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Determination of the pK_a values of some pyridine derivatives by computational methods

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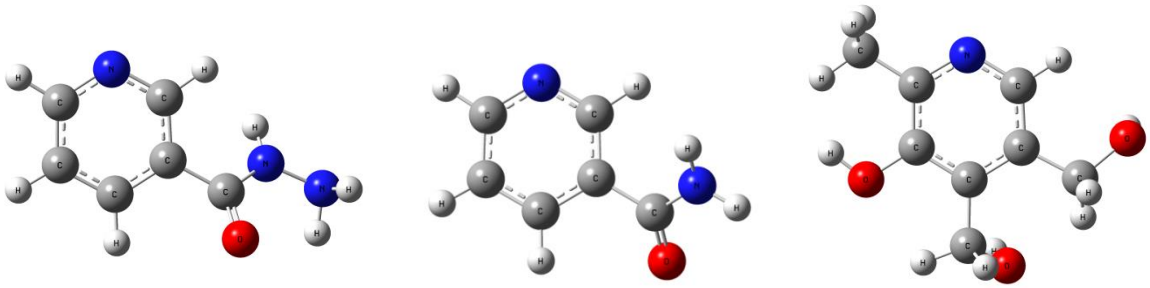
In this study, pK_a values are determined relying on density functional theory, its related methods such as WB97XD, M062X, B3LYP with 6-31+Gdp and 6-311++Gdp basis sets for three pyridine derivatives, namely isoniazid, nicotinamide and pyridoxine. When investigating the obtained values, the most accurate values are found to be obtained *via* the WB97XD method with 6-31+Gdp basis set in water phase. The pK_a values calculated in the gas phase were not satisfactory enough to compare with the experimental results.

Keywords: pK_a, DFT, M06-2X, WB97XD, B3LYP, pyridine

INTRODUCTION

Pyridine with C_5H_5N chemical formula is a basic heterocyclic aromatic compound [1]. Pyridine became a much interested compound in 1930s with the importance of its role in the disease treatment [2]. It's derivatives have been reported for a variety of biological activities and were used in clinical uses, such as anti-microbial [3-5], anti-viral [6-8], antioxidant [9], anti-diabetic [10] anti-cancer activities [11], anti-malarial agents [12], psychopharmacological antagonistic [13], iron overload disease [14], anti-amoebic agents [15], anti-inflammatory agents [16]. Pyridine derivatives in these fields also have increasing importance for modern medicinal applications, especially they have an important role to develop human medicine. There are more than hundred drugs in the market containing pyridine compounds [1]. In this study, three heterocyclic pyridine derivatives, namely isoniazid, pyridoxine hydrochloride and nicotinamide were investigated (Figure 1).



(a) (b) (c)

Figure 1. Investigated drug molecules: (a) isoniazid, (b) nicotinamide, (c) pyridoxine

Acid dissociation constants, K_a, are essential for understanding many fundamental reactions in chemistry and biochemistry of a drug precursor, such as tautomeric equilibrium, activity searches and determination of certain physical parameters. Especially determination of pK_a values of drugs gains paramount significance from the perspective of dosage form formulation, pharmaceutical analysis, and studying of drug pharmacokinetics. Solubility, lipophilicity, protein binding and membrane permeability of a given drug are also influenced by its pK_a value [17]. Several techniques have been used for pK_a determinations, such as potentiometric titration, spectrophotometric method, NMR titration, liquid chromatography (LC), capillary electrophoresis (CE) and computational methods [18]. Experimental measurements are generally less simple, as there would be considerable synthesis and purification efforts prior to the pK_a measurement. The ability of accurate computational calculating pK_a values is important for scientific advancements in biochemistry, medicinal chemistry, and other related fields [19]. In this study, the pK_a values of

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three active drug compounds were determined by a theoretical approach in order to compare computationally obtained values with the experimental values.

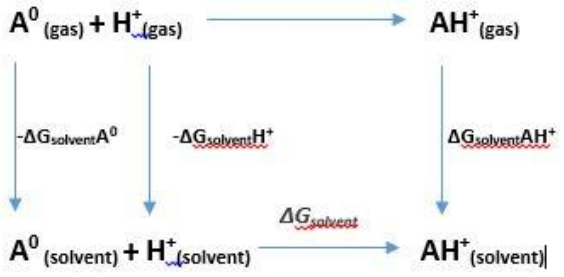
Method

Firstly, conformer search was performed with the Spartan14 [20] with a semi-empirical PM6 method [21, 22]. Geometry optimizations were performed for the obtained most stable structures in gas and water phases. The Gaussian 09 software [23] was used for all theoretical calculations, and all visulalizations were done with GaussView5 [24]. In the literature there are several studies on pKa detemination with density functional theory (DFT) [25-29]. DFT's ability to accurately compute ground-state observable properties has given its remarkable ease of use and its ability to effectively balance accuracy with computational speed when compared to traditional high-accuracy *ab initio* methods [30-32]. B3LYP [33], M062X [34] and WB97XD [35] were preferred as calculation methods with 6-31+Gdp and 6-311++Gdp basis sets in the gas and water phases for the investigated isoniazid, nicotinamide and pyridoxine molecules. IEF-PCM method [36] was applied to solvent phase calculation.

Determination of pK_a values

First principles computations have historically relied on thermodynamic cycles, taking advantage of the fact that the Gibbs energy is a state function, and therefore any convenient cycle that connects the initial reactants to the final products provides a way to calculate the Gibbs energy change for the reaction of interest [37]. The quality of calculated pK_as depends on the accuracy of the computed protonation energies and the reliability of the estimated solvation energies [28]. The pK_a values were calculated by the following Scheme 1 and Eqs.1-4:

$A + H^+ \leftrightarrow AH^+$ (protonation reaction)



Scheme 1. Thermodynamic cycles of the Gibbs free energies in gas and solvent phases [38].

The Gibbs free energy (ΔG) for the investigated compounds in the gas phase was determined by Eq.1 [39]:

$$\Delta G = \Delta H - T\Delta S \qquad \text{Eq. 1}$$

The pK_a values for the gas phase were calculated by Eq. 2:

$$pK_a = \Delta G/R/T/2.303 \qquad \text{Eq. 2}$$

On the other side, for the solvent phase, ΔΔG values were calculated *via* Eq. 3 and the obtained values were used to determine the pK_a values *via* Eq. 4 [37]:

$$\Delta\Delta G = \Delta G_{solvent} + \Delta G_{gas} + \text{correction factor } (R*T*In\ (24.46)) \qquad \text{Eq. 3}$$

$$pK_a = \Delta\Delta G/R/T/2.303 \qquad \text{Eq. 4}$$

RESULTS AND DISCUSSION

The calculated and literature data based pK_a values for the nicotinamide, isoniazid and pyridoxine compounds are listed in Table 1. The calculated results are compared with the literature data. The comparison results show that the choice of method was quite adequate. However, the pK_a values in the gas phase are somewhat different from the water phase calculations and experimental values with almost 0.2-0.9 difference in all studied methods and basis sets. The calculated pK_a value for nicotinamide with WB97XD method 6-31+Gdp basis set in water is the same (pK_a=3.35) as the literature value. In the literature, the same method has been found to provide the best correlation with the experimental data for the thiol molecules [37]. For the pyridoxine compound, the WB97XD method calculated the relevant value (pK_a=5.25) with the slightest difference (0.05) as compared to the literature value (pK_a=5.20). When the WB97XD method results are compared with experimental NMR results, we can observe that especially for the pyridoxine molecule, the experimental values (pK_a=5.24) are closer to the obtained value by the WB97XD method and this result is consistent with the literature [27]. When we look for the best pK_a value for the isoniazid compound, WB97XD/6-311++Gdp level of theory gives pK_a=3.36 (nearest obtained value through computational methods), whereas the corresponding pK_a value in the literature is 3.50. The obtained results show that WB97XD is a more suitable method for this kind of molecules.

On the other hand, M062X methods provide accurate results for the investigated molecules, especially with 6-31+Gdp basis set in water phase. For nicotinamide, the calculated pK_a value (3.39) is lower than the literature value with a small

difference (0.04) which is a quite good result in the water phase. For isoniazid molecule, the computationally obtained value by the same method is 3.23, as compared to the 3.20 value through the web-based calculation method.

The B3LYP/6-31+Gdp method has also given close results with the NMR methods for the nicotinamide molecule, pK_a= 3.57 and pK_a=3.54, respectively. The results of this method are closer to the web-based calculation results for other investigated compounds in water phase obtained as pK_a=3.29 (calculated) and pK_a=3.20 (web-based); pK_a=5.65 (calculated) and pK_a=5.60 (web-based) for isoniazid and pyridoxine compounds, respectively. In general sense, the B3LYP method has not given good matching performance with respect to other studied experimental methods in the literature.

Table 1. The calculated pK_a values with the DFT theory B3LYP, WB97XD and M062X methods, 6-31+Gdp and 6-311++Gdp basis sets in the gas and water phases

	Compound		
Method/phase	Nicotinamide	Isoniazid	Pyridoxine
B3LYP/6-31+Gdp/gas	4.17	4.12	4.98
B3LYP/6-31+Gdp/water	3.57	3.29	5.65
B3LYP/6-311++Gdp/gas	4.18	4.13	4.98
B3LYP/6-311++Gdp/water	3.42	3.30	5.64
WB97XD/6-31+Gdp/gas	4.08	4.03	4.88
WB97XD/6-31+Gdp/water	**3.35**	3.22	**5.25**
WB97XD/6-311++Gdp/gas	4.09	4.03	4.87
WB97XD/6-311++Gdp/water	3.47	**3.36**	5.34
M062X/6-31+Gdp/gas	3.85	3.79	4.69
M062X/6-31+Gdp/water	3.39	3.23	5.30
M062X/6-311++Gdp/gas	3.87	3.82	4.72
M062X/6-311++Gdp/water	3.45	3.25	5.33
NMR Method [40]	3.54	3.65	5.24
Literature	3.35 [41]	3.50 [42]	5.20 [43]
Web-Based Calculation [44]	3.60	3.20	5.60

CONCLUSION

In this study, three pyridine derivatives, namely nicotinamide, isoniazid and pyridoxine were investigated to determine the pK_a values and compare them with the experimental data. DFT theory was chosen with WB97XD, M062X and B3LYP methods using 6-31+Gdp and 6-311++Gdp basis sets. According to the obtained results the WB97XD/6-31+Gdp method has given more accurate computational values that are consistent with the experimental values in the literature. On the other hand, M062X and B3LYP methods have not reached satisfactory convergence performance to the experimental values. As an important emphasis, condensed phase results are significantly better than gas phase results. The essential result is that the WB97XD method was found as an excellent option to determine the pK_a values of pyridine family derivatives through theoretical approaches, as demonstrated by the fact that our computational findings very closely match the experimental data.

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