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Hierarchical Prediction Process of Cholic Acid Crystal Structures Based on Characteristic Helical Assemblies

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We describe here a hierarchical prediction process for crystal structures of inclusion compounds of cholic acid through a right-handed 2_1 helical assembly. This helical assembly is predictable from the distribution of three hydroxyl groups on the steroidal skeleton and can be regarded as the inherent structural unit of cholic acid. Subsequently, the carboxyl group of the side chain links neighboring 2_1 helical assemblies by means of the various hydrogen-bonding arrangements to form the corresponding structural motifs. These motifs can be built up more diversely using various guest molecules.

Keywords: cholic acid; helical assembly; hierarchical structure; hydrogen bonds; steroidal inclusion crystals

INTRODUCTION

Prediction of the crystal structures of simple aromatic hydrocarbons is currently possible based on the knowledge obtained from systematic structural studies [1]. Recently, more complicated and flexible molecules have occupied the interest of crystallographers, and some crystal structures have been designed through use of the dominant hydrogen bonds [2]. However, the involvement of the molecular skeletons in the prediction processes of crystal structures remains a challenging issue, especially in the molecules which have asymmetric molecular skeletons [3].

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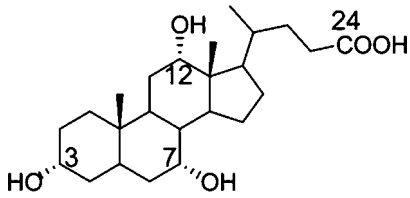
Cholic acid is known to form inclusion crystals with various guest compounds these days [4]. At first, a crossing type host framework was found containing ethanol within the small host cavity [5]. Then, next, one example of the bilayer host framework was found with acetophenone enclosed within the channel-like cavity [6]. Although these two frameworks appeared to be very different, they were sufficiently closely related to exhibit intercalation [7]. Further attempts to form inclusion crystals with various guest compounds have revealed a variety of host frameworks [8]. More than thirteen kinds of host frameworks, differing in volume, shape, polarity and chirality of guests have been found so far [9].



cholic acid

Diversity of the host framework results from the asymmetry of the steroidal skeleton and certainly complicates the structural relationship among them. These systematic structural analyses have enabled us to perform an appropriate logical explanation of these diverse host frameworks based on the amphiphilicity of steroidal molecules [10]. The structural relationships among the various bilayer structures have been revealed clearly by classifying these structures as a molecular sheet [11]. However, this sheet-like motif is not applicable to non-bilayer structures, suggesting that more general methods are needed to clarify the structural relationships.

We propose here a hierarchical structure based on a 2_1 helical assembly retained by the characteristic hydrogen-bonding network of the three hydroxyl groups of the steroidal skeleton, so that we can logically perform a well-ordered explanation and prediction of the crystal structure from the steroidal molecular structure. This hierarchical method reveals that the diversity of the host framework mainly results from the diverse arrangements of the inherent helices.

EXPERIMENTS

Cholic acid was purchased from Wako Co., and used without further purification. All other chemicals and solvents were of the commercially

available purest grades. The host compound was recrystallized from neat organic guests or their solutions. The resulting inclusion crystals were filtered and left on a filter paper for some time to remove the adhering solvents and guests. The crystals were characterized by means of IR, ^{1}H- and ^{13}C-NMR spectroscopy, thermogravimetric analysis, and X-ray powder diffraction methods. X-ray single crystal diffraction data were collected on a Rigaku RAPID diffractometer with 2D area detector with graphite-monochromatized Cu-Kα radiation. Direct methods were used for the structure solution and the structure was refined by the full matrix least-squares procedure using the program TEXSAN. Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were placed in idealized positions.

RESULTS AND DISCUSSION

The important feature of cholic acid is not only its facial amphiphilicity but also the asymmetry of the steroidal skeleton. As shown in Figure 1, the directionality of the molecule can be defined with the basic direction from tail to head, which is through O(3), C(18) and C(19). After Kitaigorodskii's studies, molecules without symmetry elements have been known to form 2_1 helical assemblies predominantly, so that close packing is attainable in the space groups $P2_1/c$, $P2_1$ or $P2_12_12_1$ [12]. Therefore, it can be assumed that cholic acid similarly forms an inherent 2_1 screw. Moreover, the facial amphiphilicity of the molecular skeleton indicates that belly-to-belly packing may be the most suitable for formation of hydrogen bonds among the three

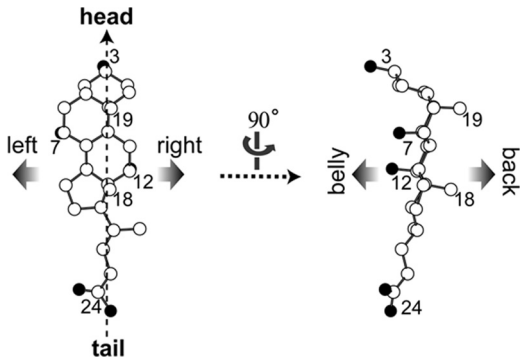


FIGURE 1 Definition of the directionality of cholic acid. Based on the asymmetry and amphiphilicity, six directions can be classified clearly. The tail-to-head direction is defined as the line passing through C(18), C(19) and O(3).

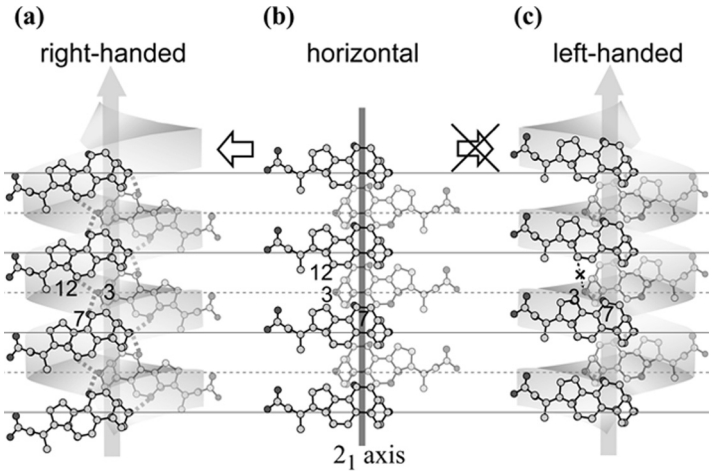


FIGURE 2 Simple simulation of (a) right-handed, (b) horizontal and (c) left-handed 2_1 helical assembly of cholic acid. The hydrogen bonds between O(3) and O(12) cannot be formed in the left handed helix.

hydroxyl groups of the steroidal skeleton. As a result, cholic acid molecules would be aligned with the tail-to-head direction vertical to the 2_1 axis as depicted in Figure 2b.

Although right-handed and left-handed 2_1 helices cannot be distinguished crystallographically, the definition of the molecular directionality makes this possible. Tilt of the molecular direction toward the horizontal state (Fig. 2b) reveals the difference between right-handed and left-handed 2_1 helices as illustrated in Figure 2a and 2c, respectively. These two helices are retained by different hydrogen-bonding networks among the three hydroxyl groups of the steroidal skeleton as shown. The right-handed helix may form a hydrogen-bonding network with the sequence O(12)···O(3)···O(7). The tilt of the right-handed helix results in the homogeneous distribution of the three hydroxyl groups along the 2_1 axis. On the other hand, the distance between O(7) and O(3) becomes shorter and the distance between O(12) and O(3) becomes longer in the left-handed helix. It can be estimated from simple simulation that the right-handed 2_1 helix is preferable to the left-handed one in the crystal of cholic acid. In this way, let us suppose this right-handed 2_1 helical assembly is the inherent unit of the host frameworks of cholic acid.

This right-handed 2_1 helical assembly, retained by the three hydroxyl groups of the steroidal skeleton, is expected to be connected to the neighboring helices by the hydrogen bonds of the carboxyl group

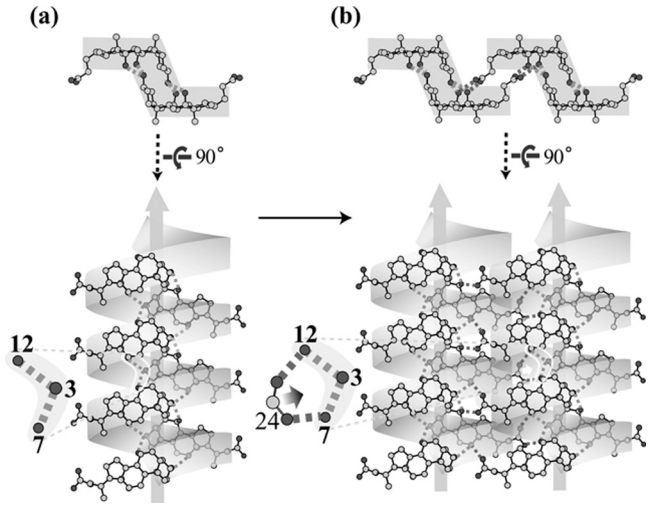


FIGURE 3 (a) Right-handed 2_1 helical assembly retained by the hydroxyl groups at the steroidal skeleton and (b) one of the possible manners of linking between the right-handed 2_1 helices by the carboxyl group at the side chain.

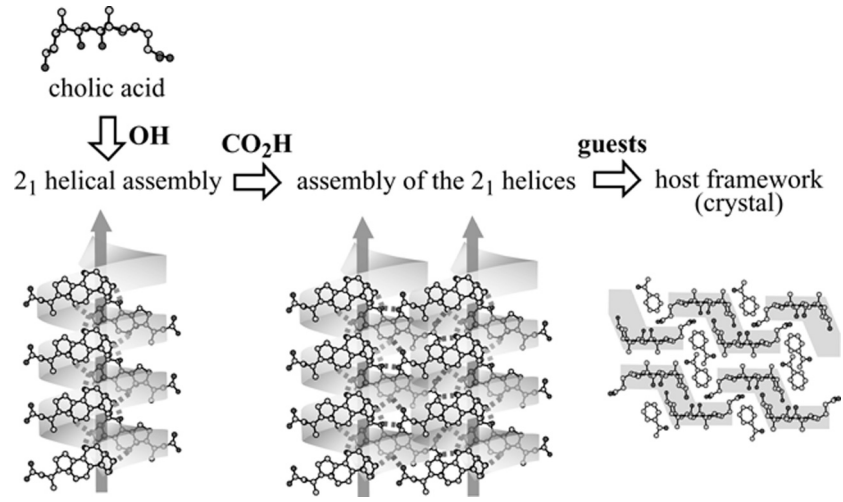


FIGURE 4 Hierarchical structures of inclusion crystals of cholic acid. This classification method is based on the inherent 2_1 helical assembly retained by hydrogen bonds of the three hydroxyl groups at C3, C7 and C12 positions.

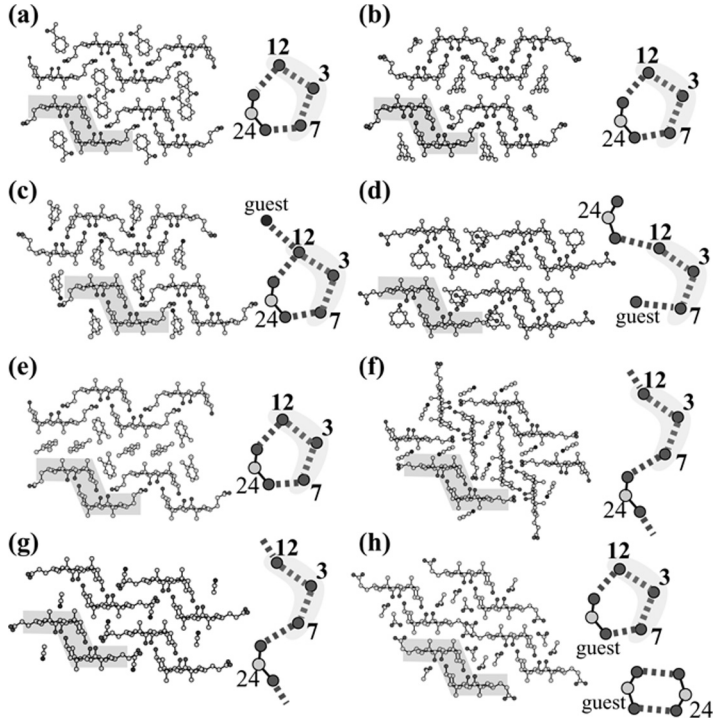


FIGURE 5 Molecular packing diagrams and hydrogen-bonding networks of eight representative host frameworks composed of the characteristic 2_1 helical assembly of cholic acid with guests: (a) acetophenone, (b) 1,3,5-trimethylbenzene + acetone, (c) 3-chloroaniline, (d) 3-chloroaniline, (e) 2-chlorotoluene, (f) acrylonitrile, (g) acetonitrile and (h) acetic acid. The shadowed parts of the packing diagrams and the hydrogen correspond to the 2_1 helical assembly.

of the side chain. Figure 3 shows one of the possible arrangements of two neighboring helices through parallel translation. The aliphatic side chain is long and thin enough to approach into the bulky axis of the neighboring helices. Therefore, the carboxyl groups can link between O(7) and O(12) to form the closed cyclic hydrogen-bonding network. As a result, this arrangement through parallel translation would result in a sheet-like motif. Actually, this sheet-like motif is observed in various inclusion crystals of cholic acid [10,11]. The bilayer structure, which is known as one of the representative host frameworks of cholic acid, is composed of the sheet-like motifs with guest compounds enclosed between the sheets in the space group $P2_1$ [6].

We have discussed the hierarchy of the bilayer structure of cholic acid so far. Figure 4 summarizes the hierarchical structure of cholic

acid. At first, cholic acid molecules assemble to form the inherent 2_1 helical assembly by using the hydroxyl groups of the steroidal skeleton. Subsequently, the carboxyl group of the side chain links to the neighboring helices to form a sheet-like motif. Finally, the motifs are built up with guest compounds to form a three-dimensional host framework. Characteristically, each structural motif is classified on the basis of the different interactions; hydrogen bonds of hydroxyl groups, hydrogen bonds of the carboxyl group, and van der Waals interactions.

It might seem unusual to treat the hydroxyl groups of the steroidal skeleton preferentially. However, the validity of this classification method is supported by other host frameworks of cholic acid. Figure 5 shows representative eight host frameworks and their corresponding hydrogen-bonding networks. Although each framework and the hydrogen-bonding network appear to be very different from the others, all the structures form common hydrogen bonds among the three hydroxyl groups of the steroidal skeleton; OH(12)···OH(3) ···OH(7) as shown in shadow. As depicted in Figure 2, this partial hydrogen-bonding network constructs the right-handed 2_1 helical assembly. In short, all these host frameworks are composed of a common 2_1 helical assembly. Alternatively, the diversity of the host frameworks results from the diverse assembly modes of the 2_1 helices with the flexible hydrogen bonds of the carboxyl group.

CONCLUSION

We have demonstrated herein a hierarchical approach to predicting and clarifying the diverse host frameworks of cholic acid from the molecular structure. The right-handed 2_1 helical assembly of cholic acid was predictable from the structure of its steroidal skeleton and was proposed as the inherent structural unit of most of the host frameworks of cholic acid. Originally, this hierarchical prediction process was applied to cholic acid by dissociating the hydroxyl groups of the steroidal skeleton from the carboxyl group of the side chain. Although such a method appears to be unusual and not logical, it does contribute to clarifying the diverse molecular assemblies of other complicated molecules that have multiple hydrogen-bonding groups.

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