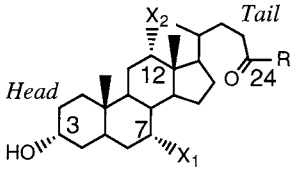
Selective Inclusion Phenomena in Lithocholamide Crystal Lattices; Design of Bilayered Assemblies through Ladder-type Hydrogen Bonding Network

Yukio Hishikawa, Yuriko Aoki, Kazuki Sada, and Mikiji Miyata*
Material and Life Science, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871

(Received September 7, 1998; CL-980697)

The substitution of lithocholic acid (**1**) to lithocholamide (**4**) led to the finding of the formation of channel-type inclusion compounds with a limited range of organic substances, such as alcohols, ketones and so on. The inclusion behavior of **4** is greatly different from those of the known hosts of bile acids and their derivatives.

Molecular design of nanoporous material is one of the most challenging concerns of crystal engineering.[1] The prominent design of hydrogen bonds brings about nanoporous frameworks suitable for lattice inclusion compounds. On the other hand, a combinatorial approach is also effective for searching the inclusion compounds.[2] A fusion of the two approaches would give us an effective way to find the compounds.



X_1	X_2	R	
-H	-H	-OH	**1**
-H	-OH	-OH	**2**
-OH	-OH	-OH	**3**
-H	-H	$-NH_2$	**4**
-H	-OH	$-NH_2$	**5**
-OH	-OH	$-NH_2$	**6**

Deoxycholic acid (**2**) and cholic acid (**3**) have been discovered to form the componds by chance.[3] Lithocholic acid (**1**) may be expected to form the inclusion compounds from a viewpoint of the combinatorial approach. So far, there is no report about the inclusion behaviors of **1** and its derivatives, though the discovery of **1** dates back to 1911.[4] Only a structure of its guest-free crystal is known.[5] However, we have found that lithocholamide (**4**) instead of **1** constructs bilayered frameworks with channels as described below.

The crystal of **1** has a slantwise assembly without channels because of helical hydrogen bonding network among 3-positioned hydroxy and pendent carboxyl groups (Figure 1a, 1b).[5] On the other hand, *N*-*n*-propylammonium deoxycholate was found to form bilayered inclusion crystals with a ladder-type hydrogen bonding network (Figure 1c, 1d).[6] This fact reminds that an amide group is an advantageous implement. The reason is that the group can commonly form ladder-type hydrogen bonding network by using

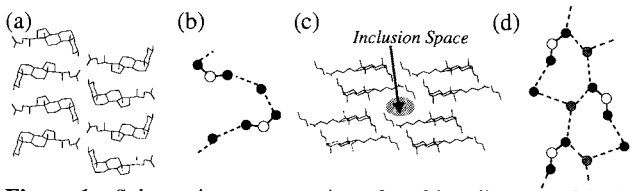


Figure 1. Schematic representation of packing diagram of **1** (a); hydrogen bonding network of **1** (b); packing diagram of *N*-*n*-propylammonium deoxycholate with 2-propanol (c); and hydrogen bonding network of *N*-*n*-propylammonium deoxycholate with 2-propanol (d).

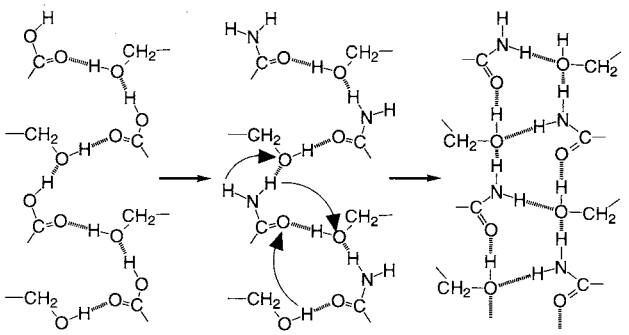


Figure 2. Schematic representation of design for ladder-type network by replacement of hydrogen bonding groups.

an additional hydrogen.[7] Transformation of carboxyl group to amide one may cause ladder-type network similar to that of the salt (Figure 2). This expectation was realized as follows.

Compound **4** was prepared from commercially available **1** as described in the literature.[8] The amide was recrystallized from neat guest components or from THF solution. The resulting crystals were characterized by IR and NMR spectroscopy, TG-DTA and powder X-ray diffraction methods. We checked over one hundred kinds of the guest candidates, such as aromatic and aliphatic alcohols, ketones, esters, nitriles and so on.

The results are summarized in Table 1. It can be seen that **4** included about twenty organic compounds among them. Although small alcohols, such as methanol, ethanol, 1- or 2-propanol, were not included, 2-methyl-2-propanol were done among four alcoholic isomers of $C_4H_{10}O$. 2-Pentanol, 3-pentanol, 2-methyl-2-butanol and 3-methyl-2-butanol were included among eight alcoholic isomers of $C_5H_{12}O$. Further inclusion experiments revealed that 1-hexanol, 2-hexanol, 3-hexanol, 2-methyl-2-pentanol, 3-methyl-3-pentanol, 3,3-dimethyl-2-butanol and 2-ethyl-1-butanol were included among alcoholic isomers of $C_6H_{14}O$. Other than these alcohols, only limited substances, such as 3-pentanone, 3-hexanone, cyclohexanone, isopentyl formate, chloroform, bromoform, bromobenzene and 2-bromofluorobenzene were included.

In contrast, **1** did not include these compounds at all. Moreover, deoxycholamide (**5**) and cholamide (**6**) flexibly included all of the aliphatic alcohols investigated.[9] Accordingly, the inclusion behavior of **4** is greatly different from those of the known hosts of bile acids and their derivatives.

In order to explain the unique inclusion behavior of **4**, we employed single crystal X-ray structural analysis. We succeeded in determining two kinds of the inclusion crystals of **4** with 3-pentanol and 3-pentanone.[10] These crystals belong to the monoclinic, space group $P2_1$. Figures 3a and 3b represent the packing diagrams of the corresponding inclusion compounds, as viewed down the crystallographic *b* axis. In each case the host molecules arrange in a head-to-tail fashion to yield bilayers, which are stacked so as to leave channels accommodating the guests. A relative po-

Table 1. Inclusion abilities of **4** towards organic compounds[a]

Guest	H : G[b]	Guest	H : G
Methanol	GF[c]	Acetone	GF
Ethanol	GF	2-Butanone	GF
1-Propanol	GF	2-Pentanone	GF
2-Propanol	GF	3-Pentanone	1 : 1
1-Butanol	GF	2-Hexanone	GF
2-Butanol	GF	3-Hexanone	1 : 1
2-Methyl-1-propanol	GF	Acetophenone	GF
2-Methyl-2-propanol	1 : 1	*n*-Butyl formate	GF
1-Pentanol	GF	Isopentyl formate	1 : 1
2-Pentanol	1 : 1	Methyl acetate	GF
3-Pentanol	1 : 1	Ethyl acetate	GF
2-Methyl-1-butanol	GF	Methyl benzoate	GF
3-Methyl-1-butanol	GF	THF	GF
2-Methyl-2-butanol	1 : 1	1,4-Dioxane	GF
3-Methyl-2-butanol	1 : 1	Anisole	GF
2,2-Dimethyl-1-propanol	GF	Acrylonitrile	GF
1-Hexanol	1 : 1	Chloroform	1 : 1
2-Hexanol	1 : 1	Bromoform	1 : 1
3-Hexanol	1 : 1	Benzene	GF
2-Methyl-2-pentanol	1 : 1	Toluene	GF
3-Methyl-3-pentanol	1 : 1	Ethylbenzene	GF
3,3-Dimethyl-2-butanol	1 : 1	Bromobenzene	2 : 1
2-Ethyl-1-butanol	1 : 1	2-Bromofluorobenzene	2 : 1

[a] Determined by TG-DTA. [b] Host : guest molar ratio. [c] GF : Guest-free crystal.

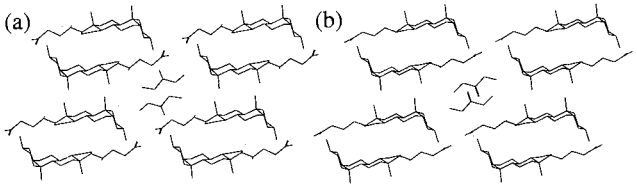


Figure 3. Schematic representation of the packing diagrams; inclusion crystals of **4** with 3-pentanol (a) and with 3-pentanone (b).

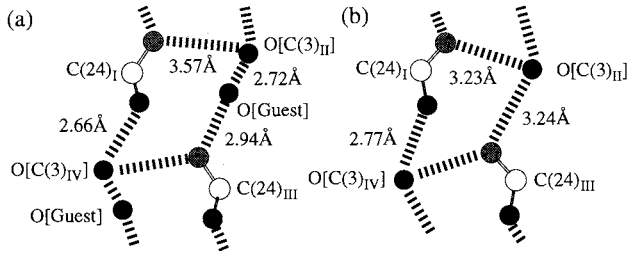


Figure 4. Schematic representation of hydrogen bonding networks; inclusion crystals of **4** with 3-pentanol (a) and with 3-pentanone (b). Empty, filled and shadowed circles represent carbon, oxygen and nitrogen atoms, respectively.

sition on lipophilic sides of the layers for 3-pentanol is similar to that for 3-pentanone.

Figures 4a and 4b show their hydrogen bonding schemes and distances. It can be seen that hydrogen bonding groups of the hosts construct common ladder-type networks instead of helical network of **1** (Figure 1b). The ladder-type networks yielded the bilayered assemblies with channels, though the helical network did the slantwise assembly without channals.[5] As shown in Figure 4a, the 3-pentanol molecules are trapped through hydrogen bonds, explaining the inclusion of many alcoholic components. On the other hand, Figure 4b shows that there is no hydrogen bond among 3-pentanone molecules and the host molecules. It is noteworthy that the bond distance (3.57 Å) of N-H[C(24)I]•••O-H[C(3)II] for 3-pentanol is longer than usual hydrogen bonding distances, but that (3.23 Å) for 3-pentanone is shortened.[5] In contrast, **1** has the short hydrogen bond lengths (2.60, 2.71 Å in Figure 1b).

The other inclusion crystals were characterized by X-ray powder diffraction patterns. The inclusion compounds with the alcohols have the crystal structures similar to that with 3-pentanol, since they have similar peaks with 2θ values of about 5.4 and 8.4°.

All of the resulting inclusion crystals gave two endothermic peaks in the DTA. One peak at higher temperature corresponds to the melting point (*ca.* 215 °C) of **4** itself. The other peak is based on the release of the guests from the host lattice. For example, the inclusion compounds of **4** with 3-pentanol and 3-pentanone gave the peaks at *ca.* 89 and 102 °C, respectively. This result indicates that the stabilization of the inclusion crystals depends on the steric terms rather than hydrogen bonding terms.

In conclusion, this study suggests that even when the acid-form of a steroidal bile acid does not yield the inclusion compound, other derivatives of the acid may form the compounds through different hydrogen bonding network. Accordingly, it is considered that molecules with steroidal skeletons and hydrogen bonding groups may have latent inclusion abilities towards organic substances.

This work was partly supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 283, "Innovative Synthetic Reactions") fro n the Ministry of Education, Science, Sports and Culture, Japan.

References and Notes

1 a) V. A. Russell, C. C. Evans, W. Li, and M. D. Ward, *Science*, **276**, 575 (1997). b) K. Kobayashi, K. Endo, Y. Aoyama, and H. Masuda, *Tetrahedron Lett.*, **34**, 7929 (1993).

2 a) K. Sada, K. Yoshikawa, and M. Miyata, *Chem. Commun.*, 1763 (1998). b) M. Miyata, K. Sada, and Y. Miyake, *Mol. Cryst. Liq. Cryst.*, **313**, 173 (1998).

3 a) M. Miyata and K. Sada, in "Comprehensive Supramolecular Chemistry," ed by D. D. MacNicol, F. Toda, and R. Bishop, Pergamon, Oxford (1996), Vol.6, p.147. b) E. Giglio, in "Inclusion Compounds," ed by J. L. Atwood, J. E. D. Davies, and D. D. MacNicol, Academic press, London (1984), Vol. 2, p. 207.

4 H. Fischer, *Z. Physiol. Chem.*, **73**, 234 (1911).

5 S.K.Arora, G.Germain, and J.P.Declercq, *Acta Crystallogr.*, **B32**, 415 (1976).

6 K. Sada, N. Shiomi, and M. Miyata, *J. Am. Chem. Soc.*, in press.

7 a) L. Leiserowitz, *Acta Crystallogr., Sect.* B, **32**, 775 (1976). b) J. Berstein, M. C. Etter, and L. Leiserowitz, in "Structure Correlation," ed by H. -B. Burgi, and J. D. Dunitz, VCH, Weinheim (1994), Vol. 2, p. 431.

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

9 a) K.Sada, T.Kondo, M.Miyata, T.Tamada, and K.Miki, *J. Chem. Soc., Chem. Commum.*, **1993**, 753. b) K. Sada, T. Kondo, and M. Miyata, *Chem Mater.*, **6**, 1103 (1994). c) K.Sada, T.Kondo, and M.Miyata, *Supramolecular Chemistry.*, **5**, 189 (1994). d) P. Briozzo, T. Kondo, K. Sada, M. Miyata, and K. Miki, *Acta Crystallogr.*, **B52**, 728 (1996).

10 Crystal structure data for **4**•3-pentanol system : ($C_{24}H_{41}O_2N_1$•$C_5H_{12}O_1$), F.W. = 463.74, Monoclinic, space group $P2_1$, a = 10.729(5), b = 8.058(2), c = 17.09(1) Å, β = 106.98(3)°, V = 1413(1) Å^3, ρ calc = 1.090 g•cm^{-3}, Z = 2, R = 0.046, Rw = 0.052. The crystal showed 2543 unique reflections(2θmax = 51.3°). 1753 [|F0|>3σ|F0|] reflections were used for further calculations after Lorenz and polarization corrections.
Crystal structure data for **4**•3-pentanone system : ($C_{24}H_{41}O_2N_1$•$C_5H_{10}O_1$), F.W. = 461.73, Monoclinic, space group $P2_1$, a = 11.145(1), b = 7.597(2), c = 17.219(2) Å, , β = 109.479(9)°, V = 1374.5(4) Å^3, ρ calc = 1.116 g•cm^{-3}, Z = 2, R = 0.044, Rw = 0.047. The crystal showed 2538 unique reflections(2θmax = 51.3°). 1851[|F0|>3σ|F0|] reflections were used for further calculations after Lorenz and polarization corrections.