Guest-participating Reversion of Molecular Arrangements in Asymmetric Multibilayers of Cholic Acid Inclusion Crystals

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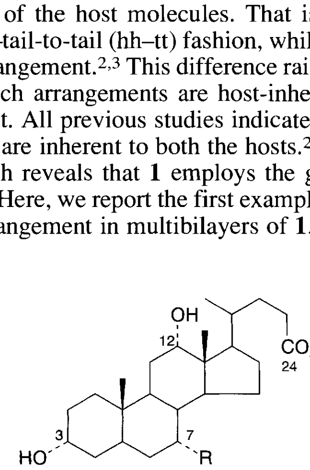
o-Xylene and 1,2,3-trimethylbenzene permit cholic acid to employ a reversed molecular arrangement in asymmetric multibilayers, in contrast to benzene, toluene and *m*- or *p*-xylene.

The correlation between molecular structures and arrangements in crystals has presented a fascinating field of research in recent years.[1] Cholic acid **1** and deoxycholic acid **2** serve as a pair of hosts suitable for such research, since they form characteristic inclusion crystals composed of asymmetric multibilayers owing to their molecular structures, characterized by their high asymmetry, facial amphiphilicity, and other factors.[2,9] The bilayers display a notable difference with respect to the arrangements of the host molecules. That is, **1** arranges in a head-to-head–tail-to-tail (hh–tt) fashion, while **2** adopts a head-to-tail (ht) arrangement.[2,3] This difference raises the question as to whether such arrangements are host-inherent or dependent upon the guest. All previous studies indicated that the adopted arrangements are inherent to both the hosts.[2–7] In contrast, our recent research reveals that **1** employs the guest-participating arrangement. Here, we report the first example of a reversion of molecular arrangement in multibilayers of **1**.



R
1 OH
2 H

We successfully produced inclusion crystals of **1** with aromatic hydrocarbons by using alcoholic solvents such as butan-2-ol.[5] This method enabled us to prepare crystals with mono-, di-, tri-, or tetra-methylsubstituted benzenes. The resulting crystals had guest-dependent molar ratios (host : guest = 2 : 1) as determined by thermogravimetry and ^{1}H NMR analysis. So for instance, while the compound with *o*-xylene had a 2 : 1 host–guest ratio, the compounds with benzene, toluene and *m*- or *p*-xylene showed a 1 : 1 ratio. Moreover, the former exhibited a sharp peak at 3580 cm^{-1} in its infrared spectrum, while the latter compounds did not.

The inclusion compounds could thus be divided into two groups. One group, the 1 : 1 inclusion compounds, were obtained with benzene, toluene, *m*- or *p*-xylene, 1,2,4- or 1,3,5-trimethylbenzene, as well as with 1,2,3,4- or 1,2,3,5-tetramethylbenzene. The other group, the 2 : 1 inclusion compounds, were obtained with *o*-xylene, 1,2,3-trimethylbenzene, 1,2,3-trichlorobenzene, 1,2-dichloro-3-methylbenzene, 1-chloro-2,6-dimethylbenzene, 1,3-dichloro-2-methylbenzene, 1,2-dibromo-3-methylbenzene, and 1-bromo-2,6-dimethylbenzene.

The X-ray powder pattern for the compound of **1** with *o*-xylene was similar to those of **2** with benzene and *o*-xylene. Previous crystallographic studies indicate that **2** arranges in the ht fashion, regardless of the guests.[6,7] Therefore, it is expected that **1** arranges in the ht fashion in 2 : 1 guests and this was verified by a single-crystal X-ray structural analysis of the *o*-xylene inclusion compound.

Recrystallization of **1** from a solution of butan-2-ol and *o*-xylene resulted in needle-like crystals of the corresponding 2 : 1 inclusion compound. The crystal† belongs to the same space group (monoclinic, $P2_1$) as those of compounds of **1** with benzene[5] and of **2** with *o*-xylene.[7] Furthermore, the cell dimensions are very similar to those of the **2**–*o*-xylene species.[7] Figs. 1(*a*) and (*b*) schematically show asymmetric multibilayers of the compounds of **1** with *o*-xylene and benzene, respectively. It can be seen that while **1** arranges in the ht fashion on the hydrophilic site in the case of *o*-xylene [Fig. 1(*a*)], (as for the **2**–*o*-xylene species), it arranges in the hh–tt fashion in the case of benzene [Fig. 1(*b*)].

The differing arrangements can be attributed to different intermolecular combinations among four discrete hydrogen-bonding groups. As shown shematically in Fig. 2, the ht and hh–tt arrangements correspond to helical or cyclic hydrogen-bonding networks, respectively. For the compound of **1** with *o*-xylene the network has a sequence of OH[C(3)]···O=C–OH[C(24)]···OH[C(12)]···OH[C(3)], where the hydrogen-bonding distances are 2.72, 2.68 and 2.68 Å, respectively [Fig. 2(*a*)],‡ and the network is very similar to that found for the compound of **2** with *o*-xylene [Fig. 2(*b*)].[7] The additional hydroxy group at the C-7 position is weakly connected to the helical network, as indicated by a relatively long distance, 3.23 Å, for OH[C(7)]···O=C–OH[C(24)]. By contrast, **1** adopts a cyclic hydrogen-bonding network in its inclusion compound with benzene [Fig. 2(*c*)].[5] In contrast to **1**, **2** cannot form a cyclic network because of the lack of a hydroxy group at the C-7 position. These results indicate that the arrangements of **1** are guest-participating, while those of **2** are host-inherent.

A computer software package for molecular graphs, MOD-RASTE,[8] enabled us to analyse the shape and size of channels formed between the lipophilic bilayers. For the hh–tt arrangement, the channel can be described as a wavy pillar with

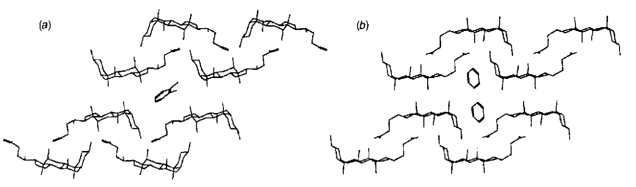


Fig. 1 Schematic representation of the crystal structures of the inclusion compounds of **1** with *o*-xylene (*a*) and benzene (*b*) viewed down the crystallographic *a* and *b* axes, respectively

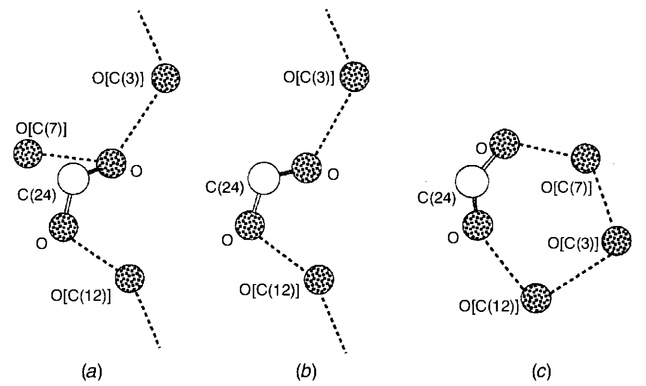


Fig. 2 Schematic representation of the hydrogen-bonding networks of the inclusion compounds of **1** with *o*-xylene (*a*), **2** with *o*-xylene (*b*) and **1** with benzene (*c*)

pentagonal cross sections. The side pockets can conveniently include methyl groups or part of a benzene ring, but are insufficiently large to accommodate trisubstituted benzenes. On the other hand, for the ht arrangement, the channel can be described as a straight pillar with a rectangular cross section of approximate dimensions 7.9 × 3.6 Å, enabling the inclusion of 'quadrilateral' trisubstituted benzenes.

In conclusion, this study demonstrates that the molecular arrangements in multibilayered crystals can be reversed by the introduction of certain kinds of guests. The host **1** can form various polymorphic crystals owing to the additional hydrogen bonding group, which is absent in **2**.

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Footnotes

† *Crystal data* for 2 × $\mathbf{1}\cdot C_6H_4Me_2$-1,2: $2C_{24}H_{40}O_5 + C_8H_{10}$, M = 923.32, monoclinic, space group $P2_1$, a = 7.515(10), b = 25.612(6), c = 13.827(9) Å, β = 90.99(8)°, V = 2661(2) Å^3, Z = 2, D_c = 1.152 g cm^{-3}, D_m = 1.15 g cm^{-3}. Intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated Mo-Kα radiation. 5816 Reflections were unique, and 3796 observed reflections with $|F_0| > 3\sigma(|F_0|)$ were used for further calculations after Lorenz and polarization corrections. The structure was solved by direct methods (MITHRIL-84) and refined against the F_0 data by full-matrix least-squares methods. All non-hydrogen atoms of the host molecules were refined anisotropically. The *o*-xylene molecule was refined isotropically with geometrical constraints. Hydrogen atoms attached to C on the host molecules were placed in calculated positions while O-H positions were obtained from difference Fourier syntheses. A total of 768 parameters were refined to final residuals R = 0.082 and R_w = 0.086. Electron densities of the guest *o*-xylene were carefully checked to seek possible disorder, but significant residual electron densities implying disorder were not detected. All calculations were performed using the TEXSAN crystallographic software package of the Molecular Structure Corporation.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ These values are for one of the two crystallographically independent molecules of **1**. The other molecule provides slightly different distances of 2.73, 2.68 and 2.71 Å for the helical hydrogen bonding and 3.31 Å for the pendant hydrogen bond.

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