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Inclusion Abilities of Bile Acids with Different Side Chain Length

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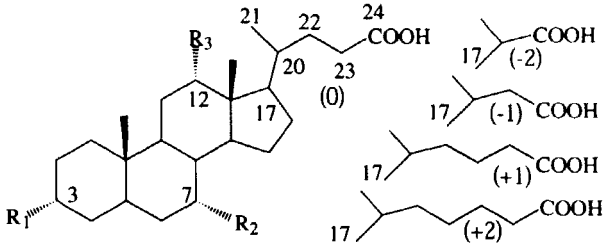
It was found that steroidal bile acids have greatly different inclusion abilities with decreasing or increasing their side chain length. Namely, the acids with intermediate side chains formed inclusion compounds with various organic compounds, while those with shorter or longer chains did not include so many. X-ray crystallographic studies clarified that the chains alter the hydrogen bonding networks among the host molecules, leading to the changes of the inclusion abilities and assembly modes.

Keywords: bile acids; side chain length; inclusion compounds; inclusion ability; crystal structures

INTRODUCTION

The identification of useful inclusion compounds is an important aspect of current crystal engineering [1]. The majority of molecular design for the compounds has focused on rigid skeletons as well as hydrogen bonding groups [2]. However, another design may originate from side chains attached to the skeletons. This idea has led us to naturally-occurring steroidal bile acids (Figure 1) which have side chains attached to polycyclic skeletons [3]. These acids enable us to investigate a relation between their inclusion abilities and side chain lengths.

This paper concerns with our recent study on inclusion abilities of these acids with different side chain length. A preliminary search indicates that their abilities clearly depend on their chain length. This result will be discussed on the basis of the structures of their guest-free or inclusion crystals.



a: R_1=OH, R_2=OH, R_3=OH ; cholic acid and its derivatives
b: R_1=OH, R_2=H, R_3=OH ; deoxycholic acid and its derivatives
c: R_1=OH, R_2=OH, R_3=H : chenodeoxycholic acid and its derivative
d: R_1=OH, R_2=H, R_3=H : lithocholic acid and its derivatives

FIGURE 1 Bile acids with different side chain length. Decreased or increased number of methylene units (-2, -1, 0, +1, or +2) of the side chains are designated in parentheses. For example, $\mathbf{a}^0$ and $\mathbf{a}^{+1}$ means cholic acid with the original side chain (0) and its derivative with the increased chain by one unit (+1), respectively.

EXPERIMENTAL

Steroidal bile acids ($\mathbf{a}^0$-$\mathbf{d}^0$) were commercially available and used without further purification. They were transformed into their derivatives with decreased or increased methylene units (Figure 1) in the conventional ways. The resulting acids were recrystallized from various organic compounds to yield guest-free or inclusion crystals. The guest incorporation was checked by IR and ^{1}H- and ^{13}C-NMR spectroscopy, as well as thermogravimetric analysis.

Some precipitated crystals were suitable for X-ray single crystal structure analysis, leading to detailed knowledge of molecular arrangements, intermolecular hydrogen bonds, inclusion spaces and so on. Since we have to compare many crystals with different crystallographic axes, we need to illustrate the molecular assemblies systematically. For example, Figure 2 depicts a projection of an assembly of the bile acid molecules. This figure is composed of three different views: top, front and right-side views. The top view is for showing a basic structure, such as layers or helices, while the front view is mainly for showing hydrogen bonding networks. The right-side view is often suitable for showing the cavities or channels.

BILE ACIDS WITH DIFFERENCE SIDE CHAIN LENGTH

TABLE 1 Approximate inclusion abilities of bile acids with different side chain length towards organic substances.

n	a	b	c	d
-2	GF	INC**	---	---
-1	INC	INC*	INC*	INC
0	INC*	INC	INC*	GF
+1	INC**	INC**	---	---
+2	INC**	INC**	INC**	GF

INC ; over 20 organic guests included,
INC* ; over 20 organic guests included or guest-free crystals obtained,
INC**; 1-10 organic guests included or guest-free crystals obtained,
GF ; only guest-free crystals obtained,
--- ; no crystals obtained and more research needed.

RESULTS AND DISCUSSION

Starting materials are commercially available bile acids, such as cholic acid ($\mathbf{a}^0$), deoxycholic acid ($\mathbf{b}^0$), chenodeoxycholic acid ($\mathbf{c}^0$) and lithocholic acid ($\mathbf{d}^0$) (Figure 1). Their side chains involve five carbons located

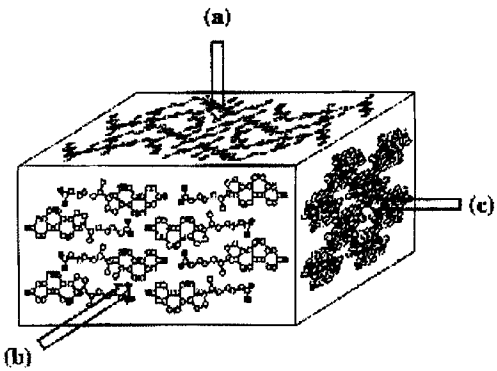


FIGURE 2 A projection of an assembly of bile acid molecules: (a) a top view, (b) a front view, (c) a right-side view.

at the corresponding 20, 21, 22, 23 and 24 positions. The carbon atoms can be decreased or increased by conventional organic reactions. Figure 1 exemplifies twenty different derivatives of the bile acids with different side chain length.

Table 1 summarizes their inclusion abilities. First of all, the results are compared among the corresponding derivatives of the original acids. Next, the results are totally compared.

Cholic Acid ($\mathbf{a}^0$) and Its Derivatives ($\mathbf{a}^{-2}$ - $\mathbf{a}^{+2}$)

It is already known that cholic acid ($\mathbf{a}^0$) forms inclusion compounds with a variety of organic substances [3]. Similarly, $\mathbf{a}^{-1}$ formed inclusion crystals with many organic compounds [4], while $\mathbf{a}^{-2}$ afforded only guest-free crystals. $\mathbf{a}^{+1}$ and $\mathbf{a}^{+2}$ lie in their intermediates.

Their crystal structures were determined by means of X-ray powder and single-crystal diffraction methods. A remarkable feature is that molecular assemblies of $\mathbf{a}^0$ and $\mathbf{a}^{-1}$ consist of bilayers so as to leave flexible channels (Figure 3(a)). The bilayers were formed between the hydrophilic faces of the skeletons by hydrogen bonds as well as between the lipophilic faces by van der Waals interaction. In contrast, $\mathbf{a}^{+2}$ exhibits diverse crystal structures. As shown in Figure 5(a), the side chains of $\mathbf{a}^{+2}$

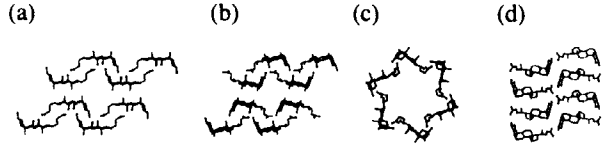


FIGURE 3 Molecular assembly modes of (a) $\mathbf{a}^0$, (b) $\mathbf{b}^0$, (c) $\mathbf{c}^0$ and (d) $\mathbf{d}^0$, respectively.

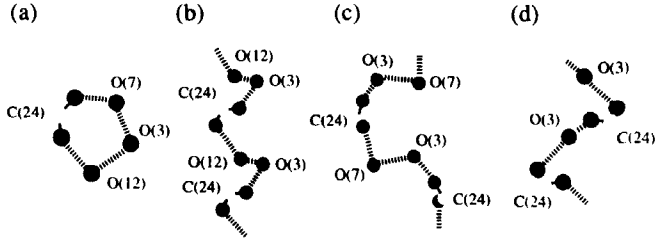


FIGURE 4 Hydrogen bonding networks of (a) $\mathbf{a}^0$, (b) $\mathbf{b}^0$, (c) $\mathbf{c}^0$ and (d) $\mathbf{d}^0$, respectively. The empty and closed circles represent carbon and oxygen atoms, respectively.

are bent, causing dense packing of the chains and skeletons. This is attributed to flexibility of the side chains elongated by two methylene groups.

$\mathbf{a}^0$ forms a cyclic hydrogen bonding network by using four hydrogen bonding groups which belong to the corresponding four molecules (Figure 4(a)). As shown in Figure 6(a), $\mathbf{a}^{+2}$ forms a different cyclic network involving two hydroxy groups located at 3 and 12 positions and one carboxylic group located at an end of the side chain. One more hydroxyl group located at 7 position is connected with the carbonyl part of the carboxylic group.

Deoxycholic Acid ($\mathbf{b}^0$) and Its Derivatives ($\mathbf{b}^{-2}$ - $\mathbf{b}^{+2}$)

$\mathbf{b}^0$ and $\mathbf{b}^{-1}$ form inclusion crystals with most of organic guests. A great

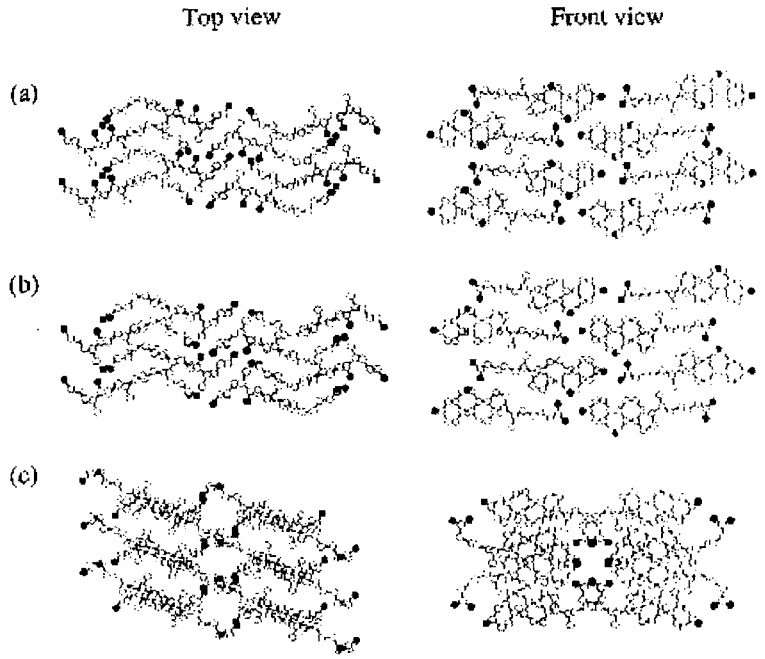


FIGURE 5 Top and front views of molecular assembly modes of guest-free crystals of $\mathbf{a}^{+2}$ (a), $\mathbf{c}^{+2}$ (b) and $\mathbf{d}^{+2}$ (c), respectively. Hydrogen atoms are omitted for clarity and the empty and closed circles represent carbon and oxygen atoms, respectively.

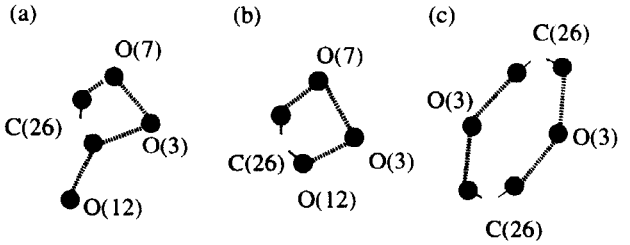


FIGURE 6 Hydrogen bond networks of guest-free (a) $\mathbf{a}^{+2}$, (b) $\mathbf{c}^{+2}$ and (c) $\mathbf{d}^{+2}$, respectively. The empty and closed cycles represent carbon and oxygen atoms, respectively.

difference is observed for their inclusion abilities towards aliphatic alcohols. That is, $\mathbf{b}^{-1}$ includes methanol, ethanol and 1-propanol, while $\mathbf{b}^{0}$ does not. This might be related to the fact that $\mathbf{b}^{0}$ employs a bilayered structure (Figure 3 (b)), while $\mathbf{b}^{-1}$ employs a monolayered structure [5]. This observation indicates that the crystal structures are significantly affected by shortening one methylene group. $\mathbf{b}^{0}$ forms a helical hydrogen bonding network by using three hydrogen bonding groups which belong to the corresponding three molecules (Figure 4(b)). On the other hand, $\mathbf{b}^{+1}$ and $\mathbf{b}^{+2}$ gave only thin crystals without guests, when recrystallized from many organic compounds. Until now we do not obtain their crystals suitable for X-ray analysis.

Chenodeoxycholic Acid ($\mathbf{c}^{0}$) and Its Derivatives ($\mathbf{c}^{-2}$ - $\mathbf{c}^{+2}$)

It was reported that hexagonal crystals of $\mathbf{c}^{0}$ with ethyl acetate have a helical assembly containing channels with a diameter of 6 to 7 Å (Figure 3(c)) [6]. As far as we know, however, there are only a few reports about the inclusion abilities of $\mathbf{c}^{0}$. Recently, we confirmed that its helical assembly can incorporate a wide range of organic guests by means of a guest exchange method with retention of the crystalline state [7]. $\mathbf{c}^{-1}$ included a relatively wide range of organic compounds by using the bilayered structure instead of the helical structure [4]. On the other hand, $\mathbf{c}^{+2}$ provided only guest-free crystals when recrystallized from many organic compounds.

Figure 5(b) shows top and front views of molecular assemblies of the guest-free crystals of $\mathbf{c}^{+2}$. The molecular arrangement is similar to that of the guest-free crystals of $\mathbf{a}^{+2}$, indicating a dense packing composed of the side chains and steroidal skeletons. Figure 6 (b) shows hydrogen bonding network of $\mathbf{c}^{+2}$. The cyclic network consists of two hydroxy groups

located at 3- and 7-positions and one carboxylic group of the side chain, as in the case of $\mathbf{a}^{+2}$. This difference between $\mathbf{c}^{0}$ and $\mathbf{c}^{+2}$ is attributed to the side chains being elongated by two methylene groups. $\mathbf{c}^{+1}$ and $\mathbf{c}^{-2}$ do not afford any suitable crystals for X-ray analysis.

Lithocholic Acid ($\mathbf{d}^{0}$) and Its Derivatives ($\mathbf{d}^{-2}$ - $\mathbf{d}^{+2}$)

It is known that $\mathbf{d}^{0}$ forms only guest-free crystals when recrystallized from many organic compounds [8]. However, $\mathbf{d}^{-1}$ included a relatively wide range of organic compounds. A remarkable feature is that the former has no bilayered structure (Figure 3(d)), while the latter has a bilayered structure. In this way, the inclusion abilities and molecular assembly modes of $\mathbf{d}^{0}$ and $\mathbf{d}^{-1}$ are significantly affected by a difference of one methylene group.

On the other hand, we do not confirm that $\mathbf{d}^{-2}$, $\mathbf{d}^{+1}$ and $\mathbf{d}^{+2}$ include organic compounds. Figure 5(c) shows the guest-free crystal structure of $\mathbf{d}^{+2}$. It can be seen that long alkyl chains pack together, indicating that the long side chains induce steric complementarity of the lipophilic parts. Hydrogen bonding network of $\mathbf{d}^{+2}$ is shown in Figure 6(c). The network involves two hydroxy groups located at 3-positions and two carboxylic groups located at the end of the chains.

Comparison among Four Bile Acid Derivatives

The original bile acids, $\mathbf{a}^{0}$- $\mathbf{d}^{0}$, have diverse inclusion abilities and crystal structures. $\mathbf{a}^{0}$ and $\mathbf{b}^{0}$ form bilayered structures, while $\mathbf{c}^{0}$ and $\mathbf{d}^{0}$ form helical and non-layer structures, respectively. In the case of the bilayers the inclusion cavities lie between the side chains due to the unbalanced molecular structures which are composed of wide steroidal skeletons and the rod-like side chains.

In contrast, the acids with the side chains involving one less carbons ($\mathbf{a}^{-1}$- $\mathbf{d}^{-1}$) have similar inclusion abilities and crystal structures, despite the different number and locations of the hydroxy groups in the skeletons [4]. This remarkable feature is based on a common bilayer structure.

On the other hand, the acids with the side chains involving two less carbons, $\mathbf{a}^{-2}$, $\mathbf{c}^{-2}$ and $\mathbf{d}^{-2}$, have no inclusion abilities, although $\mathbf{b}^{-2}$ form the inclusion compounds with several organic compounds. The acids with the chains involving one more carbons ($\mathbf{a}^{+1}$ and $\mathbf{b}^{+1}$) form the inclusion compounds with several organic compounds in spite of no inclusion abilities of $\mathbf{c}^{+1}$ and $\mathbf{d}^{+1}$.

The derivative of cholic acid with two more carbons ($\mathbf{a}^{+2}$) tend to include a larger organic substances than the original acids. This is probably because the two methylene groups can extend the inclusion spaces. The derivatives of $\mathbf{b}^{+2}$ and $\mathbf{c}^{+2}$ seem to include some large organic compounds, while $\mathbf{d}^{+2}$ does not form inclusion crystals at all.

CONCLUDING REMARKS

This study demonstrates that the inclusion abilities greatly depend on the side chain length of bile acids. The inclusion abilities are closely related to the crystal structures, indicating that the side chain length plays an important role in determining the assemblies of the host molecules. The long side chains tend to induce steric complementarity of the lipophilic parts between the long alkyl chains and skeletons. In this way the alterations of the side chain length induce subtle or drastic changes in the inclusion abilities and the crystal strucutres. Such a research may give us a new insight to the design of the inclusion compounds.

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