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Crystal Structures of β-Cyclodextrin and Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin Complexes with Carmofur

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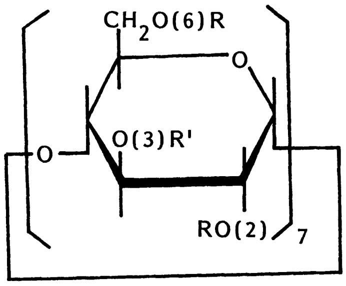
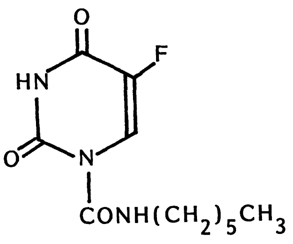
Two β-cyclodextrin molecules form a head-to-head dimer, into which the hexyl group of carmofur is inserted from the primary hydroxyl side. The fluorouracil moiety is located outside the host cavity and forms a face-to-face dimer with another one related by a pseudo twofold axis. The carmofur molecule in the heptakis(2,6-di-*O*-methyl)-β-cyclodextrin complex is disordered and occupies two sites. One is located outside the host cavity, while the hexyl group of the other is inserted into the host macrocycle.

The solubility and bioavailability of carmofur (1-hexylcarbamoyl-5-fluorouracil), which is one of the masked forms of 5-fluorouracil, are improved by the 1:1 complexation with β-cyclodextrin (β-CDx) or heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CDx).[1)] However, consisting of the fluorouracil group and a long alkyl chain of the hexyl group, carmofur is too large to be fully included by these hosts. The X-ray structure determination of the carmofur complexes with β-CDx and DM-β-CDx has been performed to elucidate how the guest carmofur is included within the host cavity.



β-CDx : R=R'=H
DM-β-CDx : R=CH_3, R'=H

Lattice parameters and diffraction intensity data were measured on a Nicolet P3/F diffractometer with graphite-monochromated Cu Kα radiation. Using θ-2θ scan mode, 5392 (β-CDx complex) and 4143 (DM-β-CDx complex) reflections with $|F_o| \geqq 3\sigma(F_o)$ were collected up to 100° (β-CDx complex) and 110° (DM-β-CDx complex) in 2θ. No corrections were made for



carmofur

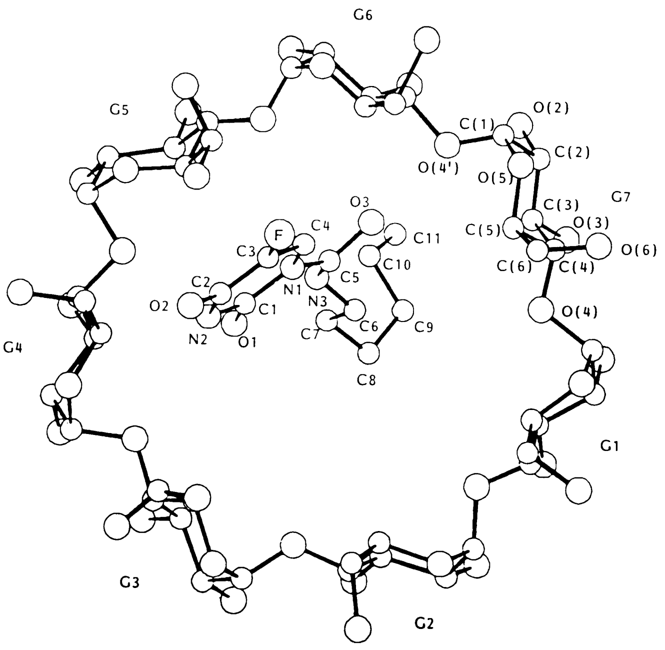


Fig. 1. The structure of the β-CDx complex with carmofur (molecule A).

absorption or extinction effects. Crystal data were: (1) β-CDx complex, $2(C_{42}H_{70}O_{35}\cdot C_{11}H_{15}O_3N_3F)\cdot 19.4 H_2O$, F.W.=3084.0, monoclinic, space group $P2_1$, Z=2, a=15.507(3), b=35.307(9), c=15.495(4) Å, β=102.68 (2)°, V=8277(3) Å^3, D_x=1.237 g·cm^{-3}, (2) DM-β-CDx complex, $C_{56}H_{98}O_{35}\cdot C_{11}H_{15}O_3N_3F\cdot 3H_2O$, F.W.=1637.7, monoclinic, space group $P2_1$, Z=2, a=15.697(3), b=18.533(3), c=15.947 (3) Å, β=106.64(2)°, V=4453(1) Å^3, D_x=1.221 g·cm^{-3}.

The structure of the β-CDx complex was elucidated by the R-map method using the β-CDx coordinates of the benzil complex.$^{2)}$ At the initial stage of the refinement, the orthorhombic space group $C222_1$ had been assumed from the intensity distribution. In the course of refinement, the guest molecule did not clearly appear in the Fourie and difference-Fourie maps owing to the disorder caused from the pseudo-orthorhombic symmetry. Then, the space group symmetry was reduced to $P2_1$ and the refinement was continued. Since the least-squares refinement of atomic parameters of carmofur was unsuccessful, the fluorouracil moiety was refined by adopting the rigid-body approximation and the hexyl group was refined by restricting the C-C bond length within a suitable range (1.50-1.55 Å). The refinement with isotropic temperature factors for β-CDx achieved the R-value of 0.16. The structure of the DM-β-CDx complex was solved by the R-map method with a model structure having a sevenfold symmetry. The DM-β-CDx molecule was anisotropically refined. The guest carmofur, which was found to be disordered, were refined by the same procedure used in the refinement of the β-CDx complex. The R-value was 0.13.

Table 1. Geometrical Data Describing the Macrocyclic Conformation of Hosts
Average values for seven residues are given with standard deviations

	β-CDx(A)	β-CDx(B)	DM-β-CDx
Radius of the O(4) heptagon (l/Å)	5.06(2)	5.05(3)	5.06(6)
O(4)---O(4') distance (l/Å)	4.39(9)	4.38(5)	4.39(5)
O(2)---O(3') distance (l/Å)	2.80(4)	2.81(6)	2.85(3)
Tilt-angle (ϕ/°)$^{a)}$	9(2)	8(2)	13(4)
Planarity of seven O(4) atoms (d/Å)$^{b)}$	0.022	0.016	0.073

a) The angle made by the O(4) plane and the plane through C(1), C(4), O(4), and O(4') of each residue. b) The root-mean-square deviation.

The β-CDx molecule has a round structure as shown in Fig. 1. Some parameters describing the macrocyclic conformation are given in Table 1. The seven O(4) atoms form a heptagon with the radius of 5.1 Å and side length of 4.4 Å. There is no significant difference in the conformation of two independent β-CDx molecules, A and B in Fig. 3. The macrocyclic conformation of DM-β-CDx resembles that of parent β-CDx except for methoxyl groups. However, each residue of the DM-β-CDx is more inclined than the glucose residue of the β-CDx as indicated by the tilt-angle (Table 1). The O(2)---O(3') distances suggest the formation of intramolecular hydrogen bonds in both hosts.

The two β-CDx molecules, which are related by a pseudo twofold axis, form a head-to-head dimer as shown in Fig. 3. The O(2), O(3) side of both molecules

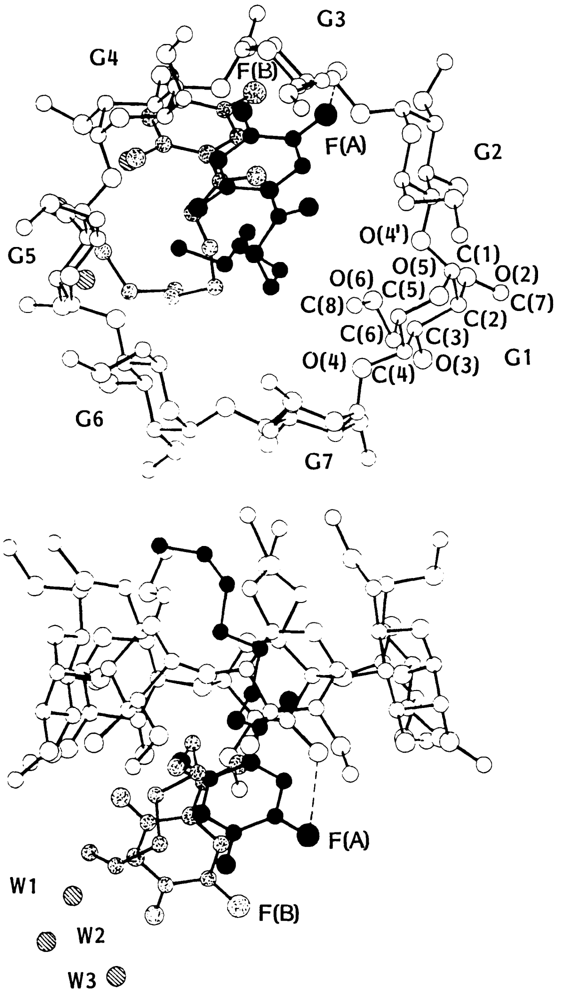


Fig. 2. The structure of the DM-β-CDx complex with carmofur. The carmofur molecule with the higher occupancy (0.6) is shown by full circles and the molecule with the lower occupancy (0.4) is shaded.

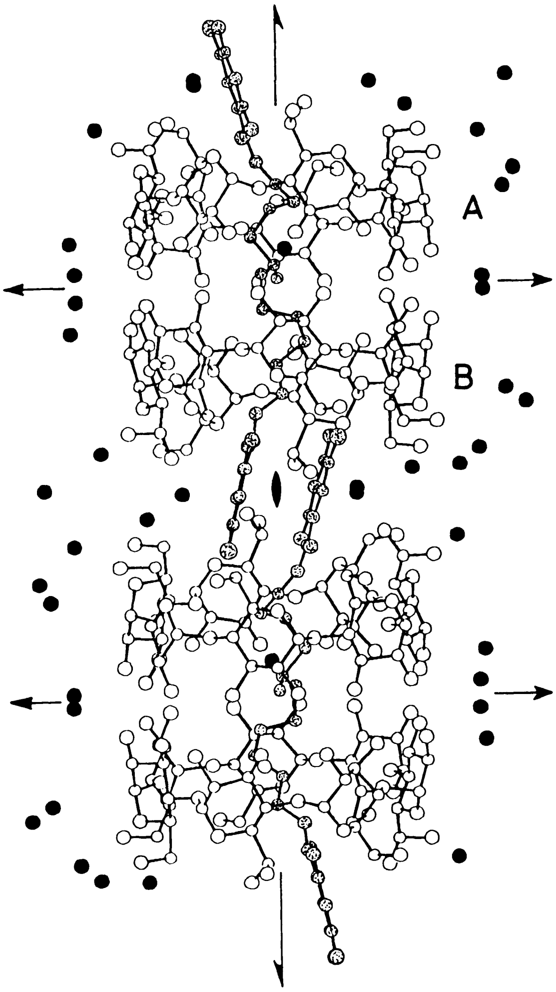


Fig. 3. The stacking feature of the β-CDx complex with carmofur. Carmofur molecules are shaded. Water molecules are shown by full circles. Pseudo twofold symmetry axes and the crystallographic twofold screw axis are shown.

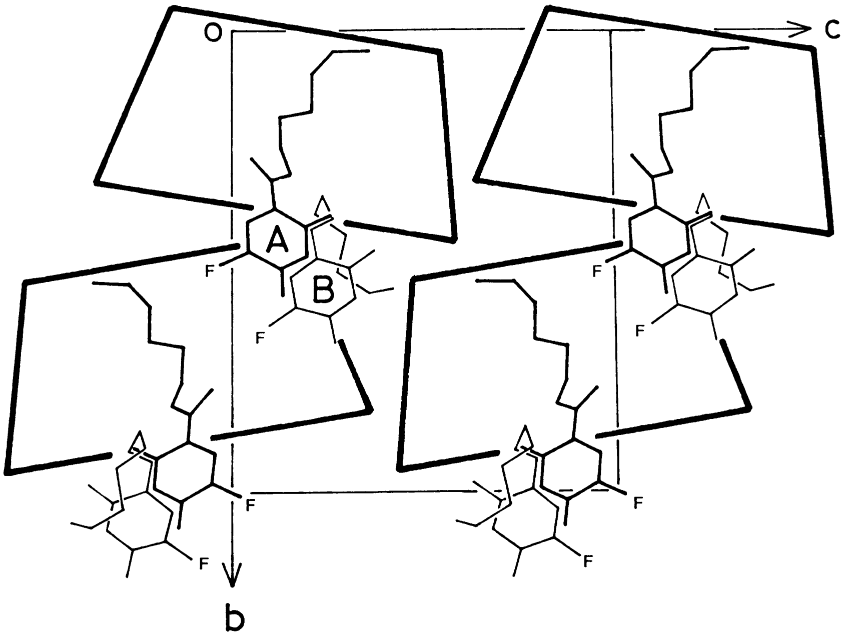


Fig. 4. A schematic drawing of the crystal structure of the DM-β-CDx complex with carmofur viewed along the a axis. The disordered guest is denoted by A and B with the respective occupancy of 0.6 and 0.4

are linked to each other by lots of hydrogen bonds. The β-CDx dimers are arranged along the twofold screw axis to form a column structure. Since the molecular plane of β-CDx makes an angle of 10.3° with the ac plane, the dimers do not form a straight channel but are arranged in a zigzag mode. The hexyl group of carmofur is inserted into the host macrocycle from the primary hydroxyl side. The fluorouracil moiety is not included within the host cavity, but located between two β-CDx dimers along the twofold screw axis and forms a face-to-face dimer with the adjacent fluorouracil moiety related by a pseudo two-fold axis.

The host-guest geometry of the DM-β-CDx differs from other DM-β-CDx complexes reported previously.[3,4] The carmofur molecule is disordered with the occupancies of 0.4 and 0.6. The hexyl group of the molecule with the higher occupancy is extended into the DM-β-CDx cavity from the secondary hydroxyl side. The carmofur molecule with the lower occupancy is not included within the host cavity, but located in the intermolecular space between DM-β-CDx molecules as shown in Fig. 4. The hexyl group is bent so as to be suitably accommodated in the limited space. The DM-β-CDx molecules are arranged parallel to the ac plane, with which the O(4) plane of DM-β-CDx makes an angle of 10.6°. Adjacent two layers are shifted to each other by about half a molecule. Therefore, DM-β-CDx molecules do not form a continuous channel and the host cavity is open to the intermolecular space where the fluorouracil moiety is located.

References

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