Novel Molecular Arrangement in Asymmetric Bilayered Crystals of the Inclusion Compounds of 3α, 12α, 24-Trihydroxy-5β-cholane

Kazuki Sada, Akemi Matsuo, and Mikiji Miyata*†
Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-11

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A novel molecular arrangement in asymmetric bilayered crystals is described. 3α, 12α, 24-trihydroxy-5β-cholane with benzene clathrate (2:1) have multibilayer structure with *parallel* fashions both in the lipophilic sites and in the hydrophilc sites.

Deoxycholic acid (R_1=H, R_2=CO_2H;(**1**)), cholic acid (R_1=OH, R_2=CO_2H;(**2**)) as well as their derivatives, are facial molecules with high asymmetry, amphiphilicity and multifunctionality, leading to clear recognition of three directions; *head* and *tail*, *right* and *left*, as well as *belly* and *back*, as schematically shown in Figure 1(a). These molecules usually associate together by various hydrogen bonds to yield different asymmetric bilayered crystals.[1] In such crystals the molecules are theoretically expected to employ diversible molecular arrangements. For example, in the case of the *head* and *tail* direction, we can distinguish two kinds of molecular arrangements, called *parallel* or *antiparallel*, in both the hydrophilic and lipophilic sites of the bilayers.[3a] Figure 1(b) exemplifies that **1** employs a *parallel* arrangement in the hydrophilic (*HP*) sites, but an *antiparallel* one in the lipophilic (*LP*)sites (the arrows indicating the direction from the *tail* to *head*). In principle, there are four combinations of the directions as shown in Table 1. The former two combinations were observed in the cases of over fifty crystal structures of **1**,[2] **2**[3] as well as their derivatives, such as deoxycholanamide (R_1=H, R_2=$CONH_2$;(**5**))[4] and cholanamide (R_1=OH, R_2=$CONH_2$;(**6**))[5] and methyl cholate (R_1=OH, R_2=CO_2CH_3;(**7**)).[6] In contrast, we first confirmed that 3α, 12α, 24-trihydroxy-5β-cholane (R_1=H, R_2=OH;(**3**)) exhibits the third arrangement (*parallel* in both sites), only when the guest is benzene, as described below.

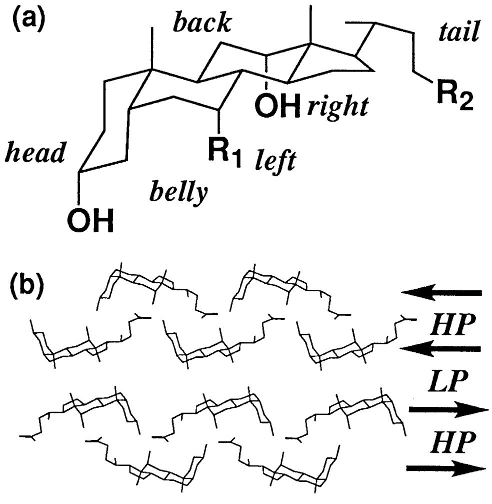

Figure 1. (a) Three directions of bile acids and their derivatives; (b) Schematic representation of a molecular arrangement; parallel in a hydrophilic site and antiparallel in a lipophilic site. The arrows indicate the direction from the tail to the head.

Table 1. Classification of molecular arrangements in asymmetric bilayers composed of steroidal molecules

Type	Hydrophilic sites	Lipophilic sites	Examples of hosts (guest)
1	parallel	antiparallel	**1** (ferrocene)[2b] **1** (p-xylene)[2c] **3** (p-xylene)
2	antiparallel	antiparallel	**2** (acetophenone)[3a] **2** (benzene)[3d] **5** (1-butanol)[4] **6** (1,4-dioxane)[5a] **7** (methanol)[6a]
3	parallel	parallel	**3** (benzene)
4	antiparallel	parallel	unknown

3 was prepared by the usual method described in literature.[7] Recrystallization resulted in the inclusion compounds of **3** with a variety of organic substances, such as aromatic or aliphatic hydrocarbons, ketones, ethers, esters and so on. As far as we know, this is the first study which establishes the inclusion ability of **3**. We assume that a high solubility of **3** prevents us from finding the inclusion ability. Addition of a large amount of less soluble liquid guests in the presence of a small amount of the good solvent for **3** gave the inclusion crystals successfully. It is noteworthy that an alcoholic derivative of **2** (R_1=OH, R_2=OH;(**4**)) exhibits no inclusion ability.[8]

The inclusion compounds of **3** with aliphatic compounds had large molar ratios of the host to guest, such as 3:1 or 4:1, which was revealed by ^{1}H nmr spectroscopy and thermogravimetry. However, the compounds with aromatic hydrocarbons, such as benzene, toluene and xylene, had 2:1 molar ratios. These results are very similar to those of **1**, indicating that **3** has a crystal structure similar to **1**. This was verified by X-ray structural analysis of the inclusion crystals, but one exception was found as follows.

Prismatic crystals were obtained from an alcoholic solution of **3** in the presence of a large amount of liquid guests. Figure 2(a) shows the bilayered crystal structure of a 2:1 complex between **3** and benzene, viewed down along the crystallographic *c* axis.[9a] The striking feature is that the host molecules arrange in a *parallel* fashion in the lipophilic sites, meaning the reverse as those of crystal structures of **1** and **2**. However, the other guests, such as toluene and xylene altered the arrangement to the *antiparallel* fashion. Figure 2(b) illustrates the crystal structure of a 2:1 complex between **3** and *p*-xylene.[9b] X-ray powder diffraction revealed that many inclusion crystals involving different guests had the *antiparallel* arrangement.

In the hydrophilic sites, the host molecules arrange in a *parallel* arrangement, which is the same as those of **1**, in the cases of all the guests mentioned above. This is responsible for a similar

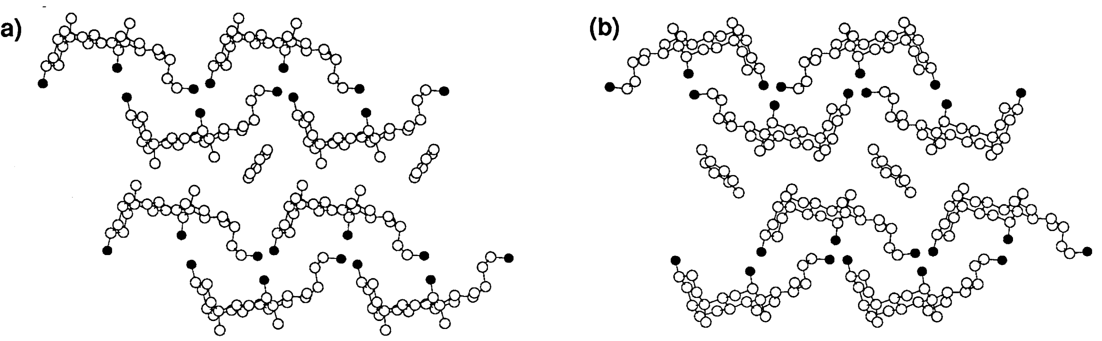

Figure 2. Crystal structures of 2:1 inclusion compounds of **3** : (a) with benzene, viewed down along the crystallographic *c* axis; (b) with p-xylene, viewed down along the crystallographic *a* axis. Carbon and oxygen atoms are represented by empty and filled circles, respectively.

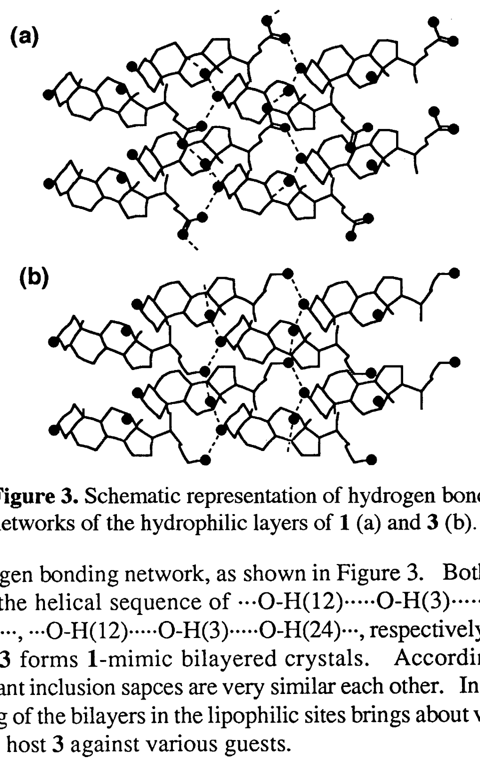

Figure 3. Schematic representation of hydrogen bonding networks of the hydrophilic layers of **1** (a) and **3** (b).

hydrogen bonding network, as shown in Figure 3. Both **1** and **3** have the helical sequence of ···O-H(12)·····O-H(3)·····O=C-O-H(24)···, ···O-H(12)·····O-H(3)·····O-H(24)···, respectively. In this way, **3** forms **1**-mimic bilayered crystals. Accordingly, the resultant inclusion sapces are very similar each other. In addition, sliding of the bilayers in the lipophilic sites brings about versatility of the host **3** against various guests.

In conclusion, this study demonstrates that chemical transformation of the steroidal molecules enables us to observe unknown molecular arrangements which can be expected theoretically. It is noteworthy that we do not find any crystals which have the fourth arrangement (*parallel* in the lipophilic site and *antiparallel* in the hydrophilic site, see Table 1). Finally, we expect that another steroidal derivatives realize this arrangement as well as another different arrangements on the basis of *head / tail*, *right / left*, and *belly / back* directions.

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References and Notes

† Present address: Material and Life Science, Faculty of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565.

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9 X-ray crystal structure analyses (a) **3**+1/2Benzene, $C_{24}H_{42}O_3 \cdot 1/2C_6H_6$, M_r=417.65, triclinic, $P1$, a=13.315(5), b=14.237(5), c=7.127(2) Å, α=99.36(3)°, β=90.22(3)°, γ=110.90(3)°, V=1242.6(8) Å^3, Z=2, D_{meas} =1.12 g cm^{-3}, D_{calcd} =1.116 g cm^{-3}, R=0.085, 1824 unique reflections with $Fo>3\sigma(Fo)$.
(b) **3**+1/2p-Xylene, $C_{24}H_{42}O_3 \cdot 1/2C_8H_{10}$, M_r= 431.68, monoclinic, $P2_1$, a=13.510(4), b=26.321(6), c=7.101(2) Å, β=90.09(2)°, V=2525.1(9) Å^3, Z=4, D_{meas} =1.12 g cm^{-3}, D_{calcd}=1.135 g cm^{-3}, R=0.076, 2568 unique reflections with $Fo>3\sigma(Fo)$.