Inclusion Phenomena of Glycine-conjugated Bile Acids and the Crystal Structure of 1 : 1 Complex of Glycodeoxycholic acid and Tetrahydrofuran

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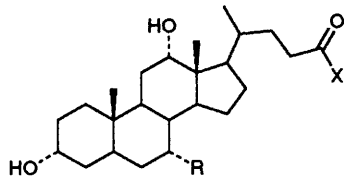
Glycine-conjugated bile acids serve as new hosts for multimolecular inclusion compounds; a novel three-leaved assembly is found in the crystal structure of a 1 : 1 complex between glycodeoxycholic acid and THF.

It has long been known that deoxycholic acid **1** forms multimolecular inclusion compounds, called 'choleic acids'.[1] More recently, we established that cholic acid **2** and its derivatives also form choleic acids.[2] For the biologically important conjugated bile acids, *e.g.* glycodeoxycholic acid **3** and glycocholic acid **4**, however, there are only a few reports on their abilities to form the compounds. More than fifty years ago, Cortese and his coworkers studied **3** and **4**[3] and concluded that the conjugated bile acids cannot form the stable choleic acids.[3b,c] In contrast, our research clearly shows that **3** and **4** can form stable inclusion compounds with some organic substances. Here, we report the first preparation of the inclusion compounds of the conjugated bile acids and a novel three-leaved assembly in the crystal structure of a 1 : 1 compound of **3** with THF.

Both **3** and **4** were prepared from the parent acids as described in literature.[4] Their inclusion abilities were checked by recrystallisation. Table 1 shows the resulting inclusion compounds of **3** and **4**. The compounds of **3** had a host : guest ratio of 1 : 1 based on ^{1}H NMR and thermal analysis. On the other hand, **4** formed compounds with only a limited number of guest molecules, such as cyclohexanone, acetophenone, oxepane, ethyl benzoate, in less than one molar ratios. Although **1** and **2** formed stable inclusion crystals with various hydrocarbons and esters, both **3** and **4** did not at all. This shows that **3** and **4** are less versatile in forming host–guest compounds than their parent bile acids.

The inclusion compounds showed two types of thermal behaviour due to thermal scanning calorimeter (DSC) and thermogravimetry (TG). We observed three endothermic peaks in the DSC diagram for the inclusion compound of **3**



1; R = H , X = OH
2; R = OH, X = OH
3; R = H , X = $NHCH_2CO_2H$
4; R = OH, X = $NHCH_2CO_2H$

Table 1 Guest release temperatures and molar ratios of **3** and **4** with various organic compounds

Guest	Host	*T*/°C	Host : Guest
Acetone	**3**	121	1 : 1
Butan-2-one	**3**	111	1 : 1
THF	**3**	115	1 : 1
1,4-Dioxane	**3**	148	1 : 1
Methyl *o*-toluate	**3**	127	1 : 1
Pyrrole	**3**	117	1 : 1
Cyclohexanone	**4**	105	1 : 1
Acetophenone	**4**	180	3 : 1
Propiophenone	**4**	175	3 : 1
Oxepane	**4**	109	4 : 1
Ethylene glycol diacetate	**4**	170	2 : 3
Nitrobenzene	**4**	173	4 : 1

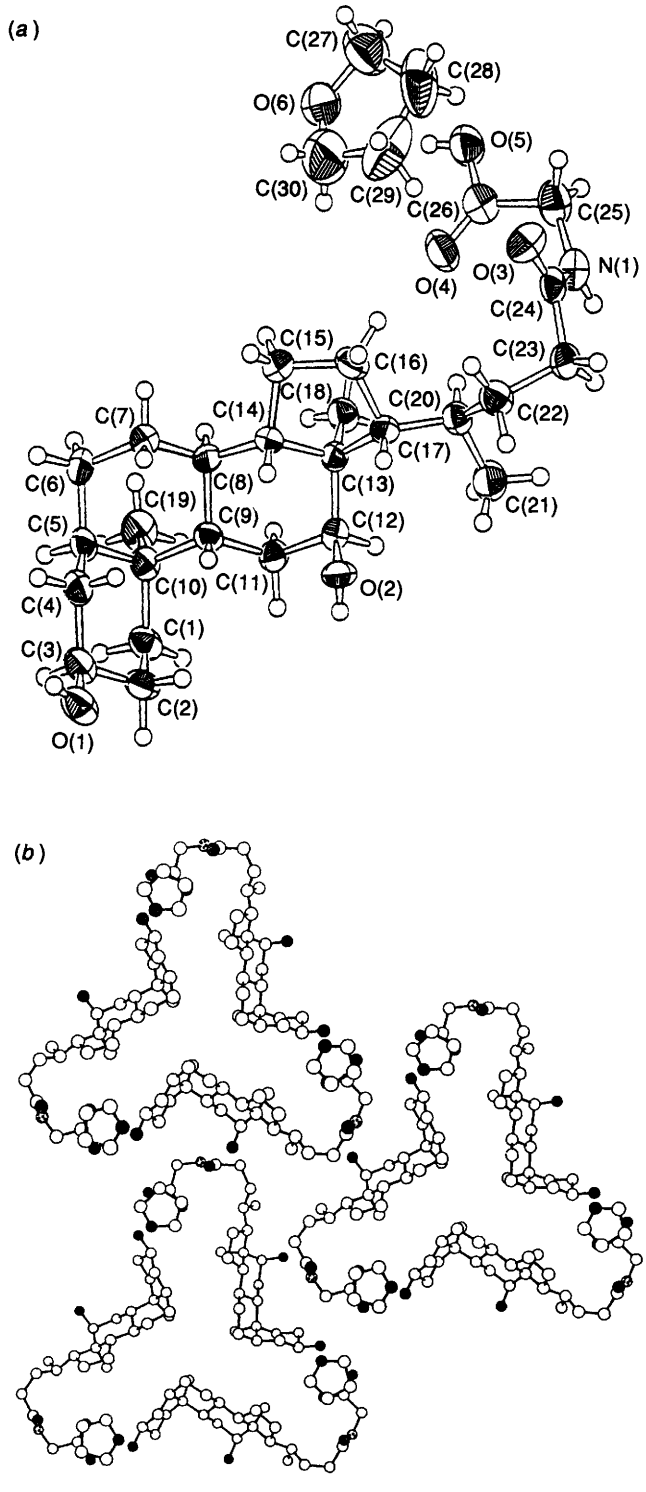


Fig. 1 The crystal structre of the inclusion compound between **3** and THF: (*a*) ORTEP drawing, (*b*) crystal packing viewed down the crystallographic *c* axis. Carbon, nitrogen and oxygen atoms are represented by empty, dotted and shadowed circles, respectively.

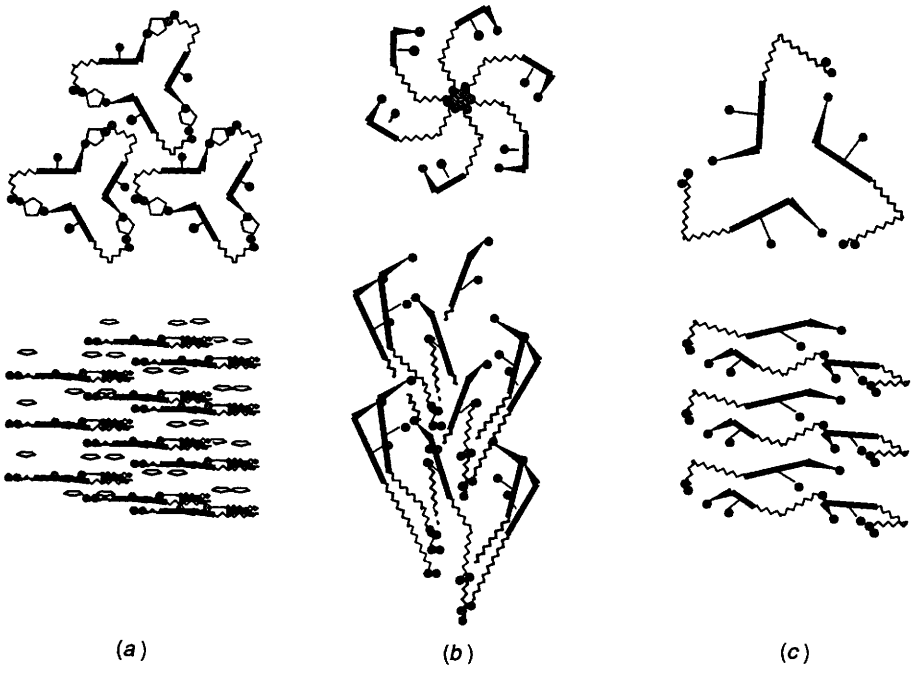


Fig. 2 Schematic representation for amphiphilic columns: (*a*) a three-leaved stacked column with a lipophilic core and a hydrophilic surface, (*b*) a helical column with a hydrophilic core and a lipophilic surface, (*c*) a helical column with a lipophilic core and a hydrophilic surface

with methyl *o*-toluate. One peak at the highest temperature (*ca.* 180 °C) corresponds to the mp of **3** itself. The other two peaks at lower temperatures (68 and 127 °C) are based on the release of the guest molecules from the host lattice, as indicated by a mass loss in the simultaneous TG measurement. In the case of other guests, *e.g.* THF, butan-2-one, we observed only one endothermic peak, but no peak for the mp of **3** itself. It is assumed that the host crystals melted or solubilized at this temperature together with the guest component.

The lower versatility of **3** and **4** suggests that the host assemblies have inclusion spaces alternative to those of **1** and **2**. This is supported by the crystal structure of a 1 : 1 complex between **3** and THF.† The ORTEP drawing of the complex is shown in Fig. 1(*a*). The torsion angles [C(16)–C(17)–C(20)–C(22); −62.2(5)°, C(17)–C(20)–C(22)–C(23); 159.6(4)°] corresponds to the *trans* conformation as in the case of the inclusion compound of **4** with γ-valerolactone.[2d] The glycine part induces the tail to be folded back to the lipophilic face of the host molecule, as confirmed by the next two dihedral angles [C(20)–C(22)–C(23)–C(24); −75.5(6)° and C(22)–C(23)– C(24)–N(1); −116.9(5)°].

The crystal packing viewed along the crystallographic *c* axis is depicted in Fig. 1(*b*). The striking feature is that three host molecules give a disk-like C_3 symmetric three-leaved assembly. The hydrophilic groups disperse on the surface of the assembly, while the lipophilic faces of the host molecules closely contact together in the core. The three-leaved assemblies stack along the crystallographic *c* axis to generate a column. The columns are connected to each other by hydrogen bonds [O(2)–O(3); 2.852(4) Å]. A THF molecule is included between the tails by a hydrogen bond [O(1)–O(6); 2.729(5) Å].

Giglio's group systematically studied the crystal structures of the conjugated bile acid salts.[5] Among them the crystal structure of sodium taurodeoxycholate hydrate[5c] is similar to that of the inclusion compound of **3** with THF. These two crystals belong to the same crystal form, and their tail conformations and assembly modes are very similar to each other. The former host molecules associate in a helical mode to give the helical column [Fig. 2(*c*)], while the latter ones associate in a cyclic mode to give the three-leaved assemblies [Fig. 2(*a*)]. Such a difference may be attributed to the existence of the corresponding ions and organic guest molecules.

It is assumed that a combination of the hydrophilic and lipophilic parts in one molecule play an important role in assembling the molecules to form crystal structures. The parent bile acids, **1** and **2**, mostly form bilayers, while additional water molecules often induce the host molecules to yield helical columns with hydrophilic cores and lipophilic outsides [Fig. 2(*b*)]. Likewise, the conjugated bile acids form amphiphilic bilayers and columns. In the case of sodium taurodeoxycholate hydrate we see a helical column [Fig. 2(*c*)]. Inclusion of THF makes **3** form columns with hydrophilic surfaces and lipophilic cores [Fig. 2(*a*)].

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Footnote

† *Crystal data*: $C_{30}H_{51}NO_6$, M = 521.74, trigonal, $R3$, $a = b$ = 32.116(1), c = 7.267(2) Å, V = 6491(1) Å^3, Z = 9, D_c = 1.201 g cm^{-3}. Intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromatized Mo-Kα radiation. The structure solved by direct methods (SHELXS86) was refined to R = 0.042 for 2086 reflections collected up to sin θ/λ = 0.65 Å^{-1}.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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