SHORT COMMUNICATION

Determination of the pK_a Values of Some 1,2,4-triazole Derivatives by the Quantum Chemical Methods

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Summary: In this study, there are eight 1,2,4-triazole derivative compounds whose acidity constants were determined by computational chemistry methods (PM6, HF/6-31Gd, M06-2X/6-31Gd) in the gas and water phases. These structures were optimized through M06-2X/6-31Gd method and single point energies were calculated additionally with M06-2X/6-311+Gdp method in the water phase. These computations were carried out via GAUSSIAN 09 academic software. The obtained results were compared to both theoretical and established experimental data as well as to earlier computational method outcomes in the literature. Our findings with the M06-2X/6-311+Gdp have provided correlation with the experimental data ($R^2 = 0.9933$).

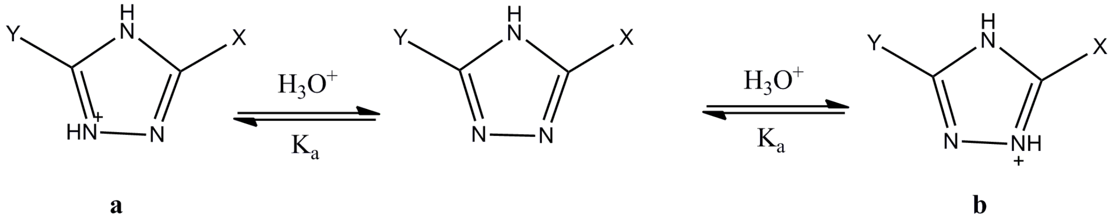
Key words: pK_a, M06-2X, PM6, 1,2,4-triazole, quantum chemical methods.

Introduction

1,2,4-triazole are chemical compounds with molecular formula C2H3N3 (a member of general triazoles group), which have a five-member ring of two carbon atoms and three nitrogen atoms (Figure 1.). As aromatic heterocycle based compounds, 1,2,4-triazole derivatives find use in a wide variety of applications [1]. Its derivatives have been presented as one of the most important biological classes of 5-membered heterocyclic compounds and their structural properties are found to form significant intermediates in the synthesis of nitrogen atom [2]. The synthesis of 1,2,4-triazole derivatives has attracted widespread attention due to their diverse biological activities, such as antibacterial [3-9], antifungal [8-10], anti-tubercular [11, 12], analgesic [13, 14], anti-inflammatory [14-16], anti-cancer [17, 18], anticonvulsant, insecticidal, anti-depressant [19-21] and antiviral properties [22]. The bioactive structures that some triazoles have displayed are comparable or even better than antibacterial and antifungal efficacy of reference drugs such as enoxacin, chloromycin and fluconazole [23].

On the other side, acid dissociation constants are essential for understanding many fundamental reactions in chemistry and biochemistry. In many cases, pK_a values can be readily measured experimentally, but the ability to computationally calculate pK_a values accurately is important for scientific advancements in biochemistry, medicinal chemistry, and other related fields [24].

In this study, our aim is to calculate the acidity constant (pK_a) of some 1,2,4-triazole derivatives. Names of studied molecules and their functional groups are listed in Table 1.



X=$-CH_3$, $-C_2H_5$, -Ph, $-NO_2$

Y=$-CH_3$, $-C_2H_5$

Fig. 1: The possible conformation of the 1,2,4-triazole derivatives.

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Table-1: Nomenclature of the studied molecules.

Molecule	IUPAC Name	X	Y
1	**4H-1,2,4-triazole**	**H**	**H**
2	**3-methyl-4H-1,2,4-triazole**	**CH3**	**H**
3	**3-ethyl-4H-1,2,4-triazole**	**C2H5**	**H**
4	**3,5-dimethyl-4H-1,2,4-triazole**	**CH3**	**CH3**
5	**3,5-diethyl-4H-1,2,4-triazole**	**C2H5**	**C2H5**
6	**3-phenyl-4H-1,2,4-triazole**	**C6H5**	**H**
7	**3-nitro-4H-1,2,4-triazole**	**NO2**	**H**
8	**3-methyl-5-nitro-4H-1,2,4-triazole**	**CH3**	**NO2**

The experimental pK_a values of these studied molecules were taken from the literature [25]. In the literature, there are two studies to determine the pK_a values of same 1,2,4-triazole molecules by E. Açıkkalp et al [26] and C. Öğretir et al [27]. The computational methods in their studies are AM1, PM3, PM5, HF/3-21G and DFT/B3LYP/6-311Gdp, respectively. An additional objective of our work is to make benchmark analysis (as compared to earlier studies) on the computational methods to determine pK_a values.

Computational Method

All of the geometry optimizations were performed by semiempirical PM6 [28, 29], ab initio Hartree-Fock (HF/6-31Gdp) and density functional theory (DFT) M06-2X/6-31Gd methods [30] in the gas phase. Solvation energies were calculated by using PM6 and M06-2X/6-311G+dp methods and the polarizable continuum model solvent was chosen as water (Eps= 78.355300). M06-2X function has been used for dispersion effects and long-range interactions and it is highly recommended for calculation of activation energy barriers [30]. In the literature to calculate pK_a values of some imidazole molecules with the theoretical approach B3LYP/6-31+G(d,p) method was chosen by Brown an coworkers [31]; HF/6-31Gdp and DFT/B3LYP/6-31G(d,p) were chosen for some organic acids by Hazarika [32]; to calculate of pK_a values of thiols compounds were chosen DFT/WB97XD/6-31+G(d,p) level of theory by Thapa[33]. All calculations were performed using the Gaussian09 suite of programs [34] and visualization was done with GaussView 5.0. The optimized structures of the studied geometries were characterized by real frequencies. The free energy of solvation $\ddot{A}G_{aq}$, and the corresponding pK_a values have been calculated by using eq.2-5.

Determination of pK_a values

To determine theoretical pK_a values of the studied molecules, following equilibrium equation were used:

$$A+H^+ \xrightleftharpoons{pK_a} AH^+ \qquad (1)$$

where K_a is the equilibrium constant of the protonation (1)

$$\Delta G=G^+_{AH} - (G_A + G^+_H) \qquad (2)$$

ΔG is the corresponding free energies difference.

$$\Delta G=-RT\ln K_a \qquad (3)$$

The acidity constant, K_a, can be calculated by using Eq.3

$$pK_a= \Delta G/2.303RT \qquad (4)$$

By representing lnK_a in terms of ΔG, R and T from Eq.3 and by converting it to proper format, pK_a expression in Eq.4 has been obtained. ΔG^o_{aq} values were calculated, one of the most common methods, proton-based thermodynamic cycle, is depicted in Figure 2, as in the following equation (Eq.5)[35];

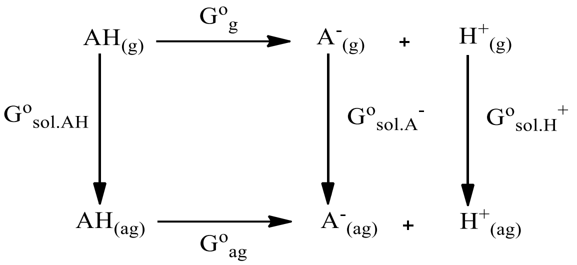


Fig. 2: Proton-based thermodynamic cycle.

$$\ddot{A}G^o_{aq} = [\ddot{A}G^o_s(A^-) + \ddot{A}G^0_s(H^+) - \ddot{A}G^o_s (AH)] + [\ddot{A}G^o_g(A^-) + \ddot{A}G^o_g (H^+) - \ddot{A}G^o_g (AH)] \qquad (5)$$

(Where R is the gas constant ($R=1.987x10^{-3}$ kcal/mol/K) and T is the absolute temperature in Kelvin as T=298 K)

Results and Discussion

In this study pK_a for eight 1,2,4-triazole derivatives were calculated (Table 2). The experimental pK_a values between the numbers of the calculated pK_a values could not be obtained from an absolute fit**.** However, when the experimental data with all of the methods is examined, regression analysis shows a good fit between calculated and experimental results (Table-3). The gas phase optimization increased in accordance with the experimental data when it is repeated in the aquatic environment. When compared with Açıkkalp and coworker's study results (Theoretical/ Experimental= R^2=0.0106-0.4808) [26] our calculated data were found to be 0.9830. The semiempirical method PM6 that we have used has given better results in both gas phase and aqueous phase than other methods, with especially a good R^2 (0.9830) value in aqueous phase. The method of PM6 has proven to give the best value compared with the other high level semiempirical methods [35].

HF/6-31Gdp method has shown to be the best fit compared with other calculated methods in the gas phase (R^2=0.9633). When Table 2 is analyzed, M06-2X/6-31Gd method results with 7 and 8 negative pK_a values conform to the experimental data obtained from molecules for only gas phase studies. On the other hand, the best correlation with the experimental data versus calculated pK_a in the water phase was obtained with the M06-2X/6-311+Gdp level of theory with R^2 value 0.9933. In literature C. Öğretir and his group (2010) obtained a good R^2 value (1) with DFT/B3LYP/6-311G (d,p) [27]. However, compound 1 was excluded from their study to reach this value (R^2 = 1). When the calculations are done including compound 1 with the M06-2X/6-311+Gdp method, the study yielded results in almost complete accordance with the experimental data by Atalay and her group [36]. The R^2 values between calculated and experimental pK_a values in the literature were obtained 0.942-0.966 for some thiol molecules with the □B97XD/6-31+Gdp calculation method. Brown and coworkers [37] established a strong correlation between experimental and calculated pK_a values for some of the benzimidazoles, that are similar to our study, whose derivatives′ calculated are obtained at the B3LYP/6-31+Gdp-PCM level of theory. This basis set is good for modeling of imidazol derivatives because of the select it take in to account polarz. In our study computational method of pK_a proves to be a good choice of determination for M06-2X method and 6-311++Gdp basis set. Schlegel and coworkers showed that to calculate the precise pK_a values polarization functions on the hydrogens and diffuse functions on the heavy atoms are needed [33].

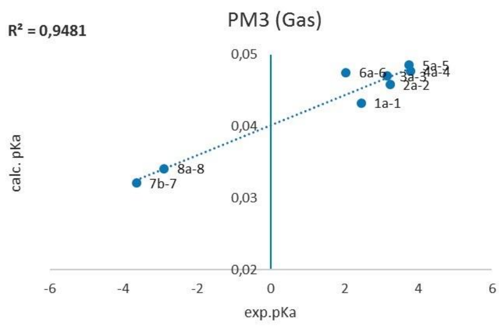
The following calculation shows obtained pK_a values graph against experimentally obtained pK_a values graph (Graph 1.). A small deviation from experimental data was observed during gas phase research (Graph 1.a, 1.c, 1.d). Also, when all aqueous phase transition was studied two methods have also caught quite a good combination (Graph 1.b, 1.e).

Table-2: Calculated and experimental pK_a values of the studied molecule.

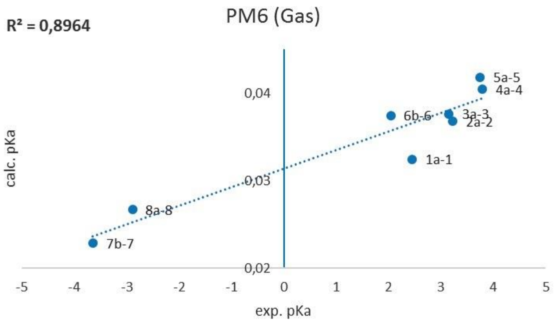
Molecule	Exp pK_a [26]	PM3 (Gas)	PM6 (Gas)	PM6 (Water)	HF/ 6-31Gdp/(Gas)	M06-2X/6-31Gd/(Gas)	M06-2X/ 6-311+Gdp/(Water)
1	2.45	0.0433	0.0325	0.0150	0.0405	0.0385	0.0231
2	3.23	0.0458	0.0368	0.0161	0.0454	0.0432	0.0252
3	3.15	0.0470	0.0376	0.0160	0.0467	0.0446	0.0251
4	3.79	0.0477	0.0405	0.0170	0.0488	0.0466	0.0265
5	3.75	0.0485	0.0418	0.0167	0.0506	0.0485	0.0262
6	2.04	0.0475	0.0375	0.0148	0.0454	0.0454	0.0231
7	-3.65	0.0321	0.0231	0.0052	0.0232	-1.1159	0.0147
8	-2.89	0.0341	0.0267	0.0083	0.0269	-1.1458	0.0156

Table-3: Regression scores depend on the method.

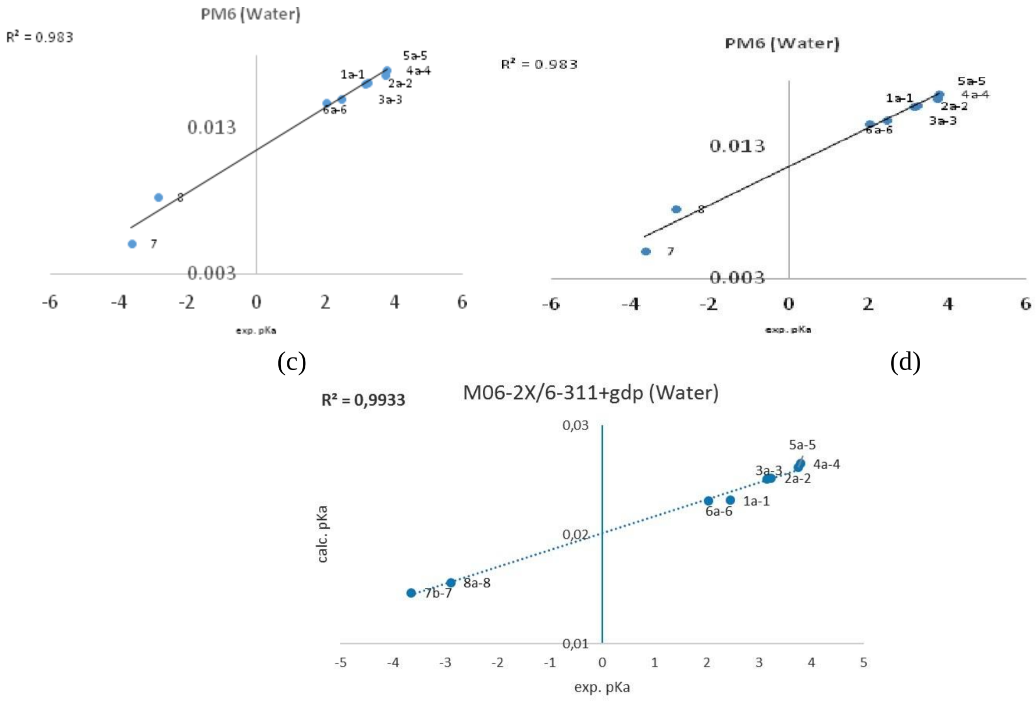
Method	PM6/	PM6/	HF/6-31Gdp	M06-2X/	M06-2X/	AM1/	PM3/	PM5/	DFT/B3LYP/	
		(Gas)	(Water)	(Gas)	6-31Gd /(Gas)	6-311+Gdp /(Water)	(Water) [26]	(Water) [26]	(Water) [26]	6-31Gdp /(Water)[27]
	R^2	0.8958	0.9830	0.9633	0.9554	0.9933	0.3561	0.4808	0.0106	1



(a)



(b)



(c) (d)

(e)

Graph 1. Experimental versus calculated pK_a values by different methods, in the gas and water phases.

Conclusion

In this study, pK_a values are calculated with computational methods for eight 1,2,4 triazole derivatives. The results obtained are compared with the experimental data in literature and the results of the selection method were observed to be very good. Especially, R^2=0.9933 values that obtained with M06-2X/6-311+gdp method (in water) and experimental data were found to be almost in complete harmony. As for R^2 values obtained from other working method it has revealed that a preferable method in theoretical pK_a determination operation with semiempirical PM6 method with the results obtained in the aqueous medium should be calculated to give values close to the high-level method M06-2X methods.

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