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Medium Effects on the Ionization Constants of some Pyridinecarboxylic Acid Derivatives

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Summary. The dissociation constants of 3-hydroxy-2-carboxypyridine (*3H2CP*), 2-hydroxy-3-carboxypyridine (*2H3CP*), and 2-mercapto-3-carboxypyridine (*2M3CP*) were determined by potentiometric titration in 20 mole% ethanol/water, dimethylsulfoxide/water, N,N-dimethylformamide/water, and dioxane/water mixtures at 25±0.1 °C applying an empirical *pH* correction for mixed aqueous solvents. The pK_n values obtained are discussed with respect to the nature of the solvent and the ionic strength of the medium as well as the molecular structure. Linearization of the titrimetric data for the second equivalence point of *3H2CP*, *2H3CP*, and *2M3CP* was carried out using the *Gran* method.

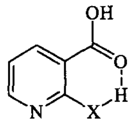
Keywords. Medium effects; Ionization constants; Acid-base equilibria; Pyridinecarboxylic acid derivatives.

Einfluß des Mediums auf die Ionisationskonstanten einiger Pyridincarbonsäurederivate

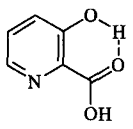
Zusammenfassung. Die Dissoziationskonstanten von 3-Hydroxy-2-carboxypyridin (*3H2CP*), 2-Hydroxy-3-carboxypyridin (*2H3CP*) und 2-Mercapto-3-carboxypyridin (*2M3CP*) wurden mittels potentiometrischer Titration in 20 mol% Ethanol/Wasser, Dimethylsulfoxid/Wasser, N,N-Dimethylformamid/Wasser und Dioxan/Wasser bei 25±0.1 °C unter Verwendung einer empirischen *pH*-Korrektur für wässrige Lösungsmittelgemische bestimmt. Die erhaltenen pK_n-Werte werden im Zusammenhang mit Lösungsmitteleigenschaften, Ionenstärken und Molekülstruktur diskutiert. Die titrimetrischen Daten für die zweiten Äquivalenzpunkte von *3H2CP*, *2H3CP* und *2M3CP* wurden mit Hilfe der *Gran*schen Methode linearisiert.

Introduction

Although there are several detailed reviews of data concerning the properties of pyridinecarboxylic acids, very few reliable results were reported on their hydroxy or mercapto derivatives [1–4]. The latter compounds are of particular interest to medicinal chemists because of the wide variety of physiological properties displayed by natural and many synthetic acids. Moreover, many of the pyridinecarboxylates are considered as versatile ligands [4–13], and their complexes with some metal ions have found use in medicine and in quantitative analysis. Accordingly it is expected that informations about pK_a values of pyridinecarboxylic acid derivatives in pure aqueous or aqueous-organic solvent media are important for such applications. Thus, in connection with our studies on acid-base equilibria of pyridinecarboxylic acid derivatives [14], this paper reports the pK_n values of some mercapto or hydroxy derivatives of pyridinecarboxylic acids in water-organic media containing 20 mole% organic solvent at constant or variable ionic strength. The organic solvents used are neutral amphiprotic (ethanol), dipolar aprotic (dimethylsulfoxide or N,N-dimethylformamide) and non-polar aprotic (dioxane). The pyridinecarboxylic acid derivatives used in this investigation are given below.



2H3CP: X = O
2M3CP: X = S



3H2CP

Results and Discussion

Treatment of data

The pK_n values of *3H2CP*, *2M3CP*, and *2H3CP* were calculated from the corresponding titration curves of 50 ml of 0.001 M reagent in organic solvent/water (20 mole% organic solvent) at constant (0.1 M) and variable ionic strength with 1.6×10^{-2} M potassium hydroxide containing the same mole percent of organic solvent. These curves are characterized by the absence of pronounced inflections corresponding to the second ionization step of H_2A. The potentiometric titration curves of the reagents investigated in water/*DMSO* containing 20 mole% DMSO at constant ionic strength are shown in Fig. 1.

The protonation scheme of diprotic acids can be represented by the following equations.

$$H_2A \overset{K_{a1}}{\rightleftharpoons} HA^- + H^+$$

$$HA^- \overset{K_{a2}}{\rightleftharpoons} A^{2-} + H^+$$

The values of pK_{a1} and pK_{a2} can be obtained from a single titration with two equivalents of standard carbonate-free alkali. If the pH is measured after each

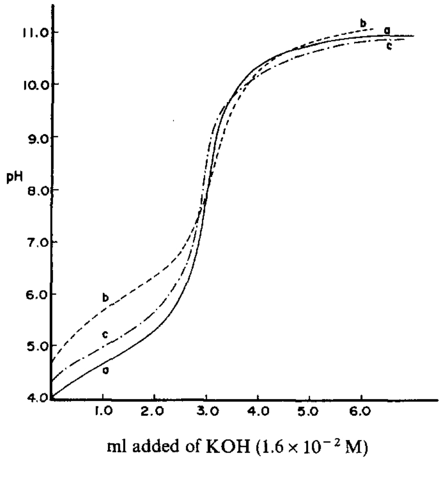


Fig. 1. pH-metric titration curves of pyridinecarboxylic acid derivatives in water/*DMSO* containing 20 mole% *DMSO*; $I = 0.1\,M$ (KNO_3), 25 °C, $C_L = 1 \times 10^{-3}\,M$; a) *3H2CP*; b) *2H3CP*; c) *2M3CP*

addition of standard alkali covering the range 0.2–0.8 mole equivalent, then pK_{a1} can be calculated from the first equivalent by equation 1 [15].

$$pK_{a1} = pH + \log\frac{C_t - C_{KOH} - C_{H^+} + C_{OH^-}}{C_{KOH} + C_{H^+} - C_{OH^-}} + \frac{A \cdot I^{1/2}}{1 + \mathring{a} \cdot B \cdot I^{1/2}} \quad 1$$

$$I = C_{K^+} + C_{H^+} \quad 2$$

For the second equivalent (*i.e.* addition of 1.2–1.8 equivalents of alkali), the value of pK_{a2} is given by

$$pK_{a2} = pH + \log\frac{2C_t - C_{KOH} - C_{H^+} + C_{OH^-}}{C_{KOH} - C_t + C_{H^+} - C_{OH^-}} + \frac{3A \cdot I^{1/2}}{1 + \mathring{a} \cdot B \cdot I^{1/2}} \quad 3$$

$$I = 2C_{KOH} - C_t + 2C_{H^+} - C_{OH^-} \quad 4$$

where C_t is the total initial concentration of diprotic acid and C_{KOH} is the total concentration of KOH added. The values of C_{H^+} and C_{OH^-} were calculated using the relations

$$-\log C_{H^+} = pH - \frac{A \cdot I^{1/2}}{1 + \mathring{a} \cdot B \cdot I^{1/2}} \quad 5$$

$$-\log C_{OH^-} = pK_w - pH + \frac{A \cdot I^{1/2}}{1 + \mathring{a} \cdot B \cdot I^{1/2}} \quad 6$$

The constants A and B of the *Debye–Hückel* equation were calculated according to the physical properties of the medium [16] (Table 1). I is the ionic strength of the

Table 1. Mean pK_{an} values for pyridinecarboxylic acid derivatives in water/organic media containing 20 mole% of organic solvents; $I = 0.1$ mol·l^{-1} (KNO_3); 25±0.1 °C

Compound	ε	A	B	pK_{a1}	pK_{a2}
H_2O/ethanol					
3H2CP				5.324±0.043	11.021±0.025
2H3CP	55.10	0.837	0.379	6.384±0.030	11.082±0.050
2M3CP				5.666±0.035	10.910±0.030
H_2O/*DMSO*					
3H2CP				5.064±0.023	11.820±0.045
2H3CP	74.55	0.570	0.349	6.133±0.033	11.387±0.040
2M3CP				5.413±0.025	11.298±0.061
H_2O/*DMF*					
3H2CP				5.071±0.030	11.890±0.035
2H3CP	70.70	0.588	0.341	6.184±0.040	11.401±0.030
2M3CP				5.462±0.020	11.303±0.020
H_2O/Dioxane					
3H2CP				5.429±0.032	11.667±0.044
2H3CP	36.22	1.654	0.492	6.720±0.030	11.570±0.046
2M3CP				6.025±0.040	11.379±0.035

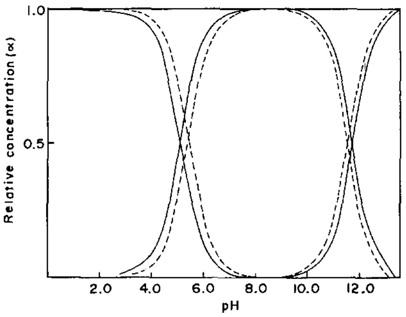


Fig. 2. Distribution curves for different acid-base forms of *3H2CP* in water/organic solvent mixture containing 20 mole% *DMSO* (solid line) or dioxane (dashed line); $I = 0.1\,M$ (KNO_3), 25 °C, $C_L = 1 \times 10^{-3}\,M$

solution and $\mathring{a}$ the "distance of closest approach" of ions. In principle, $\mathring{a}$ is a function of solvent and electrolyte, but in practice this parameter is traditionally taken as equal to 5Å [17–19].

The deviations from the mean pK_a values were evaluated from

$$\sigma(pK) = \left(\frac{1}{N-1} \cdot \sum_{n=1}^{N} (p\bar{K}_a - pK_a)^2\right)^{1/2}, \qquad 7$$

where $p\bar{K}_a$ is the mean value calculated from pK_a values obtained from titration curves. The pK_{an} values corresponding to the different ionization steps of the compounds investigated are shown in Table 1.

The distribution curves for the different species of *3H2CP* in partially aqueous medium containing 20 mole% *DMSO* or ethanol computed from the corresponding acid dissociation constant of the reagent are shown in Fig. 2.

Evaluation of the second equivalence volume

According to *Gran*, [20, 21] the linearization of the titration data for the second equivalence point of *3H2CP*, *2M3CP*, and *2H3CP* was carried out using equations 8 and 9.

$$W_t = \left(\frac{10^{-pH}}{\gamma_+} N_b V_b - \frac{10^{-pK_w}}{\gamma_- \gamma_+} V - K_{a2} \frac{10^{pH-pK_w}}{\gamma_-} V\right) \qquad 8$$

$$B_t = V(10^{pH-pK_w} - \frac{10^{-pH}}{K_{a2}} [A^{2-}] \gamma_-^2) \qquad 9$$

Here, N_b is the concentration of potassium hydroxide added and V is the total volume of solution being titrated. $[A^{2-}]$ at different pH values was obtained from the α-fraction diagram of the dianionic form of the reagent. If the values of the functions W_t and B_t are plotted against the volume of potassium hydroxide added (V_b) before and beyond the equivalence point, respectively, two straight lines are obtained which intersect the V-axis at $V = V_e$, *i.e.* at the equivalence volume.

The *Gran* plot gives reasonable agreement with the concentration of the reagent to be titrated and yields experimental uncertainties of less than 1%. The *Gran* plot of the titration of *3H2CP* in water/*DMSO* containing 20 mole% *DMSO* at constant ionic strength is shown in Fig. 3.

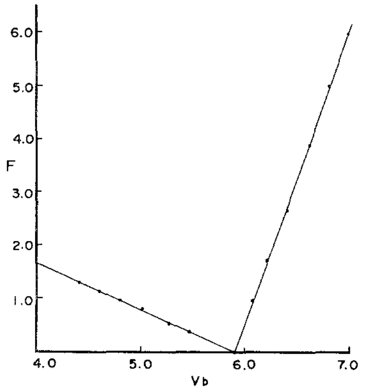


Fig. 3. *Gran* plots for the evaluation of the 2nd equivalence volume for the *pH*-metric titration of *3H2CP* in water/*DMSO* containing 20 mole% *DMSO*; $I = 0.1\ M$, 25 °C

Medium effects

The results listed in Tables 1 and 2 reveal that the pK_a values of all compounds are largely dependent on both the ionic strength of the medium and the nature of the organic cosolvent used.

According to *Coetzee* and *Ritchie* [22], the acidity constant in aqueous medium (K_a) is related to that in partially aqueous medium ($K_{a'}$) by equation 10, where γ is the activity coefficient of the subscript species in the partially aqueous medium.

$$K_a = K_{a'} \cdot \gamma_{H^+} \gamma_{A^-} / \gamma_{HA} \qquad 10$$

It is known that the electrostatic effect resulting from the change in dielectric constant of the medium will operate on the activity coefficient of the charged species only. Thus, the ionization constant of the compounds in water/organic media at constant ionic strength is expected to decrease in comparison to that in aqueous medium.

On the other hand and according to the *Debye–Hückel* equation [23] for the activity coefficient of a single ion,

$$-\log \gamma_i = \frac{AZ^2 I^{1/2}}{1 + B \cdot \mathring{a} \cdot I^{1/2}}. \qquad 11$$

Table 2. Mean pK_a value for *2H3CP* in water/ethanol medium containing 20 mole% of ethanol at variable ionic strength at 25 °C

0.016 *M* KOH ml)	*pH*	*I*	pK_a	mean pK_a
0.8	5.72	2.580×10^{-4}	6.196	
1.0	5.85	3.214×10^{-4}	6.192	
1.2	5.97	3.850×10^{-4}	6.191	
1.4	6.13	4.480×10^{-4}	6.240	6.236 ± 0.043*
1.6	6.25	5.120×10^{-4}	6.250	
1.8	6.37	5.760×10^{-4}	6.260	
2.0	6.55	6.400×10^{-4}	6.320	

*Standard deviation

The electrostatic effect resulting from the change in the ionic strength of the medium containing the same solvent at constant mole percent will also operate on the activity coefficient of the charged species. Thus, the ionization constant of these compounds is expected to decrease with increasing ionic strength of the medium containing the same organic solvent and at constant mole percent which is in accordance with the results given in Table 2.

It is known that the increase of pK_a of pyridinecarboxylic acid derivatives in water/organic media containing 20 mole% organic solvent at constant ionic strength ($I = 0.1\,M$) in comparison to that in aqueous medium can be ascribed to the high stabilization of the ionic form by solvent donor hydrogen bonding in a pure aqueous medium relative to that in partially aqueous media. This is presumably due to the greater tendency of water molecules to donate hydrogen bonds as compared with other solvent molecules [22]. The results given for these compounds in Table 1 indicate that the variation of pK_{a1} in media containing the same mole percent of organic solvent at constant ionic strength appears to be in the order *DMSO* < *DMF* < ethanol < dioxane.

The higher pK_a values of the compounds in 20 mole% ethanol is presumably due to the greater tendency of the solvent molecules to donate hydrogen bonds to the ionic form [22, 24]. Careful examination of the results reveals that the pK_a value in the presence of the poorer hydrogen bond donors *DMSO* or *DMF* is less than the one obtained in the presence of the same amount of ethanol. According to *Gutmann* [25], this can be ascribed to acceptor numbers (AN) that measures the electrophilic behaviour of a solvent (Table 3). The pK_{a1} values in presence of *DMF* or *DMSO* (lower AN) are less than the one obtained in the presence of the same amount of ethanol. In other words, this can be ascribed to the high basic character of the former solvents, reflecting itself in the strong acceptor hydrogen bond from the COOH group of the non-ionized form and thus facilitating the ionization of the COOH group (*i.e.* low pK_a).

Effect of molecular structure on pK_a

It is evident that the pK_{a1} value of *2H3CP* in the presence of the same amount of organic solvent is higher than that of *3H2CP*. This can be ascribed to the expected weak interaction of the carboxyl group at position 3 (*2H3CP*) with the heterocyclic pyridine ring compared to the carboxyl group at position 2 (*3H2CP*). This leads to easier ionization of the carboxyl group at position 2 on compared to that at position

Table 3. Some physical properties of selected solvents: donor number (DN) acceptor number (AN), density, and dielectric constant ε at 25 °C

Solvent	DN	AN	d	ε
ethanol	19.0	37.1	0.785	24.3
dimethylsulfoxide	29.8	19.3	1.096	46.7
dimethylformamide	24.0	16.0	0.9445	36.7
dioxane	14.8	10.8	1.0337	2.21

3. Moreover, careful examination of the results listed in Table 1 indicates that the dissociation constant of the 3-carboxyl proton ($K^{H}_{AH_2}$) in the case of compound *2H3CP* is lower than that in the case of compound *2M3CP*. This can be attributed to the relatively high mesomeric interaction of the OH group at position 2 with the COOH group at position 3 compared to the SH group at position 2. This reflects itself in an easier ionization of the COOH group in the case of *2M3CP* compared to *2H3CP*. The correlation of the pK_{a2} values of *2H3CP* and *2M3CP* with those of the analogous 2-hydroxy or 2-mercapto pyridine derivatives indicates that the presence of a carboxylate group at position 3 in the compounds investigated stabilizes the –OH or –SH group through intramolecular H-bonding. This renders the OH or SH proton dissociation difficult (high pK value).

Experimental

Reagents

The pyridinecarboxylic acids *3H2CP*, *2H3CP*, and *2M3CP* were purchased from Aldrich (Milwaukee, USA). Other chemicals used in this investigation and the organic solvents used were of A.R. grade. Stock solutions of the compounds (2.5×10^{-3} *M*) were prepared by dissolving the solid in the organic solvent. Standard carbonate free potassium hydroxide solutions containing 20 mole% organic solvent were prepared. Deionized water was used throughout. The ionic strength was maintained constant at $I = 0.1\,\mathrm{mol \cdot l^{-1}}$ (KNO_3).

Apparatus

Measurements of *pH* were made with a Radiometer Model M 63 *pH* meter equipped with a Radiometer combined glass electrode GK 2301C (Radiometer Copenhagen, Denmark). The *pH* meter was calibrated before use with standard buffer solutions of *pH* 4.00±0.01 and 7.00±0.01. Potentiometric *pH* titrations were performed using a Radiometer Type ABU12b autoburette accurate to ±0.001 cm^3. All measurements were carried out at a temperature of 25±0.1 °C.

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