J Incl Phenom Macrocycl Chem (2015) 81:193–203
DOI 10.1007/s10847-014-0448-9

ORIGINAL ARTICLE

# Structural studies of the inclusion complexes of the (+)- and (−)-borneol enantiomers in α- and β-cyclodextrin

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Received: 20 June 2014 / Accepted: 5 September 2014 / Published online: 11 September 2014


**Abstract** The crystal structures of the inclusion compounds of the (+)- and (−)-borneol enantiomers in α- and β-cyclodextrin (CD) were determined by X-ray crystallography at about 1 Å resolution. In all the cases, the α- or β-CDs form head-to-head dimers arranged in a "chessboard" crystal packing mode. In the cases of the (+)- and (−)-borneol/αCD inclusion complexes, one guest molecule is accommodated inside the formed dimeric cavity (2:1 host:guest stoichiometry) disordered over two and three sites respectively. In the cases of the (+)- and (−)-borneol/βCD inclusion complexes, a highly disordered guest molecule is located inside the dimeric cavity and two additional guest molecules lay at the rims of the primary hydroxyls of the dimer (2:3 host:guest stoichiometry) participating in the crystal contacts by forming H-bonds with external water molecules and –OH groups of the β-CDs of the adjacent dimers. Regarding the ability of α- and β-CD for borneol enantioseparation, the crystallographic analysis shows that no significant differences concerning the inclusion geometry and crystal packing are observed between the inclusion complexes of the borneol enantiomers with the same host CD.

**Keywords** (+)-Borneol · (−)-Borneol · α-Cyclodextrin · β-Cyclodextrin · Inclusion compounds · Crystal structures

**Electronic supplementary material** The online version of this article (doi:10.1007/s10847-014-0448-9) contains supplementary material, which is available to authorized users.

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## Introduction

Native cyclodextrins (CDs) are well known oligosaccharides consisting of six, seven or eight α-(1-4)-linked D-glucopyranose units, called respectively α-, β- or γ- CD (Fig. 1a). Due to their structural features, especially their hydrophilic external rims and hydrophobic internal cavity, they have the ability to host the hydrophobic moieties of a wide variety of guest molecules of suitable size and shape [1]. Complexation with CDs is widely used in chemical, pharmaceutical, food and other technologies as it offers significant increase of the water solubility of the guest molecules and protection from oxidation, chemical degradation, etc. Moreover, a slow release of the guest from the inclusion complex is achieved sustaining its action [2]. Another important property of CDs, is their chiral recognition ability. CDs are chiral host molecules able of chiral discrimination even if they are not chemically modified [3]. Chemical modifications are often needed to improve their physico-chemical properties (i.e. solubility) and also to graft on the macrocycle chemical functions which could allow their covalent anchoring at surfaces. The presence of free hydroxyl groups on their outer surface allows a variety of derivatives to be synthesized. This property is of major importance for CD applications in all kinds of enantioseparation techniques. However, these chemical modifications have to be done in a way that the chemical functions added do not inhibit the chiral inclusion properties of the macrocycle [4]. Moreover, some commonly modified CDs like hexakis (2,3,6-tri-*O*-methyl)-α-cyclodextrin (TM-α-CD) and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD) are also found to successfully perform selective separation [5–7].

Monoterpenes are primary compounds of plant essential oils. Borneol (or bornyl acetate; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol) is a bicyclic monoterpene present in

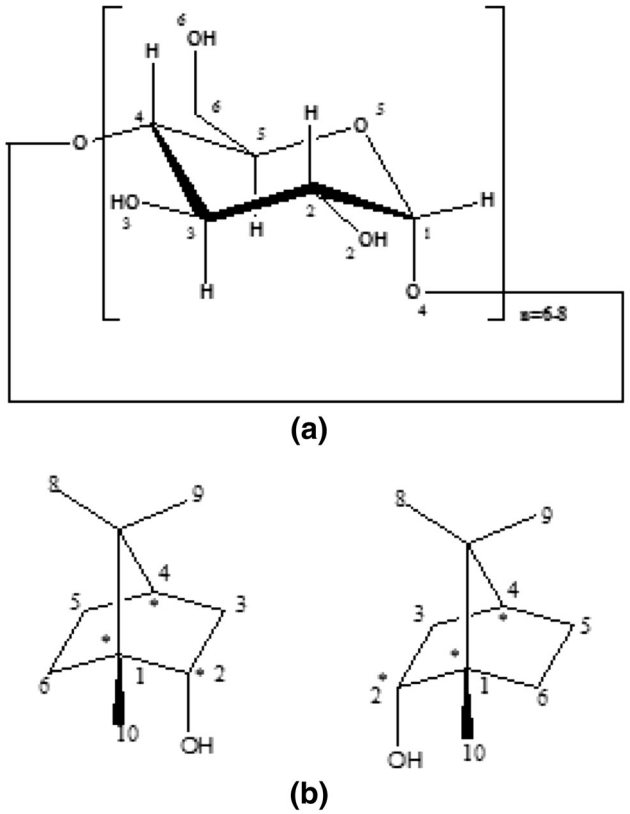


**Fig. 1** **a** Schematic representation of the chemical structure of native CDs ($n = 6$, 7, 8 for $\alpha$-, $\beta$-, and $\gamma$-CD respectively) **b** the (1R, 2S, 4R)-(+)-borneol and (1S, 2R, 4S)-(−)-borneol guests

the essential oils of numerous medicinal plants used for analgesia and anesthesia in traditional Chinese and Japanese medicine [8]. It is a volatile chiral alcohol occurring in two enantiomeric forms the (+)- and (−)-borneol (Fig. 1b) having the ability to be transformed to camphor by oxidation. In folk remedies, borneol is used for treatment of abdominal pain, particularly stomachache. Recently it has been demonstrated to show antithrombotic and antiplatelet activity [9]. Some studies have shown that borneol could be a candidate to improve the oral bioavailability of some drugs. More specific, borneol can be used as a messenger drug, since it has little pharmacological activity, and is capable of permeating blood–brain barrier, introducing drug to the target site, and increasing therapeutic efficacy [10], [11]. These properties are attributed to its highly efficacious positive modulated action at human $GABA_A$ receptors [8].

Borneol, natural or synthetic, has the potential to be widely used in the medical and functional food fields. However, the disadvantages of instability in the preparation and storage process due to its easy sublimation and degradation to noxious camphor and the low water solubility have limited its application. The formation of inclusion complexes of volatile compounds of essential oils with cyclodextrins is widely used to improve their characteristics [12]. In particular, the characterization of the complex of natural borneol in native $\beta$-CD has shown a significant improvement of borneol stability and solubility [13]. Moreover, thermodynamic studies on chiral recognition of borneol by modified $\beta$-CD have also been carried [14], [15]. However, the crystal structures of the inclusion complexes of the borneol enantiomers in $a$- or $\beta$- native CDs have not been studied yet.

In an ongoing study of inclusion complexes of essential oil compounds with native CDs, we report here the investigation of the crystal structures of the (+)- and (−)-borneol enantiomers encapsulated in $\alpha$-CD ((+)-borneol/$\alpha$CD **(1)**, (−)-borneol/$\alpha$CD) **(2)** and $\beta$-CD ((+)-borneol/$\beta$CD **(3)**, (−)-borneol/$\beta$CD **(4)**) by X-ray crystallography. Our final aim is to use the structural knowledge (stoichiometry, inclusion geometry, crystal packing, etc.) of the inclusion complexes in order to give a direct evidence of the CD enantiodifferentiation ability.

## Experimental

### Single-crystal preparation

(+)- or (−)-borneol were purchased from Sigma–Aldrich and were used without further purification. The host compounds $\alpha$- and $\beta$-CD were purchased from Fluka. 30 mg of $\alpha$-CD (0.03 mmol) were weighted into vials and 2 mL of distilled water was added. An equimolar quantity (4.756 mg, 0.03 mmol) of (+)-borneol was added for the formation of the (+)-borneol/$\alpha$CD **(1)** inclusion compound. The (−)-borneol/$\alpha$CD **(2)** inclusion compound was formed in a similar way. In addition, 30 mg of $\beta$-CD (0.026 mmol) were weighted into vials, 2 mL of distilled water was added and an equimolar quantity (4.055 mg, 0.026 mmol) of (+)-borneol was added for the (+)-borneol/$\beta$CD **(3)** inclusion compound. Finally, the (−)-borneol/$\beta$CD **(4)** inclusion compound was formed in a similar way. All mixtures were stirred in sealed vials for about 4 h at 343 K until they were limpid. Then they were gradually cooled to room temperature over a seven-day period in order to produce crystals suitable for X-ray data collection.

### Data collection and crystal structure determination

Crystals of approximate 0.3 × 0.3 × 0.3 mm were removed from the mother liquor and they were cryoprotected by rapid immersion in tab oil and flash frozen in $N_2$ stream for data collection at 100 K using a MarCCD imaging plate detector at the EMBL X13 or X11 beamline at the DORIS storage ring, DESY, Hamburg. Diffraction data at about 1 Å resolution were collected and processed with the DENZO and

SCALEPACK program [16]. Initial data processing indicated that the crystals are orthorhombic and the space group of both α-CD complexes is $P2_12_12_1$ whereas both β-CD complexes crystallize in the $C222_1$ space group.

Both structures of the complexes of the borneol enantiomers with α-CD were solved by molecular replacement using the atomic coordinates of the α-CD macrocycle of the isomorphous isosorbide dinitrate/αCD complex [17]. The structures of the complexes of the borneol enantiomers with β-CD were also solved by molecular replacement using the atomic coordinates of the macrocycle of the isomorphous 4-tert-butylbenzylalcool/βCD complex [18]. The molecular replacement solutions were obtained by a Patterson vector search method and Fourier recycling with the program DIRDIF99 [19]. All the atomic positions of the host, guest and the water molecules were located and refined using the least-squares procedures based on $F^2$ with the SHELXL97 program [20]. Dirdif99 and Shelxl97 were used under the interface and the graphical display support of the WINGX suite [21]. Hydrogen atom positions linked to primary, secondary or tertiary carbon atoms of the host molecules were placed in calculated positions for temperature of 100 K and their thermal parameters were set to 1.2 Uiso of the isotropic thermal parameter of the corresponding carbon atom. The number of the observed reflections was not sufficient to allow the introduction of anisotropic thermal parameters for all the non-hydrogen atoms. Therefore, only some atoms of the host molecules, non-disordered over 2 or 3 sites, have been treated as anisotropic. 5 ((+)-borneol/*a*CD) **(1)**, 8 ((−)-borneol/*a*CD) **(2)**, 8 ((+)-borneol/βCD **(3)**) or 7 ((−)-borneol/βCD **(4)**) reflections exhibiting poor agreement were given zero weight during the final refinement cycles. Extinction correction was applied in all cases. Final lattice parameters along with all data collection parameters of the complexes are quoted in Table 1.

The geometrical analysis and the validation of the crystal structures have been carried with the programs Olex2 [22] and Platon [23]. The graphics programs used to illustrate the crystal structures are Mercury 3.1 [24] and Pymol [25].

## Results and discussion

### The encapsulation of (+,−)-borneol enantiomers in α-CD

#### *Description of the crystal structures*

The structures of the (±)-borneol/*a*CD **(1 and 2)** inclusion complexes have strong similarities with those of the (*R*, *S*)-camphor/αCD [26]. Their asymmetric units contain two *a*-CD host molecules (HostA and HostB) arranged in a head-to-head mode being hydrogen bonded via their -O3*n*H hydroxyl groups and forming dimers. In the case of the (+)-borneol/αCD **(1)** inclusion complex, one (+)-borneol molecule, disordered over two sites (denoted as (+)A and (+)B), with occupancies of 0.80 and 0.20 respectively) is accommodated inside the dimeric cavity. Similarly, in the (−)-borneol/αCD **(2)** complex, one (−)-borneol molecule is located inside the dimeric cavity, disordered over three sites (denoted as (−)A, (−)B and (−)C), with occupancy factors of 0.60, 0.20 and 0.20 respectively). Thus, in both cases the host:guest stoichiometry is 2:1. Moreover, 13.4 and 12.3 water molecules distributed over 27 and 29 sites were found in the asymmetric units of the (+)-borneol/*a*CD **(1)** and (−)-borneol/*a*CD **(2)** complexes, respectively.

The borneol molecules are accommodated at the interfaces of the dimers between the mean planes of the glucosidic O4*n*A and O4*n*B atoms. In the case of the (+)-borneol/*a*CD **(1)** complex, the orientation of the guest is similar in both occupied sites. The C2-OH bond of the encapsulated (+)-borneol always points towards the O4*n*A mean plane and the hydroxyl group is hydrogen bonded with a water molecule located at the rim of the primary hydroxyls of the HostA (Fig. 2a). The oxygen atoms of the hydroxyl groups of the disordered guest molecules are found at 0.664(3) Å (OA) or 0.717(3) Å (OB) distances from the O4*n*A mean plane and the C9 carbon atoms of the methyl groups are at distances of 1.429(3) Å (C9A) and 1.374(3) Å (C9B) from the O4*n*B mean plane. Moreover, the two occupied sites ((+)A, (+)B) are very close to each other, the distance between their centroids being at 0.453(3) Å.

The overall mean square displacement parameter of the (+)A site ($U_{(+)A}$) is equal to 0.0868(16) $Å^2$, while the $U_{(+)B}$ value is 0.122(9) $Å^2$. The two sites have the same orientation and they are differentiated only by a slight rotation (Fig. 2a). The distances of their centroids from the centroid of the O4n atoms of the hostA of the α-CDs dimer are 0.4407(18) Å (for the (+)A site) and 0.461(4) Å (for the (+)B site).

In the case of the (−)-borneol/*a*CD inclusion complex **(2)**, noticeable differences between the position and orientation of the three occupied sites ((−)A, (−)B and (−)C) are observed. The (−)B and (−)C sites are close to each other ((−)B-(−)C centroids distance = 0.387(6) Å) whereas they are not so close to the (−)A site (centroids distances: (−)A-(−)B = 0.949(4) Å and (−)A-(−)C = 1.143(2) Å). Moreover, the orientation of the guest molecule occupying the (−)A site differs significantly from that of the (−)C site and it is quite the opposite to the orientation of the (−)B site (the hydroxyl group of the (−)B is found at the anti-diametric position of that of the hydroxyl of the (−)A site) (Fig. 2b,c). The oxygen atom of the hydroxyl group of the guest molecule is located at distances of 0.6662(17) Å (OA) and

**Table 1** Experimental details experiments were carried out at 100 K. H-atom parameters were constrained

| | (+)-borneol/αCD | (+)-borneol/βCD | (−)-borneol/αCD | (−)-borneol/βCD |
|---|---|---|---|---|
| Crystal data | | | | |
| Chemical formula | $2(C_{36}H_{31}O_{30})\cdot(C_{10}H_{18}O)\cdot13.1(H_2O)$ | $(C_{42}H_{46}O_{35})\cdot1.5(C_{10}H_{18}O)\cdot10.8(H_2O)$ | $2(C_{36}H_{34}O_{30})\cdot(C_{10}H_{18}O)\cdot12.3(H_2O)$ | $(C_{42}H_{43}O_{35})\cdot1.5(C_{10}H_{18}O)\cdot8.6(H_2O)$ |
| $M_r$ | 2,243.00 | 1,487.74 | 2,224.56 | 1,449.51 |
| Crystal system, space group | Orthorhombic, $P2_12_12_1$ | Orthorhombic, $C222_1$ | Orthorhombic, $P2_12_12_1$ | Orthorhombic, $C222_1$ |
| $a$, $b$, $c$ (Å) | 13.758 (1), 24.342 (1), 30.737 (1) | 19.055 (1), 23.696 (1), 32.357 (1) | 13.889 (1), 24.477 (1), 30.848 (1) | 19.293 (1), 24.063 (1), 32.873 (1) |
| $V$ (Å$^3$) | 10,293.7 (9) | 14,610.1 (11) | 10,487.1 (9) | 15,261.2 (11) |
| $Z$ | 4 | 8 | 4 | 8 |
| Radiation type | Synchrotron, λ = 0.80150 Å | Synchrotron, λ = 0.80150 Å | Synchrotron, λ = 0.80510 Å | Synchrotron, λ = 0.81600 Å |
| μ (mm$^{-1}$) | 0.13 | 0.12 | 0.13 | 0.11 |
| Crystal size (mm) | 0.30 × 0.30 × 0.30 | 0.30 × 0.30 × 0.30 | 0.30 × 0.30 × 0.30 | 0.30 × 0.30 × 0.30 |
| Data collection | | | | |
| Diffractometer | MARCCD 165 mm diffractometer | MARCCD 165 mm diffractometer | MARCCD 300 mm diffractometer | MARCCD 300 mm diffractometer |
| Absorption correction | – | – | – | – |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 44,312, 5,894, 5,729 | 4,093, 4,093, 4,027 | 10,194, 10,194, 10,080 | 4,337, 4,337, 4,299 |
| $R_{int}$ | 0.082 | 0.036 | 0.046 | 0.051 |
| $\theta_{max}$ (°) | 23.6 | 23.6 | 29.4 | 24.1 |
| $(\sin\theta/\lambda)_{max}$ (Å$^{-1}$) | 0.500 | 0.500 | 0.610 | 0.500 |
| Refinement | | | | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.095, 0.295, 1.14 | 0.100, 0.300, 1.18 | 0.076, 0.224, 0.98 | 0.096, 0.297, 1.17 |
| No. of reflections | 5,894 | 4,093 | 10,194 | 4,337 |
| No. of parameters | 828 | 561 | 1,318 | 586 |
| No. of restraints | 37 | 44 | 46 | 28 |
| | $w = 1/[\sigma^2(F_o^2) + (0.280P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ | $w = 1/[\sigma^2(F_o^2) + (0.280P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ | $w = 1/[\sigma^2(F_o^2) + (0.1906P)^2 + 13.6975P]$ where $P = (F_o^2 + 2F_c^2)/3$ | $w = 1/[\sigma^2(F_o^2) + (0.280P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| | 0.082 | 0.020 | 0.136 | 0.055 |
| $\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å$^{-3}$) | 0.80, −0.56 | 1.00, −0.49 | 1.15, −0.66 | 0.85, −0.52 |

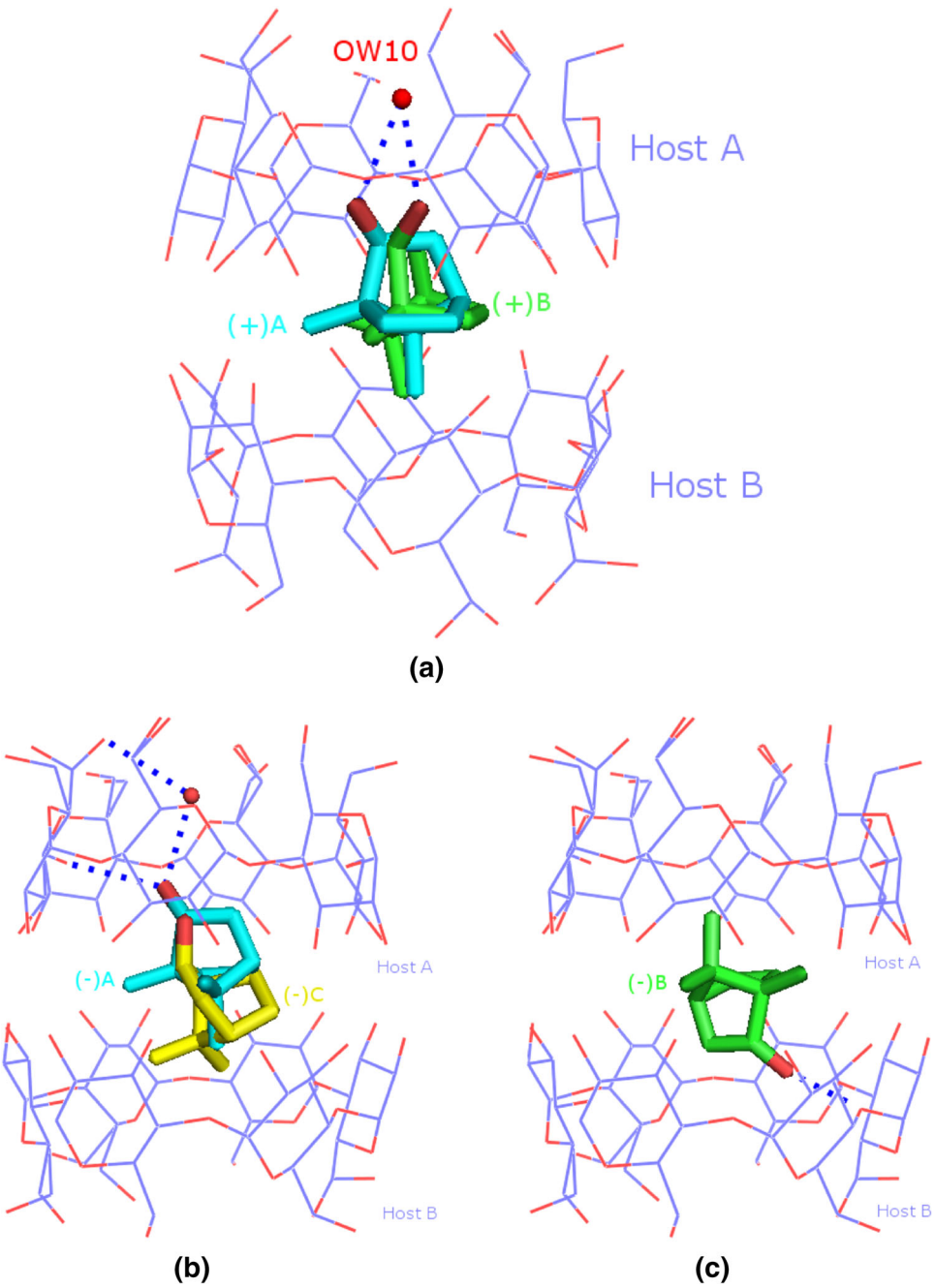


**Fig. 2** **a** (+)-borneol/αCD inclusion complex. The guest (+)-borneol is disordered over two sites, (+)A (*cyan*) and (+)B (*green*) with occupancy factor (o.f.) 0.80 and 0.20 respectively. **b**, **c** (−)-borneol/αCD inclusion complex. The guest (−)-borneol is disordered over three sites, (−)A (*cyan*), (−)B (*green*) and (−)C (*yellow*), with o.f. 0.60, 0.20 and 0.20 respectively). For clarity the (−)B occupied site has been drawn separately from the (−)A and (−)B in (**c**)

1.6052(15) Å (OC) from the O4*n*A mean plane when the guest occupies the (−)A and (−)C site respectively whereas when it occupies the "flipped over" (−)B site this distance is 0.7859(17) Å (OB) from the O4*n*B mean plane. The C9 carbon atom is found at distances of 1.5791(14) Å (C9A of the A-site) and 0.7538(16) Å (C9C of the C-site) from the O4*n*B mean plane whereas C9B of the B-site is located closer to the O4*n*A mean plane at a distance of 1.5097(15) Å.

The overall mean square displacement parameters $U_{(-)A}$, $U_{(-)B}$ and $U_{(-)C}$ are equal to 0.0451(8), 0.196(18) and 0.105(6) $Å^2$, respectively. The (−)B and (−)C sites are characterized by low occupancy factors and high overall atomic displacement as they interpret the almost spherical residual electron density distribution observed inside the dimeric cavity.

In both inclusion complexes, one water molecule is located at the primary hydroxyl groups rim of the HostA. It is accommodated between the C6*n*A and O4*n*A mean planes at distances of 0.80(2) and 1.92(2) Å respectively in the (+)-borneol/*a*CD **(1)** complex (denoted by OW10) and 0.69(2) and 2.04(2) Å respectively in the (−)-borneol/*a*CD **(2)** complex (denoted by OW17). This OW10 water molecule is hydrogen bonded with OA and OB hydroxyls of the (+)A and (+)B sites (Fig. 2a). On the other hand, only

**Table 2** Hydrogen bond network hydrogen bonds between borneol, cyclodextrin and water molecules present at the four complexes

| | O···O (Å) | | C–O···O (°) | Symmetry operation |
|---|---|---|---|---|
| Alpha-CD dimers | | | | |
| (+)-borneol | | | | |
| OA···OW10 | 2.86(2) | C2A-OA···OW10 | 106.9(4) | – |
| OB···OW10 | 2.75(2) | C2B-OB···OW10 | 112.7(5) | – |
| (−)-Borneol | | | | |
| OA···OW17 | 2.83(2) | C2A-OA···OW17 | 114.9(4) | – |
| O64C·····OW17 | 3.05(3) | C64C-O64C···OW17 | 103.1(10) | – |
| OA·····O44A | 3.016(4) | C2A-OA···O44A | 129.70(7) | – |
| Beta-CD dimers | | | | |
| (+)-borneol | | | | |
| OA···OW4 | 2.716(10) | C2A-OA···OW4 | 118.4(6) | – |
| OA···O66 | 2.727(10) | C2A-OA···O66 | 118.7(6) | x, −y, 1−z |
| | | OA···O66-C66 | 126.9(6) | |
| O64···OW4 | 2.734(10) | C64-O64···OW4 | 122.2(5) | −1/2 + x, −1/2−y, 1−z |
| (−)-Borneol | | | | |
| OA···OW2 | 2.769(14) | C2A-OA···OW2 | 125.5(9) | 1/2−x, 1/2−y, −1/2 + z |
| O65···OW2 | 2.758(13) | C65-O65···OW2 | 119.7(6) | −1/2 + x, 1/2−y, −z |
| OA···O67 | 2.723(12) | C2A-OA···O67 | 109.1(9) | x, 1−y, −z |
| | | C67-O67···OA | 125.2(7) | |

the hydroxyl group of the (−)A site of the guest molecule of the (−)-borneol/*a*CD **(2)** complex is hydrogen bonded with the OW17 water molecule. This water molecule is also hydrogen bonded with the oxygen atom of the primary hydroxyl group of the HostA of the (−)-borneol/*a*CD **(2)** complex (Fig. 2b). The hydroxyl group of the (−)A site is also hydrogen bonded with the glucosidic oxygen atom O44A. Indicative hydrogen bonds (distances and angles) are quoted in Table 2.

*Conformation of the host molecules*

The host molecules of both *a*-CD complexes have the usual (replace: conical) molecular conformation of the truncated cone with the glycosidic O4*n* atoms lying on a plane within 0.129(4) Å and forming an almost regular hexagon (see Online Resource, Table S1).

Three primary hydroxyl groups of both (+)-borneol/*a*CD **(1)** hosts are disordered over two sites. In the (−)-borneol/*a*CD **(2)** complex two (of the HostA) or three (of the HostB) primary hydroxyl groups are disordered over two sites and two primary hydroxyl groups of the HostA are disordered over three sites. More than half of the hydroxyl groups have the *gauche-trans* orientation pointing inwards the cavity and the rest of them have the *gauche–gauche* orientation pointing outwards from it. The same conformation of the primary hydroxyl groups has been observed in the camphor/αCD complexes [26]. Moreover, the C64 and C65 atoms of two hydroxyl groups of both host molecules of the (+)-borneol/*a*CD **(1)** complex are also disordered.

*Molecular packing*

Both complexes crystallize in the space group $P2_12_12_1$ with similar cell dimensions. The dimers form layers parallel to the *ab* plane. The successive layers are linked by the twofold screw *a*-axis (Fig. 3a). Camphor/α-CD inclusion complexes, in which the guest molecules have similar size and shape with the borneol molecules, have been found crystallizing in the same space group with similar cell dimensions and following the same molecular packing with borneol/α-CD inclusion complexes [26]. The six-fold molecular axis of the dimers forms an angle of about 9° with the *c*-axis in both complexes. The distance of the projection of the centers of the dimers of the successive layers on the *ab* plane is 5.85(3) Å ((+)-borneol/*a*CD **(1)**) or 5.98(4) Å ((*gauche-trans* orientation )-borneol/*a*CD **(2)**). Therefore, the molecular packing of the dimers may be characterized as a chessboard. The same packing mode has been observed in *β*-CD dimeric inclusion complexes crystallizing in the space group $C222_1$, the shift of the successive dimeric layers being about 8.7 Å in those cases due to the larger size of the *β*-CD molecule [18].

The encapsulation of (+,−)-borneol enantiomers in *β*-CD

*Description of the crystal structures*

The (+)-borneol/*β*CD **(3)** and (−)-borneol/*β*CD **(4)** complexes crystallize in the space group $C222_1$. Their

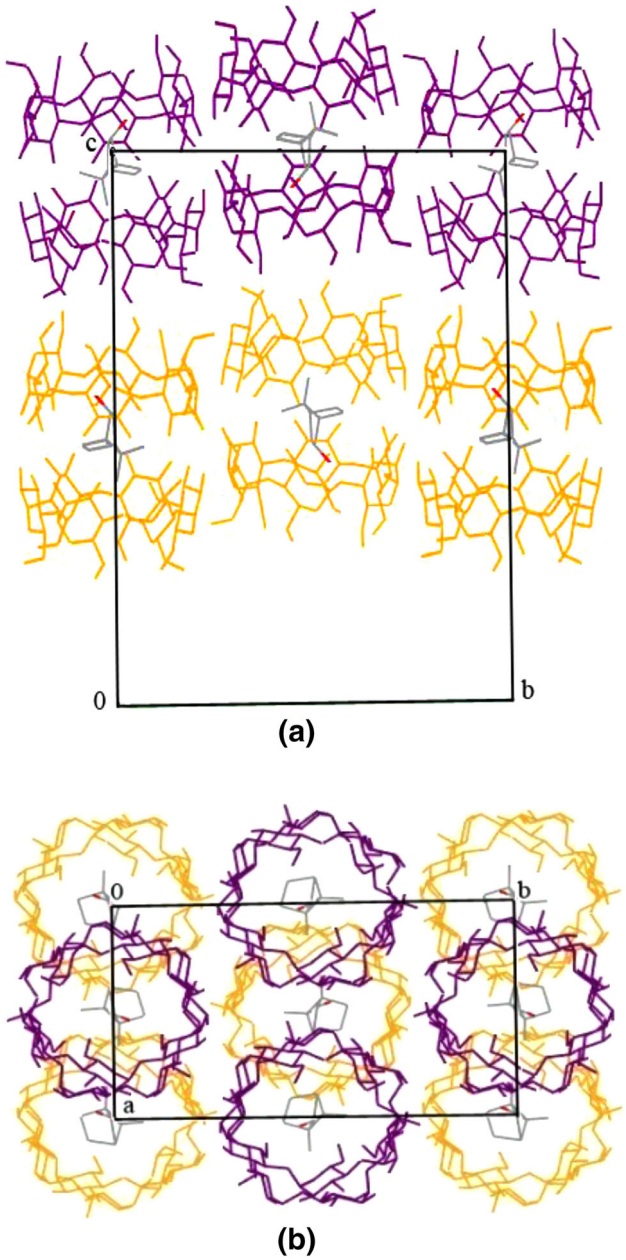


**Fig. 3** The crystal packing of the (+)-borneol/αCD and (−)-borneol/αCD inclusion complexes. For clarity, only one site of the encapsulated molecule and no water molecules are drawn **a** The dimeric complexes form layers that are stacked along the *c*-axis. **b** The dimers of αCD stack along the c-axis forming a "chessboard" molecular packing mode. αCD dimers of two successive layers are drawn with *purple* and *yellow* color, respectively

asymmetric units contain one host molecule. Two symmetry related host molecules form a head-to-head dimer via the O3*n*···O'3(8-*n*) hydrogen bonds. In both complexes, the *β*CD dimers host 3 guest molecules, the host:-guest stoichiometry being 2:3 (Figs. 4b, c, e, f). Two of them are accommodated at the rims of the primary *β*CD hydroxyls. These guest molecules, denoted by (+)A for the (+)-borneo/*β*CD **(3)** complex and (−)A for the (−)-borneol/*β*CD **(4)** complex, are only partially included inside the *β*CD cavity due to steric effects (see Fig. 4 c, f). The C8A and C9A atoms of their corresponding methyl groups are found inside the host's cavity, their C7A atom lies almost onto the mean plane of the C6*n* atoms of the host *β*CD whereas the OA atom of their hydroxyl group is located outside the cavity at a distance of about 3.9 Å from the host's C6*n* mean plane. Moreover these guests' hydroxyl groups participate in the crystal contacts as following: The hydroxyl group of the (+)A site is hydrogen bonded with the water molecule OW4 and with a primary hydroxyl group of the *β*CD of the adjacent dimer. The OW4 water molecule is also hydrogen bonded with the primary hydroxyl group of the host of the adjacent dimer (Fig. 5a). Similarly, the hydroxyl group of the (−)A is hydrogen bonded with the OW2 water molecule which in turn is hydrogen bonded with a primary hydroxyl group of the host molecule of the adjacent dimer. Moreover, the OA atom of the guest molecule occupying the (−)A site, is hydrogen bonded with a hydroxyl group of the adjacent dimer (Fig. 5b). Indicative hydrogen bonds (distances and angles) are quoted in Table 2.

The third guest molecule of the *β*CD dimer is fully encapsulated inside the dimeric cavity and therefore its total occupancy factor in the assymmetric unit is 0.5. In the case of the (+)-borneol/*β*CD **(3)** complex, this guest molecule is found disordered over two sites, denoted by (+)B and (+)C and having occupancies of 0.2 and 0.3 respectively (Fig. 4a). In both occupied sites the hydroxyl group of the guest molecule is oriented towards the secondary hydroxyls whereas the C1–C10 bond points toward the "poles" of the *β*-CD dimer, the C10 methyl group being at a distance of 1.91(9) Å ((+)B site) and 1.817(2) Å ((+)C site) from the mean plane of the O4*n* atoms (Fig. 4a, b). In the case of the (−)-borneol/*β*CD **(4)** complex, only one highly disordered site, denoted by (−)B, could be determined for the encapsulated (−)-borneol. The orientation of the guest occupying the (−)B site is quite different to that of the encapsulated (+)-borneol molecule. The oxygen atom of the hydroxyl group of the (−)B site, denoted by OB, lies inside the hydrophobic *β*-CD cavity at a distance of 0.749(3) Å from the O4n atoms mean plane with the C2B-OB bond of the guest forming an angle of about 51° with the sevenfold molecular axis of the host. The C8B and C10B methyl groups of the guest are located at the dimeric interface pointing towards the secondary hydroxyls whereas the other, C9B methyl group, is oriented towards the poles of the *β*-CD dimer (Fig. 4c, d).

Furthermore, in the asymmetric units of the crystal structures of these inclusion complexes, 10.8 ((+)-borneol/βCD **(3)**) or 8.6 ((−)-borneol/*β*CD **(4)**) water molecules distributed over 13 or 12 sites are located in the free space around the hosts.

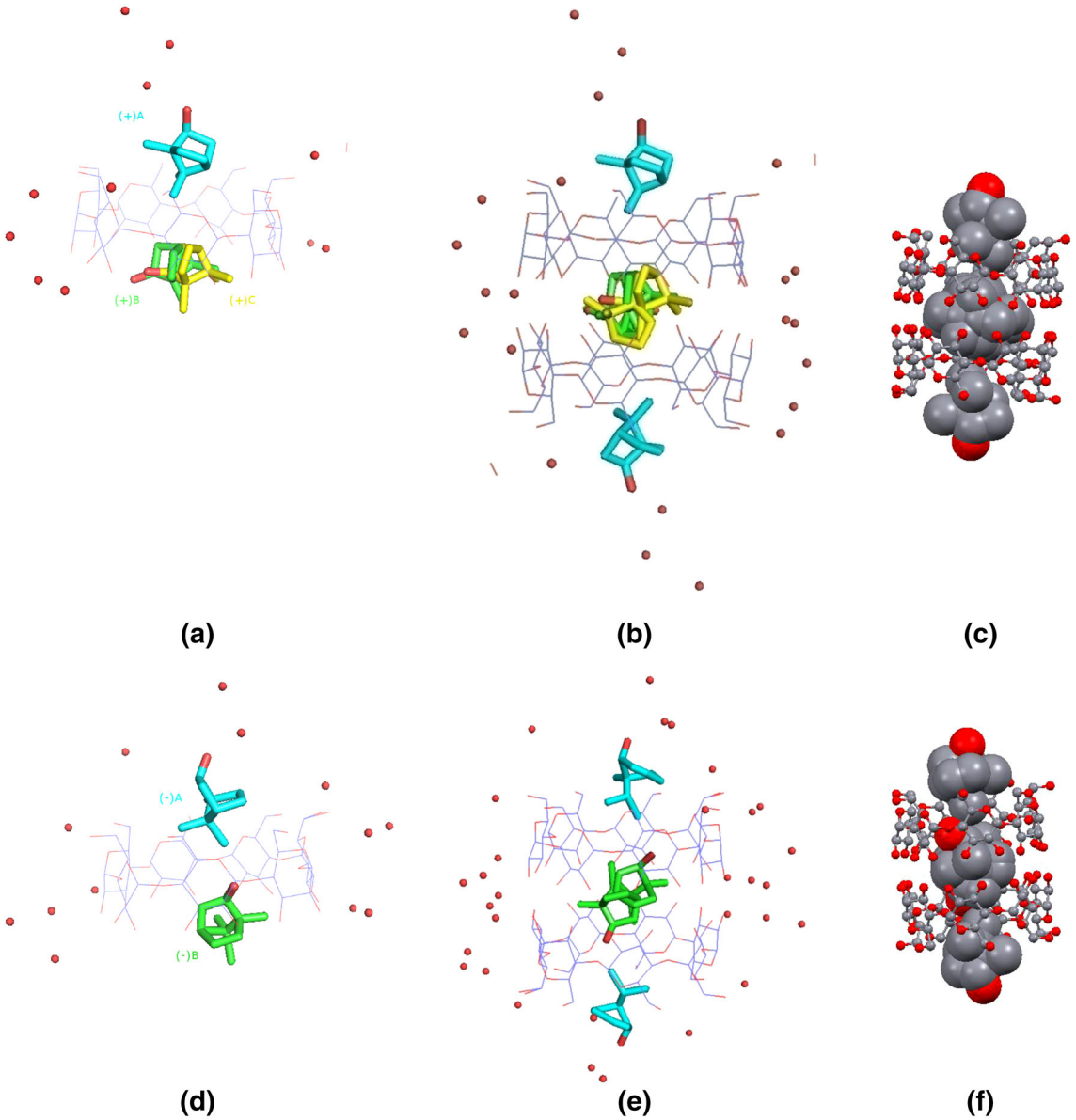


**Fig. 4** **a**, **b**, **c** (+)-borneol/*β*CD complex. **a** In the crystallographic asymmetric unit, one (+)-borneol molecule (*cyan*) protrudes outside the rim of the primary hydroxyls of the *β*-CD and an other guest is accommodated at the rim of the secondary hydroxyls disordered over two sites ((+)B: *green*, with occupancy factor (o.f.) = 0.2; (+)C: *yellow*, o.f. = 0.3) **b** the formed (+)-borneol/*β*CD dimer. One (+)-borneol is encapsulated inside the dimeric cavity of the *β*-CDs and two guest molecules are located at the primary rims. **c** the (+)-borneol/*β*CD dimer with the guest molecules displayed with the space filling model illustrating the partial inclusion of the (+)A guests due to steric effects **d**, **e**, **f** (−)-borneol/*β*CD complex **d** In the asymmetric unit, one (−)-borneol molecule (*cyan*) protrudes outside the primary rim whereas an other (*green*) with o.f. = 0.5 is located at the secondary rim of the *β*CD. **e**, **f** the (+)-borneol/*β*CD dimer. For clarity the water molecules are omitted in the space filling display model figures **c** and **f**

The guest molecule found encapsulated inside the dimeric cavity of the *β*-CDs is highly disordered. In the case of the (+)-borneol/*β*CD **(3)** complex this guest molecule presents a $U_{(+)B}$ value of 0.154(11) Å$^2$ and a $U_{(+)C}$ value of 0.133(7) Å$^2$. The mean atomic displacement of this (+)-borneol molecule being 0.141(8) Å$^2$. On the other hand, in the case of the (−)-borneol/*β*CD **(4)** structure only one site could be modeled for the encapsulated (−)-borneol ((−)B with $U_{(-)B}$ = 0.269(13) Å$^2$).

*Conformation of the host molecules*

In both (+),(−)-borneol/*β*CD inclusion complexes the *β*CD host molecules maintain their rigid shape of a truncated cone. The O4*n* glycosidic atoms are almost coplanar, their maximum distance from the mean plane being 0.057(5) Å, and they form almost regular heptagons. (see Online Resource, S_Table 2). This is similar to what is observed in the cases of the (+),(−)-borneol/*α*CD inclusion

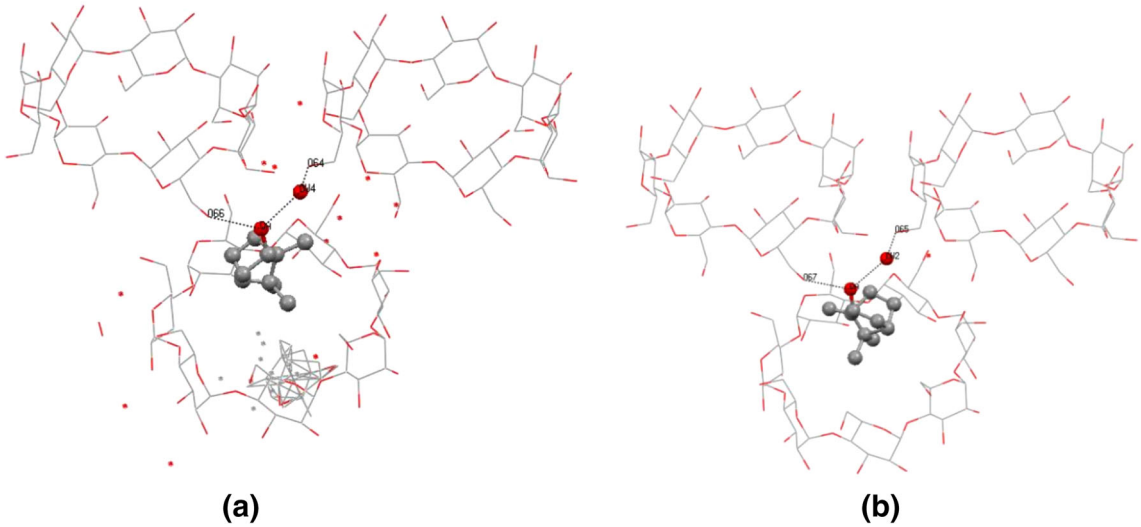


**Fig. 5** The hydroxyl group of the (+)A site is hydrogen bonded either directly with the O66 atom of an adjacent *β*-CD or through a water bridge (OW4) with the O64 atom of an adjacent *β*-CD. **b** The hydroxyl group of the (−)A site is hydrogen bonded either directly with the O67 atom of an adjacent *β*-CD or through a water bridge (OW2) with the O66 atom of an adjacent *β*-CD

complexes. In general, the *α*- or *β*-CD hosts rigidity caused by the intramolecular H-bonds is enhanced by the intermolecular H-bonds that form the dimers. Borneol guest molecules are also rigid. As it was expected, given the shape and size of the guest molecules and the inflexible cavities of the hosts, no significant changes in the conformation of the host or the guest molecules and therefore no induced-fit complexation is observed.

Furthermore, the geometrical study of the host molecules of the (+),(−)-borneol/*β*CD inclusion complexes shows that only one primary hydroxyl group is disordered and all of them have the *gauche–gauche* orientation pointing outwards the host cavity (see Online Resource, S_Table 2). This is not observed often in the *β*-CD complexes and is related to the fact that the larger part of the guest molecules occupying the (+)A or (−)A sites protrudes outside the host cavity from the rim of the primary hydroxyl groups.

*Molecular packing*

Both complexes crystallize in the $C222_1$ space group and in the chessboard packing mode (Fig. 6a,b) according to the classification of the crystal packing modes of the *β*-CD dimeric complexes by Mentzafos et al. [18]. The dimeric complexes related by the *b*-axis form layers that are stacked along the *c*-axis. The inclination between two successive layers, indicated by the angles of the O4n mean planes, is about 20.81(7) and 20.28(3)° for the (+)-borneol/*β*CD **(3)** and (−)-borneol/*β*CD **(4),** respectively (Fig. 6a). The shift between the successive layers, measured by the projection of the centroids of the dimers on the *ab* plane, is about 8.952(4) Å (complex **(3)**) and 8.948(3) Å (complex **(4)**). The guest molecules that protrude outside the dimeric cavity participate in the crystal contacts directly via hydrogen bonds with the host molecules of adjacent complexes along the *c*-axis or indirectly through water bridges (Fig. 5).

## Concluding remarks

The final conclusion of this study is that the structural knowledge of the (+) and (−)-borneol enantiomers in *α*- and *β*-cyclodextrin can give no clear evidence of the CD enantiodifferentiation ability. The structural distinction is not pronounced because the inclusion geometry and the crystal packing of the inclusion complexes of borneol enantiomers with the same host are very similar. Despite the fact that these guest enantiomers clearly contribute to the crystal contacts, no major differences between the crystal packing of the two structures are observed. Thus, it seems that enantioselectivity cannot be achieved by crystallization of the borneol enantiomers complexes with *β*- (or *a*-) CDs.

By comparing the complexes of the same enantiomers with different hosts in terms of the atomic displacement parameters, it is clear that the encapsulated molecules are found, as expected, less disordered within the smaller *a*-CD dimeric cavity than the larger cavity of the *β*-CD dimers. Certainly, the comparison between the atomic displacement parameters of the guests of the complexes of different crystal structures should be made with cautiousness as the final model is highly affected by the quality of the crystal and the data collection conditions (e.g. temperature,

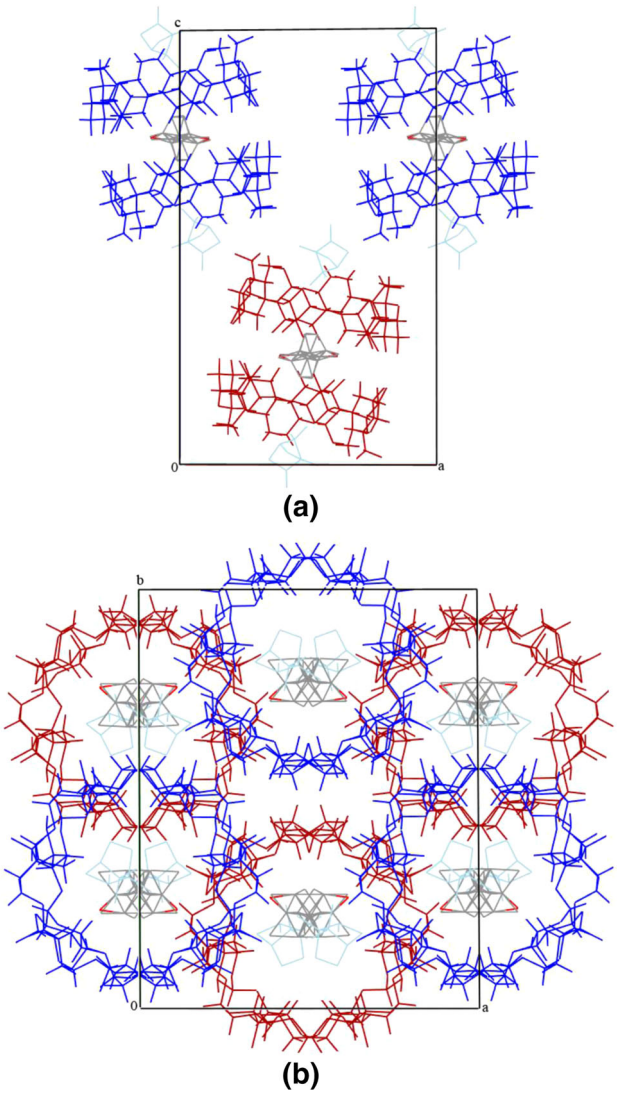


**Fig. 6** The crystal packing of the (+)-borneol/*β*CD and (−)-borneol/*β*CD complex. For clarity no water molecules are drawn. The dimeric complexes form layers that are stacked along the c-axis forming a "chessboard" molecular packing mode. *β*CD dimers of two successive layers are drawn with *blue* and *red* color, respectively. **a** projection onto ac plane **b** projection onto ab plane

radiation intensity, etc.). In the present case, data collection for all crystals was performed using sychrotron radiation of nearly the same wavelength (∼0.8 Å) and at the same temperature (100(2) K). A quantitative comparison of the disorder between the guest molecules of the (±)-borneol/*a*CD **(1 and 2)** and the (±)-borneol/*β*CD **(3 and 4)** complexes can be safely made by using the relative guest atomic displacement to the host atomic displacement. In the case of 1 and 2 complexes the overall atomic displacement of the guest is about 2.4–3.3 times higher than that of the host molecule whereas in the case of 3 and 4 complexes this ratio is significantly higher (about 3.4–5.7 times).

## Supplementary data

CCDC 1021395-1021398 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Acknowledgments** We thank the EMBL staff for the valuable support in data collection at the EMBL X11 and X13 beamlines at the DORIS storage ring, DESY, Hamburg (2011, Project no.: PX-11-151; Group leader: K. Bethanis).

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