Spectroscopic Determination of Acid Dissociation Constants of Some Pyridyl-Substituted 2-Aminothiazole Derivatives

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The acid dissociation constants, K_a, of nine biologically active 2-amino-4-(*x*-pyridyl)-thiazole, 2-methylimino-3-methyl-4-(*x*-pyridyl)-2,3-dihydrothiazole, and 2-methylamino-4-(*x*-pyridyl)-2,3-dihydrothiazole were determined using UV−vis spectroscopic technique.The acidity constants for the first protonation, pK_{a1}, of parent molecules and their fixed model molecules are found to be associated with the protonation of aza or imino nitrogen atom. The acidity constants for the second proton uptake, pK_{a2}, are found to correspond to aza, imino, or amino nitrogen atom protonation. The contribution of the imino tautomeric form to tautomeric equilibria was found to be considerably important.

Introduction

The thiazole derivatives exhibit pharmacological and biological activities.[1,2] Some of them with their activity are known to be a ligand of estrogen receptors[3] as well as a novel class of adenosine receptors antagonists.[4] Some thiazole derivatives found application in development and preparation of antibiotic or anti-inflammatory drugs.[2] The others show insecticidal fungitoxicity,[5] antispasmodic, antihistaminic,[6] schistosomicidal, anthelminitic,[7] or dopaminergic[8] activity. Furthermore, some thiazole derivatives are being used as azo dyes.[9] These important and useful application of thiazole derivatives have made these compounds attractive to work on. Many researchers have been reporting their research results of theoretical[10−14] and experimental[15−20] studies. We now report on experimentally obtained acid dissociation constants, K_a values, and tautomeric equilibrium of some newly synthesized 4-(*x*-pyridyl)-2-aminothiazole derivatives.

Experimental Section

Materials and Solutions. The studied compounds were of spectroscopic grade, and the procedures of synthesis have been described elsewhere.[21,22]

Methanol, ethanol, glycine, KOH, H_2SO_4, HC1, CH_3COOH, CH_3COONa, NaOH, KH_2PO_4, Na_2CO_3, $NaHCO_3$, NaCl, methyl red indicator, and standard buffer solutions were from Merck and were not purified further.

Apparatus. pH measurements were performed using a glass electrode. Standard buffer solution of pH values of 1.0, 7.0, and 14.0 were used in the calibration of the INOLAB pH level 1 pH-meter and the Sartorious balance; a Unicam UV2 UV−vis scanning spectrometer was used for measurements.

Procedure. Acid solutions, CO_2-free NaOH solutions, and pH solutions were prepared by using the methods described in the literature (refs 23−26, respectively). As well-explained in ref 26, for bases the ionization is

$$BH^+ = H^+ + B \tag{1}$$

and

$$K_a = \frac{a_{H+}a_B}{a_{BH+}} \tag{2}$$

where *a* represents the activity of each species. At a given temperature, the constants expressed above are thermodynamic quantities also known as thermodynamic ionization constants, which we can refer to henceforth as K_a. These constants are independent of concentration because all terms involved are in terms of activities. Another type of constant that we can make use of it is the concentration ionization constant, K_C, which is defined for bases as shown in eq 3:

$$K_C = \frac{[H^+][B]}{[BH^+]} \tag{3}$$

In which the square brackets denote the concentration (as opposed to the activity) of each ionic species. Equation 3 is generally used in the following form (eq 4), in which pK_a is the negative logarithm of the ionization constant:

$$pK_a = pH + \log[BH^+]/[B] \tag{4}$$

The main difference between thermodynamic and concentration constants is that the activities of the ions have to be taken care of in calculating the former. These activities compensate for the attraction that ions can exert on one another (ion-pair) as well as the incomplete hydration of ions in solutions that are too concentrated. The lower the concentration, the less this interaction becomes until, at infinite dilution, the concentration becomes numerically equal to the thermodynamic constant. Equation 3 can be used for the sake of simplicity, provided that the constant is determined in solution not stronger than 0.01 mol·L^{-1} and only univalent ions are present.

For the present, it need only be noted that the activity of a neutral species (molecule) does not differ appreciably from its concentration and that pH, as commonly determined, is nearer to hydrogen ion activity than to hydrogen ion concentration,

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Table 1. Formula and IUPAC Names for 2-Amino-4-(*x*-pyridyl)-thiazoles (1 to 9)

compound	IUPAC name	R^1	R^2	X
1	2-amino-4-(2-pyridyl)-thiazole	H	H	2-pyridyl
2	2-amino-4-(3-pyridyl)-thiazole	H	H	3-pyridyl
3	2-amino-4-(4-pyridyl)-thiazole	H	H	4-pyridyl
4	2-methylimino-3-methyl-4-(2-pyridyl) 2,3-dihydrothiazole	CH_3	CH_3	2-pyridyl
5	2-methylimino-3-methyl-4-(3-pyridyl) 2,3-dihydrothiazole	CH_3	CH_3	3-pyridyl
6	2-methylimino-3-methyl-4-(4-pyridyl)-2,3 dihydrothiazole	CH_3	CH_3	4-pyridyl
7	2-methylamino-4-(2-pyridyl)-2,3-dihydrothiazole	H	CH_3	2-pyridyl
8	2-methylamino-4-(3-pyridyl)-2,3-dihydrothiazole	H	CH_3	3-pyridyl
9	2-methylamino-4-(4-pyridyl)-2,3-dihydrothiazole	H	CH_3	4-pyridyl

Table 2. UV Spectral Data and Acidity Constants, pK_{a1}, Values of 1 to 9 for the First Protonation

	spectral maximum λ/nm		acidity measurements				
compound	neutral[a] species (log ϵ_{max})	monocation[b] (log ϵ_{max})	λ^c/nm	$H^{1/2}$ [d]	pK_{a1}[e]	K_T[f]	corr.[g]
1	300 (3.85)	252 (4.03)	302	4.90 ± 0.50	3.96	$2.69 \cdot 10^{-4}$	0.90
2	224 (4.22)	201 (4.12)	224	3.85 ± 0.10	1.61	$5.62 \cdot 10^{-6}$	0.95
3	226 (4.27)	256 (3.96)	257	1.90 ± 0.30	1.54	$2.13 \cdot 10^{-8}$	0.95
4	227 (3.89)[i]	254 (4.10)	254	9.50 ± 0.10	5.90	−	0.97
5	259 (4.08)[i]	250 (4.17)	250	8.80 ± 0.20	6.59	−	0.94
6	259 (4.11)[i]	327 (3.84)	327	8.80 ± 0.18	8.80	−	0.98
7	224 (4.11)	258 (4.08)	224	4.30 ± 0.19	2.33	−	0.94
8	292 (3.81)	229 (4.24)	229	4.40 ± 0.08	1.34	−	0.94
9	311 (3.78)	260 (4.04)	260	1.90 ± 0.60	1.13	−	0.99

[a] Measured in pH = 7 buffer solution for **1** to **3** and **7** to **9** and measured in pH = 12 buffer solution for **4** to **6**. [b] Measured in pH = 1 buffer. [c] The analytical wavelength for pK_a determination. [d] Half-protonation values and uncertainties for the standard errors for the first protonation. [e] Acidity constant value. [f] K_T (from Carlton equation).[27] [g] Correlations for log *I* as a function of pH graph.

Table 3. UV Spectral Data and Acidity Constants, pK_{a2}, Values of Compounds 1 to 9 for the Second Protonation

	spectral maximum λ/nm		acidity measurements			
compound	monocation[a] (log ϵ_{max})	dication[b] (log ϵ_{max})	λ^c/nm	$H^{1/2}$ [d]	pK_{a2}[e]	corr.[f]
1	247 (4.03)	321 (3.96)	302	0.60 ± 0.10	0.53	0.66
2	201 (4.12)	244 (4.05)	245	6.20 ± 0.10	1.48	0.84
3	260 (3.72)	326 (3.99)	326	2.80 ± 0.0	1.11	0.98
4	251 (4.13)	318 (3.79)	318	1.60 ± 0.60	2.21	0.94
5	252 (4.08)	306 (3.59)	306	2.20 ± 0.02	1.98	0.99
6	331 (3.94)	253 (4.14)	327	2.10 ± 0.20	1.06	0.88
7	251 (4.14)	327 (3.98)	257	0.50 ± 0.60	0.20	0.62
8	229 (4.24)	248 (4.16)	229	−1.05 ± 0.20	−1.13	0.71
9	261 (3.99)	337 (4.07)	357	2.30 ± 0.11	0.85	0.85

[a] Measured in pH = 7 buffer solution for **1** to **3** and **7** to **9** and measured in pH = 12 buffer solution for **4** to **6**. [b] Measured in 50 % H_2SO_4. [c] The wavelength for pK_a determination. [d] Half-protonation value and uncertainties for the standard error for the second protonation. [e] Acidity constant value. [f] Correlations for log *I* as a function of pH graph.

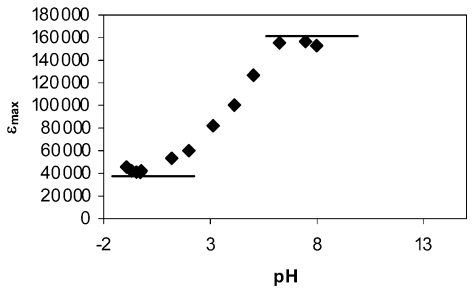


Figure 1. ϵ_{max} as a function of pH (at 224 nm) plot for the first protonation of 2-amino-4-(3-pyridyl)-thiazole molecule (**2**).

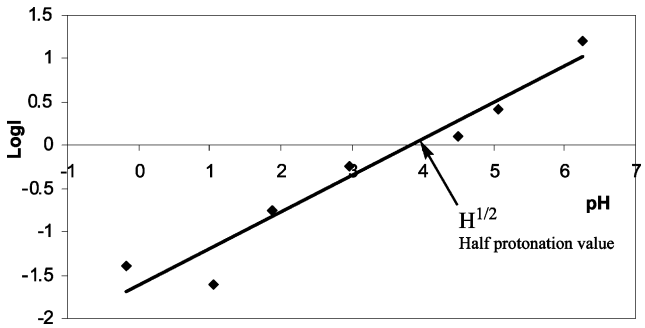


Figure 2. pH as a function of log *I* (at 224 nm) plot for the first protonation of 2-amino-4-(3-pyridyl)-thiazole molecule (**2**).

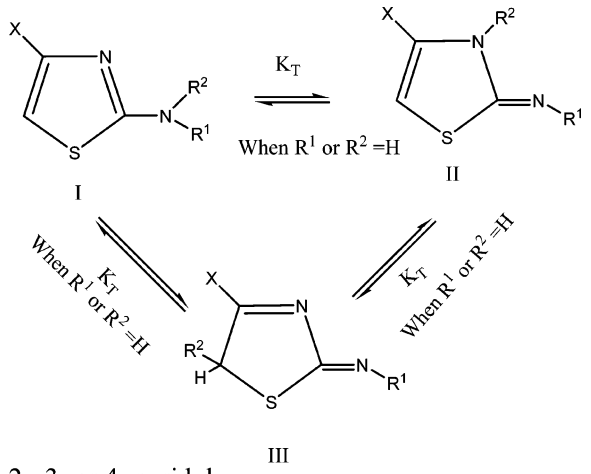
although at low ionic strength ($I < 0.01$ M) these terms do not differ greatly between pH 2 and pH 10. Hence, a_{BH+} is the only unfamiliar quantity in eq 2, because a_{BH+} can be substituted for a_B, and a_{H+} is read from the measuring instruments.

Since the spectroscopy is an ideal method[26] when a substance is not soluble enough for potentiometry or when its pK_a value is particularly low or high (e.g., less than 2 or more than 11), that method had applied in the present work.

Depending on the direct determination of the ratio of the molecular species, that is, the neural molecules corresponding to the ionized species in a series of nonabsorbing buffer solutions for which pH values are either known or measured, to provide a series of buffers. For a weak base B, which ionizes by simple proton addition, the pH values at half-protonation were measured for several compounds during the course of the present work using the UV−vis spectrophotometric method.[23]

The general procedure applied as follows; a stock solution of the compound under investigation was prepared by dissolving the compound about 10 to 20 mg in water in a volumetric flask. Aliquots (1 mL) of this solution were transferred into 10 mL volumetric flask and diluted to the mark with buffers of various

Scheme 1. Tautomeric Forms for the Studied Molecules 1 to 9



X= 2-, 3- or 4- pyridyl

for molecules **1-3** and **7-9** *imino*

for molecules **4-6** *amino*

pH values. The pH was measured before and after addition of the new solution. The optical density of each solution was then measured in 1 cm cells, against solvent blanks, using a constant temperature cell-holder Unicam UV2 UV−vis scanning spectrometer thermostated at 25 °C (to within ± 0.1 °C). The wavelengths were chosen such that the fully protonated form of the substrate had a much greater or a much smaller extinction coefficient than the neutral form. The analytical wavelengths, the half-protonation values, and the UV absorption maximums for each substrate studied are shown in Tables 2 and 3.

Calculations of half-protonation values were carried out as follows: the sigmoid curve of optical density or extinction coefficients at the analytical wavelength (OD, λ) was first obtained (Figure 1). The optical density of the fully protonated molecule (OD_{ca}, optical density of conjugated acid) and the pure free base (OD_{fb}, optical density of free base) at an acidity were then calculated by linear extrapolation of the arms of the curve. Equation 10 gives the ionization ratio where the OD_{obs} (the observed optical density) was in turn converted into molar extinction, ϵ_{obs}, using Beers' law of OD $= \epsilon \cdot b \cdot c$, ($b$ = cell width, cm; c = concentration, mol·dm^{-3}):

$$I = \frac{[BH^+]}{[B]} = \frac{(OD_{obs} - OD_{fb})}{(OD_{ca} - OD_{obs})} = \frac{(\epsilon_{obs} - \epsilon_{fb})}{(\epsilon_{ca} - \epsilon_{obs})}$$

The linear plot of log I against pH, using the values $-1.0 <$ log $I < 1.0$, had slope m, yielding half-protonation value as $pH^{1/2}$ or more generally $H^{1/2}$ at log $I = 0$ (Figure 2).

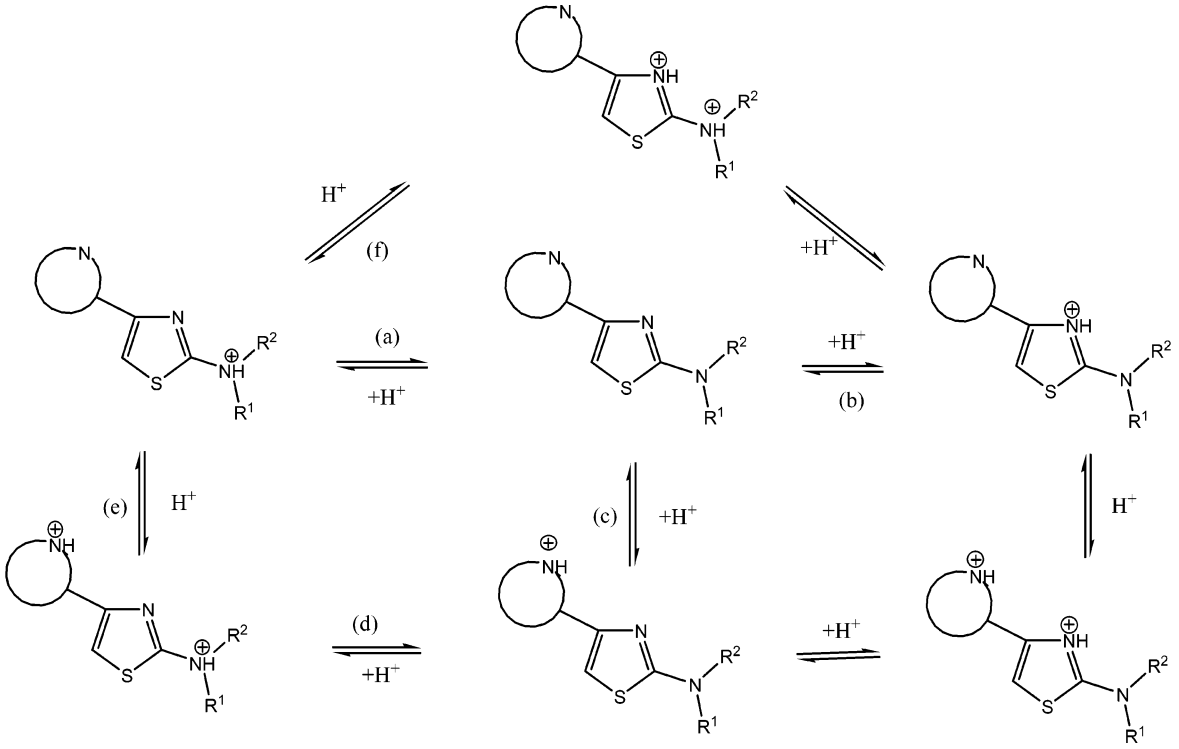
Carlton's equation[27] (eq 5) is of great importance in calculating the azole equilibrium. In this method the pK_a values of fixed model compounds, in which the proton migration is eliminated by replacing the mobile protons by methyl groups, of the corresponding tautomers are known the prediction of the equilibrium position for any asymmetrically substituted azole will be possible by using eq 5:

$$pK_T = pK_{a(reactant)} - pK_{a(product)} \quad (5)$$

Result and Discussion

The acid dissociation constants have been used in various areas of research such as stereochemical and conformational structure determinations,[28,29] the directions of nucleophilic and electrophilic attack, the stabilities of intermediates, the size of activation energies in organic reactions,[30] and the determination of the active centers of enzymes in biochemistry.[31] In the present work, we are reporting on the experimental acid dissociation constants of some biologically active 4-(*x*-pyridyl)-2-aminothia-

Scheme 2. Possible First and Second Protonation Pathways for the Amino Forms of Studied 4-Pyridylthiazole Derivatives (1 to 9)[a]



[a] R^1 = H, CH_3; R^2 = H, CH_3.

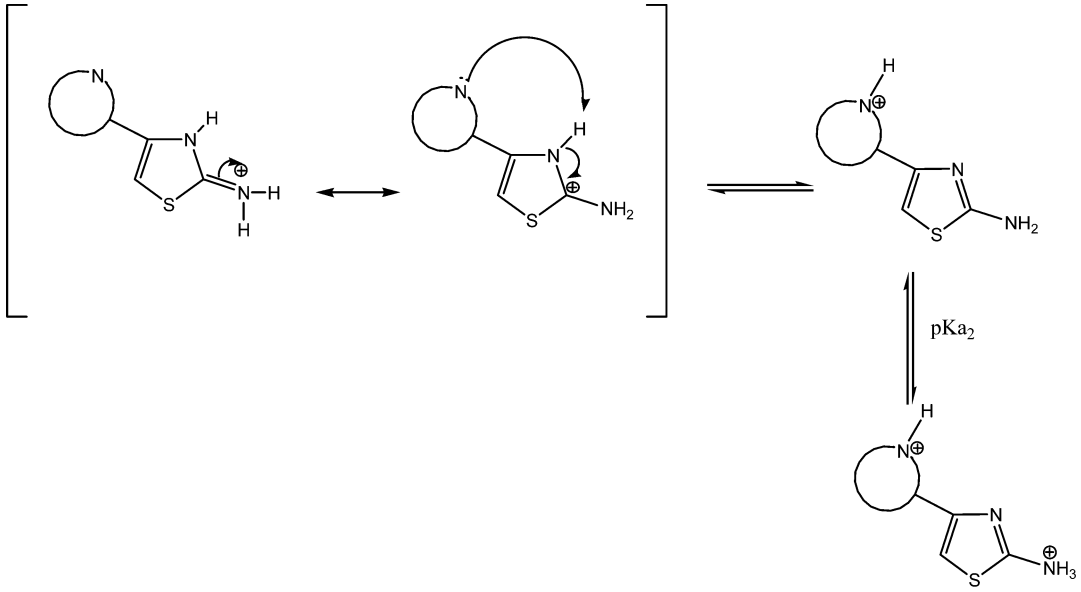
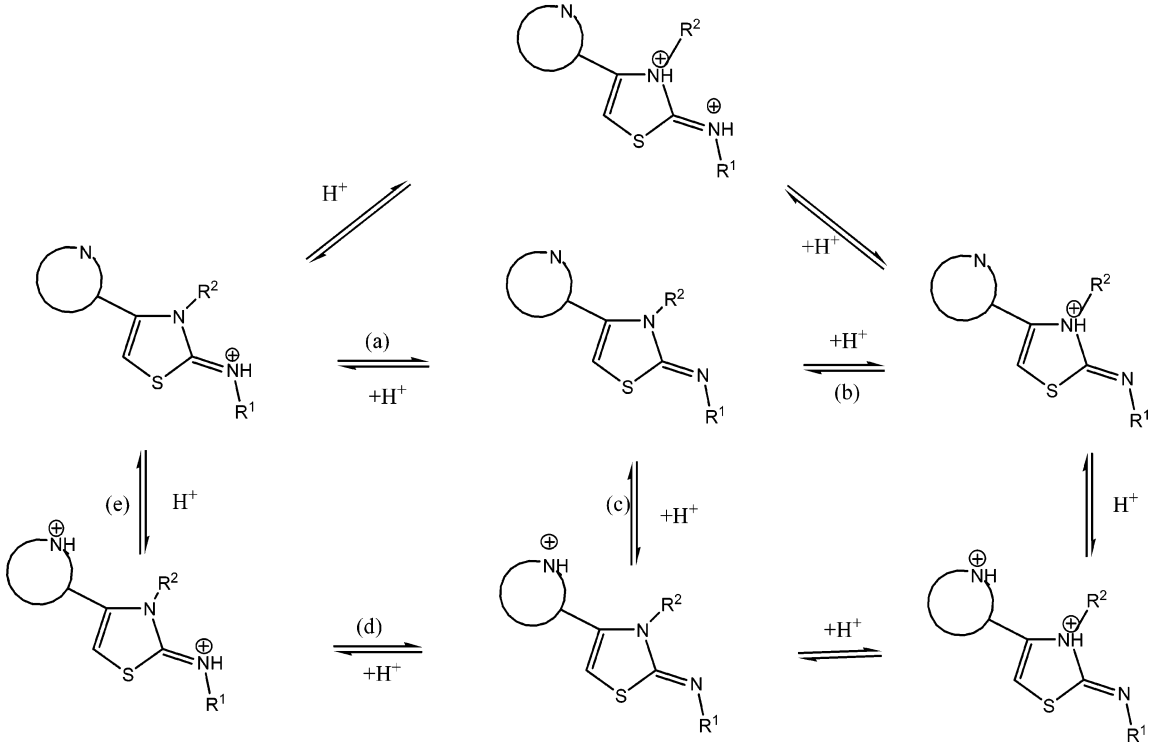


Figure 3. Possible second protonation path for **2**.

Scheme 3. Possible First and Second Protonation Pathways for the Imino Forms of Studied 4-Pyridylthiazole Derivatives (1 to 9)[a]



[a] R^1 = H, CH_3; R^2 = H, CH_3.

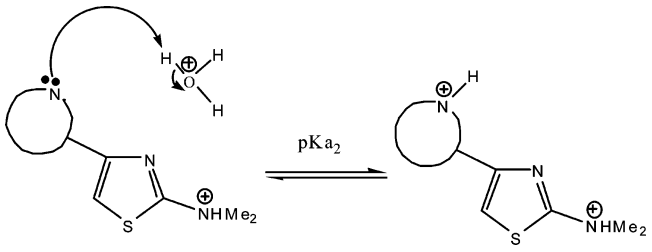


Figure 4. Possible second protonation path for **5**.

zole bases to elucidate the structure−reactivity relations. Since existence of two tautomeric forms (i.e., amino and imino) in aqueous media is possible in discussion of the protonation pathways, the tautomeric equilibrium had to be taken into account (Schemes 1 to 3).

Protonation Patterns. The nomenclature, UV spectra, and protonation data for studied **1** to **9** were depicted in Tables 1 to 3. The possible protonation patterns were shown in Schemes 2 and 3. It can even implicitly be seen from the structure of studied compounds that there are three potential protonation centers in each molecule. Furthermore, in molecules that have a mobile hydrogen atom, two tautomeric forms are possible (Scheme 1).

The only method to determine the protonation centers for the first and second protonation seems to compare the obtained data with the literature values and to compare the data for parent

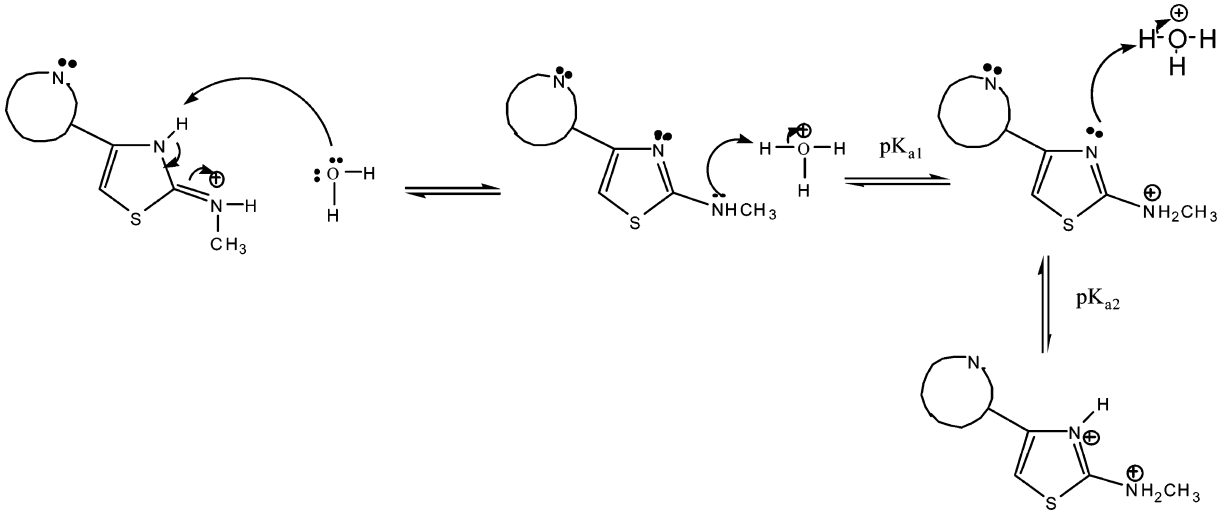
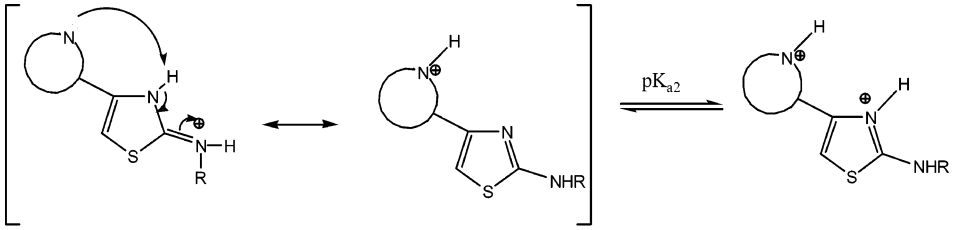


Figure 5. Possible second protonation path for **8**.



R=H for compound **3**
R=CH_3 for compound **9**

Figure 6. Possible protonation pattern for second protonations of parent compound **3** and it's imino protonated model compound **9**.

compounds with the data for fixed model compounds in which the possibility of proton migration is eliminated by replacing the acidic protons with methyl group. We will discuss the first and second protonation data separately to clear up the protonation patterns.

First Protonation. The measured half-protonation values, $H^{1/2}$, for the parent compound **1** and its model compounds **4** and **7** (i.e., amino and imino models) were found as 4.90, 9.50, and 4.30, respectively (Table 2). It seems that the half-protonation values of **1** and its imine model **7** are closer to each other, and we can say that they protonate with the same mechanism (Scheme 3, path a). Whereas, the half-protonation value of molecule **4** is too much bigger than others. So we can conclude that it protonates at the amino group (i.e., molecule **4** cannot be in imino form) (Scheme 2, path a).

Similarly, the measured half-protonation values, $H^{1/2}$, for parent compound **2** and its model compounds **5** and **8** (i.e., amino and imino models) were found as 3.85, 8.80, and 4.40, respectively. It seems that half-protonation values of parent compound **2** and its imine model **8** are closer to each other, and we can say that they protonate with the same mechanism (Scheme 3, path a) as its imino protonation. Whereas, the half-protonation value of molecule **5** is far bigger than others, so we can conclude that it is because of its amino protonation (Scheme 2, path a).

The half-protonation values for parent compound **3** and its model compounds **6** and **9** were found as 1.90, 8.80, and 1.90, respectively. It seems that the half-protonation value of parent compound **3** and its imine model **9** are exactly the same, so we can conclude that they protonate with the same mechanism (Scheme 3, path a). Where as, the half-protonation value of molecule **6** is too big than others. So we can predict its amino protonation (i.e., molecule **6** cannot be in imino form) (Scheme 2, path a).

Second Protonation. The measured half-protonation values, $H^{1/2}$, for the second protonation are depicted in Table 3. The obtained half-protonation values for monoprotonated (i.e., imino protonated) parent compound **1** and its amino and imino models **4** and **7** were found as 0.60, 1.60, and 0.50, respectively. The half-protonation value for the second protonation of imino protonated parent compound **1** and its imino protonated model molecule **7** are close enough to indicate a similar protonation mechanism for the second protonation, and it should be aza protonation at pyridine ring (Scheme 3, path e). Whereas, the half-protonation value of amino protonated model molecule **4** for the second protonation seems to be more basic and not the pyridine protonation, but it must be aza protonation at thiazole ring (Scheme 2, path f).

The obtained half protonation values for imino protonated parent compound **2** and its mono protonated (i.e., amino and imino protonated) amino and imino models **5** and **8** were found as 6.20, 2.2, and −1.05, respectively. It seems that the basicity of monoprotonated molecules of **2**, **5**, and **8** decrease regularly, and there is no similarities between obtained half-protonation values. So the mechanisms for the second protonation for those molecules are all different, and tautomerism plays an important role in the second protonation values. It seems that for the parent compound **2** after first protonation a tautomeric change occur in the structure in a way that it gets amino form (Figure 3) (Scheme 2, path a).

For **5** however, we have less basic form for the second protonation. A possible protonation pattern then can be as shown in Figure 4. Since its amino protonated already, it can protonate easily at azo nitrogen atom of pyridine ring, which is further

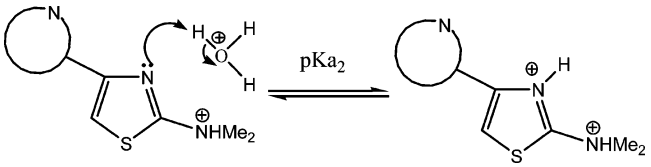


Figure 7. Possible protonation pattern for the second protonation of amino protonated model compound **6**.

away from the positively charged $^{+}NHMe_2$ group (Scheme 2, path e).

For **8**, which is already imino protonated, we can suggest a different mechanism as shown in Figure 5 (Scheme 2, path f).

The half-protonation values for monoprotonated parent compound **3** and its amino protonated model compound **6** and imino protonated model compound **9** were found as 2.80, 2.10, and 2.30, respectively. It seems that the half-protonation values are very close to each other, and the mechanism for the second protonation seems to be smilar for **3**, **6**, and **9**. The half-protonation values for pK_{a1} and pK_{a2} measurement for the first protonation of parent compound **3**, and its imino protonated model **9** did not change much whereas for the amino protonated model **6** we have a considerable amount of change so the mechanism for the second protonation of molecule **3** and its model **9** can be similar (Figure 6) (Scheme 3, path e).

For the amino protonated model molecule **6**, we can suggest a different protonation pattern as shown in Figure 7 (Scheme 2, path f). We can immediately notice that basicity decreases a little bit for that compound is very little because the second plus charge is located nearby the first one.

Tautomerizm. Using Carton's approach,[27] the tautomeric equilibrium constants, K_T values, were calculated (Table 2). The obtained K_T values are indicating overwhelming predominance of amino forms over the imino forms in aqueous media. The aza nitrogen of pyridine ring which is in ortho, meta, and para position in **1**, **2**, and **3**, respectively. So the electron-withdrawing effect of this aza nitrogen will be different in each position, and it will effect the protonation mechanism and the value of acidity constants, pK_a values, as well as the tautomeric equilibrium constants (i.e., K_T values). Therefore, decrease in K_T values from **1** to **3** in the expected one.

Literature Cited

(1) Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer Press: Berlin, 1998; Vol. 2, pp 416−420.

(2) Kazzouli, S. E.; Raboin, S. B.; Mouaddib, A.; Guillaumet G. Solid support synthesis of 2,4-disubstituted thiazoles and aminothiazoles. *Tetrahedron Lett.* **2002**, *43*, 3193−3196.

(3) Fink, B. A.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens. *Chem. Biol.* **1999**, *6*, 205.

(4) Mujlwıjk, K.; Jacqueline, E.; Timmermon, H.; Vallinga, R. C. Thiazole and thiadiazole anologs as a novel class of adenosine receptor antagonists. *J. Med. Chem.* **2001**, *44*, 749−762.

(5) Harrison, W. A.; Hubbard, W. L.; Grahane, R. E. Insecticidial 2-(3-pyridyl) thiazole derivatives. *Chem. Abstr.* **1973**, *78*, 492.

(6) Nayak, A.; Misra, S. B. Synthesis of 5-diethylaminomethyl−2-substituted-aminothiazoles−their fungitoxicity, antispasmodic and antihistaminic activities. *J. Indian Chem. Soc.* **1986**, *63*, 986.

(7) Metzger, J. V. *Comprehensive Heterocyclic Chemistry I*; Pergamon Press: New York, 1984; Vol. 6, p 328.

(8) Campbell, M. M.; Cosford, N. D. P.; Rae, D. R.; Sainsbury, M. Ethano- and etheno-bridged 2-pyridyl isoxazoles and thiazoles, and their reduced variants. *J. Chem. Soc., Perkin Trans. 1* **1981**, *4*, 765−770.

(9) Kim, J. J.; Funabiki, K.; Muramatsu, H.; Shibata, K.; Kim, S. H.; Shiozaki, H.; Hartmann, H.; Matsui, M. Synthesis, structure, and UV−Vis absorption spectra of azo dyes derived from (dialkylamino)thiazole dimers. *J. Chem. Soc.. Perkin Trans. 2* **2001**, 379−387.

(10) Jagodzınskı, T.; Dzıembowska, T.; Szczodrowska, B. *Trans. Khim. Get. Soed.* **1988**, *24*, 3.

(11) Katritzky, A. K. *Handbook of Heterocyclic Chemistry*; Pergamon Press: New York, 1985.

(12) Forlani, L. Reactivity and tautomerizm of 2-thiazoleamine derivatives. Universita di Bologna, Viale Risorgimento 4, Bologna Italia, 1988.

(13) Forlani, L.; Lunazzi, L.; Medici, A. Conformational studies by dynamic nuclear magnetic resonance. Part XI. The detection of restricted rotation in 2- *N*,*N*-dimethylaminothiazoles. *Tetrahedron Lett.* **1977**, *18*, 4525−4526.

(14) Forlani, L.; Bernardi, F.; Todesco, P. E.; Colonna, F. P. ; Distefano, G. A pes study on 1,3-thiazole and its monosustituted halogen derivatives. *J. Electron Spectrosc. Relat. Phenom.* **1976**, *9*, 217−226.

(15) Forlani, L.; Medici, A.; Todesco, P. E. Unusual amino group activation towards nucleophilic substitution, reactions between 2-amino-5-halogenthiazoles and nucleophiles. *Tetrahedron Lett.* **1976**, *17*, 201−202.

(16) Vernin, G.; Lebreton, M. A.; Dou. H. J. M.; Metzger, J. Heterocyclic radicals. X. Pseudo-Gomberg reaction. *Tetrahedron* **1974**, *30*, 4171−4180.

(17) Kane, J. L.; Hirth, H. B.; Liang, B.; Gourlie, B. B.; Nahill, S. Barsomian, G. Ureas of 5-aminopyrazole and 2-aminothizole inhibit growth of Gram-positive bacteria *Bioinorg. Med. Chem.* **2003**, *13*, 4463−4466.

(18) Gorczynski, M. J.; Leal, M.; Mooberry, S. L.; Bushweller, J. H.; Brown M. L. Synthesis and evaluation of substituted 4-aryloxy- and 4-arylsulfanyl-phenyl-2-aminothiazoles as inhibitors of human breast cancer cell proliferation. *Bioinorg. Med. Chem.* **2004**, *12*, 1029−1036.

(19) Helal, J. C.; Sanner, M. A.; Cooper, C. B.; Lucas, J. C.; Kang, Z.; Kupchinsky, S.; Ahlijanian, M. K.; Tate, B.; Menniti, F. S.; Kelly, K.; Peterson, M. Discovery and SAR of 2-aminothiazole inhibitors of cyclin-dependent kinase 5/p25 as a potential treatment for Alzheimer's disease. *Bioinorg. Med. Chem.* **2004**, *14*, 5521−5525.

(20) Katritzky, A. R.; Ogretir, C.; Tarhan, O. H.; Dou, H. M.; Metzger, J. V. The kinetics and mechanism of the electrophilic substitution of heteroaromatic compounds. Part XLII. The nitration of thiazoles and thiazolones. *J. Chem. Soc. Perkin Trans. 2* **1975**, 1614−1620.

(21) Taurins, A.; Blaga, A. *J. Heterocyclic Chemistry*, synthesis of Pyridyl- and Quinolyl substituted 2-aminothizoles, **1970**, *7*, 1137−1141.

(22) Funda Tay Ph.D. Thesis, Eskişehir Osmangazi University, Eskisehir, Turkey, 2005.

(23) Cookson, R. F. The determination of acidity constants. *Chem. Rev.* **1974**, *74*, 1.

(24) Bowden, K. Acidity functions for strongly basic solutions. *Chem. Rev.* **1966**, *66*, 2.

(25) Perrin, D. D. *Buffers for pH and Metal Ion Control*; Chapman and Hall: London, 1971.

(26) Albert, A.; Serjeant, E. P. *The Determination of Ionisation Constants*; Chapman and Hall: London, 1984.

(27) Elguero, J.; Marzin, C.; Katritzky, A. R. *Advances in Heterocyclic Chemistry, Supplement 1*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: London, 1976; pp 26−27.

(28) Brown, H. C.; Daniel, O. H. Mc.; Haflinger, O. *Determination of Organic Structure by Physical Methods;* Academic Press: New York, 1985.

(29) Chilton, J.; Stenlake, J. B. Dissociation constants of some compounds related to lysergic acid. II. *J. Pharm. Pharmacol.* **1962**, *14*, 367.

(30) Johnson, C. D. *The Hammett Equation;* Cambridge University Press: Cambridge, 1973.

(31) Frey, P. A.; Kokesh, F. O.; Wcstheimer, F. H. a reporter group at the active site of acetoacetate decarboxylase. I. Ionization constant of the nitrophenol. *J. Am. Chem. Soc.* **1971**, *93*, 7266−7270.

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