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Equilibrium Studies of 5-Substituted 4-Hydroxy-2-methylpyrimidines. VI.[1] Ethereal Solvents Effect on the Lactim-Lactam Tautomerism

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The lactim form, I, one of the tautomers of 5-carbethoxy-4-hydroxy-2-methylpyrimidine (1), in *n*-hexane was changed into the lactam form, IIb (4(3H)-pyrimidone) on addition of the ethereal solvents (ethyl ether, *n*-propyl ether, isopropyl ether, *n*-butyl ether and *p*-dioxane). The lactam form, IIb, increased with increasing the concentration of the ether in *n*-hexane. The following association equilibria were examined.

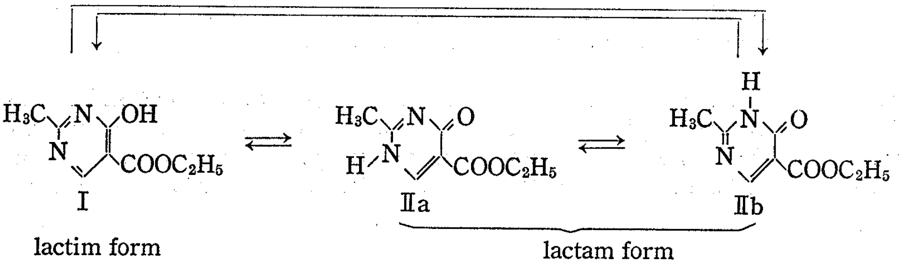
$$\mathrm{I} + S \rightleftharpoons \text{associated lactim form (I')}$$
$$\mathrm{IIb} + S \rightleftharpoons \text{associated lactam form (IIb')}$$

S: ether

The over-all association constant which was defined as K_0 ($K_0=([\mathrm{I}]+[\mathrm{IIb}])[S]/([\mathrm{I'}]+[\mathrm{IIb'}])$) was estimated. The K_0 values increased in that order: *p*-dioxane <isopropyl ether< ethyl ether<*n*-propyl ether<*n*-butyl ether.

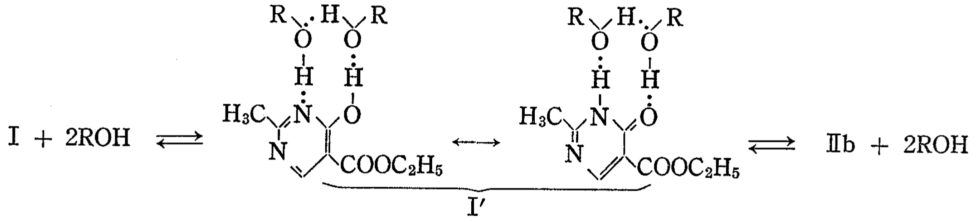
Keywords——5-carbethoxy-4-hydroxy-2-methylpyrimidine; lactim-lactam tautomerism; UV-spectrophotometry; *n*-hexane; association equilibria with ethers

The lactim-lactam tautomerism of 5-carbethoxy-4-hydroxy-2-methylpyrimidine (**1**) is shown as



(Equil. I)

In the previous paper,[3] the effect of alcohols (MeOH and *n*-BuOH) on the tautomerism was examined. It was found that the addition of such a hydrogen-donor solvent into *n*-hexane solution of **1** yielded the equilibria as shown



(Equil. II)

When ethers are added to the solution in exchange for alcohols, a new effect may be brought about into the lactim-lactam tautomerism of **1** in *n*-hexane because of the hydrogen accept-

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[1] Part V: T. Kitagawa, K. Matsumoto, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), 26, 1415 (1978).

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[3] T. Kitagawa, S. Mizukami, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), 26, 1403 (1978).

ing property of ethers. In the present paper, a solvent effect on the tautomerism was examined using some ethers: ethyl ether, *n*-propyl ether, isopropyl ether, *n*-butyl ether and *p*-dioxane.

Results and Discussion

An effect of ethyl ether on the ultraviolet (UV) spectrum of **1** in *n*-hexane was shown in Fig. 1. A series of spectra passed through an isosbestic point, 282.6 nm. A decrease of a 270 nm band and an appearance of a new band at 305 nm were brought with adding ethyl ether. These bands at 270 nm and 305 nm correspond to those of the lactim form (I) and the lactam form (IIb), respectively.[3] A similar phenomenon was observed with adding other various ethers to the solution of **1** in *n*-hexane. Hence, it seems that ethers affect on the lactim-lactam tautomerism. Such an effect of ethers was also found for methyl 2-hydroxynicotinate (**2**) in *n*-hexane. Compound **2** will form a similar lactim-lactam tautomerism to that of **1**. In order to analyze the spectral change, equilibria were assumed as follows:

$$\begin{tikzcd}
\underset{\mathrm{I}}{\text{lactim form} + S} \arrow[rr, shift left, "K_1"] \arrow[d, shift left] & & \underset{\mathrm{I}'}{\text{associated lactim form}} \arrow[ll, shift left, "\text{(Equil. III)}"] \arrow[d, shift left] \\
\underset{\mathrm{II}}{\text{lactam form} + S} \arrow[rr, shift left, "K_2"] \arrow[u, shift left, "K_\mathrm{t}\ \text{(Equil. VI)}"] & & \underset{\mathrm{II}'}{\text{associated lactam form}} \arrow[ll, shift left, "\text{(Equil. V)}"] \arrow[u, shift left, "K_\mathrm{t}'\ \text{(Equil. IV)}"']
\end{tikzcd}$$

Here, we assumed associated forms, I′ and II′, as intermediates which were formed by association of ethers to **1** and **2**. The ether was expressed as S. The equilibrium constants in equilibria, III, IV, V and VI are defined as K_1, K_t', K_2 and K_t, respectively. The constants are expressed by eq(1), (2) (3) and (4), respectively.

$$K_1 = \frac{[\mathrm{I}']}{[\mathrm{I}][S]} \tag{1}$$

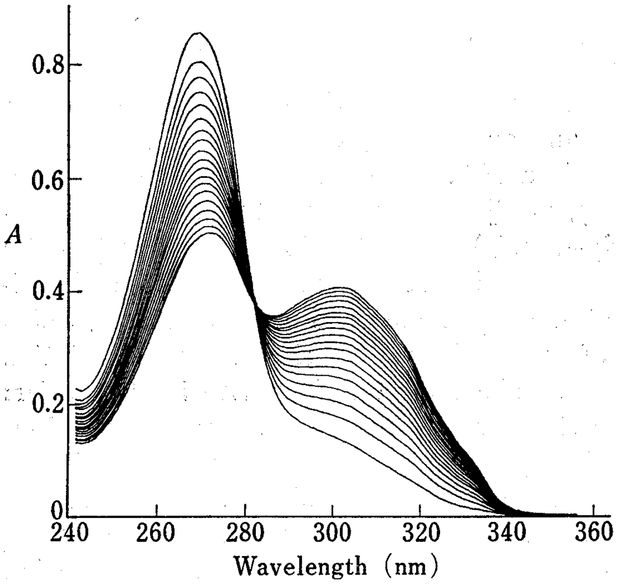

Fig. 1. Spectral Change on Addition of Ethyl Ether for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in *n*-Hexane

concentration of ethyl ether: 0.128—1.53 M.

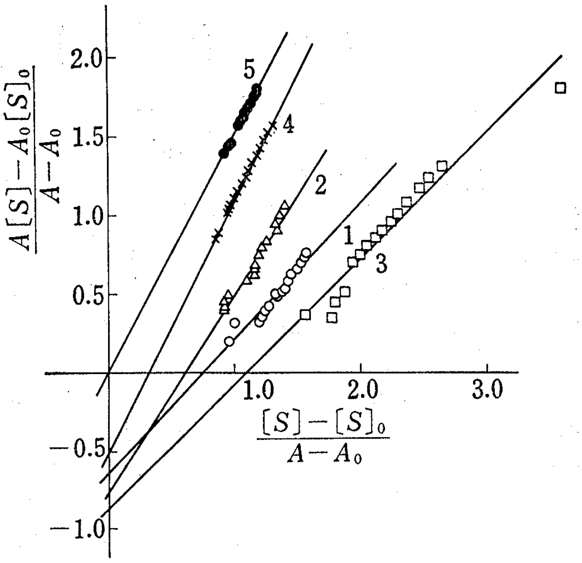

Fig. 2. Plot of $(A[S]-A_0[S]_0)/(A-A_0)$ against $([S]-[S]_0)/(A-A_0)$ for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine

(1) *p*-dioxane; (2) isopropyl ether; (3) ethyl ether; (4) *n*-propyl ether (+0.50); (5) *n*-butyl ether (+1.00).

$$K_t' = \frac{[\mathrm{II}']}{[\mathrm{I}']} \tag{2}$$

$$K_2 = \frac{[\mathrm{II}']}{[\mathrm{II}][\mathrm{S}]} \tag{3}$$

$$K_t = \frac{[\mathrm{II}]}{[\mathrm{I}]} \tag{4}$$

The over-all association constant, K_0, is defined as

$$K_0 = \frac{([\mathrm{I}]+[\mathrm{II}])[S]}{[\mathrm{I}']+[\mathrm{II}']} \tag{5}$$

The ratio of the concentration of the lactam form to that of the lactim form observed on the spectra is defined as R. Assuming that the spectra of both associated forms, I′ and II′, are approximately identical with those of I and II, respectively, R is expressed by

$$R = \frac{[\mathrm{II}]+[\mathrm{II}']}{[\mathrm{I}]+[\mathrm{I}']} = \frac{\varepsilon-\varepsilon_{\mathrm{I}}}{\varepsilon_{\mathrm{II}}-\varepsilon} \tag{6}$$

where ε_{I} and $\varepsilon_{\mathrm{II}}$ are the molar extinction coefficients at a given wavelength of the lactim and the lactam form, respectively, and ε is the coefficient at the same wavelength apparently observed for the test solution. As a total concentration of **1** is constant through all measurements of UV spectra, $(\varepsilon-\varepsilon_{\mathrm{I}})/(\varepsilon_{\mathrm{II}}-\varepsilon)$ is converted into $(A-A_{\mathrm{I}})/(A_{\mathrm{II}}-A)$ using the absorbances at the same wavelength.

In order to estimate the K_0 value, a method was deviced. By use of eq(1), (2), (3) and (5), eq(6) is converted into

$$\frac{A-A_{\mathrm{I}}}{A_{\mathrm{II}}-A} = \frac{\{K_0(K_1+K_1K_t')-1\}+K_1K_t'[S]}{1+K_1[S]} \tag{7}$$

One spectrum which is measured in the solution containing a given amount of the ether is chosen. When the A value in this spectrum is expressed as A_0 and the ether content as $[S]_0$, eq(7) is

$$\frac{A_0-A_{\mathrm{I}}}{A_{\mathrm{II}}-A_0} = \frac{\{K_0(K_1+K_1K_t')-1\}+K_1K_t'[S]_0}{1+K_1[S]_0} \tag{8}$$

Combining eq(8) with eq(7) yields

$$\frac{A[S]-A_0[S]_0}{A-A_0} = \left(\frac{A_{\mathrm{II}}K_t'+A_{\mathrm{I}}}{1+K_t'}\right)\frac{[S]-[S]_0}{A-A_0} - K_0 \tag{9}$$

Eq (9) means that plot of $(A[S]-A_0[S]_0)/(A-A_0)$ against $([S]-[S]_0)/(A-A_0)$ yields a straight line with a slope equal to $(A_{\mathrm{II}}K_t'+A_{\mathrm{I}})/(1+K_t')$ and an intercept equal to $-K_0$.

This plot was attempted using the spectral data of **1**. The concentration of the ether ($[S]$) was much larger than that of the sample (C_{S}), so $[S]$ can be replaced by the total concentration of the ether, C_{E}. Fig. 2 shows plots of $(A[S]-A_0[S]_0)/(A-A_0)$ against $([S]-[S]_0)/(A-A_0)$ for **1**. The plot for **2** was also attempted. The spectral data observed by addition of *p*-dioxane were used.[4] The regression lines were obtained by the method of least-squares, which were shown in Table I. From the intercepts of the straight lines, the over-all association constants, K_0's, for various ethers were estimated. The K_0 values increased in that order: *p*-dioxane<isopropyl ether<ethyl ether<*n*-propyl ether<*n*-butyl ether. In the previous paper,[1] it was found that the tautomerism of **1** in *p*-dioxane was different from those in the other ethereal solvents: the compound in *p*-dioxane existed predominantly in the lactam form, but in other ethers the lactim form existed to a considerable extent. It was found that the predominance of the lactam form in *p*-dioxane was due to the strongest association of the lactim form with the solvent.

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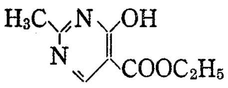
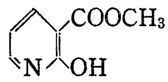
4) Since the other ethers did not alter the tautomerism significantly, no analysis was done for any solvent but *p*-dioxane.

TABLE I. Results of the Plot of $(A[S]-A_0[S]_0)/(A-A_0)$ against $([S]-[S]_0)/(A-A_0)$ for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine and Methyl 2-Hydroxynicotinate

Compound	Solvent	Slope	Intercept($=-K_0$)	$r^{a)}$	n	K_t'	K_1
	*p*-Dioxane	$0.863\pm0.125^{b)}$	$-0.644\pm0.168^{b)}$	0.9695	16	8.0	0.17
	Isopropyl ether	1.262 ± 0.150	-0.763 ± 0.177	0.9833	15	5.3	0.21
	Ethyl ether	0.796 ± 0.120	-0.872 ± 0.249	0.9722	16	5.2	0.18
	n-Propyl ether	1.618 ± 0.020	-1.012 ± 0.021	0.9998	16	60	0.016
	n-Butyl ether	1.536 ± 0.037	-1.014 ± 0.040	0.9993	13	24	0.039
	*p*-Dioxane	2.586 ± 0.158	-1.023 ± 0.074	0.9967	11	88	0.011

a) Correlation coefficient.
b) 95% confidence interval.

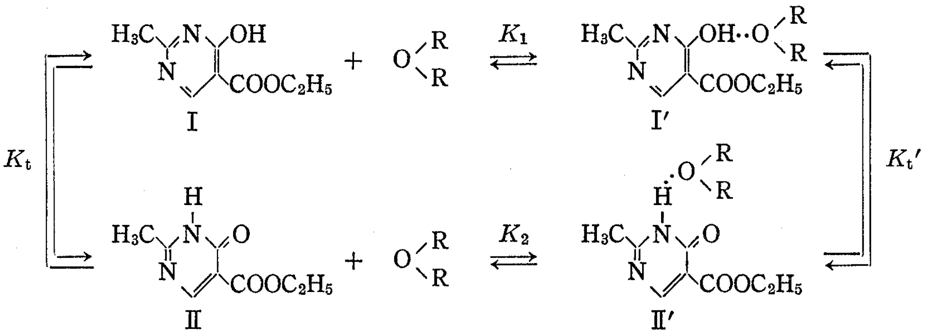
The absorbance of **1** and **2** in *n*-hexane may be regarded as A_{I}, because the compounds exist almost completely in the lactim form.[3] The absorbance of the solution containing a small amount of MeOH (0.7%(v/v) for **1** and 2% (v/v) for **2**) may be used as A_{II}, because the compounds exist almost completely in the lactam form.[3] Hence, K_t' was calculated from the slope. The tautomeric equilibrium constant, K_t', was found to be much larger than 1. The result shows that the amount of I′ is very little as compared with that of II′.

From eq(1), (2), (4) and (5), K_1 is expressed

$$K_1=\frac{1+K_t}{K_0(1+K_t')} \tag{10}$$

Since K_t is much smaller than 1, K_1 is calculated using K_0 and K_t'. The equilibrium constants, K_t' and K_1, are shown in Table I.

The mechanism of the tautomerism of **1** can be shown as the following scheme.



The lactim form associates with one molecule of ether. Associated lactim form, I′, is formed, which is changed into more stable associated form, II′.

Experimental

Materials——*n*-Hexane and the ethers were purified by the same method as described previously.[1,3] 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (**1**) and methyl 2-hydroxynicotinate (**2**) were prepared in the same manner as described in the previous paper.[3,5]

Determination of K_0 of 1 and 2——The UV spectra of **1** and **2** were measured in *n*-hexane using 100 mm cell (C_S: 1.2×10^{-5}—3.5×10^{-5} M). The ether (50—400 μl) was added to the *n*-hexane solution. The spectra were consecutively recorded in various amounts of the ether (C_E: 0.03—1.5 M). From the spectra of **1** and **2**, the absorbances at 303 nm and 335 nm were respectively read. Since the total volume was changed by

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5) T. Kitagawa, S. Mizukami, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **22**, 1239 (1974).

the addition of the ether, the observed A values were corrected to give the absorbance at the initial volume, that is

$$A_{\text{corrected}} = A_{\text{observed}} \frac{V_0 + V}{V_0}$$

where V_0 and V are the initial volume of the n-hexane solution and the volume of the ether added, respectively.

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