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New crystalline forms of permethylated β-cyclodextrin†

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Two new crystalline forms of permethylated β-cyclodextrin are reported that contain methylglucose residues exclusively in the $^4C_1$ conformation, in contrast to the known monohydrate, in which a single methylglucose residue adopts the $^1C_4$ conformation.

In recent reports, we have focused on two intriguing aspects of the solid-state chemistry of cyclodextrins, namely isostructurality and polymorphism, both of which have practical implications for the continued use of these molecules as drug carriers. Systematic classification of the crystal structures of native and derivatised cyclodextrins, and their inclusion complexes, into isostructural series has proven useful in our laboratory for the definitive identification from X-ray powder diffraction of new inclusion complexes formed by these macrocyclic oligosaccharides.[1] On the other hand, crystal polymorphism, the inverse of isostructurality,[2] was also demonstrated for cyclodextrins in our recent report on the structural characterization of two crystalline forms of the inclusion complex β-cyclodextrin–methyl paraben, isolated at different temperatures.[3]

The present report relates to the polymorphism of permethylated β-cyclodextrin [heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin, commonly known as TRIMEB], widely used as a solubilising agent and as host for the encapsulation of organic molecules,[4] including drugs.[5] In 1994, we isolated single crystals of this host as the monohydrate from an aqueous solution of TRIMEB maintained at 50 °C. X-Ray structural analysis revealed that six of the seven methylglucose residues adopt the normal $^4C_1$ conformation while the seventh is in the inverted $^1C_4$ conformation.[6] A second structure determination of this phase was subsequently reported.[7] To our knowledge, this remains the only known case of ring-inversion in cyclodextrin solid-state chemistry. The resultant, highly distorted conformation of the TRIMEB molecule contrasted strongly with the more regular conformations it adopts in its inclusion complexes.

We refer to the above crystal monohydrate as Form 1, in view of our recent isolation of two new crystalline modifications of TRIMEB, namely a trihydrate (Form 2) and an anhydrate (Form 3), which are the subject of this report. These new forms are isostructural with respect to the host molecule, the latter having all seven methylglucose residues in the normal $^4C_1$ conformation. Both crystal forms were isolated from failed attempts to obtain inclusion complexes of TRIMEB with drug molecules.‡ In all of the experiments performed, the starting host material corresponded to the known monohydrate, Form 1. The trihydrate (Form 2) crystallised from a solution containing TRIMEB and the antihypertensive drug atenolol (4-[2-hydroxy-3-[(1-methylethyl)-amino)propoxy]benzeneacetamide, either in the form of enantiopure (*S*)-atenolol or as the racemate), in 1 : 1 host–guest molar ratio, as well as from a solution containing TRIMEB and the analgesic drug bucetin (*N*-(4-ethoxyphenyl)-3-hydroxybutanamide) in 1 : 1 molar ratio. When the crystal of Form 2 obtained in the latter case was maintained at 50 °C for several weeks, the anhydrate Form 3 resulted. X-Ray diffraction data from single crystals of both Forms 2 and 3 were collected and the structures were solved and refined by routine procedures.§ The structure and conformation of the host molecule in the anhydrate Form 3 are shown in Fig. 1, where the view is from the wider, secondary side of the macrocycle. All methylglucose units adopt the usual $^4C_1$ conformation and the structure is remarkably free of disorder.

Deviation from toroidal symmetry is usually described in terms of the 'tilt angle',[8] defined for each glucose residue G*n* as the angle between the plane O4G*n*, C1G*n*, C4G*n*, O4G(n − 1) and the mean plane through the seven glycosidic oxygen atoms O4G*n* (n = 1–7). For the molecule depicted in Fig. 1, the tilt angle magnitudes span a very wide range, namely 8.4(1)° for G4 to 72.0(1)° for G6, indicating very significant distortions. The primary side of the molecule is effectively blocked due to the unique orientation of residue G6 coupled with the extended conformation of C5 → C9.

Although the tilt angle magnitudes in the TRIMEB molecule in Form 1 span a similar range (4.6–72.9°), the presence of one methylglucose residue in the inverted $^1C_4$ conformation results in the molecule adopting a distinctly elliptical shape.[6] This collapsed overall conformation was attributed mainly to the tendency for the molecule to minimise the hydrophobic cavity size in the absence of a guest molecule. The extent of ellipticity is measured by the seven 'radial' distances O4G*n*···Cg, where Cg is the centre of gravity of the seven O4G*n* atoms. For Form 1, these radii span the range 3.41–5.94 Å, whereas in Form 3 (Fig. 1), the range is much narrower *viz.* 4.49–5.50 Å. Examination of the crystal packing revealed that the more 'round' shape of the TRIMEB molecule in Form 3 is due to a much greater degree of 'self-inclusion' than is observed in Form 1. Specifically, two primary methoxy groups of one molecule insert into the secondary side of a neighbouring molecule, as shown in Fig. 2. Space-filling models show that these methoxy groups make van der Waals contacts with residue G6 and its extended side chain C5 → C9.

The molecular conformation of TRIMEB in the trihydrate,

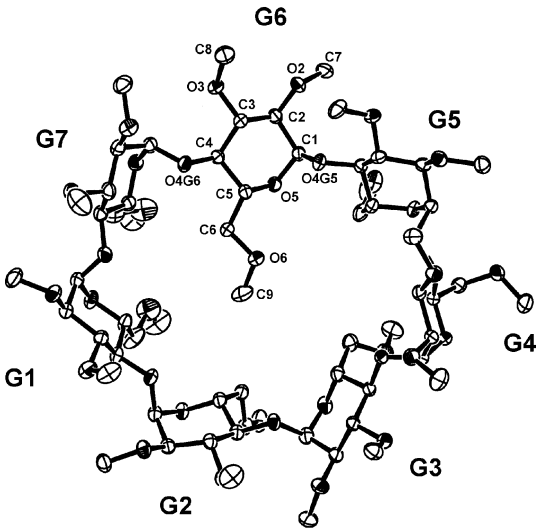

Fig. 1 Conformation of the TRIMEB molecule in Form 3.

† Electronic supplementary information (ESI) available: PXRD patterns for Forms 1–3. See http://www.rsc.org/suppdata/cc/b4/b408660k/

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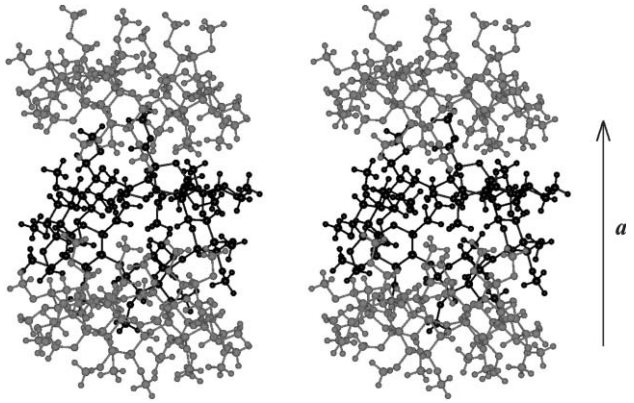

Fig. 2 Self-inclusion in Form 3 for molecules related by the screw axis parallel to *a*.

Form 2, closely resembles that in Form 3, but interestingly, there is molecular disorder in the former case (primary methoxy groups on G1 and G3, each disordered over two positions; primary methoxy C atom on G7 disordered over two positions). In addition, the three water molecules associated with each TRIMEB molecule are located outside the host cavity and are disordered over five sites. They are arranged in discontinuous channels parallel to the crystal *b*-axis where they are extensively hydrogen bonded to one another and to host oxygen atoms.

The packing coefficients[9] for Forms 2 and 3 are comparable at 67 and 64% respectively. Computation of the voids in the trihydrate (Form 2) yielded a total potential solvent volume[9] of only 51.5 Å^3 per unit cell (0.6%), whereas for the anhydrate (Form 3), the void volume is 467.2 Å^3 (6.1%). The latter could accommodate ~3 water molecules per host molecule, which therefore implies that dehydration of Form 2 to yield Form 3 leaves the crystal structure essentially intact but more porous than the trihydrate phase. Close examination showed that the positions of the relatively large voids remaining in the Form 3 crystal structure coincide with cavities that would result if the water molecules in Form 2 were to be artificially removed. The dehydration process and its possible reversibility have yet to be investigated but the mechanism of the former is likely to involve small conformational changes of the host molecules to permit the diffusion of water molecules through the bulk crystal, as has been postulated for β-cyclodextrin hydrates,[10] in which no permanent channels exist.

We were first alerted to the existence of these new modifications of TRIMEB from their unusually large crystal sizes (longest dimension ~3 mm) and their rounded, rhombic prismatic habits, which contrast strongly with the flat, elongated prisms of Form 1. In addition, the unit cell parameters for these crystal forms could not be reconciled with those of previous crystals containing the TRIMEB host molecule. Another distinguishing feature is the common lower melting point of Form 2 (following dehydration) and Form 3, namely 148 °C, compared with 157 °C for Form 1.[11] Powder X-ray patterns of Forms 1, 2 and 3 were generated[12] using the single crystal X-ray data. As expected from the isostructurality of Forms 2 and 3, their PXRD peak positions show very good correlation, especially in the lower 2θ angular range (see ESI†).

In conclusion, our report of the precipitation of Form 2 from solutions of TRIMEB containing at least two different drug substances suggests that this new crystal form of the host may be encountered more frequently in future and the characterization data provided here should ensure its unequivocal identification. We have noted the close structural analogy between the molecules of atenolol and bucetin. This may be a factor in the crystallization of Form 2 of TRIMEB in preference to the usual Form 1; we are therefore investigating the effects of their analogues in crystallization experiments with this host.

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Notes and references

‡ 4 cm^3 distilled water at 20 °C were added to a mixture of 10 mg (0.038 mmol) of either (*S*)-atenolol or racemic atenolol and 50 mg TRIMEB monohydrate, Form 1 (0.035 mmol). The mixture was placed on ice and stirred for 19 h, filtered (0.45 μm) and the solution placed in an oven at 60 °C. Crystals of Form 2 appeared after one month. Thermogravimetry yielded a 3.3 ± 0.2% mass loss indicating 2.6–2.9 water molecules per TRIMEB molecule. 1 cm^3 of distilled water at 20 °C was added to a mixture of 10 mg (0.045 mmol) bucetin and 64.8 mg (0.045 mmol) TRIMEB monohydrate (Form 1) and the resultant stirred in a glass vial on ice for 24 h. Further heating at 70 °C for 30 min and stirring for 30 min on ice followed. The resulting solution was filtered (0.45 μm) and placed in an oven at 50 °C. Large crystals of Form 2 appeared under the mother liquor. The latter was allowed to evaporate and the crystals on the side of the vial (uncovered by mother liquor) were harvested after one month and found to be those of Form 3.

§ Intensity data were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo–Kα X-rays (λ = 0.71069 Å). Both crystals were coated in Paratone oil (Exxon Chemical Co., TX, USA) immediately after isolation and cooled in a stream of nitrogen vapour on the diffractometer. The structures were solved by direct methods with program SHELXS-97[13] and refined using SHELXL-97.[14] *Crystal data for Form 2:* $C_{63}H_{112}O_{35}\cdot 3H_2O$, M = 1483.57, orthorhombic, space group $P2_12_12_1$, a = 16.2051(1), b = 16.2870(1), c = 30.0989(3) Å, U = 7944.1(1) Å^3, Z = 4, D_c = 1.240 g cm^{-3}, T = 193(2) K, μ(Mo–Kα) = 0.102 mm^{-1}. Full-matrix least-squares refinement was based on 17 741 reflection data and yielded *wR2* = 0.176 (all data), *R1* [13 791 data with $F^2 > 2\sigma(F^2)$] = 0.0632, and goodness-of-fit on F^2 = 1.026 (CCDC 239740). *Crystal data for Form 3:* $C_{63}H_{112}O_{35}$, M = 1429.53, orthorhombic, space group $P2_12_12_1$, a = 15.9509(1), b = 16.5772(1), c = 28.9413(2) Å, U = 7652.7(1) Å^3, Z = 4, D_c = 1.241 g cm^{-3}, T = 173(2) K, μ(Mo–Kα) = 0.101 mm^{-1}. Full-matrix least-squares refinement was based on 14 499 reflection data and yielded *wR2* = 0.130 (all data), *R1* [13 091 data with $F^2 > 2\sigma(F^2)$] = 0.0531, and goodness-of-fit on F^2 = 1.107 (CCDC 239741). See http://www.rsc.org/suppdata/cc/b4/b408660k/ for crystallographic data in .cif format.

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