Inclusion Crystals of Cholic Acid and Cholanamide with Alcohols: Importance of Hydrogen Bond "Double Hooks"

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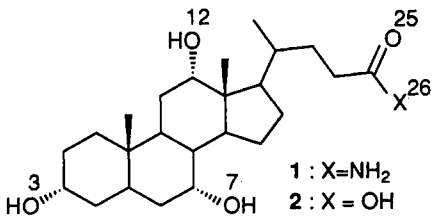
Lattice inclusion compounds are now one of the most interesting topics in organic solid-state chemistry.[2] Our attention has been focused on the inclusion compounds of bile acids and their derivatives because of their fascinating molecular structures.[3] Recently, we found that cholanamide (3α,7α,12α-trihydroxy-5β-cholan-24-amide, **1**) forms the inclusion compounds with a variety of organic



substances, as in the case of cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid, **2**). X-ray crystallographic study on a 1:1 complex of **1** with 1,4-dioxane illustrated that amide nitrogen acts as a "hook" to hold the guest molecule in a channel by a hydrogen-bonding from the host to the guest.[4]

However, the question of much different affinity of both hosts to various alcohols remains open. And no simple explanation has been given for the selective inclusion ability of **2** to the alcohols since last century.[5] This paper deals with strong evidence for dissolving this subject, which has been brought about by our further work on the inclusion compounds of **1** and **2** with the alcohols and on the crystal structure of a 1:1 complex of **1** with 2-propanol. **1** efficiently includes the alcohols into channels by hydrogen-bond "double hooks", while **2** does not.

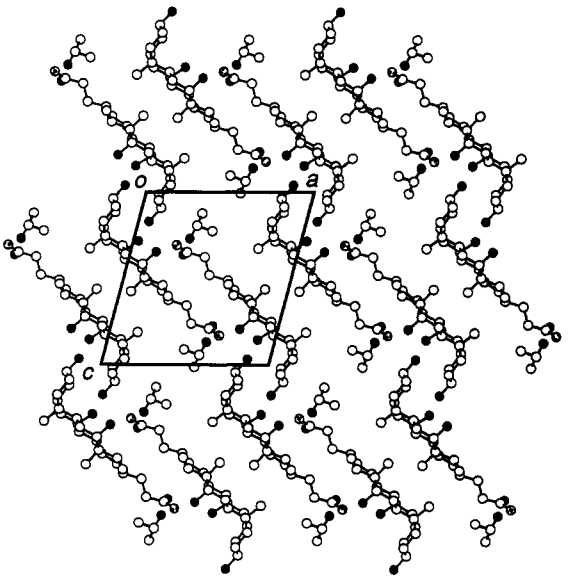


Figure 1. Crystal structure of a 1:1 complex between **1** and 2-propanol as viewed along the *b* axis. The carbon, nitrogen, and oxygen atoms are represented by open, dotted, and shadowed circle, respectively.

Inclusion compounds of **1** were prepared by recrystallization from neat alcohols and characterized by TGA-DSC, solid-state IR spectroscopy, X-ray powder diffraction, and their melting points. All alcohols examined formed the inclusion crystals generally at a 1:1 stoichiometry (Table 1). The guests with low-boiling points were released from the host lattice at higher temperatures than their boiling points due to the thermal analysis. In the case of the guest with high boiling points, the lattice was collapsed about 150 °C and simultaneously the guest molecules were released. This indicates that hydrogen bonding between the host and the guest plays an important role in forming the stable inclusion compounds.

X-ray crystallographic study of a crystal of **1** with 2-propanol illustrates that **1** forms the channel-type structure with hydrogen bond "double hooks" (Figure 1 and 2c).[6] This crystal structure is isomorphous to that of **1** with 1,4-dioxane. Both the structures have 10-membered

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(3) (a) Miyata, M. *Nippon Kagaku Kaishi* **1993**, 128. (b) Miyata, M.; Shibakami, M.; Goonewardena, W.; Takemoto, K. *Chem. Lett.* **1987**, 605. (c) Miyata, M.; Shibakami, M.; Takemoto, K. *J. Chem. Soc., Chem. Commun.* **1988**, 655. (d) Miki, K.; Masui, A.; Kasai, N.; Miyata, M.; Shibakami, M.; Takemoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 6594. (e) Miyata, M.; Shibakami, M.; Chirachanchai, S.; Takemoto, K.; Kasai, N.; Miki, K. *Nature* **1990**, *343*, 446. (f) Miki, K.; Kasai, N.; Shibakami, M.; Takemoto, K.; Miyata, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1757.

(4) Sada, K.; Kondo, T.; Miyata, M.; Tamada, T.; Miki, K. *J. Chem. Soc., Chem. Commun.* **1993**, 753.

(5) Mylius, F. *Chem. Ber.* **1887**, *20*, 1968.

(6) Structural determination summary: X-ray data were collected at 20 °C using a Rigaku automated four-circle diffractometer and Ni-filtered Cu Kα radiation. $C_{24}H_{41}NO_4 \cdot C_3H_8O$ (M = 467.69) belongs to the monoclinic space group $P2_1$, (a = 13.103(1), b = 7.799(1), c = 14.092(2) Å, β = 104.68(1)°, V = 1393.0(2) Å^3, Z = 2, D_c = 1.115 g cm^{-3}). 2213 reflections were collected and merged to 2116 independent reflections (R_{int} = 0.010). The crystal is essentially isomorphous with those of the inclusion compound of **1** with 1,4-dioxane.[4] Its atomic coordinates of non-hydrogen atoms for **1** were employed as an initial model. The 2-propanol molecule were located in a difference Fourier map. The structure was refined by the block-diagonal least-squares procedure with *HBLS*-V program[7] using 1958 observed reflections [$|F_o| \geq 3\sigma(|F_o|)$]. On the difference Fourier maps all the H atoms were found at the expected positions. Their positional parameters were refined in the further refinement, whereas their temperature factors were fixed to the B_{eq} values of connecting C and O atoms. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = (\sigma(F_o)^2 + 0.0035|F_o| + 0.0015|F_o|^2)^{-1}$; R = 0.047 for 1958 reflections collected up to $\sin\theta/\lambda$ = 0.55 Å^{-1}. The atomic temperature factors in the guest 2-propanol molecule were extremely large as found in the other molecules of the cholic acid/cholanamide inclusion compounds. Electron densities of the guest molecule were carefully checked to seek possible disorder, but significant features which imply disorder could not be detected. The six hydrogen bond distances are as follows: N(26)-H···O(G) = 2.933(15), N(26)-H···O(7) = 3.000(8), O(7)-H···O(3) = 2.689(5), O(3)-H···O(12) = 2.871(5), O(12)-H···O(25) = 2.728(7), and O(G)-H···O(12) = 3.085(13) Å, respectively. All the computations were carried out on an ACOS 930 computer at the Research Center for Protein Engineering, Institute for Protein Research, Osaka University. See the supplementary material for further details.

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Table 1. Inclusion Complexes of 1 with Alcohols[a]

guest	release temp[b,c] (°C)	H:G[b]	guest	release temp[b,c] (°C)	H:G[b]
methanol	80	1:1	2-methyl-1-hexanol	148	1:1
ethanol	121	1:1	1-octanol	138, 142	1:1
1-propanol	142, 153	1:1	1-decanol	121	1:1
2-propanol	143	1:1	methyl lactate	128	1:1
1-butanol	140, 147	1:1	*n*-butyl lactate	128	1:1
2-butanol	141, 145	1:1	benzyl alcohol	125	1:1
2-methyl-1-propanol	149, 156	1:1	phenethyl alcohol	130	1:1
2-methyl-2-propanol	138	1:1	cyclohexanol	149	1:1
1-pentanol	141, 149	1:1	2-methylcyclohexanol	144	1:1
2-pentanol	144	1:1	3-methylcyclohexanol	138, 149	1:1
3-methyl-2-butanol	151	1:1	4-methylcyclohexanol	145, 153	1:1
2-methyl-1-butanol	150, 158	1:1	2,6-dimethylcyclohexanol	135, 143	1:1
2,2-dimethyl-1-propanol	139	1:1	3,5-dimethylcyclohexanol	135, 143	1:1
1-hexanol	140	1:1	2,5-dimethylcyclohexanol	138, 146	1:1
2-hexanol	116	1:1	1-chloro-2-propanol	146	1:1
2-methyl-1-pentanol	145, 151	1:1	ethylene chlorohydrin	132, 142	1:1
4-methyl-2-pentanol	140	1:1	1-(dimethylamino)-2-propanol	122	1:1

[a] Recrystallization from neat *alcohols*. [b] Determined by TGA-DSC. [c] Endothermic peak top temperature for guest-release.

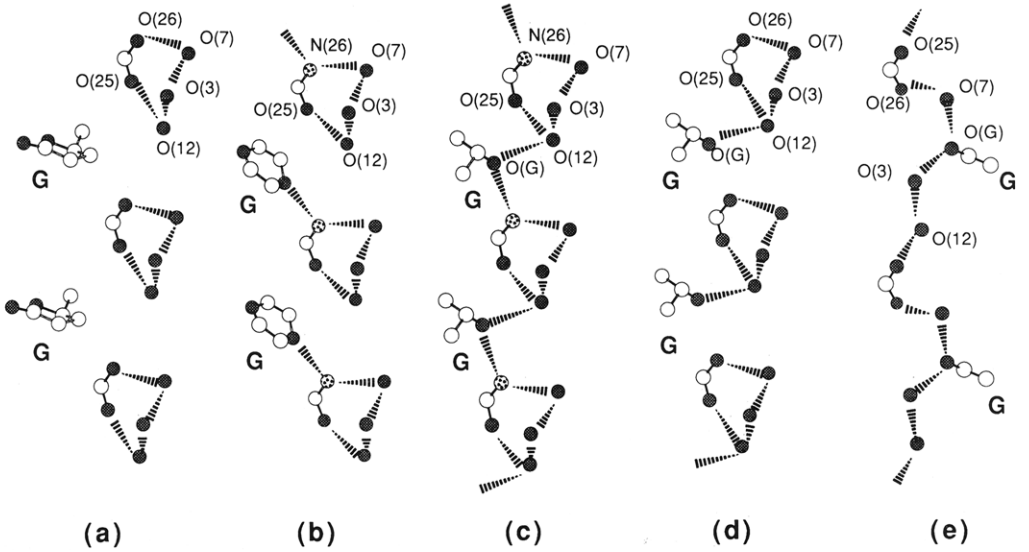

Figure 2. Schematic drawings of hydrogen-bonding networks: (a) **2**-γ-valerolactone, (b) **1**-1,4-dioxane, (c) **1**-2-propanol, (d) postulated channel-type **2**-2-propanol, (e) **2**-ethanol.

circular intermolecular hydrogen bonding networks consisting of four different host molecules which are related by symmetry (2-fold screw axis of space group $P2_1$): Figure 2b,c. As found in the case of 1,4-dioxane, the 2-propanol molecule is caught with the amide nitrogen "hook" on the wall of the channel by hydrogen bonding from the host to the guest.[4] The striking feature is an additional hydrogen bonding from the guest to the host. The hydroxy group of the guest acts as a hydrogen bond donor to the oxygen atom of the host hydroxy group O(12) and bridges between 10-membered hydrogen-bond rings (Figure 2c). Such double hydrogen bonds serve as a driving force to form thermally stable inclusion crystals where the guest molecules are tightly fixed in the channel. The large cavity of the channel-type structure and the double hydrogen bondings between the host and the guest are responsible for the inclusion of **1** with a wide range of alcohols.

Both crystal structures of inclusion crystals of **1** mentioned above are quite similar to those of the channel-type inclusion crystals of **2** with acetophenone or γ-valerolactone.[3d,f] That is, hydroxy and carboxyl groups of the latter host molecules are likewise associated to form the 10-membered hydrogen bond rings (Figure 2a). Therefore, as in the case of **1**, an alcoholic guest molecule may be bound by the oxygen atom O(12) of **2** as a "hook" (Figure 2d). However, since no proton donors are provided as a "hook" on the wall of the channel, it is considered that single hydrogen bonding from the guest to the host, as compared with "double hooks" of the clathrates of **1**, might be so weak that **2** does not form the thermally stable inclusion compounds with alcohols in the same manner. In fact, **2** selectively included only small aliphatic alcohols with less than three carbon atoms, such as methanol, ethanol, and 1-propanol among the alcohols listed in Table 1.[5,8b] In these cases, the guests are included in small cages, indicating the structural complementary.[8] In this manner, the selective inclusion by **2** and the versatile inclusion by **1** can be explained not only by the structural complementary to the cage or the channel but also by different hydrogen bondings between the hosts and the guests.

In conclusion, the comparison of the inclusion behaviors and the crystal structures between **1** and **2** gave us a reasonable explanation for formation of inclusion compounds of **1** and **2** with alcohols as guests.[3,4] In addition, this result supports the idea that all proton donors and all

(7) Ashida, T. *HBLS-V. The Universal Crystallographic Computing System—Osaka*; Computation Center, Osaka University, 1979, pp 53–59.

(8) (a) Johnson, P. L.; Schaefer, J. P. *Acta Crystallogr.* **1972**, *B28*. 3083. (b) Jones, E. L.; Nassimbeni, L. R. *Acta Crystallogr.* **1990**, *B46*. 399.

proton acceptors in one molecule participate in hydrogen-bonding networks.[9] Due to the highly asymmetric structure of 1, the versatile clathrate formation of 1 with alcohols implies a possibility of efficient optical recognition of racemic alcohols. Finally, the hydrogen-bonding "hook" may also provide us a design for inclusion polymerization of polar monomers.[10]

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Supplementary Material Available: Tables of atomic coordinates and equivalent isotropic thermal parameters of non-hydrogen atoms, atomic coordinates and equivalent isotropic thermal parameters of hydrogen atoms, anisotropic thermal factors of non-hydrogen atoms, and all bond distances and bond angles (9 pages); tables of observed and calculated structural factors (6 pages). Ordering information is given on any current masthead page.

(9) For recent reviews on hydrogen bonding architectures see: Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. Whiteside, G. M.; Mathias, J. P.; Seto, C. T. *Science (Washington, DC)* **1992**, *254*, 1312.

(10) Reviews on inclusion polymerization, see: Miyata, M. In *Polymerization in Organized Media*; Paleos, C. M., Ed.; Gordon and Breach: Philadelphia, 1992; p 327.