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Tautomerism of 4-Pyridones

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The tautomeric constants, K_t, of several 4-pyridones were determined by measurement of pK_a values. For 2-substituted 5-methoxy-4-pyridones, the K_t values were correlated to the substituent constants σ, the equation $\log K_t = 2.98 + 2.93\sigma_m - 6.18\sigma_0$ being obtained.

The tautomerism of simple 4-pyridones having chlorine atom[1] or methoxycarbonyl group[2] in an α-position to nitrogen atom has been investigated in detail. Gordon *et al.* showed that the tautomeric equilibrium of 4-pyridones is displaced in favour of 4-hydroxypyridine form by electron-withdrawing groups of α-position.

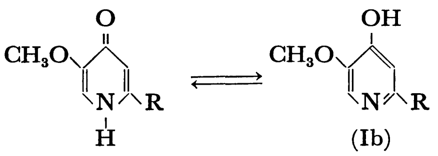
We report the tautomerism of several 2-substituted 5-methoxy-4-pyridones and discuss the substituent effects by the Hammett equation. Little is known about the application of the Hammett equation to 4-pyridones.

Results and Discussion

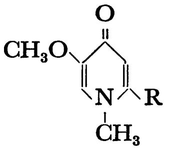
Dissociation Constants. The dissociation constants of 4-pyridones (I), *N*-methyl-4-pyridones (II), and 4-methoxypyridines (III) were determined spectrophotometrically in water at 20 °C. The results are summarized in Table 1, where pK_1 and pK_2 represent respectively the first and second dissociation constants for 4-pyridones (I), and pK_{NCH_3} and pK_{OCH_3} correspond to the dissociation constants for *N*-methyl-4-pyridones (II) and 4-methoxypyridines (III), respectively.

Table 1. Dissociation constants

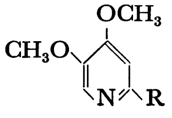
Substituent	(I)		(II)	(III)
	pK_1	pK_2	pK_{NCH_3}	pK_{OCH_3}
CH_3	3.42	11.29	3.39	7.10
H	3.04	11.08		
CH_2OH	3.06	10.48	3.06	5.89
CH_2OCH_3	2.99	10.23	2.88	5.42
CHO				4.25
$COOCH_3$	2.17	8.23	2.18	3.16



(Ia) (Ib)



(II)



(III)

Since activity coefficients were not introduced into the calculation, the dissociation constants do not represent thermodynamic terms, giving only a relative measure of base strength.

The pK_a values of 4-pyridones and 4-methoxypyridines decrease by electron-withdrawing groups attached to 2-position, the degree of decrease for 4-methoxypyridines being the greatest of all. It is concluded that these changes are related to the distance between the substituent and the reaction site.

Tautomeric Ratio. The tautomeric constants K_t which represent the ratio of NH-form (Ia) to OH-form (Ib), are given by the following equation[3] (Table 2).

$$\log K_t = pK_{OCH_3} - pK_{NCH_3} \qquad (1)$$

Table 2. Tautomeric constants

Substituent	$\log K_t$
CH_3	3.7
CH_2OH	2.8
CH_2OCH_3	2.5
$COOCH_3$	1.0

The K_t values for 4-pyridones are affected by the substituents in the 2-position, decreasing by electron-withdrawing groups.

UV Spectra. The UV spectra of neutral species of 5-methoxy-4-pyridones (I) having methyl, hydroxymethyl, and methoxymethyl groups in the 2-position are similar to those of their *N*-methyl derivatives (II), but differ a great deal from those of their *O*-methyl derivatives (III). That is to say, these 4-pyridones exist essentially in the NH-form (Ia). However, 5-methoxy-2-methoxycarbonyl-4-pyridone exists in both NH-form (Ia) and OH-form (Ib) in water (Fig. 1).

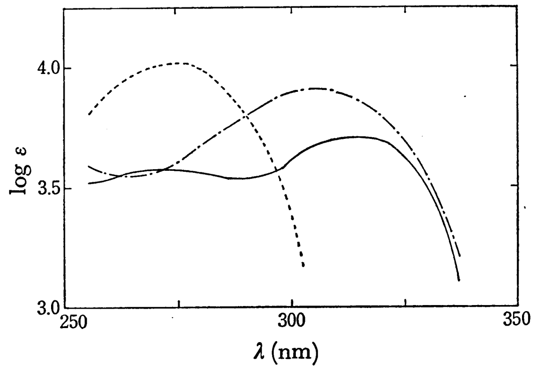


Fig. 1. The UV spectra of the neutral species of 5-methoxy-2-methoxycarbonyl-4-pyridone series.
——: 5-Methoxy-2-methoxycarbonyl-4-pyridone,
–·–·–: 5-methoxy-2-methoxycarbonyl-1-methyl-4-pyridone,
······: 4,5-dimethoxy-2-methoxycarbonylpyridine.

Substituent Effects. The substituent constants σ_o for ortho-substituted pyridines were obtained from their dissociation constants by Clark and Perrin.[4] However, the σ_o values for hydroxymethyl and methoxymethyl groups are unknown. We obtained them by the following method. When the pK_a values of 2-substituted 4,5-dimethoxypyridines, 4-methoxypyridine (pK_a=6.62),[5] and 2-chloro-4-methoxypyridine (pK_a=1.93)[1] are plotted against the apparent substituent constants σ_o[4] for the 2-position and the substituent constants σ_m[6] for the 5-position, the plot gives a straight line, the following equation for 2,5-disubstituted 4-methoxypyridines being obtained by the least square methods.

$$pK_{OCH_3} = 6.75 - 6.07(\sigma_o + \sigma_m) \quad (r = 0.992) \quad (2)$$

The regression of Eq. 1 gives the σ_o values which are 0.02 and 0.10 for hydroxymethyl and methoxymethyl groups, respectively.

The following Eqs. 3 and 4 are obtained for the proton gain and proton loss, respectively, of 2-substituted 5-methoxy-4-pyridones (I).[6,7]

$$pK_1 = 3.11 - 3.01\sigma_m \quad (r = 0.989) \quad (3)$$

$$pK_2 = 10.77 - 4.94\sigma_o \quad (r = 0.989) \quad (4)$$

Equations 5 and 6 are obtained for the proton gain of 2-substituted 5-methoxy-1-methyl-4-pyridones (II) and the proton loss of 2-substituted 4,5-dimethoxypyridines (III), respectively.

$$pK_{NCH_3} = 3.09 - 2.93\sigma_m \quad (r = 0.978) \quad (5)$$

$$pK_{OCH_3} = 6.07 - 6.18\sigma_o \quad (r = 0.985) \quad (6)$$

In Eq. 5, the value 0.01 obtained from the regression of Eq. 3 was assigned to the substituent constants σ_m for the hydroxymethyl group.

When Eqs. 4 and 5 are substituted into Eq. 1, the following equation is derived.

$$\log K_t = 2.98 + 2.93\sigma_m - 6.18\sigma_o \quad (7)$$

The electron-withdrawing groups in the 2-position stabilize the keto form for the carbonyl group and the hydroxy form for the nitrogen atom in the ring. In Eq. 7, the K_t values are defined as [NH]/[OH]. The ρ-value −6.18 for the substituent constants σ_o shows that the ratio of (Ib) increases with electron-withdrawing groups in the 2-position. In contrast, the ρ-value +2.93 for the substituent constants σ_m indicates the decrease of (Ib) owing to the stabilization of the carbonyl group by electron-withdrawing groups in the 2-position. Thus, Eq. 7 shows to what extent the substituents in the 2-position participate in the two reaction sites relating to the tautomerism of 4-pyridones. For 2-substituted 5-methoxy-4-pyridones, the electron-withdrawing substituents in the 2-position increase the ratio of the hydroxy form (Ib). Gordon *et al.*[2] showed that the K_t values are little affected by the substituents in β-position as compared with α-position, supporting our results.

It is concluded that most of the factors for the tautomerism of 4-pyridones are due to the electronic effect (including steric effect) of the substituents in the 2-position.

Experimental

All the melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. The IR spectra were taken on a JASCO IRA-1 spectrophotometer, and the NMR spectra on a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz).

The pK_a values of 4-pyridones, *N*-methyl-4-pyridones, and 4-methoxypyridines were measured specrophotometrically in water at 20 °C by the method of Albert and Serjeant.[8] The absorption spectra were taken on a Hitachi EPS-3T spectrophotometer, while the pH values were measured by a Hitachi-Horiba F-7 pH meter.

Materials. All the known compounds were prepared according to the methods described in references: 3-methoxy-4-pyridone, mp 170—172 °C (lit,[9] 173 °C); 5-methoxy-2-methyl-4-pyridone, mp 104—105 °C (lit,[10] 102—103 °C); 5-methoxy-1,2-dimethyl-4-pyridone, mp 145—147 °C (lit,[11] 150 °C); 4,5-dimethoxy-2-methylpyridine, bp 76—80 °C/1 Torr (lit,[10] 78—80 °C/1 Torr); 5-methoxy-2-hydroxymethyl-4-pyridone, mp 170—171°C (lit,[11] 172 °C); 5-methoxy-2-hydroxymethyl-1-methyl-4-pyridone, mp 203—205 °C (lit,[11] 203—205 °C); 4,5-dimethoxy-2-hydroxymethylpyridine, mp 117—118 °C (lit,[12] 117—118 °C); 5-methoxy-2-methoxymethyl-4-pyridone, bp 200—204 °C/1 Torr (lit,[13] 200 °C/1 Torr); 5-methoxy-2-methoxymethyl-1-methyl-4-pyridone, mp 58—59 °C (lit,[14] 59°C).

4,5-Dimethoxy-2-methoxymethylpyridine was obtained by methylation of 5-methoxy-2-methoxymethyl-4-pyridone[13] with diazomethane: Yield, 22%; mp 49—50 °C (from petroleum ether); IR ($CHCl_3$) 1590 cm^{-1} (C=C); NMR ($CDCl_3$) δ: 3.45 (s,3H), 3.95 (s,6H), 4.50 (s,2H), 6.97 (s,1H), 8.19 (s,1H). Found: C, 58.88; H, 7.13; N, 7.71%. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65%.

4,5-Dimethoxy-2-formylpyridine was obtained by manganese dioxide oxidation of 4,5-dimethoxy-2-hydroxymethylpyridine[12]: Yield, 59%; mp 136—137°C (from petroleum ether); IR ($CHCl_3$) 1730(C=O), 1580(C=C) cm^{-1}; NMR ($CDCl_3$) δ: 3.98(s,3H), 4.05(s,3H), 7.47(s,1H), 8.27(s,1H), 9.91(s,1H). Found: C, 57.57; H, 5.50; N, 8.41%. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38%.

5-Methoxy-2-methoxycarbonyl-4-pyridone was obtained by esterification of 5-methoxy-2-carboxy-4-pyridone[11] with methanol in the presence of dry hydrogen chloride: Yield, 15%; mp 174—177 °C (from ethyl acetate); IR ($CHCl_3$) 1730(C=O), 1615(C=O) cm^{-1}; NMR ($CDCl_3$) δ: 3.95(s,3H), 3.97(s,3H), 7.55(s,1H), 7.95(s,1H). Found: C, 52.17; H, 4.87; N, 7.71%. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65%.

5-Methoxy-2-methoxycarbonyl-1-methyl-4-pyridone was obtained from 5-methoxy-2-carboxy-4-pyrone[15] by *N*-methylation with methylamine and by esterification with methanol in the presence of hydrogen chloride: Yield, 21%; mp 147—149 °C (from benzene); IR ($CHCl_3$) 1750(C=O), 1620(C=O) cm^{-1}; NMR ($CDCl_3$) δ: 3.82(s,3H), 3.88(s,3H), 3.91(s,3H), 7.02(s,2H). Found: C, 54.65; H, 5.60; N, 7.11%. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10%.

4,5-Dimethoxy-2-methoxycarbonylpyridine was obtained by methylation of 5-methoxy-2-carboxy-4-pyridone[11] with a large excess of diazomethane: Yield, 29%; mp 125—126 °C (from ethyl ether); IR ($CHCl_3$) 1735(C=O,) 1580(C=C) cm^{-1}; NMR ($CDCl_3$) δ: 3.99(s,6H), 4.01(s,3H), 7.68(s,1H), 8.21 (s,1H). Found: C, 54.96; H, 5.69; N, 7.19%. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10%.

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