

Substituent Effects on 6-Substituted 3-Hydroxy-1-methyl-4-pyridones

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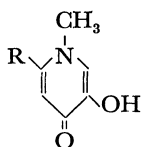
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Acid dissociation constants and UV and NMR spectra of a series of 6-substituted 3-hydroxy-1-methyl-4-pyridones have been measured. The acid dissociation constants have been analyzed in terms of the Hammett equation to give linear relationships, with $\rho=1.16$ for the conjugate acids and $\rho=1.06$ for the neutral compounds. Halochromism in the UV spectra gave the equation: $\Delta\bar{\nu}=689\text{ p}K_a-9399$, and the Hammett plots of the chemical shifts of the 2-H, 5-H, and CH_3 protons gave linear relationships, with $\rho=1.78$, 2.56, and 1.39, respectively.

In 1967 Choux and Benoit¹⁾ reported the substituent effects on the physical properties such as the acid dissociation constants and UV and NMR spectra of 4-pyrone derivatives. However, little is known about the 4-pyridone derivatives. The substituent effect on tautomerism of 6-substituted 3-methoxy-4-pyridones has been examined and it has been reported that the tautomeric ratios are affected by the substituents.²⁾

In this paper the substituent effects on the acid dissociation constants and UV and NMR spectra of 6-substituted 3-hydroxy-1-methyl-4-pyridones will be reported in which tautomerism does not exist.



Results and Discussion

Acid Dissociation Constants. The acid dissociation constants of five 6-substituted 3-hydroxy-1-methyl-4-pyridones have been determined spectrophotometrically in water at 25 °C. The results are summarized in Table 1, where the $\text{p}K_2$ and $\text{p}K_1$ values represent the acid dissociation exponent ($\text{p}K_a$) of a neutral compound and that of its conjugate acid, respectively. The $\text{p}K_1$ values are comparable to the $\text{p}K_1$ values for 4-pyridone (3.37)³⁾ and *N*-methyl-4-pyridone (3.33).⁴⁾ The $\text{p}K_2$ values are slightly larger than the $\text{p}K_2$ values for the 3-hydroxy-4-pyrones,¹⁾ i.e. the 3-hydroxy-1-methyl-4-pyridones are less acidic than the 3-hydroxy-4-pyrones.

A correlation between $\text{p}K_2$ and the Hammett σ_p constants⁵⁾ has been established for the 6-substituted 3-hydroxy-1-methyl-4-pyridones, as shown in Fig. 1,

and gives the following equation by the least-squares method:

$$\text{p}K_2 = 9.13 - 1.06\sigma \quad (r=0.969, s=0.03)$$

The reaction constant ($\rho=1.06$) is apparently smaller than that for the proton loss of 6-substituted 3-methoxy-4-pyridones ($\rho=4.94$).²⁾ In the latter case tautomerism produces the 4-pyridinols but since tautomerism does not exist in the former, transmission of the substituent effect is decreased.

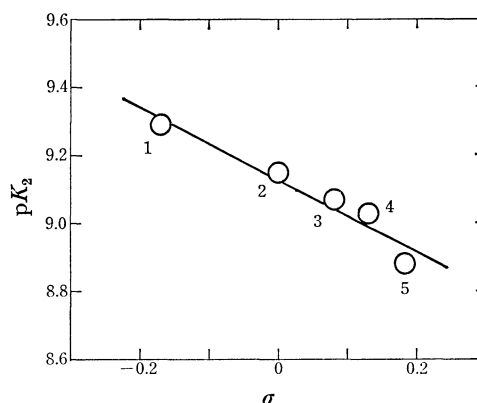


Fig. 1. The Hammett plot of $\text{p}K_2$ values.

The Hammett plots of the $\text{p}K_1$ values gave the equation:

$$\text{p}K_1 = 3.17 - 1.16\sigma \quad (r=0.860, s=0.06)$$

Although the correlation is not good, the transmission of the substituent effect is enhanced by the existence of a conjugated double bond, but is considerably smaller than that in the 3-methoxy-4-pyridones ($\rho=3.01$).²⁾

Halochromism in UV Spectra. The UV spectra of the 6-substituted 3-hydroxy-1-methyl-4-pyridones have been measured in neutral and alkaline solutions. The wavelengths and wave numbers are listed in Table 2 as λ_{HA} and $\bar{\nu}_{\text{HA}}$ for the neutral species and λ_{A^-} and $\bar{\nu}_{\text{A}^-}$ for the conjugate bases, respectively. The $\Delta\bar{\nu}$ values are the differences between the $\bar{\nu}_{\text{A}^-}$ and $\bar{\nu}_{\text{HA}}$ values.

A general relationship between the electronic spectra and dissociation constants has been established for 4-substituted 2-nitrophenols.⁶⁾ Plots of the $\Delta\bar{\nu}$ values against $\text{p}K_a$ ($\equiv \text{p}K_2$) values give a linear relationship as shown in Fig. 2, which is represented by the following equation.

$$\Delta\bar{\nu} = 689\text{ p}K_a - 9399 \quad (r=0.959, s=31)$$

TABLE 1. $\text{p}K_a$ VALUES

No. ^{a)}	R	σ	$\text{p}K_1$	$\text{p}K_2$
1	CH_3	-0.170	3.43	9.29
2	H	0	3.07	9.15
3	CH_2OH	0.08 ^{b)}	3.07	9.07
4	COO^-	0.132		9.03
5	CH_2Cl	0.184	3.02	8.88

a) Numbers correspond to those in Fig. 1. b) Ref. 1.

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TABLE 2. UV SPECTRAL DATA

No. ^{a)}	R	Neutral species			Conjugate base			$\Delta\bar{\nu}$ cm ⁻¹
		λ_{HA} nm	$\bar{\nu}_{HA}$ cm ⁻¹	$\log \epsilon_{HA}$	λ_{A^-} nm	$\bar{\nu}_{A^-}$ cm ⁻¹	$\log \epsilon_{A^-}$	
1	CH ₃	278	35970	4.08	304	32890	3.96	-3080
2	H	282	35460	4.12	309	32360	3.97	-3100
3	CH ₂ OH	283	35340	4.11	311	32150	3.99	-3190
4	COO ⁻	284	35210	4.04	312	32050	3.90	-3160
5	CH ₂ Cl	283	35340	4.00	312	32050	3.89	-3290

a) Numbers correspond to those in Fig. 2.

TABLE 3. NMR SPECTRAL DATA

No. ^{a)}	R	δ			
		2-H	5-H	1-CH ₃	Others
1	CH ₃	7.43 (s)	6.40 (s)	3.61 (s)	2.30 (s) for 6-CH ₃
2	H	7.59 (d) ^{b)}	6.58 (d) ^{c)}	3.82 (s)	7.58 (dd) ^{d)} for 6-H
3	CH ₂ OH	7.71 (s)	6.80 (s)	3.89 (s)	e)
4	COOH	7.88 (s)	7.13 (s)	3.98 (s)	
5	CH ₂ Cl	8.11 (s)	7.31 (s)	4.14 (s)	e)

a) Numbers correspond to those in Fig. 3. b) $J_{2,6}=3$ Hz. c) $J_{5,6}=7$ Hz. d) $J_{6,2}=3$ Hz and $J_{6,5}=7$ Hz. e) The δ values for 6-CH₂OH and 6-CH₂Cl could not be measured accurately because of overlapping with the signal of HOD.

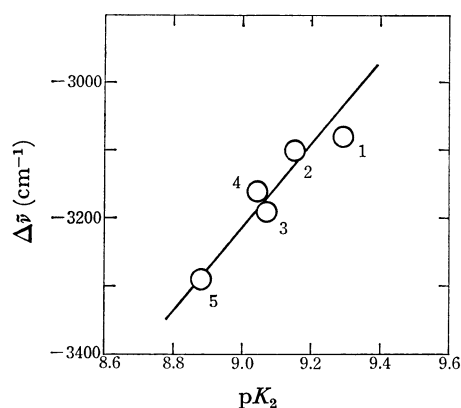


Fig. 2. The relationship between $\Delta\bar{\nu}$ and pK_a .

NMR Spectra. The ¹H-NMR spectral data in deuterium oxide are listed in Table 3. The chemical shifts of 3-OH could not be determined because of hydrogen exchange with deuterium in the solvent. The chemical shifts of 2-H, 5-H, and 1-CH₃ have been plotted against the respective σ_p constants (Fig. 3). The plots have yielded the following equations.

$$\delta_{2-H} = 1.78\sigma + 7.66 \quad (r=0.937, s=0.05)$$

$$\delta_{5-H} = 2.56\sigma + 6.73 \quad (r=0.939, s=0.11)$$

$$\delta_{CH_3} = 1.39\sigma + 3.83 \quad (r=0.977, s=0.03)$$

From this data the substituents have a stronger effect on the chemical shifts of the 5-H proton than on that of the 2-H proton. The chemical shifts of the 1-CH₃ are less sensitive to the substituent effects than those of the 2-H and 5-H protons. Transmission of the substituent effects was apparently larger than for the 4-pyrones.¹⁾

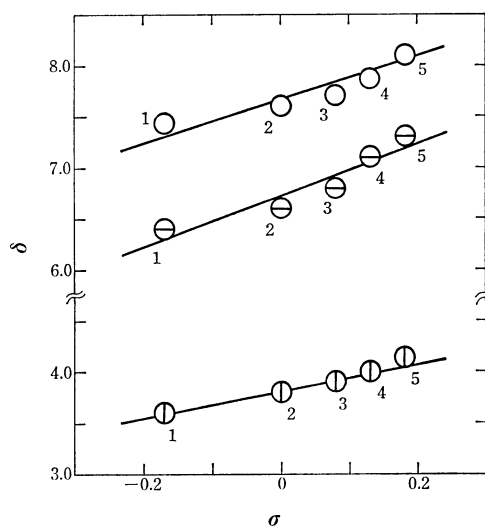


Fig. 3. The relationships of the chemical shifts with σ constants. $\circ$: δ_{2-H} , $\ominus$: δ_{5-H} , $\oplus$: δ_{CH_3} .

Experimental

All the melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. The IR, UV, and NMR spectra were taken on JASCO IRA-1, Hitachi EPS-3T, and Hitachi-Perkin-Elmer R-24 (60 MHz) spectrometers, respectively. The pH values were measured by a Hitachi-Horiba F-5 pH meter. The pK_a values were obtained by the method of Albert and Serjeant.⁷⁾

Materials. All the known compounds were prepared from kojic acid according to the methods in the literature: 3-hydroxy-1-methyl-4-pyridone, mp 215–217 °C (lit.⁸⁾ 212–216 °C); 1,2-dimethyl-5-hydroxy-4-pyridone, mp 270–274 °C (lit.⁹⁾ 273–274 °C); 5-hydroxy-2-hydroxymethyl-1-methyl-4-

pyridone, mp 220 °C (lit.⁸) 225—227 °C).

2-Chloromethyl-5-hydroxy-1-methyl-4-pyridone was obtained by the treatment of 5-hydroxy-2-hydroxymethyl-1-methyl-4-pyridone⁸ (1.0 g) with thionyl chloride (4.0 ml) at 60—70 °C for 30 min. Yield, 0.38 g (34.0%); mp 220—230 °C (from methanol-ethyl acetate); IR (KBr): 1628 cm⁻¹. Found: C, 48.36; H, 4.87; N, 8.06%. Calcd for C₇H₈ClNO₂: C, 48.43; H, 4.64; N, 8.07%.

2-Carboxy-5-hydroxy-1-methyl-4-pyridone was obtained by reaction of comenic acid (1.1 g) with 48% methylamine solution (2.5 g) at 60—80 °C for 4 h. Yield, 0.28 g (23.5%); mp 224—230 °C (dec) (from water); IR (KBr): 1630, 1607 cm⁻¹. Found: C, 49.68; H, 4.37; N, 8.27%. Calcd for C₇H₇NO₄: C, 49.71; H, 4.17; N, 8.28%.

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