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# Improvement of thermal and photochemical stability of benzaldehyde by cyclodextrin complexation

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## Summary

Inclusion complexes of benzaldehyde (BA) with α-, β- and γ-cyclodextrins (α-, β- and γ-CyD) in water and in the solid phase were investigated by the solubility method, infrared spectroscopy, X-ray diffractometry and thermal analysis. The solid complexes of BA with all 3 CyDs were prepared, and their molar ratios were found to be 1 : 1 (BA/α-CyD), 3 : 2 (BA/β-CyD) and 2 : 1 (BA/γ-CyD). The volatility and photo-oxidation of BA were significantly retarded by the CyD inclusion complexation. The oxidation of BA was completely inhibited by 3 CyD complexes. The improved thermal and photochemical stabilities of BA by inclusion complexation suggest ease of handling with prolonged storage time.

## Introduction

In the past decade cyclodextrins (CyDs) have received considerable attention because they are able to modify the physical and chemical properties of the drug molecules by inclusion complexation (Uekama, 1979, 1981; Saenger, 1980). Recently, Uekama and coworkers (1979, 1981a and b, 1982) have succeeded in improving the chemical stability, the solubility and the bioavailability of various drugs including prostaglandin derivatives, steroid hormones, and digoxin by means of CyD complexation. Benzaldehyde (BA) is known to be a light- and oxygen-sensitive oil and its pharmaceutical use is therefore limited. Ikeda et al. (1982) have recently reported that the volatility and photo-oxidation of essential oils were significantly retarded after formation of inclusion complexes with α- and β-CyDs. In

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these continuing investigations, the inclusion complexes of BA with 3 CyDs ($\alpha$-, $\beta$- and $\gamma$-CyDs) in water and in the solid state were studied in the hope of improving the thermal and photochemical stabilities of BA.

## Materials and methods

*Materials*

BA (Tokyo Kasei, Tokyo, Japan) was distilled before use under reduced pressure and in the dark. The $\alpha$-, $\beta$- and $\gamma$-CyDs were purchased from Nippon Shokuhin Kako (Tokyo, Japan) and recrystallized twice from water. All other materials and solvents were of analytical reagent grade. Deionized and double-distilled water was used throughout the study.

*Solubility studies*

Solubility measurements were carried out according to Higuchi and Lach (1954). Excess amounts of BA were added to aqueous CyD solutions saturated with nitrogen and were shaken at $25 \pm 0.5$°C in the dark. After equilibration was attained (approximately 5 days), an aliquot was centrifuged and pipetted through a cotton filter. A portion of the sample (0.5 ml) was then diluted with water and analyzed spectrophotometrically. No degradation of BA was observed under these experimental conditions.

*Preparation of solid complexes*

The solid complexes were obtained by mixing appropriate amounts of the CyD and BA in water. Amounts were calculated from the descending portion of the phase solubility diagram (see Fig. 1). For example, 0.15 g of BA and 1.75 g of $\alpha$-CyD were added in 10 ml water and sealed in a flask under an atmosphere of nitrogen. The mixture was then agitated at 25°C for 5 days. The precipitated complex was filtered and dried under vacuum at room temperature for 24 h. This powder corresponded to a 1 : 1 BA–$\alpha$-CyD complex which had a molecular weight of 1078.

*X-Ray diffractometry*

The powder X-ray diffraction patterns were obtained using a Rigaku Denki Geiger Flex 2012 (Tokyo, Japan) with Ni-filtered Cu-$K_\alpha$ radiation.

*Infrared (IR) spectroscopy*

The IR spectra were measured as a KBr disc or a nujol dispersion, using a Jasco DS-701 double-beam spectrophotometer (Tokyo, Japan).

*Thermal analyses*

Differential thermal analysis (DTA) and thermal gravimetric analysis (TG) were carried out using a scanning rate of 10°C/min on a Shimadzu DT-20B thermal analyzer (Kyoto, Japan). The sample weight was 2–10 mg.

*Oxidation and photo-oxidation studies*

BA (50 mg) or its equivalent amounts of CyD complexes were put in glass-stoppered tubes and sealed under the oxygen-saturated conditions in the dark. In the photolysis experiments, BA (50 mg) or its equivalent amounts of CyD complexes were put in glass-stoppered 1 cm quartz cells and sealed under the oxygen-saturated conditions. Then, these samples were irradiated with a Yoko-lamp (Toshiba DR 250/T, 25,000 lux) at 30°C. Intact BA was quantitatively analyzed by high-performance liquid chromatography (HPLC).

*HPLC analysis*

HPLC was performed using an ATTO model HSLC-013 (Tokyo, Japan). The eluent was monitored spectrophotometrically at 249 nm. The separation utilized a reversed-phase column (LiChrosorb RP-18, 5 $\mu$m, 4$\phi$ × 250 mm; Merck; Darmstadt, F.R.G.) operating at a flow rate of 48 ml/h with methanol–water (7 : 5) as the mobile phase. Ethyl *p*-hydroxybenzoate was used as an internal standard.

## Results and discussion

*Inclusion complexes of BA with CyDs*

Fig. 1 shows the phase solubility diagrams obtained for BA with the 3 CyDs. The differences in solubility curves were clearly noted. The $\alpha$-CyD system showed a typical $B_S$-type (Higuchi and Connors, 1965) solubility curve with the micro-crystalline complex precipitating at the higher $\alpha$-CyD concentration. On the other hand, $\beta$- and $\gamma$-CyD systems showed $B_I$-type solubility curves and yielded insoluble com-

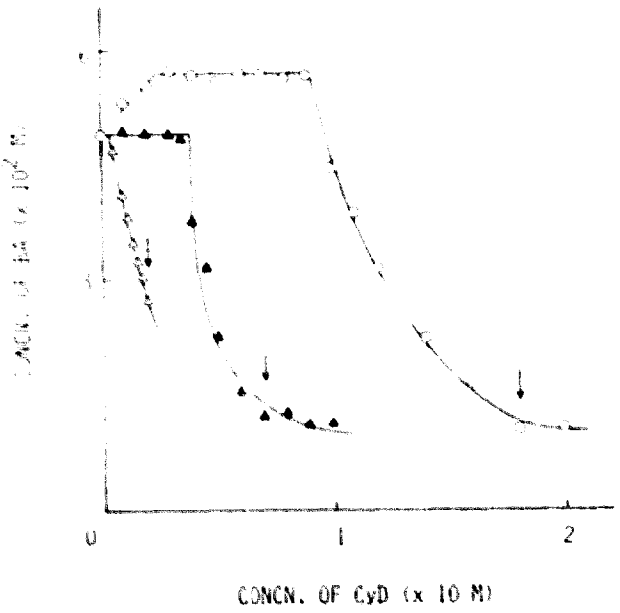


Fig. 1. Phase solubility diagrams of BA–CyD systems in water at 25°C. ○, $\alpha$-CyD; △, $\beta$-CyD; ▲, $\gamma$-CyD. Arrows showing experimental conditions for the preparation of the solid complex (see text).

plexes. The stoichiometries of the complexes in solid phase were analyzed on the basis of data in the plateau region of the solubility diagrams, and were estimated to be 1 : 1 for BA–α-CyD, 3 : 2 for BA–β-CyD, and 2 : 1 for BA–γ-CyD, respectively. These results were in good agreement with those obtained by isolation and analysis of the solid complexes. From the initial rising portion of the solubility curve for the BA–α-CyD system, 1 : 1 stability constant was calculated to be 7 $M^{-1}$, according to the method of Higuchi and Connors (1965). The relatively small stability constant obtained for this system may be due to the less hydrophobic nature of BA molecule compared to other mono-substituted benzene derivatives (Saenger, 1980). Although the shapes of the solubility curves have not been explained fully, the spatial relationship between host and guest molecules seems to also be responsible for the stability constant and stoichiometry of the complexes.

In order to further confirm the complexation of BA with the 3 CyDs in the solid state, the micro-crystalline complexes of BA with 3 CyDs were examined by X-ray diffractometry and IR spectroscopy. Fig. 2 shows the powder X-ray diffraction patterns of these complexes and the CyDs. The diffraction patterns of the complexes were apparently different from those of the CyDs. The β- and γ-CyD complexes

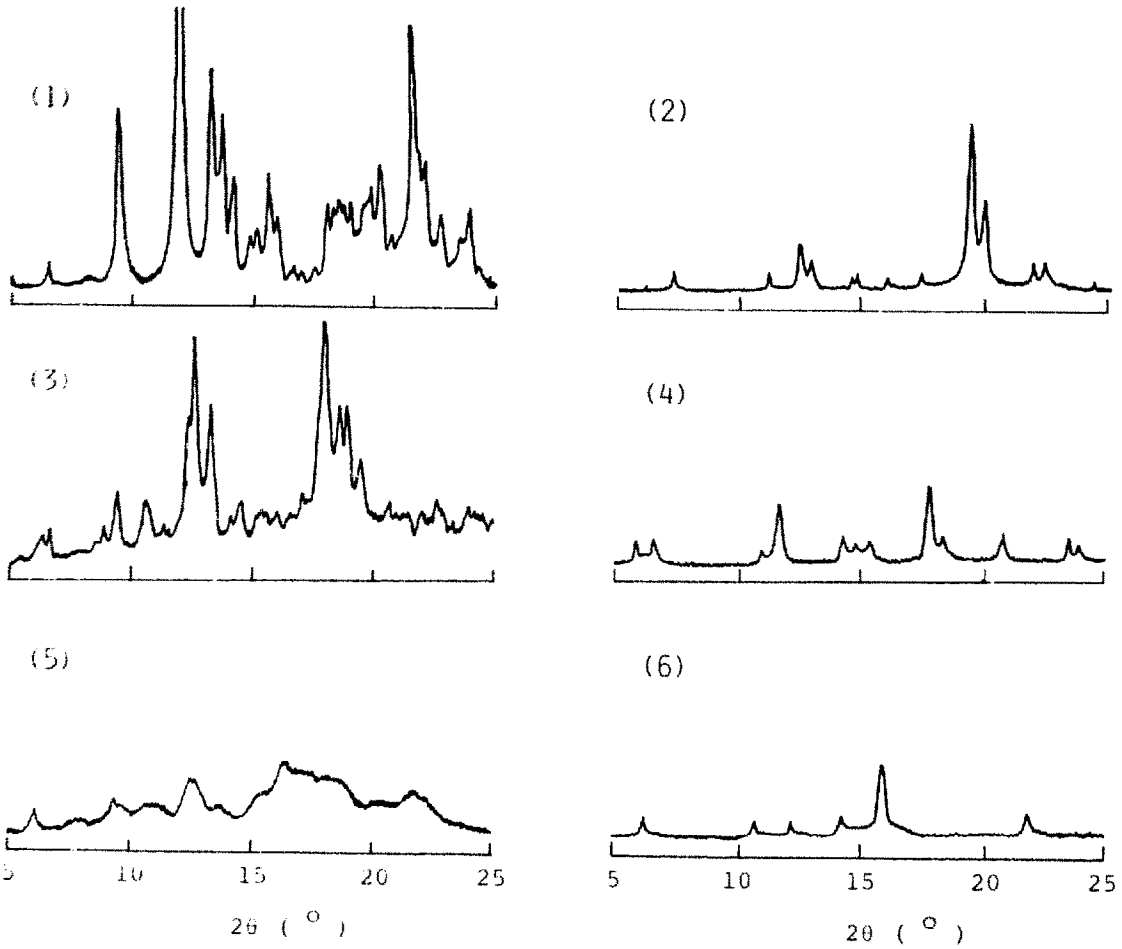


Fig. 2. Powder X-ray diffraction patterns of BA–CyD systems. (1) α-CyD alone; (2) α-CyD complex; (3) β-CyD alone; (4) β-CyD complex; (5) γ-CyD alone; (6) γ-CyD complex.

gave somewhat diffuse diffraction patterns compared with the α-CyD complex and 3 CyDs, suggesting that they are much less crystalline than α-CyD complex and the CyDs. Actually, the single crystal of α-CyD complex is easily obtained (Harata et al.,

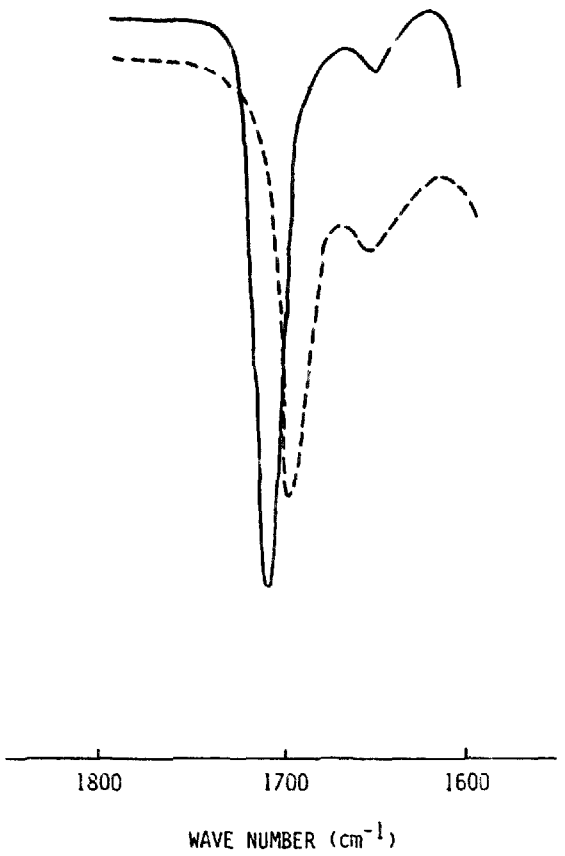


Fig. 3. IR spectra of BA–α-CyD systems. ———, BA alone; - - - - - -, complex.

1981), but those of β- and γ-CyD complexes were difficult to obtain.

Fig. 3 shows IR spectra of BA and its α-CyD complex in the carbonyl-stretching region. In the case of the α-CyD complex, the 1708 $cm^{-1}$ band was found to shift to 1692 $cm^{-1}$. Similar results were obtained for β- and γ-CyD complexes, where the shifts were smaller than that for the α-CyD complex. These spectral changes may be due to differences in geometries of the guest molecule within the cavity of CyDs.

*Thermal behavior of inclusion complexes*

Effects of CyD complexation on the thermal behavior of BA were examined by the thermal analyses since BA is a volatile liquid. Fig. 4 shows DTA and TG thermograms of the various BA–CyD systems. BA showed an endotherm around 210°C corresponding to its boiling temperature. However, the endotherm of BA disappeared with the formation of inclusion complex. The broad peaks around 100–150°C observed for the β- and γ-CyD complexes may be due to the crystalline- or adhesional-water molecules, as suggested by the TG curves. The volatility of BA

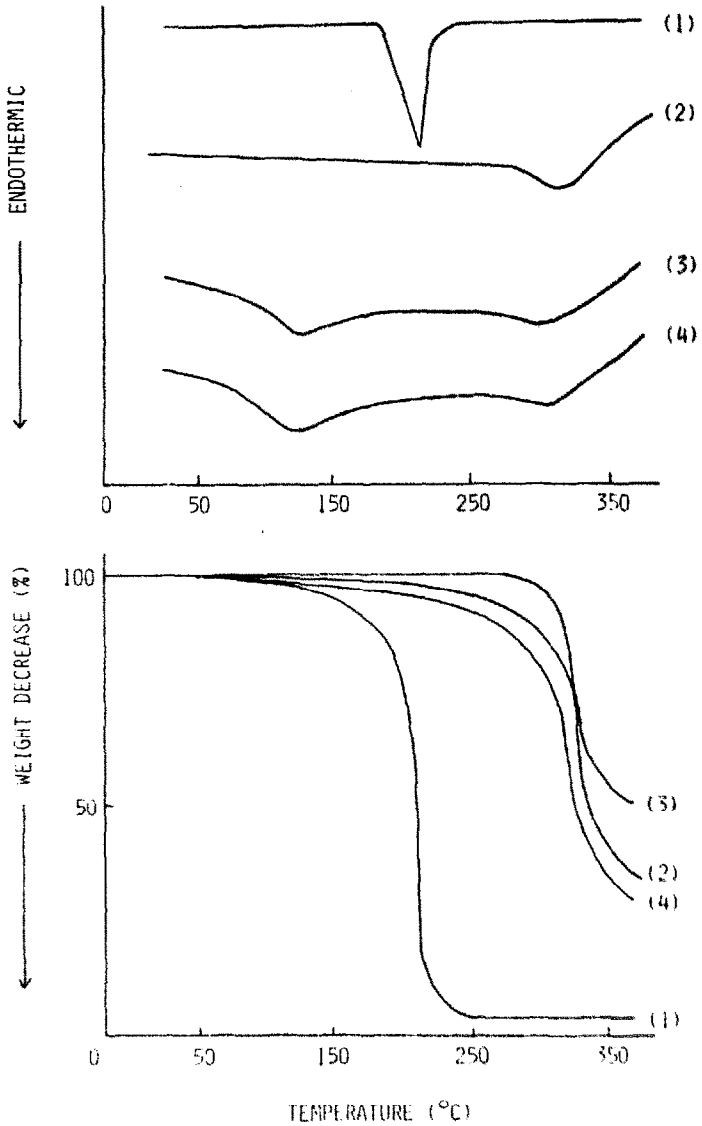


Fig. 4. DTA and TG thermograms of the BA–CyD systems. (1) BA alone; (2) α-CyD complex; (3) β-CyD complex; (4) γ-CyD complex.

was significantly lowered by the CyD inclusion complex, as described previously (Uekama et al., 1979). These results indicate that the CyD complexes may be easier to handle and store than volatile BA.

*Oxidative and photochemical behavior of inclusion complexes*

Fig. 5 shows the oxidation curves of BA and 3 CyD complexes. The oxidation of BA was completely inhibited by complexation. Fig. 6 shows the time courses of the photolysis of BA and the complexes under aerobic conditions. The photodegradation of BA was significantly retarded by the complex formation. It should be noted that the photodegradation of BA was completely suppressed by α-CyD. The differences in photochemical stabilities observed for the 3 complexes can be explained on the

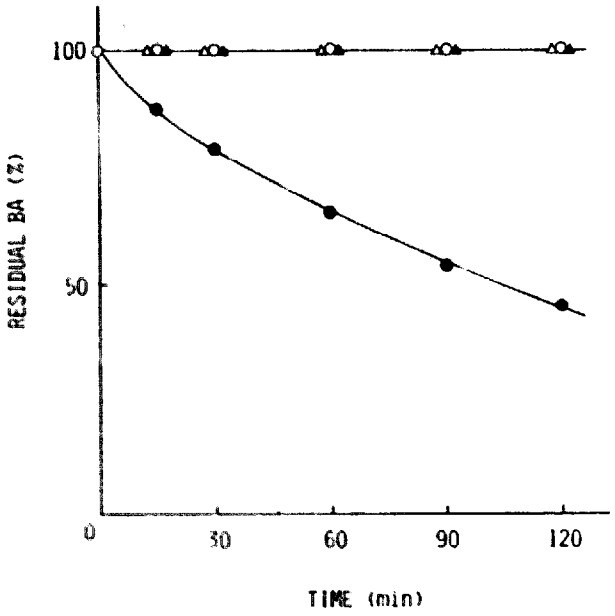


Fig. 5. Degradation curves of BA and its CyD complexes under aerobic condition. ●, BA alone; ○, α-CyD complex; △, β-CyD complex; ▲, γ-CyD complex.

basis of the structure and stoichiometries of the solid complexes. In the case of 1 : 1 α-CyD complex, the BA molecule can be suitably oriented within the cavity of α-CyD to prevent the oxidation reaction. On the other hand, in the case of 3 : 2 β-CyD complex or 2 : 1 γ-CyD complex, the BA molecule could not be tightly included within the cavity of β- or γ-CyD because of the larger cavities. In addition, the crystal lattice of α-CyD complex seems to be stronger than those of β- and

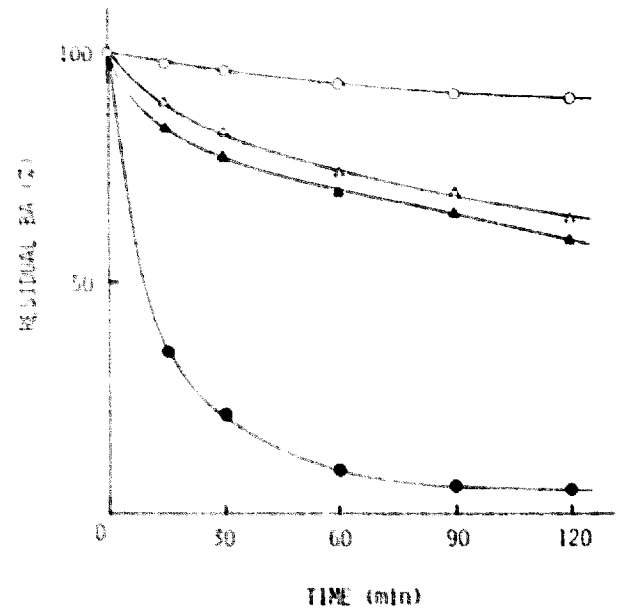


Fig. 6. Photodegradation curves of BA and its CyD complexes under aerobic condition. ●, BA alone; ○, α-CyD complex; △, β-CyD complex; ▲, γ-CyD complex.

γ-CyD complexes since it is harder to release the crystalline- or adhesional-water molecule from the α-CyD complex than the β- and γ-CyD complexes. This consideration is supported by the crystal structure of BA–α-CyD hexahydrate complex (Harata et al., 1981).

Since BA is known to yield mainly benzoic acid by the oxidation, the effects of CyDs on the appearance of benzoic acid were examined by thin-layer chromatography of BA and its complexes. Two spots, assigned to BA ($R_f \sim 0.86$) and benzoic acid ($R_f \sim 0.34$), were observed for the oxidation of BA, while the 3 complexes show only one spot corresponding to BA. Similar results were obtained for the photo-oxidation of the complexes. This clearly indicates that the main product of oxidation for BA is benzoic acid and that the CyD complex is chemically stable. On the other hand, no appreciable degradation was oberved for BA and its CyD complexes under anaerobic conditions since this reaction is known to be oxygen-dependent (Moore, 1976).

The present data indicate that the thermal and photochemical stabilities of BA are improved by all three CyDs, and particularly by α-CyD. Therefore, the formation of solid (powder) inclusion complexes of BA with CyDs improves the ease of handling and decreases the problems encountered upon prolonged storage of BA.

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