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X-ray Structure and Thermal Properties of a 1:1 Inclusion Complex Between Permethylated β-Cyclodextrin and Psoralen

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The phytoalexin psoralen (7*H*-furo[3,2-*g*][1]benzopyran-7-one) has been included in heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) to yield a solid crystalline complex of formula TRIMEB—psoralen—H_2O. Its X-ray structural elucidation provides an accurate model for cyclodextrin–furocoumarin interaction. Thermal analysis (hot stage microscopy, differential scanning calorimetry, thermogravimetry) indicated complex dehydration in the range 40–100°C followed by melting at 137.1°C. The X-ray analysis showed that the elongated guest molecule induces elliptical distortion in the host molecule, with which it interacts *via* C—H···O hydrogen bonding and hydrophobic interactions. The host molecule adopts a very similar conformation to that in the isostructural complex with L-menthol as guest. Water molecules bridge symmetry-related TRIMEB molecules by hydrogen bonding.

Keywords: Permethylated β-cyclodextrin; Psoralen; Inclusion complex; Thermal analysis; X-ray analysis

INTRODUCTION

Psoralen (7*H*-furo[3,2-*g*][1]benzopyran-7-one, Fig. 1) is the parent compound of a family of naturally occurring furocoumarins used by plants as phytoalexins to combat attacks from fungi and insects [1]. Well-known members of the psoralen family include 5-methoxypsoralen (5-MOP, bergapten), 8-methoxypsoralen (8-MOP, methoxsalen) and trimethylpsoralen (TMP). The structurally related compound khellin (5,8-dimethoxy-2-methyl-6,7-furanochromone) also possesses antipsoriatic activity. These compounds are able to intercalate into DNA, with which they form mono- and di-adducts when exposed to long-wave UV light. They are used in dermatological preparations for PUVA therapy (psoralens plus UVA radiation) to treat vitiligo, psoriasis and mycosis fungoides [2].

Inclusion of these furocoumarins in cyclodextrins (CDs) has been pursued primarily for analytical and medicinal applications. Examples in the former category include HPLC fluorimetric detection of psoralen, 5-MOP and 8-MOP, with various CDs [3] as well as liquid chromatographic detection of 5-MOP using β-CD in the mobile phase and a cross-linked β-CD column [4].

Our interest in the psoralens stems from their photochemotherapeutic applications. Formulation of psoralens for oral or topical administration is hampered by their poor aqueous solubilities, which leads to erratic bioavailability. One approach to their solubilisation is inclusion in cyclodextrins. An earlier study showed that the aqueous solubility of khellin is enhanced significantly by inclusion complex formation with γ-CD, hydroxypropyl-β-CD (HP-β-CD) and heptakis(2,6-di-*O*-methy)-β-CD (DIMEB) [5]. Recently it was reported that the aqueous solubility of the β-CD-psoralen inclusion complex exceeds that of psoralen [6]. Other complexes that have been identified, or for which association constants have been determined, include that between DIMEB and 8-MOP [7] and those between HP-β-CD and the guests 5-MOP, 8-MOP and TMP [8].

Pertinent to the present report is a study in which 1:1 inclusion complexes between the parent compound psoralen and the hosts β-CD, DIMEB and TRIMEB [heptakis(2,3,6-tri-*O*-methyl)-β-CD, or

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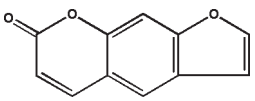

FIGURE 1 Molecular structure of the guest psoralen.

permethylated β-CD] were revealed by phase solubility measurements [9]. Stability constants of 663, 603 and 69.6 M^{-1} were reported for the respective complexes. Complexation led to increased solubility and dissolution rates but evidently did not affect the strength of binding of psoralen to DNA. While much evidence has thus been accumulated for both the ability of CDs to complex with psoralens and the advantages to be gained by this strategy, no details of the mode of inclusion of a psoralen in a cyclodextrin have hitherto been elucidated. This report describes the preparation, and the thermal and X-ray structural characterization of an inclusion complex formed between psoralen and TRIMEB. The rigidity of the guest molecule contributes to a remarkably ordered structure, which thus serves as a reliable model for inclusion of a furocoumarin in a cyclodextrin. Systems of this type have been noted as appropriate models for the study of lipophilic interactions in biological systems [10]. The title structure is discussed in relation to known isostructural complexes [11] including TRIMEB·(L)-menthol·2H_2O [12].

MATERIALS AND METHODS

Complex Preparation and Preliminary Characterization

TRIMEB was purchased from Cyclolab (Hungary) and psoralen was obtained from Sigma Chemical Co. (MO, USA). A mass of 0.077 g of TRIMEB (0.054 mmol) was dissolved in 0.6 mL distilled water in a vial kept under ice. An equimolar amount of psoralen (0.010 g) was added with stirring overnight. This did not, however, result in solubilisation of the drug. The vial was placed in an oven at 50°C for 1 week, after which solubilisation was achieved by adding a few drops of ethanol. After 1 week, colourless prismatic crystals of the inclusion complex appeared. Water content was determined on fresh crystals by thermogravimetry (Mettler Toledo TGA/SDTA 851^e) under N_2-purge (flow rate 30 mL/min) using samples of mass ~1 mg and a scan rate of 10 K/min over the range 30–200°C. The host–guest ratio was determined from UV spectrophotometric absorbance measurements recorded at 294 nm on a Cintra 20 UV system. DSC analysis was performed on a Perkin-Elmer PC7 system calibrated with high-purity indium and zinc standards.

Crystal Structure Analysis

Intensity data were collected on a Nonius Kappa CCD diffractometer from a crystal coated with Paratone N oil (Exxon) and cooled using a Cryostream cooler (Oxford Cryosystems). The crystal system and space group were deduced from the Laue symmetry and systematic absences, respectively. Data-collection (COLLECT software [13]) involved a combination of ϕ- and ω-scans of 0.8–1.0° and a crystal to detector distance of 51 mm. Program DENZO-SMN [14] was used for unit cell refinement and data reduction. The structure was solved by isomorphous replacement using the co-ordinates of the host non-hydrogen atoms (excluding O6, C7, C8 and C9 atoms) of all methylglucose residues of the isostructural L-menthol complex [12]. Guest atoms were located in difference electron density maps. The single water molecule in the asymmetric unit (see TG data below) was disordered over two sites whose occupancies refined to 0.5 each. Except for the water molecules and one disordered host methyl C atom, which were treated isotropically, all non-H atoms of host and guest refined anisotropically. Hydrogen atoms were added in idealised positions in a riding model with $U_{iso} = 1.2$ times those of their parent atoms. H atoms on the disordered water molecule could not be located. Full-matrix least-squares refinement against F^2 (SHELXL97 [15]) was employed with a weighting scheme $w = [\sigma^2(F_o^2) + (0.0720P)^2 + 3.00P]^{-1}$ and $P = [\max(F_o^2, 0) + 2F_c^2]/3$. The CIF file for the structure has been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC 223556).

RESULTS AND DISCUSSION

Thermal Analysis

A one-step TGA weight loss of 0.9 ± 0.2% ($n = 2$) indicated a monohydrate (calcd. 1.1%). Crystal dehydration in this temperature range was confirmed by hot stage microscopy. The DSC trace was unremarkable, yielding a single endotherm for fusion with extrapolated onset 133.1°C and peak temperature 137.1°C. This differs sufficiently from the melting points of both host (157–159°C) and guest (163–164°C) to be useful as a means of complex identification. The anhydrous complex begins to decompose at 140°C.

X-Ray Analysis

General Description of the Structure

Crystal data and details of the structural refinement are listed in Table I. The complex unit TRIMEB·psoralen·H_2O with atoms drawn as thermal

TABLE I Crystal data and refinement details

Complex formula	$C_{63}H_{112}O_{35}\cdot C_{11}H_6O_3\cdot H_2O$
Formula weight	1633.70
Temperature	203(2) K
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 10.9445(1)$Å $b = 25.6523(3)$Å $c = 29.9394(4)$Å
Volume	8405.5(2)Å^3
Z	4
Density (calculated)	1.291 g cm^{-3}
Radiation, wavelength	MoKα, 0.71073 Å
Absorption coefficient	0.104 mm^{-1}
F (000)	3504
Crystal size	0.35 × 0.35 × 0.20 mm
θ range	1.02 to 27.10°
Index ranges	$-13 \le h \le 13$, $-32 \le k \le 32$, $-38 \le l \le 38$
Reflections collected	16174
Observed reflections [$I > 2\sigma(I)$]	13146
Data/restraints/parameters	16174/0/1036
Goodness-of-fit on F^2	1.049
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0508$, $wR^2 = 0.1267$
R indices (all data)	$R_1 = 0.0689$, $wR^2 = 0.1386$
Largest diff. peak and hole	−0.66, 0.34 eÅ^{-3}

ellipsoids as well as the atomic numbering is shown in Fig. 2, where the symbols Gn (n = 1–7) refer to the methylglucose residues. The comparable level of thermal motion of host and guest atoms is evident, indicating a tight fit of the psoralen molecule in the cavity.

The guest molecule is planar (maximum deviation from the LS plane including all non-H atoms 0.038(4) Å, rms deviation 0.019 Å). Interestingly, the molecular parameters observed in this study, for psoralen included in TRIMEB, are more accurate and precise than those reported for uncomplexed psoralen [16] owing to the difficulty of obtaining good crystals of the free guest. Figure 3 shows the extent of encapsulation of the guest molecule in the TRIMEB cavity. The latter is generally roughly bowl-shaped with the primary side capped to variable extents by methoxy groups. In this case, guest entry from the secondary side places the pyranone residue in contact with the host 'lid' while a portion of the furan ring protrudes from the host secondary side, making a shallow entry into the primary side of a host molecule related by translation along the short a-axis (see below). The host molecule is elliptically distorted to accommodate the elongated guest molecule.

Details of Host Geometry and Guest Inclusion Mode

All seven methylglucose residues adopt the $^4C_1$ conformation. Only host atom C7G1 displays disorder (Fig. 2), the two positions having site-occupancy factors of 0.69 and 0.31. The C6—O6 bonds generally point away from the TRIMEB cavity, in the (−)-*gauche* conformation, except in the cases

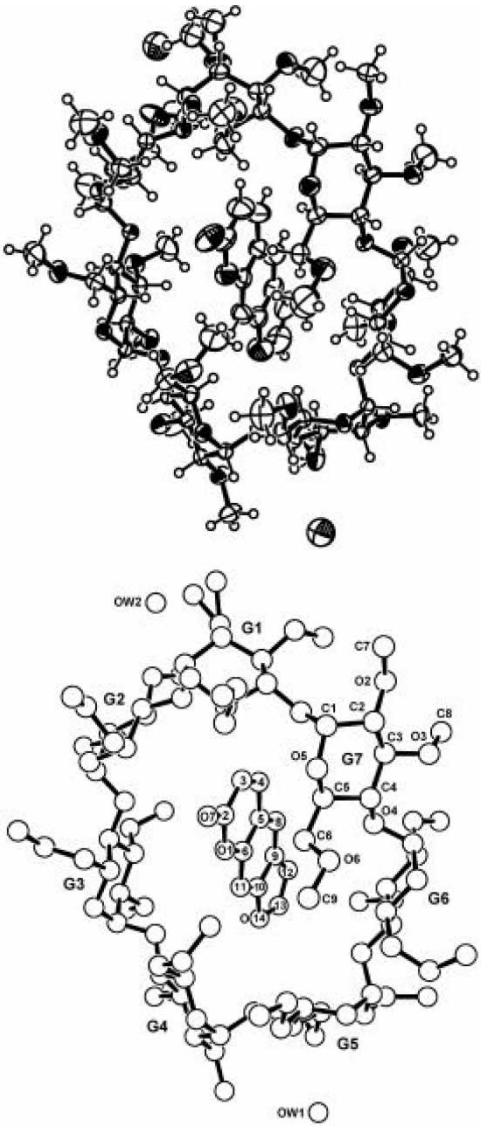

FIGURE 2 The complex unit viewed from the host primary side showing thermal ellipsoids drawn at the 50% probability level (top) and atomic numbering (bottom) with H atoms omitted for clarity. Guest carbon atoms are labelled with numerals only.

of G4 and G5, where a (+)-*gauche* conformation is assumed. The O6—C9 bonds of all residues are generally *trans* to the corresponding C5—C6 bonds (torsion angle range 161.4–177.7°) but those in G4 and G6 adopt a *gauche* relationship. The net result is

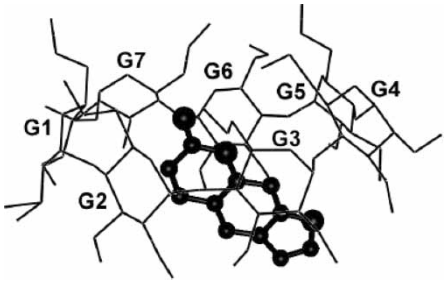

FIGURE 3 Side view of the title complex.

TABLE II Geometrical data for the host TRIMEB

(i) Glycosidic oxygen angle (°) and radius (Å) of the O4 heptagon measured from the centre of gravity of the seven O4 atoms to each O4 atom

O4G7···O4G1···O4G2	118.9	G1	5.29
O4G1···O4G2···O4G3	119.8	G2	5.47
O4G2···O4G3···O4G4	132.8	G3	4.69
O4G3···O4G4···O4G5	138.1	G4	4.65
O4G4···O4G5···O4G6	113.4	G5	5.60
O4G5···O4G6···O4G7	126.2	G6	5.07
O4G6···O4G7···O4G1	143.5	G7	4.30

(ii) O4···O4′ distance (Å)

O4G1···O4G2	4.23	O4G5···O4G6	4.22
O4G2···O4G3	4.43	O4G6···O4G7	4.51
O4G3···O4G4	4.63	O4G7···O4G1	4.44
O4G4···O4G5	4.30		

(iii) Glucose residue number, value of tilt angle (°),[a] glycosidic O4 atom label and deviation (Å) of each O4 atom from the least-squares plane through the seven O4 atoms

G1	25.7(2)	O4G1	0.540(2)
G2	11.0(1)	O4G2	−0.014(2)
G3	6.6(1)	O4G3	−0.409(1)
G4	41.0(1)	O4G4	0.116(1)
G5	22.3(1)	O4G5	0.440(1)
G6	11.6(1)	O4G6	−0.336(1)
G7	50.5(1)	O4G7	−0.336(2)
			RMS deviation: 0.357

[a] Dihedral angle between the mean O4*n* plane (*n* = 1–7) and atoms O4G(*n*)—C1G(*n*)—C4G(*n*)—O4G(*n* + 1).

partial capping of the primary side, mainly by the methoxy groups of G4, G5 and G7.

Table II lists the geometrical parameters for the TRIMEB molecule. These include the glycosidic oxygen angle O4G(*n* − 1)···O4G(*n*)···O4G(*n* + 1), the radius of the heptagon (measured from the centroid of the seven O4 atoms to each O4 atom), the glycosidic O4G*n*···O4G(*n* + 1) distance, the tilt angle of each glucose residue (defined in Table II) and the deviation of each O4 atom from the least-squares plane defined by all seven O4 atoms. The angle between the plane of the guest molecule and that defined by the seven glycosidic host O4 atoms is 79.4(1)°.

Encapsulation of the guest involves considerable distortion of the host molecule, as reflected in the wide ranges of the listed parameters. Significantly smaller ranges, reflecting a more 'round' host structure, were observed in, *e.g.* the TRIMEB· (*S*)-naproxen complex [17], namely 120.1–139.0° (glycosidic oxygen angle), 4.64–5.21 Å (O4···O4(centroid)distance), 4.25–4.54 Å (glycosidic O4G*n*···O4G(*n* + 1)distance) and 9.4–44.3° (tilt angle magnitudes). The smaller deviation from 'roundness' is associated with insertion of the (*S*)-naproxen molecule with its molecular axis nearly parallel to that of the host and with a major portion of the guest protruding from the secondary side.

Host–guest interactions are predominantly hydrophobic. Only two hydrogen bonds of type C—H···O were found (Table III); in one of these (C5G2—H···O7), the guest carbonyl O atom accepts a host methine H atom within the cavity, and in the other (C13—H···O6G4) a guest furan H atom is donated to O6G4 on the primary side of a TRIMEB molecule translated along the *x*-axis. Several C6G*n*—H···O5G(*n* − 1) hydrogen bonds [12,17] stabilise the observed conformation (Table III). A detailed comparison of the host conformation with that in the L-menthol complex [12] reveals remarkable similarities. The guest molecules psoralen and L-menthol occupy similar volumes within their respective host cavities and protrude from their host secondary sides to similar extents. These common features probably account for the isostructurality of these complexes. Stacking of the complex units by translation along the *x*-axis results in the crystal packing resembling channel formation (Fig. 4).

TABLE III C—H···O hydrogen bond data

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
C5G2-H··· O7	0.99	2.55	3.497(4)	159.6
C13-H···O6G4[a]	0.94	2.48	3.342(5)	152.8
C6G1-H···O5G7	0.98	2.42	3.244(4)	141.0
C6G2-H···O5G1	0.98	2.46	3.199(4)	132.4
C6G3-H···O5G2	0.98	2.58	3.203(3)	121.7
C6G5-H···O5G4	0.98	2.33	3.224(4)	152.1
C6G6-H···O5G5	0.98	2.45	3.195(3)	132.3
C2G5-H··· O6G3[b]	0.99	2.48	3.384(3)	151.2
C1G2-H···OW1[c]	0.99	2.49	3.179(8)	126.7
C7G4-H···OW1	0.97	2.56	3.328(8)	136.2
C8G2-H···OW1[d]	0.97	2.52	3.373(8)	147.5

[a] 1 + x, y, z. [b] 1 − x, 1/2 + y, 3/2 − z. [c] 1 − x, −1/2 + y, 3/2 − z. [d] 3/2 − x, 1 − y, −1/2 + z.

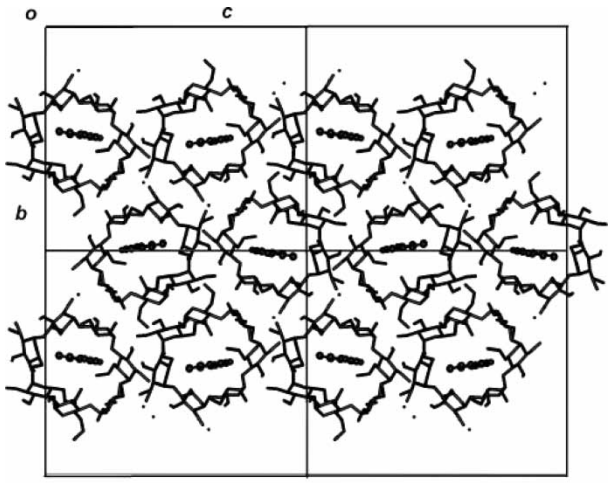

FIGURE 4 Crystal structure of the title complex viewed down [100]. The guest is shown in ball-and-stick mode while water oxygen atoms are shown as dots.

TABLE IV Hydrogen bonds involving water molecules

Atoms	Symmetry code for OW*n*	D···A (Å)
O3G5···OW1	*x,y,z*	2.646(7)
O5G2···OW1	$1-x,-1/2+y,3/2-z$	3.239(8)
O3G2···OW2	*x,y,z*	2.583(7)
O2G1···OW2	*x,y,z*	3.237(8)
O6G2···OW2	$-1/2+x,1/2-y,1-z$	2.855(8)

The disordered water molecules engage in hydrogen bonding (Table IV). OW1 links two TRIMEB molecules by hydrogen bonding to O3G5 (Fig. 2) and a symmetry-related O5G2. OW1 is also involved in C—H···O hydrogen bonding (Table III). OW2 bridges residues G1 and G2 by hydrogen bonding to atoms O2G1 and O3G2, respectively, and forms an intermolecular hydrogen bond to a symmetry-related atom O6G2.

Following the first report of a TRIMEB inclusion complex with unit cell dimensions $a \sim 11$, $b \sim 26$, $c \sim 29$ Å, space group $P2_12_12_1$ [12], several analogues have been identified. The guests in this series, like the present psoralen, tend to be relatively small, predominantly lipophilic molecules (methylcyclohexane [18], (*S*)-1,7-dioxaspiro(5.5)undecane [19], clofibric acid [20]). The other known isostructural series of TRIMEB complexes, with $a \sim 15$, $b \sim 21$, $c \sim 28$ Å, also crystallizing in space group $P2_12_12_1$, includes those with guests such as flurbiprofen, ibuprofen and naproxen [11,21]. In this series, a significant portion of the guest molecule protrudes from the secondary face, preventing the type of close stacking of host molecules observed here.

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