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Soluble Complex Formation of Theophylline with Aliphatic Di- and Monoamines in Aqueous Solution

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The interactions of theophylline with aliphatic diamines and aliphatic monoamines were studied by measurements of solubility in aqueous solution. Diamines such as 1,3-propanediamine, 1,4-butanediamine, 1,6-hexanediamine and ethylenediamine, and monoamines such as triethylamine, diethylamine, *n*-propylamine, allylamine, 2-methoxylamine, ethanolamine and triethanolamine were used. The solubility of theophylline increased in the presence of amine and increased in proportion to the pK_a of the amine. The amount of the complex formed was found to be proportional to the pK_a of the amine and the apparent stability constant of complex formation tended to increase as the pK_a of the amine increased.

Keywords——theophylline; aliphatic diamine; aliphatic monoamine; pK_a of theophylline; solubility method; soluble complex formation; stability constant

It is well known that the solubility of theophylline (TP) in an aqueous solution of ethylenediamine (ED) rises more significantly that would be expected from the pH change caused by ED, because TP forms a soluble complex with ED.[1] Indeed, aminophylline (a solid complex of TP with ED) has been a useful drug for the treatment of asthma. The present paper describes the interactions of TP with aliphatic diamines such as 1,3-propanediamine (PD), 1,4-butanediamine (BD) and 1,6-hexanediamine (HD) and with aliphatic monoamines such as ethanolamine (EA), *n*-propylamine (PA), diethylamine (DEA), triethylamine (TEA), allylamine (AA), 2-methoxyethylamine (2-MA) and triethanolamine (TNA). The interactions of TP with amines were studied by measurements of the solubility in aqueous solution. As the experimental conditions for ED reported previously[1] are different from ours, the interaction of TP with ED was also studied for comparison with other amines.

Experimental

Materials——TP used was the same material as described in the previous paper.[2] Amines were commercial products of guaranteed grade, which were distilled under reduced pressure in a nitrogen stream and stored in a desiccator containing sodium hydroxide. Water that had been deionized and doubly distilled in all-glass apparatus was used.

Dissociation Constant (K_a) of Theophylline——According to the established method,[3] pH titrimetry was carried out using 0.1 N KOH (f=1.000) in carbon dioxide-free water. An aqueous solution of TP (47.5 ml)

which was prepared to become 0.01 M at half-neutralization was poured into a beaker and ten 0.50 ml portions of 0.1 N KOH were added successively from a 1 ml buret. pH measurements were carried out for the solutions obtained, while nitrogen gas was continuously blown through the solutions. pK_a ($-\log K_a$) was calculated by means of equation (1). All the measurements were conducted at a temperature of 25 ± 0.05°C.

$$pK_a = pH + \log \frac{[TH]+[OH^-]}{[T^-]-[OH^-]} \quad (1)$$

where [TH] and [T^-] stand for the concentrations of unionized species and ionized species of TP, respectively, and [OH^-] is the concentration of the hydroxyl ion in aqueous solution, which can be obtained from the ionic product of water[3] based on the pH of the solution. A Hitachi-Horiba F-7 meter was used for pH measurement. The pK_a value of TP was found to be 8.64 ± 0.03. The pK_a of TP was previously reported to be 8.6 at 20°C.[4]

Measurement of Solubility——A 20 ml aliquot of amine solution of appropriate concentration and excess solubilizate were taken in 25 ml test tubes, which were sealed. The test tubes were kept at 25 ± 0.05°C under shaking for one week until a solubility equilibrium was established. Test solutions were taken up in a pipette with a cotton filter, diluted with an appropriate amount of acetate buffer solution (pH 5.0) and analyzed for solute by UV spectrophotometry. The wavelength used was 272 nm for TP. The remaining supernatant solutions were used for pH measurement.

Results and Discussion

Interactions of Theophylline with Diamines

Fig. 1 shows the solubility of TP in the presence of various concentrations of HD. The solubility of TP was also increased by other diamines, and increased with increasing pK_a1 and pK_a2 of the protonated diamine. Table I lists the pK_a1 and pK_a values of the diamines. It is probable that the observed solubility includes the increment of solubility due to the pH elevation (S_t) in the presence of HD according to equation (2)

$$S_t = (S_0)\left\{1+\frac{K_a}{[H^+]}\right\} \quad (2)$$

where (S_0) stands for the solubility of unionized species of TP (measured as 3.58×10^{-2} M); K_a represents the dissociation constant of TP; [H^+] is the hydrogen ion concentration. In Fig. 1, S_t is represented by the solid circles. As the solubility is always higher than St, HD, like ED, is considered to form a soluble complex with TP in aqueous solution. The obser-

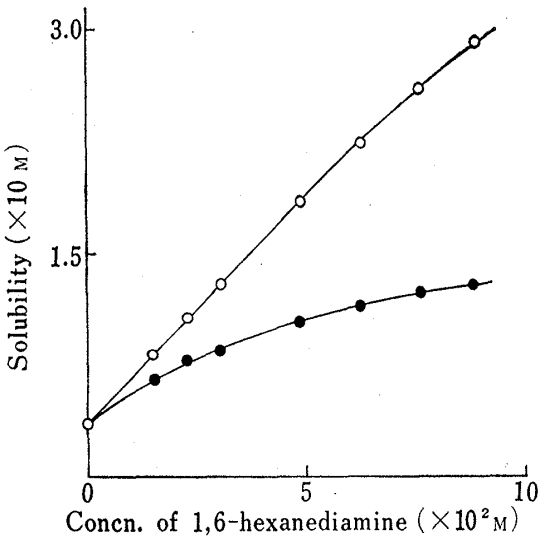

Fig. 1. Solubilization of Theophylline by 1,6-Hexanediamine in Water at 25°C

—○—: solubility curve of theophylline in the presence of 1,6-hexanediamine.
—●—: calculated solubility curve of theophylline at found pH.

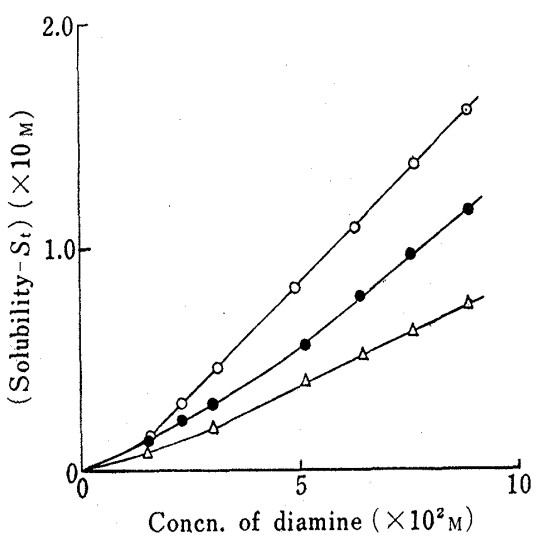

Fig. 2. Correlation between the Amount of Soluble Complex and Concentration of Diamine added in Water at 25°C

—○—: 1,6-hexanediamine, pK_{a1} 9.83, pK_{a2} 10.93.
—●—: 1,3-propanediamine, pK_{a1} 8.29, pK_{a2} 10.30.
—△— : ethylenediamine pK_{a1} 6.85, pK_{a2} 9.93.

vation that the solubility is larger than S_t was confirmed with all the diamines employed, indicating the formation of a soluble complex with TP in each case. Thus solubility is considered to be the sum of S_t and the concentration of the complex, [Complex](equation 3)

$$\text{solubility} = S_t + [\text{complex}] \quad (3)$$

In Fig. 2, (solubility-S_t) values are plotted against the concentration of diamines. It was found that the increment of the solubility (solubility-S_t) due to the complex formation or the amount of complex formed was more significant in the cases of other diamines tested than in the case of ED. In addition, the amount of the complex was positively related to the magnitude of pK_a1 and pK_a2 of the diamines. In the case of BD, the phase solubility diagram was a typical Type Bs[5] and a solid complex was formed in aqueous solution when the concentration of BD was above 7.6×10^{-2} M (Fig. 3). The composition of the solid complex can be calculated from the data in the plateau region of Fig. 3, and the molar ratio of TP to BD was 2:1. By X-ray analysis, the solid complex of BD was proved to be identical with the one prepared as described in the previous paper.[2] As the solid complex was thermally stable,[2] the thermal stability of the solid complex is presumed to be related to the ease of the solid complex formation.

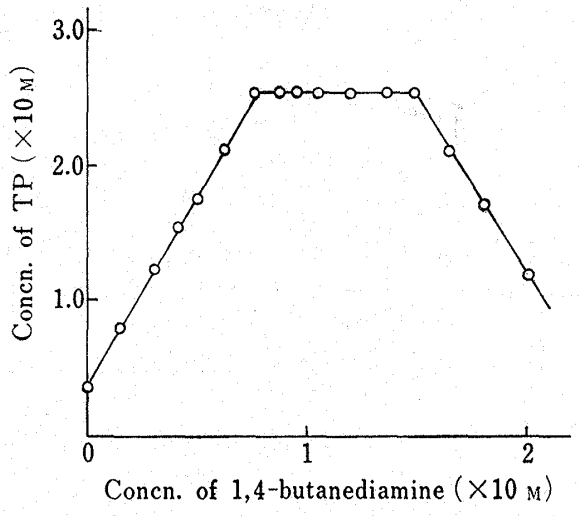

Fig. 3. Phase Solubility Diagram of the Theophylline-1,4-butanediamine System in Water at 25°C

TP is reported to form a soluble complex of ion pair type with ED in aqueous solution almost in a molar ratio of 1:1.[1] Judging from the greater pK_a1 and pK_a2 values and the greater increase of solubility due to the complex formation (solubility-S_t), it is assumed that TP forms a substantial amount of 2:1 complex, in addition to a 1:1 complex with PD and forms almost entirely 2:1 complexes with BD and HD in aqueous solution. The apparent stability constant of the complex formation at a molar ratio of 2:1 in the cases of BD and HD may be defined as follows:

Table I. Dissociation Constants of Amines (pK_a) and Apparent Stability Constants ($K_{C1:1}$, $K_{C2:1}$) of Theophylline–Amine Complexes in Aqueous Solution at 25°C

Amine	pK_a[a]		$K_{C1:1}$	$K_{C2:1}$
Ethylenediamine	6.85	9.93[b]	62	
1,3-Propanediamine	8.29	10.30[b]	—[c]	—[c]
1,4-Butanediamine	9.20	10.65[b]		1310
1,6-Hexanediamine	9.83	10.93[b]		1350
Diethylamine	10.63		74	
Triethylamine	10.87		77	
n-Propylamine	10.53		65	
Ethanolamine	9.50		47	
Allylamine	9.69		51	
Triethanolamine	7.82		34	
2-Methoxyethylamine	9.45		42	

a) Dissociation constant of protonated amine at 25°C (ref. 3 and 6).
b) Second dissociation constant (pK_a2).
c) Stability constant was not determined because, in addition to a 1 : 1 complex, a 2 : 1 complex was assumed to be formed in substantial amount.

$$K_{c2:1} = \frac{[T_2D]}{[T^-]^2[D^{+2}]} \quad (4)$$

where $[T_2D]$ is the concentration of 2:1 complex and $[T^-]$ and $[D^{+2}]$ represent the concentrations of TP ion and divalent diamine ion, respectively. These values were calculated from the following stoichiometric equations (5)—(9).

$$\text{solubility} = (S_o) + [T^-] + 2[T_2D] \quad (5)$$

$$\text{Total concentration of diamine} = [D] + [D^+] + [D^{+2}] + [T_2D] \quad (6)$$

$$K_a1 = \frac{[D^+][H^+]}{[D^{+2}]} \quad (7)$$

$$K_a2 = \frac{[D][H^+]}{[D^+]} \quad (8)$$

$$K_a = \frac{[T^-][H^+]}{[TH]} \quad (9)$$

where $[D]$ and $[D^+]$ represent the concentrations of unionized species of diamine and monovalent diamine ion, respectively. K_a1 and K_a2 are the primary and secondary dissociation constants of protonated diamine, respectively (Table I). Table II shows the process of calculation of the apparent stability constant $K_{C2:1}$ of HD.

TABLE II. Calculation of Apparent Stability Constant of Theophylline (TP)–1,6-Hexanediamine (HD) Complex at 25°C

Concn. of HD ($\times 10^2$ M)	Solubility of TP ($\times 10^2$ M)	pH Found	Concn. of complex (T_2HD) ($\times 10^2$ M)	T^- ($\times 10^2$ M)	HD^{+2} ($\times 10^2$ M)	$K_{C2:1}$
0	3.58	6.35	—	—	—	—
1.52	8.17	8.55	0.805	2.98	0.679	1335
2.28	10.67	8.69	1.54	4.00	0.739	1307
3.04	12.97	8.79	2.28	4.83	0.700	1396
4.87	18.53	8.91	4.14	6.67	0.653	1423
6.24	22.30	8.98	5.44	7.84	0.700	1263
7.61	26.09	9.04	6.86	8.80	0.649	1366
8.82	29.06	9.07	8.03	9.42	0.671	1348
						(1350±54) a)

a) The mean±standard deviation.

Interactions of Theophylline with Monoamines

Fig. 4 shows the changes of solubility of theophylline due to the addition of EA. The other monoamines similarly elevated the solubility of TP. The magnitude of solubility increased depending on pK_a of the protonated monoamine (Table I). It is considered that the solubility includes S_t, the increment of solubility resulting from the pH elevation produced by the presence of monoamine (equation 2). S_t is shown by the solid circles in Fig. 4. These results suggest that, as is the case with diamine, monoamines form soluble complexes of ion pair type. Thus, equation (3) can be written. Some of the experimental results are shown in Fig. 5 by plotting (solubility-S_t) values against the concentration of monoamines. It is clear that at the same concentration of monoamines the amounts of the complexes formed depend on the magnitude of pK_a.

Provided that TP and monoamine form a soluble complex of ion pair type in a molar ratio of 1:1 in aqueous solution, since monoamine has only monovalent ion as an ionized species, the apparent stability constant can be defined by the following equation (10).

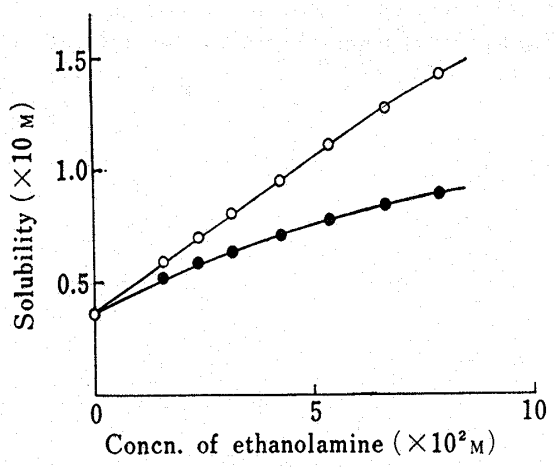

Fig. 4. Solubilization of Theophylline by Ethanolamine in Water at 25°C

—○—: solubility curve of theophylline in the presence of ethanolamine.
—●—: calculated solubility curve of theophylline at found pH.

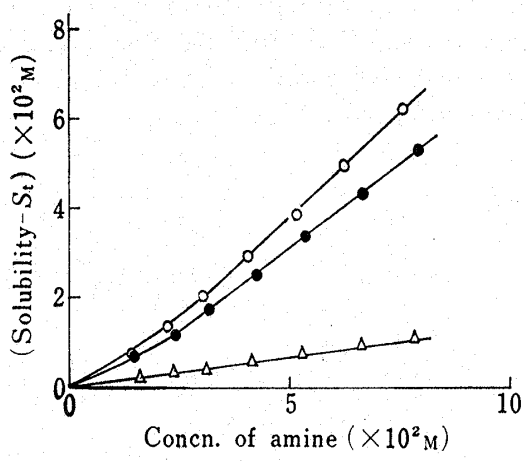

Fig. 5. Correlation between the Amount of Soluble Complex and Concentration of Monoamine added in Water at 25°C

—○—: *n*-propylamine, pK_a 10.53.
—●—: ethanolamine, pK_a 9.50.
—△—: triethanolamine, pK_a 7.82.

$$K_{C1:1} = \frac{[TA]}{[A^+][T^-]} \tag{10}$$

where [TA] and [A+] represent the concentrations of 1:1 complex and ionized species of monoamine, respectively. These values were calculated from equations (9), (11), (12) and (13).

$$S_t = (S_o) + [T^-] + [TA] \tag{11}$$

$$\text{Total concentration of monoamine} = [A] + [A^+] + [TA] \tag{12}$$

$$K_a = \frac{[A][H^+]}{[A^+]} \tag{13}$$

where [A] and K_a represent the concentration of unionized species of monoamine and the dissociation constant of protonated monoamine. Table III presents the process for calculating the apparent stability constant $K_{C1:1}$ of EA. The apparent stability constants thus obtained are listed in Table I. To investigate whether or not there is a correlation between $K_{C1:1}$ and pK_a of amine, $K_{C1:1}$ values were plotted against pK_a values of amines at 25°. As pK_a increased, $K_{C1:1}$ gradually tended to increase. In other words, a more basic amine tends to form a complex more easily. This finding agrees with the results reported previously on the formation of the soluble complex of tioxacin with aliphatic amine.[7] It can be assumed that an

Table III. Calculation of Apparent Stability Constant of Theophylline (TP)–Ethanolamine (EA) Complex at 25°C

Concn. of EA (×10²M)	Solubility of TP (×10²M)	pH Found	Concn. of complex (×10²M)	T⁻ (×10²M)	EA+ (×10²M)	$K_{C1:1}$
0	3.58	6.35				
1.57	5.88	8.30	0.660	1.64	0.862	46.7
2.35	6.98	8.44	1.14	2.26	1.05	48.0
3.13	8.08	8.53	1.73	2.78	1.27	49.0
4.24	9.60	8.63	2.52	3.50	1.52	47.5
5.35	11.12	8.71	3.32	4.21	1.75	45.1
6.61	12.72	8.77	4.31	4.83	1.94	46.0
7.87	14.27	8.82	5.27	5.42	2.15	45.2
						(47.0±1.5[a])

a) The mean±standard deviation.

amine with a greater pK_a value yields a large amount of the ionized species of amine and TP in aqueous solution, and therefore mutual attraction between the positive charged amine and the negative charged TP results in easier ion pair formation, and $K_{C1:1}$ of an amine with a greater pK_a has a greater value.

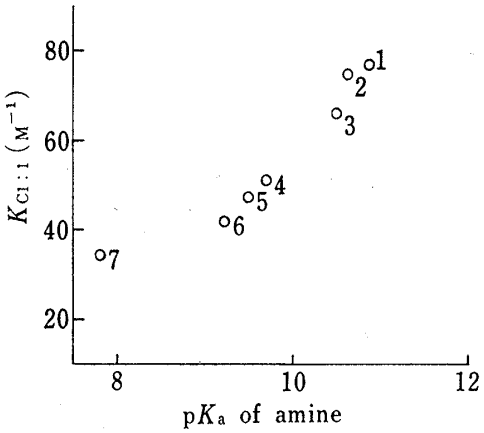

Fig. 6. Relationship between K_c of Theophylline–Monoamine Complex and pK_a of Monoamine

1: triethylamine, 2: diethylamine, 3: *n*-propylamine, 4: ethanolamine, 5: allylamine, 6: 2-methoxyethylamine, 7: triethanolamine.

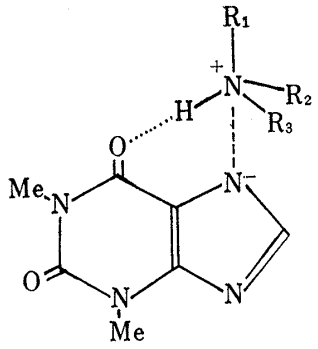

Chart 1. Proposed Structure of Theophylline–Amine Complex

In the previous paper,[8] it was reported that DEA, TEA, AA, 2-MA, and TNA formed no solid complex with TP. As described in the present paper, these amines each form a soluble complex with TP, indicating that complexes formed in aqueous solution can not always be obtained in the solid state. Based on the bonding mode of solid complex and the fact that all types of amine form a soluble complex in aqueous solution, the soluble complex is assumed to have the structure presented in Chart 1. As the ease of soluble complex formation in aqueous solution is governed by the pK_a of the amine, the substituents R_1, R_2 and R_3 (Chart 1) may affect the complex formation through control of the basicity of the amine. On the other hand, as the solid complex formation is governed by the pK_a of the amine, the proportion of hydrophobic groups in the amine molecule and the type of amine, these substituents (R_1, R_2 and R_3) may affect the solid complex formation through both control of the basicity of the amine and by introducing additional interactions which might promote crystallization of the complex, or the formation of the crystal lattice of the complex.

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