Crystal Structure Determination of the 1:1 Complex of Deoxycholic Acid and Acetic Acid

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Summary The 1:1 crystal complex of deoxycholic acid and acetic acid (a so-called choleic acid) is an inclusion compound, in which chains of acetic acid molecules, hydrogen bonded as in the crystal structure of acetic acid, are held in tunnels between hydrogen-bonded sheets of deoxycholic acid molecules.

THE so-called 'choleic acids'[1] are stoicheiometric crystalline inclusion complexes in which the bile acid deconjugate deoxycholic acid is host and one of a variety of organic molecules is the guest.[2] The acholic component may be an aliphatic hydrocarbon, alcohol, acid, or ester ranging from ethyl alcohol up to molecules with chains of at least 20 carbon atoms. Other choleic acids contain flat aromatic molecules such as anthracene, or cage-like molecules such as camphor.

The 1:1 acetic acid complex, m.p. 145°, formed needle-like, orthorhombic crystals from a solution of deoxycholic acid in glacial acetic acid: $a = 25{\cdot}55$, $b = 13{\cdot}81$, $c = 7{\cdot}109$ Å; space group $P2_12_12_1$. The *X*-ray intensity data (1795 reflections) were measured on a computer-controlled three-circle diffractometer using Cu-K_α radiation. The phase problem was solved by a combination of Patterson and direct methods. All 44 hydrogen atoms have been found from a difference Fourier synthesis. After refinement by block-diagonal least-squares, the *R* factor is currently 0·10 for all reflections and 0·08 if the 422 unobservably weak reflections are omitted.

In the crystal structure, deoxycholic acid molecules hydrogen bond only with each other, forming pleated sheets which extend in the *y* and *z* directions [Figure (a)]. The hydrogen bonds form a spiral arrangement about the *z*-axis direction, with the sequence ···O=C–OH···O(12)–H···O(3)–H···O=C–OH···.† The O···O distances are 2·67, 2·73, and 2·76 Å respectively, with e.s.d.'s of 0·01 Å. The hydrogen-bonded pleated sheets of deoxycholic acid molecules are stacked in the *x* direction so as to leave tunnels which are parallel to *z*. There are only weak van der Waals interactions between adjacent sheets, *i.e.*, across the planes $x = \frac{1}{4}$ and $\frac{3}{4}$. The acetic acid molecules are hydrogen bonded to form chains [Figure (b)] which are very similar to those found in the crystal structure of acetic acid itself.[3] The O···O hydrogen bonding distance is 2·67 Å. The

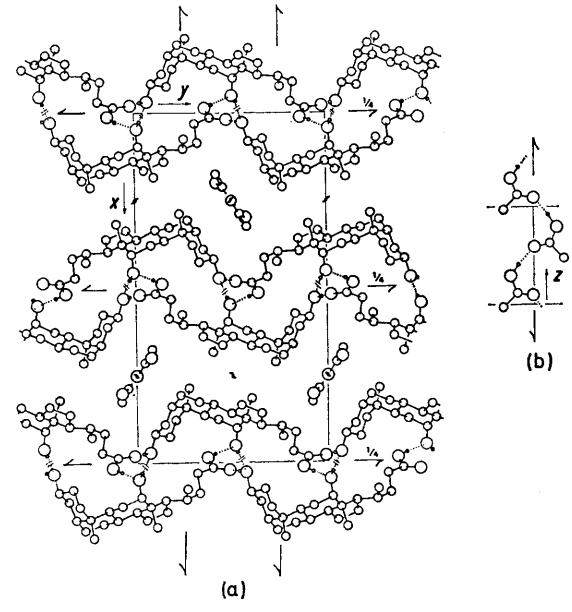

FIGURE. *The crystal structure of the* 1:1 *complex of deoxycholic acid and acetic acid. Hydrogen atoms are omitted except for those involved in hydrogen bonding.* (a) *Projection in the* z*-direction.* (b) *A chain of hydrogen bonded acetic acid molecules. This projection is on to the plane passing through the carboxy-carbon atoms.*

shortest non-bonded C···C distances between molecules of acetic and deoxycholic acids are 3·56 Å, involving the carboxy-carbon atom of acetic acid and C(6), and 3·87 Å between the methyl carbon atom of acetic acid and C(22). There is no evidence of disordering of acetic acid molecules.

In each tunnel, a model shows that the acetic acid chain could be replaced by one and perhaps two parallel hydrocarbon chains. There are also tunnel side pockets which could

† The deoxycholic acid atoms are numbered according to the convention for steroid molecules.

hold methyl branchings. Alternatively, the tunnels are large enough for anthracene or camphor molecules. Earlier *X*-ray studies[4] show that choleic acids containing butyric, lauric, palmitic, stearic, and α-bromostearic acids have similar cell dimensions to that of the acetic acid complex, but with space group $P2_12_12$ rather than $P2_12_12_1$.‡ A structure in $P2_12_12$ can be derived by stacking of the deoxycholic acid sheets as in the Figure with a slip of $\pm c/4$ between adjacent sheets.

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‡ The detailed crystal structures which have been proposed for these complexes are dissimilar from that of the acetic acid complex, but are unreliable, since they are based on inadequate diffraction data.

[1] H. Wieland and H. Sorge, *Z. physiol. Chem.*, 1916, **97**, 1.
[2] H. Sobotka, *Chem. Rev.*, 1934, **15**, 311; L. F. Fieser and M. Fieser, 'Steroids', Reinhold, New York, 1959; C. Asselineau and J. Asselineau, *Ann. Chim.*, 1964, **9**, 461; W. C. Herndon, *J. Chem. Educ.*, 1967, **44**, 724.
[3] R. E. Jones and D. H. Templeton, *Acta Cryst.*, 1958, **11**, 484.
[4] Y. Go and O. Kratky, *Z. physik. Chim.*, 1934, **B26**, 439; V. Caglioti and G. Giacomello, *Gazzetta*, 1939, **69**, 245; H. Fischmeister, *Monatsh.*, 1954, **85**, 182.