A Novel Molecular Channel with a Hydrogen Bond 'Hook'; Inclusion Phenomena of Cholanamide and the Crystal Structure of a 1 : 1 Complex of Cholanamide and 1,4-Dioxane

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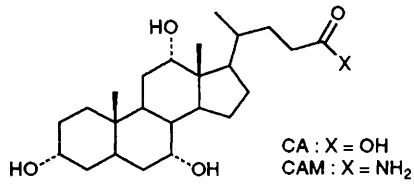
A new host, cholanamide (CAM), is described; CAM forms lattice inclusion compounds with a variety of organic substances, particularly hydrogen bond acceptors, which are trapped in channels by hydrogen bonding to the amide nitrogen.

'Designed' hosts in lattice inclusion compounds are mostly symmetrical and have a rigid well defined shape.[1] Functional groups are often arranged in fixed orientations to form three-dimensional frameworks. Our approach for the design of host molecules has two essentials: one is a rigid structure which produces the molecular assemblies, and the other is associated with flexible and modifiable functional groups attached to the rigid segments to control the surroundings of the channels or cages at the molecular level.[1]

Cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid, CA), a steroidal bile acid, has both a rigid structure and flexible 'tail'. We have reported that CA forms channel-type lattice inclusion compounds with a variety of organic substances.[2] The channels of CA inclusion crystals are hydrophobic, in which less polar organic compounds are incorporated. Chemical modification of the flexible 'tail' part of the CA molecule might lead to functionalization of the cavities and control of their size or shape.[3] We have investigated the amide of CA as a novel host which has an NH_2 group capable of forming hydrogen bonds. It forms channels similar to those formed in CA inclusion crystals, in which the guest molecules are accommodated not only by hydrophobic interactions but also by host–guest hydrogen bonds.

Crystallization of 3α,7α,12α-trihydroxy-5β-cholan-24-amide (CAM)[4] from the guest components as solvents afforded the inclusion compounds, which were characterized by TGA, solid-state IR spectroscopy, and their melting points. A wide variety of organic compounds: alcohols, ethers, heterocycles, carboxylic acids and aromatic amines were included at a host : guest ratio of 1 : 1 (Table 1). Oligo(ethylene glycol) also formed inclusion crystals with a host : guest ratio varying from 1 : 1 to 2 : 1, depending on its size. The size and shape of the guests included in CAM were similar to those included in CA. However, higher aliphatic alcohols and ethers were incorporated into the lattice of CA whereas they were not included in CA.[2a]

The channel-type structure of CAM host aggregates affords a similar versatility in clathrate formation as that shown by CA (see Table 1). An X-ray crystallographic study confirmed that CAM forms inclusion crystals with a channel-type structure (Fig. 1).† The CAM clathrates are isomorphous to those of



† *Crystal Data*: $C_{24}H_{41}NO_4 \cdot C_4H_8O_2$, M = 495.70, monoclinic, $P2_1$, a = 13.170(1), b = 7.868(1), c = 14.098(1) Å, β = 104.97(1)°, Z = 2, D_c = 1.167 g cm^{-3}, D_m = 1.16 g cm^{-3}. The structure solved by direct methods (SHELXS-86) was refined to R = 0.050 for 2064 reflections collected up to sin θ/λ = 0.55 Å^{-1} (Cu-Kα radiation). All the computations were done on an ACOS 930 computer at the Research Center for Protein Engineering, Institute for Protein Research, Osaka University.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Table 1 Guest release temperatures and molar ratios of CAM inclusion crystals with various organic compounds.

Guest	Guest release temperature/°C[a,c]	ΔT/°C[b]	Molar ratio[c] host : guest	Guest	Guest release temperature/°C[a,c]	ΔT/°C[b]	Molar ratio[c] host : guest
Methanol	75	+11	1 : 1	THF[d]	109	+43	1 : 1
Ethanol	110	+31	1 : 1	1,4-Dioxane	121	+21	1 : 1
Propan-1-ol	129	+32	1 : 1	DME[d]	97	+13	1 : 1
Pentan-1-ol	120	−18	1 : 1	Diglyme	77	−85	1 : 1
Octan-1-ol	123	−72	1 : 1	Triglyme	100	−116	3 : 2
Cyclohexanol	122	−39	1 : 1	Tetraglyme	92	−174	2 : 1
Benzyl alcohol	99	−106	1 : 1	Collidine	83	−88	1 : 1
Acetic acid	96	−20	1 : 1	Pyrrole	93	−37	1 : 1
Chloroform	105	+44	1 : 1	Aniline	117	−67	1 : 1

[a] Onset temperature of the guest release. [b] ΔT = T (guest release) − T (b.p.). [c] Determined by TGA–DSC. [d] THF = tetrahydrofuran; DME = 1,2-dimethoxyethane.

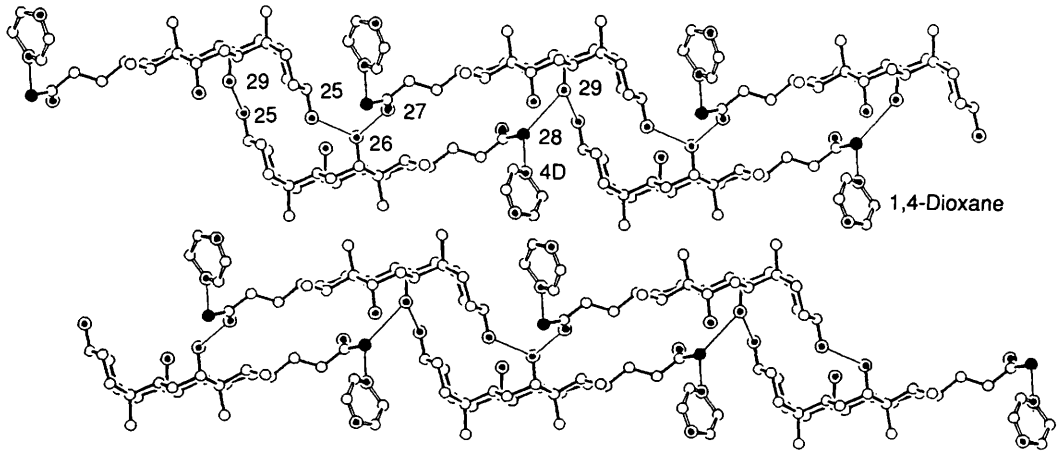


Fig. 1 The crystal structure of the inclusion compound between CAM and 1,4-dioxane viewed down the crystallographic b axis. Carbon, oxygen and nitrogen atoms are represented by empty, half-filled and filled circles, respectively. The hydrogen bond network, together with the numbering scheme of the atoms concerned, is shown: O(26)^{I}–H···O(27)^{II}=C(24)^{II}–N(28)^{II}–H···O(29)^{III}–H···O(25)^{IV}–H···O(26)^{I}, and N(28)^{II}–H···O(4D)^{II} where the five O···O distances are 2.785(5), 2.989(6), 2.690(5), 2.871(5) and 2.946(5) Å and the symmetry codes I–IV are $(x, -1 + y, z)$, $(1 - x, -1/2 + y, z)$, (x, y, z) and $(2 - x, -1/2 + y, 2 - z)$, respectively.

CA clathrates, and the conformations of the host molecule are identical to those for the corresponding channel-type CA clathrates.[2c,d] The head-to-tail double-layered arrangements and the cyclic hydrogen-bond network of the host molecules are the same as those of the channel-type CA clathrates.[2c] The assembly mode of the hosts in the molecular complex of CAM with 1,4-dioxane is identical to that in CA inclusion crystals with γ-valerolactone.[2d]

The striking structural feature of the inclusion crystals of CAM with 1,4-dioxane is the hydrogen bonding between the host and the guest. A schematic representation of the hydrogen-bond geometry of CAM and CA inclusion is shown in Fig. 2. In the case of the channel-type CA clathrate, hydroxy and carboxy groups from a hydrogen-bond network which stabilizes the aggregation of the host molecules, but does not contribute to the host–guest interaction [Fig. 2(*b*)].[2c,d] In the CAM inclusion crystal, one of two amide protons is used for the host–host hydrogen bonds in the same manner as that of CA. The other amide proton protrudes from the wall of the channel, and acts as a 'hook' for hydrogen-bond acceptors such as ethers and alcohols. The N–O distance between the oxygen atom of 1,4-dioxane and the amide nitrogen atom of CAM is 2.946(6) Å, which is similar to that of the host–host hydrogen bonds [2.989(6) Å]. Thermal analysis of CAM clathrates showed that the release of the guests from the lattice occurred at the higher temperature than their boiling points. Thus, the channel-type CAM clathrates

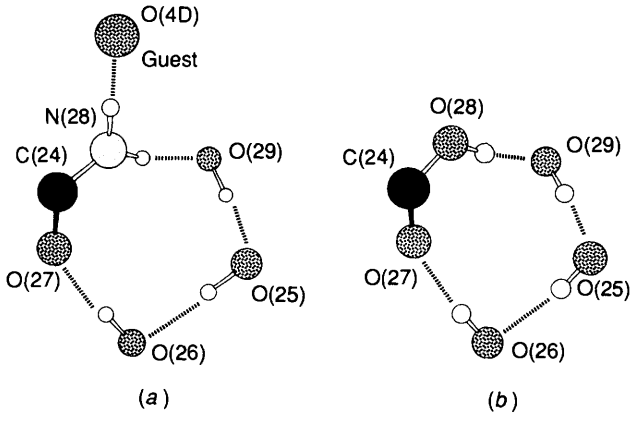


Fig. 2 Schematic representation of the hydrogen-bonding networks: (*a*) CAM–1,4-dioxane inclusion crystal, (*b*) CA–γ-valerolactone inclusion crystal

have an NH 'hook' which attracts hydrogen bond acceptors. Molecular models show that the size and shape of the channel of CAM clathrates are similar to those of CA clathrates.[2d] The formation of the hydrogen bond between the guest and the NH group of the host is an important factor contributing to the stability of CAM clathrates. Weak hydrogen-bond acceptors, such as ketones or esters, did not form stable inclusion crystals

with CAM, but were accommodated into the channels of CA only by hydrophobic interactions.

Chemical modification of the functional groups that contribute to the framework of the host assembly usually leads to collapse of the original host arrangements in the molecular assemblies and a restructuring of the size and/or shape of the cavities.[1] In our system, modification of the functional group did not change the assembly mode of the host. The size and shape of the channel in CAM were essentially identical to those of the parent CA host. Among channel-type inclusion compounds of CA derivatives, these are the first examples of inclusion compounds which have hydrophilic channels. We believe that cholic acid derivatives should provide a variety of molecular-level channels, and that the environment of the channels should be controllable by small modifications of the host. Molecular recognition, for example the optical resolution of chiral alcohols, and inclusion polymerization in the clathrate of CAM are now under investigation.[5]

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