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INTERCALATION PHENOMENA AND POLYMORPHISM OF CHOLIC ACID CRYSTALS

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Abstract Cholic acid affords polymorphic crystal forms. The molecular assemblies have a guest-dependent bilayered structure. Insertion and replacement of guest molecules between the layers took place with retention of the crystalline state. The intercalation phenomena give us an opportunity to understand a structure-property relationships in organic solids.

Keywords: Intercalation, Polymorphism, Cholic Acid, Bilayered Structure

INTRODUCTION

Cholic acid[1] and its derivatives[2] form inclusion compounds with a variety of organic substances. An X-ray crystallographic study indicated that the inclusion compound of cholic acid with acetophenone is a new channel-type one.[3] By chance, we also obtained crystals with no guest molecules.[4] We observed that the crystals spontaneously absorbed guest molecules, such as acetophenone, with retention of the crystalline state. On the basis of the bilayered structure of the assemblies, we interpret this as an intercalation phenomenon, much like that occurring in inorganic compounds, such as graphite and clay.[5] Here we report our subsequent study on both polymorphism of the cholic acid crystals and the interconversion of the polymorphic crystal forms induced by guest components. The scanning electron micrography gives us valuable information for understanding the behavior of the crystals.

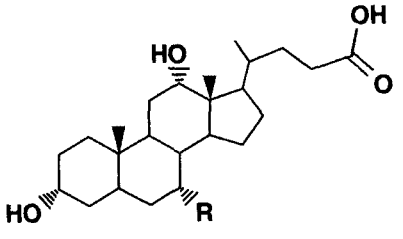

FIGURE 1 Host molecules.
R=OH:Cholic acid
R=H:Deoxycholic acid

POLYMORPHISM OF CHOLIC ACID CRYSTALS

The recrystallization of cholic acid from various organic liquids yields beautiful crystals with various forms, such as needles, plates, columns, prisms, and hexagons. We have systematically investigated their crystal structures by X-ray diffraction methods. Table I summarizes crystal data for the inclusion compounds of cholic acid.

The crystal structures may be conveniently organized into three groups. The first is an orthorhombic crystal. The steroidal molecules are linked to each other to form helical hydrogen-bonded networks. Ethanol molecules join the networks, while acrylonitrile molecules are accommodated in the cavities. The second is a monoclinic one. The carboxylic groups hydrogen bond with hydroxy groups to form bilayers so as to leave channels. The guest molecules are included into channels between the layers. The conformation of the steroidal side chains is trans in the case of γ-valerolactone, but it is gauche in the case of acetophenone. The channels are closed, and in some cases retain a bilayer structure. For example, 3-methylcyclohexanone molecules join the hydrogen-bonded networks with the trans conformation of the steroidal chain, while water molecules join the networks with the gauche conformation. The third type of structure is a hexagonal one. We obtain such crystals when cholic acid is recrystallized from liquid guests that do not form the inclusion compounds.

TABLE I Crystal data for cholic acid inclusion compounds.

Guest	Crystal system	Space group	a (Å)	b (Å)	c (Å)	β (°)	Ref.
None	Orthorhombic	$P2_12_12_1$	16.48	8.39	16.99	90.0	4
Ethanol	Orthorhombic	$P2_12_12_1$	14.65	11.74	15.05	90.0	9,10
Acrylonitrile	Orthorhombic	$P2_12_12_1$	16.90	8.54	17.86	90.0	8
Water	Monoclinic	$P2_1$	12.79	8.16	12.89	117.6	11
Acetophenone	Monoclinic	$P2_1$	13.72	8.09	14.23	113.7	3
γ-Valerolactone	Monoclinic	$P2_1$	13.01	8.00	14.05	104.8	7
Acetylacetone	Triclinic	$P1$	12.31	8.20	14.47	105.4	8
3-Methylcyclohexanone	Monoclinic	$C2$	22.15	8.23	16.90	109.7	8

The detailed crystal structure is unknown. The helical arrangement of the molecules is a plausible crystal structure.

INTERCALATION PHENOMENA

We have been studying one-dimensional inclusion polymerization by using deoxycholic acid (Figure 1) and apocholic acid as the host component since 1973.[12] In the polymerization process, we usually obtain inclusion compounds with monomers by a method[14] that consists of the replacement of acetone by diene monomers in channels. Since the crystals of deoxycholic acid molecules are composed of bilayers, it should involve an intercalation of guest molecules between the layers. However, we could not prove the phenomenon by X-ray crystallographic study, because the host molecules do not afford crystals in the absence of guest molecules.

We discovered crystals of cholic acid with no guest molecules and succeeded in determining the crystal structure. Furthermore, the crystals spontaneously absorbed organic liquid guests, as in the case of deoxycholic acid, which enabled us to interpret the phenomenon by intercalation between the layers.[5] However, we need much time for obtaining a few single crystals suitable for the X-ray analysis.

We searched for the interconversion between the polymorphic crystals by scanning electron micrography. We have found that the replacement of guest molecules can take place in the channels with

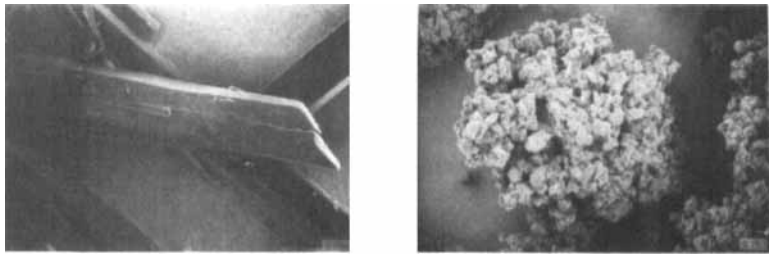

FIGURE 2 Scanning electron microscopic photographs of crystals of cholic acid after soaking for 42 days in acetylacetone (left) and for 5 minutes in ethanol (right). The original inclusion crystals were obtained from recrystallization from γ-valerolactone.

retention of the crystalline state. Figure 2 shows an example of this phenomenon. In contrast, the crystals are destroyed in the case of ethanol.

CONCLUDING REMARKS

Small molecules, such as bile acids and their derivatives, form molecular assemblies composed of pleated bilayers.[2,3] There are several stacking modes of the layers.[8] The assemblies have guest-responsive and dynamical structures, which lead to an intercalation of guest molecules into the layers. The sliding of the layers yields interlayer spacings, called channels, for inclusion of guest molecules.[5] Depending on the structures of the host molecules, the channels have characteristic shapes and sizes, which results in the corresponding molecular recognition behavior.[6,7] In some cases, the channels serve as molecular-level spaces suitable for one-dimensional inclusion polymerization[12] and photoreaction.[13]

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