# Unusual $^1C_4$ Conformation of a Methylglucose Residue in Crystalline Permethyl-β-cyclodextrin Monohydrate

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The severely distorted conformation adopted by the uncomplexed TRIMEB molecule in the solid state is attended by ring-inversion of one of the seven methylglucose residues.

Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) as a pharmaceutical carrier molecule offers various advantages over its unmethylated counterpart, amongst which are higher aqueous solubility and greater protection from hydrolysis both in solution and in the solid state.[1] The 'roundness' of the parent β-cyclodextrin molecule is maintained by intramolecular O(2)···O(3') hydrogen bonding.[2,3] It has therefore been suggested that permethylation of β-cyclodextrin results in greater conformational flexibility owing to the loss of its O(2)···O(3') hydrogen bonding capability and consequently accounts for the distortion of the macrocycle observed in TRIMEB complexes.[4–7]

We report here the preparation, X-ray structure and thermogravimetric analysis of a monohydrate of TRIMEB.† Fig. 1 shows the observed conformation of TRIMEB in the solid state.

All methylglucose residues are in the $^4C_1$ chair conformation, except that of G2, which adopts the $^1C_4$ conformation; the latter has not been observed previously in the cyclodextrins or their complexes in the solid state. The O(6) and C(9) atoms of residue G2 are disordered over two sites each, with occupancies of 0.63 and 0.37. The C(6) and O(6) atoms of G3 are similarly disordered with occupancies of 0.67 and 0.33. However, C(9G3) is not disordered.

The O(2)–C(7) bonds are directed away from the cavity and the O(3)–C(8) bonds are directed towards the cavity as observed in TRIMEB complexes,[3–6] except in G2, where the inverted chair conformation causes O(2) and O(3) to be axial [torsion angle O(2G2)–C(2G2)–C(3G2)–O(3G2) 162.6°] instead of equatorial. This, together with a rather large negative tilt angle of 24.5° for G2, results in the C(7) methyl group pointing into the cavity and the C(8) methyl group pointing outwards. The C(6)–O(6) bonds of G1, G5, G6 and G7 are directed away from the cavity and are in the *–gauche* conformation,[2] while those of G3 and G4 are directed towards the cavity in the *+gauche* conformation. The C(6)–O(6) group of G2 is also in the *+gauche* conformation, but is directed away from the cavity on account of the inverted chair conformation and negative tilt angle of G2. The O(6)–C(9) bonds are *trans* to the C(5)–C(6) bonds, except those of G1 and G5, where the relationship is *gauche*.

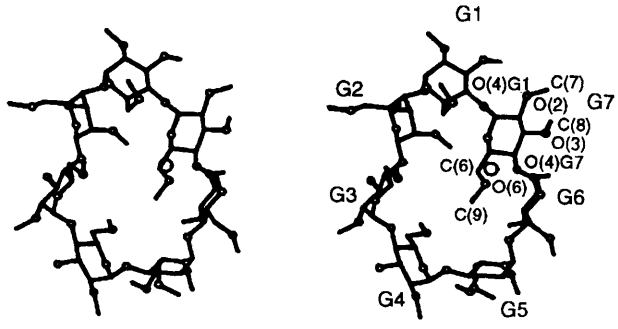


**Fig. 1** The title compound viewed perpendicular to the least-squares plane through the seven O(4) atoms. H-atoms are omitted. The small open circles represent oxygen atoms. The large open circle represents the water molecule.

The tilt angles for the other six glucose residues are: G3 24.7°, G4 38.0°, G5 21.0°, G6 −4.6°, G7 72.9° and G1 57.3°. The largest positive and negative tilt angles reported in inclusion complexes of TRIMEB are 51.7° and −16.3° respectively. O(4)···O(4')···O(4'') angles in TRIMEB monohydrate range from 91.9° to 161.6°. These extreme values are approximately 22° lower and higher respectively than the lowest and highest values found in TRIMEB complexes. The average, 124.5°, is slightly less than the averages for TRIMEB complexes which span a narrow range from 126.9° to 127.1°, close to the ideal value of 128.6° for a regular heptagon. The largest deviation from the least-squares plane of the seven O(4) atoms is 1.09 Å, compared with a maximum of only 0.66 Å in TRIMEB complexes. The radii of the O(4) heptagon range from 3.41 to 5.94 Å with an average of 4.82 Å. The *m*-iodophenol TRIMEB complex (MIP)[7] has a minimum radius of 4.16 Å and a maximum radius of 5.47 Å with an average of 5.00 Å. The averages for the other TRIMEB complexes range from 4.98 to 5.01 Å. From these data it is evident that the conformation of the uncomplexed TRIMEB molecule is distorted to a remarkable extent, even when compared with the rather distorted conformations observed in its complexes.

The O(6)–C(9) group of G7, which has the largest positive tilt angle, acts as a 'lid', closing off the O(6) side of the TRIMEB molecule and making it cup-shaped. The water molecule occupies a site at the periphery of the O(2), O(3) side.

† Single crystals were grown from an aqueous solution of TRIMEB maintained at 50 °C. Thermogravimetry was performed on a Perkin-Elmer PC7 system at a heating rate of 10 °C min$^{-1}$ in the range 40–140 °C with $N_2$ purge at a flow rate of 40 cm$^3$ min$^{-1}$. Crystal data for $C_{63}H_{112}O_{35}\cdot H_2O$, $M_r$ = 1447.57, orthorhombic, space group $P2_12_12_1$ (No. 19), $a$ = 14.818(4), $b$ = 19.362(9), $c$ = 26.51(2) Å, $Z$ = 4, $D_c$ = 1.264 g cm$^{-3}$, crystal size = 0.43 × 0.50 × 0.50 mm. Intensity data were collected at 294 K on an Enraf–Nonius CAD4 diffractometer using Mo-Kα radiation ($\lambda$ = 0.7107 Å) to $\theta_{max}$ = 25°; 6366 unique reflections were collected. The structure was solved by direct methods using program SHELX86[9] and the least-squares refinement (SHELX76[10]) converged to a final $R$ = 0.063 for 4286 reflections with $I > 2\sigma(I)$: $R_w$ = 0.067 with $w = [\sigma(F_o) + 1.882 \times 10^{-3} F_o^2]^{-1}$. Residual electron density (max, min) = 0.31, −0.25 e Å$^{-3}$. All non-hydrogen atoms, except the disordered atoms and the water molecule were treated anisotropically and hydrogen atoms were fixed at idealised positions (C–H = 1.00 Å) in a riding-model. Molecular parameters with esds were calculated with program PARST[11] and the figure was drawn with PLUTO.[12] Atomic coordinates, thermal parameters, bond distances, angles and torsion angles have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1.

Atom O(1W) occupies only one site and the formulation of the title compound as a monohydrate is based on thermogravimetric analysis which yielded a 1.2 weight percent loss between 40 and 140 °C, corresponding to 0.96 water molecules per TRIMEB molecule.

The conformation of the TRIMEB molecule is stabilised by a number of intramolecular C–H · · · O hydrogen bonds, a common interaction found in carbohydrate crystal structures.[8] Parameters quoted below are based on idealised H-atom positions. A significant interaction which appears to stabilise the $^1C_4$ conformation of G2 is C(5G2)–H · · · O(5G1) with C · · · O 3.18(1), H · · · O 2.53 Å and C–H · · · O 123°. The orientation of residue G7, with the largest tilt angle, is partly maintained by the interaction C(1G6)–H · · · O(3G7) with C · · · O *3.02(1)*, H · · · O 2.28 Å and C–H · · · O 130°. In addition, we find four C($6G_n$)–H · · · O($5G_{n-1}$) interactions with parameters in the ranges C · · · O 3.12–3.37, H · · · O 2.35–2.48 Å, C–H · · · O 128–148°. We conclude that these interactions are also attractive and that they are partly responsible for the larger tilt angles observed both here and in complexes of TRIMEB, as compared with those found in complexes of unsubstituted cyclodextrins. Thus far, only steric repulsions and the absence of O(2) · · · O(3′) hydrogen bonds have been invoked to explain unusually large tilt angles.[4–6] We note that in the known crystal structures of TRIMEB complexes, five of the relevant C(6) · · · O(5) distances are in the range 3.0–3.4 Å; the two remaining (> 3.4 Å) involve O(5) atoms of those glucose residues with negative tilt angles.

The somewhat collapsed structure of the uncomplexed TRIMEB molecule is due to numerous factors amongst which is an attempt to minimise the hydrophobic cavity in the absence of a hydrophobic guest, thereby facilitating more efficient packing whilst avoiding accommodation of water molecules in a relatively hydrophobic environment.

We are using NMR and X-ray diffraction techniques to study the conformational changes induced in the TRIMEB molecule upon inclusion of non-steroidal anti-inflammatory drugs.

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