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COMMUNICATION

Channel-type inclusion crystal with hydrogen bond 'hooks' of deoxycholanamide

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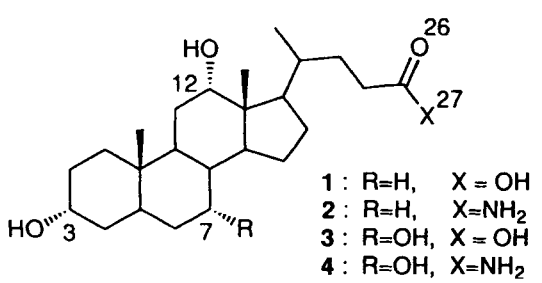
Deoxycholanamide forms lattice inclusion compounds with a variety of organic substances; the 1:1 inclusion crystal of the amide with 1-butanol has a bilayer structure involving channels with hydrogen bond hooks for the guests.

Deoxycholic acid (3α, 12α-dihydroxy-5β-cholan-24-oic acid, **1**) is a classical host molecule which forms lattice inclusion compounds with many organic compounds.[1] However, little is known about the inclusion compounds of the long-known derivatives of **1**, leading us to a comprehensive investigation of their inclusion abilities and crystal structures. In this communication, we describe that deoxycholanamide (3α, 12α-dihydroxy-5β-cholan-24-amide, **2**) forms inclusion compounds with a wide variety of organic substances, and that the host assembly has a bilayer structure involving molecular channels on the basis of X-ray crystallography. The crystal structure is completely different from those of the methyl ester and the glycine conjugate of **1**.[2,3] The host molecules arrange in a *head-to-head/tail-to-tail* manner in the hydrophilic layers, which is the reverse of that of **1**.[1b] Among the derivatives of **1**, the host **2** is the first example to exhibit the same molecular orientation as cholic acid (3α, 7α, 12α-trihydroxy-5β-cholan-24-oic acid, **3**) and cholanamide (3α, 7α, 12α-trihydroxy-5β-cholan-24-amide, **4**).[4,5]

A wide variety of organic compounds such as alcohols, ethers, ketones, carboxylic acids and aromatic amines were included in the crystal lattices of **2**. As shown in Table 1, aromatic and cyclic guests were included in a 2:1 molar ratio, suggesting a similar inclusion behaviour to that of **1**. But many aliphatic alcohols were included in a 1:1 molar ratio of the host to guest. This is in contrast to the case of **1**, since **1** does not form channel-type inclusion crystals with the aliphatic alcohols.[1] It is considered that the relation between **1** and **2** is similar to that between **3** and **4**. The result may be attributed to an additional hydrogen atom of the amide group of the side-chain. The amide group must affect the hydrogen bond networks to yield the different inclusion ability, just like the case of **4**.[5]

This is supported by an X-ray crystallographic study of an inclusion compound of **2**.[6] Figure 1 depicts the crystal structure of the 1:1 inclusion compound of **2** with 1-butanol. The conformation of the side chain of **2** is *gauche*, similar to those of the inclusion compounds of **1**.[1b] It can be seen that a multifunctional and facially amphiphilic structure of **2** plays a decisive role in determining the assembly mode. The one is a bilayer structure, which comes from intermolecular hydrogen bonds of hydrophilic faces as well as van der Waals interaction of lipophilic faces. This structure is a common assembly mode of facially amphiphilic bile acids and their derivatives.[1b,4,5] The other is an arrangement of the host molecules, which is greatly different in the hydrophilic layer. The molecules of **2** arrange in a *head-to-head/tail-to-tail* manner like those of **3** and **4**,[4,5] in contrast to the *head-to-tail* arrangement of **1**.[1b]



1 : R=H, X = OH
2 : R=H, X=NH_2
3 : R=OH, X = OH
4 : R=OH, X=NH_2

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Table 1 Guest release temperatures and molar ratios of **2** with various organic compounds

Guest	*Release temperature/°C*	*Molar ratio (host : guest)*	*Guest*	*Release temperature/°C*	*Molar ratio (host : guest)*
Methanol	99	1 : 1	2-methyltetrahydrofuran	176	2 : 1
Ethanol	90	1 : 1	tetrahydropyran	141,176	2 : 1
1-Propanol	130	1 : 1	Acetophenone	177	2 : 1
1-Butanol	126,147	1 : 1	Cyclohexanone	146,166	2 : 1
1-Hexanol	95,158	1 : 1	Methyl benzoate	160,170	2 : 1
Cyclohexanol	123, 153	1 : 1	Benzonitrile	175	2 : 1
Phenethyl alcohol	126	1 : 1	Collidine	174	2 : 1
2-Butanol	122,140	1 : 1	Chloroform	159	2 : 1
2-Octanol	156	1 : 1	Aniline	149,155	2 : 1

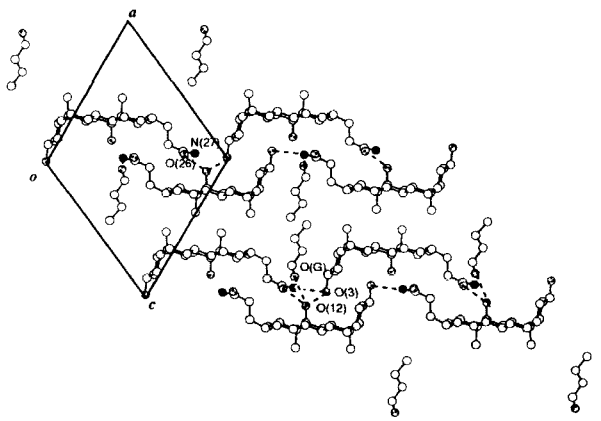

Figure 1 The crystal structure of the inclusion compound between **2** and 1-butanol viewed down the crystallographic *b* axis. Carbon, nitrogen and oxygen atoms are represented by empty, dotted and shadowed circles, respectively. The hydrogen bond network, together with the numbering scheme of the atoms concerned, is shown by dotted lines. The six hydrogen bond distances are followings: O(3)-H•••O(12) = 2.904(6), O(12)-H•••O(26) = 2.738(6), N(27)-H•••O(3) = 3.058(8), N(27)-H•••O(G) = 2.88(1), and O(G)-H•••O(12) = 3.03(1) Å, respectively.

The arched molecular shape as well as the bilayer sliding construct molecular channels between the lipophilic layers along the crystallographic *b* axis. The guest molecules are caught into the channels by hydrogen bonds. As indicated from the molecular arrangements, **2** has similar channels in size and shape to **3** and **4**, but different channels from **1**.[4,5] The flexible bilayer structure explains the versatility of the host **2** to aliphatic alcohols.

The different molecular arrangements and inclusion abilities between **1** and **2** originate from the hydrogen bonding schemes. Figure 2 shows the motifs of hydrogen bonds of **1–4**.[1b,4,5] **2**, **3** and **4** form cyclic hydrogen bond networks, while **1** forms a helical network. The cyclic networks of **2** are composed of two different hydroxy and one amide groups of the corresponding different host molecules. An oxygen atom of the guest molecule bridges the adjacent hydrogen bond circles to yield the 2D(two-dimensional)-hydrogen bond network in the hydrophilic layer.[7] In this way the channels of **2** have the hydrogen bond 'double hooks'.[5b]

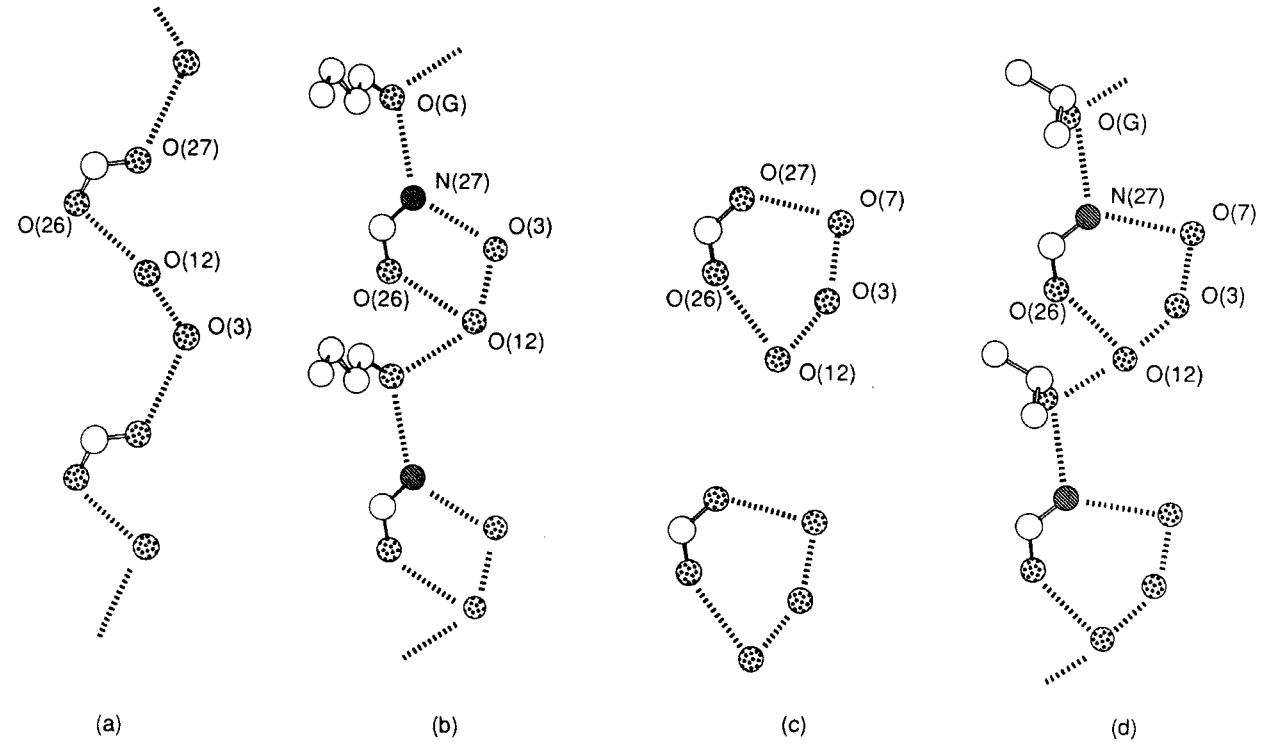

Figure 2 Schematic representation of the hydrogen bond networks: (a) **1**-ferrocene[1e], (b) **2**-1-butanol, (c) **3**-γ-valerolactone[4b], (d) **4**-2-propanol[5b].

Even when the host molecules lack the hydroxy group at the 7 position of the steroidal B-ring, the arrangement of host molecules and the intermolecular hydrogen bond patterns in the amide hosts are maintained.[5] The functional groups in the side chain of bile acids, 'tail', play a more important role for the assembly mode of the hosts than the hydroxyl groups in the steroidal skeleton, since amide and carboxylic acid groups may be stronger hydrogen bond donors or acceptors rather than hydroxy groups.

The versatile formation of the inclusion crystals with organic substances, such as aromatic and cyclic compounds, suggests that **2** has the potential to form guest-dependent polymorphic crystals. Successive structural investigations may reveal the mechanism of the molecular recognition of organic guests and the self-assembly of the host molecule **2**.

ACKNOWLEDGEMENTS

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6 Crystal Data: $C_{28}H_{51}NO_4$, M=465.72, monoclinic, $P2_1$ a = 13.693 (2), b = 7.750 (2), c = 14.195 (1) Å, β = 113.666(8)°, V = 1379.8(4) Å^3, Z = 2, D_c = 1.121 g/cm^3. Intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromatized Mo-Kα radiation. The structure solved by direct methods (SHELXS86) was refined to R = 0.050 for 1733 reflections collected up to $2\theta_{max}$ = 50°. All computations were performed using TEXSAN crystallographic software package of Molecular Science Corporation.

7. Hydrogen bonding networks of the cholic acid derivatives see also, (a) Miyata, M.; Sada, K.; Yasuda, Y.; Miki, K. *Mol. Cryst. Liq. Cryst.* **1994**, *240*, 183; (b) Sada, K.; Kondo, T.; Yasuda, Y.; Miyata, M.; Miki, K. *Chem. Lett.* **1994**, 727.