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Spectroscopic Determination of Acid Dissociation Constants of Some Novel Drug Precursor 6-Acylbenzothiazolon Derivatives

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The acid dissociation constants, as pK_a values, of eight drug precursor 6-acylbenzothiazolon derivatives were determined using UV−vis spectroscopic technique. The protonation and deprotonation behaviors of the investigated molecules were studied from super basic to super acid regions (i.e., 8 mol·L^{-1} KOH to 98 % H_2SO_4) including the pH region. It was observed that protonation occurs only at the amid group in the super acid region. By validating the obtained acid dissociation constants, elucidation of the structure and protonation mechanisms of the studied molecules was attempted.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) which have important side effects have been used worldwide. 2-Benzothiazolinone derivatives are belong to the NSAIDs group. These drugs, however, have important side effects such as gastrointestinal lesions, kidney functional disorders, and hematological toxicities.[1] Therefore, medical chemistry researchers have aimed to develop NSAID drugs which are effective as opiates but do not have side effects. As a result of these investigations, there exist nowadays many heterocyclic compounds being investigated for anti-inflammatory activity, and they have different effects from the above-mentioned side effects.

It was previously reported that 2-benzothiazolinone, 2-benzoxazolinone, and oxazolo pyridazinone derivatives exhibit a variety of pharmacological effects, including analgesic and anti-inflammatory activity.[2–9] Early studies had indicated that 2-benzothiazolinone, 2-benzoxazolinone, and oxazolo pyridazinone derivatives exhibit a variety of pharmacological effects, including analgesic and anti-inflammatory activity.[2–9] For instance, 6-benzoyl-2-benzothiazolinone was screened for analgesic activity and reported as a peripheral acting by release of an endogenous circulating opioid-like substance with a certain anti-inflammatory and antipyretic activity.[10] These derivates are known as antibacterial, anticonvulsive, diuretic, antihistaminic, antiarithmic, and analgesic reagents and have a wide spectrum of biological activity.

The piperazine moiety has been classified as a privileged structure which is frequently found in biologically active compounds. Therefore, the piperazine moiety has been used intensively in many therapeutic areas such as antifungal, antidepressants, antiviral, serotonin receptor (CS-HT), and antagonists/agonists binding.[11–13] Piperazines and substituted piperazines are important pharmacophores that can be found in many marketed drugs, such as the Merck HIV protease inhibitor.[14–16] Several compounds that contain the piperazine moiety in their molecule bind to serotonin receptors.[17] Although as a group the piperazine-like compounds cannot be considered as selective compounds for serotonin receptors, they can made be more site-selective with the appropriate substituents.[18]

The knowledge of the acidity constant is a key parameter for understanding the chemical interactions between the compound of interest and its pharmacological target. Relationships between the acid−base dissociation constant, pK_a, and the structure may prove to be useful information in drug design studies and in explaining the biopharmaceutical properties of substances like benzoxa- or benzothiazolinone.[19,20] The aim of this work is to determine the acid−base dissociation constant, pK_a values, of a series of novel drug precursor 6-acylbenzothiazolon derivatives using UV spectrophotometric methods.

Experimental Section

Materials and Solutions. The studied compounds (Table 1) were of spectroscopic grade, and the procedures of synthesis are described in ref 21. Methanol, ethanol, glycine, KOH, H_2SO_4, HC1, CH_3COOH, CH_3COONa, NaOH, KH_2PO_4, Na_2CO_3, $NaHCO_3$, NaCl, methyl orange indicator, phenolphthalein indicator, and standard buffer solutions were used without further purification and were obtained from Sigma Aldrich.

Apparatus. pH measurements were performed using a glass electrode. Standard buffer solutions of pH values of 4, 7, and 9 were used in the calibration of the Hanna instruments HI 221 pH meter; the UV-2550 Shimadzu UV−vis spectrophotometer was used for measurements. Measurements were made at (25.0 ± 0.1) °C.

Methods of Theoretical Calculations. Prior to any calculations, all structures were submitted to the HF/3-21G level of theory for geometry conformational search. A conformational search of investigated molecules was performed by Spartan08.[22] Only those conformations, which are most stable for a given compound, have been used. The other calculations were performed with Gaussian 03W software.[23] The molecular structures of the 6-acylbenzothiazolon derivatives, in the ground state, are optimized by using the B3LYP method with the standard 6-31G(d) basis set.[24]

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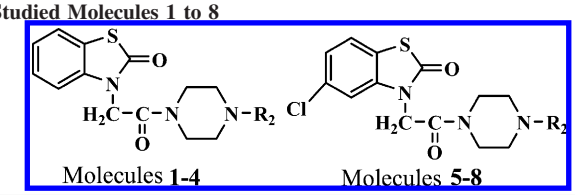
Table 1. IUPAC Nomenclature of the Studied Molecules 1 to 8



compound	IUPAC name	R_2
1	3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	CH_3
2	3-(2-(4-ethylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	C_2H_5
3	3-(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	$CH(CH_3)_2$
4	3-(2-(4-butylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	$CH_2CH_2CH_2CH_3$
5	5-chloro-3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	CH_3
6	5-chloro-3-(2-(4-ethylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	C_2H_5
7	5-chloro-3-(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)benzo[d]thiazol-2(3*H*)-one	$CH(CH_3)_2$
8	3-(2-(4-butylpiperazin-1-yl)-2-oxoethyl)-5-chlorobenzo[d]thiazol-2(3*H*)-one	$CH_2CH_2CH_2CH_3$

Table 2. UV−vis Spectral Data, Acidity Constants, and pK_a Values of Studied Compounds for the Protonation

UV spectra data and acidity constants, pK_a, values of **1** to **8** for the protonation									
	spectral maximum λ/nm					acidity measurements			
compound	neutral species ($\log \epsilon_{max}$)[a]		monocation ($\log \epsilon_{max}$)[b]		λ/nm[c] $_{max}$	$H^{1/2}$[d]	m[e]	pK_a[f]	corr.[g]
1	242 (shoulder)	3.90	241.5	3.80	282	−5.193 ± 0.07	0.7105	−3.69 ± 0.07	0.99
	278.5	3.69	274	3.53					
	285.5	3.66	281.5	3.54					
2	243 (shoulder)	3.89	244	3.79	282	−5.402 ± 0.08	0.4279	−2.311 ± 0.08	0.98
	278.5	3.68	275	3.52					
	286	3.65	281.5	3.53					
3	244 (shoulder)	3.92	243	3.78	282	−5.477 ± 0.02	0.4175	−2.286 ± 0.02	0.99
	278.5	3.70	275	3.52					
	285.5	3.68	281.5	3.52					
4	244 (shoulder)	3.92	242.5	3.77	282	−6.187 ± 0.12	0.6071	−3.756 ± 0.12	0.99
	278	3.71	274	3.53					
	285.5	3.68	281.5	3.52					
5	287	3.65	283.5	3.63	290.5	−4.336 ± 0.13	0.3672	−1.592 ± 0.13	0.98
	294	3.66	291	3.66					
6	286.5	3.64	283.5	3.63	291.5	−3.687 ± 0.02	0.5421	−1.998 ± 0.02	0.99
	294	3.66	291	3.66					
7	286.5	3.70	283.5	3.67	291	−4.490 ± 0.10	0.5940	−2.667 ± 0.10	0.99
	293.5	3.71	291	3.66					
8	286.5	3.69	283	3.67	290.5	−4.444 ± 0.08	0.7435	−3.300 ± 0.08	0.98
	294	3.69	291.5	3.68					

[a] Measured in 0.3 mol·L^{-1} H_2SO_4. [b] Measured in 98 % H_2SO_4. [c] The analytical wavelength for pK_a determination. [d] Half-protonation values and ± uncertainties for standard errors for the protonation. [e] Slopes of the $\log I - H_0$ plot. [f] Acidity constant values. [g] Correlations for the $\log I$ against H_0 graph.

Procedure. Acid, KOH, and pH solutions were prepared by using methods described in the literature.[25–28] The potentiometric measurements were performed by measuring the hydrogen ion concentration (under nitrogen atmosphere) at (25.0 ± 0.1) °C, and ionic strengths of the media were maintained at 0.1 using NaCl.

Spectrometry is an ideal method[28] of potentiometry when a substance is not soluble enough or when its pK_a values are particularly low and high (i.e., less than 2 or more than 11). This method depends on the direct determination of the ratio of the molecular species concentration, 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.[28] For determining the acid dissociation constants of very weak bases, solutions of known H_0 (designed for H_2SO_4) take the place of the buffer solutions mentioned above. This method takes into account any effect of the medium on the wavelength of the maximum UV absorption and the corresponding extinction coefficient. This effect is particularly at high acidities. The protonation of a weak base can be defined as follows,

$$HX + SH \rightleftharpoons X^- + SH_2^+ \quad (1)$$

where SH is the solvent. Then, the equilibrium constant might be expressed in terms of activity (eq 2)

$$K_a = \frac{a_{x^-} \cdot a_{SH_2^+}}{a_{HX}} \quad (2)$$

By inserting the equivalence of a in eq 2 (where $a = c\gamma$; a: activity; γ: activity coefficient; c: concentration), we can derive eq 3

$$K_a = \frac{[X^-]}{[HX]} \cdot \frac{\gamma_{X^-}}{\gamma_{HX}} \cdot a_{SH_2^+} = h_X \frac{[X^-]}{[HX]} \quad (3)$$

and bearing in mind that

$$h_X = \frac{\gamma_{X^-}}{\gamma_{HX}} \cdot a_{SH_2^+} \quad (4)$$

When we insert the h_X value in eq 3, we obtain eq 5.

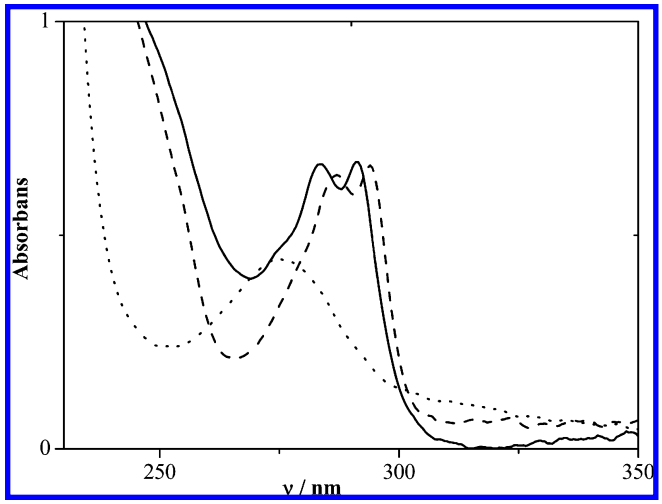


Figure 1. UV−vis spectrum of compound **5**. —, 98 % H_2SO_4; ---, pH = 7; •••, 8 mol·L^{-1} KOH.

$$H_X = -\log h_X = pK_a - \log \frac{[HX]}{[X^-]} \quad (5)$$

where H_X is an acidity function. The H_0 scale is defined such that for the uncharged primary aniline indicators used a plot of log I (i.e., log ([HX]/[X^-])) against H_0 has a unit slope. It was observed from work on bases other than the Hammett-type that the slopes of the plots of log I against H, shown by m, were not always unit. Thus, a series of structurally similar bases, like triarylmethanols, primary amides, and tertiary aromatic amines, defined individual acidity functions, H_R, H_A, and H''', which have a linear relationship to H_0.

An experimental plot of log I against H_0 does not yield the pK_a at log $I = 0$, unless it is a Hammett base, but rather the H_0 at half-protonation ($H^{1/2}$). The general eq 3 may therefore be applied. By rearranging eq 5, we can get eq 6,

$$pK_a = H^{1/2} + \log I \quad (6)$$

and mathematically it can be expressed as a straight line ($y = mx + n$) with a slope of m so it becomes as follows (eq 7);

$$pK_a = m \cdot H^{1/2} + \log I \quad (7)$$

Since at the half-protonation point log I will be equal to zero, we will end up with eq 8.

$$pK_a = m \cdot H^{1/2} \quad (8)$$

The general procedure is applied as follows: a stock solution of the compound under investigation was prepared by dissolving the compound (∼ (10 to 20) mg) in water or sulfuric acid of known strength (25 mL) in a volumetric flask. Aliquots (1 mL) of this solution were transferred into 10 mL volumetric flasks and diluted to the mark with sulfuric acid solutions of various strengths or buffers of various pH values. The total mass of solution in each flask was measured and the mass percent of sulfuric acid in each and the total mass of the final solution added. In the case of buffer solutions, 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 of UV-2550 Shimadzu UV−vis spectrophotometer. 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 Table 2.

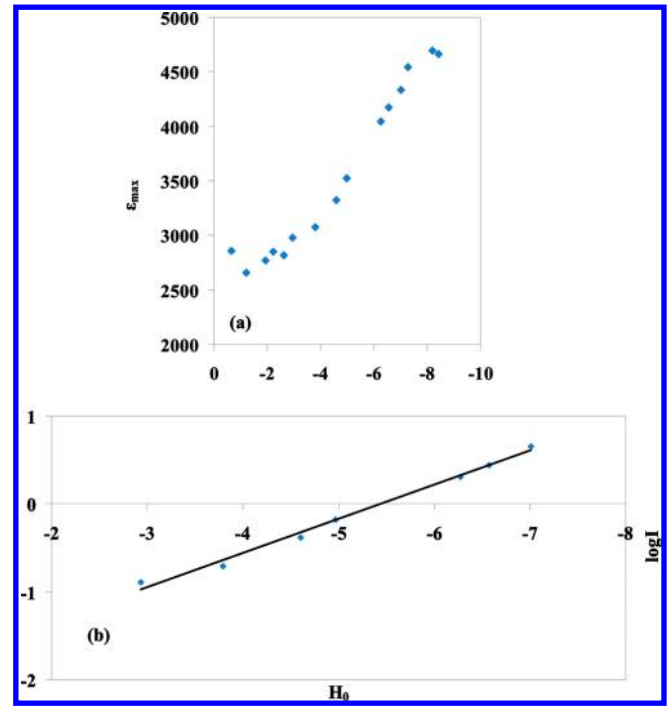
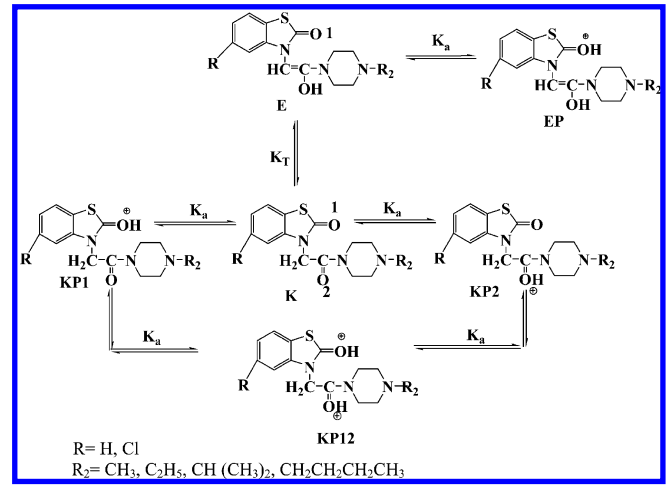


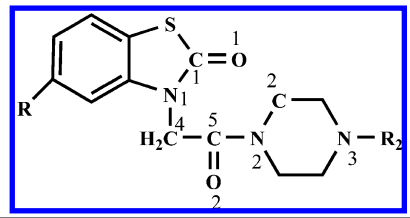
Figure 2. (a) ε_{max} as a function of $-H_0$ (obtained from the 0.1 % to 98 % H_2SO_4 vs $-H_0$ table of the ref 28) (at 282 nm) plot for the protonation of molecule **3**. (b) H_0 as a function of log I (at 282 nm) plot for the protonation of molecule **3** ($y = -0.4175x - 2.2867$, $R^2 = 0.9983$).

Scheme 1. Possible Protonation Pattern for Studied Molecules 1 to 8



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 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 = ϵbc, (b = cell width, cm; c = concentration, mol·dm^{-3}).

Table 3. Sum of Energy, Dipole Moment, Atomic Charge, and Dihedral Angle Calculated at the B3LYP/6-31G(d) Level of Theory for the Investigated Molecules 1 to 8



	sum of energy		charges						dihedral angle	
compound	kcal·mol^{-1}	dipole moment (Debye)	O(1)	O(2)	R	N(1)	N(2)	N(3)	N1−C4−C5−N2	O1−C1−N1−C4	O2−C5−N2−C2
1	−788560	2.04	−0.500	−0.516	0.141 (*R* = H)	−0.513	−0.421	−0.386	76.570	6.640	−175.906
2	−813229	2.39	−0.500	−0.517	0.141 (*R* = H)	−0.514	−0.420	−0.390	−74.758	−6.644	177.530
3	−837892	2.78	−0.493	−0.526	0.141 (*R* = H)	−0.515	−0.412	−0.404	62.572	4.876	−176.803
4	−862570	2.09	−0.501	−0.513	0.141 (*R* = H)	−0.513	−0.419	−0.397	75.599	6.644	−175.980
5	−1076960	2.37	−0.495	−0.513	−0.012 (*R* = Cl)	−0.515	−0.421	−0.385	−77.246	−6.617	175.909
6	−1101629	2.59	−0.495	−0.514	−0.012 (*R* = Cl)	−0.516	−0.422	−0.380	−76.972	−6.435	176.919
7	−1126299	2.69	−0.495	−0.515	−0.012 (*R* = Cl)	−0.516	−0.420	−0.400	77.372	6.324	2.770
8	−1150963	2.22	−0.495	−0.512	−0.011 (*R* = Cl)	−0.515	−0.424	−0.387	64.308	5.589	−177.070

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

The linear plot of log I against H_0, using the values $-1.0 < \log I < 1.0$, had slope m, yielding the half-protonation value as $H^{1/2}$ at log $I = 0$ (Figure 2).

Results and Discussion

The nomenclature and UV−vis spectroscopic data related to protonation processes are depicted in Tables 1 and 2. A possible protonation pattern for investigated molecules was represented in Scheme 1. The UV spectrum of compound **5** was shown in Figure 1. The spectral characteristics of all compounds were used for determining the acidity constant, pK_a, values. For example, the absorption spectrum of compound **5** in 98 % H_2SO_4 solution showed two absorption bands centered at (283 and 291) nm, while in pH = 7 solution, both absorption bands shifted from (283 to 287) nm and from (291 to 294) nm, and spectral overlaid shows two isosbestic points. However, the absorption spectrum of compound **5** in 8 mol·L^{-1} KOH solution showed one absorption band centered at 274 nm, while in pH = 7 the solution showed two absorption bands. The absorption spectra of the other molecules have similar behaviors.

Molecules **1**, **2**, **3**, and **4** show the following trend with the increasing of their half protonation, $H^{1/2}$, values.

Molecule	:	1	2	3	4
$H^{1/2}$	:	-5.193 >	-5.402 >	-5.477 >	-6.187
R_2(substituent):		methyl	ethyl	isopropyl	butyl

→ Increasing acidity or decreasing basicity

It is observed that the increase in substituent size of **1**, **2**, **3**, and **4** molecules gives rise to increase of acidity caused by the steric effects of the ethyl, methyl, isopropyl, and butyl group.

The half protonation, $H^{1/2}$, values for the protonation the molecules **5**, **6**, **7**, and **8** can be put in increasing acidity orders as follows.

There is no correlation between the substituent size and acidity values of **5**, **6**, **7**, and **8** molecules.

Molecule	:	6	5	8	7
$H^{1/2}$	:	-3.687 >	-4.336 >	-4.444 >	-4.490
R_2 (substituent):		ethyl	methyl	butyl	isopropyl

→ Increasing acidity or decreasing basicity

It seems that the addition of an alkyl group to the nitrogen of piperazine of **1**, **2**, **3**, and **4** molecules causes the lowering of pK_a values and increases the acidic power. Similar behaviors were reported for the piperazine, 1-methylpiperazine, 1-ethylpiperazine, and 1,4-dimethylpiperazine molecules earlier.[29]

The m values given in Table 2 of **2**, **3**, **5**, **6**, and **7** molecules, which are about of 0.5, suggest the oxo-protonation of amid moiety for all studied molecules. The possible protonation pattern (KP2 protonation) for **2**, **3**, **4**, **5**, **6**, and **7** molecules was depicted in Scheme 1. The pK_a value for oxo-protonation of acetamid supports this result.[30] The m values of **1**, **4**, and **8** molecules are bigger than those of the other molecules. So, we can conclude that it is because of their enol form oxo-protonation (EP protonation).

Half-protonation values indicated that replacement of the R group by a weak electron acceptor such as the Cl substituent on the aromatic ring did not influence the acidity character. However, the presence of the Cl atom lets the global electron density on **5**, **6**, **7**, and **8** molecules increase which, in turn, increases the basicity.

The sum of energy, dipole moment, atomic charge, and dihedral angle calculated at the B3LYP/6-31G(d) level of theory for the investigated molecules **1** to **8** are depicted in Table 3. The abnormal behavior of molecule **7** can easily be interpreted if we look at the geometric optimization data of Table 3. All of the dihedral angles of this molecule are different from the molecules **5**, **6**, and **8**. The isopropyl substituent of molecule **7** gives rise to strong steric hindrance on the molecule forcing the O2−C5−N2−C2 dihedral angle to be 2.770°. Thus, the difference in $H^{1/2}$ value of molecule **7** can be attributed to the steric hindrance depending on the orientation of piperazine−isopropyl moiety.

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