Isostructural Replacement of an N–H···O by a C–H···O Hydrogen Bond in Complex Stabilisation: Crystal Structures of β-Cyclodextrin Complexed with Diethanolamine and with Pentane-1,5-diol

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In the isomorphous crystal structures of the inclusion complexes β-cyclodextrin–diethanolamine and β-cyclodextrin–pentane-1,5-diol, the flexible guest molecules have identical conformations; they form the same intermolecular contacts, with a structure-stabilizing N–H···O hydrogen bond in the former being replaced by a C–H···O interaction in the latter.

In recent years, the nature of C–H···O hydrogen bonds has been extensively studied,[1–5] and numerous examples of small molecule crystal structures were reported which play a key role in determining molecular conformations and crystal packing arrangements.[1,2,6–10] Much less is known about the role of these weak interactions in large molecular assemblies or even in macromolecular systems.[2,10] Here we describe crystal structures of hydrated inclusion complexes of biological interest, in which C–H···O hydrogen bonding crucially contributes to structure stabilisation.

The crystalline inclusion complexes of the macrocyclic oligosaccharide β-cyclodextrin (cyclomaltoheptaose, β-CD), which consists of seven α(1–4) linked D-glucoses, are excellent model systems to study hydrogen bond properties and host–guest interactions.[2] To explore the behaviour of small molecules in larger molecular voids, we are performing a series of studies with guest molecules which are systematically too small to completely fill the relatively hydrophobic cavity of β-CD.[11–14] The remaining space is then filled with water molecules, and normally guest and water molecules are dynamically disordered over several sites. However, we also found two strikingly well-ordered inclusion complexes, the structural relations of which are discussed here: β-CD–diethanolamine·6.4 H_2O **1**, and β-CD–pentane-1,5-diol·6.2 H_2O **2**.‡

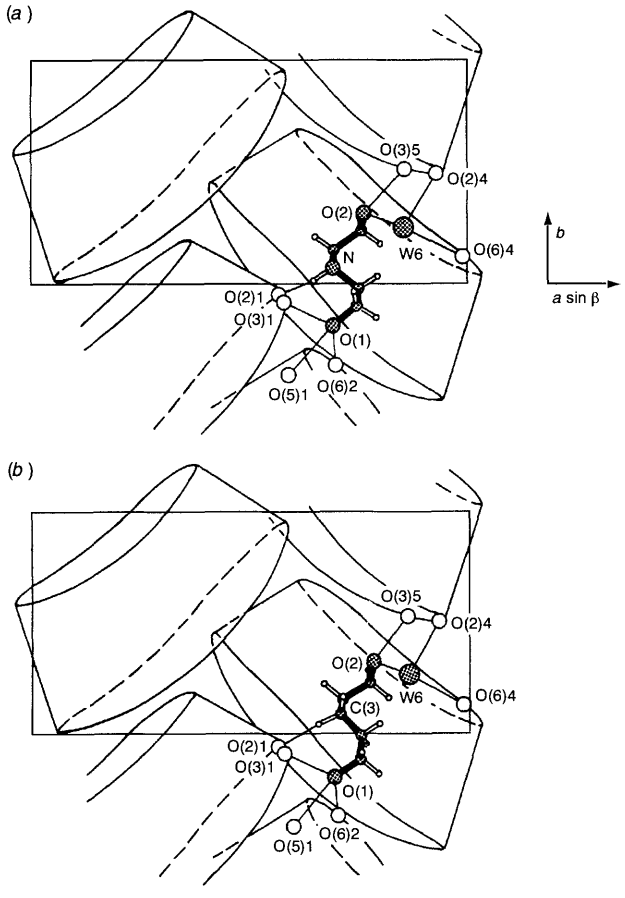


Fig. 1 Crystal packing arrangement, inclusion geometry, and hydrogen bond network of the guest molecules in (*a*) β-CD–diethanolamine·6.4 H_2O, and (*b*) β-CD–pentane-1,5-diol·6.2 H_2O. β-CD molecules are drawn schematically (as in our earlier studies),[11–13] with small spheres representing β-CD O-atoms involved in hydrogen bonding with the guest molecules. The interstitial water sites are omitted for clarity.

In the crystal structures of **1** and **2**, Fig. 1, the β-CD molecules are packed in a herringbone pattern which is isomorphous to the packing of β-CD–butane-1,4-diol·6.25 H_2O.[12] In both complexes, the β-CD cavities contain one linear guest and one water molecule, W6. The guest molecules extend axially through the β-CD cavities, and adopt almost identical low-energy conformations, with all internal torsion angles around ± *gauche* or *trans*. The space between the β-CD macrocycles is filled by 5.4 and 5.2 water molecules distributed over 10 and 9 partially occupied sites (**1** and **2**, respectively), which are of minor interest in the present context (not shown in Fig. 1).

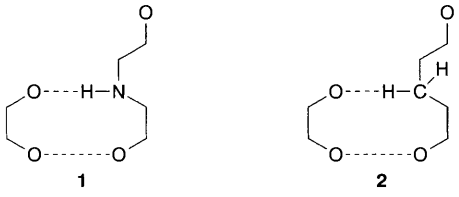
For the complexed diethanolamine molecule in **1**, the terminal hydroxy groups are placed near the cavity openings, and are tightly fixed by O–H···O hydrogen bonds, Fig. 1(*a*) and Table 1. The N–H group points towards the O(2)–O(3) cavity opening and forms an N–H···O hydrogen bond with the hydroxy group O(2)1 of a neighbouring β-CD molecule. The $(CH_2)_2$ moieties are located in the central part of the cavity, with their C–H bonds pointing towards C–H groups of the cavity lining. This way, hydrogen bonding potentials as well as hydrophobic (van der Waals) interactions are very favourably satisfied, hence the exceptionally stable and ordered inclusion geometry. For the included pentane-1,5-diol molecule in **2**, not only the molecular conformation, but also the pattern of intermolecular contacts is almost identical as in **1**, Fig. 1(*b*) and Table 1. This includes the central CH_2 group which is replacing N–H: instead of the hydrogen bond N–H···O(2)1, a contact C–H···O(2)1 is formed, with the only difference that the C···O distance is 3.42 Å, compared to the N···O distance of 2.81 Å (the calculated H···O distances are 2.49 Å for **2** and 1.81 Å for **1**). These C···O

Table 1 Donor–acceptor contacts (Å) of the guest molecules suggestive for hydrogen bonding. For simplicity, O···O contacts > 3.1 Å are not listed, although they may be associated with hydrogen bonds.[16] O(*n*)*m* denotes oxygen atom *n* of glucose residue *m*

Contact	1	2
O(1)···O(3)1	2.675 (9)	2.697 (9)
O(1)···O(5)1	2.990 (8)	2.910 (8)
O(1)···O(6)2	2.72 (1)	2.78 (1)
N/C(3)···O(2)1[a]	2.811 (8)	3.42 (1)
O(2)···O(3)5	2.78 (1)	2.66 (2)
O(2)···W6	2.94 (1)	2.94 (2)
W(6)···O(2)4	2.90 (1)	2.85 (1)
W(6)···O(6)4	2.98 (1)	2.83 (1)

[a] Theoretical H···O separations and angles at H (for bond lengths of C–H = 1.09, N–H = 1.04 Å): 1.81 Å and 161° for N–H···O(2)1; 2.49 Å and 142° for C(3)–H···O(2)1.

and H···O separations are in the typical range for C–H···O hydrogen bonds involving weaker types of C–H donors and O acceptors.[3,5] The contact pattern with the hydroxy groups O(2)1 and O(3)1 of the neighbouring β-CD molecule is schematically shown for **1** and **2**.



The identity of the patterns immediately suggests that the C–H···O contact in **2** is in fact a hydrogen bond, which structurally and functionally takes the role of the N–H···O bond in **1** (analogous conclusions from identity of patterns were drawn earlier for small molecule crystal structures, *e.g.* for the system urea–barbital, acetamide–barbital).[7] Further support for this view is provided by the structure of the complex between β-CD and the related molecule diethyleneglycol,§ where the hydrogen bond donors N–H in **1** and C–H in **2** are substituted by an ether O atom. As the X–H···O(2)1 interaction is deleted, the guest molecule becomes severely disordered.

It was surprising to find an ordered geometry for the inclusion of pentane-1,5-diol, since $(CH_2)_n$-chains in β-CD cavities tend to be disordered over alternative low-energy conformations (as must be expected for entropic reasons). In the related complex with butane-1,4-diol, the $(CH_2)_4$ chain adopts at least two alternative conformations.[12] For the complexes with propane-1,3-diol¶ and ethanediol,[13] even more pronounced disorder is observed. If, as in **2**, one of the possible low-energy conformations is associated with sterically favourable C–H···O hydrogen bonding, however, it can be sufficiently stabilized to be ordered. The general conclusion is that in formation and stabilisation of macromolecular complexes, C–H···O interactions may tip the scales in a subtle balance of weak interactions and may decide whether a molecular assembly is ordered or not.

This study was supported by the Deutsche Forschungsgemeinschaft, Sa 196/25-1, by Bundesministerium für Forschung und Technologie, 03-Sa3FUB, and by Fonds der Chemischen Industrie.

Received, 7th December 1994; Com. 4/07481E

Footnotes

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‡ Topography of Cyclodextrin Inclusion Complexes, Part 36. For Part 35, see Th. Steiner and W. Saenger, *Carbohydr. Lett.*, 1994, **1**, 143. For Part 34, see Th. Steiner and K. Geßler, *Carbohydr. Res.*, 1994, **260**, 27.

Crystal data for **1**: β-Cyclodextrin–Diethanolamine·6.4 H_2O $[(C_2H_{10}O_5)_7 \cdot C_4H_{11}O_2N \cdot 6.4\ H_2O]$. Crystallized by slow cooling of hot concentrated aqueous solutions. Monoclinic $P2_1$; a = 21.310(13), b = 9.987(2), c = 15.247(12) Å, β = 111.85(3)°, V = 3012(3) Å^3, Z = 2, D_c = 1.49 g cm^{-3} (room temperature). Enraf–Nonius CAD4 diffractometer, Ni-filtered Cu-Kα X-rays, λ/2 sin θ_{max} = 0.89 Å, 4508 unique reflections, 4386 with $F_o > \sigma(F_o)$. Initial structure solution by using atomic coordinates of the β-CD molecule in β-CD–butane-1,4-diol hexahydrate,[12] anisotropic refinement with SHELX76,[15] H atoms bonded to C and N included in ideal positions, hydroxy and water H atoms not located. One β-CD primary hydroxy group two-fold disordered, O(6)1 [O(6)1 A, occ. = 0.78; O(6)1B, occ. = 0.22]. R = 0.063 [for reflections $F_o > \sigma(F_o)$].

For **2**: β-Cyclodextrin–Pentane-1,5-diol·6.2 H_2O $[(C_2H_{10}O_5)_7 \cdot C_5H_{12}O_2 \cdot 6.2\ H_2O]$. Crystallization, data collection and structure solution and refinement as for **1**. Monoclinic $P2_1$; a = 21.451(11), b = 10.014(2), c = 15.240(8) Å, β = 111.25(2)°, V = 3051(2) Å^3, Z = 2, D_c = 1.47 g cm^{-3}. 4547 unique reflections, 4342 with $F_o > \sigma(F_o)$. No disorder in the β-CD molecule. R = 0.065 [for reflections $F_o > \sigma(F_o)$].

Atomic coordinates, bond lengths and angles, and thermal parameters for **1** and **2** have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ *Crystal data* for β-Cyclodextrin–Diethyleneglycol·*ca.* 6 H_2O. Monoclinic $P2_1$; a = 21.288(11), b = 9.969(2), c = 15.276(11) Å, β = 111.62(2)°, V = 3014(2) Å^3 (preliminary crystal structure determined).

¶ *Crystal data* for β-Cyclodextrin–Propane-1,3-diol·*ca.* 7 H_2O. Monoclinic $P2_1$; a = 21.116(4), b = 9.976(1), c = 15.274(3) Å, β = 110.88(1)°, V = 3006(1) Å^3 (preliminary crystal structure determined).

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