Spectroscopic and Calculated Ionization Constants of Some Pyrazines and Pyridazines

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The pH dependence of the electronic spectra of some pyrazines and pyridazines was measured in the region between pH 14.3 and H_0 −10.02. The experimental data were used to investigate the structure of some ionic forms and to calculate the ionization constants. Many constants were also calculated by the CNDO/2 method. The experimental constants show a correlation with the calculated ones.

The investigation of acid–base equilibria of heterocyclic compounds has become more and more important for the chemical and pharmaceutical industry. Albert and his co-workers began the determination of ionization constants of pyrazines and pyridazines by spectroscopic methods.[1] Series of papers have subsequently been published by him,[2–5] Barlin,[4–11] and Mason.[12–14] Some other publications have dealt with similar problems.[15–26]

Most of these papers have dealt only with the first protonation. Only moderate attention has been given to the second proton gain.[21,26–35] Thus, so, in contrary we extended our investigations to the second proton gain by the ring and in some cases (depending on the substituents) to the second proton loss.

Similarly, few data have been published on quantum chemical calculations of ionization constants for these compounds. Ueda and Amano[36] have carried out calculations of this kind by the Hückel MO method for some azines.

The purpose of our work was the experimental determination of the ionization constants and their comparison with the calculated (CNDO/2) ones.

Experimental

Ionization constants in water were determined through the pH dependence of the electronic spectra. They were recorded on a Unicam SP 1800 spectrometer. Absorption maxima were manually controlled.

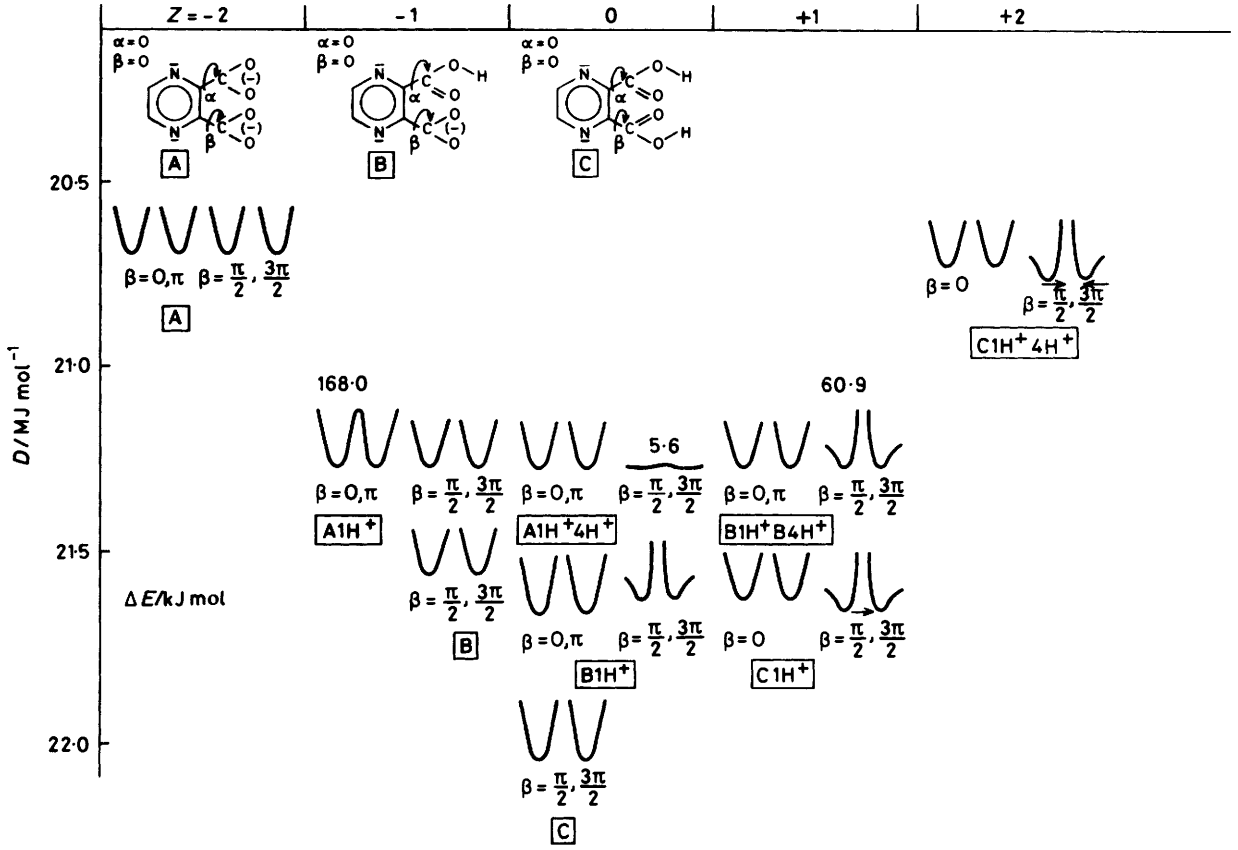

Figure 1. Calculated energy levels of 2,3-dicarboxypyrazine (CNDO/2), D = binding energy, ΔE = rotational barrier, α and β are rotational angles, with value 0 if the substituent is in the plane of the pyrazine ring

Table 1. pH dependence of electronic absorption maxima [$\lambda_{max.}$/nm (log ε)] of substituted pyrazines*

Substituents	Ionic state −2	−1	0	+1	+2
			2.22	*−1.00*	*−7.82*
			261 (3.76)	268 (2.85)	284 (4.29)
			268 (3.69)		
			302 (2.88)		
		13.98	*0.87*	*−5.51*	*−8.14*
2-COOH		267 (3.86)	209 (3.83)	209 (3.87)	209 (2.87)
		314 (2.81)	270 (3.90)	278 (3.91)	293 (3.90)
			0.55	*−3.03*	*−8.14*
2-$CONH_2$			210 (3.89)	210 (3.87)	215 (3.88)
			270 (3.89)	276 (3.91)	279 (3.94)
			313 (2.81)		
	7.06	*2.50*	*0.55*	*−6.54*	*−8.14*
2,3-$(COOH)_2$	282 (3.81)	278 (3.77)	213 (3.76)	215 (3.78)	215 (3.81)
			270 (3.80)	283 (3.85)	280 (3.86)
			2.21	*−5.51*	*−8.14*
2,3-$(CONH_2)_2$			213 (3.91)	241 (4.00)	225 (3.89)
			269 (3.81)	268 (3.78)	278 (3.82)
		10.91	*3.90*	*0.22*	*−8.14*
2-NH_2-3-COOH		243 (3.98)	246 (3.98)	242 (4.01)	240 (4.15)
		340 (3.76)	346 (3.75)	356 (3.85)	393 (3.84)
			5.30	*−1.00*	*−8.00*
2-NH_2-3-$COOCH_3$			246 (4.03)	243 (4.03)	241 (4.17)
			344 (3.81)	355 (3.85)	392 (3.87)
			2.00	*−2.22*	*−10.02*
2-NH_2-3-$COOCH_3$-5-Cl			256 (4.10)	251 (4.07)	253 (4.03)
			372 (3.76)	380 (3.80)	428 (3.72)

* pH and H_0 values are in italics.

The pH range of the measurements was between those of 2.000 mol dm^{-3} NaOH solution (pH 14.30) and 17.98 mol dm^{-3} H_2SO_4 (H_0 −10.02).[37] In the pH range 1—12 Britton–Robinson buffer, at higher pH values sodium hydroxide solutions, and at lower values sulphuric acid solutions were applied.

25—40 spectra were recorded at different pH (H_0) values for each compound investigated.

All compounds were Aldrich products. They were redistilled and recrystallized, respectively, before preparing fresh solutions for measurements.

Calculations

Calculations were carried out by an Elwro ODRA-1305 computer. A variant of the CNDO/2 procedure was applied. Binding energies and charge distributions were calculated for nine compounds. The calculations were extended to all possible ions which may occur in the acid–base equilibria, their tautomers, and conformers.

From these data the barriers of rotation were determined for the tautomers. Since the CNDO/2 parametrization somewhat overestimates the energy of in-plane conformers compared to the perpendicular ones, the determination of the most probable conformer is not completely reliable in this sense. For a given ionic state the tautomer with maximal binding energy was chosen as the structure of the ion.

Since the calculations refer to individual compounds neglecting the molecular environment the results have to be handled with care when drawing conclusions for solvated molecules.

Figure 1 presents an example of our calculations. Geometric parameters for pyridazine,[27] 3,6-dichloropyridazine,[27] and pyrazine[28] were measured by electron diffraction and for pyrazine carboxylic acid by *X*-ray diffraction.[29] For parameters of other investigated compounds recommended substituent bond lengths and bond angles were used.[30,31]

From a knowledge of the binding energies of the most probable structures, ionization constants were calculated. Assuming the proportionality of the binding energy (D) differences to the ionization constants one has equation (1) where equation (2) holds. The more negative ion has charge z.

$$pK_a^{z/(z+1)} = \frac{D_{z/(z+1)}}{RT \ln 10} \quad (1)$$

$$D_{z/(z+1)} = D_z - D_{z+1} \quad (2)$$

Results and Discussion

pH *Dependence of Spectra.*—Tables 1 and 2 contain the most important spectral data for the pyrazines and pyridazines, respectively.

Figure 2 illustrates our measurements in strongly acidic media. The u.v. spectra of 2-amino-3-carboxypyrazine also indicates with the two isosbestic points the precision of the measurements.

Pyrazines. The *B* band ($\pi \longrightarrow \pi^*$) with its vibrational structure (261 and 268 nm) and the *R* band (302 nm) appear in the spectrum of neutral pyrazine. In course of the protonation the *R* band ($n \longrightarrow \pi^*$) vanishes, the *B* band shifts to higher wavelengths, and the second proton gain increases the *B* band intensity, as expected.

With 2-carboxy substitution the *K* band (209 nm) appears in

Table 2. pH dependence of electronic absorption maxima [$\lambda_{max.}$/nm (log ε)] of substituted pyridazines*

Substituents	−2	−1	Ionic state 0	+1	+2
			4.05	*−0.49*	*−8.14*
			242 (3.13)	215 (3.26)	216 (3.36)
			247 (3.12)	238 (3.23)	235 (3.26)
			300 (2.40)		
	14.28	*7.11*	*3.71*	*−2.49*	*−10.02*
3,6-$(OH)_2$	335 (3.46)	331 (3.36)	304 (3.40)	213 (3.82)	215 (3.81)
				287 (3.43)	274 (3.18)
		13.98	*2.48*	*−2.94*	*−10.02*
3-Cl-6-OH		235 (3.89)	213 (3.81)	213 (3.79)	212 (3.71)
		309 (3.41)	225 (3.70)	284 (3.31)	276 (3.35)
			290 (3.31)		
			5.47	*0.58*	*−10.02*
3-NH_2-6-Cl			210 (4.07)	215 (4.16)	215 (4.16)
			239 (4.02)	228 (3.93)	
			310 (3.30)	300 (3.38)	300 (3.39)
			~7†	*−1.72*	*−8.13*
3-NH_2-6-CH_3			214 (4.05)	216 (4.14)	216 (3.89)
			225 (sh)		
			309 (3.30)	303 (3.42)	270 (3.42)
			~7†	*−5.70*	*−10.02*
3,6-Cl_2			217 (3.82)	217 (3.96)	217 (3.87)
			272 (3.14)	275 (3.31)	276 (3.35)

* pH and H_0 values are in italics.
† Distilled water solution.

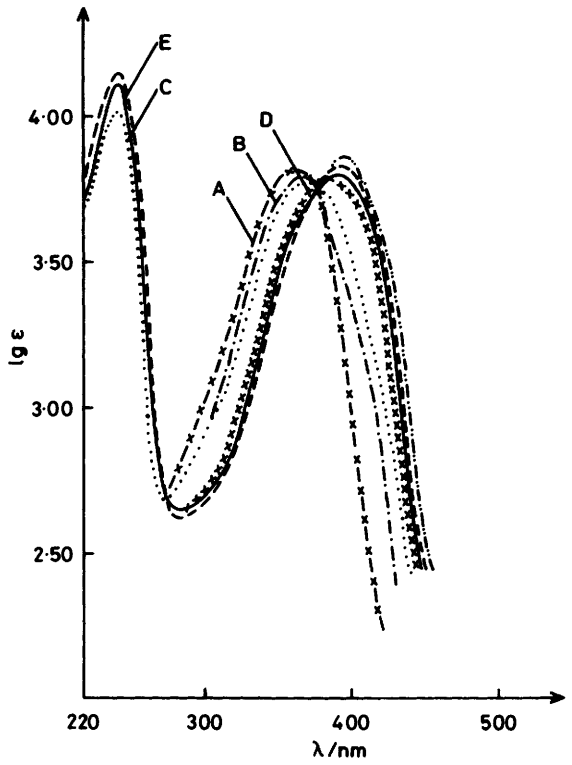

Figure 2. U.v. spectra of 2-amino-3-carboxypyrazine in strong acidic media (A, 7.15 mol dm^{-3} H_2SO_4; B, 10.88 mol dm^{-3} H_2SO_4; C, 11.82 mol dm^{-3} H_2SO_4; D, 13.12 mol dm^{-3} H_2SO_4; E, 13.98 mol dm^{-3} H_2SO_4). Because of the small changes in log ε only three spectra are presented between 220 and 275 nm

strongly acidic ($H_0 > 0.8$) solutions. The *R* band is observable only in the spectrum of the proton-deficient form ($z -1$) (314 nm). The *B* band positions of neutral (z 0) and anionic ($z -1$) forms are similar to those of benzoic acid [32] [z 0, 273 nm (log ε 3.00); $z -1$, 268 nm (log ε 3.98)]. This band shifts to higher wavelengths on gaining a proton.

The spectra of the z 0 and -1 forms of the 2-carboxamide derivative are close to those of the corresponding 2-carboxypyrazine forms, apart from the appearance of the *K* band in the z 0 form. For z 2 the *K* band has a 5 nm bathochromic shift, whereas the *B* band has a 14 nm hypsochromic shift related to the 2-carboxypyrazine spectrum, but the intensities are nearly the same. The hypsochromic shift demonstrates that the $-M$ effect of the $CONH_2$ group is stronger than that of the COOH group.

For derivatives with two vicinal carboxy groups the spectra of the z 0 and +1 states are very similar to those of the monocarboxylic acid. These, and the ionization constant of the equilibrium of the anionic and neutral forms (see Table 3), seem to prove the perpendicular position of the carboxy groups in the z 0 ionic states. The second carboxy group hinders the gain of the second proton and therefore the spectrum in the z 2 state is nearly the same as that of the 2-carboxamidopyrazine.

Two vicinal carboxamide groups alter the pyrazine spectrum in the neutral state in the same manner as two vicinal carboxy groups, showing that one of the carboxamides is perpendicular to the ring. Upon decreasing the H_0 value, at $z +1$ a new *K* band appears at 241 nm.

In stronger acidic solution this band disappears and the *K* band lies at 225 nm and the *B* band at 278 nm. The *B* band shift (12 nm from z 0 to +2) is the result of the increasing conjugation of the carboxamide group in strong acidic media.

The substitution of an amino group decreases the energy of the $n \longrightarrow \pi^*$ transition (*R* band), so in the spectrum of 2-

Table 3. Acidic ionization constants (as pK_a values) of some pyrazines (PZ) and pyridazines (PD)

Compound		Ionic state							
Parent	Substituent	−2		−1		+1		+2	
PZ						0.60 (0.02)	0.65 [21, 26]	−6.60 (0.09)	−5.78 [21, 26]
	2-COOH			5.55 (0.05)	2.70 [26]	0.90 (0.02)	−0.7	−7.81 (0.13)	< −3
	2-$CONH_2$					−0.29 (0.02)		−5.10 (0.13)	
	2,3-$(COOH)_2$	4.20 (0.03)	3.57, 2.84	2.26 (0.05)	−0.9 [12, 26]	−3.39 (0.13)	< −2 [12, 26]	−7.13 (0.15)	
	2,3-$(CONH_2)_2$					−2.15 (0.10)	−3	−7.02 (0.07)	
	2-NH_2-3-COOH			7.60 (0.05)	3.70 [2, 36]	−2.66 (0.11)	<1 [2]	−5.58 (0.12)	
	2-NH_2-3-$COOCH_3$					2.58 (0.10)		−5.62 (0.08)	
	2-NH_2-3-$COOCH_3$-5-Cl					−0.74 (0.04)		−8.64 (0.05)	
PD						2.29 (0.03)	2.33 [35, 3]	−7.78 (0.14)	−7.10 [35]
	3,6-$(OH)_2$	12.92 (0.21)	13.0 [3]	5.70 (0.10)	5.67 [3, 23]	−2.64 (0.10)	−2.2 [23]	−8.06 (0.08)	
	3-Cl-6-OH			9.11 (0.18)	8.91 [23]	−1.55 (0.18)	−1.86 [23, 25]	−6.94 (0.12)	
	3-NH_2-6-Cl					3.79 (0.18)	3.85 [25]	−6.21 (0.08)	
	3-NH_2-6-OCH_3					4.39 (0.09)		−5.90 (0.10)	
	3,6-Cl_2					−4.42 (0.10)		< −10	

amino-3-carboxypyridazine the *K* band shifts with decreasing pH (H_0) to the higher wavelengths, from 340 to 393 nm. From the last entry (z +2) one can conclude that the second protonation takes place at the amino group. The *B* band position is practically independent of the acidity of the solution. Esterification of this compound by methanol does not modify the spectra dramatically except for the fact that the z −1 state does not exist for this compound.

On substituting this ester by chlorine in position 5, the $+M > -I$ effect of Cl shifts both *B* and *R* bands bathochromically by nearly 10 and 30 nm, respectively.

Pyridazines.—In the spectrum of the neutral form of the parent compound the *R* band has practically the same position as in the spectrum of pyrazine but the *B* band with vibrational structure shows a 20 nm hypsochromic shift relative to the pyrazine *B* band. On increasing the acidity the *R* band (300 nm) disappears gradually without shifting, the *B* band shows hypsochromic shift, while the *K* band as a result of a bathochromic shift becomes observable. These shifts give evidence that the protonation of the 1,2-diazine leads to a far greater structural change than in the case of the 1,4-diazine.

With two hydroxy groups in the positions vicinal to the nitrogens, two types of spectra may be observed depending on the acidity. In the states with z 0 the double lactim tautomers [C(OH)–N=], and at $z < 0$ the double lactam ones (CO–NH) are predominant. The spectra for z 1 and 2 are therefore very similar and only the *R* bands are measurable. At lower pH the *R* band shifts to lower wavelengths. The shift from z 1 to 0 is 27 nm, indicating the decrease in the positive electronic effect.

On changing one of the hydroxy groups to chlorine, the spectra of states with $z > 0$ remain practically unaltered. The *K* band at 235 nm for z −1 shifts to 225 nm for z 0. The *B* band also shows a hypsochromic shift. The spectrum of the neutral form is a mixture of the enol- and the keto-type spectra.

The spectrum of the neutral form of 3-amino-6-chloropyridazine contains three bands. The large shift of the *B* band relative to the pyridazine *B* band (63 nm) is the result of the combined effect of the two substituents.[33,34]

The strong effect of the amino group is demonstrated by the spectra of 3-amino-6-methoxypyridazine. For z 0 and +1 the *B* bands have nearly the same position as in 3-amino-6-chloropyridazine. The drastic hypsochromic *B* band shift in very strongly acidic solution suggests that the second protonation was carried out at the amino group.

The spectrum of 3,6-dichloropyrazine is practically independent of the pH (H_0), only the *B* band intensity increasing with increasing acidity of the solution.

Measured Ionization Constants.—Our measurements and the literature data are in Table 3. The standard deviations of our results are less than 0.21 pK_a units, mostly *ca.* 0.10 units. The mean values and standard deviations were calculated from 4—9 data.

The acidity function behaviour of protonation in sulphuric acid was investigated by plot logarithms of the concentration rates c_{BH^+}/c_{BH} and $c_{BH^{2+}}/c_{BH^+}$ determined from the spectra against the H_0 values corresponding to the sulphuric acid concentrations.[38] The linear dependence which resulted proved in all cases the applicability of the H_0 function.

The comparison of our results with those of others, if any data exist, often shows deviations.[2,12,23,26,35,37,39] The main reasons for these deviations are the different solvents, the H_0 scale, and the method of determination.

Pyrazines. The first proton gain by the ring is in accord with the mesomeric effects of the substituents. For the second protonation, however, some deviations occur.

The pK_a for the +1 to +2 equilibrium is smaller in the case of the dicarboxy compounds than for the monocarboxy one. The same phenomenon is not observable in the case of carboxamides. This behaviour of the dicarboxy derivative confirms the out-of-plane position of one of the carboxy groups. With this we have further evidence for the irregular behaviour of 2,3-dicarboxypyrazine.

The non-coplanarity of the second carboxy produces the relatively high acidity of the 2,3-dicarboxy compounds. It is a far stronger acid for both the first and the second proton loss than the monocarboxylic acid. The geometry of the carboxy group decreases the mesomeric interaction and this way increases the acidity.

All the other ionization constants show the expected shifts.

Pyridazines. The ionization constants of 3,6-dihydroxypyridazine show an unexpected shift from those for pyridazine. For the first proton gain the pK_a decreases by 4.93 units. In the case of the hydroxypyridazine the shift is −3.69.[7] We can explain these results only by invoking tautomerism; the molecule is in the double lactam form, as concluded from the electronic spectra. The corresponding pK_a value of 3-methoxypyridazine is 2.52,[3] confirming this change in structure, since here no tautomerism may occur.

Table 4. Calculated ionization constants

Compound		Ionic	Ionization constant (as pK_a)		
Parent	Substituent	state	Calculated	Scaled	Measured
Pyrazine		1	−45.5	−0.83	0.60
		2	−163.6	−6.25	−6.60
	2-COOH	−1	78.5	4.86	5.55
		1	−47.3	−0.92	−0.90
		2	−153.4	−5.79	−7.81
	2-$CONH_2$	1	−5.52	1.00	−0.29
		2	−117.9	−4.15	−5.10
		3	−230.9	−9.34	
	2,3-$(COOH)_2$	−2	142.3	7.79	4.20
		−1	75.8	4.73	2.26
		1	−48.9	−0.98	−3.39
		2	−153.4	−5.79	−7.13
	2-NH_2-3-$COOCH_3$	1	−39.8	−0.57	2.58
		2	−159.9	−6.08	−5.62
		3	−246.2	−10.04	
	2-NH_2	1	−56.0	−1.31	2.93[18]
		2	−248.1	−10.13	
		3	−771.3	−34.85	
Pyridazine		1	−72.8	−2.08	2.29
		2	−187.2	−7.33	−7.78
	3-Cl-6-OH	−1	97.4	5.73	9.11
		1	−60.5	−1.52	−1.55
		2	−177.0	−6.87	−6.94
	3.6-Cl_2	1	−69.0	−1.91	−4.42
		2	−181.2	−7.06	−10

For the first proton gain of 3-chloro-6-hydroxypyridazine the shift in pK_a is only −3.84 relative to the pyridazine. This value seems too low taking into account the electronic effects of both substituents. So we have good reason to assume the lactam structure in this case also.

The values of the other ionization constants are in accord with their electronic effects, with the exception of the second proton gains for the mentioned compounds. The reason for the deviations is again tautomerism.

Calculated Ionization Constants.—Results are listed in Table 4. The values are prone to error for the following reasons. CNDO/2 is only an approximate method and our calculations neglect the molecular environment totally. Besides, the ionization energy of the hydrogen atom was neglected compared with its atomic energy, and constant vibrational partition functions were assumed. Thus care is needed in drawing conclusions from the calculated ionization constants.

A correlation of the calculated and measured data was carried out. The 20 data pairs show a correlation coefficient of 0.801 which is not very high but gives evidence for the existence of a correlation. The regression line fits equation (3) where $K_{a,m}$ are the measured and $K_{a,c}$ the calculated ionization constants.

$$pK_{a,m} = 0.0459\ pK_{a,c} + 1.256 \qquad (3)$$

By applying equation (3) the calculated ionization constants were related to the measured ones. Table 4 also gives these ionization constants.

The deviation between these and the measured ionization constants is sometimes very high, but there is also excellent agreement. The method is only a rough approximation, but we hope to refine the calculation of ionization constants by taking into account the molecular environment.

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