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Characterization by Simultaneous X-ray Diffractometry and Differential Scanning Calorimetry of the Exothermic Change of Dimethyl-β-cyclodextrin Prepared by Drying after Solvent Dissolution

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Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CD), prepared by dissolution in either pure water or acetone and dried at 40 °C, showed a characteristic exothermic change in the range 160–185 °C. Simultaneous X-ray diffractometry and differential scanning calorimetry (XRD-DSC) clearly showed the transition of DM-β-CD from an amorphous to a crystalline state during exothermic reactions.

Cyclodextrin (CD) has the ability to form an inclusion compound with many guest molecules. Several kinds of modified CD have been synthesized to improve their physicochemical properties and their inclusion ability. For instance, heptakis-(2,6-di-*O*-methyl)-β-CD (DM-β-CD) has such a characteristic property that increases its water solubility by almost 30-fold when compared with the parent β-CD, and dissolves well in cold water with exothermic dissolution.[1] Several preparation methods to obtain inclusion compounds with CD, coprecipitation,[2,3] kneading,[4,5] co-grinding,[6–8] and sealed heating,[9] have been available in the fields of organic chemistry and pharmacy. Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) have been used to investigate the formation of inclusion compounds by thermal reactions in the solid phase for the ground mixture of benzoic acid (BA) and either DM-β-CD[9,10] or heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD)[11] by the methods of co-grinding or co-grinding and sealed heating in a glass ampoule.

We have reported our thermal analyses of several types of CD in the solid state, but we did not observe any exothermic change of DM-β-CD before the initiation of thermal decomposition.[12] Recently, we found that the dried powder of DM-β-CD dissolved in either pure water or acetone showed a characteristic exothermic change without any loss of weight as observed by thermogravimetry and differential thermal analysis (TG-DTA). Therefore, in the study reported here, we use the new technique of simultaneous X-ray diffractometry and differential scanning calorimetry (XRD-DSC)[13] to elucidate this exothermic change of DM-β-CD.

Experimental

Sample Preparation. Cyclodextrins, α-CD, β-CD, γ-CD, DM-β-CD, and hydroxypropyl-β-CD (HP-β-CD) were provided by Nihon Shokuhin Kako Co., Ltd (Tokyo, Japan). TM-β-CD was purchased from Wako Pure Chemicals (Osaka, Japan) and used without further purification. Another DM-β-CD was purchased from Nakalai Tesque Ltd (Kyoto, Japan), and heptakis(2,3,6-tri-*O*-acetyl)-β-CD (TA-β-CD) was synthesized according to the previously published method.[14] The samples of DM-β-CD produced by Nihon Shokuhin Kako and Nakalai Tesque are indicated as DM-β-CD (A) and DM-β-CD (B), respectively.

The samples for thermal analysis were prepared as follows. The CD was dissolved in pure water or acetone and dried in a drying oven at 40 °C for several hours or half an hour, respectively. These samples are named "dissolved" in this study. For the other preparation method described in the literature (i.e., grinding the powder of DM-β-CD and TM-β-CD by a vibration mill),[15] we used a SpectroMill ball Pestle Impact Grinder (Model 1100, Chemplex Industries, Inc., NY, U.S.A.).

Thermal Analyses. TG-DTA and DSC were accomplished using a Rigaku TG 8120 and DSC 8230L (Tokyo, Japan), respectively, under the following conditions: heating rate 5 °C min^{-1} and N_2 flow 50 mL min^{-1}. Simultaneous XRD-DSC analysis was done using a Rigaku RINT Ultima under the following conditions: (1) X-ray diffractometry: Cu K (40 kV, 50 mA), scanning 20° min^{-1}, sampling step 0.020°; (2) DSC: heating rate 3 °C min^{-1}, N_2 flow 50 mL min^{-1}.

Results and Discussion

The DM-β-CD (A) powder obtained by dissolution in pure water and dried at 40 °C showed a characteristic exothermic change in the range 177–186 °C (peak temp 182 °C) on TG-DTA (Fig. 1), without any weight-loss other than from dehydration (−2.79%) at less than 100 °C. The same result was obtained for DM-β-CD (A) powder prepared from acetone (not shown); the exothermic change in the range 174–186 °C (peak temp 182 °C) was observed, and the weight loss below 100 °C by dehydration was −4.76%. Similar results were obtained for the samples of DM-β-CD (B) powder prepared from water and acetone.

XRD-DSC analysis was carried out to elucidate the exothermic change of each solid powder (i.e. non-dissolved and dissolved) and Figures 2 and 3 show the respective XRD-DSC patterns. The XRD pattern of the dissolved DM-β-CD (A) clearly changed at 164–172 °C during an exothermic change, and new diffractions appeared in the 2θ range of 8–22° (8.3, 9.8, 10.2, 11.8, 12.2, and 16.8°), which were the same as those for the non-dissolved DM-β-CD (A). Thus, TG-DTA showed that the amorphous state of the dissolved DM-β-CD transformed exothermally to a crystalline structure; the process was irreversible because there was no endothermic peak from the successive cooling process (not shown). Moreover, when the DM-β-CD (A) that was dissolved in water was dried at temperatures higher than 50 °C, the compound had no exothermic peak around 182 °C on TG-DTA (i.e., the exothermic peak of the sample

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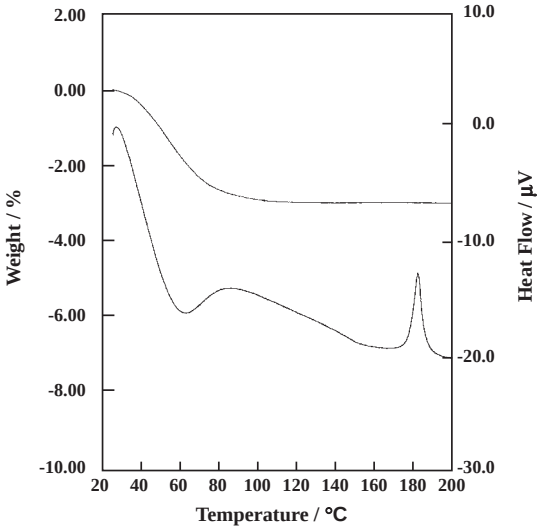

Fig. 1. Thermograms of DM-β-CD (A) powder prepared by dissolution in pure water and dried at 40 °C. Upper, TG; lower, DTA.

prepared at 40 °C had vanished), which indicates crystallization even took place during the drying process at 50 °C.

In contrast, both the non-dissolved and dissolved TM-β-CD gave two endothermic peaks similar to methylated CD: one at 45 °C that was attributable to dehydration with 0.9% weight-loss until 90 °C and the other one attributed to fusing at 156 °C. Moreover, in our experiments, there was a very small exothermic change at around 89 °C on the DTA curve of non-dissolved TM-β-CD due to the glass transition change reported by Tsukushi,[16] but it was not observed in the case of dissolved TM-β-CD. Thus, DM-β-CD was notably different from TM-β-CD.

We also used TG-DTA to examine other types of CD (i.e., α-CD, β-CD, HP-β-CD, TA-β-CD, TM-β-CD, or γ-CD) prepared by drying at 40 °C after being dissolved in water or acetone, and none of them showed an exothermic peak around 182 °C. It is very interesting that only DM-β-CD had an exothermic peak near 182 °C (on TG-DTA), which might be attributable to its characteristic properties. The estimated crystallization energy and peak temperature by DSC of DM-β-CD (A) prepared from water and acetone was $16.7 \pm 2.3\,J\,g^{-1}$ (183 °C) and $18.3 \pm 1.6\,J\,g^{-1}$ (184 °C), respectively.

In order to compare our preparation method with the grinding method, TG-DTA analysis was performed under the same analytical conditions as for dissolved CD. The powder of non-dissolved β-CD and non-dissolved DM-β-CD (A) were ground for 5 min with the steel impact grinder. The β-CD did not show an exothermic peak, but DM-β-CD had a small exothermic peak at 156 °C (in the range 151–161 °C) with a crystallization energy of $2.6\,J\,g^{-1}$ (value corrected for water content −2.62%). This amount of energy was too small a value and the peak temperature was ca. 24 °C lower in comparison with that obtained by solvent removal preparation. Moreover, a very small exothermic change of $0.4\,J\,g^{-1}$ at 90 °C (in the range 89–91 °C) was observed. Then, we extended the grinding time for DM-β-CD (A) to 15 min, which gave a crystallization energy of $7.1\,J\,g^{-1}$ (value corrected for water content −2.65%) at 156 °C (in the range 151–161 °C), but gave no exothermic change at 90 °C. The energy of $7.1\,J\,g^{-1}$ was about 43% of that of the DM-β-CD (A) obtained by the solvent removal preparation method ($16.7\,J\,g^{-1}$). Therefore, not even grinding for 15 min was sufficient for amorphization. According to the literature,[11] the diffusion of molecules can be activated in an amorphous solid, and then the inclusion reaction should be enhanced. Thus, our method of drying at low temperature after dissolution in solvent might be more convenient and complete than mechanical grinding for the creation of the amorphous state of DM-β-CD.

Conclusion

DM-β-CD powder, obtained by drying at 40 °C after dissolution in either pure water or acetone, formed the amorphous state and revealed a characteristic irreversible exothermic change on TG-DTA at around 180 °C without weight loss. The recent technique of XRD-DSC analysis clearly showed the transition of DM-β-CD from the amorphous to the crystalline state during the exothermic process, and the crystallization energy was estimated.

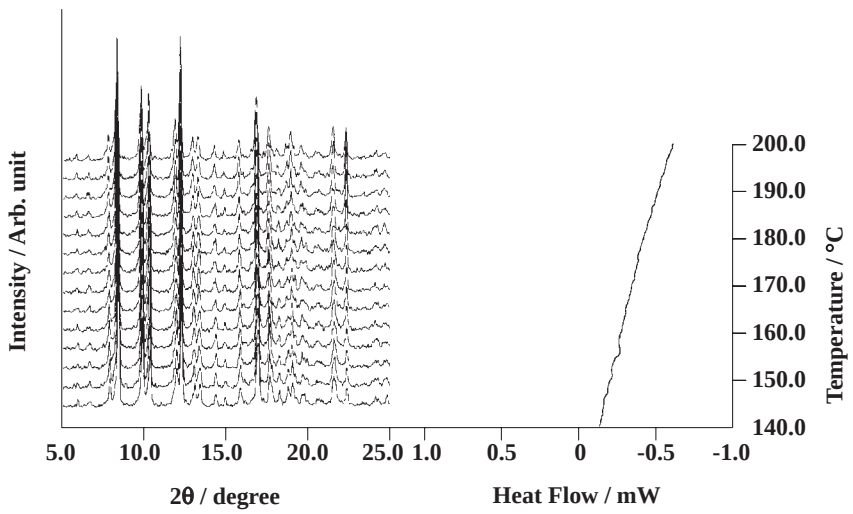

Fig. 2. XRD-DSC patterns of non-dissolved DM-β-CD (A) powder.

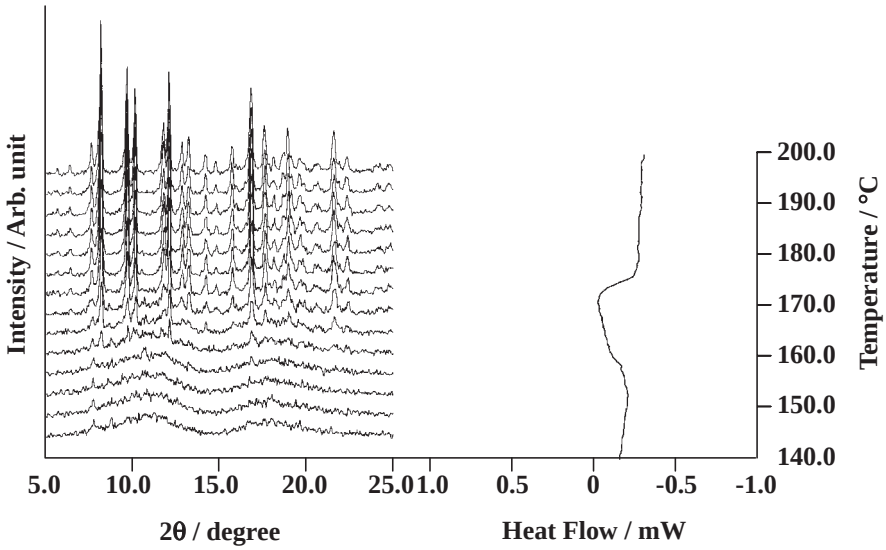

Fig. 3. XRD-DSC patterns of DM-β-CD (A) powder prepared by drying at 40 °C after dissolution in pure water.

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