Crystal Structures of Cholic Acid–Aniline and –3-Fluoroaniline Inclusion Compound; Fluorine Atom Effect on Channel and Hydrogen Bonding Pattern

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X-Ray crystallographic studies of cholic acid (CA)–aniline and –3-fluoroaniline (3-FA) show that F substitution changes the structure: introducing a second channel and altering the hydrogen bonds around the amino group.

During the past several decades, numerous X-ray studies have been undertaken to clarify the crystal structures of inclusion compounds.[1] Naturally occurring cholic acid (CA), deoxycholic acid (DCA) and apocholic acid (ACA) have been known to form inclusion compounds with a variety of 'guest' molecules[2,3] and several crystal structures of CA, DCA and ACA complexes have been reported.[4] Almost all the X-ray studies have shown that these inclusion compounds form amphiphilic layered structures, with only one kind of channel within hydrophobic layers. Here we report the crystal structures of inclusion complexes of CA–aniline† and –3-fluoroaniline (3-FA), demonstrating that in the CA–3-FA complex novel channel-like spaces are formed besides the conventional channels only by adding F atoms into aniline. To our knowledge this is the first example of 'double channel' type inclusion complex of bile acids.

Colourless needle-like crystals of the CA–aniline and –3-FA complexes were obtained from solutions of CA in aniline and 3-FA, respectively. The crystal structures are depicted in Fig. 1.‡ The molecular conformation of CA for CA–aniline is essentially the same as that observed in CA–3-FA besides the side chains.§ The packing of CA molecules and the arrangement of hydrogen bonds is similar in the two compounds; CA molecules are arranged to form the amphiphilic layered structure, presenting the channels (channel A) within hydrophobic layers, in which guest molecules are accommodated. It must be noted that CA molecules of CA–3-FA form another kind of channel (channel B) between the steroidal *B*, *C* and *D* rings within the hydrophobic layers, in which 3-FA molecules are also included. The formation of channel B is indirectly due to the steric repulsion between adjacent 3-FA molecules inside channel A. The hypothetical structure of CA–3-FA based on

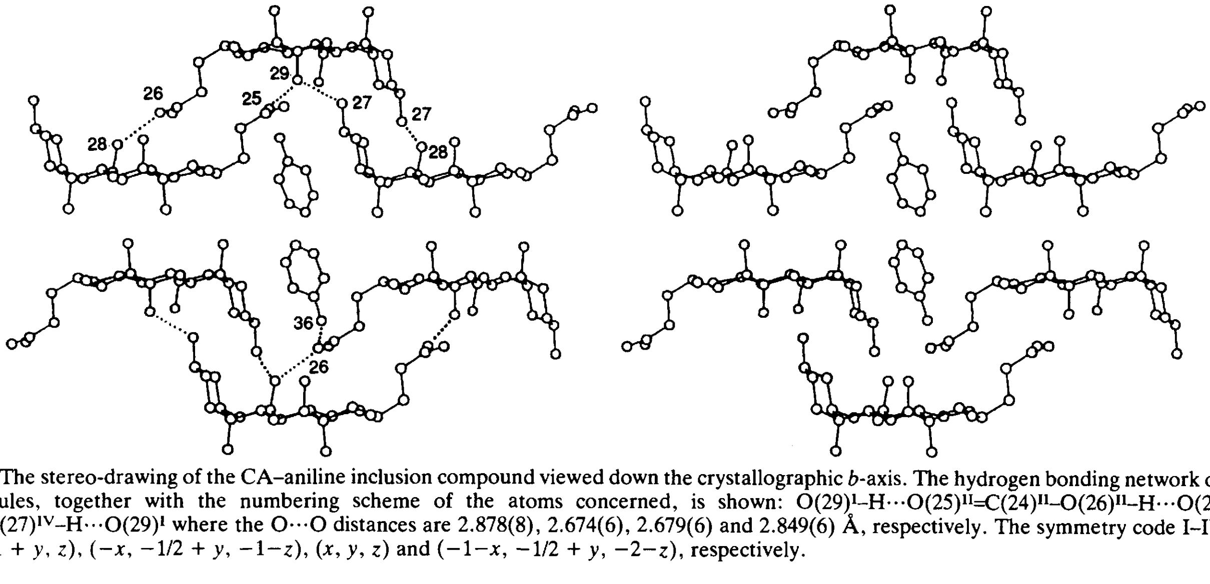


Fig. 1 The stereo-drawing of the CA–aniline inclusion compound viewed down the crystallographic *b*-axis. The hydrogen bonding network of CA molecules, together with the numbering scheme of the atoms concerned, is shown: $\mathrm{O(29)^{I}–H\cdots O(25)^{II}{=}C(24)^{II}–O(26)^{II}–H\cdots O(28)^{III}–H\cdots O(27)^{IV}–H\cdots O(29)^{I}}$ where the O···O distances are 2.878(8), 2.674(6), 2.679(6) and 2.849(6) Å, respectively. The symmetry code I–IV are $(x, -1 + y, z)$, $(-x, -1/2 + y, -1-z)$, (x, y, z) and $(-1-x, -1/2 + y, -2-z)$, respectively.

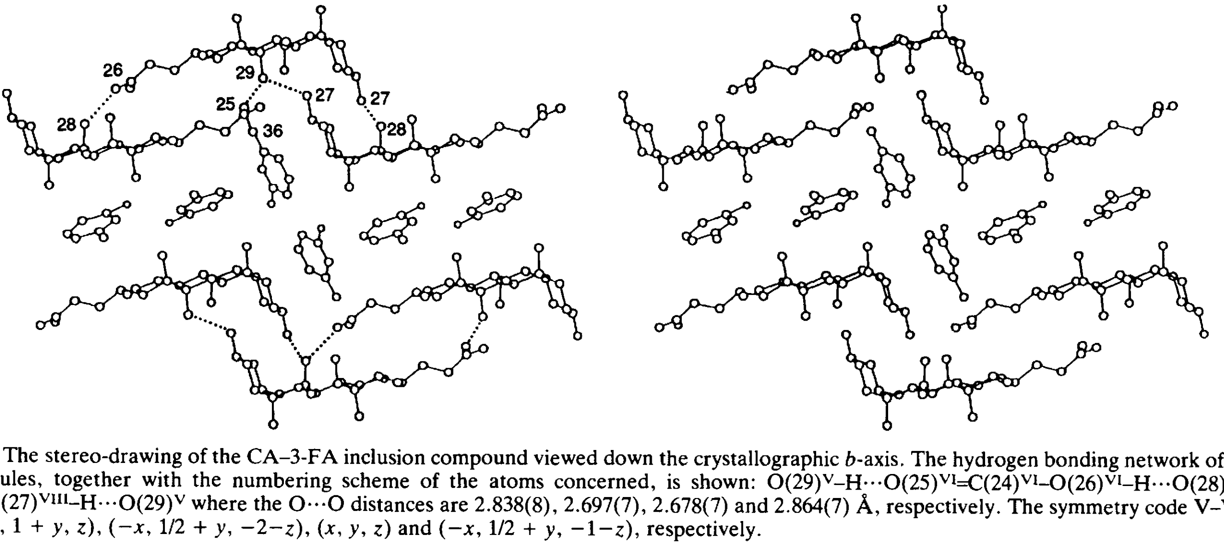
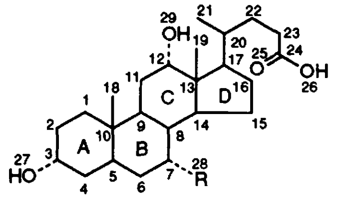
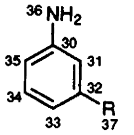


Fig. 2 The stereo-drawing of the CA–3-FA inclusion compound viewed down the crystallographic *b*-axis. The hydrogen bonding network of CA molecules, together with the numbering scheme of the atoms concerned, is shown: $\mathrm{O(29)^{V}–H\cdots O(25)^{VI}{=}C(24)^{VI}–O(26)^{VI}–H\cdots O(28)^{VII}–H\cdots O(27)^{VIII}–H\cdots O(29)^{V}}$ where the O···O distances are 2.838(8), 2.697(7), 2.678(7) and 2.864(7) Å, respectively. The symmetry code V–VIII are $(x, 1 + y, z)$, $(-x, 1/2 + y, -2-z)$, (x, y, z) and $(-x, 1/2 + y, -1-z)$, respectively.

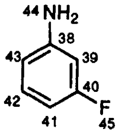


Cholic acid : R = OH
Deoxycholic acid : R = H
Apocholic acid : R = H (8, 14 en)

In channel A:



In channel B:



Aniline R = H
3-Fluoroaniline R = F

CA–aniline structure would support this idea.¶ In this hypothetical structure, there are several too close contacts (distances of 1.939 and 2.125 Å) between the F and atomatic H atoms inside channel A.|| Therefore, the deformation of channel A occurs approximately along the *c*-axis to avoid steric repulsion, followed increase in the separation of the hydrophobic layers. Channel B would emerge in this manner.

As shown in Fig. 1,[7] the N atom of aniline is hydrogen bonded to O(26)$^{\mathrm{II}}$ and O(29) at distances of 3.26(2) and 3.23(1) Å, respectively. Fig. 2 shows that 3-FA molecule is situated in channel A in a similar manner to aniline. The N atom is hydrogen bonded to O(25)$^{\mathrm{IX}}$ [IX: $(-1-x, -1/2+y, -2-z)$] and O(29)$^{\mathrm{X}}$ [X: $(-1+x,y,z)$] at distances of 3.20(1) and 3.136(10) Å, respectively. That is, the N atom of 3-FA is hydrogen bonded to the carbonyl O atom of the CO_2H group. By contrast, that of aniline is hydrogen bonded to hydroxy O atom of the CO_2H group. The change in the hydrogen bonding pattern shows that the character of the amino group changes from hydrogen bonding acceptor to donor by the addition of an F atom into the benzene ring. One explanation is that the acidity of the amino H increases by adding an F atom to the benzene ring so that amino group prefers to bond to the carbonyl O rather than the hydroxy O atoms of the CO_2H group. The F atom also alters the bonding mode between the amino group and the O(29) atom, as can be seen from the difference of symmetry code. However, no intermolecular hydrogen bonds are observed between CA and 3-FA in channel B, in contrast to 3-FA in channel A. This lack of hydrogen bonding would cause large thermal vibration of 3-FA in channel B. Temp. factors [B(eq) (Å^2)] of 3-FA are as follows: C(38) 21(1), C(39) 12.4(9), C(40) 14(1), C(41) 12.3(7), C(42) 24(1), C(43) 21(1), N(44) 27(1), F(45) 35.1(10).

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Footnotes

† When the X-ray structural work on the CA–aniline complex was completed, it came to our notice that Caira and coworkers had carried out the X-ray analysis of this complex.[5]

‡ *Crystal data* for CA–aniline: $C_{24}H_{40}O_5{+}C_6H_7N$, M = 501.71, monoclinic, space group $P2_1$, a = 13.801(3) Å, b = 8.066(3) Å, c = 14.094(3) Å, β = 116.01(1)°, V = 1409.9(7) Å^3, Z = 2, D_c = 1.182 g cm^{-3}. For CA-3-FA: $C_{24}H_{40}O_5{+}2C_6H_6FN$, M = 630.81, monoclinic, space group $P2_1$, a = 14.326(3) Å, b = 7.847(3) Å, c = 16.125(3) Å, β = 106.58(1)°, V = 1737.4(7) Å^3, Z = 2, D_c = 1.206 g cm^{-3}. Intensity data were collected by ω–2θ scan mode with 2θ up to 120.1 and 120.2° for CA–aniline and -3-FA, respectively on a Rigaku AFC7R diffractometer using Cu-Kα radiation. The structures were solved by the direct methods (MULTAN 88 & DIRDIF92 for CA–aniline and SHELXS86 and DIRDIF92 for CA-3-FA) and refined by full-matrix least-squares procedure. The final R values are 0.050 for 1448 [$I > 3.00\sigma(I)$] reflections for CA–aniline and 0.060 for 1925 [$I > 3.00\sigma(I)$] reflections for CA-3-FA. The absolute configurations were established by Hamilton's method.[6] That is, the final R values are 0.053 and 0.063 for the inverted CA–aniline and -3-FA structures with molecules of opposite hand, respectively. Consequently, we determined the original configurations are correct. In fact, both the configurations of the present structures are in accord with those of previously reported structures.[4c,d,5] All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation. 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.

§ The C(17)–C(20)–C(22)–C(23) dihedral angles for CA–aniline and -3-FA are 61.2(8) and −166.1(8)°, respectively: these values correspond to *gauche* and *anti*, respectively. The difference would be due to the deformation of channel A.

¶ The hypothetical CA-3-FA structure was made merely by replacing the H atom attached to C(34) in benzene ring with F atom in CA–aniline structure. The C–F distance is fixed at 1.360 Å.

|| The close contacts take place between the F atom and the H atoms attached to C(32) and C(33) of adjacent 3-FA [symmetry code: $(-x, 1/2+y, -2-z)$].

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