Journal of Inclusion Phenomena and Macrocyclic Chemistry **47:** 39–45, 2003.

Crystal Structures of β-Cyclodextrin Complexes with Formic Acid and Acetic Acid

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(Received: 14 January 2003; in final form: 20 August 2003)

Key words: acetic acid, crystal structure, β-cyclodextrin, formic acid, hydrogen bond, inclusion complex, X-ray analysis

Abstract

β-Cyclodextrin (β-CD)–formic acid (**1**) and β-CD–acetic acid (**2**) inclusion complexes crystallize as β-CD·0.3HCOOH·7.7H_2O and β-CD·0.4CH_3COOH·7.7H_2O in the monoclinic space group $P2_1$ with comparable unit cell constants. Anisotropic refinement of atomic parameters against X-ray diffraction data with $F_o^2 > 2\sigma(F_o^2)$ (986/8563 and 991/8358) converged at *R*-factors of 0.051 and 0.054 for **1** and **2**, respectively. In both complexes, the β-CD molecular conformation, hydration pattern and crystal packing are similar, but the inclusion geometries of the guest molecules are different. The β-CD macrocycles adopt a "round" conformation stabilized by intramolecular, interglucose O3(n)···O2(n + 1) hydrogen bonds and their O6–H groups are systematically hydrated by water molecules. In the asymmetric unit, each complex contains one β-CD, 0.3 formic acid (or 0.4 acetic acid), and 7.7 water molecules that are distributed over 9 positions. Water sites located in the β-CD cavity hydrogen bond to the guest molecule. In the crystal lattice, β-CD molecules are packed in a typical "herringbone" fashion. In **1**, the formic acid (occupancy 0.3) is entirely included in the β-CD cavity such that its C atom is shifted from the O4-plane center to the β-CD O6-side by 2.90 Å and C=O, C—O bonds point to this side. In **2**, the acetic acid (occupancy 0.4) is completely embedded in the β-CD cavity, in which the carboxylic C atom is displaced from the O4-plane center to the β-CD O6-side by 0.87 Å; the C=O bond directs to the β-CD O6-side and makes an angle of 15° to the β-CD molecular axis. Furthermore, both dimethyl-β-CD-acetic acid and β-CD-acetic acid complexes form a cage structure, showing that the small guests enclosed entirely in the cavity either in β-CD or in dimethyl-β-CD do not affect the packing of the host macrocycles.

Introduction

α-, β-, γ-Cyclodextrins (CDs) are cyclic oligosaccharides consisting of 6, 7, 8 D-glucose units linked by α-(1 → 4) glycosidic bonds [1]. They have the shape of a truncated cone and are amphiphilic with an apolar cavity coated by C—H groups and O4, O5 atoms, and hydrophilic rims lined by O6-H groups on the narrower side, and O2–H, O3–H groups on the wider side (Figure 1).

CDs are well known for their ability to form inclusion complexes [2] with a variety of guest molecules fitting partially or completely into the host CD cavity as shown by many CD crystal structures [3]. In the crystal lattice, CDs are arranged in two different types according to the feature of the formed cavity: (i) cage (herringbone or brick motifs) and (ii) channel depending on the size and shape of the guest molecule [4].

Inclusion complexes of α-CD with a series of aliphatic carboxylic acids with 2–5 C atoms have been investigated by Saenger *et al.* since 30 years ago [5]. Although the crystal structures were not determined, the crystallographic data gave information on crystal packing. Clearly, the complexes with small guest-molecules like acetic acid, propionic acid, butyric acid, crystallize in the orthorhombic space group $P2_12_12_1$ and have a cage structure, whereas the complex with the longer molecule, valeric acid, crystallizes in a hexagonal space group and forms a channel structure. In past years, Mavridis *et al.* studied the inclusion complexes of β-CD with long aliphatic monocarboxylic and α,ω-dicarboxylic acids [6–12]. Both complexes with aliphatic monoacids and with aliphatic diacids likely crystal-

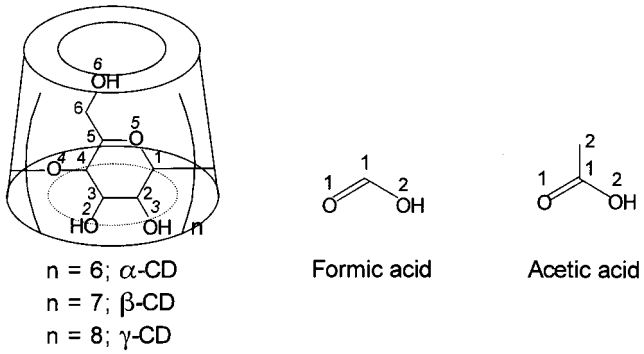

Figure 1. Chemical structures and atomic numbering of CD, formic acid, and acetic acid.

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lize in the triclinic space group $P1$ and β-CDs form dimer enclosing the guest molecules. In the monoacids with 12–16 C atoms the packing pattern is a channel structure [6–9], whereas in the diacids with 10–16 C atoms the packing style is an intermediate between cage (brick motif) and channel [10–12]. In addition, an inclusion complex of dimethyl-β-CD with acetic acid has been reported [13]. The complex crystallizes in the monoclinic space group $P2_1$ and the CD molecules are stacked in a herringbone cage-type.

Because the inclusion complexes of β-CD with formic acid and acetic acid have not yet been evidenced crystallographically so far. Therefore, it is of interest to determine the crystal structures of the β-CD complexes with small aliphatic carboxylic acids and to compare them to the corresponding complex of α-CD and other relevant complexes.

Experimental

Crystallization and X-ray diffraction

β-CD purchased from Cyclolab (Budapest, Hungary), formic acid and acetic acid from Fluka were used without further purification. Each 0.05 mmol of β-CD was dissolved in 2 mL of 5% formic acid and 10% acetic acid at RT. The rodlike, colorless single crystals grew in two weeks by slow solvent evaporation.

A single crystal of each complex was mounted in a glass capillary sealed at both ends by a drop of mother liquor. X-ray diffraction experiments were carried out at RT using a SMART CCD (Bruker) with MoKα radiation (α = 0.71073 Å) operating at 50 kV, 30 mA. A total of 15,883 (β-CD–formic acid complex) and 16,086 (β-CD–acetic acid complex) reflections were measured in the θ-range 1.0–30.5° (0.7 Å resolution). Data were corrected for Lorentz, polarization, and absorption effects and merged by SADABS [14] and SHELXTL [15] to yield 10,384 and 10,886 unique reflections for the formic acid and acetic acid complexes, respectively. The crystals of both complexes belong to monoclinic space group $P2_1$ (further details, see Table 1).

Structure determination and refinement

The crystal structures were determined by molecular replacement with program PATSEE [16] using the structure of β-CD–ethylene glycol complex [17] as a phasing model (only the β-CD skeleton was used for the calculations, O6 atoms were omitted). β-CD O6 atoms, guest molecules, water oxygen atoms, and most of CH, CH_2 H-atoms of β-CD could be located by difference Fourier electron density maps aided by the graphic program XTALVIEW [18]. The remaining H atom positions were placed according to the "riding model" [19]. The structures were refined by full-matrix least-squares on F^2 with program SHELXL-97 [19]. Anisotropic refinement of atomic parameters against X-ray diffraction data with $F_o^2 > 2\sigma(F_o^2)$ (986/8563 and 991/8358) converged at R-factors of 0.051 and 0.054 for the formic acid and acetic acid complexes, respectively (except for the guest molecules that were refined isotropically). The O6 atoms of glucose residues 1, 7 are twofold disordered with occupancies for sites A, B are 0.6, 0.4; 0.7, 0.3 (formic acid); 0.45, 0.55; 0.85, 0.15 (acetic acid). The β-CD cavity accommodates both the disordered guest and water molecules (e.g., W8, W9 (formic acid); W1, W2, W3 (acetic acid)). The 7.7 water molecules are distributed over 9 sites with average occupancy 0.86. Both β-CD structures show normal thermal motion with U_{eq} in the ranges 0.042–0.095 Å^2 (β-CD skeleton), 0.069–0.142 Å^2 (β-CD O6), whereas some water sites and guest molecules exhibit higher thermal motion with U_{eq} 2–3 times more.

A summary of crystallographic data and the geometrical parameters for both the inclusion complexes are given in Tables 1 and 2, respectively. The final fractional atomic coordinates and equivalent isotropic thermal displacement factors are deposited at the Cambridge Crystallographic Data Center [20].

The atomic numbering scheme is that used conventionally for carbohydrates (i.e., the first number denotes the position in the glucose and the second number the glucose number in the CD macrocycle), Figure 1. Letters A, B indicate disordered atoms. For example, O61A stands for site A of the disordered O6 of glucose unit 1. In addition, letters M and T show the formic acid and acetic acid, respectively; the β-CD-formic acid complex is given as **1** and β-CD–acetic acid **2**.

Results and discussion

Isomorphous β-CD macrocycle

In both complexes, the structures of host β-CD molecules are identical as shown by very small rms deviation of superposition 0.05 Å (all C, O atoms were used for the calculations). The 14 glucose units adopt a regular $^4C_1$ chair conformation as indicated by the Cremer–Pople puckering parameters Q, θ [21] and torsion angles ϕ, ψ, in the ranges 0.54–0.59 Å, 1–9° and 102.2–117.3°, 113.9–140.8°, respectively (Table 2, Figures 2(a,b)). The annular geometry of the β-CD macrocycles is stabilized by intramolecular, interglucose O3(n)$\cdots$O2($n+1$) hydrogen bonds with O$\cdots$O distances 2.78–3.00 Å (Table 2, Figures 2(a,b)). Tilt angles showing inclination of glucose to the β-CD central cavity are in the range 4.0–13.3°, except for those of glucose residues 1, 5, 7 that are 17.4–26.5° (Table 2, Figures 2(a,b)). In addition, the lines connecting the seven O4-atoms give a well-defined heptagon as indicated by the O4($n-1$)$\cdots$O4(n)$\cdots$O4($n+1$) angles 123.9–133.9° and the deviations of O4 atoms from their common least-squares plane < 0.28 Å (Table 2, Figures 2(a,b)).

The orientation of C6–O6 groups is generally described by the torsion angle O5–C5–C6–O6. All C6–O6 groups point "away" from the β-CD cavity (*-gauche* orientation) as shown by the torsion angle O5–C5–C6–O6 in the range −59.1° to −72.0° (Table 2, Figures 2(a,b)). Exceptions are

Table 1. Crystallographic data of β-CD·0.3HCOOH·7.7H_2O and β-CD·0.4CH_3COOH·7.7H_2O

Chemical formula	$(C_6H_{10}O_5)_7$·0.3CH_2O_2·7.7H_2O	$(C_6H_{10}O_5)_7$·0.4$C_2H_4O_2$·7.7H_2O
Formula weight	1287.51	1297.72
Crystal habit, color	Rod, colorless	Rod, colorless
Crystal size (mm^3)	0.4 × 0.6 × 1.0	0.5 × 0.6 × 0.9
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$
Unit cell dimensions		
a (Å)	15.171(1)	15.263(4)
b (Å)	10.169(1)	10.157(2)
c (Å)	20.986(1)	21.044(5)
β (°)	110.92(1)	110.67(1)
Volume ($Å^3$)	3024.2(1)	3051.8(1)
Z	2	2
D_x (g cm^{-3})	1.400	1.397
μ (mm^{-1})	0.13	0.13
$F(000)$	1348	1356
Diffractometer	SMART CCD (Bruker)	
Wavelength, MoKα (Å)	0.71073	
Temperature (°C)	20	20
θ range for data collection (°)	1.04 to 30.54	1.03 to 30.52
Resolution (Å)	0.70	0.70
Measured reflections	15883	16086
Unique reflections	10384	10886
R_{int}	0.026	0.032
Index ranges	$0 \le h \le 20, -14 \le k \le 12,$ $0 \le l \le 27$	$0 \le h \le 19, -14 \le k \le 12,$ $0 \le l \le 30$
Unique reflections $[F^2 > 2\sigma(F^2)]$	8563	8358
Structure solution	Molecular replacement (PATSEE)	
Refinement method	Full-matrix least-squares on F^2	
Weighting scheme	$w = [S^2(F_o^2) + (0.1085P)^2 + 0.0350P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$	$w = [S^2(F_o^2) + (0.1000P)^2 + 0.0218P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$
Data/parameters	10384/986	10886/991
R $[F^2 > 2\sigma(F^2)]$	$R^a = 0.051$, $wR^6 = 0.140$	$R^a = 0.054$, $wR^b = 0.139$
R (all data)	$R^b = 0.060$, $wR^b = 0.145$	$R^a = 0.067$, $wR^b = 0.146$
Goodness of fit	1.006	0.995
Highest peak/ Deepest hole (e $Å^{-3}$)	0.25/−0.19	0.30/−0.19

[a] $R = \sum \| F_o| - |F_c \| / \sum |F_o|$.
[b] $wR = \sum\{w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2\}^{1/2}$.

C61–O61B, C65–O65, C67–O67B groups that point "toward" the β-CD cavity (+*gauche* orientation) as shown by the corresponding angles of 58.9–77.6° (Table 2, Figures 2(a,b)). This is because these O6–H groups hydrogen bond to the guest molecules and to water molecules embedded in the β-CD cavity (Figures 2(a,b)).

Different inclusion geometries of the guest molecules

Although the structures of formic acid and acetic acid are similar, each small acid are oriented differently in the large β-CD cavity to yield a stable complex with sufficient host–guest interactions. In **1**, the formic acid (occupancy 0.3) is located at the β-CD O6-side such that its C-atom shifts from the O4-plane center by 2.90 Å and C=O, C—O bonds point to this side (Figure 2(a)). It is maintained in position by hydrogen bonding to the surrounding water sites and β-CD OH groups. For example, O25···O1M(x, $y-1$, z), O65···O1M, O67B···O1M, W3···O1M, O34···O2M(x, $y-1$, z), O25···O2M(x, $y-1$, z), O67B···O2M, W1···O2M, W3···O2M (O···O separation 2.66–3.49 Å, Figures 2(a), 4(a)). In **2**, the acetic acid (occupancy 0.4) is almost placed at the center of β-CD cavity, in which the carboxylic C-atom is displaced from the O4-plane center to the O6-side by 0.87 Å and the C=O bond points to the O6-side and makes an angle of 15° to the β-CD molecular axis (Figures 2(b), 3). It is sustained by hydrogen bonding in similar way, as is the formic acid, but has fewer number of O—H···O interactions. For example, W8···O1T, W7···O1T(x,

Table 2. Geometrical parameters of β-CD macrocycles in the formic acid and acetic acid inclusion complexes (distances in Å and angles in °)

Residue	1	2	3	4	5	6	7
Q^a, θ^b	0.58, 2	0.54, 5	0.57, 2	0.58, 5	0.55, 6	0.56, 2	0.58, 9
	0.57, 3[i]	**0.54, 5**	**0.57, 1**	**0.59, 5**	**0.55, 6**	**0.56, 3**	**0.58, 9**
ϕ^c, ψ^c	106.6(3)	102.6(3)	108.2(3)	113.2(3)	117.2(3)	103.0(3)	115.8(3)
	135.3(3)	118.7(3)	128.3(3)	129.9(3)	130.8(3)	113.9(3)	140.9(3)
	107.3(3)	**102.4(3)**	**106.8(3)**	**113.6(3)**	**117.3(3)**	**102.2(3)**	**115.5(3)**
	133.9(3)	**117.9(3)**	**128.1(3)**	**130.1(3)**	**130.2(3)**	**115.0(3)**	**140.8(3)**
Tilt angle[d]	26.5(2)	10.9(2)	5.4(1)	12.4(2)	20.2(2)	4.1(2)	17.4(2)
	26.3(2)	**10.6(2)**	**5.6(1)**	**13.3(2)**	**20.3(2)**	**4.0(2)**	**17.7(2)**
O4 angle[e]	127.5(1)	124.4(1)	133.8(1)	128.0(1)	124.0(1)	131.6(1)	129.0(1)
	127.4(1)	**124.0(1)**	**133.9(1)**	**128.4(1)**	**123.9(1)**	**130.8(1)**	**129.9(1)**
Distance							
O4 deviation[f]	−0.12	0.20	0.05	−0.26	0.11	0.17	−0.15
	−0.12	**0.22**	**0.04**	**−0.28**	**0.14**	**0.17**	**−0.17**
O3(n)···O2($n+1$)	2.88(1)	2.87(1)	2.82(1)	2.78(1)	2.89(1)	2.88(1)	3.00(1)
	2.87(1)	**2.89(1)**	**2.80(1)**	**2.78(1)**	**2.94(1)**	**2.90(1)**	**2.97(1)**
Torsion angle							
O5-C5-C6-O6	58.9(6)[g]	−61.0(3)	−63.0(4)	−70.7(4)	64.0(4)	−63.9(4)	−67.5(4)[g]
	−59.9(6)[g]						77.6(14)[g]
	−60.7(5)[h]	**−59.2(3)**	**−62.6(4)**	**−72.0(4)**	**62.5(4)**	**−63.4(3)**	**−66.4(5)**[h]
	59.1(7)[h]						**69.5(7)**[h]

[a] Cremer–Pople puckering amplitude [21].
[b] Indicates the deviation from the theoretical chair conformation (ideal value: $\theta = 0$).
[c] Torsion angles ϕ and ψ at glycosidic O4, defined as O5(n)–C1(n)–O4($n-1$)–C4($n-1$) and C1(n)–O4($n-1$)–C4($n-1$)–C3($n-1$), respectively.
[d] Tilt angles, defined as the angles between the O4 plane and the planes through C1(n), C4(n), O4(n) and O4($n-1$).
[e] Angle at each glycosidic O4: O4($n+1$)–O4(n)–O4($n-1$).
[f] Deviation of O4 atoms from the least-squares plane through the seven O4 atoms.
[g] Values for sites A, B of the twofold disordered O61, O67 with the occupancy factors 0.6, 0.4; 0.7, 0.3, respectively (formic acid).
[h] Values for sites A, B of the twofold disordered O61, O67 with the occupancy factors 0.45, 0.55; 0.85, 0.15, respectively (acetic acid).
[i] Bold numbers are the values of the acetic acid inclusion complex.

$y-1$, z), O67B···O1T, W9···O2T, W8···O2T (O···O separation 2.71–3.30 Å, Figures 2(b), 4(b)).

In comparison to the inclusion complex of dimethyl-β-CD with acetic acid [13], the appended methyl groups have little effect on the β-CD macrocycle, but much on the inclusion geometry of acetic acid in the β-CD cavity. Figure 3 shows the similarity between the structures of β-CD–acetic acid and dimethyl-β-CD–acetic acid [13] complexes which is indicated by the small rms deviation of superposition 0.27 Å (only CD C1–C6, O2–O5 atoms were used for the calculations). The acetic acid (occupancy 0.5) is located below the O4-plane such that its carboxylic C-atom shifts from the O4-plane center by 0.82 Å and the C—C bond inclines 50° to the dimethyl-β-CD molecular axis (Figure 3). It is in van der Waals contacts to the CD macrocycle and has no hydrogen bond interactions to the water molecules. This suggests that the acetic acid in the cavity of methylated derivative is probably less energetically favored than in that of native β-CD, although its occupancy factor in the former (0.5) is higher than that in the latter (0.4).

Water molecules as hydrogen bonding mediator

Each inclusion complex contains 7.7 water molecules that are distributed over 9 positions (average occupancy 0.86). In **1**, the water sites W1, W3, W4 are disordered with occupancies 0.6, 0.3, 0.8 and the rest is fully occupied. Water sites W1, W2, W3 located in the β-CD cavity hydrogen bond to the formic acid (Figure 2(a)). In **2**, the disordered water sites W3, W4, W7 (occupancies 0.8, 0.2, 0.7) are located outside the β-CD cavity and the others are fully occupied. Water sites W8 and W9 located at the O6-side and O2-, O3-side of the β-CD cavity hydrogen bond to the acetic acid (Figure 2(b)). Similar hydration patterns are observed in both complexes (Figures 4(a,b)). The β-CD O6–H groups are systematically hydrated by water sites (e.g., W4, W5/W6, W9, W7/W8, W7/W9, W7, W4 (**1**); W9, W1/W2, W5, W3/W6, W3/W8, W3, W8/W9 (**2**)). Some water sites bridge O5 to O6–H of the glucose units 1, 2, 4, 5 (e.g., W4, W5, W8, W7 (**1**); W9, W1, W6, W3 (**2**)). Some water sites link O3(n)–H to O2($n+1$)–H (e.g., O32···W5···O23, O34···W1···W8···W9···O25 (**1**); O32···W1···O23, O34···W7···W6···W5···O25 (**2**)). The O···O distances of the above-mentioned $O_{CD}\cdots O_W$ hydrogen bonds are in the range 2.71–3.15 Å, except for

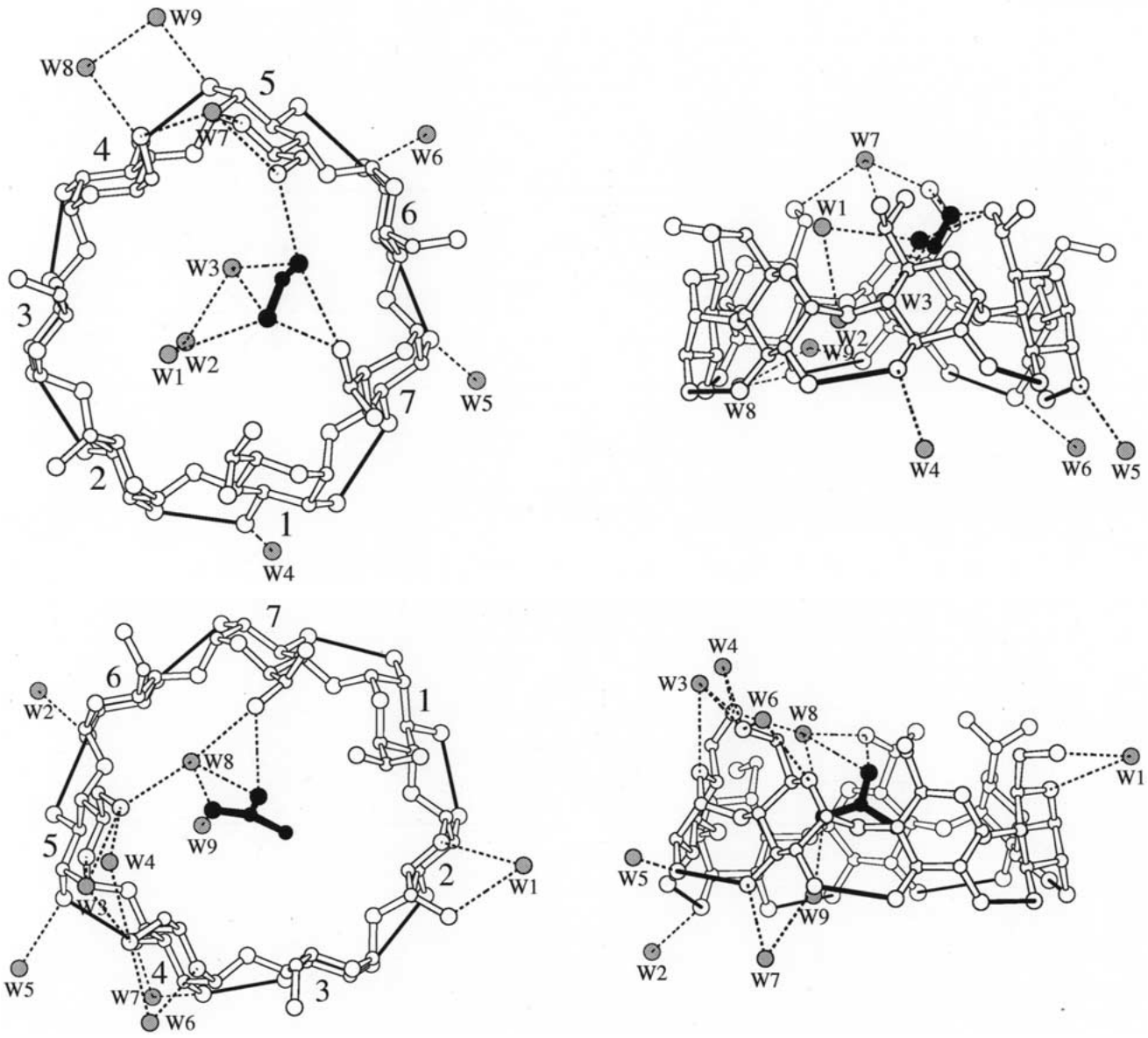

Figure 2. Ball-and-stick representation of (a) β-CD–formic acid and (b) β-CD–acetic acid inclusion complexes; top views on the left and side views on the right. Annular geometry of β-CD is stabilized by intramolecular, interglucose O3(n)$\cdots$O2($n+1$) hydrogen bonds (solid lines). For clarity, β-CDs are shown in white ball-and-stick and acids in black, water sites in grey balls, and hydrogen atoms are not shown. O—H$\cdots$O hydrogen bonds are represented with dashed lines. Drawn with MOLSCRIPT [30].

O61A$\cdots$W4 3.38 Å for **1**, O61B$\cdots$W9 3.39 Å, O64$\cdots$W4 3.45 Å for **2**. Water molecules play a crucial role as hydrogen bonding mediator in stabilizing the crystal structure.

Crystal packing

In **1** and **2**, the β-CD molecules are packed in a herringbone cage-type [4] as observed in the β-CD hydrates [22, 23] and in the β-CD inclusion complexes with small guest molecules like methanol [24], ethanol [25], DMSO [26]. The unit cell volumes of the above-mentioned β-CD inclusion complexes (this work and Refs. 24–26) are so comparable to those of β-CD hydrates [22, 23] with only 1% difference. This shows that when the small guest molecules are entirely included in the β-CD cavity, the herringbone packing structure of CD host molecules is intact. The inclusion complexes of α-CD and β-CD with acetic acid have different packing styles. The former [5] crystallizes in the orthorhombic space group $P2_12_12_1$ and is arranged in a brick cage-type, whereas the latter crystallizes in the monoclinic space group $P2_1$ and prefers a herringbone cage-type. However, albeit the complexes of α-CD with long aliphatic carboxylic acids have not yet been determined, it is expected that they should have a channel structure as observed in the complexes with long molecules (e.g., α-CD–polyiodides [27] and α-CD–4,4′–biphenyldicarboxylic acid [28]). This will be similar to the corresponding complexes of β–CD [6–9]. Furthermore, both dimethyl-β-CD–acetic acid [13] and β-CD–acetic acid complexes form a cage structure, showing that the small guests enclosed entirely in the cavity either in β-CD or in dimethyl-β-CD do not affect the packing of the host macrocycles.

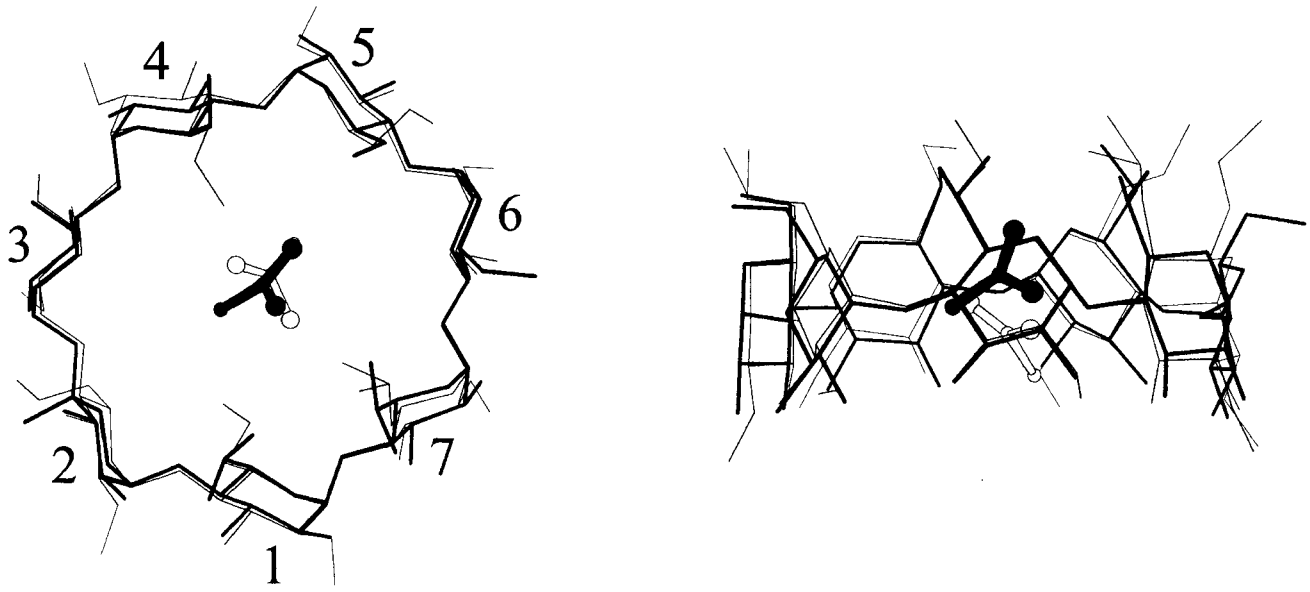

Figure 3. Superposition of β-CD–acetic acid (thick line-black ball-and-stick) on dimethyl-β-CD–acetic acid[13] (thin line-white ball-and-stick); small balls are C and bigger O. For clarity, water molecules and hydrogen atoms not shown. Top view on the left and side view on the right. Drawn with MOLSCRIPT [30].

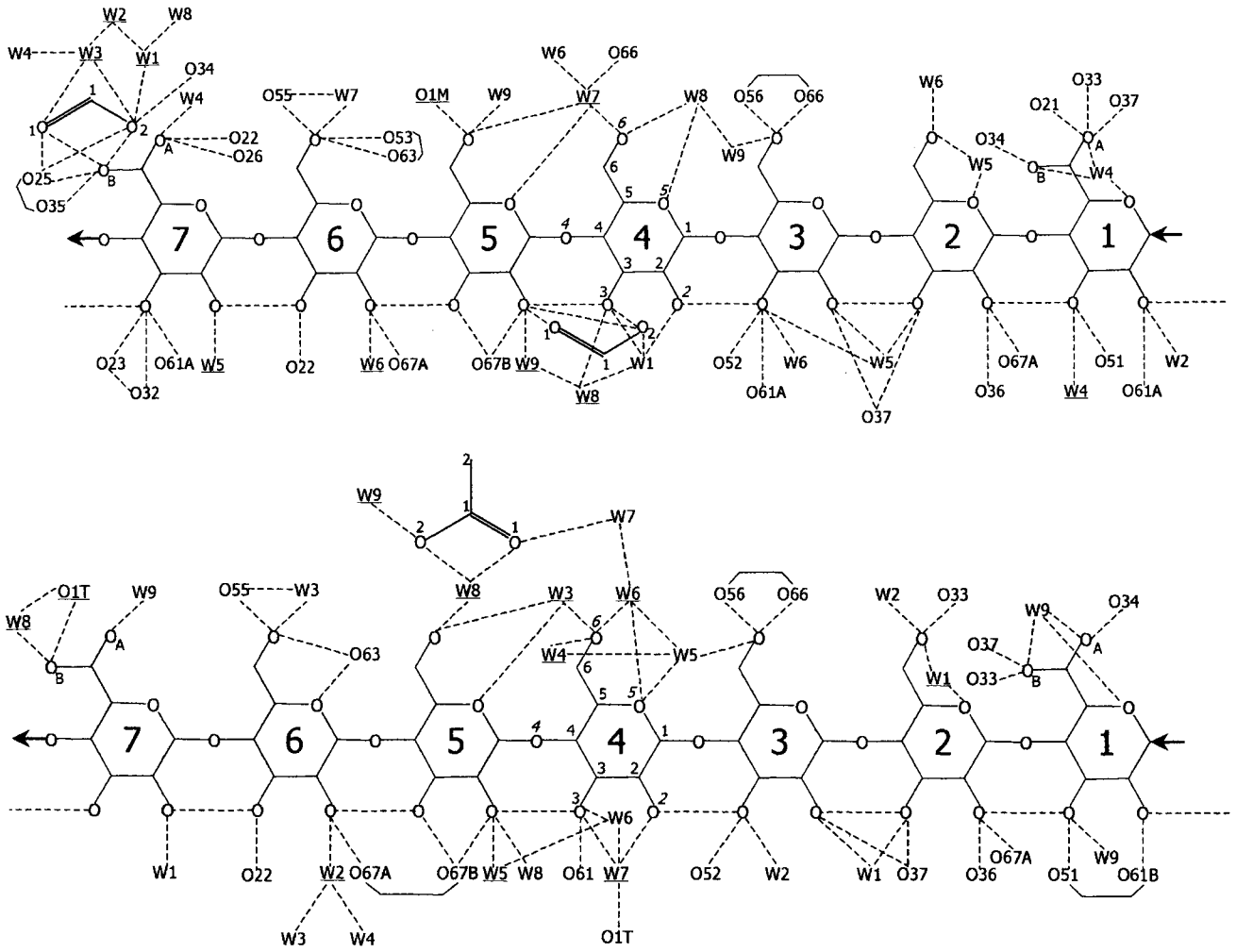

Figure 4. Possible O—H···O hydrogen bonds (dashed lines) in the (a) β-CD·0.3HCOOH·7.7H_2O and (b) β-CD·0.4CH_3COOH·7.7H_2O inclusion complexes with O···O distances within 3.5 Å. Underlined atomic names indicate atoms in the general position x, y, z; the others are in symmetry related positions. Arrows show connection of glucose units in β-CD. Atomic numbering of the β-CD and acids is also given.

Conclusions

The β-CD–formic and β-CD–acetic acid inclusion complexes show similarity both in terms of molecular structure (β-CD macrocycle, hydration pattern) and crystal packing. A striking difference is observed only in the orientation of guest molecules in the β-CD cavity. When each small aliphatic acid (e.g., formic acid, acetic acid) is totally included in an individual β-CD cavity, the β-CD is arranged in a herringbone cage-structure. As the number of C atoms in the aliphatic acids increases, each long acid occupies more than one β-CD cavity; the β-CD prefers to form dimer and exhibits a channel structure [6–9]. The results are consistent with the previous structure elucidations of CD inclusion complexes [29].

Acknowledgements

This work was supported by grants for development of new faculty staff of Chulalongkorn University and by the Thailand Research Fund. We thank the Austrian-Thai Center (ATC) for Computer-Assisted Chemical Education and Research, in Bangkok for providing computer time in data analysis.

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