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Acid-Base Equilibria of some Pyridinol Derivatives in Binary Water / Organic Solvent Systems

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Summary. pK_a values of 2-hydroxy 3-pyridinol (*HHP*), 2-mercapto 3-pyridinol (*MHP*), and 2-carboxy-3-pyridinol (*CHP*) were determined by potentiometric titration in water/organic solvent mixtures containing 20 mole% of organic solvent at 25 ± 0.1 °C and 0.1 *M* ionic strength (KNO_3) applying an empirical *pH* correction for mixed aqueous solvents. The influence of the organic solvents on the dissociation constants and tautomeric equilibria of the pyridinol derivatives is discussed. The effect of the molecular structure of the compounds on pK_a is also explained. Titrations of a mixture of two weak diprotic acids (*HHP* and *CHP*) in a water/dimethylsulphoxide medium containing 20 mole% organic solvent at constant ionic strength were evaluated using the *Gran* method.

Keywords. Acid-base equilibria; Pyridinol derivatives; Tautomeric equilibria; Medium effects; Ionization constants.

Säure-Basen-Gleichgewichte einiger Pyridinolderivate in binären Systemen aus Wasser und organischen Lösungsmitteln

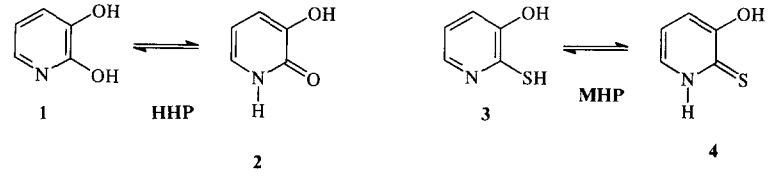
Zusammenfassung. Die pK_a-Werte von 2-Hydroxy-3-pyridinol (*HHP*), 2-Mercapto-3-pyriodinol (*MHP*) und 2-Carboxy-3-pyridinol (*CHP*) wurden durch potentiometrische Titration in wäßrigen Systemen mit 20 mol% organischem Lösungsmittelanteil bei 25 ± 0.1 °C und einer Ionenstärke von 0.1 *M* KNO_3 unter Anwendung einer empirischen *pH*-Korrektur für Lösungsmittelgemische bestimmt. Der Einfluß der organischen Lösungsmittel auf die Dissoziationskonstanten und die tautomeren Gleichgewichte der untersuchten Verbindungen und der Einfluß der molekularen Strukturen auf die pK_a-Werte werden diskutiert. Die Titration eines Gemisches von zwei schwachen zweibasigen Säuren (*HHP* und *CHP*) in Wasser/Dimethylsulfoxid bei konstanter Ionenstärke wurde mit Hilfe der *Gran*schen Methode ausgewertet.

Introduction

This paper is part of our research on the dissociation of pyridinecarboxylic acid derivatives in various water/organic solvent systems [1–3] with special reference to acid strength as a function of, the solvent nature and the molecular structure of the acid. Generally, pyridinol derivatives are of particular interest to medicinal chemists because of their wide variety of physiological properties displayed by natural and many synthetic compounds. Moreover, many of the pyridinol derivatives are versatile ligands [3–15], and their complexes with some metal ions have found use in medicine and in quantitative analysis.

The acid dissociation constants of pyridinol derivatives are remarkably influenced by the solvent-solute interactions [16–18]. These interactions are generally interpreted on the basis of donor power (DN), acceptor power (AN), dielectric constant values (DEC), and hydrogen bonding ability, which all influence the ionization behaviour of the species present.

Since no work has been reported before on the medium effect on the ionization process of pyridinol derivatives, this paper reports the pK_{an} values of some pyridinol derivatives (2-hydroxy-3-pyridinol (*HHP*), 2-mercapto-3-pyridinol (*MHP*), and 2-carboxy-3-pyridinol (*CHP*)) in water-organic solvent mixtures containing 20 mole% organic solvent at constant ionic strength. The organic solvents used are ethanol, dimethylsulfoxide (*DMSO*), and dioxane. These solvents can also influence the tautomeric equilibria of the considered pyridinols.



A method for titrations of mixtures of *HHP* and *CHP* in water/*DMSO* containing 20 mole% organic solvent at constant ionic strength was also deduced using the *Gran* method [19, 20].

Results and Discussion

The pK_a values of pyridinol derivatives were calculated from the corresponding titration curves of 50 ml of 0.001 *M* reagent in organic solvent/water mixtures containing 20 mole% organic solvent at constant ionic strength (0.1 *M*) 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 steps of H_2A. The potentiometric titration curves are shown in Fig. 1.

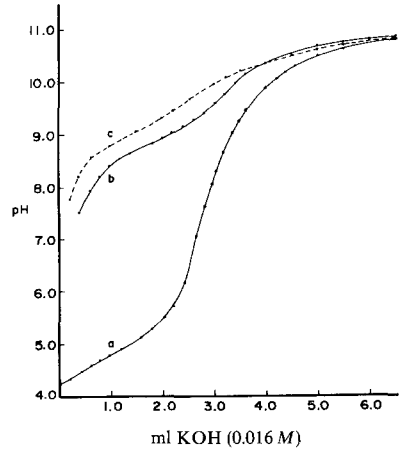


Fig. 1. *pH*-metric titration curves of pyridinol derivatives in water/ethanol (20 mole% ethanol); $I = 0.1\,M$ (KNO_3), 25 °C, $C_L = 1 \times 10^{-3}\,M$; a) *CHP*, b) *MHP*, c) *HHP*

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 addition of standard alkali covering the range 0.2–0.8 mole equivalents, then pK_{a1} can be calculated from equation 1 [21].

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

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

For the second equivalent (*i.e.* addition of 1.2–1.8 equivalents), the pK_{a2} value will be given by equation 3.

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

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

Here 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 relations 5 and 6.

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

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

The constants A and B of the *Debye–Hückel* equation were calculated according to the physical properties of the medium [22]. I is the ionic strength of the 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 [23–25]. The pK_{an} values corresponding to the different ionization steps of the compounds investigated are given in Table 1.

The results listed in Table 1 show that the pK_a values of all compounds are largely dependent on the nature of the organic cosolvent used. 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. Furthermore, one can ascribe the observed increase of pK_a of pyridinol derivatives in water organic media in comparison to that in aqueous medium to the low stabilization of the ionic form by solvent donor hydrogen bonding in partially aqueous media relative to pure aqueous medium. This is due to the greater tendency of water

Table 1. Mean pK_{an} values for pyridinol derivatives in water/organic media containing 20 mole% of organic solvents; $I = 0.1\ M$ (KNO_3), 25 ± 0.1 °C

Compound	Dielectric constant	*A*	*B*	pK_{a1}	pK_{a2}
H_2O/ethanol					
HHP	55.10	0.837	0.379	9.261 ± 0.005	11.721 ± 0.01*
MHP				8.896 ± 0.002	11.608 ± 0.02
CHP				5.324 ± 0.001	11.021 ± 0.025
H_2O/*DMSO*					
HHP	74.55	0.570	0.349	9.520 ± 0.003	12.260 ± 0.016
MHP				9.119 ± 0.001	12.184 ± 0.014
CHP				5.064 ± 0.003	11.820 ± 0.025
H_2O/dioxane					
HHP	36.22	1.654	0.492	9.990 ± 0.007	12.526 ± 0.03
MHP				9.478 ± 0.005	12.580 ± 0.03
CHP				5.429 ± 0.002	11.667 ± 0.034

*standard deviation

molecules to donate hydrogen bonds as compared with the other solvent molecules [26].

The data obtained allow us to formulate some hypotheses concerning the influence of the organic solvent on the ionization constant of pyridinol derivatives. The results given in Table 1 for 2-carboxy-pyridinol indicate that the variation of pK_{a1} in media containing the same mole percentage of organic solvent at constant ionic strength appears to be in the order *DMSO* < ethanol < dioxane.

Careful examination of the results reveals that the pK_{a1} values in presence of the poorer hydrogen bond donor *DMSO* is lower than that obtained in presence of the same amount of ethanol. This fact is in accordance with the *Gutmann* [27] acceptor number (AN) that measures the electrophilic behaviour of a solvent.

Regarding 2-hydroxy- or 2-mercapto-pyridinol, the variation of pK_a values in media containing the same mole percent of organic solvent at constant ionic strength appears to be in the order ethanol < *DMSO* < dioxane.

The lower pK_a values of the compounds in ethanol can be interpreted on the principle that the "model system" [13] changes. In particular, the compounds exist mainly in the oxo- or mercapto-hydroxy forms (**2** and **4**) in ethanoic medium, whereas in *DMSO* or dioxene they exist predominantly in the diol form (**1**, **3**). This interpretation is in agreement with the assumption that the hydrogen bonding ability of the solvent plays an obvious role as hydrogen bond donors stabilize the oxo or mercapto forms (keto forms) whereas hydrogen bond acceptors stabilize the diol forms [28].

Titration of a mixture of two weak diprotic acids

In the evaluation of binary component titration data, the uniqueness of each titration curve is one factor which governs the accuracy of prediction. The degree

to which curves do not overlap is given by the difference between the pK_{a1} values of the acids in the mixture. This means that the effective *pH* interval for specification is set by the pK_{a1} values of the two diprotic weak acids in the mixture, *i.e.* that the viable *pH* interval lies between the dissociation of the first proton in *CHP* ($pK_{a1} = 5.064$) and that in *HHP* ($pK_{a1} = 9.520$).

In this respect it can be observed that the pK_{a1} values of *CHP* in presence of the poorer acceptor number *DMSO* is lower than the one obtained in presence of the same amount of ethanol. The results given in Table 1 for *HHP* indicate that a higher pK_{a1} value is obtained in presence of *DMSO*. It is therefore not surprising that the resolution of acid strength of the mixture is greater in presence of *DMSO* than of ethanol. Accordingly, titration of a mixture of *CHP* and *HHP* can be carried out in presence of 20 mole% *DMSO* at constant ionic strength with $1.6 \times 10^{-2}\,M$ potassium hydroxide solution containing the same amount of *DMSO* (Fig. 2). The distribution curves for different species of *CHP* and *HHP* in partially aqueous medium containing 20 mole% *DMSO* computed from the corresponding acid dissociation constant of the reagents are shown in Fig. 3.

According to *Gran* [19, 20], linearization of the titration data for the first and second equivalence points of a mixture of *CHP* and *HHP* was carried out using

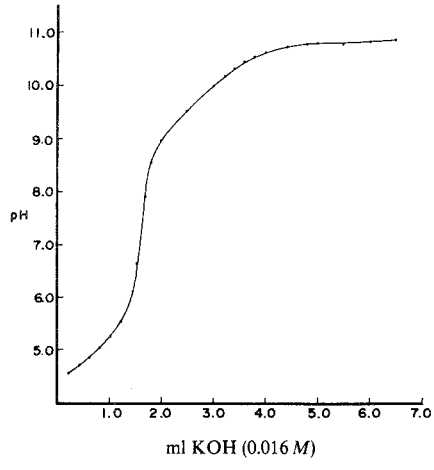


Fig. 2. *pH*-metric titration of a mixture of *CHP* and *HHP* in water/*DMSO* (20 mole% *DMSO*); $I = 0.1\,M$ (KNO_3), 25 °C, $[CHP] = [HHP] = 5 \times 10^{-4}\,M$

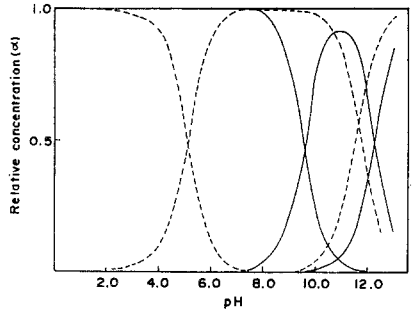


Fig. 3. Distribution curves for different acid-base forms of *HHP* (solid line) and *CHP* (dashed line) in water/*DMSO* (20 mole% organic solvent); $I = 0.1\,M$ (KNO_3), 25 °C, $C_L = 1 \times 10^{-3}\,M$

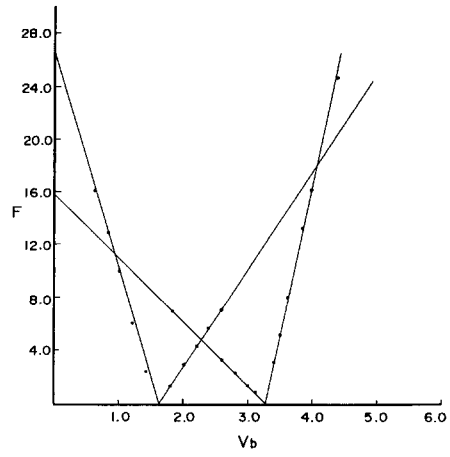


Fig. 4. *Gran* plots for the evaluation of equivalence volumes of a mixture of *CHP* and *HHP* in water/*DMSO* (20 mole% *DMSO*); $I = 0.1\ M$, $V_{e1} = 1.62 \pm 0.01$, $V_{e2} = 3.24 \pm 0.01$

equations 7–9.

$$w_{t1} = 10^{-pH} \cdot Vb/\gamma_+ \qquad 7$$

$$w_{t2} = 10^{-pH} \cdot VbNb/\gamma_+ - 10^{-pK_w} \cdot V/\gamma_+^2 - 10^{pH-pK_w} \cdot K_a \cdot V/\gamma_- \qquad 8$$

$$B_t = 10^{pH-14} \cdot V/\gamma_- \qquad 9$$

Nb is the concentration of potassium hydroxide added and *V* is the total volume of solution being titrated. This investigation is based on the use of stepwise addition of equal portions of the titrant. Straight lines were obtained from the *Gran* expression. If the values of the functions w_{t1} or w_{t2} and B_t were plotted against the volume of potassium hydroxide added (*Vb*) before and beyond the first and second equivalence point, respectively, straight lines are obtained which intersect the *V*-axis at $V = V_{e1}$ and $V = V_{e2}$.

The *Gran* plot gives agrees reasonably with the concentrations of the mixture to be titrated within experimental uncertainties of less than 2%. The *Gran* plots of the potentiometric titration of a mixture of *CHP* and *HHP* in water/*DMSO* containing 20 mole% *DMSO* at constant ionic strength are shown in Fig. 4.

Effect of molecular structure

Generally, due to resonance effects, the proton dissociation of the substituent at position 2 is easier than at position 3. Accordingly, for *HHP* or *MHP* the highest acidity of the OH or SH group at position 2 corresponds to that of the OH group at position 3. For the OH group at position 3, the negative charge of the ionized form is almost completely localized on the oxygen atom. On the other hand, for OH or SH at position 2 the negative charge of the ionized form is only partially localized on the oxygen or sulfur atom. This behaviour reflects itself in a high equilibrium concentration of the ionized form in the case of OH or SH at position 2, *i.e.* high acidity. Moreover, it is evident that the pK_{a1} value of *CHP* in presence of the same amount of organic solvent and constant ionic strength is lower than that of *MHP* or *HHP*. The observed high acidity of the COOH group can be ascribed to its contribution in an intramolecular hydrogen bond with the OH group at position 3.

The data obtained compared with those reported in previous papers [1–3] allows us to formulate some considerations concerning the influence of the nature of the substituent on acidity of pyridinol derivatives.

i) In *HHP* or *MHP*, the hydroxy or mercapto group at position 2 is more acidic than that at position 3 in both compounds. This is due to the fact that the resonance of the negative oxygen atom at position 2 with the heterocyclic nitrogen atom results in high stabilization of the ionized form at position 2.
ii) In *MHP*, the mercapto group at position 2 is more acidic than the hydroxy group at the same position in the case of *HHP*. This is due to the inductive effect of the OH group at position 2 which tends to intensify the negative charge on the OH group and results in relatively low acidity.
iii) In *CHP*, the presence of a hydroxy group in α-position to the COOH group stabilizes the ionized form because of the intramolecular hydrogen bond. This leads to a high acidity of the COOH group.

The correlation of the pK_a values of *HHP*, *MHP*, and *CHP* with that of 3-pyridinol indicates that the presence of hydroxy, mercapto or carboxy groups at position 2 decreases the acidic strength of the OH group because the negative charge of the ionized form tends to intensify the charge on the hydroxy group at position 3 and consequently renders its proton dissociation more difficult.

Experimental

Reagents

The pyridinol derivatives *HHP*, *MHP*, and *CHP* were purchased from Aldrich (Milwaukee, USA). Other chemicals used in this investigation and the organic solvents were of A.R. grade. Stock solutions 2.5×10^{-3} *M* of the compounds were prepared by dissolving the solid in the organic solvent. Standard carbonate free potassium hydroxide solutions containing 20 mole% of organic solvent were prepared. Deionized water was used throughout. The ionic strength was maintained constant at $I = 0.1$ mol·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 titrations were performed using a Radiometer Type ABU 12b autoburette accurate to ± 0.001 cm^3. All measurements were carried out at a temperature of 25 ± 0.1 °C.

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