Medium Effect on the Ionization of Pyrazine Carboxylic Acid and Its 2-Amino Derivatives

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Introduction

The ionization constants of pyrazine carboxylic acid (I) and 2-amino pyrazine-3-carboxylic acid (II) were determined pH metrically at 25°C and 0.01, 0.05, 0.1 and 0.2 ionic strength (NaCl) and 35°C (u=0.1 M) by the Bjerrum - pH titration technique as modified by Irving. The effect of different solvents on the ionization constants of the two compounds (I and II) shows a decrease in the following order DMF > Methanol > Ethanol > Dioxane > H_2O. Also, the thermodynamic ionization constants of (I) and (II) were determined and from which the free energy change ΔG° was calculated in ethanol at 25°C. The other thermodynamic parameters as ΔH and ΔS were calculated. An attempt was made to calculate the number of solvent molecules surrounding the solute molecule and the number of water molecules in three solvation zone (J) for two solvent mixtures (ethanol-water) and (Dioxane-water).

Pyrazine and its derivatives have been found, recently, to be one of the major constituents in certain products of biological importance and at the same time display antibacterial properties [1]. As a matter of fact, the advent of the sulfa drugs, led to a general revival in pyrazine research after the excellent bacteriostatic properties of sulfapyrazine and some of its derivatives were discovered. Pyrazine is a weak base (pK_a = 0.6) [2], the presence of different substituents on the pyrazine ring exerts a considerable effect on their ionization.

In the present investigation, the ionization constants of pyrazine carboxylic acid and 2-amino pyrazine-3-carboxylic acid were studied in presence of different solvents, different ionic strengths and temperatures, in an attempt to throw more light on their behaviours.

Results and Discussion

The ionization constants of (I) and (II) were determined pH-metrically in different solvents at constant ionic strength (0.1 M) and constant temperature (25°C) (Table 1). The effect of varying

both ionic strength and temperature on the ionization of (I) and (II) was studied in ethanolic aqueous solutions (Table-2). Also, the effect of percentage (0 to 100 %) of two of the above solvents (ethanol and dioxane) on the ionization constants of two investigated compounds was studied in an attempt for the determination of the number of solvent molecules and water molecules surrounding each compound (Table 3). Theoretical considerations and the mode of calculations lead to the following logarithmic equation:

Table-1: pK values of I and II in different solvents (at 25°C and u = 0.1 M)

Solvent	Dielectric constant	pK	
		I	II
Water	78.5	2.8	3.7
Dioxane	2.2	3.6	3.4
Methanol	32.0	5.3	8.4
Ethanol	24.0	5.5	5.6
D.M.F.	36.6	5.7	6.4

Table-2: pK values of I and II by different methods in aqueous ethanolic solutions.

Temp. (°C)	u(M)	pK					
		Ist method		2nd method		Mean	
		I	II	I	II	I	II
25	0.01	5.9	6.2	5.9	6.2	5.9	6.2
	0.05	5.7	5.9	5.7	5.9	5.7	5.9
	0.10	5.5	5.6	5.5	5.6	5.5	5.6
	0.20	5.2	5.3	5.2	5.3	5.2	5.3
35	0.1	5.0	5.2	5.0	5.2	5.0	5.2

Ist method: nA - pH method; 2nd method: Point-wise method; I = Pyrazine-carboxylic acid.; II = 2-Aminopyrazine-3-carboxylic acid.

Table-3: pK values of I and II in different percentage of ethanol and dioxane.

Percentage %	pK			
	Ethanol		Dioxane	
	I	II	I	II
00	2.8	3.7	2.8	3.7
20	3.0	3.9	3.1	3.9
40	3.4	4.4	3.6	4.3
60	3.6	4.8	4.3	5.3
80	4.3	5.4	5.3	7.6

$$\log K_a = \log y + n \log S$$

where K is the ionization constant, y is a constant rate value, S is the percentage weight of the solvent and n is the number of the solvent molecules in the transition state of the reaction, respectively [3,4].

A plot of pK values against log S for the investigated compounds in dioxane-water and ethanol-water mixtures is given Fig. (1). From the slopes of the lines obtained the n values were calculated.

The calculated formation constant (Table 1) reveals that pK increases in the order: water <

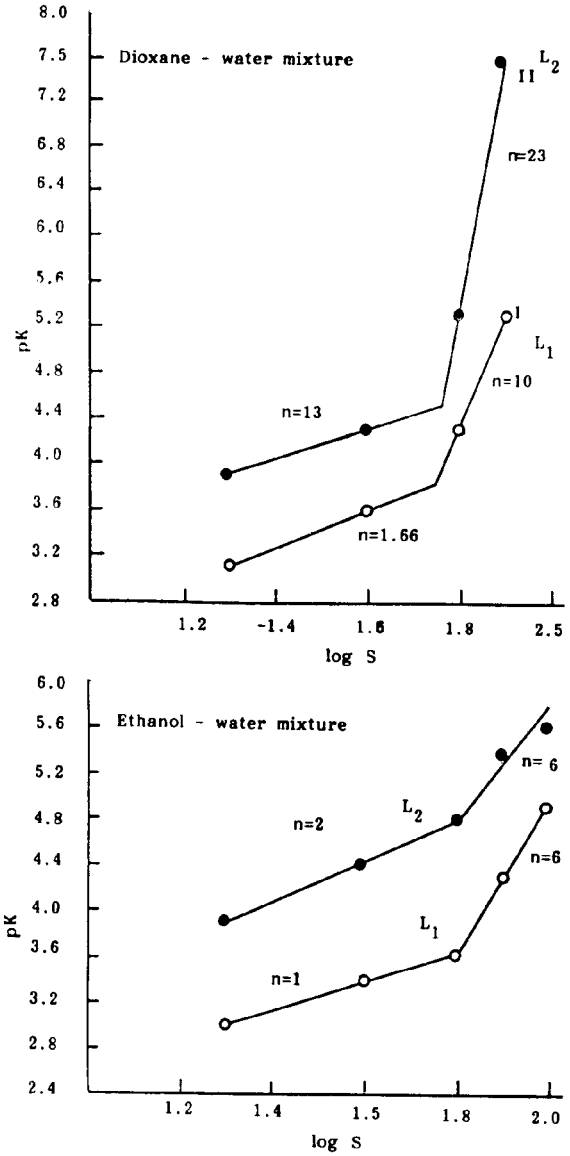
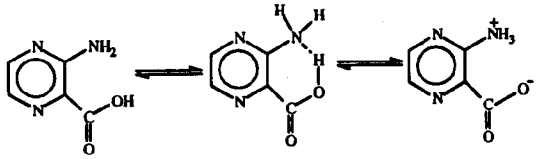


Fig. 1: pK values against log S in dioxane-water and ethanol-water mixtures.

dioxane < ethanol < methanol < DMF. The formation constants are not well correlated with increasing or decreasing dielectric constant of the organic solvents. This is attributed to the fact that the dielectric constant is not the only factor affecting stabilization of the compounds. Other factors may be involved, such as solvolysis of the different species (ionic, non ionic), proton acceptor, hydrogen bonding, refractive index and sterric hindrance. Also, it is clear from Table (1) that the pK values of (II) are higher than (I) denoting higher stability. This confirms the formation of ZWITTER ION in compound (II) as a result of the presence of an amino group in o-position to the carboxylic group. Also, the possibility of hydrogen bond formation may lead to higher pK values in case of (II), thus:



The effect of ionic strength on the ionization constants of (I) and (II) is given in Table (2). The pK of both compounds decreases with increasing ionic strength in accordance with Debye theory [5] that is to say, increasing the ionic strength facilitates the ionization of both compounds to a more or less the same extent showing a marked influence on the ionization of the investigated compounds.

Also, from Table (2), it is obvious that the ionization of either compound (I) or (II) decreases with rise of temperature. The calculated thermodynamic parameters, ΔH and ΔS, Table (4), are negative. The negative ΔH indicates evolution of heat during the combination of the proton to the negative anion while the negative ΔS value, i.e. the decrease in entropy, is a result of the orientation of the solvent molecules around the neutral (non ionized) species leading to a more ordered structure.

For evaluating the number of water molecules associated with the two compounds (I) and (II) in ethanol and dioxane, the following simplified equation dealing with this phenomena is used [6,7].

$$J \log [S] + \log K = - G/2.3\,RT - w \log [H_2O]/[S]$$

J is the solvation zone taking values 1,2,3.... and w is the number of water molecules in each zone. By putting log $[H_2O]/[S]$ = x and j log [S] + log K = y, Table 5, a plot of y versus x at different values of J for the investigated compounds gives a straight line, Fig. 2, the slope of which is the value of w.

According to Helpler [6] and Mackellar [7] the question of solvation and equation of solute molecules surrounded by solvent and water molecules in different manner is discussed in terms of the relative value of w with respect to the solvation zone value (J = 1,2,3, ...). If w is greater than the J number then the solute molecules are better aquated than solvated and the opposite is true.

Table-4: Thermodynamic parameters for the protonation constants of I and II (u = 0.1 M, T = 35°C).

	pK 25°C	pK 35°C	Free energ change -ΔGKJ/mole	Enthalpy change ΔH KJ/mole	Engropy change ΔS J/deg/mole
I	5.5	5.0	29.706	-88.324	-383.213
II	5.6	5.2	30.836	-123.637	-501.546

ΔG° for I = -17.778 KJ/mol; ΔG° for II = - 19.213 KJ/mole; I = Pyrazine carboxylic acid; II = 2-Aminopyrazine-3-carboxylic acid.

Table-5: n value for I and II

Solvent	log S	-X	y I J=1	I J=2	I J=3	II J=1	II J=2	II J=3
	1.30	-0.600	4	6	8	5	7	8
	1.60	-0.177	5	7	9	6	8	9
Ethanol								
	1.77	+0.177	5	7	9	7	8	10
	1.90	+0.600	6	8	10	7	9	11
	1.30	-0.600	4	6	7	5	7	9
	1.60	-0.177	5	6	8	6	8	9
Dioxane								
	1.77	+0.177	6	8	10	7	9	11
	1.90	+0.60	7	9	11	10	11	13

Table-6: J and W values for I and II

Compound No.	Ethanol water J	Ethanol water W	Dioxane water J	Dioxane water W
I	1	1.5	1	2.5
	2	2.0	2	3.0
	3	2.5	3	3.5
II	1	1.5	1	2.75
	2	2.5	2	2.75
	3	3.0	3	3.5

I = Pyrazine carboxylic acid; II = 2-Aminopyrazine-3-carboxylic acid.

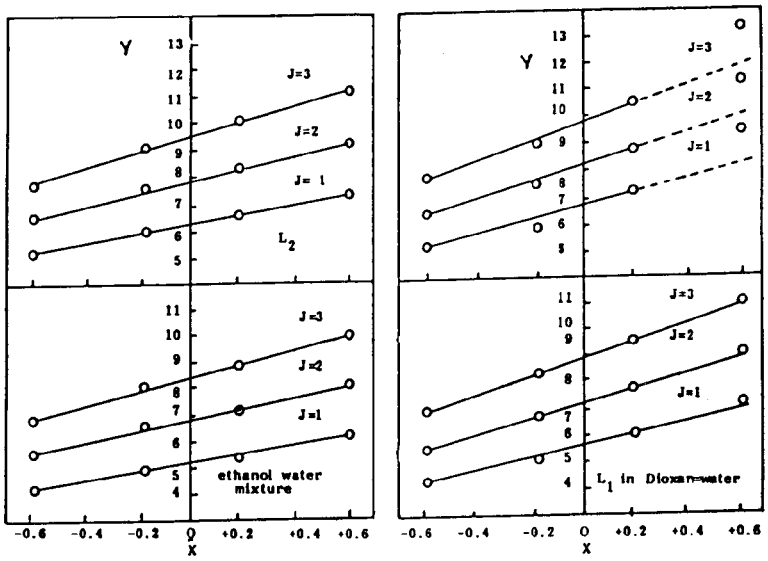


Fig. 2: Y versus X at different values of J.

It is clear from Table 6 that for the investigated compounds in the two solvents for all J values the number of water molecules (w) is greater than J. This indicates equation.

In dioxane-water, system aquation is more prominent than in ethanol - water system due to the low polarity of dioxane, which favours solute-water interaction as result of the high polarity of the solute molecules (I and II).

Experimental

The pyrazine carboxylic acid (I) and 2-amino pyrazine-3-carboxylic acid (II) were of highest purity provided by Fluka, all other chemicals were from BDH and water used was always doubly distilled. All solvents used were of spectroscopic grade (BDH), their purities were comparable to the reported values in terms of refractive index and diclectric constants.

pH-measurements were carried out as reported earlier [8]. The following mixture (total volume 50 ml ionic strength adjusted with 1M NaCl in different solvents, dioxane-, ethanol-, methanol-, and dimethylformamide-water) were titrated pH-metrically against standard 0.1 M sodium hydroxide.

(i) 3.0 ml HCl (0.1 M) + x ml 1 M NaCl

(ii) 3.0 ml 0.1 M HCl + x ml 1 M NaCl + 20 ml pyrazine carboxylic acid or 2-amino pyrazine-3-carboxylic acid.

The value of the pH measured was corrected according to the following relation.

$$pH_{corrected} = -\log[H^+] = B + \log V_H$$

where B is the pH-meter reading, $\log V_H$ is a correction factor which accounts for the residual junction potential and is given by the following relation [9,10].

$$-\log V_H = \frac{0.5 Z.u\ 1/2}{1 + u\ 1/2} - 0.1\,u$$

where u is the ionic strength of the solution.

The pK values of the investigated compounds at different ionic strengths were evaluated by plotting nA versus pH (interpolation at half nA values) and the point wise method i.e. plotting log nH/(1-nH) versus pH. Linear plots of intersect equal to pK were obtained.

The thermodynamic formation constants were obtained by extrapolation of the overall stability constants to zero ionic strength (u), in the plot of log K versus u. The free energy change

ΔG° at 25°C was calculated by the relation $\Delta g^\circ = -2.3$ RT log K also, ΔH and ΔS were calculated from the log K value at two different temperatures (25° and 35°C).

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