Effect of peracetylation on the conformation of γ-cyclodextrin†

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The well-known, fourfold symmetry of the γ-CD molecule in its solid inclusion complexes is lost on peracetylation, which yields a highly distorted host molecule in which self-inclusion of acetyl residues divides the macrocyclic cavity into two distinct sub-cavities that accommodate solvent molecules.

Derivatisation of a native cyclodextrin (CD) renders it more specific in its action as a solubiliser, a drug carrier or a catalyst.[1] CD derivatives are employed as carriers to increase the solubility of poorly water-soluble drugs or to impart controlled release properties in pharmaceutical dosage forms.[2] Peracylation of parent CDs, for example, produces hydrophobic derivatives with potential use as bio-absorbable sustained-release carriers for hydrophilic drugs.[3] Such chemical modification of a parent CD molecule is expected to induce significant conformational changes, since it not only eliminates the intramolecular $O2\cdots O3'$ hydrogen bonding responsible for maintaining the 'round' shape of the parent molecule, but should also induce severe tilting of the glucose residues through steric congestion of acyl residues, especially those on the more crowded host secondary rim. Furthermore, peracylation is likely to modify the inclusion ability of the parent CD significantly.

Macrocyclic distortion resulting from acylation was recently reported for the series of host molecules heptakis(2,3,6-tri-*O*-acetyl)-β-CD (TAβCD), heptakis(2,3,6-tri-*O*-propanoyl)-β-CD (TPβCD), and heptakis(2,3,6-tri-*O*-butanoyl)-β-CD (TBβCD).[4] Single-crystal X-ray analyses of these β-CD derivatives revealed that in both TAβCD and TPβCD, one glucose unit adopts the highly strained $^0S_2$-skew-boat conformation and an acyl chain blocks the O6 side, while in TBβCD, though all seven glucose units adopt the common $^4C_1$-conformation, there is self-inclusion of a single butanoyl chain in the host cavity. Tests of the inclusion ability of these host molecules in ethanolic solution were negative, a result attributed to both their low aqueous solubility and the intramolecular inclusion of acyl chains. Furthermore, no solvent of crystallization was located within the macrocyclic cavities.

In a recent study investigating the thermal and structural properties of hexakis(2,3,6-tri-*O*-acetyl)-α-CD (TAαCD), heptakis(2,3,6-tri-*O*-acetyl)-β-CD (TAβCD), and octakis(2,3,6-tri-*O*-acetyl)-γ-CD (TAγCD),[5] Bettinetti *et al.* discovered that these novel substituted CDs display a rich solid-state chemistry. Numerous forms of each host molecule, including amorphs, solvates and polymorphs, were isolated and characterized, and the thermodynamic stability relationships amongst these forms were established. The availability of single-crystal X-ray data for TAαCD[6] and TAβCD[4] proved useful in the interpretation of thermal and X-ray powder diffraction (XRPD) data for species containing these host compounds, but the lack of solid-state structural information for TAγCD (Fig. 1) limited the discussion of analogous data for solid forms derived from this host.

We have crystallized the inclusion compounds TAγCD$\cdot$2EtOH$\cdot$H$_2$O **1** and TAγCD$\cdot$1$\cdot$5Pr^{i}OH$\cdot$H$_2$O **2**, representative members of a series of isostructural solvated forms of TAγCD, and report here the first single-crystal X-ray structures containing this host. A unique feature of the TAγCD molecule is the partitioning of the macrocyclic cavity by self-inclusion of acetyl residues, into two distinct sub-cavities that are filled with solvent molecules.

The space group $P42_12$ characterizes the parent CD in its inclusion complexes,[7] the 'round' shape of the γ-CD molecule, maintained by $O2\cdots O3'$ hydrogen bonds, being compatible with its location on the crystallographic fourfold rotation axis. Compounds **1** and **2** instead crystallize in the tetragonal space group $P4_12_12$,‡ with the TAγCD molecule occupying a general position in this space group due to the severe conformational distortion induced by acetylation. The stereoview in Fig. 2 shows the structure and conformation of the host in **1** (as representative) viewed from the primary side, with the eight, fully acetylated glucose rings labelled A-H and the solvent molecules removed for clarity.

Examination of glucose residues A–H shows that six of them adopt conformations that are very close to the regular chair form ($^4C_1$), but both rings B and D adopt $^0S_2$-skew-boat conformations, with the substituents at C2 and C3 in a pseudo-axial relation. For

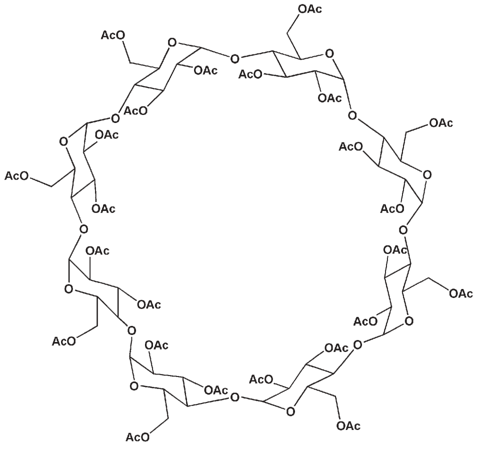

Fig. 1 Chemical structure of peracetylated γ-cyclodextrin.

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† Electronic supplementary information (ESI) available: DSC and TG data for a series of five TAγCD solvates. See DOI: 10.1039/b616681d

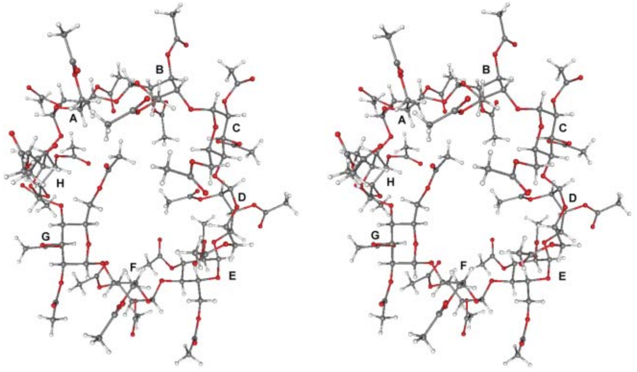

Fig. 2 Stereoview of the structure of TAγCD in compound **1**.

both rings, the acetyl group associated with C2 enters the macrocyclic cavity ('self-inclusion') while that associated with C3 is directed away from the cavity. In ring G, displaying the most severe 'tilt' with respect to the glycosidic O4-octagon, the substituent –CH_2–O–CO–CH_3 on the primary rim adopts the very unusual staggered conformation,[4] accounting for significant 'self-inclusion'. The only evidence of molecular disorder is that of the acetyl group on the primary face of ring H, which occupies two orientations with equal probability (Fig. 2).

The O4-octagon in TAγCD is shown in Fig. 3, drawn as a side-view perspective (top) and normal to the mean plane (bottom) using the refined atomic coordinates of O4A–O4H. A least-squares plane calculation yields deviations ranging from −0.662(2) Å for O4H to +1.076(2) Å for O4F. The distinctly concave surface generated contrasts strongly with the nearly planar O4-octagon occurring in parent γ-CD complexes where the deviations are of the order of only 0.2 Å.[7] Further indications of severe distortion following peracetylation include the wide distance ranges for O4$\cdots$O4′ (Fig. 3), for the octagon centroid$\cdots$O4 distances (4.761–6.248 Å) and for the O4$\cdots$O4′$\cdots$O4″ angles (115.2–143.2°).

Self-inclusion of the acetyl groups of rings B, D and G divides the macrocyclic cavity into two voids (stereoview, Fig. 4), one near the host primary side, accommodating an ethanol molecule, and one near the secondary side that is occupied by the second ethanol molecule and a water molecule. The former EtOH molecule is tethered to the host molecule *via* bifurcated hydrogen bonds (OH$\cdots$O4C, OH$\cdots$O2D with O$\cdots$O 2.93(1) and 3.27(1) Å, respectively). In the second void, the water molecule accepts a hydrogen bond from the EtOH molecule (O$\cdots$O 3.14(1) Å) and acts as donor to acetyl oxygen atom O11E and atom O8C of a symmetry-related host molecule (inferred from O$\cdots$O distances of 3.13(1), 3.23(1) Å, respectively). Solvent molecules are enclathrated within their respective sub-cavities by acetyl residues from neighbouring molecules abutting the host primary and secondary faces.

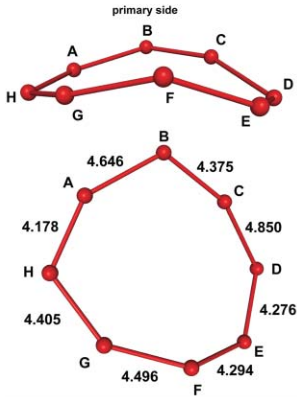

Fig. 3 Views of the O4-octagon (distances in Å).

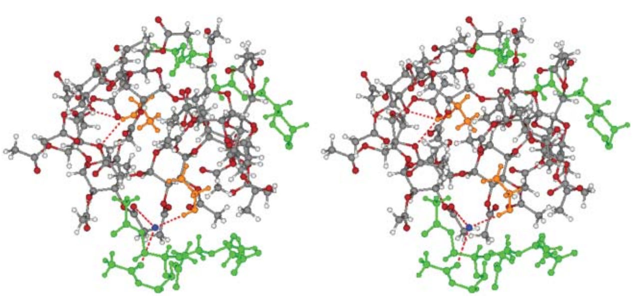

Fig. 4 Stereoview of compound **1** (EtOH molecules = orange; H_2O oxygen atom = blue; atoms from neighbouring TAγCD molecules = green).

Compounds **1** and **2** display a high degree of isostructurality. An overlay of the respective host molecules is shown in Fig. 5. In compound **2**, the 2-propanol and water molecules occupy analogous positions to those occupied by the solvent molecules in **1**, with the differences that the 2-propanol molecule located near the host primary side in **2** is present at half-occupancy and its hydroxyl group engages in bifurcated hydrogen bonding to acetyl carbonyl atoms O13C and O15C. Refinement of this 2-propanol molecule with full occupancy yielded abnormally high U_{iso} values (average 0.30 Å^2). When the site-occupancy was set at 0.5, the average refined U_{iso} (0.16 Å^2) was comparable with those for the second 2-propanol molecule and the water molecule (0.15 and 0.16 Å^2, respectively). This model is also consistent with the TG data that indicated one water molecule and 1.5 2-propanol molecules per host molecule.† This result may indicate more hindered inclusion at the primary side for the sterically more bulky 2-propanol molecule relative to the EtOH molecule in **1**.

The isostructurality of **1** and **2**, unequivocally established by single crystal X-ray analysis, is reflected in very close correspondence of their XRPD patterns, which in turn correspond with those for solvates of TAγCD containing acetone, *n*-propanol, and ethanol (see ESI data).[5] Fig. 6 and 7 show the experimental and

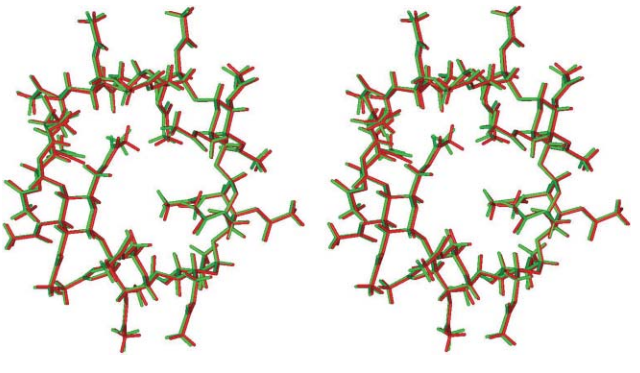

Fig. 5 Overlay of the host molecules in **1** (red) and **2** (green). For clarity, the red image was slightly displaced to the right following the LS fit.

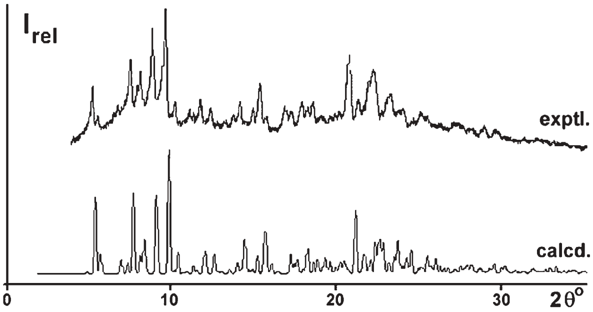

Fig. 6 Experimental and computed XRPD patterns for **1**.

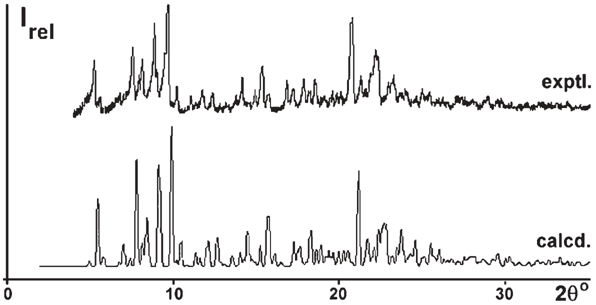

Fig. 7 Experimental and computed XRPD patterns for **2**.

computed XRPD patterns for **1** and **2**, respectively (Cu-Kα radiation, λ = 1.5418 Å). The level of agreement in each case is convincing evidence that the single crystals are representative of the respective bulk phases. A general shift of the computed peaks to higher 2θ values is due to the shrinkage of the unit cells at the low temperature of X-ray data collections.

All of these isostructural species show biphasic desolvation profiles in thermal analysis. For compounds **1** and **2**, containing water, TG and DSC data indicate loss of this solvent as the first step. This observation can be reconciled with the somewhat weaker hydrogen bonds involving the included H_2O molecules (range 3.01(2)–3.23(1) Å), as well as the small size of the water molecule which facilitates its diffusion out of the crystal. For the isostructural solvates containing only acetone, *n*-propanol or ethanol molecules, we attribute the observed biphasic desolvation to their accommodation within distinct micro-environments analogous to those identified in crystals of **1** and **2**.

The common host conformation observed in this isostructural series of compounds, featuring distinct sub-cavities, strongly suggests that in its interaction with guest molecules larger than those reported here, the host TAγCD molecule could engage in 'bi-inclusion', accommodating the same or different moieties from two guest molecules entering from the primary and secondary sides. Studies of the affinity of TAγCD for larger guest molecules are underway in our laboratory.

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Notes and references

‡ TAγCD (10.0 mg) purchased from Cyclolab (Budapest, Hungary) was added to 3.0 mL of aqueous ethyl alcohol (96.4% by wt EtOH) pre-heated to 60 °C. The suspension was stirred for 2 h at 60 °C during which time all of the TAγCD dissolved. The hot solution was filtered (0.45 μm) into a clean vial and allowed to cool spontaneously to room temperature. Colourless, prismatic crystals of solvate **1** appeared after one day.

Preparation of **2** and the other solvates of TAγCD is described in ref. 5. Prior to X-ray analysis, solvent content in the crystals of **1** and **2** was determined by TG analysis (triplicate measurements) using 4–7 mg samples in alumina crucibles heated on a Mettler Toledo TG/SDTA 851e system (β = 10 K min^{-1}) under nitrogen gas purge at a flow rate of 30 mL min^{-1}. Intensity data for both crystals were collected on a Nonius Kappa CCD diffractometer. The structure of **2** was solved using program SHELXD[8] and that of **1** by isomorphous replacement using the host atom coordinates of **2**. Two ethanol molecules and one water molecule per host molecule were located in **1** by difference Fourier methods and were included with unit site-occupancy factor (s.o.f.) in accord with the TG data (calculated total mass loss for $C_{96}H_{128}O_{64}\cdot 2C_2H_5OH\cdot H_2O$: 4.6%, found 4.6 ± 0.3%). TG data for **2** and the other solvates are provided in the ESI.† One of the two 2-propanol molecules located in **2** showed significantly higher average thermal motion and was modelled with s.o.f. 0.5 to yield a total 2-propanol content of 1.5 molecules per complex unit, in accord with the TG data. In both crystal structures, the acetyl group on the primary side of ring H was found to be disordered over two positions. Bond length restraints were included for the disordered components and least-squares refinement of their s.o.f.s yielded values in the range 0.48–0.52. Both structures were refined against F^2 with SHELXL-97.[9]

Crystal data for **1**: $C_{100}H_{142}O_{67}$, M = 2416.14, tetragonal, space group $P4_12_12$ (no. 92), $a = b$ = 25.0841(1), c = 38.2760(2) Å, V = 24083.7(2) Å^3, Z = 8, D_c = 1.333 g cm^{-3}, F_{000} = 10224, Mo-Kα radiation, λ = 0.710 73 Å, T = 113(2) K, $2\theta_{max}$ = 50.7°, μ = 0.113 mm^{-1}. 43 624 reflections collected, 21 912 unique (R_{int} = 0.0229). Final GooF = 1.037, $R1$ = 0.0699, $wR2$ = 0.1939, R indices based on 10 396 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1473 parameters, 7 restraints. CCDC 627127.

Crystal data for **2**: $C_{100.50}H_{142}O_{66.50}$, M = 2414.14, tetragonal, space group $P4_12_12$ (no. 92), $a = b$ = 25.0996(1), c = 38.1856(2) Å, V = 24056.6(2) Å^3, Z = 8, D_c = 1.333 g cm^{-3}, F_{000} = 10216, Mo-Kα radiation, λ = 0.71073 Å, T = 113(2) K, $2\theta_{max}$ = 46.6°, 101 708 reflections collected, 17 157 unique (R_{int} = 0.0750). Final GooF = 1.034, $R1$ = 0.0872, $wR2$ = 0.2300, R indices based on 8392 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1162 parameters, 20 restraints. CCDC 626126.

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b616681d

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