Anadolu Üniversitesi Bilim ve Teknoloji Dergisi A- Uygulamalı Bilimler ve Mühendislik
Anadolu University Journal of Science and Technology A- Applied Sciences and Engineering

2016 - Volume: 17 Number: 2
Page: 263 - 272
DOI: 10.18038/btda.96904
Received: 07 January 2016 Revised: 08 April 2016 Accepted: 09 May 2016

DETERMINATION AND EVALUATION OF ACIDITY CONSTANTS OF SOME IMIDAZOLE AND THIAZOLE LINKED ACETAMIDE COMPOUNDS

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ABSTRACT

In this work, the effect of substituents on the acidity constants of some acetamide derivatives was investigated. The acidity constants of nine acetamide derivatives were determined at 25 °C using a UV spectrophotometric method. When the molecules possessed different substituents the values of the acidity constants changed from 6.01 to 8.22 for the first protonation and from 3.07 to 4.73 for the second protonation. The first protonation under these circumstances was observed to occur on the nitrogen atom of the 2-mercaptoimidazole ring. The second protonation was observed to occur on the nitrogen atom of the thiazole ring.

Keywords: Imidazole, Thiazole, Acetamide, Protonation paths, UV spectroscopy, pK_a

1. INTRODUCTION

During the last few years, numerous articles detailing the determination of the acid–base properties of organic molecules have been reported [1-12]. The acid dissociation constant, pK_a, is defined as tendency of an acid to release a proton in an aqueous solution. The acidity constants of organic reagents play a fundamental role in numerous chemical and biological processes, such as analytical procedures, acid-base titrations, solvent extraction, ion transport, complex formation, chemical synthesis, electrochemical properties, pharmacokinetics, drug design, drug metabolism and enzymatic reactions [13-15]. Acidity constants are very important in the analysis of the mechanisms of action of drugs because they are the key parameters for predicting the extent of the ionization of a molecule in solution at different pH [16].

Spectrophotometric methods are highly sensitive and suitable for the determination of acidity constants. Different spectroscopic methods for the experimental determination of acidity constants have been developed, including UV–Vis absorption, ^{1}H NMR, FT-IR, and Raman techniques [17-20]. Knowledge of the acidity constant of a molecule is one of the most important parameters in explaining the physicochemical behavior of drugs and in investigating pharmaceutical synthesis methods [21]. Changes in pK_a values in molecules depend on intramolecular interactions [22].

Imidazole and thiazole represent an interesting class of heterocyclic compounds. Phenyl thiazole and imidazole-2-thione were observed to play important roles in biological functions, such as antimicrobial, antidiabetic, antiviral, anti-inflammatory, antituberculosis, and anticancer activities [23-31]. In particular, 2-amino-4-phenyl-1,3-thiazole has pharmaceutical characteristics and it is used in industrial applications [32-34]. Thiazole compounds have also been used in electrochemical applications [35-42].

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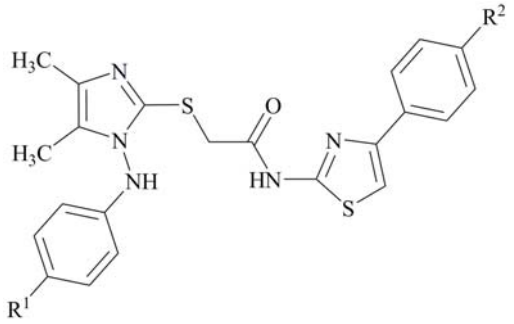
In this study, UV-visible spectrophotometry and a physicochemical approach are used to determine the acidity constants of nine 2-(4,5-dimethyl-1-(arylamino)-1*H*-imidazol-2-yl)thio)-*N*-(4-arylthiazol-2-yl)acetamide derivatives (Figure 1).



Comp.	R^1	R^2
1	H	H
2	H	OCH_3
3	H	Cl
4	OCH_3	H
5	OCH_3	OCH_3
6	OCH_3	Cl
7	Cl	H
8	Cl	OCH_3
9	Cl	Cl

Figure 1. Structures of 2-(4,5-dimethyl-1-(arylamino)-1*H*-imidazol-2-yl)thio)-*N*-(4-arylthiazol-2-yl) acetamide derivatives

2. MATERIAL AND METHOD

The studied acetamide derivatives were synthesized according to the methods described in our previous work [31]. The buffer solutions used were prepared from: (a) HCl-KCl, pH = 1.0; (b) KH_2PO_4-NaOH, pH = 7.0; (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 [43]. The percentage of sulfuric acid solution [(1 to 98%) H_2SO_4] was determined by titration with Na_2CO_3 using methyl red as an indicator.

An Orion model 720A+ pH/ion analyzer with a combination glass electrode was used for pH measurements after being calibrated against standard buffers of pH 4, 7 and 9. A Unicam UV2 UV-Vis scanning spectrophotometer was used to record the electronic absorption spectra. The UV-Vis spectra, which were obtained to determine the values of the acidity constants, were recorded at pH which are (1-14) and H_o (acidity range) which is -0.20 and -10.72. The spectrophotometer was equipped with quartz cells with a 1 cm path length and the spectra were recorded over the wavelength range of 220-400 nm.

Acid solutions, CO_2-free NaOH solutions, and pH solutions were prepared by using the methods described in the literature [44-46]. For bases ionization process can be described as in Eq.1.

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

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

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

Where *a* represent 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 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 in which the square brackets denote the concentration of each ionic species.

$$K_c = [H^+]\ [B] / [BH^+] \tag{3}$$

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 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 infinite dilution, the concentration becomes numerically equal to the thermodynamic constant. Equation 3 can be used for the simplicity, provided that the constant is determined in solution not stronger than 0.01 mol/L and only univalent ions are present. For the present, it needs only to be noted that activity of neutral species does not differ appreciably from its concentration and that pH, as commonly determined, is nearer to hydrogen ion activity than that to hydrogen ion concentration, although at low ionic strength (I <0.01) 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 form the measuring instruments.

Spectroscopy is an ideal method [46] when a substance is not soluble enough for potentiometry. We have therefore preferred this method in the present work. This methods, depend on the direct determination of the ratio of the molecular species, that is, the neutral 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 [45]. The general procedure applied as follows;

The stock solution of compound (10^{-5}M) under investigation was prepared by dissolving the compound in ethanol in a volumetric flask. Aliquots (1mL) of this solution were transferred into 10 mL volumetric flask and diluted to the mark with buffers of various pH values. The pH was measured before and after the addition of the new solution. The optical density of each solution was then measured in 1 cm cells against solvent blanks using a Unicam UV-2 UV-Vis spectrophotometer equipped with a constant-temperature cell holder. The scanning spectrophotometer was thermostated at 25 °C (to within ±1 °C). The UV spectra of the same compounds were retaken, after the sample in buffer during 48 hours. The UV spectra were compared, it was observed that those were the same spectra. In other words there is no interaction between the sample solution and the buffer solution.The UV spectra of compound **2** are shown in Figure 2a for the pH=7, 50% H_2SO_4 and 98% H_2SO_4. The wavelengths were chosen such that the fully protonated form of the substrate had a much greater or much smaller extinction coefficient than the neutral form.

Calculation of half protonation values were carried out as follows: the sigmoid curve of the optical density at the analytical wavelengths (OD, λ) was first obtained. Observed optical density (OD_{obs}) data were converted to the observed molar extinction (ε_{obs}) using Beer's law of OD = ε.b.c (b: cell width, cm; c: concentration, mol/dm^3). Data in the H_o range -3 and -8.25 (monoprotic acid behavior) were fitted in its linear transformation. (Eq. 5) (Figure 2b)

The optical densities of the fully protonated molecule ($OD_{ca,}$ optical density of the conjugated acid) , pure free base ($OD_{fb,}$ optical density of the free base) and (ODobs, optical density of the observed) at acidity were then calculated by linear extrapolation of the arms of the curve. The following equation (Eq.5) gives the ionization ratio [46]:

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

I is the ionization ratio

The linear plot of log I as a function of pH using the values -1 < log I < 1 had slope m, which yielded the half-protonation value as $pH^{1/2}$ or, more generally, $H^{1/2}$ at log I=0 (Figure 2c). The acidity constant was calculated as follows (Eq.6) :

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

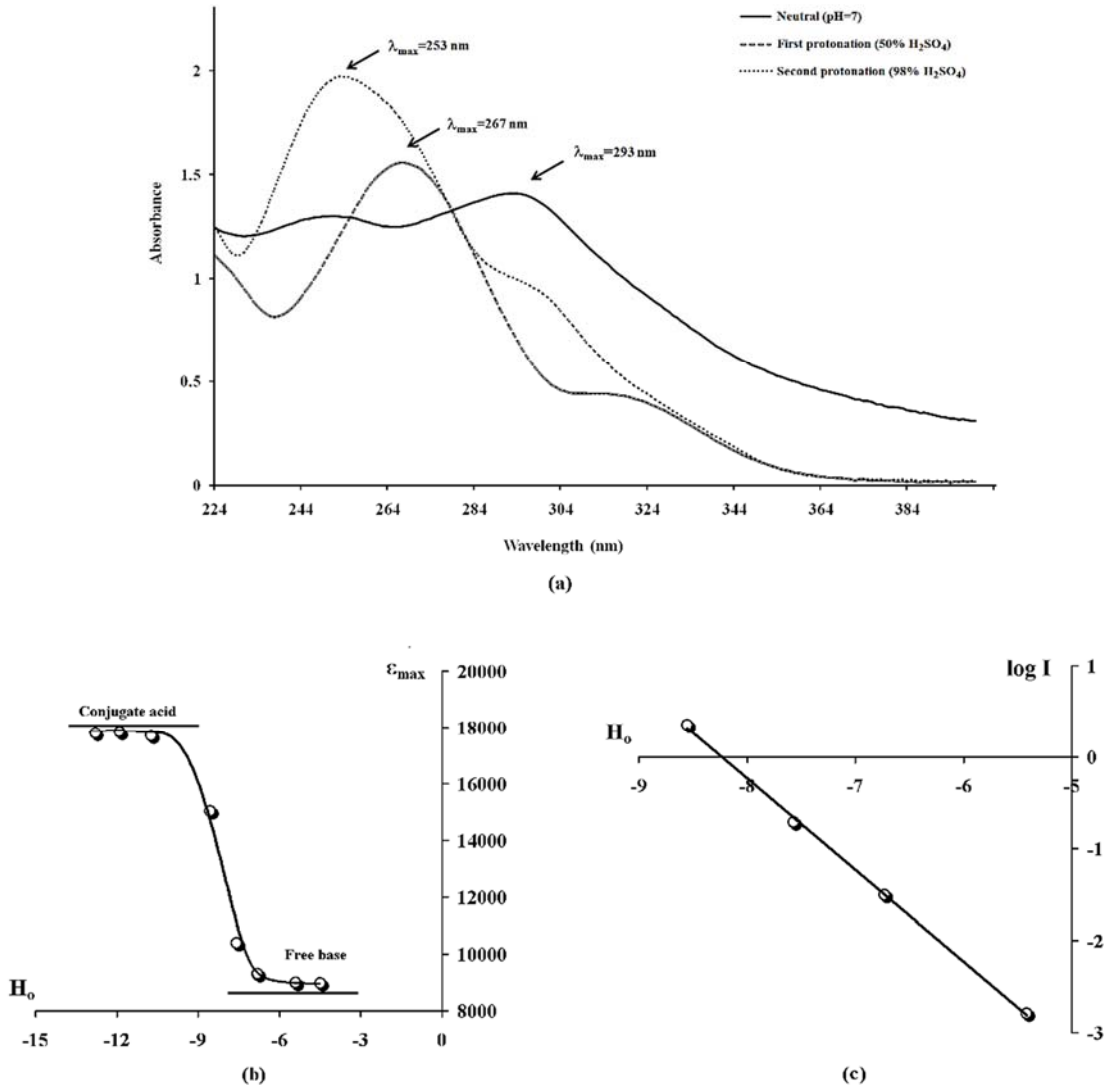


Figure 2. (a)Absorption spectra at different acidity range, (b)ε_{max} as a function of H_o and (c) H_o as a function of log I of compound **2**

3. RESULTS AND DISCUSSION

3.1. Absorbtion Spectra

It is known that an absorbance diagram is a plot of the absorbance at one wavelength against the absorbance at second wavelength. As a result, an absorbance diagram shows the relative absorbance changes at two wavelengths as a function of the pH of the buffer solutions. For example the absorption spectrum of compound 2 shows (Figure 2a) two absorption band which have two absorption maximum at 267 nm and 253 nm. This absorption bands are attributed to the acidic forms (monocation and dication) of compound 2.

3.2. Determination of Acidity Constants

The acidity constants (*i.e.*, the pK_a values) of some 2-(4,5-dimethyl-1-(arylamino)-1*H*-imidazole-2-yl)thio)-*N*-(4-arylthiazol-2-yl)acetamide derivatives were determined using the previously described UV spectroscopic method. The nomenclature and protonation data for studied derivatives 1 to 9 are presented in Tables 1.

Table 1. IUPAC Nomenclature for studied compounds (**1-9**)

Comp.	IUPAC Name
1	2-(4,5-dimethyl-1-(phenylamino)-1*H*-imidazol-2-ylthio)-*N*-(4-phenylthiazol-2-yl)acetamide
2	2-(4,5-dimethyl-1-(phenylamino)-1*H*-imidazol-2-ylthio)-*N*-(4-(4-methoxyphenyl)thiazol-2-yl)acetamide
3	*N*-(4-(4-chlorophenyl)thiazol-2-yl)-2-(4,5-dimethyl-1-(phenylamino)-1*H*-imidazol-2-ylthio)acetamide
4	2-(1-(4-methoxyphenylamino)-4,5-dimethyl-1*H*-imidazol-2-ylthio)-*N*-(4-phenylthiazol-2-yl)acetamide
5	*N*-(4-(4-methoxyphenyl)thiazol-2-yl)-2-(1-(4-methoxyphenylamino)-4,5-dimethyl-1*H*-imidazol-2-ylthio)acetamide
6	*N*-(4-(4-chlorophenyl)thiazol-2-yl)-2-(1-(4-methoxyphenylamino)-4,5-dimethyl-1*H*-imidazol-2-ylthio)acetamide
7	2-(1-(4-chlorophenylamino)-4,5-dimethyl-1*H*-imidazol-2-ylthio)-*N*-(4-phenylthiazol-2-yl)acetamide
8	2-(1-(4-chlorophenylamino)-4,5-dimethyl-1*H*-imidazol-2-ylthio)-*N*-(4-(4-methoxyphenyl)thiazol-2-yl)acetamide
9	*N*-(4-(4-chlorophenyl)thiazol-2-yl)-2-(1-(4-chlorophenylamino)-4,5-dimethyl-1*H*-imidazol-2-ylthio)acetamide

Table 2. The first protonation values of the compounds and their UV-spectral data

Comp.	Spectral Maximum λ (nm)		Acidity Measurements			
	Neutral species[a] (log ε_{max})	Monocation[b] (log ε_{max})	λ[c]	$H^{1/2}$ [d]	pK_{a1}	Corr.[e]
1	307 (4.23)	264 (4.34)	227	13.25	8.46 ± 0.24	0.95
2	293 (4.45)	267 (4.19)	302	-8.25	8.22 ± 0.28	1.00
3	291 (4.44)	271 (4.45)	271	-7.82	7.67 ± 0.35	0.96
4	282 (4.35)	265 (4.34)	261	-6.72	7.51 ± 0.34	0.97
5	290 (4.43)	268 (4.47)	235	10.85	7.89 ± 0.34	0.97
6	272 (4.43)	271 (4.46)	233	13.50	7.79 ± 0.30	0.95
7	274 (4.31)	267 (4.40)	227	10.70	6.93 ± 0.11	0.99
8	287 (4.19)	267 (4.24)	268	15.15	8.04 ± 0.23	0.96
9	286 (4.43)	263 (4.45)	308	9.15	6.01 ± 0.13	0.98

[a] Measured in pH=7; [b] measured in 1% or 50% H_2SO_4; [c] measurement of the dissociation constant on the wavelength (nm); [d] half protonation values; [e] correlation coefficient

Table 3. The second protonation values of the compounds and their UV-spectral data

Comp.	Spectral Maximum λ (nm)		Acidity Measurements			
	Monocation[a] (log ε_{max})	Dication[b] (log ε_{max})	λ[c]	$H^{1/2}$ [d]	pK_{a2}	Corr.[e]
1	264 (4.34)	249 (4.60)	249	-7.72	5.23 ± 0.25	1.00
2	267 (4.19)	253 (4.60)	253	-7.45	4.00 ± 0.13	0.99
3	271 (4.45)	253 (4.54)	253	-7.90	3.07 ± 0.36	0.93
4	265 (4.34)	260 (4.37)	301	5.30	4.16 ± 0.24	0.93
5	268 (4.47)	262 (4.71)	296	-8.12	3.92 ± 0.37	0.89
6	271 (4.46)	261 (4.66)	310	4.65	4.73 ± 0.19	0.99
7	267 (4.40)	250 (4.69)	300	7.20	4.17 ± 0.35	0.90
8	267 (4.24)	254 (4.36)	290	5.70	3.31 ± 0.10	0.99
9	263 (4.45)	252 (4.61)	252	4.50	3.25 ± 0.30	0.97

[a] Measured in 1% or 50% H_2SO_4; [b] measured in 98% H_2SO_4; [c] measurement of the dissociation constant on the wavelength (nm); [d] half protonation values; [e] correlation coefficient

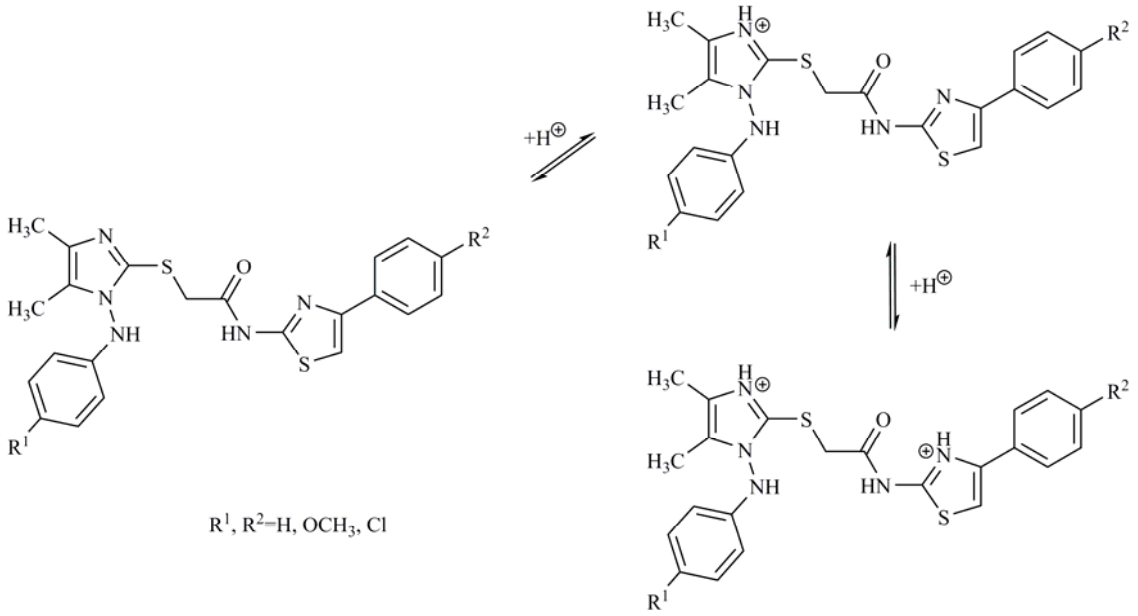


Figure 3. Possible protonation pattern for the first and second protonation of compounds (**1-9**)

The acetamides share the same structural backbone, such that one arylamino group and one phenyl ring attached to a thiazole ring are bridged via an acetamide (-CH_2-CO-NH-) linkage. These heterocyclic rings are responsible for the acid behavior of the studied compounds. Figure 3 indicates the presence of two possible protonation centers (the imidazole-ring and thiazole-ring nitrogen atoms) in each molecule.

One method for determining the protonation centers for the first and second protonation involves a comparison of the obtained data with the literature values. According to the literature, the pK_a values are 7.00 and 4.10 for the imidazole and 4-phenyl-2-aminothiazole, respectively [47-48]. As indicated in Table 2, the first acidity constant values of the acetamide derivatives are greater than 7.00. In this case, the imidazole can be protonated. According to these data, the first protonation pK_a values of compound **1** were observed to be the lowest (*i.e.*, 8.46) and the protonation pK_a values of compound **9** were observed to be the highest (*i.e.*, 6.01) among the investigated derivatives. The acidity of the acetamide derivatives is influenced by the substituents on the aromatic phenyl ring. The low acidity of compound **1** can be attributed to the high electron density at the imidazole ring system that results from the electron-donor character of the substituent phenyl group; therefore, the proton bonds more strongly to the heterocyclic nitrogen atom, affording a lower acidity constant for compound. Compound **9** possesses an electron-withdrawing Cl group, which decreases the electron density on the imidazole ring. Consequently, the bond between the hydrogen atom and the imidazole nitrogen atom is weakened, leading to easier ionization, that is, high acidity. The results in Table 2 reveal that the pK_{a1} values increase in the following order:

Compd.	**1** <	**2** <	**8** <	**5** <	**6** <	**3** <	**4** <	**7** <	**9**
R^1, R^2	H, H	H, OCH_3	Cl, OCH_3	OCH_3, OCH_3	OCH_3, Cl	H, Cl	OCH_3, H	Cl, H	Cl, Cl
Exp. pK_{a1}	8.46	8.22	8.04	7.89	7.79	7.67	7.51	6.93	6.01

increasing acidity →

As evident from the results in Table 3, the values of the second acidity constants (pK_{a2}) were found to be 5.23 between 3.07, which are close the value of thiazole protonation. According to the obtained results, the pK_{a2} values increase as follows:

Compd.	**1** <	**6** <	**7** <	**4** <	**2** <	**5** <	**8** <	**9** <	**3**
R^1, R^2	H,H	OCH_3, Cl	Cl,H	OCH_3,H	H,OCH_3	OCH_3, OCH_3	Cl, OCH_3	Cl,Cl	H, Cl
Exp. pK_{a2}	5.23	4.73	4.17	4.16	4.00	3.92	3.31	3.25	3.07

increasing acidity →

This order of increasing acidity is logical since it gives the electron-donating effect of the phenyl group and the inductive electron-withdrawing effect of the Cl group in the *para* position on the phenyl ring. Therefore, the second protonation value of compound **1** was observed to be the lowest (*i.e.*, 5.23) and that of compound **3** was observed to be the highest (*i.e.*, 3.07).

4. CONCLUSION

We have determined the acidity constants of nine acetamide derivatives in ethanol using a UV spectroscopic method. A comparison of the data given in Tables 2 and 3 reveals that the lowest pK_a values were observed for molecules **9** and **3**, both of which carry an inductive electron-withdrawing substituent (*i.e.*, a chloro group).

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