Supramolecular Chirality and Isomerism in Cinchonidine Crystals: Hierarchical Analysis on the Basis of the Asymmetric 2_1 Helical Columnar Assembly

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We obtained the first cinchonidine inclusion crystal with benzene as a neutral guest. Comparison of the inclusion and guest-free crystal structures by the qualitative hierarchical analysis clarified their supramolecular isomerism of asymmetric 2_1 helical columnar assembly with supramolecular chirality.

Supramolecular isomerism is of great interest in connection with the diverse molecular arrangements due to the combinations of host and guest components.[1] Because of appearance of unexpected supramolecular isomers, it is impossible at this moment to predict organic crystal structures from the molecular structures.[2] To clarify the supramolecular isomerism, we have so far prepared over three hundreds of inclusion crystals of steroidal bile acids and brucine,[3,4] and elucidated their supramolecular isomeric crystal structures from their asymmetric molecular structures. On the basis of a series of the studies, we have proposed that the supramolecular isomerism in crystals of asymmetric molecules can be interpreted by the qualitative hierarchical analysis through supramolecular chirality.[4] The analysis is performed in the following three phases; (i) fixing a conformation of an asymmetric molecule, (ii) forming a bimolecular aggregation, and piling up the bimolecular aggregation to form a columnar assembly with supramolecular chirality, (iii) stacking the columns into a bundle.

Cinchonidine has been known to form inclusion crystals with acidic guest molecules.[5] Recently, we obtained the first cinchonidine inclusion crystal with benzene as a neutral guest molecule. The resulting benzene-included crystal was found to have a different space group from the known guest-free crystal,[6] enabling us to consider supramolecular chirality and isomerism due to the asymmetric host molecule. In this paper, we describe the crystal structures of cinchonidine with and without benzene, **1** and **2**, respectively, and interpret the formation of the supramolecular isomers of cinchonidine assemblies on the basis of the hierarchical analysis through supramolecular chirality.

Crystal **1** was obtained by crystallization from benzene solution of cinchonidine. X-ray diffraction analysis revealed that crystal **1** belongs to a space group of $P2_1$, and that the intermolecular hydrogen bonds give rise to chains of molecules along screw axes parallel to b.[7] The intermolecular hydrogen bond is formed between O(1)–H and N(1^i), where $i = -1 - x$, $1/2 + y, -1 - z$. The bond length is 2.743 Å.

The crystal structure of **1** is shown in Figure 1 together with that of **2**.[6,7] It can be seen that the former has the same bimolecular-based columnar structure as the latter (along b for **1** and along c for **2**), but different arrangements of the columns from the latter, indicating that they are the supramolecular isomers. We interpreted a formation process of the isomers by the following hierarchical analysis.

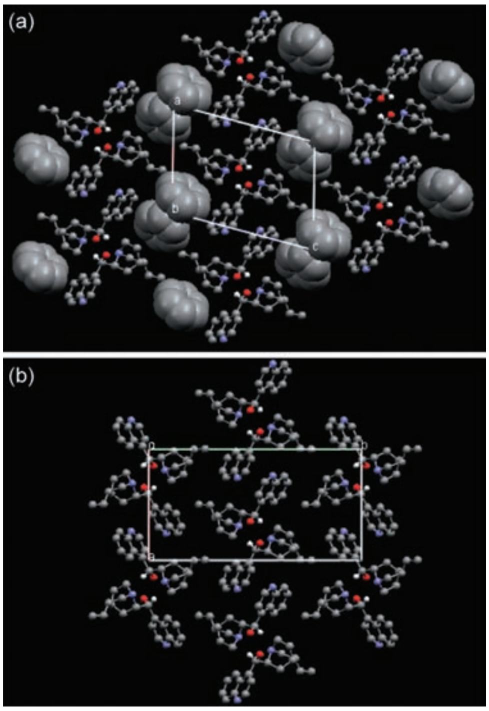

Figure 1. Crystal structures of **1** and **2**. (a) A view up b in **1**. Benzene molecules are shown by van der Waals representations. (b) A view down c in **2**. Hydrogen atoms were omitted except those bonding to oxygen and C(8) atoms for clarity. Atoms are colored by gray (C), white (selected H), red (O), and blue (N).

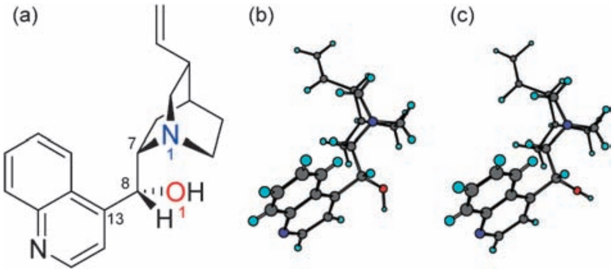

Figure 2. Chiral molecular structure of cinchonidine (a) and its conformations (b) and (c) observed in crystals **1** and **2**, respectively.

In the first phase, we compared the molecular conformations of cinchonidine in crystals **1** and **2**. As shown in Figure 2, they have similar conformations to one another, which are classified in the anti-open form.[8] This conformational geometry is predicted to be the most stable in apolar solvents such as benzene on the

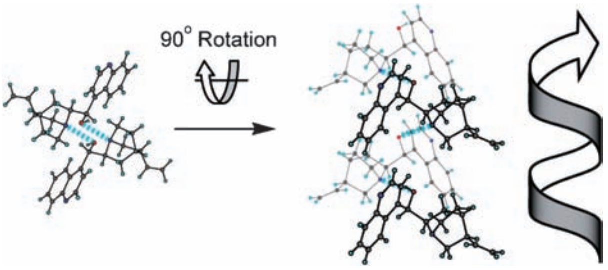

Figure 3. Supramolecular chirality of asymmetric helical columnar assembly of cinchonidine. Dashed lines mean intermolecular hydrogen bonds.

basis of the theoretical study by using ab initio or density functional reaction field calculations.[9] The conformer distribution with the computed conformational energy difference often corresponds to molecular conformations in the crystal structures statistically.[10] Therefore, observation of the anti-open form in the crystal state is also reasonable.

Next, in the second phase, we focus on bimolecular aggregation and asymmetric 2_1 helical columnar assembly. In Figure 3, partial crystal structure of **1** is shown, where cinchonidine molecules are connected through intermolecular hydrogen bonds to form the bimolecular aggregation followed by the asymmetric helical columnar assembly with 2_1 screw axis. Guest-free crystal **2** also has almost the same 2_1 helical column. The columns constitute left-handed screws, and are displayed with arrows, as exemplified in Figure 3.[4d] It is reasonable for cinchonidine molecule to assemble into the 2_1 helical column according to the Kitaigorodskii's report that molecules without symmetry elements form 2_1 helical assemblies predominantly.[11]

The final phase consists of stacking of the asymmetric helical columns to form bundles, which correspond to the whole crystal structures. As shown in Figure 4, the arrangements of the columns are different between crystals **1** and **2**; the columns are combined in parallel (for **1**) or anti-parallel (for **2**) fashion. The parallel stacking leads to a bundle with monoclinic, $P2_1$ space group, while the anti-parallel one with orthogonal, $P2_12_12_1$. Only in the case of the parallel stacking, benzene molecules are included in the cavities probably due to the steric effect. Two benzene molecules make a pair through CH–π interaction. Thus, the crucial step for the formation of the supramolecular isomers in cinchonidine crystals is the stacking of the asymmetric 2_1 helical columns to form the different bundles.

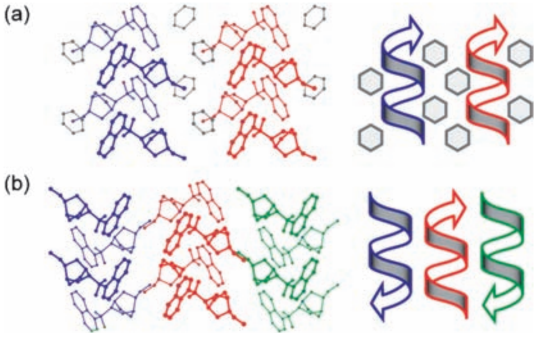

Figure 4. Supramolecular isomers of bundles of the helical columns. (a) A parallel fashion of the columns in crystal of **1**. (b) An anti-paralel fashion of the columns in crystal of **2**.

In summary, we obtained the first example of inclusion crystal of cinchonidine with a neutral guest molecule. The inclusion crystal was elucidated by the hierarchical analysis, leading to the fact that the molecules form the common 2_1 helical columnar assemblies, and that the columns stack in different ways to give the supramolecular isomers. In this way, the qualitative hierarchical analysis is useful to understand the supramolecular chirality and isomerism starting from chiral molecules.

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7 Crystallographic data for benzene-included crystal of cinchonidine **1**; $C_{19}H_{22}N_2O{\bullet}C_6H_6$, MW = 372.51, monoclinic, $P2_1$ (#4), $a = 10.471(3)$ Å, $b = 7.363(1)$ Å, $c = 14.136(3)$ Å, $\beta = 104.220(8)°$, $V = 1936(2)$ Å^3, $Z = 2$, $\rho_{\text{calcd}} = 1.171\ \text{g cm}^{-1}$, $2\theta_{\text{MAX}} = 136.5°$, 9347/2011 measure/independent reflections, $R = 9.3$, $Rw = 26.1$. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-607834. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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