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Note

Crystal structures of cyclomaltohexaose (α-cyclodextrin) complexes with *p*-chlorophenol and *p*-cresol

Shin Muraoka, Osamu Matsuzaka, Shigehiro Kamitori *, Kenji Okuyama

Department of Biotechnology and Life Science, Faculty of Technology,
Tokyo University of Agriculture and Technology, 2-24-16 Naka-cho, Koganei, Tokyo 184-8588, Japan

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Abstract

Crystal structures of cyclomaltohexaose (α-cyclodextrin) complexes with *p*-chlorophenol and *p*-cresol have been determined by single-crystal X-ray diffraction studies. The space group of the α-cyclodextrin–*p*-chlorophenol complex is $P2_12_12_1$ with unit cell dimensions of $a = 15.299(3)$, $b = 24.795(5)$, $c = 13.447(5)$ Å, and that of the α-cyclodextrin–*p*-cresol complex is $P2_1$ with unit cell dimensions of $a = 7.927(7)$, $b = 13.568(7)$, $c = 24.54(1)$ Å, $\beta = 90.41(8)°$. In spite of the similar structures of guest molecules, both complexes have different inclusion modes and packing structures. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: X-ray structure; Cyclodextrin; Inclusion compounds; Crystal

1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are cyclic oligosaccharides with α-(1 → 4)$_n$-linked glucose units, where $n = 6$ (α-CD), $n = 7$ (β-CD), or $n = 8$ (γ-CD). These compounds form inclusion complexes with a variety of molecules [1]. CDs have a truncated conical structure (a torus) with the primary hydroxyl groups at the narrow side (head) and the secondary hydroxyl groups at the wide side (tail), as shown in Fig. 1. Many crystal structures of α-CD complexes with various guests have been reported [2], suggesting that a para-substituted phenol is a suitable guest for α-CD. Crystal structures of α-CD complexes with *p*-hydroxybenzoic acid (*p*-$COOHC_6H_4OH$), *p*-nitrophenol (*p*-$NO_2C_6H_4OH$), *p*-iodophenol, and *p*-fluorophenol have been successfully determined [3–5]. Interestingly, in spite of the similar structures of the guest molecules, inclusion modes and packing structures of these complexes are classified into two types. In the complexes of *p*-$COOHC_6H_4OH$, *p*-$NO_2C_6H_4OH$ and *p*-IC_6H_4OH, guest molecules enter deeply into the cavity of the α-CD by way of the para-substituent groups (Type 1 inclusion mode) giving a layered packing structure in their respective crystals. On the other hand, in the complex of *p*-FC_6H_4OH, the guest molecule only shallowly enters the cavity of α-CD by way of the hydroxy group (Type 2 inclusion mode), giving a column-type packing in its crystal. These differences are thought to be due to the differ-

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* Corresponding author. Tel.: + 81-42-388-7028; fax: + 81-42-388-7209.
E-mail address: kamitori@cc.tuat.ac.jp (S. Kamitori)

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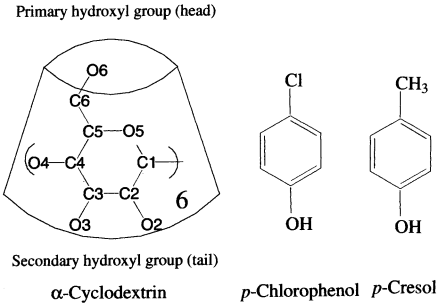

Fig. 1. A schematic diagram of α-CD with the atomic numbering for the glucose unit and chemical structures of *p*-chlorophenol and *p*-cresol.

ences in the bulkiness, the electronegativity, and the capacity to form hydrogen bonds of the various para-substituent groups of the guest molecules. In order to elucidate how the para-substituent groups affect the inclusion modes and the packing structures in detail, the crystal structures of α-CD–*p*-chlorophenol and α-CD–*p*-cresol complexes have been determined by single-crystal X-ray diffraction. As shown in Fig. 1, *p*-chlorophenol has as its para substituent a chlorine atom, and *p*-cresol has a methyl group, which is not electronegative. The relative bulkiness of the substituent groups is in the order $\text{–COOH} > \text{–NO}_2 > \text{–I} \geqslant \text{–CH}_3 > \text{–Cl} > \text{–F}$.

2. Experimental

Crystallization.—A crystal of the α-CD–*p*-chlorophenol complex was prepared by dissolving α-CD (0.1 mmol) and *p*-chlorophenol (0.1 mmol) in water (5 mL) at 50 °C. By slow evaporation of this solution at 25 °C, a suitable crystal for X-ray data collection was obtained. Single crystals of the α-CD–*p*-cresol complex were obtained by a similar method.

X-ray analysis.—For the α-CD–*p*-chlorophenol complex, diffraction data up to $2\theta = 140°$ were collected by a Rigaku AFC7R diffractometer on a Rigaku rotating anode X-ray generator with graphite monochromated Cu K_α radiation using the $2\theta/\omega$ scan mode. The initial phase angles were determined by a direct method using the TEXSAN crystallographic software package of Molecular Structure Corporation [6]. Water molecules were located on a difference Fourier map. Non-hydrogen atoms of α-CD and *p*-chlorophenol were refined anisotropically, and oxygen atoms of water were refined isotropically. Hydrogen atoms, except hydroxyl hydrogen atoms, were introduced by geometrical calculations and were not refined. The crystal structure was refined to $R = 0.102$ (5188 reflections, all unique reflections) and $R_1 = 0.073$ (3990 reflections with $F_o > 4\sigma(F_o)$) by a full matrix least-squares method using the program SHELX97 [7], based on 704 parameters and 653 restraints. For the α-CD–*p*-cresol complex, data collection up to $2\theta = 120°$ and the structure determination were done in a similar manner to that used for the α-CD–*p*-chlorophenol complex. The crystal structure was refined to $R = 0.143$ (4120 reflections, all unique reflection) and $R_1 = 0.085$ (2496 reflections with $F_o > 4\sigma(F_o)$) by a full matrix least-squares method using the program SHELX97 [7], based on 704 parameters and 650 restraints. The distinction between the methyl group and hydroxyl group of the *p*-cresol was determined by the refined temperature factors (B_{eq}). When the methyl group is at the correct site, the B_{eq}s of the carbon and oxygen atoms are 11.86 and 12.25 Å^2, respectively, and when it is at the opposite site, the B_{eq}s of the carbon and oxygen atoms are 7.00 and 16.89 Å^2, respectively. The solved structure is also supported by the fact that the hydroxyl group forms hydrogen bonds. Crystal data are shown in Table 1 (see Section 4).

3. Results and discussion

In the α-CD–*p*-chlorophenol complex, α-CD forms a 1:1 complex with *p*-chlorophenol, as shown in Fig. 2(a and b) [8]. There are an α-CD and a *p*-chlorophenol in the asymmetric unit. The guest is deeply included into the α-CD, making its molecular axis almost perpendicular to the α-CD plane (Type 1 inclusion mode). The six O-4 atoms make up a plane (O-4 plane) within 0.2 Å, and the angle between the molecular axis of the guest (the axis giving the minimum moment of inertia) and the perpendicular axis to the O-4 plane of α-CD is 9.8°. On account of the included phenyl ring of *p*-chlorophenol, the α-CD is

Table 1
Crystal data

	α-CD–*p*-chlorophenol	α-CD–*p*-cresol
Chemical formula	$C_{36}H_{60}O_{30}\cdot C_6H_5OCl\cdot 5H_2O$	$C_{36}H_{60}O_{30}\cdot C_7H_8O\cdot 6H_2O$
Molecular weight	1191.5	1189.1
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
Cell dimensions		
a (Å)	15.299(3)	7.927(7)
b (Å)	24.795(5)	13.568(7)
c (Å)	13.447(5)	24.54(1)
β		90.41(8)°
Cell volume (Å^3)	5101.3	2640.5
Z value	4	2
D_m (g cm^{-3})	1.52(1)	1.47(1)
D_{calc} (g cm^{-3}) [a]	1.55	1.50

[a] D_{calc} was calculated based on molecular weight and cell volume.

distorted to an ellipsoid shape, as shown in Fig. 2(b). The chlorine atom is situated at the center of the C-5 plane of the α-CD. Although the chlorine atom does not have any hydrogen bonds with hydroxyl groups, it seems to form weak electrostatic interactions with the hydrogen atoms attached to the C-5 atoms (C-5 hydrogen atoms) that are involved in hydrogen bonds in other oligosaccharides [9,10]. The distances between them are 3.09, 3.17, 3.60, 3.43, 3.24 and 3.68 Å, as shown in Fig. 2(b), and the large deviations between them are due to the ellipsoid distortion of the α-CD. All of the distances are greater than the van der Waals contacts (3.05 Å) in the *p*-chlorophenol complex; however, a slightly shorter distance between the iodine and C-5 hydrogen atom (3.18 Å, which is shorter than the usual van der Waals contact of 3.35 Å) is found in the *p*-iodophenol complex [4], suggesting that a weak electrostatic interaction certainly exists between the iodine and the C-5 hydrogen atoms. Since all of the C-5 hydrogen atoms in the α-CD direct to the center of the torus, the center of the C-5 plane is very much suited for an electronegative atom, as shown in Fig. 2(b). These interactions between the chlorine atom and the C-5 hydrogen atoms is thought to determine the position of chlorine and the orientation of a guest, giving rise to the Type 1 inclusion mode.

The α-CD–*p*-chlorophenol complex has a layered packing structure. The secondary hydroxyl groups of an α-CD have intermolecular hydrogen bonds to the primary hydroxyl group and the secondary hydroxyl groups of other α-CDs, as shown in Fig. 2(a). The hydroxyl group of *p*-chlorophenol, which is located on the center axis of a host α-CD, forms hydrogen bonds with the O-6 and O-2 atoms of other host α-CDs. These distances are 2.68 and 2.61 Å, respectively.

In the α-CD–*p*-cresol complex, α-CD forms a 1:1 complex with *p*-cresol, as shown in Fig. 3(a and b). Both α-CD and *p*-cresol are in the asymmetric unit. The guest is shallowly included into α-CD, making an angle of 33.3° between its molecular axis and the perpendicular axis to the O-4 plane of the α-CD. The methyl group enters the cavity of the α-CD and makes van der Waals contacts with three C-5 atoms of the α-CD (3.94, 4.01, and 4.11 Å), and with three O-4 atoms of the α-CD (3.64, 3.81, 3.82 Å) as shown in Fig. 3(b). The relative orientation and location of the guest in the α-CD–*p*-cresol complex are almost the same as those in the *p*-fluorophenol complex, but the para-substituent group is located at the opposite side of the torus. Therefore, the inclusion mode of the α-CD–*p*-cresol complex can be referred as Type 2′ inclusion mode. The position in the center of the C-5 plane is not suitable for the methyl group since it is not electronegative and cannot establish attractive electrostatic interactions with the C-5 hydrogen atoms of the α-CD as in the case of the chlorine atom of the *p*-chlorophenol. Thus the methyl group is situated on the O-4 plane with hydrophobic interactions with the C-5 atoms and the CH···O electrostatic interactions with the O-4 atoms [11], which gives a Type 2′ inclusion mode. As in the case of *p*-chlorophenol, the α-CD is slightly distorted to an ellipsoid shape by the phenyl moiety as shown in Fig. 3(b).

The α-CDs are arranged in an one-dimensional column structure along the crystallographic *a*-axis in a head-to-tail orientation. The secondary hydroxyl groups of an α-CD have intermolecular hydrogen bonds to the primary hydroxyl groups of other α-CDs as shown in Fig. 3(a). The hydroxyl group of *p*-cresol forms hydrogen bonds with two O-6 atoms of another host α-CD (2.44 and 3.06 Å), one of which is disordered, as shown in Fig. 3(a). Since the hydroxyl group of a guest slips out of the center axis of a host α-CD, it can make hydrogen bonds with another α-CD arranged in a column structure.

The location of the hydroxyl group of a guest induced by the inclusion modes is closely related to the packing structure. If the

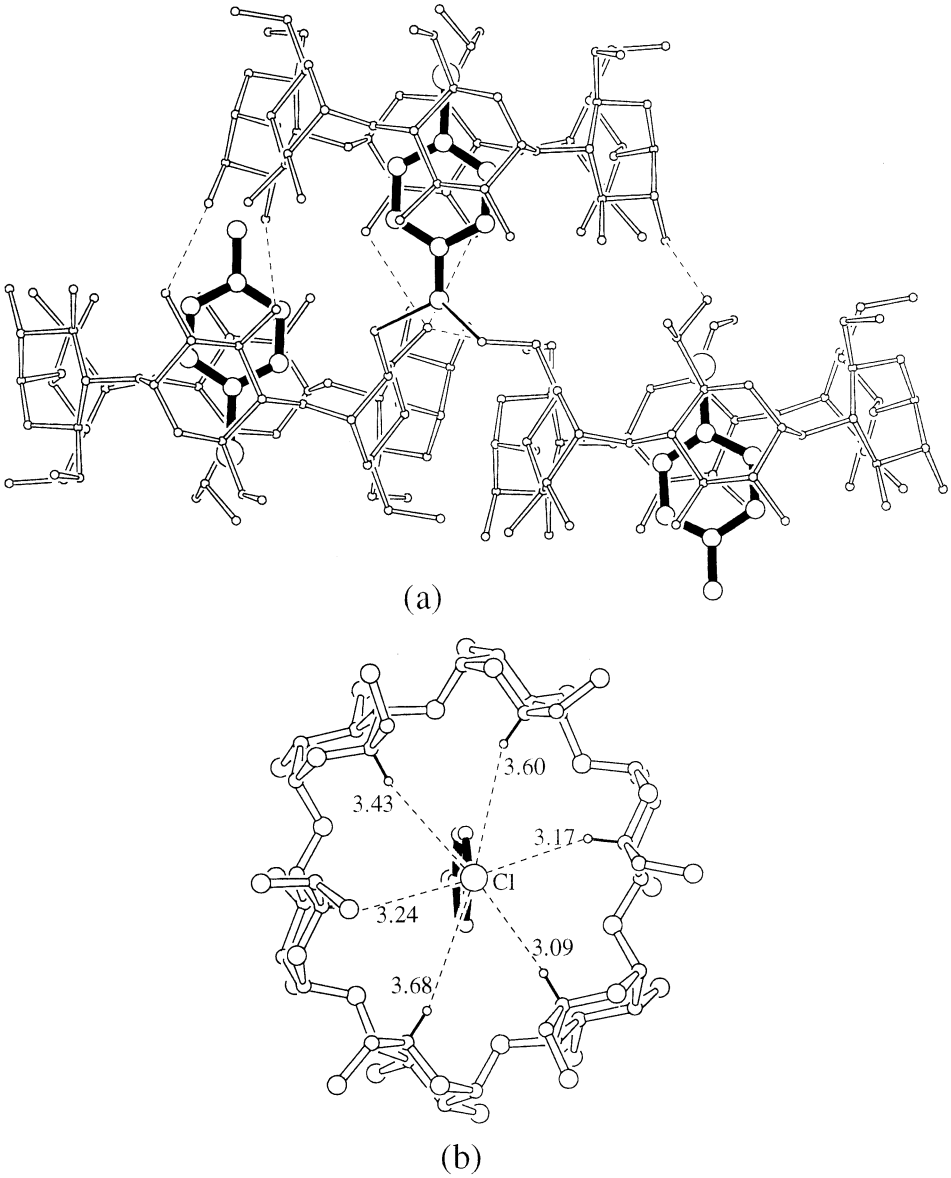

Fig. 2. (a) The crystal structure of the α-CD–*p*-chlorophenol complex. The hydrogen bonds (less than 3.1 Å) between α-CDs are shown by dashed lines. The hydrogen bonds of *p*-chlorophenol are shown by thin lines. Water molecules are not shown. (b) The α-CD complex viewed along the vertical axis of the O-4 plane of the α-CD. The hydrogens attached to the C-5 atoms are shown by small circles, and the distances from them to the chlorine atom are also indicated.

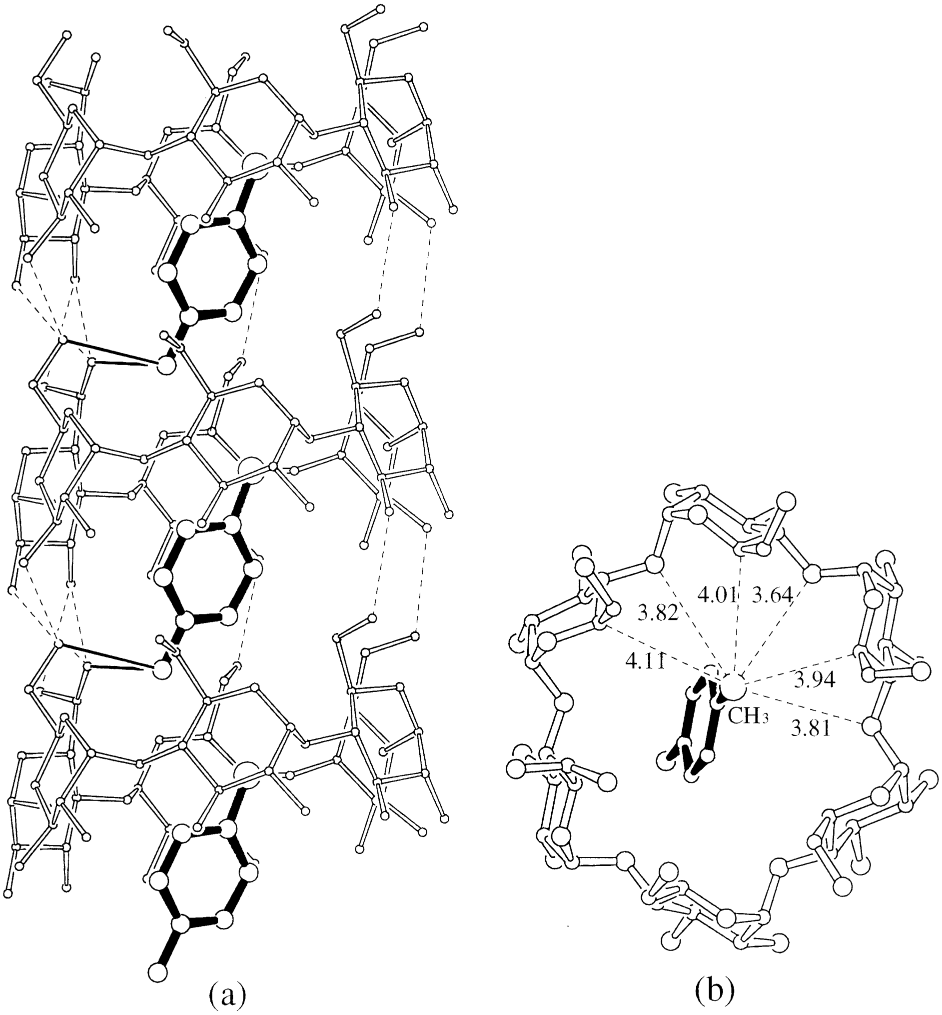

Fig. 3. (a) The crystal structure of the α-CD–*p*-cresol complex. The hydrogen bonds (less than 3.1 Å) between α-CDs are shown by dashed lines. The hydrogen bonds of *p*-cresol are shown by thin lines. Water molecules are not shown. (b) The α-CD complex viewed along the vertical axis of the O-4 plane of α-CD. The short distances between the methyl group of *p*-cresol and α-CD are indicated.

α-CDs are arranged in a column structure in the complex with a Type 1 inclusion mode, the hydroxyl groups of a guest cannot form hydrogen bonds with the hydroxyl groups of other α-CDs. The formation of a column structure of an α-CD has never arisen from the Type 1 inclusion mode, as it has always required the Type 2′ or Type 2 inclusion mode.

This study shows that, when an α-CD includes a para-substituted phenol, the inclusion mode is determined by the bulkiness, the electronegativity and the capacity to form hydrogen bonds of para-substituent groups, and the packing structure is closely related to the location of the hydroxyl group of a guest induced by the inclusion mode. In the *p*-$COOHC_6H_4OH$ and *p*-$NO_2C_6H_4OH$ complexes, the carboxyl and nitro groups are so bulky that they cannot be situated at the position occupied by the methyl group in the *p*-cresol complex with the Type 2′ inclusion mode. It is more favorable for them to be located at the center of the primary site and interact with the primary hydroxyl groups of the α-CD, giving the Type 1 inclusion mode. In the *p*-iodophenol and *p*-chlorophenol complexes, the electronegative iodine and chlorine atoms are suitably located at the center of the C-5 plane of the α-CD, giving rise to the Type 1 inclusion mode. The methyl group of the *p*-cresol complex leads to the Type 2′ inclusion mode, as described above. In the complex of *p*-fluorophenol with the Type 2 inclusion mode, the hydroxyl group of the guest is situated in an unusual manner in the cavity of the α-CD. Although the atomic diameter of fluorine might be too small to be located at the center of the C-5 plane of the α-CD where it would form weak electrostatic interactions with C-5 hydrogen atoms, the precise reasons for this unusual inclusion mode of *p*-fluorophenol have not yet been determined.

Supplementary material

Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 133557 for α-CD–*p*-chlorophenol complex and 133556 for α-CD–*p*-cresol complex. These data may be obtained free of charge, on request, from The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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