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Calculation of Acidity Constants of Some Substituted Thiazole Derivatives Using DFT and UV Spectroscopic Methods

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Abstract

The acidity constants of the compounds, including five-membered heterocyclic (pyrrole, thiophene, furan or thiazole) ring systems were determined at 25^{o}C in aqueous solitions, applying UV-Vis spectroscopic method that uses absorbance diagrams,. In order to explain the pK_a values obtained, also the molecule conformations of the bases and their corresponding conjugate acids were investigated, applying density functional theory methods. Basis set at the B3LYP/ 6-31 G(d) level of theory was used for calculations. The results obtained from the calculations were compared with the experimental findings. It seems that high coefficient of correlation for the calculation in determination of acidity constants were observed.

Keywords: *Pyrrole, Thiophene, Furan*

Özet

Beş üyeli (pirol, tiyofen, furan veya tiyazol) heterosiklik halka sistemlerini içeren bileşiklerin asitlik sabitleri sulu ortamda ve oda sıcaklığında UV-Vis spektroskopik metodu kullanılarak hesaplanmıştır. Hesaplanan pKa değerlerinin açıklanması için aynı zamanda moleküllere ait bazları ve karşılık gelen konjuge asitleri yoğunluk fonksiyonu teorisi metotları uygulanarak incelenmiştir. Temel olarak hesaplamalarda B3LYP/ 6-31 G(d) metodu kullanılmıştır. Hesaplamalardan elde edilen sonuçlar ile deneysel sonuçlar karşılaştırılmıştır. Asitlik sabitlerinin incelenmesinde yüksek korelasyon katsayıları elde edildiği gözlenmiştir.

Anahtar Kelimeler: *Pirol, Tiyofen, Furan*

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1. Introduction

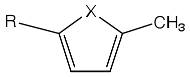
It is well-known that the acidity constants are considerable for the development of new compounds with biological activity. For the determination of acidity constants; capillary electrophoresis [1-2], calorimetric adsorption method [3], potentiometric titration method [4-6], chromatographic methods [7,8] and IR, NMR or UV-visible spectrometric [9-17] determinations in water or in mixtures of solvents are used .

In addition to experimental methods, quantum chemical methods has been developed for the calculation of pK_a values based on chemical structures. Therefore, there exist some studies dealing with the acid–base properties of compounds in aqueous solutions and in gas phase [18-21]. It is useful, therefore, to have reliable and accurate means of calculating relative and/or absolute pK_a values and to have an understanding is essential for the measured effective pK_a values in molecules.

Pyrrole, furan, thiophene and thiazole are well known examples of five-membered heterocyclic aromatic organic compounds [22-24]. The thiazole is a crucial part of vitamin B1 and epothilone [25]. Pyrroles are components of larger aromatik rings, including the porphyrins of heme, the clorins and bacteriochlorins of chlorophyll, and the corrin ring of vitamin B12 [26]. Thiophenes are important heterocyclic compounds and are recurring building blocks in organic chemistry with applications in pharmaceuticals. The benzene ring of a biologically active compound may often be replaced by a thiophene without loss of activity. This is seen in examples such as the NSAID lornoxicam, the thiophene analog of piroxicam. Thiophenes are used as synthetic intermediates, taking advantage of the susceptibility of the carbon atoms adjacent to S toward electrophilic reactions. The polymer formed by linking thiophene through its 1,5 positions is called polythiophene. Polythiophenes become electrically conductive upon partial oxidation, i.e. they become organic metals [27].

Due to existence of five membered rings in natural structures they have been prepared synthetically and theoritical or spectroscopic calculations done in the literature [28, 29]. In this work I report the theoretical and experimental calculations of the synthesized pyrrolyl, furanyl and thiophenyl, 2-thiazole- derivatives (TABLE I) in the aqueous phase. The results obtained from quantum chemical calculations have been compared with the experimental values. Physicochemical properties of molecular compounds strongly depend on the protonation pattern. Therefore, computational methods that reliably predicted protonation patterns in terms of pK_a values would be of general use.

Table 1. The compounds that studied in this work.



Compound	R	X	IUPAC Name
1	2-thiazolyl	NH	2-methyl-5-(2-thiazolyl)pyrrole
2	2-thiazolyl	O	2-methyl-5-(2-thiazolyl)furan
3	2-thiazolyl	S	2-methyl-5-(2-thiazolyl)thiophene

2. Experimental

The determination of acidity constants by UV spectroscopy is an ideal method when the compound is too insoluble for potentiometry or when its pK_a value is particularly low or high. Under suitable conditions, it is the most accurate method, as all measurements being taken in very dilute solutions [30]. The spectroscopic technique is based on the fact that, for solutions containing only the fully protonated or the totally nonprotonated species, there will be an absorption due to both the free base (neutral molecule) and conjugate acid. An analytical wave length is chosen where there is the greatest diffrence between the absorbances of the two species and the procedures depends upon the the direct determination of the ratio of neutral molecule to ionized species in series of non-absorbing buffer solutions of known *pH* (Fig 1).

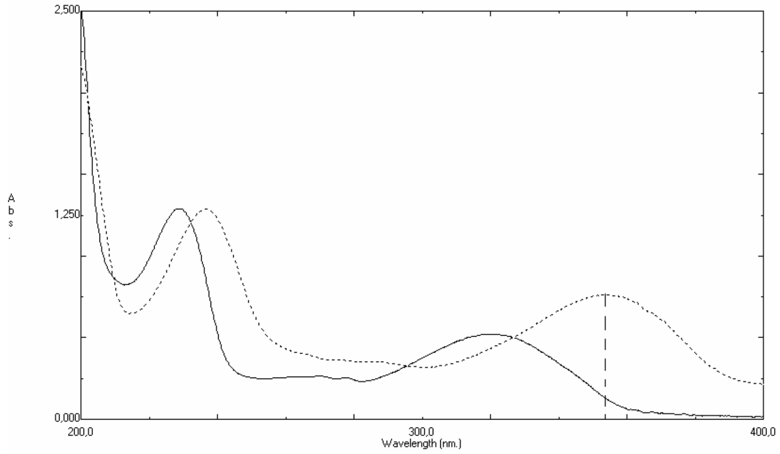


Fig.1. Absorption spectra of 2-methyl-5-(2-thiazolyl)pyrrole at different pH. The arrow indicate the selected wavelength for the absorbances measured.

Measurement of the absorbance at chosen wavelength for solution over a range of *pH* values gives the ratio of neutral to ionized species and the pK_a of the compound can be calculated [31]. For the calculations of the two species present at any *pH*, it is assumed that Beer's law is obeyed for both species. Thus, the absorbance, *A*, at the chosen wavelength will be equal to the sum of the absorbances of the free base, A_{BH+}, and conjugate acid A_{BH+}. By using Beer Lambert's law:

$$A = \varepsilon \times C \times l \qquad (1)$$

where ε = extinction coefficient, *C*= concentration, and *l*= optical path length of the cell. Below equation can be used to determine the pK_a of the compound.

$$pK_a = pH + \log \frac{A_B - A}{A - A_{BH+}} \qquad (2)$$

Thus, from a knowledge of the absorbance of the base and its conjugate acid and by measuring the variation of the absorbance of the solution with its acidity, the pK_a can be calculated (eq. 2). As the acidity is increased the solution changes from 100% free base to 100% conjugate acid giving a sigmoidal curve for the absorbance as a function of *pH* (H_o) (Fig. 2).

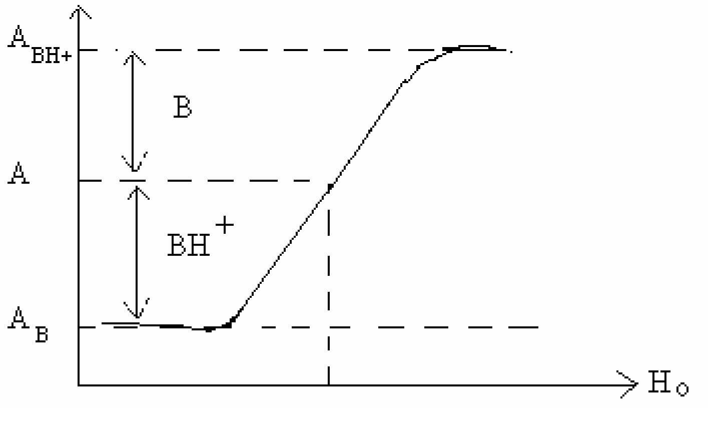


Figure 2. The e_{max}. as a function of *pH* for the protonation of molecule.

In an ideal case, the spectra of a set of solutions, in which free base and conjugate acid are present in different amounts, show a common point of intersection known as the isobestic point.

2.1. Reagents

Sulphuric acid , hydrochloric acid and sodium hydroxide were from Merck and were not purified further. Acid solutions were standartized by titration against 1N standart sodium hydroxide. *pH* solutions for UV technique were prepared using 1N sulphuric acid, sodium acetate, sodium dihydrogen phosphate and disodium hydrogenphosphate.

2.2. Procedure.

pH measurements were performed using a glass electrode. Standart buffer solutions of *pH* values of 1, 7, and 14 were used in the calibration of the Corning *pH*/ion analyzer 350 Meter and the Ohaus Adventurer balance; a Shimadzu UV2101 PC UV-vis scanning spectrometer was used for measurements. For the sodium acetate- sulphuric acid system, 200ml. 1N solution of sodium acetate was used in each buffer, whilst fort he sodium dihydrogen phosphate-sulphuric acid system, 250ml. 1N solution of the phosphate was used in each buffer. All buffers were calibrated on a *pH*-meter.

The general procedure applied was as follows [32]: A stock solution studied was prepared by dissolving an accurately weigth sample of the compound in ethanol. A 1ml of this solution was diluted to 100ml. with the buffer solutions of different *pH*. The *pH* of the buffered solutions was measured before and after addition of the compound. The optical density of each solution was then measured in a 1cm. cell, against the solvent blanks at 25^{o}C. Measurements of the absorbance were made at a number of frequencies, some at the absorption maxima of the species involve where the absorbance of one species is very high and the absorbance of the other is fairly low. Other frquencies were also chosen, for example onthe side peak where there was a shoulder, where possible the absorbance region measured lay between 0.2 and 1, since this is the most accurate region of the instrument. The ε values of the protonated molecule (ε_p) and the free base (ε_{fb})were calculated by using Beer Lambert’s law. The ionization ratio, where the ε is the measurement of extinction coefficient of the solution at the analytical wavelenth;

$$I = \frac{[BH^+]}{[B]} = \frac{\varepsilon - \varepsilon_{fb}}{\varepsilon_p - \varepsilon} \tag{3}$$

An approximate value of the pK_a of the compound was first obtained using equation (3), and a set of buffer solution were then made up at *pH* values equal to this pK_a. The pK_a values, obtained from measurements of the spectra in these solutions where $-1.0 < \log I < +1.0$ gave an exact values of pK_a with its the standart deviation.

$$pK_a = pH + \log I \tag{4}$$

3. Calculations

Ab initio Hartree-Fock and density functional geometry optimizations were performed with the Gaussian 03W program system[32]. The optimizations were done using HF/3-21G method. The results were re-optimized 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 acidity constants is directly related to the free energy of the deprotonation reaction

$$AH \rightleftarrows A^- + H^+$$

and defined as given in Equation 5

$$pK_a = \Delta G_R / 27.303\, RT \tag{5}$$

The deprotonation of a compound in aqueous solution can be represented as a part of a thermodynamic cycle (Fig. 3).

$$\begin{tikzcd}
AH_{(g)} \arrow[r, "\Delta G_{gas}"] \arrow[d, "\Delta G_{sol}\,(AH)"'] & A^-_{(g)} \arrow[d, "\Delta G_{sol}\,(A^-)"'] & + & H^+_{(g)} \arrow[d, "\Delta G_{sol}\,(H^+)"] \\
AH_{(aq)} \arrow[r, "\Delta G_R"] & A^-_{(aq)} & + & H^+_{(aq)}
\end{tikzcd}$$

Figure 3. Interrelationship between the gas phase ans solution thermodynamic parameters

Figure 3 explains the interrelationship between the gas and solution thermodynamic parameters[33]. One part of this cycle, ΔG_{gas} is the gas-phase deprotonation energy of the molecule. Three other parts $\Delta G_{sol}\ (AH)$, $\Delta G_{sol}\ (A^-)$, $\Delta G_{sol}\ (H^+)$ are the free energy of solvation of the protonated and deprotonated form of the molecule and the proton, respectively. The last part of the cycle ΔG_R, is the free energry of deprotonation in solution and can be calculated as given in Equation 6.

$$\Delta G_R = \Delta G_{gas} + \Delta G_{sol}\ (A^-) + \Delta G_{sol}\ (H^+) - \Delta G_{sol}\ (AH) \qquad (6)$$

The total energies are given in Hartrees using the conversation factor 1 Hartree = 627.5095 kcal mol^{-1}. The value of $\Delta G_{sol}(H^+)$ was taken as -259.375kcal mol^{-1}, the mean value of range between -220 and -270 kcal mol^{-1}.

4. Results and Discussion

Absorbance values, the pK_a values calculated as shown in procedure, and the corelations obtained for the various compounds under investigation are listed in Table 2.

Table 2. Acidity constants pK_a, of compounds 1-6 for protonation.

Compound	λ^a/nm	$H^{1/2b}$	m^c	pK_a	Corr.^{d}
1	354,0	3,34	0,73	3,34	0,92
2	360,3	4,67	0,55	2,43	0,94
3	355,4	4,22	0,54	2,28	0,92

^{a}Analytical wavelength for pK_a measurements, ^{b}Half-protonation value, ^{c}Slopes of log$I$ as a function of pH graph, ^{d}Correlations for log$I$ as a function of pH graph.

The pK_a values are subject to base weaking electron withdrawing inductive effects and mesomeric the base stregthening electron donating effects of the heteroaryl groups. The protonation may be from thiazole nitrogen as shown in Figure 4.

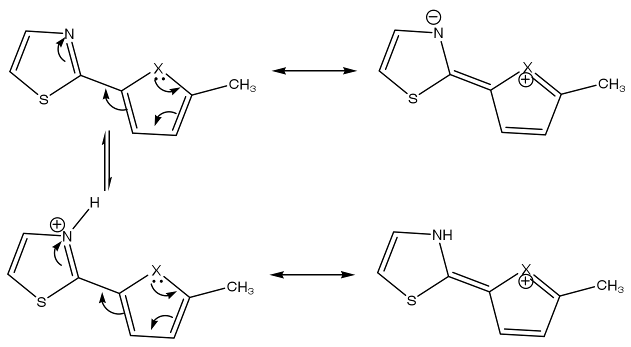


Figure 4. The possible tautomers and the rezonance of the compounds

Acidity constants and physical parameters of the studied molecules which were calculated with DFT and experimental acidity constants are indicated in Table 3.

Table 3. Standart and solvation free energies, ΔG_{sol} and ΔG_{gas} calculated by DFT method for the compounds. experimental and calculated acidity constants pK_a values

Comp.	Standart free energy G_{gas} (kcal mol^{-1})	Solvation free energy $G_{sol(A)}$ (kcal mol^{-1})	Standart free energy $G_{gas(AH)}$ (kcal mol^{-1})	Solvation free energy $\Delta G_{sol(AH)}$ (kcal mol^{-1})	pK_a (calc.)[a]	pK_b (exp,)[b]
1	-512,812.78	-5.15	-513,038.33	-53.15	3.34	3,34
2	-525,349.61	-4.81	-525,519.30	-49.26	2.31	2,28
3	-727,958.65	-4.58	-728,165.01	-46.81	2.64	2,43

[a] Calculated from $pKa = [\Delta G_{gas} + \Delta G_{sol(A-)} - \Delta G_{sol(AH)} + \Delta G_{sol(H+)}]/2.303RT$

The calculated pK_a values by DFT calculation method seems closer to the experimental pK_a values, so Fig. 5 showes a perfect correlation between calculated and experimental pK_a values. The acidity constants of the molecules arranged in order to 1>3>2.

The pyrrolyl-, furanyl- and thienyl- thiazole derivatives, show stronger basicty than the thiazole (pK_a: 2.5). The thiazole derivatives show stronger basicty than the thiazole as found from the experimental results. This effect can be related to a reduction in mesomeric effect of aryl groups, as a result of greater steric hindrance, and also by increased importance of the inductive effect of aryl groups. The thienyl- derivatives show a little effect to reduce the basicity of the thiazole but the furanyl- derivatives show much more effect because of the oxygen. The unpaired electrons of the oxygen can not easily delocalize towards the quinoline ring.

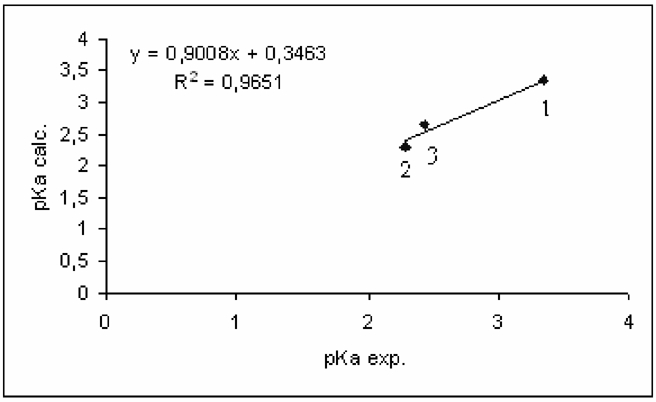


Figure 5. The plot of DFT aqueus phase calculated acidity constants, p$K_{a(calc.)}$,againstexperimental acidity constants, p$K_{a(expt.)}$.

It can be seen that PA values is increased by 2-pyrroly substituents (electron-donating) while they are increased by 2-thienyl and 2- furyl substituents (electron-withdrawing). We can conclude that from the above data that this trend of decrease in proton accepting power is the same as the one which was obtained experimentally obtained pK_a values.

Table 4. B3LYP/6-31G(d) calculated E and Proton Affinities (PA) values

Molecule	B3LYP/6-31G(d) E (kcal/mol)	Zero point correction energy (ZPE) (kcal/mol)	PA^a
1	-512716.44	87.32	227.86
1p	-512955.65	98.67	
2	-525266.30	83.31	224.01
2p	-525498.00	90.99	
3	-727936.67	85.92	224.22
3p	-728164.80	89.83	

$PA = (E_{(B)} + ZPE_{(B)}) – (E_{(BH^+)} + ZPE_{(BH^+)})$

The aqueous phase DFT calculated nucleophilicities are indicating that the previous discussion of decrease in basicity is correct and the nucleophilicity as well as the basicities of molecules 3 and 2 are not effected by thienyl and furanyl very much because of its low electron-withdrawing effect. Whereas, the nucleophilicity of molecule 1 influenced more and consequently they have bigger nucleophilic power than that of molecule 3 and 2, respectively. These results also indicate that the nucleophilicity of studied molecules changed parallel with basicity.

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