Novel channel-type inclusion compounds of 3-epiursodeoxycholic acid

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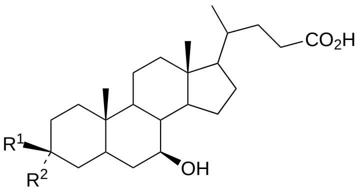
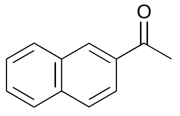
A new host, 3-epiursodeoxycholic acid, forms inclusion crystals with naphthalene derivatives with 1 : 1 stoichiometry.

Ursodeoxycholic acid (3α,7β-dihydroxy-5β-cholan-24-oic acid **1**), one of the bile acids, is well-known as a medicine,[1] originally isolated from the gall of bears.[2] Compound **1** and its 3β-isomer, 3-epiursodeoxycholic acid **2**, were believed to yield only guest-free crystals in the presence of organic substances,[3,4] although other bile acids, such as deoxycholic acid and cholic acid, tend to form inclusion crystals.[5] In contrast, our recent research has revealed that **2** includes a wide range of organic compounds. Here we report that **2** forms a layered assembly with large channels where naphthalene derivatives are included in a 1 : 1 host-to-guest ratio.



1 R^1 = H, R^2 = OH
2 R^1 = OH, R^2 = H



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Compound **2** was prepared from commercially available **1** as described in the literature.[6] The acid was recrystallized from neat organic liquids, or from alcoholic solvents dissolving the third solid components.[7] The resulting crystals were characterized by thermogravimetric analysis, and solid state IR and ^{1}H NMR spectroscopy. A wide variety of organic compounds, such as aromatic and aliphatic alcohols, ketones, ethers, esters and so on, were included by **2** as a host, whereas they were not included by **1**. Table 1 shows a number of the inclusion compounds. It is noteworthy that **2** includes both small ketones such as pentan-3-one and naphthalene derivatives such as 2′-acetonaphthone **3** in a 1 : 1 molar ratio of host to guest. We did not observe such an inclusion in the case of other bile acids and their derivatives. For example, deoxycholic acid formed inclusion compounds with **3** in a 3 : 1 molar ratio of host to guest.

Table 1 Inclusion ability of **2** with various organic compounds

Guest	Host–guest ratio
4-Methylpentan-2-ol	1 : 1^{a,b}
2-Methylpentan-1-ol	1 : 1^{a,b}
Isobutyl acetate	1 : 1^{a,b}
Propyl propionate	1 : 1^{a,b}
Ethyl benzoate	1 : 1^{a,b}
Pentan-2-one	1 : 1^{a,b}
Pentan-3-one	1 : 1^{a,b}
4-Methylcyclohexanone	1 : 1^{a,b}
Acetophenone	1 : 1^{a,b}
Anisole	1 : 1^{a,b}
Ethylbenzene	1 : 1^{a,b}
n-Propylbenzene	1 : 1^{a,b}
Styrene	1 : 1^{a,b}
o-Xylene	1 : 1^{a,b}
2′-Acetonaphthone	1 : 1^{b}
1′-Hydroxy-2′-acetonaphthone	1 : 1^{b}
2-Methylnaphthalene	1 : 1^{b}
1-Methoxynaphthalene	1 : 1^{b}

[a] Determined by thermogravimetric analysis–differential scanning calorimetry. [b] Determined by ^{1}H NMR spectroscopy.

X-Ray powder diffraction studies showed that the inclusion compounds have very similar structures, indicating that the inclusion crystals have similar molecular assembly modes. This was confirmed by single crystal X-ray structural analysis. Single crystals suitable for analysis were obtained by recrystallization of **2** with **3**.† Fig. 1 depicts the crystal packing of the inclusion compound viewed along the crystallographic *c* axis. It can be seen that the host molecules are arranged in a ‘chicken-wire’ network with large channel-type inclusion spaces. The molecular assembly mode is quite unique, as inclusion crystals of other bile acids tend to form bilayered structures.[5] All the host molecules are connected by hydrogen bonds. The helical network has the sequence O(3)H··O(7)H··O(24a)=C–O(24b)H··O(3)H, where the hydrogen bonding distances are 2.744(5), 2.894(5) and 2.595(4) Å, respectively.

The channel was analysed as a space filling model, which showed that the channel could be described as a straight pillar with a rectangular cross-section of approximate dimensions 7.4 × 11.5 Å. The guest molecules are accommodated in the channels with only van der Waals contacts. It is interesting that **3** arranges perpendicular to the channel and forms a column along the crystallographic *c* axis. In the column, **3** stacks with a distance of 3.51 Å, which corresponds to half of the crystal *c* dimension (7.020 Å). The space filling model of one column is depicted in Fig. 2.

In addition, we obtained single crystals *via* recrystallization of **2** from pentan-3-one. The X-ray measurement at 193 K indicated that the guest molecules were disordered in the channels. This indicates that the guest molecules are too small in size to provide thermally stable inclusion compounds.

In conclusion, this study demonstrates that **2** forms inclusion compounds with a wide range of organic compounds. These form a new channel-type large inclusion space as compared with any other bile acids, enabling the inclusion naphthalene derivatives with 1 : 1 stoichiometry.

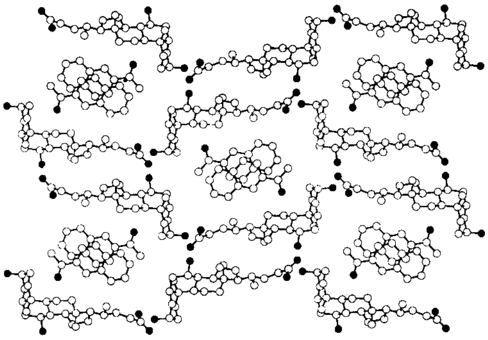

Fig. 1 The crystal structure of a 1 : 1 complex between **2** and **3** viewed down the crystallographic *c* axis. Carbon and oxygen atoms are represented by empty and filled circles, respectively. Hydrogen atoms are omitted for clarity.

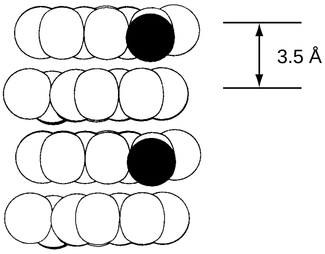

Fig. 2 Schematic drawing of one column of **3** in the inclusion space. Carbon and oxygen atoms are represented by empty and filled circles, respectively.

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Footnotes and References

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† *Crystal data* for **2**·**3**: $C_{24}H_{40}O_4 \cdot C_{12}H_{10}O_1$, M = 562.79, orthorhombic, space group $P2_12_12_1$, a = 15.81(1), b = 28.106(3), c = 7.0207(8) Å, V = 3120(1) Å^3, Z = 4, D_c = 1.198 g cm^{-3}. Intensity data were collected on Rigaku RAXIS-IV diffractometer with graphite-monochromated Mo-Kα radiation. 2683 Reflections were unique, and 1583 observed reflection with $|F_o| > 3\sigma(|F_o|)$ were used for further calculations after Lorentz and polarization corrections. The structure was solved by direct methods (SIR92) and refined against the F_o data by full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to carbon were placed in calculated positions, while O–H positions were obtained from difference Fourier synthesis. A total of 370 parameters were refined to final residuals R = 0.037 and Rw = 0.040. All calculations were performed using the TEXSAN crystallographic software package of the Molecular Structure Corporation. CCDC 182/665.

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