Functionalization of Inclusion Cavities of Bile Acid Hosts. Channel-Type Inclusion Compounds of Cholamide

Kazuki Sada,*,# Takashi Kondo, Masahiko Ushioda, Yoshiaki Matsuura, Kazunori Nakano, Mikiji Miyata,*,# and Kunio Miki*,†

Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1112

†Department of Chemistry, Graduate School of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606-8502

(Received March 9, 1998)

Clathrate formation and crystal structures of 3α, 7α, 12α-trihydroxy-5β-cholan-24-amide (cholamide) have been investigated. Cholamide forms inclusion compounds with various organic compounds having hydrogen-bond (H-bond) donors. X-Ray crystallographic studies showed that cholamide has bilayer structures with molecular channels. The crystal structures are quite similar to those of channel-type inclusion crystals of cholic acid. Steric dimensions of the host cavities are identical, but cholamide has an H-bond 'hook' on the wall of the channels, while cholic acid does not. This difference is correlated with not only the inclusion abilities but also the molecular structures. Two H-bond donors of the amide group yield a hydrophilic inclusion cavity that includes H-bond acceptors, and one H-bond donor of the carboxylic acid gives a lipophilic inclusion cavity that includes non-polar or less polar compounds.

Molecular design of organic microporous materials is now one of the most interesting topics in supramolecular chemistry. A large number of designed organic host compounds have been reported.[1,2] However, even now no general method to construct a desired host cavity in crystalline lattice is available. Chemical modification of known host compounds is a promising approach to design host cavities. We present here a pair of host compounds that construct host cavities having quite similar steric dimensions but different hydrogen bond environments.

Steroids are one of the best sources as host compounds due to their multi-functionality and ridged steroidal structure.[3] We recently found that cholic acid (3α, 7α, 12α-trihydroxy-5β-cholan-24-oic acid, **2**) forms channel type inclusion compounds with various organic substances.[4] Structural investigation of cholic acid clathrates found that they have bilayer structures with the lipophilic molecular channels. The facially amphiphilic molecular structure of **2** yields a characteristic bilayer structure. Here, we introduce its amide, 3α, 7α, 12α-trihydroxy-5β-cholan-24-amide (**1**) as a host molecule (Chart 1). The chemical modification from **2** and **1** leads to change of the inclusion abilities and the host cavities. Comparison of inclusion abilities and crystal structures gives us a new insight for designing inclusion cavities. Moreover, within our knowledge, they are the first examples for organic host compounds that have inclusion cavities with identical steric dimensions and different H-bond properties.

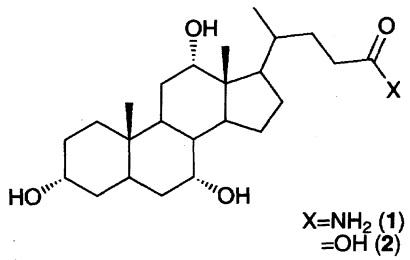

Chart 1.

Results and Discussion

Formation of Inclusion Crystals. Amide **1** forms inclusion compounds with various organic substances. The guest compounds are summarized in Table 1. Chart 2 shows the organic compounds that give guest-free powder of **1** by recrystallization. More than one hundred organic compounds form inclusion compounds with **1** and about seventy compounds do not. The following points are remarkable about the inclusion ability of **1**. (1) Amide **1** is effective in clathration with H-bond acceptors. All examined aliphatic alcohols, aliphatic diols, various cyclic ethers, and cyclic ketones give inclusion crystals. (2) Weak H-bond acceptors and non-polar compounds such as nitriles, esters, acyclic ketones, hydrocarbons, and halides do not form inclusion compounds. (3) Aliphatic amides do not give good crystalline materials at all due to high solubility. (4) In contrast with aliphatic compounds, various aromatic compounds form inclusion compounds with **1**, regardless of the presence of H-bond donors.

Host-to-guest ratios of the inclusion complexes are generally 1 : 1. Methanol and ethanol complexes have 1 : 2 host–guest ratios and 1,7-heptanediol, oligoethylene glycol

Present address: Material and Life Science, Graduate School of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565-0871, Japan.

Table 1. Guests and the Host–Guest Ratios

Guest	Molar ratio host : guest[a)]	Guest	Molar ratio host : guest[a)]	Guest	Molar ratio host : guest[a)]
Methanol	1 : 2	1,2-Propanediol[b)]	1 : 1	Ethylbenzene	1 : 1
Ethanol	1 : 2	1,3-Propanediol[b)]	1 : 1	Propylbenzene	1 : 1
1-Propanol	1 : 1	1,2-Butanediol[b)]	1 : 1	*o*-Xylene	2 : 1
2-Propanol	1 : 1	1,3-Butanediol[b)]	1 : 1	*m*-Xylene	1 : 1
1-Butanol	1 : 1	1,4-Butanediol[b)]	1 : 1	*p*-Xylene	1 : 1
2-Methyl-1-propanol	1 : 1	2,3-Butanediol[b)]	1 : 1	*o*-Chrolotoluene	2 : 1
2-Butanol	1 : 1	1,2-Pentanediol[b)]	1 : 1	*m*-Chrolotoluene	1 : 1
2-Methyl-2-propanol	1 : 1	1,5-Pentanediol[b)]	1 : 1	*p*-Chrolotoluene	1 : 1
1-Pentanol	1 : 1	2,4-Pentanediol[b)]	1 : 1	*o*-Bromotoluene	2 : 1
2-Methyl-1-butanol	1 : 1	1,2-Hexanediol[b)]	1 : 1	*m*-Bromotoluene	1 : 1
3-Methyl-1-butanol	1 : 1	2,5-Hexanediol[b)]	1 : 1	*o*-Dichlorobenzene	2 : 1
2,2-Dimethyl-1-propanol	1 : 1	1,7-Hexanediol[b)]	2 : 1	Styrene	1 : 1
2-Pentanol	1 : 1				
3-Methyl-2-butanol	1 : 1	Methyl lactate	1 : 1	Acetophenone	1 : 1
3-Pentanol	1 : 1	Ethyl lactate	1 : 1	Propiophenone	1 : 1
1,1-Dimethyl-1-propanol	1 : 1	Propyl lactate	1 : 1	Methyl benzoate	1 : 1
1-Hexanol	1 : 1	Isopropyl lactate	1 : 1	Anisole	1 : 1
2-Methyl-1-pentanol	1 : 1	Butyl lactate	1 : 1	Phenetole	1 : 1
3-Methyl-1-pentanol	1 : 1			Benzonitrile	1 : 1
4-Methyl-1-pentanol	1 : 1	Tetrahydrofuran	1 : 1		
2-Ethyl-1-butanol	1 : 1	Tetrahydropyran	1 : 1	Phenol	1 : 1
3,3-Dimethyl-1-butanol	1 : 1	1,4-Dioxane	1 : 1	*o*-Cresol	1 : 1
2-Hexanol	1 : 1	Cyclohexene oxide	1 : 1	*m*-Cresol	1 : 1
3-Hexanol	1 : 1	Oxacycloheptane	1 : 1	*p*-Cresol	1 : 1
2-Methyl-2-pentanol	1 : 1	3-Methyltetrahydrofuran	1 : 1	*m*-Ethylphenol	1 : 1
3-Methyl-2-pentanol	1 : 1	2-Methyltetrahydrofuran	1 : 1	*p*-Ethylphenol	1 : 1
4-Methyl-2-pentanol	1 : 1	1,2-Dimethoxyethane	1 : 1	*o*-Methoxyphenol	1 : 1
2-Methyl-3-pentanol	1 : 1	Diglyme	1 : 1	Methyl salicylate	1 : 1
2,3-Dimethyl-2-butanol	1 : 1	Triglyme	3 : 2	Benzyl alcohol	1 : 1
3,3-Dimethyl-2-butanol	1 : 1	Tetraglyme	2 : 1		
3-Methyl-3-pentanol	1 : 1			Aniline	1 : 1
1-Heptanol	1 : 1	Acetone	1 : 1	*N*-Methylaniline	1 : 1
2-Heptanol	1 : 1	Cyclohexanone	1 : 1	*N*,*N*-Dimethylaniline	1 : 1
1-Octanol	1 : 1	2-Methylcyclohexanone	1 : 1	*o*-Toluidine	1 : 1
2-Octanol	1 : 1	3-Methylcyclohexanone	1 : 1	*m*-Toluidine	1 : 1
1-Decanol	1 : 1	4-Methylcyclohexanone	1 : 1	*p*-Toluidine	1 : 1
				Pyrrole	1 : 1
Cyclohexanol	1 : 1	Water	1 : 1	Phenylhydrazine	1 : 1
2-Methylcyclohexanol	1 : 1	Acetic acid	1 : 1		
3-Methylcyclohexanol	1 : 1				
4-Methylcyclohexanol	1 : 1				

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

dimethyl ethers, and 1,2-disubstituted benzenes yield the inclusion crystals at 3 : 2 or 2 : 1 host–guest stoichiometries. A wide range of alcohols, for example from 1-propanol to 1-decanol, form 1 : 1 inclusion compounds with **1**. Therefore, the host–guest ratios of **1** are independent of the steric dimensions of the guest alcohols. This indicates that the host **1** have several polymorphs of the host assemblies in response to the guest molecules.

Crystal Structures of Inclusion Crystals. X-Ray crystallographic studies showed that crystal structures of **1** divided into three groups (I, II, III) dependent on the guest molecules. Figure 1 shows typical forms and Table 2 summarizes the crystallographic data of inclusion crystals with the guest compounds having various functional groups. 2-Propanol, 1,4-dioxane, (*RS*)-2-butanol, and *m*-cresol belong to form I[8a,8b,8d)] and 4-methylcyclohexanone, aniline, and *p*-toluidine to form II.[8c)] *m*-Xylene and (*RS*)-butyl lactate consist of form III.

In all forms, host **1** has bilayer structures due to H-bonds between the hydrophilic faces of **1** and van der Waals force between the lipophilic faces. Moreover, the bent molecular shape of **1** produces a one-dimensional host cavity, a channel, that run along a two-fold screw axis in the lipophilic layers, where the guest molecules are incorporated.

These crystal structures are characterized by the conformation of the steroidal side chain and the relative positions in the lipophilic layers. This yields three kinds of the inclusion cavities with different steric dimensions. Guest molecules

Hexane	Propionic acid	Ethylene diacetate
Cyclohexane	*N*,*N*-Dimethylforamide	*s*-Butyl acetate
Dichloromethane	Acetamide	Ethyl butyrate
1,2-Dicholoethane	Dimethyl sulfoxide	Ethyl isobutyrate
Heptane	Pyridine	Methyl sorbate
Carbon tetrachloride	2-Methylpyridine	Butyl acrylate
	2,6-Dimethylpyridine	Pentyl acetate
Diethyl ether	2,4,6-Trimethylpyridine	Phenyl acetate
Diisopropyl ether	Nitromethane	Ethyl benzoate
		Propyl benzoate
2-Butanone	Methyl formate	Isopropyl benzoate
2,4-Pentanedione	Ethyl formate	Butyl benzoate
2-Pentanone	Methyl acetate	Isobutyl benzoate
3-Methyl-2-butanone	Ethyl acetate	*t*-Butyl benzoate
2-Heptanone	Allyl acetate	
	Isopropyl acetate	γ-Butyrolactone
Acetonitrile	Ethyl acrylate	γ-Valerolactone
Acrylonitrile	Methyl crotonate	4-Hexanolide
Propionitrile	Methyl methacrylate	
Crotononitrile	Propyl acetate	
Methacrylonitrile	Methyl butyrate	
Butyronitrile	Methyl isobutytae	
Isobutyronitrile	Ethyl crotonate	
	Ethyl methacrylate	
Benzene	Methyl tiglate	
Toluene		
Chlorobenzene		
Bromobenzene		
p-Bromotoluene		
1-Phenyl-1-propene		

Chart 2. Non-included Organic Compounds for **1**.

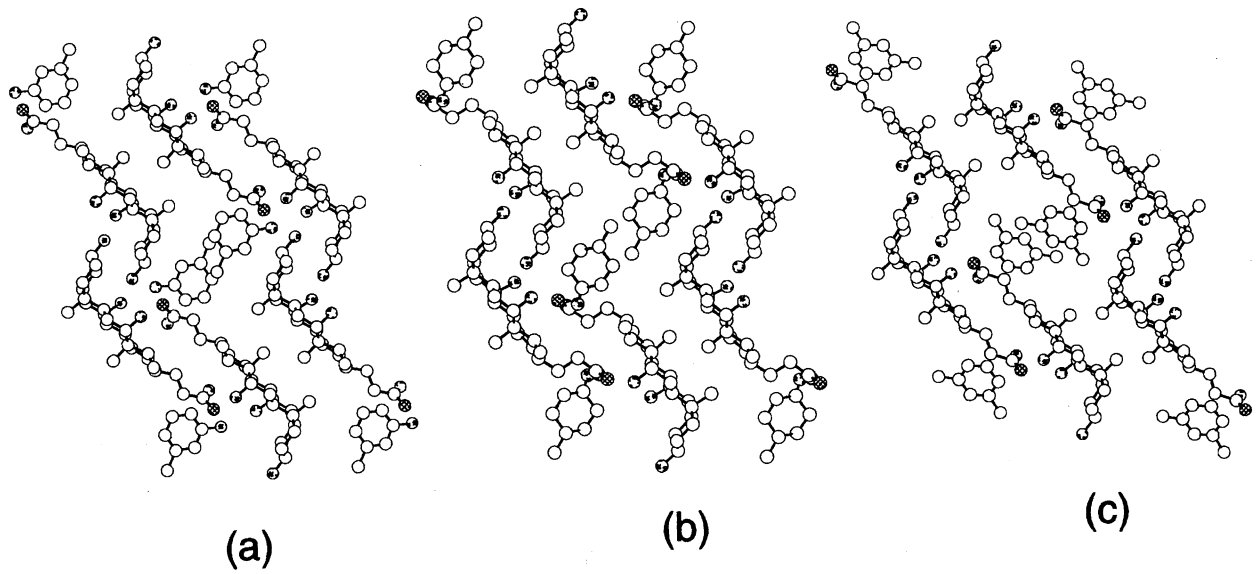

Fig. 1. Crystal structures of 1 : 1 complexes of **1** (a) with *m*-cresol (1 : 1) as form I, (b) with 4-methylcyclohexanone (1 : 1) as form II, and (c) with *m*-xylene (1 : 1) as form III, viewed along the crystallographic *b* axis. The carbon, nitrogen, and oxygen atoms are represented by open, shadowed and dotted circle, respectively.

are incorporated in the suitable channels. Small guests such as 2-propanol and 1,4-dioxane are included in form I having the narrowest channels and large guests such as *m*-xylene and (*RS*)-butyl lactate in form III having the widest ones. The channel-type structures and three polymorphs of the host assemblies dependent on guests enables **1** to form inclusion compounds with a wide range of guest molecules.

Hydrogen Bonds Motifs. H-bond networks between

Table 2. Lattice Parameters of Inclusion Crystals of **1**

Guest	2-Propanol	(*RS*)-2-Butanol	*m*-Cresol	(*RS*)-Butyl lactate	1,4-Dioxane
Host : guest ratio	1 : 1	1 : 1	1 : 1	1 : 1	1 : 1
Molecular formula	$C_{27}H_{49}NO_5$	$C_{28}H_{51}NO_5$	$C_{31}H_{49}NO_5$	$C_{31}H_{55}NO_7$	$C_{28}H_{41}NO_6$
Formula weight	515.73	481.71	515.73	553.78	495.70
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
a/Å	13.103(1)	13.251(2)	13.431(4)	12.082(4)	13.170(1)
b/Å	7.799(1)	7.869(1)	7.788(4)	8.103(3)	7.868(1)
c/Å	14.092(2)	14.045(1)	14.311(6)	16.852(5)	14.098(1)
β/°	104.68(1)	104.82(1)	105.23(3)	110.40(2)	104.97(1)
V/Å^3	1393.0(2)	1415.9(3)	1444(1)	1546.4(9)	1411.2(2)
D_c/g cm^{-1}	1.12	1.13	1.19	1.19	1.16
Z	2	2	2	2	2
R	0.047	0.051	0.044	0.045	0.050
Polymorph	I	I	I	III	I
Reference	8b	8d	This work	This Work	8a
Guest	4-Methylcyclohexanone	Aniline	*p*-Toluidine	*m*-Xylene	
Host : guest ratio	1 : 1	1 : 1	1 : 1	1 : 1	
Molecular formula	$C_{31}H_{53}NO_5$	$C_{30}H_{48}N_2O_4$	$C_{31}H_{50}N_2O_4$	$C_{32}H_{51}NO_4$	
Formula weight	519.76	500.12	514.75	513.76	
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	
a/Å	13.8043(9)	14.018(1)	14.068(1)	12.231(3)	
b/Å	8.234(1)	7.936(2)	7.9532(9)	8.001(2)	
c/Å	13.8388(8)	14.1591(7)	14.135(2)	16.075(3)	
β/°	110.080(4)	115.402(6)	114.001(7)	108.41(1)	
V/Å^3	1477.4(2)	1422.8(3)	1444.8(3)	1492.7(5)	
D_c/g cm^{-1}	1.17	1.17	1.18	1.14	
Z	2	2	2	2	
R	0.040	0.040	0.045	0.075	
Polymorph	II	II	II	III	
Reference	This work	8c	This Work	This Work	

host molecules in the forms are identical. They all have a cyclic intermolecular H-bond network involving three hydroxy groups and one amide group of four different host molecules, which are related by symmetry (two-fold screw axis of space group $P2_1$). Figure 2 is a schematic drawing of the H-bond network. One of two amide protons participates in the host–host H-bond cycle.

Another amide proton comes out on the wall of the channel and forms a H-bond with guest molecules. Oxygen atoms of the guests are caught by an amide hydrogen bond 'hook'.[8a] Alcohols and phenols have an additional hydrogen bond from the guest to the host. The hydroxy group bridges between host–host H-bond cycles. Such double hydrogen bonds serve as a driving force to form thermally stable inclusion crystals.

Comparison of Inclusion Compounds between 1 and 2. Systematic comparison of the guest compounds of **1** with **2** showed that inclusion ability of **1** is complementary to that of **2**. Chart 3 represents the ratios between the number of the compounds that were recrystallized and that of the guest compounds of **1** or **2**. Prominent features are as follows: (1) amide **1** forms inclusion compounds with various alcohols, more than 40 aliphatic alcohols, but acid **2** does with only limited alcohols such as methanol, ethanol, and 1-propanol.[5] Higher alcohols form guest-free crystals or hemihydrate crystals of **2**.[6,7,9] (2) Various nitriles, esters acyclic ketones, and

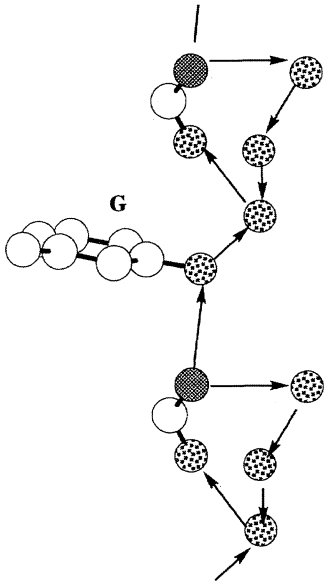

Fig. 2. Schematic drawing of the hydrogen bond network of **1** with *m*-cresol (G). The carbon, nitrogen, and oxygen atoms are represented by open, shadowed, and dotted circle, respectively. Arrows represent hydrogen bond direction from a donor to an acceptor.

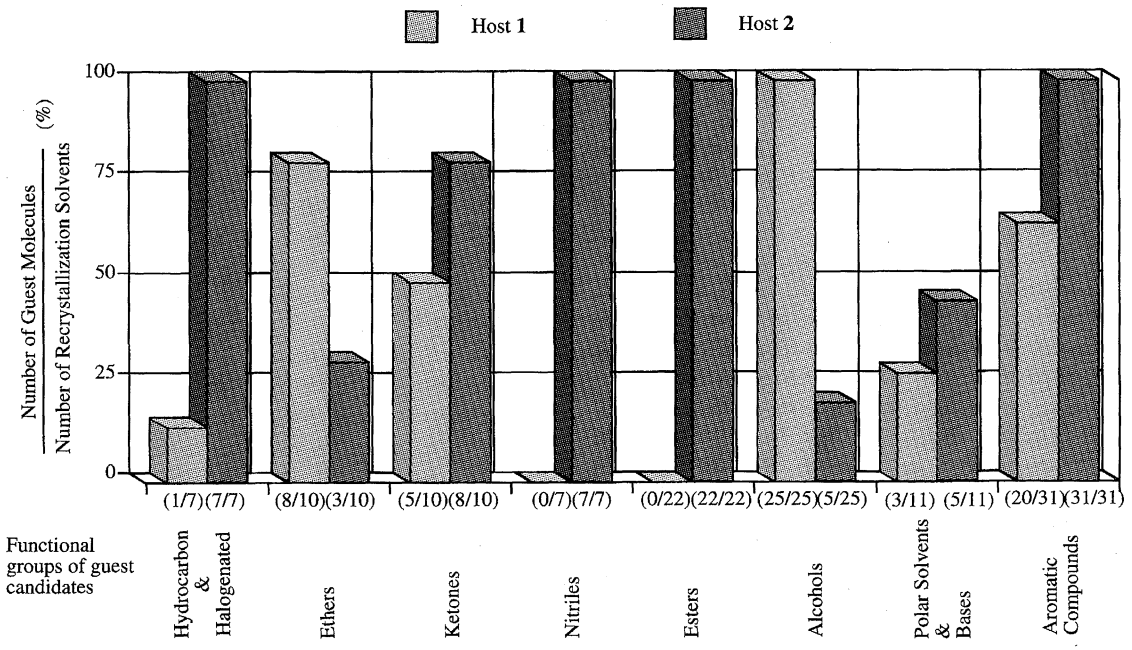

Chart 3. Comparison of functional groups of guest molecules of **1** and **2**.

hydrocarbons form inclusion compounds with **2**, not with **1**. (3) Benzene, toluene, chlorobenzene, and bromobenzene do not form inclusion compounds with **1**. However, all mono-substituted benzenes form inclusion compounds with **2**.[4f] (4) Cyclic ketones and cyclic ethers form inclusion compounds with both **1** and **2**. (5) Amides and other polar solvents do not give good crystalline material in both. Therefore, aliphatic alcohols and ethers form inclusion compounds with **1**, and less polar compounds form inclusion compounds with **2**. This indicates that inclusion by **1** of the aliphatic compounds is complementary to that of **2**.

Comparison of crystal and molecular structures of both hosts gives some explanation of the complementary inclusion abilities. The crystal structures of the inclusion compounds of **2** have already been reported.[4,5] Acid **2** forms two kinds of major polymorphs of the host assemblies, dependent on guest molecules; one is a channel-type form that includes less and non-polar compounds and the other is a cage-type that includes alcoholic guests.[4,5] The channel-type structure of **2** resembles those of **1**. Replacement of the amide group by the carboxylic acid group in the H-bond network of **1** yields the H-bond network of the channel-type form of **2**. The proton of the carboxylic acid participates in the cyclic host H-bond network and no proton donors are provided as a 'hook' to guest molecules on the wall of the channel in the channel-type form of **2**. A single H-bond from the alcoholic guest to the host, as compared with 'double hooks' of the clathrates of **1**, would be so weak that **2** does not form thermally stable inclusion compounds with various alcohols in the channel-type structure. Consequently, the alcohols form another cage-type form, which has a linear H-bond network involving host-to-guest and guest-to-host double H-bonds. The lack of H-bond donors to guest molecules in the channel-type structure of **2** allows the formation of inclusion compounds with a wide range of weak H-bond donors and non-polar guest molecules.

Although both **1** and **2** form similar channel-type structures, **1** has H-bond donors in the channel and **2** has not. Consequently, **1** prefers to form inclusion compounds with hydrophilic compounds rather than lipophilic compounds and **2** has the opposite preference. This difference of inclusion abilities is derived from that of the molecular structures themselves. The number of the H-bond donors at the terminal functional groups plays a decisive role in host–guest interactions.

Modification of H-Bond Environment of Inclusion Cavities. The H-bond is the strongest and most directional intermolecular interaction in organic crystals. Chemical modification of H-bond functional groups of host compounds generally transforms the crystal structures and reforms the environment of host cavities, including steric dimensions and the H-bond environment.[1,2] However, the bile acid hosts described above do not change the host frameworks at all. Size and shape of the channel of **1** are essentially identical to those of **2**.[4] The additional hydrogen atom of **1** allows the host–guest H-bonds in the channel. A small modification of the functional group of the bile acid **2** to **1** leads to a small modification of H-bond properties of the inclusion cavities without any transformation of the steric dimensions. This indicates that modification of the bile acids will give us lots of host compounds having inclusion cavities with various steric dimensions and H-bond environments.

Experimental

IR spectra were taken on a JASCO IR-810 or a JASCO IR Report 100 grating spectrometer using KBr disk. ^{1}H NMR spectra were recorded on a JEOL 270 MHz or 400 MHz FT-NMR spectrometer, and chemical shifts are reported in parts per million (ppm) from tetramethylsilane. TGA-DSC was measured by a Rigaku Thermoflex TG 8110 instrument. All solvents and chemicals were of

reagent grade quality, purchased commercially and used without further purification. **1** was prepared by the conventional condensation reaction from **2** and ammonia by mixed anhydride method at −20 °C.[10]

Preparations of Inclusion Crystals. Preparation of inclusion crystals usually involves recrystallization of **1** from organic substances. A typical procedure is as follows: a recrystallization experiment involves dissolving 30 mg of **1** in 3.0 mL of 2-butanol with heating at its boiling point. The solution was allowed to be cool to room temperature until crystals began to form. Crystals were collected and air-dried on a filter paper for several minutes. The resulting crystals were characterized by IR and the host-guest ratios were measured by TGA or solution ^{1}H NMR in DMSO-d_6.

The following organic compounds were recrystallized to compare guest specificity of **1** and **2** (see Chart 3). In parentheses, the number of the compounds are shown: Hydrocarbons & halogenated hydrocarbons (7): hexane, heptane, cyclohexane, carbon tetrachloride, chloroform, dichloromethane, 1,2-dichloroethane; Ethers (10): diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxane, 2-methyltetrahydrofuran, 3-methyltetrahydrofuran, cyclohexene oxide, oxacycloheptane; Ketones (10): acetone, 2-butanone, 2,4-pentanedione, 2-pentanone, 3-methyl-2-butanone, 2-heptanone, cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone; Nitriles (7): acetonitrile, acrylonitrile, propionitrile, crotononitrile, methacrylonitrile, butyronitrile, isobutyronitrile; Aliphatic esters (22): methyl formate, ethyl formate, methyl acetate, ethyl acetate, allyl acetate, isopropyl acetate, ethyl acrylate, methyl crotonate, methy methacrylate, propyl acetate, methyl butyrate, methyl isobutyrate, ethyl crotonate, ethyl methacrylate, methyl tiglate, ethylene diacetate, *s*-butyl acetate, ethyl butyrate, ethyl isobutyrate, methyl sorbate, butyl acrylate, pentyl acetate, γ-butyrolactone, γ-valerolactone, 4-hexanolide; Aliphatic alcohols (25): methanol, ethanol, 1-propanol, 2-propanol, 2-propyn-1-ol, allyl alcohol, 1-butanol, 2-butanol, 2-methyl-1-propanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol, 1,1-dimethyl-1-propanol, 3-methyl-2-butanol, 1-hexanol, 2-hexanol, 3-hexanol, 4-methyl-2-pentanol, 1-heptanol, 2-heptanol, 1-octanol, 2-octanol, 1-decanol; Polar solvents and bases (11): acetic acid, propionic acid, *N*,*N*-dimethylforamide, acetamide, dimethyl sulfoxide, water, pyridine, 2-methylpyridine, 2,6-dimethylpyridine, 2,4,6-trimethylpyridine, pyrrole; Aromatic compounds (31): phenol, *o*-cresol, *m*-cresol, *p*-cresol, benzyl alcohol, acetophenone, propiophenone, benzonitrile, chlorobenzene, bromobenzene, anisole, *N*-methylaniline, aniline, *o*-toluidine, *m*-toluidine, *p*-toluidine, phenyl acetate, methyl benzoate, ethyl benzoate, propyl benzoate, isopropyl benzoate, butyl benzoate, isobutyl benzoate, *t*-butyl benzoate, benzene, toluene, propylbenzene, styrene, *o*-xylene, *m*-xylene, *p*-xylene.

Crystal Structure Determinations. X-Ray diffraction data were collected on Rigaku AFC5R diffractometer with graphite-monochromatized Cu $K\alpha$ radiation at Osaka University and the Tokyo Institute of Technology or Rigaku AFC7R diffractometer with graphite-monochromatized Mo $K\alpha$ radiation at Gifu University. All measurements were done at room temperature. Lattice parameters were obtained by least-squares analysis of 25 reflections. Direct methods (SHELX 86) were used for the structure solution. The structure was refined by the block-diagonal least-squares procedure with the program HBLS-V at Osaka University, or by the full matrix least-squares procedure with the TEXSAN software package at Gifu University using observed reflections ($|F_o| > 3\sigma(|F_o|)$, except for *m*-xylene clathrate ($|F_o| > 2\sigma(|F_o|)$). On the difference Fourier maps all the hydrogen atoms were found at the expected positions. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms of host molecule were refined isotropically as the constant thermal parameters. Hydrogen atoms of guest molecules are not refined. All the computations were done on an ACOS 930 computer at the Research Center for Protein Engineering, Institute for Protein Research, Osaka University or on an IRIS workstation at Gifu University. Tables of positional and thermal parameters and bond angles and distances and full experimental detail have been deposited as Document No. 71042 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Support of our work by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, and by Ciba-Geigy Foundation (Japan) for the Promotion of Science are gratefully acknowledged.

References

1) Reviews on inclusion compounds: a) D. D. MacNicol, J. J. McKendrick, and D. R. Wilson, *Chem. Soc. Rev.*, **7**, 65 (1978); b) J. E. D. Davies, W. Kemula, H. M. Powell, and N. O. Smith, *J. Inclusion Phenom.*, **1**, 3 (1983); c) *Top. Curr. Chem.*, **140**, (1988) and **149**, (1988); d) "Inclusion Compounds," ed by J. L. Atwood, J. E. D. Davies, and D. D. MacNicol, Academic Press, London (1984), Vol. 1—3; Oxford Press, Oxford (1991), Vol. 4—5; e) "Comprehensive Supramolecular Chemistry," ed by D. D. MacNicol, F. Toda, and R. Bishop, Pergamon Press, Oxford (1996), Vol. 6: Solid-State Supramolecular Chemistry: Crystal Engineering.

2) a) X. Wang, M. Simard, and J. D. Wuest, *J. Am. Chem. Soc.*, **116**, 12119 (1994); b) G. B. Gardner, D. Venkataraman, J. S. Moore, and S. Lee, *Nature*, **374**, 792 (1995); c) O. M. Yaghi, G. Li, and H. Li, *Nature*, **378**, 703 (1995).

3) a) W. C. Herndon, *J. Chem. Educ.*, **44**, 724 (1967); b) E. Gigilo, "Inclusion Compounds," ed by J. L. Atwood, J. E. D. Davies, and D. D. MacNicol, Academic Press, London (1984), Vol. 2, p. 207; c) M. Miyata and K. Sada, Ref. 1e, p. 147, and references sited in.

4) Channel-type clathrates of **2**: a) K. Miki, A. Masui, N. Kasai, M. Miyata, M. Shibakami, and K. Takemoto, *J. Am. Chem. Soc.*, **110**, 6594 (1988); b) K. Miki, N. Kasai, M. Shibakami, K. Takemoto, and M. Miyata, *J. Chem. Soc., Chem. Commun.*, **1991**, 1757; c) M. R. Caira, L. R. Nassimbeni, and J. L. Scott, *J. Chem. Soc., Chem. Commun.*, **1993**, 612; d) M. R. Caira, L. R. Nassimbeni, and J. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 623; e) M. R. Caira, L. R. Nassimbeni, and J. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 1403; f) K. Nakano, K. Sada, and M. Miyata, *Chem. Lett.*, **1994**, 137; g) M. Shibakami and A. Sekiya, *J. Chem. Soc., Chem. Commun.*, **1994**, 429; h) K. Nakano, K. Sada, and M. Miyata, *J. Chem. Soc., Chem. Commun.*, **1995**, 953; i) J. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, **1995**, 495; j) M. Shibakami, M. Tamura, and A. Sekiya, *J. Am. Chem. Soc.*, **117**, 4499 (1995).

5) Alcoholic complexes of **2**: a) P. L. Jonson and J. P. Schaefer, *Acta Crystallogr., Sect. B*, **B28**, 3083 (1972); b) E. Jones and L. R. Nassimbeni, *Acta Crystallogr., Sect. B*, **B46**, 399 (1990); c) M. Shibakami and A. Sekiya, *J. Inclusion Phenom.*, **18**, 397 (1994).

6) Hydrate of **2**: a) L. Lessinger, *Struct. Commun.*, **11**, 1787 (1982); b) L. Lessinger and B. W. Low, *J. Crystallogr. Spectrosc. Res.*, **23**, 85 (1993).

7) Guest-free **2**: K. Miki, N. Kasai, M. Shibakami, S. Chirachanchai, K. Takemoto, and M. Miyata, *Acta Crystallogr.*,

Sect. C, **C46**, 2442 (1990).

8) a) K. Sada, T. Kondo, M. Miyata, T. Tamada, and K. Miki, *J. Chem. Soc., Chem. Commun.*, **1994**, 753; b) K. Sada, T. Kondo, M. Miyata, and K. Miki, *Chem. Mater.*, **6**, 1103 (1994); c) K. Sada, Y. Matsuura, and M. Miyata, *Mol. Cryst. Liq. Cryst.*, **276**, 121 (1996); d) P. Briozzo, T. Kondo, K. Sada, M. Miyata, and K. Miki, *Acta Crystallogr., Sect. B*, **B52**, 728 (1996).

9) F. Mylius, *Ber. Dtsch. Chem. Ges.*, **20**, 1968 (1887).

10) A. M. Bellini, M. P. Quaglio, M. Guarneri, and G. Cavazzini, *Eur. J. Med. Chem.*, **18**, 185 (1983).