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Inclusion Compounds of Hyocholic Acid with Specific Alcohols

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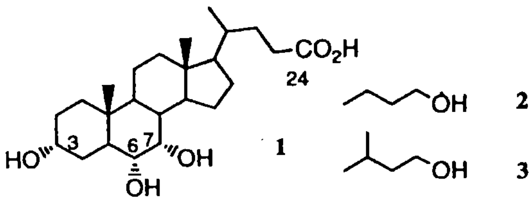
Hyocholic acid forms lattice-type inclusion compounds with specific aliphatic alcohols. In these compounds, water molecules are also included and they play an important role in the formation of inclusion spaces.

Keywords: Inclusion compounds, Hyocholic acid, butanol

Hyocholic acid (3α, 6α, 7α-trihydroxy-5β-cholan-24-oic acid 1), a natural bile acid, was discovered in 1956 [1, 2]. So far, there were neither reports about its inclusion ability nor those about its crystal structure. However, we have found that 1 has an inclusion ability towards specific organic substances. This paper concerns structural analyses of both guest-free and inclusion crystals of 1, accompanied by an interesting role of water.



SCHEME

Recrystallization of 1 from various organic substances mostly yielded prismatic crystals, which were characterized by thermogravimetric analysis, IR and ^{1}H-NMR spectroscopy, and powder X-ray diffractometer. It was found that the resulting crystals were guest-free except for the cases of 1-butanol (2) and 3-methyl-1-butanol (3). Detailed analyses clarified that these crystals also included water molecules, and that the stoichiometry (host: alcohol: water) was 2:1:1 for 2, and 4: 2: 1 for 3. It is noteworthy that use of dried 2 or 3 gave only guest-free crystals. This result indicates that the inclusion crystals were formed in the presence of water.

Next we analyzed single crystals by means of X-ray diffraction method. The guest-free crystals belong to the orthorhombic space group $P2_12_12_1$ [4]. Figure 1(a) depicts the crystal structure viewed along the crystallographic *c* axis. It can be seen from the figure that 1 arranges almost linearly each other on the *ab* plane. The host molecules constitute a 2_1 column along the *c* axis with a hydrogen-bonding network which consists of helical main chains with pendent carboxyl groups. The main chain has a sequence

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*Corresponding author.

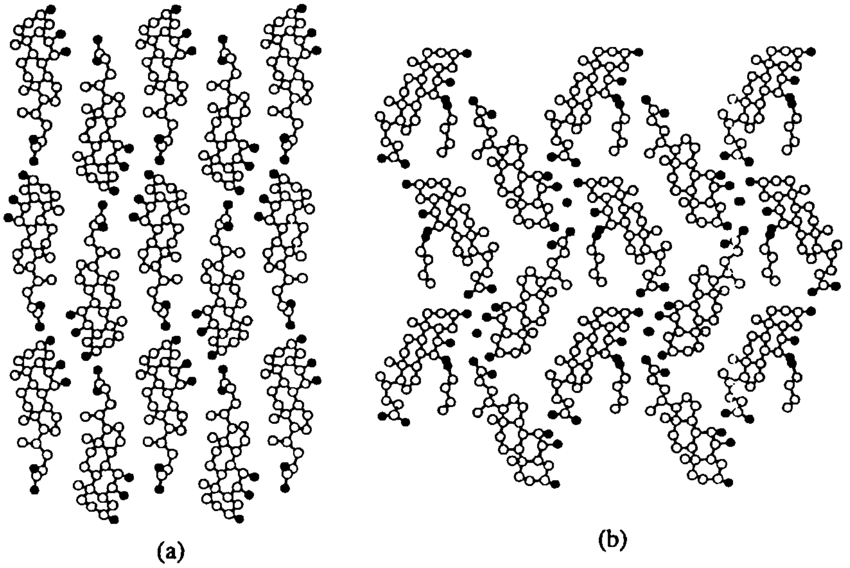


FIGURE 1 The crystal structures of guest-free and inclusion crystal of 1; (a) guest-free crystal viewed down the crystallographic *c* axis, (b) inclusion crystal between 1 and 2 viewed down from crystallographic *a* axis. Carbon and oxygen atoms are represented by empty and shaded circles, respectively. Hydrogen atoms are omitted for clarity.

of O(3)H···O(6)H···O(3)H···, where the hydrogen bonding distances are 2.809(4) and 2.998(4) Å, respectively. The side chain is composed of O(7)H···O(24a) = C —O(24b)H (the distance is 2.951(5) Å), and the O(24b)H is connected to the main chain at O(3) by hydrogen bonding (2.661(5) Å).

On the other hand, the crystals of the inclusion compound of 1 with 2 belong to the monoclinic space group $P2_1$. Figure 1(b) presents the crystal structure of the compound, viewed along the crystallographic *a* axis. It can be seen that host molecules arrange in a zig-zag fashion so as to leave inclusion spaces for guests. Figure 2 shows the relationship between guest-free 1 and the inclusion crystal of 1 and 2. Both molecular assembly modes have a similar arrangement that are composed of four molecules of 1. In the guest-free crystals, the four molecules arrange in linear, while in inclusion crystal of 1 and 2, the four molecules arrange in cross manner by insertion of water molecules.

Figure 3 schematically illustrates the correlation between the guest-free and inclusion crystals of 1. Hydrogen bonding networks in the guest-free crystals correspond to a closed "pantograph", while the networks in the inclusion crystals correspond to an open "pantograph". This change takes place in the presence of water

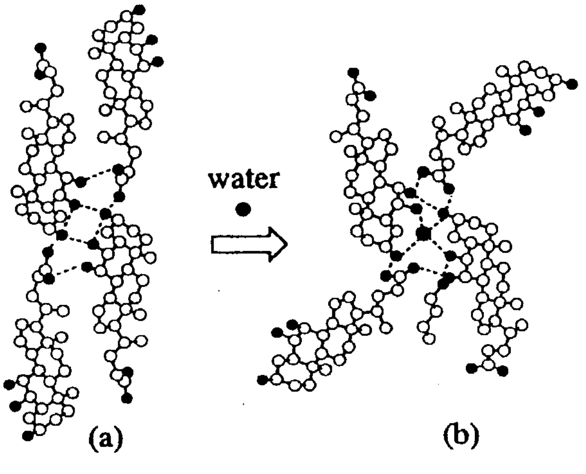
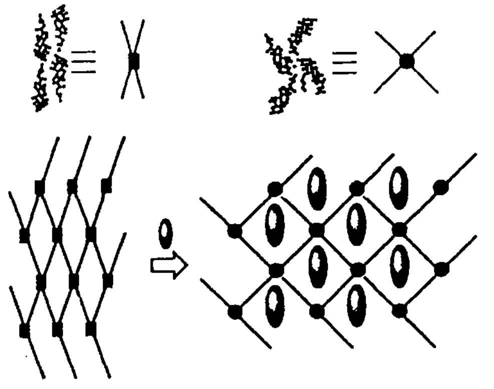


FIGURE 2 Comparison of molecular arrangements that are composed of four molecules of 1; (a) guest-free crystal of 1, (b) inclusion crystal of 1 and 2. Dotted lines that connect between O atoms show hydrogen bonding networks. Hydrogen atoms are omitted for clarity.



(a) (b)

FIGURE 3 Schematic representation of the crystal structures of 1; (a) guest-free crystal of 1. (b) inclusion crystal of 1 and 2. Lines, filled circles and shadowed circles show host molecules, hydrogen bonding parts and guest molecules, respectively.

molecules. One can say that water molecules function as "joints" to open the "pantograph", leading to a formation of inclusion spaces for accommodating guest molecules.

In addition, the crystal structure of the inclusion compound of 1 with 3 is similar to that of 1 with 2. In fact, both crystals belong to the same space group (monoclinic, $P2_1$) [4], and the guest molecules are included in the same cavity. However, additional methyl group of the guest molecule expel half of water to give a different hydrogen-bonding network. This result indicates that water plays an important role in modifying the inclusion space for specified guests.

We have systematically been studying inclusion compounds of deoxycholic acid and related compounds [3], leading to the following propose: even long-known compounds, which are believed to form no inclusion compounds with organic substances, may serve as latent hosts. In order to discuss the inclusion abilities of the host compounds it is necessary to check at least a hundred kinds of organic guests. This proposition is supported by the finding of the inclusion ability of 1.

Acknowledgement

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[4] Crystal data for (**a**) **1**: $C_{24}H_{40}O_5$, $M = 408.68$, orthorhombic, space group $P2_12_12_1$, $a = 11.375(3)$, $b = 30.417(4)$, $c = 6.349(4)$ Å, $V = 2196(1)$ Å^3, $Z = 4$, $D_c = 1.235$ g cm^{-3}. For (**b**) **1**-**2**-**water** (2:1:1): $2C_{24}H_{40}O_5 + C_4H_{10}O_1 + H_2O$, $M = 909.29$, monoclinic, space group $P2_1$, $a = 6.660(1)$, $b = 24.25(1)$, $c = 16.067(3)$ Å, $\beta = 98.42(1)°$, $V = 2567(1)$ Å^3, $Z = 2$, $D_c = 1.176$ gcm^{-3}. For (**c**)**1**-**3**-**water** (4:2:1): $4C_{24}H_{40}O_5 + 2C_5H_{12}O_1 + H_2O$, $M = 1828.62$, monoclinic, space group $P2_1$, $a = 13.002(3)$, $b = 25.552(6)$, $c = 15.81(1)$ Å, $\beta = 102.14(4)°$, $V = 5134(3)$ Å^3, $Z = 2$, $D_c = 1.183$ gcm^{-3}. Intensity data were collected on Rigaku AFC-7R diffractometer with graphite-monochromated Mo-Kα radiation for **a** and Rigaku RAXIS-IV diffractometer with graphite-monochromated Mo-Kα radiation for **b** and **c**. 2934, 4195 and 7646 reflections for the crystals **a**, **b** and **c** were unique. 1586, 3306 and 4562 observed reflection with $|Fo| > 3\sigma(|Fo|)$ were used for further calculations after Lorenz and polarization corrections. The structure was solved by direct methods (SHLEX86 for **a**, SIR92 for **b** and SnB for **c**) and refined against the Fo data by full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to carbon were placed in calculated position while O —H positions were obtained from difference Fourier synthesis. The final R values are 0.047, 0.043 and 0.045 respectively. All calculations were performed using the TEXSAN crystallographic software package of the Molecular Structure Corporation. Atomic coordinations, bond length and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.