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Spectroscopic Determination of Acid Dissociation Constants of Some Imidazole Derivatives

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The acid dissociation constants, pK_a, of eight biologically active imidazole derivatives were determined using a spectroscopic technique. Using the obtained acid dissociation constants, attempts were made to elucidate the structures and protonation mechanisms of these derivatives. Four of eight molecules were found to behave as Hammett base for the first protonation.

Introduction

The imidazole ring is present in the structure of some important biologically active compounds such as pilocarpine.[1] Several imidazole derivatives have been used in chemotherapy.[2] Our research group has been doing experimental and theoretical studies on imidazoles since 1990.[3−6] In the present work the acid dissociation constants were determined by a UV spectroscopic technique, and the results were evaluated.

Experimental Section

Materials and Solutions. The studied compounds (Figure 1) were of spectroscopic grade, and the procedures of synthesis have been reported elsewhere.[7]

Methanol, glycine, KOH, H_2SO_4, HCl, CH_3COOH, CH_3COONa, NaOH, KH_2PO_4, Na_2CO_3, $NaHCO_3$, NaCl, and standard buffer solution were from Merck and were not purified further.

Apparatus. pH measurements were performed using a glass electrode. Standard buffer solution of pH values of 1, 7, and 14 were used in the calibration of the Cole Parmer Digital Benchtop pH-Meter and the Shinco Denski PF-150 balance; a Shimadzu UV2101 PC UV−vis scanning spectrometer was used for measurements.

Methods of Theoretical Calculations. Theoretical calculations were carried out by a molecular mechanics program of CS Chem Office Pro for Windows,[8] followed by full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles), without any symmetry constraint.

Procedure. Acid solutions were prepared with H_2SO_4 % (w/w) (0.0049−96% H_2SO_4) in water.[9] The CO_2-free KOH solutions were prepared with KOH pellets (1−16.67 M KOH) in water.[10] pH solutions were prepared with various reagents (pH 1−3 buffer solutions, 0.1−0.3 M HCl + 0.3 M glycine; pH 4−6 buffer solutions, 0.2 M CH_3COOH + 0.2 M CH_3COONa; pH 7−8 buffer solutions, 0.2 M KH_2PO_4 + 0.2 M NaOH; pH 12−13 buffer solutions, 0.1 M NaOH).[11] The potentiometric measurements were performed by measuring the hydrogen ion concentration (under nitrogen atmosphere) at 25 ± 1 °C, and ionic strengths of the media were maintained at 0.1 using NaCl.

Spectrometry is an ideal method[12] when a substance is not soluble enough for potentiometry or when its pK_a value is particularly low or high (e.g., <2 or >11).

The method depends 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 in highly acid regions, acidity functions H_x were used.[13] Thus, for determining the acid dissociation constant of very weak bases, solutions of known H_0 take the place of the buffer solutions mentioned above. For the protonation of the anion of a strong acid, which yields the neutral molecule, the function H_- was used.[13] This scale was constructed by the use of optically absorbing acids just as bases were used for the H_0 scale. The H_0, H_-, or pH values at half-protonations were measured for several compounds during the course of the present work, using the UV spectrophotometric method of Johnson.[14] This method takes into account of any effect of the medium on the wavelength of the maximum UV absorption and the corresponding extinction coefficient. This effect is particularly significant at high acidities.

The general procedure was applied as follows. A stock solution of the compound under investigation was prepared by dissolving the compound (∼10−20 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 solution was than calculated from the known mass of sulfuric acid added and the total mass of the final solution. 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 Shimadzu UV2101 PC UV−vis scanning spectrometer thermostated at 25 °C. The wavelengths were chosen such that the fully protonated form of the substrate had a very

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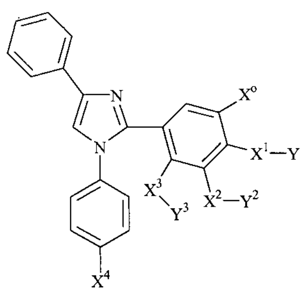


Compound	X^0	X^1	Y^1	X^2	Y^2	X^3	Y^3	X^4	Compound Name
1	-H	-H		-H		-H		-H	1,2,4-Triphenylimidazol
2	-H	-O-	$-CH_3$	-O-	$-CH_3$	-H		-H	4-(1,4-Diphenylimidazol-2-yl)-1,2-dimethoxybenzen
3	-H	-H		-O-	$-CH_3$	-O-	$-CH_3$	-H	1-(1,4-Diphenylimidazol-2-yl)-2,3-dimethoxybenzen
4	-H	-H		-H		-H		$-CH_3$	1-(4-Methylphenyl)-2,4-diphenylimidazol
5	-O-	-O-	X^0-CH_2- X^1	-H		-H		-H	5-(1,4-Diphenylimidazol-2-yl)-2H-benzo[d]1,3-dioxolen
6	-H	-O-	-H	-O-	$-CH_3$	-H		-H	4-(1,4-Diphenylimidazol-2-yl)-2-methoxyphen
7	-H	-O-	-H	-O-	$-CH_3$	-H		$-CH_3$	2-Methoxy-4-[1-(4-methylphenyl)-4-phenylimidazol-2-yl]phen
8	-H	-H		-H		-H		$-OCH_3$	1-(2,4-Diphenylimidazolyl)-4-methoxybenzen

Figure 1. Structures of the studied imidazole derivatives.

Table 1. UV and pK_a Data for the Studied Imidazole Derivatives for Proton Loss

	spectral maximum λ (nm)			acidity measurements			
compd	neutral[a] species	anion[b] (log ϵ_{max})	λ^c (nm)	$H^{1/2\ d}$	m^e	pK_a	corr[f]
5	273 (3.96)	318 (4.56)	318	15.77 ± 0.12	1.13	17.82	0.976
6	275 (4.36)	302 (4.53)	275	8.68 ± 0.18	1.12	9.72	0.948
7	277 (4.96)	301 (4.36)	306	9.00 ± 0.03	0.82	7.38	0.997

[a] Measured in pH 7 buffer. [b] Measured in 8 M KOH. [c] Analytical wavelength for pK_a measurements. [d] Half-protonation value ± uncertainties refer to the standard error. [e] Slopes of log I − pH (or H_-) graphs. [f] Correlations for I − pH (or H_-) graphs.

Table 2. UV and pK_a Data for the Studied Imidazole Derivatives for Proton Gain

	spectral maximum λ (nm)				acidity measurements				
compd	neutral[a] species	monocation[b]	dication[c] (log ϵ_{max})	λ^d (nm)	$H^{1/2\ e}$	m[f]	pK_{a1}[g]	pK_{a2}[h]	corr[i]
1	270 (4.02)	256 (4.31)		256	4.75 ± 0.03	0.63	3.00		0.995
		256 (4.10)	287 (4.38)	287	−8.80 ± 0.14	0.56		−5.00	0.882
2	273 (4.08)	300 (4.21)		300	5.08 ± 0.07	0.60	3.05		0.972
		300 (4.11)	310 (4.26)	310	−3.65 ± 0.03	0.57		−2.08	0.991
3	267 (4.26)	254 (4.38)		254	4.00 ± 0.03	0.50	2.00		0.994
		252 (8.90)	246 (4.17)	295	−7.30 ± 0.01	0.23		−1.68	0.988
4	272 (3.66)	254 (4.11)		272	4.67 ± 0.11	1.00	4.67		0.959
		254 (4.12)	284 (4.26)	254	−7.85 ± 0.06	0.45		−3.53	0.976
5	276 (4.54)	305 (4.90)		255	4.67 ± 0.04	0.95	4.68		0.993
		291 (4.72)	255 (4.90)	291	−8.55 ± 0.02	0.42		−3.60	0.993
6	275 (4.52)	302 (4.30)		275	5.76 ± 0.03	0.45	2.60		0.976
		253 (4.30)	296 (4.48)	261	−6.10 ± 0.03	0.52		−3.17	0.986
7	254 (4.02)	277 (4.31)		254	5.51 ± 0.05	0.81	4.46		0.987
		279 (4.20)	263 (4.41)	263	−4.78 ± 0.02	0.40		−1.91	0.995
8	269 (3.94)	257 (4.42)		260	4.78 ± 0.12	0.98	4.68		0.953
		257 (4.13)	283 (4.46)	290	−8.87 ± 0.20	0.54		−4.79	0.703

[a] Measured in pH 7 buffer. [b] Measured in pH 1 buffer. [c] Measured in 98% H_2SO_4. [d] Analytical wavelength for pK_a measurements. [e] Half-protonation value ± uncertainties refer to the standard error. [f] Slopes of log I − pH (or H_0) graphs. [g] First protonation. [h] Second protonation. [i] Correlation for log I − pH (or H_0) graphs.

much greater or very 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 shown in Tables 1 and 2.

Calculations of half-protonation values were carried out as follows. The sigmoid curve of optical density or extinction coefficient at the analytical wavelength (OD, λ) was 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 of the arms of the curve. Equation 1 gives the ionization

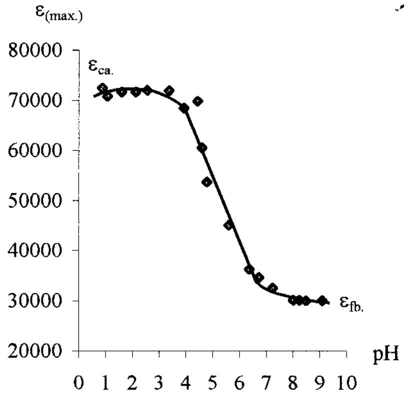


Figure 2. Sigmoid curve of ϵ_{max}−pH for the pK_a determination of 5-(1,4-diphenylimidazol-2-yl)-2*H*-benzo[*d*]1,3-dioxolen.

ratio; the OD_{obsd} (the observed optical density) was converted into molar extinction ϵ_{obsd} using Beers' law of $OD = \epsilon bc$.

$$I = \frac{[BH^+]}{[B]} = \frac{OD_{obsd} - OD_{fb}}{OD_{ca} - OD_{obsd}} = \frac{\epsilon_{obsd} - \epsilon_{fb}}{\epsilon_{ca} - \epsilon_{obsd}} \tag{1}$$

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

The pK_a values were calculated by using eq 2.

$$pK_a = mH_x{}^{1/2}\ (\text{or } pH^{1/2}) \tag{2}$$

When the value of the obtained slope *m* is around unity, then that base is called a Hammett base[15] and it is an indication of a pyridine-type nitrogen atom protonation.

Results and Discussion

As can be seen from Table 1 the acid dissociation constants of compounds **5**−**7** were found to be 17.82, 9.72, and 7.38, respectively, in basic media (i.e., pH 7 buffer to 8 M KOH region and it is a deprotonation process), which are comparable with the literature values of 14.20, 13.40, 13.50, and 12.60 of imidazole, 2-phenylimidazole, 4-phenylimidazole, and 2,5-diphenylimidazole molecules, respectively.[15] The optimized geometries of these molecules (Table 3) had indicated that phenolic protons, which are lying out of plane of the phenyl ring B, can leave more easily than the protons of the $-OCH_2O-$ group, which are lying on the plane of the phenyl ring B, and both molecules of **6** and **7** are found to be more acidic than molecule **5**, as expected. Although it is rather ambiguous, it seems that the *p*-CH_3 group on phenyl ring C makes the 4-(1,4-diphenylimidazol-2-yl)-2-methoxyphenol molecule, via inductive effect, more basic or less acidic than the 2-methoxy-4-[1-(4-methylphenyl)-4-phenylimidazol-2-yl]phenol molecule up to 2.34 pK_a units.

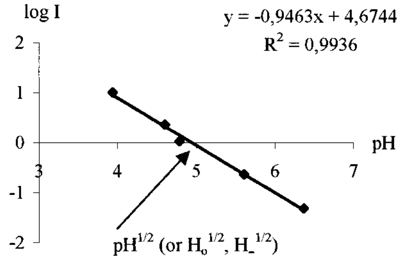


Figure 3. Linear plot of log *I* − pH for the pK_a determination of 5-(1,4-diphenylimidazol-2-yl)-2*H*-benzo[*d*]1,3-dioxilene. $m = 0.95$; $pH^{1/2} = 4.67$; p$K_a = 4.44$.

As far as the first protonations are concerned, the slopes of log *I* − pH (or H_0) graphs indicate (Table 2) that the protonation mechanism in compounds **1**−**3** and **6** is different from that of compounds **4**, **5**, **7**, and **8**. The latter compounds act as Hammett bases. Taking into account the half-protonation values (Table 2), we can arrange all eight compounds in increasing acidity or decreasing basicity strength as follows:

$H_o{}^{1/2}$: 5.76 > 5.51 > 5.08 > 4.93 > 4.78 > 4.75 > 4.67 > 4.00

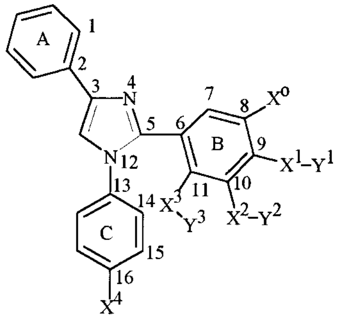
6 > **7** > **2** > **5** > **8** > **1** > **4** > **3**

Decreasing basicity or increasing acidity ⟶

⟵ Increasing basicity or decreasing acidity

The abnormal behavior of the 1-(1,4-diphenylimidazol-2-yl)-2,3-dimethoxybenzene molecule, **3**, 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 others, and full mezomeric and inductive

Table 3. Molecular Mechanics Optimized Dihedral Angles for the Studied Imidazole Derivatives



	dihedral angles							
compd	1, 2, 3, 4	4, 5, 6, 7	5, 12, 13, 14	7, 8, X^0, Y^1	8, 9, X^1, Y^1	9, 10, X^2, Y^2	10, 11, X^3, Y^3	14, 15, 16, X^4
1	−18.4	−48.1	−39.5					
2	−18.7	−48.5	−40.8		61.8	1.0		
3	17.3	−89.7	46.3			−2.5	73.9	
4	−18.4	−47.6	−40.1					179.7
5	−18.2	−49.8	−40.8	179.5	0.4			
6	−18.2	−46.0	−40.5		2.1	35.7		
7	−18.4	−45.5	−41.0		2.0	35.8		180.0

effects may not be exerted over 3N of the imidazole ring, whereas a steric effect is being applied with full strength to shield the 3N of the imidazole ring from the approaching proton. With the cooperation of all effects indicated above, the basicity of this molecule decreased effectively. The 4-(1,4-diphenylimidazol-2-yl)-2-methoxyphenol molecule, **6**, and 2-methoxy-4-[1-(4-methylphenyl)-4-phenylimidazol-2-yl]phenol molecule, **7**, are expected to act parallel to each other due to their similar structures, and they are indeed found to behave similarly and have very close half-protonation values of 5.76 and 5.51, respectively.

The 4-(1,4-diphenylimidazol-2-yl)-1,2-dimethoxybenzene molecule, **2**, may not exhibit a greater basic strength as expected due to the value of 61.8° for the dihedral angle of 8, 9, X^1, Y^1, which indicates that the methoxy group is twisted out of the plane of ring B.

For the second protonations the slopes of log $I - H_0$ graphs indicate (Table 2) that the protonation mechanisms for all studied compounds, **1**−**8**, are the same and the values of slopes are ~0.5, indicating a double-bond protonation (i.e., most probably C5 protonation). The different behavior of the 1-(1,4-diphenylimidazol-2-yl)-2,3-dimethoxybenzene molecule, **3**, was also observed here as happened in the first protonation and has a slope of 0.23 due to a geometric anomaly. The arrangement of the studied compounds in increasing acidity or decreasing basicity for the second protonation is as follows

$H_o^{1/2}$: -3.65 > -4.78 > -6.10 > -7.30 > -7.85 > -8.55 > -8.80 > -8.87

2 > **7** > **6** > **3** > **4** > **5** > **1** > **8**

Decreasing basicity or increasing acidity ⟶

⟵ Increasing basicity or decreasing acidity

The unexpected difference in basic strength between the 4-(1,4-diphenylimidazol-2-yl)-1,2-dimethoxybenzene molecule, **2**, and the 1-(2,4-diphenylimidazol)-4-methoxybenzene molecule, **8**, may arise from the full conjugative effects of the two methoxy groups, which are located at meta and para positions of the phenyl ring B in molecule **2**. In this way compound **2** becomes more basic than compound **8**, in which the methoxy group is located at the para position of the phenyl ring of C and cannot exert a fully conjugative effect on the imidazole ring due to the 1N atom, which behaves as a kind of electron filter.

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