Spectroscopic Determination of Acid Dissociation Constants of Some Biologically Active 6-Phenyl-4,5-dihydro-3(2*H*)-pyridazinone Derivatives

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The acid dissociation constants, pK_a, of twelve biologically active 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone derivatives were determined using spectroscopic techniques. Elucidation of the structure−reactivity relationships was attempted from structural considerations based on the acid dissociation constants.

Introduction

It is well-known that biological processes are based on chemical reactions. The main factors of life such as providing energy, transmission of pulses, metabolism, and transfer of genetic information are all chemical reactions in which heteroaromatic molecules take part. Therefore, knowledge about the structure of heteroaromatic molecules is invaluable in understanding their reactivity. The acid dissociation constants have been used in various areas of research, such as stereochemical and conformational structure determinations,[1,2] the directions of nucleophilic and electrophilic attack, the stabilities of intermediates, the size of activation energies in organic reactions,[3] and determination of the active centers of enzymes in biochemistry.[4]

In the present work we report on the acid−base behavior of some 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone derivatives with potential *antihypertensive* effects.[5−8] The acid dissociation constants, pK_a, were determined by means of the UV technique. The results were used to interpret the structure−reactivity relations.

Experimental Section

Reagents. The studied compounds were synthesized and reported elsewhere.[9] Sulfuric acid, nitric acid, and sodium hydroxide were all Analar grade reagents and were not purified further. The weight percentage acidities were checked with a densitometer for sulfuric acid solutions lower than 90%. For higher percentages, they were titrated with a 0.1 N sodium hydroxide solution using methyl orange/xylene cyanol as the indicator. The buffer solution was prepared using Analar hydrochloric, boric, and acetic acids, a standard 0.1 N sodium hydroxide solution, and potassium dihydrogen phosphate.

Determinations of Acidity Constants. 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[10,11] (e.g. less than 2 or more than 11). The method depends on the direct determination of the ratio of the molecular species, that is, the neutral molecules to the corresponding ionized species in a series of nonabsorbing buffer solutions where pH values are either known or measured. To provide a series of solutions in highly acid and highly basic regions, the acidity functions H_0 and H_- were used.[12] In strong acid solutions in which the ionic strength is high, the proton-donating ability of the medium is no longer measured by the concentration of hydrogen ions, since the molar activity coefficients of the ions in the solution are not unity. As a measure of the acidity degree to which a weak organic base is protonated, Hammett and Deyrup established the H_0 acidity scale.[13] This scale was improved by Jorgensen and Harterr[14] and then Johnson, Katritzky, and Shapiro.[15] For a weak base B which ionizes by simple proton addition, we have

$$BH^+ \rightleftharpoons B + H^+$$

that is

$$K_a = \frac{[B][H^+]}{[BH^+]}\frac{\gamma_B\gamma_{H^+}}{\gamma_{BH^+}} = \frac{[B]}{[BH^+]}\frac{\gamma_B\gamma_{H^+}}{\gamma_{BH^+}} \quad (1)$$

Therefore,

$$pK_a = \frac{[BH^+]}{[B]} + H_x \quad (2)$$

where H_x is an acidity function. The H_0 scale is defined such that, for the uncharged primary aniline indicators used, the plot of log I (i.e. log([BH^+]/[B])) against H_0 has unit slope. It was observed from work on bases other than the Hammett type that the slopes of the plots of log I against $-H_0$, donated by m, were not always unity. Thus, series of structually similar bases, like triarylmethanols,[16] primary amides,[17,18] and tertiary aromatic amines[19] defined individual acidity functions, H_R, H_A, and H_0'', which have a linear relationship to H_0 with m values of 2.0, 0.6, and 1.3, respectively. Yates proposed that any acidity function H_x would be proportional to H_0 over the entire acidity range, that is $H_x = mH_0$, with a common point $H_0 = 0$.[20]

Therefore, 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 ($H_0^{1/2}$). The general

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Table 1. Nomenclature of the Studied Compounds (1−12)

compound	name	R	X	Y
1	6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone	H	H	H
2	6-(4-methylphenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	H	H	CH_3
3	6-(4-methoxyphenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	H	H	OCH_3
4	6-(4-chlorophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	H	H	Cl
5	6-(3,4-dichlorophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	H	Cl	Cl
6	6-(4-bromophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	H	H	Br
7	2-methyl-6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone	CH_3	H	H
8	2-methyl-6-(4-methylphenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	CH_3	H	CH_3
9	2-methyl-6-(4-methoxyphenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	CH_3	H	OCH_3
10	2-methyl-6-(4-chlorophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	CH_3	H	Cl
11	2-methyl-6-(3,4-dichlorophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	CH_3	Cl	Cl
12	2-methyl-6-(4-bromophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone	CH_3	H	Br

eq 3 may therefore be applied.

$$\log I = m.(H_0^{1/2} - H_0) \quad (3)$$

It follows that

$$pK_a = mH_0^{1/2} \quad (4)$$

Generally, those bases for which m lies roughly between 0.85 and 1.15 are called "Hammett Bases" and m is taken as unity. Therefore, its important to measure m as well as $H_0^{1/2}$ for each base studied.

It is evident that yet other acidity functions could exist at the extreme alkaline edge of the pH range, namely, above pH 14, for measuring the pK_a values of weak acids and strong bases, the former with an H_- scale and the latter with an H_0 scale. This is a more difficult region of pH than the acidic strength dealt with in the foregoing, insofar as the glass electrode becomes increasingly inaccurate and strong OH^- absorption swamps the reading. It is well established that the basic properties of aqueous alkalies increase in nonlinear fashion, with concentration.[21] The use of H_- in highly alkaline solution was described in the literature.[22,23] The sigmoid curve approach (see below) should be carried out carefully in this region to make sure that the function being used is a relevant one. Any discussion about the acid dissociation constants in this region should be done by taking the half protonation values rather than the pK_a values.

The calculation of half protonation values (i.e. $H^{1/2}$) was carried out as follows: the sigmoid curve of optical density against pH, H_0, and H_- at the analytical wavelength (OD, λ) was first obtained. The optical densities of the fully protonated (OD_{ca}) and nonprotonated compounds (OD_{fb}) were then calculated by linear extrapolation of the arms of the curve. The ionization ratio was given by eq 5, where the OD_{obs} is the measured optical density of the solution at the analytical wavelength

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

The linear plot of log I against pH, H_0 or H_-, using $-1.0 < \log I < 1.0$, had slope m, yielding half protonation values $H^{1/2}$ at $\log I = 0$, as defined in eq 3. The multiplication of the slope m with the half protonation value gives the pK_a values, as show in eq 4. At high acidity ($-H_0 > 3$), the values of Shapiro[15] were used; in the region $3 > -H_0 < 3$, the values of Bascombe and Bell[24] were used. Typical determinations of $H^{1/2}$ and pK_a values were given in Figures 1 and 2.

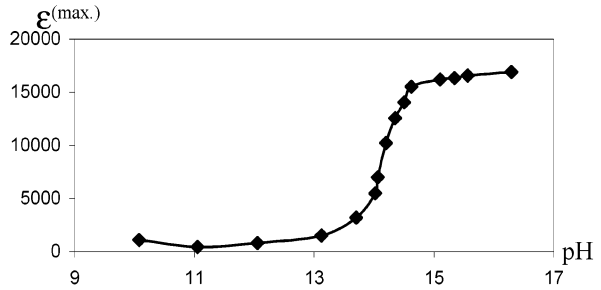


Figure 1. Sigmoid curve of ϵ_{max} vs pH for the pK_a determination of 6-(4-bromophenyl)- 4,5-dihydro-3(2*H*)-pyridazinone.

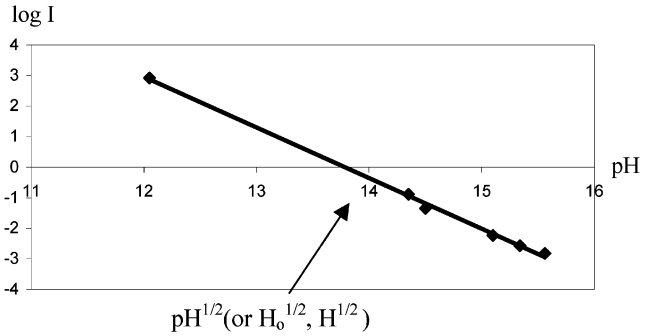
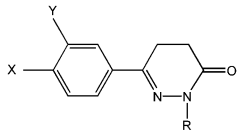


Figure 2. Linear plot of log I vs pH for the pK_a determination of 6-(4-bromophenyl)-4,5-dihydro-3(2*H*)-pyridazinone. $m = 1.65$; $pH^{1/2} = 22.87$; $pK_a = 13.86$.



R = H (for parent compounds, 1-6) ; CH_3 (for model molecules compounds, 7-12)

X= H, CH_3 , OCH_3 , Cl , Br Y = Cl

Figure 3. Structures of studied molecules (**1**−**12**).

Results and Discussion

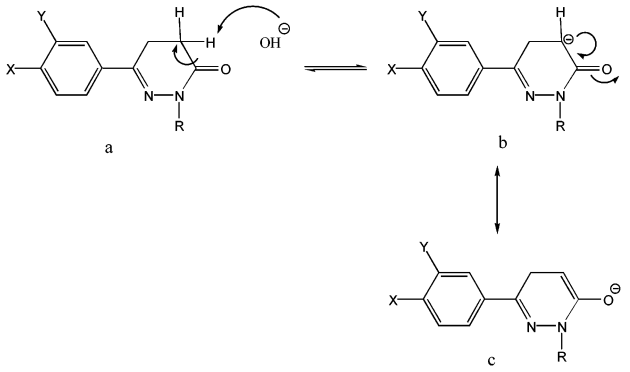
The structures of studied molecules indicate that the first six molecules (**1**−**6**) have one proton-loss and two proton-gain centers whereas the N−Me derivatives (**7**−**12**) normally should have only two proton-gain centers and no deprotonation center (Table 1; Figure 3). The obtained results, however, indicated that the model compounds (**7**−**12**) also have deprotonation centers, most probably the hydrogen atoms to the carbonyl groups, which are acidic enough to be removed in basic media (Table 2; Scheme 1). Presumably the driving force to form structure **c** according to the above suggested mechanism (Scheme 1) is to gain more conjugation. In the case of the parent compounds (**1**−**6**), however, there is a possibility of N−H proton loss (Scheme 2). The latter possibility is rather stronger because

Table 2. pK_a Data for the Studied Compounds (1−12) for the Proton-Loss Process

	spectral maximum (λ_{max}(abs)/nm)		acidity measurements				
compound	anion[a]	neutral[b]	λ[c] (nm)	$H^{1/2}$ [d]	m[e]	pK_a	correlation[f]
1	296.5 (0.625)	281.2 (1.187)	322.0	14.35 ± 0.03	1.26	18.14	0.997
2	300.0 (0.485)	288.0 (0.880)	315.0	14.20 ± 0.03	3.76	53.38	0.995
3	320.0 (1.014)	307.3 (0.849)	245.0	15.23 ± 0.03	2.17	33.05	0.881
4	296.0 (0.860)	282.0 (0.600)	320.0	13.29 ± 0.03	1.85	24.71	0.994
5	275.0 (0.737)	285.0 (0.975)	315.0	13.67 ± 0.11	2.37	32.39	0.960
6	324.8 (0.780)	293.6 (0.440)	324.0	13.79 ± 0.04	1.66	22.87	0.993
7	307.7 (1.087)	290.4 (0.915)	313.0	14.08 ± 0.03	1.13	15.94	0.986
8	327.2 (0.339)	292.0 (0.263)	320.0	16.67 ± 0.05	1.67	22.74	0.987
9	295.0 (0.785)	292.8 (1.060)	329.0	14.24 ± 0.03	1.74	24.77	0.960
10	305.7[g] (0.513)	304.4[g](0.441)	305.2	13.73 ± 0.11	0.33	4.48	0.970
11	325.7 (0.877)	280.5 (0.889)	335.0	14.05 ± 0.04	1.97	27.65	0.990
12	314.0 (1.000)	304.9 (0.432)	315.0	13.60 ± 0.01	1.80	24.44	0.988

[a] Measured in 8 M KOH. [b] Measured in pH = 7 buffer. [c] λ for pK_a measurements. [d] Half protonation value ± uncertainties refer to standard errors. [e] Slopes of log I versus pH (or H_-) graphs. [f] Correlation for log I versus pH (or H_-) graphs. [g] Measured in pH = 13 buffer.

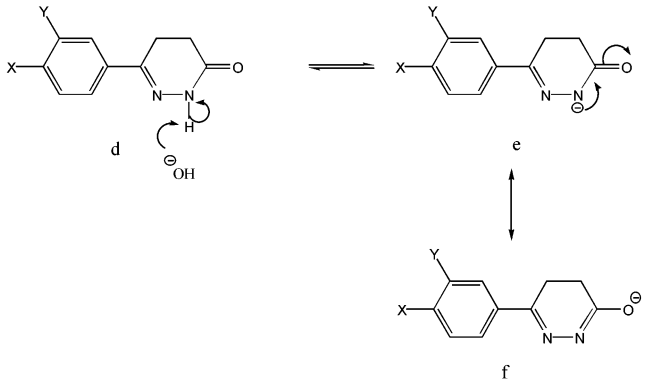
Scheme 1. Possible Mechanism for Deprotonation of the Studied Compounds (1−12)



R = H (for parent compounds, 1-6) ; CH_3 (for model molecules compounds, 7-12)

X= H, CH_3 , OCH_3 , Cl , Br Y = Cl

Scheme 2. Possible Mechanism for Deprotonation of the Parent Compounds (1−6)



R = H (for parent compounds, 1-6) ; CH_3 (for model molecules compounds, 7-12)

X= H, CH_3 , OCH_3 , Cl , Br Y = Cl

the resultant molecule **f** has more conjugation than molecule **c**.

We can arrange the parent molecules (**1**−**6**) in order of increasing acidity or decreasing basicity strength by taking into account the proton-loss half protonation values as follows:

$H^{1/2}$(deprot) 15.23 > 14.35 > 14.20 > 13.79 > 13.67 > 13.29
compd **3** > **1** > **2** > **6** > **5** > **4**
−MeO −H −Me −Br −Cl,Cl −Cl
decreasing basicity or increasing acidity→
←increasing basicity or decreasing acidity

Since the concept of slope (see Experimental Section) is rather unreliable in basic solutions, we have concentrated our discussion on the half protonation values for proton-loss processes.

It seems that the MeO group in the *para*-position of the phenyl ring makes compound **3** the least acidic or the most basic one within the series by providing electrons to the pyridazine ring mesomerically and keeping the proton more firmly. However, *p*-Me cannot do the same because of the weak inductive effect in compound **2** whereas, in compounds **4**−**6**, the halogens pull electrons from the ring inductively and keep the protons less firmly. Observation of a different trend of acidic and/or basic strengths for the model molecules **7**−**12** could indicate different deprotonation mechanisms between the parent molecules **1**−**6** and their N−CH_3 derivatives (i.e. fixed models) **7**−**12**.

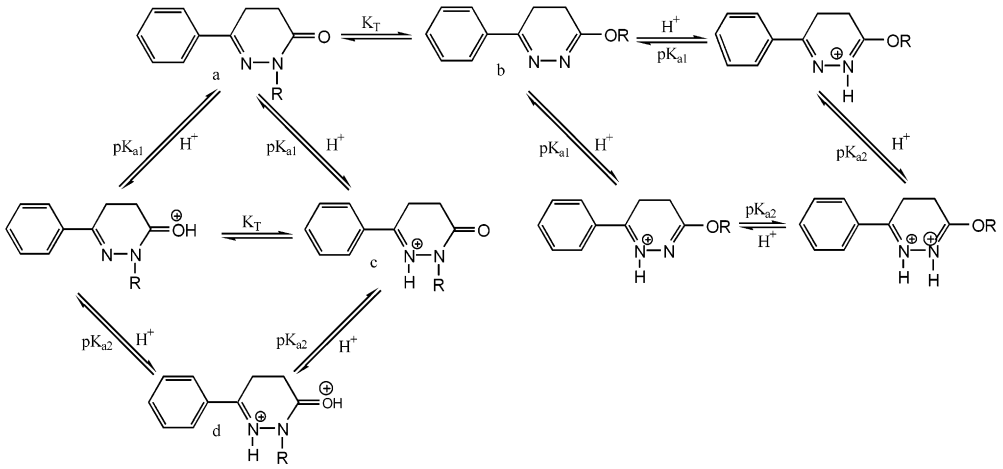
A dissimilar trend of acidic and/or basic strengths for the model molecules **7**−**12**, however, was observed, as shown below:

$H^{1/2}$(deprot) 16.67 > 14.24 > 14.08 > 14.05 > 13.73 > 13.60
compd **8** > **9** > **7** > **11** > **12** > **10**
−H −MeO −Me −Br −Cl,Cl −Cl
decreasing basicity or increasing acidity→
←increasing basicity or decreasing acidity

It seems that the MeO group in the *para*-position of the phenyl ring cannot make compound **9** the least acidic or the most basic one within this. This phenomenon led us to conclude that there are two different deprotonation pathways for the parent molecule **3** (i.e. most probably N−H deprotonation) and its model molecule **9** (i.e. have to be removal of the α-carbonyl proton) and that the mesomeric electron donating effect of the MeO group is not effective here. The N−Me group in compound **9** is also partly responsible for this basicity increase. The N−Me group in compound **8** makes this compound less acidic than compound **2**, as expected. In compounds **10**−**12** the halogens pull electrons inductively and decrease the basicity, as expected.

The data of acid dissociation constants for the studied compounds **1**−**12** for the first and second proton-gain processes are presented in Table 3. The slopes of the log I versus pH (H_0) graphs for the first proton-gain of compound **1** and its model compound **7**, in which the proton migration

Scheme 3. Suggested Protonation Patways for Molecules 1 and 7 for the First and Second Protonations



R= H (for molecule **1**) ; CH_3 (for molecule **7**)

Table 3. Spectral and Calculation Data for Studied Compounds (1−12) for Proton-Gain Processes

	spectral maximum ($\lambda_{max.}$(abs)/nm)			acidity measurements					
compound	neutral[a]	monocation[b]	dication[c]	λ[d] (nm)	$H^{1/2}$ [e]	m[f]	pK_{a1}[g]	pK_{a2}[h]	correlation[i]
1	321.0 (0.605)	318.3 (0.104)		308.0	1.37 ± 0.01	1.03	1.41		0.980
		316.5 (0.402)	319.5 (0.532)	308.0	−4.65 ± 0.03	0.99		−4.63	0.994
2	302.9 (0.516)	303.0 (0.486)		285.0	1.89 ± 0.06	0.77	1.45		0.976
		303.0 (0.486)	309.6 (0.751)	270.0	−1.96 ± 0.03	0.47		−0.92	0.986
3		307.6 (0.854)	335.6 (1.531)	292.0	−0.51 ± 0.05	0.77	−0.39		0.987
		307.6 (0.854)	335.6 (1.531)	348.0	−1.45 ± 0.04	1.34		−1.94	0.982
4		313.0 (0.460)	318.4 (0.883)	330.0	−3.29 ± 0.04	1.50	−4.92		0.993
		313.0 (0.460)	318.4 (0.883)	330.0	−6.88 ± 0.07	0.79		−5.46	0.972
5		306.9 (0.534)	321.6 (0.771)	325.0	−3.44 ± 0.02	2.06	−7.09		0.988
		306.9 (0.534)	321.6 (0.771)	340.0	−8.05 ± 0.02	1.96		−15.81	0.995
6		310.5 (0.722)	322.5 (1.119)	340.0	−3.46 ± 0.03	1.45	−5.00		0.986
		310.5 (0.722)	322.5 (1.119)	340.0	−6.68 ± 0.03	1.05		−7.01	0.991
7	312.8 (0.211)	316.4 (0.239)		319.2	−2.48 ± 0.03	1.86	−4.62		0.986
		316.4 (0.239)	313.3 (3.617)	325.0	−8.45 ± 0.03	0.80		−6.74	0.991
8	303.3 (0.505)	303.5 (0.566)		295.0	6.09 ± 0.07	0.82	5.01		0.972
		317.3 (0.806)	327.7 (1.310)	335.0	−3.18 ± 0.05	0.47		−1.51	0.987
9		304.0 (1.445)	335.2 (2.126)	292.5	−0.83 ± 0.03	1.07	−0.90		0.991
		335.2 (2.126)	368.4 (0.889)	292.5	−6.36 ± 0.03	0.85		−5.39	0.994
10		302.8 (1.694)	304.8 (1.636)	333.0	−3.16 ± 0.03	1.82	−5.78		0.995
		304.8 (1.636)	325.9 (2.939)	333.0	−7.66 ± 0.01	1.96		−15.06	0.988
11	307.7 (0.265)	203.0 (0.045)		300.0	1.49 ± 0.06	1.45	2.16		0.971
		203.0 (0.045)	312.0 (0.200)	300.0	1.36 ± 0.01	0.30		−1.86	0.988
12		309.7 (0.403)	310.0 (0.403)	330.0	−3.64 ± 0.03	1.01	−3.70		0.997
		310.0 (0.403)	340.0 (1.428)	330.0	−8.24 ± 0.02	1.16		−8.33	0.995

[a] Measured in pH = 7 buffer. [b] Measured in 50% H_2SO_4. [c] Measured in 98% H_2SO_4. [d] λ for pK_a measurements. [e] Half protonation value ± uncertainties refer to standard errors. [f] Slops of log I versus pH (or H_0) graphs. [g] First protonation. [h] Second protonation. [i] Correlation for log I versus pH (or H_0) graphs.

is eliminated by replacing the mobile *N*-hydrogen atom with the *N*-methyl group, were found to be 1.03 and 1.86, respectively (Table 3). Since the values of the slopes of log I versus pH (H_0) graphs are indicative of the protonation mechanism, it seems that compounds **1** and **7** are protonating by different mechanisms; in another words, originally they were not in the same tautomeric form, since the tautomeric form of compound **7** is fixed as the keto form **7a** while compound **1** is most probably in the enol form **1b**. The slope of 1.03, indicating pyridine type protonation, favors tautomeric form **b**. Furthermore, we can claim that the first protonation in molecule **1** takes place at the 2N position because of the mesomeric effect of the hydroxy group located at 3C of the pyridazine ring (Figure 2). For compound **7**, however, we can suggest a proton attack on the carbonyl oxygen with a subsequent rearrangement into tautomeric form **7c** by a positive charge transfer to 1N, as suggested in in the literature, vide infra.[25] In fact, the slope of the log I versus pH (H_0) graph for the second protonation of compound **7** to **7d** was found to be 0.79, and this value, within experimental error, falls into the carbonyl (oxo) protonation range, whereas the value of 1.86 for the first pronation indicates amide type protonation. This point is also supported by theoretical studies.[9] On the other hand, the slope of the log I versus H_0 graph (i.e. 0.99) for the second protonation for compound **1** suggests the 1N protonation is in a fashion to keep the two positive charges away from each other, and that point has also been confirmed theoretically.[9]

The very same trend of the first protonation seems to be applicable for the parent molecules **2** and **4** and for the model molecules **7**, **8**, **9**, and **11**. For the rest of the molecules, protonation seems to take place at a pyridine type of nitrogen via tautomeric rearrangements (i.e. slopes of around 2), as indicated in the literature as unusual protonation behaviors of pyridazin-3-ones.[25] The trend of

$H^{1/2}$(deprot)	1.89	>	1.37	>	−0.51	>	−3.29	>	−3.44	>	−3.46
compd	**2**	>	**1**	>	**3**	>	**4**	>	**5**	>	**6**
	−Me		−H		−MeO		−Cl		−Cl,Cl		−Br
$H^{1/2}$(2nd prot)	−1.45	>	−1.96	>	−4.65	>	−6.68	>	−6.87	>	−8.05
compd	**3**	>	**2**	>	**1**	>	**6**	>	**4**	>	**5**
	−MeO		−Me		−H		−Br		−Cl		−Cl,Cl

decreasing basicity or increasing acidity→
←increasing basicity or decreasing acidity

substituent effects seems better displayed for the second protonation rather than the first protonation of the parent molecules. Compound **3** was found to be the most basic one within the series because of the mesomeric electron donating effect of the *p*-OCH_3 group, but compound **5** was found to be the least basic, as expected, because of the inductive electron withdrawing effects of *p*-Cl and *m*-Cl atoms. The weaker inductive electron donor *p*-CH_3 group makes molecule **2** less basic than molecule **3** whereas it makes it more basic than molecules **1**, **6**, **4**, and **5**, as expected. All these points explain that the second protonations occur in a way that the substituents are included in the conjugation of the whole system and that the mechanism of protonation is different from that of the first protonation, which takes place probably at a center which is not included in the conjugation.

Literature Cited

(1) Brown, H. C.; Daniel, O. H. Mc.; Haflinger, O. *Determination of Organic Structure by Physical Methods*; Academic Press: New York, 1985.
(2) Chilton, J.; Stenlake, J. B. *J. Pharm. Pharmacol.* **1962**, *14*, 367.
(3) Johnson, C. D. *The Hammett Equation;* Cambridge University Press: 1973.
(4) Frey, P. A.; Kokesh, F. O.; Westheimer, F. H. *J. Am. Chem. Soc.* **1971**, *93*, 7266−7270.
(5) Tishler, M.; Stanovnik, B. *Pyridazines*, *Advances in Heterocyclic Chemistry;* Academic Press: New York, 1968, 1979, and 1990.
(6) Szasz, G.; Budvavi, Z. *Bavauy Pharmaceutical Chemistry of Antihypertensive Agents*; CRC Press: Boca Raton, FL, 1991.
(7) Henisch, G.; Kopelent-Frank, H. Pharmacalogically Active Pyridazine Derivatives. *Prog. Med. Chem.* **1992**, *29*, 141−183.
(8) Zwieten, P. A. V.; Greenlee, W. J. *Antihypertensive Drugs*; Harwood Academic Publishers: New York, 1997.
(9) Yarligan, S. Synthesis, Experimental and Theoretical Studies on Some Pyradizinon Derivatives. Ph.D. Thesis, Osmangazi University, Eskisehir, Turkey, 2001.
(10) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall Ltd.: London, 1984.
(11) Ögretir, C.; Berber, H.; Asutay, O. *J. Chem. Eng. Data* **2001**, *46*, 1540−1543.
(12) Wiberg, B. K. *Physical Organic Chemistry*; Academic Press: New York, 1963.
(13) Hammett, L. P.; Deyrup, A. J. *J. Am. Chem. Soc.* **1932**, *54*, 3413.
(14) Jorgenson, M. J.; Harterr, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 878.
(15) Johnson, C. D.; Katritzky, A. R.; Shapiro, S. A. *J. Am. Chem. Soc.* **1969**, *91*, 6654.
(16) Deno, N. C.; Jaruzelski, J. J. *J. Am.Chemic. Soc.* **1955**, *77*, 3044.
(17) Orloff, M. K.; Fitts, D. D. *Tetrahedron* **1963**, *19*, 1961.
(18) Yates, K.; Stevens, J. B.; Katritzky, A. R. *Canad. J. Chem.* **1964**, *42*, 1957.
(19) Arnett, E. M.; March, G. W. *J. Am. Chem. Soc.* **1964**, *86*, 2671.
(20) Yates, K.; McClelland, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 2686.
(21) Schawarzenbach, G.; Sulzberger, R. *Helv. Chim. Acta* **1944**, *27*, 348.
(22) Rochester, C. H. *Acidity Functions*; Academic Press: London, 1970.
(23) Jones, J. R. *The Ionization of Carbon Acids*; Academic Press: New York, 1973.
(24) Bascombe, K. N.; Bell, R. P. *J. Chem. Soc.* **1959**, 1096.
(25) Katritzky, A. R.; Elguero, E.; Linda, P. *The Tautomerism of Heterocycles Supplement 1, Advanced Heterocyclic Chemistry*; Academic Press: New York, 1976.

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