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Review

Supramolecular Chirality in Crystalline Assemblies of Bile Acids and Their Derivatives; Three-Axial, Tilt, Helical, and Bundle Chirality

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Abstract: Steroidal bile acids and their derivatives exhibit characteristic inclusion behaviors in the crystalline state. Their crystals present varied assemblies due to asymmetric molecular structures, which relate to supramolecular properties through cooperative weak interactions. An overview indicates that the steroidal assemblies lie in an intermediate position among various molecules and have hierarchical structures such as primary, secondary, tertiary, and host-guest assemblies like proteins. Such an interpretation brought about the idea that the assemblies with dimensionality present supramolecular chirality such as three-axial, tilt, helical, bundle, and complementary chirality. This concept of the supramolecular chirality enables us to understand formation of chiral crystals starting from the molecular chirality of the steroidal molecules.

Keywords: Steroidal bile acids; inclusion crystal; supramolecular chirality; helices; molecular tilt

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1. Introduction

Crystalline molecular assemblies of steroidal bile acids and their derivatives (Scheme 1, Table 1) have aroused our interests for a long time, because the assemblies include various organic guest components through cooperative weak interactions [1–4]. The resulting host-guest complexes, termed as inclusion compounds [5,6], were found to have a variety of assembly structures by means of X-ray crystallographic analysis.

Scheme 1. Steroidal bile acids and their derivatives with the traditional atomic numbering.

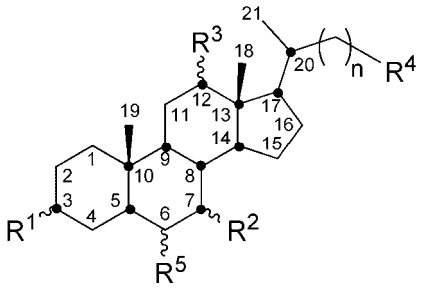
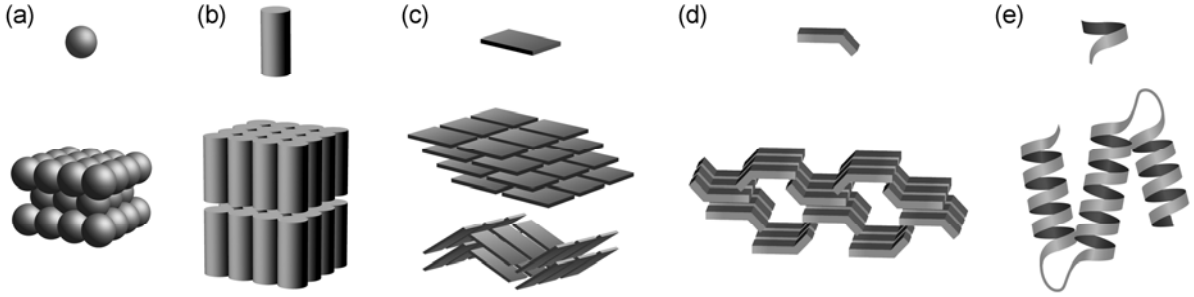


Table 1. Steroidal bile acids and their derivatives.

R^1	R^4	R^5	n	R^2=α-OH, R^3=α-OH	R^2=α-H, R^3=α-OH
α-OH	COOH	H	2	Cholic acid (**Ia**)	Deoxycholic acid (**IIa**)
α-OH	$CONH_2$	H	2	Cholamide (**Ib**)	Deoxycholamide (**IIb**)
α-OH	$COOCH_3$	H	2	Methyl cholate (**Ic**)	Methyl deoxycholate (**IIc**)
α-OH	COOCH	H	2	3α,7α,12α,24-Tetrahydroxy-5β-cholane (**Id**)	3α,12α,24-Trihydroxy-5β-cholane (**IId**)
α-OH	COOH	H	1	Norcholic acid (**Ie**)	Nordeoxycholic acid (**IIe**)
α-OH	COOH	H	4	Bishomocholic acid (**If**)	Bishomodeoxcholic acid (**IIf**)
β-OH	COOH	H	2	3-Epicholic acid (**Ig**)	3-Epideoxycholic acid (**IIg**)
R^1	R^4	R^5	n	R^2=α-OH, R^3=α-H	R^2=α-H, R^3=α-H
α-OH	COOH	H	2	Chenodeoxycholic acid (**IIIa**)	Lithocholic acid (**IVa**)
α-OH	$CONH_2$	H	2	Chenodeoxycholamide (**IIIb**)	Lithocholamide (**IVb**)
α-OH	$COOCH_3$	H	2	Methyl chenodeoxycholate (**IIIc**)	Methyl lithocholate (**IVc**)
α-OH	CH_2OH	H	2	3α,7α,24-Trihydroxy-5β-cholane (**IIId**)	3α,24-dihydroxy-5β-cholane (**IVd**)
α-OH	COOH	H	1	Norchenodeoxycholic acid (**IIIe**)	Norlithocholic acid (**IVe**)
α-OH	COOH	H	4	Bishomochenodeoxcholic acid (**IIIf**)	Bishomolithocholic acid (**IVf**)
β-OH	COOH	H	2	3-Epichenodeoxycholic acid (**IIIg**)	3-Epilithocholic acid (**IVg**)
α-OH	COOH	α-OH	2	Hyocholic acid (**IIIh**)	Hyodeoxycholic acid (**IVh**)
R^1	R^4	R^5	n	R^2=R^3= =O	
=O	COOH	H	2	Dehydrocholic acid (**Vi**)	

This experimental result prompted us to consider a relationship between the molecular structures and the assembly structures. These studies led us to the fact that the assemblies lie in an intermediate among the other known molecular assemblies and biopolymers, as schematically shown in Figure 1. Thus, spherical [Figure 1(a)], axial [Figure 1(b)], and flat [Figure 1(c)] molecules make face- (or body) centered, layered, and herringbone (or stacked) assemblies, respectively, whereas biopolymers such as proteins [Figure 1(e)] form folded structures. Compared with these molecules, the steroidal molecules [Figure 1(d)] have arched skeletons with about ten chiral carbons and multiple hydrogen-bonding groups, making the intermediate assemblies which relate to supramolecular properties, such as host-guest, inclusion, reaction, chirality, recognition, dynamics, information, and so on. In other words, the steroidal assemblies serve as a fascinating entity for supramolecular chemistry in the crystalline state [7,8].

Figure 1. Relationship between molecular structures and crystal structures; (a) spherical, (b) axial, (c) flat, (d) arched, and (e) chain molecules.



The research into the crystalline assemblies of bile acids and their derivatives can be briefly summarized from the viewpoint of the inclusion as follows. A classical host, deoxycholic acid (**IIa**), has been known to include various organic substances over a century [9–11]. Craven and DeTitta reported the first crystal structure involving acetic acid in 1972 [12], and clarified that the inclusion comes from a bilayer structure with channels. The subsequent crystallographic research by Giglio established a common occurrence of the channel-type bilayer structures [13]. In contrast, few studies of the inclusion behavior of cholic acid (**Ia**) have been published [9–11]. Johnson and Schaefer reported a cage-type structure of the inclusion crystal of **1a** with ethanol in 1972 [14]. In 1988, Miyata, Miki and their coworkers reported a channel-type structure of the inclusion crystal of **Ia** with acetophenone [15–17]. Until now, such inclusion properties have been extended to their related derivatives. Several reviews are concerned with these assemblies in 1996 [1], 2004 [2, 3], 2007 [4].

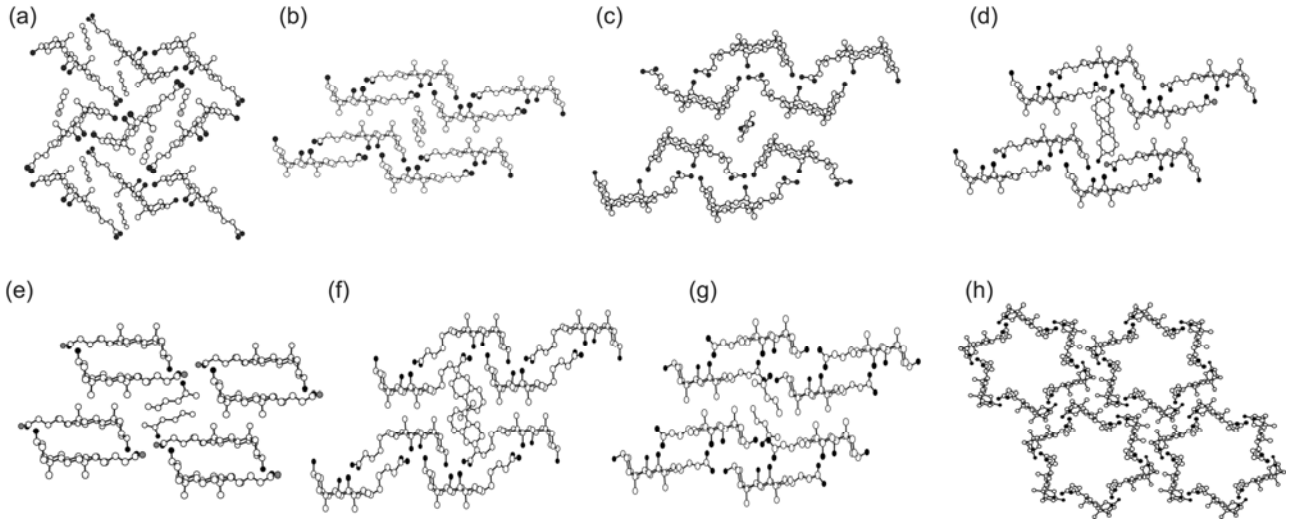
In this article, comprehensive studies on inclusion behaviors and crystal structures of bile acids and their derivatives are briefly summarized in Chapter 2, followed by a hierarchical interpretation of the crystalline assemblies (Chapter 3). Chapter 4 deals with an understanding of supramolecular chirality of the hierarchical assemblies, followed by illustrative description of the supramolecular chirality of the steroidal assemblies (Chapter 5). Final chapter deals with perspectives of these studies.

2. Diverse Structures of Inclusion Crystals of Bile Acids and Their Derivatives

2.1. Basic Patterns of Assembly Modes

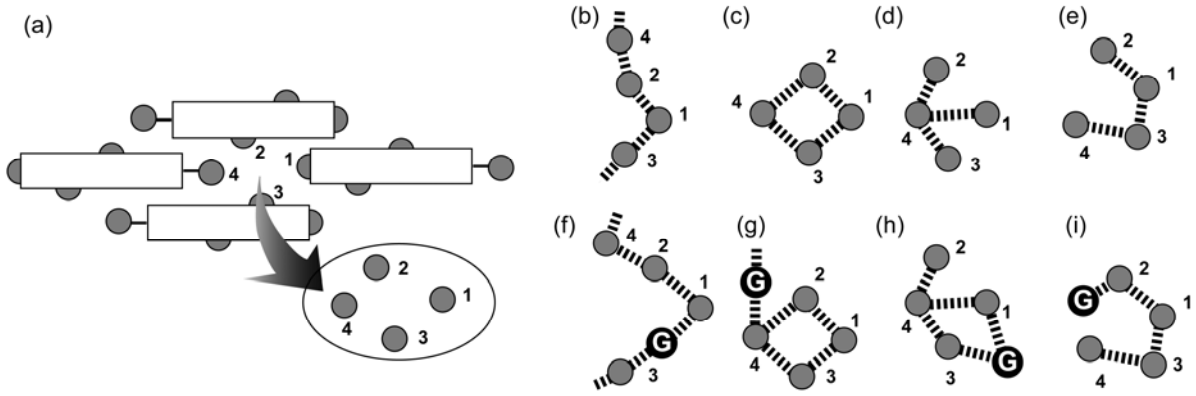
Molecular structures of bile acids and their derivatives are generally shown in Scheme 1, and their nomenclature and abbreviations in this article are shown in Table 1. We usually searched for inclusion abilities of the steroidal derivatives by using more than one hundred organic compounds as guest candidates. It was so far confirmed that each steroidal derivative exhibits a corresponding inclusion ability and assembly mode based on a set of hydrogen bonding groups involving guest components. Figure 2 shows representative crystal structures of the steroidal derivatives. Their collected X-ray crystallographic data provides a treasure trove with respect to cooperative interactions composed of multiple non-covalent bonding groups.

Figure 2. Representative crystal structures of steroidal bile acids and their derivatives; a crossing structure with cage-like cavities for **Ia** (a), bilayered structures with channel-like cavities for **Ia** (b), **IIa** (c), **Ib** (d), **IVb** (e), **If** (f), **Ig** (g), and a honeycomb structure with hexagonal channels for **IIIa** (h).



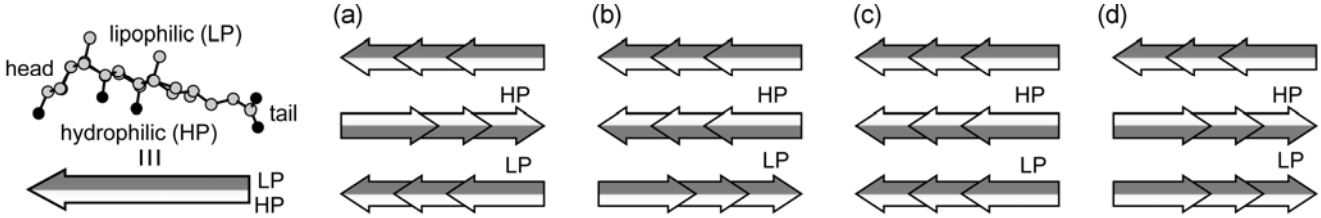
In order to classify the crystal structures, it is essential to understand the basic patterns of hydrogen bonding networks and molecular arrangements. Figure 3 exemplifies a typical assembly pattern of four molecules with the corresponding hydrogen bonding groups, neglecting donor-acceptor relationships. The neighboring four groups [Figure 3(a)] produce four kinds of networks; linear [Figure 3(b)], cyclic [Figure 3(c)], branched [Figure 3(d)] and arched [Figure 3(e)] ones, respectively. These networks vary with number of the groups as well as corporation of guest components. Figures 3(f)–(i) show examples of the modified networks involving guest components.

Figure 3. Association among four hydrogen bonding groups of four host molecules (a). Four kinds of hydrogen bonding networks; linear (b), cyclic (c), branched (d), and arched (e). The networks involving guest components; linear (f), cyclic (g), branched (h), and arched (i).



The hydrophilic and lipophilic sides separately meet together to produce a bilayer structure. Figure 4 schematically depicts four kinds of molecular arrangements in the bilayers. In this Figure, we distinguish a tail-to-head direction by means of an arrow on the basis of an arched skeleton and chain parts of the steroidal molecules [Figure 4(a)]. The arrows combine together to yield two types of molecular arrangements, parallel and anti-parallel. These two arrangements theoretically combine together on both the hydrophilic and lipophilic sides to yield four types of the arrangements in Figures 4(b) to 4(e).

Figure 4. Asymmetric layers with a tail-to-head alignment on their hydrophilic side (HP) and lipophilic side (LP). Four kinds of the arrangements of the layers; anti-parallel on both HP and LP (a), parallel on HP and anti-parallel on LP (b), anti-parallel on both HP and LP (c), and anti-parallel on HP and parallel on LP sides (d).



2.2. Carboxylic Acid Hosts

Cholic acid (**Ia**) and deoxycholic acid (**IIa**) mostly make bilayered assemblies, and **Ia** has larger channels in size than **IIa**. **Ia** includes small aliphatic alcohols and nitriles in cage-type cavities [Figure 2(a)] with a linear hydrogen bonding network among four groups [Figures 3(b) and 3(f)] [14,18,19]. On the other hand, a variety of aliphatic and aromatic compounds are included within a cyclic hydrogen bonding network [Figure 3(c)] in channel-type cavities between the bilayers [Figure 2(b)] [16,20–25].

Water molecules are also caught in three types of crystal structures [26–28]. Similarly, **IIa** forms inclusion crystals with a wide range of organic substances in the channels [Figure 2(c)] with a linear network among three groups [12,13,29]. **Ia** mostly arranges in an anti-parallel fashion on both hydrophilic and lipophilic sides [Figure 4(b)] [30–32], while **IIa** arranges in a parallel fashion on the hydrophilic side and in an anti-parallel fashion on the lipophilic side [Figure 4(c)]. The bilayers of **Ia** and **IIa** cause flexibilities due to conformational changes of the side-chains as well as sliding and reversion on the lipophilic sides, explaining the versatile inclusion behaviors mentioned above [13,24]. Chenodeoxycholic acid (**IIIa**) forms a honey-combed structure with hexagonal channels where various guest compounds are included [Figure 2(h)] [33–36]. In contrast, lithocholic acid (**IVa**) does not include any organic guests [37].

2.3. Amide, Ester, and Alcohol Hosts

Bile amide hosts can include many aliphatic alcohols, in contrast to the original bile acids. This is because one additional hydrogen bond donor acts as a hook for catching a guest molecule with hydrogen bond acceptor. **Ib** forms the same bilayer structure as **Ia**, with almost the same cavity dimensions [Figure 2(d) [38–42]. The hydroxyl groups of the guest molecules are linked between two cyclic hydrogen bonding networks [Figure 3(g)]. **IIb** includes alcoholic guests with an additional N-H like **Ib**, but forms guest-dependent bilayers, unlike **Ib** [43]. **IIIb** does not yield inclusion crystals with organic guest molecules. In contrast, **IVb** forms a bilayer structure with channels for including over five carbon atoms [Figure 2(e)] [44].

Esterification of the carboxylic acid decreases the number of the hydrogen bond donor groups on the steroidal side-chain, leading to a lowering of their inclusion abilities. Thus, **Ic** includes small aliphatic alcohols and nitriles with a linear and arched [Figure 3(i)] hydrogen bonding network, respectively [45-47], while **IIc** includes only methanol [48]. **IIIc** and **IVc** do not seem to include any organic compounds. On the other hand, reduction to alcohols of the carboxylic group causes a lowering of the inclusion ability. **Id** does not include organic guests at all and gives only guest-free crystals [49], while **IId** tends to form inclusion compounds with non-polar guests such as aromatic compounds [50]. The host arrangements and linear hydrogen bond networks of **IId** are similar to those of **IIa**. Inclusion crystal of **IId** with benzene takes a rare parallel arrangement on both sides [Figure 4(d)]. **IIId** and **IVd** form a bilayer structure including only a few small alcohols.

2.4. Hosts with Different Side-Chain Length and Reversed Hydroxyl Groups

Changes of the side-chain length of the hosts induce different inclusion abilities [51]. Shortening by one methylene unit brings about a change of the orientation of the carboxyl group, leading to a great change of the hydrogen bond networks. Norbile acids, which have shorter side-chain length by one methylene unit than original bile acids, form inclusion crystals with various organic substances [52–54]. Among them, **IIe** exhibits a notable inclusion ability [54]. On the other hand, the elongation of the side-chain may give rise to expansion of the host cavity. In fact, **If**, which has longer side-chain length by two methylene units than **Ia**, form inclusion compounds with larger aromatic compounds, such as 1-methylnaphthalene in a 1:1 host-to-guest ratio [Figure 2(f)] [55]. Epimerization at the 3-position alters

the inclusion abilities due to a change of the direction of the hydroxyl group [56]. **Ig** gives inclusion crystals with various aliphatic alcohols having bilayer structures [Figure 2(g)] and branched hydrogen bond networks (Figure 3(h)). **IIg** has an inclusion ability similar to **Ig**. Epimerization at the 7- and/or 12-positions yields different molecular assemblies from the original acids. For example, 3-epiurso-deoxycholic acid forms an interesting inclusion compound [57].

2.5. Other Hosts

Apocholic acid, which has a double bond between the 8 and 14 positions in its skeleton, forms inclusion crystals with channels like **IIa** [58]. Hyocholic acid (**IIIh**) and hyodeoxycholic acid (**IVh**) form inclusion compounds with aliphatic alcohols and pyridine, respectively [59, 60]. Bile acid salts with various primary amines serve as the hosts for including aliphatic alcohols [61,62]. Their crystals have bilayered structures with a ladder hydrogen-bonding network similar to those of **Ia** and **IIa**. *N*-alkyl derivatives of **Ib** and **IIb** include water [63] and small guests [64,65]. Glycine-conjugated bile acids make inclusion crystals with a three-leaved structure [66].

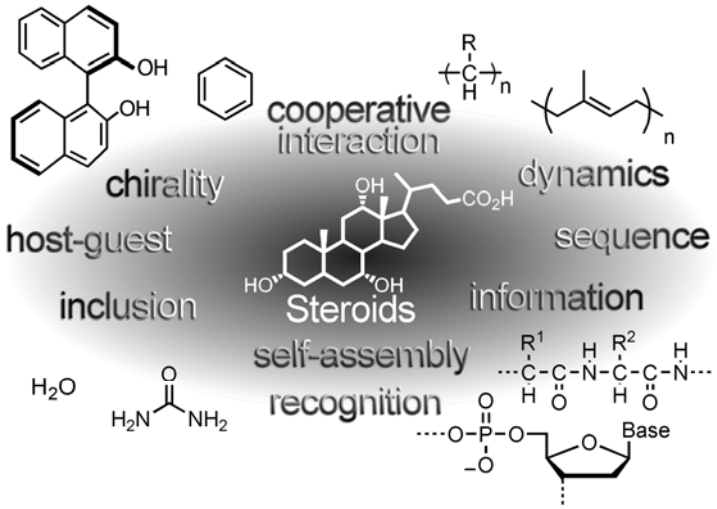
3. Hierarchical Assemblies of Bile Acids and Their Derivatives

3.1. Intermediate among Various Molecules and Assemblies

As described above, we obtained comprehensive experimental results about inclusion behaviors and crystal structures of bile acids and their derivatives. Their remarkable features hinge on the following two matters. The first is that the inclusion behaviors vary from one case to another, and depend on subtle differences in donor-acceptor relationships among the hydrogen bonding groups. The other is that the steroidal molecules form diverse assemblies, such as monolayers, bilayers, helical tubes, and so on. The assembly modes are host-inherent in some cases but guest-dependent in the other cases. These results brought about the idea that the steroidal molecules are located in an intermediate among small molecules and biopolymers from various viewpoints of host-guest, inclusion, recognition, polymorphism [67–72], dynamics [17,73–77], polymerization [78–83], separation [3,84,85], and so on, as shown schematically in Figure 5.

Theoretically, there exist many possible combinations of intermolecular non-covalent bonds, enabling us to simulate many possible assemblies among the host and guest components. Along with this simulation study, an overview study directed us toward a research for any relationships between the molecular structures and assemblies. We expected that the relationship might be closely connected with various fundamental concepts established for proteins, since multiple non-covalent bonds play a critical role in both the steroidal molecules and proteins. In addition, it may be considered that the steroidal molecules form various crystal structures owing to environmental effects of organic solvents, while proteins form various folded structures in water.

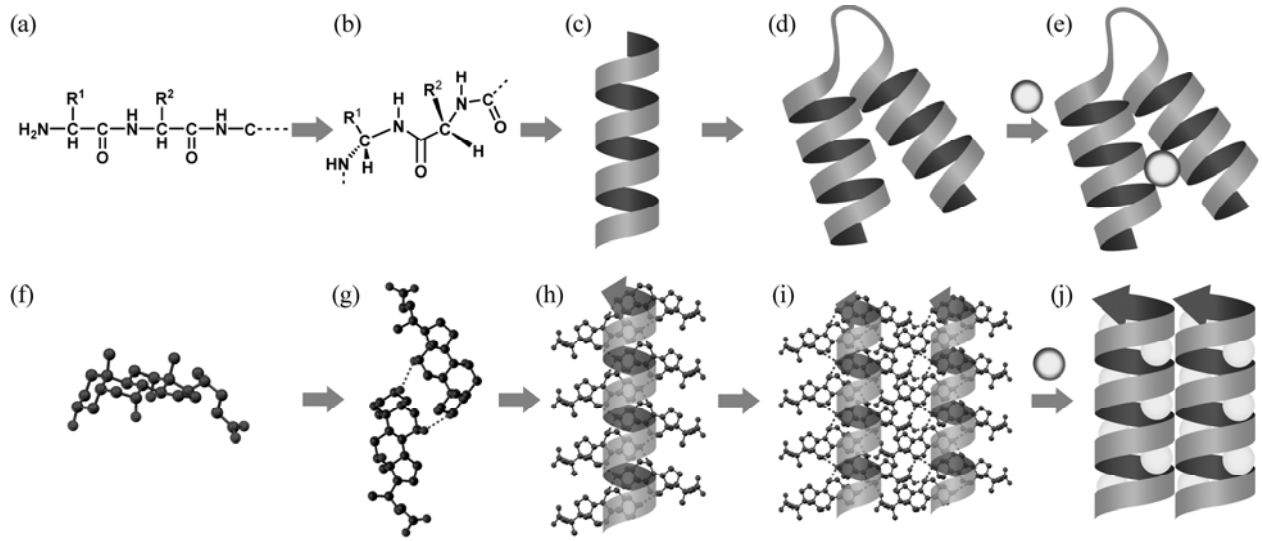
Figure 5. Intermediate properties of crystalline assemblies of steroidal bile acids and their derivatives, which relate to supramolecular chemistry.



3.2. Hierarchical Interpretation of the Steroidal Assemblies

The research is focused on the following question; how the steroidal host molecules assemble in corporation with guest molecules. Before going ahead with the question, we have to confirm the current situation that prediction of crystal structures still remains a challenging subject for many chemists [86–88].

Figure 6. Hierarchical structures in proteins (upper) and steroids (lower). The peptide chain (a) is folded with a relative position between the two units (b), yielding a helical chain (c) and a bundle of the helical chains (d), followed by a host-guest complexation (e). The steroidal molecules (f) associate to make a bimolecular assembly (g) and a helical assembly (h), followed by a bundle of the chains (i). The cavities among the helices accommodate guest components (j).



We now tried to obtain a qualitative answer to the question on the basis of the simulation and overview studies. The first thing we noticed is that most of the steroidal assemblies consist of helical moieties, which reminds us of helical structures of proteins. This is attributed to the well-known fact that proteins express their molecular information through non-covalent bonds via the following hierarchical processes; sequential chains as primary structures, helical stereostructures as secondary ones, bundles of the helices as tertiary ones, and so on [Figures 6(a)–(e)].

Therefore, an analogy emerged between the steroidal molecules and proteins. That is, the steroidal molecules also construct a hierarchical structure involving primary, secondary, tertiary structures [Figures. 6(f)–(j)] [89–92]. Thus, the steroidal molecules themselves constitute primary structures [Figure 6(f)], followed by the subsequent bimolecular [Figure 6(g)] and helical [Figure 6(h)] assemblies, as secondary structures. The helical assemblies are combined to produce their bundles as tertiary structures [Figure 6(i)]. When the bundles leave cavities for accommodating guest components, host-guest complexes are constructed as quaternary structures [Figure 6(j)].

3.3. Molecular Information and Expression of Chiral Chains

Such a hierarchical understanding of the steroidal assemblies reminded us of the concept of molecular information and expression. It is well-known that peptide chains serve as storage of the molecular information, which are expressed in the process for making three-dimensional structures and accommodating other molecules. It is also known that the steroidal molecules originate from hexamers of isoprene, suggesting that the steroidal molecules are substantially composed of the carbon-chains, which may serve as information storages for constructing any three-dimensional assemblies [1–4,17,93–97]. This analogy between the chains indicates that various informational molecules are theoretically created by means of chemical modifications of the carbon-chains, as shown in Figure 7.

Figure 7. A polymethylene chain with various substituents (a) serves as storage of molecular information. The sequential carbon chain can be theoretically modified to a polypeptide chain (b), a polynucleotide chain (c), a polysaccharide chain (d), and a polycyclic chain (e).

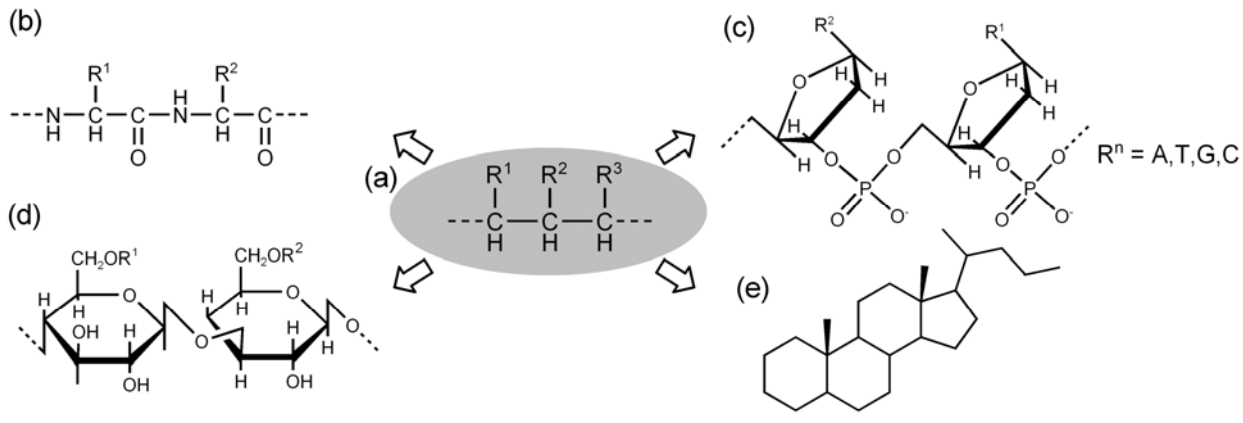


Figure 7(a) shows a chiral carbon-chain composed of methylene units with various substituents and absolute configurations. In case of the chains, we should notice that a beginning and terminal points define directionality of the chains. The methylene units can arrange in different ways, and each carbon-chain is termed as a sequential chain with molecular information at a nanometer level. Such a chain can be chemically modified to make the best use of non-covalent bonds. Thus, the carbon-chain is converted to proteins with amide bonds [Figure 7(b)], nucleic acids with phosphate and sugar moieties [Figure 7(c)], polysaccharides with sugar moieties [Figure 7(d)], and steroidal molecules with polycycles [Figure 7(e)].

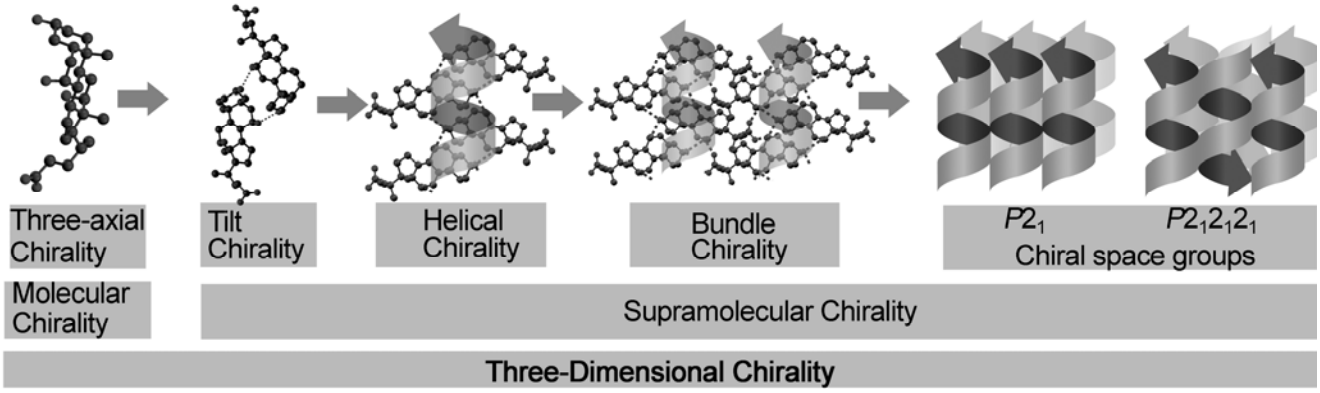
The remarkable feature of these chains is that chirality of the carbon atoms is essential for constructing definite three-dimensional structures with chirality. This concept induced the subsequent idea that the steroidal molecules must make their hierarchical assemblies with chirality in the crystalline state. In other words, the assemblies may exhibit supramolecular chirality in the crystalline state. The next chapter deals with our research directed toward the supramolecular chirality in each hierarchical assembly.

4. Supramolecular Chirality in Crystalline Molecular Assemblies

4.1. Chirality of the Hierarchical Assemblies, Especially 2_1 Helical Assemblies

As described above, we obtained the idea that the chiral chains may dominate chirality of the subsequent assemblies, such as helices, bundles, and host-guest complexes. Namely, each hierarchical assembly of the steroidal molecules must have its own three-dimensional structures with chirality, starting from the original molecular chirality, as shown in Figure 8 [4,92].

Figure 8. Molecular and supramolecular chirality of various molecular assemblies. Tilt chirality in a bimolecular assembly causes helical chirality in the resulting helical assembly. The helices are tied up to make various bundles as chiral crystals. The three-dimensional chirality of the molecular assemblies are interpreted in a hierarchical way.



Such an idea is universal for proteins, but not for the steroidal molecules. To the best of our knowledge there seemed to be no studies which clarified a correlation among their molecular structures, helical assemblies and crystal space groups from the viewpoint of both molecular and

supramolecular chirality. In other words, we have to search for systematic ways of describing the supramolecular chirality of the steroidal assemblies in the crystalline state.

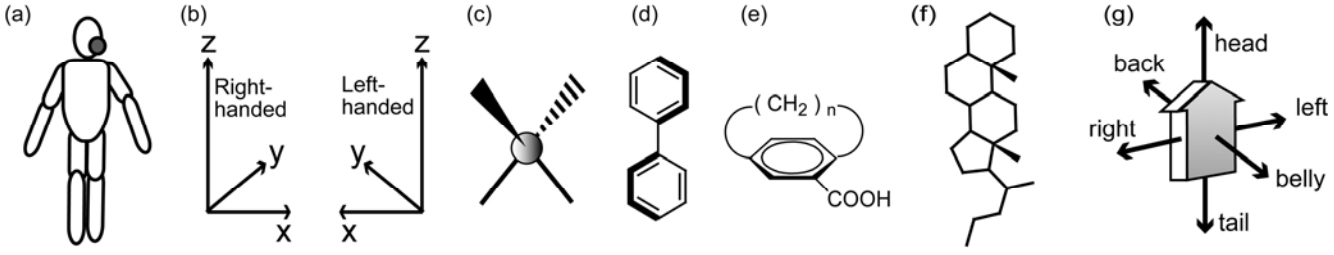
In this manner we encountered a new subject; how to define supramolecular chirality of molecular assemblies starting from molecular chirality. The first idea is that the steroidal molecules are analogous to vertebrate animals or humans with three-axial chirality [1–4]. Secondly, as Kitaigorodskii pointed out [98], organic molecules without symmetry elements predominantly form 2_1 helical assemblies with chiral space groups, such as $P2_1$, $P2_12_12_1$, and so on. Since the steroidal molecules have no symmetry elements, it may be assumed that the molecules form the 2_1 helical assemblies related to the corresponding chiral space groups. Thirdly, if the three-axial chirality of the starting molecules would be transferred to three-axial chirality of the 2_1 helical assemblies, we would be further able to interpret supramolecular chirality of the subsequent bundles and space groups. Therefore, the key for interpreting their chirality lies in handedness of the 2_1 helical assemblies.

We stopped due to a mysterious problem, that there are no general rules to determine handedness of the 2_1 helical assemblies. In the present situation, the handedness of the 2_1 helical assemblies is not conventionally discussed, even when we employ highly asymmetric molecules, such as steroids. In daily life, however, we have experiences of going up and down right- or left-handed stairs with 2_1 helical arrangements, indicating that the key structures, 2_1 helical assemblies, may have their handedness which can be defined in some ways. Recently, we have introduced the term, three-axial and tilt chirality for defining the handedness of the bimolecular as well as 2_1 helical assemblies [99–101]. This definition has been proven to be powerful in the elucidation of many structural problems of the assemblies.

4.2. Three-axial Chirality of Molecules

We live in three-dimensional space world, and naturally understand stereostructures of materials in three dimensions. For example, we daily use a set of words for our bodies, head-and-leg, right-and-left, and belly-and-back [Figure 9(a)]. Mathematically, there is an orthogonal coordinate system with x, y, and z-axes, which accompanies right- or left-handedness [Figure 9(b)].

Figure 9. Three-axial chirality of materials. Human (a), mathematical three axes with right-handed or left-handedness (b), molecules with center (c), axial (d), and plane (e) chirality, a steroidal molecule (f), and a facial material with three-axial chirality (g).



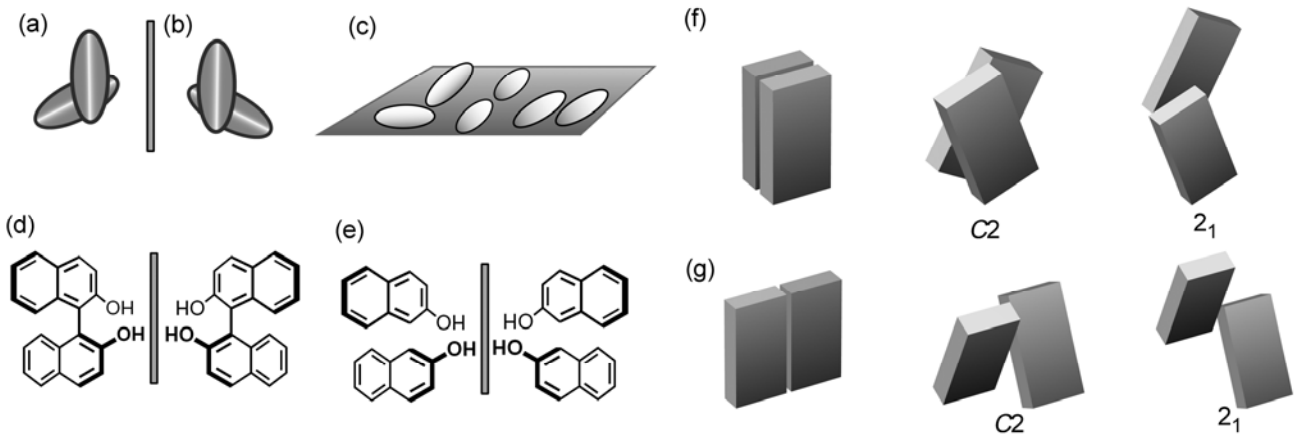
In the field of chemistry, molecular asymmetry has been conventionally expressed in terms of center- [Figure 9(c)], axis- [Figure 9(d)], and plane-chirality [Figure 9(e)]. These terms suggest an understanding of molecular chirality based on zero- (center), one- (axis), two- (plane) dimensional characteristics, although the molecules substantially have three-dimensional stereostructures.

However, these terms in chemistry are not suitable to express the whole chirality of arched and polycyclic molecules such as bile acids, although the terms are enough to express the local chirality of these molecules. Instead, we notice total characteristics of the steroidal molecules, that is, three-axial chirality. Since the steroidal molecules have an arched skeleton with a side chain [Figure 9(f)], the molecule is connected with a vertebrate animal, whose body is expressed by the daily words; head and tail (leg), right and left, as well as belly and back [Figure 9(a)]. In general, the facial molecule with three-axial chirality is schematically shown in Figure 9(g).

4.3. Tilt Chirality of Bimolecular Assemblies Based on Three-Axial Chirality

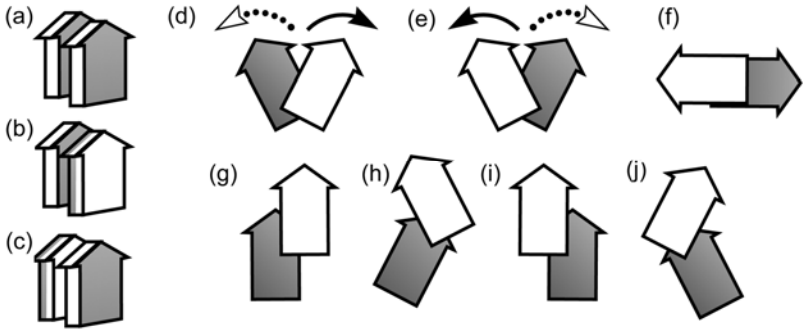
From a mathematical viewpoint, an assembly composed of two objects can form distinguishable enantiomorphic polyhedrons in three-dimensional world [102]. For example, the assembly of polyhedrons [Figure 10(a)] is not superimposable on its mirror image [Figure 10(b)], as in the case of right- or left-handed orthogonal coordination system [Figure 9(b)]. However, when the assembly composed of the two objects is put on an identical plane without stacking in various ways [Figure 10(c)], the assembly can be superposed on its mirror image. In general, a three-dimensional assembly with three-axial chirality cannot be superposed upon each other, while the assembly with two-axial chirality can be done. In other words, the appearance of supramolecular chirality requires a tilt between two objects, as shown in Figures 10(a) and 10(b). We have proposed to use the term, supramolecular tilt chirality, for expressing such chirality [99,100].

Figure 10. Supramolecular tilt chirality of assemblies of two materials. An assembly of two polyhedrons with tilt chirality (a), its mirror image (b), their assemblies without tilt chirality (c), 1,1'-bi-2-naphthol with axial chirality (d), mirror images of hypothetical assemblies made by a bond collapse of 1,1'-bi-2-binaphthol (e), bimolecular assemblies of planar molecules with 2_1 or *C*2 symmetry in a face-to-face (f) or an edge-to-edge mode (g).



First of all, we shall recall a single molecule with axis-chirality, such as 1,1'-bi-2-naphthol [Figure 10(d)], where two benzene rings have a tilt conformation. Hypothetical removal of the covalent bond between the rings would result in a tilt bimolecular assembly [Figure 10(e)]. This situation of the hypothetical assemblies is briefly displayed as models composed of two plates [Figures 10(f) and 10 (g)]. The former model shows an assembly in a face-to-face stacked alignment, while the latter does in an edge-to-edge one. A tilt between the plates yields a chiral object with twofold axis (*C*2), and further sliding yields another chiral object with twofold screw axis (2_1). The hypothetical bimolecule in the right part of Figure 10 (e) corresponds to the object with twofold axis (*C*2) in Figure 10 (g).

Figure 11. Tilt chirality of assemblies of two materials with three-axial chirality. Three association modes with a head-to-head mode in addition to a belly-to-back (a), belly-to-belly (b), back-to-back (c) modes. Inclination between two materials with right-tilt (d), left-tilt (e), rotation by 90 degrees (f). Combination of sliding and tilt; right and up sliding (g), left-tilt after the right and up sliding (h), left and up sliding (i), right-tilt after the left and up sliding (j).



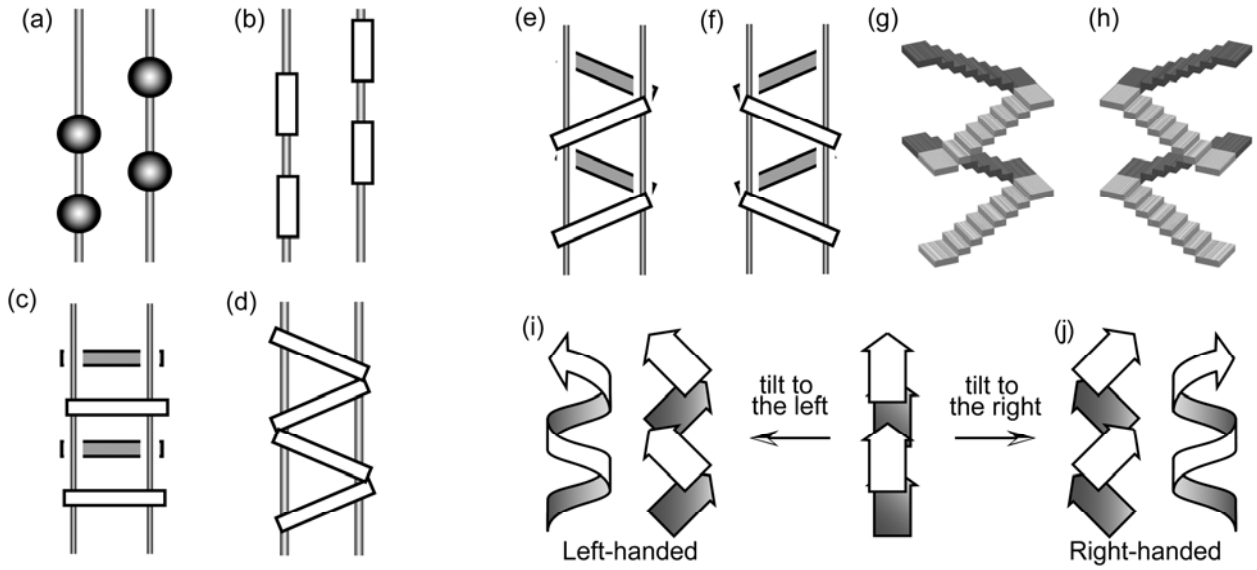
The first step toward molecular assemblies is logically the formation of a bimolecular assembly. When the materials with three-axial chirality [Figure 9(g)] align in a head-to-head fashion, they have the following three association modes; belly-to-back [Figure 11(a)], belly-to-belly [Figure 11(b)] as well as back-to-back [Figure 11(c)]. Each of the bimolecular assemblies can be rotated toward reverse directions at the same time. As for belly-to-belly association [Figure 11(b)], a clockwise rotation of the upper and an anti-clockwise rotation of the lower yield a right-tilt position [Figure 11(d)]. The reverse rotations yield a left-tilt position [Figure 11(e)]. Figure 11(f) illustrates a tail-to-tail association after the rotation by 90 degrees. Moreover, the belly-to-belly assembly [Figure 11(b)] can slide toward up-to-right as well as up-to-left yield another positions [Figures 11(g) and 11(i)], which further can tilt to the left [Figure 11(h)[or to the right [Figure 11(j)].

4.4. Helical Chirality of 2_1 Helical Assemblies Based on Three-axial and Tilt Chirality

Conventionally, it has been considered from a mathematical viewpoint that right- or left-handedness of the 2_1 helical assemblies cannot be distinguished, since the twofold screw axis operation includes rotation by 180 degrees and translation. This is true when we consider spherical materials [Figure 12(a)], but the situation changes when we consider other non-spherical materials. For example,

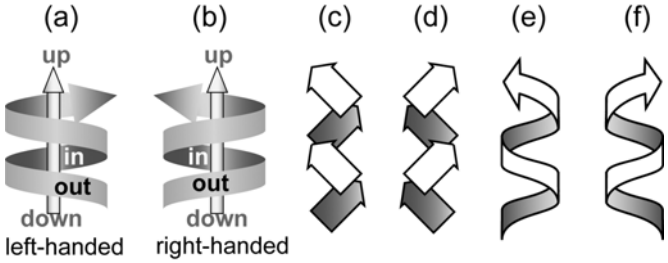
when bars can be regularly arranged in a parallel [Figure 12(b)], perpendicular [Figure 12(c)], and zigzag [Figure 12(d)] fashion against an axis on the same plane, the mirror images can be superposed upon each other. However, when they are arranged in a zigzag fashion alternating on two sides of a plane [Figure 12(e)], the bars cannot be superposed upon their mirror image [Figure 12(f)]. As in the case of stairs in daily life [Figures 12(g) and 12(h)], we can define handedness of the 2_1 helical assemblies on the basis of the supramolecular tilt chirality. As schematically shown in Figure 12(i), when the aligned bars incline to the right or left in front of a 2_1 screw axis, the assemblies are defined to be right- or left-handed, respectively. Graphically, the helical assemblies are designated with the corresponding helical tapes.

Figure 12. Helical chirality based on tilt chirality. 2_1 Helical assemblies of spheres (a), bars parallel to a 2_1 axis (b), bars perpendicular to a 2_1 axis (c), bars with a zigzag arrangement (d), bars with right-tilt arrangement (e) and a left-tilt arrangement (f), right-handed stairs with tilt chirality (g), left-handed stairs with tilt chirality (h). Definition of handedness of the 2_1 helical assemblies of planar molecules with left-handedness (i) and right-handedness (j).



In general, helices with three-axial chirality are designated by the following three-axes; left and right, up and down as well as in and out [Figures 13(a) and 13(b)]. When the up and in sides of the helix may correspond to the head and belly sides of the molecule with three-axial chirality, respectively, the molecules are stacked in the belly-to-belly mode on the in side of the helix. Therefore, helical chirality of the 2_1 helical assemblies is defined on the basis of the three-axial and tilt chirality of the bimolecular assembly as follows [101]. The sliding assembly in the belly-to-belly and left-tilt fashion [Figure 11(h)] can be expanded with a 2_1 symmetry operation to give its left-handed 2_1 helical assembly [Figure 13(c)], whereas the assembly in the right-tilt fashion [Figure 11(j)] can be expanded to give its right-handed 2_1 helical assembly [Figure 13(d)]. These 2_1 helical assemblies [Figures 13(c) and 13(d)] are displayed with tape-like expression in Figures 13(e) and 13(f), respectively.

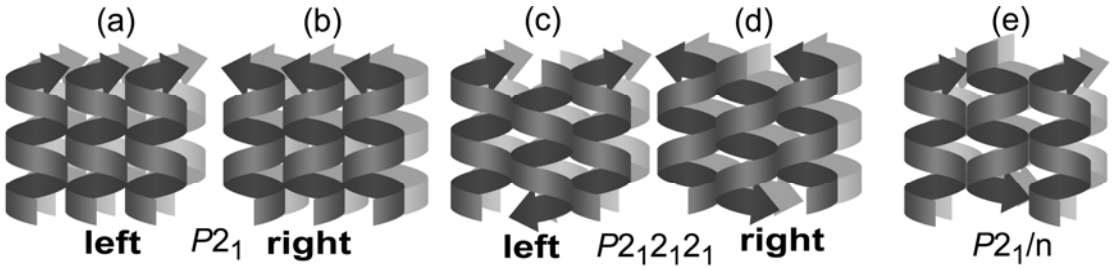
Figure 13. Helices with three directions; up and down, in and out, as well as right and left. Right-handed helix (a) and left-handed helix (b). 2_1 Helical assemblies of molecules with three-axes; left-tilt, left-handed helix (c) and right-tilt, right-handed helix (d). Ribbon-like expression of the left-handed helix (e) and right-handed helix (f).



4.5. Bundle Chirality Based on Three-axial, Tilt, and Helical Chirality

The 2_1 helical assemblies are tied up to yield bundles as tertiary structures. A basic hexagonal packing is that one helical assembly is surrounded by six other ones. Although there are many theoretical ways to assemble the helices with three-axial chirality, the representative bundles consist of helices with a parallel and anti-parallel alignment. Figure 14 shows five typical kinds of the bundles. A uniform bundle of either left- or right-handed helices gives chiral crystals with space group $P2_1$ in Figures 14(a) and 14(b), respectively. Another bundle of either left- or right-handed helices with the reverse up-down directions give the corresponding chiral crystals with space group $P2_12_12_1$ [Figures 14(c) and 14(d)]. Figure 14(e) depicts a bundle of both the left- and right-handed helices with the reverse up-down directions, which corresponds to the crystal structure with space group $P2_1/n$. These space groups containing the twofold screw axes frequently appear in organic crystals [103].

Figure 14. Bundles of helices with three-axial, tilt, and helical chirality. Stacking in an identical direction with left-handed helices (a) and right-handed helices (b), in the reversed direction with left-handed helices (c) and right-handed helices (d), with both left- and right-handed helices (e).



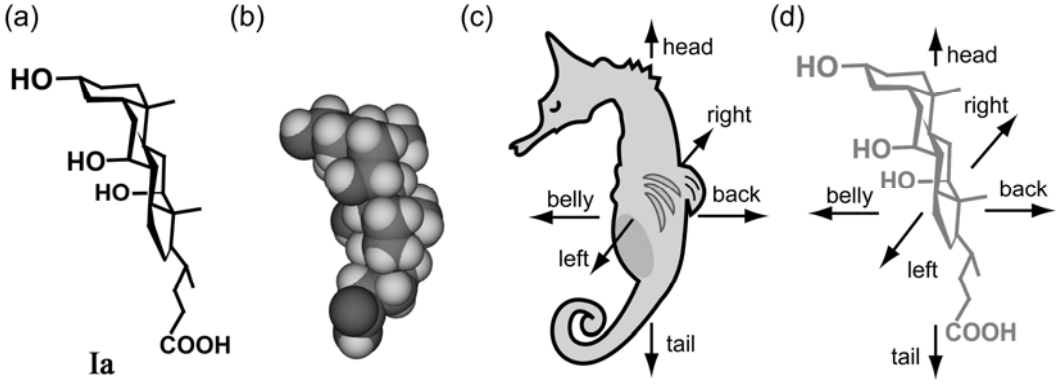
5. Supramolecular Chirality of Crystalline Assemblies of Bile Acids and Their Derivatives

5.1. Steroidal Molecules with Three-Axial Chirality

When we saw the conventional structural formulae of **Ia,** for instance [Figure 15(a)], we did not get any ideas suitable for understanding its whole chirality. However, when we freely rotated a stereo model of the molecule [Figure 15(b)], we noticed that the molecule is like a vertebrate with three distinguishable directions [Figure 15(c)]. Accordingly, we proposed to use the common words head and tail (or leg), right and left, and belly and back, for defining the directions of the steroidal molecules.

The assignment of the three directions is as follows. The key is a curved steroidal skeleton and various groups attached. As shown in Figure 15(d), the molecular structure of **Ia** consists of a skeleton and a side-chain. The skeleton possesses three hydroxyl and two methyl groups to form a hydrophilic and a lipophilic face, respectively. This facial structure enables us to distinguish three axes as follows. First, we designate the hydrophilic and lipophilic sides as belly and back, respectively. Second, we recognize the side-chain as the tail, and the reverse arched part of the skeleton as the head. Third, we discriminate the hydroxyl groups at the 7 and 12 positions as left and right, respectively. In addition, molecule **Ia** is asymmetric owing to the methyl and tail groups on the right side of the skeleton, meaning that naturally-occurring bile acids and their derivatives are right-handed molecules with three-axial chirality.

Figure 15. A stereostructure of **Ia** (a), its space-filling model (b), a hypothetical animal (c), and a stereostructure of **Ia** with three-axial chirality (d).

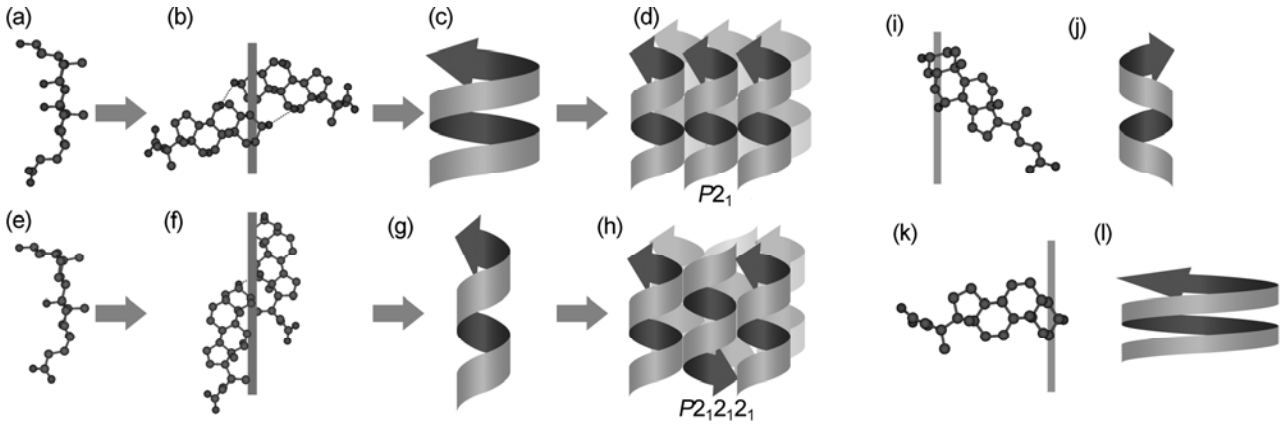


5.2. Steroidal Assemblies with Three-axial, Tilt, Helical, and Bundle Chirality

On the basis of the considerations described above, we can explain how to form crystals with chiral space groups starting from the steroidal molecules with three-axial chirality. Figures 16(a) to (d) show the hierarchical structure of **Ia**. The molecules of **Ia** [Figure 16(a)] are connected with a hydrogen bonding network among three hydroxyl groups at the 3-, 7-, and 12-positions. The resulting bimolecular assembly has a belly-to-belly association, an up-to-left sliding, and a right-tilt inclination [Figure 16(b)], and is expanded with 2_1 symmetry operation to construct a right-handed 2_1 helical assembly [Figure 16(c)]. The helices align in a parallel fashion with carboxylic groups to yield a crystal

structure with monoclinic, $P2_1$ space group [Figure 16(d)]. This Figure corresponds to that obtained with a rotation upward by 90 degrees of Figure 2(b), which shows a parallel stacking of bilayers.

Figure 16. Hierarchical assemblies of steroidal bile acids and their derivatives. The molecules of **Ia** (a) and **IIa** (e) form right-tilt bimolecular assemblies (b) and (f), 2_1 helical assemblies with right handedness (c) and (g), and bundles of the helices as chiral crystals with $P2_1$ (d) and $P2_12_12_1$ (h) space groups, respectively. The molecules of **IIIa** (i) form a left-handed 2_1 helical assembly (j), and the molecules of **IVa** (k) form a slightly right-handed helix (l).



The hierarchical structure of **IIa** is shown in Figures 16(e) to 16(h). The molecules of **IIa** [Figure 16(e)] are connected with the network among two groups at the 3- and 12-positions. The connection results in a right-tilt bimolecular assembly [Figure 16(f)], followed by a right-handed 2_1 helical assembly [Figure 16(g)]. The helices align in an anti-parallel fashion with the carboxylic groups to yield a crystal with orthogonal, $P2_12_12_1$ space group [Figure 16(h)], which shows an anti-parallel stacking of bilayers. This Figure corresponds to that obtained by a rotation up and right by 90 degrees of Figure 2(c), which shows an anti-parallel stacking of bilayers. On the other hand, **IIIa** has a left-tilt [Figure 16(i)] and a left-handed 2_1 helical assembly [Figure 16(j)] owing to the bias of the hydroxyl groups at the 3- and 7-positions towards the left side. In contrast, **IVa** has a helical hydrogen bonding network with hydroxyl groups and carboxylic groups, so that the molecules lay in a perpendicular and slightly right-tilt position to the 2_1 axis [Figure 16(k)]. The resulting 2_1 helical assembly [Figure 16(l)] is right-handed. These results indicate that the tilt and handedness of the steroidal assemblies strongly depend on substituted positions of the hydroxyl groups in the steroidal skeleton.

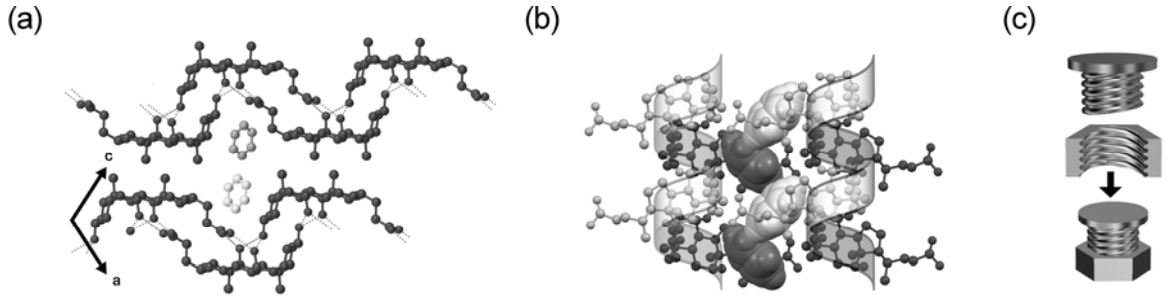
5.3. Complementary Chirality in Host-Guest Complexes

The bundles of helices may leave cavities where the other organic substances are accommodated. Since the steroidal molecules have both hydrophilic and lipophilic sides, the resulting helices usually have lipophilic outsides where any sliding may take place. Such sliding enables the assemblies to accommodate the guest components in various ways, resulting in guest-dependent polymorphism of the host components. Key and lock mechanism is widely accepted as a principle of molecular recognition [104]. This concept is based on stereo and electronic complementarity between concave host cavities

and convex guest compounds. Therefore, complementary compounds are usually included in the host cavities.

The 2_1 helical assemblies of the host components may leave 2_1 helical assemblies of the cage- or channel-like cavities, indicating that the guest components may produce the 2_1 helical assemblies by using the cavities. Therefore, not only chiral but also achiral guest molecules may yield handedness of the 2_1 helical assemblies. Indeed, inclusion crystals of **Ia** with benzene [Figure 17(a)] exhibit right-handed 2_1 helical assemblies of both **Ia** and benzene on the basis of supramolecular tilt chirality [Figure 17(b)] [105]. Moreover, we confirmed that about 40 kinds of benzene derivatives exhibit right-handed 2_1 helical assemblies in the inclusion crystals of **Ia**. Such a complementary relationship is compared to a right-handed bolt and nut [Figure 17(c)], and are observed for many crystalline host-guest inclusion systems. We consider that this complementary chirality should be more frequently discussed as one of supramolecular chirality in the crystalline state.

Figure 17. Complementary chirality of the 2_1 helical assemblies of host and guest components. The inclusion crystal of **Ia** with benzene (a), bundles of right-handed helical assemblies of **Ia** and benzene (b), and a combination of a right-handed bolt and nut (c).



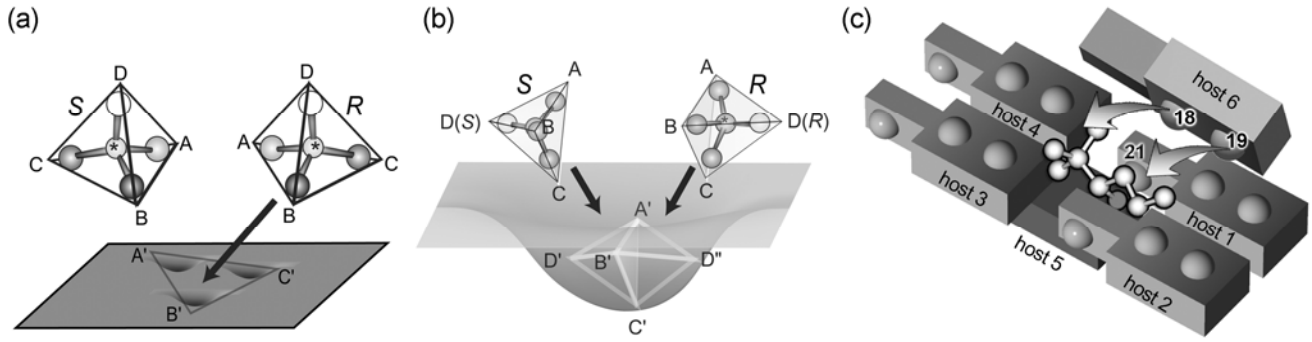
5.4. Chirality Recognition Based on Supramolecular Chirality

The steroidal assemblies form chiral spaces which function to accommodate chiral guest components. We performed systematic studies on enantioresolution of various secondary alcohols [3,106]. This is because hosts such as **Ib**, **IIb**, **IVb**, **IIe**, **Ig**, and **IIg** include aliphatic and aromatic alcohols, as described in Chapter 2. **Ib** prefers (*R*)-isomers to (*S*)-isomers, and the efficiency depends on alkyl groups of the alcohols in size and shape [107, 108]. Most of the guest components are included in the channels, but (*S*)-2,2-dimethyl-3-hexanol is exclusively included in the cage-like cavities [109]. **IVb** includes aliphatic alcohols involving over four carbon atoms [110], and prefers (*R*)-isomers of the secondary alcohols to (*S*)-isomers. **IIe** is useful for 4-methyl-2-pentanol [111]. **Ig** and **IIg** display efficient chiral recognition for the aliphatic alcohols, especially 3-methyl-2-pentanol [112]. **Ia** functions for enantioresolution of lactones [113–116], cyclic ketones as well as epoxides with phenyl rings [117]. Dehydrocholic acid (**Vi**) is known to be an effective host for the enantioresolution of sulfoxides and cyclic amides [118–121]. It is noteworthy that **Ia** includes chiral conformers of achiral compounds [122–124].

We studied the detailed mechanism of chirality recognition by using bile acids and their derivatives. Unexpectedly, the mechanism for enantioresolution using inclusion crystals remains unclear. In fact,

the three-point attachment model has been so far accepted for enantioselective complexation [125]. Figure 18(a) shows a simple description of the model which has a flat surface for accommodating the guest molecules. In this model, three locations (A, B, and C) of a guest component meet three locations (A', B', and C') on the flat surface. However, falling of the surface may induce the following change. Four substituents at a chiral carbon attach to the wall of the dip. When the fourth substituent is the smallest atom, hydrogen, both the enantiomers may be included into a deep dip. In such a case we have to fix a location of the fourth substituent. Therefore, we should employ a four location model [126], as shown in Figure 18(b). To fix the hydrogen attached with chiral carbon, it is important that location of chiral carbon should be fixed through some weak interactions or a bulky substituent. Figure 18(c) depicts one example of the crystal structure of the inclusion crystal of **Ib** with 2,2-dimethyl-3-hexanol [109]. It can be seen that the cage composed of six host molecules is occupied by three substituents attached to the chiral carbon; hydroxyl, *n*-propyl, and *tert*-butyl groups. The feature is that the *n*-propyl group has some close contacts with a methyl group at 21-position of the host (1) and at 19-position of the host (6), and that one methyl group of the *tert*-butyl group has a close contact with a methyl group at 18-position of the host (6). Namely, three methyl groups at 18, 19, and 21-positions of the steroidal molecules are related to the chirality recognition. This result indicates that chirality recognition may be accomplished by cooperative work through multiple weak interactions.

Figure 18. Models for chirality recognition. A three-location model (a) and a four-location model (b). Chirality recognition in a cage of the inclusion crystal of **Ia** with (*S*)-2,2-dimethyl-3-hexanol (c).



6. Conclusions and Perspectives

We have presented the fact that steroidal crystalline assemblies exhibit the hierarchical structures with supramolecular three-axial, tilt, helical, and bundle chirality, according to the order of weak interactions. Alternatively, we continue to study polymerization of conjugated diene monomers in the inclusion and crystalline state. The latter study aims to obtain optically active polymers with quantitative chiral centers starting from achiral monomers, forcing us to prepare chiral assemblies of the monomers as chiral crystals. During this study we noticed the research for preparing chiral crystals from achiral molecules [127], and wanted to understand a mechanism how to acquire such crystals. This research gave a chance to consider three-dimensional chirality of materials, especially steroidal

assemblies with complete three-dimensional chirality, leading us to the interpretation of supramolecular chirality in the hierarchical crystal structures.

The research naturally moves in the direction of supramolecular crystal engineering. Now our study is spreading from steroidal molecules to the surrounding natural compounds, such as brucine [128], cinchona alkaloids, and further to the surrounding organic substances, such as organic salts [129–131]. Supramolecular chirality of assemblies of these substances fascinates us so much. Our approach would provide an efficient view for creating new chiral crystals from chiral and/or achiral compounds, finding possible application to electronics, optics, photonics, informatics, and so on. Further studies are in progress for the crystal engineering, the fabrication of new materials, and so on.

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