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Effect of perethylation on the conformation of γ-cyclodextrin: an X-ray diffraction study

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Effect of perethylation on the conformation of γ-cyclodextrin: an X-ray diffraction study

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The X-ray structure of octakis(2,3,6-tri-*O*-ethyl)-γ-cyclodextrin (perethylated γ-cyclodextrin (CD)), isolated as a trihydrate, is reported. It crystallises in the monoclinic space group *C*2 with $Z = 2$. As a result of perethylation, the host molecule, located on a two-fold axis, adopts a conformation that differs from those of permethylated and peracetylated γ-CDs, being divided into two identical halves connected at kink sites. A particular feature of the kink sites is their stabilisation via hydrogen bonding with included water molecules. Significant 'self-inclusion' of two fully extended $-CH_2OCH_2CH_3$ chains from the primary sides of two diad-related glucose residues occurs, leading to considerable steric congestion in the CD cavity.

Keywords: cyclodextrin derivatives; alkylated cyclodextrins; hydrates; X-ray structure

Introduction

Derivatisation of cyclodextrins (CDs) is undertaken to alter their solubilities, to render them more biocompatible as drug carriers, to develop enzyme models and to optimise the fit between the CD and specific guest molecules in enantioselective separations (*1*). Common CD derivatives include those obtained by alkylation, hydroxyalkylation, acylation and sulphation or sulphoalkylation of the free hydroxyl groups of the parent molecules (*2*). Among the alkylated CD derivatives, much attention has focused on the partially and fully methylated compounds, including the 2,6-di-*O*-methylated and 2,3,6-tri-*O*-methylated analogues, that display the anomalous property of a negative temperature coefficient of solubility in water (*3*), as well as differences in their modes of guest inclusion, as exemplified by the well-known hosts heptakis(2,6-di-*O*-methyl)-β-CD and heptakis(2,3,6-tri-*O*-methyl)-β-CD.

Fully methylated α-, β- and γ-CDs have attracted much interest since intramolecular $O(2n)\cdots O3(n-1)$ hydrogen bonding is precluded, leading to severe distortions of the macrocycles and significantly reduced cavity volumes relative to the native CDs. For the largest of the native CDs, viz. γ-CD, with eight glucose rings in the macrocycle, permethylation results in remarkable distortions to relieve steric strain, namely 'flipping' and 'kinking', that had only previously been identified as novel structural motifs in larger CDs such as cyclodeca- and cyclotetradecaamylose (ι-CD and ε-CD, respectively) (*4*). In two of the known crystalline forms of octakis(2,3,6-tri-*O*-methyl)-γ-CD (TRIMEG), two kinks and two flips characterise the molecular conformation (*5, 6*). In a third form of TRIMEG, however, a 'round' conformation occurs (*7*) with all glucose residues oriented *syn*.

As the structures of higher alkylated homologues of γ-CD have not been reported hitherto, we were prompted to establish what effect lengthening the alkyl chain from methyl to ethyl might have on the conformation of γ-CD. We duly crystallised the fully ethylated derivative, octakis(2,3,6-tri-*O*-ethyl)-γ-CD **1** (Figure 1), as a trihydrate and herein report its molecular and crystal structure. This compound is used as a solubiliser and as a chiral selector in gas chromatography (GC) and capillary electrophoresis (CE) techniques. Reported applications of ethylated γ-CDs include enantioselective high-resolution GC separation of toxaphene congeners in human milk (*8*), and very efficient GC separation of atropisomeric polychlorinated biphenyls (PCBs) and methylsulphonated PCBs (*9*). In the latter case, the CD contained 3.8 free hydroxyl groups per molecule.

Experimental

A 10-mg sample of octakis(2,3,6-tri-*O*-ethyl)-γ-CD (purity >98%, supplied by Cyclolab, Budapest, Hungary) was added to 1 cm^3 of 99.9% ethanol pre-heated to 60°C, in which it dissolved rapidly. Water was added dropwise until the solution became turbid. The hot solution was filtered (0.45 μm) into a clean vial and allowed to cool to 20°C. Colourless single crystals, corresponding to a hydrate of **1**, appeared within 2 days. Estimation of water content by thermogravimetry and Karl Fischer methods was complicated by an initially rapid partial dehydration. Duplicate elemental analyses of fresh, surface-dried

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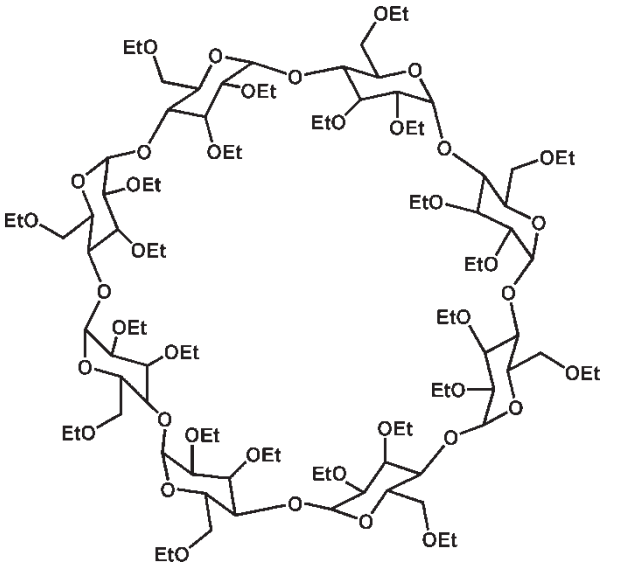

Figure 1. Chemical structure of perethylated γ-cyclodextrin.

crystals yielded average values, %C, 57.6 and %H, 9.1, suggesting a composition $C_{96}H_{176}O_{40}{\cdot}n\,H_2O$ with $n \sim 2$ (calcd %C, 57.46; %H, 9.04), though this was considered an underestimate (see below). Behaviour of the crystals on heating was examined on a Linkam THMS 600 hot stage fitted with a Linkam TP92 temperature control unit. Images were captured on a real-time Sony Digital Hyper HAD colour video camera fitted to a Nikon SMZ-10 stereomicroscope while crystals were heated at 1 K min^{-1}.

Powder X-ray diffraction (PXRD) traces were recorded on a Huber Imaging Plate Guinier Camera 670 with Ni-filtered Cu-Kα_1 radiation ($\lambda = 1.5406$ Å) produced at 40 kV and 20 mA by a Philips PW1120/00 generator fitted with a Huber long fine focus tube PW2273/20 and a Huber Guinier Monochromator Series 611/15. The samples were gently ground and packed in Lindemann capillaries for multiple-scan data collections with exposure times of 30 min over the 2θ range of 4–100° with a step size of 0.005° in 2θ.

Single-crystal intensity data were collected on a Nonius Kappa CCD diffractometer and the structure was solved using the program SHELXD (*10*). The ethyl groups attached to O6A of glucose residue A, and to atoms O3D and O6D of residue D, were disordered over two sites each and modelled accordingly with appropriate bond length restraints. Water oxygen atom O3, with an assigned site-occupancy factor (s.o.f.) of 1.00 behaved normally, refining with $U_{iso} = 0.086$ Å^2. Significantly lower, and virtually equal, electron densities for each of the water oxygen atoms O1 and O2, located on the diad, indicated their partial occupancy. They were initially assigned the same U_{iso} values as O3, their s.o.f.s refining to ~0.25 each. In the final refinement, the latter were held constant and the refined U_{iso} values were physically reasonable and comparable to those of O3 viz. 0.085 (O1) and 0.068 Å^2 (O2). This model corresponds to a trihydrate, $C_{96}H_{176}O_{40}{\cdot}3H_2O$ (calcd %C 57.0; %H 9.1). Though hydrogen atoms on the water molecules could not be located, the role of the water molecules in hydrogen bonding could be inferred. The structure was refined against F^2 with SHELXL-97 (*11*). Friedel opposites were merged since the absolute structure was not reliably indicated by the Flack parameter, though the chirality of the host molecule was known.

Table 1. Crystallographic data for perethylated γ-cyclodextrin trihydrate.

Formula	$C_{96}H_{176}O_{40}{\cdot}3H_2O$
Formula weight	2024.42
Temperature (K)	133(2)
Crystal system	Monoclinic
Space group	*C*2
a (Å)	30.5544(5)
b (Å)	10.5839(3)
c (Å)	20.1300(5)
β (°)	119.565(1)
Volume (Å^3)	5662.1(2)
Z	2
Density (calcd, g cm^{-3})	1.187 g cm^{-3}
Radiation, wavelength (Å)	Mo-Kα, 0.71073
Absorption coefficient (mm^{-1})	0.092
F(000)	2204
Crystal size (mm^3)	0.32 × 0.24 × 0.16
Theta range (°)	1.00–25.35
Index ranges	*h*: −36, 36; *k*: −12, 12; *l*: −24, 24
Reflections collected/unique	10315/5467
Observed reflections [$I > 2\sigma(I)$]	3989
Data/restraints/parameters	5467/15/584
Goodness of fit on F^2	1.048
Final *R* indices R_1, wR^2 [$I > 2\sigma(I)$]	0.0841/0.2242
R indices R_1, wR^2 (all data)	0.1126/0.2469
Largest diff. peak and hole (eÅ^{-3})	−0.35 and 0.59

Details of the crystal parameters, data collection and refinement of the structure are summarised in Table 1. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, as CCDC No. 676952. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Results and discussion

The typical prismatic morphology of crystals of **1**·3H$_2$O is shown in Figure 2. Upon heating the crystal under silicone oil, fine cracks appear at ~100°C and the melting process follows over the range 108–112°C, with the release of a small bubble of vapour representing accumulated water.

X-ray analysis of **1** revealed that the host molecule is located on a crystallographic two-fold axis and adopts the

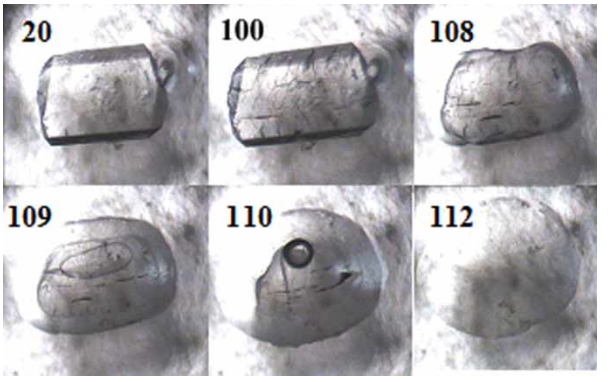

Figure 2. Morphology and behaviour on heating of a crystal of **1**·3H_2O (temperatures in °C).

conformation as shown in Figure 3, where the symbols A–D indicate the four glucose units of the chosen asymmetric unit and A′–D′ their diad-related equivalents (′ = $-x$, y, $1 - z$). All glucose units are in the regular $^4C_1$ chair conformation. The most striking features afforded by this view are the undulating backbone of sugar residues in the macrocycle and the penetration into the CD cavity of the two fully extended —$CH_2OCH_2CH_3$ chains from the primary sides of the glucose residues D and D′.

The novel features of the molecular conformation of **1** are highlighted first in Figure 4 (top), where all 24 ethyl substituents have been omitted for clarity to give the γ-CD 'skeleton'. Glucose units A–D are essentially oriented *syn*, but proceeding through this sequence, the steric bulk of the O2—Et and O3—Et residues (not shown) causes progressive twisting of the chain (ϕ range: 107.7–115.1°, ψ range 149.1–149.3°) (*12*). Between glucose residues D and A′, however, there is a 'kink' ($\phi = 61.6°$, $\psi = 77.7°$), where the two glucose ring planes are nearly orthogonal. The two-fold crystallographic symmetry, therefore, results in the molecule being divided into two identical halves connected at the kink sites. Figure 4 (bottom) shows, for comparison, the distinctly different conformation of the corresponding skeleton occurring in TRIMEG·2H_2O (CSD ref code GIWMAA) (*5*). Here, two 'kinks' as well as two 'flips' characterise the conformation, the eight-ring system having pseudo-two-fold symmetry and a distinctly elliptical shape. At the flip site, adjacent glucose units are rotated by ~180° and adopt *anti* orientations. Very similar conformations to this are observed for the four independent molecules of TRIMEG occurring in the crystal form [4 TRIMEG]·19.3H_2O (CSD ref code BEBJAT) (*6*).

The most recent study of TRIMEG crystal forms revealed a third crystalline modification (TRIMEG·4.5H_2O, CSD ref code XERSIW) (*7*), in which the macrocycle remarkably displays a 'round' form, with all glucose units oriented *syn*. Comparison with **1** revealed that four contiguous glucose rings adopt a conformation similar to that of the glucose sequence B–C–D–A′ in **1**. Figure 5 shows the extent of overlap of the two structures, drawn with their respective methyl and ethyl carbon atoms included. The 'round' shape of the TRIMEG molecule (in blue) is quite evident, as is the increasing divergence of the conformation of **1** (in red) from the former beyond the overlapping sequence of glucose residues. The more distorted structure of **1** is associated with *anti* orientations of glucose ring D and its diad-related counterpart, which allow their bulky —OEt chains to point into the macrocyclic cavity and effectively block it (Figure 3).

Water molecules included in the crystal of **1** play a pivotal role in stabilising the formation of the kinks (Figure 4, top) that confer a unique character to the observed macrocyclic conformation. This is shown in Figure 6, where the water oxygen atom O3, with full site occupancy, is hydrogen bonded to atoms O2A′ and O6D (O···O distances 2.99(1) and 3.01(1) Å, respectively, and angle O2A′···O3···O6D 103(1)°). The identical hydrogen bonding motif is repeated by the two-fold symmetry

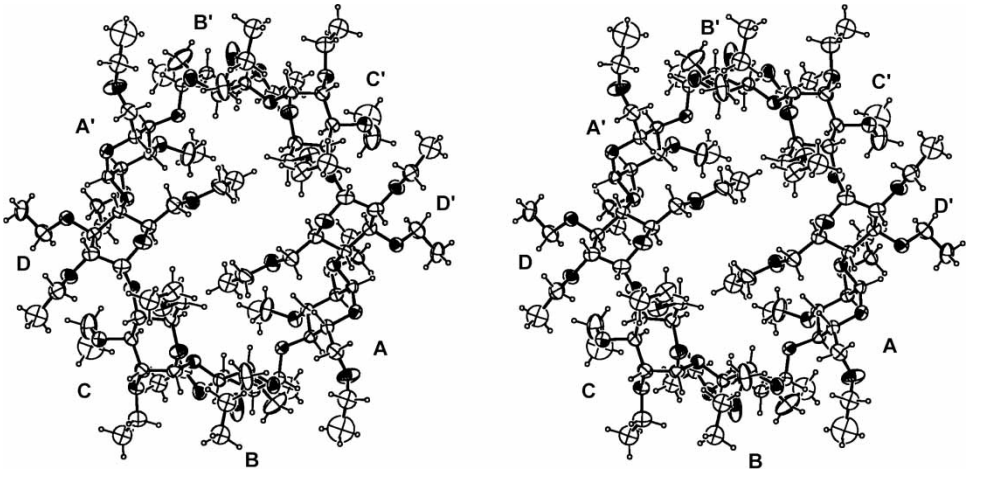

Figure 3. Stereoview of **1** viewed down the crystallographic two-fold axis. Included water molecules are not shown.

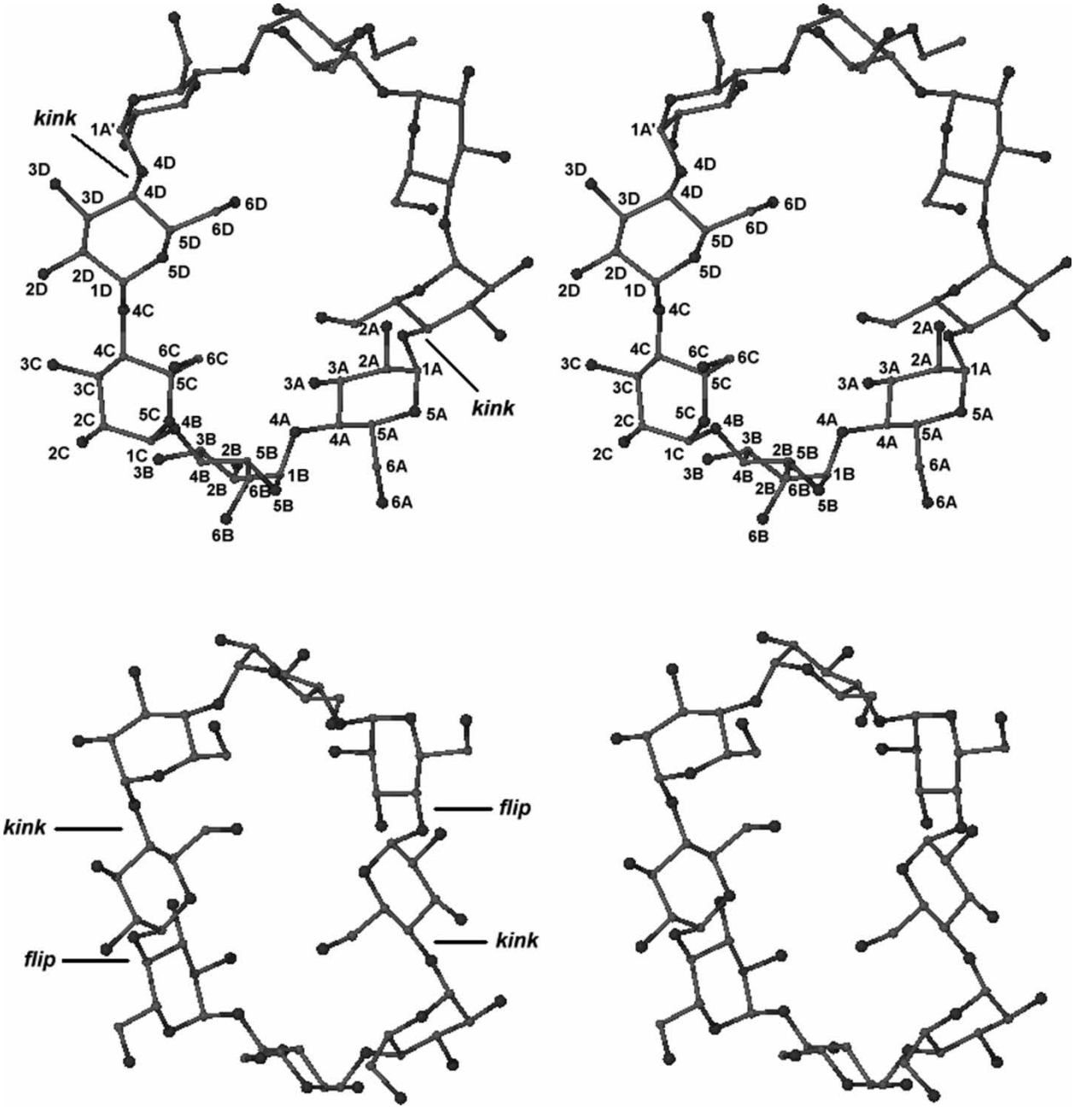

Figure 4. Stereoviews of the γ-CD skeleton in the perethylated compound **1**·3H_2O (top) and in permethylated γ-CD TRIMEG·2H_2O (bottom). Kinks and flips characterising the conformations are indicated.

at glucose rings A and D′. 'Self-inclusion' of the —CH_2—OEt moieties of rings D and D′ is thus stabilised by H-bonding to water molecules O3 and O3′. Water oxygen atom O2 (located on the two-fold axis with partial site occupancy) bridges O3 and O3′ by hydrogen bonding (O2···O3 2.85(1) Å) and forms a third H-bond with O1 (also located on the two-fold axis) having O2···O1 2.71(3) Å. Water oxygen atom O1 is not within the hydrogen bonding distance of any atoms of the lower, translated host molecule.

The well-defined hydration pattern observed in **1** differs from that in, for example, BEBJAT (*6*), where the four independent TRIMEG molecules are hydrated to different extents, with, however, a single water molecule (invariably located on the pseudo-two-fold axis) bridging the O6 atoms of the diametrically opposed glucose units by hydrogen bonding.

Distinct conformational differences are also noted between perethylated γ-CD **1** and peracetylated γ-CD, whose structure was recently reported (*13*). Introduction of

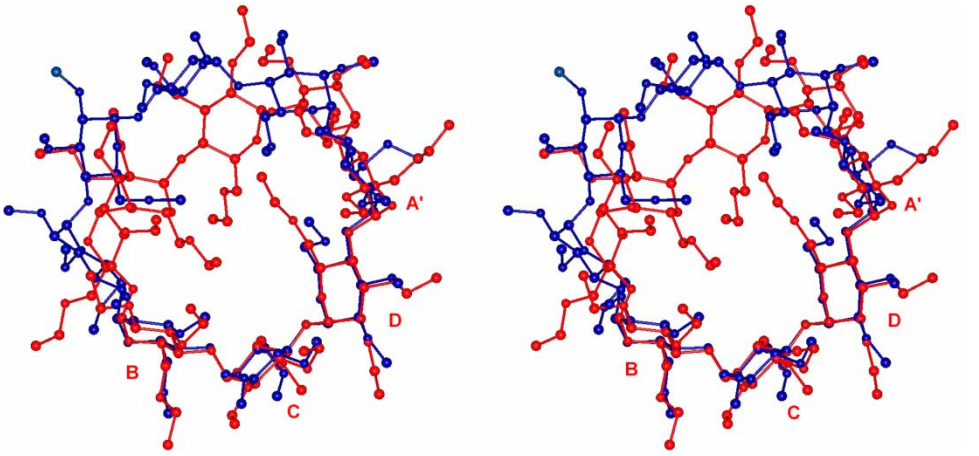

Figure 5. Stereoview showing partial overlap of four glucose rings B–C–D–A′ of **1** (red) with a sequence of four glucose rings in TRIMEG·4.5H_2O (blue).

bulky acetyl groups in the latter case results in two of the eight rings adopting $^0S_2$–skew–boat conformations, and significant self-inclusion of —CH_2—O—CO—CH_3 residues that partition the macrocyclic cavity into two subcavities, each capable of accommodating a small solvent molecule.

The PXRD trace (Cu-Kα_1 radiation, $\lambda = 1.5406$ Å) of single crystals of **1**·3H_2O after manual grinding and that of the commercially available raw material are shown in Figure 7. The level of agreement indicates that they are essentially the same phase. Discrepancies may be attributed to differences in solvent content (loss on drying is calculated as 1.0% for the raw material and 2.7% for the trihydrate), as well as the declared possible presence of traces of under-ethylated CDs in the former. Comparison of the experimental PXRD trace of the recrystallised material and the calculated PXRD trace from the single-crystal X-ray structure reported here also indicates no substantial differences, save for the expected shifts in the angular positions of the peaks to higher 2θ values for the calculated pattern owing to the low temperature of the X-ray data-collection.

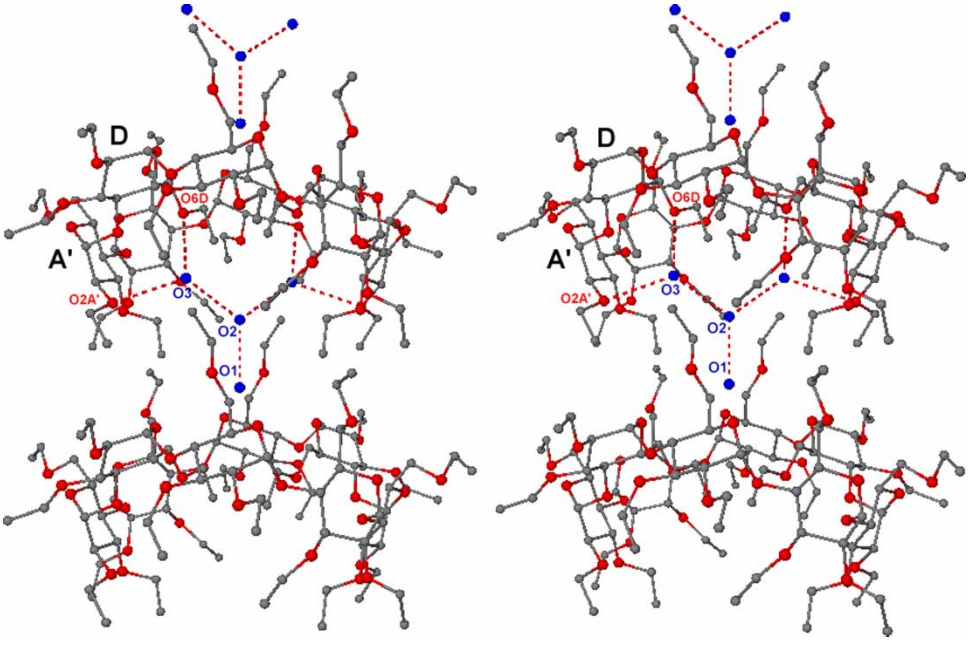

Figure 6. Stereoview illustrating the inclusion of water molecules (blue spheres) in the crystal of **1**·3H_2O and their role in stabilising the host conformation. The two host molecules are related by translation along the *b*-axis.

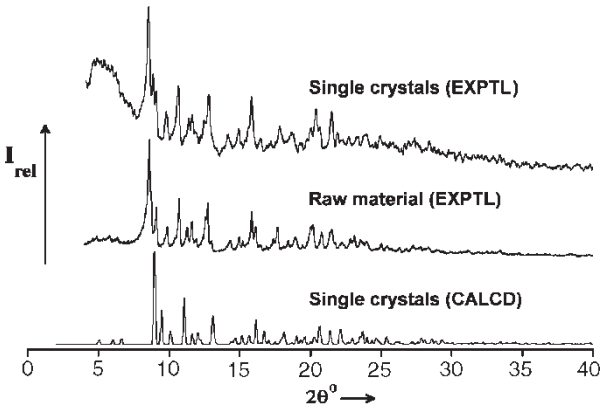

Figure 7. PXRD traces of the three samples described in the text.

Conclusion

The X-ray analysis of perethylated γ-CD, in the form of its trihydrate, reveals a distinctly different molecular conformation from that observed in recent studies of related γ-CD derivatives. Stabilisation of the 'kink' regions mediated by water molecules is a novel feature of this conformation. This analysis, indicating also that the cavity of fully ethylated γ-CD is considerably congested by the 'self-inclusion' of two sterically bulky $-CH_2OCH_2CH_3$ chains, provides a plausible reason for the reported lack of enantioselectivity of certain substrates by the fully ethylated compound and the contrasting highly efficient enantioselectivity of under-ethylated γ-CDs (*9*), where stereorecognition by the expected deeper penetration of guest molecules into the chiral cavity should be enhanced.

Steiner and Saenger (*5*) have noted that crystallisation of a methylated CD from hot or cold water influences both the extent of crystal hydration and the location of H_2O molecules. We are exploring such variations in the conditions to establish whether other forms of **1** can be isolated.

Acknowledgements

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