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Equilibrium Studies of 5-Substituted 4-Hydroxy-2-methylpyrimidines. II.[1] Photometric Titration in Methanol[2]

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Photometric titration was performed in MeOH using nitroaniline derivatives as an indicator and fluorosulfuric acid as titrant. 5-Substituted 4-hydroxy-2-methylpyrimidine and its three methyl derivatives were used as samples. Most of the samples could be determined using this method. Some samples, 5-carbethoxy-4-hydroxy-2-methylpyrimidine (**1d**) and its three methyl derivatives (**2d**, **3d** and **4d**) could not be determined successfully because of the appearance of large errors. These results show that the method is undesirable for determination of a very weak base with basicity less than pK_a 2. A modification of the method was attempted in order to titrate such weaker base.

The dissociation constant (pK_{BH}) of the sample in MeOH was estimated from the slope of the straight line by Type II or the modified Type II plot. The basicity of the samples in MeOH generally increased by 10 to 100 times as compared with that in water. The degrees of the increase of the basicity were different among the compounds. Much larger increase of the basicity than the other compounds (about 100 times) was found for 5-substituted 1,2-dimethyl-4(1H)-pyrimidones.

Keywords——photometric titration in MeOH; Higuchi's Type II plot; 5-substituted 4-hydroxy-2-methylpyrimidines; dissociation constant of the pyrimidines; dissociation constant of the nitroanilines; fluorosulfuric acid titrant

Photometric titration method has commonly been used as a mean of the volumetric analysis in various types of titrations: redox titration, neutralization titration, *etc.* Since Higuch, *et al.*[4] applied this method to neutralization titration, it has more widely been used as a mean of not only volumetric analysis, but also dissociation constant determination. The photometric titration method which was named by them Type II plot was useful for detection of the end point and simultaneous evaluation of the equilibrium constant, K_{ex}, at the equilibrium

$$B + IH^+ \overset{K_{ex}}{\rightleftarrows} BH^+ + I \qquad (I)$$

where B and I mean the sample and the indicator, respectively. The equilibrium constant, K_{ex}, is defined as the expression

$$K_{ex} = \frac{[BH^+][I]}{[B][IH^+]} \qquad (1)$$

They have already confirmed the application of the Type II plot method in aqueous solution of high dielectric constant and glacial acetic acid of low dielectric constant.[5] The method, however, has not been applied to the titration in the solvent having a medium dielectric constant (D). Then, the photometric titration was attempted in MeOH(D=32.6) in view of its analytical usefulness.

1) Part I: T. Kitagawa, S. Mizukami, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **22**, 1239 (1974).
2) This work was presented at the 23rd Annual Meeting of the Japan Society for Analytical Chemistry, Osaka, Oct, 1974.
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); S.P. Friksen and K.A. Connors, *J. Pharm. Sci.*, **53**, 465 (1964).
5) K.A. Connors and T. Higuchi, *Anal. Chem.*, **32**, 93 (1960); T. Higuchi, C.H. Barnstein, H. Ghassemi, and W.E. Perez, *ibid.*, **34**, 400 (1962).

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Results and Discussion

Photometric titration was performed in anhydrous MeOH using 5-substituted 4-hydroxy-2-methylpyrimidines(R; H(**1a**), CH_3(**1b**), OCH_3(**1c**) and $COOC_2H_5$(**1d**)) and its methyl derivatives: 1,2-dimethyl-4(1H)-pyrimidones(R; H(**2a**), CH_3(**2b**), OCH_3(**2c**) and $COOC_2H_5$(**2d**)), 2,3-dimethyl-4(3H)-pyrimidones(R; H(**3a**), CH_3(**3b**), OCH_3(**3c**) and $COOC_2H_5$(**3d**)) and 4-methoxy-2-methylpyrimidines(R; H(**4a**), CH_3(**4b**), OCH_3(**4c**) and $COOC_2H_5$(**4d**)). Fluorosulfuric acid was used as titrant. This acid acts as a very strong acid.[6] Nitroaniline derivatives were chosen as indicators. Use of the nitroaniline derivatives was advantageous because the large difference in absorbance in visible region between the base (I) and its conjugate acid (IH^+) could facilitate the spectrometric determination.

The equation of Type II plot derived by Higuchi[4] is

$$\frac{[I]}{[IH^+]} = K_{ex}V_{eq}\left(\frac{1}{V} - \frac{1}{V_{eq}}\right) \qquad (2)$$

where V is the volume of the titrant added and V_{eq} is the volume equivalent to the sample. The quotient $[I]/[IH^+]$ in eq(2) was defined as P. The P values were calculated from the absorbance(A) of the titrating solution at a given wavelength.

$$P = \frac{[I]}{[IH^+]} = \frac{A - A_{IH}}{A_I - A} \qquad (3)$$

where A_I and A_{IH} are the absorbances at a given wavelength of the indicator and the conjugate acid, respectively. Plots of P against $1/V$ for **1a**, **2a**, **3a** and **4a** were shown in Fig. 1. Linear relationships were observed. The intercept on the abscissa of each straight line crossed at the equivalence point. The end point was determined from the regression equation of the straight line which was obtained by treatment of the least square method. The recoveries of **1a**, **2a**, **3a** and **4a** were shown in Table I. The same plots for the other 4-hydroxypyrimidine

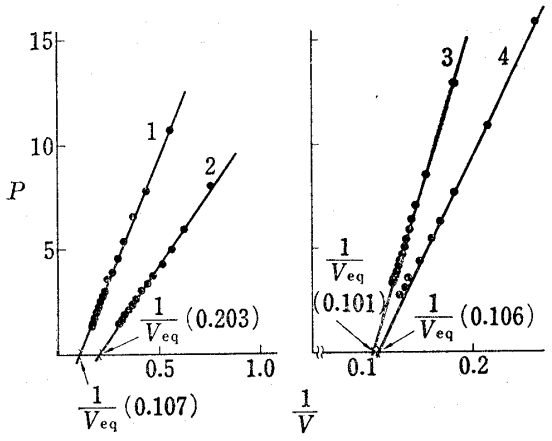

Fig. 1. Type II Plot in MeOH: 4-Hydroxy-2-methylpyrimidine (1), 2,3-Dimethyl-4(3H)-pyrimidone (2), 4-Methoxy-2-methylpyrimidine (3) and 1,2-Dimethyl-4(1H)-pyrimidone (4)

1: $P=-2.552+24.093\ 1/V$; $s=0.054$; $n=15$
2: $P=-2.744+13.943\ 1/V$; $s=0.102$; $n=13$
3: $P=-15.393+158.81\ 1/V$; $s=0.086$; $n=14$
4: $P=-10.335+99.139\ 1/V$; $s=0.033$; $n=6$

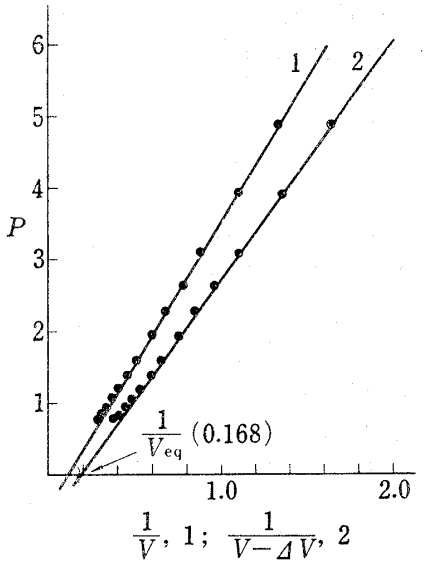

Fig. 2. Type II and Modified Type II Plots (1 and 2) in MeOH for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine

2: $P=-0.558+3.319\ 1/(V-\Delta V)$; $s=0.020$; $n=10$ ($\Delta V=[H^+](V+Vo)/N$)

6) R.C. Paul and S.S. Pahil, *Anal. Chim. Acta.*, **30**, 466 (1964).

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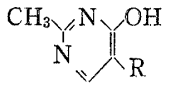
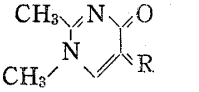
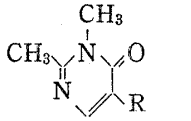
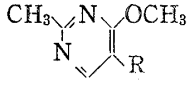
TABLE I. Photometric Titration Data of 5-Substituted 4-Hydroxy-2-methylpyrimidine and Its Methyl Derivatives in MeOH

Compound		Indicator[a]	Sample taken (mg)	0.1N $FSOH_3$ Calcd. (ml)	0.1N $FSOH_3$ Obsd. (ml)	Slope	Recov. (%)	log K_{ex}	pK_{BH} (MeOH)	pK_a (H_2O)	ΔpK[b]
	**1a** H	4MNA[d]	115.49	9.33	9.44	24.093	101.2	0.407	4.01	2.51	1.50
	1b CH_3	4MNA	89.32	6.43	6.54	58.893	101.7	0.954	4.55	3.23	1.32
	1c OCH_3	4MNA	80.60	5.12	5.15	15.636	100.6	0.482	4.08	2.58	1.50
	1d $COOC_2H_5$[c]	3NA[e]	117.02	5.96	5.95	3.319	99.8	−0.253	2.66	1.27	1.39
	**2a** H	4MNA	132.48	9.44	9.59	99.139	101.6	1.014	4.61	2.69	1.92
	2b CH_3	TB[f]	166.80	10.39	10.48	129.78	100.9	1.093	5.79	3.46	2.33
	2c OCH_3	4MNA	84.36	4.87	4.91	71.213	100.8	1.161	4.76	2.79	1.97
	2d $COOC_2H_5$[c]	3NA	107.24	5.23	5.10	14.339	97.5	0.449	3.36	1.50	1.86
	**3a** H	4MNA	68.66	4.92	5.08	13.943	103.3	0.438	4.04	2.74	1.30
	3b CH_3	4MNA	98.85	6.39	6.55	49.739	102.5	0.880	4.48	3.42	1.06
	3c OCH_3	4MNA	61.44	3.53	3.65	10.862	103.4	0.473	4.07	2.72	1.35
	3d $COOC_2H_5$[c]	3NA	56.64	2.76	2.79	1.331	101.1	−0.321	2.59	1.38	1.21
	**4a** H	4MNA	139.48	9.92	9.97	158.81	100.5	1.202	4.80	3.99	0.81
	4b CH_3	TB	173.29	10.79	10.94	174.03	101.4	1.202	5.90	4.79	1.11
	4c OCH_3	4MNA	176.96	10.13	10.15	277.86	100.2	1.437	5.04	4.11	0.93
	4d $COOC_2H_5$[c]	3NA	65.55	3.19	3.18	7.571	99.7	0.377	3.29	2.36	0.93

a) Concentration of the indicator in titration cell: 0.9×10^{-4}—1.3×10^{-4} M.
b) $\Delta pK = pK_{BH}$ (MeOH) − pK_a (H_2O).
The pK_a (H_2O) values of the pyrimidines were determined in the previous paper.[1]).
c) Analyzed by use of Modified Type II Plot.
d) 4MNA: 4-methy-3-nitroaniline.
e) 3NA: *m*-nitroaniline.
f) TB: thymol blue (concentration in titration cell: 3.7×10^{-6} M).
pK_{IH} (MeOH)=4.7; L.S. Guss and I.M. Kolthoff, *J. Am. Chem Soc.*, **62**, 249 (1940).

derivatives with substituents at 5-position (CH_3 and OCH_3) also gave straight lines with the intercept equal to the reciprocal of the equivalent volume. The recoveries for these compounds were also quantitative. These data were summarized in Table I. Type II plot method for these compounds was successful in MeOH. However, the results of the same plot for 5-carbethoxy-4-hydroxy-2-methylpyrimidine (**1d**) and its methyl derivatives (**2d**, **3d** and **4d**) were different from those obtained for the above compounds. For example, the intercept of the straight line for **1d** did not cross in the vicinity of the equivalence point and the recovery was about 130% as shown in Fig. 2. A similar behavior was also found for **2d**, **3d** and **4d**. Recoveries for these compounds were widely exceeding over 100%. Thus, the treatment by Type II plot method failed for the weaker bases having a strong electron-withdrawing substituent.

In eq(2), the existence of the dissociated H^+ from the conjugate acid, BH^+, of the sample base has been neglected. Such an assumption seemed to be appropriate for the relatively strong bases, **1a**, **1b**, **1c** and their methyl derivatives. In the case of very weak bases containing strong electron-withdrawing substituent, such as **1d**, **2d**, **3d** and **4d**, however, the existence of the dissociated H^+ from the conjugate acid may not be negligible. In this case electroneutrality rule is

$$[X^-] = [H^+] + [BH^+] + [IH^+] \quad (4)$$

where X^- is the anion of the titrant acid. Since the concentration of the indicator was negligible as compared with that of the sample, eq(4) becomes

$$[X^-] = [H^+] + [BH^+] \quad (5)$$

The total concentrations of the titrant acid and the sample base are respectively expressed as

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$$C_{HX} = [X^-] \tag{6}$$

$$C_B = [B] + [BH^+] \tag{7}$$

Introducing eq(5), (6) and (7) into eq(1) yields

$$P = \frac{[I]}{[IH^+]} = K_{ex}\frac{C_B-(C_{HX}-[H^+])}{C_{HX}-[H^+]} \tag{8}$$

Eq(8) is converted into eq(9) using the volume of the titrant added, V.

$$P = K_{ex}V_{eq}\left(\frac{1}{V-[H^+]\frac{V_0+V}{N}}-\frac{1}{V_{eq}}\right) \tag{9}$$

where V_0 is the volume of sample solution at $V=0$ and N is the normality of the titrant. Eq(9) suggests that plot of P against $1/\{V-[H^+](V_0+V)/N\}$ falls on a straight line with an intercept on the abscissa corresponding to $1/V_{eq}$ and with a slope being equal to K_{ex} V_{eq}: the same type of plot as Type II.

Hydrogen ion concentration in the titrating solution can be estimated from eq(10).

$$IH^+ \overset{K_{IH}}{\rightleftarrows} H^+ + I \tag{II}$$

$$K_{IH} = \frac{[H^+][I]f_H}{[IH^+]f_{IH}} \tag{10}$$

where K_{IH} is the dissociation constant of the indicator. According to Kolthoff,[7] activity coefficient is written

$$f_H = f_{IH} \tag{11}$$

From eq(3), (10) and (11),

$$\frac{1}{P} = \frac{1}{K_{IH}}[H^+] \tag{12}$$

If K_{IH} value is known, $[H^+]$ can be estimated using the observed P value. Therefore, it is possible to plot P *vs.*

$$\frac{1}{V-[H^+]\frac{V_0+V}{N}}.$$

The K_{IH} values in MeOH for indicators, nitroaniline derivatives, were estimated elsewhere. When a strong acid is added to the solution of the indicator, an equilibrium (II) will form. In this case electroneutrality rule is

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

The concentration, $[IH^+]$, may be calculated using the P value (eq(3)) and the total concentration of the indicator (C_I).

$$[IH^+] = \frac{C_I}{1+P} \tag{14}$$

From eq(6), (13) and (14), $[H^+]$ in the solution was calculated.

$$[H^+] = C_{HX} - \frac{C_I}{1+P} \tag{15}$$

Plot of $1/P$ (eq(12)) against $[H^+]$ fell on a straight line. Table II shows the result of the plot. According to eq(12), the slope of the straight line corresponds to $1/K_{IH}$.

The K_{IH} value of *p*-nitroaniline was obtained by the following method. Since the amount of the acid enough to make this indicator completely change into the conjugate acid

7) 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).

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TABLE II. pK_{IH} (MeOH) Values of Nitroanilines

Nitroanilines	C_I (10^5)	Wave length (nm)	$S^{a)}$	$r^{b)}$	n	pK_{IH} (MeOH)
p-Nitroaniline	8.464	371	0.006	0.9986	14	1.32±0.02[c]
m-Nitroaniline	9.242	375	0.047	0.9992	15	2.91±0.10
4-Methyl-3-nitroaniline	9.170	368	0.063	0.9991	14	3.60±0.12
5-Nitronaphthylamine	9.518	400	0.032	0.9996	10	3.78±0.01

a) Standard deviation.
b) Correlation coefficient.
c) Range calculated from 95% confidence interval.

form was unknown, the K_{IH} value was estimated using the following equation which was derived from eq(3) and (12):

$$A = A_{IH} + K_{IH}\frac{A_I - A}{[H^+]} \qquad (16)$$

Plot of A against $(A_I - A)/[H^+]$ yielded a straight line with an intercept corresponding to A_{IH} and the slope being equal to K_{IH}.

Titration data of **1d** were analyzed according to eq(9). Plot of P against $1/\{V-[H^+](V_0+V)/N\}$ was found to be linear and the intercept of the straight line agreed with $1/V_{eq}$, as shown in Fig. 2. The base was recovered in quantity of 99.8%. The recoveries for the other weaker bases, **2d**, **3d** and **4d**, were also satisfactory by the plots of eq(9), as shown in Table I. The K_{ex} values were calculated from the straight line by dividing its slope by newly observed V_{eq}. It was shown that such photometric titration was applicable to the quantitative analysis of the bases and simultaneously to the way of K_{ex} determination. The constant, K_{ex}, is expressed by the ratio of the dissociation constant, K_{IH} for indicator base to K_{BH} for sample base, from eq(1). Since K_{IH} has already been determined (Table II), K_{BH} values of the titrated compounds were calculated, which were shown in Table I.

The dissociation constants of these compounds in MeOH were compared with pK_a values.[1] It was found that the basicities of the compounds generally more increased in MeOH than those in aqueous solution. The degrees of the increase are different among the compounds, ranging from 0.8 to 2.3 pK unit.[8] The basicity for a series of 1,2-dimethyl-4(1H)-pyrimidones is more increased than those for 4-hydroxy-2-methylpyrimidines, 2,3-dimethyl-4(3H)-pyrimidones and 4-methoxy-2-methylpyrimidines in MeOH. Protonation of 1,2-dimethyl-4(1H)-pyrimidones is performed at the ring N_3, while 2,3-dimethyl-4(3H)-pyrimidones and 4-methoxy-2-methylpyrimidines at the ring N_1.[1] Since 4-hydroxy-2-methylpyrimidines exist predominantly in the corresponding 4(3H)-pyrimidone form in MeOH, as discussed in the following paper of this series, the protonation site is also the ring N_1. Such difference of enhancement in basicity may be dependent on the site of protonation.

Experimental

Apparatus——Titrations were carried out using the photometric titrator set up by the combination of a Hitachi EPU-2A spectrophotometer with a Hitachi titrimetric attachment (Photoelectric Titration). To minimize errors on the determination of the titrant volume and absorbance, the apparatus was improved.

8) Since the pK_{BH} values of **2b** and **4b** could not be determined by use of 4-methyl-3-nitroaniline as an indicator, thymol blue was used instead. The pK_{IH} value of thymol blue could not be measured by the above method because of its strong basicity. Thus, we used the value which Kolthoff, *et al.*[9] determined using a different method from ours as such. The difference in the pK_{BH} values which was apparently observed between the two indicators, the nitroaniline and thymol blue may be due to the difference of the method.

9) See footnote *f* in Table I.

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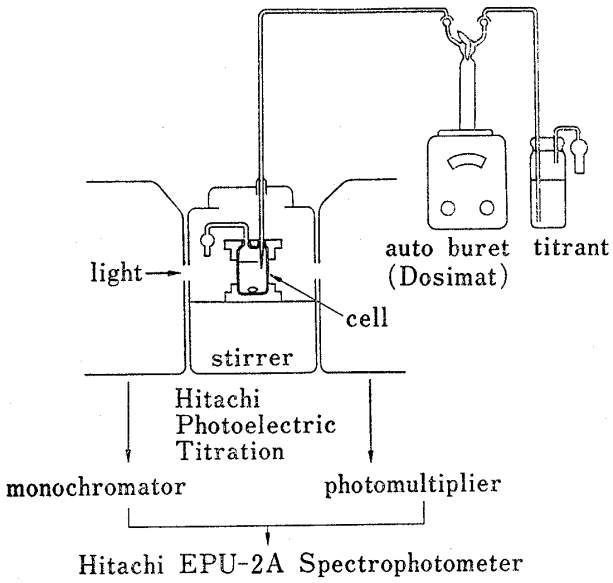

Chart 1

Buret was substituted for Metrohm Dosimat. Instead of the round cell (beaker), a cubic cell (40 mm square and 55 mm in height) was used. The cell was held in the cell-holder. The shape of the holder was fitted to that of the cell. The holder was inlaid on the bottom of the cell-compartment of the titrator. The outline of the apparatus are shown in Chart 1.

Reagents——Methanol was distilled after refluxing with metal magnesium ribbon. Water content of the distillate by Karl Fischer titration was within the range of 0.013 to 0.018%. Fluorosulfuric acid (FSO_3H) used as titrant was synthesized by the method of Paul, *et al.*[10] The titrant was standardized in MeOH using diphenylguanidine as standard material and methyl yellow as an indicator. 5-Substituted 4-hydroxy-2-methylpyrimidine and its methyl derivatives were synthesized in the previous paper.[1] Commercial nitroaniline derivatives were purified by recrystallization.

Procedure——An accurately weighed sample (50—170 mg) was dissolved in 60 ml of MeOH in the cell. One ml of the indicator solution (nitroanilines: 5—8×10^{-3} M; thymol blue: 2.24×10^{-4} M) was then added. Absorbance of the indicator (A_I) was recorded at the maximum wavelength, then 0.1 N FSO_3H was added until the change of the absorbance reached more than 0.02. Absorbances were recorded following the addition of the titrant. As titration approached the end point, the absorbance decreased and reached almost constant value despite new further addition. Then, titration was stopped. On the other hand, 1 ml of the indicator solution was added to 60 ml of 0.1 N FSO_3H. Absorbance (A_{IH}) was determined. Observed absorbances were corrected to eliminate the dilution effect according to Underwood's method.[11]

The dissociation constants of the nitroanilines were measured using the above procedure without sample. To the nitroaniline solution was added 0.1—0.5 N FSO_3H.

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10) R.C Paul, S.K. Vasisht, K.C. Malhotra, and S.S. Pahil, *Anal. Chem.*, 34, 820 (1962).
11) A.L. Underwood, "Advances in Analytical Chemistry and Instrumentation, "Vol. 3, ed. by C.N. Reilley, John Wiley and Sons, Inc., New York, 1964, pp. 31—104.

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