ELSEVIER

www.elsevier.nl/locate/carres

Carbohydrate Research 328 (2000) 135–140

CARBOHYDRATE RESEARCH

The crystal structure of the 1:1 complex of β-cyclodextrin with *trans*-cinnamic acid

Areti Kokkinou [a], Stella Makedonopoulou [b], Dimitris Mentzafos [a,*]

[a] *Physics Laboratory, Agricultural University of Athens, Iera Odos 75, GR-11855 Athens, Greece*
[b] *Institute of Physical Chemistry, National Center for Scientific Research 'Demokritos', Aghia Paraskevi, GR-15310 Athens, Greece*

Received 19 January 2000; accepted 23 March 2000

Abstract

The crystal structure of the 1:1 complex of β-cyclodextrin (cyclomaltoheptaose) with *trans*-cinnamic acid was studied by X-ray diffraction. Two β-cyclodextrin molecules related by a twofold crystal axis form dimers in the hydrophobic cavity of which, two guest molecules are entirely buried. The complex crystallizes in the monoclinic *C*2 space group with channel-type molecular packing. The oxygen atoms of the carboxylate group of the *trans*-cinnamic acid molecule form strong hydrogen bonds with two water molecules lying in the interdimeric space of the hydrophobic channel. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Crystal structure; β-Cyclodextrin; *trans*-Cinnamic acid; Inclusion compound

1. Introduction

trans-Cinnamic acid (tCA) has several effects on plant growth and development probably associated with membrane perturbations like the alteration of membrane potential [1]. It exhibits a notable regulatory action as a plant growth inhibitor: (i) it blocks phenylalanine uptake by barley embryos and lettuce seedling [2], (ii) it inhibits photosynthetic mechanisms [3], (iii) it can stop entirely the growth of *Brassica campestris* roots [4], (iv) it is an important root exude compound of *cucumis sativus* and strongly inhibits NO_3^-, K^+ and Ca^{2+} uptake [5]. On the other hand, cyclomaltooligosaccharides (cyclodextrins, CD) are utilized as solubilizers in biotechnological processes, where plant cells are involved [6]. Studying the uptake of plant growth hormones from their CD complexes, we also undertook the determination of their structures. We have prepared single crystals of the complex of tCA with β-cyclodextrin (β-CD), the structure of which we report here. A comparison is made between the molecular packing of the title compound and of the 1:1 complex of ethyl cinnamate with β-CD (ECBC) [7]. Biological studies concerning the effect of the title compound on the rooting of certain species will be presented elsewhere.

2. Experimental

Crystallization.—Colorless crystals of the title complex were obtained from an aq soln of β-CD (purchased from Cyclolab) to which tCA (obtained from Sigma), dissolved in a few drops of ethyl alcohol, was added in a

---

* Corresponding author.
E-mail address: mentz@auadec.aua.gr (D. Mentzafos).

PII: S0008-6215(00)00091-4

host:guest molar ratio of 1:1. The formed precipitate was redissolved in water at 65 °C and allowed to cool gradually over a period of 7 days to rt.

X-ray data collection.—Final lattice parameters, determined from 32 reflections, are given in Table 1 along with other information on data collection and refinement. A crystal suitable for data collection was enclosed in a Lindermann glass capillary to prevent loss of water. The data were collected on a Syntex P2$_1$ diffractometer, upgraded by Crystal Logic, with Ni-filtered Cu Kα radiation, by the ω–2θ scan mode, at a scan rate of 3°/min and a scan width of 2.7° (2θ) plus α_1-α_2 divergence. Three standard reflections, monitored every 97 reflections, showed an intensity fluctuation of less than 3%. The crystal diffracted up to $2\theta = 57.47°$. This poor diffracting power appears in all the CD crystals, because of the variability and disorder of the water content and disorder of the guest molecule. The intensities were corrected for Lp and absorption (by the Psi-scan process) effects.

Table 1
Crystal data and structure refinement for the tCA/β-CD complex

Empirical formula	$C_{42}H_{70}O_{48}\cdot C_9H_8O_2\cdot (H_2O)_{10.9}$
Formula weight	1482.76
Temperature (K)	295(2)
Wavelength (Cu Kα) (Å)	1.54180
Crystal system	monoclinic
Space group	*C*2
Unit cell dimensions	
a (Å)	19.422(3)
b (Å)	24.461(3)
c (Å)	15.9415(19)
β (°)	108.648(4)
Volume (Å^3)	7176(9)
Z	4
D_{calcd} (Mg/m^3)	1.369
Absorption coefficient (mm^{-1})	1.077
F(000)	3142
θ Range for data collection (°)	2.93–57.47
Limiting indices	$-21 \leq h \leq 0$, $0 \leq k \leq 26$, $-16 \leq l \leq 17$
Reflections collected/unique/observed [$I_o > 2\sigma(I_o)$]	5196/5016/2394
Parameters	627
R_{int}	0.0455
Completeness to theta	57.47
Goodness-of-fit on F^2	1.043
R indices [$I_o > 2\sigma(I_o)$]	$R = 0.0875$, $wR = 0.2298$
R indices (all data)	$R = 0.1836$, $wR = 0.3153$
Weighting scheme	$1/[\sigma^2(F_o^2) + (0.2P)^2]$ [a]
Absolute structure parameter	0.3(7)
$(\Delta/\sigma)_{\max}$	−0.451
Extinction coefficient	0.00099(18)
Largest difference peak and hole (e/Å^3)	0.426 and −0.308

[a] $P = [\max(F_o^2) + 2(F_c^2)]/3$.

Structure solution and refinement.—The structure was solved by isomorphous replacement using the coordinates of the skeleton atoms of the β-CD molecule of the β-CD /(*Z*)-9-dodecen-1-ol complex [8]. Sequential $\Delta\rho$ maps revealed the positions of the remaining atoms of the host, 19 water molecules and the guest molecule atoms. The refinement, based on F^2, proceeded by using the SHELXL-97 program [9]. Hydrogen atoms linked to carbon atoms of the β-CD molecule were used at calculated positions with a C–H distance of 0.98 Å for the secondary and 0.97 Å for the tertiary ones, while their thermal parameters have been set to 1.2 U_{iso} of the isotropic thermal parameter of the corresponding C atom. The atomic positions of the guest molecule were improved by fitting them on the maxima of an electron density map, using the molecular graphics program 'O' [10], on an O$_2$ Silicon Graphics workstation. The benzyl ring was considered to be planar and its atomic distances and angles were optimized (C–C distances 1.38 Å, angles 120°). After optimization, all the atom coordinates of the guest molecule were kept constant and refinement of their occupation factor resulted in 1.00. The small number of observations led to a ratio of observed reflections to parameters of 5016/627 (Table 1), not allowing an anisotropic refinement for all the non-H atoms. Thus, only the non-disordered oxygen atoms, the C-6*n* atoms linked to non-disordered O-6*n* atoms of the host molecule and some water molecules were refined anisotropically. Extinction correction was applied, while 33 reflection intensities exhibiting poor agreement or being negative were given zero weight during the final refinement cycles. The refinement converged at $R =$ 0.0875 and 0.1544 for observed

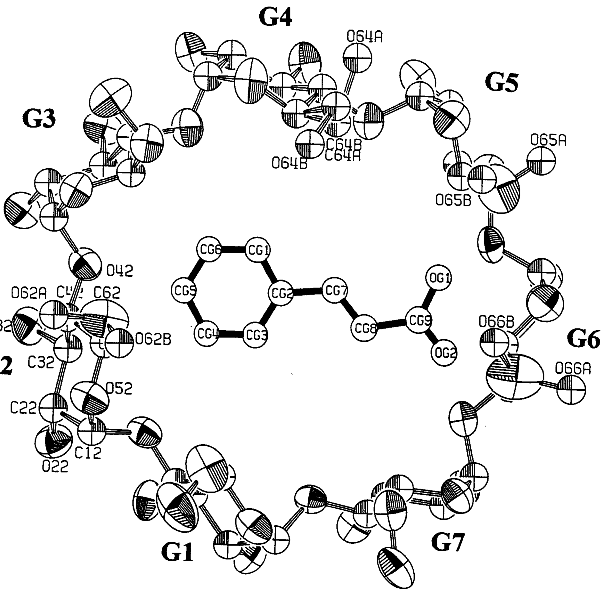

Fig. 1. Numbering scheme of the host and guest molecules. C-*mn* and O-*mn* denote the *m*th atom within the *n*th glucosidic residue.

($F_o > 4.0\sigma(F_o)$) and all reflections, respectively. The numbering scheme of the host and guest molecules is given in Fig. 1, C-*mn* and O-*mn* denoting the *m*th atom within the *n*th glucosidic residue.

3. Results and discussion

Molecular geometry and conformation of β-CD.—Three primary hydroxyl groups of the β-CD molecule, O-62, O-65 and O-66, are disordered over two sites, the occupancies of their major sites being 0.80, 0.71 and 0.56, respectively. The C-64–O-64 group is also disordered over two sites with occupancies of 0.58 and 0.42. As the values of the torsion angles show (Table 2), the disordered atoms of all the major sites exhibit a *gauche–gauche* orientation pointing outwards to the β-CD cavity, while the minor ones have a *gauche–trans* orientation pointing inwards. The glycosidic O-4*n* atoms lie in a plane within 0.024 (8) Å, the O-4*n*···O-4(*n* + 1) distances vary between 4.27 and 4.52 Å and the values of the O-4(*n* − 1)···O-4*n*···O-4(*n* + 1) angles range from 123.5 to 132.6°. The tilt angles of glycopyranose residues, defined as the angles between the O-4*n* plane and the individual planes defined by O-4(*n* − 1)···C-1*n*···C-4*n*···O-4*n* atoms, range between 6.8(3) and 14.5(4)° (Table 2). Two β-CD molecules, related by the twofold crystal axis parallel to *b*, form dimers in a head-to-head fashion, that stack along the *c* crystal axis forming an angle of 79.6° with the O-4*n* best plane. As a consequence a 1:1 complex is formed, which crystallizes in the channel packing mode, the space group being *C*2 [11].

Water molecules (10.9) distributed over 19 sites form the usual network of hydrogen bonds [12] with the hydroxyl groups of the β-CD molecule and among themselves. Two water molecules, O-WG1 and O-WG2, were found in the interface of the vicinal dimers, lying along the *c* crystal axis, on (O-WG1) or very close (O-WG2) to the twofold axis parallel to *b*. This is rare since, in the channel

Table 2

Selected torsion angles and tilt angles (°) formed between the O-4*n* mean plane and the individual O-4(*n* + 1)···C-1*n*···C-4*n*···O-4*n* mean planes for the tCA/β-CD complex [a]

Residue Torsion angles	Site	*n* = 1	*n* = 2	*n* = 3	*n* = 4	*n* = 5	*n* = 6	*n* = 7
C-4*n*–C-5*n*–C-6*n*–O-6*n*	A	58(2)	54(2)	58.8(1.7)	38(4)	60(3)	72(3)	51.8(1.8)
O-5*n*–C-5*n*–C-6*n*–O-6*n*	A	−61(2)	−68(2)	−59.3(1.6)	−74(4)	−57(2)	−48(3)	−71.2(1.5)
C-4*n*–C-5*n*–C-6*n*–O-6*n*	B		157(4)		174(4)	176(4)	−163(3)	
O-5*n*–C-5*n*–C-6*n*–O-6*n*	B		35(4)		45(5)	59(4)	77(3)	
Tilt angles		13.1(3)	13.4(3)	8.5(2)	14.5(4)	13.4(5)	13.9(7)	6.8(3)

[a] Standard deviations in parentheses.

Table 3
Hydrogen bonds and van der Waals contacts of the guest molecule of the tCA/β-CD complex [a]

Distances (Å) and angles (°) of the hydrogen bonds			
O-G1···O-WG1	2.596	C-G9–O-G1···O-WG1	130.1
O-G2···O-WG2	2.569	C-G9–O-G2···O-WG2	135.5
	2.308		142.4
Distances between the guest atoms of the dimer less than 4.00 Å		**Distances between host and guest atoms less than 4.00 Å**	
C-G1···C-G1	3.45	C-G1···C-35	3.79
C-G1···C-G5	4.00	C-G4···C-32	3.78
C-G2···C-G4	3.87	C-G5···O-42	3.76*
C-G2···C-G6	3.70	C-G6···O-33	3.76*
C-G3···C-G4	3.86	C-G7···O-45	3.69*
C-G5···C-G7	3.54	O-G1···C-64B	3.54*
C-G6···C-G7	3.81	O-G1···C-55	3.89*
C-G1···C-G2	3.91	O-G2···C-57	3.73*
C-G1···C-G6	3.50	C-G4···O-41	3.91*
C-G2···C-G5	3.68	C-G5···C-32	3.95
C-G3···C-G3	3.80	C-G6···C-33	3.58
C-G4···C-G8	3.91	C-G6···O-43	3.79*
C-G5···C-G8	3.60	C-G8···O-46	3.83*
		O-G1···O-64B	3.64
		O-G2···O-66B	3.74
		O-G2···C-57	3.73

[a] C–H···O contacts are indicated by an asterisk (*).

packing mode, the interdimeric space is hydrophobic.

The guest molecules.—Many van der Waals contacts between the host and guest molecules of the dimer are observed, their non H-atom distances ranging from 3.54 to 3.95 Å (Table 3). The mean planes of the phenyl rings of the two guest molecules of the dimer are almost perpendicular to the glycosidic O-4*n* atoms plane, forming an angle of 84.0(4)° with it, and nearly parallel to each other, their mutual angle being 8.6°. The distances of the atoms of one phenyl ring from the plane of the other range from 3.39 to 3.75 Å, their mean value being 3.57 Å. These distances and the mutual angles between the phenyl rings of the two guest molecules of the dimer, although both greater than observed elsewhere [13,14], suggest a π–π interaction. Due to this interaction, the phenyl rings are located in the secondary level of the host molecules of the dimer (Fig. 2), which is wide enough to accommodate the two phenyl rings. The guest molecules are totally buried inside the hydrophobic dimeric cavity, the oxygen atoms of the carboxylic group of the guest, O-G1 and O-G2, being at distances of 0.70 and 0.51 Å below the C-6*n* atoms mean plane, still inside the β-CD cavity.

The O-WG1 and O-WG2 water molecules form strong hydrogen bonds with the oxygen atoms of the guest molecules of two vicinal dimers (Fig. 3). Thus, because the carboxylate groups of the tCA molecules are not close enough to form hydrogen-bonded dimers inside the hydrophobic channel, they entrap water molecules in order to satisfy their H-bonding potential and thus the solid state photodimerization of the tCA molecules is prevented [15]. Although carboxylate groups are found in both sides of the dimer, the complex forms channels as the β-CD/monoacid complexes [16].

In ECBC [7], the crystal structure and the accommodation of the guest molecules are different from those of the title complex. EBCD crystallizes in space group *P*1 and packs in the intermediate packing mode [11].

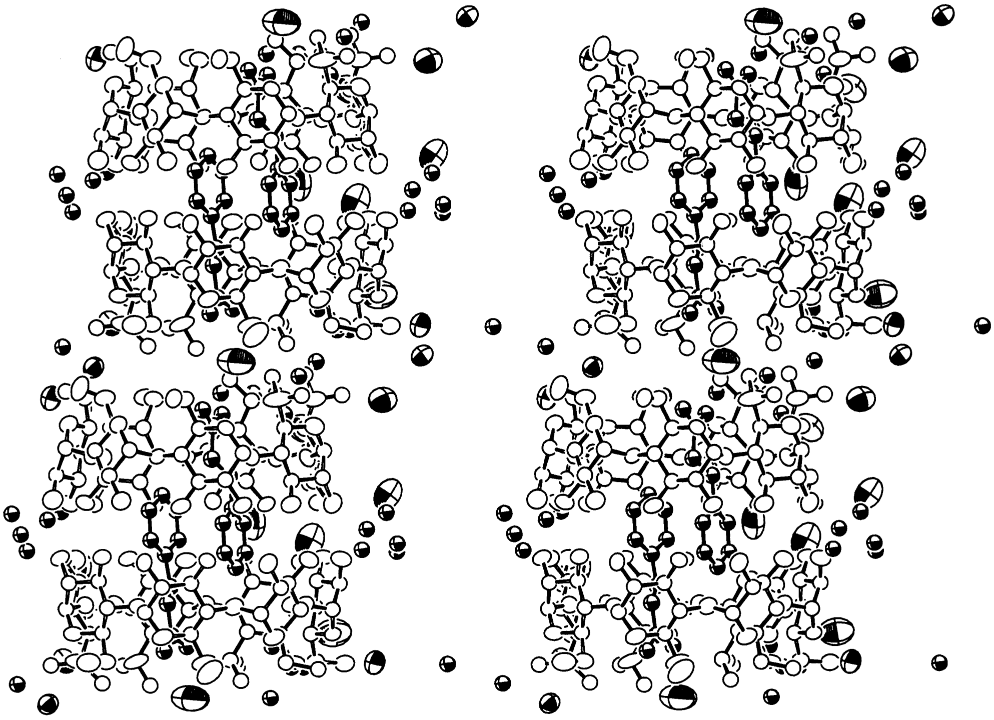

Fig. 2. A stereo diagram of the dimeric channel of the complex.

The angle between its phenyl rings of the two guest molecules of the dimer is 15°, and the distances of the atoms of the one phenyl group from the mean plane of the other range between 3.36 and 4.10 Å, their mean value being 3.71 Å. Both indicate a weaker π–π interaction than in the title complex, if any. Nearly all the atoms of the aliphatic part of the guest molecule of the ECBC complex are found in the interdimeric interface, protruding sufficiently from the dimeric cavity to force the β-CD dimers to pack in the intermediate packing mode [16]. The ester moiety, although less hydrophilic than the carboxylate group, forms a weak hydrogen bond of 2.95 Å between the free oxygen atom of the guest and a water molecule.

4. Supplementary material

Full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Center. Deposition Number: CCDC 141591. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel.: + 44-1223-336408; fax: + 44-1223-

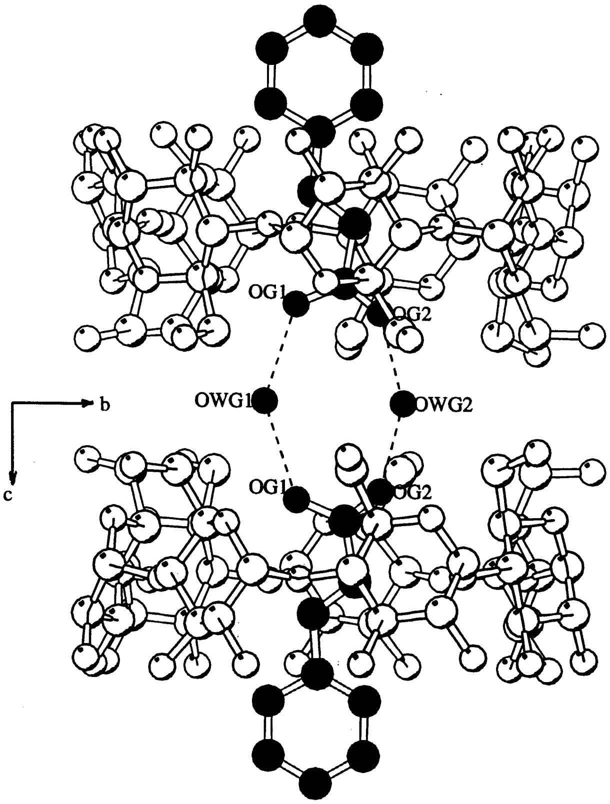

Fig. 3. A diagram indicating the hydrogen bonds of the O-WG1 and O-WG2 water molecules. Lengths are given in Table 3.

336033, e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk

Acknowledgements

The authors are indebted to Dr I.M. Mavridis for several pertinent comments.

References

[1] F.A. Einhellig, *ACS Symp. Ser.*, 582 (1995) 96–116.

[2] C.F. Van Sumere, J. Cottenie, J. DeGreef, J. Kint, *Rec. Adv. Phytochem.*, 4 (1971) 165–221.

[3] D.T. Patterson, *Weed Sci.*, 29 (1981) 53–59.

[4] H. Matsuoka, T. Kotani, M. Saito, K.-B. Oh, *J. Biotechnol.*, 62 (1998) 187–193.

[5] J.Q. Yu, Y. Matsui, *J. Chem. Ecol.*, 23 (1997) 817–827.

[6] W. van Uden, H.J. Woerdenbag, N. Pras, *Plant Cell, Tissue Org. Cult.*, 38 (1994) 103–113.

[7] M. Hursthouse, C. Smith, M. Thornton-Pett, J. Utley., *J. Chem. Soc., Chem. Commun.*, (1982) 881–882.

[8] D. Mentzafos, I.M. Mavridis, M.B. Hursthouse, *Acta Crystallogr., Sect. C*, 52 (1996) 1220–1223.

[9] G.M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1993.

[10] T.A. Jones, M. Kjedgaad, ‘O’, version 5.10, Molecular Modelling Program, Uppsala, Sweden, 1995.

[11] D. Mentzafos, I.M. Mavridis, G. Le Bas, G. Tsoucaris, *Acta Crystallogr., Sect. B*, 47 (1991) 746–757.

[12] G. Le Bas, G. Tsoucaris, *Supramol. Chem.*, 4 (1994) 13–16.

[13] D. Sriram, T. Lakshmanan, D. Loganathan, S. Srrinivasan, *Carbohydr. Res.*, 309 (1998) 227–236.

[14] C.M. Hartshorn, P.J. Steel, *Inorg. Chem.*, 35 (1996) 6902–6903.

[15] G.M.J. Schmidt, *Reactivity of the Photoexcited Organic Molecules*, Interscience, New York, 1967, pp. 227–228; and references therein.

[16] S. Makedonopoulou, I.M. Mavridis, K. Yannakopoulou, J. Papaioannou, *Chem. Commun. (Cambridge)*, (1998) 2133–2134.