Chinese Journal of Chemistry, **2009**, *27*, 2097—2101 **Note**

Crystal Structure of *β*-Cyclodextrin-Felbinac Inclusion Complex

WANG, Enju*(王恩举) CHEN, Guangying(陈光英) LIU, Hong(刘红)

Hainan Provicial Key Laboratory of Tropical Pharmaceutical Herb Chemistry, School of Chemistry & Chemical Engineering, Hainan Normal University, Haikou, Hainan 571158, China

The crystal structure of the inclusion complex of *β*-cyclodextrin (*β*-CD) synthesized with felbinac (4-biphenylacetic acid) was determined by single crystal X-ray diffraction at 150 K. The complex contains two *β*-CDs, two felbinac molecules, twenty-two water molecules in the asymmetric unit, and could be formulated as $(C_{42}H_{70}O_{35})_2$•$(C_{14}H_{12}O_2)_2$•22(H_2O). In the crystal lattice, the two *β*-CD moieties form a head-to-head dimer jointed through hydrogen bonds, and the felbinacs that interact by face-to-face π-π stacking are included in the *β*-CD dimer cavity with their carboxyl groups protruding out from cavity opening. In crystals the dimer units of *β*-CD are stacked in an intermediate type (IM) that consists of closely packed *β*-CD dimer layers.

Keywords *β*-cyclodextrin, 4-biphenylacetic acid, Felbinac, inclusion complex, crystal structure

Introduction

Felbinac (4-biphenylylacetic acid), an active metabolite derived from fenbufen, is a potent non-steroidal anti-inflammatory agent, which is used to treat muscle inflammation and arthritis. It could induce severe gastrointestinal side effects such as gastric erosions and ulcer when given orally, which limits its widespread use *in clinic*.[1] The optimum choice for felbinac is to become a medicament for topical treatment in order to overcome its undesirable secondary effect, for instance, it is applied to the skin surface for the relief of local pain and inflammation induced by sprains, strains, rheumatism, and mild arthritis.[2]

β-Cyclodextrin (*β*-CD) is a macrocyclic oligosaccharide consisting of seven *α*-(1→4)-linked *D*-glucose units. It has a hydrophilic exterior and a hydrophobic central cavity, which results in its ability to form inclusion complexes with a variety of hydrophobic molecules in aqueous solution.[3-6] The physicochemical properties of the included molecules are different from the uncomplexed ones. This beneficial property has been applied to the pharmaceutical field,[7,8] and several studies have been performed on felbinac. After oral administration of *β*-CD-felbinac complex to rats, quicker and higher drug plasma concentrations can be achieved, and parallel studies demonstrate a greater anti-inflammatory activity and a better gastric tolerability.[9,10] Colon-specific delivery systems of felbinac have been constructed through an ester or amide linkage with CD.[11] Furthermore, *β*-CD and its derivatives can enhance the cutaneous permeation of felbinac.[12,13] The single crystal X-ray structure of the inclusion complex between felbinac and heptakis-(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin (TM-*β*-CD) has been reported.[14] In this work, we wish to report the crystal structure of felbinac complexed with *β*-CD. The inclusion geometry and the crystal packing structure are discussed in details.

Results and discussion

The *β*-CD-felbinac inclusion complex crystallizes as a face-to-face *β*-CD dimer (*β*-CD-A and *β*-CD-B, Figure 1) containing two included felbinac molecules in the extended cavity and twenty-two water molecules in interstices between the dimers. Each glucose residue of *β*-CD dimer adopts the usual $^4C_1$ chair conformation, and the overall *β*-CD molecule has an approximate 7-fold-axis symmetry. The geometric parameters for the *β*-CD molecules are listed in Table 1. The O(4*n*) atoms of glucose residues are almost co-planar, with the largest displacement from the average plane observed for *β*-CD-A being the O(6) and O(11) atoms (−0.0370 and 0.0420 Å, respectively), for *β*-CD-B being the O(46) and O(51) atoms (0.0331 and −0.0250 Å, respectively). The O(4*n*)···O[4(*n*+1)] distances vary between 4.230(3) and 4.555(0) Å. The distances from the center of seven O(4) atoms to each individual O(4) atom are in the range of 4.867(6)—5.299(6) Å for *β*-CD-A and in the range of 4.959(5) — 5.119(8) Å for *β*-CD-B. The O[4(*n*−1)]···O(4*n*)···O[4(*n*+1)] angles, varying from 122.2(2)° to 132.4(3)° for *β*-CD-A and from 126.4(6)° to 130.2(0)° for *β*-CD-B, are within 6.35° from the regular heptagon of 128.57°. The annular shape of *β*-CD is stabilized by interglucose O[2(*n*+1)]—H···O(3*n*) hydrogen bonds.

* E-mail: enjuwang@163.com; Tel.: 0086-0898-65780881
Received March 11, 2009; revised May 20, 2009; accepted June 26, 2009.
Project supported by the Natural Science Foundation of Hainan Province (No. 808145).

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

		Residue						
		1	2	3	4	5	6	7
ϕ	A	122.2(2)	132.4(3)	131.4(5)	124.7(3)	127.1(0)	132.1(8)	129.7(7)
	B	126.9(8)	130.2(0)	129.0(4)	126.4(6)	130.1(2)	128.1(4)	129.0(4)
D_1	A	4.379(8)	4.230(3)	4.555(0)	4.301(7)	4.384(5)	4.431(6)	4.476(3)
	B	4.350(9)	4.326(3)	4.477(6)	4.243(5)	4.462(6)	4.338(2)	4.404(5)
Tilt angle	A	9.2	7.8	13.9	11.6	9.5	5.1	7.3
	B	9.4	7.1	12.0	7.0	12.9	6.2	2.8
d	A	−0.0370	0.0420	−0.0295	0.0231	-0.0268	0.0187	0.0095
	B	0.0082	−0.0177	−0.0043	0.0300	-0.0250	-0.0029	0.0106
O(3n)−O[2(n+1)]	A	2.8(7)	2.8(3)	2.8(5)	2.8(5)	2.8(2)	2.7(0)	2.7(9)
	B	2.7(1)	2.7(4)	2.8(3)	2.7(9)	2.8(8)	2.7(7)	2.8(0)
Torsion angle	A	-61.1, 45.6	−64.3	−66.4	−61.6	63.9	−69.0	−55.9
	B	-62.0	−66.7	−61.7	−65.2	−65.0	−62.2	−67.0
D_2	A	5.299(6)	4.914(2)	4.884(6)	5.220(3)	5.134(5)	4.867(7)	5.001(0)
	B	5.039(5)	5.094(2)	4.959(5)	5.039(2)	5.119(8)	4.999(2)	5.042(0)

ϕ = angle between atoms O[4(n−1)]-O(4n)-O[4(n+1)]; D_1 = distance between atoms O[4(n−1)]···O(4n); Tilt angle is the angle between the O(4) plane and the planes defined by O[4(n−1)], C(1n), C(4n), and O(4n); d = deviation of O(4n) atom from the least-squares optimum plane formed by the seven O(4n) atoms; Torsion angle: O(5n)-C(5n)-C(6n)-O(6n); D_2 = distance between atoms O(4n) and the center of seven O(4).

Conclusively, the geometrical parameters indicate that upon complex formation, the guest molecule has slightly distorted the macrocyclic conformation of the β-CD. The orientation of the C(6n)—O(6n) bond is generally described by the torsion angles of O(5n)-C(5n)-C(6n)-O(6n). For β-CD-A, five of the seven primary hydroxyl groups exhibit the (−)-*gauche* orientation pointing outwards from the β-CD cavity. One [O(25)—H] of them has (+)-*gauche* orientation pointing inwards and forming hydrogen bond O(71)—H···O(25) contributing to the interlinkage between β-CD and felbinac. The last one is disordered at two sites, in which one points outwards from the β-CD cavity, the other points inwards with the occupation of 0.53 [O(5A)] and 0.47 [O(5B)], respectively. For β-CD-B, all seven primary hydroxyl groups point away from the β-CD cavity.

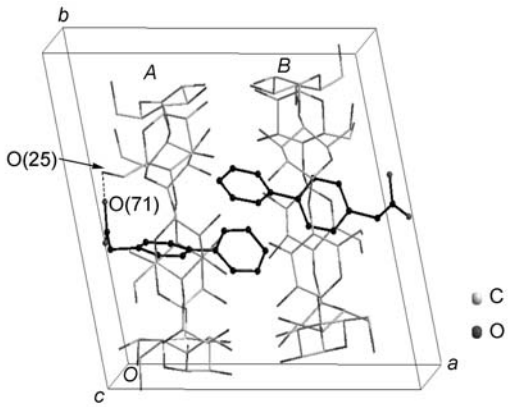

Figure 1 View of β-CD-felbinac inclusion complex. There is a face-to-face π-π stacking interaction between two phenyl rings in β-CD dimer center. Hydrogen bond between the β-CD and guest is shown as dashed line.

Two guest molecules reside within the dimer cavity in a similar manner with their carboxyl groups protruding from the cavity of β-CD dimer. The two-fold axis of biphenyl unit is inclined about 19° with respect to the normal of the O(4) plane. In the β-CD dimer, two felbinac molecules also form a dimer by face-to-face π-π stacking interaction. For two phenyl rings involving in stacking, the distance is about 0.36 Å and the angle is 13.9°. One carboxyl group of two 4-biphenylacetic acids in each β-CD dimer is linked to a primary hydroxyl group of β-CD, which includes it via an O(71)—H···O(25) hydrogen bond, being crucial for the felbinac to avoid disorder. The other carboxyl group of two guests is linked to adjacent β-CD by a direct hydrogen bond [O(10)—H···O(73)] and an indirect hydrogen bond through a water molecule as a bridge [O(74)—H···O(85)—H···O(15)].

The two β-CD molecules form a head-to-head dimmer, which is assembled through O(3)—H···O(3) intermolecular hydrogen bonds.[15] The dimers crystallize in an intermediate mode (IM) in which they stack along *a*-axis with a significant lateral translation of 6.0 Å in *c* direction (Figure 2).[16] The offset is close to the inner diameter of β-CD (about 6.0—6.5 Å), which means that the cavity opening of β-CD dimers is blocked by the rim of adjacent dimers. The result is a nearly cage-like environment for the guest molecules. There is no interaction between guests in adjacent dimer cavities, but an interaction between β-CD and the felbinac included in adjacent dimers exists, that is O(73)···H—O(10), in which O(73) is from the carboxyl group of guest and O(10)—H is an primary hydroxyl of β-CD. The hydrogen bond contributes to fixed location of guest. Beside interaction between the guest and adjacent β-CD dimers, the intermediate packing type favors solvation

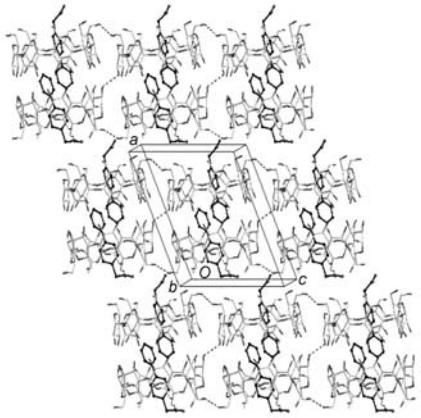

Figure 2 Crystal packing in an intermediate mode (IM) in which they stack along *a*-axis with a significant lateral translation in *c* direction.

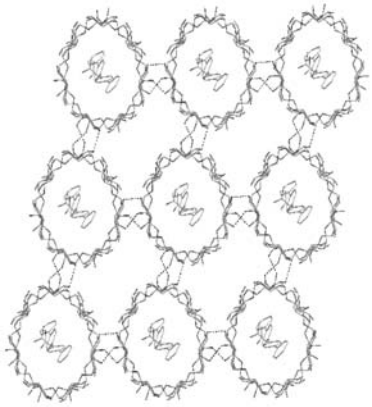

Figure 3 *β*-CD dimer layer in *bc*-plane linked by direct hydrogen bonds between adjacent *β*-CD dimers.

of guests, which is also an important factor to keep order.

There are seven direct hydrogen bond interactions between *β*-CD dimers. Three of them contribute to the interaction in *c* direction, and other three of them bond adjacent *β*-CD dimers in *b* direction, but there is no direct hydrogen bond between *β*-CD dimers in *a* direction. All the above six hydrogen bonds link the *β*-CD dimers into layers in *bc*-plane, which stack along *a*-axis to form three-dimensional structure (Figure 3). There are a hydrogen bond between *β*-CD dimers and a hydrogen bond between *β*-CD dimer and felbinac contributing to the interaction between layers. A summary of intermolecular hydrogen bonds that are crucial for packing is given in Table 2, excluding the hydrogen bonds in which water molecules are involved in.

Crystal water plays the most important role in crystal packing by forming extended hydrogen-bond networks with hydroxyl groups of *β*-CD and carboxyl groups of guests. In the networks, the hydrogen-bonds have cooperative effect which contributes additional energy to the individual hydrogen bond.[17] The fact that the crystals would decompose due to escaping of crystal water when exposed in air at room temperate further shows the significance of crystal water. But these hydrogen bonds could not be assigned, because hydrogen atoms of water molecules were not located.

In a previous paper, the crystal structures of derivatives of biphenyl in *β*-CD have been summarized.[18] Because these guests are too big to be included in *β*-CD, two *β*-CD molecules form a face-to-face dimmer, which has larger cavity than twice of one *β*-CD cavity. 4-Biphenylacetic acid and flurbiprofen (2-fluoro-*α*-methyl-4-biphenylacetic acid) have similar molecular framework, so the inclusion complexes of them crystallize in the same mode.

Conclusion

The inclusion complex of felbinac in *β*-CD has been synthesized and characterized by single crystal X-ray diffraction. In the crystal lattice, two *β*-CD moieties form a head-to-head dimer that enclose two felbinacs. The two guests also form a dimer by face-to-face π-π stacking and oritent themselves with the hydroxyl groups residing at the open ends of *β*-CD dimer. The

Table 2 Intermolecular hydrogen bonds [distance in Å and angles in (°)]

D—H	*d*(H···A)	∠DHA	*d*(D···A)	A
In *c*-axis direction				
O(30)—H(30)	1.907	172.29	2.722	O(10) [*x*, *y*, *z*+1]
O(45)—H(45A)	2.017	162.91	2.811	O(65) [*x*, *y*, *z*−1]
O(42)—H(42)	2.068	152.19	2.819	O(27) [*x*, *y*, *z*−1]
In *b*-axis direction				
O(20)—H(20A)	2.133	169.69	2.944	O(35) [*x*, *y*+1, *z*]
O(67)—H(67A)	1.952	164.99	2.752	O(17) [*x*, *y*−1, *z*1]
O(70)—H(70A)	1.941	162.88	2.735	O(55) [*x*, *y*−1, *z*]
Between *β*-CD dimer layers				
O(10)—H(10C)	1.916	165.22	2.717	O(73) [*x*−1, *y*, *z*−1]
O(60)—H(60)	2.479	120.77	2.983	O(4) [*x*+1, *y*+1, *z*+1]
Between *β*-CD and guest				
O(71)—H(71A)	2.221	111.05	2.629	O(25)

complex are arranged in a brickwork pattern in *ac*-plane and forms layer in *bc*-plane by hydrogen-bonds.

Experimental

Preparation and crystallization of the inclusion compound

β-CD•12H_2O was re-crystallized prior to use. 4-Biphenylacetic acid was purchased from Merck and used as received. 4-Biphenylacetic acid (0.2 mmol) was suspended in 8 mL of aqueous solution of *β*-CD (0.2 mmol) and heated until the solid dissolved. Cooling of the solution produced a saturated aqueous solution of the title inclusion complex. Slow evaporation of the filtered solution at room temperature afforded colorless flake-like crystals in one week.

X-ray crystallography

The crystallographic data are summarized in Table 3. X-ray diffraction data were collected on an Oxford Diffraction Xcalibur Nova instrument with Cu Kα radiation (λ=1.54178 Å) at 150 K. The data were processed using CrysAlis.[19] The structure was solved by isostructural replacement of the *β*-CD coordinates from an isomorphous structure, *β*-CD complex with 7-hydroxyl-4-methylcoumarin.[20] In solving the structure, except that the relatively rigid backbone of *β*-CD was used for the calculations, all atoms of *β*-CD O(6), guests and water were omitted, which could be located from the difference Fourier maps. One of the O(6) atoms of *β*-CD-A is disordered over two positions and all the other atoms in an asymmetric unit are fully occupied. Except for those hydrogen atoms attached to the water molecules, all the other hydrogen atoms were added in ideal positions and refined as riding models. The structure was refined using full-matrix least-squares based on F^2 with program SHELXL.[21]

Table 3 Crystallographic data

Chemical formula	$(C_{42}H_{70}O_{35})_2$•$(C_{14}H_{12}O_2)_2$•22(H_2O)
Formula weight	3090.78
Temperature/K	150
Wavelength/Å	1.54178
Crystal system	Triclinic
Space group	*P*1
a/Å	17.842(4)
b/Å	15.394(2)
c/Å	15.463(4)
α/(°)	103.108(16)
β/(°)	113.33(2)
γ/(°)	99.201(15)
V/Å^3	3647.1(12)
Z	1
D_{calcd}/(Mg•m^{-3})	1.407
F(000)	1648
Crystal size/mm^3	0.25×0.2×0.1
θ range/(°)	2.81—70.40
Index ranges	−20≤*h*≤21; −18≤*k*≤18; −18≤*l*≤16
Reflections collected/unique	30237/16967 [*R*(int)=0.0271]
Data completeness	0.917
Data / restraints/parameters	16967/3/1928
Goodness-of-fit on F^2	1.047
Final *R* indices [$I>2\sigma(I)$]	R_1=0.0743, wR_2=0.2052
R indices (all data)	R_1=0.0803, wR_2=0.2227
Largest diff. peak and hole/(e•Å^{-3})	1.137 and −0.479

Supplementary data

Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with CCDC No. 711404. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: 0044-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

References

1 Arima, H.; Kondo, T.; Irie, T.; Uekama, K. *J. Pharm. Sci.* **1992**, *81*, 1119.
2 Ramuzei, M. P.; Soondaasu, R. U. *JP 5194208*, **1993** [*Chem. Abstr*. **1993**, 2079420].
3 Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.
4 Hapiot, F.; Tilloy, S.; Monflier, E. *Chem. Rev.* **2006**, *106*, 767.
5 Song, L. X.; Wang, H. M.; Teng, C. F.; Bai, L.; Xu, P.; Guo, X. Q. *Chin. J. Chem.* **2008**, *26*, 1702.
6 Fan, Z.; Diao, C.-H.; Song, H.-B.; Jiang, Z.-L.; Yu, M.; Chen, X.; Guo, M.-J. *Acta Chim. Sinica* **2007**, *65*, 1449 (in Chinese).
7 Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045.
8 Pan, T. T.; Chu, Y. Q.; Zhou, M. F.; Ding, C. F. *Acta Chim. Sinica* **2008**, *66*, 2462. (in Chinese).
9 Puglisi, G.; Santagati, N. A.; Ventura, C. A.; Pignatello, R.; Panico, A. M.; Spampinato, S. *J. Pharm. Pharmacol.* **1991**, *43*, 430.
10 Puglisi, G.; Ventura, C. A.; Spadaro, A.; Campana, G.; Spampinato, S. *J. Pharm. Pharmacol.* **1995**, *47*, 120.
11 Minami, K.; Hirayama, F.; Uekama, K. *J. Pharm. Sci*. **1998**, *87*, 715.
12 Castelli, F.; Puglisi, G.; Giammona, G.; Ventura, C. A. *Int. J. Pharm*. **1992**, *88*, 1.
13 Arima, H.; Miyaji, T.; Irie, T.; Hirayama, F.; Uekama, K. *Chem. Pharm. Bull.* **1996**, *44*, 582.
14 Harata, K.; Hirayama, F.; Arima, H.; Uekama, K.; Miyaji, T. *J. Chem. Soc., Perkin. Trans. 2* **1992**, 1159.
15 Makedonopoulou, S.; Mavridis, I. M. *Acta Crystallogr., Sec. B* **2000**, *56*, 322.
16 Mentzafos, D.; Mavridis, I. M.; LeBas, G.; Tsoucaris, G. *Acta Crystallogr., Sect. B* **1991**, 746.
17 Saenger, W.; Jacob, J.; Gessler, K.; Hoffmann, D.; Sanbe,

H.; Koizum, K.; Smith, S. M.; Takaha, T. *Chem. Rev.* **1998**, *98*, 1787.

18 Wang, E. J.; Yan, Z.; Cai, J. *Carbohydr. Res.* **2007**, *342*, 1530.

19 *CryAlis CCD and RED*, Version 1.171.31.7, Oxford Diffraction Ltd, **2006**.

20 Brett, T. J.; Alexander, J. M.; Stezowski, J. *J. Chem. Soc., Perkin. Trans. 2* **2000**, 1105.

21 Sheldrick, G. M. *SHELXL-97, Program for Crystal Structure Solution and Refinements*, University of Göttingen, Germany, **1997**.

(E0903112 Lu, Y.)