Inclusion Compounds of Methyl Esters of Cholic and Deoxycholic Acids; Structure of a 1 : 1 Complex between Methyl Cholate and Methanol

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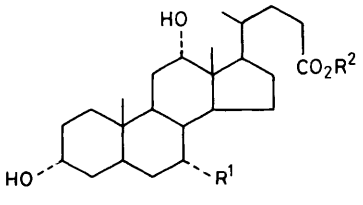
Methyl cholate forms crystalline inclusion compounds with a wide variety of organic substances; the crystal structure of a 1 : 1 complex between methyl cholate and methanol indicated that the methanol molecules are trapped in the host molecules by hydrogen bonds.

The inclusion compounds of deoxycholic acid [3α,7α-dihydroxy-5β-cholan-24-oic acid] (**3**) have been extensively studied since the last century.[1] However, little is known about the inclusion behaviour of other bile acids and their derivatives.[2] In a series of extensive studies on inclusion polymerization using deoxycholic acid and apocholic acid as the host components,[3,4] we have found that some bile acids and their derivatives form inclusion compounds with a variety of organic substances.[5] We report here the inclusion behaviour of methyl esters of cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid) (**1**) and deoxycholic acid as well as a structure of a 1:1 complex between methyl cholate and methanol, as established by *X*-ray crystallography.

The inclusion compounds of methyl cholate (**2**) were generally obtained by recrystallization of the host compound from liquid components. In case of solid or viscous guest compounds, a solvent such as acetone or acetone–diethyl ether was used. For example, the recrystallization of methyl cholate from methanol afforded the corresponding inclusion compound. The differential thermal analysis (d.t.a.) of the compound showed two endothermic peaks. The peak at higher temperature (152 °C) corresponded to the melting point of the pure host compound. The peak at lower temperature (117 °C) accompanied a rapid weight loss in the simultaneous thermogravimetric analysis, indicating the release of the guest molecules from the host lattice. The release amount corresponded to a 1:1 molar ratio of host to guest components, which was ascertained also by ^{1}H n.m.r. analysis. The release temperature (117 °C) is higher by 52 °C than the boiling point of methanol itself (65 °C). These results suggest that the guest molecules are accommodated into the host lattice by hydrogen bonds, which was proved by *X*-ray crystal structure analysis. Figure 1 shows the crystal structure of a 1:1 complex between methyl cholate and methanol.† It can be seen from Figure 1 that the host molecules form a layered structure composed of one hydrophobic site and another hydrophilic site, and that the methanol molecules are trapped in the hydrophilic site by hydrogen bonds with the hydroxy groups at C(12) of the host molecules. The distance and angle of O(26)–H(26) · · · O(methanol) are 2.69 Å and 170°, respectively.‡



Cholic acid (**1**); R^1 = OH, R^2 = H
Methyl cholate (**2**); R^1 = OH, R^2 = Me
Deoxycholic acid (**3**); R^1 = H, R^2 = H
Methyl deoxycholate (**4**); R^1 = H, R^2 = Me

† *Crystal data*: $C_{25}H_{42}O_5 \cdot CH_4O$, M = 454.65, monoclinic, $C2$, a = 25.184(3), b = 7.797(1), c = 15.174(3) Å, β = 121.05(1)°, Z = 4, D_c = 1.183 g cm^{-3}. Intensity data were collected by the θ—2θ scan mode with sin θ/λ up to 0.55 on a Rigaku automated four-circle diffractometer using Cu-K_α radiation. The structure was solved by direct methods and refined by block-diagonal least-squares procedure. After several cycles of anisotropic refinement for the non-hydrogen atoms, all the hydrogen atoms were found on a difference Fourier map, and then refined isotropically in the further cycles. The final R value is 0.035 for 1844 [$|F_o| > 3\sigma(|F_o|)$] reflexions. Computations were carried out on an ACOS 850 computer at the Crystallographic Research Centre, Institute for Protein Research, Osaka University. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

‡ The atomic numbering system is in accord with the convention for steroid molecules (ref. 1)

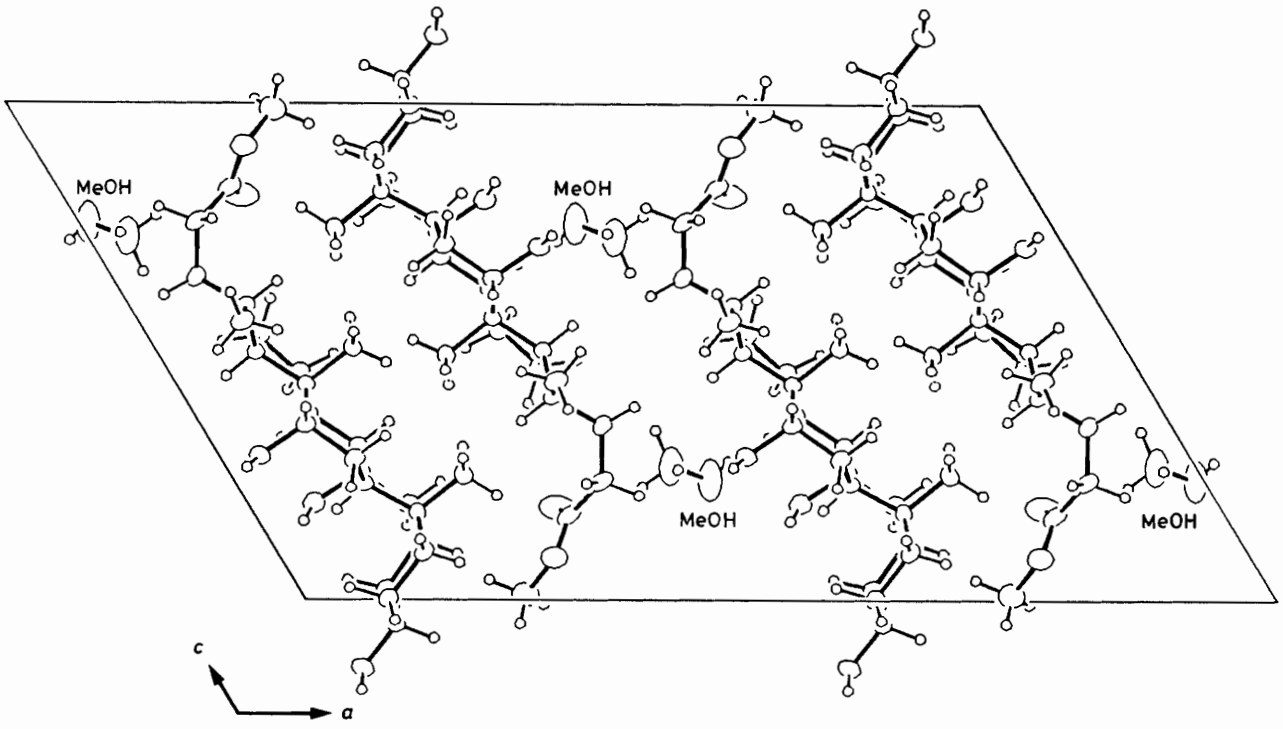


Figure 1. The crystal structure of a 1:1 complex between methyl cholate and methanol as viewed along the *b* axis.

Table 1. Release temperature and molar ratio of the inclusion compounds of methyl cholate with various organic substances.

Guest	B.p. of guest/°C	Release temperature/°C	Molar ratio host : guest
MeOH	65	117	1 : 1
MeCN	82	113	1 : 1
PhCOMe	202	117	1 : 1
PhCHO	179	47	1 : 1
HCO_2Et	54	110	1 : 0.5
HCO_2H	101	107	1 : 1
HCO_2NMe_2	153	85	1 : 1
$MeNO_2$	101	103	1 : 1
CCl_4	77	95	1 : 1
$\overline{OCH_2CH_2OCH_2CH_2}$	101	74	1 : 1

We have found that methyl cholate forms inclusion compounds with over fifty different organic substances, such as aliphatic and/or aromatic alcohols, ketones, aldehydes, ethers, carboxylic acids, esters, nitriles, halides, and nitro compounds. Table 1 shows a list of the inclusion compounds of methyl cholate with various liquid organic substances. The release temperatures vary from one case to another, reflecting the stability of the inclusion compounds. In the case of methanol, acetonitrile, carbon tetrachloride, and ethyl formate, the release of the guest molecules from the host lattice occurred rapidly at temperatures 20 to 50 °C higher than the boiling points of the guest compounds themselves. However, in the case of dioxane and acetone, the release of the guest molecules occurred gradually even at the beginning of the measurement, which indicates that these compounds are relatively unstable. The aromatic compounds also provided stable compounds, with release or melting temperatures different from the boiling or melting points of the guest compounds themselves.

However, methyl deoxycholate (**4**) showed a marked decrease in ability to form inclusion compounds, as compared with methyl cholate. Methyl deoxycholate did not form stable inclusion compounds with the various liquid guest components shown in Table 1, but it did complex with relatively large aromatic compounds such as benzalacetophenone, phenyl benzoate, diphenyl carbonate, *etc.*

It is known that deoxycholic acid forms inclusion compounds with the hydrophobic channel running through the host lattice.[1] In this case the hydrophobic sites of the host molecules are used to accommodate the guest molecules, while the host molecules are linked through the hydrophilic sites. The reverse relationship was found for the inclusion compound of methyl cholate with methanol on the basis of the crystal st r cture analysis.

In conclusion, the bile acids and their derivatives form different types of inclusion compounds with a variety of organic substances through the different combinations of the hydrophobic and hydrophilic sites of the molecules.

The inclusion compounds of methyl cholate can be classified as co-ordinatoclathrates,[6] in the same way as derivatives of binaphthyl[7] and diacetylene diol.[8]

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