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Guest-dependent conformations of side chains in cholic acid inclusion compounds

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An attractive role of a side chain of cholic acid is described. X-ray crystallographic studies made clear that the side chain employs guest-dependent conformations (called *trans* or *gauche*) in its channel-type inclusion compounds in contrast to that of deoxycholic acid. The flexibility of the side chain originates from a fact that the host molecules arrange in a *tail-to-tail* fashion to form cyclic hydrogen-bonding network. Guest molecules affect the network, leading to very sensitive infrared spectra to the guests. Molecular graphics study shows that there are two kinds of pockets in the channels. The conformational change is responsible for a change of shape of the pockets composed of the chains.

INTRODUCTION

Most of known hosts for lattice-type inclusion compounds (clathrates) are composed of only rigid skeletons.[3] However, proteins remind us of a role of pendent groups of amino acids, which cause flexibility of the molecular architectures. In addition, as for macrocyclic compounds, it is known that pendent groups attached to the cycles play unique roles.[4] Also as for the above inclusion compounds, we may expect any effects of flexible side chains attached to the rigid skeletons of the hosts.

To this end, a series of natural compounds seem to be favorable. They are steroidal bile acids, such as cholic acid[5a] and deoxycholic acid[5b] (hereafter referred to as CA and DCA, respectively). As shown in Figure 1, they consist of rigid skeletons as well as flexible side chains. However, the classical host, DCA, did not enable us to find such an effect of the side chain. The reason is that the side chain employs a very similar conformation for all of the channel-type inclusion compounds of DCA. In contrast, CA serves as a desirable host as described below.

In 1986 we confirmed that CA[6] and its derivatives[7] form inclusion compounds with a wide range of organic compounds. Since then, we met a number of fascinating behaviors of the molecular assemblies. These are related to chiral recognition,[8] molecular arrangements,[9] intercalation in organic crystals,[10,11] inclusion polymerization,[12] expression of molecular information[10,11,13] and so on.

In the course of this study, we have found that the side chains of CA and its derivatives employs guest-dependent conformations. The conformational change induces not only statical changes of inclusion spaces for guests, but also dynamical changes of the molecular assemblies. Here we report a new inclusion and molecular recognition on the basis of the guest-dependent conformations of the side chains.

RESULTS AND DISCUSSION

Molecular arrangements in CA assemblies

X-ray crystallographic studies established that the inclusion compounds of CA have guest-dependent polymorphic structures.[9,14–20] This phenomenon is based on a fact that four hydrogen-bonding groups connect CA molecules each other in different modes. The first mode brings up a channel-type structure. Typical examples are the inclusion compounds of CA with acetophenone[9] and γ-valerolactone.[15] The second yields no channel-type structure exemplified by the compounds of CA with alcohols[16,18] and no guest.[14] Our study tells us that the channel-type structure includes larger guest molecules than the no channel-type one. The third lies in the compound of CA with water.[17]

The channel-type structures are constructed by stacking and sliding of bilayers. Figure 2 shows a bilayer (I) composed of CA molecules[9] in addition to that (II) of DCA,[21] on the basis of the corresponding inclusion compounds with acetophenone. As shown in Figure 1, we distinguish the two sides of the molecules, that near the steroidal A ring and that of side chains, as the *head* and *tail*, respectively. It can

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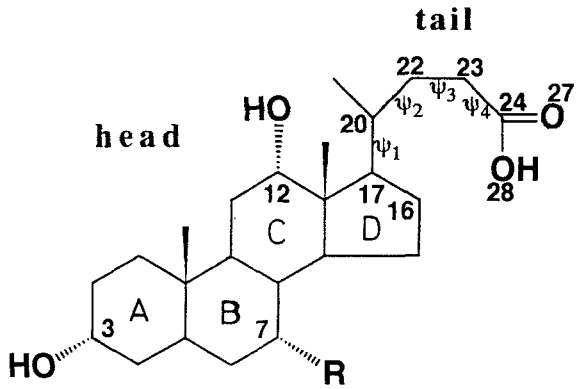

Figure 1 Cholic acid (R = OH; CA) and deoxychholic acid (R = H; DCA). Atomic numbering of the molecules and torsion angles of the side chain are shown.

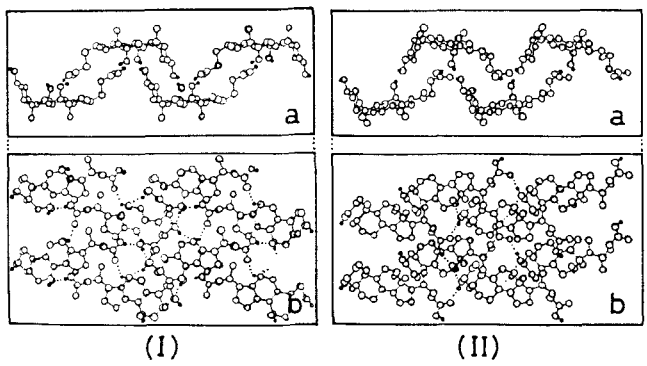

Figure 2 Top-side views (a) and front-side views (b) of bilayers composed of CA (I) and DCA (II) molecules in the case of the inclusion compounds with acetophenone.

be seen from Figure 2 that DCA employs a *head*-to-*tail* arrangement, while CA does a *head*-to-*head* and *tail*-to-*tail* one. In the former case the *tail* part is constrained by the *head* part, leading to a unchangeable conformation of the side chain. However, the latter arrangement enables the chain to employ the conformation suitable for the guest molecules.

Conformations of side-chains

Figure 1 shows atomic numbering of the host molecules and four torsion angles of the side-chain. The conformations with $\psi_2 \sim 190$ and ~ 60 can be indicated as *trans* and *gauche*, respectively. It is confirmed that the conformation of the side chain of DCA is always gauche for each channel-type structure, and that the lattice constants lie in a narrow range.[22] This result indicates that the bilayers of DCA are relatively rigid. In contrast, the conformation of CA is different. Figure 3 and Table 1 show the molecular structures and the torsion angles determined by X-ray crystallography, respectively.[9,15,21] It can be seen that the conformation is gauche in the case of acetophenone

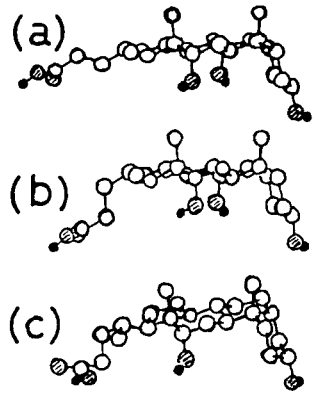

Figure 3 Molecular structures of CA and DCA in the inclusion compounds. (a) CA-γ-valerolactone, (b) CA-acetophenone, and (c) DCA-acetophenone.

Table 1 Torsion angles of side-chains of CA and DCA

Host guest	*CA γ-valerolactone*	*CA acetophenone*	*DCA acetophenone*
$\psi 1$	59.8	57.4	54.2
$\psi 2$	190.5	58.3	63.0
$\psi 3$	175.7	185.6	179.4
$\psi 4$	147.9	265.1	120.9

as the guest, while it is trans in the case of γ-valerolactone.

X-ray powder diffraction gave various patterns corresponding to kinds of the inclusion compounds. It is useful to distinguish between the no channel-type structure (Figure 4(a)) and the channel-type ones (Figures 4(b)(c)(d)). However, we do not confirm the usefulness for distinguishing between the *trans* (Figures 4(b)(d)) and *gauche* (Figure 4(c)) conformations of the side-chain. The reason is that we do not always succeed in indexing the peaks due to the great difference of the intensity of the peaks.

Distinction of the conformations by infrared spectra

We noticed that infrared spectra of the CA inclusion compounds show a strong dependence on the guest components, while those of DCA does not. Figure 5 illustrates the spectra of the inclusion compounds of CA with no guests (no channel-type; Figure 5(a)) and four kinds of guests (channel-type; Figures 5(b)–(e)). In a region of stretching vibration of hydroxyl groups, the absorption is sensitive to the guests. The absorption of CA crystals with no guests (Figure 5(a)) is greatly different from those of inclusion compounds of CA with acetophenone (Figure 5(b)) and γ-valerolactone (Figure 5(d)). So, the no channel-type structure is distinguishable from the channel-type structure.

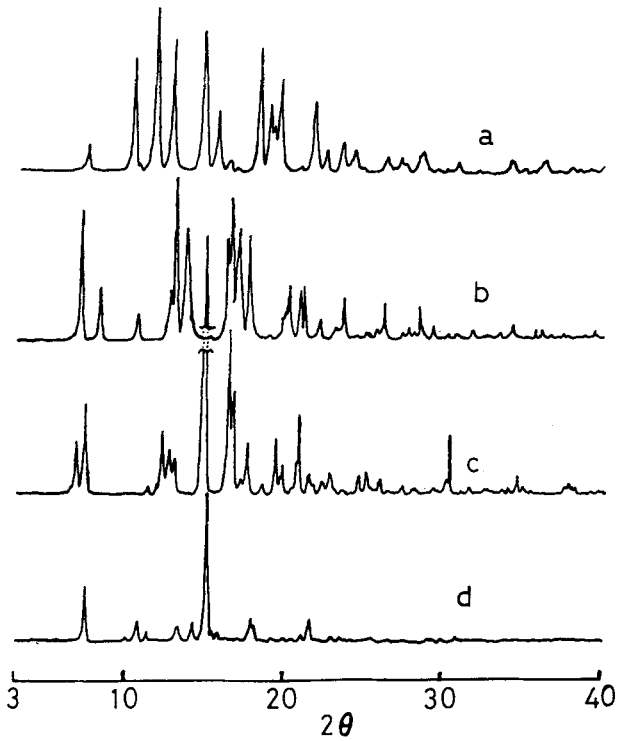

Figure 4 X-ray powder diffraction. (a) CA with no guest, (b) CA-3-valerolactone, (c) CA-acetophenone, and (d) CA-propiophenone.

In order to distinguish between *trans* and *gauche* conformations, we can use an absorption band in a region of stretching vibration of carbonyl groups. Figure 5(b) shows that the carbonyl band of the inclusion compound is split into two bands in the case of acetophenone, while Figure 5(d) shows that it is not in the case of γ-valerolactone. The splitting of the band can be seen clearly in the case of benzonitrile (Figure 5(c)). It was strange at first that the infrared spectrum of the compound with propiophenone shows a single carbonyl band, as shown in Figure 5(e). It was solved by the report that the inclusion compound of CA with propiophenone has *trans* conformation on the basis of X-ray crystallography.[19] In addition, we can use another absorption band in the region of 1150–1000 cm^{-1}.

These differences of the infrared spectra are related to hydrogen-bonding network among the CA molecules. Figure 6 shows the network in the inclusion compounds of CA and DCA. In the case of DCA (Figure 6(c)), the network is helical and rigid. This is supported by a fact that the lattice constants are practically identical.[22] So, the inclusion compounds of DCA with various organic compounds give similar infrared spectra as for the host. However, in the case of CA, the cyclic network is composed of four different molecules. It can be seen from the Figures 6(a) and 6(b) that the network is slightly different in the length and angles of the

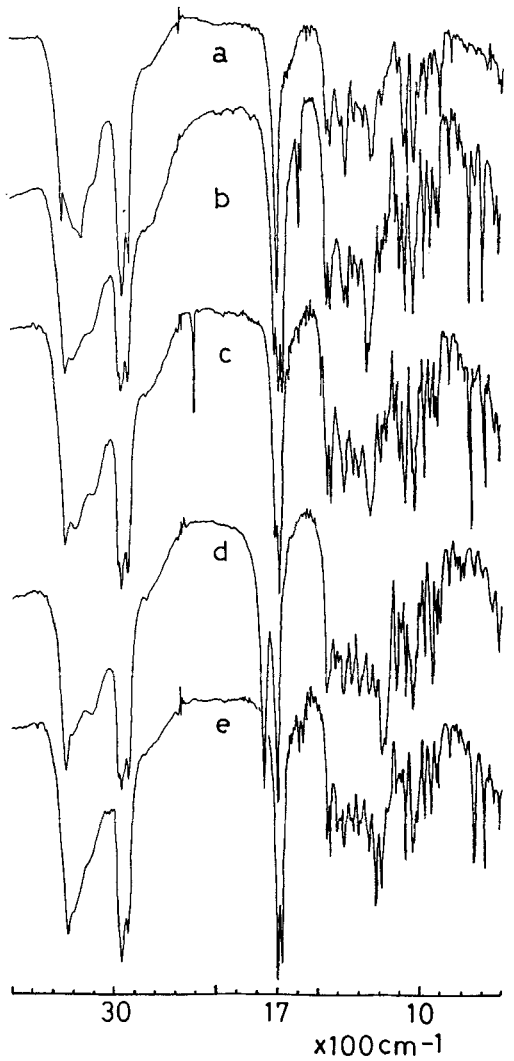

Figure 5 Infrared spectra of inclusion compounds of (a) CA with no guest, (b) CA-acetophenone, (c) CA-benzonitrile, (d) CA-γ-valerolactone, and (e) CA-propiophenone.

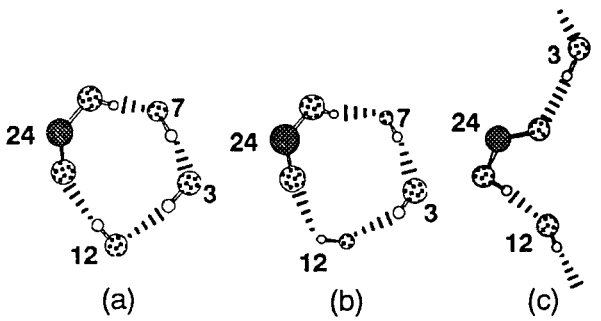

Figure 6 Hydrogen bonding network of bilayers. (a) CA-γ-valerolactone, (b) CA-acetophenone, and (c) DCA-acetophenone.

hydrogen bonds. Since the hydroxyl bands of the infrared spectra are very sensitive to the guests, we may expect that the network consists of slightly different length and angles of the hydrogen bonds corresponding to the kind of guest molecules.

It is noteworthy that the hydrogen bonds between carbonyl groups and hydroxyl groups (C12) are different in both inclusion compounds of CA (Figures 6(a) and 6(b)). Especially, in the case of *gauche* conformation, the angle of O–H···O is relatively smaller than that in the case of *trans*. It is considered that the X-ray crystallographic study evaluates a thermodynamically stable network. Perhaps the splitting of the carbonyl band is attributable to a dynamical equilibrium in other unstable state.

On the basis of these results, we extensively checked which conformations various aromatic guests allow CA to employ. The results are partly shown in Figure 7. According to thermogravimetric analysis, these inclusion compounds show a 1:1 molar ratio of host to guest. It can be seen that the selection of *trans* or *gauche* conformation depends on the functional groups as well as the relative positions of two groups. Among the compounds with one functional group, only anisole selects *trans* conformation. The guests involving two functional groups tend to select *trans* conformation except for a few cases.

Additional interesting example is provided by guests involving two benzene rings. Benzophenone allows CA to employ *trans* conformation, while phenyl benzoate and diphenyl carbonate *gauche*. Similarly, diphenyl ether allows CA to employ *trans*, while dibenzyl ether *gauche*. These results suggest that the relative orientation of the two benzene rings are related to the conformation of the side chains.

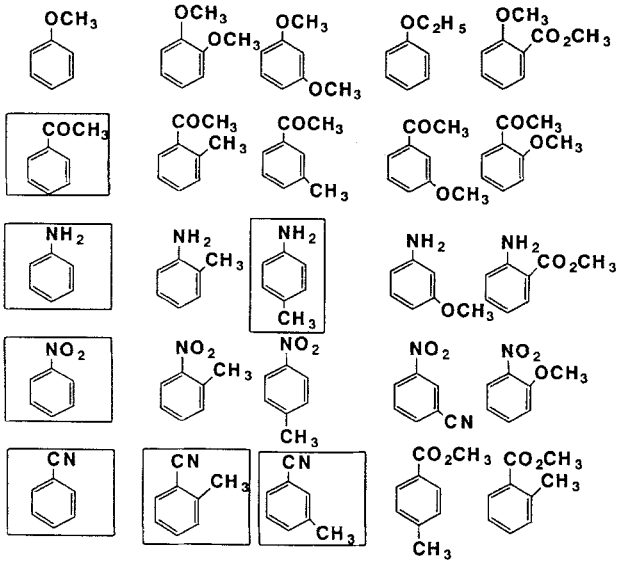

Figure 7 List of aromatic compounds included in CA. The side chain of CA is gauche conformation in the case of guests in brackets, while trans in the case of others.

Dynamical changes with retention of the molecular assemblies

We reported earlier that intercalation phenomena in organic crystals take place in the CA crystals.[10] In a similar way, we observed spontaneous replacement of guest molecules by using CA crystals. For example, the infrared spectra showed that the replacement of guest molecules from γ-valerolactone to acetophenone took place gradually with retention of the crystalline state in appearance. The replacement saturated after 18 days at ambient temperature. The scanning electron microscopic photographs of the crystals indicate that the whole structure of the crystals was maintained after the replacement, although the surface of the crystals displays a little damage. This observation tells us that the conformation of the side chain of CA changed to *gauche* from *trans*. In this way we reconfirmed that the CA molecular assemblies are flexible and dynamical molecular crystals.

Description of inclusion spaces

Since CA is a highly asymmetric molecule, it has completely separated sides. For example, three hydroxyl groups and two methyl groups form a hydrophilic and lipophilic side, respectively. In addition, we can distinguish three directions of the molecule; *head*-and-*tail*, *left*-and-*right*, *back*-and-*belly*. On other words, the molecule resembles an animal having backbone. Therefore, we can characterize each part of the molecule by using our daily words. Thus, the molecule is composed of various parts, such as a head, a face, an eye, a neck, a shoulder, a right hand, a left hand, a breast, a belly, a back, and a tail. The use of such words help us to understand how the host molecules construct the molecular architectures and the inclusion spaces for the guests.

Molecular graphics study enables us to discuss the construction. MODRASTE[23] is a convenient software for personal computers. This is very excellent for studying the inclusion compounds, because we can cut and slice the molecular assemblies freely in all of the directions, just like Computer Tomography (CT) for human body. Lots of sectional views enable us to express the inclusion spaces composed of CA molecules by using our daily words, as mentioned above.

Figure 8 shows an example of the cross-sectional views in the case of the inclusion compound of CA with acetophenone. Figure 8(a) shows a horizontal section view of the channels as viewed along the crystallographic *b* axis. It can be seen that a guest molecule is in the deformed pentagonal channel. The wall of the inclusion space are constructed of different parts of five host molecules, being a breast and belly part of molecule (**1**), a neck part of molecule (**2**), a tail part of molecule (**3**), a head part of molecule (**4**), and tail part of molecule (**5**). From two vertical section

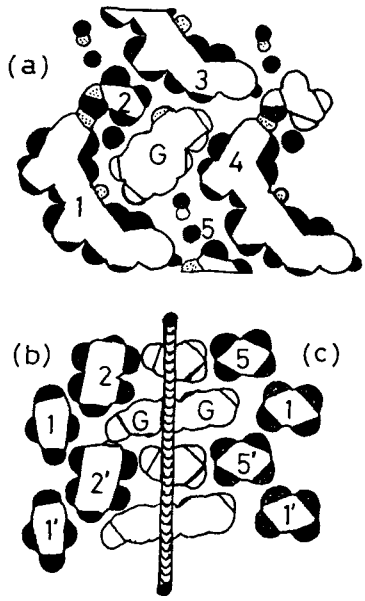

Figure 8 Schematic drawings of cross-sections of the CA channels (0.2 Å thickness) using space-filling models. (a) A horizontal section view of the CA deformed pentagonal channel as viewed along the crystallographic *b* axis. Vertical section views of the channel wall consisted of the head parts (b) and the wall consisted of the tail parts (c). Guest (G) is acetophenone.

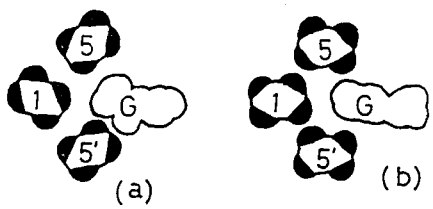

Figure 9 Schematic drawings of the pockets in the CA channels. (a) CA-γ-valerolactone and (b) CA-acetophenone. G; guest.

views (Figures 8(b) and 8(c)), we see two kinds of pockets in the channel. The one is between a left shoulder part of molecule (**2**) and a right shoulder part of another below molecule (**2'**). Another pocket is between a tail part of molecule (**5**) and a tail part of another below molecule (**5'**).

The latter pocket is formed by the two side chains. Therefore, the conformational changes of the side chains of CA molecules lead to a change in shape and size of the inclusion spaces for the guests. Figures 9(a) and 9(b) show the shape of the pockets in the case of the inclusion compounds of CA with γ-valerolactone and acetophenone, respectively. It can be seen that the orientation of the tail parts of the hosts are different. Therefore, we can readily distinguish the shape of the pockets in Figure 9. The side chains with *gauche* conformation form a square pocket (Figure 9(b)), while the ones with *trans* form a round one (Figure 9(a)). When the guest molecules are flat ones with a benzene ring, the *gauche* conformation can be selected. But the compounds with more longer chain prefer the latter. In the case of the compounds with two benzene rings, the length of the spacer is important. The long spacers make two benzene rings relatively parallel, leading to a selection of the square pocket.

EXPERIMENTAL SECTION

Commercially available CA was used without further purification. Inclusion compounds of CA were formed by recrystallization of the CA from the corresponding liquid guests. In the case of solid guests, 2-butanol or ethyleneglycol diacetate was used as the solvent. The resulting crystals were filtered or dried on filter paper immediately before use.

Infrared spectra were measured with a JASCO IR-Report-100 spectrometer. Differential thermal analysis (DTA) and thermogravimetry (TG) were measured with Rigaku TAS-100 and TG-8110. X-ray powder diffraction were recorded by using RIGAKU RINT-1100.

Molecular graphics study was carried out by using MODRASTE prepared by Nakano.[23] We modified this software for crystals. We first form one unit of the molecular assembly composed of sixteen host and sixteen guest molecules on the basis of the data obtained by X-ray crystallography, and then slices the unit in various ways by using a personal computer NEC PC-9801VX.

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