A Novel Host-Guest Supramolecular Architecture of Dehydrocholic Acid in the Enantioselective Inclusion of R-(+)-Methyl *p*-Tolyl Sulfoxide

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The first crystal structure of a 1 : 1 inclusion complex between dehydrocholic acid and R-(+)-methyl *p*-tolyl sulfoxide, formed by intercalation layers, is reported.

Steroids, in particular bile acids, have shown to be particularly efficient as hosts for the resolution of a number of organic molecules.[1] Noteworthy is the observation that alkyl aryl sulfoxides are the first example of guest molecules able to form inclusion compounds with bile acid derivatives lacking steroidal hydroxyl groups, such as dehydrocholic acid **1**.[2] In this respect and as reported in our previous paper[2] the methyl *p*-tolyl sulfoxide **2** forms a 1 : 1 inclusion compound with dehydrocholic acid, according to a number of different procedures. In particular, the crystallization method, in which both the host and the racemic guest are dissolved in ethyl acetate followed by partial evaporation of the solvent, provides single crystals suitable for the X-ray analysis that is described and discussed later on in this communication.

Figure 1 displays the crystal structure[3] of dehydrocholic acid, obtained from a solution of **1** in ethyl acetate, used for comparison with the inclusion complex. Dehydrocholic acid crystallises in the space group *P1* using two independent molecules in the asymmetric unit linked in dimers by means of two hydrogen bonds, O28–H···O27, between the carboxylic groups [O28A···O27B = 2.67(2) Å and O28B···O27A = 2.67(2) Å]. The independent molecules **1A** and **1B** differ in the conformations of the carboxylic side chain, being ttgt and tttt respectively (see Table 1). Since the packing does not show the channels, which characterise the crystal structures of many steroid compounds, the inclusion compounds of dehydrocholic acid displays a novel host-guest supramolecular architectures, completely different from those observed in the inclusion compounds of cholic[4] and deoxycholic[5] acids.

The crystal structure[6] of the (1 : 1) inclusion compound between dehydrocholic acid **1** and (R)-(+)-methyl *p*-tolyl sulfoxide **2** is shown in Figure 2. The guest molecules are linked to the host ones by means of the hydrogen bond O28-H···O1 [O28···O1 = 2.645(2) Å] between the carboxylic group of **1** and the oxygen of the sulfoxide. The conformation of the side chain of dehydrocholic acid **1C** is ttgt. Although the crystals of dehydrocholic acid and of the inclusion complex belong to two different systems, the molecular frameworks of **1** in both crystals are oriented in the same manner with respect to the cell edges. In the inclusion compound the molecules of sulfoxide are accommodated in between the carboxylic groups, forming an intercalation layer parallel to *ab* plane, as shown in Figure 2, with a lengthening of the c_2 axis of about 4.50 Å, with respect to c_1 axis of the crystal of dehydrocholic acid, which correspond to the tickness of the layer occupied by the guest molecules. The remaining cell parameters turn out to be very similar. Furthermore, the crystal data reveal that the inclusion compound is obtained by intercalation of molecules of sulfoxide in the crystal

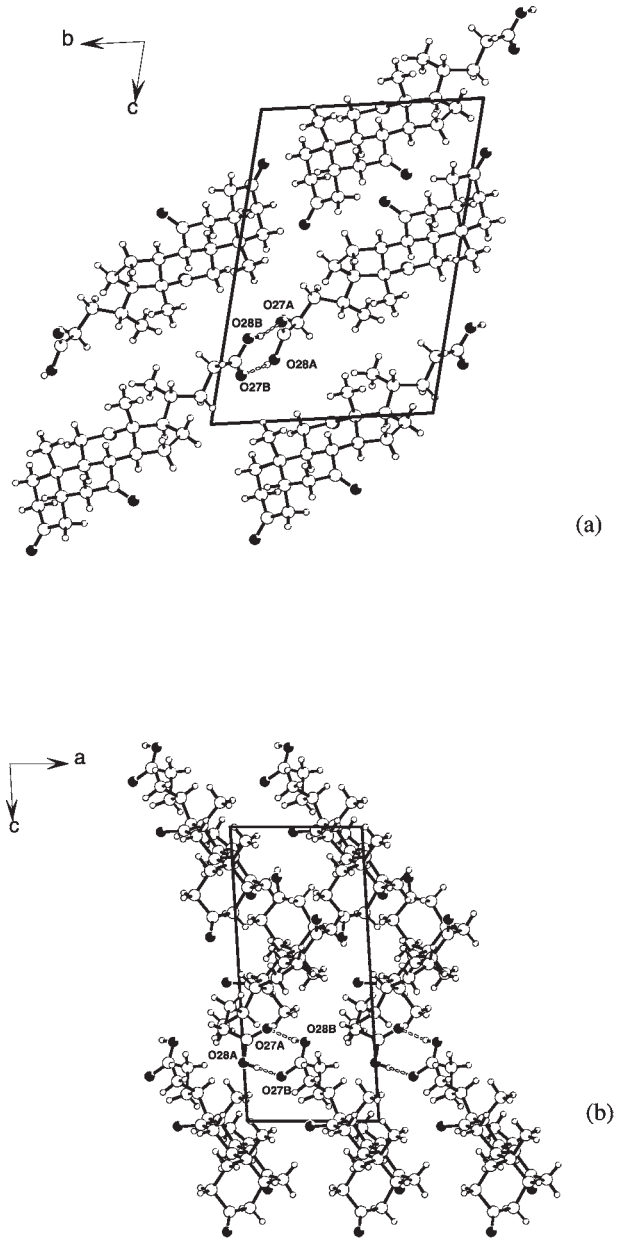

Figure 1. (a) The crystal structure of dehydrocholic acid **1** as viewed down the crystallographic *a* axis; (b) as viewed down the crystallographic *b* axis.

Table 1. Torsion angles (°) and conformations of the carboxylic side chains of the dehydrocholic acid molecules in the crystals of **1** and of the 1 : 1 inclusion derivative

Molecule	ψ_1 [a]	ψ_2 [b]	ψ_3 [c]	ψ_4 [d]	Conf.
1A	−175.4(8)	−163.1(9)	77.2(13)	−165.5(11)	ttgt
1B	179.6(9)	−154.5(10)	−152.1(12)	−169.2(12)	tttt
1C	−172.5(3)	−165.1(3)	80.4(4)	172.3(3)	ttgt

[a]C13–C17–C20–C22. [b]C17–C20–C22–C23. [c]C20–C22–C23–C24. [d]C22–C23–C24–O28.

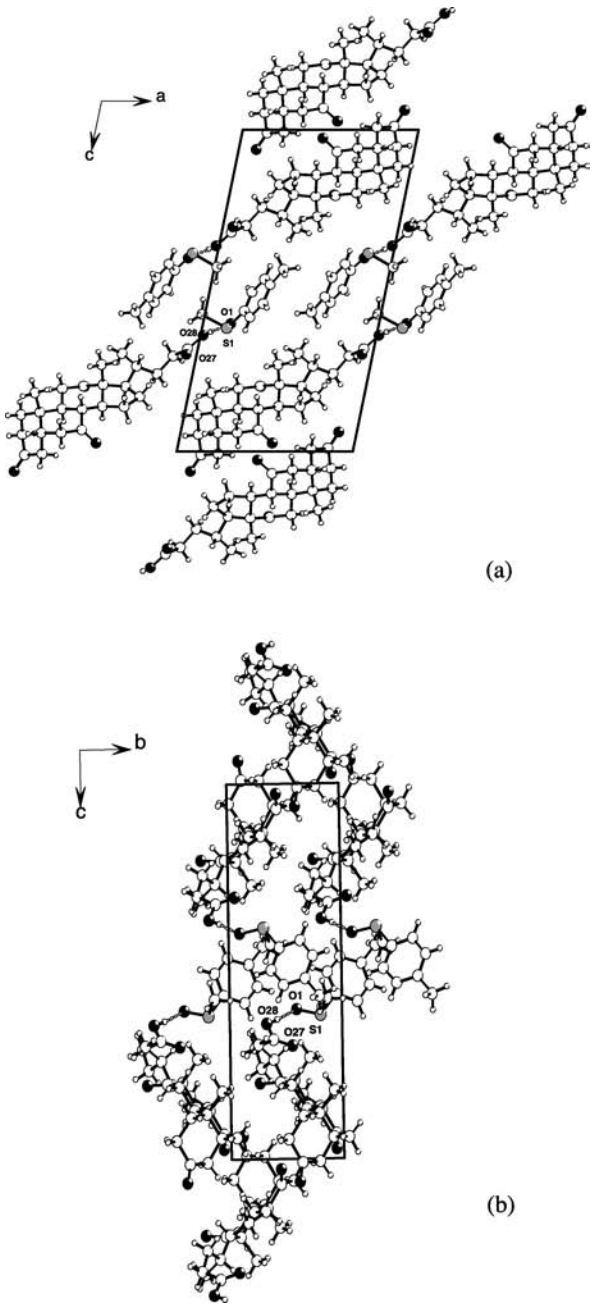

Figure 2. (a) The crystal structure of the inclustion compound dehydrocholic acid **1** with (R)-(+)-methyl *p*-tolyl sulfoxide **2**, as viewed down the crystallographic *b* axis; (b) as viewed down the crystallographic *a* axis.

lattice of **1**, giving rise to: *a*) formation of hydrogen bonds between of the carboxylic group and the oxygen of sulfoxide [$d_{O\cdots O} = 2.645(2)$ Å] shorter than those observed between the carboxylic groups in dehydrocholic acid crystal; *b*) conformational modification of the carboxylic side chain of molecule **1B** from tttt to ttgt; *c*) small variations of the cell parameters except for *c* which shows a lengthening of 4.50 Å; *d*) space group change from triclinic *P1*, $Z = 2$, to monoclinic $P2_1$, $Z = 2$. It can be concluded that the host molecules are able to include the pure (*R*)-enantiomer probably because only this chiral accommodation allows to obtain a closer face-to-face packing of the molecules of dehydrocholic acid, Figure 2, similar to that observed in the crystals of dehydrocholic acid itself, Figure 1.

A further characterization of the inclusion compound has been obtained by differential thermal analysis (DTA) and thermogravimetry (TG). The DTA spectrum showed two endothermic peaks at 245.0 and 166.9 °C, respectively. The peak at higher temperature corresponds to the melting point of the pure host compound, whereas the signal at 166.9 °C is associated with the release of the guest molecule from the host lattice, as indicated by the weight loss observed during the simultaneous TG analysis. This evidence in combination with ^{1}H NMR measurements confirmed a 1 : 1 host-guest molar ratio pertaining to the inclusion complex.

The present X-ray structure is the first case of a bile acid displaying a novel host-guest supramolecular architecture formed by intercalation layers.

References and Notes

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2 O. Bortolini, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *Chem. Commun.*, **2000**, 365.

3 Crystal data for **1**: $C_{24}H_{34}O_5$, fw = 402.53, triclinic, space group *P1*, $Z = 2$, $a = 6.8583(4)$, $b = 10.5646(10)$, $c = 15.7879(17)$ Å, $\alpha = 78.25(1)$, $\beta = 86.68(1)$, $\gamma = 89.29(1)°$, $V = 1118.1(2)$ Å^3, $D_c = 1.196$ g cm^{-3}. The structure solved by direct methods (SIR92[7]) was refined (SHELXL-97[8]) to $R = 0.094$ for 3472 observed reflections [$I > 2\sigma(I)$] up to $\theta = 26°$ (Mo Kα radiation) on a Nonius Kappa CCD diffractometer.

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6 Crystal data for the inclusion complex: $C_{24}H_{34}O_5 + C_8H_{10}OS$, fw = 556.76, monoclinic, space group $P2_1$, $Z = 2$, $a = 10.8984(5)$, $b = 6.8112(3)$, $c = 20.2949(10)$ Å, $\beta = 101.57(1)°$, $V = 1475.9(1)$ Å^3, $D_c = 1.253$ g cm^{-3}. The structure solved by direct methods (SIR92[7]) was refined (SHELXL-97[8]) to $R = 0.047$ for 2860 observed reflections [$I > 2\sigma(I)$] up to $\theta = 27.5°$ (Mo Kα radiation) on a Nonius Kappa CCD diffractometer.

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