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Equilibrium Studies of 5-Substituted 4-Hydroxy-2-methylpyrimidines. III.[1] Photometric Titration in *n*-Butanol[2]

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Photometric titration for 5-substituted 4-hydroxy-2-methylpyrimidine and its methyl derivatives was performed in *n*-BuOH. An equation for the titration was derived in consideration of ion pair formation in *n*-BuOH.

$$P = \frac{\dfrac{K_{\mathrm{B}}}{K^{\circ}_{\mathrm{HX}}}(K_{\mathrm{BHX}}+[\mathrm{X}^-]f^2)}{\dfrac{K_{\mathrm{I}}}{K^{\circ}_{\mathrm{HX}}}(K_{\mathrm{IHX}}+[\mathrm{X}^-]f^2)} V_{\mathrm{eq}}\left(\frac{1}{V}-\frac{1}{V_{\mathrm{eq}}}\right)$$

It was proved that Higuchi's Type II plot method was applicable only under a condition, $K_{\mathrm{BHX}}=K_{\mathrm{IHX}}$, from the analysis of the titration curves.

The over-all dissociation constant of the pyrimidines ($K_{\mathrm{BH}}^{n\text{-BuOH}}=K^{\circ}_{\mathrm{HX}}/K_{\mathrm{B}}K_{\mathrm{BHX}}=[\mathrm{H}^+][\mathrm{B}]f_{\mathrm{H}}/[\mathrm{BH}^+]f_{\mathrm{BH}}$) was estimated from the slope of the titration curve. The basicities of the compounds in *n*-BuOH generally increased as compared with those in water ($\Delta\mathrm{p}K=\mathrm{p}K_{\mathrm{BH}}^{n\text{-BuOH}}-\mathrm{p}K_{\mathrm{a}}=-0.1$—$2.3$). The degrees of the increase differed largely among the compounds. Much larger increase of the basicity than the other compounds ($\Delta\mathrm{p}K$; 2.1—2.3) was found for 5-substituted 1,2-dimethyl-4(1H)-pyrimidones.

Keywords——photometric titration in *n*-BuOH; Higuchi's Type II plot; 5-substituted 4-hydroxy-2-methylpyrimidines; dissociation constant in *n*-BuOH; ion pair dissociation constant; perchloric acid titrant

In the previous paper,[1] it was shown that Higuchi's photometric titration method[4] could be applied to the titration in MeOH as well as in water. In MeOH this method was useful for the detection of an end point and was also effective for the estimation of the dissociation constant. Such photometric titration, however, has been scarcely attempted in a lower dielectric constant (D) alcohols than MeOH(D=32.6). In this paper, *n*-BuOH(D=17.1) was chosen as a lower dielectric constant solvent. The dissociation of the electrolytes is complicated in this solvent, because cation and anion exist as ion pair in more stable form than do as a single ion.[5,6] An application, therefore, to the photometric titration in such a dielectric constant solvent may be limited.

Results

Photometric titration was performed in *n*-BuOH using the same technique as that reported in our previous paper.[1] 5-Substituted 4-hydroxy-2-methylpyrimidine and its methyl derivatives were titrated. 4-Methyl-3-nitroaniline was used as an indicator. The acid,

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[1] Part II: T. Kitagawa and S. Mizukami, *Chem. Pharm. Bull.* (Tokyo), 26, 53 (1978).

[2] Presented in part at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, 1975.

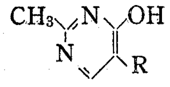
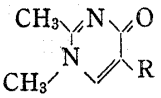
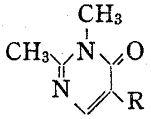
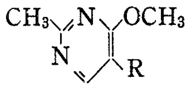
[3] Location: *5-12-4, Sagisu, Fukushima-ku, Osaka, 553, Japan.*

[4] T. Higuchi, C. Rehm, and C. Barnstein, *Anal. Chem.*, 28, 1506 (1956); C. Rehm and T. Higuchi, *ibid.*, 29, 367 (1957).

[5] T. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), 26, 59 (1978).

[6] I.M. Kolthoff and S. Bruckenstein, "Treatise on Analytical Chemistry," Part I, Vol. 1, ed. by I.M. Kolthoff, P.J. Elving, and E.B. Sandell, The Interscience Encyclopedia, Inc., New York, 1959, pp. 475—542 and references therein.

Table I. Photometric Titration Data of 5-Substituted 4-Hydroxy-2-methylpyridine and Its Methyl Derivatives

Compound			Sample taken (mg)	0.1 N $HClO_4$ Calcd. (ml)	0.1 N $HClO_4$ Obsd. (ml)	Recovery (%)
	H	**1a**	11.30	1.062	1.222(1.101)[a]	115.1(103.7)[a]
	CH_3	**1b**	47.95	3.995	4.026	100.8
	OCH_3	**1c**	37.33	2.764	2.866	103.7
	H	**2a**	13.17	1.098	1.115	101.5
	CH_3	**2b**	14.78	1.098	1.122	102.2
	OCH_3	**2c**	4.10	2.744[b]	2.771[b]	101.0
	H	**3a**	25.99	1.068[c]	1.229[c](1.128)[a]	115.1(105.6)[a]
	CH_3	**3b**	17.56	1.316	1.345	102.2
	OCH_3	**3c**	16.46	1.101	1.228(1.104)[a]	111.5(100.3)[a]
	H	**4a**	30.13	2.519	2.558	101.5
	CH_3	**4b**	55.50	4.155	4.137	99.6
	OCH_3	**4c**	15.11	1.011	1.029	101.8

a) Corrected by eq(31).
b) 0.01N $HClO_4$.
c) 0.2N $HClO_4$.

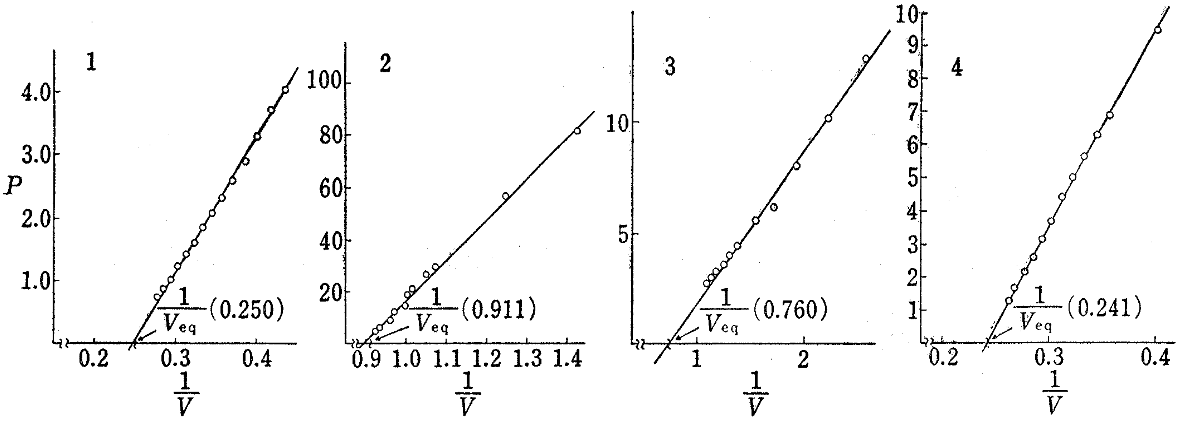
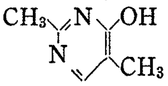
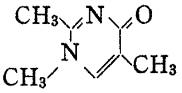


Fig. 1. Plot of P against $1/V$ in n-BuOH: 2,5-Dimethyl-4-hydroxypyrimidine(1), 1,2,5-Trimethyl-4(1H)-pyrimidone(2), 2,3,5-Trimethyl-4(3H)-pyrimidone(3) and 2,5-Dimethyl-4-methoxypyrimidine(4)

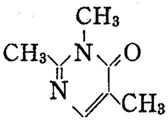
1: $P=-5.400+21.739\ 1/V$; $s=0.036$; $n=10$



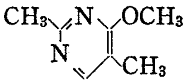
2: $P=-137.71+154.56\ 1/V$; $s=1.150$; $n=11$



3: $P=-5.178+6.966\ 1/V$; $s=0.260$; $n=8$



4: $P=-14.728+60.926\ 1/V$; $s=0.068$; $n=12$



$HClO_4$, in n-BuOH was used as titrant, which was prepared from the reaction of $AgClO_4$ with HCl.[5] When the ratio of the concentration of the indicator ([I]) to that of its conjugate acid (ion, $[IH^+]$; ion pair, $[IH^+X^-]$) is defined as P;

$$P = \frac{[I]}{[IH^+]+[IH^+X^-]} = \frac{A-A_{IH}}{A_I-A} \tag{1}$$

P is calculated using the absorbance (A) of the titrating solution and the absorbances, A_I and A_{IH}, which correspond to the indicator itself and its conjugate acid, respectively.

Plots of P against the reciprocal of the added titrant volume ($1/V$) for the tested pyrimidines (Table I) were shown in Fig. 1. Linear relationships were observed. The intercept on the abscissa of each straight line crossed at the reciprocal of the equivalent volume($1/V_{eq}$)[7] except 4-hydroxy-2-methylpyrimidine(**1a**), 2,3-dimethyl-4(3H)-pyrimidone(**3a**) and 2,3-dimethyl-5-methoxy-4(3H)-pyrimidone(**3c**). The end point was determined from the regression equation of the straight line which was obtained by the method of least-squares.[8] The recoveries for **1a**, **3a** and **3c** were widely exceeding 100%, as shown in Table I.

Discussion

Plot of P against $1/V$ yielded a straight line with an intercept on the abscissa equal to $1/V_{eq}$. However, the phenomenon only showed apparent obedience to Higuchi's Type II plot, because formation of ion pair is not negligible in n-BuOH. The phenomenon may be explained as follows:

When a base (B) is titrated with an acid, HX, in the presence of the indicator (I), the following equilibria exist.

$$B + HX \overset{K_B}{\rightleftharpoons} BH^+X^- \overset{K_{BHX}}{\rightleftharpoons} BH^+ + X^- \tag{I}$$

$$I + HX \overset{K_I}{\rightleftharpoons} IH^+X^- \overset{K_{IHX}}{\rightleftharpoons} IH^+ + X^- \tag{II}$$

$$HX \overset{K_{HX}^i}{\rightleftharpoons} H^+X^- \overset{K_{HX}^d}{\rightleftharpoons} H^+ + X^- \tag{III}$$

The equilibrium constants, K_B, K_{BHX}, K_I, K_{IHX}, K_{HX}^i and K_{HX}^d are defined as follows:

$$K_B = \frac{[BH^+X^-]}{[B][HX]} \tag{2}$$

$$K_{BHX} = \frac{[BH^+][X^-]}{[BH^+X^-]} f_{BH} f_X \tag{3}$$

$$K_I = \frac{[IH^+X^-]}{[I][HX]} \tag{4}$$

$$K_{IHX} = \frac{[IH^+][X^-]}{[IH^+X^-]} f_{IH} f_X \tag{5}$$

$$K_{HX}^i = \frac{[H^+X^-]}{[HX]} \tag{6}$$

$$K_{HX}^d = \frac{[H^+][X^-]}{[H^+X^-]} f_H f_X \tag{7}$$

The over-all dissociation constant of the acid, K_{HX}°, is defined as

$$K_{HX}^\circ = K_{HX}^i K_{HX}^d = \frac{[H^+][X^-]}{[HX]} f_H f_X \tag{8}$$

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[7] See eq (23) in this report.

[8] The points in the vicinity of the equivalence point which deviated from the straight line were excluded.

According to Kolthoff,[9] activity coefficient is written

$$f_H = f_{BH} = f_{IH} = f_X = f \tag{9}$$

In *n*-BuOH, Debye-Hükel equation for f is shown[5]

$$-\log f = 5.02\sqrt{\mu} \tag{10}$$

The total concentrations of the base, the indicator and the added acid, C_B, C_I and C_{HX}, are expressed as eq(11), (12) and (13), respectively.

$$C_B = [B] + [BH^+] + [BH^+X^-] \tag{11}$$

$$C_I = [I] + [IH^+] + [IH^+X^-] \tag{12}$$

$$C_{HX} = [HX] + [H^+X^-] + [X^-] + [BH^+X^-] + [IH^+X^-] \tag{13}$$

From the rule of the electroneutrality

$$[X^-] = [BH^+] + [IH^+] + [H^+] \tag{14}$$

The ratio of the concentration of the base to that of its conjugate acid was defined as Q.

$$Q = \frac{[B]}{[BH^+]+[BH^+X^-]} \tag{15}$$

From eq(1), (4), (5), (8) and (9)

$$P = \frac{1}{\frac{K_I}{K^\circ_{HX}}[H^+](K_{IHX}+[X^-]f^2)} \tag{16}$$

From eq(2), (3), (8), (9) and (15)

$$Q = \frac{1}{\frac{K_B}{K^\circ_{HX}}[H^+](K_{BHX} + [X^-]f^2)} \tag{17}$$

Combination of eq(16) with eq(17) gives

$$P = \frac{\frac{K_B}{K^\circ_{HX}}(K_{BHX} + [X^-]f^2)}{\frac{K_I}{K^\circ_{HX}}(K_{IHX}+[X^-]f^2)} Q \tag{18}$$

When the amount of the indicator used is extremely small as compared with that of the base ($C_B \gg C_I$), Q is converted into

$$Q = V_{eq}\left(\frac{1}{V} - \frac{1}{V_{eq}}\right) \tag{19}$$

Because eq(18) involves the variables, $[X^-]$ and f, in the right-hand side, the photometric titration could not be revealed as a simple straight line of P *vs.* $1/V$. However, the fact that the titrations for most of the pyrimidine bases tested exhibited such a linear relationship between P and $1/V$, may be explained by any one of the following assumptions:

Assumption 1 $\begin{cases} K_{BHX} \ll [X^-]f^2 \text{ \textit{i.e.}, } [BH^+] \ll [BH^+X^-] & (20a) \\ K_{IHX} \ll [X^-]f^2 \text{ \textit{i.e.}, } [IH^+] \ll [IH^+X^-] & (20b) \end{cases}$

Assumption 2 $K_{BHX} = K_{IHX}$ (21)

Assumption 3 $\begin{cases} K_{BHX} \gg [X^-]f^2 \text{ \textit{i.e.}, } [BH^+] \gg [BH^+X^-] & (22a) \\ K_{IHX} \gg [X^-]f^2 \text{ \textit{i.e.}, } [IH^+] \gg [IH^+X^-] & (22b) \end{cases}$

Under each assumption, P will be expressed as a function involving only one variable, Q. Since the ion of the indicator, 4-methyl-3-nitroaniline, in *n*-BuOH existed in more amounts than the ion pair did,[5] Assumption 1 cannot occur. Success of the plot, therefore, will be attributed to either condition: Assumption 2 or Assumption 3. Under each of the two assump-

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[9] I.M. Kolthoff and M.K. Chantooni, Jr., *J. Am. Chem. Soc.*, **87**, 4428 (1965); I.M. Kolthoff and M.K. Chantooni, Jr., *J. Phys. Chem.*, **70**, 856 (1966).

tions, plot of P against $1/V$ will give a straight line with a slope $(K_B K_{BHX}/K^{\circ}_{HX})V_{eq}/(K_I K_{IHX}/K^{\circ}_{HX})$ and with an intercept on the abscissa equal to the reciprocal of the equivalent volume of the titrant (V_{eq}), that is,

$$P = \frac{\dfrac{K_B}{K^{\circ}_{HX}} K_{BHX}}{\dfrac{K_I}{K^{\circ}_{HX}} K_{IHX}} V_{eq} \left(\frac{1}{V} - \frac{1}{V_{eq}}\right) \tag{23}$$

The value of the slope means the ratio of the over-all dissociation constant of the indicator to that of the base, because

$$K_{BH}^{n\text{-BuOH}} = \frac{K^{\circ}_{HX}}{K_B K_{BHX}} = \frac{[H^+][B]}{[BH^+]} \tag{24}$$

and

$$K_{IH}^{n\text{-BuOH}} = \frac{K^{\circ}_{HX}}{K_I K_{IHX}} = \frac{[H^+][I]}{[IH^+]} \tag{25}$$

In the previous paper,5) the $K_{IH}^{n\text{-BuOH}}$ value of the indicator, 4-methyl-3-nitroaniline, was measured. Then, the $K_{BH}^{n\text{-BuOH}}$ value of the titrated sample can be calculated from the slope by use of the $K_{IH}^{n\text{-BuOH}}$ value.

The hydrogen ion concentration, $[H^+]$ was estimated by a successive approximation procedure.

(1) As a first approximation, $[H^+]$ is calculated from eq(16), assuming $[X^-]=0$.

(2) Estimation of $[IH^+X^-]$; $[IH^+]$ is calculated from eq(25) using the $K_{IH}^{n\text{-BuOH}}$ value (3.013×10^{-4}), [I] and an approximate value of $[H^+]$. The concentration, [I], is calculated:

$$[I] = \frac{P}{P+1} C_I \tag{26}$$

Thus, $[IH^+X^-]$ can be calculated from eq(12).

(3) Estimation of $[BH^+X^-]$; since $HClO_4$ dissociates almost completely in the concentrations less than 2×10^{-2} M,5) [HX] or $[H^+X^-]$ can be neglected as compared with $[X^-]$. Then,

$$C_{HX} = [BH^+X^-] + [IH^+X^-] + [X^-] \tag{27}$$

Combination of eq(14) with eq(27) gives

$$[BH^+] + [BH^+X^-] = C_{HX} - [IH^+] - [IH^+X^-] - [H^+] \tag{28}$$

When $[H^+]$ is known, ($[BH^+]+[BH^+X^-]$) can be calculated. The concentration, [B], is also calculated from eq(11). Since $[BH^+]$ is calculated from eq(24) using the $K_{BH}^{n\text{-BuOH}}$ value, $[H^+]$ and [B], $[BH^+X^-]$ can be calculated.

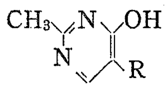
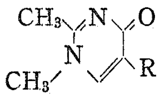
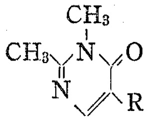
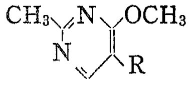
(4) From eq(27), a new $[X^-]$ is calculated, and f is also calculated from eq(10)($\mu = [X^-]$).

TABLE II. Estimation of the K_{BHX} Value of 2,5-Dimethyl-4-hydroxy-2-methylpyrimidine

C_{HX} (10^2)	V (ml)	No.	(X^-) (10^2)	$[H^+]$ (10^4)	$[BH^+]$ (10^2)	$[IH^+]$ (10^5)	$[BH^+X^-]$ (10^2)	$[IH^+X^-]$ (10^5)	K_{BHX} (10^3)
1.196	2.40	1	0.0000	0.8004	1.17095	3.0737	0.0140	0.0000	
		2	1.1820	0.6118	0.89294	2.3495	0.2939	0.7242	
		3	0.9014	0.6049	0.88279	2.3229	0.3041	0.7508	
		4	0.8911	0.6047	0.88250	2.3223	0.3044	0.7514	
		5	0.8908	0.6047	0.88250	2.3223	0.3044	0.7514	2.913
1.409	2.90	1	0.0000	1.4192	1.4186	4.5665	−0.0284	0.000	
		2	1.4374	1.1006	1.0938	3.5414	0.2996	1.025	
		3	1.1084	1.0810	1.0739	3.4782	0.3197	1.088	
		4	1.0882	1.0800	1.0729	3.4750	0.3207	1.092	
		5	1.0872	1.0800	1.0729	3.4748	0.3207	1.092	3.265

The entire cycle, (1)—(4), is iterated until constant values of $[H^+]$ are obtained. Then, all the chemical species in the solution can be determined. As an example, Table II shows the results calculated at $V=2.40$(ml) and $V=2.90$(ml) on the titration curve of **1b**, respectively. After four times iterations, $[H^+]$ and the concentrations of all the chemical species reached the constant values. From the values determined, the K_{BHX} values were calculated to be 2.91×10^{-3} and 3.27×10^{-3}, respectively. It was found that the ion pair of the base existed in significant amounts and that both K_{BHX} values were in good agreement with the K_{IHX} value (3.11×10^{-3}). Such calculations at the other points on the titration curve gave similar results to those obtained at these two points: the K_{BHX} values almost agreed with the K_{IHX} value ($K_{BHX}=3.18\times10^{-3}$; $\sigma=0.27\times10^{-3}$; $n=14$). This result indicates that Assumption 2 holds more appropriately rather than Assumption 3. The titration curves of the other compounds were similarly analyzed by the above method. A similar result was also obtained. The K_{BHX} values of pyrimidine bases were approximately identical with the K_{IHX} value as shown in Table III.

TABLE III. Equilibrium Constants, $pK_{BH}^{n\text{-BuOH}}$, $\log K_B/K_{HX}^{\circ}$ and pK_{BHX} of 5-Substituted 4-Hydroxy-2-methylpyrimidine and Its Methyl Derivatives

Compound			$pK_{BH}^{n\text{-BuOH}}$ (Stand. Dev.)	$\log K_B/K_{HX}^{\circ}$	pK_{BHX} (Stand. Dev.)	pK_a[a]	ΔpK[b]
	H	**1a**	3.71(0.022)[c]	—	—	2.51	1.20
	CH_3	**1b**	4.26	6.76	2.50(0.04)	3.23	1.03
	OCH_3	**1c**	3.76	6.28	2.52(0.04)	2.58	1.18
	H	**2a**	4.97	7.48	2.52(0.06)	2.69	2.28
	CH_3	**2b**	5.67	8.30	2.63(0.12)	3.46	2.21
	OCH_3	**2c**	4.91	7.45	2.54(0.22)	2.79	2.12
	H	**3a**	3.68(0.037)[c]	—	—	2.74	0.94
	CH_3	**3b**	4.24	6.83	2.59(0.11)	3.42	0.82
	OCH_3	**3c**	3.68(0.049)[c]	—	—	2.72	0.96
	H	**4a**	4.10	6.59	2.49(0.05)	3.99	0.11
	CH_3	**4b**	4.69	7.07	2.37(0.14)	4.79	−0.10
	OCH_3	**4c**	4.40	7.01	2.62(0.06)	4.11	0.29

a) Ref. 11.
b) $\Delta pK = pK_{BH}^{n\text{-BuOH}} - pK_a$.
c) Estimated on the basis of the assumption: $K_{BHX}=K_{IHX}$.

The three compounds, **1a**, **3a** and **3c**, were not determinable satisfactorily from the plot by eq(23). The dissociation constant of ion pair of these compounds, K_{BHX}, will be closely equal to K_{IHX} by analogy with other pyrimidine bases. The deviation from the equivalence point, therefore, may be resulted from the term of $V_{eq}(1/V-1/V_{eq})$ in eq(23). In order to calculate properly this term, it was attempted to estimate the concentrations of all the species by a successive approximation procedure.

(1) As a first approximation, $[H^+]$ was calculated from eq(16), assuming $[BH^+X^-]=0$ and $[IH^+X^-]=0([X^-]=C_{HX})$.

(2) Estimation of $[BH^+X^-]$: when

$$K_{BHX} = K_{IHX} \tag{29}$$

is assumed, $[BH^+]$ can be calculated from eq(3), (5), (28) and (29).

$$[BH^+] = \frac{C_{HX} - ([IH^+]+[IH^+X^-]) - [H^+]}{1+\dfrac{[X^-]f^2}{K_{IHX}}} \tag{30}$$

Since $([BH^+]+[BH^+X^-])$ can be known from eq(28), $[BH^+X^-]$ can be calculated.

(3) Estimation of $[IH^+X^-]$: from eq(25) and (26), $[IH^+]$ can be calculated. From eq(12) and (26), $[IH^+X^-]$ can be calculated.

(4) From eq(27), a new $[X^-]$ is calculated, and f is also calculated from eq(10)($\mu=[X^-]$).

The entire cycle, (1)—(4), is iterated until constant values of $[H^+]$ are obtained. Then, all the chemical species in the solution can be determined. Table IV shows the results calculated at $V=0.32$(ml) and $V=0.85$(ml) for the titration of **1a**. After four times iterations, $[H^+]$ and the concentrations of all the species reached the constant values.

Table IV. Estimation of the $K_{BH}^{n\text{-BuOH}}$ Value of 4-Hydroxy-2-methylpyrimidine

C_{HX} (10^3)	V (ml)	No.	$[BH^+X^-]$ (10^3)	$[IH^+X^-]$ (10^5)	$[H^+]$ (10^4)	$[X^-]$ (10^3)	$[BH^+]$ (10^3)	$[IH^+]$ (10^5)	$K_{BH}^{n\text{-BuOH}}$ (10^4)
1.786	0.32	1	0.0000	0.0000	0.6853	1.786	1.3829	2.923	
		2	0.2990	0.6319	0.6971	1.481	1.4057	2.973	
		3	0.2750	0.5817	0.6961	1.505	1.4037	2.969	
		4	0.2771	0.5861	0.6962	1.503	1.4039	2.969	
		5	0.2769	0.5857	0.6962	1.503	1.4039	2.969	2.104
4.603	0.85	1	0.0000	0.0000	3.4817	4.603	3.1791	7.287	
		2	0.9804	2.2471	3.5337	3.600	3.2225	7.396	
		3	0.9318	2.1385	3.5303	3.650	3.2196	7.388	
		4	0.9350	2.1456	3.5306	3.647	3.2199	7.389	
		5	0.9347	2.1450	3.5305	3.647	3.2198	7.389	1.748

As shown in Table IV, $[H^+]$ in the solution increases with proceeding of titration and is not negligible on addition of a large volume of acid. Therefore, it is desirable that the term $(1/V-1/V_{eq})$ is converted into

$$\left(\frac{1}{V-([H^+]+[IH^+]+[IH^+X^-])\dfrac{V_0+V}{N}}-\frac{1}{V_{eq}}\right)$$

Thus, the equation of the photometric titration is obtained.

$$P=\frac{K_{IH}^{n\text{-BuOH}}}{K_{BH}^{n\text{-BuOH}}}V_{eq}\left(\frac{1}{V-([H^+]+[IH^+]+[IH^+X^-])\dfrac{V_0+V}{N}}-\frac{1}{V_{eq}}\right) \qquad (31)$$

where V_0 is the volume of the sample solution at $V=0$ and N is the normality of the titrant. Eq(31) means that plot of P against $1/(V-\Delta V)$ yields a straight line with a slope equal to $K_{IH}^{n\text{-BuOH}}V_{eq}/K_{BH}^{n\text{-BuOH}}$ and with an intercept on the abscissa equal to $1/V_{eq}$. Here,

$$\Delta V=([H^+]+[IH^+]+[IH^+X^-])\frac{V_0+V}{N} \qquad (32)$$

This plot was performed using $[H^+]$ and $([IH^+]+[IH^+X^-])$ estimated. As shown in Fig. 2, plot of P against $1/V$ (curve 1) did not give a correct value of the equivalent volume, but plot of P against $1/(V-\Delta V)$ (curve 2). The same plot as the above for the other samples, **3a** and **3c**, also gave satisfactory results, which were shown in Table I. Thus, it was clarified that the failure of the plot (P *vs.* $1/V$) was due to negligence of the significant amounts of $([H^+]+[IH^+]+[IH^+X^-])$.

From the calculated values of $[H^+]$, $[B]$ and $[BH^+]$, the $K_{BH}^{n\text{-BuOH}}$ values of **1a** were calculated (by eq(24)) to be 2.104×10^{-4} and 1.748×10^{-4} at $V=0.32$(ml) and $V=0.85$(ml), respectively. By the calculations at all the points on the titration curve, almost constant values were obtained.

The over-all dissociation constants of the compounds in n-BuOH(p$K_{\mathrm{BH}}^{n\text{-BuOH}}$) were compared with the pK_a values. It was found that the basicities of the compounds generally more increased in n-BuOH than those in aqueous solution. The results may be explained on the basis of less basicity of n-BuOH than water as suggested by Bell for increasing in basicity of various anilines and benzoate anions in MeOH or EtOH.[10] The basicity for a series of 1,2-dimethyl-4(1H)-pyrimidone is more increased than those for 2,3-dimethyl-4(3H)-pyrimidones and 4-methoxy-2-methylpyrimidines in n-BuOH. The phenomenon may be explained by difference in solvation for these compounds. In the case of 1,2-dimethyl-4(1H)-pyrimidones, protonation is performed at the ring N_3.[11] Solvation at the position by n-BuOH of a large molecule is more weakened than that by H_2O, because of steric hindrance by the neighboring groups, 2-methyl and 4-carbonyl group. Protonation at the position, therefore, may be facilitated in n-BuOH. In the case of 2,3-dimethyl-4(3H)-pyrimidones and 4-methoxy-2-methylpyrimidines, on the contrary, protonation is performed at the ring N_1,[11] which is not so hindered sterically as the ring N_3. There may be little difference in solvation at the ring N_1 between H_2O and n-BuOH. The effect of solvation on protonation may not vary exceedingly between both the solvents.

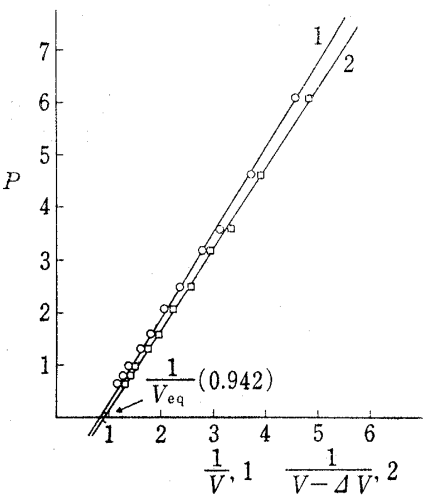


Fig. 2. Plot of P *vs.* $1/V$ (1) and Plot of P *vs.* $1/(V-\Delta V)$ (2) for 4-Hydroxy-2-methylpyrimidine

$(\Delta V=([H^+]+[IH^+]+[IH^+X^-])\ (Vo+V)/N)$
1: $P=-1.322+1.615\ 1/V;\ s=0.071;\ n=8$
2: $P=-1.407+1.548\ 1/(V-\Delta V);\ s=0.078;\ n=8$

Since 4-hydroxypyrimidines exist predominantly in the corresponding 4(3H)-pyrimidone form in n-BuOH, as discussed in the following paper of this series, the solvation effect on protonation also may not vary exceedingly between n-BuOH and H_2O (as well as the case of 2,3-dimethyl-4(3H)-pyrimidone).

Experimental

Apparatus——The apparatus for the photometric titration has already shown in our previous paper.[1] Twenty seven millimeter square and 52 mm height of titration vessel was used.

Materials——Preparation of 5-substituted 4-hydroxy-2-methylpyrimidine and its methyl derivatives and dehydration of the solvent (n-BuOH) were done by the same method as described in the previous paper.[5]

Determination of $K_{\mathrm{IH}}^{n\text{-BuOH}}$ and K_{IHK} of 4-Methyl-3-nitroaniline——The equilibrium constants, $K_{\mathrm{IH}}^{n\text{-BuOH}}$ and K_{IHX}, of 4-methyl-3-nitroaniline were determined by the method in the previous paper.[5] Both values were $3.013 \pm 0.370 \times 10^{-4}$ and $3.11 \pm 1.52 \times 10^{-3}$, respectively ($n=5$).

Procedure of the Photometric Titration——Titration was carried out according to the same technique as described in the previous paper.[1] An accurately weighed sample (10—50 mg) was dissolved in 16—37.5 ml of n-BuOH in the titration vessel. One milliliter of the solution of the indicator ($2.81 \times 10^{-3}-3.51 \times 10^{-3}$ M) was then added. The absorbance of the solution (A_{I}) was recorded at the maximum wavelength (370 nm). Then, 0.1 N $HClO_4$ was added and absorbances, A's, were recorded. The absorbance of the cation of the indicator (A_{IH}) was measured in 0.1 N $HClO_4$. On the titration of **2c**, the precipitates appeared before the end point. In this case, more dilute solution (1.56×10^{-3} M) was used (titrant; 0.01 N $HClO_4$).

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