

2₁ Helical Assemblies of Cinchona Alkaloids in Crystals: Definition of Their Handedness Based on the Molecular Tilt

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Cinchona alkaloids form 2₁ helical assemblies in their crystals. We firstly define the handedness of the assemblies on the basis of the molecular tilt. It is revealed that cinchonine and its pseudo-enantiomer, cinchonidine form 2₁ helical assemblies with right- and left-handedness, respectively.

Supramolecular chirality, which is defined as chirality derived from the asymmetric arrangement of chiral and achiral molecules,¹ is a remarkably important concept for studies on molecular assemblies and self-organized systems. We became interested in supramolecular chirality in crystals of cinchona alkaloids **1–4** (Chart 1) because cinchona alkaloids have been attractive substantial interests from the following point of views: 1) some of them have antimalarial activity and are sodium channel blockers used in the prevention and treatment of a wide variety of cardiac arrhythmias,² 2) they are used as enantiomer separators such as in chromatography³ and as powerful chiral auxiliaries and catalysts as well as chiral reagents in asymmetric and enantio selective reactions.⁴ Because of these aspects, a number of their derivatives have been prepared and conformational studies of them including original cinchona alkaloids have been investigated both theoretically and experimentally. However, supramolecular chirality of the assemblies of cinchona alkaloids in crystals has not been investigated.

Recently, we reported supramolecular chirality and isomerism of cinchonidine in its inclusion crystals with benzene. In the systems, arrangement of 2₁ helical assemblies composed of the molecules plays a crucial role on the hierarchical structural analysis, which we proposed to understand the appearance of the supramolecular chirality and isomerism.⁵ During the series of studies, we faced the requirement to define the supramolecular chirality of 2₁ helical assemblies for well understanding of the supramolecular systems hierarchically. In this paper, we describe the supramolecular chirality and determination of the handedness in the 2₁ helical assemblies of cinchona alkaloids.

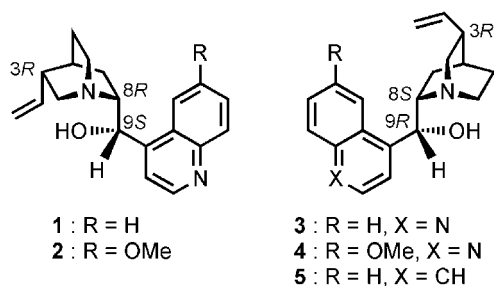


Chart 1.

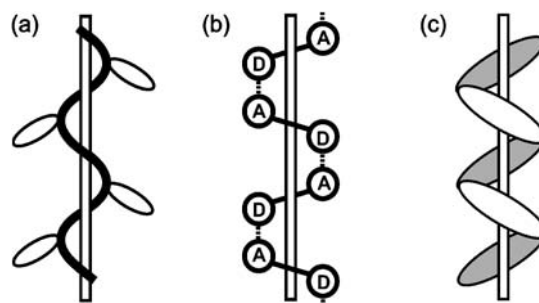


Figure 1. Schematic representation of helical structures with polymeric backbone (a), noncovalent-bonded linkage (b), and distinguishable molecular tilt (c).

In crystals of organic and organometallic compounds without symmetry elements, 2₁ helical structures are observed predominantly.⁶ 2₁ Helical symmetry is exhibited in crystals with space groups such as $P2_1/c$, $P2_12_12_1$, and $P2_1$, and according to Motherwell, more than 52,000 organic crystal structures belonging to these space groups are registered in Cambridge Structural Database.⁷ In connection with helical handedness of 2₁ symmetric structures, one can not determine it from the theoretical view point because the screw axis operation includes 180° rotation as well as translation, leading to impossibility to distinguish right- or left-handed rotation. However, if objects ordered in 2₁ symmetry are connected with a line like a polymer backbone, the handedness can be easily determined from its appearance (Figure 1a). Similarly, helical handedness of 2₁ symmetrical assemblies with networks composed of noncovalent bond such as hydrogen bond⁸ is often determined based on complement of the line with noncovalent bonds (Figure 1b). Thus, the sense of noncovalent bonded network is important for the supramolecular chirality. On the other hand, relative position of a molecule against another molecule in a 2₁ assembly should be crucial for its supramolecular chirality, because physical properties of the assemblies such as CD activity often depend on it. From this view point, we defined supramolecular chirality, i.e. helical handedness, in 2₁ helical assemblies of cinchona alkaloids on the basis of the molecular tilt (Figure 1c), which is well corresponding to the relative location, as described below.

Figures 2a and 2b show selective crystal structures (side and top views) of cinchonidine **3**^{9,10} and cinchonine **1**,^{9,11} respectively. The molecules form 2₁ helical columnar assemblies through intermolecular hydrogen bond between the hydroxy group and nitrogen atom in the quinuclidine ring. The structures of **3** and **1** belong to the space groups of $P2_1$ and $P2_12_12_1$, respectively. Two-fold screw axes are described by yellow poles. In Figure 2c, crystal structure of deaza-cinchonidine **5**, reported

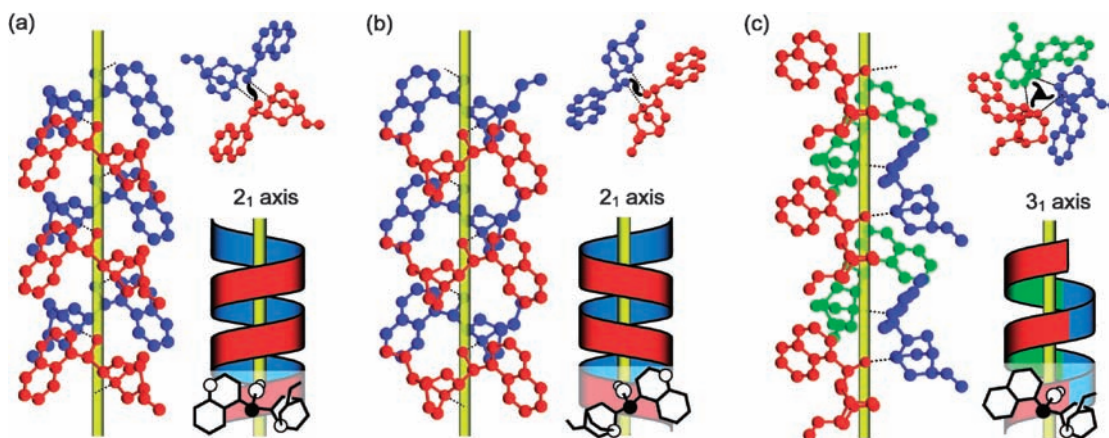


Figure 2. 2_1 Helical columnar assemblies of cinchonidine **3** (a) and cinchonine **1** (b) and 3_1 helical structure of deaza-cinchonidine **5** (c), where side and top views of respective crystal structures and cartoon representations of the helices are described. Hydrogen atoms are omitted for clarity. Yellow bars denote three- or two-folds screw axes. (a) and (c) exhibit right-handed helical sense while (b) exhibits left-handed sense.

by Dehmlow et al.,¹² are shown for comparison.⁹ Deaza-cinchonidine **5** has CH group in its aromatic ring instead of nitrogen atom and forms 3_1 helical assembly through intermolecular hydrogen bond. The 3_1 helical assembly obviously shows right-handed sense, where the molecules colored by red tilt into the right in the assembly (see the cartoon in Figure 2c). As in the case of **5**, molecules of **3** colored red incline into the right as shown in Figure 2a. Although the degree of the molecular tilt is less than that of **5**, the handedness of 2_1 helical assembly of **3** can be constitutively defined as right-handed sense. Notice that the helical handedness of **3** is not corresponding to that based on the hydrogen-bonded network, which exhibits left-handedness. However, in this context, we adopt the helical sense based on the relative position of the molecules, i.e. molecular tilt. Cinchonine **1**, which is a pseudo-enantiomer of **3**, forms 2_1 helical assembly in similar fashion with **3**. The resulting assembly also exhibits a pseudo-enantiomeric structure with that of **3**, and the helical handedness of the assembly of **1** exhibits left-handed sense (Figure 2b). Although the structure of the columnar assemblies of **3** and **1** are almost the same except their chirality, their packing mode is different; the former stacks with parallel manner, leading to $P2_1$ space group, while the latter with antiparallel, to $P2_12_12_1$, probably due to the diastereotopic position of the vinyl group attaching at C3 of quinuclidine ring.

Moreover, it is revealed that other cinchona alkaloid derivatives such as quinidine **2**,¹³ 10,11-dihydrocinchonidine,¹⁴ and 10,10-difluoro-11-hydroquinine,¹⁵ also formed the similar 2_1 helical assemblies in the crystals, the helicity of which can be determined by our method on the basis of the molecular tilt. To clarify supramolecular chirality of 2_1 helical assemblies in various systems other secondary alcohols, further investigations are proceeding in our laboratory.

In summary, we focused on the supramolecular chirality in the 2_1 helical assemblies of cinchona alkaloids in crystalline state and defined their handedness to be consistent with the 3_1 helical system on the basis of the molecular tilt.

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