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High guest inclusion in 3β-amino-7α,12α-dihydroxycholan-24-oic acid enabled by charge-assisted hydrogen bonds

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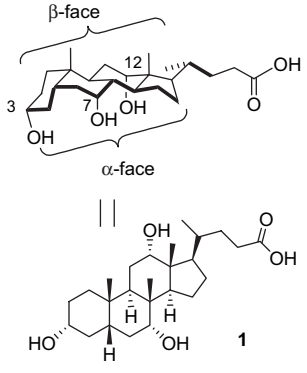
Abstract—3β-Amino-7α,12α-dihydroxycholan-24-oic acid (**2**) forms inclusion compounds with high ratio (host/guest=1/4) of guest methanol. Both hydrogen bonds and hydrophobic interactions are important to the solid structure. The cholates assemble in a head-to-tail fashion to form infinite hydrogen-bonded chains. The chains are interconnected between cholates and also through the guests. Large channels are formed along the crystallographic *a* axis where most of the methanol molecules are located. Presence of a dominant hydrogen-bonding motif (i.e., ammonium-carboxylate ion pairing) is probably responsible for high guest incorporation.

1. Introduction

Cholic acid (**1**) has an unusual distribution of functional groups: the α face is hydrophilic with three hydroxyl groups and the β face is hydrophobic consisting of only hydrocarbons. Because of its unique structure and commercial availability, cholic acid is a popular building block in supramolecular chemistry.[1] In recent years, it has been used to construct environmentally responsive molecules.[2–4] Taking advantage of the facial amphiphilicity of cholates,[5] we prepared molecular baskets that undergo transitions between micelle-like and reversed-micelle-like conformations induced by solvent changes[6] and cholate foldamers with nanometer-sized hydrophilic cavities.[7]



Another interesting feature of cholic acid (and bile acids in general) is their ability to form inclusion compounds with various organic compounds.[8] This is an attractive application because bile acids are chiral and can be used for enantiomeric and diastereomeric separation of guest molecules.[9,10] The number and the orientation of hydrogen bonds greatly influence the solid state structures of the bile acids as well as the inclusion compounds that can be formed. For example, deoxycholic acid, only different from cholic acid (**1**) by missing one hydroxyl group at C-7, is known for over a hundred years to form inclusion compounds with a wide variety of organic molecules including hydrocarbons, alcohols, ethers, ketones, acids, esters, and nitriles.[8,11] The ability of cholic acid to form inclusion compounds, however, was discovered much later, but received increased attention in recent years.[8] Its crystal lattice is quite stable and can survive reversible incorporation and removal of guest molecules in some cases,[12,13] making it potentially useful as 'organic zeolite' for separation and chemical reactions.

In our recent study of cholate derivatives, we synthesized 3β-amino-7α,12α-dihydroxycholan-24-oic acid (**2**) and found it could include guest molecule such as methanol. Most interestingly, large void volumes can be formed in the solid structure so that four solvent molecules can be incorporated per host molecule. In contrast, the number of guest molecules in preciously reported bile acid inclusion compounds almost never goes above two.

2. Results and discussion

Synthesis of **2** was adopted from literature procedures (Scheme 1).[14] Cholic acid was treated with catalytic amount

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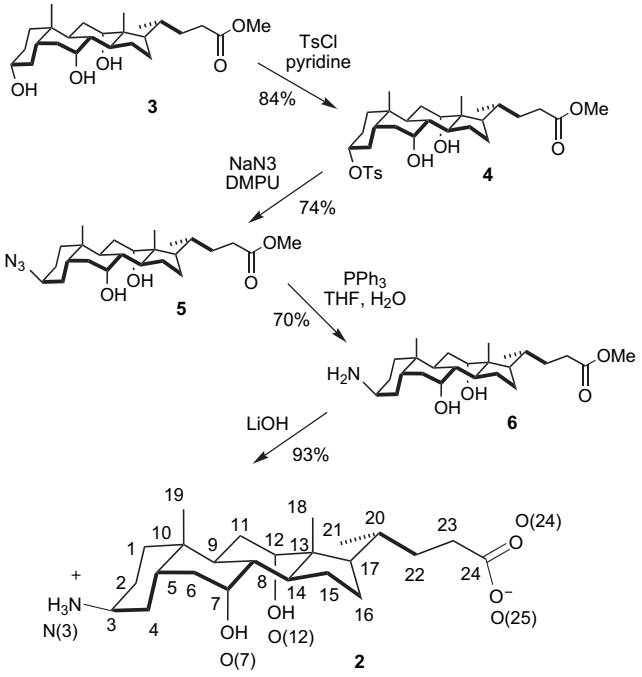
of sulfuric acid in refluxing methanol to give methyl ester **3**. Among the three hydroxyl groups, the one at 3α position is most reactive and was selectively tosylated in 84% yield. Tosylate **4** was replaced by azide through nucleophilic substitution with sodium azide in 74% yield. The azide intermediate **5** was then reduced by triphenylphosphine in aqueous THF and was hydrolyzed to give the final product **2** in good yield.



Scheme 1. Synthesis of compound **2**.

3β-Amino-7α,12α-dihydroxycholan-24-oic acid (**2**) has low solubility in many organic solvents including chloroform, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and even dimethyl sulfoxide (DMSO)—the latter two typically dissolve cholate derivatives very easily. Apparently, charges from the ammonium and carboxylate interact more strongly than neutral hydrogen-bonding donors and acceptors in most bile acids and give exceptionally high stability to the solid. It is insoluble in water at neutral pH but is soluble under both acidic and basic conditions, presumably due to formation of micellar aggregates. The compound is soluble in hot methanol and easily forms large transparent needle-like crystals upon cooling.

According to single crystal X-ray structure determination one independent molecule of **2** and four methanol solvent molecules were found in asymmetric unit of orthorhombic cell (space group $P2_12_12_1$). The molecule assembles in a head-to-tail fashion with the amine and the carboxyl group hydrogen bond to each other (Fig. 1). The α faces of the cholates tilt up and down alternately along the chain. In fact, every other molecule along the chain is equivalent and can be converted to one other by translational operation. Similar to other bile acids, each repeating unit propagates along the crystallographic *c* axis in a helical fashion,[15] possibly as a result of the bent backbone caused by the cis-fused A/B rings. Along the *a* axis, the chains are completely parallel. These chains are bridged by methanols to give pleated sheets in this direction. The chains are zigzagged and antiparallel between neighboring layers. Along the crystallographic *b* axis, the chains are connected by hydrogen bonds between the carbonyl oxygen O(24) of one cholate and the hydroxyl group O(7) of another.

Amphiphilicity is important in the structure as both hydrophilic and hydrophobic portions of the molecules are clearly segregated (Fig. 1). Hydrophobic contact is maintained by closely packed methyl groups on the β faces of cholates between neighboring chains. Unlike most bile acids,[8] however, the hydrophobic layers are discontinuous along the *c* axis. This is the direct result of alternating α and β faces along the chains (which is likely caused by strong interactions between the amine and the carboxyl group and the β orientation of the amine). The hydrophobic contact is continuous along the *a* axis, forming multiple hydrophobic 'belts' in this direction. Hydrophilic region is located around the amine/carboxyl pair and the two hydroxyl groups O(7) and O(12) of another cholate molecule.

There are four cholates and 16 methanol molecules in one unit cell. This guest/host ratio (4/1) is unusually high for bile acid inclusion compounds. For example, cholic acid (**1**) only incorporates one or two methanol in its crystal.[16–18] Deoxycholic acid does not form inclusion compounds with simple alcohols. In fact, the guest/host ratio in the majority of bile acid inclusion compounds is 1:1 or lower.[8] Figure 2 shows the hydrogen-bonding network formed by the cholates and methanol. Not surprisingly, all the polar atoms (i.e., oxygen and nitrogen) from both the hosts and the guests are involved in hydrogen bonding. Each cholate is hydrogen bonded to six methanol molecules. The carboxylate of cholate A is bonded to the amine of cholate B and to hydroxyl

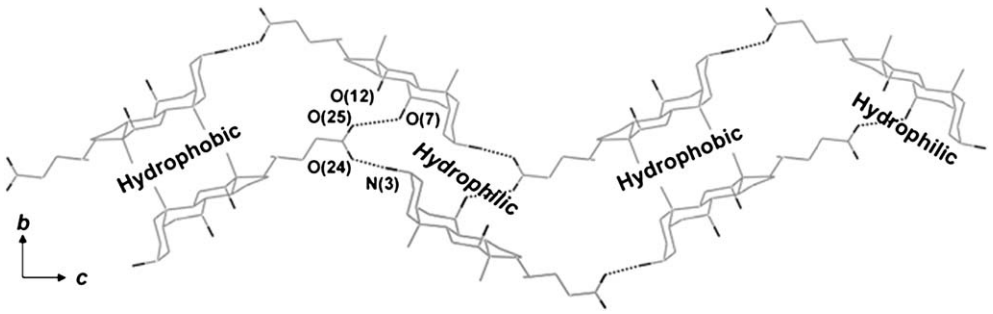


Figure 1. Two hydrogen-bonded chains of **2** viewed along the crystallographic *a* axis. Hydrogen bonds are shown in dotted lines. Hydrogen atoms are omitted for clarity.

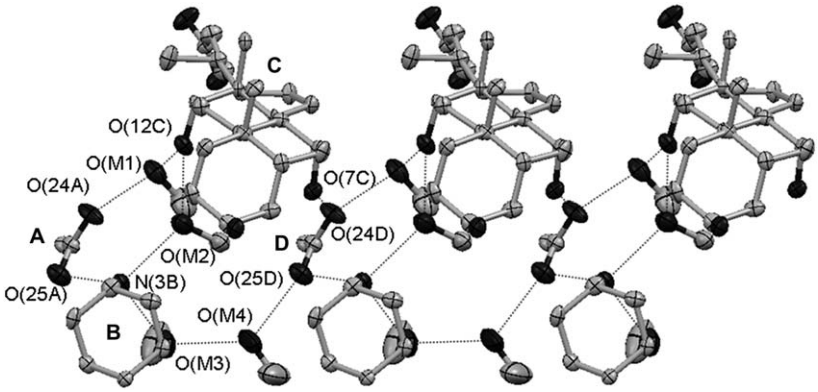


Figure 2. Hydrogen-bonding network within the crystal lattice of **2**. Hydrogen atoms and parts of cholates A, B, and D are omitted for clarity. O(M1), O(M2), O(M3), and O(M4) are the oxygen atoms on the four methanol molecules.

O(12) of cholate C through methanol M1. The hydroxyl O(12) of cholate C is then reconnected back to the amine of cholate B through methanol M2. Interestingly, two additional methanol molecules (M3 and M4) sit between closely bonded amine/carboxylate pairs from cholates A and B.

Typical hydrogen-bonded O···O distances range from 2.36 to 3.69 Å, with the latter being the van der Waals cutoff value.[19] Table 1 summarizes the hydrogen-bond distances and bond angles in the crystal structure. The O···O distance in our structure ranges from 2.65 to 2.79 Å, representing medium-strengthened (2.65–2.80 Å) hydrogen bonds according to literature classification.[19,20] Strong hydrogen bonds tend to have linear geometry. Many of the D–H–A bond angles, however, are smaller than 160°, possibly because the shape of **2** prevents optimal alignment of the donor and the acceptor atoms. Among all the polar atoms, O(7) is the only one that hydrogen bonds strongly to just one other polar atom—the next closest distance between O(7) and another polar atom is 3.30 Å. The O···N distance ranges from 2.70 to 2.86 Å (entries 7–9), similar to the values (2.66–3.12 Å with an average of 2.84 Å) found in amino acids and peptides.[21]

As in most supramolecular systems, the final product formed (crystal structure in this case) represents a minimum in either the global or local energy landscape (corresponding to the thermodynamically controlled or kinetically trapped structures). Multiple intermolecular forces have to work together and balance among themselves to reach the best compromise (i.e., to obtain at least a local energy minimum) in a crystal structure. In typical bile acid inclusion compounds, the most important interactions are hydrogen bonds and hydrophobic interactions.[8] Since all hydrogen bonds (O–H···O) are of similar nature, no one can dominate in a bile acid that is functionalized only with hydroxyl and carboxylic acid groups. Under such a circumstance, the molecules have many ways of optimization and can form tightly packed structures fairly easily. This probably explains why bile acid inclusion compounds rarely incorporate more than one or two guest per host even for small guests like methanol.

Table 1. Hydrogen-bond distances (with H···A distances <2.5 Å) and angles in the solid structure of **2**

Entry	Hydrogen bond[a]	D–H (Å)	H···A (Å)	D···A (Å)	D–H–A bond angle (°)
1	O(7C)–H···O(24D)	0.84	2.14	2.785(6)	133.4
2	O(12C)–H···O(M1)	0.84	1.99	2.755(7)	150.9
3	O(M3)–H···O(M4)	0.84	1.88	2.655(11)	153.6
4	O(M1)–H···O(24A)	0.84	1.86	2.660(8)	158.5
5	O(M2)–H···O(12C)	0.84	1.82	2.653(8)	171.0
6	O(M4)–H···O(25D)	0.84	1.83	2.660(10)	168.2
7	N(3B)–H···O(M2)	0.91	1.82	2.700(9)	162.5
8	N(3B)–H···O(25A)	0.91	2.02	2.831(8)	147.6
9	N(3B)–H···O(M3)	0.91	2.06	2.855(10)	145.5

[a] See Figure 2 for atom numbering. A, B, C, and D are the four labeled cholates. M1, M2, M3, and M4 are the four labeled methanol molecules.

In the current structure, however, the ammonium-carboxylate is the dominant force. In fact, charge-assisted hydrogen bonds are well known to be stronger than neutral ones[20,22,23] and are, therefore, generally maintained in the solid state. Görbitz surveyed 749 amino acids and peptides and found that ammonium carboxyl is always maintained despite the presence of many other hydrogen-bond donors and acceptors in the structures.[21] Aakeröy and co-workers had the same observation in a series of substituted benzylammonium benzoate derivatives.[24] Presence of a dominant force puts a severe constraint on the number of possible ways to optimize the structures. The price of maintaining a particular interaction is to sacrifice other hydrogen bonds and/or close packing of the molecules. Therefore, it should be much easier to incorporate a larger number of guests in such a system.

The crystal structure has channels along the *a* axis (Fig. 3). These channels are fairly hydrophobic except at the corners where the polar atoms are clustered. They are nearly triangular in shape and are fairly large in size: the shorter edge is about 5 Å and the longer ones roughly 7 Å in length. Three (M1, M3, and M4) of the methanol molecules are located within the channels and are connected to the 'wall' through hydrogen bonds. All three of them have their methyl groups pointing to the hydrophobic side of the wall. M1 has lower mobility because it is bonded to the wall via two connections (see also Fig. 2). M3 and M4, on the other hand, are interconnected to each other and are hydrogen bonded to the wall only through a one-point contact. As a result, they have the largest thermal motions among all the atoms, presumably because they can move up and down easily without significantly changing the hydrogen-bonding network. The fourth

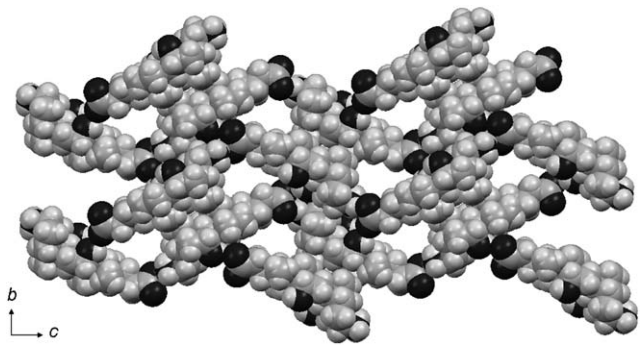


Figure 3. Space filling models of crystal structure of **2** viewed along the crystallographic *a* axis (carbon and hydrogen shown in light gray; oxygen and nitrogen shown in black). Methanol molecules are omitted to show the channels.

methanol (M2) is located in the hydrophilic region in between the carboxyl, amine, and hydroxyl O(7). It is tightly held in a narrow space, which explains the smallest thermal motion observed for this methanol among all the solvents.

3. Conclusions

Ammonium-carboxylate interaction is maintained in the crystal structure of 3β-amino-7α,12α-dihydroxycholan-24-oic acid (**2**). Combination of a dominant hydrogen-bonding interaction with shape awkwardness of the steroid backbone is probably responsible for incorporation of an unusually large number of guest molecules in the inclusion compound. Such a feature can be very useful in preparing inclusion compounds with high loading capacities. Another potentially beneficial feature of **2** as a supramolecular host is its low solubility in a range of polar and nonpolar solvents. This could be useful in reversible incorporation and release of guest molecules for separation and chemical reactions.[9,10]

Bile acid inclusion compounds occupy a unique position in the field of crystal engineering. They have multiple polar groups to stabilize the crystal lattice, facial amphiphilicity allowing incorporation of both hydrophilic and hydrophobic guests, chirality for enantiomeric and/or diastereomeric selectivity, and awkward shapes to avoid close packing. Many systematic modifications on the basic structures have been performed including variation on the number and the orientation of hydroxyl groups, on the type of functionality (e.g., acid, ester, amide, alcohol) at the C24 carbon, and the length of the carboxy tail.[8] In contrast, amino-derived cholates have received little or no attention in their inclusion abilities. Since charge-assisted hydrogen bonds are commonly used to rationally design molecular solids,[22,23] amino-derived bile acids as a group may become highly valuable host compounds for crystal engineering.

4. Experimental

4.1. General

Anhydrous tetrahydrofuran (THF) was dried by passage through a column of activated alumina under compressed nitrogen. All reagents and solvents were of A.C.S. certified grade or higher, and were used as received from commercial suppliers. All glassware and syringes were dried in an oven at least overnight prior to use. All Routine ^{1}H spectra were recorded on a Varian VXR-300 and VXR-400 spectrometer.

4.2. Synthesis

4.2.1. 3β-(4-Methylphenyl)sulfonyloxy-7α,12α-dihydroxycholan-24-oic acid methyl ester (4). This compound was prepared according to adopted literature procedures.[14,25] Methyl cholate **3** (3.03 g, 7.17 mmol) was dissolved in anhydrous pyridine (20 mL). Toluenesulfonyl chloride (1.95 g, 10.79 mmol) was added under N_2. The reaction mixture was stirred for 4 h at 50 °C. Solvent was removed in vacuo. The residue was dissolved in ethyl acetate (50 mL), washed with 2 N HCl (50 mL) and water (2×50 mL), dried with $MgSO_4$, and concentrated in vacuo to give a white powder (3.58 g, 6.21 mmol, 87% yield). This material was generally used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz, δ) 7.74 (d, 2H, J=8.4 Hz), 7.42 (d, 2H, J=8.4 Hz), 4.21 (m, 1H), 3.71 (s, 1H), 3.52 (s, 3H), 2.58–0.78 (m, 33H), 0.54 (s, 3H).

4.2.2. 3β-Azido-7α,12α-dihydroxycholan-24-oic acid methyl ester (5). This compound was prepared according to literature procedures.[14] Tosylate **4** (3.58 g, 6.21 mmol) and NaN_3 (2.16 g, 33.22 mmol) were dissolved in *N*,*N*′-dimethylpropyleneurea (DMPU, 20 mL). The reaction mixture was stirred for 12 h at 60 °C. Water (100 mL) was added. The precipitate was collected by filtration and washed with water (2×50 mL). The residue was purified with column chromatography over silica gel using ethyl acetate/hexane (1/4) as the eluent to give a white powder (2.05 g, 4.59 mmol, 74% yield). ^{1}H NMR (DMSO-d_6, 400 MHz, δ) 3.95 (br s, 1H), 3.73 (br s, 1H), 3.57 (br s, 1H), 3.53 (s, 3H), 2.58 (m, 1H), 2.32–0.73 (m, 29H), 0.54 (s, 3H).

4.2.3. 3β-Amino-7α,12α-dihydroxycholan-24-oic acid methyl ester (6). This compound was prepared according to literature procedures.[14] Azide ester **5** (203 mg, 0.459 mmol) and PPh_3 (168 mg, 0.641 mmol) were dissolved in THF (5 mL) and water (0.3 mL). The reaction mixture was heated to reflux for 12 h. Solvent was removed in vacuo. The residue was purified by column chromatography over silica gel using first ethyl acetate/hexane (4/1) and then methanol/triethylamine (50/1) as the eluents to give a white solid (135 mg, 0.321 mmol, 70% yield). Mp 225–230 °C dec. ^{1}H NMR (CD_3OD, 400 MHz, δ) 3.94 (br s, 1H), 3.80 (m, 1H), 3.64 (s, 3H), 3.09 (s, 1H), 2.57 (m, 1H), 2.42–2.11 (m, 3H), 1.96–0.91 (m, 26H), 0.71 (s, 3H).

4.2.4. 3β-Amino-7α,12α-dihydroxycholan-24-oic acid (2). This compound was prepared according to adopted literature procedures.[26] LiOH (2 M, 5 mL) was added to the solution of compound **5** (135 mg, 0.321 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 21 h. HCl (2 N) was added until pH=7–8. Solvent was removed in vacuo. Residue was purified by column chromatography using MeOH/triethylamine (50/1) as eluent to give white solid (121 mg, 0.298 mmol, 93% yield). Mp 240–245 °C dec. ^{1}H NMR (CD_3OD/D_2O=1/1, 400 MHz,

δ) 3.59 (s, 1H), 3.26 (s, 1H), 2.00–0.75 (m, 30H), 0.52 (s, 3H).

4.3. X-ray crystallography

A colorless small solvent dependent crystal ($0.25\times 0.18\times 0.13$ mm^3) was covered with epoxy glue and immediately mounted and centered in the stream of cold nitrogen. The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer at 193 K, Mo Kα (λ=0.71073 Å) radiation, detector to crystal distance of 5.03 cm. The data were collected using the full sphere routine (0.3° scans in ω, 30 s per frame). This dataset was corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements[27] using SADABS software.[28] The structure was solved using direct methods and was refined in full-matrix anisotropic approximation for all nonhydrogen atoms. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The crystals of **2** are orthorhombic, $C_{24}H_{41}NO_4\times 4(CH_4O)$, space group $P2_12_12_1$; at 193(2) K, a=7.606(2), b=13.516(4), c=29.156(8) Å, V=2997.2(14) Å^3, Z=4, M=535.75, D_{calcd}=1.187 Mg m^{-3}, μ=0.085 mm^{-1}, $F(000)$=1184, $R1$=0.0814, $wR2$=0.2189 (data/parameters=2819/348), GOF=1.085.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 600390 copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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28. All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrick, Bruker Analytical X-ray Systems, Madison, WI).