Determination and Evaluation of Acid Dissociation Constants of Some Substituted 2-Aminobenzothiazole Derivatives

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The acid dissociation constants of some 4- and/or 6-substituted 2-aminobenzothiazole and 4-substituted thiazole derivatives were determined spectroscopically. With the exception of a few, the first protonation was found to occur on the amino group. In some molecules where prototropic tautomerism is possible, a change-over in the protonation mechanism was observed. The first protonation under these circumstances was found to occur on the imino nitrogen atom. The second protonation takes place on the thiazole ring nitrogen atom.

Introduction

Some 2-substituted benzothiazole derivatives have been found to be biologically active and have been used particularly in *breast cancer* treatment.[1] Some benzothiazole derivatives have found application in the development and preparation of *anti-inflammatory* drugs and analgesics.[2] The others show *local anesthestic*,[3] *antifungal*,[4,5] *antitumor*,[6] and *antimicrobial*[7] activity. Furthermore, some benzothiazole derivatives are being used as azo dyes[8,9] and corrosion inhibitors[10–12] The important and useful usage of benzothiazole derivatives has made the compounds attractive to work on. Many researchers have studied the IR and Raman spectroscopic properties of the compounds in detail.[13–16] Taking into account the important role of the acidity−basicity of drug precursor compounds in transport phenomena, in partitioning in a medium, and in binding to a receptor and following our work on thiazoles and benzothiazoles,[17] we now here report on acid dissociation constants, K_a values, and proton tautomerism of some 4- and/or 6-substituted 2-amino benzothiazole derivatives.

Experimental Section

Materials and Solutions. The synthesis of the studied compounds was achieved by using procedures described in the literature.[18]

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 further purified.

Apparatus. pH measurements were performed using a glass electrode. Standard buffer solutions with pH values of 1.0, 7.0, and 14.0 were used in the calibration of the INOLAB pH level 1 pH-meter and a five-digit analytical balance; a Unicam UV2 UV–vis scanning spectrophotometer was used for measurements.

Procedure. Acid solutions, CO_2-free NaOH solutions, and pH solutions were prepared by using methods described in the literature.[19–22]

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It is well explained in ref 22 that for weak bases the aqueous ionization process can be described as in eq 1.

$$BH^+ \underset{\text{deprotonation}}{\rightleftharpoons} H^+ + B \quad (1)$$

A mathematical expression of the acid ionization constant can be written as in eq 2.

$$K_a = \frac{a_{H^+}\, a_B}{a_{BH^+}} \quad (2)$$

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 which we can make use of is *the concentration ionization constant*, K_C, which is defined for bases by eq 3.

$$K_c = \frac{[H^+][B]}{[BH^+]} \quad (3)$$

in which the square brackets denote the *concentration* (as opposed to 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 and only applicable if $[H^+] \cong a_{H^+}$, i.e., $\lambda_{H^+} \approx 1$, as indicated below.

$$pK_a = pH + \log[BH^+]/[B] \quad (4)$$

The 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 ions which can exert on one another (ion pair) as well as for the incomplete hydration of ions in solutions that are 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 solutions no stronger than about 0.01 $mol \cdot L^{-1}$ and only univalent ions or unchanged molecules are present.

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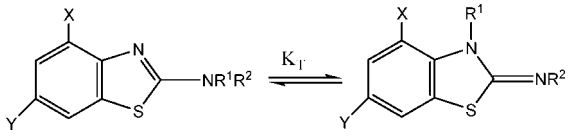
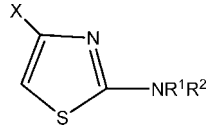
Table 1. Formulas and IUPAC Nomenclature for 4- and/or 6-Substituted 2-Aminobenzothiazole Derivatives (1 to 16)



compound	IUPAC name	substituents X	Y	R^1	R^2
1	benzothiazole	H	H	–	–
2	2-amino	H	H	H	H
3	2-methylamino	H	H	CH_3	H
4	2,2-dimethylamino	H	H	CH_3	CH_3
5	4-methyl-2-amino	CH_3	H	H	H
6	4-methyl-2-methylamino	CH_3	H	CH_3	H
7	4-methyl-2,2-dimethylamino	CH_3	H	CH_3	CH_3
8	6-methyl-2-amino	H	CH_3	H	H
9	6-methyl-2-methylamino	H	CH_3	CH_3	H
10	4,6-dimethyl-2-amino	CH_3	CH_3	H	H
11	4,6-dimethyl-2-methylamino	CH_3	CH_3	CH_3	H
12	6-methoxy-2-amino	H	OCH_3	H	H
13	6- methoxy –2-methylamino	H	OCH_3	CH_3	H
14	6-floro-2-amino	H	F	H	H
15	6-floro-2-methylamino	H	F	CH_3	H
16	6-chloro-2,2-dimethylamino	H	Cl	CH_3	CH_3

Table 2. Formulas and IUPAC Nomenclature for 4-Substituted 2-Amino Thiazole Derivatives (17 to 24)



compound	IUPAC name	substituents X	R^1	R^2
17	thiazole	–	–	–
18	2-amino	H	H	H
19	2-methylamino	H	CH_3	H
20	2-dimethylamino	H	CH_3	CH_3
21	4-(1-napthyl)-2-amino	1-napthyl	H	H
22	4-(l-napthyl)-2-dimethylamino	1-napthyl	CH_3	CH_3
23	4-(2-napthyl)-2-amino	2-napthyl	H	H
24	4-(2-napthyl)-2-dimethylamino	2-napthyl	CH_3	CH_3

For the present study, it needs to 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 the hydrogen ion activity than to the hydrogen ion concentration, although at low ionic strength ($I < 0.01$ M) these terms do not differ greatly between pH 2 and 12.

Spectroscopy is an ideal method[22] when a substance is not soluble enough for potentiometry or when its pK_a value is particularly low or high and requires a very small amount of substance.We have therefore preferred this method in the present work. This method depends on the direct determination of the ratio of the molecular species, that is, the neutral molecules and their corresponding ionized species, in a series of nonabsorbing buffer solutions for which $[H^+]$ 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.[19–22]

The general procedure applied was as follows: a stock solution of the compound under investigation was prepared by dissolving about (10 to 20) mg of the compound in water in a volumetric flask. Aliquots (1 mL) of this solution were transferred into 10 mL volumetric flasks and diluted to the mark with buffers of various pH. 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. The scanning spectrophotometer was thermostatted 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 maxima for each substrate studied are given in Tables 1 to 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 densities 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 3 gives the ionization ratio where the OD_{obsd} (the observed optical density) was converted into molar extinction ϵ_{obsd} using Beers' Law of OD = $\epsilon.b.c$, (b = cell width, cm; c = concentration, mol·dm^{-3}).

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

The linear plot of log I against pH, using the values $-1.0 < \log I < 1.0$, had slope m, yielding the half-protonation value as $pH^{1/2}$ or more generally $H^{1/2}$ at $\log I = 0$ (Figure 2). The half-protonation value for the protonation of molecule **15** then can be obtained as $H^{1/2}$ = pH = 3.30.

Result and Discussion

Acid dissociation constants can be used in various areas of research, such as stereochemical and conformational structure determinations,[23,24] the directions of *nucleophilic* and *electrophilic* attack, the stabilities of intermediates, the size of activation energies in organic reactions,[25] and determination of the active centers of enzymes in biochemistry.[26] In the present work, we report on the experimental acid dissociation constants of some biologically active 4- and/or 6-substituted 2-amino benzothiazole bases to elucidate the structure–reactivity relationships and to evaluate the linear free energy relationship.

Protonation Patterns

The nomenclature, UV spectra, and protonation data for the studied compounds **1** to **24** are given in Tables 1 to 3.

First Protonation

The half-protonation, $H^{1/2}$, values for the first protonation of 4- and/or 6-substituted 2-amino benzothiazole derivatives and their model molecules (1 to 16) can be put in increasing basicity order as follows:

Compound	:	11		6		16		14		5		8
Half protonation ($H^{1/2}$):		4.00	<	9.20	<	9.80	<	11.4	<	13.00	<	13.45

→ increasing basicity

When we take the acidity constant value of 9.65[27] for the protonation of 2-amino-3-methyl thiazole into account, we can say that the molecules **5**, **8**, **14**, and **16** have larger half-protonation values, whereas molecules **6** and **11** have smaller half-protonation values. Since the half-protonation values are close enough to the pK_a value of the 2-amino-3-methyl thiazole

Table 3. UV Spectral Data, Acidity Constants, and pK_{a1} and pK_{a2} Values of Compounds 1 to 24 for the First and/or Second Protonation

compound	spectral maximum λ/nm			acidity measurements							
neutral[a]	species (log ϵ_{max})	monocation (log ϵ_{max})[b]	dication (log ϵ_{max})[c]	λ^d/nm	$H^{1/2e}$	pK_{a1}[f]	corr.[g]	λ^d/nm	$H^{1/2e}$	pK_{a2}[f]	corr.[g]
1	–	–	–	–	–	–	–	–	–	1.84[29]	–
2	–	–	–	–	–	–	–	–	–	4.51	–
3	273(4.09)	216(4.39)	–	–	–	–	–	275	2.91 ± 0.1	2.17	0.96
4	257(4.42)	242(4.03)	–	–	–	–	–	257	−1.3 ± 0.3	−1.75	0.92
5	271(4.12)	260(4.07)	262(4.03)	271	13.00 ± 0.03	7.28	0.97	260	−0.88 ± 0.3	−0.98	0.81
6	269(4.15)	220(4.31)	–	269	9.2 ± 0.07	5.33	0.93	–	–	–	–
7	278(4.00)	264(3.87)	–	–	–	–	–	278	2.3 ± 0.07	2.32	0.97
8	266(2.83)	290(0.65)	–	290	13.45 ± 0.01	2.28	0.98	–	–	–	–
9	225(4.41)	261(3.99)	–	–	–	–	–	231	3.7 ± 0.05	2.59	0.98
10	226(4.26)	275(4.10)	–	–	–	–	–	231	4.1 ± 0.06	4.46	0.99
11	228(4.26)	208(4.36)	273(3.93)	259	4.00 ± 0.09	2.36	0.95	273	−0.84 ± 0.22	−1.05	0.90
12	267(4.06)	209(4.46)	–	–	–	–	–	267	0.65 ± 0.04	0.31	0.97
13	212(4.46)	270(4.14)	–	–	–	–	–	224	3.8 ± 0.07	1.83	0.99
14	220(4.16)	255(3.83)	–	220	11.4 ± 0.1	7.8	0.93	–	–	–	–
15	222(4.43)	208(4.25)	–	–	–	–	–	222	3.3 ± 0.05	2.17	0.97
16	261(3.50)	230(3.60)	–	230	9.8 ± 0.1	6.40	0.87	–	–	–	–
17	–	–	–	–	–	2.53	–	–	–	–	–
18	–	–	–	–	–	5.39	–	–	–	–	–
19	–	–	–	–	–	9.65	–	–	–	–	–
20	–	–	–	–	–	–	–	–	–	–	–
21	223(4.55)	272(3.88)	–	272	4.1 ± 0.1	2.58	0.97	–	–	–	–
22	372(4.09)	259(3.99)	–	372	0.85 ± 0.08	1.00	0.97	–	–	–	–
23	295(4.10)	260(4.34)	–	260	3.6 ± 0.05	3.80	0.99	–	–	–	–
24	382(4.03)	227(4.44)	–	382	0.6 ± 0.14	0.51	0.86	–	–	–	–

[a] Measured in pH = 7 buffer solution for compounds 3, 5 to 16, 21 to 22, and 24 and measured in 50 % H_2SO_4 for compounds 4 and 23. [b] Measured in pH = 1 buffer for compounds 3, 5 to 7, 9 to 16, and 21 to 24 and measured in 98 % for compound 4. [c] Measured in 50 % H_2SO_4 for compounds 5 and 11. [d] The analytical wavelength for pK_a determination [e] Half-protonation value ± uncertainties refer to the standard error for the first and/or second protonation. [f] Acidity constant value. [g] Correlations for log *I* as a function of pH graph.

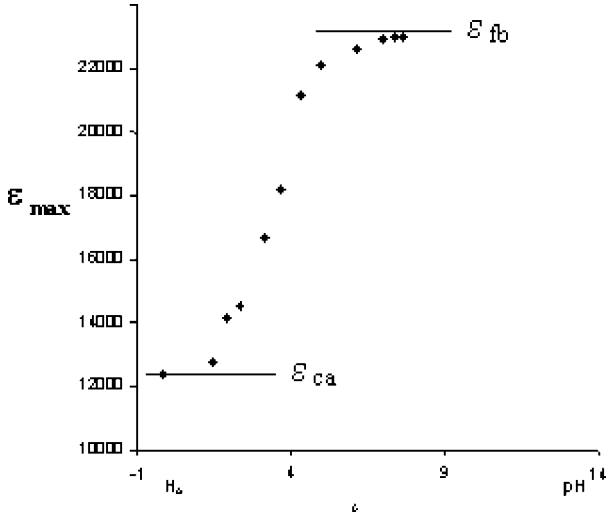


Figure 1. ϵ_{max} as a function of pH and $-H_o$ (obtained from the % H_2SO_4 vs $-H_o$ table of ref 22) (at 222 nm) plot for the protonation of 6-floro-2-methylamino benzothiazole molecule **15**.

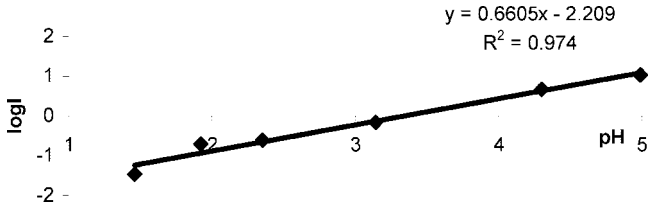
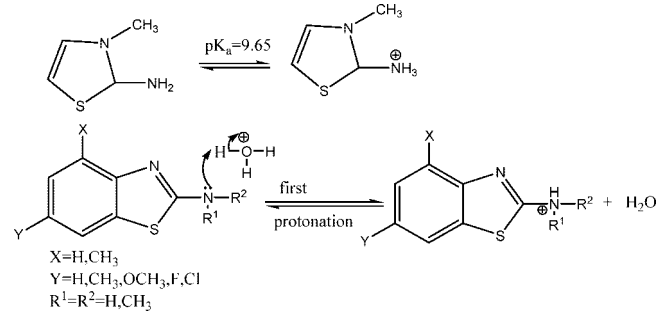


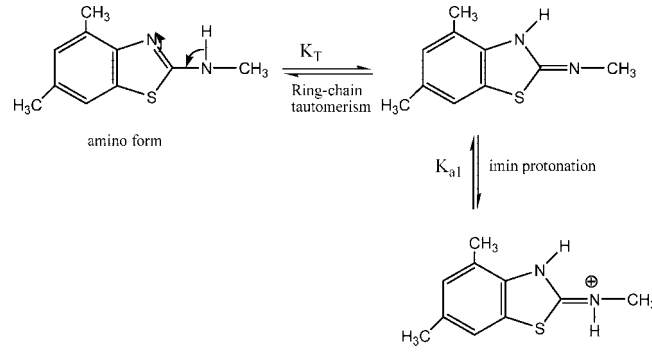
Figure 2. pH as a function of log *I* (at 222 nm) plot for the protonation of 6-floro-2-methylamino benzothiazole molecule **15**.

molecule, the protonation pattern of this model molecule and the molecules **5**, **6**, **8**, **11**, **14**, and **16** should be similar and had to be amino protonation (Scheme 1). The differences of up to five orders of magnitute can only be justified with a change-over in the protonation mechanism.

Scheme 1. Possible Protonation Pattern for the First Protonation of Molecules (1 to 16)



Scheme 2. Possible Protonation Pattern for Molecule 11 for the First Protonation



Molecule **8** has the largest basicity because of the inductive effect of the methyl group at position six (6C) (i.e., the Hammett substituent constant for the *p*-Me group is −0.17[28]), whereas in molecule **5** the methyl group is located at 4C which has a smaller inductive effect. In molecule **14**, the flouride atom at position six (6C) (i.e., the Hammett constant for the *p*-F atom is 0.06[28]) withdraws electrons from the ring and reduces the

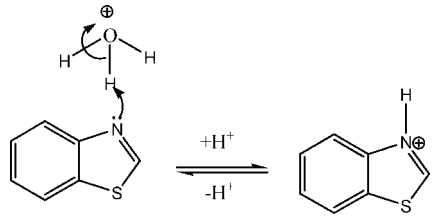


Figure 3. Protonation pattern for the benzothiazole molecule.

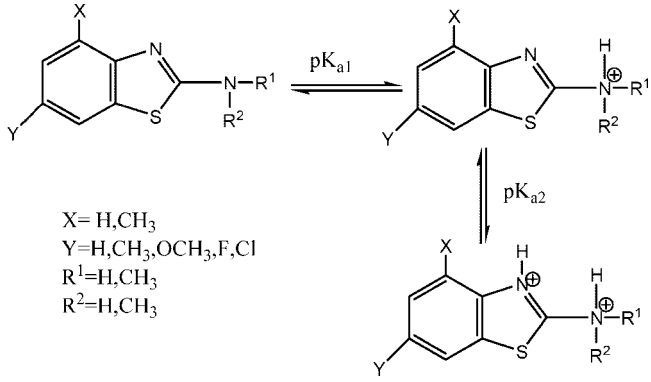


Figure 4. Protonation pattern for studied compounds for the second protonation.

electron density on the amino group. Consequently, the basicity decreases. In molecule **16**, the chloride atom is placed at the 6C position (i.e., the Hammett substituent constant for *p*-Cl is 0.23[28]) and withdraws electrons inductively, making the molecule less basic. In this molecule, the steric effect of the two methyl groups on the amino group should also be considered. These two methyl groups cause the formation of a bulky group and do not permit an easy access of the hydronium ion to the nitrogen atom of the amino group. In molecule **6**, a methyl group placed at 4C has no inductive effect. The methyl group on the amino group also causes a steric obstacle for easy protonation. In molecule **11**, however, the basicity drops down enormously (i.e., half-protonation value is 4.00). This abnormallity can be explained only with a change in protonation mechanism. It seems that in molecule **11**, amino−imino tautomerism becomes effective, and the pattern in Scheme 2 is suggested.

The protonation pattern for molecule **11** then will be different from the other members of the series, and the basicity will drop down considerably.

Second Protonation

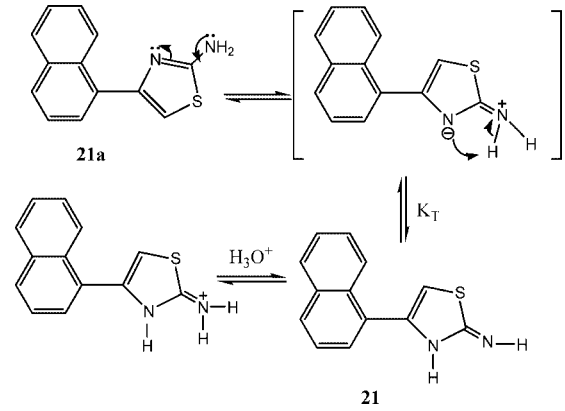
The half-protonation values for the second protonation of 2- and/or 4-substituted 2-amino-benzothiazole derivatives can be put in increasing basicity order as follows:

Compound : **4 5 11 12 7 3 15 9 13 10 2 1**

$H^{1/2}$: -1.30<-0.88<-0.84<0.65<2.30<2.91< 3.30< 3.70<3.80< 4.10< 4.51<5.39

increasing basicity
decreasing acidity

Scheme 3. Possible Protonation Pattern for Molecule 21



Molecule **1** seems to have the biggest half-protonation value, and the protonation occurs at 3N of the thiazole ring (Figure 3).

In molecule **2**, however, the first protonation occurs on the amino group, and the protonated amino group withdraws an electron from the thiazole ring. The 3N atom becomes electron poor, so the basicity decreases. The basicity decreases more in molecule **10** because, in addition to the electron-withdrawing effect of the protonated amino group, the steric effect of the 4-CH_3 group comes to action (Figure 4).

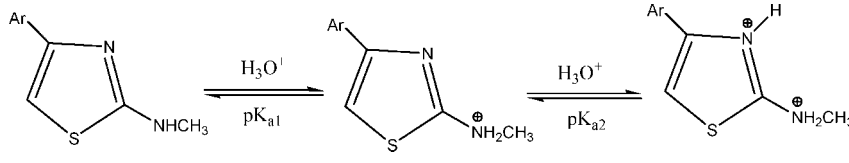
In molecules **13** and **9**, the decrease of basicity is caused by the steric effect of the 2-methylamino group. In molecule **15**, in addition to the steric effect of the 2-methylamino group, the strong inductive electron-withdrawing effect of the fluoride atom becomes effective and the basicity drops further. In molecule **3**, there is no substituent on the benzene ring to increase the basicity, so after the first protonation the methylamino group turns into a methylammonium group and withdraws an electron inductively and, at the same time, sterically decreases the possibility of a proton approach. In compound **7**, the protonation of the dimethyl amine group creates a bigger steric effect, and basicity drops further. Compound **4** seems to be the least basic molecule. Obviously, the dimethyl amino group is protonated and becomes effective because the dimethylammonium ($-^{+}NH(CH_3)_2$) ion can withdraw electrons inductively as well as sterically. Compound **5** shows a slightly larger basicity than compound **4** because the protonated ammonium group ($-^{+}NH_3$) withdraws electrons less than the diammonium group and so has a smaller steric effect. In molecule **11**, the methylammonium ($-^{+}NH_2CH_3$) group has effects similar to those in molecule **5**. The electron-donating effect of the methoxy group in molecule **12** however increases basicity by almost one pK_a unit.

Thiazole Derivatives

The acidity constants, pK_a values, of investigated thiazole derivatives **17** to **24** can be put in increasing order as follows:

The pK_a value of the thiazole molecule **17** and 2-aminothiazole **18** have been reported as 2.53 and 5.39, respectively, for the ring protonation. We can say therefore that the amino group at 2C of the thiazole ring has increased the basicity of the

Scheme 4. Possible Protonation Pattern for Molecules 22 and 24



Molecule : **24** **22** **17** **21** **23** **18** **19**

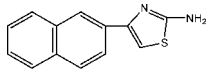
pK_a :0.51 < 1.00 < 2.53 < 2.58 < 3.80 < 5.39 < 9.65

basicity increase

acidity decrease

ring by a strong electron-donating effect. This effect however seems to not be that effective on molecule **21** probably due to the possibility of amino−imino tautomerism. In this way, the protonation can take place on the imino nitrogen atom (Scheme 3).

In molecule **23**, however, the geometry seems to be different than in molecule **21**, and the dihedral angle between 2-napthyl and the thiazole ring is different from zero. Unlike molecule **21**, the full conjugation is not effective. The electron-withdrawing effect of the napthyl group is not effective because it is substituted at the β position.



23

This structure lets the electron density on the 3N atom increase which, in turn, increases the basicity. For molecule **19**, however, the first protonation takes place on the amino group because the hydrogen atom of the amino group is replaced with a methyl group, becoming a secondary amine. The pK_a value of 9.65[27] of 3-methyl-2-amino thiazole can be taken as a reference for molecule **19**.

The protonation mechanism for molecules **22** and **24** seems to take place with a similar mechanism. It seems that the second protonation takes place on the thiazole ring because the methylamino group has already protonated (Scheme 4) and becomes an electron-withdrawing methylammonium group, letting the basicity decrease.

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