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Inclusion Compounds of Cholic Acid with Various Hydrocarbons and the Crystal Structure of a 1:1 Complex of Cholic Acid and Benzene

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Cholic acid was found to form crystalline inclusion compounds with various hydrocarbons and related compounds. Some alcohols do not form inclusion crystals at all, but serve as solvents. The crystal structure of a 1:1 inclusion compound of cholic acid with benzene was determined. Comparative studies on inclusion behaviors of cholic acid and deoxycholic acid are now possible.

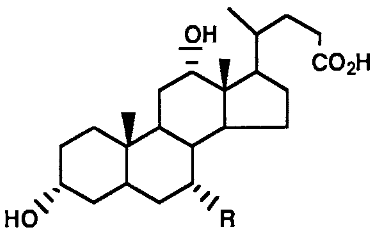

Fig .1. R=OH: Cholic Acid, R=H: Deoxycholic Acid.

Cholic acid(CA)[1)] is a new host, while deoxycholic acid(DCA)[2,3)] is an old one(Fig.1). They serve as a fascinating pair of hosts for multimolecular inclusion compounds.[4)] The reason is that the hosts enable us to prove that only a slight difference in their molecular structures brings about great differences in their molecular assemblies. We observed such differences in hydrogen bonding networks,[5,6)] molecular arrangements,[5,6)] polymorphism,[7)] dynamics,[8)] and molecular recognition.[9)] However, we so far could not compare a scope of guests precisely, since we could not obtain the inclusion compounds of CA with various hydrocarbons and related compounds, which are common guests for DCA,[2)] due to their low solubilities. This problem has now been resolved on the basis of our studies on a correlation of molecular recognition with polymorphism of CA crystals. Here we report the first preparation of inclusion compounds of CA with hydrocarbons and related compounds as well as crystallographic evidence for the simplest inclusion compound of CA with benzene.

We usually determine solvents for preparing inclusion compounds by the method of trial and error. For example, in the case of DCA, methanol and ethanol have been empirically used as solvents.[2)] But these alcohols can not be applied to CA, since they form stable crystals with CA. Therefore, we so far obtained the inclusion compounds of CA by direct recrystallization from liquid guests.[1)] Recently, we gave a plausible mechanism for selective inclusion of CA against alcoholic guests via hydrogen bonding double hooks.[10)] This suggests that the other alcohols should serve as appropriate solvents, and that we can reasonably find solvents for preparing the inclusion compounds.

First, we studied on preparation of the inclusion compound of CA with benzene using various alcohols as solvents. Excess amounts of benzene were added to saturated alcoholic solutions of CA. The resulting crystals had completely different components for guests, as shown in Table 1. In the case of methanol, ethanol and 1-propanol, CA exclusively yielded the stable inclusion compounds with the corresponding alcohols, but not with benzene.

Table 1. Formation of inclusion compounds of CA in the presence of alcoholic solvents

Solvents	Volume of Solvents[a) / mL	Included Guests[b)	Inclusion Crystals / mg	Solvents	Volume of Solvents[a) / mL	Included Guests[b)	Inclusion Crystals / mg
Methanol	0.6	Methanol	60	1-Pentanol	0.4	Benzene	83
Ethanol	1.6	Ethanol	69	2-Pentanol	0.6	Benzene	85
1-Propanol	1.4	1-Propanol	77	3-Methyl-1-butanol	0.4	Benzene	81
2-Propanol	1.0	Benzene	15	2-Methyl-2-butanol	0.7	Benzene	88
1-Butanol	0.4	Benzene	86	1-Hexanol	0.4	Benzene	80
2-Butanol	0.5	Benzene	80	2-Hexanol	0.6	Benzene	77
2-Methyl-1-propanol	0.4	Benzene	81	1-Octanol	0.4	Benzene	86
2-Methyl-2-propanol	1.0	Benzene	82	2-Octanol	0.6	Benzene	80

a) 100 mg of CA was dissolved in alcoholic solvents.
b) 1.0 mL of benzene was added to saturated alcoholic solutions.

The reverse was observed in the case of other alcohols, such as various butanols and pentanols. Among the alcohols checked, 2-butanol and 2-methyl-1-propanol were easy to treat owing to moderate solubilities and viscosity against CA and various guests.

Next, inclusion compounds with various hydrocarbons were prepared in the same way by using 2-butanol. Molar ratios and release temperatures of the resulting crystals were determined by simultaneous measurements of differential scanning calorimetry (DSC) and thermogravimetry (TG). A partial list is shown in Table 2. Most of aromatic hydrocarbons employed gave thermally stable inclusion compounds. For example, benzene molecules were released from the crystals at 123 °C, which is 43 degrees higher than the boiling point itself. Introduction of a methyl or ethyl group led to a decrease of the release temperature. In the case of ethylbenzene and tetralin, a two-step-release was observed. Although naphthalene gave no complex, 1-methylnaphthalene gave a 2:1 complex.

Aliphatic hydrocarbons also yielded inclusion compounds. For example, cyclohexane gave an unstable compound, while methyl or ethylcyclohexane did stable ones. Saturated hydrocarbons such as hexane, 2,3-dimethylbutane and decalin gave crystals without any guests. Unsaturated hydrocarbons such as cyclohexene, 1,5-hexadiene and 2,3-dimethyl-1,3-butadiene gave the thermally unstable compounds, while 2,5-norbornadiene did

Table 2. Guest release temperatures and molar ratios of inclusion compounds of CA with hydrocarbons and related compounds

Guests	Guest release temperature/°C[a)	Molar ratio host : guest	Guests	Guest release temperature/°C[a)	Molar ratio host : guest
Benzene	123	1 : 1[a)	Cyclohexane	Not Clear	3 : 2[a)
Toluene	89	1 : 1[a)	Ethylcyclohexane	110	2 : 1[a)
Ethylbenzene	70, 116	1 : 1[a,b)	2,5-Norbornadiene	142	1 : 1[a)
Tetralin	89, 113	3 : 2[a,b)	Chlorobenzene	122	1 : 1[a)
1-Methylnaphthalene	126	2 : 1[a)	Dibutyl ether	109	2 : 1[a)
1,5-Hexadiene	Not Clear	1 : 1[a)	β-Ionone	142	2 : 1[a)
Myrcene	117	2 : 1[a)	Methyl Decanoate	118	2 : 1[a)

a) Determined by TG-DSC. b) Determined by ^{1}H-NMR.

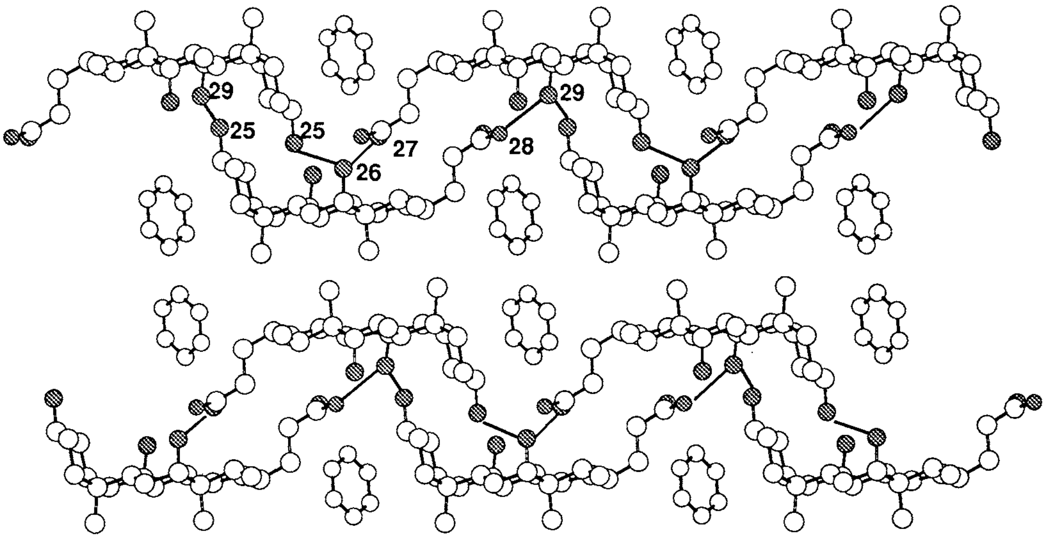

Fig. 2. The crystal structure of the inclusion compound of CA with benzene (1:1) viewed down along the crystallographic *b* axis. Carbon and oxygen atoms are represented by empty and shadowed circles, respectively. The hydrogen bond network, together with the numbering scheme of the atoms concerned, is shown: O(26)^{I}-H···O(27)^{II}=C(24)^{II}-O(28)^{II}-H···O(29)^{III}-H···O(25)^{IV}-H···O(26)^{I}, where the four O···O distances are 2.783(10), 2.656(8), 2.702(8) and 2.833(7)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, 1-z), respectively.

stable ones. Terpenes such as myrcene and (+)-limonene were also included. It is noteworthy that aromatic or long-chain compounds involving functional groups, such as chlorobenzene, dibutyl ether, β-ionone and methyl decanoate yielded stable inclusion compounds.

The inclusion compound of CA with benzene is a standard one necessary to compare the crystal structures with that of CA. Needle-like crystals were obtained by recrystallization from a solution of CA in benzene and 2-butanol. X-ray crystallographic study confirmed that the resulting single crystal consists of a 1:1 channel-type and bilayered inclusion compound,[12)] as depicted in Figure 2. The structure is isomorphous to those with γ-valerolactone,[6)] acetophenone,[5)] nitrobenzene[11)] and aniline.[11)] Tails of CA molecules adopt *gauche* conformation as in the case of acetophenone. Facial amphiphilicity forces the molecules to yield bilayers composed of hydrophilic and lipophilic sides. On the hydrophilic side four hydrogen bonding groups form cyclic networks shown in Figure 2, leading to a molecular arrangement in a head-to-head and tail-to-tail fashion. On the lipophilic side the steroidal skeletons stack together so as to leave channels between them. The channels have large side-pockets where benzene molecules fit closely, explaining the thermal stability of the inclusion compound mentioned above.

As reported earlier,[7,8)] CA forms guest-dependent polymorphic crystals, which is caused by different networks among hydrogen bonding groups, conformations of the tails, and sliding of the bilayers. The different conformations of the tails were conveniently detected by different infrared absorptions owing to stretching vibration of carbonyl group.[13)] The inclusion compound of CA with benzene had two peaks at 1698 and 1717 cm^{-1}, indicating the *gauche* conformation of the tail. This result is consistent with the crystal structure of the compound mentioned above.

In this way it is now possible to compare inclusion behavors of CA and DCA. It has been long known that DCA forms the inclusion compounds with a great variety of organic substances.[2,3] CA also can include polar as well as nonopolar guest components, as mentioned above. Therefore, it is considered that both hosts do not select polarity of the guest component. The important difference is that CA channels have large side pockets, while DCA channels very small ones.[5] Such a consideration would lead us to the idea that CA provides a molecular-level space for inclusion polymerization larger than DCA.[14,15]

In conclusion, this study demonstrates that we can reasonably find an efficient solvent for preparing inclusion compounds on the basis of a correlation between selective inclusion and guest-dependent polymorphism of host crystals.

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12) Crystal data for CA-benzene(1:1): $C_{24}H_{40}O_5+C_6H_6$, M=486.69, monoclinic, $P2_1$, a=13.627(4), b=8.038(9), c=14.076(4)Å, β=114.25(2)°, V=1405.8(6) Å^3, Z=2, Dc=1.150 gcm^{-3}. Intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromatized Mo-Kα radiation. Based on 3473 unique reflections [$|F_o|>3\sigma(F)$] the structure was solved by direct methods(SHELXS-86) and refined by the full-matrix least-squares method to R=0.054, Rw=0.035.
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