

X-Ray Crystallographic Study of Fluorine Atom Effect on Guest Orientation inside the α -Cyclodextrin Cavity

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X-Ray crystallographic studies of α -cyclodextrin (α -CD)-2- and -4-fluorophenol complexes indicate that the fluorine atom determines the guest orientations inside the α -CD cavity in both complexes, and accordingly that the hydroxy groups of 4-FC₆H₄OH and 2-FC₆H₄OH are located inside and outside the cavity, respectively.

Special attention has been drawn to cyclodextrin (CD) inclusion complexes from the standpoint of enzyme modelling. This is mainly because CD has a hydrophobic cavity which has the ability to include some compounds in a similar way to enzymes. Thus far many crystallographic studies of α -CD complexes have been carried out to clarify the inclusion phenomena of α -CD; most crystallographic analyses have supported the generally accepted concept that the α -CD cavity includes hydrophobic moieties in preference to hydrophilic moieties of guest molecules. We now report the unique crystal structures of α -CD-2-fluorophenol (2-FPhOH) and -4-fluorophenol (4-FPhOH) complexes, which indicate that both the fluorine atoms are located outside the α -CD cavity, and consequently that the hydroxy groups of 4-FPhOH and 2-FPhOH are situated inside and outside the cavity, respectively (PhOH \equiv C₆H₄OH). We find that this is mainly owing to the ability of the fluorine atom to form an intermolecular hydrogen bond.

Colourless prismatic crystals of the present compounds were obtained from aqueous solutions containing α -CD and 2-FPhOH or 4-FPhOH in 1:1 molar ratios. The crystal structure of α -CD-4-FPhOH is depicted in Fig. 1.† The α -CD molecules are arranged in a one-dimensional array along the crystallographic *a*-axis, forming a head to tail channel-type structure. To our surprise, the hydrophobic cavity includes the hydrophilic hydroxy group in preference to the fluorine atom; the fluorine atom is located outside the cavity, *i.e.* in the hydrophilic environment filled with water molecules.‡ The

orientation of 4-FPhOH inside the cavity would be due to the intermolecular hydrogen bond between the fluorine atom and the primary hydroxy group of adjacent α -CD-C-F...H-O intermolecular hydrogen bond, as shown in Fig. 1.§ Murray-Rust *et al.* have reported that the ability to form an intermolecular hydrogen bond by fluorine atoms is weaker than that of hydroxy groups in the crystalline state.³ So, the fact that fluorine atom takes part in forming the inter-

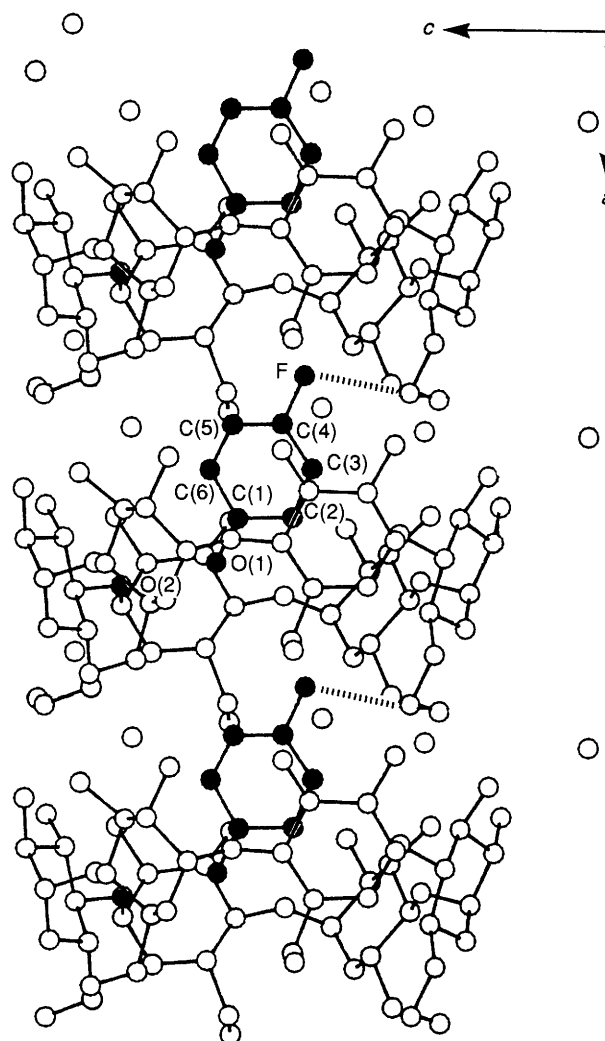


Fig. 1 Crystal structure of α -CD-4-FPhOH, as viewed down along the crystallographic *b*-axis. The hydrogen bond is shown by dotted line. Selected temperature factors [B(eq)] and interatomic distance (Å): C(1) 9.6(7), C(2) 6.9(5), C(3) 5.8(4), C(4) 6.2(5), C(5) 9.1(7), C(6) 10.0(8), O(1) 11.8(6), F 12.1(6); O(1)...O(2) 3.23(1).

† Crystal data: 1 α -CD-4-FPhOH: C₃₆H₆₀O₃₀C₆H₅OF·6H₂O, [ratio established to be 1:1:9 by thermogravimetric analysis (TGA); for both 1 and 2 some water molecules were not found on the electron density map probably owing to the thermal instability of the crystals]. *M* = 1193.0, monoclinic, space group *P*2₁/*a* = 7.845(2), *b* = 13.587(2), *c* = 24.557(2) Å, β = 91.75(1)°, *V* = 2616.3(6) Å³, *Z* = 2, *D_c* = 1.377 g cm⁻³. For 2 α -CD-2-FPhOH: C₃₆H₆₀O₃₀·C₆H₅OF·5H₂O, (ratio established to be 1:1:6 by TGA), *M* = 1175.0, monoclinic, space group *P*2₁, *a* = 7.842(2), *b* = 13.615(2), *c* = 24.550(2) Å, β = 92.27(1)°, *V* = 2619.0(8) Å³, *Z* = 2, *D_c* = 1.376 g cm⁻³. Intensity data were collected by ω -2 θ scan mode with $\sin^2\theta/\lambda$ up to 0.63 Å⁻¹ for α -CD-4-FPhOH and α -CD-2-FPhOH on a Rigaku AFC5R diffractometer using Cu-K α radiation. The structures were solved by the direct methods (MITHRIL, DIRDIF) and refined by full-matrix least-squares procedure. The final *R* values are 0.055 for 3459 [*F_o*] > 3 σ (*F_o*)] reflections for α -CD-4-FPhOH and 0.062 for 3896 [*F_o*] > 3 σ (*F_o*)] reflections for α -CD-2-FPhOH. 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 Notice to Authors, Issue No. 1.

‡ The guest molecule vibrates as a rigid body inside the α -CD cavity. Thus, the temperature factors of F and O(1) should be of nearly equal magnitude and be larger than those of aromatic carbons since the two atoms are situated in almost equivalent positions from the centre of gravity. However, in the case of the 'erroneous' structure obtained by interchanging F and O(1), these conditions are not satisfied with the temperature factors: C(1) 9.6(7), C(2) 6.8(5), C(3) 5.8(4), C(4) 6.3(5), C(5) 9.2(7), C(6) 9.9(8), O(1) 9.5(5), F 14.7(7). In addition, the distance between F and O(2) [3.23(1) Å] is too short for van der Waals contact. On the contrary, the structure in Fig. 1 is consistent with the conditions of the factors and the distance.

§ In a previous paper,¹ we have indirectly suggested that the C-F...H-O intermolecular hydrogen bond exists in α -CD-fluorinated substance complexes in aqueous solution. Further, we have confirmed the existence of the C-F...H-O bond also in solution.²

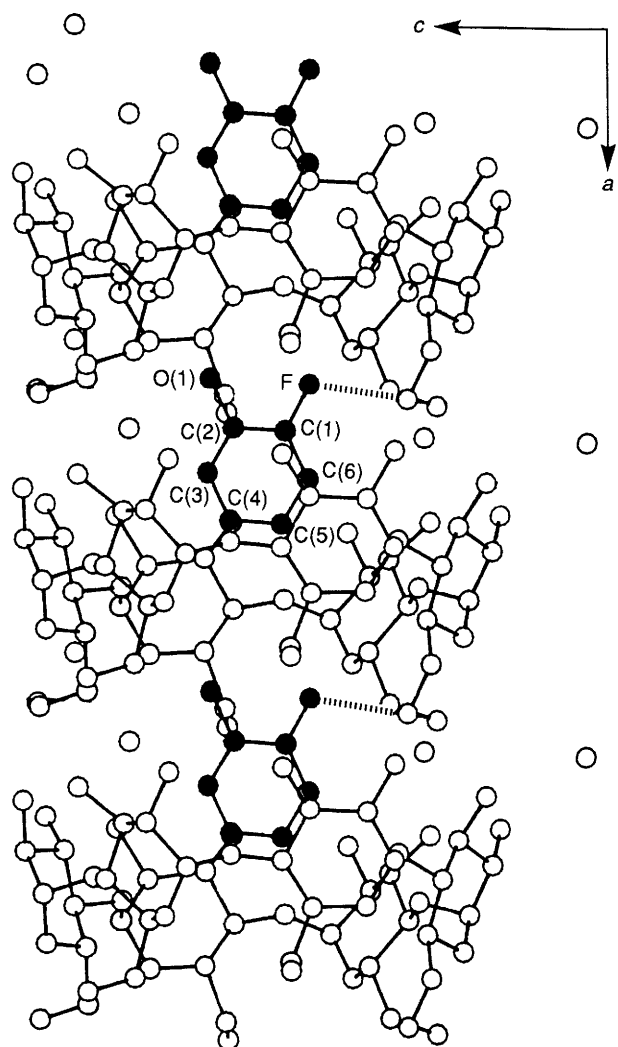


Fig. 2 Crystal structure of α -CD-2-FPhOH, as viewed down along the crystallographic b -axis. The hydrogen bond is shown by dotted line. Selected temperature factors [B(eq)]: C(1) 4.5(5), C(2) 6.2(7), C(3) 8.5(9), C(4) 8(1), C(5) 7.6(8), C(6) 5.2(6), O(1) 8.6(6), F 8.7(5).

molecular hydrogen bond instead of the hydroxy group of 4-FPhOH is in contrast to their report. Whereas, Harata has previously reported the crystal structure of α -CD-4-iodophenol (4-IPhOH):⁴ the structure shows that the cavity includes the hydrophobic iodine atom, whereas the hydroxy group is located outside the cavity and the intermolecular hydrogen bond between the iodine atom of 4-IPhOH and α -CD cannot be observed. These results were distinct from the α -CD-4-FPhOH structure, although both fluorine and iodine atom are in group 7. By comparing α -CD-4-FPhOH with α -CD-4-IPhOH structures, it appears that the orientational difference between 4-FPhOH and 4-IPhOH inside the cavity is principally due to the C-F...H-O intermolecular hydrogen bond and the hydrophobicity difference.

A similar head to tail channel-type structure is observed with α -CD-2-FPhOH as shown in Fig. 2†.¶ The primary hydroxy group of α -CD forms the intermolecular hydrogen bond with fluorine atom similar to α -CD-4-FPhOH complex, nevertheless both the fluorine atom and hydroxy group of 2-FPhOH are located near the α -CD hydroxy group. Further, the spatial position of the fluorine atom of 2-FPhOH in a unit cell is essentially identical to that of 4-FPhOH, so that it appears that the fluorine atoms indeed determine the orientations of 2-FPhOH or 4-FPhOH inside the cavity by forming the C-F...H-O intermolecular hydrogen bond; the hydroxy group, by contrast, has no effect on the orientation.

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¶ Because of similar reasons as for α -CD-4-FPhOH, the structure in Fig. 2 is correct. That is, supposing the structure obtained by interchanging F and O(1) is correct, the conditions of the temperature factors mentioned above cannot be satisfied with the factors: C(1) 4.4(4), C(2) 5.8(5), C(3) 8.3(7), C(4) 8.5(8), C(5) 7.4(7), C(6) 5.4(5), O(1) 6.5(4), F 10.1(5).