

Water-participation in the Formation of a Triangular Pillar-like Assembly in Deoxycholamide Inclusion Crystals

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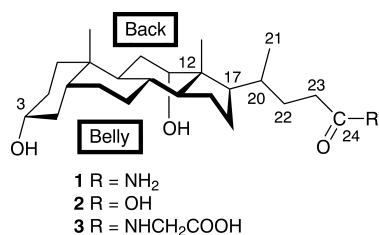
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Addition of water enables deoxycholamide to form a triangular pillar-like assembly with a core involving water and a surface involving organic compounds.

Water molecules participate in constructing supramolecular assemblies of bioorganic substances such as proteins, nucleic acid, *etc.*¹ With inclusion crystals, host molecules having multiple hydrogen-bonding groups often form guest-dependent assemblies.² Accordingly, we may obtain any inclusion crystals with different assembly modes by an intended addition of water into a host–guest system. Here we report that deoxycholamide ($3\alpha,12\alpha$ -dihydroxy- 5β -cholane-24-amide, **1**) forms such a novel crystalline assembly which has a triangular pillar-like structure in the presence of a large amount of water.



Compound **1** was prepared from commercially available deoxycholic acid **2** with ammonia according to the mixed anhydride method.³ The resulting **1** (*ca.* 80 mg, 0.20 mmol) was recrystallized from homogeneous mixtures of water (*ca.* 0.2 ml) and organic guest components (*ca.* 0.4 ml). The precipitated crystals were characterized by TG-DTA, IR and ¹H NMR spectroscopy, and X-ray crystallographic analysis. Such analyses revealed that **1** includes water as well as organic guests, such as small aliphatic alcohols, ketones, carboxylic acids, *etc.*

Table 1 summarizes the results. A typical example of the inclusion of **1** with acetic acid and water is as follows. The compound gave three endothermic peaks (*ca.* 94, 153 and 186 °C) in the DTA. The peak at the highest temperature corresponds to the melting point of **1**. The other two peaks are based on the release of the guest molecules from the host lattice, as indicated by a mass loss in the simul-

taneous TG measurement. In the IR spectrum, the inclusion compound exhibited a clear absorption peak at 1750 cm⁻¹ in the C=O stretching region, indicating the existence of hydrogen-bonded acetic acid. Two additional peaks were observed at 1675 and 1630 cm⁻¹ in the region of amide I and II. Moreover, large crystals were triangular prismatic. In the X-ray powder diffraction pattern, the crystals had two clear peaks with *d* values of 6.1 and 12.3 Å, while those involving no water had different peaks with *d* values of 6.4, 7.2, 9.3 and 12.1 Å.

The existence of water was confirmed by an X-ray analysis of the single crystal of the inclusion compound (**1**/acetic acid/water). Slow evaporation of the mixed solution containing **1** at room temperature led to the growth of single crystals suitable for X-ray analysis. The colourless crystals belong to the trigonal crystal system, space group *P*3₁.† It is noteworthy that the employment of double the length of the *c*-axis parameter [*c* = 22.925(1) Å] led us to a reasonable structure consisting of two crystallographically independent molecules of **1** (H-I and H-II), water (W-I and W-II) and acetic acid (G-I and G-II). When the single length of the *c*-axis parameter (*c* = 11.463) was employed, two unreasonable results were obtained: (i) a bond length of C=O at a 24-position of **1** was almost at the same as that of C–N at a 24-position of **1**, and (ii) a donor–acceptor relation among the hydrogen-bonding groups was not completely satisfied. A remarkable difference between H-I and H-II was found in the conformations of their amide groups. Their dihedral angles {C(22)–C(23)–C(24)–N[C(24)]} are 37.4 and –135.5° respectively.

Figs. 2(a) and 2(b) depict the crystal packings as viewed along the crystallographic *c*- and *a*-axis, respectively. The striking feature is that the host molecules arrange along a left-handed three-fold screw axis parallel to the *c*-axis to yield a triangular pillar with a core involving water and a surface involving acetic acid. The pillars are packed so as to

Table 1 Guest-release temperatures and molar ratios in the inclusion compounds of **1** with organic substances and water^a

Organic guests	Guest-release temperatures (T/°C)	Molar ratio (1:guest:water)
Methanol	92	1:1:1
Ethanol	92	1:1:1
Propan-1-ol	92	1:1:1
Propan-2-ol	87, 142	1:1:1
Ethylene glycol	76, 153	1:1:1
Propylene glycol	74, 94, 110	1:1:1
Trimethylene glycol	100, 129	1:1:1
Acetic acid	94, 153	1:1:1
Acetone	90, 139	1:1:1

^aDetermined by TG-DTA and ¹H-NMR spectroscopy.

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†Crystal structure data for the **1**/acetic acid/water system: (C₂₄H₄₁O₃N₁·C₂H₄O₂·H₂O)₂, trigonal, space group *P*3₁, *a* = *b* = 13.9654(7), *c* = 22.925(1) Å, *V* = 3872.0(3) Å³, ρ_{calc} = 1.208 g cm⁻³, *Z* = 3, *R* = 0.055, *R*_w = 0.079. Intensity data of this crystal were collected by a Rigaku RAXIS-IV imaging plate with a two-dimensional area detector with graphite-monochromatized Mo-Kα radiation (λ = 0.71070 Å) at *ca.* 200 K. The crystal showed 4032 unique reflections (2θ_{max} = 51.2°). Some 2757 [|*F*_o| > 3σ|*F*_o|] reflections were used for further calculations after Lorentz and polarization corrections. The structures were solved by direct methods (SIR92) and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically. The estimated standard deviations for the geometrical parameters involving non-hydrogen atoms lie within the following ranges: bond lengths, 0.007–0.01 Å; bond angles, 0.4–1.0°. Hydrogen atoms attached to carbon atoms were located in the calculated positions. The positions of hydrogen atoms attached to oxygen and nitrogen atoms were obtained from difference Fourier syntheses. All hydrogen atoms were fixed. All calculations were performed by using TEXSAN crystallographic software package of the Molecular Structure Corporation.

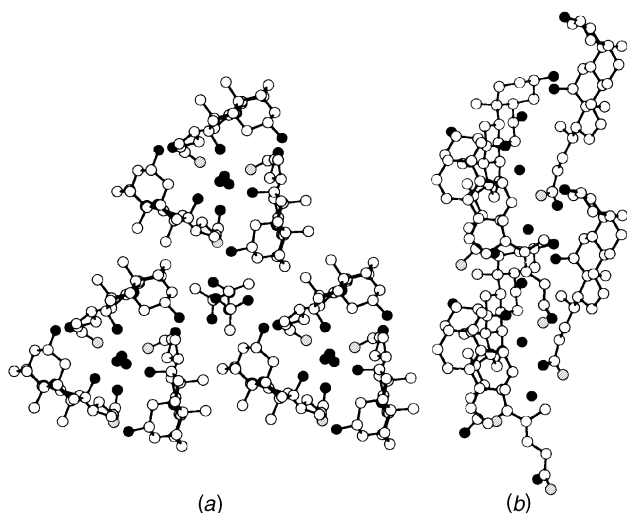


Fig. 2 Schematic representation of the triangular pillar-like assembly composed of **1**/acetic acid/water (1:1:1) as viewed down the crystallographic *c*-axis (a), and the *a*-axis (b). Empty, dotted and filled circles represent carbon, nitrogen and oxygen atoms, respectively. Hydrogen atoms are omitted for clarity

leave channels that accommodate acetic acid. The cross-sections of the channel have equilateral triangular shapes with edges of about 5 Å [Fig. 2(a)].

A complicated hydrogen-bonding network is separately drawn in Fig. 3, where each hydrogen-bonding group with the same designation (e.g. [C(24)_{H-I}]) is identical. Fig. 3(a) shows the core part. It can be seen that W-I and W-II arrange along the three-fold screw axis. The NH₂ of the amide groups of H-I as well as C=O of those of H-II are directed toward the core to bridge the water molecules. These hydrogen-bonding groups as well as OH[C(12)] groups of H-I and H-II form two kinds of spiral hydrogen-bonding sequences. One is N—H[C(24)_{H-I^a}]···O—H[O_{W-I^b}]···O—H[C(12)_{H-II^b}]···O[O_{W-II^b}]···H—N[C(24)_{H-I^a}], where the hydrogen-bonding distances are 2.912(7), 2.744(6), 2.810(6) and 2.963(7) Å, respectively. The other is O—H[C(12)_{H-I^b}]···O—H[O_{W-I^b}]···O=C[C(24)_{H-II^a}]···H—O—H[O_{W-II^b}]···O—H[C(12)_{H-I^b}], where the distances are 2.844(5), 2.791(6), 2.764(6) and 2.747(5) Å, respectively.

Fig. 3(b) shows the surface part. It can be seen that acetic acid molecules span the host molecules through hydrogen-bonds. This network has a sequence of C=O[C(24)_{H-I^f}]···H—O[C(3)_{H-I^g}]···H—O—C=O[C(3)_{H-I^g}]···H—N—H[C(24)_{H-II^e}]···O—H[C(3)_{H-II^d}]···O=C—O—H[C(3)_{H-I^g}]···O=C[C(24)_{H-I^b}], where the hydrogen-bonding distances are 2.797(5), 2.685(7), 2.845(8), 2.943(6), 2.787(9) and 2.678(8) Å, respectively. In this way the employment of crystallographically independent molecules enabled us to satisfy a donor–acceptor relationship among the hydrogen-bonding groups.

We previously reported that glycodeoxycholic acid (**3**) gave a C₃ symmetric pillar which belongs to the trigonal system, space group R3.^{4a} Comparison between the two different trigonal assemblies reveals that the direction of back and belly sides of the steroidal molecules are opposite, i.e. the hydrophilic belly sides of **1** are directed toward the core, while those of **3** are toward the surface.

E. Giglio's group has reported that **2** forms hexagonal crystals which belong to space group P6₅.⁵ These water-containing crystals only include ethanol or DMSO as organic guests. It is noteworthy that recrystallization of **1** and **2** from organic liquids containing no additional water gave inclusion crystals which have usual bilayered structures, as reported earlier.^{4b,c}

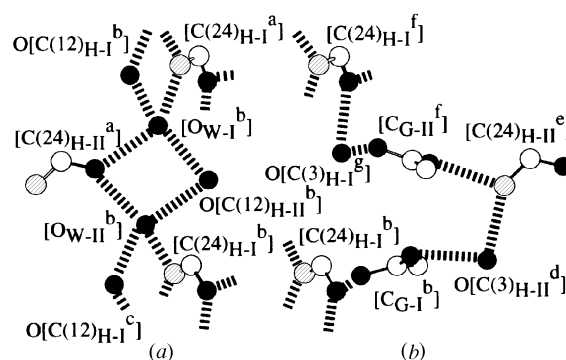


Fig. 3 Schematic representation of the sequential hydrogen-bonding networks of the core (a) and the surface (b). Hydrogen atoms are omitted for clarity. The symmetry codes a–g are $(-x + y, -z, z + 2/3)$, $(-y + 1, x - y + 1, z + 1/3)$, $(x + 1, y, z)$, $(x + 2, y + 1, z)$, $(-x + y + 1, -z + 1, z + 2/3)$, $(-x + y + 1, -z, z + 2/3)$, and $(x + 2, y, z)$, respectively

In conclusion, this study shows that the deliberate addition of water can give unexpected molecular assemblies. Further studies on other derivatives of steroidal bile acids are now in progress.

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Techniques used: IR, ¹H NMR, TGA, DTA, single crystal X-ray diffraction

References: 5

Fig. 1: Schematic representation for the conformations of the side chains of H-I (a) and H-II (b). Empty, striped and filled circles represent carbon, nitrogen and oxygen atoms, respectively. Hydrogen atoms are omitted for clarity.

Table 2: Crystallographic data for **1**/acetic acid/water

Appendix: Tables of atomic coordinates, *B*_{iso}/*B*_{eq} and anisotropic displacement parameters. ORTEP drawing of **1**

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