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Crystal architecture and conformational properties of the inclusion complex, neohesperidin dihydrochalcone–cyclomaltoheptaose (β-cyclodextrin), by X-ray diffraction

Luciana Malpezzi,[a] Giovanni Fronza,[b] Claudio Fuganti,[a] Andrea Mele[a,*] and Sergio Brückner[c]

[a]*Dipartimento di Chimica, Materiali ed Ingegneria Chimica 'G. Natta'—Politecnico di Milano, Via L. Mancinelli 7, I-20131 Milan, Italy*
[b]*CNR—Istituto di Chimica del Riconoscimento Molecolare, Via L. Mancinelli 7, I-20131 Milan, Italy*
[c]*Dipartimento di Scienze e Tecnologie Chimiche, Università di Udine, Via Cotonificio, 108–I-33100 Udine, Italy*

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Abstract—The crystal structure of the host–guest noncovalent complex of cyclomaltoheptaose (β-cyclodextrin, βCD) with the *O*-diglycosyl flavonoid neohesperidin dihydrochalcone [(3,5-dihydroxy-4-(3-hydroxy-4-methoxyhydrocinnamoyl)phenyl-2-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranoside, NDC] has been determined from single-crystal X-ray diffraction data collected at low temperature (130 K), using synchrotron radiation. The crystal data are as follows: $a = 15.125(5)$, $b = 30.523(5)$, $c = 41.332(5)$ Å, orthorhombic, space group $C222_1$. The structure contains 19 molecules of water, of which 11 appeared well positioned, whereas 9 are disordered over 23-positions. The βCD–NDC complex is characterized by one aromatic part of NDC deeply inserted into the hydrophobic cavity of the βCD through the primary OH rim, and it is present in the crystal as a dimer. The dimeric units, formed by head-to-head assemblies of CD molecules, each with its guest, are self-assembled in columns. The stability of the columns is provided by host–guest and guest–guest attractive interactions, thus showing a key role of the guest molecules in the crystal architecture. The guest conformation in the complex is different from that reported in the literature for uncomplexed NDC. The host-induced conformational changes on NDC provide the optimum geometry requirements for the assembly of the dimeric units.
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1. Introduction

Cyclomaltoheptaose (β-cyclodextrin, βCD, **1**, Fig. 1) is a cyclic, torus shaped, oligomer of amylose characterized by an inner hydrophobic cavity and an external hydrophilic surface. These features make βCD capable of hosting molecular guests via inclusion of the whole guest, or part of it, into the void cavity, thus giving rise to noncovalent host–guest complexes. Both fundamental research and applied technology focused their interest on such systems, whose relevance is nowadays well established.[1,2] Several factors are recognized to be responsible for the formation of inclusion complexes of cyclodextrins (CDs) with suitable guest molecules: van der Waals forces, hydrogen bonds, hydrophobic, and dipole–dipole interactions. Single-crystal X-ray diffraction studies of host–guest (H–G) complexes of CDs provide detailed information on the role of such weak interactions for establishing host–guest supramolecular

* Corresponding author. Tel.: +39-02-23993006; fax: +39-02-239930-80; e-mail: andrea.mele@polimi.it

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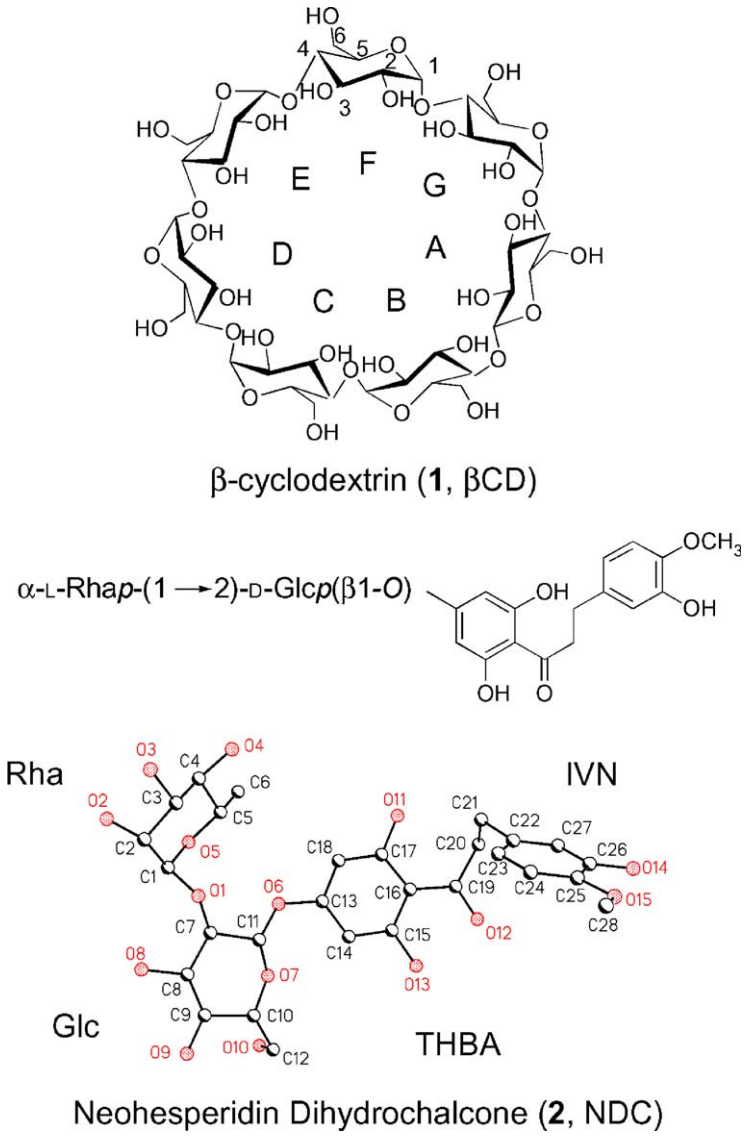


Figure 1. Top: molecular formula and atom numbering of βCD. The glucose residues are labeled by the capital letters (A–G) showed inside the macro-ring. Bottom: chemical structure of NDC. The ball-and-stick structure of NDC taken from X-ray analysis is also reported along with the numbering system used. For the sake of clarity, the abbreviations for the building blocks of NDC are also reported (Rha: rhamnose; Glc: glucose; THBA: trihydroxybenzoic acid and IVN: isovanillin).

assemblies,[3,4] molecular recognition, and stereodifferentiation.[5] This information is complementary to that achievable in the solution state by NMR spectroscopy[6,7] and in the gas phase by mass spectrometry.[8–11]

The ideal guest molecule able to bind CD via the different interaction mechanisms described above 'should have a hydrophobic body and hydrophilic 'ends', which can form hydrogen bonds to the hydroxyl groups on both sides of the host molecule to stabilize the inclusion complex'.[12] To this end we decided to explore the complexation features of aromatic compounds conjugated to oligosaccharides, starting from the *O*-diglycosyl flavonoid neohesperidin dihydrochalcone (NDC, **2**, Fig. 1). The aglycon is made of two aromatic systems derived from isovanillin (IVN) and 2,4,6-trihydroxy benzoic acid (THBA), respectively, and mutually connected through a flexible CH_2–CH_2 spacer. One of the phenolic OH groups of the THBA is bound to the α-L-Rha*p*-(1 → 2)-D-glucopyranosyl residue via β-*O*1 glycosidic linkage (the glycan is often referred to as β-neohesperidosyl residue). The present study reports on the crystal structure of the 1:1 inclusion complex of βCD with NDC. The geometry of the complex and the crystal packing provide valuable information on the role of both the glycan and the aglycon in the mechanism of interaction with the amphiphilic host βCD. Special emphasis is given to the description of the different types of host–host (H–H), host–guest (H–G), and, if any, guest–guest (G–G) interactions and their contribution to the crystal architecture.

2. Experimental

2.1. Materials, crystal preparation and data collection

β-CD and NDC were purchased from Aldrich Chemical Company (Milan, Italy) and Sigma Chemical Co. (Milan, Italy), respectively. Both products were used as received. The formation of the inclusion complex was achieved by simply mixing equimolar amounts of host and guest in distilled water at room temperature. Suitable crystals for X-ray analysis were obtained after several attempts by precipitation from an aqueous solution and successive slow evaporation of the solvent within 10–15 days. The selected crystal was sealed in a capillary tube in the presence of a small amount of mother liquor. Previous sample preparations pointed out that degradation of the crystals occurred in few hours due to evaporation of crystallization water. Data collection was performed at the X-ray diffraction beamline of the ELETTRA Synchrotron Radiation Laboratory (Trieste, Italy, web address: http://www.elettra.trieste.it) using an MAR345 Image Plate. The first experiments carried out with a conventional single-crystal automatic diffractometer (Cu cathode, working conditions: 36 mA × 44 kV) operating at room temperature did not allow us to solve the structure and prompted us to the exploitation of a more efficient radiation source, such as synchrotron light, operating at low temperature (130 K). Indeed, low-temperature data acquisition greatly enhanced the intensity of the high-angle reflections, due to a decreased conformational disorder of the host–guest ensemble. This provided us with a larger dataset for solving and refining the structure.

2.2. Solution and refinement of the structure

The structure of the complex was determined by direct methods using the program SIR97 that revealed almost all the non-H atoms of the complex. The refinement was then accomplished by SHELXL97.[13] The main parameters used in structure refinement are summarized in Table 1. Due to the high number of parameters to be refined, the least-squares refinement was carried out in two blocks, one containing the βCD molecule and one containing the guest molecule plus all water molecules. Among the 19 water molecules found, 11 are well positioned, whereas 9 are disordered over 23-positions. Refinement on F^2 converged to $R1 = 0.0579$ and $wR2 = 0.1685$. No effort was made to find the positions of H atoms from difference Fourier maps; the H atoms were located by using the interactive editing method of the molecular graphics XP program that generates hydrogen atoms in idealized positions. In the case of O–H terminal groups, the choice between equivalent positions was based on optimizing possible hydrogen bonds.

Table 1. Crystallographic data: data collection, structure determination and refinement

	βCD–NDC
Empirical formula	$C_{42}H_{70}O_{35}\cdot C_{28}H_{36}O_{15}\cdot 19.7H_2O$
Formula weight	2067.51
Temperature (K)	130
Radiation type	Synchrotron light
Wavelength (Å)	1.2040
Crystal system	Orthorhombic
Space group	$C222_1$
a (Å)	15.125(5)
b (Å)	30.523(5)
c (Å)	41.332(5)
V (Å^3)	19,081(7)
Z	8
D_{calcd} (Mg m^{-3})	1.439
Absorption coefficient (mm^{-1})	0.132
$F(0\,0\,0)$	8688
Crystal size (mm)	0.3 × 0.4 × 0.6
θ Range for data collection (°)	3.34°–54.46°
Limiting indices	$0 \leqslant h \leqslant 18$, $0 \leqslant k \leqslant 40$, $0 \leqslant l \leqslant 55$
Reflections: collected/unique/obsd	12,277/12,277/12,277
Completeness to $\theta = 28.70$	93.3%
Data/restraints/parameters	12,277/0/1319
Goodness-of-fit on F^2	1.123
Final R indices [$I \geqslant \sigma(I)$]	$R1 = 0.0579$, $wR2 = 0.1685$
R indices (all data)	$R1 = 0.0582$, $wR2 = 0.1690$
Structure solution	Direct method (SIR97)
Refinement method	Full-matrix-block least-squares on F^2 (SHELXL97)

During the last refinement the H atoms were allowed to ride on their carrier atoms, with the isotropic displacement parameter fixed to 1.2 or 1.5 times the value of the equivalent isotropic displacement parameter (U_{eq}) of the atom to which they are attached. In the last difference Fourier map, some minor peaks of electron density, especially near the disordered water oxygen atoms, were still present, but they were considered too weak to be assigned.

A complete set of geometrical data together with the list of atomic parameters has been deposited at Cambridge Crystallographic Data Center (see Supplementary material).

3. Results and discussion

3.1. Structural features of βCD macro-ring and inclusion complex

The most relevant geometrical parameters of the βCD ring are given in Table 2; the molecular structure of the complex is shown in Figure 2. The βCD/NDC host–guest inclusion complex shows, in the crystal, the same 1:1 stoichiometry already found in solution[16] and vapor phase.[17] The IVN terminus of the guest is deeply included in the CD cavity via the primary hydroxyl

Table 2. Selected geometric parameters for βCD ring in the βCD–NDC complex

Parameter	Glucose unit of βCD						
	A	B	C	D	E	F	G
dC1[a]	0.67	0.655	0.67	0.694	0.644	0.657	0.698
dC4[b]	−0.66	−0.643	−0.694	−0.61	−0.692	−0.693	−0.644
Tor1[c]	82.4	82.1	89.1	68.9	72.7	84.8	84.8
Tor2[d]	−4.75	−2.64	−5.08	−3.4	3.62	−0.26	−2.4
d(C1···C4)[e]	2.899	2.887	2.86	2.878	2.904	2.849	2.859
T[f]	9.77	9.28	1.66	26.89	17.28	7.62	10.98
$D4$[g]	4.421	4.384	4.436	4.265	4.517	4.433	4.259
$A4$[h]	125.7	129.34	131.94	125.89	125.6	132.37	128.22
dO4[i]	−0.11	−0.081	0.144	0.044	−0.209	0.111	0.101
$D2$[j]	2.767	2.828	3.164	3.078	2.973	2.835	2.801
$D6$[k]	6.389	4.87	5.623	5.478	5.596	5.536	6.216
$A6$[l]	105.67	152.71	96.92	134.43	134.69	124.97	127.77
ϕ[m]	115.1	116.0	98.9	107.7	108.5	108.6	116.0
ψ[n]	125.3	131.9	114.4	135.9	135.9	126.9	127.6
Q[o]	0.566	0.555	0.583	0.561	0.574	0.584	0.577
θ[o]	173.8	175.9	178.3	173.3	173.7	176.9	175.3
ϕ[o]	−101	−119	−42	−178	65	−58	−162

[a] Distance (Å) of atoms C1 from the least-square plane defined by the atoms C2, C3, C5, and O5.
[b] Distance (Å) of atoms C4 from the least-square plane defined by the atoms C2, C3, C5, and O5.
[c] Dihedral angles (°) between the planes defined by the atoms C2, C3, C5, and O5 and the plane of all seven O4 atoms.
[d] Torsion angles O4($n+1$)–C1···C4(n)–O4(n).
[e] Distance between atoms C1(n)···C4(n) within a glucose residue.
[f] Tilt angle, dihedral angle between the O4 plane and the plane through O4($n+1$), C1(n), C4(n), O4(n).
[g] Distance between atoms O4(n)···O4($n+1$).
[h] Angle between atoms O4($n-1$)···O4(n)···O4($n+1$).
[i] Distance of O4(n) from the least-squares plane defined by the seven O4 atoms.
[j] Distance between atoms O2(n)···O3($n+1$).
[k] Distance between atoms O6(n)···O6($n+1$).
[l] Angle between atoms O6($n-1$)···O6(n)···O6($n+1$).
[m] Torsion angle O5($n+1$)–C1($n+1$)–O4(n)–C4(n).
[n] Torsion angle C1($n+1$)–O4(n)–C4(n)–C3(n).
[o] Cremer and Pople puckering parameters:[14] Q, the total puckering amplitude; θ and ϕ, the two angular variables specifying the distortion type of the ring. Parameters were calculated with PARST.[15]

groups' rim. Interestingly, this is the same inclusion geometry proposed for the complex in D_2O solution on the basis of intermolecular NOE data.[16] The THBA aromatic residue and the β-neohesperidosyl residue of NDC are outside the cavity.

The geometrical features of the CD macro-ring in the complex are not substantially different from those described for hydrated β-CD.[18] The seven glucose units of βCD are in the usual $^4C_1$ conformation; the glycosidic oxygen atoms (O4, see Fig. 1) show a fairly regular heptagonal arrangement, with the maximum out-of-plane distance, 0.21 Å, of each O4 from the average plane defined by the seven O4 atoms. Other geometrical descriptors of the glycosidic oxygen atoms heptagon, such as the mean O4(n)–O4($n+1$) distance (4.39 Å, $\sigma = 0.12$) and the mean O4($n-1$)–O4(n)–O4($n+1$) angle (128.4°, $\sigma = 3.8$), are close to those reported for the crystal structure of the host alone (4.38 Å and 125.2°).[18] The conical shape of the macro-cyclic ring can be described by the dihedral angles between the average plane of the O4 oxygen atoms and the planes defined by C2(n)–C3(n)–C5(n)–O5(n). In the βCD–NDC complex five of these angles fall in the range of 82°–89°, whilst the two glucose units D and E show marked deviations (68.9° and 72.7°, respectively. See also Fig. 2). The latter dihedral angles are related to the hydrogen-bond network present in the crystal cell (vide ultra). As a consequence, the macro-cycle shows a slight distortion from ideal C_7 symmetry.

The linkage between glucose residues through glycosidic oxygen atoms is classically described by the torsion angles ϕ and ψ listed in Table 2 for all seven glucose units. No significant variations were found along the macro-cycle with the only exception of the junction between the C and D residues, where some significant deviation occurs in connection with the already mentioned tilt of the D residue relative to the mean plane of the seven O4 atoms.

In cyclodextrins, intramolecular hydrogen bonds between hydroxyl groups O2(n) and O3($n+1$) are responsible for the remarkable rigidity of the macrocyclic structure; the O2(n)–O3($n+1$) distance lies normally in the range 2.7–3.1 Å. In the structure of the present complex, the majority of these hydrogen bonds are replaced by hydrogen bonds connecting the two monomers within each dimer.

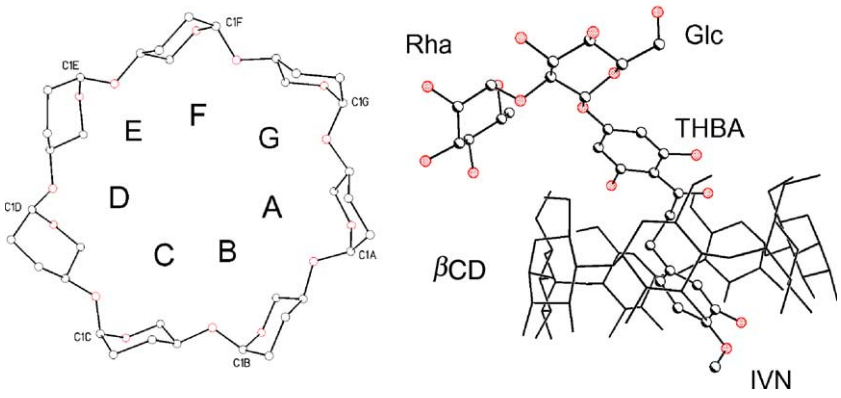


Figure 2. Left: ball-and-stick model of the macro-ring of βCD derived from crystallographic coordinates. Glucose rings are labeled A–F. Right: view of the 1:1 inclusion complex in the solid state as derived from crystallographic coordinates. The main residues have been labeled according to the text.

Primary hydroxyl groups O6 have (+)*gauche*/(−)*gauche* orientation relative to C4–C5 and O5–C5 bonds, respectively, and are therefore directed away from the cavity with the exception of the hydroxyl group C6B–O6B, which is in (+)*gauche* conformation relative to bond O5B–C5B (torsion angle 68.1°) and in *trans* relative to C4B–C5B bond (torsion angle 171.5°). This geometry is not new in CD complexes; in fact it is often observed that five or six C6–O6 groups have a *gauche*/*gauche* orientation, whereas two or one groups, respectively, have a *trans*/(+)*gauche* orientation or are affected by conformational disorder on the two conformations.

Table 3. Summary of short contacts

Entry	D–H···A	*d*(D–H)[a]	*d*(H–A)[a]	*d*(D–A)[a]	D–H···A[b]	Contact type[c]
Intramonomer						
1	O2A–H···O3B	0.82	1.98	2.765(3)	159.7	$H_k(i)$–$H_k(i)$
2	O2B–H···O3B	0.82	2.48	2.885(3)	111.6	$H_k(i)$–$H_k(i)$
3	O3E–H···O2E	0.82	2.50	2.895(5)	111.2	$H_k(i)$–$H_k(i)$
4	C3E–H···O14	0.98	2.38	3.345(4)	166.8	$H_k(i)$–$G_k(i)$
5	O11–H···O6B	0.82	1.77	2.590(3)	172.8	$G_k(i)$–$H_k(i)$
6	O10–H···O7	0.82	2.41	2.801(3)	110.3	$G_k(i)$–$G_k(i)$
7	O13–H···O12	0.82	1.73	2.467(5)	148.3	$G_k(i)$–$G_k(i)$
Intradimer						
8	O3A–H···O3A	0.82	1.96	2.764(4)	167.8	$H_k(i)$–$H_k(i+1)$
9	O2B–H···O3G	0.82	2.20	3.021(3)	158.6	$H_k(i)$–$H_k(i+1)$
10	O2B–H···O2F	0.82	2.56	2.904(3)	106.8	$H_k(i)$–$H_k(i+1)$
11	O3B–H···O3G	0.82	1.97	2.777(3)	170.0	$H_k(i)$–$H_k(i+1)$
12	O3C–H···O3F	0.82	2.06	2.864(3)	166.1	$H_k(i)$–$H_k(i+1)$
13	O14–H···O14	0.82	2.55	3.056(9)	120.9	$G_k(i)$–$G_k(i+1)$
Interdimer						
14	O6E–H···O8	0.82	2.22	2.947(3)	147.1	$H_k(i+1)$–$G_k(i+2)$
15	C6D–H···O5	0.98	2.43	3.281(4)	146.6	$H_k(i+1)$–$G_k(i+2)$
16	O2–H···O6D	0.82	2.02	2.730(3)	145.3	$G_k(i+1)$–$H_k(i+2)$
17	O10–H···O13	0.82	2.03	2.784(4)	153.5	$G_k(i+1)$–$G_k(i+2)$
Intercolumn						
18	C1F–H···O2B	0.98	2.42	3.298(4)	148.2	$H_k(i)$–$H_{k+1}(i)$
19	C2F–H···O3C	0.98	2.50	3.420(4)	155.7	$H_k(i)$–$H_{k+1}(i)$
20	O2F–H···O2F	0.82	2.02	2.799(5)	159.0	$H_k(i)$–$H_{k+1}(i+1)$
21	O6F–H···O6C	0.82	2.12	2.866(4)	151.9	$H_k(i)$–$H_{k+1}(i)$
22	O3–H···O8	0.82	2.07	2.801(4)	147.7	$G_k(i)$–$G_{k+2}(i-1)$
23	O8–H···O3i	0.82	2.03	2.801(4)	157.7	$G_k(i)$–$G_{k+3}(i-1)$
24	O9–H···O2	0.82	2.06	2.771(3)	144.7	$G_k(i)$–$G_{k+3}(i-1)$

[a] Distance (Å).
[b] Angle (deg).
[c] Code for labeling of components: H = host; G = guest. Index *i* is referred to the *i*th cyclodextrin molecule within a given column. Index *k* indicates the column location. Refer to Scheme 1 for a graphical sketch.

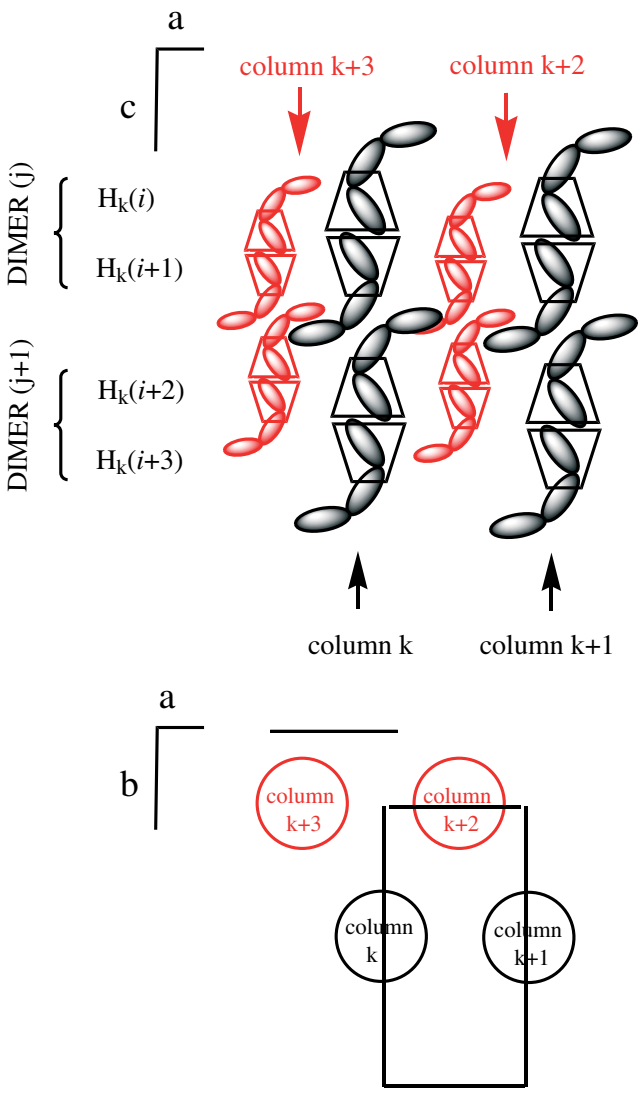
It has been argued that the *gauche*/*trans* orientation is only required by packing reasons or by the formation of a hydrogen bond with the guest molecule. In our case the O6 hydroxyl group oriented toward the cavity displays a strong hydrogen bond between the O6 atom of the B glucose residue of the host (acceptor) and one of the phenolic oxygen (O11, see Fig. 1 for numbering) of the THBA moiety of the guest molecule (donor) [$O6B_{host}\cdots O11_{guest}$ distance: 2.59 Å; $O6B_{host}\cdots H6_{guest}$–$O6_{guest}$ angle: 172.8°]. The same O6 atom of glucose residue B acts as donor in a hydrogen bond of comparable strength with a fully occupied water molecule [O6B···O9W distance: 2.727 Å; O6B···H9W–O9W angle: 160.5°].

A hydrogen bond of the kind $C–H_{host}\cdots O_{guest}$[19] is also detectable between the C3E carbon atom of βCD and one of the phenolic OH of isovanillin ($C3E_{host}\cdots O14_{guest}$ distance: 3.345 Å; C3E–H···O14 angle: 166.8°, see Table 3).

3.2. Crystal packing

The βCD–NDC complex is actually present in the crystal as a dimer. Dimeric units are formed by head-to-head assemblies of CD molecules, each with its guest, and are arranged in columns. A simple sketch of such arrangement is reported in Scheme 1, whilst Figure 3 shows the crystal packing viewed along the *b* direction. Each H–G unit can thus be identified by specifying the column to which it belongs (*k* index, Scheme 1) and the position along the column (*i* index, Scheme 1).

In terms of inclusion properties, the formation of dimeric hosts provides the guest molecules with a large apolar cavity. Their overall volume is larger than the sum of the void volumes of two CDs, as it also includes the void space between the wider rims of the two CD that is confined within the hydrogen-bond network mentioned above. Two guest molecules are located in this extended hydrophobic cavity generating a dimer. Each guest penetrates the cavity with the IVN moiety from the primary hydroxyl groups' rim; the geometry of the inclusion is such that the IVN residues of each dimer are stacked together (mean interplanar separation 3.64 Å). The dimers, in turn, are self-assembled in columns. An overall description of all nonbonded interactions present both within the dimer and among dimers is given in Table 3. The data of Table 3 are organized in a hierarchical way, grouping together the short contacts associated to the formation of the 1:1 complexes, the dimers, the columns of dimers, and the assembly or the columns, respectively. Inspection of data of Table 3 point out that the formation of dimeric units and their assembly in columns is promoted and stabilized by a large repertoire of attractive interactions, also including C–H···O hydrogen bonds (entries 4, 15, 18, and 19), along with the classic hydrophobic host–guest interactions and O–H···O hydrogen bonds. The guest molecule appears to play a key role in the process of packing of the dimeric units. Indeed, the main interactions responsible of the assembly of dimers into columns are host–guest hydrogen bonds [$H_k(i+1)$–$G_k(i+2)$] and guest–guest attractive interactions [$G_k(i+1)$–$G_k(i+2)$]. This is due to the fact that the bulky residues of NDC protruding outside the CD cavity prevent the establishment of host–host interdimer hydrogen bonds involving the primary OH groups of cyclodextrin. These latter interactions have been reported as the main stabilizing factor of some head-to-head dimeric inclusion complexes of βCD with less sterically demanding guest molecules, such as tridecanoic acid,[20] 1,12-dodecandiol,[21] *S*-ibuprofen,[22] and ethanol.[23] Finally, the guest



Scheme 1. Top: sketch of crystal packing of the 1:1 complex in the ac crystallographic plane. The i, $i+1$, $i+2$, $i+3$ sequence is an arbitrary notation used for sequential monomers and does not correspond to crystallographic symmetry translation. The dimeric units are identified by the j index. $H_k(i)$ means the host of the ith monomer within the kth column.

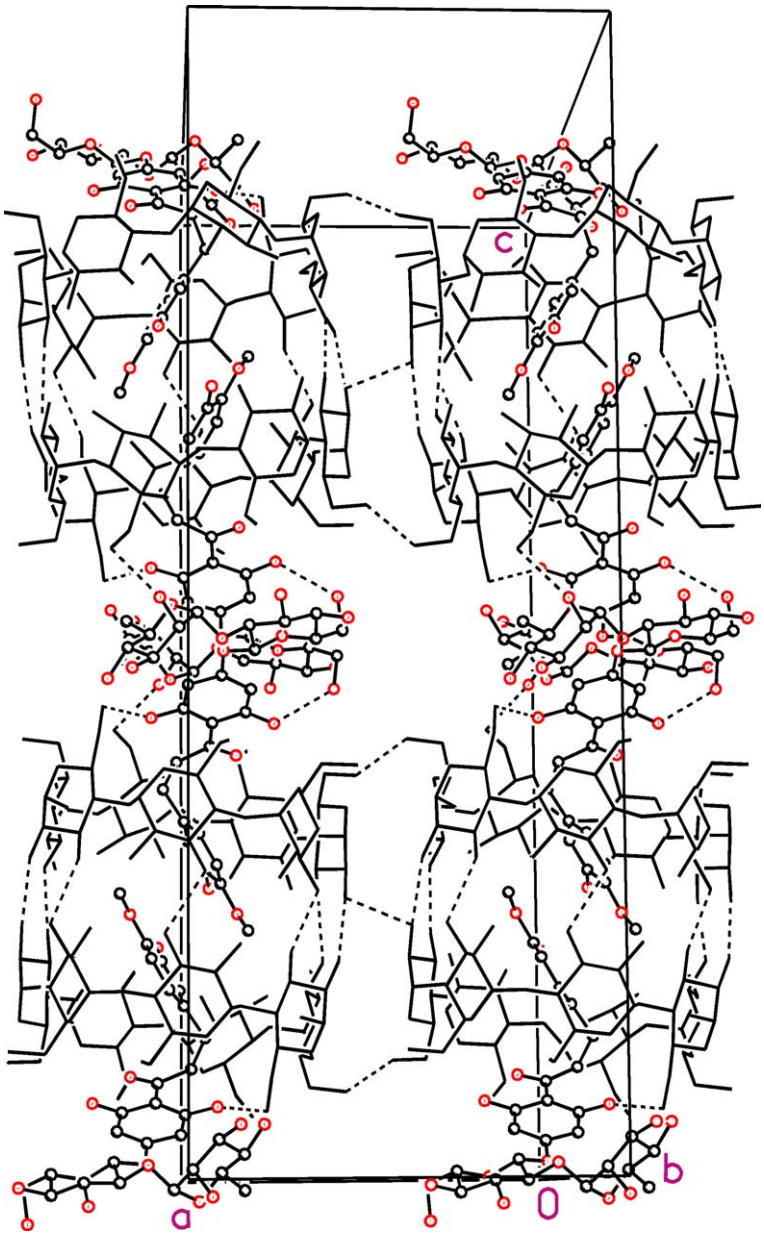


Figure 3. Crystal packing of the complex βCD–NDC. Projection on the *ac* crystallographic plane.

contribution to the assembly of the columns of βCD–NDC dimers is demonstrated by entries 22, 23 and 24 of Table 3, where significant short contacts of type $G_k(i)$–$G_{k+2}(i-1)$ and $G_k(i)$–$G_{k+3}(i-1)$ are highlighted. These contacts correspond to intermolecular hydrogen bonds involving rhamnose (Rha) and glucose (Glc) of different guest molecules.

3.3. Host-induced conformational changes of the guest molecule and consequences on crystal packing

The molecular conformation of the guest molecule is mainly dictated by the values of the torsion angles around the chemical bonds connecting the different residues that is, Rha, Glc, THBA, and IVN, along with the torsions of the freely rotating functional groups, namely primary, secondary, and phenolic OHs, CH_3, and OCH_3. The crystal structure of free NDC, reported in 1986,[24] presented two crystallographically independent molecules, labeled by the authors as A and B, whose key difference was in the values of the torsion angle around the C21–C22 bond (atom numbering according to Fig. 1), −112.9° and 47.1°, respectively, whilst the torsions around C20–C21 are nearly identical (−176.3° and −179.4°, respectively), thus allowing the carbonyl carbon and C22 to arrange in an *anti* relationship. When encapsulated into βCD, NDC assumes a single conformation. The formation of the inclusion

complex forces the guest molecule to rotate the IVN residue around the C20–C21 bond in such a way that the carbonyl carbon and C22 assume a *gauche* relationship (torsion angle around C20–C21 = 60.0°). The *anti* to *gauche* conformational transition is worth of consideration for a number of reasons: (a) the inclusion process is sometimes reported to induce conformational changes in the host molecules, such as macro-ring distortion,[12] or individual glucopyranose ring deviation from the normally observed $^4C_1$ conformation;[25–27] nevertheless, the complementary phenomenon, host-induced conformational change of the guest, was reported only in few cases by NMR spectroscopy in solution[6] and never by direct comparison of crystallographic data. (b) The formulation of a rational model for structure–activity relationships among biologically active molecules such as NDC, commonly used as nonsucrose sweetener, often require detailed knowledge of the populated conformations.[28] Thus any observed change induced by the molecular environment is worthy of attention. (c) The observed conformational transition due to the molecular encapsulation plays a role in the self-assembly of the dimeric units in the channel-type packing. From the point of view of the crystal architecture, the *trans* to *gauche* transition has three main consequences: (i) the IVN residues belonging to the two halves of the same dimeric unit and in the same columns [$G_k(i)$ and $G_k(i+1)$, see Scheme 1] are in the optimum geometry for inclusion into the CD cavity. (ii) The THBA residues are protruding outside the cavity and fill the interdimeric region along the column axis. The THBA residues belonging to consecutive dimeric units [$G_k(i+1)$ and $G_k(i+2)$] are parallel, thus in a conformation with minimum steric repulsion. However, the long distance between the aromatic ring planes (4.6 Å) rules out any significant π–π interactions. (iii) Each β-neohesperidosyl residue is located in the intercolumn void space (Fig. 3) that is outside the hydrophobic channel generated by the self-association of the dimeric units in columns. The disaccharide residues are in a suitable geometry for interacting with both host and guest of the adjacent dimeric unit of the same column [$H_k(i+1)$–$G_k(i+2)$ and $G_k(i+1)$–$G_k(i+2)$] and of different columns [$G_k(i)$–$G_{k+2}(i-1)$ and $G_k(i)$–$G_{k+3}(i-1)$], as discussed in the previous section.

4. Conclusions

The crystal architecture of the βCD–NDC complex can be sketched as a four-step process: (i) the formation of the 1:1 H–G inclusion complex, (ii) the assembly of the complexes in dimeric units, (iii) the formation of columnar structures by head-to-head stacking of the dimers, and (iv) the self-assembly of the columns. Significant interactions of the α-L-rhamnosyl-β-D-glucopyranoside moiety of the guest molecule with βCD are observed, along with intermolecular interactions between the glycan of two different guest molecules. These carbohydrate–carbohydrate interactions provide significant contribution to the crystal packing. The importance of these interactions seems to increase in passing from step (i) to step (iv). The conformational change of the guest due to the complex formation provides optimum geometry for both the inclusion process and the assembly of columns.

Supplementary material

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 230691. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0)12233336033 or e-mail: deposit@ccdc.cam.ac.uk).

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