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Publisher's version / Version de l'éditeur:

<https://doi.org/10.1039/b920581k>

CrystEngCom, 12, 5, pp. 1450-1453, 2010-01-01

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Complex packing motifs templated by a pseudo-spherical guest: the structure of β -cyclodextrin–adamantane inclusion compounds†

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Received 2nd October 2009, Accepted 20th November 2009

First published as an Advance Article on the web 23rd December 2009

DOI: 10.1039/b920581k

β -Cyclodextrin has been shown to form inclusion compounds with a wide variety of suitably sized guest molecules. In the present study a pseudo-spherical van der Waals guest molecule, adamantane, has been shown to template surprisingly complex packing motifs when incorporated into β -cyclodextrin host frameworks.

Introduction

The supramolecular assembly of inclusion compounds is sensitive to the size, shape and bonding abilities of the guest species. In addition subtle changes in the crystallization conditions can lead to polytypes, polymorphs and pseudopolymorphs of the same inclusion complex components. It is clear that several factors, such as kinetic effects, packing efficiency and especially weak intermolecular interactions (H-bonding and van der Waals), all play a role in determining the structures of these compounds.

A number of crystallographic studies of inclusion complexes of cyclodextrin molecules with a wide variety of suitably sized guest molecules have been reported and several different packing motifs have been identified.^{1–4} Attempts to correlate the type of packing observed with guest molecule properties have been somewhat successful for α - and γ -cyclodextrins but not with the more commonly employed β -cyclodextrin (BCd) host.²

Our laboratory had been actively studying the guest dynamics in cyclodextrin inclusion compounds for a number of years.^{5,6} Preliminary solid state ¹³C MAS NMR spectra of the BCd–adamantane inclusion compound had indicated a complex packing motif with several BCd host molecules in the asymmetric unit (AU).

The BCd host molecule consists of seven 1,4-linked *gluco*-pyranose residues that take the form of a truncated cone (Fig. 1a) with seven primary hydroxyl groups lining the narrow rim and 14 secondary hydroxyl groups lining the wider rim. The inner cavity is large enough to accommodate guest molecules less than about 7 Å in diameter. The numbering scheme for the *gluco*-pyranose residues is indicated in the figure. Adamantane (Ad), C₁₀H₁₆, is a pseudo-spherical function-free hydrocarbon that is approximately 6.5 Å in diameter (Fig. 1b). The poor solubility of Ad in water is significantly enhanced when the Ad molecules are included in the hydrophobic cavities of the BCd molecules. The Ad guest molecules are small enough that they should just pass through the conical cavity of BCd.

The first high resolution (~0.8 Å), single-crystal dataset of BCd–Ad was obtained on a CAD4 diffractometer in 1995.

Between 1996 and 1999 several more such datasets were collected on a SMART 1000 CCD diffractometer. All unambiguously indicated an orthorhombic unit cell, space group *P*2₁2₁2 with an estimated 350 non-hydrogen atoms in the asymmetric unit (AU). As there were no previously reported BCd structures with this space group, and the number of non-hydrogen atoms was too large for direct methods we were unable to solve the structure at the time of data collection. In 2001 programs such as SIR2000 and SHELXD that employ “dual space recycling” methods, adapted from protein crystallography became available to small molecule crystallographers⁷ and the structure was solved. The AU was found to contain four BCd host molecules, four Ad guest molecules and 31.7 water molecules. Over the intervening years least squares refinement of the structure proceeded very slowly due in part to the complexity of the disorder that is present.

In 2007 a vial containing crystals in solution that had initially been grown and screened for a 1999 data collection was discovered. A number of crystals from this vial were screened for data collection on a KAPPA APEXII CCD diffractometer. Surprisingly all crystals screened were found to be triclinic, space group *P*1 with the AU comprised of six BCd molecules, seven Ad molecules and 71 water molecules.

Experimental

The crystals described above were formed from an equimolar solution of BCd and Ad dissolved in hot water. The solution was stored in an oven at 70 °C. After several days crystals suitable for

Fig. 1 BCd host molecule (a) with numbering scheme and included Ad guest molecule (b).

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† CCDC reference numbers 750246–750248. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b920581k

single-crystal analysis were formed. All crystals formed in this manner were observed to be orthorhombic (**1**). A sealed vial containing single crystals of **1** immersed in solution was stored at room temperature. After eight years the crystals were observed to have been transformed into a triclinic phase (**2**). Several crystals were screened and one was chosen for a full data collection. All were found to have the same triclinic unit cell. Crystals were also grown from a saturated aqueous solution formed with excess amounts of both BCd and Ad. Such crystals (**3**) had a significantly different stoichiometry with one BCd host molecule, 1.5 Ad guest molecules and 10.1 water molecules in the AU. Crystals of **3**, isostructural to previously reported BCd inclusions, were solved and refined in the orthorhombic space group $C22_1$.

The solutions obtained from SHELXD were used as the starting point for least squares refinement. The initial solution clearly revealed the positions of the BCd molecules and many sites that could be identified as the oxygen atoms of water molecules. Both compounds **1** and **2** had the BCd molecules stacked on top of each other forming a channel motif with disordered guest molecules filling the channels within the columns of BCd molecules. In the crystals the columns of BCd molecules pack in distorted square-grid arrangements. Water molecules are located in the channels formed between columns. The refinement proceeded slowly due to widespread disorder, particularly in **1**. H-Atoms of BCd were either placed in calculated positions or located with distance and angle constraints (as for the hydroxyl groups). Both the primary and the secondary hydroxyl groups of the BCd molecules exhibited occasional disorder that was modeled as two possible sites, with complementary occupancies, for the oxygen atoms. One BCd molecule in the asymmetric unit of **1** had a glucose fragment that was disordered over two sites, related by a rotation about the bridging "O4" atoms. The Ad guest molecules were severely disordered. In **1** three of the four unique sites were modeled as disordered over three distinct overlapping orientations, a fourth site required four orientations. For **2** one of the seven Ad sites did not appear to be disordered and the remaining six sites were modeled as two overlapped orientations. All the electron density in the channels between the BCd columns was modeled as water molecules. For **1** a total of 31.7 water molecules were distributed over 59 sites with occupancies varying from 1.0 to 0.20. For **2** there were a total of 71.2 water molecules distributed over 122 sites in the AU. For the water sites H-atoms were located from electron density maps when possible. For low occupancy sites,

particularly for **2** this was not possible. In modeling disorder first and second neighbor distance restraints were employed to insure the bond distances and angles matched expected values. Restrained, anisotropic thermal parameters were applied to all the non-hydrogen atoms of sufficient occupancy (≥ 0.33). As the crystals of **3** diffracted weakly at high angles, the data were limited to a resolution of ~ 0.90 Å. Due to the lower resolution it was not possible to resolve the highly disordered Ad sites or to locate hydrogen atoms on the water molecules. The BCd molecules in **3** pack in the so-called checkerboard (CB) arrangement that has been described elsewhere. The crystal data and final refinement parameters for **1**, **2** and **3** are given in Table 1.

Results and discussion

Most of the reported BCd structures adopt a channel packing motif. The most common channel arrangement consists of the host molecules forming head to head hydrogen bonded dimers (*via* the secondary hydroxyl groups) which stack in columns. A head to tail stacking arrangement has also been occasionally observed. Recently, an apparently unique stacking motif has also been reported in which the BCd molecules are stacked as trimers,⁸ with three crystallographically unique molecules. In the present study the observed packing motifs in **1** and **2** appear to be unique.

In **1** the columns are formed as stacked tetramers (Fig. 2a) consisting of one dimer, denoted by the arrow and two molecules oriented head to tail. In this arrangement three of the four BCd molecules in the AU are stacked in a column with the primary hydroxyl groups on the same side, while the fourth molecule is flipped by 180° to form a head to head dimer with its neighbor. The columns align along the *c* axis and pack in a distorted square-grid arrangement (Fig. 3a). Nearest neighbor columns along the *a* and *b* directions are antiparallel and aligned such that the nearest neighbor BCd molecules are shifted by ~ 2.2 Å along the *c* direction with respect to each other. The column axes are displaced from ideal square-grid locations by a small rotation, within the unit cell, about the $(\frac{1}{2} \frac{1}{2} z)$ axis. As a result each column has seven nearest neighbors, five of which are in close contact. Surrounding each column are two wide and three narrow channels, all of which are filled with water molecules (not shown). The planes defined by the bridging oxygen atoms (*Onm4*, Fig. 1) of the four distinct BCd molecules are all perpendicular (within 1°) to *c* and the molecules exhibit no significant deviation

Table 1 Crystal data collection and final refinement parameters for **1–3**

Crystal	1	2	3
Formula	$4(C_6H_{10}O_5)_7 \cdot 4(C_{10}H_{16}) \cdot 31.7(H_2O)$	$6(C_6H_{10}O_5)_7 \cdot 7(C_{10}H_{16}) \cdot 71.2(H_2O)$	$1(C_6H_{10}O_5)_7 \cdot 1.5(C_{10}H_{16}) \cdot 10.1(H_2O)$
Temperature/K	173(2)	100(1)	173(2)
<i>a</i> /Å	29.4201(10)	15.4573(8)	19.156 (4)
<i>b</i> /Å	29.8907(2)	20.2952(10)	24.075(5)
<i>c</i> /Å	30.6856(3)	35.9970(17)	32.596(7)
$\alpha, \beta, \gamma/^\circ$	90.0, 90.0, 90.0	101.17(1), 102.11(1), 98.02(1)	90.0, 90.0, 90.0
<i>V</i> /Å ³	29984.5(3)	10639.4(9)	15032(5)
Space group	$P2_12_12$	$P1$	$C22_1$
Crystal size/mm	$0.30 \times 0.20 \times 0.20$	$0.30 \times 0.20 \times 0.06$	$0.30 \times 0.25 \times 0.10$
# Reflections/unique	263 907/29 178	130 467/43 474	34 326/5819
<i>R</i> (int)	0.1278	0.0599	0.1038
<i>R</i> Indices ($>2\sigma$) (all data)	$R1 = 0.078, wR2 = 0.1859$	$R1 = 0.076, wR2 = 0.2322$	$R1 = 0.051, wR2 = 0.1269$

Fig. 2 The BCd host molecule stack in columns in both **1** (a) and **2** (b). The H-bonded BCd dimers are indicated by the double-headed arrows. The crystallographically unique molecules are color coded.

Fig. 3 The packing of the BCd columns for **2** (a) and **3** (b).

from planar. The centroids of the disordered Ad guest sites are not distributed evenly along the channel axis (separations: 10.21, 6.98, 6.65, 6.84 Å). In crystalline adamantane the distance between nearest neighbor centroids is 6.39–6.50 Å.

In **2** the columns are formed as stacked hexamers (Fig. 2b). All of the host molecules form head to head dimers, denoted by the arrows, such that three crystallographically distinct dimers stack to form the hexameric repeat unit found in the columns. One of the dimers contains three Ad guest sites while the remaining two dimers (upper and lower dimers in Fig. 2b) each contain two guest sites. The columns, aligned along the $a + 2b + c$ direction, are also packed in a distorted square-grid fashion where the angle of the grid is not 90° (Fig. 3b). As a result each column has eight nearest neighbors, four of which are in close contact. Surrounding each column are four elongated channels filled with

Fig. 4 BCd bilayers in **2** (a) and as seen in the commonly observed channel packing motif (b). The crystallographically unique molecules are color coded.

Fig. 5 The BCd dimers in **3** encapsulate three Ad guest molecules. The crystallographically unique molecules are color coded.

water molecules. The planes defined by the bridging oxygen atoms of the six distinct BCd molecules are all parallel to each other (within 1°) but tilted approximately 9° off perpendicular to the $a + 2b + c$ column direction (Fig. 2b). This gives rise to a small undulation in the channels in which the Ad molecules reside. None of the BCd host molecules exhibits any significant deviation from planar. The centroids of the disordered guest sites in **2** are much more evenly distributed along the channel axis (separations: 6.61, 6.60, 6.99, 7.12, 6.75, 6.96, 6.42 Å) than in **1**. The smallest separation (6.42 Å) occurs between the lone ordered site (coded as green in Fig. 2b) and one of its neighbors.

The structure of the host molecule framework in compound **2** can also be described in terms of BCd bilayers. BCd dimers from adjacent columns lie in the (0 1 1) plane, with crystallographically equivalent dimers forming rows along the a direction. Parallel rows of inequivalent dimers line up in sequence along $a - b + c$ to form bilayers (Fig. 4a). Adjacent bilayers are aligned such that the host molecules form the columns as depicted in Fig. 2b. The BCd framework can be seen to be a variant of the most commonly observed BCd packing motif depicted in Fig. 4b. In this motif all the dimers are equivalent with the two BCd molecules related either by a crystallographic twofold axis and described in space group $C2$, or by a pseudo-twofold axis in space group $P1$ (as illustrated in Fig. 4b). The dashed lines in Fig. 4 indicate the location of pseudo-twofold axes of the BCd frameworks.

A more detailed examination of the packing in **2** shows that the dimer centroid-to-centroid distances along a , $a - b + c$ and $a + 2b + c$ in **2** fall well within the range of lattice constants (a , b , c) that have been reported for the common BCd channel inclusions.

In **3** the Ad guest positions are clearly visible (Fig. 5) and an electron count of the disordered sites supports an inferred stoichiometry of a 2 : 3 : 20.2, BCd : Ad : H₂O ratio. In **3**, two AU's, related by a twofold axis, form a dimer as shown in Fig. 5. Within the dimer are three fully disordered guest sites. As such this dimer is similar to the central dimer depicted in Fig. 2b. The dimers in **3** adopt a CB motif.

Conclusions

Two distinct structural forms, **1** and **2**, of an approximately 1 : 1 BCd–Ad inclusion complex have been structurally characterized. In both forms the Ad guest molecules pack in channels formed by stacked BCd host molecules. Form **1** appears to be kinetically favored as it was the only form initially observed from an equimolar aqueous solution of BCd and Ad. When form **1** was stored in solution at room temperature it transformed, over several years, to form **2** which appears to be a structural variant of the common BCd channel inclusion compound. The BCd : Ad (host : guest) ratio is 1 : 1 in **1** and 6 : 7 in **2**, which appears to allow more efficient filling of the hydrophobic channels. The number of included water molecules per BCd host molecule is ~6.5 in **1** and ~11.8 in **2**. This can be explained by the relative increase in

volume of the hydrophilic channels located between the columns of BCd molecules.

A completely different form, compound **3**, appears to be favored when crystallization occurs from a saturated aqueous solution. In this case it is expected that the concentration of cyclodextrin dimers is much higher in the natant solution and, as a consequence, the building block depicted in Fig. 5 will be more readily available for crystal formation.

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