Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 342 (2007) 767–771
Carbohydrate RESEARCH

Note

The crystal structure of the 1:1 inclusion complex of β-cyclodextrin with benzamide

En-Ju Wang,[a] Zhao-Xun Lian[a] and Jiwen Cai[a,b,*]

[a]School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, PR China
[b]School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510080, PR China

Received 5 September 2006; received in revised form 21 November 2006; accepted 7 December 2006
Available online 12 December 2006

Abstract—The 1:1 inclusion complex of β-cyclodextrin and benzamide was prepared and characterized by single crystal X-ray diffraction, PXRD, TGA, and IR. This complex crystallizes in the monoclinic $P2_1$ space group with unit cell constants $a = 15.4244(16)$, $b = 10.1574(11)$, $c = 20.557(2)$ Å, $\beta = 110.074(2)°$, $V = 3025.1(6)$ Å^3. The guest molecule projects into the β-cyclodextrin cavity from the primary hydroxyl side. The amide group protrudes from the primary hydroxyl side and forms hydrogen bonds with the adjacent β-cyclodextrin molecule. There are six crystallized water molecules, which play crucial roles in crystal packing.

Keywords: β-Cyclodextrin; Benzamide; Inclusion complex; Crystal structure

β-Cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of seven α-(1→4)-linked D-glucose units. It has the shape of a truncated cone with a hydrophobic central cavity, that results in its ability to form inclusion complexes with a variety of guest molecules, including organic compounds,[1] pharmaceutical compounds,[1,2] and organometallic compounds.[3] In order to explore the details of intermolecular interactions, a large number of crystallographic studies on the inclusion complexes of cyclodextrins have been performed, which has led to a better understanding of the inclusion phenomenon at the molecular level.[4,5] However, the structural factors that could influence the molecular conformation and packing mode are so intricate, and the complexes formed by β-CD and molecules of structural analogs could have different modes of molecular interactions due to the difference both in the functional groups as well as space configuration.[6–9] Therefore, studying individual crystal structure remains to be the major approach to understand the host–guest molecular recognition of each unique β-CD inclusion complex. Herein, we wish to report the crystal structure of benzamide complexed with β-CD. The intermolecular interactions including hydrogen bonds and Van der Waals interactions are discussed in details, as well as the crystal packing structure.

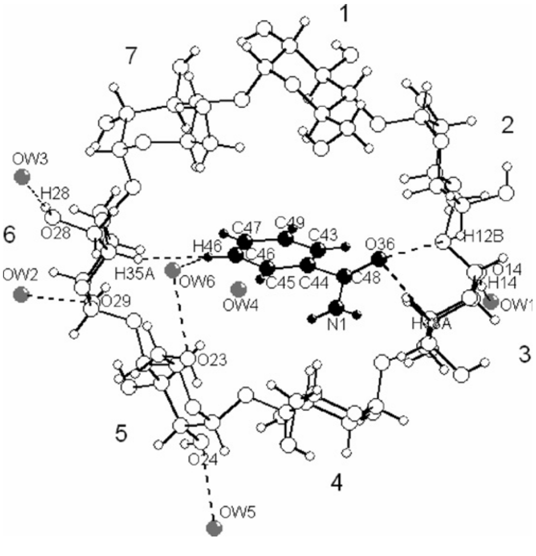

Figure 1. Crystal structure of the inclusion complex and crystallization water molecules.

---

* Corresponding author. E-mail: puscjw@mail.sysu.edu.cn

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.12.004

As shown in Figure 1, the asymmetric unit consists of one β-CD, one benzamide and six water molecules. Each glucose residue of β-cyclodextrin adopts the usual $^4C_1$ chair conformation, and the overall β-cyclodextrin molecule has an approximate 7-fold axis. The geometric parameters for the β-CD molecule are listed in Table 1. The O4n atoms are almost co-planar, with the largest displacement from the average plane observed for O11 and O21 atoms (0.2182 and −0.2524 Å, respectively). The O4n···O4($n+1$) distances vary between 4.241(5) and 4.497(0) Å. The distances from the center of gravity of seven O4 atoms to each individual O4 atom are in the range of 4.833(5)–5.212(1) Å. The O4($n-1$)···O4n···O4($n+1$) angles, varying from 124.08(0)° to 132.60(3)°, are within 4.49° from the regular heptagon of 128.57°. The tilt angles of the glycopyranose residues, defined as the dihedral angle between the O4n plane and the individual planes defined by O4($n-1$), C1n, C4n, and O4n atoms, are in the range of 2.8–26.4°. The annular shape of β-CD is stabilized by interglucose O3n···O2($n+1$) hydrogen bonds with O···O distances 2.732(1)–2.952(1) Å. Overall, the geometrical parameters indicate that there is a small deviation of the β-CD molecule from the 7-fold symmetry in this complex compared to its hydrated form,[10] which is a well-defined heptagon.

The orientation of the C6n–O6n bond is generally described by the torsion angles C4n–C5n–C6n–O6n and O5n–C5n–C6n–O6n. Five out of the seven primary hydroxyl groups exhibit the *gauche–gauche* orientation pointing outwards from the β-CD cavity, as shown by the torsion angle of O5n–C5n–C6n–O6n in the range of −61.1° to −68.1°. The other two primary hydroxyl groups have *gauche–trans* orientation pointing inwards, as indicated by the corresponding torsion angles of 57.9° and 61.9°, respectively.

The β-CD cage is large enough to fully accommodate the mono-substituted benzene molecule, since its diameter is comparable to the length of the long axis of the benzene ring.[4] The phenyl group of benzamide is embedded inside the β-CD cavity with its long axis parallel to the mid-plane of the macrocycle defined by the glycosidic oxygen atoms (O4n). The amide group is located at the primary hydroxyl side, forming hydrogen bond with adjacent β-CD molecules. The benzene ring center of benzamide is 1.4541(1) Å away from the O4-plane center to the O6-side of β-CD. The benzene ring plane inclined 72.9° with respect to the O4-plane. The angle between the benzamide molecular axis to the O4-plane is 46.9°. Each inclusion complex contains six water molecules that are all fully occupied. Water molecules Ow4 and Ow6 located in the β-CD cavity, while the others located outside the β-CD cavity.

There is no conventional hydrogen bond observed between β-CD and its guest molecule. However, benzamide forms hydrogen bonds with the adjacent β-CD molecule that is related to the host molecule by a 2-fold screw axis. Two C–H···O interactions are observed for C12–H12B···O36 and C18–H18A···O36, and O23 is bridged to H46 through Ow6. One host–guest intermolecular H···H contact between H46···H35A is 2.3220(2) Å, less than 2.4 Å (twice the Van der Waals radius of hydrogen atom) , indicating weak Van der Waals interactions between the guest benzamide molecule and β-CD.

The β-CD molecules are stacked along the crystallographic *b*-axis in cage-type mode, as frequently observed in the β-CD complex with small guest molecules such as ethanol,[11] ethylene glycol,[12] squaric acid,[13] and hexamethylenetetramine.[14] β-CD forms a herringbone pattern along the 2-fold screw axis, as shown in Figure 2. The angle between two cyclodextrins related by screw symmetry is 86.60(3)°.

The intermolecular hydrogen bonds are listed in Table 2. Water molecules form extensive hydrogen bonding networks in the crystal structure. The amide group forms one hydrogen bond with the adjacent β-CD (N1···O18), and the two β-CD are linked by water molecules through four hydrogen bonding bridges (O8···Ow2···Ow3···O23, O13···Ow5···O24, O23···Ow5···O12, O23···Ow3···Ow2···O15). Each β-CD is linked to the adjacent β-CD in *c* direction by two bridging water molecules (O34···Ow1···O8, O5···Ow4···O3 and O33), and to

Table 1. Geometrical parameters for the β-CD molecule (distance in Å and angles in °)

	Residue						
	1	2	3	4	5	6	7
ϕ	129.61(5)	124.08(0)	129.61(8)	132.60(3)	124.10(4)	128.65(6)	129.40(5)
D	4.318(1)	4.311(3)	4.497(0)	4.241(5)	4.288(1)	4.442(3)	4.436(6)
Tilt angle	26.4	7.6	10.1	11.9	20.9	2.8	21.1
d	−0.0261	0.2182	−0.0359	−0.2524	0.1800	0.1545	−0.2455
O3n–O2($n+1$)	2.863(1)	2.922(8)	2.732(1)	2.743(9)	2.952(1)	2.950(5)	2.933(7)
Torsion angle 1	−179.2	59.6	58.7	54.6	176.6	52.3	52.1
Torsion angle 2	61.9	−61.1	−61.7	−66.4	57.9	−67.0	−68.1

ϕ = angle between atoms O4($n-1$)–O4n–O4($n+1$); D = distance between atoms O4n···O4($n+1$); Tilt angle is the angles between the O4 plane and the planes defined by O4($n-1$), C1n, C4n, and O4n; d = deviation of O4n atom from the least-squares optimum plane formed by the seven O-4n atoms; Torsion angle 1: C4n–C5n–C6n–O6n; Torsion angle 2: O5n–C5n–C6n–O6n.

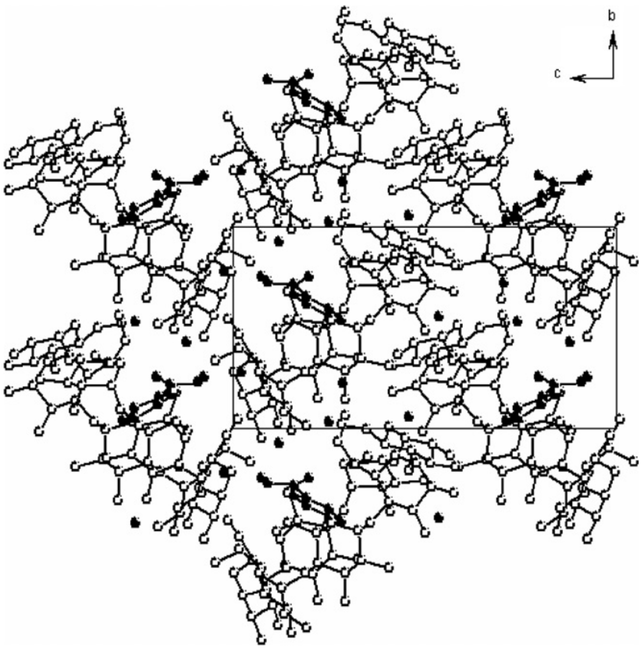

Figure 2. Crystal packing viewed along the *a*-axis.

another β-CD in *b* direction by another five hydrogen bonds (O8···Ow2···O15, O24···Ow5···O23, O8···Ow1···O14, O28···Ow3···Ow2···O29, O23···Ow6···O24, and O25). In addition, a number of hydrogen bonding bridges are found between neighboring *bc* planes, for example, O34···Ow1···O10, O23···Ow3···O28, O28···Ow3···Ow2···O8, O29···Ow2···O15, O29···Ow2···Ow3···O18, and O23.

Similar guest molecules as that of benzamide complexed with β-CD have been reported, including nicotinamide,[6] nicotinic acid,[7] benzoic alcohol,[8] and benzoic acid.[9] The complexes of nicotinamide[6] and nicotinic acid[7] have almost the same inclusion geometry and packing pattern as the present crystal structure. The complex of benzoic acid is different, crystallizing in the triclinic *P*1 space group while stacking in the channel mode. The benzoic acid is embedded deeper in the β-CD cavity than the benzamide molecule, with the distance of the aromatic ring center to the O-4-plane center being 1.0 and 1.5 Å for the benzoic acid and benzamide complex, respectively. The angle between the aromatic plane and the O-4-plane is 52° and 72.8° for the benzoic acid and benzamide complex, respectively. The benzoic acid complex is stacked in the alternative head-to-head and tail-to-tail channel mode.[9] Meanwhile, the benzoic alcohol complex crystallizes in the monoclinic $P2_1$ space group,[8] with the hydroxyl group locating at the secondary hydroxyl side and forming hydrogen bonds with adjacent β-CD molecules.

In summary, we report here a new addition to the crystal structures and supramolecular chemistry of β-CD inclusion complexes. Although the mode of inclusion of benzamide in β-CD is not essentially different of that of guests with comparable framework, the crystal structure, packing and intermolecular hydrogen bonding as well as the presence of water molecules differ in each case. A comparison of the crystal structures suggests that different host–guest hydrogen bonding modes as well as spatial fitting contributed to the difference.[4,8]

1. Experimental

1.1. Materials and methods

β-CD·12H_2O was re-crystallized prior to use. Benzamide was purchased from E. Merck and used as received. Elemental analysis was conducted by the Vario EL elemen-

Table 2. Intermolecular hydrogen bonds

D–H	*d*(H···A)	∠DHA	*d*(D···A)	A
Between β-CD molecules and water molecules or benzamide				
O3–H3	1.982	157.25	2.756	Ow4 [$x, y+1, z$]
O5–H5	2.071	150.84	2.815	Ow4 [$-x+1, y+1/2, -z+1$]
O8–H8	2.064	167.40	2.870	Ow1 [$x, y+1, z$]
O14–H14	2.000	158.80	2.780	Ow1
O18–H18	2.163	151.54	2.911	N1 [$-x+2, y-1/2, -z+2$]
O23–H23	2.018	169.62	2.828	Ow3 [$-x+1, y-1/2, -z+2$]
O24–H24	2.016	158.71	2.796	Ow6 [$x, y-1, z$]
O28–H28	1.938	168.12	2.745	Ow3
N1–H1A	2.069	165.79	2.911	O18 [$-x+2, y+1/2, -z+2$]
N1–H1B	2.588	143.87	3.321	Ow5 [$x, y+1, z$]
Between β-CD molecules				
O10–H10	2.628	110.67	3.016	O35 [$-x+1, y-1/2, -z+1$]
O13–H13	2.093	135.41	2.738	O28 [$x+1, y, z$]
O13–H13	2.534	125.02	3.078	O27 [$x+1, y, z$]
O19–H19	1.953	158.56	2.733	O36 [$x, y-1, z$]
O29–H29	2.280	125.42	2.835	O33 [$x, y-1, z$]
O33–H33	2.026	168.85	2.835	O29 [$x, y+1, z$]

tal analyzer. Powder XRD data were performed on a Rigaku D/max-IIA diffractometer. TGA was performed on a Netzsch TG 209 analyzer, using a heating rate of 10 °C min^{-1} in flowing air atmosphere. FTIR were obtained on a Mattson 700 FTIR spectrometer with KBr pellets.

1.2. Synthesis of the inclusion compound

β-CD·12H$_2$O (0.2 mmol) was dissolved in water (4 mL) at 60 °C and benzamide (0.4 mmol) was added. The resulting mixture was stirred for 6 h then cooled down slowly. The resulting suspension was filtered and the white powder was air dried. Yield 0.22 g (80%). Anal. Calcd for $C_{42}H_{70}O_{35}$·$C_7H_7O_1N_1$·$6H_2O$: C, 43.12; H, 6.58; N, 1.03. Found: C, 42.44; H, 6.83; N, 0.87. Recrystallization of white powder in water affords colorless block-like crystals in 1 week.

1.3. X-ray crystallography

The crystallographic data are summarized in Table 3. X-ray diffraction data were collected on a Bruker Smart 1000 CCD diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 293(2) K. Absorption corrections were applied using SADABS.[15] The structure was solved by direct methods and refined using full-matrix least-squares/Fourier difference techniques using SHELXTL.[16,17] All non-hydrogen atoms of the asymmetric unit were refined with anisotropic thermal displacement parameters. All hydrogen atoms were calculated in the ideal positions (riding model), except those of the water molecules.

Table 3. Crystallographic data

Empirical formula	$C_{42}H_{70}O_{35}$·C_7H_7ON·$6(H_2O)$
Formula weight	1364.21
Temperature	293(2) K
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
A (Å)	15.4244(16)
b (Å)	10.1574(11)
c (Å)	20.557(2)
β (°)	110.074(2)
V (Å^3)	3025.1(6)
Z	2
D_{calcd} (Mg/m^3)	1.498
Absorption coefficient (mm^{-1})	0.132
$F(000)$	1452
Crystal size (mm)	0.50 × 0.40 × 0.20
θ Range for data collection (°)	1.05–27.08
Index ranges	$-19 \leqslant h \leqslant 19$, $-8 \leqslant k \leqslant 12$, $-24 \leqslant l \leqslant 26$
Reflections collected	23,535
Independent reflections	6998 [$R_{\mathrm{int}} = 0.0244$]
Reflections observed (>2σ)	6203
Data completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.94
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6998/1/834
Goodness-of-fit on F^2	1.046
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0475$, $wR2 = 0.1304$
R (all data)	$R1 = 0.0551$, $wR2 = 0.1404$
Absolute structure parameter	0(10)
Largest diff. peak and hole (e/Å^3)	0.681 and −0.471

1.4. PXRD characterization

As shown in Figure 3, the PXRD pattern of the physical mixture of benzamide and β-CD is the superposition of the patterns contributed by benzamide and β-CD. The β-CD–benzamide adduct has a different pattern, which is consistent with the stimulated PXRD pattern of the single crystal structure.

1.5. TGA analysis

The TGA for the inclusion complex, the 1:1 physical mixture, β-CD and benzamide are illustrated in Figure 4. The benzamide–β-CD complex presents a 7.7% mass loss before 100 °C corresponding to the loss of water molecules (calcd 7.9%). There is no further mass loss in the temperature range of 100–220 °C. Between 220 and 300 °C, a 9.3% further mass loss contributed by the release of benzamide was observed (calcd 8.9%). Finally, an abrupt mass loss at roughly 300 °C suggests the onset of chemical decomposition of β-CD. The 1:1 mechanical mixture of benzamide and β-CD was dehydrated before 100 °C, melted, and subsequently decomposed after 300 °C. Interestingly, the physical mixture did not behave as the superposition of the two pure substances as usual, but experienced a mass loss in a very

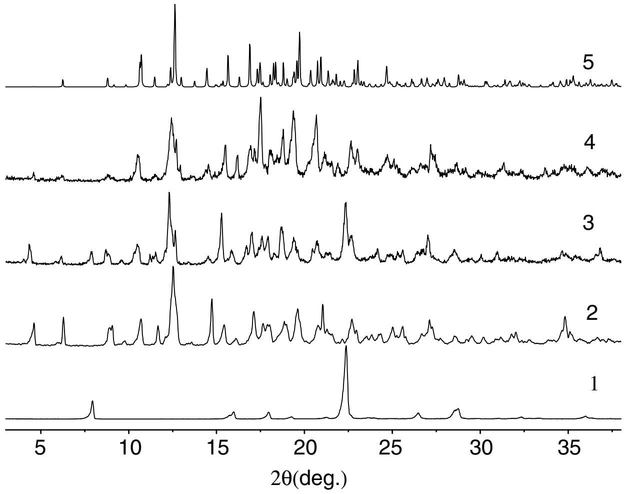

Figure 3. PXRD: (1) benzamide; (2) β-CD·12H$_2$O; (3) 1:1 mechanical mixture of benzamide and β-CD·12H$_2$O; (4) complex of benzamide and β-CD; (5) stimulated PXRD from single crystal structure.

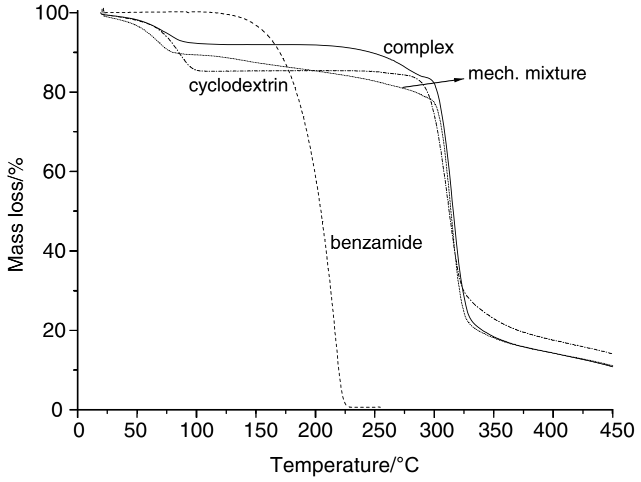

Figure 4. TGA of benzamide, β-CD·$12H_2O$, 1:1 mechanical mixture of benzamide and β-CD·$12H_2O$, and complex of benzamide and β-CD.

gradual and smooth way between 130 and 300 °C. It could be accounted as the occurrence of some interactions between benzamide and cyclodextrin after benzamide melted (the melting point of benzamide is 129–130 °C).

1.6. IR characterization

The IR spectra are shown in Figure 5. Since there are seven repeating units in the β-cyclodextrin molecule, the spectra of both the inclusion complex and the mechanical mixture are largely dominated by the vibrational bands of the cyclodextrin molecule. There is no obvious difference between the spectrum of the inclusion compound and that of the corresponding physical mixture. Benzamide has a carbonyl band of 1660 cm^{-1}. In the physical mixture, the absorption position of the carbonyl band remains the same. While in the corresponding complex, it shifts to 1666 cm^{-1} and its intensity decreases correspondingly, indicating the involvement of intermolecular interaction of the carbonyl group.

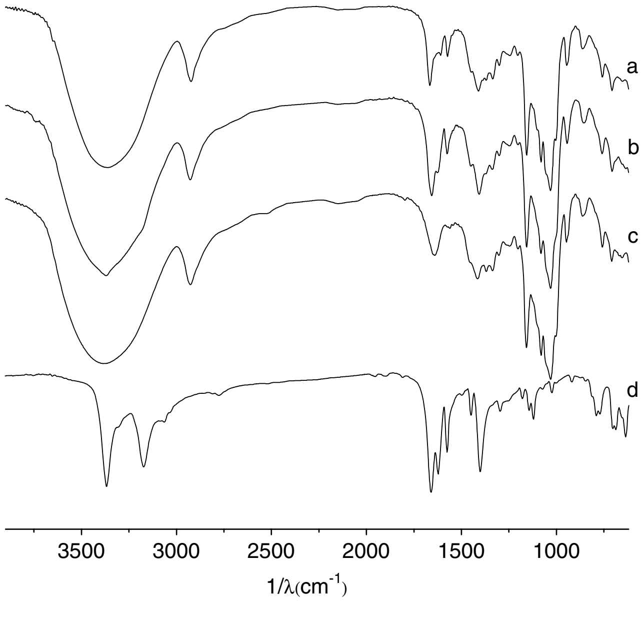

Figure 5. FT-IR spectra: (a) benzamide and β-CD complex; (b) 1:1 mechanical mixture of benzamide and β-CD·$12H_2O$; (c) β-CD·$12H_2O$; (d) benzamide.

Supplementary data

Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with CCDC No. 619082. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgment

We are grateful for the financial support from the Natural Science Foundation of Guangdong (Grant No. 04105493).

References

1. Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1917.
2. Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045–2076.
3. Hapiot, F.; Tilloy, S.; Monflier, E. *Chem. Rev.* **2006**, *106*, 767–781.
4. Harata, K. *Chem. Rev.* **1998**, *98*, 1803–1827.
5. Saenger, W.; Jacob, J.; Gessler, K.; Steiner, T.; Hoffmann, D.; Sanbe, H.; Koizumi, K.; Steven, M. S.; Takaha, T. *Chem. Rev.* **1998**, *98*, 1787–1802.
6. Harata, K.; Kawano, K.; Fukunaga, K.; Ohtani, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1428–1430.
7. Zhou, W. H.; Wang, J. L.; Miu, F. M. *Acta Chim. Sinica* **2001**, *59*, 1135–1138.
8. Harata, K.; Uetama, K.; Otagiri, M.; Hirayama, F.; Ohtani, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1234–1238.
9. Aree, T.; Chaichit, N. *Carbohydr. Res.* **2003**, *338*, 439–446.
10. Lindner, K.; Saenger, W. *Carbohydr. Res.* **1982**, *99*, 103.
11. Tokuoka, R.; Abe, M.; Fujiwara, T.; Tomita, K.; Saenger, W. *Chem. Lett.* **1980**, 491–494.
12. Gessler, K.; Steiner, T.; Saenger, W. *Carbohydr. Res.* **1993**, *249*, 327–344.
13. Crisma, M.; Fornasier, R.; Marcuzzib, F. *Carbohydr. Res.* **2001**, *333*, 145–151.
14. Harata, K. *Carbohydr. Res.* **2003**, *338*, 353–359.
15. Blessing, R. *Acta Crystallogr., Sect. A* **1995**, *51*, 33.
16. Bruker AXS, SHELXTL, Version 5.1, Bruker AXS, Madison, WI, 1998.
17. Sheldrick, G. M. SHELXL-97, *Program for Crystal Structure Solution and Refinements*; University of Göttingen: Germany, 1997.