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The 2,3-anhydro-α-cyclomannin−1-propanol hexahydrate: topography, lipophilicity pattern and solid-state architecture†

Stefan Immel,[a,*] Frieder W. Lichtenthaler,[a] Hans J. Lindner,[a] Kahee Fujita,[b] Makato Fukudome [b] and Yasuyoshi Nogami [c]

[a]*Institut für Organische Chemie, Technische Universität Darmstadt, D-64287 Darmstadt, Germany*
[b]*Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852-8131, Japan*
[c]*Daiichi College of Pharmaceutical Sciences, Tamagawa-cho, Fukuoka 815, Japan*

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Abstract

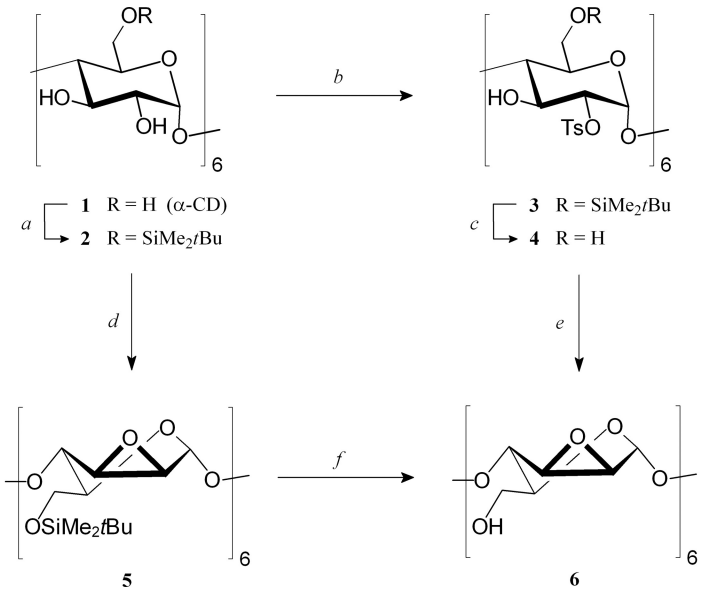
As evidenced by its X-ray structural analysis, 2,3-anhydro-α-cyclomannin **6**, a cyclooligosaccharide consisting of six α-(1→4)-linked 2,3-anhydro-D-mannopyranose units, readily incorporates 1-propanol into its cavity such that hydrophobic and hydrophilic surface regions of guest and host match at their interfaces. Together with water, the macrocycle and its guest assemble into a unique solid-state architecture, featuring layers of head-to-head dimers of the macrocycle with its guest, separated by equally distinct layers of water molecules, which are engaged in an intense hydrogen bonding network with the 6-CH_2OH and the propanol-OH groups. The overall guest–host topography is thus reverse to that of the respective ethanol inclusion complex.[1]

1. Introduction

2,3-Anhydro-α-cyclomannin **6**,[2] a cyclooligosaccharide composed of six α-(1→4)-linked 2,3-anhydro-D-mannopyranose units, is readily accessible from α-cyclodextrin via simple reaction sequences, the key steps being — in the 6-*t*-butyldimethylsilyl-blocked α-CD **2**[3] — the selective sulfonation of the more acidic 2-OH and subsequent displacement of the 2-sulfonyloxy groups by the vicinal 3-OH to elaborate the oxirane rings. Of the two protocols that have been advanced for this conversion,[4,5] the one allowing sulfonation and epoxide formation to proceed in a one-pot operation, i.e. **2**→**5**, appears to be preparatively more propitious (44% overall yield for **1**→**6**[5]) than the other performing sulfonation (**2**→**3**) and generation of the oxirane ring (**4**→**5**) in separate operations (19% for **1**→**6**[4]) (Scheme 1).

* Corresponding author. E-mail: lemmi@sugar.oc.chemie.tu-darmstadt.de

† Part 26 of the series Molecular Modelling of Saccharides. For Part 25, see Immel et al.[1]



Scheme 1. Key: (a) *t*BuMe$_2$SiCl/imidazole, DMF, 75%;[3] (b) TsCl/DMAP, pyridine, 55%;[4] (c) $BF_3 \cdot Et_2O$, $CHCl_3$, 51%;[4] (d) NaH/DMF, then $C_6H_5SO_2Cl$, 64%;[5] (e) K_2CO_3, MeOH, 90%;[4] (f) Bu_4NF, THF, 92%[5]

Thus, unlike other non-glucose cyclooligosaccharides with α-(1→4)-linked hexose units,[6–8] 2,3-anhydro-α-cyclomannin is available in sufficient amounts to broadly study its molecular recognition properties, and in particular its capability to form inclusion complexes. Indeed, when recrystallized from aqueous ethanol, **6** was shown to accumulate as a hydrate with ethanol included in its cavity (Fig. 1, left entries).[1] The three crystal engineering entities — **6**, ethanol, and water — assemble to a unique superstructure in the solid-state, characterized by layers of head-to-head dimers of the macrocycle, stabilized by OH···OH hydrogen bonding between the cavity-included guest–ethanol molecules, followed by layers of water. The crystal engineering operative is unusual in that the hydrophilic and hydrophobic surface regions at the guest–host interface are non-complementary as the guest's OH group is placed at the hydrophobic, epoxide ring-carrying rim of the macrocycle.[1] This behavior is strongly contrasted by various inclusion complexes of the cyclodextrins of which the lipophilicity profiles have been determined,[9,10] as they reveal the guest–host matching of hydrophilic and hydrophobic surface regions to be a decisive factor for the orientation of the guest in the cavity.

We wish to report here the peculiar finding that simply by enlarging the guest molecule by a CH_2 group, i.e. by including 1-propanol instead of ethanol into the cavity of 2,3-anhydro-α-cyclomannin, the self-assembly of the three crystal engineering components — **6**, 1-propanol, and water — leads to a distinctly different solid-state architecture (Fig. 1, right entries), the guest now having the inverse orientation in the cavity, i.e. one in which hydrophobic and hydrophilic surface areas at the guest–host interface are complementary.

2. Results and discussion

2,3-Anhydro-α-cyclomannin **6**, when recrystallized from aqueous 1-propanol, accumulated as its 1-propanol inclusion complex of which the X-ray analysis, invited by the high crystallinity of the product, revealed it to be a hexahydrate. The geometry of the complex (Fig. 1, right entries) unfolds a high degree of regularity, with the backbone of the macrocycle best approximated by six-fold rotational symmetry

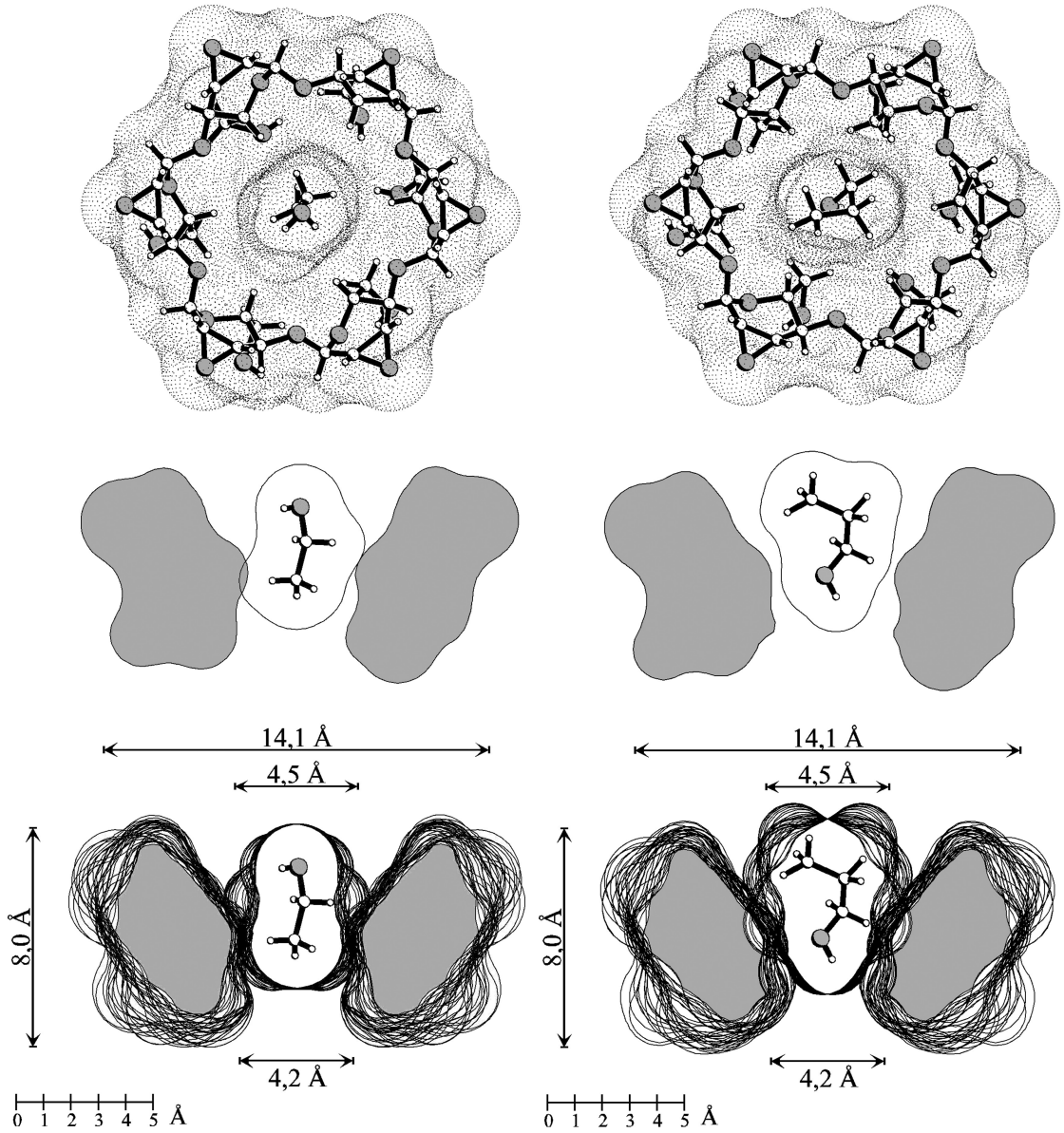


Fig. 1. Comparison of the inclusion complexes of 2,3-anhydro-α-cyclomannin **6** with ethanol[1] (left) and 1-propanol (right), clearly showing the inverse orientation of the guests in the macrocyclic cavity. Top: solvent-accessible surfaces in dotted form, with the oxirane rings pointing towards the front and the 6-CH_2OH groups to the rear; disordered atomic positions and water molecules of crystallization have been left off for clarity. Center: single surface slice through the complexes to visualize the opposite mode of inclusion of ethanol and 1-propanol (approx. molecular dimensions in Å; the 6-CH_2OH groups point downward). Bottom: superimposed surfaces cross-section cuts obtained from stepwise 10° rotation around the center of geometry (only one ball-and-stick model of the guest molecule is shown)

(C_6). All epoxide rings are lined up on the larger aperture of the cone-shaped molecule with their oxygens directed towards the outside of the macro-ring. The overall shapes of the macrocycle and the hexose residues are almost identical to the geometry realized in the ethanol complex;[1] some geometry parameters are listed and compared for both inclusion complexes in Table 1. On the basis of the Cremer–Pople

ring puckering parameters,[11] the pyranose rings invariably adopt $^{O}H_5$ half-chair conformations with very small fluctuations in the *endo*- and *exo*-cyclic torsion angles. In the propanol complex, the 6-CH_2OH groups adopt *gauche–trans* and *gauche–gauche* conformations with statistical weights of 2:4. As illustrated by the solvent-accessible surface (Fig. 1) and, more lucidly, by the space-filling model (Fig. 2, left) and the side-view plots, the propanol guest is fully immersed into the host, with its OH group located next to the six CH_2OH groups at the narrow opening of the conically shaped cavity.

Table 1
Cremer–Pople ring puckering parameters,[11] pyranose conformations, and some selected torsion angles in the crystal structure of the 2,3-anhydro-α-cyclomannin–1-propanol complex (**6**·PrOH·6H_2O) as compared to those of the corresponding ethanol complex (**6**·EtOH·3.5H_2O)[1]

	6 · PrOH · 6 H_2O [a]	**6** · EtOH · 3.5 H_2O [a]
Cremer-Pople parameters		
Q [Å]	0.498 (0.02)	0.488 (0.02)
θ [°]	51.3 (3.0)	51.1 (2.6)
ϕ [°]	335.7 (6.4)	337.8 (4.9)
pyranose conformation	$^{O}H_5$	$^{O}H_5$
ring torsion angles [°]		
O5-C1-C2-C3	19.1 (4.3)	20.2 (4.0)
C1-C2-C3-C4	0.5 (3.9)	0.5 (3.4)
C2-C3-C4-C5	11.8 (3.2)	10.7 (3.2)
C3-C4-C5-O5	-43.1 (3.3)	-41.0 (2.5)
C4-C5-O5-C1	69.3 (2.1)	67.2 (1.6)
C5-O5-C1-C2	-55.6 (3.5)	-55.4 (3.2)
other torsions		
O1-C1-C2-O2	-170.9 (2.8)	-170.5 (2.5)
O5-C1-C2-O2	-48.9 (4.3)	-46.4 (3.4)
O5-C5-C6-O6	82 (14)[b,c]	69.5 (5.7)[b,d]
	-66.4 (6.7)[b,c]	-59.2 (3.7)[b,d]

[a] Parameters averaged over six pyranose units with root-mean-square (RMS) deviations in parenthesis; [b] independently averaged values for the *gauche-trans* (*gt*, $\omega \approx +60°$) and *gauche-gauche* (*gg*, $\omega \approx -60°$) arrangements of the 6-CH_2OH groups; [c] statistical weights *gt* : *gg* = 2 : 4; [d] *gt* : *gg* = 3 : 3.

In the crystal lattice, the 2,3-anhydro-α-cyclomannin–propanol inclusion complex forms architecturally intricate layered structures: two guest–host macrocyclic units are 'fused together' to head-to-head dimers with the wider, oxirane ring-bearing sides facing each other, and each of these dimeric units is separated by a layer of water molecules (Fig. 3). Table 2 lists a selection of intermolecular non-hydrogen-bonding distances between heavy atoms of the crystal components, indicating the close contacts between the macrocycles in each layer, and particularly between the O-2 and C-2 atoms of stacked 2,3-anhydro-α-cyclomannins. The guest is held in the cavity by van der Waal's contacts to the host's O-1, 3-CH, and 5-CH groups, and the C-2 and C-3 atoms of two symmetry related 1-propanol molecules in the dimer approach each other to about 2.8–2.9 Å (cf. Table 2).

The crystal structure is characterized by an intense network of intermolecular hydrogen bonding interactions between the 6-hydroxyls of the macrocycle, 1-propanol, and water, with only one intramolecular H-bond of the 6-OH···O-6 type being realized; Table 3 gives a list of these hydrogen bonds and Fig. 4 provides a schematic drawing of the three-dimensional network of interactions which determine the crystal architecture. Most notably, the 1-propanol guest is not engaged in hydrogen bonding to the pyranose 6-CH_2OH groups, but forms a distinct H-bond towards a water molecule (labeled OW4 in Fig. 4).

In this respect, the crystal structure of the **6**·PrOH complex is entirely different to the one observed

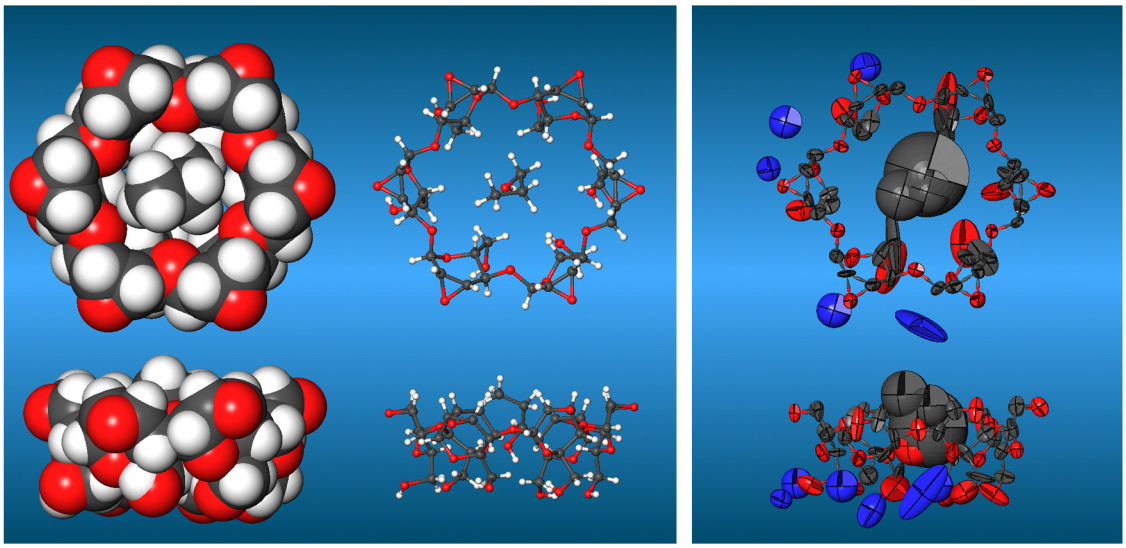


Fig. 2. Left: solid-state molecular geometry of the 2,3-anhydro-α-cyclomannin–1-propanol complex (**6**·PrOH·6H_2O) in space-filling (CPK) form and as a ball-and-stick model. The inclusion complex is shown perpendicular (top) and parallel (bottom) to the ring plane of the macrocycle (water molecules of crystallization are omitted for clarity). Right: anisotropic thermal 50% probability ellipsoids for all non-hydrogen atoms (water oxygens in blue; the 1-propanol oxygen is hidden behind the disordered carbon atoms of the guest) in the asymmetric unit of the crystal structure

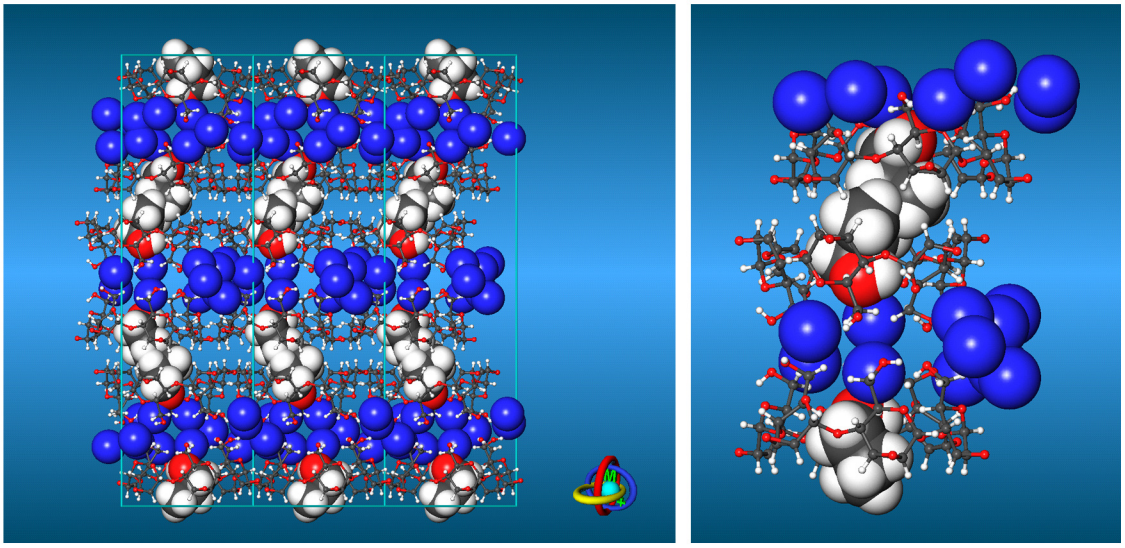


Fig. 3. Left*:* in the crystal lattice, the 2,3-anhydro-α-cyclomannin–1-propanol hexahydrate forms three layers of head-to-head arranged dimers, i.e. a total of six stacked macrocycles per unit-cell in the direction of the *c*-axis of the trigonal space group $P3_212$ (view down the *b*-axis). The crystal water molecules (shown as blue spheres) likewise form distinct layers alternating with those of dimeric macrocycles, this unique crystal engineering obviously being effected by an intense hydrogen-bonding texture with the primary 6-OH groups of the macrocyclic host and the 1-propanol-OH. Right: section cut, illustrating in more detail the intricate assembly of the three crystal engineering components

Table 2
Selected intermolecular (non-hydrogen bonding) heavy atom distances in solid-state structure of the 2,3-anhydro-α-cyclomannin–1-propanol complex (**6**·PrOH·6H_2O); labeling of the mannose units corresponds to Fig. 4, additional parameters on host–water distances are listed in Table 3

distances (d<3.35 Å)	d [Å]	symmetry	distances	d [Å]	symmetry
host-host (layered):[a]			**host-guest:**		
C(4D) ··· O(2A)	3.337	c	O(1G) ··· C(6E)	3.355	h
O(2E) ··· C(1A)	3.324	d	O(1G) ··· C(5E)	3.680	h
O(2B) ··· C(1D)	3.178	e	O(1G) ··· C(5A)	3.942	h
C(3B) ··· O(2E)	3.213	e	C(1G) C(5B)	3.459	h
O(2B) ··· C(3E)	3.254	e	C(1G) ··· C(6B)	3.921	h
O(2B) ··· C(4E)	3.286	e	C(1G) ··· O(1A)	3.555	h
C(4B) ··· O(2E)	3.330	e	C(1G) ··· O(1B)	3.734	h
C(3C) ··· O(2F)	3.153	f	C(2G) ··· O(1C)	3.947	h
O(2C) ··· C(3F)	3.186	f	C(3G) ··· C(2D)	3.511	h
C(4C) ··· O(2F)	3.191	f	C(3G) ··· C(3D)	3.513	h
O(2C) ··· C(4F)	3.205	f	C(3G) ··· O(1D)	3.828	h
C(1B) ··· O(2F)	3.349	f			
host-host (stacked):			**guest-guest:**		
O(2A) ··· C(2A)	3.296	g	C(2G) ··· C(2G)	2.788	h
O(2A) ··· O(2A)	3.297	g	C(2G) C(3G)	2.922	h
			C(3G) ··· C(3G)	2.991	h

[a] Atomic distances between 2,3-anhydro-cyclomannins contained in the same layer. Symmetry operations: [b] x,y,z; [c] x,y-1,z; [d] x+1,y,z; [e] x-1,y,z; [f] x-1,y-1,z; [g] x,x-y,-z; [h] x,x-y+1,-z.

for the respective ethanol inclusion compound (cf. Fig. 4, bottom left), which displays a hydrogen bond between the ethanol molecules trapped inside the dimeric cavity.

The unique packing features become more comprehensible on analyzing the molecular lipophilicity patterns (MLPs) of guest and host. Their generation with the MOLCAD program[12] and their visualization by projection onto the contact surface of Fig. 2 in color-coded form[13] results in Fig. 5, clearly showing the macrocycle to have its most hydrophobic (yellow) areas at the wider, oxirane ring-carrying opening of the torus, obviously due to the 2-H and 3-H ring protons of the sugar units forming its rim. The hydrophilic (blue) domains are centered on the opposite side around the 6-hydroxyl groups. Thus, the lipophilicity distribution in **6** is strikingly different from that manifested in the native cyclodextrins,[9,14] where the wider 2-OH/3-OH side of the respective macrocycles is distinctly hydrophilic versus the pronouncedly lipophilic domains at the opposite, narrower 6-CH_2OH side and inside the cavity.

3. Conclusion

The solid-state structure of the 2,3-anhydro-α-cyclomannin–1-propanol hexahydrate detailed here, and the respective ethanol inclusion complex unraveled previously,[1] provide unique examples of the subtle intricacies operative in the crystal engineering. The three components involved — a cyclooligosaccharide, an alcohol, and water — self-assemble to substantially different superstructures by enlarging the alcohol component to be enclosed in the cavity by as little as one CH_2 group (cf. Fig. 4, bottom part). Obviously due to the fact that 1-propanol can fill out the hydrophobic, oxirane-carrying section of the macrocycle's cavity better than ethanol (cf. Fig. 1), it is included in such a way that hydrophobic and hydrophilic surface regions match at the guest–host interface (Fig. 5). The smaller ethanol occupies the cavity in an inverse way, whereby the non-complementarity in non-polar guest–host interactions is counterbalanced by the establishment of hydrogen-bonding between the cavity-inserted ethanol-OHs. The factors underlying this enthralling interplay of steric, polar, and non-covalent interactions between such

Table 3
Hydrogen bond patterns in the solid-state structure of the 2,3-anhydro-α-cyclomannin–1-propanol complex (**6**·PrOH·6H_2O), listed for distances d(H···O)<2.5 Å and/or d(O···O)<3.5 Å only; the water molecules are labeled OW1–OW6, the mannose labeling A–F and the indices given in italics in the first column correspond to Fig. 4

no. (cf. Fig. 4)	hydrogen bond	d(H···O) [Å][a]	d(O···O) [Å]	φ(O···O) [°][a]	symmetry
intramolecular host-host hydrogen bonds:					
1	O(6D) ··· O(6C)	-	3.093	-	[b]
intermolecular host-host hydrogen bonds:					
2	O(6A) ··· O(6B)	-	3.012	-	[c]
3	O(6F) ··· O(6C)	-	2.654	-	[c]
4	O(6E) ··· O(6E)	-	3.251	-	[c]
5	O(6E) ··· O(6D)	-	3.001	-	[c]
host-water hydrogen bonds:					
6	O(6A) ··· O(W5)	-	2.804	-	[b]
7	O(6A) ··· O(W3)	-	3.039	-	[b]
8	O(6C) ··· O(W4)	-	3.202	-	[b]
9	O(6D)H ··· O(W4)	2.252	2.890	134.9	[b]
10	O(6E) ··· O(W6)	-	3.372	-	[b]
11	O(6F)H ··· O(W1)	2.057	-	141.7	[b]
12	O(6B) ··· O(W2)	-	3.391	-	[d]
13	O(6B)H ··· O(W1)	2.475	3.093	132.6	[c]
14	O(6B)H ··· O(W3)	2.421	2.710	101.7	[c]
15	O(6A) ··· O(W5)	-	2.803	-	[c]
16	O(6D) ··· O(W2)	-	3.305	-	[c]
guest-water hydrogen bonds:					
17	O(1G)H ··· O(W4)	1.653	2.531	172.0	[b]
water-water hydrogen bonds:					
18	O(W1) ··· O(W3)	-	2.660	-	[b]
19	O(W1) ··· O(W6)	-	3.012	-	[e]
20	O(W3) ··· O(W6)	-	2.793	-	[e]
21	O(W2) ··· O(W5)	-	3.172	-	[f]
22	O(W2) ··· O(W5)	-	3.171	-	[g]
23	O(W1) ··· O(W6)	-	3.397	-	[h]

[a] Hydrogen bond H···O-distances and O-H···O-angles omitted if hydrogen atoms were not located explicitly. Symmetry operations: [b] x,y,z; [c] -y-1,-x-1,-z+1/3; [d] x-1,y,z; [e] x,y+1,z; [f] x+1,y,z; [g] -y,-x-1,-z+1/3; [h] y-1,-x,-z+1/3.

structurally incomparable crystal engineering components as water, a non-glucose cyclooligosaccharide, and a suitable guest are being further studied with the aim to eventually understand their intricacies.

4. Experimental

2,3-Anhydro-α-cyclomannin **6**[2] was prepared in a three-step procedure from α-cyclodextrin **1** involving protection of its six primary hydroxyl groups by the *t*-butyl-dimethylsilyl group (**1**→**2**[3]), followed by per-sulfonation at *O*-2 with benzenesulfonyl chloride/NaH in DMF (→**5**), and tetrabutylammonium fluoride-promoted desilylation.[5] A 30 mg sample of the resulting product — presumably the methanol inclusion compound due to its precipitation from methanol[1] — was suspended in 1 mL of 2:1 water:1-propanol, followed by brief warming to 60°C to effect dissolution, filtration through a membrane filter (TOSOH, H-13-2), and subsequent standing of the filtrate at ambient temperature for several days. This resulted in the generation of well-formed crystals having m.p. 267°C (decomp.) and $[\alpha]_D^{20}$=+83

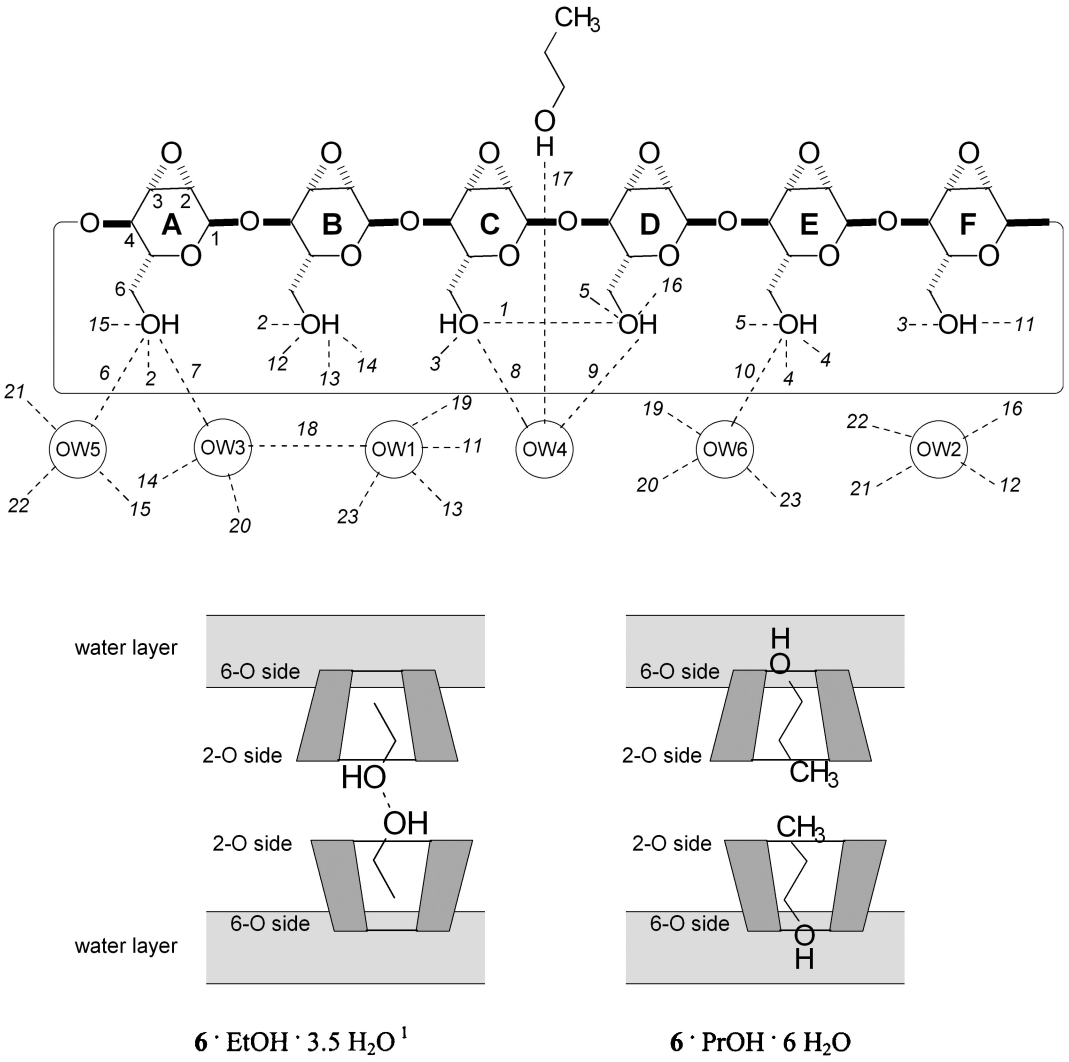


Fig. 4. Top: schematic drawing of the hydrogen-bonding pattern in the 2,3-anhydro-α-cyclomannin–1-propanol hexahydrate crystal structure. The pyranose residues are labeled A–F and the water positions OW1–OW6. The numbers in italics correspond to the indices given in Table 3; 'open-ended' dashed lines indicate H-bonds formed between symmetry-related positions. The cavity-inserted 1-propanol-OH forms a single hydrogen bond to a water molecule (OW4), yet none to the host's 6-CH_2OH groups. Bottom: comparative sketch of the opposite directional modes with which ethanol (left[1]) and 1-propanol (right) are embedded into the macrocyclic cavity, resulting in distinctly different interactions with the respective water layers

(*c* 0.3, DMSO). The analytical sample, vacuum dried over P_2O_5 for 1 d, analyzed for the dihydrate $C_{36}H_{48}O_{24}\cdot C_3H_7OH\cdot 2\ H_2O$ (960.86): calcd. C, 48.75; H, 6.29; found C, 48.55; H, 6.20.

The prismatic crystal used for the X-ray structure analysis, of the dimensions 0.25×0.25×0.1 mm, turned out to be a hexahydrate: $C_{36}H_{48}O_{24}\cdot C_3H_7OH\cdot 6\ H_2O$, M_r=1032.95, trigonal, space group $P3_212$, $a=b$=14.105(2), c=41.787(6) Å, V=7199(18) Å^3, Z=6, ρ=1.402 g cm^{-1}, $\mu(Mo_{K\alpha})$=0.080 mm^{-1}, T=293(2) K. A total of 5018 reflections were collected on an Enraf–Nonius CAD-4 diffractometer using graphite-monochromated $Mo_{K\alpha}$ (λ=0.71093 Å) radiation, of which 4761 were independent (R_{int}=0.1004). The structure was solved by direct methods (SHELXS-97[15]) and successive Fourier difference syntheses. Refinement (on F^2) was performed by full-matrix least squares method with

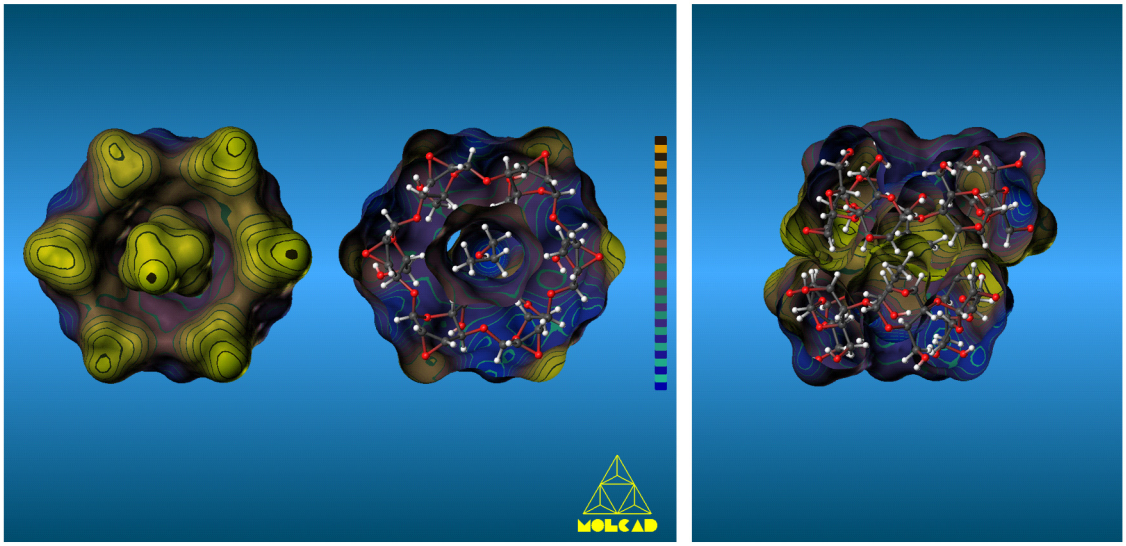


Fig. 5. Molecular lipophilicity patterns (MLPs) of the 2,3-anhydro-α-cyclomannin−1-propanol inclusion complex: the relative hydrophobicity of guest and host was mapped in color-coded form onto their individual contact surfaces, with the colors ranging from dark blue (most hydrophilic areas) to yellow–brown (hydrophobic domains). Computation and scaling of the MLPs was done separately for the guest and host, followed by reassembly of the complex. Left: view onto the wider opening of the macrocycle with the six oxirane rings, displaying the hydrophobic (yellow) side. The front-opened version *(*center) with the ball-and-stick model insert exposes the distinctly hydrophilic (blue) rear side bearing the 6-CH_2OH groups. Right: MLP of one head-to-head dimeric unit, 'fused together' via their hydrophobic oxirane ring-carrying faces; in the crystal lattice these dimers assemble in horizontal layers that are enclosed on either of their hydrophilic 'tails' by layers of water

SHELXL-97.[15] $R(F)$=0.0817 for reflections with $I \geq 2\sigma I$, $\omega R(F^2)$=0.2822 for all 4761 reflections with $\omega=1/(\sigma^2(F_o^2)+(0.1584\,P)^2+0.00\,P$, where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms except for the 1-propanol carbon atoms were refined anisotropically, 1-propanol was refined as a rigid body molecule; hydrogen atoms on the 2,3-anhydro-α-cyclomannin were considered in calculated positions with the $1.2\times U_{eq}$ value of the corresponding bound atom. All hydroxyl groups were treated as idealized HO groups, the hydroxyl proton of 1-propanol was subsequently positioned geometrically.

Crystallographic data for the **6**·1-propanol hexahydrate have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-138832. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

5. Computational details

Calculation of the molecular contact surfaces and the respective hydrophobicity potential profiles (MLPs) was performed using the MOLCAD molecular modeling program.[12,13] Scaling of the MLP profiles was performed in relative terms (most hydrophilic to most hydrophobic surface regions) and no absolute values are displayed. Molecular Graphics were generated using MolArch$^+$.[16]

Acknowledgements

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2. As outlined previously,[1] we prefer the term 2,3-anhydro-α-cyclomannin[1,5] for **6** rather than *cyclo*-α-1,4-hexamanno-2,3-epoxide,[4] or cyclohexakis-(1→4)-2,3-anhydro-α-D-mannopyranosyl (systematic name required by IUPAC recommendations of *Carb. Res.* **1997**, *297*, 79, Rule 2-Carb-37.4.2), which is not only less handy, but inconsequential, since **6** is not a series of 'glycos*yl*s', but a glycos*ide* — a hexasaccharide in fact.
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