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Quantum chemical studies on protonation of some substituted thiazole derivatives

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Abstract

The acidity constants, pK_a values for protonation of some substituted thiazole derivatives were calculated by using AM1 and PM3 basis sets of semi-empirical methods and B3LYP/6-31G(d) basis sets of density functional theory (DFT) calculated physical and thermodynamic parameters. Correlation search among the experimental and calculated acidity constants, pK_a values, revealed that the best correlation exist between the experimental and *ab initio* calculated pK_a values with a regression of $R^2 = 0.98$.

Keywords: Protonation; Substituent constants; Acidity; Basicity; Proton affinity; Electronic charge; Thiazole; Nucleophilicity

1. Introduction

The acidity or basicity of a molecular site is 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 of processes. The basicity, besides being related to the acidity, can easily be related to the nucleophilicity of the basic site. Whether, the application is polymers or pharmaceuticals, the understanding of the acidity or basicity of molecule is fundamental to molecular design and mechanistic understanding. If the acidity and basicity can be reliably and quickly estimated without the normal synthesis and experimental determination, the efficiency and productivity will greatly be enchanted. Recently several computational approaches have been applied in estimating acidities and basicities which are used in interpretation of structure reactivity relations safely [1,2].

Since thiazole moiety is present in the structure of many biologically active compounds such as thiamine, penicillin G, amphetamine drugs and used an analytical reagent in analysis of heavy metals such as cadmium, lead, copper and gold [3], as an active centre we believe that thiazole derivatives deserve a close theoretical investigation to study structure–reactivity relationships, and performed some quantum chemical calculation on some thiazole derivatives (Table 1) and we are now reporting on the obtained results and evaluation of them.

2. Methods of calculations

Ab inito Hartree-Fock and density functional geometry optimisations were performed with the Gaussian 98 program system [4]. The optimisations were done using HF/3-21G method. These results were re-optimised at the B3LYP type of Density Functional Theory by using the larger basis set 6-31G(d). The *ab initio* geometries were employed in calculating the solvation free energies carried out using at the B3LYP/6-31G(d). The total energies are given in hartree using the conversation factor 1 hartree = 627.5095 kcal mol^{-1}. The value of $\Delta G_s(H^+)$ was taken as -259.5 kcal mol^{-1} [5].

Semi-empiric theoretical calculations were carried out at the restricted Hartree-Fock level (RHF) using AM1 and PM3 [6] semi-empirical SCF-MO methods in MOPAC 7.0 program [7] implemented on an Intel Pentium Pro 133 MHz computer, using a relative permittivity of 78.4 corresponding to water, with up to 60 surface segments per atom for the COSMO model being used to construct a solvent accessible surface area based on van der Waals radii [8]. All structures were optimised to a gradient norm of <0.1 in the gas phase and 0.1–1.0 in the

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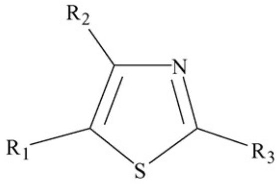
Table 1
Nomendate of the studied thiazole derivative



	R$_1$	**R$_2$**	**R$_3$**
1	–H	–H	–H
2	–H	–H	–CH$_3$
3	–CH$_3$	–H	–H
4	–H	–CH$_3$	–H
5	–H	–H	–NO$_2$
6	–NO$_2$	–H	–H
7	–H	–NO$_2$	–H
8	–CH$_3$	–H	–CH$_3$
9	–H	–CH$_3$	–CH$_3$
10	–CH$_3$	–CH$_3$	–H
11	–CH$_3$	–H	–NO$_2$
12	–H	–CH$_3$	–NO$_2$
13	–NO$_2$	–H	–CH$_3$
14	–NO$_2$	–CH$_3$	–H
15	–CH$_3$	–NO$_2$	–H
16	–H	–NO$_2$	–CH$_3$
17	–CH$_3$	–CH$_3$	–NO$_2$
18	–NO$_2$	–CH$_3$	–CH$_3$
19	–CH$_3$	–NO$_2$	–CH$_3$

aqueous phase. The absolute entropies of all structures were calculated from a complete vibrational analysis. Enthalpies were corrected to free energies using calculated enthalpies. Initial estimates of all the structures were obtained by a molecular mechanics program (CS Chem Office Pro for Windows) [9], followed by full optimisation of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using the semi-empirical AM1 and PM3 quantum chemical methods in the MOPAC 7.0 program.

2.1. Absolute and relative pK_a calculations

The interrelationship between gas–liquid phase acidities can be seen in Scheme 1 and taking the general equilibrium (1) into account, where n can have negative, positive or zero value, the Eq. (2) can be driven for the free energy calculation. Eqs. (3) and (4) describe the absolute and relative pK_a values, respectively. In Eq. (3) ΔG_g and ΔG_a are the gas phase and solutions free energies of the ionisation, respectively. The ΔG_s's are solvation free energies. For *ab initio* calculations ΔG_g is the differences between thermal and solvation energies of the protonated and unprotonated species. The appropriate $\Delta G_{s(H^+)}$ values were appointed by the program with a changing values from -240 to -270 kcal mol^{-1} for *ab initio* calculations.

$$BH^{n+} \rightleftharpoons B^{(n-1)+} + H^+ \qquad (1)$$

$$\delta\Delta G_{(BH^+)} = [\Delta G_{(B)} + \Delta G_{(H_3O^+)}] - [\Delta G_{(BH^+)} + \Delta G_{(H_2O)}] \qquad (2)$$

Absolute pK_a :

$$pK_a = [\Delta G_g + \Delta G_{s(B)} - \Delta G_{s(BH)} + \Delta G_{s(H^+)}]/2.303RT \qquad (3)$$

Relative pK_a : $$pK_{a(BH^+)} = \delta\Delta G_{(BH^+)}/2.303RT \qquad (4)$$

3. Results and discussion

A list of the studied thiazole derivatives and their protonation pattern are given in Table 1 and Scheme 2, respectively. Both semi-empirical and *ab initio* gas phase calculated physical parameters and aqueous phase calculated acidity constants are depicted in Tables 2–7.

Comparing to semi-empirically calculated pK_a values the *ab initio* calculated pK_a values which were calculated using the computed parameters and were depicted in Tables 2–4, respectively are much closer to that of experimental ones (Table 5). The correlation search between calculated and experimental pK_a values indicate that the best correlation exists between the pK_a (*ab initio* calc.) and pK_a (experimental) values (Fig. 1) (i.e. $R^2 = 0.98$ and the slope is 1.18) with the exception of the pK_a value of thiazole molecule itself. The next best correlation was observed between the experimental, and PM3 calculated pK_a values for the increasing order of basicity.

As it can be seen in Scheme 2 the only potential protonation centre in the studied molecules is the azo nitrogen atom of the thiazole ring. The changes in strength of basicity or acidity inevitably arises from the different substituents at different positions which in turn may causes changes in geometries and perturbate the electronic configuration of molecules. So taking these points into account in discussion of basicity and/or acidity power is a necessity.

Expectedly, the basicity of a molecule increases when an electron-donating group such as methyl (i.e. donates electron to the ring inductively) is placed at 2C, 4C or 5C positions. The increasing order of basicity was found as follows:

$$\begin{array}{cccccccl}
\mathbf{1} & & \mathbf{2} & & \mathbf{3} & & \mathbf{4} & \\
\text{H} & < & \text{5-Me} & < & \text{4-Me} & < & \text{2-Me} & \text{by experimental } pK_a \text{ values} \\
\mathbf{1} & & \mathbf{2} & & \mathbf{4} & & \mathbf{3} & \\
\text{H} & < & \text{5-Me} & < & \text{2-Me} & < & \text{4-Me} & \text{by AM1 } pK_a \text{ values} \\
\mathbf{1} & & \mathbf{2} & & \mathbf{3} & & \mathbf{4} & \\
\text{H} & < & \text{5-Me} & < & \text{4-Me} & < & \text{2-Me} & \text{by PM3 } pK_a \text{ values} \\
\mathbf{3} & & \mathbf{2} & & \mathbf{4} & & \mathbf{1} & \\
\text{4-Me} & < & \text{5-Me} & < & \text{2-Me} & < & \text{H} & \text{by ab initio } pK_a \text{ values}
\end{array}$$

← decrease of basicity increase of basicity →