A robust structural motif in inclusion crystals of norbile acids

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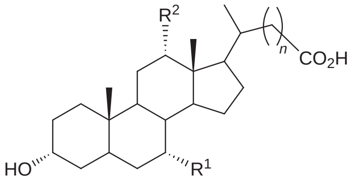
Four norbile acids (norcholic, nordeoxycholic, norchenodeoxycholic and norlithocholic acids) include various organic compounds and have a common robust motif in their crystal structures based on a cyclic hydrogen bond network and steric complementarity in the lipophilic parts.

The development of robust structural motifs in the crystalline state has attracted much attention as 'supramolecular synthons'[1] for the design of molecular cavities in nanoporous organic materials. However, most focus on directional strong intermolecular interactions such as multiple hydrogen bonding groups.[2] The design of robust motifs using steric complementarity or other weak interactions is still in its infancy: layer structures of long alkyl compounds,[3] herring-bone motifs or π–π stacking of polyaromatic compounds[4] or tetraarylporphyrins[5] are known. We describe here a novel robust motif based on the steric complementarity of the liophilic parts in inclusion crystals of norbile acids.

Norbile acids (**1a**–**4a)** were prepared from commercially available bile acids (**1b**–**4b**) by degradation of the side chain.[6]



n = 1 **1a** R^1 = OH, R^2 = OH **2a** R^1 = H, R^2 = OH
3a R^1 = OH, R^2 = H **4a** R^1 = H, R^2 = H
n = 2 **1b** R^1 = OH, R^2 = OH **2b** R^1 = H, R^2 = OH
3b R^1 = OH, R^2 = H **4b** R^1 = H, R^2 = H

Trace formation of inclusion crystals was investigated by recrystallization from more than eighty organic compounds. The guest incorporation and stoichiometries were determined by thermogravimetric analysis, IR spectroscopy and using a Karl Fischer moisture content meter. Table 1 shows the guest compounds, the host–guest ratios and the structural type of the host assemblies. Inclusion compounds of **2a** have already been reported by us,[7] and the other three norbile acids also form inclusion crystals with many organic compounds as **2a** does. In some cases, **1a** includes guest compounds as well as one molecule of water. Compared to the lack of inclusion ability of **4b**,[8] various organic compounds are included in **4a**.

The X-ray diffraction patterns of the inclusion crystals indicate that they exhibit several types of host framework, depending on the guest molecules. It is noteworthy that the B type structure in Table 1 is observed in the crystal structures of all four norbile acids. The crystal structures of the inclusion crystals of acetone were further characterized by X-ray crystallography (Fig. 1).† They are all isostructural, despite the different number and locations of the hydroxy groups in the steroidal skeleton. This remarkable structural feature is a bilayer structure that is formed by hydrogen bonding between the hydrophilic faces (α-faces) of the steroidal plane and van der Waals association between the lipophilic faces (β-faces). In the hydrophilic layer, a cyclic hydrogen-bond network involves two hydroxy groups in the 3-positions and two carboxylic acids in the side chains from four different host molecules (Fig. 2). This cyclic hydrogen bond network forms a wavy sheet structure, which stacks in an antiparallel manner without any void space in the liopophilic layers. A caged inclusion cavity forms between the side chains due to the unbalanced molecular structure with the wide steroidal plane and the rod-like side chain. The guest compounds are included in 2:1 host–guest stoichiometry in the cavity.

In contrast, bile acids have diverse crystal structures. That is, **1b** and **2b** form bilayer structures,[9] while **3b** and **4b** form helical[10] and non-layer[8] structures, respectively. In these cases all hydrogen bond groups contribute to the formation of such

Table 1 Guest molecules of **1a**, **2a**, **3a** and **4a**, and their host–guest ratios and molecular assembly modes[a]

	1a		**2a**		**3a**		**4a**	
Guest (G1)	H : G1 : G2	Mode	H : G1 : G2	Mode	H : G1 : G2	Mode	H : G1 : G2	Mode
MeOH	1 : 1	A	1 : 0 : 1		1 : 1	B	1 : 1	A
EtOH	1 : 1	A	1 : 1	C	1 : 1	A	1 : 1	A
PrOH	2 : 1	B	1 : 1	C	1 : 1	A	2 : 1	B
Pr^{i}OH	2 : 1 : 1	B	1 : 1	C	2 : 1	B	2 : 1	B
BuOH	2 : 1	B	2 : 1 : 1	B	2 : 1	B	1 : 0 : 1	
Bu^{s}OH	nc		1 : 1	C	2 : 1	B	2 : 1	B
Ethylene glycol	1 : 1	A	1 : 0 : 1		1 : 1	A	2 : 1	B
Acetone	2 : 1 : 1	B	2 : 1	B	2 : 1	B	2 : 1	B
MeCOEt	2 : 1 : 1	B	2 : 1	B	2 : 1	B	2 : 1	B
MeCOPr	2 : 1	B	2 : 1	B	2 : 1	B	2 : 1	B
Pentane-2,4-dione	2 : 1	B	2 : 1	B	2 : 1	B	2 : 1	B
γ-Valerolactone	2 : 1 : 1	B	2 : 1	B	2 : 1 : 1	B	2 : 1	B
MeCN	2 : 1 : 1	B	1 : 1	B	1 : 1	B	1 : 1	B
EtCN	2 : 1 : 2	B	2 : 1	B	2 : 1	B	2 : 1	B
Acrylonitrile	2 : 1	B	2 : 1	B	2 : 1	B	2 : 1	B

[a] G2 = water; mode A = bilayered cage (I); mode B = bilayered cage (II); mode C = monolayered; H : G = host–guest molar ratio; nc = not crystalized; GF = homocrystals of host without incorporation of the guest.

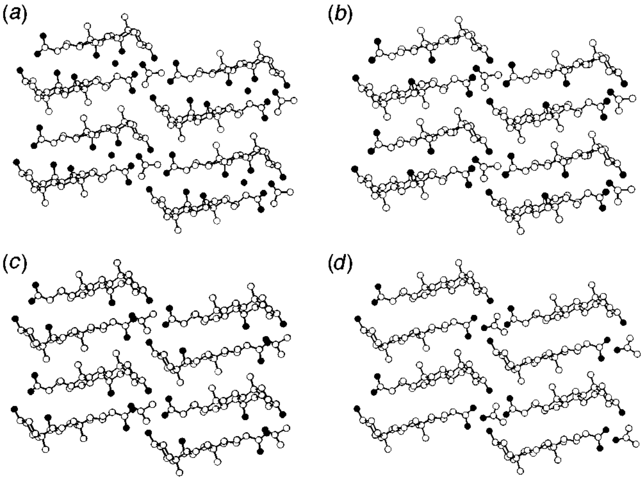


Fig. 1 Crystal structures of (a) **1a**·with acetone·water (2:1:1), (*b*) **2a**·acetone (2:1), (*c*) **3a**·acetone (2:1) and (*d*) **4a**·acetone (2:1), respectively. Hydrogen atoms are omitted for clarity and the empty and closed cycles represent carbon and oxygen atoms, respectively.

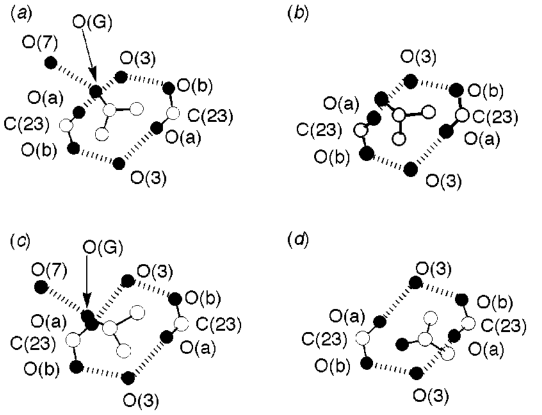


Fig. 2 Hydrogen bond networks of (*a*) **1a**, (*b*) **2a**, (*c*) **3a** and (*d*) **4a** with acetone, respectively. The empty and closed cycles represent carbon and oxygen atoms, respectively. The distances of the cyclic host–host hydrogen bond sequence, O(3)H•••O(23a)=C–O(23b)H•••O(3)•••O(23a)=C–O(23b)H•••O(3) are 2.63, 2.73, 2.61 and 2.79 Å for **1a**, 2.64, 2.75, 2.61 and 2.79 Å for **2a**, 2.71, 2.64, 2.76 and 2.65 Å for **3a**, 2.72, 2.60, 2.79 and 2.62 Å for **4a**.

host-inherent assemblies involving different hydrogen bond networks. In the case of norbile acids, however, the groups at the 7 and 12 positions do not join the networks, yielding the common assembly mentioned above. This is attributed to the side chains being shortened by one methylene group. The restrained chains have carboxy groups orientated in different directions, explaining the different hydrogen bond networks. Moreover, the wavy structure of the host molecules causes steric complementarity of the lipophilic β-faces. Accordingly, the molecules form the wavy layers which stack with good complementarity, leading to the robust structural motif.

This paper describes the new robust motif in the crystal structures of the norbile acids. The robustness is mainly caused by steric complementarity between the lipophilic layers. Molecular recognition and guest-dependent polymorphism of the host assemblies is currently under investigation.

Footnotes and references

† *Crystal data* for (*a*) **1a**·acetone·water (2:1:1), (*b*) **2a**·acetone (2:1), (*c*) **3a**·acetone (2:1) and (*d*) **4a**·acetone (2:1): (a) $C_{46}H_{76}O_{10}•C_3H_6O•H_2O$ (−63.9 °C), M = 865.20, triclinic, space group $P1$, a = 10.657(1), b = 15.309(6), c = 7.556(2) Å, α = 93.75(1), β = 106.19(2), γ = 79.15(2)°, V = 1162.6(5) Å^3, Z = 1, D_c = 1.236 g cm^{-3}; (b) $C_{46}H_{76}O_8•C_3H_6O$ (-63.8 °C), M = 815.18, triclinic, space group $P1$, a = 10.5710(9), b = 15.269(2), c = 7.583(3) Å, α = 92.47(2), β = 104.61(2), γ = 80.221(9)°, V = 1 167.1(4) Å^3, Z = 1, D_c = 1.160 g cm^{-3}; (c) $C_{46}H_{76}O_8•C_3H_6O$ (-62.8 °C), M = 815.18, triclinic, space group $P1$, a = 10.490(1), b = 15.257(1), c = 7.567(3) Å, α = 92.758(3), β = 104.24(2), γ = 79.999(8)°, V = 1155.9(4) Å^3, Z = 1, D_c = 1.171 g cm^{-3}; (d) $C_{46}H_{76}O_6•C_3H_6O$ (−63 °C), M = 783.18, triclinic, space group $P1$, a = 10.466(4), b = 15.243(2), c = 7.555(3) Å, α = 92.36(2), β = 103.08(3), γ = 80.78(2)°, V = 1158.8(6) Å^3, Z = 1, D_c = 1.122 g cm^{-3}. (a) 3609, (b) 3696, (c) 3603 and (d) 3462 reflections were unique, and (a) 3534, (b) 3619, (c) 3531 and (d) 3351 observed reflections with $I > 1.5\sigma(I)$ were used for further calculations after Lorentz and polarization corrections. In the case of **4d**, the guest molecule is disordered so that the position and thermal parameters of the guest molecule were refined isotropically as a ridged model. A total of (a) 550, (b) 523, (c) 523 and (d) 476 parameters were refined to final residuals (a) R = 0.152 and R_w = 0.256, (b) R = 0.134 and R_w = 0.220, (c) R = 0.130 and R_w = 0.221 and (d) R = 0.149 and R_w = 0.267 (refinement on F^2). CCDC 182/1137. Crystal data are available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/293.

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