First Columnar Monolayer Structure of Bile Acids Inclusion Crystal. Inclusion Compounds of 23-Nordeoxycholic Acid

Kazuki Sada, Michihiro Sugahara, Yoshihiro Nakahata,† Yoshitaka Yasuda,† Akinori Nishio,† and Mikiji Miyata
Material and Life Science, Graduate School of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565
†*Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-11*

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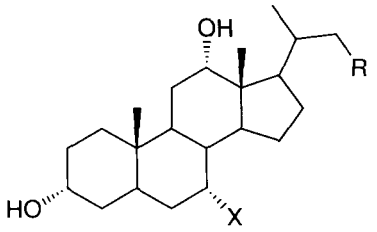
A new host, 23-nordeoxycholic acid, which forms inclusion compounds with many organic compounds, have a novel monolayer columnar structure in spite of a facially amphiphilic molecular structure.

Deoxycholic acid (3α, 12α-dihydroxy-5β-cholan-24-oic acid **1**) and cholic acid (3α, 7α, 12α-dihydroxy-5β-cholan-24-oic acid **2**) are much of interest due to facially amphiphilic molecular structures.[1] In recent years, they have been employed as a building block for supramolecular architecture.[2] The facial amphiphilic molecular structure can be recognized as a design of organic crystals.[5,6] They have a bilayer structure through hydrogen bonding between the hydrophilic faces and association of the lipophilic faces.[3,5] However, we report herein an unprecedented *monolayer* structure in an inclusion crystal of 24-nordeoxycholic acid (3α,12α-dihydroxy-23-nor-5β-cholan-23-oic acid **3**). **3** is the first bile acid that has the monolayer structure. We present here crystal structures and the inclusion abilities of **3**.



1: X=H, R=CH_2COOH
2: X=OH, R=CH_2COOH
3: X=H, R=COOH

3 was prepared by the side chain degradation of **1**.[7] More than 40 organic compounds such as alcohols, ketones, and aromatic compounds, were included in **3**. Guest molecules are summarized in Table 1. **3** forms the inclusion compounds with as many organic compounds as **1**.[3] Compared to the large host-to-guest ratios of **1**, **3** had generally 1:1 or 2:1 host-guest ratios. This result shows that **3** has the larger host cavity and more polymorphic forms of the host assemblies than **1**. Indeed, XRD indicated that at least five polymorphs exist responsively on the guest molecules. Among them, ethanol and benzyl alcohol clathrates were characterized crystallographically.[8]

The ethanol clathrate has the unique monolayer structure. Figure 1 shows the crystal structures of the ethanol clathrate. The carboxyl group of one host molecule is hydrogen bonded to two hydroxy groups from another host molecule. This hydrogen bond yields a monolayer column along two-fold screw axis. The guest molecule is incorported between the columns and the alcoholic oxygen atom bridges the columns by the double hydrogen bonds.

On the other hand, the benzyl alcohol clathrate has the bilayer structure. Figure 2 shows the crystal structures of the benzyl alcohol clathrate. Hydrogen bonds between the hydrophilic faces provides the bilayer structure. Molecular arrangement in the structure is similar to those in the bilayer clathrates of **1**.[3] Compared with the chain hydrogen bond network of **1**, a cyclic hydrogen bond network is observed in the bilayer structure of **3** due to the shorter side chain. Host channels run in the lipophilic layer, in which the phenyl group is incorporated.

Table 1. Guest Molecules of **3**

Guest	host:guest ratio[a]	Guest	host:guest ratio[a]
ethanol	1:1	acetone	2:1
1-propanol	1:1	2-butanone	2:1
2-propanol	1:1	2-pentanone	2:1
1-butanol	2:1	2,4-pentandione	2:1
2-butanol	1:1	methyl formate	2:1
2-methyl-1-propanol	2:1	ethyl formate	2:1
2-methyl-2-propanol	1:1	n-propyl formate	2:1
1-pentanol	2:1	n-butyl formate	2:1
2-pentanol	1:1	methyl benzoate	2:1
3-methyl-2-butanol	1:1	m-tolyl acetate	2:1
1-hexanol	2:1	acetonitile	1:1
benzyl alcohol	1:1	benzonitrile	2:1
1,4-dioxane	2:1	o-xylene	1:1
tetrahydrofuran	2:1	water	1:1

[a]Determined by TGA.

The large inclusion cavities and the host polymorphism dependent on guest molecules enable **3** to include various oragnic compounds. The guest molecules are included in the most suitable host cavities. XRD diffrations revealed that 1:1 clathrates with various aliphatic alcohols formed the monolayer structure and that aromatic compounds yielded the bilayer structure.

Length of the steroidal side chain affects structural variation of the host assemblies. **3** forms the monolayer and the bilayer structures, and **1** forms only the bilayer structure.[3] The shorter side chain of **3** by one methylene than **1** induces the conformational change of the terminal carboxyl group. The carboxyl plane of **3** is nearly perpendicular to the steroidal plane. This conformation directs one of the two oxygen atoms to the lipophilic face and enables to form the hydrogen bonds from both sides (Figure 3). On the other hand, **1** has the parallel conformation and both of two oxygen atoms are directed to the hydrophilic face. Hydrogen bonding from the hydrophilic face are preferable in the crystal sturctures of **1**.

In summary, we have been demonstrated the inclusion properties and the crystal structure of **3**. **3** can form both the monolayer and bilayer structure in crystalline state. Comparison of the crystal structures of **1** with those of **3** shows that the

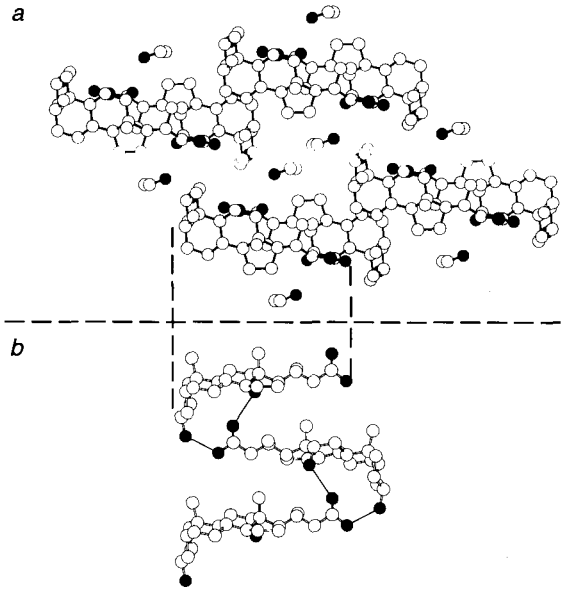


Figure 1. (a) Crystal strcuturc of **3** with ethanol (1:1) viewed from crystallographic *b*-axis; (b) side view of the monolayer column. Solid lines represent hydrogen bonds. Full and open cirlces represent oxygen and carbon atoms, respectively.

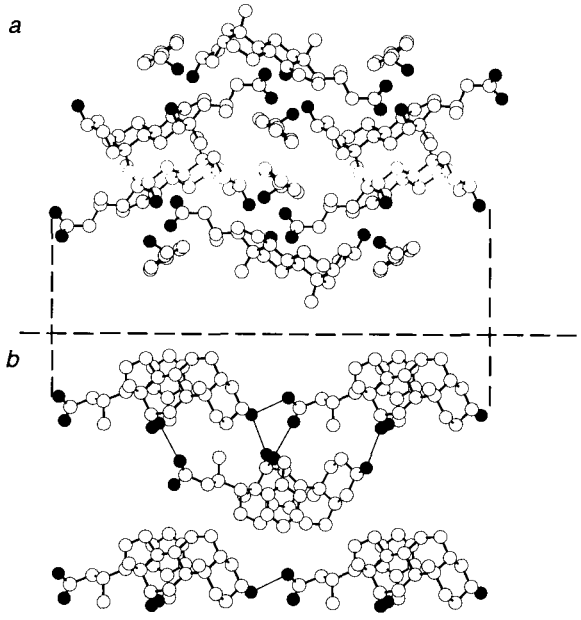


Figure 2. (a) Crystal strcuture of **3** with benzyl alcohol (1:1) viewed from crystallographic *c*-axis; (b) side view of the hydrophilic layer. Solid lines represent hydrogen bonds. Full and open cirlces represent oxygen and carbon atoms, respectively.

conformation of the carboxy group at the side chain plays an important role for the structures of the host assemblies. Exploring inclusion properties and the crystal structures of the steroidal bile acids and their derivatives must give us new insight to design inclusion cavities or molecular crystals. Successive structural studies of other polymorphs of **3** are under investigation to elucidate

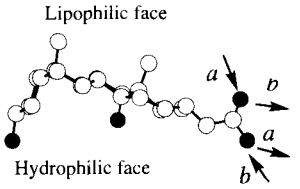


Figure 3. Ball-stick models and the directions of hydrogen bondings of the carboxy group of **3**. *a*: found in **3**+ethanol, and *b*: in **3**+benzyl alcohol. Full and open cirlces represent oxygen and carbon atoms, respectively. Arrows shows the directions of hydrogen bonding.

specific recognition of the crystal structures by the guest molecules.

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8 Crystal data for (a) **3**+ethanol(1:1): $C_{25}H_{44}O_5$, monoclinic $P2_1$, a=11.247(10) Å, b=10.303(5) Å, c=12.059(7) Å, β=117.13(4) °, V=1243(1) Å^3 , Z=2, D_c=1.17 g•cm^{-3} (b) **3**+benzyl alcohol(1:1): $C_{30}H_{46}O_5$, orthorhombic $P2_12_12_1$, a=14.700(3) Å, b=16.437(4) Å, c=11.481(5) Å, V= 2773(1) Å^3 , Z=4, D_c=1.17 g•cm^{-3} Intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromatized Mo-Kα radiation. 3026 and 3586 reflections were unique for the crystals (a) and (b). 2715 and 1549 observed reflections with [$|F_o|>3\sigma(|F_o|)$] were used for further calculations after Lorenz and polarization corrections, respectively. The structures were solved by direct methods (SHELXS86) and refined by full-matrix least-squares procedure. All non-hydrogen atoms were refined anisotropically. C-H were located in calculated positions and O-H positions were obtained from difference Fourier syntheses. The final R values are 0.041 and 0.050 respectively. All calculations were performed using the TEXSAN crystallographic software package of the Molecular Structure Corporation.