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Solid Complexes of Theophylline with Several Aliphatic Monoamines

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The formation of solid complexes of theophylline with 16 aliphatic monoamines was attempted from aqueous and absolute ethyl alcohol solutions. Theophylline forms solid complexes with methylamine, ethylamine, *n*-propylamine, monoethanolamine, *n*-propanolamine, and isopropanolamine, in a molar ratio of 1:1. The solid complex of methylamine contains one molecule of water of crystallization. The ability to form solid complexes was considered to be related to the pK_a value, type, and hydrophobic property of the amine. The thermal and physico-chemical properties of these solid complexes were investigated by differential thermogravimetry, differential scanning calorimetry, X-ray powder diffractometry, and infrared spectroscopy. It was found that the thermal stabilities of the solid complexes of amines with a hydroxyl group are higher than those of amines without a hydroxyl group; however, the incremental thermal stabilities of the complexes of amines without a hydroxyl group are higher than those of amines with a hydroxyl group upon formation of the solid complex. The heats of reaction for formation of the solid complexes of theophylline with monoamines and the activation energies of deamination reactions of the solid complexes were determined and are discussed.

Keywords——solid complex formation; theophylline; aliphatic monoamine; thermal behavior of solid complex; heat of reaction; activation energy

A solid complex of theophylline with ethylenediamine, called aminophylline, is a drug described in the Japanese Pharmacopeia and is effective for controlling the symptoms of bronchial asthma and other complaints. In connection with aminophylline, the authors have previously reported some solid complexes of theophylline with ethylenediamine analogs.[1] On the other hand, little work has been done on complexes of theophylline with aliphatic monoamines. It seemed useful in order to clarify the driving forces of solid complex formation and to obtain fundamental data on theophylline complexes to determine what structures of amines are suitable for solid complex formation or can yield thermally stable complexes. Solid complex formation of theophylline with 16 monoamines was attempted. The physico-chemical properties of 6 complexes obtained were studied by using X-ray diffraction, thermal analysis, infrared spectroscopy(IR), *etc.* The results are described in the present paper.

Experimental

Materials——Theophylline, special grade, was recrystallized from water and converted to the anhydrous form at 80°C (about 2 h). Theophylline monohydrate was prepared by keeping theophylline in a desiccator saturated with water vapor after recrystallization from water. Monoamines of the highest purity among those available from Nakarai Chemicals Co. Ltd. (Kyoto) were purchased. Methylamine (40% aqueous solution) and ethylamine (70% aqueous solution) were used without further purification. Other amines were purified by distillation under reduced pressure in a stream of nitrogen and kept in a desiccator containing sodium hydroxide. Distilled water was employed throughout these experiments. All other reagents were of special grade.

Formation of Solid Complexes——a) Complexation from Absolute Ethanol: Theophylline and a monoamine were reacted in a molar ratio of 1: 2. The experimental conditions were the same for all the monoamines. For example, 2.04 g (0.0334 mol) of monoethanolamine was dissolved in 25.0 ml of absolute ethanol and then 3.0 g (0.0167 mol) of theophylline was added in portions to the solution with vigorous stirring. After 3 h, the precipitate was filtered off, washed with cold ethanol, and dried in a refrigerator to a constant weight. Prior to use, the product was kept in a refrigerator (4°C—5°C).

b) Complexation from Aqueous Solution: Preliminary experiments revealed that theophylline forms solid complexes with monoamines in a molar ratio of 1: 1. Consequently, theophylline was reacted with monoamines in a molar ratio of 1: 1. The experimental conditions were the same for all the monoamines. For example, 3.0 g (0.0167 mol) of theophylline and 1.02 g (0.0167 mol) of monoethanolamine were dissolved together in about 15 ml of water. The vessel containing the solution was loosely stoppered to permit evaporation of the solvent and kept in the refrigerator until most of the solvent had evaporated. The resulting crystals were kept in the refrigerator until their weight became constant. The crystals were stored in a container in the refrigerator prior to use.

Determination of Each Component in a Solid Complex——Sample of each solid complex was dissolved in acetate buffer (pH 5.0) and ultraviolet spectrophotometry was carried out at 272 nm to determine theophylline. Monoamines were determined by titration with a standardized solution of HCl using BPB as an indicator. Water of crystallization was determined by the method of Karl Fisher and by differential thermogravimetric analysis (DTA-TG), as reported previously.[1]

Thermal Analysis——DTA-TG was carried out in air, the temperature being elevated at the rate of 2.5°C/min. A standard type differential scanning calorimeter produced by Rigaku Denki Co. Ltd. was used to measure the amount of heat. An aluminum cell was used as a sample container and a heating rate of 2.5°C/min was adopted. Heat of vaporization of monoamine was measured in nitrogen gas using the liquid sample cell, which was loosely sealed. For the calculation of the amount of heat, the heat of transition of potassium nitrate, 1.29 kcal/mol (128°C) was employed as a standard.

X-Ray Diffraction (Powder Method)——The apparatus and the procedures were the same as those reported in the previous paper.[1]

IR——The apparatus and the procedures were the same as those reported in the previous paper.[2]

Results and Discussion

Solid Complex Formation

Theophylline and each monoamine were reacted by the two methods described in "Experimental" and we examined whether or not a solid complex was formed. Solid complex formation was confirmed by disappearance of the X-ray diffraction pattern of theophylline and the appearance of a new X-ray diffraction pattern. As an example, X-ray diffraction patterns of the case of monoethanolamine (which formed a solid complex) are shown in Fig. 1. The compositions of solid complexes were estimated based on the amounts of theophylline, monoamine, and water of crystallization determined by the methods described in "Experimental." Whether or not the solid complex between theophylline and an aliphatic monoamine was formed and, if it was formed, the composition are summarized in Table I. The solid complexes of *n*-propylamine and monoethanolamine were formed by both methods. According to the X-ray diffraction patterns and results of DTA–TG, the solid complex obtained from aqueous solution was identical with that obtained from absolute ethanol in each case. In the cases of *n*-propanolamine and isopropanolamine, however, the solid complexes were exclusively obtained from aqueous solution.

As methylamine and ethylamine are available only as aqueous solutions, the solid complex formations of these amines from absolute ethanol were not tried. However, the solid complexes of these amines are presumed to be formed from absolute ethanol, because the solid complexes obtained from aqueous solution could stand for 1 h in absolute ethanol without any change. On the other hand, the solid complexes of *n*-propanolamine and isopropanolamine decomposed to theophylline and monoamine on the same treatment. The molar ratio of

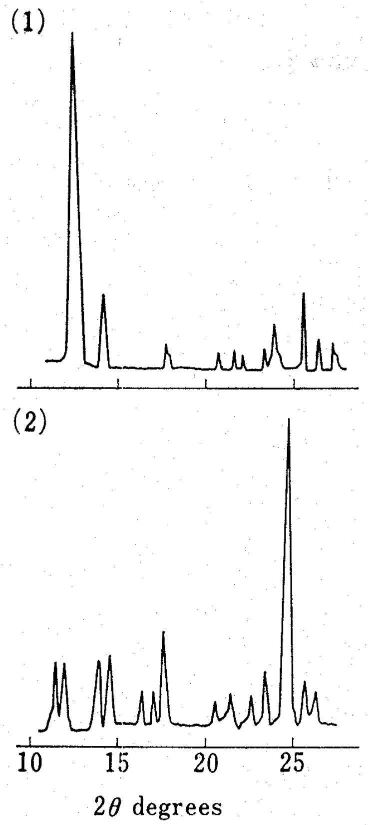

Fig. 1. X-Ray Powder Diffraction Patterns of Anhydrous Theophylline (1) and the Complex of Theophylline with Monoethanolamine (2)

Table I. Abilities of Monoamines to form Solid Complexes with Theophylline (TP), and Compositions of the Solid Complexes

Monoamine	pK_a[a] (25°C)	Composition	
		Solvent: ethanol	Solvent: water
Methylamine (M)	10.62	[b]	$TP \cdot M \cdot H_2O$
Ethylamine (E)	10.63	[b]	$TP \cdot E$
Diethylamine	10.77	—	—
Triethylamine	9.80	—	—
n-Butylamine	10.60	—	—
tert-Butylamine	10.45	—	—
n-Propylamine (P)	10.53	$TP \cdot P$	$TP \cdot P$
Isopropylamine	10.63	—	—
Cyclohexylamine	10.64	—	—
Allylamine	9.69	—	—
2-Methoxyethylamine	9.45	—	—
Monoethanolamine (ME)	9.50	$TP \cdot ME$	$TP \cdot ME$
Diethanolamine	8.88	—	—
Triethanolamine	7.76	—	—
n-Propanolamine (PA)	9.96	—	$TP \cdot PA$
Isopropanolamine (iPA)	9.43	—	$TP \cdot iPA$

a) From reference (3).
b) Experiment not carried out (see text).

theophylline and monoamine was 1:1 without exception for the complexes thus obtained. The solid complex between theophylline and methylamine included one molecule of water of crystallization. Amines other than the above did not form solid complexes. The results shown in Table I reveal that, with respect to the ability to form a solid complex, monoamines are inferior to the diamines studied previously.[1] It is considered that the pK_a value of the monoamine is an important factor in solid complex formation. However, the experimental results can not be explained in terms of pK_a values alone. The effect of hydrogen bonding due to the hydroxyl group of monoethanolamine seems to contribute to the formation of a solid complex between theophylline and monoethanolamine. Neither diethanolamine nor triethanolamine forms a solid complex with theophylline from either solvent. For these results, the following two possible explanations can be offered. (1) The pK_a values of both amines are smaller than that of monoethanolamine. (2) For these amines, self-association may occur preferentially. The latter is suggested by the fact that the boiling points of these amines are much higher than that of monoethanolamine. Neither *n*-propanolamine nor isopropanolamine formed a solid complex with theophylline when absolute ethanol was used as a solvent. It is likely that the amines having a hydroxyl group are more easily bound to ethanol than to theophylline.

It may be concluded that the proportion of hydrophobic groups in the monoamine molecule as well as the type of monoamine may be related to the ability to form a solid complex with theophylline. In other words, a primary monoamine with a small proportion of hydrophobic groups seems most likely to form a solid complex with theophylline.

Thermal Decompositions of Solid Complexes

The thermal decompositions of the solid complexes were monitored by DTA–TG and

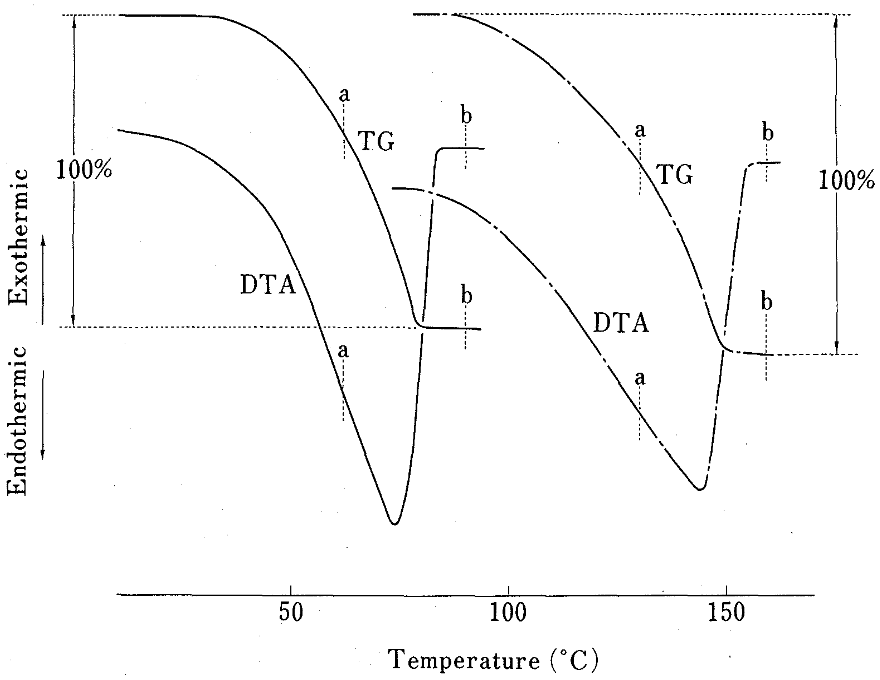

Fig. 2. DTA–TG Curves of Complexes of Theophylline with Methylamine (——) and Monoethanolamine (-—-)

Amount of sample: complex of methylamine 11.62 mg: complex of monoethanolamine 15.00 mg.
Sensitivity: 100 μV.

by X-ray analysis. Fig. 2 shows the results of DTA–TG for the solid complexes of methylamine and monoethanolamine as examples. Each solid complex starts to decrease in weight accompanying the thermal change; the weight loss and the thermal change finish at point b in Fig. 2. The X-ray patterns of the samples collected at point b coincide with the pattern of anhydrous theophylline shown in Fig. 1-(1). The samples collected in the middle of the decomposition, at point a in Fig. 2, gave the X-ray patterns of the initial material, the solid complex, and anhydrous theophylline. Consequently, the solid complex of methylamine always eliminates methylamine and water of crystallization in a molar ratio of 1: 1. On the other hand, the solid complex of monoethanolamine eliminates monoethanolamine to form anhydrous theophylline. DTA–TG curves obtained from other solid complexes involving the other amines are almost the same as those mentioned above. These results suggest that the solid complexes release either amine or both amine and water of crystallization, with an endothermic peak, apparently due to an elementary reaction, and produce anhydrous theophylline.

As there was no evidence of melting when the deamination reaction was observed microscopically and no exothermic peak on the DTA–TG curves, the eliminations of amine and water of crystallization from the solid complex appear to occur with slight modification, but not destruction, of the crystal lattice of the solid complex to leave anhydrous theophylline.

IR Spectra

In IR spectra of the solid complexes, the absorption bands of $\rangle C=O$[4] at positions 2 and 6 of theophylline shifted to lower frequencies compared with those of theophylline alone and the characteristic absorption bands for $-NH_3^+$[4] appeared coupled with disappearance of absorption bands of $-NH_2$ of amine. These observations suggest that, as reported previously[5] for aminophylline, a proton migrated from $\rangle N-H$ of theophylline to $-NH_2$ of the monoamine and the resulting $-NH_3^+$ formed specific hydrogen bonds both to $\rangle C=O$ at position 6 and to $\rangle N^-$ of theophylline. The absorption bands of $\rangle C=O$ at position 2 in theophylline shifted considerably to lower frequency when theophylline formed a solid complex (Table II). Although

Table II. ν_{CO} Absorption Bands (cm^{-1}) in the IR Spectra of Theophylline and Its Complexes (Nujol Mulls)

	Theophylline	Complex of methylamine	Complex of ethylamine	Complex of *n*-propylamine	Complex of monoethanolamine	Complex of *n*-propanolamine	Complex of isopropanolamine
$\nu_{C_2=O}$	1722	1673	1680	1679	1683	1686	1678
$\nu_{C_6=O}$	1673	1635	1625	1636	1635	1633	1634

no role has been assigned to >C=O at position 2, this >C=O is considered to contribute to the solid complex formation through hydrogen bonding with one of the hydrogen atoms of $-NH_3^+$, which does not take part in the specific hydrogen bonds mentioned above. In addition, taking into account that only primary amines form the solid complexes, the bonding mode shown in Chart 1 may be presumed in the solid state. A similar bonding mode was reported previously for a complex of tioxacin on the basis of IR spectra.[6]

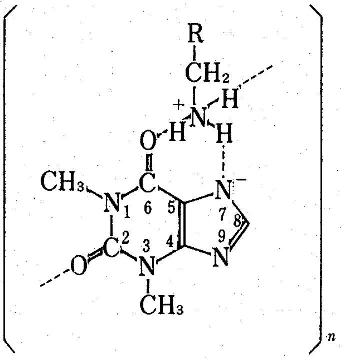

Chart 2

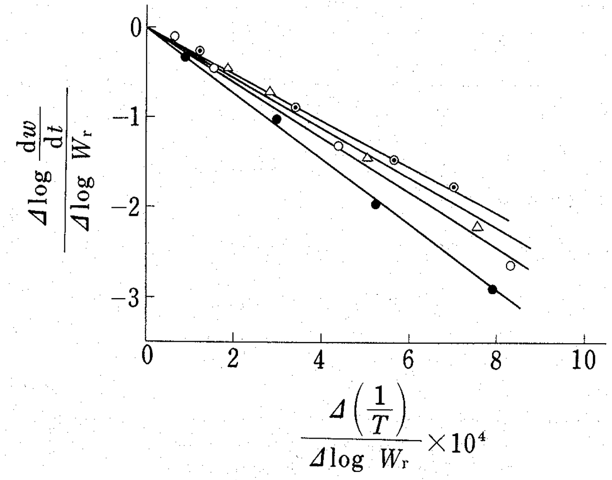

Fig. 3. Kinetics of Deamination of the Solid Complexes

—○—: complex of methylamine.
—●—: complex of *n*-propanolamine.
—⊙—: complex of *n*-propylamine.
—△—: complex of monoethanolamine.

Activation Energies and Orders of Reaction of Deamination Reactions of Solid Complexes

The activation energies and orders of reaction in the deamination of the solid complexes were determined from the TG curves according to Freeman and Carrol.[7]

Products is volatile, *i.e.*,

A(solid) —— B(solid) + C(gas)

Eq. 1 is considered to be valid:

$$-\frac{E}{2.3R}\cdot\frac{\varDelta\left(\frac{1}{T}\right)}{\varDelta\log W_r}=-n+\frac{\varDelta\log\frac{dw}{dt}}{\varDelta\log W_r} \qquad (1)$$

E: activation energy
R: gas constant
T: absolute temperature
W_r: residual weight loss
$\frac{dw}{dt}$: rate of change in sample weight
n: order of reaction

Based on Eq. 1, $\Delta(1/T)/\Delta\log W_r$ were plotted against $\Delta\log(dw/dt)/\Delta\log W_r$ and the activation energy and order of reaction were determined from the slope and the intercept of the line, respectively. Fig. 3 shows some examples of the results of TG-curve analysis. The values of activation energies thus obtained are listed in Table III. The orders of reaction are apparently 0 for all the solid complexes. The activation energies of the solid complexes between theophylline and monoamines are generally smaller than those of the solid complexes between theophylline and diamines.[1] The activation energies of the solid complexes in the cases of amine with a hydroxyl group are slightly larger than those of the solid complexes of amines with no hydroxyl group. In addition, the activation energy of the solid complex of methylamine is that of elimination of methylamine and water of crystallization.

Table III. Thermal Properties of Amines and Their Complexes

Amine	Boiling point of amine (°C)	Temperature range of elimination of amine from the complex (°C)	$\Delta T^{a)}$ (°C)	ΔH_v Heat of vaporization of amine (kcal/mol)	ΔH_d Enthalpy change due to deamination from the complex (kcal/mol)	$-\Delta H_r^{e)}$ (kcal/mol)	$E^{g)}$ (kcal/mol)
Methylamine	−6.3	37.4—76.4	63.2	6.1$^{b)}$	32.9	26.8 (13.0)$^{f)}$	14.3
Ethylamine	16.6	40.6—95.5	51.5	6.4$^{c)}$	18.9	12.6	11.4
n-Propylamine	48.0	51.5—97.0	26.2	6.7 (38.3°C)$^{d)}$	18.0	11.3	11.8
Monoethanolamine	170.8	91.0—148.1	−51.2	17.9 (136.5°C)$^{d)}$	24.6	6.7	14.3
Isopropanolamine	173.0	67.7—125.0	−76.6	16.2 (138.3°C)$^{d)}$	21.7	5.5	16.0
n-Propanolamine	188.0	81.1—129.0	−82.9	20.4 (150.4°C)$^{d)}$	23.9	3.5	16.2

a) Difference in temperature between the average temperature of initiation and termination of deamination of the solid complex and the boiling point of each amine.
b) From reference (8).
c) Value estimated from methylamine and *n*-propylamine.
d) Peak temperature from DTA curve.
e) Heat of reaction for the solid complex formation of theophylline with amine.
f) Enthalpy change due to elimination of water of crystallization.
g) Activation energy of deamination of the solid complex.

Incremental Thermal Stabilities of Amines on Solid Complex Formation

Ranges of temperature at which deamination of the solid complexes occurs given in Table III. The thermal stabilities of the solid complexes of amines with a hydroxyl group are higher than those of the solid complexes of amines without a hydroxyl group. This fact suggests that the hydrogen bonds between hydroxyl groups enhance the thermal stabilities of the solid complexes. This view was confirmed by the finding that, in the IR spectra, the streching vibrations of hydroxyl group of the amine shifted to lower frequencies on solid complex formation. The deamination of solid complexes of amines with a hydroxyl group takes place in higher temperature ranges than those of the solid complexes of amines without a hydroxyl group. This does not necessarily mean, however, that amines with a hydroxyl group are much more stabilized than amines without a hydroxyl group by solid complex formation because the amines with a hydroxyl group are intrinsically more stable than those without a hydroxyl group due to the stronger hydrogen bonds among amine molecules. In order to study the incremental thermal stability of amine due to solid complex formation, the effect of solid complex formation on the temperature at which the amine is vaporized was investigated. A boiling point under 1 atmospheric pressure was taken to represent the temperature of vaporization of the amine, while the average temperature of initiation and termination of the deamination reaction of the solid complex was taken as the temperature of liberation of amine vapor from the solid complex. The difference in temperature between the boiling point and the average temperature, ΔT, is included in Table III. As ΔT increases, the amine is considered to be more stabilized by solid complex formation. On the basis of this view, it is concluded that the amines without a hydroxyl group such as methylamine, ethylamine and *n*-propylamine, are much more stabilized than the amines with a hydroxyl group by solid complex formation.

Heats of Reaction for the Formation of Solid Complexes

The heat of vaporization, ΔH_v, and the change in enthalpy of deamination reaction, ΔH_d, were calculated for amine and the solid complex, respectively, by the methods described in "Experimental" (Table III). The difference, $-\Delta H_r = \Delta H_d - \Delta H_v$, was taken as the heat of reaction for formation of the solid complex, as given below

$$\text{monoamine (liquid)} + \text{theophylline (crystal)} \longrightarrow \text{solid complex (crystal)}$$

In the case of the solid complex of methylamine, which contains one molecule of water of crystallization, the heat of reaction for the formation of solid complex ,not involving water of crystallization, was approximately estimated. Namely, the change in enthalpy for elimination of one molecule of water of crystallization from theophylline monohydrate was first determined and this value was subtracted from ΔH_d. The heats of reaction for the formation of solid complexes thus obtained are given in Table III. The heats of reaction $-\Delta H_r$ were all exothermic and were correlated with the incremental thermal stabilities of amines upon solid complex formation.

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