Weak Polar Host–Guest Interactions Stabilizing a Molecular Cluster in a Cyclodextrin Cavity: C–H···O and C–H···π Contacts in β-Cyclodextrin–But-2-yne-1,4-diol Heptahydrate†

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In the crystalline title complex, the guest molecules are ordered and the inclusion geometry is stabilized by a system of host–guest O–H···O, C–H···O and C–H···π contacts; this is an example of weak but crucial polar interactions between the surface of a cyclodextrin cavity and a cluster of polar guest molecules.

The cyclodextrins are macrocyclic molecules composed of α(1–4) linked D-glucoses (that with seven residues is called β-cyclodextrin, β-CD), which readily form inclusion complexes with guest molecules of suitable size.[1,2] The molecular cavity is lined by C–H groups and the glycosidic linker atoms O(4), and therefore is more hydrophobic than the exterior surface, which carries three hydroxy groups per glucose. If hydrophilic guest molecules are included in these cavities, they have little opportunity to form conventional hydrogen bonds with the host. Normally, one or two of the primary hydroxy groups CH_2–O(6)–H are then folded 'inwards' to become available for O–H···O bonds from inside the molecular cavity. The glycosidic O(4) atoms are sterically poorly accessible, and act only occasionally as acceptors of O–H···O or N–H···O hydrogen bonds donated by guest molecules.[3]

Until recently, hydrogen bonds with O(4) and O(6) were regarded as the only polar host–guest interactions occurring in CD complexes. In an analysis of neutron diffraction data, however, we found strong evidence that host–guest C–H···O hydrogen bonds can be formed between CDs and substrates,[4,5] and for the complex αCD–(benzyl alcohol)$_2$–6 H_2O, we observed short C–H···π contacts between the outer jacket of α-CD and a benzyl group.[6] C–H···O[7] and X–H···π[8–10] interactions have typical binding energies in the range 1–2 kcal mol^{-1} (1 cal = 4.184 J), and can therefore be regarded as weak hydrogen bonds (O–H···O: typically around 4–5 kcal mol^{-1}). The general role of such weak bonds in complex stabilisation is as yet poorly investigated. In the crystal structure of the inclusion complex β-CD–but-2-yne-1,4-diol–7 H_2O, **1**, we observe an exceptional variety of weak polar host–guest contacts.§

In **1**, Fig. 1, the β-CD molecules are packed in a herringbone pattern which is observed for many other complexes of β-CD with small molecules.[11–13] The β-CD cavity contains one but-2-yne-1,4-diol and two water molecules, which have well defined and ordered positions (the other five water molecules per asymmetric crystal unit fill the space between the macrocyles and are of minor interest here). The linear diol molecule extends axially through the β-CD cavity, and its hydroxy groups form O–H···O hydrogen bonds with neighbouring molecules. At first glance, this parallels inclusion complexes with other linear diols (pentane-1,5-diol,[11] butane-1,4-diol[13]), where related guests also extend axially through the β-CD channel. Unlike in the other complexes, however, the guest in **1** is displaced from the channel axis and forms tight contacts with the cavity wall, Fig. 2. This gives room for two co-complexed water molecules, W6 and W7, to form a two-membered water chain that is roughly parallel to the diol molecule.

The intermolecular contacts of the guest molecules, which are indicative of significant polar interactions, are shown in Figs. 1 and 2. The O···O contacts suggestive of hydrogen bonding (< 3.2 Å) are typical of those observed in β-CD complexes.[3] One hydroxy group of the diol molecule, O(1)B, is favourably coordinated by β-CD hydroxy groups and water molecule W7, so that its hydrogen bond potential is fully satisfied. The other hydroxy group, O(2)B, however, has only one fully occupied O hydrogen bond partner in its vicinity, O(2)4 of a neighbouring β-CD molecule. A second hydrogen bond partner, O(6)2B of the host molecule, is only 23% occupied. This means that the O–H···O hydrogen bond coordination of O(2)B is unfavourable, leaving acceptor potentials available for weaker hydrogen bond donors like C–H.

Fig. 2 shows the short contacts within the β-CD cavity. Apart from the 'normal' O···O hydrogen bond contacts, there are a number of weak polar interactions: (*a*) The diol hydroxy group O(2)B is in contact with C(5)3–H of the cavity wall. The geometry is typical for C–H···O hydrogen bonding[4,5,7] (H···O = 2.53, C···O = 3.38 Å, angle at H = 134°). This interaction is presumably formed as a compensation for the poor O–H···O coordination of O(2)B. (*b*) A CH_2 group of the guest molecule donates a long C–H···O hydrogen bond to atom O(4)5 of the cavity wall (H···O = 2.74, C···O = 3.69 Å, angle at H = 145°). (*c*) Water molecule W6 contacts two C(5)–H groups with H···O distances of 2.66 and 2.83 Å [C···O = 3.56 and 3.70 Å, angle at H = 139 and 137° for C(5)6–H and C(5)7–H, respectively]. This is similar to our earlier observations on water molecules in β-CD cavities.[5] (*d*) Most remarkable is a C–H···π contact directed from C(5)4–H to the C≡C triple bond of the guest. The two H···C distances are 2.78 and 2.82 Å, respectively (angles at H = 164 and 155°, respectively); the distance to the midpoint of the C≡C bond is even shorter: H···M(C≡C) = 2.74 Å (angle at H = 163°). For alkynyl C–H···C≡C contacts of similar geometry, a hydrogen-bond-like nature could be clearly shown from IR spectroscopic data.[10] Therefore, bonding character is also expected for the C–H···C≡C contact observed here.

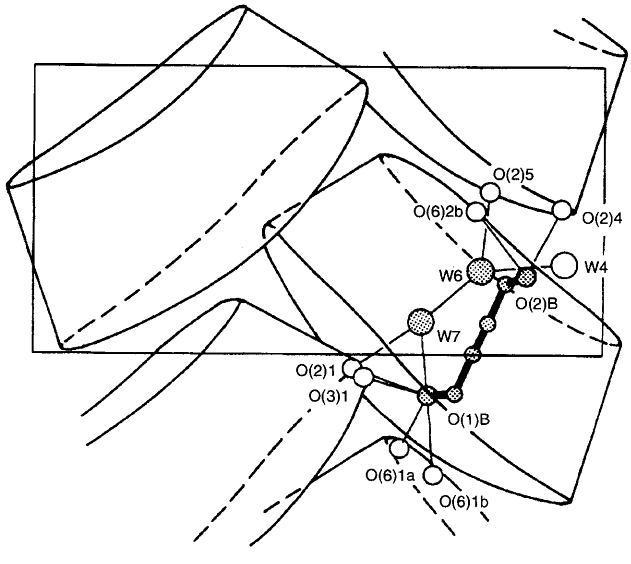

Fig. 1 Crystal packing arrangement, inclusion geometry and O···O contacts suggestive of hydrogen bonding (< 3.2 Å) in β-CD–but-2-yne-1,4-diol–7 H_2O. β-CD molecules are drawn schematically as in our earlier studies,[11,13] with small spheres representing β-CD O-atoms involved in hydrogen bonding with the guest molecules. The interstitial water molecules are omitted for clarity, except for W4 which is in hydrogen bond distance with the guest water molecule W6.

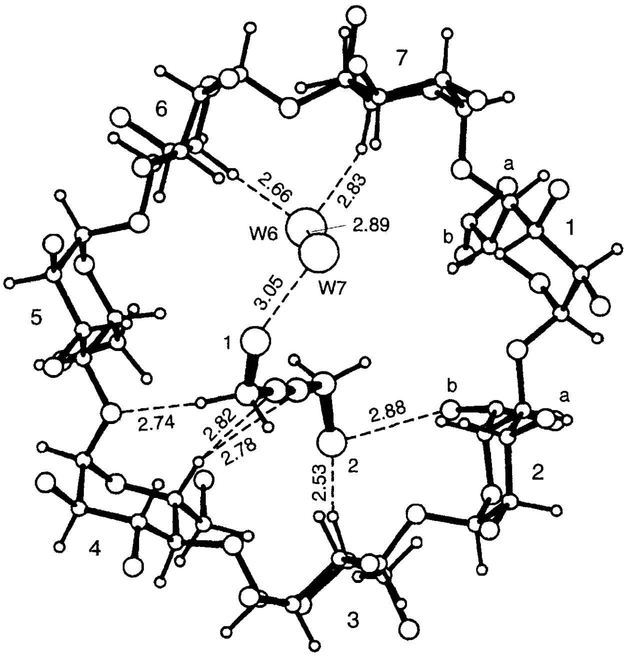

Fig. 2 Inclusion geometry of the title complex. H···X distances are given for the theoretical H-positions based on a bond length C–H = 1.09 Å. These values are realistic because for the relevant C–H groups, the H-positions are reliably determined by the non-H molecular skeletons.

If small molecules and additional water molecules are included in β-CD cavities, there is a pronounced tendency for dynamic disorder within the cluster of guest molecules.[11–13,15,16][¶] This is readily explained by entropic considerations: if there are several possible arrangements of guest molecules on a similar energy level, there should be permanent fluctuations between these arrangements (at room temperature). We explain the ordered nature of **1** by the unusually large number of weak polar interactions of the guest molecules with the cavity surface, which sufficiently favour one of the many possible arrangements of the guest molecules to keep them in an ordered state. This example indicates that the bonding situation for molecular clusters in more or less hydrophobic cavities is an extremely delicate matter. Weak hydrogen bonding interactions may crucially determine the geometrical arrangement and also whether the cluster is disordered or not.

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Footnotes

[†] Topography of Cyclodextrin Inclusion Complexes, Part 38. Part 37: T. Steiner and W. Saenger, *Carbohydr. Res.*, in the press. For Part 36, see ref. 11.

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[§] *Crystal Data* for **1**: β-cyclodextrin–but-2-yne-1,4-diol–heptahydrate [$(C_6H_{10}O_5)_7 \cdot C_4H_6O_2 \cdot 7.0\ H_2O$]. Crystallized by slow evaporation of aqueous solutions. M = 1347.18. Monoclinic $P2_1$; a = 20.988(9), b = 10.092(2), c = 15.223(10) Å, β = 110.30(6)°, V = 3024(3) Å^3, Z = 2, D_c = 1.48 g cm^{-3} (room temp.). Enraf-Nonius CAD4 diffractometer, Ni-filtered Cu-Kα X-rays, μ = 11.1 cm^{-1}, $\lambda/2\sin\theta_{max}$ = 0.89 Å, 0.2 × 0.15 × 0.04 mm^3 crystal mounted in a glass capillary together with some mother liquor, 4998 unique reflections, 3064 with $F_o > 3\sigma(F_o)$. Initial structure solution by using atomic coordinates of the β-CD molecule in β-CD–diethanolamine–heptahydrate,[11] anisotropic refinement with SHELX-76,[14] H atoms bonded to C included in ideal positions, hydroxy and water H atoms not located. Two β-CD primary hydroxy groups and one interstitial water molecule are each two-fold disordered, O(6)1, O(6)2, W3 [O(6)1A, occ. = 0.73; O(6)1B, occ. = 0.27; O(6)2A, occ. = 0.77, O(6)2B, occ. = 0.23; W3A, occ. = 0.76, W3B, occ. = 0.24; each pair constrained to Σocc. = 1.0]. R = 0.078 [for reflections $F_o > 3\sigma(F_o)$].

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallograpic Data Centre. See Information for Authors, Issue No. 1.

[¶] We have solved but not yet published the crystal structures of a number of β-CD complexes, in which guest and water molecules in the β-CD cavity are heavily disordered (all in the same space group $P2_1$): β-CD–propane-1,3-diol; β-CD–but-2-ene-1,4-diol; β-CD–diethylene glycol; β-CD–cyclohexane-1,4-diol; β-CD–ethoxyethanol.

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