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Note

Quantum chemical calculations on the weak polar host–guest interactions in crystalline cyclomaltoheptaose (β-cyclodextrin)-but-2-yne-1,4-diol heptahydrate

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Abstract

X-ray diffraction analysis of the crystalline inclusion complex β-cyclodextrin-but-2-yne-1,4-diol heptahydrate has shown that a number of C–H...O and C–H...π interactions occur between the cavity wall and the guest molecules. The interaction energies of these contacts are estimated by *ab initio* quantum chemical calculations. They are in the range 0.7 to 1.1 kcal mol^{-1}, which is far below values of conventional hydrogen bonding (4 to 6 kcal mol^{-1} for O–H...O hydrogen bonds in carbohydrates), but appreciably above energies of van der Waals contacts.

Keywords: β-cyclodextrin; Weak hydrogen bond; Quantum chemical calculations

1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are macrocyclic host molecules composed of α-(1→4)-linked-D-glucoses (with seven residues called β-cyclodextrin, β-CD) [1,2]. The molecular cavity is lined by C–H groups and by the O-4 atoms linking the glucose residues, rendering the cavity surface relatively hydrophobic in nature. If polar guest molecules are included in these cavities, they have limited opportunity to satisfy their hydrogen bond potentials. Typically, guest molecules carrying hydroxyl groups are oriented in such a way that hydrogen bonds can be formed through the cavity openings to neighboring CD or crystal water molecules. Hydrogen bonds can also be formed with the primary O-6 hydroxyl groups which are placed at the narrower of the two cavity openings. The interglycosidic O-4 atoms are sterically poorly accessible, and serve only occasionally as acceptors of O–H···O hydrogen bonds [3,4].

O/N–H···O hydrogen bonds with hydroxyl groups and O-4 atoms are often regarded as the only possible host-guest hydrogen bonds in cyclodextrin inclusion complexes. However, we have found structural evidence for C–H···O hydrogen bonding [5–8], and also for directional C–H···π

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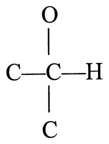
interactions [6] in a number of cyclodextrin inclusion complexes (for background on C–H...O and C–H···π hydrogen bonds, see Refs 9–11). The typical energies of C–H···O and C–H···π hydrogen bonds depend on the nature of the C–H donor. For the very weakly polarized methyl donors, C–H···O bond energies are around 0.5 kcal mol^{-1}, not much above the energies of van der Waals interactions. For strongly polarised ('activated') C–H groups like in chloroform or in terminal alkynes, C–H···O energies may be >2 kcal mol^{-1} [11] (i.e. comparable with the 4 to 6 kcal mol^{-1} for O–H···O hydrogen bonds between hydroxyl groups or water molecules [2]). For the other types of C–H donors, hydrogen bond energies are in between these extremes. The C–H groups forming the surface of cyclodextrin cavities, C-3–H and C-5–H, are of a significantly activated type:



$$\mathrm{C{-}\overset{\overset{O}{|}}{\underset{\underset{C}{|}}{C}}{-}H}$$

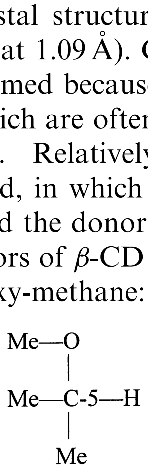
For this kind of donor, C–H···X interactions have not yet been the subject of theoretical investigations.

To get an impression on the energy contibution of weak hydrogen bonds in the stabilisation of CD inclusion complexes, quantum chemical calculations were performed on the weak polar host-guest interactions in the crystalline inclusion complex β-cyclodextrin—but-2-yne-1,4-diol—heptahydrate, **1**, for which the X-ray crystal structure has been published previously [8]. This particular structure is selected because it contains an exceptional variety of weak hydrogen bonds.

2. Computational technique

Quantum chemical *ab initio* molecular orbital calculations were performed in the MO LCAO SCF (HF + MP2) approximation using the GAUSSIAN 92/DFT package [12]. Atomic partial charges (Mulliken scheme) and intermolecular bond energies were calculated using the 6-31** basis set by taking into account electron correlation and the basis set superposition error (BSSE). The computations were performed on the CRAY Y-MP4D/464 of the Konrad-Zuse-Zentrum, Berlin.

Hydrogen bond energies were calculated for molecular fragments in the contact geometry defined by the crystal structure of **1** (C–H bond lengths normalised at 1.09 Å). Geometry optimisation was not performed because this leads to idealised geometries which are often far away from the experimental ones. Relatively large molecular fragments were used, in which the covalent bonding situation around the donor or acceptor is conserved. C–5-H donors of β-CD were approximated by dimethyl-methoxy-methane:



$$\mathrm{Me{-}\overset{\overset{Me{-}O}{|}}{\underset{\underset{Me}{|}}{C\text{-}5}}{-}H}$$

The interglycosidic O-4 acceptors of β-CD were approximated by dimethylether (Me–O–Me), the C–H donor of but-2-yne-1,4-diol by the analogous C–H donor of prop-2-yne-ol [HO–CH$_2$–CCH], the hydroxyl acceptor of but-2-yne-1,4-diol by that in prop-2-yne-ol and the C≡C acceptor of but-2-yne-1,4-diol by that of but-2-yne (Me–C≡C–Me).

The "noise-level" of this kind of calculations is a few 0.1 kcal mole^{-1}. Therefore, the energies of ca. 1 kcal mole^{-1} that are computed below, are reliable in their order of magnitude, but small differences between similar values cannot be relied on.

Since hydroxyl and water H-atoms had not been located in the crystal structure determination, energies of O–H···O hydrogen bonds could not be calculated.

3. Results and discussion

The crystal packing of **1** is schematically shown in Fig. 1, and the inclusion geometry is shown in detail in Fig. 2. The β-CD host molecules are packed in a herringbone pattern in which the cavity openings are closed by the rims of neighboring β-CD molecules (Fig. 1). Five water molecules per β-CD are placed in interstitial voids.

The β-CD cavity contains one but-2-yne-1,4-diol and two water molecules in fully ordered positions (Fig. 2). The butynediol molecule is parallel to the axis of the β-CD cavity, and its hydroxyl groups form O–H···O hydrogen bonds with neighboring β-CD molecules. The guest molecule is displaced from the β-CD molecular axis, and forms close contacts with the cavity wall. This gives place for

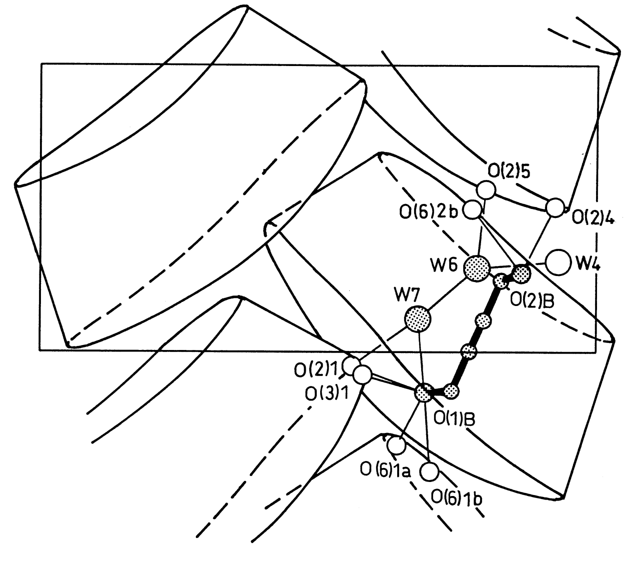


Fig. 1. Crystal packing, inclusion geometry and intermolecular O···O contacts suggestive of hydrogen bonding. Redrawn after Ref. [8]. Guest molecules are drawn shaded.

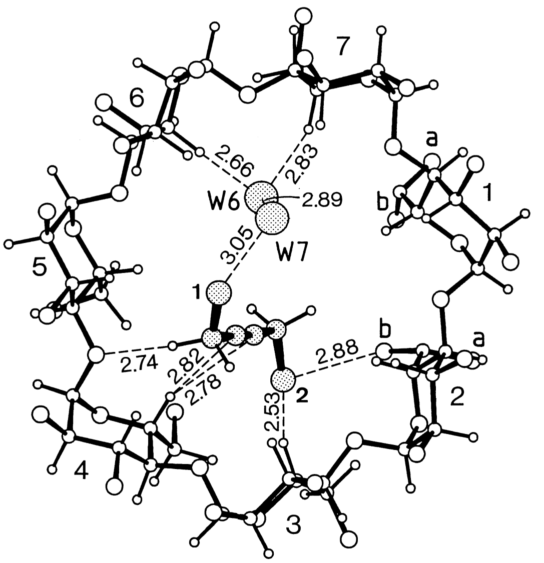


Fig. 2. Inclusion geometry of the title complex. H···X distances are given for theoretical hydrogen atom positions based on a normalised bond length of C–H = 1.09 Å. Redrawn after Ref. [8]. Guest molecules are drawn shaded.

two water molecules which are also contained in the β-CD cavity.

Apart from O–H...O hydrogen bonds, the but-2-yne-1,4-diol and water molecules in the β-CD cavity are engaged in several short contacts with the cavity lining, which we have interpreted as weak hydrogen bonds [8]. The geometries of these contacts and the energies of the calculated interactions are given in Table 1. The results are, in detail:

(a) Water molecule W6 accepts two $\text{C–H}\cdots\text{O}_\text{W}$ hydrogen bonds from C-5–H donors. Both bond energies are calculated to be 1.1 kcal mol^{-1}. This kind of hydrogen bond occurs frequently if water molecules are enclosed in cyclodextrin cavities [5].

(b) One of the diol hydroxyl groups (O-2) is engaged in a C–H···O interaction with C-5^3–H of the cavity wall. The calculated bond energy of 0.7 kcal mol^{-1} is lower than that for the water acceptor W6. This might be because hydroxyl groups are known to be weaker acceptors than water molecules in general [2].

(c) One of the CH$_2$ groups of the guest molecule donates a C–H···O hydrogen bond to the interglycosidic oxygen atom O-4^5. The bond

Table 1
Geometric parameters of the D–H···A host-guest contacts in **1**,[a] and corresponding bond energies (kcal mol^{-1}) estimated by quantum chemical calculations. O···O distances < 3.2 Å suggestive of O–H···O hydrogen bonding between guest molecules are also given

Contact	H···A	D···A	D-H···A	Energy
Host-guest contacts				
C-5^6-H···O-W6	2.66	3.56	137	1.1
C-5^7-H···O-W6	2.83	3.70	135	1.1
C-5^3-H···O-2$^\text{But}$	2.53	3.38	135	0.7
C-5^4-H···$\text{M}_{C\equiv C}^{\text{But}}$ [b]	2.74	3.79	163	0.7
C-1$^\text{But}$-H···O-4^5	2.74	3.69	145	1.1
O-6^{2}b···O-2$^\text{But}$		2.88		
Possible O-H···O hydrogen bonds between the guest molecules				
O-W6···O-W7		2.89		
O-W7···O-1$^\text{But}$		3.05		

[a] given in Å and degrees, based on a bond length of C–H = 1.09 Å.
[b] The two individual H···C contacts have distances of H···C-2$^\text{But}$ = 2.82 Å and H···C-3$^\text{But}$ = 2.78 Å.

energy of 1.1 kcal mol^{-1} is as to be expected for this weakly activated donor.

(d) The C≡C triple bond of the guest molecule accepts a C–H···π interaction from C-5^4–H, which is directed almost exactly at the center of the π-bond. The energy is calculated to be 0.7 kcal mol^{-1}. For more acidic C–H donors, energies of C–H···π interactions can exceed 2 kcal mol^{-1} [9].

The calculated bond energies for the weak polar interactions in **1** are low with numeric values in the range 0.7 to 1.1 kcal mol^{-1}. This is roughly a quarter (or even less) of O–H···O hydrogen bonds in carbohydrates, but clearly above the dispersion energies. It is expected that these energies are typical also for other C–H···O hydrogen bonds in carbohydrates [5].

This is a situation which can be interpreted only with care. With the donors and acceptors occurring in carbohydrates, C–H···X hydrogen bond energies are small and far below those of conventional hydrogen bonds. Carbohydrates carry large numbers of O–H donors and O acceptors, so that dense networks of co-operative O–H···O–H···O hydrogen bonds can be formed [2]. In the normal situation, these conventional hydrogen bonds will dominate the solid-state interactions, and the far weaker C–H···O hydrogen bonds play only secondary roles. Still, since they add about one kcal mol^{-1} each to the total energy, they should not be simply neglected. The situation changes if dominant networks of O–H···O hydrogen bonds cannot be formed for some reason, such as local lack of suitable functional groups or steric hindrance. Then, the weaker hydrogen bond types gain of importance because they can satisfy hydrogen bonding potentials which would otherwise be vacant. This is a situation which is typical if hydrophilic molecules are enclosed in cyclodextrin cavities, or any other molecular cavity with partly hydrophobic walls. To satisfy their hydrogen bonding potentials, the guest molecues have no other choice than engaging in weak types of hydrogen bonds.

It is obvious that arrangements involving weak hydrogen bonds are more prone to disorder than those stabilised by conventional hydrogen bonds: the entropy gain due to disorder can easily exceed the enthalpy loss due to breaking the weak hydrogen bonds. This is a phenomenon that occurs very frequently with guest molecules enclosed in cyclodextrin cavities. The case of **1** is one of the contrary examples where an ordered guest arangement is in fact stabilised by weak hydrogen bonds of energies around 1 kcal mol^{-1}.

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