Hydrogen Bond of 4-Amino-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one Derivatives with Alcohols. I. Experimental Considerations

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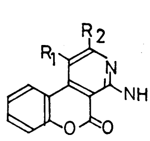
The hydrogen bond between 4-amino-5*H*-[1]benzopyrano[3,4-*c*]-pyridin-5-one (benzopyranopyridine) derivatives including their related compounds (pyridine, aniline, and coumarin) and alcohols (methanol and ethanol) is discussed experimentally in detail. The formation of a hydrogen bond between the nitrogen atom of the benzopyranopyridine ring and the hydroxyl group of methanol was investigated by IR spectral measurements. The equilibrium constants for the formation of hydrogen-bonded 1:1 complexes were determined from the UV spectral data. The enthalpy changes accompanying complex formation were obtained from a knowledge of the temperature dependence of the equilibrium constants. The values of the enthalpy changes range approximately from 4.5 to 5.2 kcal/mol in the benzopyranopyridine–ethanol systems. It may be concluded that the hydrogen bond of the benzopyranopyridine–ethanol system occurs mainly at the nitrogen atom of benzopyranopyridine ring, because the thermodynamic properties for hydrogen bond formation between benzopyranopyridine and ethanol showed a striking resemblance to those of the pyridine–ethanol system. In addition, the presence of an intramolecular hydrogen bond between the amino and carbonyl groups of benzopyranopyridine derivatives was confirmed by means of IR spectra.

The hydrogen bond of organic compounds has been studied by many workers in recent years.[1] However, the hydrogen bond of 4-amino-5*H*-[1]benzopyrano-[3,4-*c*]pyridin-5-one (benzopyranopyridine) derivatives has not been investigated except in the benzopyranopyridine derivative–acetic acid systems.[2] In this paper the hydrogen bond between the benzopyranopyridine derivatives and alcohols was investigated in detail by means of IR and UV spectra. The spectra for the systems of the related compounds of benzopyranopyridine derivatives (pyridine, aniline, and coumarin) and alcohols were also measured. Some discussions were made of the hydrogen bond by comparing the IR and UV spectra of the benzopyranopyridine–alcohol systems with those of the related compound–alcohol systems.

Experimental

Six benzopyranopyridine derivatives **1**—**6** (Fig. 1) were prepared by the methods described by Sakurai *et al.*[3]



1	R_1= CH_3	R_2=H
2	R_1= n-C_5H_{11}	R_2=H
3	R_1= n-C_9H_{19}	R_2=H
4	R_1= H	R_2=CH_3
5	R_1= H	R_2=n-C_5H_{11}
6	R_1= H	R_2=n-C_9H_{19}

Fig. 1. Benzopyranopyridine derivatives; 4-amino-1-methyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**1**), 4-amino-1-*n*-pentyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**2**), 4-amino-1-*n*-nonyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**3**), 4-amino-2-methyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**4**), 4-amino-2-*n*-pentyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**5**), and 4-amino-2-*n*-nonyl-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (**6**).

These compounds were purified by recrystallization from ethanol several times and then by sublimation *in vacuo* at *ca.* 230 °C. Pyridine was refluxed over barium oxide and distilled. Aniline was dried over potassium hydroxide for a long time, and then fractionated under reduced pressure. Coumarin was recrystallized from ethanol and ligroin several times. The purifications of methanol, ethanol, carbon tetrachloride, and isooctane (2,2,4-trimethylpentane) were done in the usual ways.[4]

The IR and UV spectra were measured using the Hitachi Model 215 infrared spectrophotometer and Hitachi Model 323 spectrophotometer, respectively. All the infrared absorption measurements were carried out at room temperature in carbon tetrachloride solution. All the UV absorption spectra were measured in isooctane solution. The temperature of the UV absorption cells was regulated by use of the Komatsu-Yamato Model CTR-120 electronic cooling circulator within the temperature range between 10 and 50 °C.

Results and Discussion

The compounds **1** and **4** which have the simplest structure among the benzopyranopyridine derivatives synthesized by Sakurai *et al.*[3] are soluble only in carbon tetrachloride (6×10^{-3} mol/l) and isooctane (4×10^{-5} mol/l) at room temperature. However, **2**, **3**, **5**, and **6** have higher solubility in these solvents than **1** and **4** at room temperature. Consequently, the IR and UV spectra of these compounds were measured more easily than those of **1** and **4**. On the basis of these data of **1**—**6** the intermolecular interaction between the benzopyranopyridine derivatives and alcohols was investigated in the non-polar solvents.

First, the formation of an intramolecular hydrogen bond by the benzopyranopyridine derivative was studied by the IR spectral measurement in CCl_4 solution. The asymmetric (ν_{as}) and symmetric (ν_s) stretching frequencies for the NH_2 group of a primary amine can be expressed by the following empirical equation:[5]

$$\nu_s = 345.5 + 0.876\nu_{as}, \tag{1}$$

where ν_s is attributed to the lower frequency and ν_{as}

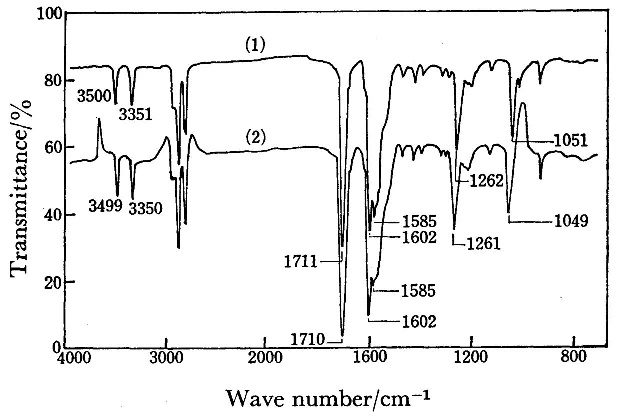


Fig. 2. IR spectra of **6** (1) and the **6**–methanol system (2) in carbon tetrachloride solution. Concentration of **6**: 1.2×10^{-2} mol/l. Concentration of methanol: 9.9×10^{-2} mol/l.

to the higher one. As is shown in Fig. 2, the two bands of the amino group of **6** appear at 3500 and 3351 cm^{-1}. The value of ν_s calculated using Eq. 1 with the value of ν_{as} (3500 cm^{-1}) became 3412 cm^{-1}. This value is higher than the observed value (3351 cm^{-1}). A similar example has been seen for the NH_2 group of *o*-nitroaniline[6] in chloroform. In the case of the *o*-nitroaniline, the corresponding bands appear at 3510 and 3380 cm^{-1}. The observed value (3380 cm^{-1}) for the symmetric frequency is lower than the calculated value (3420 cm^{-1}). This discrepancy in the two values of *o*-nitroaniline may be attributed to an intramolecular hydrogen bond between the NH_2 and NO_2 groups. On the analogy of *o*-nitroaniline, the discrepancy between the calculated and observed frequency values of **6** would be due to the formation of an intramolecular hydrogen bond between the NH_2 and C=O groups. The formation of the intramolecular hydrogen bond of benzopyranopyridine derivative is further confirmed by the following experimental results:

(1) The IR absorption bands of the NH_2 and C=O groups of **6** were measured in concentration from 2.1×10^{-3} to 4.3×10^{-1} mol/l, but there was no variation in the frequencies of these bands.

(2) The C=O stretching vibration of **6** appeared at 1711 cm^{-1} (Fig. 2), while the C=O bands of coumarin appeared at 1757 and 1742 cm^{-1} (Fig. 5). The decrease in the C=O frequency of **6** may be attributed to an intramolecular hydrogen bond.

Another consideration of this intramolecular hydrogen bond will be given in a subsequent paper[7] in further detail.

Benzopyranopyridine has four positions (the ring nitrogen atom, the oxygen atoms of carbonyl group and coumarin ring, and the hydrogen atom of amino group) for the hydrogen bond formation with alcohol. Therefore, there are four kinds of 1 : 1 hydrogen-bonded complexes in the benzopyranopyridine–methanol system. The IR spectral techniques were employed to determin which hydrogen-bonded complex is predominant among the four complexes. The IR spectrum of the **6**–methanol system is presented in Fig. 2. The position of the IR absorption bands corresponding to the NH_2 and C=O groups, and that of the absorption bands of each type (1262, 1051 cm^{-1}) shifted to the lower frequency side by about 1—2 cm^{-1}, and the intensity of these absorption bands did not change, compared with the IR spectrum of **6**. Nevertheless, the absorption band at 1585 cm^{-1} corresponding to the stretching vibration of the benzopyranopyridine ring disappeared, while a new shoulder was observed at 1590 cm^{-1} (Fig. 3) after an addition of methanol. In the IR spectra of the systems of each compound from **1** to **5** and of methanol a similar new shoulder was observed near 1590 cm^{-1}. Furthermore, when ethanol was used in the place of methanol, the new shoulder band was observed near 1590 cm^{-1}. This result indicates that there is no difference between the two alcohols with respect to the hydrogen bond with benzopyranopyridine.

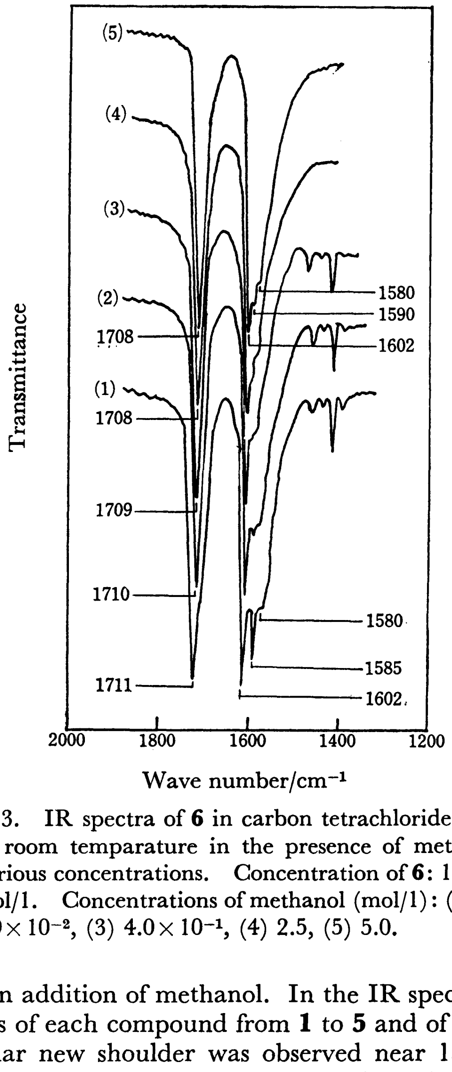


Fig. 3. IR spectra of **6** in carbon tetrachloride solution at room temparature in the presence of methanol of various concentrations. Concentration of **6**: 1.2×10^{-2} mol/l. Concentrations of methanol (mol/l): (1) 0, (2) 9.9×10^{-2}, (3) 4.0×10^{-1}, (4) 2.5, (5) 5.0.

The IR spectra of the pyridine–methanol system were measured and compared with those of the benzopyranopyridine–methanol system. The spectra of this system are shown in Fig. 4. The two absorption peaks corresponding to the stretching vibration of the pyridine ring at 1597 and 1577 cm^{-1} disappeared with an increase of methanol concentration, while a new peaks appeared at 1590 cm^{-1}. The present results of the pyridine–methanol system are compatible with those reported by Takahashi *et al.*[8] (Fig. 4). In high concentrations of methanol, the two absorption bands of the NH_2 group of **6** could not be observed owing to the

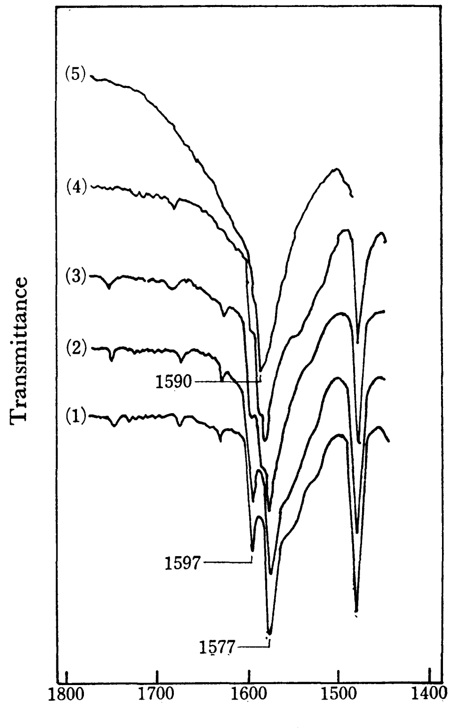


Fig. 4. IR spectra of pyridine in carbon tetrachloride solution at room temperature in the presence of methanol of various concentrations. Concentration of pyridine: 1.3×10^{-1} mol/l. Concentrations of methanol (mol/l): (1) 0, (2) 9.9×10^{-2}, (3) 2.5×10^{-1}, (4) 4.5×10^{-1}, (5) 5.0.

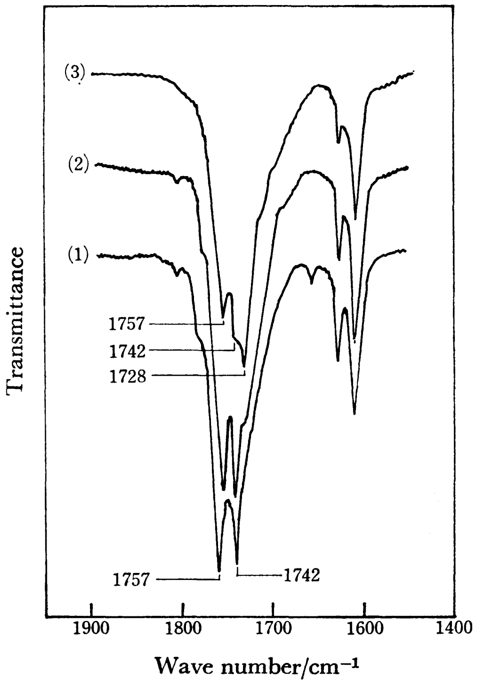
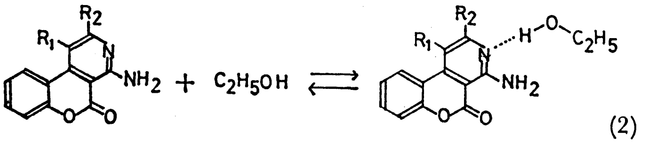


Fig. 5. IR spectra of coumarin in carbon tetrachloride solution at room temperaure in the presence of methanol of various concentrations. Concentration of coumarin: 2.0×10^{-2} mol/l. Concentrations of methanol (mol/l): (1) 0, (2) 8.7×10^{-1}, (3) 3.5.

overlap of an intense absorption band of the OH group of the alcohol. However, the absorption bands of this amino group were observed in the concentration range of 0 to 3×10^{-1} mol/l. The corresponding bands of the amino group shifted to the lower frequency side with increasing methanol concentration. But this spectral shift was smaller than that of the amino group for the aniline–methanol system. It is thought that the hydrogen-bonded species formed between the amino group of benzopyranopyridine and the hydroxyl group of alcohol is negligibly small in concentration.

The C=O absorption bands of coumarin were observed at 1757 and 1742 cm^{-1}, as shown in Fig. 5. When methanol was added to the coumarin system, a new band appeared at 1728 cm^{-1}. This band may be due to the formation of a hydrogen bond between the C=O group of coumarin and the OH group of methanol. However, in the case of the benzopyranopyridine derivative–methanol system the C=O absorption band of **6** at 1711 cm^{-1} shifts by 3 cm^{-1} (Fig. 3). This spectral shift is very small compared with that of the coumarin–methanol system. Therefore, the C=O group of benzopyranopyridine is weaker than that of coumarin in hydrogen bonding ability. Another example is found in the salicylaldehyde–*n*-butyl alcohol system. The C=O stretching vibration of salicylaldehyde appears at 1668 cm^{-1} in CCl_4 solution and 1667 cm^{-1} in *n*-butyl alcohol solution.[9] Its C=O stretching frequency changes only by 1 cm^{-1} in *n*-butyl alcohol solution. The reason may be attributed to the intramolecular hydrogen bond of the C=O group. With increasing concentration of methanol, the absorption band at 1051 cm^{-1} of **6**, which may be assigned to the ether type absorption, was hidden by the intense absorption band of the OH group of alcohol, while the absorption band at 1261 cm^{-1} corresponding to the ether type of **6** was not so effected by an addition of methanol. This result suggests that the hydrogen-bonded complex formed at the oxygen atom of the coumarin ring may be negligible. From the above experimental results, it may be concluded that the hydrogen-bonded species formed at the nitrogen atom of the benzopyranopyridine ring is the most predominant among the four hydrogen-bonded ones.

The equilibrium constant (K), enthalpy changes ($-\Delta H$), and entropy changes ($-\Delta S$) were obtained by means of the UV spectroscopic method, as given below. As is partly shown in Figs. 6 and 7, remarkable changes are produced in the UV spectra of **3** and **6** by the addition of ethanol to the isooctane solution. It may safely be assumed that these spectral changes are due to the formation of a hydrogen-bonded species between the benzopyranopyridine derivatives and alcohols. In this case the hydrogen bond is represented by the following equilibrium:



(2)

where benzopyranopyridine derivative acts as a proton acceptor and ethanol as a proton donor. No considera-

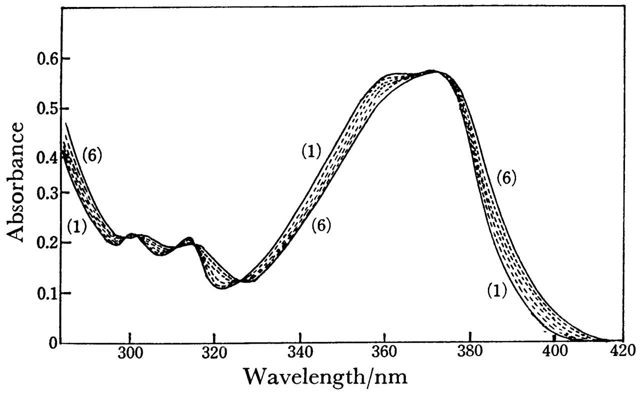


Fig. 6. UV spectra of **3** in isooctane solution at 25.0 °C in the presence of ethanol of various concentrations. Concentration of **3**: 6×10^{-5} mol/l. Concentrations of ethanol (mol/l): (1) 0, (2) 7.0×10^{-2}, (3) 1.0×10^{-1}, (4) 5.0×10^{-1}, (5) 1.0, (6) 2.0.

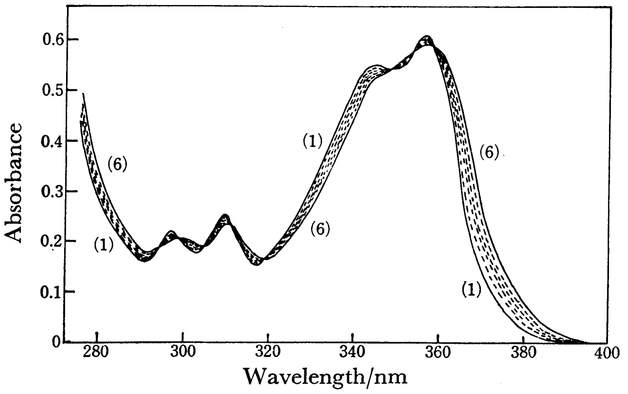


Fig. 7. UV spectra of **6** in isooctane solution at 27.0 °C in the presence of ethanol of various concentrations. Concentration of **6**: 5.3×10^{-5} mol/l. Concentrations of ethanol (mol/l): (1) 0, (2) 7.0×10^{-2}, (3) 1.0×10^{-1}, (4) 5.0×10^{-1}, (5) 1.0, (6) 2.0.

tion is given here to the hydrogen-bonded form in which one benzopyranopyridine is associated with two or more ethanols, because several clear isosbestic points are observed from the UV spectra. The **1**–ethanol and **2**–ethanol systems showed a remarkable resemblance to the **3**–ethanol system in spectral behavior. However, the spectral changes of the **4**–ethanol and **5**–ethanol systems were similar to that of the **6**–ethanol system.

The equilibrium constants K of the hydrogen bonding reactions were obtained by the use of

$$1/(\varepsilon-\varepsilon_f) = [1/\{K(\varepsilon_b-\varepsilon_f)\}](1/C) + [1/(\varepsilon_b-\varepsilon_f)],^{10)} \qquad (3)$$

where ε_f is the molar absorption coefficient of the non-hydrogen-bonded or free solute species, and ε_b is that of the hydrogen-bonded species. ε is the molar absorption coefficient observed for a solution in which the initial concentration of ethanol is C. All these absorption coefficients refer to a given wavelength.

The enthalpy changes ($-\Delta H$) accompanying hydrogen-bond formation can be obtained from a knowledge of the variation of K with temperature, according to the well known-equation,

$$-\Delta H = R[\mathrm{d}\ln K/\mathrm{d}(1/T)]. \qquad (4)$$

In the present experiment the values of K were determined for each system at five points of temperature within the range from 10 to 50 °C. The free energy changes ΔG were calculated by

$$\Delta G = -RT\ln K. \qquad (5)$$

The entropy changes were obtained from

$$\Delta G = \Delta H - T\Delta S. \qquad (6)$$

TABLE 1. THERMODYNAMIC PROPERTIES OF HYDROGEN-BOND FORMATION IN BENZOPYRANOPYRIDINE DERIVATIVE–ETHANOL SYSTEMS (1 cal=4.184 J)

Compd	$K^{a)}$ / $\mathrm{l\ mol^{-1}}$	$-\Delta H$ / $\mathrm{kcal\ mol^{-1}}$	$-\Delta S$ / $\mathrm{cal\ K^{-1}\ mol^{-1}}$
1	2.90	4.6	13.3
2	3.05	4.5	12.9
3	3.00	4.7	13.6
4	3.35	5.0	14.4
5	4.05	5.2	14.7
6	3.25	5.0	14.4
Pyridine	1.60	4.2	13.2
Aniline	0.35	2.1	9.2
Coumarin	1.01	3.8	12.7

a) The values were interpolated at 25.0 °C.

The values of K, $-\Delta H$, and $-\Delta S$ for the systems of benzopyranopyridine derivatives, pyridine, aniline, and coumarin with ethanol are given in Table 1. From Table 1 it is found that the $-\Delta H$ values are *ca.* 4.6 kcal/mol for the 1-alkyl derivative–ethanol systems, and *ca.* 5.1 kcal/mol for the 2-alkyl derivative–ethanol systems. The values of K, $-\Delta H$, and $-\Delta S$ of 2-alkyl derivative–ethanol systems are slightly larger than those of 1-alkyl derivative–ethanol systems. The nitrogen atom of 2-alkyl derivatives is activated by the nearest-neighbour alkyl group which is situated at the

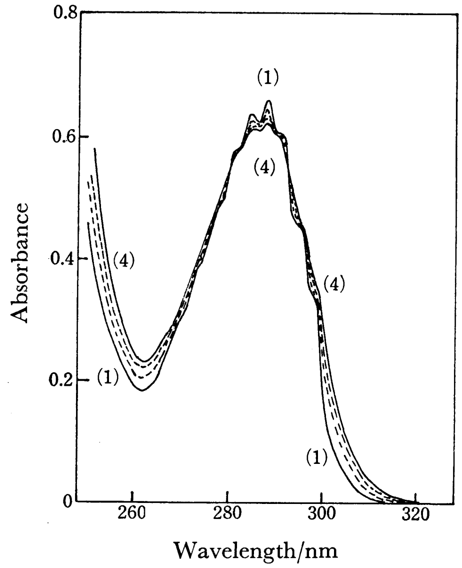
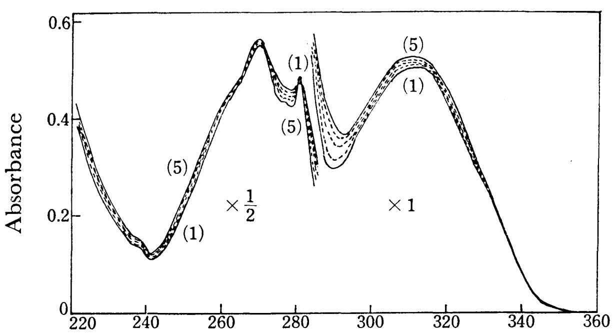


Fig. 8. UV spectra of aniline in isooctane solution at 24.8 °C in the presence of ethanol of various concentrations Concentration of aniline: 2.3×10^{-4} mol/l. Concentrations of ethanol (mol/l): (1) 0, (2) 1.0×10^{-1}, (3) 5.0×10^{-1}, (4) 2.0.

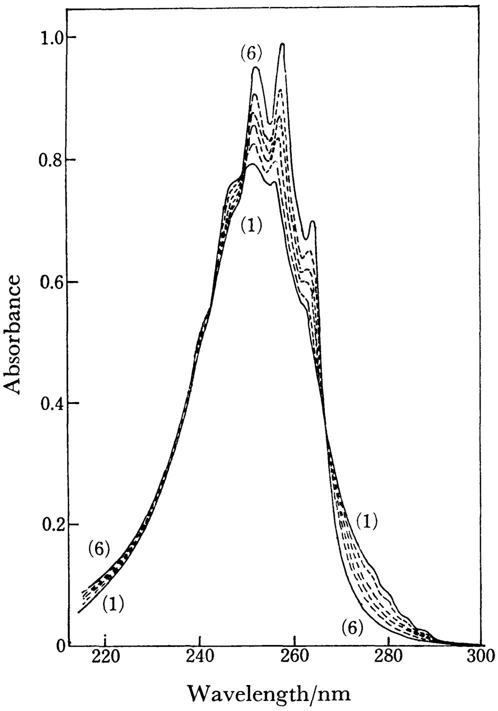


Wavelength/nm

Fig. 9. UV spectra of coumarin in isooctane solution at 28.0 °C in the presence of ethanol of various concentrations. Concentration of coumarin: 2.3×10^{-4} mol/l. Concentrations of ethanol (mol/l): (1) 0, (2) 1.0×10^{-1}, (3) 3.0×10^{-1}, (4) 5.0×10^{-1}, (5) 1.0.

α-position with respect to the ring nitrogen atom, but the 1-alkyl group which is substituted at the β-position cannot activate the ring nitrogen atom.

The UV spectral change of the aniline–ethanol system was not so large when ethanol was added in a fairly large amount (Fig. 8). The $-\Delta H$ of this system is smaller than that of benzopyranopyridine derivative–ethanol system. This result indicates that the hydrogen-bonded complex formed between the amino group of benzopyranopyridine and ethanol is not so important. The UV spectra for the coumarin–ethanol system is shown in Fig. 9. The value of $-\Delta H$ for the coumarin–ethanol system is 3.8 kcal/mol. This value indicates that the carbonyl group of coumarin has a fairly strong hydrogen bonding ability. However, in the case of benzopyranopyridine the hydrogen bonding ability of its carbonyl group is not so strong as that of the carbonyl group of coumarin, because the carbonyl group of benzopyranopyridine is already occupied by an intramolecular hydrogen bond.



Wavelength/nm

Fig. 10. UV spectra of pyridine in isooctane solution at 19.2 °C in the presence of ethanol of various concentrations. Concentration of pyridine: 4.4×10^{-4} mol/l. Concentrations of ethanol (mol/l): (1) 0, (2) 7.0×10^{-2}, (3) 2.0×10^{-1}, (4) 5.0×10^{-1}, (5) 1.0, (6) 2.0.

The UV spectral data of the pyridine–ethanol system is presented in Fig. 10. As is listed in Table 1, the values of K, $-\Delta H$, and $-\Delta S$ for the pyridine–ethanol system obtained by this study are 1.60 l/mol, 4.2 kcal/mol, and 13.2 kcal/(K mol), respectively. These values are in fair agreement with the K (2.31 l/mol), $-\Delta H$ (4.4 kcal/mol), and $-\Delta S$ (11.7 cal/(K mol))[11] for the pyridine–methanol system obtained by the IR spectral experiment. It is to be noted that these values of the pyridine–ethanol system are approximately equal to those of the benzopyranopyridine–ethanol system, although the values of K and $-\Delta H$ for the benzopyranopyridine–ethanol system are slightly larger than those of the pyridine–ethanol system. This is because the nitrogen atom of the benzopyranopyridine ring is activated by the adjacent alkyl and amino groups. In addition, as the π-conjugation of the benzopyranopyridine molecule is larger than that of the pyridine molecule, the hydrogen bond makes the benzopyranopyridine–ethanol system more stable than the pyridine–ethanol system.

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