[Chem. Pharm. Bull. 30(6)2219—2222(1982)]

Interaction of Theophylline with Benzylamine in the Solid State

JUZIRO NISHIJO, KUMIKO OHNO, and KEIKO NISHIMURA

Kobe Women's College of Pharmacy, Motoyama-Kitamachi, Higashinada-ku, Kobe 658, Japan

(Received October 29, 1981)

Complexation of theophylline with 4 amines having a benzene moiety was studied in water and in absolute ethanol. Theophylline forms a solid complex with benzylamine in a molar ratio of 1:1 from both solvents. However, no solid complex is formed between theophylline and aromatic amines, such as aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline. The physico-chemical properties of the complex formed were studied by powder X-ray diffractometry, differential thermogravimetric analysis (DTA-TG), differential scanning calorimeter (DSC) and infrared spectroscopy. The DTA-TG thermograms of the solid complex obtained at a heating rate of 2.5°C/min in air showed that deamination occurred in the temperature range of 53—90°C to yield anhydrous theophylline with two endothermic peaks, a large endothermic peak followed by a broad but small endothermic peak. The reaction was first-order, and the activation energy of determination 29 kcal/mol. The heat of reaction for solid complex formation was estimated to be 21.3 kcal/mol. Hydrogen bonding was the major attractive force between the components of the complex.

Keywords——theophylline; benzylamine; DTA-TG; activation energy; heat of reaction; hydrogen bond

A solid complex of theophylline with ethylenediamine, called aminophylline, is a drug described in the Japanese Pharmacopoeia and is effective for controlling bronchial symptoms and other complaints. The authors have previously reported some complexes of theophylline with ethylenediamine analogs[1] and aliphatic monoamines.[2] The ability to form a solid complex is considered to be related to the pK_a value, class, and hydrophobic properties of the amines. On the other hand, no work has been done on complexes of theophylline with amines which have a benzene moiety. The present study was therefore undertaken to investigate the ability of theophylline to form a solid complex with amines having a benzene moiety and to investigate the physico-chemical properties of the complex obtained.

Experimental

Materials——Theophylline, benzylamine, aniline, *N*-methylaniline, *N*,*N*-dimethylaniline, and absolute ethanol were all of reagent grade. Distilled water was used.

Preparation of Solid Complex——a) Complexation from Aqueous Solution: In about 20 ml of water 3.0 g (0.0167 mol) of theophylline and 1.78 g (0.0167 mol) of benzylamine were dissolved. The vessel containing the solution was allowed to stand in a refrigerator, being loosely stoppered to permit the evaporation of solvent. The crystals obtained were dried in the refrigerator until constant weight was attained. The crystals, in tightly stoppered container, were stored in the refrigerator until use. In the cases of other amines, whose solubilities in water are small, 0.0015 mol (0.27 g) of theophylline and 0.0015 mol (for example, aniline 0.14 g) of amine were dissolved in about 50 ml of water and the aqueous solutions obtained were treated by the same method as in the case of benzylamine.

b) Complexation from Absolute Ethanol: Theophylline and amine were reacted in a molar ratio of 1:2 to accelerate the complex formation. For example, 3.57 g (0.034 mol) of benzylamine was dissolved in absolute ethanol, and 3.0 g (0.0167 mol) of theophylline was gradually added to the mixture with vigorous stirring.

The reaction mixture was allowed to stand for 3 h, and the precipitates formed were filtered off with suction, washed with cold ethanol, and dried in a refrigerator until constant weight was attained. The product, in a tightly stoppered container was stored in a refrigerator until use.

Chemical Analysis of the Solid Complex——Determination of each component of the solid complex was carried out according to the method reported previously.[2]

X-Ray Diffraction——X-Ray diffraction was carried out using the apparatus reported previously.[2]

Thermal Analysis——Differential thermogravimetric analysis (DTA-TG) was conducted using the apparatus reported previously.[2] Measurement of the amount of heat was carried out using a standard type differential scanning calorimeter (produced by Rigaku Denki Co. Ltd.) according to the method reported previously.[2]

Infrared Absorption (IR) Spectra——IR spectra were recorded using the apparatus reported previously.[2]

Results and Discussion

Solid Complex Formation

Solid complex formation was confirmed by the disappearance of the X-ray diffraction pattern of theophylline and the appearance of a new X-ray diffraction pattern. It became clear that a solid complex was formed between theophylline and benzylamine and the structure of the complex obtained from aqueous solution was identical with that of the complex obtained from absolute ethanol since the X-ray diffraction patterns of both samples were identical, differing from that of component theophylline. Fig. 1 shows the X-ray diffraction patterns of anhydrous theophylline and solid complex. The molar ratio of the complex was 1 : 1. However, no solid complex was formed between other aromatic amines (aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline) and theophylline by method. It is apparent that aromatic amines such as aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline having small pK_a values,[3] 4.60, 4.58, and 4.85 at 25°C, respectively, do not formed a solid complex with theophylline. On the other hand, the pK_a[3] of benzylamine is 9.34 at 25°C.

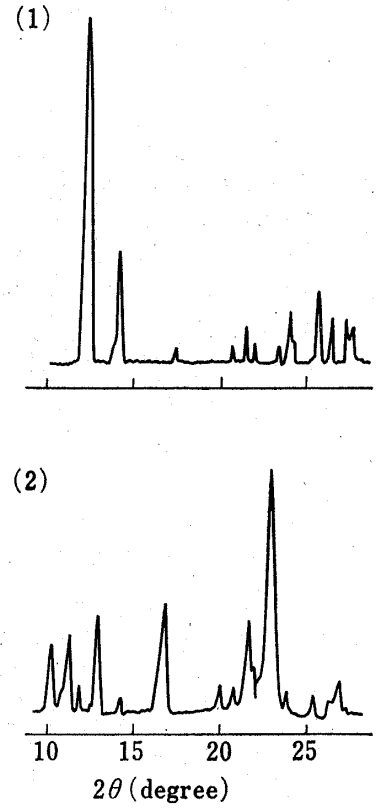

Fig. 1. Powder X-ray Diffraction Patterns of Anhydrous Theoplylline (1) and Its Solid Complex with Benzylamine (2)

Thermal Decomposition of the Solid Complex

The thermal decomposition of the solid complex was monitored by DTA-TG and X-ray diffractometry. Fig. 2 shows the results of DTA-TG. The solid complex starts to decrease in weight at about 54°C with a large endothermic peak, followed by a small but broad endothermic peak, which terminates at about 90°C where the decrease in weight ends. The X-ray diffraction pattern of a sample taken at point b of Fig. 2 coincides with that of anhydrous theophylline, as shown in Fig. 1-(1). Accordingly, the solid complex decomposes to anhydrous theophylline with liberation of benzylamine. An X-ray diffraction pattern of a sample taken at point a where the DTA curve starts to show the small endothermic peak reveals the patterns of the starting solid complex and anhydrous theophylline. When the sample is allowed to stand in air, the intensity of diffraction peaks of theophylline increases a liittle. Observation of the deamination of the solid complex on a micro melting point apparatus showed that partial liquefaction took place. From these experimental results, it is considered that deamination occurs with the disintegration of the crystal lattice of the solid complex to yield amorphous theophylline (endothermic), which then crystallizes into theophylline (exothermic) and the large endothermic peak shifts to the small broad one because of this crystallization energy. It is assumed that the small endothermic peak became broad since

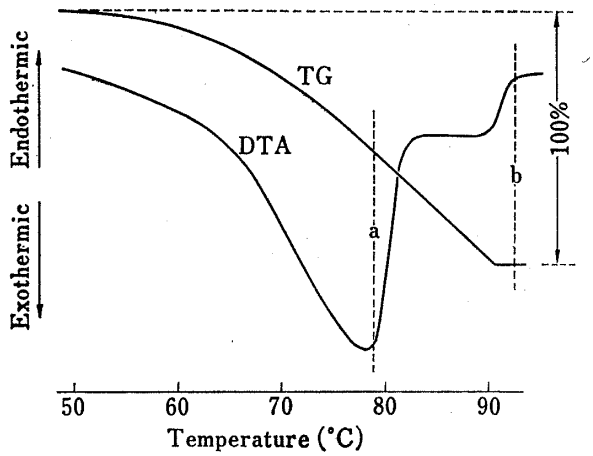

Fig. 2. DTA–TG Thermograms of the Solid Complex of Theophylline with Benzylamine in Air

Sample amount, 8.95 mg; heating rate, 2.5°C/min; Sensitivity, ±100 μV.

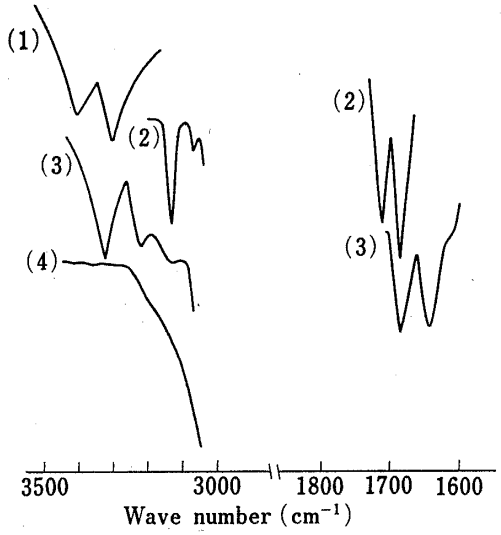

Fig. 3. IR Spectra of Benzylamine (1), Theophylline (2), Solid Complex of Theophylline with Benzylamine (3), and Benzylamine Hydrochloride (4)

deamination and the crystallization of amorphous theophylline at this stage were in a stationary state.

IR Spectra

Fig. 3 shows IR spectra of the complex and theophylline in the regions of 3500—3000 cm^{-1} and 1800—1600 cm^{-1}. The IR spectra of benzylamine, and benzylamine hydrochloride, which was prepared by the usual method, were also measured in the region of 3500—3000 cm^{-1}. It was ascertained by determination of each component of the complex and by DTA-TG that this complex contains no water of crystallization. Accordingly, the absorptions at 3320 and 3220 cm^{-1} are ascribed to stretching vibrations of the $-NH_2$ group,[4] indicating that there is no proton migration from the >N–H group of theophylline to the nitrogen atom of benzylamine, within the time scale of IR measurement. On the other hand, the IR spectrum of benzylamine hydrochloride, in which an $-NH_3^+$ group is considered to exist, showed almost no absorptions in these regions. In the solid complex, however, it is considered that the >C=O groups at the 2 and 6 positions of theophylline are hydrogen-bonded with $-NH_2$ of benzylamine since the absorptions of the two >C=O groups and $-NH_2$ group are shifted to lower wave numbers than in theophylline and benzylamine alone. From the fact that caffeine forms no complex with ethylenediamine,[5] the >NH group of theophylline is considered to play an important role in the complex formation. In the solid complex of theophylline with aliphatic amine,[2] proton transfers from the >NH group of theophylline to the nitrogen atom of the amine and the specific hydrogen bonds which the resulting $-NH_3^+$ group forms with >C=O groups at the 2 and 6 positions and the $>N^-$ group of theophylline may be the driving force for solid complex formation. In the case of benzylamine, the assumed hydrogen bonding shown in Chart 1 and the interaction between electrons of the benzene ring of benzylamine and the α,β-unsaturated ketone of theophylline[6] may be the driving force for solid complex formation.

Order of Reaction and Activation Energy of Deamination of the Solid Complex

The order of reaction and the activation energy of deamination were determined from TG curves in air according to the method of Freeman and Carrol[7] in the same manner as reported previously.[2] The reaction and the activation energy were estimated to be first order and 29 kcal/mol (Fig. 4), respectively.

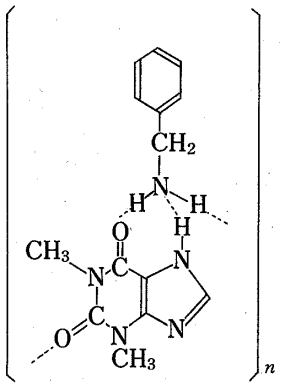

Chart 1. Proposed Hydrogen Bonding between Theophylline and Benzylamine in the Solid State

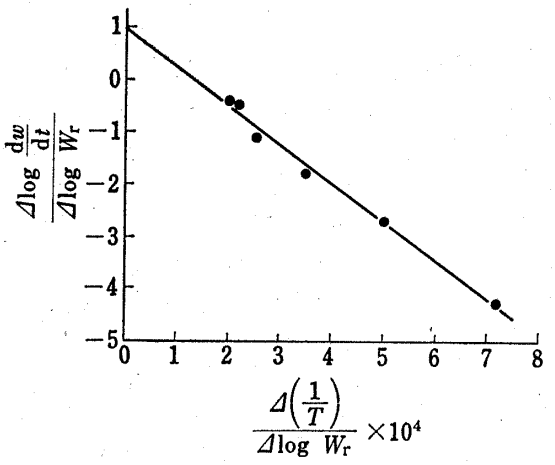

Fig. 4. Kinetics of Elimination of Benzylamine from the Solid Complex

W_r: (weight loss at completion of reaction) − (total weight loss up to time, t).
$\frac{dw}{dt}$: rate change of sample weight.
T: absolute temperature.

Heat of Reaction of Formation of Solid Complex

In the same manner as reported previously,[2] the heat of evaporation ΔH_v of benzylamine and the enthalpy change ΔH_d of deamination of the solid complex were determined. They were 14.2 kcal/mol and 35.5 kcal/mol, respectively, and the difference $\Delta H_r = \Delta H_v - \Delta H_d$ may be considered as the heat of solid complex formation represented by the equation;

benzylamine(liquid) + theophylline(crystal) ⟶ solid complex(crystal)

The heat of reaction $-\Delta H_r$ thus determined was 21.3 kcal/mol (exothermic), being considerably larger than that for the aliphatic amine reported previously. To determine the thermal stabilization due to formation of the solid complex of benzylamine, the difference ΔT between the average temperatures at the start and termination of deamination and the boiling point of benzylamine (185°C) under atmospheric pressure was determined to be −121°C. Therefore, the increase in thermal stability of benzylamine produced by solid complex formation was not large. It is presumably because benzylamine is an aromatic compound and the energy of crystallization of formation of the solid complex from benzylamine and theophylline is greater than that in the case of aliphatic amine, due to the stacking effect ΔH_r for the solid complex formation of theophylline with benzylamine is larger.

References and Notes

1) J. Nishijo, H. Hurukawa, and M. Nakano, *Yakugaku Zasshi*, **100**, 493 (1980).
2) J. Nishijo, K, Ohno, K. Nishimura, M. Hukuda, and H. Ishimaru, *Chem. Pharm. Bull.*, **30**, 391 (1982).
3) A. Albert, E.P. Serjeant, "Ionization Constants of Acids and Bases," Methuen Co., Ltd., London, 1962.
4) L.J. Bellamy, "The Infra-red Spectra of Complex Molecules, Methuen Co., Ltd., London, 1958.
5) T. Okano, K. Aita, K. Ikeda, *Chem. Pharm. Bull.*, **15**, 1621 (1967).
6) *a*) E. Shefter, *J. Pharm. Sci.*, **58**, 710 (1969); *b*) E. Shefter, *J. Pharm. Sci.*, **57**, 350 (1968).
7) E.S. Freeman and B. Carrol, *J. Phys. Chem.*, **62**, 394 (1958).