

Factors Affecting the Formation in the Solid State of the Metastable Complex between Naphthalene and Dimethyl- β -Cyclodextrin

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Abstract. An equimolar mixture of naphthalene and amorphous heptakis-(2,6-di-*O*-methyl)- β -cyclodextrin (DM β CD) was heated at 70 or 90 °C in a sealed container. After heating for 15 min at 90 °C, the mixture was crystallized to show an excimer fluorescence of naphthalene, and the fluorescence spectrum changed to a monomer emission by further prolongation of heating time, accompanied by a slight change in its powder X-ray diffractogram. It is suggested that a metastable complex showing the excimer emission of naphthalene was transformed to a stable complex showing the monomer emission. The mixing molar ratio of naphthalene to DM β CD was also found to affect the transformation temperature of the complex.

Key words: Naphthalene, heptakis-(2,6-di-*O*-methyl)- β -cyclodextrin, sealed heating, metastable complex, solid–solid reaction.

1. Introduction

Polymorphism is one of the important issues in pharmaceutical technology, since different polymorphic forms of a given solid differ from each other in regard to many physical properties such as solubility, crystal form and solid-state stability, which affects the properties of pharmaceutical preparations. Numerous investigators have therefore studied and characterized polymorphic forms of drugs by appropriate techniques, such as powder X-ray diffraction, thermal analysis, IR spectroscopy, Raman spectroscopy, and solid-state NMR [1–6]. Nakanishi *et al.* reported the crystal structures of two forms of β -cyclodextrin–barbital complexes [7]. A comparison of the crystal data showed that the unit cell volume of form **I** is about a half that of the form **II**, and that the host/guest ratio is 1/1 in both forms.

We have already reported that an inclusion compound of cyclodextrin was obtained by heating a mixture of a guest and cyclodextrin in a sealed contain-

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er [8–12]. In our previous paper [13], we reported that two kinds of complexes were formed when an equimolar physical mixture of naphthalene and amorphous heptakis-(2,6-di-*O*-methyl)- β -cyclodextrin (DM β CD) was heated in a glass ampoule. Depending on the heating temperature, each form of the complex displayed excimer or monomer fluorescence emission of naphthalene [14–16]. In the present study, in order to clarify the mechanism of the inclusion behavior, we have investigated the effects of heating time and mixing molar ratio on the complex formation by the sealed heating method, using powder X-ray diffractometry and solid-state fluorescence spectroscopy.

2. Experimental

2.1. MATERIALS

Heptakis-(2,6-di-*O*-methyl)- β -cyclodextrin (DM β CD; lot No. 43) was purchased from Toshin Chemical Co. (Tokyo, Japan), and was dried *in vacuo* at 105 °C for 6 h. The purity was ascertained by a single spot on TLC. Naphthalene (Wako Pure Chemical Industries, Ltd.) was of reagent grade.

2.2. PREPARATION OF PHYSICAL MIXTURE

DM β CD was amorphized by grinding for 10 min in a Heiko Seisakusho model TI-200 vibrational mill (Tokyo, Japan). The physical mixtures of naphthalene and the amorphous DM β CD were prepared at definite mixing molar ratios of naphthalene to DM β CD (naphthalene/DM β CD in molar ratios 0.5–2.0) by simple blending in a vial.

2.3. SEALED HEATING PROCEDURE

A physical mixture (300 mg) was sealed in a 2 mL glass ampoule, and then heated in an oil bath maintained at temperatures in the range 40–120 °C with a thermostat.

2.4. X-RAY DIFFRACTOMETRY

X-ray diffraction patterns for powdered samples were obtained with a Rigaku 2027 diffractometer (Tokyo, Japan). Conditions: target Cu, filter Ni, voltage 30 kV, current 5 mA, receiving slit 0.15 mm, count range 2000 cps, scanning speed 4°/min.

2.5. SOLID-STATE FLUORESCENCE SPECTROSCOPY [17]

Fluorescence spectra were measured using an FP-770F spectrofluorometer (Japan Spectroscopy Co., Ltd., Tokyo, Japan) equipped with a cell holder for the solid sample. Sample powder beds were prepared by light manual packing of the holder. Measurements were carried out at an excitation wavelength of 256 nm.

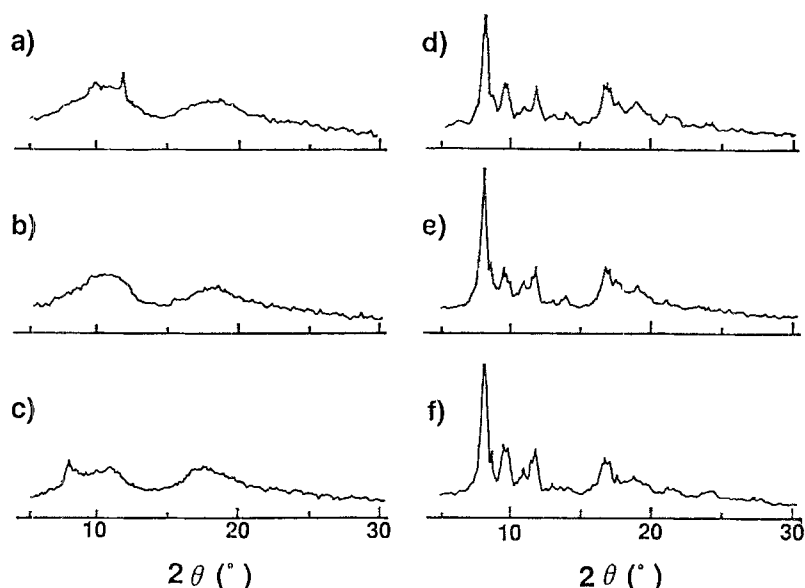


Fig. 1. Changes in the powder X-ray diffraction pattern of an equimolar physical mixture of naphthalene and DM β CD during heating at 70 °C. (a) An equimolar physical mixture of naphthalene and amorphous DM β CD after sealed-heating at 70 °C for: (b) 15 min; (c) 1 h; (d) 2 h; (e) 4 h; (f) 24 h.

3. Results and Discussion

3.1. EFFECT OF HEATING TIME ON THE PROPERTIES OF SEALED-HEATING SAMPLE

Figures 1 and 2 show changes in the powder X-ray diffractograms and solid-state fluorescence emission spectra of an equimolar physical mixture of naphthalene and amorphous DM β CD during sealed-heating at 70 °C. As shown in Figure 1(b), heating for 15 min revealed no change in the X-ray diffractogram from that of the physical mixture. After heating for over 2 h, crystallization took place with the appearance of a characteristic diffraction peak at $2\theta = 8.5^\circ$, the diffraction pattern of which was different from that of DM β CD crystals. Fluorescence emission spectra of the samples heated at 70 °C showed that the excimer peak around 390 nm grew in intensity as heating was prolonged; heating for over 2 h provided only the excimer emission.

The results of sealed heating at 90 °C are shown in Figures 3 and 4. Heating at 90 °C for 15 min provided the same diffraction pattern and fluorescence spectrum as those observed after heating at 70 °C for 2 h [Figures 1(d) and 2(d)]. After heating at 90 °C for 24 h, only monomer fluorescence emission was observed in the solid state fluorescence spectra, and the powder X-ray diffraction pattern showed characteristic peaks around $2\theta = 11^\circ$ and 18° , which was different from that of the sealed sample heated at 70 °C for 24 h, as reported in our previous

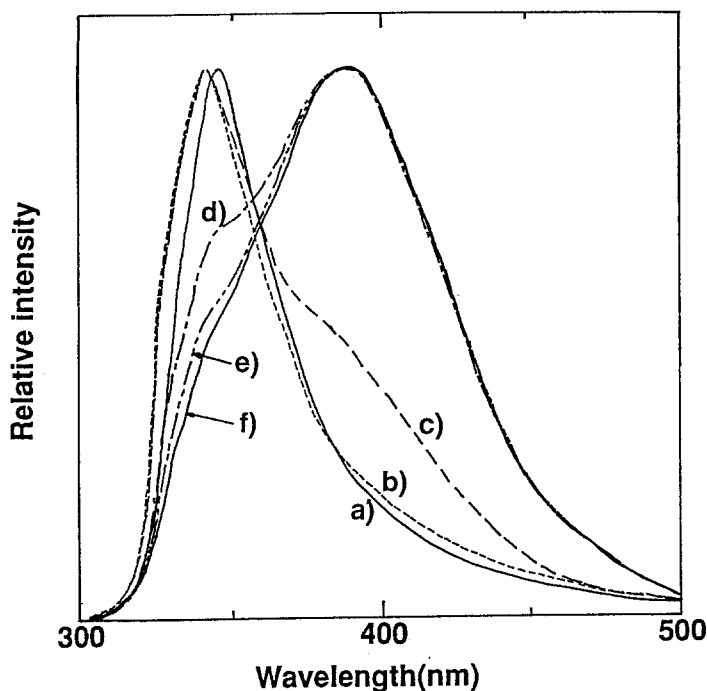


Fig. 2. Changes in the solid-state fluorescence emission spectrum of an equimolar physical mixture of naphthalene and DM β CD during sealed heating at 70 °C ($\lambda_{\text{ex}} = 256$ nm). (a) An equimolar physical mixture of naphthalene and amorphous DM β CD after sealed heating at 70 °C for: (b) 15 min; (c) 1 h; (d) 2 h; (e) 4 h; (f) 24 h.

paper [13]. These results indicate that a complex showing an excimer emission was formed immediately after heating at 90 °C, accompanied by crystallization, the naphthalene molecules then gradually changing their molecular arrangement to form another complex showing a monomer emission. It seems reasonable to state that the complex showing the excimer emission was metastable, having a transition to a stable state showing the monomer emission; i.e., a structural stabilization took place during the process of sealed heating at 90 °C.

3.2. EFFECT OF MIXING MOLAR RATIO (NAPHTHALENE/DM β CD) ON COMPLEX FORMATION

Nakai *et al.* reported that the initial mixing ratio affected the inclusion behavior in a system of benzoic acid and DM β CD which were sealed and heated together [12]. Figure 5 shows the solid-state fluorescence spectra of physical mixtures at initial molar ratios of 1.0, 1.5 and 2.0 (naphthalene/DM β CD) after heating at 70 °C for 24 h in a 2 mL glass ampoule. The fluorescence spectrum of the 1 : 1 mixture showed only an excimer emission. In the case of the 1.5 : 1 mixture, both the monomer and excimer peaks were observed. Further, the spectral pattern of the 2 : 1 mixture showed only a monomer emission, even though it was considered

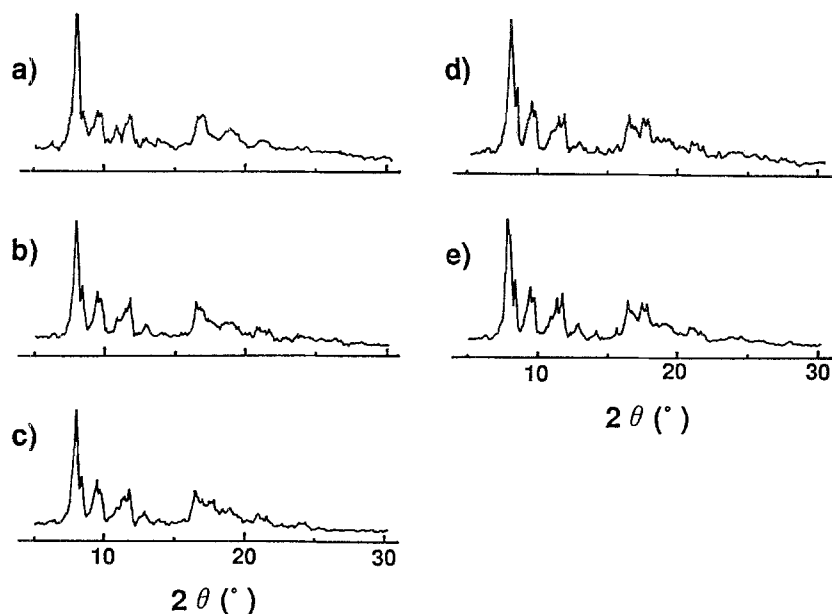


Fig. 3. Changes in the powder X-ray diffraction pattern of an equimolar physical mixture of naphthalene and DM β CD during sealed heating at 90 °C. After sealed-heating of an equimolar physical mixture of naphthalene and amorphous DM β CD at 90 °C for: (a) 15 min; (b) 1 h; (c) 2 h; (d) 4 h; (e) 24 h.

that the excimer state had once existed as an intermediate state during the heating. Increasing the mixing molar ratio caused the rapid transformation from the excimer state to the monomer state under the same conditions. It seems convenient to define the fluorescence intensity ratio at 341 and 390 nm, $I_{390\text{nm}}/I_{341\text{nm}}$, as an objective indication of the fractional ratio of the excimer state to the monomer state. Figure 6 illustrates a plot of $I_{390\text{nm}}/I_{341\text{nm}}$ against sealed-heating temperature at various mixing ratios upon heating for 24 h. At any mixing ratio, the value of $I_{390\text{nm}}/I_{341\text{nm}}$ decreased as the heating temperature increased, indicating that the complex showing the monomer fluorescence emission was produced in higher amount at higher heating temperature. Furthermore, the temperature at which the metastable state transformed to the stable state reduced with an increase in the mixing ratio. We may say that the transformation in the solid state from the metastable state to the stable state is kinetically unfavorable, to some extent requiring molecular activation. In the present equimolar system of naphthalene–amorphous DM β CD, there is insufficient molecular activation at 70 °C, but sufficient at 90 °C. Therefore, heating the equimolar physical mixture at 70 °C, even for long periods, could not ensure the formation of the stable complex. On the other hand, increasing the mixing molar ratio of naphthalene to DM β CD makes the transformation easy, resulting in a lowering of the transformation temperature.

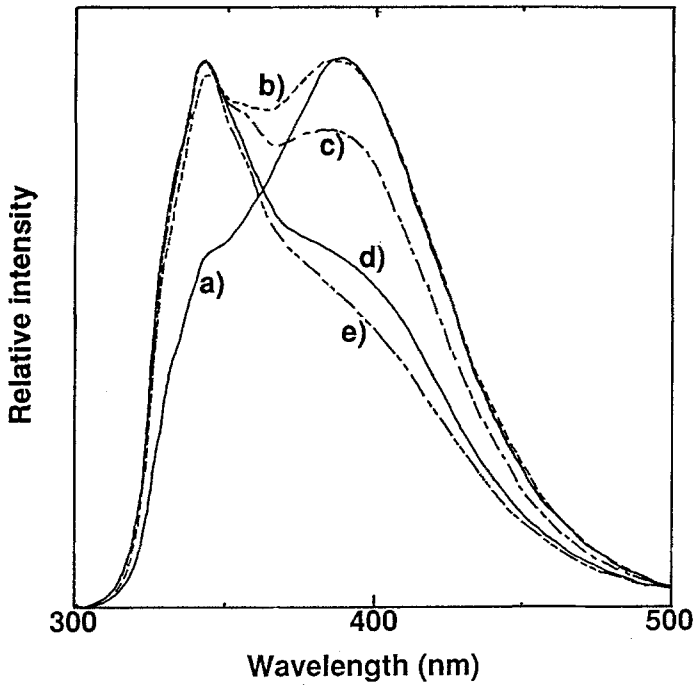


Fig. 4. Changes in the solid-state fluorescence emission spectrum of an equimolar physical mixture of naphthalene and DM β CD during sealed heating at 90 °C ($\lambda_{\text{ex}} = 256$ nm). After sealed heating of an equimolar physical mixture of naphthalene and amorphous DM β CD at 90 °C for: (a) 15 min; (b) 1 h; (c) 2 h; (d) 4 h; (e) 24 h.

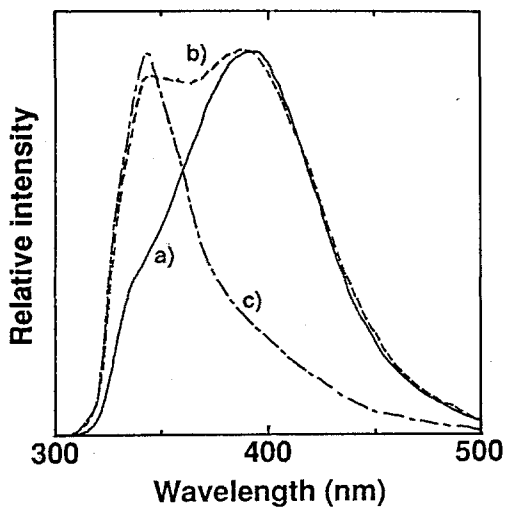


Fig. 5. Solid-state fluorescence emission spectra of sealed samples heated at 70 °C for 24 h in various mixing molar ratios ($\lambda_{\text{ex}} = 256$ nm). Mixing molar ratio (naphthalene mol:DM β CD mol): (a) 1:1; (b) 1.5:1; (c) 2:1.

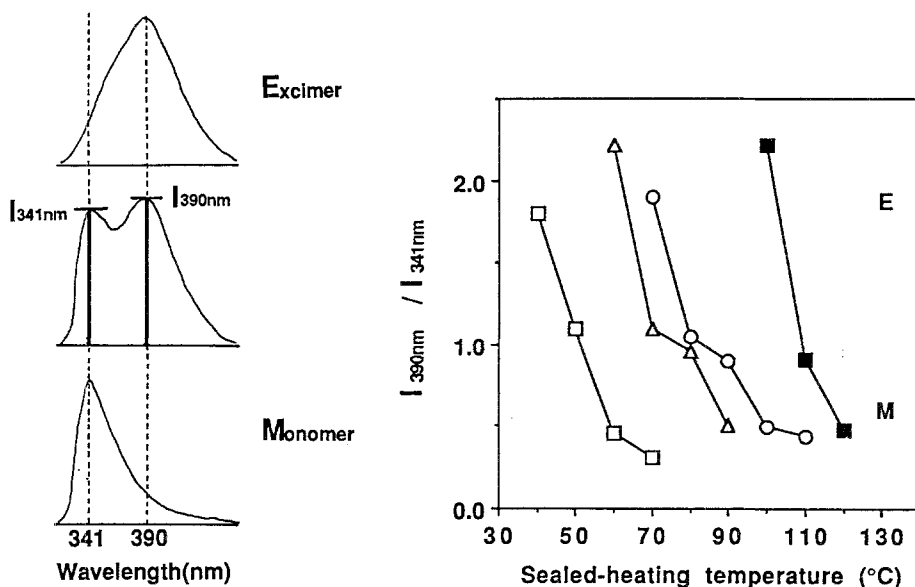


Fig. 6. Effect of sealed-heating temperature on the ratio $I_{390\text{nm}}/I_{341\text{nm}}$ of sealed samples heated at various mixing ratios. Mixing ratio (naphthalene mol/DM β CD mol): (—■—) 0.5; (—○—) 1.0; (—△—) 1.5; (—□—) 2.0.

In conclusion, the results of the sealed-heating process at 90 °C in an equimolar naphthalene–amorphous DM β CD system showed that the solid complex displaying an excimer emission was in a metastable state and was formed under mild conditions. An increase of the mixing ratio induced the transformation to a stable state under definite heating conditions. The structures of these complexes should be elucidated; these are currently under investigation.

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