Spectroscopic Determination and Evaluation of Acidity Constants for Some Drug Precursor 2-Amino-4-(3- or 4-substituted phenyl) Thiazole Derivatives

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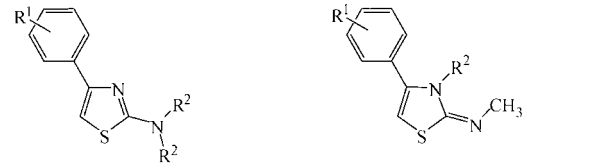
Acid dissociation constants, K_a, of eight drug precursor 2-amino-4-(3- or 4-substituted phenyl) thiazole derivatives were determined using a UV−vis spectroscopic technique. The obtained K_a values were evaluated by structure elucidation and a protonation mechanism. The obtained tautomerization equilibrium constants, K_T, indicated the predominance of amino forms for all studied compounds.

Introduction

Sulfur-containing compounds are present in many important living organisms.[1] One important class of heterocyclic compounds which has the etheric sulfur atom is the five-membered thiazole ring.[2] As they possess several biological properties, thiazole derivatives are the main tools in pharmaceutical research.[3−10] 2-Aminothiazoles and their derivatives on the other hand have been used as precursors for the synthesis of many active molecules for a long time.[11] These compounds have various applications, related to agriculture, pharmacy, photography, or similar activities.[12] They have also been considered as one of the key building blocks in drug discovery. There are more than 500 structures containing the 2-aminothiazole moiety reported in the Derwent World Drug Index.[13] 2-Aminothiazole derivatives also are well-known common motifs in medicinal chemistry due to their broad applications in drug development for treatment of allergies, hypertension, inflammation, and bacterial infections[14−17] as well as displaying high affinity for the NPY5 (neuropeptide Y5) receptor for the treatment of nutrition disorders such as obesity and hyperphagia.[18] All these observed properties of 2-aminothiazole derivatives seemed to be very attractive to us to work on some physical properties of these drug precursor compounds.

The acidity constant, pK_a, of a compound is an important property in both the life sciences and in chemistry.[19] The most important of the parameters are lipophilicity, solubility, permeability, and apparent acid dissociation constants (K_a) because these factors determine the absorption and bioavailability of the molecule.[20−23] The acid dissociation constant (K_a value) is an important parameter to estimate the extent of ionization of drug molecules at different pH values, which is of fundamental importance in the consideration of their interaction with biological membranes and in their synthesis.[24,25] The ability to cross the blood−brain barrier toward the site of action can be characterized by some physicochemical parameters, such as acidity constants, pK_a, which can predict the behavior of biologically active compounds in living organisms governing their ionization degree at the physiological pH value.[26] Following our work on 2-aminobenzothiazoles,[27] we now report the acidity constants of some drug precursor 2-amino-4-(3- or 4-substituted phenyl) thiazole derivatives.



amino form (**1, 1a**) imino or semi-imino form (**1b, 1c**)

R^1 = H, 4-Cl, 4-OMe, 4-CH_3, 4-NO_2, 3-Cl, 3-OCH_3, 3-NO_2
R^2 = H, CH_3

Figure 1. Structures of 4-(3- or 4-substituted phenyl)thiazol-2-amine and *N*-(3- or 4-substituted phenyl thiazol-2(3*H*)-ylidene) methanamine derivatives.

Experimental Section

For the determination of pK_a values, one commonly applied approach is the spectrophotometric method based on the measurement of the ratio of protonated/deprotonated forms.[28,29] Spectrometry is an ideal method 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).[30] Samples, however, must possess chromophore(s) close to ionizable groups in a way that the neutral and ionized forms have different absorption spectra. The largest change in absorbance occurs at the pH corresponding to the pK_a value.

Synthesis. The studied compounds were synthesized by our group and reported elsewhere.[31] The structure and nomenclature of the studied 2-amino-4-(3- or 4-substituted phenyl) thiazole derivatives are shown in Figure 1 and Table 1.

Materials and Solutions. The buffer solutions employed were prepared from: (a) HCl−KCl, pH = 1; (b) KH_2PO_4−NaOH, pH = 7; (c) borax−HCl, pH = 8.0 to 9.0; (d) borax−NaOH, pH = 9.3 to 10.7. All these materials and buffer solutions were from Merck and were not further purified.[32]

Equipment. The pH values were measured by a pH/ion analyzer Orion 720 A+ pH meter which is furnished with a combined glass electrode, and it was standardized at 25 °C by using standard buffers of pH 4, 7, and 9. The UV−vis spectra, obtained to determine absorptiometric pK_a values, were recorded at each pH using a Hitachi 150-20 double beam spectropho-

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10.1021/je9005739
Published on Web 01/08/2010

Table 1. UV Data and Acidity Constants of Studied 2-Amino-4-(3- or 4-substituted phenyl) Thiazole Derivatives

		λ_{max} (nm) (10^3 ε)			
form	IUPAC names	cation[a]	neutral[b] molecule	$H_x^{(1/2)c}$	λ (nm)[d]
1	4-phenylthiazol-2-amine	264 (14.35)	226 (20.35)	3.91	230
2	4-(4-chlorophenyl)thiazol-2-amine	268 (13.63)	232 (19.05)	3.56	237
3	4-(4-methoxyphenyl)thiazol-2-amine	270 (16.23)	240 (11.43)	3.83	234
4	4-(4-methylphenyl)thiazol-2-amine	266 (17.33)	230 (20.03)	3.84	234
5	4-(4-nitrophenyl)thiazol-2-amine	326 (10.05)	346 (4.01)	3.56	334
6	4-(3-chlorophenyl)thiazol-2-amine	266 (14.55)	228 (19.58)	3.76	234
7	4-(3-methoxyphenyl)thiazol-2-amine	266 (13.91)	226 (22.22)	4.16	306
8	4-(3-nitrophenyl)thiazol-2-amine	262 (22.93)	222 (23.98)	3.36	227
1a	*N*,*N*-dimethyl-4-phenylthiazol-2-amine	432 (0.40)	404 (5.57)	1.79	417
2a	4-(4-chlorophenyl)-*N*,*N*-dimethylthiazol-2-amine	366 (0.99)	398 (4.42)	1.61	418
3a	4-(4-methoxyphenyl)-*N*,*N*-dimethylthiazol-2-amine	362 (0.69)	406 (5.51)	2.16	430
4a	4-(4-methylphenyl)-*N*,*N*-dimethylthiazol-2-amine	364 (5.85)	404 (2.18)	1.61	352
5a	4-(4-nitrophenyl)-*N*,*N*-dimethylthiazol-2-amine	372 (1.07)	414 (6.75)	1.89	438
6a	4-(3-chlorophenyl)-*N*,*N*-dimethylthiazol-2-amine	364 (4.84)	406 (1.43)	1.81	356
7a	4-(3-methoxyphenyl)-*N*,*N*-dimethylthiazol-2-amine	372 (4.98)	414 (3.03)	1.60	230
8a	4-(3-nitrophenyl)-*N*,*N*-dimethylthiazol-2-amine	266 (23.90)	234 (24.63)	3.74	260
1b	*N*-(3-methyl-4-phenylthiazol-2-ylidene)methanamine	258 (12.33)	252 (9.33)	10.00	301
2b	*N*-(4-(4-chlorophenyl)-3-methylthiazol-2-ylidene)methanamine	260 (11.65)	222 (17.13)	9.93	308
3b	*N*-(4-(4-methoxyphenyl)-3-methylthiazol-2-ylidene)methanamine	260 (13.03)	236 (14.30)	10.28	262
4b	*N*-(4-(4-methylphenyl)-3-methylthiazol-2-ylidene)methanamine	258 (10.35)	218 (14.85)	10.35	298
5b	*N*-(4-(4-nitrophenyl)-3-methylthiazol-2-ylidene)methanamine	260 (14.15)	266 (16.88)	8.86	276
6b	*N*-(4-(3-chlorophenyl)-3-methylthiazol-2-ylidene)methanamine	260 (19.07)	252 (15.60)	9.18	304
7b	*N*-(4-(3-methoxyphenyl)-3-methylthiazol-2-ylidene)methanamine	260 (8.47)	250 (7.47)	9.96	306
8b	*N*-(4-(3-methylphenyl)-3-methylthiazol-2-ylidene)methanamine	208 (23.90)	216 (25.25)	10.71	224
1c	*N*-(4-phenylthiazol-2-ylidene)methanamine	266 (14.40)	230 (22.80)	4.01	234
2c	*N*-(4-(4-chlorophenyl)thiazol-2-ylidene)methanamine	270 (23.28)	238 (21.88)	4.11	276
3c	*N*-(4-(4-methoxyphenyl)thiazol-2-ylidene)methanamine	270 (19.20)	246 (22.33)	3.50	236
4c	*N*-(4-(4-methylphenyl)thiazol-2-ylidene)methanamine	268 (17.93)	236 (23.18)	4.00	240
7c	*N*-(4-(3-methoxyphenyl)thiazol-2-ylidene)methanamine	268 (14.13)	234 (18.48)	3.98	240

[a] Measured in pH = 1 buffer. [b] Measured in pH = 7 buffer. [c] Half protonation values. [d] Wavelengths of measurements.

tometer controlled by a computer and equipped with a 1 cm path length quartz cell for UV−vis spectra acquisition. After each pH adjustment, the solution was transferred into the cuvette, and the absorption spectra were recorded. Spectra were acquired between (205 and 325) nm (1 nm resolution).

Procedure for Spectrophotometric Measurement. A stock solution of 4-(3- or 4-substituted phenyl)-2-amino thiazole derivatives (10^{-3} mol·dm^{-3}) was prepared in ethanol−water (1:1). Sample solutions were prepared by adding 0.50 mL of stock solution to 9.5 mL of buffer solution in a series of 10 mL volumetric flasks. We have prepared the sample solutions which have absorbance values in the UV−vis spectrum between 0.5 and 1. All the series of standard solutions were placed in UV cells, hermetically closed, and thermostatted at 25 °C for 15 min. The UV−vis spectra were then recorded on a spectrophotometer within the range (205 to 325) nm. Simultaneously, the corresponding absorbance values were measured at the optimum wavelength. This process was followed for each molecule.

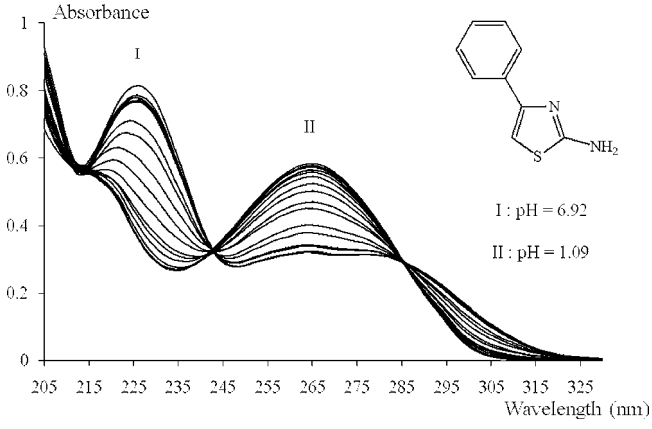
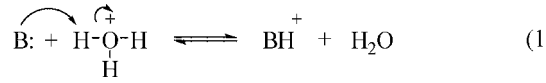


Figure 2. UV spectrum of molecule **1** in 1:1 water:ethanol.

The method depends on the direct determination of the ratio of the molecular species in a series of nonabsorbing buffer solutions for which pH values are either known or measured. 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 spectrophotometric method of Johnson.[33] This method takes into account any medium effect on the wavelength of the maximum UV absorption and the corresponding molar absorptivity. The protonation of a weak base can be defined as follows (eq 1)



(1)

then the equilibrium constant might be expensed in terms of concentration and activity coefficient as shown in eq 2.

$$K_a = \frac{[BH^+]}{[B][H^+]}\frac{\gamma_{BH^+}}{\gamma_B\gamma_{H^+}} \quad (2)$$

Assuming that $\gamma_{BH^+}/\gamma_B = 1$, the p$K_a$ value can be expressed as follows (eq 3)

$$pK_a = -\log\frac{[BH^+]}{[B]} + pH \quad (3)$$

An experimental plot of log I (i.e., log [BH$^+$]/[B]) against pH will be equal to pK_a when log $I = 0$ is the measure of the half protonation value. Equation 4 may therefore be applied

$$pK_a = m{\cdot}H_x^{1/2} \quad (4)$$

where $H_x^{1/2}$ represents the half protonation value and "m" is the slope of the log I−pH plot. The wavelengths were chosen such that the fully protonated form of the substrate had a very

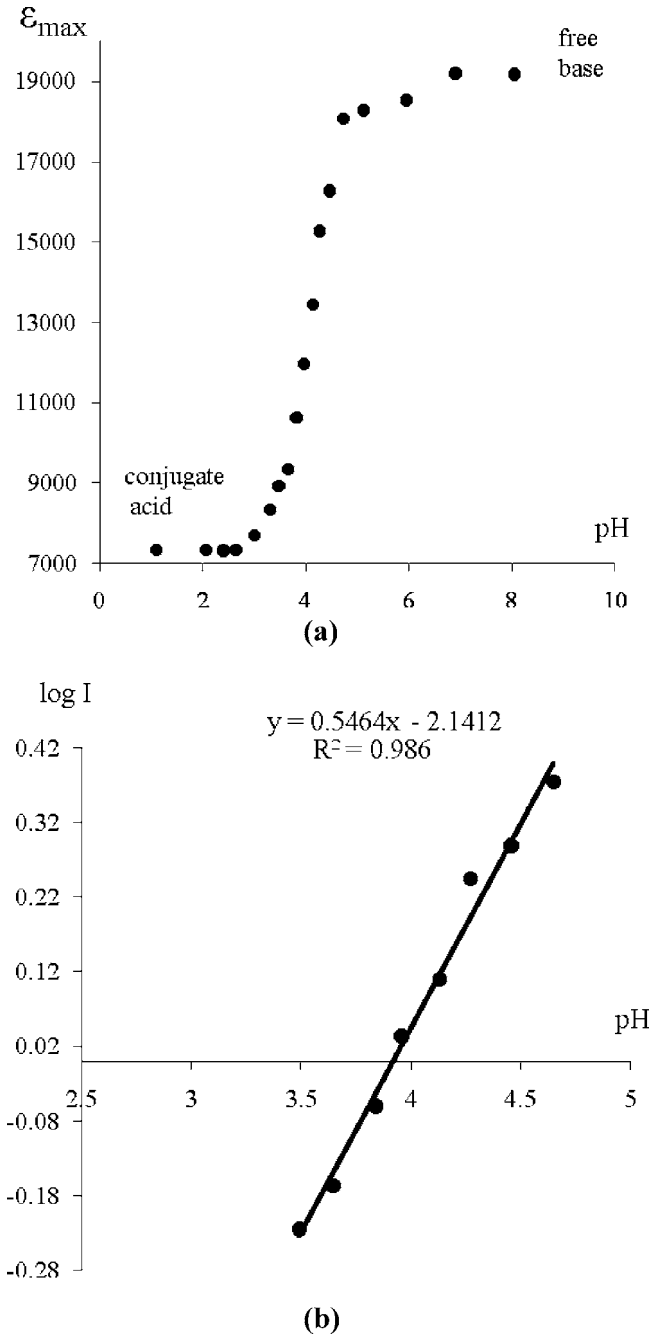


Figure 3. pH−ε_{max} (at 230 nm) (a) and log I−pH (b) plots of the molecule **1**.

much greater or a very much smaller molar absorptivity than the neutral form. Calculations of half protonation values were carried out as follows: the sigmoid curve of optical density or molar absorptivities at the analytical wavelength (OD, λ) were first obtained (Figure 2). 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 from the arms of the curve. Equation 5 gives the ionization ratio of the $OD_{obs.}$ (the observed optical density) which in turn was converted into molar extinction $\varepsilon_{obs.}$ using Beers' Law of OD $= \varepsilon \cdot b \cdot c$.

$$I = \frac{[BH^+]}{[B]} = \frac{(OD_{obs.} - OD_{fb.})}{(OD_{ca.} - OD_{obs..})} = \frac{(\varepsilon_{obs} - \varepsilon_{fb.})}{\varepsilon_{obs} - \varepsilon_{fb.}} \quad (5)$$

The linear plot of log I against pH, using the values $-1.0 <$ log $I < 1.0$, had a slope m, yielding the half protonation value as $H_x^{1/2}$ or $pH^{1/2}$ at log $I = 0$ as shown in Figure 3.

The pK_a values were calculated using eq 6.

$$pK_a = pH^{1/2} \quad (6)$$

Results and Discussion

The acidity constants and tautomeric equilibrium constants, K_T, are given in Table 1 and Table 2. The possible protonation pathways along with the tautomeric equilibrium are given in Scheme 1. We evaluated the obtained data in the following order

pK_a and Prototropic Equilibrium, K_T. As expected, 2-aminothiazole is more basic (pK_a = 5.28) than thiazole (pK_a = 2.52).[34] It is recorded in the literature that the first protonation occurs at the ring nitrogen within the pH range[35] of 1 to 7. Therefore, our results seem to be logical. In strongly acidic media, however, exocyclic nitrogen protonation (i.e., amine protonation) was suggested.[36,37] That point is also cleaned out in our work.

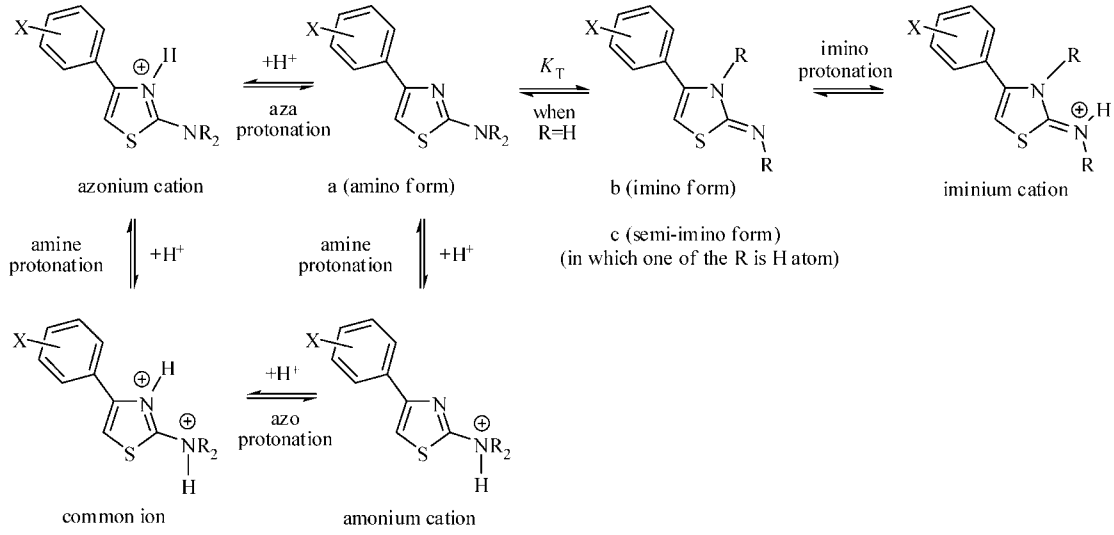
The pK_a value of the 4-phenyl-2-aminothiazole molecule is reported as 4.10 in the literature.[38] In the present study, we have measured this pK_a value as 3.91 for molecule **1** which is very close to the literature value of 4.10 (Table 1, Scheme 2). Angyal and Angyal measured the pK_a of 2-aminothiazoles and 2-imino-4-thiazolines to obtain the prototropic equilibrium constants and K_T values,[39] and they stated that the higher pK_a values of the imino derivative (9.26) compared with that of 2-aminothiazole (5.68) indicate that the amino form is highly predominant. In the present study, the pK_a value of 4-phenyl-2-(*N*-methyl)-3-methyl iminothiazole **1b** (i.e., model molecule for compound **1** in which the proton migration is eliminated by replacing the acidic hydrogen with methyl group) was determined to be 10.00. The higher pK_a value of the imino derivative **1b** compared with that of molecule **1** (3.91) proves that the amino form is highly predominant. The pK_a value of 4-phenyl-2-(*N*,*N*-dimethyl) amino derivative **1a** (i.e., model molecule for amino form) was calculated to be 1.79. This pK_a value of model molecule **1a** is not close enough to the pK_a value of the parent molecule **1** to

Table 2. pK_T and K_T Values for the Studied Compounds

tautomeric equilibria	K_T	pK_T[a]	tautomeric equilibria	K_T	pK_T[a]
1a ⇌ 1b	$6.16 \cdot 10^{-9}$	−8.21	1a ⇌ 1c	$6.02 \cdot 10^{-3}$	−2.22
2a ⇌ 2b	$4.78 \cdot 10^{-9}$	−8.32	2a ⇌ 2c	$3.16 \cdot 10^{-3}$	−2.50
3a ⇌ 3b	$7.58 \cdot 10^{-9}$	−8.12	3a ⇌ 3c	$4.57 \cdot 10^{-2}$	−1.34
4a ⇌4b	$1.81 \cdot 10^{-9}$	−8.74	4a ⇌ 4c	$4.07 \cdot 10^{-3}$	−2.39
5a ⇌ 5b	$1.07 \cdot 10^{-7}$	−6.97	-	-	-
6a ⇌ 6b	$4.26 \cdot 10^{-8}$	−7.37	-	-	-
7a ⇌ 7b	$4.36 \cdot 10^{-9}$	−8.36	7a ⇌ 7c	$4.16 \cdot 10^{-3}$	−2.38
8a ⇌ 8b	$1.07 \cdot 10^{-7}$	−6.97	-	-	-

[a] Calculated by using the Charton method and the following equations: $pK_T = pK_{a(\text{model for imino form})} - pK_{a(\text{model for amino form})}$ and $pK_T = pK_{a(\text{model for semi imino form})} - pK_{a(\text{model for amino form})}$. The minus sign of the pK_T value indicates the predominance of the amino form. a: represents the amino form. b: represents the imino form. c: represents the semi amino or semi imino form.

Scheme 1. Possible Protonation Patterns for Studied 4-(3- or 4-Substituted phenyl)-2-amino Thiazole Derivatives and for Their Model Molecules



R = H or Me (for model compounds),
X = H, 4-Cl, 4-MeO, 4-Me, 4-NO_2, 3-Cl, 3-MeO, 3-NO_2

Table 3. Calculated Substituent Constants, σ Values, and Dihedral Angles (ABCD)[a]

		σ		dihedral angles °
compound	substituent X	calcd$_{\text{for amino form}}$	lit.$_{\text{for amino form}}$	difference between neutral and N-protonated form
2	*p*-Cl	0.07	0.23	35
3	*p*-MeO	0.02	−0.27	145
4	*p*-Me	0.01	−0.17	146
5	*p*-NO_2	0.06	0.78	148
6	*m*-Cl	0.03	0.37	146
7	*m*-MeO	−0.04	0.12	146
8	*m*-NO_2	0.09	0.71	31

[a] $pK_{a(\text{substituent})} - pK_{a(\text{unsubstituent})} = \rho\cdot\sigma$ equation was used. The ρ value of the pyridine type nitrogen atom was taken into account, and the value of ρ was −5.77.[41] [b] Taken from ref 41.

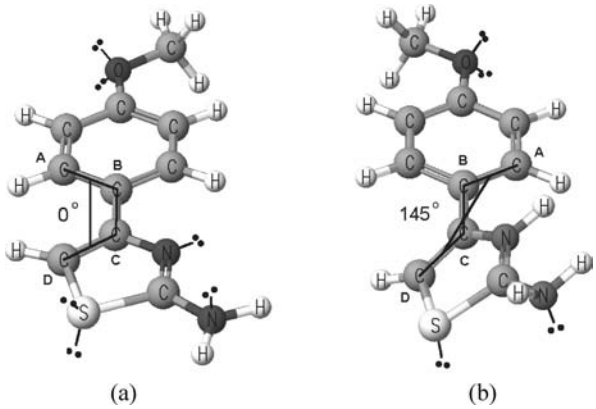
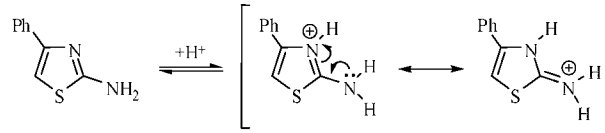


Figure 4. Dihedral angles (ABCD) of unprotonated (a) and protonated (b) forms for molecule **2** (calculated using the demo version of the semiempirical CAChe 7.5 packet program).[42]

predict that they protonate with the same mechanism. However, the pK_a value of 4.01 for molecule **1c** (i.e., model molecule for semiamino form) is very close to the pK_a value of molecule **1**. So we can predict that they protonate via the same mechanism as shown in Scheme 1. That is, the protonation equilibrium at the ring nitrogen for compound **1c** is 1c ⇌ 1c-3 Np and 1 ⇌ 1-3 Np for compound **1**. The calculated pK_T value of −8.21 for the 1a ⇌ 1b equilibrium with the Charton method using the corresponding model molecules indicates that the formation of

Scheme 2. Possible Protonation Pathway for Compound 1



the amino form is highly feasible. However, a subsequent proton migration is inevitable (Scheme 2).

For molecule **2**, a pK_a value of 3.56 was obtained. The electron-withdrawing effect of the chlorine atom at the para position of the phenyl ring of molecule **2** is being reflected in an increment of the acidity. The similarity of the pK_a value to molecule **2c** (i.e., 4.11) indicates that the protonation pattern is the same as for molecule **1**. Here again the higher pK_a value of the imino derivative **2b** indicates the predominance of the amino form. The calculated pK_T value of −8.32 (i.e., $K_T = 4.78\cdot10^{-9}$) indicates that the amino form is overwhelmingly predominant (Table 2).

Similarly for molecule **3**, the obtained pK_a value of 3.83 indicates the electron-donating effect of the methoxy group at the *para* position of the phenyl ring. The higher pK_a value of the imino derivative (i.e., 10.28) compared to amino derivative **3a** (i.e., 2.16) indicates the predominance of the amino form. The calculated pK_T value of −8.12 (i.e., $K_T = 7.58\cdot10^{-9}$) indicates also the overwhelming predominance of the amino form.

This protonation mechanism and predominance of the amino forms seems to be applicable to other studied molecules **4** to **8** (Scheme 1, Table 1).

When we put the studied molecules in an increasing acidity order, we have obtained the following trend

Molecule:	**7**		**1**		**4**		**3**		**6**		**2**		**5**		**8**
Half protonation value ($H^{1/2}$):	4.16	<	3.91	<	3.84	<	3.83	<	3.76	<	3.56	=	3.56	<	3.36
increasing acidity	→														

(7)

Although the difference between the maximum and minimum pK_a values is not big (i.e., 0.8 pK_a units), the differences between the two individual molecules indicate the electronic effect of the substituent, and the dimension of this effect can be calculated by using the Hammett equation. The calculated substituent constants then can be compared with literature values as has been done by LFER (linear free energy relationship) workers.[40]

Evaluation of pK_a Values for LFER. The Hammett equation (eq 8) can be applied to the obtained data. The calculated substituent constants and σ values are depicted in Table 3.

The Hammett Equation can be written as follows

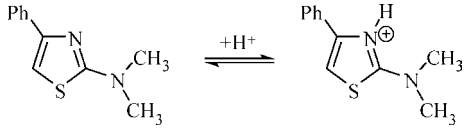
$$\log K/K_o = \rho\cdot\sigma \tag{8}$$

where σ is the substituent constant; ρ is the equilibrium constant and is −5.77 for pyridine-type nitrogen atom protonation; K is the ionization constant for the model compound of the substituted molecule; and K_o is the ionization constant for the model compound of the unsubstituted molecule.

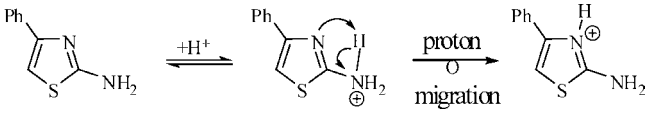
We can deduce from the obtained substituent constant values (i.e., σ values) that electron-donating substituents ($\sigma < 0$) will favor the imino tautomer **b** and electron-withdrawing groups ($\sigma > 0$) the amino tautomer **a**.

Acidity Constant and Protonation Mechanism. The possible protonation pattern for studied 4-(3- or 4-substituted phenyl)-2-amino thiazole derivatives and their model molecules in which the proton migration is eliminated by replacing the mobile protons with methyl groups is described in Scheme 1.

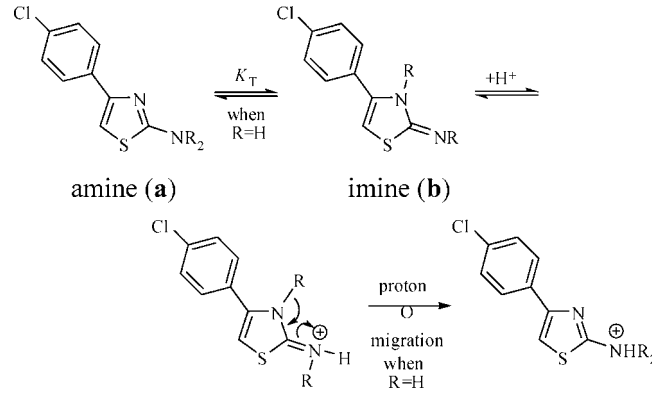
The difference between the pK_a values of molecule **1** (i.e., pK_a value 3.91) and molecule **1a** (i.e., pK_a value 1.79) indicates that they do not protonate with the same mechanism. For molecule **1a**, one possible protonation exists site, which is the aza nitrogen atom of the thiazole ring, and so we can predict a protonation path as follows



In molecule **1**, however, a direct aza protonation seems not to be feasible because the amino group protonated easier in this molecule. However, a subsequent proton migration makes molecule **1** have the same structure as molecule **1a** with the following mechanism



For molecule **2**, the small difference between **2** and **2b** forms is 0.17 pK_a units. Therefore, we can predict that they protonate with the same mechanism as follows



As subsequent proton migration causes molecule **2** to take the form of a 2-amonium derivative and the strong electron-withdrawing effect of the ammonium group causes a drop of the pK_a value of molecule **2** to 2.84, the difference of 0.17 pK_a units between molecule **2** and **2b** originates from that change.

When we attempt to compare the calculated substituent constants with that of literature values, we observe that the fully conjugative and inductive effect becomes impossible in studied molecules **1** to **8**, and this point is reflected in the σ values. The reason for that much difference between the calculated and literature values of σ can be attributed to the drastic change in dihedral angles as shown in Figure 4, which is about 145° for molecules **3** to **7** and about 30° for compounds **2** and **8** in which the rotation about the single bond between two rings is rather rendered.

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Received for review July 7, 2009. Accepted December 24, 2009. Financial support from the Eskişehir Osmangazi University Research Fund (Project Number 200319010) is gratefully acknowledged.

JE9005739