The X-Ray Structure of an Inclusion Complex of Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin with 2-Naphthoic Acid

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An X-ray structure determination of heptakis(2,6-di-*O*-methyl)-β-cyclodextrin–2-naphthoic acid inclusion complex reveals that the naphthyl group is lengthwise inserted into the host cavity with an inclination angle of *ca.* 30° to the pseudosymmetry axis of the host molecule.

Cyclodextrins form inclusion complexes with a variety of guest molecules.[1] Complex formation affects both the physicochemical properties of the guest and chemical reactions involving the complexation reaction.[2] The inclusion of aromatic side-chain groups by cyclodextrins destabilizes native conformations of globular proteins by shifting the equilibrium in favour of the unfolded polypeptide chain.[3] The sulfonation of β-cyclodextrin (β-CD) with 2-naphthylsulfonyl chloride produces 6-*O*-substituted β-CD in pyridine while 3-*O*-substituted β-CD is a major product in aqueous solution where the naphthyl group has been considered to be included in the β-CD cavity.[4] The elucidation of such a regioselective reaction requires the knowledge of the structure of inclusion. The disposition of the guest molecule within the host cavity largely depends on its size and shape. In complexes with β-CD with substituted naphthalenes, two possible orientations of the napthalene ring have been discussed. In a previous paper on the circular dichroism study,[5] we suggested that the 2-substituted naphthalene ring is included with its long axis parallel to the pseudosymmetry axis of β-CD. On the other hand, crosswise inclusion has been suggested for complexes with other naphthalene derivatives.[6,7] We report herein the structure of heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CD) complex with 2-naphthoic acid.‡ This is the first crystallographic structure of the inclusion of the naphthalene moiety in the β-CD cavity.

Fig. 1 shows the structure of the DM-β-CD complex with naphthoic acid. The DM-β-CD molecule is in a round structure that is maintained by seven O(3)–H···O(2) inter-residue hydrogen bonds. The distance between O(2) and O(3) of the adjacent reside is in the range 2.80–2.91 Å. The average values of radius and side length of the heptagon composed of O(4) atoms, 5.03 and 4.39 Å, are in good agreement with

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‡ *Crystal data for*: $C_{56}H_{98}O_{35}\cdot C_{11}H_8O_2\cdot 3H_2O$, M = 1557.6, orthorhombic, space group $P2_12_12_1$, a = 15.436(2), b = 18.922(1), c = 27.852(2) Å, U = 8149(1) Å^3, Z = 4, D_x = 1.270 g cm^{-3}. 4458 Independent reflections with $|F_o| > 3\sigma(F)$ were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu-Kα radiation (θ–2θ scan mode). The structure was solved by the molecular replacement method using a computer-generated molecular model with the sevenfold symmetry and refined to R = 0.073 by the block-diagonal least-squares method. Atomic coordinates, bond distances and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

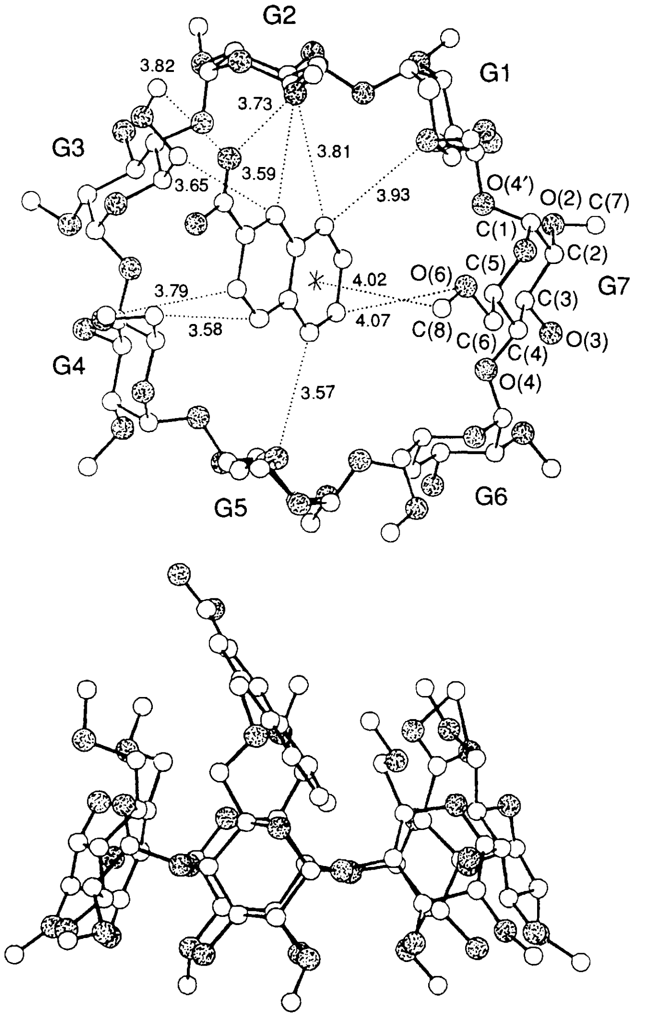

Fig. 1 Structure of the DM-β-CD complex with 2-naphthoic acid. Oxygen atoms are shown by shaded circles. * in the naphthalene ring denotes the centre of the six-membered ring. The O(6) atom of the G1 residue is disordered and the C(6)–O(6) bond shows *gauche–gauche* [to the C(5)–O(5) and C(4)–C(5) bonds, respectively] and *gauche–trans* conformations.

those of native β-CD.[8] The naphthyl group is lengthwise inserted into the host cavity from the O(6) side and makes an angle of *ca.* 30° with the molecular axis of DM-β-CD. The naphthalene moiety is included within the host cavity while the carboxy group is found outside the cavity. The naphthyl group inclines towards the G3 and G4 residues and is in van der Waals contact with the 6-CH_2 groups and 8-Me groups. The C(6)–O(6) bond of these residues is in a *gauche–gauche* conformation, which avoids unfavourable short contact between O(6) oxygen atoms and the naphthyl group. On the other hand, the C(6)–O(6) bond of the G7 residue is in a *gauche–trans* conformation and the 8-Me group is located on the naphthyl plane with the distance of 4.0 Å. The O(6) oxygen atoms of the G2 and G5 residues are also in van der Waals contact with the naphthyl group. Therefore, the guest molecule is favourably accommodated at the O(6) side of the cavity. Further penetration into the cavity may reduce the van der Waals contact since the O(2), O(3) side of the cavity is wider than the O(6) side. The 8-Me group seems to play an important role to fix the guest molecule in the cavity. We have tried to solve several β-CD complexes with naphthalene derivatives but failed to locate the guest molecule because of the disorder. The 6-OMe group of DM-β-CD changes its conformation to be in good contact with the guest molecule. The O(6) oxygen atoms contact with hydrogen atoms of the naphthyl group while the 8-Me and 6-CH_2 groups have contacts with π-electrons of the aromatic ring.

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