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Interpretation of Variable Inclusion Abilities of Cholic Acid and Its Derivatives on the Basis of the Crystal Structure of 5β-Petromyzonol

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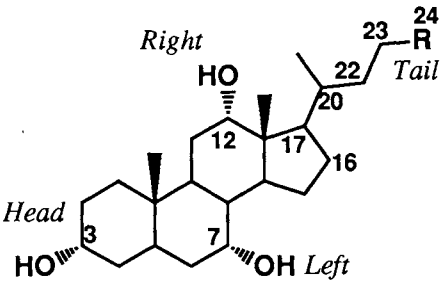
5β-Petromyzonol does not form crystalline inclusion compounds with organic substances in contrast to cholic acid, cholanamide and methyl cholate. The crystal structures of these hosts give direct evidence for such an inclusion feature. 5β-Petromyzonol forms greatly different bilayered crystals from other hosts with respect to the hydrogen bonding networks, molecular arrangements, and stacking modes.

Cholic acid (**1**) and its derivatives are highly asymmetric and facially amphiphilic compounds involving four discrete hydrogen bonding groups. Such characteristic molecular structures would enable us to study various features of asymmetric bilayered crystals from various viewpoints.[1,2] The one is how their functional groups affect their hydrogen bonding networks, leading to different molecular arrangements and inclusion abilities. We have reported that **1** preferentially includes nonpolar substances such as aromatic compounds[3b,e] and lactones,[3c] while cholanamide (**2**) includes polar substances such as ethers[4a] and alcohols,[4b] and that methyl cholate (**3**) is intermediate between them.[5a] In contrast, 5β-petromyzonol (**4**) has not been confirmed to form the inclusion compounds with a variety of organic substances. We now found that the crystal of **4** has a specific molecular arrangement derived from a different hydrogen bonding network from those of **1**-**3**. This paper concerns with the interpretation of variable inclusion abilities of these hosts on the basis of their crystal structures.



R=CO_2H; Cholic acid(**1**)
R=$CONH_2$; Cholanamide(**2**)
R=CO_2CH_3; Methyl cholate(**3**)
R=CH_2OH; 5β-Petromyzonol(**4**)

4 was prepared from commercially available **1** by the method described in literature.[6] **4** was recrystallized from over fifty different organic substances, such as alcohols, carboxylic acids, esters, lactones, ketones, nitriles, and so on. The resulting crystals gave no evidence for inclusion and polymorphism, because the crystals had the same infrared spectra and diagrams of thermal analysis. For comparison Table 1 illustrates the inclusion behaviour of **1**-**4** against eight kinds of alcohols together with data reported earlier. It can be seen that their inclusion abilities vary from one case to another. That is, **2** included all the alcohols employed, whereas **1** included only methanol, ethanol, and 1-propanol. **3** exhibits another behaviour, especially in the case of butanols. In contrast, **4** did not include these alcohols at all. The disappearance of the inclusion ability of **4**

Table 1. Molar ratios of the inclusion compounds of cholic acid and its derivatives with various alcohols[a)]

Hosts \ Alcohols	MeOH	EtOH	Pr^nOH	Pr^iOH	Bu^nOH	Bu^iOH	Bu^sOH	Bu^tOH
1	1:1 c)	1:1 c)	1:1 c)	—b)	—b)	—b)	—b)	—b)
2	1:1 d)	1:1 d)	1:1 d)	1:1	1:1	1:1	1:1	1:1
3	1:1 e)	1:1 e)	1:1 e)	1:1 e)	—b)	—b)	1:1	2:1
4	—b)	—b)	—b)	—b)	—b)	—b)	—b)	—b)

a) The inclusion compounds were prepared by the usual recrystallization method. Molar ratios were determined by thermogravimetry. b) Alcohols were not included. c) Ref.7. d) Ref.4a. e) Ref.5a.

suggests that **4** constitutes a molecular assembly different from those of **1-3**. In order to clarify this from a structural viewpoint, we carried out X-ray crystal structural analysis of **4**.

Single crystals suitable for the analysis were grown at room temperature by slow evaporation of methanol solutions of **4**. They belong to a different crystal system (tetragonal, space group $P\,4_12_12$) from those of **1-3** (monoclinic, $P\,2_1$ or orthorhombic, $P\,2_12_12_1$).[8)] The observed bond distances and angles are the normal values for the standard steroidal compounds within experimental errors. The side chain adopts *trans* conformation as in the case of the inclusion compound of **1** with γ-valerolactone,[3c,d)] that of **2** with 1,4-dioxane[4a)] and that of **3** with acrylonitrile.[5c)] The torsion angles of (C(16)-C(17)-C(20)-C(22)), (C(17)-C(20)-C(22)-C(23)), and (C(20)-C(22)-C(23)-C(24)) are 60.8°, -169.6°, and 172.3°, respectively. Figure 1 shows the crystal packing viewed along the diagonal *a* and *b* axes. It can be seen that the asymmetric molecules associate in a *head*-to-*tail* and *right*-to-*left* fashion to yield asymmetric sheets which extend in the *a* and *b* directions. Each sheet is composed of one hydrophilic and another lipophilic sites. The amphiphilic sheets are stacked on each site along the crystallographic *c* axis to produce bilayered crystals with no inclusion spaces.

The striking feature is that the stacking modes of **4** are greatly different from those of **1-3** on both hydrophilic and lipophilic sites of the sheets. Figures 2 (a) and (b) show an overlap and a rotation of steroidal skeletons on the hydrophilic and lipophilic sites, respectively. The overlap is caused by a unique hydrogen bonding network among the host molecules. Figure 3 shows a schematic representation of the network of **4** as compared with those of **1-3**. **1** and **2** form similar networks of the cyclic sequence of OH[C(3)]---OH[C(12)]---O=C(24)-OH---OH[C(7)]---OH[C(3)], where four different

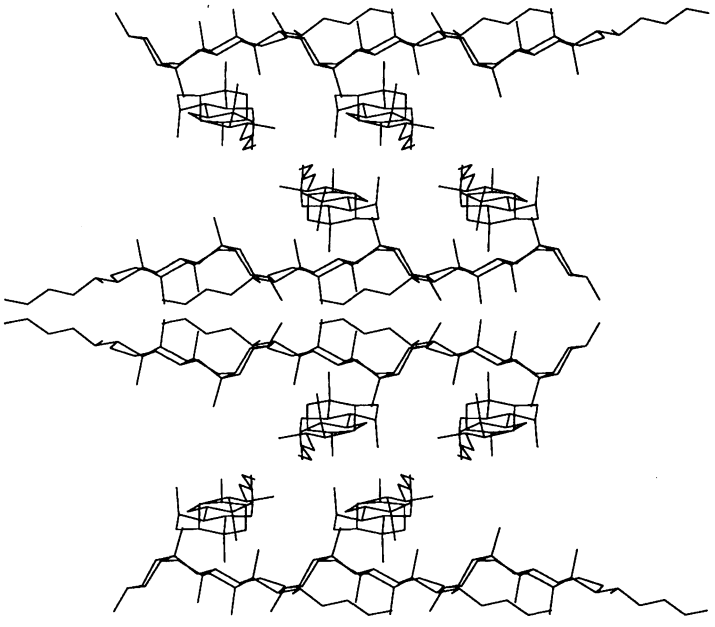


Fig.1. The crystal structure of **4** viewed down along the diagonal *a* and *b* axes.

host molecules provide each one functional group. **3** forms open networks of the similar sequence. On the other hand, **4** forms another networks with the different sequence of OH[C(7)]---OH[C(12)]---OH[C(24)]---OH[C(3)].[10] The introduction of a hydroxyl group into the side chain led to the greatly different hydrogen bonding networks.

Such different networks cause different arrangements of the host molecules, as schematically shown in Figs. 4 (a) and (b). In the case of **1**-**3** the molecules locate on vertices and long sides of rectangles (Fig. 4(a)), while in the case of **4** the molecules locate on vertices and diagonals of squares (Fig. 4(b)). In the former case guest molecules are trapped into the concavity on the lipophilic site of the bilayers. **2** has additional hydrogen bonding hooks thereon suitable for inclusion of ethers and alcohols. On the other hand, in the case of **4**

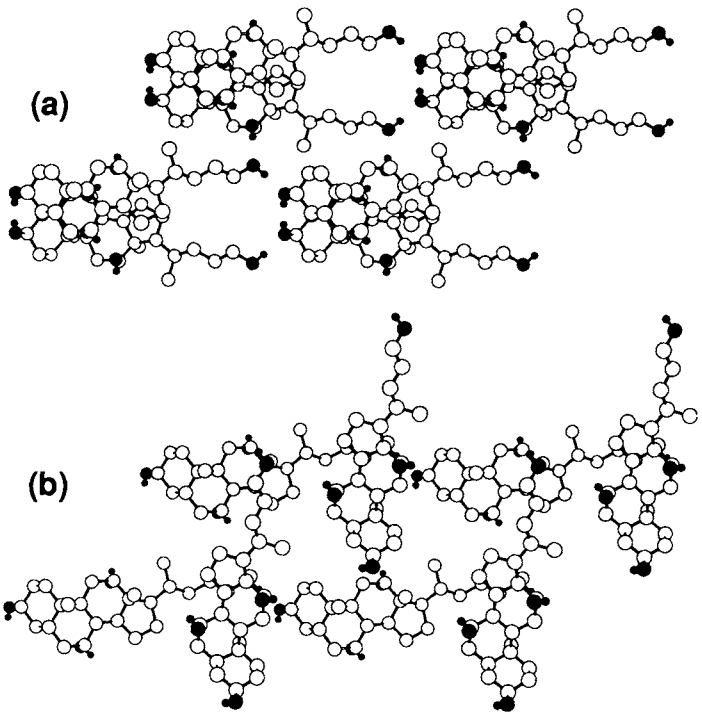


Fig.2. Stacking of amphiphilic sheets of **4** on hydrophilic sides (a) and lipophilic sides (b) viewed down along the crystallographic *c* axis.

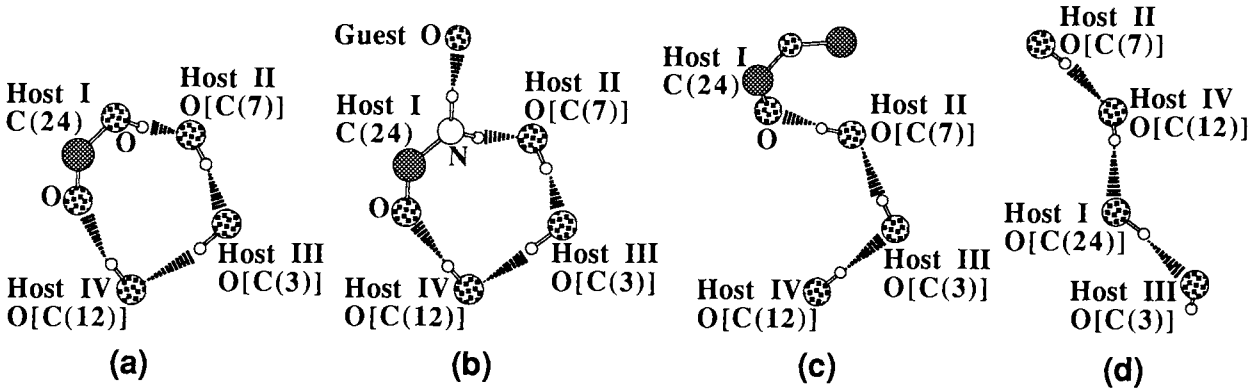


Fig.3. Schematic representation of hydrogen bonding networks ; (a) **1** - benzene,[3e] (b) **2** - 2-propanol,[4b] (c) **3** - acrylonitrile,[5c] and (d) **4**.[10]

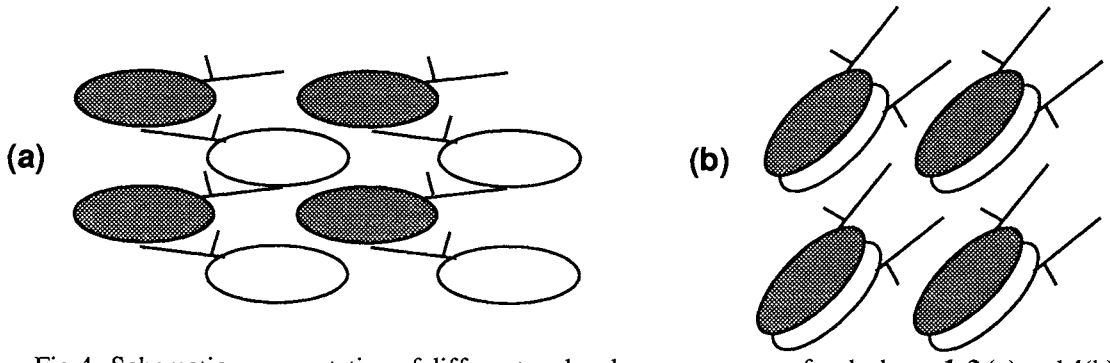


Fig.4. Schematic representation of different molecular arrangements for the hosts **1**-**3** (a) and **4**(b).

the concavity in the center of squares are compensated by the convexity of the neighboring sheet, explaining the fact that **4** has no inclusion ability. In this way the crystal structures give us clear evidence for variable inclusion abilities of **1**-**4** on the basis of different molecular arrangements.

In conclusion, this study demonstrates that molecular associations greatly or slightly change with the transformation of functional groups of the flexible side chains attached to the rigid skeletons. Although the molecular design for multimolecular inclusion compounds has so far been concentrated on rigid skeletons,[9] this study indicates that the side chains could play a fascinating role in determining the inclusion abilities.

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8) Crystal data for $C_{24}H_{42}O_4$, M = 394.60, tetragonal, $P\,4_12_12$, $a = b = 11.836(1)$ Å, $c = 32.626(2)$ Å, $V = 4570.3(4)$ Å^3, $Z = 8$, $D_c = 1.147$ g cm^{-3}. Intensity data were collected by the θ-2θ scan mode with sin θ/λ up to 0.55 Å^{-1} on a Rigaku automated four-circle diffractometer using Ni-filtered Cu-Kα radiation. The structure was solved by direct methods(SHELXS-86) and refined by the full-matrix least-squares method. The final R value is 0.039 for 1811 [$|Fo|>3\sigma(|Fo|)$] reflections. All the computaions were done on an ACOS 930 computer at the Research Center for Protein Engineering, Institute for Protein Research, Osaka University.

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10) There exists another hydrogen bonding with reverse direction. Details will be published.

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