Communications to the Editor

[Chem. Pharm. Bull. 31(4)1428—1430(1983)]

STRUCTURE OF β-CYCLODEXTRIN INCLUSION COMPLEX WITH NICOTINAMIDE

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The crystal structure of the β-cyclodextrin–nicotinamide (1:1) complex hexahydrate was determined by the X-ray method. The β-cyclodextrin ring is round in shape with seven intramolecular hydrogen bonds between secondary hydroxyl groups. The nicotinamide molecule is included in the host β-cyclodextrin cavity with the pyridine moiety being located at the center of the cavity. The amido group protrudes outside from the primary hydroxyl side of β-cyclodextrin and forms hydrogen bonds with adjacent β-cyclodextrin and water molecules.

KEYWORDS———β-cyclodextrin; nicotinamide; inclusion complex; single crystal; X-ray analysis; crystal structure

Cyclodextrins form a number of inclusion complexes with biologically and pharmaceutically important substances. Some chemical and physical properties of guest molecules are affected by the complex formation. For instance, the solubility of many sparingly water-soluble materials increases in the presence of cyclodextrins, so cyclodextrins have been investigated for use as a solubilizing and/or stabilizing reagent for pharmaceuticals.[1,2] On the other hand, cyclodextrins also form crystalline complexes with oily or volatile materials and compounds with high solubility in water.[3] The β-cyclodextrin complex with nicotinamide has been obtained from a β-cyclodextrin–nicotinamide ground mixture and an aqueous solution containing an excess amount of nicotinamide.[4] It has been suggested that the crystal of this complex has a cage-type structure in spite of a relatively large guest molecule. In the present paper, we deal with the crystal structure of the β-cyclodextrin–nicotinamide complex, showing direct evidence for the formation of an inclusion complex.

The β-cyclodextrin–nicotinamide complex was crystallized from an aqueous solution containing 200 mg β-cyclodextrin and 2 g nicotinamide in 5 ml hot water, and allowed to stand for a month in a refrigerator. The lattice parameters and diffraction intensities were measured on a Nicolet P3/F diffractometer with graphite-monochromated CuKα radiation. The crystal data were as follows: $C_{42}H_{70}O_{35}\cdot C_6H_6N_2O\cdot 6H_2O$; F.W.=1365.2; monoclinic; space group $P2_1$; $Z=2$; $a=15.373(2)$; $b=10.367(1)$, $c=20.433(2)$, $\beta=110.46(1)°$; $V=3051.1(6)$ Å^3; $D_x=1.486$, $D_m=1.47$ g·cm^{-3}. By using θ-2θ scan mode, intensity data of 5508 independent reflections with $|F_o| \geqq 3\sigma(F)$ were obtained up to 150° in 2θ. The orientation of the molecular axis of β-cyclodextrin was deduced

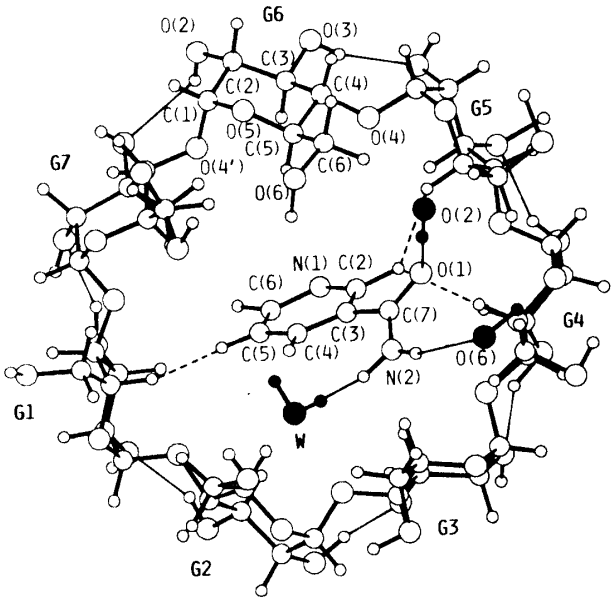

Fig. 1. An Inclusion Feature of the Complex
Black circles denote atoms in water (W) and hydroxyl groups (O(2) and O(6)) of symmetry-related adjacent β-cyclodextrin molecules. Hydrogen bonds are denoted by thin lines. Dashed lines indicate host–guest contact less than 2.4 Å.

from a Patterson map. The atomic positions in the unit cell were determined by the trial-and-error method combined with rotation about the molecular axis and the rigid-body least-squares technique. The block-diagonal least-squres refinement, including 86 hydrogen atoms found on a difference-Fourier map, achieved the R-value of 0.040.

The β-cyclodextrin molecule is in the shape of a truncated heptagonal cone; the O(4)···O(4) distances between adjacent glucose residues are in the range 4.283—4.471 Å, and the distances from the center of gravity of seven O(4) atoms to each individual O(4) atom are in the range 4.887—5.195 Å. Four of the primary hydroxyl groups in G1, G4, G5, and G6 residues show a *gauche-gauche* conformation, while those in the G2 and G3 residues are in a *gauche-trans* conformation. A statistical disorder between *gauche-gauche* and *gauche-trans* conformations is found in the orientation of the C(6)–O(6) bond in the G7 residue. Secondary hydroxyl groups form intramolecular hydrogen bonds between adjacent glucose residues: four O(3)–H··· O(2) and three O(2)–H···O(3) hydrogen bonds. The tilt-angle of glucose residues, defined as a dihedral angle between two planes, that is, one through seven O(4) atoms and the other through C(1), C(4), O(4), and O(4') atoms of each residue, varies from -3.3° to 27.9°. These indicate that the macrocyclic ring has an almost round but somewhat distorted heptagonal structure.

As shown in Fig. 1, the nicotinamide molecule is included into the β-cyclodextrin cavity. The pyridine moiety is located nearly at the center of the cavity, while the amido group protrudes outside from the O(6) side of the cavity. The amido group forms three hydrogen bonds with symmetry-related adjacent β-cyclodextrin and water molecules. Three host–guest intermolecular hydrogen···hydrogen contacts less than 2.4 Å (twice the van der Waals radius of hydrogen atom) suggest that the guest nicotinamide molecule is bound in the host cavity by van der Waals force and hydrogen bonds. Six water molecules are distributed to fill the intermolecular spaces, and form a hydrogen bond network in the crystal. β-Cyclodextrin molecules are

stacked along the crystallographic b axis, as shown in Fig. 2. Both ends of the β-cyclodextrin cavity are blocked by adjacent β-cyclodextrin molecules to form a typical cage-type structure. Previously, a similar cage-type structure has been found in β-cyclodextrin complexes with a quite small guest molecule, such as water[5] and ethanol.[6] The present complex indicates that the individual cavity, being isolated, is sufficiently large to accommodate the nicotinamide molecule.

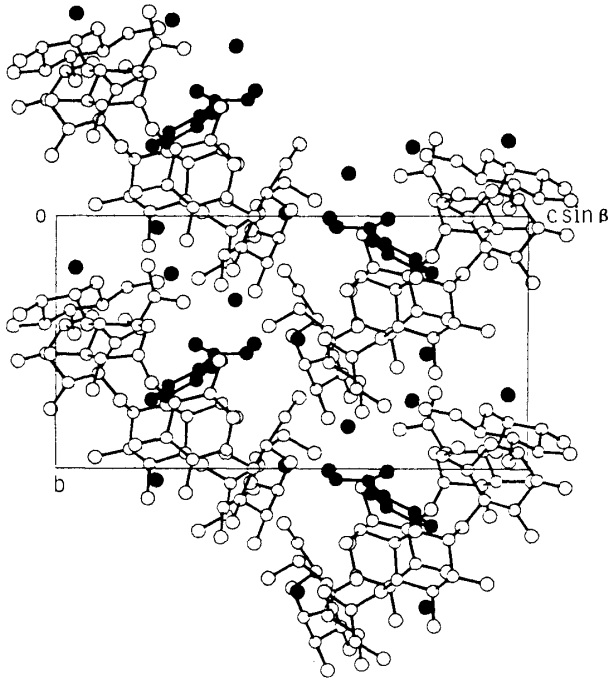

Fig. 2. The Crystal Structure Viewed along the a Axis
Atoms in the nicotinamide and water molecules are shown by black circles.

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(Received February 14, 1983)