Crystal Structure of Cholesteryl 17-Bromoheptadecanoate

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Summary The structure of cholesteryl 17-bromoheptadecanoate has been determined by *X*-ray diffraction; the 2 molecules in the asymmetric unit differ mainly in the conformation about the chain carbon atoms near the ester group and there are alternating regions with cholesterol and hydrocarbon chain packing ($O_{\perp}$).

IN connection with our studies of lipids of relevance to the structure of biological membranes, *X*-ray single crystal analyses are being performed on cholesteryl esters to provide information on the molecular packing and conformation of compounds containing both a steroid skeleton and a hydrocarbon chain. As cholesteryl esters are the major component in atherosclerotic lesions, detailed structural information is also desirable for an understanding of the deposition phenomena from the plasma micelles.

Unit cell data on cholesteryl esters were reported by Abrahamsson and Selin[1] who also indicated that the stearate was isostructural with the ω-bromine substituted cholesteryl ester. Later, cell dimensions of a whole series of esters were reported by Barnard and Lydon,[2] and phase analyses have been performed by Wendorff and Price.[3] The complete three-dimensional structure of the bromine-substituted ester ($C_{44}H_{77}BrO_2$) has now been determined. The compound was prepared from 17-bromoheptadecanoic acid chloride and cholesterol in the presence of pyridine. Crystals, m.p. 77·0—77·5 °C, were grown from acetic acid–ethyl acetate. The unit cell is monoclinic, space group

$P2_1$, with $a = 7{\cdot}663(2)$, $b = 10{\cdot}311(5)$, $c = 55{\cdot}963(22)$ Å, $\beta = 103{\cdot}10(3)°$. (This represents a cell transformation compared to that given in ref. 1). The asymmetric unit contains two independent molecules. 2848 reflexions were recorded on a Picker FACS1 diffractometer. Of these, 2112, with $I > 4\sigma(I)$ were used in the structure analysis. The structure was determined by the heavy-atom technique and refined by full-matrix least-squares methods. Hydrogen atoms were included at their calculated positions (C–H 1·00 Å). Owing to the large number of parameters when using anisotropic temperature factors for all non-hydrogen atoms the structure was divided into four parts which were varied separately. The present R-value is 0·089.

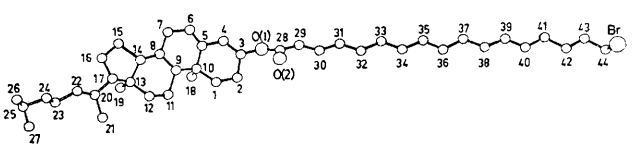

FIGURE 1. Spacial drawing of cholesteryl 17-bromoheptadecanoate showing the atomic numbering.

The structure is shown in Figures 1 and 2. Regions with packing of steroid skeleta alternate with regions of hydrocarbon chain packing. Through a 'head to tail' arrangement of the molecules the cross sectional area of each cholesterol residue corresponds to that of two carbon chains. A similar situation exists in glycolipids.[4] The carbon-chain axes make an angle of 27° with the direction of maximum extension of the steroid skeleta [C(3) and C (17)] thereby effectively increasing the area of the chains by 12% compared to that in a fully extended molecule. The steroid skeleta are translated relative to each other in the direction of maximum extension so that C(19) on the five-membered ring is in packing contact with C(7) of a neighbouring molecule (3·85 Å). In cholesterol sulphate[5] the corresponding closest contact of C(19) with the ring system is to C(17). In both structures the cholesterol side packing leaves space around the side chains, with resulting large thermal vibrations and/or disorder. Thus, whereas the atomic co-ordinates of most atoms are well determined, the ends of the side chains [C(25)—C(27)] have very large standard deviations. Considering this, all bond distances and angles are as expected.

The hydrocarbon chain side packing is of the common orthorhombic type ($O_\perp$) with the subcell dimensions $a_s = 7{\cdot}50$, $b_s = 5{\cdot}16$, $c_s = 2{\cdot}54$ Å.

The structure solution was complicated by the fact that the heavy atoms do not lie as expected forming an all *trans* extended chain. Instead the arrangement around the C(43)—C(44) bonds is *gauche* with torsion angles of *ca.* 80° in both molecules. A similar conformation was found earlier in an ω-iodine-substituted long-chain compound.[6] With a *trans* conformation the bromine atoms would have

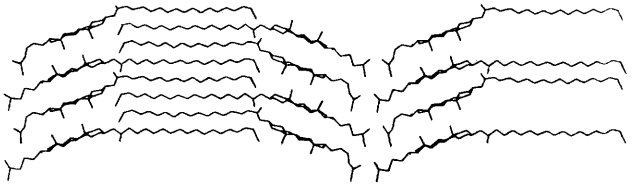

FIGURE 2. Molecular packing in cholesteryl 17-bromoheptadecanoate.

come too close to the steroid skeleta whereas now the heavy atoms have normal, symmetrical van der Waals environments. Although the two molecules of the asymmetric unit differ only slightly in the torsion angles about the C(43)—C(44) bonds, there are large conformational differences near the ester group. Thus, in one molecule the torsion angle about the C(28)—C(29) bond is −170°, *i.e.* the ester oxygen O(1) extends the zig-zag chain, but in the other molecule the corresponding angle is 82°. The side-chains of the molecules also differ in conformation.

During the course of this analysis it became known to us that the crystal structure of cholesteryl myristate has been determined.[7] The two compounds are not isostructural but the general packing principles are the same with alternating regions of cholesterol and hydrocarbon chain packing.

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