

# Crystalline Host–Guest Assemblies of Steroidal and Related Molecules: Diversity, Hierarchy, and Supramolecular Chirality

MIKIJI MIYATA,\* NORIMITSU TOHNAI, AND ICHIRO HISAKI

Department of Material and Life Science, Graduate School of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565-0871, Japan

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## ABSTRACT

Steroidal bile acids and over 50 of their derivatives serve as the hosts of inclusion crystals. These hosts each exhibit their own characteristic inclusion behaviors, which have been explored through more than 300 crystallographic data. The molecules with three-axial chirality combine in asymmetric fashion to form diverse assemblies, which have supramolecular properties, such as recognition and dynamics, through cooperative weak interactions. From an overview of these results, an analogy emerged: the steroidal assemblies may have hierarchical structures, such as primary, secondary, tertiary, and host–guest assemblies, similar to proteins. Accordingly, the assemblies with dimensionality bear supramolecular chirality, such as three-axial, tilt, helical, bundle, and complementary chirality. Such a concept can be extended to other organic substances, such as alkaloids and organic salts. These results move in the direction of supramolecular crystal engineering.

## Introduction

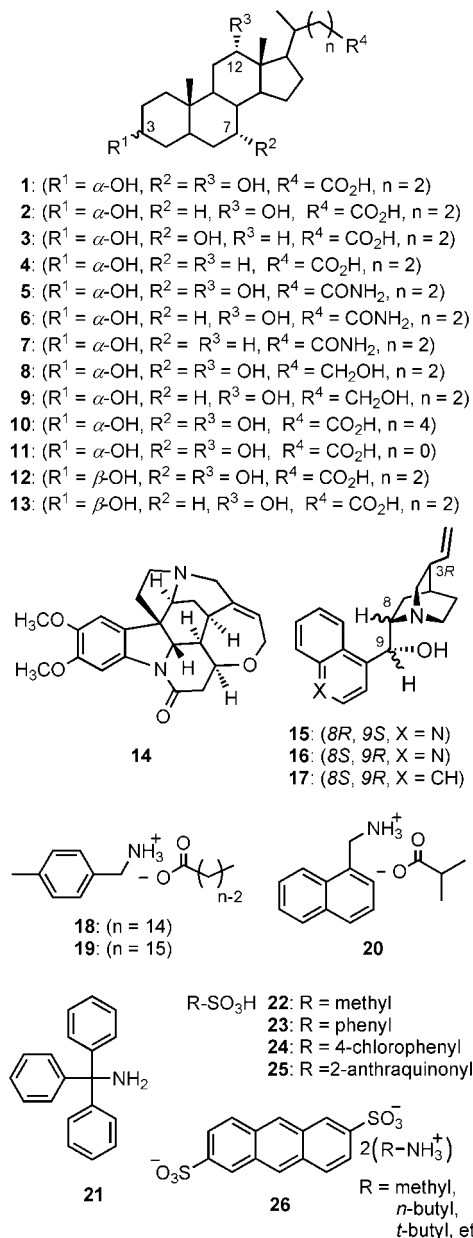
Natural compounds, steroidal bile acids (1–13 in Scheme 1), have fascinating molecular structures. Their representative cholic acid (1) involves an arched polycyclic skeleton with 11 chiral carbons, a short side-chain, and 4 discrete hydrogen-bonding groups. From the viewpoint of crystalline molecular assemblies, we may expect that properties

Mikiji Miyata is a Professor of the Department of Material and Life Science, Graduate School of Engineering, Osaka University, Japan. He joined the Department of Applied Chemistry, Faculty of Engineering, Osaka University, as an Assistant Professor in 1973. He received his Ph.D. degree under Prof. K. Takemoto from Osaka University in 1979. In 1989, he moved to the Department of Applied Chemistry, Faculty of Engineering, Gifu University, as an Associate Professor. Since 1995, he has been at his current position. His current research interests include steroidal inclusion compounds, molecular recognition, supramolecular chirality, and crystal engineering.

Norimitsu Tohnai is an Associate Professor of the Department of Material and Life Science, Graduate School of Engineering, Osaka University, Japan. He received his Ph.D. degree from Osaka University in 1999. He joined Miyata's group in 2002 as an Assistant Professor and obtained his current position in 2005. His research activities are in the field of supramolecular chemistry, crystal engineering, and photophysics.

Ichiro Hisaki is an Assistant Professor of the Department of Material and Life Science, Graduate School of Engineering, Osaka University, Japan. He received his Ph.D. degree from the Graduate School of Engineering Science, Osaka University, in 2005. He joined Miyata's group in 2005 as an Assistant Professor. His current research interests include supramolecular chirality, crystal engineering, and the construction of new supramolecular systems.

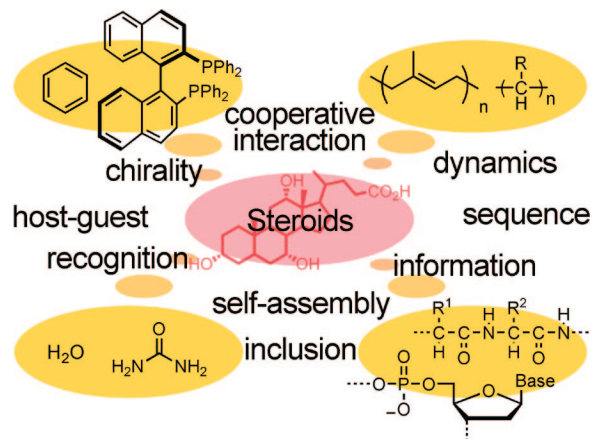
Scheme 1. Organic Molecules and Salts Described in This Paper



of the steroidal molecules are intermediate between those of small ones, such as benzene, and large ones, such as biopolymers (Figure 1). The intermediate properties are concerned with chirality, cooperative interaction, inclusion, self-assembly, host–guest, recognition, dynamics, sequential information, and so on.

To date, much research has been devoted to elucidating relationships between organic molecules and their assemblies.<sup>1,2</sup> Well-known examples cover face- or body-centered assemblies from spherical molecules, hexagonal-packed layered ones from axial ones, and herringbone ones from flat ones. The molecules having hydrogen-bonding groups, such as urea and biopolymers, form honeycombed or folded structures accommodating so-

\* To whom correspondence should be addressed. Fax: +81-6-6879-7404. E-mail: miyata@mls.eng.osaka-u.ac.jp.



**FIGURE 1.** Relationship between molecules and their properties. Crystalline assemblies of steroidal molecules exhibit various intermediate properties, bridging the gaps between these molecules.

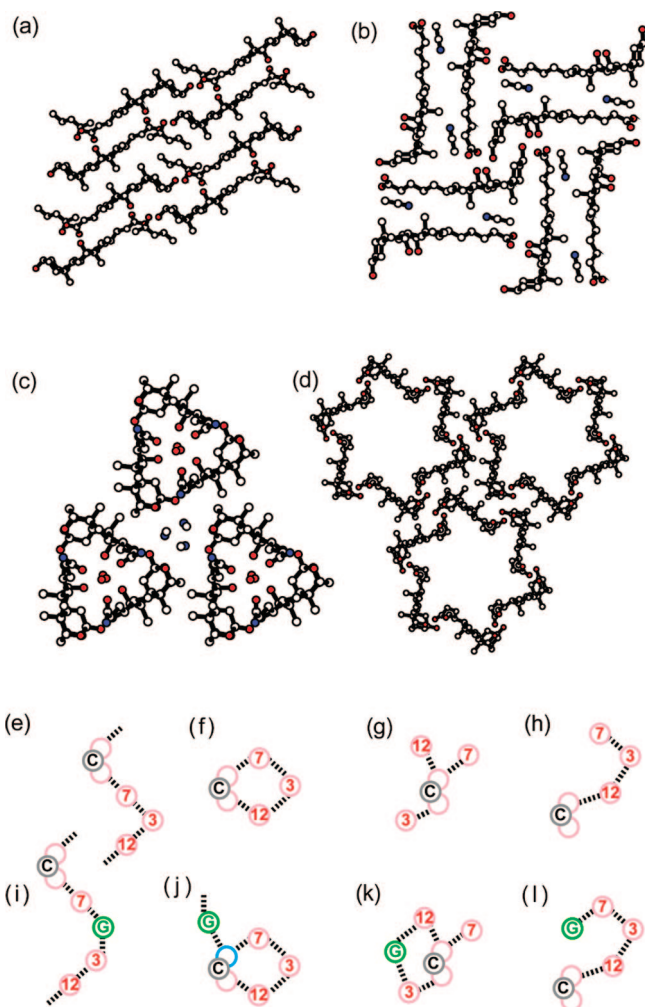
called guests. In the last decades, the supramolecular self-organization strategy<sup>3</sup> has been directed toward crystal engineering with synthons.<sup>4</sup> Considering the strategy, the steroidal bile acids, as well as over 50 of their derivatives, correspond to highly chiral diverse synthons and construct host–guest assemblies, termed as inclusion compounds.<sup>5</sup> Therefore, a systematic study on the steroidal assemblies would clarify any relations between organic molecules and their assemblies through cooperative interactions, bridging the gap between small molecules and biopolymers.

In contrast to a classical host, deoxycholic acid (**2**),<sup>6</sup> **1** was found to function as a new host by one of the authors (M. Miyata) and K. Miki in 1986.<sup>7</sup> Since then, we have been studying crystalline assemblies of the steroidal molecules based on X-ray crystallographic data.<sup>8,9</sup> Lengthy research led to the finding that each host molecule exhibits unique inclusion behavior because of diverse crystal structures. In the course of this research, we noticed that the steroidal assemblies bear a resemblance to proteins and yield novel concepts for elucidating the relations between organic molecules and their assemblies. Such concepts may be expected to hold for other related organic molecules. This paper deals with our systematic study as follows: The first part is concerned with the diversity of crystalline steroidal assemblies, and the subsequent parts are concerned with hierarchy and supramolecular chirality of the assemblies, followed by extension to organic salts.

## Diversity of Crystalline Steroidal Assemblies with Host–Guest Relationships

Main bile acids involve **1**, **2**, chenodeoxycholic acid (**3**), and lithocholic acid (**4**), which are logically converted to hundreds of derivatives by conventional procedures. We employed the following three modifications: (i) transformation of functional groups at their side chains, (ii) changes of their side-chain length, and (iii) changes of the direction of hydroxyl groups on their skeletons.

**Inclusion Behaviors and Crystal Structures.** More than 100 guest candidates were screened as guests. The resulting feature was that each host exhibits unique inclusion ability and that a subtle change of the molecular structure



**FIGURE 2.** Representative crystal structures of bile acids and their derivatives: bilayer (a), herringbone (b), triangular prism (c), and honeycomb (d). Hydrogen-bonding networks among hosts: linear (e), cyclic (f), branched (g), and arched (h). Networks accompanied with guest: linear (i), cyclic (j), branched (k), and arched (l).

always brings about a great change in the inclusion behavior. Therefore, enormous comparative studies are derived by using a pair or set of the steroidal hosts. Thus, **1** and **2** include a wide range of organic substances,<sup>8–10</sup> while **3** includes a little and **4** has none at all. Their amides **5**, **6**, and **7** can include many aliphatic alcohols in contrast to the original acids.<sup>11</sup> An alcoholic derivative **8** does not include organic guests at all, while **9** includes many aromatic compounds. Bishomocholeic acid (**10**) with two additional methylene units includes various organic substances,<sup>12</sup> while bisnorcholeic acid (**11**) with two decreased units does not. Epimers **12** and **13** include various aliphatic alcohols, in contrast to their original acids.

The bile acids and their derivatives construct variable crystal structures.<sup>8,9</sup> Parts a–d of Figure 2 illustrate the bilayer for **13**, herringbone for **10**, triangular prism for **5**, and honeycomb for **3**, respectively. The representative bilayer structures show facile guest-dependent polymorphism with the following two features. One is that the bilayers can slide on the lipophilic sides accompanied by conformational changes of the side chains to give versatile inclusion behaviors mentioned above. The other is that

the bilayers are constructed by the connection of the  $2_1$  helical assemblies through their side chains, whose length decisively influences assembly modes of the helices. Commonly, the asymmetric amphiphilic molecules bring about various combinations of the hydrophilic and lipophilic sides in a parallel or antiparallel direction. For example, in the case of the bilayers, the combinations yield four types of the cumulated bilayers. In addition, real and pseudo-polymorphic crystals, including guests, are also obtained with many steroidal hosts.

**Molecular Recognition and Dynamics.** Combinations of three or four hydrogen-bonding groups make linear, cyclic, branched, or arched networks with the cooperation of the guests (parts e–l of Figure 2).<sup>8,9</sup> Subtle differences in the groups are sufficient to account for the networks. The interesting feature is whether the networks among the host molecules are opened to guest molecules or not. Thus, the linear network of **1** (Figure 2e) is opened to several aliphatic alcohols (Figure 2i), while the cyclic network of **1** (Figure 2f) is not opened to the alcohols. Additional hydrogen in the cyclic network of **5** (Figure 2j) is enough to catch over 50 alcoholic guests. On the other hand, **12** prefers the branched network (Figure 2g) to the cyclic one, which needs insertion of aliphatic alcohols between the two hydrogen-bonding groups (Figure 2k). The arched networks (parts h and l of Figure 2) are observed in rare cases.

The packing coefficient of the host cavity, PC cavity, functions as the parameter for evaluating the fitness of the guest volumes in the host cavities. The PC-cavity values of inclusion crystals **1** and **5** were evaluated in a wide range of the guest volumes.<sup>10,11</sup> The resulting values are in a range of approximately 45–75% for inclusion crystals and tend to increase with increasing guest volumes. This result means that it would be difficult to form inclusion crystals out of this range because of too tight or loose packing. To avoid this, it is necessary to adopt different assembly modes or molar ratios. Otherwise, they may form guest-free crystals or none at all. Moreover, the PC-cavity values can be compared with other organic assemblies.<sup>13</sup> It is reasonable that the values of the inclusion crystals are intermediate between those in the liquid (44–56%) and crystalline (66–77%) states.

We expect that efficient enantioresolution would take place in the steroidal crystals, because the host molecules are highly asymmetric. However, it is not so easy to perform the resolution in more than 90 % enantiomeric excess (ee), owing to guest-dependent crystal structures. Successful enantioresolution of secondary alcohols is recorded for the remarkable recognition of the (2*R*,3*S*) isomer among four isomers of 3-methyl-2-pentanol by **12**.<sup>14</sup> As for the recognition mechanism, we suggest that a four-location model is more suitable rather than the conventional three-point attachment model. The reason is that the former is based on deformed holes, while the latter is based on a planar surface. It is important that the smallest hydrogen atom should be recognized together with the chiral carbon.

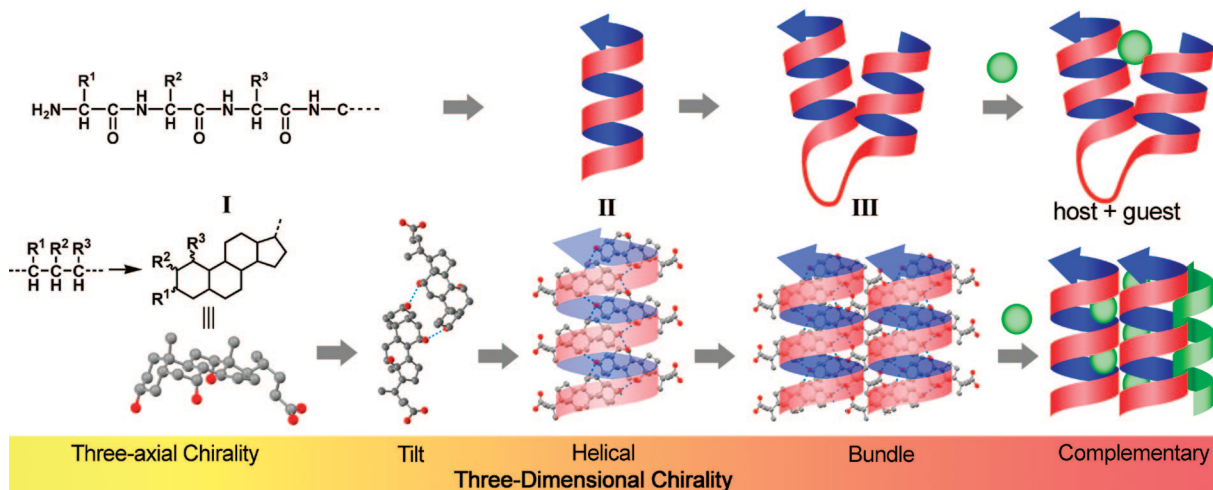
The steroidal crystals exhibit dynamic behaviors. In comparison to inorganic compounds, such as clays and graphite, we first proved intercalation in organic crystals of **1**.<sup>15</sup> Recently, a sandwich-type crystal was found to show a dynamic behavior similar to inorganic layered materials.<sup>16</sup> On the other hand, a dynamic process of monomeric guests was reflected upon inclusion polymerization.<sup>17</sup> Early studies revealed highly stereoregular and asymmetric polymers, followed by significant knowledge of the space effects at the molecular level. Currently, inclusion polymerization is classified into one of low-dimensional and space-dependent polymerizations.

## Hierarchy and Three-Dimensional Chirality

The above-mentioned comparative studies made clear various static and dynamic relations between the inclusion behaviors and the crystal structures. On the other hand, overview studies suggested an analogy with proteins and vertebrate animals, resulting in an interpretation of hierarchy and three-dimensional chirality of the crystalline assemblies, particularly the  $2_1$  helical assemblies, as described below. The crystal structures full of variety make it difficult to understand a mechanism to assemble the steroidal molecules, and there are no general principles for explaining crystal-growth processes at present. However, it may be postulated that relatively small assemblies can be formed before total crystal structures, leading to the idea that the molecules construct a hierarchical structure, as in the case of proteins (Figure 3).<sup>8,9</sup> Thus, the steroidal molecules serve as primary structures and associate because of their accompanied hydrogen-bonding groups and side chains. The simplest secondary structures are naturally bimolecular assemblies, followed by helical assemblies, and so on. The helices are tied up in a bundle, which corresponds to tertiary structures and leaves cavities for accommodating guest components. The resulting host–guest complexes are characterized by recognition and dynamics. In addition, chirality of the starting molecules should be responsible for the chirality of subsequent assemblies.

This hierarchical interpretation recalls the concept of molecular information and its expression. Specifically, proteins consist of sequential chains of  $\alpha$ -amino acids, while steroidal molecules consist of chains of methylene units with various substituents. These chains are considered to function as molecular information storages, and their information is expressed through three-dimensional architectures by the best use of noncovalent bonds. The architectures are folding structures of proteins as well as assemblies of the steroidal molecules. To confirm this concept, we further employed brucine (**14**), one of the alkaloids, which has a facial, asymmetric structure with a polycyclic and aliphatic skeleton. Its crystals exhibit the hierarchical structure similar to the steroidal crystals.<sup>18</sup>

It may be considered that the hierarchical assemblies have the corresponding three-dimensional structures with supramolecular chirality, starting from molecular chirality. This view yields a new subject: how to describe such



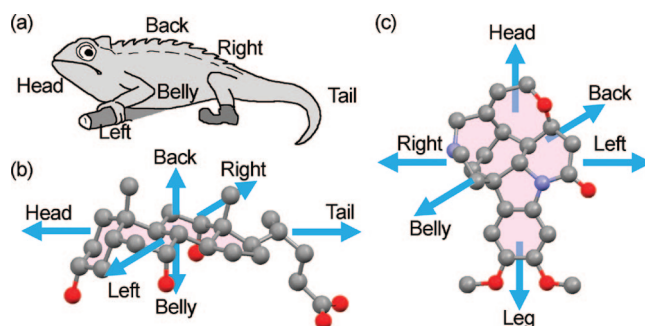
**FIGURE 3.** Hierarchical structures of proteins and crystalline steroidal assemblies with three-dimensional chirality. I, II, and III represent the corresponding primary, secondary, and tertiary structures, respectively.

chirality. The idea is that the steroidal molecules are analogous to vertebrate animals with three-axial chirality, enabling us to determine three axes of the helical assemblies, as in the case of helices of proteins and DNA. As Kitaigorodskii pointed out,<sup>19</sup> molecules without symmetry elements tend to form the  $2_1$  helical assemblies predominantly to induce close packing with the following chiral space group,  $P2_1$ ,  $P2_12_12_1$ , and so on. This applies to the steroidal and alkaloidal molecules. However, this poses the problem that there are no general rules to determine handedness of the  $2_1$  helical assemblies, and therefore, we cannot determine their handedness despite highly asymmetric molecules, such as steroids and alkaloids. The next part deals with our research directed toward this problem.

### Supramolecular Chirality of the Hierarchical Assemblies

We have introduced the term three-axial and tilt chiralities for defining the handedness of the bimolecular and helical assemblies. This definition has proven to be powerful in the elucidation of many structural problems of the assemblies, prompting further research for the surrounding organic molecules.

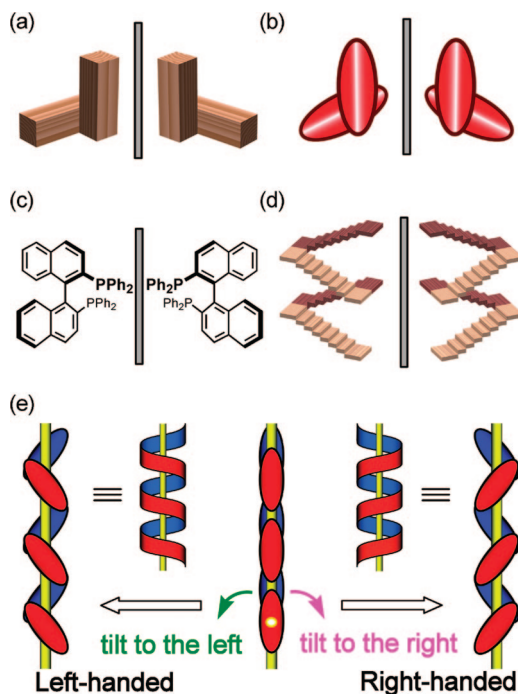
**Three-Axial Chirality.** Conventionally, molecular asymmetry has been expressed in terms of center, axis, and plane chirality. In the case of the steroidal and alkaloidal molecules, these terms are enough to express the local chirality of these molecules but not suitable for the whole chirality. These molecules have asymmetric, amphiphilic, and facial structures with multiple chiral carbon atoms, indicating the existence of three-axial chirality (Figure 4). Such characteristic structures connect the molecules with vertebrate animals, whose bodies are expressed by the general terms: head and tail (leg), right and left, as well as belly and back, as shown in Figure 4a.<sup>8,9</sup> Therefore, it seems natural to depict the whole three-dimensional chirality of the molecules on the basis of the orthorhombic three axes. Thus, we employ these words to define the three-axial chirality of the steroidal molecules, such as **1**



**FIGURE 4.** Illustrations of a vertebrate animal (a), cholic acid **1** (b), and brucine **14** (c) with orthorhombic three axes.

(Figure 4b), and the alkaloidal ones, such as **14** (Figure 4c).

**Tilt Chirality.** When we attempted to define handedness of the  $2_1$  helical assemblies, we encountered Gardner's book.<sup>20</sup> One chapter deals with an assembly composed of two achiral objects, such as polyhedrons, from a mathematical viewpoint (Figure 5a), telling us that the assembly can form distinguishable enantiomorphous polyhedrons. This description suggests the common appearance of such supramolecular chirality in bimolecular assemblies (Figure 5b) and reminds us of axis chirality in a single molecule, such as [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (BINAP) (Figure 5c). It is to be emphasized that a tilt between the two molecules is indispensable for the appearance of supramolecular chirality, as in the case of the axis chirality. Therefore, such chirality in bimolecular assemblies may be referred to as supramolecular tilt chirality.<sup>21</sup> Furthermore, as in the case of stairs (Figure 5d), the bimolecular assemblies are expanded with  $2_1$  symmetry operation to yield the corresponding  $2_1$  helical assemblies (Figure 5e). Conventionally, it has been considered from a mathematical viewpoint that right- or left-handedness of the  $2_1$  helical assemblies cannot be distinguished, because the two-fold screw axis operation includes  $180^\circ$  rotation and translation. However, it is reasonable to define the handedness of the  $2_1$  helical assemblies on the basis of the tilt chirality. As schemati-

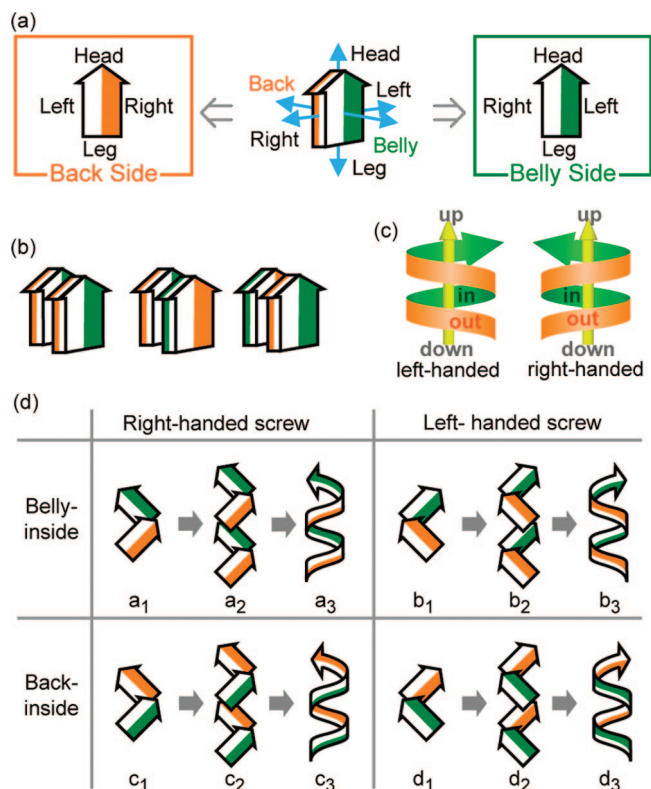


**FIGURE 5.** Concept of supramolecular tilt chirality. Mirror image pair of an assembly of polyhedrons (a), molecules (b), BINAP (c), stairs (d), and definition of handedness of the  $2_1$  helical assemblies (e).

cally shown in Figure 5e, given molecules inclined to the right or left in front of a  $2_1$  screw axis, the assemblies are defined to be right- or left-handed, respectively.

**Helical Chirality Based on Three-Axial and Tilt Chiralities.** The first step directed toward the molecular assemblies is logically the formation of bimolecular assemblies. Normally, a simplified example is adequate for our purpose. When the molecules with three-axial chirality (Figure 6a) align in the same head-to-tail direction, they have the following three association modes: belly-to-belly, back-to-back, and belly-to-back (Figure 6b). Each mode may have a right or left tilt. The bimolecular assemblies with the former two modes can be expanded with  $2_1$  symmetry operation to form the corresponding asymmetric  $2_1$  helical assemblies. In general, an asymmetric helix is designated by the following three axes: right and left, up and down, and in and out (Figure 6c). A combination of the three-axial and tilt chiralities enables us to define the helical chirality of the  $2_1$  helical assemblies. For example, the up and in side of the helix may correspond to the head and belly side of the asymmetric molecule, respectively. As shown in Figure 6d, the molecules are stacked with combinations of the belly-to-belly or back-to-back mode on the in side, accompanied by the tilt, to give four kinds of the bimolecular assemblies ( $a_1$ )–( $d_1$ ). They are extended to the corresponding  $2_1$  helical assemblies ( $a_2$ )–( $d_2$ ) and helical tapes ( $a_3$ )–( $d_3$ ).<sup>22</sup>

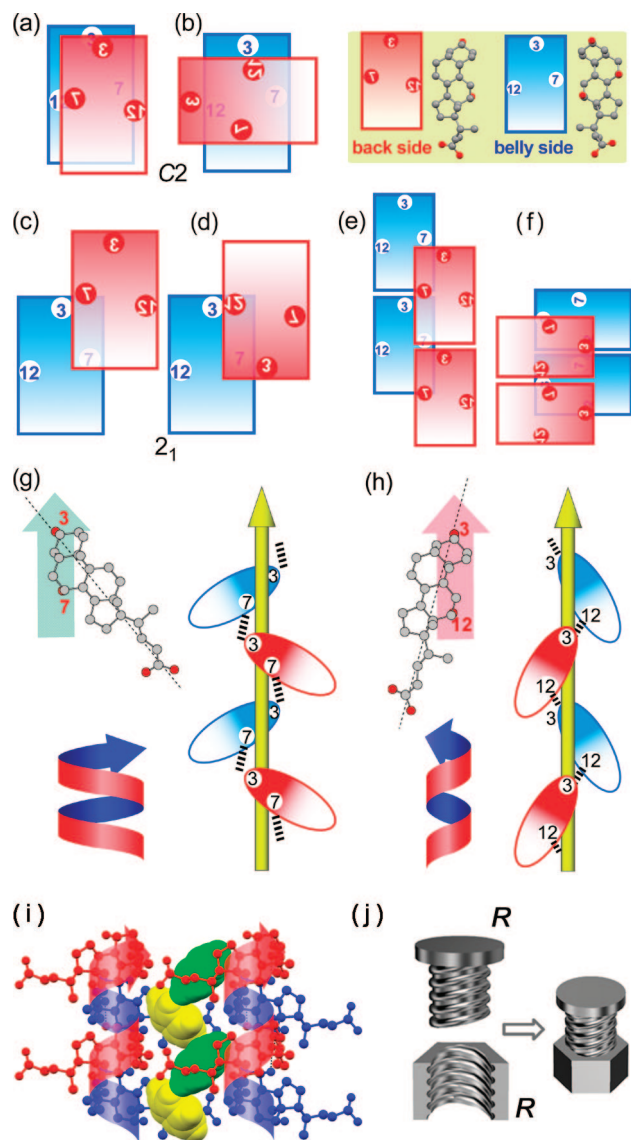
**Bimolecular and  $2_1$  Helical Assemblies with the Supramolecular Chirality.** Such helical assemblies are actually proven by taking for instance the steroidal molecules, which have the largest size in the head-to-tail direction (Figure 4b). A simplified consideration of their assemblies may be limited to the belly-to-belly association mode on



**FIGURE 6.** Schematic representation of a chiral molecule with three axes (a), three bimolecular association modes (b), an asymmetric helix with three axes (c), and four kinds of bimolecular and  $2_1$  helical assemblies by combination of three-axial and tilt chiralities (d).

their hydrophilic sides (Figure 7). Parts a–d of Figure 7 show the representative four modes of the bimolecular assemblies observed. Parts a and b of Figure 7 illustrate bimolecular assemblies with a parallel association mode and its left-tilt mode, respectively. Figure 7c displays a bimolecular assembly with a sliding head-to-tail association mode, which can be expanded with  $2_1$  symmetry operation to give its  $2_1$  helical assembly (Figure 7e). Tilt to the left produces its left-handed  $2_1$  helical assembly of **3** (Figure 7g). In contrast, **2** has the right-handed assembly owing to biased hydroxyl groups [OH(3) and OH(12)] toward the right side (Figure 7h). On the other hand, Figure 7d displays a bimolecular assembly with a sliding head-to-head (tail-to-tail) association mode, given its right-handed  $2_1$  helical assembly of **1** (Figure 7f). These results indicate that the tilt and handedness of the steroidal assemblies strongly depend upon substituted positions of the hydroxyl groups in the steroidal skeleton. Another example is given by cinchonine (**15**), cinchonidine (**16**), and deaza-cinchonidine (**17**), whose fixed conformations are known to have facial structures with three-axial chirality.<sup>22,23</sup>

**Complementary Assemblies between the Host and Guest.** The  $2_1$  helical assemblies can also be formed from achiral molecules. Indeed, **1** makes inclusion crystals with the  $2_1$  helical assembly of benzene, which is determined to be right-handed on the basis of supramolecular tilt chirality (Figure 7i).<sup>24</sup> Moreover, we confirm that 38 kinds of benzene derivatives exhibit the right-handed  $2_1$  helical assemblies in the inclusion crystals of **1**. In these host–guest



**FIGURE 7.** Representative bimolecular assembly modes of steroidal molecules: a parallel mode (a), left-tilt mode (b), sliding head-to-tail mode (c), and sliding head-to-head (tail-to-tail) mode (d). The  $2_1$  Helical assemblies from the sliding head-to-tail mode (e) and the ones from the sliding head-to-head (tail-to-tail) mode (f). Schematic representation of helical tapes of **3** (g) and **2** (h). Illustration of the inclusion crystal of **1** with benzene by using helical ribbons (i). The complementary relationship between helical assemblies of **1** and benzene can be compared to the combination of a right-handed bolt and nut (j).

systems, the host **1** constructs right-handed  $2_1$  Helical assemblies to leave right-handed helical cavities in which the guest molecules are accommodated in the form of right-handed helical assemblies. Such a complementary relationship is compared to a right-handed bolt and nut (Figure 7j) and can be observed for many crystalline host–guest inclusion systems. This relationship was termed as lock-and-key by Emil Fischer in 1894.<sup>25</sup> However, the important point here is the direction of rotation of the key, right or left.

**Bundle of the Assemblies.** Next, we discuss how to bundle the  $2_1$  helical assemblies with three-axial chirality. Figure 8 shows three typical kinds of bundles of these

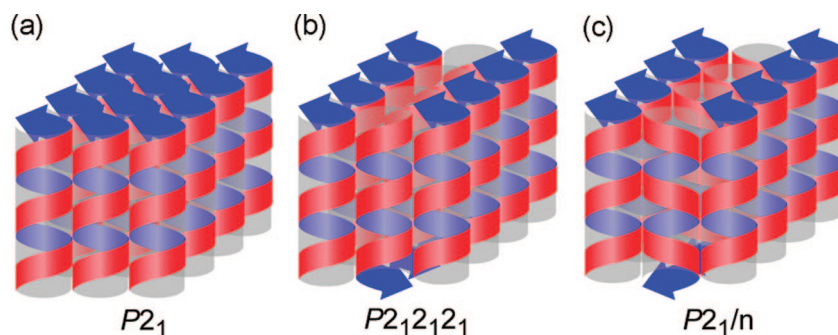
helices. Figure 8a exhibits a bundle of right-handed helices with uniformed direction, leading to chiral crystals with space group  $P2_1$ . The crystals are frequently observed for **1** and **14**. Figure 8b displays a bundle of right-handed helices with the reverse up–down directions, which corresponds to the crystal structure with space group  $P2_12_12_1$ . Most of the crystals of **2** belong to this space group. In addition, Figure 8c depicts a bundle of both the right- and left-handed helices with the reverse up–down directions, which corresponds to the crystal structure with space group  $P2_1/n$ . These space groups containing two-fold screw axes frequently appear in organic crystals, and more than 52 000 organic crystals are registered in the Cambridge Structural Database.<sup>26</sup> In this way, determination of handedness of the  $2_1$  helical assemblies might indicate a new way to understand how to create chiral crystals with chiral space groups. It may be expected that such chirality can be detected with the help of a linear-polarized laser.

## Supramolecular Properties and Functions of Organic Salts

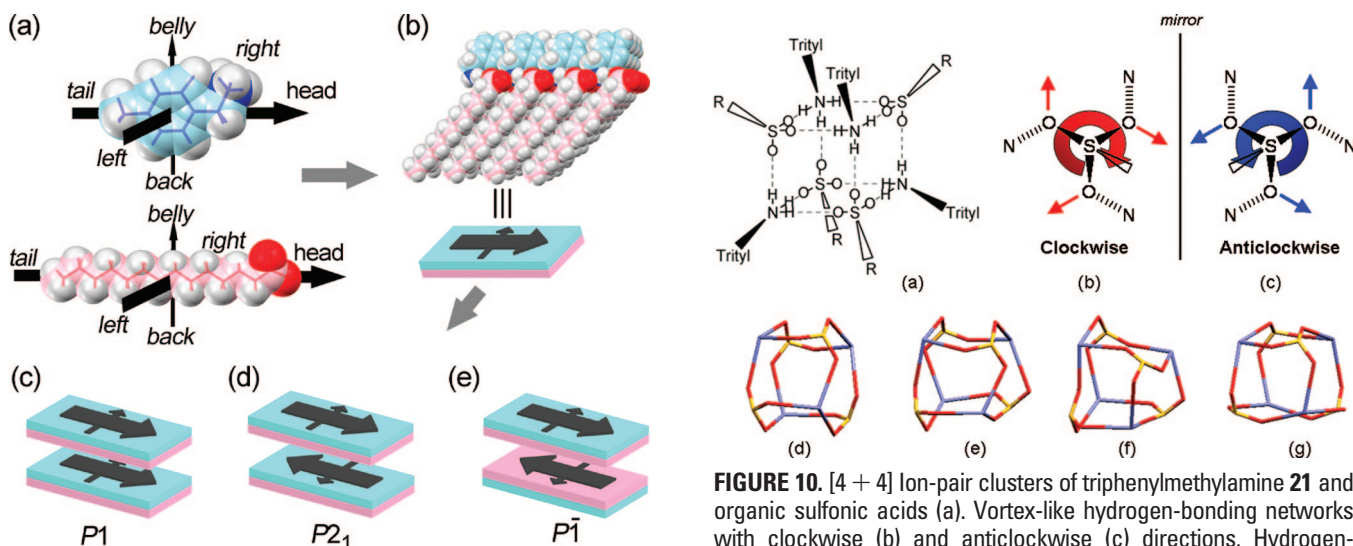
Because of the results described above, our research in crystal engineering has been extended to supramolecular assemblies of organic salts, such as carboxylate, sulfonate, and phosphonate ammonium. From the viewpoint of supramolecular design, organic salts are quite interesting materials, because they are constructed by charge-assisted hydrogen bonds with different directionality and length. Therefore, it may be expected that crystalline assemblies of organic salts would exhibit the hierarchical structures with supramolecular three-axial and tilt chiralities, even if their components are achiral in appearance.

### Creation of Chiral Crystals from Achiral Molecules.

In the course of our study on layered crystals of organic salts,<sup>27</sup> we encountered the fact that chiral crystals can be made from organic salts of achiral amines and carboxylic acids. To reveal the mechanism of chirality creation, we applied the above-mentioned concepts: hierarchical interpretation and three-axial chirality.<sup>28</sup> Figure 9 shows the interpretation in the case of chiral crystals of 4-methylbenzylammonium salts with myristic acid (**18**) and pentadecanoic acid (**19**). First, their possible conformations are fixed to generate their conformers with three-axial chirality (Figure 9a). The chiral conformers arrange in an asymmetric two-dimensional fashion through hydrogen bonds to yield chiral layered assemblies with three-axial chirality (Figure 9b). The chiral layers stack in a parallel or antiparallel fashion to give the corresponding chiral crystals with space group  $P1$  for **18** (Figure 9c) or  $P2_1$  for **19** (Figure 9d), respectively. Another stacking produces an achiral crystal with space group  $P\bar{1}$  (Figure 9e). On the other hand, in the case of 1-naphthylmethylammonium salt with isobutyric acid (**20**), their chiral conformers alternatively arrange in an asymmetric one-dimensional fashion through hydrogen bonds to yield chiral  $2_1$  helical assemblies with three-axial and tilt chiralities. The directional helices are tied up in a bundle in an antiparallel fashion to yield chiral crystals with space group  $P2_12_12_1$ .



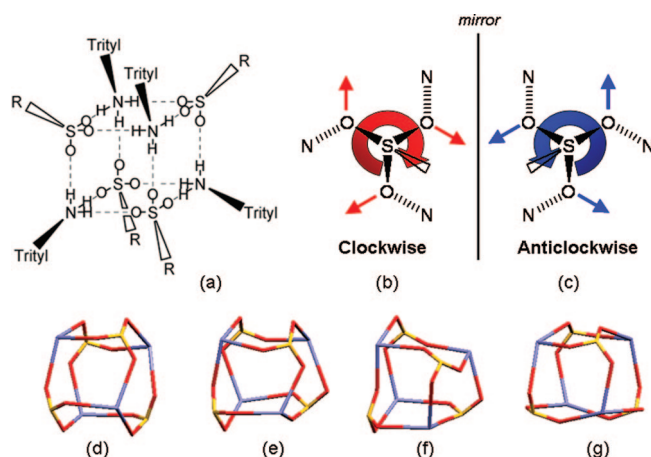
**FIGURE 8.** Three kinds of bundles composed of the  $2_1$  helical assemblies. Bundles composed of right-handed helices with uniform directions (a), right-handed helices with the reverse up–down directions (b), and both the right- and left-handed helices with the reverse up–down directions (c).



**FIGURE 9.** Hierarchical interpretation of chiral crystals from achiral molecules. Chiral conformers (a), chiral layers composed of the chiral conformers (b), chiral  $P1$  crystal composed of the chiral layers stacked in a parallel fashion (c), chiral  $P2_1$  crystal in an antiparallel fashion (d), and achiral  $P\bar{1}$  crystal in the reversed stacking (e).

Considering chiral crystals from achiral molecules, it should be emphasized that an orthorhombic coordinate system consists of right- or left-handed three axes, relating to right- or left-handed crystals.

**Creation of Hydrogen-Bonding Clusters.** In a combinatorial approach for screening new host compounds, we learned how to control dimensionalities of hydrogen-bonding networks based on bulky substituents of organic salts.<sup>29–31</sup> Such control would be expected to bring about novel materials, such as artificial clusters, clays, zeolites, and so on. Thus, bulky triphenylmethyl groups cause a core-shell structure with a cubic hydrogen-bonding network.<sup>32–34</sup> Figure 10a shows a  $[4 + 4]$  ion-pair cluster of organic salts composed of four triphenylmethylenamines (**21**) and four organic sulfonic acids (**22–25**) in the crystalline state. Such clusters from various carboxylates are obtained only in a limited range of combinations, whereas the ones from sulfonates are obtained in a wide range. The retention of the sulfonate clusters in solution was confirmed by  $^1\text{H}$  nuclear magnetic resonance (NMR) and mass spectroscopy. It is interesting that the cubic clusters exhibit supramolecular chirality, such as dice in

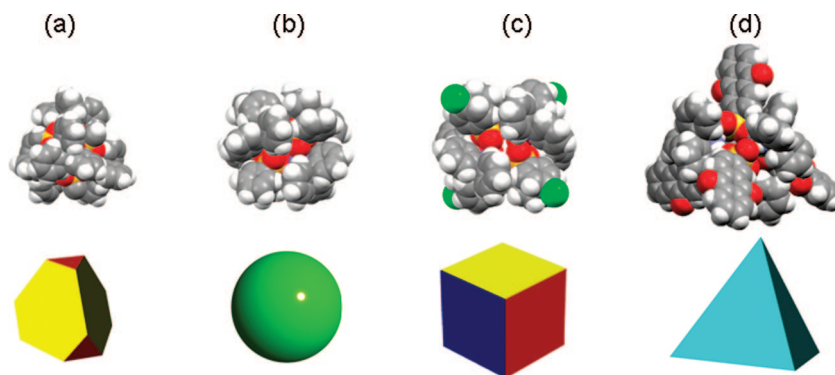


**FIGURE 10.**  $[4 + 4]$  Ion-pair clusters of triphenylmethylenamine **21** and organic sulfonic acids (a). Vortex-like hydrogen-bonding networks with clockwise (b) and anticlockwise (c) directions. Hydrogen-bonding networks of the clusters with **23** (4:0) (d), **25** (4:0) (e), **22** (3:1) (f), and camphorsulfonic acid (2:2) (g). The ratios of clockwise to anticlockwise directions are indicated in parentheses.

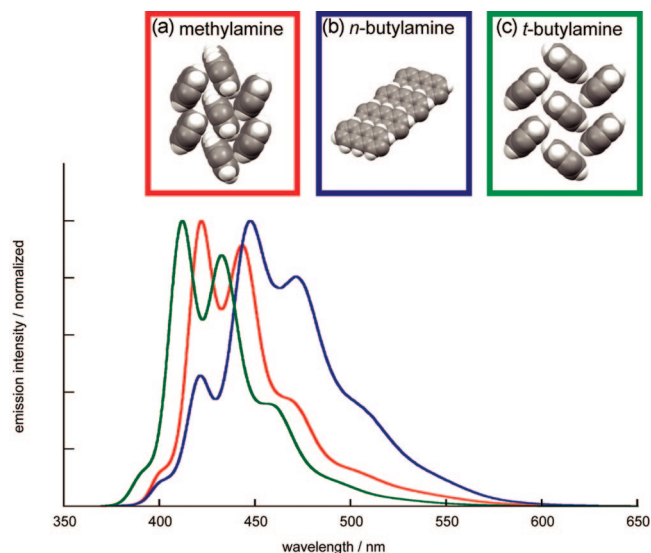
daily life. Thus, the clusters have the two vortex-like patterns of the hydrogen-bonding network: clockwise (Figure 10b) or anticlockwise (Figure 10c). Parts d–g of Figure 10 show four kinds of hydrogen-bonding networks of the clusters with the pattern ratios of 4:0, 4:0, 3:1, and 2:2, respectively.

Comprehensive construction of such gigantic monodisperse clusters would open a fascinating research field in nanotechnology as well as material science, because proteins are basically regarded as gigantic clusters with high-order folded structures. For example, we can prepare diverse clusters with inherent shapes and sizes based on various substituents of the sulfonic acids. Parts a–d of Figure 11 schematically illustrate four kinds of hydrogen-bonding clusters composed of the salts of **21** with **22**, **23**, **24**, and **25** in the forms of the corresponding truncated tetrahedron, spherical, cubic, and tetrahedron, respectively. We suggest that this robust cubic hydrogen-bonding network functions as a promising supramolecular synthon, which may lead to the construction of higher order architectures, such as artificial zeolites.

**Control of Solid-State Fluorescence.** Solid-state emission properties may change because of the dimensionalities of molecular assemblies. We have recently adopted



**FIGURE 11.** Characteristic shapes of the ion-pair clusters composed of organic salts of **21** with **22** (a), **23** (b), **24** (c), and **25** (d).



**FIGURE 12.** Solid-state fluorescence emission spectra of crystalline salts **26** with methylamine (a), *n*-butylamine (b), and *tert*-butylamine (c). The excitation wavelength is 340 nm in all samples.

organic salts of anthracene-2,6-disulfonic acid (**26**) with various primary amines as a tunable solid-state fluorescence system.<sup>35,36</sup> Although **26** shows the same fluorescence properties in solution, it does both the spectral shifts and intensity changes of the fluorescence in the solid state. Figure 12 partly shows the arrangements of anthracene moieties and fluorescence spectra of **26** with methylamine (Figure 12a), *n*-butylamine (Figure 12b), and *tert*-butylamine (Figure 12c), respectively. It is considered that substituents of the amines alter arrangements of anthracene moieties and the corresponding solid-state fluorescence properties. Anthracene itself has only one molecular-packing manner, whereas **26** has many kinds of the packing manners because of different hydrogen-bonding networks.

In this way, such organic salts would serve as an efficient system for the development of solid physics and material science because of the following practical advantages: (1) simple preparation without the requirements of skill or technique in organic syntheses, (2) possible systematic investigation based on a wide variety of combinations between the acids and bases, and (3) a wide variety of crystal structures with robust hydrogen-bonding networks. Current research toward excellent materials

requires a speedy resolution of the relationship between the molecular arrangements and the corresponding solid-state properties. Accordingly, crystal engineering of organic salts is promising for exploring sophisticated functions beyond the molecules themselves.

## Conclusion and Outlook

We have demonstrated that steroidal bile acids and their derivatives give us crystalline molecular assemblies with overwhelmingly diverse structures, leading to the novel concept of diversity, hierarchy, and supramolecular chirality. Such a concept is now spreading from natural compounds to the surrounding organic substances and prompts us to create chiral crystals with chemical and physical properties suitable for electronics, optics, photonics, informatics, and the like. Hopefully, this will contribute to the development of crystal engineering, the prediction of crystal structures, the fabrication of new materials, and so on. At the beginning, the diverse structures seemed to contradict the hierarchical ones, but analogy with proteins directed us to the solution. As a result, we reached the unique concept that chiral carbon chains of steroidal molecules are similar to sequential peptide chains. The steroidal molecules derived from hexamers of isoprene correspond to one of the beautifully designed sequential isomers, because such isomers exceed more than one billion. This reminds us of a style of Japanese poetry with 31 syllables, called Tanka or Waka. These poems may be brief but allow for infinite expression, much as the steroidal molecules do.

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