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COMBINATORIAL CHEMISTRY OF INCLUSION COMPOUNDS BY USING STEROIDS

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Steroidal acids and their derivatives form inclusion compounds with a variety of organic substances. Over one thousand derivatives are candidates for hosts of the compounds. The study on steroidal inclusion compounds provides systematic data for considering relationships between molecular structures and molecular assemblies, indicating that combinatorial chemistry can be applied to inclusion chemistry.

Keywords: steroids; bile acids; inclusion compounds; host-guest assemblies; hydrogen bonding networks; combinatorial chemistry

INTRODUCTION

We have been studying on inclusion compounds of steroids, particularly bile acids and their derivatives[1]. The reason is that the steroids are regarded as

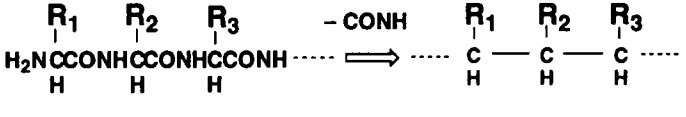
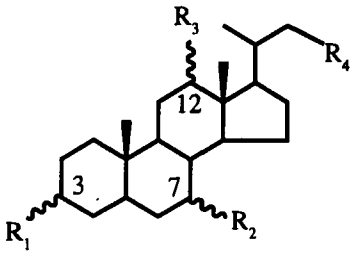


FIGURE 1 Information carriers composed of sequential carbon-chains.

sequential carbon-chain oligomers, which are conceptually made by removal of amide groups from peptides (Fig. 1). The units of the chains are substituted methylenes which may combine to yield practically infinite kinds of latent hosts (Fig. 2). This means that these hosts may function as information carriers at a molecular level[2]. This idea directed us to combinatorial chemistry of the inclusion compounds by using the steroids.

Here we describe some relationships between molecular structures and assemblies of the steroids, leading to an interpretation of their inclusion behaviors.



R_1; R_2; R_3 : H, α-OH, β-OH
R_4 : CO_2H, CH_2CO_2H, $CH_2CH_2CO_2H$
$CONH_2$, CH_2CONH_2, $CH_2CH_2CONH_2$
CO_2CH_3, $CH_2CO_2CH_3$, $CH_2CH_2CO_2CH_3$
CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$
etc.

FIGURE 2 Steroids composed of substituted methylene units.

TABLE 1 Approximate inclusion abilities of steroidal acids (R_4=CH_2CO_2H) towards organic substances. The acids are designated by numbers in parentheses in the text.

R_1	R_2			R_3
	H	α-OH	β-OH	
α-OH	(14) −	(9) − −	(11) *	H
	(4) − −	(1) − −	nd	α-OH
	(6) +	(5) *	nd	β-OH
β-OH	(15) ++	(10) +	(12) − −	H
	(3) +	(2) ++	(13) +	α-OH
	(8) + and −	(7) +	nd	β-OH

(+): hydrophilic guests included; (++): more hydrophilic guests included;
(-): lipophilic guests included; (- -) : more lipophilic guests included;
(*) : guest-free crystals obtained; (nd): more research needed.

INCLUSION BEHAVIORS AND ASSOCIATION MODES OF THE STEROIDAL ACIDS AND THEIR DERIVATIVES

Starting from commercially available bile acids,such as cholic acid(**1**), deoxycholic acid(**4**), chenodeoxycholic acid(**9**), lithocholic acid(**14**), their epimerization affords many kinds of the steroidal derivatives. They have different inclusion abilities towards various organic guests, as shown in Table 1; ones include hydrophilic guests, while others include lipophilic guests. Such selectivities are attributed to diversible association modes of the host molecules through intermolecular hydrogen bonds.

These host molecules associate to give a crossing, a layered and a helical structures, as schmatically shown in Fig. 3. Fig. 4 exemplifies a schematic representation of a hydrogen bonding network in the layered structure.

Cholic Acid (1) and 3-Epicholic Acid (2)

1 includes only methanol, ethanol and 1-propanol among saturated aliphatic alcohols involving one to six carbon atoms, while **2** includes most of the alcohols. In the case of the layered structure, **1** forms cyclic hydrogen bonding networks by using four hydogen bonding groups which belong to different molecules (Fig. 5(a)). The alcoholic guests do not join the network, explaining the limited inclusion ability of **1**. On the other hand, **2** forms branched networks, since the directional change forces 3-positioned hydroxy groups to combine with carboxyl groups of the side-chains (Fig. 5(b)). The alcoholic guest is inserted between the 3-positioned hydroxy group and the 12-positioned one, enabling us to explain

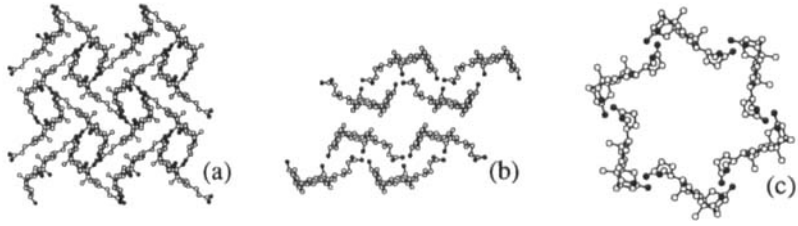


FIGURE 3 Representative assemblies; crossing(a), layer(b) and helix(c).

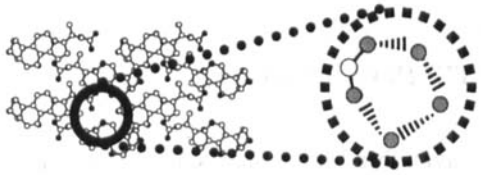


FIGURE 4 Schematic drawing of a hydrogen bonding network.

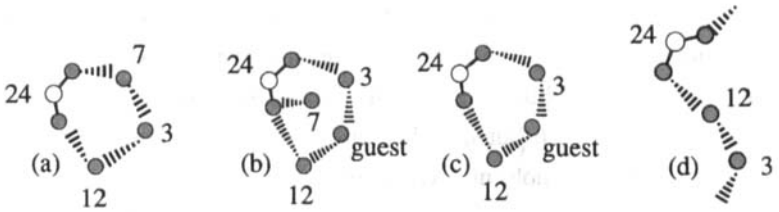


FIGURE 5 Changes of hydrogen bonding networks in the layered structures in the case of hosts; 1 (a), 2 (b), 3(c), and 4(d).

the inclusion of the alcohols.

In contrast, 3-epideoxycholic acid (**3**) includes only 2-methyl-1-propanol among four kinds of butanols, 2-pentanol and 2-methyl-1-butanol. The common alcoholic guests yield isomorphous bilayered crystals in the case of both **2** and **3**. Removal of 7-positioned hydroxy group from **2** may weaken the branched hydrogen bonding network (Fig.5 (c)), explaining that **3** includes a limited range of the alcohols.

Cholic Acid (1) and Deoxycholic Acid (4)

4 does not include methanol, ethanol and 1-propanol, in contrast to **1**. This is based on different polymorphic crystals of these hosts. **1** employs a crossing structure for the alcohols, while **4** does not. Both the hosts can include a wide range of lipophilic substances by using bilayered structures. But their hydrogen bonding networks are greatly different. Namely, **4** takes a stable helical network, as can be seen in Fig. 5(d). This difference brings about a reverse arrangement of the host molecules in the hydrophilic sites of the bilayers. An antiparallel arrangement gives **1** large pockets at the channel walls, while a parallel arrangement gives **4** very small pockets.

12-Epicholic acid (**5**) does not include organic guests employed, while 12-epideoxycholic acid (**6**) includes only 2-methyl-2-butanol. 3,12-Epicholic aicd (**7**) includes methanol, acetonitrile and so on. In contrast, 3,12-epideoxycholic acid (**8**) includes both hydrophilic and lipophilic guests. This is because the host molecules form a helical assembly with a channel. Further three kinds of epimers of **1** remain unclarified.

Cholic Acid (1) and Chenodeoxycholic Acid (9)

Removal of 12-positioned hydroxy group from **1** causes a dramatic change of the molecular arrangements. It is known that **9** forms a helical assembly with a large channel (Fig. 3(c))[3]. Therefore, **9** may include a wide range of organic guests. However, there are only several reports about the inclusion abilities so far. Recently, we have found that **9** forms large crystals in the presence of some esters. The usage of the crystals enables us to obtain various inclusion compounds of **9** by spontaneous replacement of the included guests.

In contrast, 3-epichenodeoxycholic acid (**10**) includes only 3-methyl-2-pentanol among aliphatic alcohols involving one to six carbon atoms. Moreover, 7-epichenodeoxycholic acid (**11**), called ursodeoxycholic acid, does not form the inclusion compounds at all. However, we have found that 3,7-epichenodeoxycholic acid (**12**) and 3,7-epicholic acid (**13**) include various organic substances, such ketones and naphthalene derivatives. This finding is attributed to large channels between monolayers. An additional hydroxy group of **13** is expected to function as a hydrogen donor to catch the polar guests.

Cholic Acid (1) and Lithocholic Acid (14)

There is a report on a crystal structure of **14** without guest[4]. We have searched the inclusion ability of **14** towards various organic substances. This thorou investigation brought us the finding of inclusion of aromatic guests, but further X-ray structural study is necessary for describing the compounds.

On the other hand, 3-epilithocholic acid (**15**) clearly forms the inclusion crystals with many aliphatic alcohols. Untill now we obtained only thin inclusion crystals which are not suitable for X-ray crystallographic analysis.

Transformation of Hydrogen Bonding Groups of Side-Chains

We observed dramatic changes of inclusion behaviors of the hosts by transformation of hydrogen bonding groups of steroidal side-chains. For example, an amide derivative of **1** includes all of the aliphatic alcohols mentioned above, in contrast to **1**. This can be interpreted by an additional hydrogen which functions as a hydrogen donor for catching the alcoholic guests. On the other hand, an alcohol derivative of **1** does not include any organic guests. Both elongation and shortening of the side-chains cause subtle or great changes of the inclusion behaviors as compared with the original hosts. For example, norcholic and nordeoxycholic acids with one less carbon than **1** and **4** include various aliphatic alcohols, similar to amide derivatives of **1** and **4**, respectively.

CONCLUDING REMARKS

In principle we can get more than one thousand derivatives of bile acids. We aim to search for the inclusion abilities of as many hosts as possible. This is because such studies may lead us to establishment of the concept; information and expression by small molecules which are composed of sequential and chiral carbon-chains.

Acknowledgements

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