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

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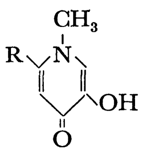
Acid dissociation constants and UV and NMR spectra of a series of 6-substituted 3-hydroxy-1-methyl-4-pyridones have been measured. The acid dissociation constants have been analyzed in terms of the Hammett equation to give linear relationships, with $\rho=1.16$ for the conjugate acids and $\rho=1.06$ for the neutral compounds. Halochromism in the UV spectra gave the equation: $\Delta\bar{\nu}=689\,\mathrm{p}K_a-9399$, 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 Benoit[1] 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-hydroxyl-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 pK_2 and pK_1 values represent the acid dissociation exponent (pK_a) of a neutral compound and that of its conjugate acid, respectively. The pK_1 values are comparable to the pK_1 values for 4-pyridone (3.37)[3] and *N*-methyl-4-pyridone (3.33).[4] The pK_2 values are slightly larger than the pK_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 correlarion between pK_2 and the Hammett σ_p constants[5] has been established for the 6-substituted 3-hydroxyl-1-methyl-4-pyridones, as shown in Fig. 1, and gives the following equation by the least-squares method:

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

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.

TABLE 1. pK_a VALUES

No.[a]	R	σ	pK_1	pK_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.

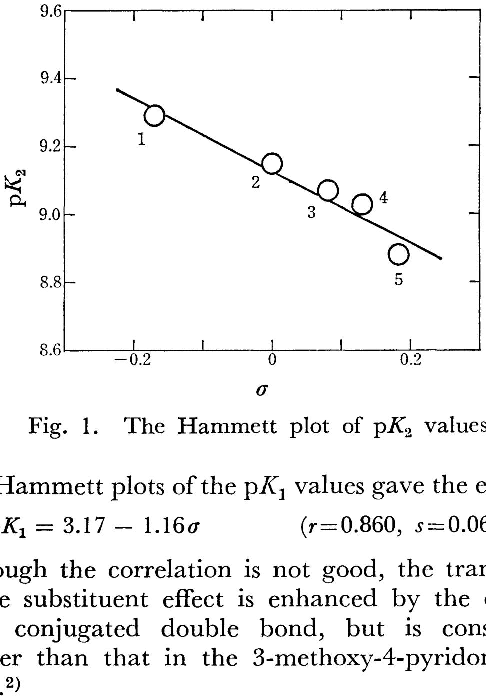


Fig. 1. The Hammett plot of pK_2 values.

The Hammett plots of the pK_1 values gave the equation:

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

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 $\bar{\nu}_{HA}$ for the neutral species and λ_{A^-} and $\bar{\nu}_{A^-}$ for the conjugate bases, respectively. The $\Delta\bar{\nu}$ values are the differences between the $\bar{\nu}_{A^-}$ and $\bar{\nu}_{HA}$ 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 pK_a ($\equiv$pK_2) values give a linear relationship as shown in Fig. 2, which is represented by the following equation.

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

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Table 2. UV spectral data

No.[a]	R	Neutral species			Conjugate base			$\Delta\tilde{\nu}$
		λ_{HA} / nm	$\tilde{\nu}_{HA}$ / cm^{-1}	$\log \varepsilon_{HA}$	λ_{A^-} / nm	$\tilde{\nu}_{A^-}$ / cm^{-1}	$\log \varepsilon_{A^-}$	cm^{-1}
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_2OH	283	35340	4.11	311	32150	3.99	−3190
4	COO^-	284	35210	4.04	312	32050	3.90	−3160
5	CH_2Cl	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_2OH	7.71(s)	6.80(s)	3.89(s)	e)
4	COOH	7.88(s)	7.13(s)	3.98(s)	
5	CH_2Cl	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-$\mathbf{CH_2}$OH and 6-$\mathbf{CH_2}$Cl could not be measured accurately because of overlapping with the signal of HOD.

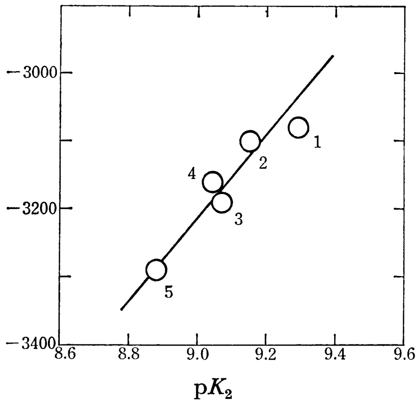

Fig. 2. The relationship between $\Delta\tilde{\nu}$ and pK_2.

NMR Spectra. The ^{1}H-NMR spectral data in deuterium oxide are listed in Table 3. The chemical shifts of 3-OH could not be determined becasue of hydrogen exchange with deuterium in the solvent. The chemical shifts of 2-H, 5-H, and 1-CH_3 have been plotted against the respective σ_p constants (Fig. 3). The plots have yielded the following equations.

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

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

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

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-CH_3 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]

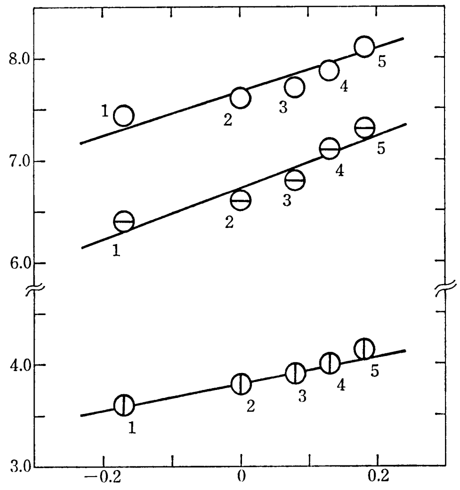

Fig. 3. The relationships of the chemical shifts with σ constants. ○: $\delta_{2\text{-H}}$, ⊖: $\delta_{5\text{-H}}$, ⦶: δ_{CH_3}.

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-hydroxymethxl-1-methyl-4-pyridone[8] (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 $C_7H_8ClNO_2$: 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 $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28%.

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