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Inclusion of Anesthetics in Cyclodextrins: Structural Investigation of Solid Inclusion Complexes of Butamben

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Single crystal and powder X-ray diffraction techniques were used to characterize inclusion complexes formed between the local anesthetic butamben (4-aminobenzoic acid butyl ester) and various cyclodextrins (CDs). Kneading butamben with the native hosts β- and γ-CD yielded microcrystalline products, unequivocally identified as inclusion complexes by powder X-ray diffraction. Single crystals of a 1:1 inclusion complex between butamben and permethylated β-CD (TRIMEB) were isolated. X-ray analysis revealed that the guest is included with the ester moiety fully encapsulated in the TRIMEB cavity. However, a major part of the phenylamine residue protrudes from the host primary side, entering the secondary side of a translated TRIMEB molecule to which it hydrogen bonds, both directly [$-NH_A\cdots O(host)$] and indirectly [$-NH_B\cdots O(water)\cdots O(host)$]. This unusual mode of guest inclusion is associated with a novel channel-like complex packing arrangement in the monoclinic space group $P2_1$. The included drug molecule adopts a more extended conformation than that found in the crystal of butamben, whose X-ray structure was also determined in this study.

INTRODUCTION

Enhancement of drug-delivery performance using formulations based on cyclodextrin (CD)-drug inclusion complexes is well known. Among the advantages to be gained from this approach are improved drug stability, solubility, dissolution rate and, in some instances, reduction of adverse side effects [1]. For local anesthetics, administration of dosage forms based on their CD inclusion complexes leads to slow release, thus prolonging anesthetic action and reducing cardiac and nervous system toxicity [2]. Recent patent applications for formulated products based on anesthetic/CD technology include those for the systems benzocaine–γ-CD (lozenge, topical cream) [3] and propofol-sulfobutyl ether β-CD (pharmaceutically stable injectable dosage form) [4]. For a medicinal formulation based on a solid CD-drug complex, structural characterization of the latter is essential for reproducible manufacture and processing. The importance of the X-ray technique in elucidating the structures of CD derivatives, modes of guest inclusion in CD complexes and crystal packing arrangements has been highlighted in a recent review [5]. Examples of drugs whose CD inclusion complexes have been determined by X-ray analysis include non-steroidal anti-inflammatory agents (e.g. flurbiprofen, fenoprofen, naproxen, diclofenac, acetylsalicylic acid, acetaminophen, piroxicam) and drugs from other classes, e.g. the sedative barbital and the antiemetic cyclizine [6]. As regards CD-anesthetic complexes, however, very little structural information is available. Here we report the structural characterization of solid complexes resulting from the interaction between the local anesthetic butamben (4-aminobenzoic acid butyl ester, Figure 1) and several CDs. In a previous study of this drug, complexes between butamben and the hosts heptakis(2,6-di-O-methyl)-β-CD and hydroxypropyl-β-CD (HPBCD) were prepared by freeze-drying and incorporated into fatty suppositories [7]. *In vivo* tests showed increased drug absorption from the butamben/HPBCD-containing formulation compared with suppositories containing the drug alone.

In this report, we present unequivocal evidence of inclusion of butamben in β-CD, γ-CD and heptakis(2,3,6-tri-O-methyl)-β-CD (TRIMEB).

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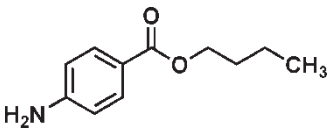

FIGURE 1 Molecular structure of the guest butamben.

Single crystal X-ray analysis of the TRIMEB·butamben inclusion complex revealed a relatively ordered structure, in contrast to the situation described for β-CD·benzocaine [8], a CD complex containing a drug guest in the same anesthetic class as the title drug. Furthermore, the mode of inclusion of the butamben molecule leads to channel-like crystal packing, which is very unusual for TRIMEB complexes. The conformation of the included guest molecule differs significantly from that of the uncomplexed drug, whose crystal structure is also reported here.

MATERIALS AND METHODS

Preparation of Complexes and Preliminary Characterization

The native CDs (α-, β-, γ-CD) and TRIMEB were purchased from Cyclolab (Hungary). Butamben was obtained from Sigma Chemical Co. (MO, USA). To investigate the interaction between the drug and the native CDs, butamben was kneaded for 1 h with each CD, with the addition of small amounts of distilled water to maintain a pasty consistency. Only 1:1 host–guest ratios were tested. The kneaded products were examined by X-ray powder diffraction (PXRD) on a Huber Imaging Plate Guinier Camera 670 using CuKα-radiation ($\lambda = 1.5405981$ Å) produced at 40 kV, 20 mA by a Philips PW1120/00 generator with a Huber monochromator attached to the X-ray tube.

Single, acicular crystals of butamben suitable for X-ray analysis were obtained by dissolving 2 mg of the powder in 1.5 ml ethanol at 60°C, and allowing the solution to evaporate spontaneously at 24°C.

To prepare the TRIMEB complex, 0.37 g (0.26 mmol) TRIMEB was dissolved in 1 ml distilled water under ice and 0.05 g (0.26 mmol) butamben was added to the solution with stirring overnight, resulting in the formation of a thick paste. 60 ml of water were added to dissolve the paste and the clear solution was filtered into a vial and left to concentrate on a hot-plate at 50°C. The concentrate was sealed, and crystals of the TRIMEB·butamben complex appeared after one week. These were analysed by thermogravimetry (TG), elemental analysis and differential scanning calorimetry (DSC). TG analysis was performed on a Mettler Toledo TGA/SDTA 851^e apparatus in the range 30–220°C at a scan rate of 10 K min^{-1} with nitrogen purge at 30 ml min^{-1} and samples in the mass range 3–4 mg. A mass loss of $0.40 \pm 0.08\%$ ($n = 2$) indicated the loss of 0.36 water molecules per complex unit. Elemental analysis yielded %C 54.6, %H 8.03, %N 0.84 (calcd. for $C_{63}H_{112}O_{35} \cdot C_{11}H_{15}NO_2 \cdot 0.36H_2O$: %C 54.55, %H 7.90, %N 0.86), corresponding to 1:1 CD-drug stoichiometry. DSC traces for pure butamben and the inclusion complex were recorded on a Perkin Elmer PC7 system calibrated with high-purity indium and zinc standards. Conditions were: scan rate 5 K min^{-1}; nitrogen purge 30 ml min^{-1}; sample mass range 2–4 mg.

Single Crystal X-ray Analyses

The structure of butamben was determined from intensity data collected on a Nonius Kappa CCD diffractometer. Data collection (COLLECT software [9]) involved a combination of ϕ- and ω-scans of 1.0° each and a crystal to detector distance of 30 mm. Laue symmetry $2/m$ indicated that the monoclinic system and the systematic absences were consistent with the space group $P2_1/c$. Program DENZO-SMN [10] was used for unit cell refinement and data reduction. The structure was solved by direct methods [11] and refined routinely by full-matrix least-squares on F^2 (SHELXL97 [12]) with a weighting scheme $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$ where $P = [\max(F_o^2, 0) + 2F_c^2]/3$. H atoms were located and added in idealised positions with U_{iso} values set to 1.2 times those of their parent atoms. All non-H atoms refined anisotropically. Further details are given in Table I.

An initial attempt to refine the crystal structure of the TRIMEB·butamben complex using intensity data collected at low temperature (173 K) resulted in unsatisfactorily large residual factors ($R_1 = 0.159$, $wR2 = 0.439$), due to an increase in crystal mosaicity upon cooling from ambient temperature. Intensity data for the structure reported were collected at 293(1) K using a similar strategy to that employed for butamben, with a crystal-to-detector distance of 40 mm. The monoclinic crystal system and space group $P2_1$ were deduced from the Laue symmetry ($2/m$) and systematic absences ($0\,k\,0$ $k = 2n + 1$) respectively. The structure was solved by Patterson search methods [13] using selected fragments of the host molecule of the TRIMEB·naproxen inclusion complex [14]. Except for nine atoms (mainly methyl C atoms) modelled isotropically, host atoms refined anisotropically. Remarkably, there were no alternative atom sites interpretable as host disorder. Guest atoms were located in difference electron density maps. Due to the generally high level of guest thermal motion, these atoms appeared with relatively low electron densities. They were treated

TABLE I Crystal data and refinement details

Formula	$C_{11}H_{15}NO_2$	$C_{63}H_{112}O_{35}\cdot C_{11}H_{15}NO_2\cdot 0.36H_2O$
Formula weight	193.25	1629.25
Temperature/K	298(2)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1$
a/Å	8.3508(5)	10.8911(2)
b/Å	5.2093(4)	14.8575(2)
c/Å	25.626(2)	27.5834(5)
β/°	95.372(2)	99.62(3)
Volume/Å^3	1109.9(1)	4400.6(1)
Z	4	2
Density (calc.)/g m^{-3}	1.156	1.230
Radiation, wavelength/Å	MoKα, 0.71073	MoKα, 0.71073
Absorption coefficient/mm^{-1}	0.079	0.098
$F(000)$	416	1755
Crystal size/mm^3	0.45 × 0.25 × 0.14	0.40 × 0.40 × 0.30
Theta range/°	1.02 to 21.49	1.02 to 24.11
Index ranges	$-7 \le h \le 8$, $-4 \le k \le 5$, $-25 \le l \le 25$	$-12 \le h \le 12$, $-17 \le k \le 16$, $-31 \le l \le 31$
Reflections collected	4588	23230
Observed reflections [$I > 2\sigma(I)$]	1761	9498
Data/restraints/parameters	2435/0/129	13146/9/877
Goodness-of-fit on F^2	1.062	1.329
Final R indices R_1, wR^2 [$I > 2\sigma(I)$]	0.0584, 0.1515	0.1108, 0.3009
R indices R_1, wR^2 (all data)	0.0820, 0.1718	0.1382, 0.3296
Largest diff. peak and hole/e Å^{-3}	−0.15, 0.25	−0.67, 0.62

with a common, fixed isotropic displacement parameter of 0.20 Å^2 (the average of the individual U_{iso} values on free refinement). The phenyl ring was modelled as a regular hexagon, and several distance restraints (taken from the structure of the uncomplexed drug) were applied to maintain reasonable guest geometry. Compared with the molecular structure of the uncomplexed drug, the precision of that of butamben included in TRIMEB is therefore relatively low, but more than adequately defined to describe its interaction with the host. The partial water molecule was located, modelled with a fixed site-occupancy factor 0.36 (in accord with the TG data) and refined isotropically ($U_{iso} = 0.147$ Å^2). Hydrogen atoms were added to both host and guest in idealised positions in a riding model with $U_{iso} = 1.2$ times those of their parent atoms. H atoms on the partial water molecule could not be located. Full-matrix least-squares refinement on F^2 was employed, with weighting as for butamben above. Crystal and refinement details appear in Table I. The CIF files for the structures have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 226560 and 226561).

RESULTS AND DISCUSSION

Interaction between Butamben and Native CDs

The PXRD pattern of the product of kneading butamben and α-CD resembled that of the 1:1 physical mixture, indicating that no inclusion had taken place. However, the PXRD patterns of the products obtained by kneading butamben with β- and γ-CD gave convincing matches with published reference patterns for CD inclusion complexes [15]. Figure 2 shows the comparison in the case of the host β-CD. The PXRD pattern for the kneaded material yields peaks with angular values in excellent agreement with those for the reference pattern for dimeric β-CD inclusion complexes crystallizing in the space group $P1$ with $a \sim 15.6$, $b \sim 15.6$, $c \sim 15.9$ Å, $\alpha \sim 102$, $\beta \sim 102$, $\gamma \sim 104°$. (It should, however, be noted that there is a close correspondence between the reference pattern shown and that for monoclinic dimeric β-CD inclusion complexes crystallizing in the space group $C2$ with $a \sim 19.3$, $b \sim 24.4$, $c \sim 15.9$ Å, $\beta \sim 109°$, owing to a simple lattice transformation relating the respective triclinic and monoclinic unit cells.) As explained earlier [15], since the peak intensities in the reference patterns have been artificially generated by averaging computed PXRD patterns of known isostructural

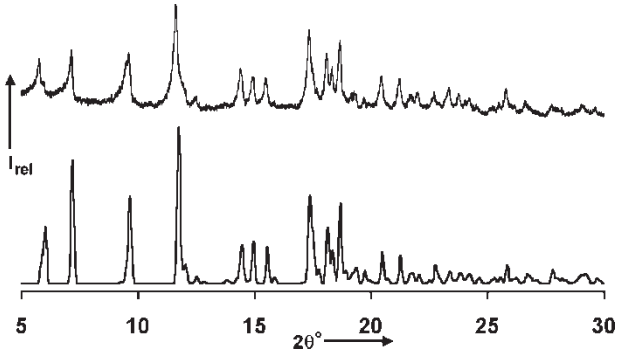

FIGURE 2 Experimental (top) and reference (bottom) PXRD patterns for the inclusion complex between β-CD and butamben.

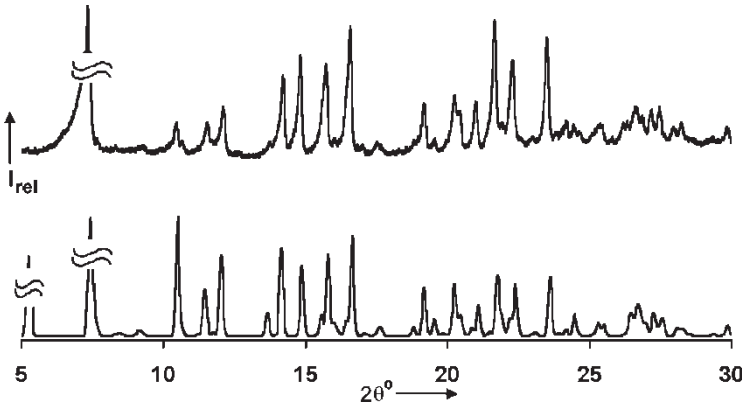

FIGURE 3 Experimental (top) and reference (bottom) PXRD patterns for the inclusion complex between γ-CD and butamben.

compounds, less attention is necessarily given to intensity matching than peak position matching when applying this procedure for detecting complex formation. Figure 3 compares the PXRD pattern for the product of kneading butamben and γ-CD, and the reference pattern for γ-CD inclusion complexes. The match in this case indicates that butamben definitely forms a γ-CD inclusion complex crystallizing in the tetragonal space group $P42_12$ with approximate unit cell dimensions $a \sim 23.8$, $c \sim 23.2$ Å.

We attempted to grow single crystals of the β- and γ-CD complexes of butamben, both by recrystallization from water of the microcrystalline complexes from kneading and by the co-precipitation method, but neither produced satisfactory results. However, the definitive information deduced from the PXRD patterns above provides a sound basis for possible future modelling of the structures from high-resolution PXRD data that might be obtained using e.g. synchrotron radiation.

Structure of Uncomplexed Butamben

Crystal data and refinement details are listed in Table I. Figure 4 shows the molecular and crystal structure of the uncomplexed drug. Molecular parameters are in the expected ranges [6]. The *n*-butyl chain is in an extended conformation with its mean plane nearly orthogonal to the rest of the molecule. The L-shaped molecular conformation allows the amino- and carbonyl groups to engage in intermolecular hydrogen bonding (N7–H7A···O9^{i} with N···O 2.950(3) Å, $i = 1 + x,\ y,\ z$; N7–HB···N7^{ii} with N···N 3.253(3) Å, ii $= 2 - x,\ 1/2 + y,\ 1/2 - z$) and the hydrophobic alkyl chains to interdigitate in the crystal. As discussed below, the butamben molecule adopts a distinctly different conformation when the interactions shown in Figure 4 are replaced by those associated with its isolation and encapsulation by the host TRIMEB.

Structure of the TRIMEB·butamben Inclusion Complex

The crystals of the TRIMEB inclusion complex yielded a DSC trace showing a single endotherm with onset and peak temperatures of 126.3 and 128.9°C respectively. The melting point of the drug is 57–59°C and its inclusion in TRIMEB therefore significantly increases its thermal stability. Since the host m.p. (157–159°C) is also significantly different from that of the complex, DSC is a useful technique for complex identification. From TG analysis, it was evident that complex decomposition commences around 160°C.

The complex unit, viewed from the host primary side, is shown in Figure 5. The guest is included with the hydrophobic ester moiety occupying the interior of the TRIMEB cavity, while a significant portion of the phenylamine residue protrudes from the host primary side. This mode of inclusion differs from that observed for TRIMEB inclusion complexes with other drugs (e.g. (S)-ibuprofen [16], (L)-menthol [17] and clofibric acid [18]). In the latter complexes, the host primary side is blocked by several methoxyl groups and a significant portion of the drug molecule protrudes instead from the host secondary side. The conformation of the butamben molecule is an extended one, in contrast to the L-shaped conformation of the uncomplexed guest (Figure 4).

The methylglucose residues in Figure 5 are labelled G*n* ($n = 1 - 7$) and the numbering of key atoms in the representative residue G1 follows previous convention [14]. A striking feature of the host structure is the uniform *trans*-conformation of the C5–C6–O6–C9 residues (except for G7), with the C6–O6 bonds directed away from the host cavity in all cases. This unusual and uniform 'opening' of the host primary side is a result of steric clashes between

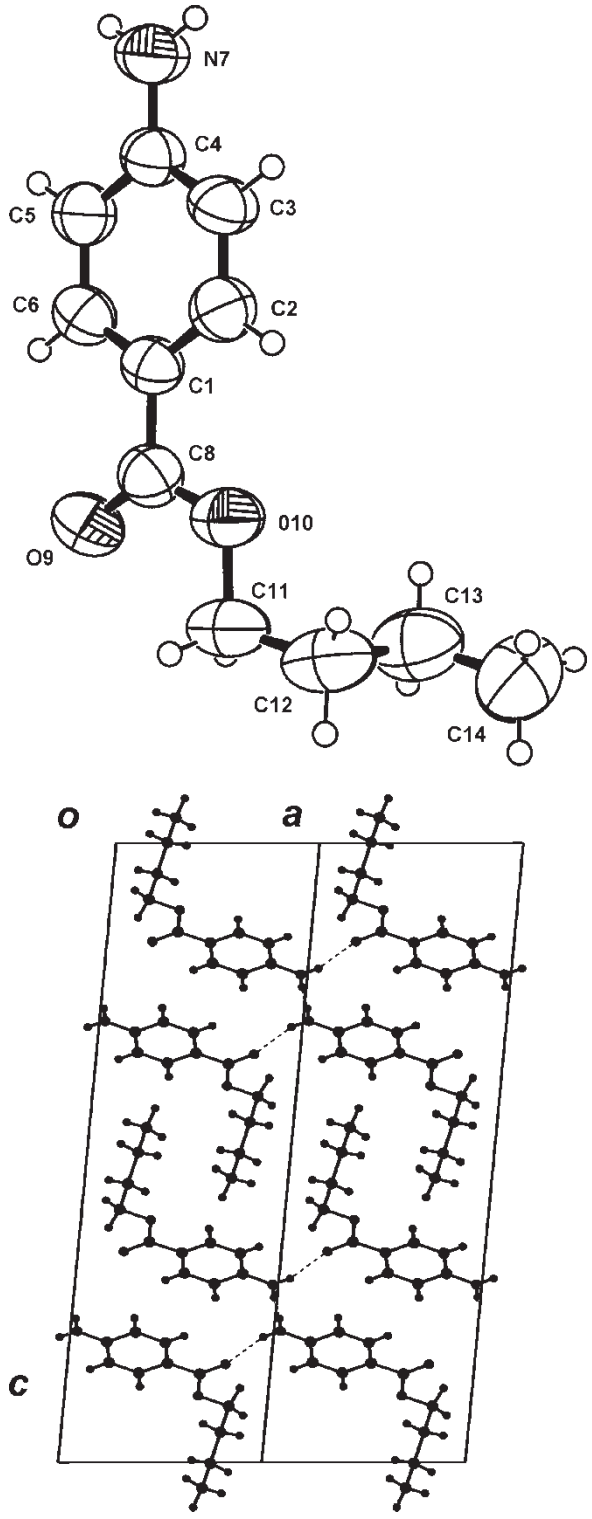

FIGURE 4 Molecular structure (top) and crystal structure (bottom) of butamben. Thermal ellipsoids are drawn at the 50% probability level.

the protruding guest phenylamine residue and the chains attached to C5 of each methylglucose residue, which otherwise tend to form a 'lid' on the primary side. The torsion angles C5–C6–O6–C9 (τ_1) are in the magnitude range 169(1)–178(1)°, except for G7 where the conformation is *gauche* with $\tau_1 = 75(1)°$.

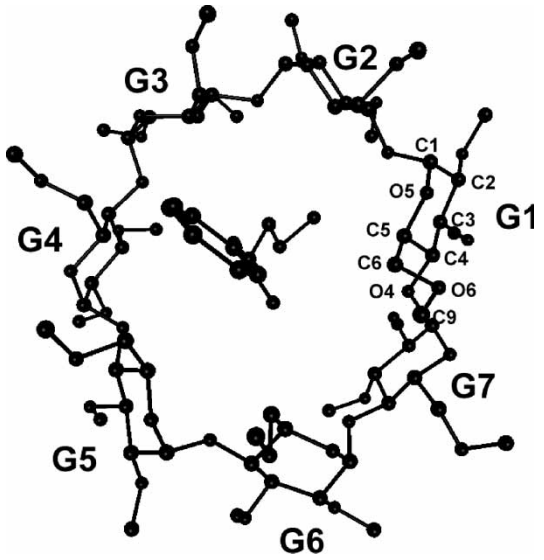

FIGURE 5 TRIMEB·butamben complex unit viewed from the host primary side showing atomic numbering. H atoms and the water O atom are omitted for clarity.

The directions of the C6–O6 bonds (away from the host cavity) are defined by the torsion angles O5–C5–C6–O6 (τ_2), all of which are (−)-*gauche* with magnitude range 61(1)–77(2)°.

Table II lists other standard geometrical parameters defining the host conformation. 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 O4Gn···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. An elliptical host conformation is evident from the ranges of values for the heptagon radii (4.40–5.31 Å) and the glycosidic oxygen angles (119.4–141.3°). Five of the seven methylglucose residues have positive tilt angles, indicating that their primary sides incline towards the host cavity. Four hydrogen bonds of type C6Gn − H···O5G($n-1$) [19], with C···O in the range 3.21(1)–3.36(1)Å, stabilize the distorted host conformation.

The protrusion of the guest phenylamine residue from the host primary side was emphasised above. This residue enters the secondary side of a translated complex unit (Fig. 6), thus giving rise to a channel-like stacking, in contrast to the more frequently encountered cage-like packing motifs associated with TRIMEB complexes. The translated units are separated by the *a*-axis length of ~10.9 Å. Both H atoms of the guest amino group are donors in hydrogen bonds (Fig. 6), one to a methoxyl O atom on the secondary side of the penetrated host (N7–HA···O2G4^{i}, N···O 3.09(2) Å, i = 1 + x, y, z) and the other to the disordered water

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	141.3	G1	4.40
O4G1···O4G2···O4G3	120.8	G2	5.14
O4G2···O4G3···O4G4	123.0	G3	5.30
O4G3···O4G4···O4G5	129.1	G4	4.86
O4G4···O4G5···O4G6	134.6	G5	4.72
O4G5···O4G6···O4G7	119.4	G6	5.31
O4G6···O4G7···O4G1	121.8	G7	5.15
(ii) O4···O4′ distance (Å)			
O4G1···O4G2	4.35	O4G5···O4G6	4.31
O4G2···O4G3	4.30	O4G6···O4G7	4.27
O4G3···O4G4	4.36	O4G7···O4G1	4.42
O4G4···O4G5	4.58		
(iii) Glucose residue number, value of tilt angle (°)*, glycosidic O4 atom label and deviation (Å) of each O4 atom from the least-squares plane through the seven O4 atoms			
G1	38.6(4)	O4G1	−0.497(4)
G2	24.0(4)	O4G2	0.472(4)
G3	12.6(3)	O4G3	0.198(4)
G4	−6.2(1)	O4G4	−0.436(4)
G5	34.7(2)	O4G5	−0.111(3)
G6	41.3(2)	O4G6	0.622(3)
G7	−22.5(3)	O467	−0.248(4)
			RMS deviation: 0.407

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

molecule located in the host cavity (N7–H7B···O1W, N···O 2.74(3) Å). The water molecule is in turn hydrogen-bonded to a host glycosidic O atom (O1W–H···O4G6^{i}, O···O 3.01(2) Å, i = $1 + x, y, z$).

The closest analogue of the complex presented here is the β-CD·benzocaine complex [8], the guest (4-aminobenzoic acid ethyl ester) being a lower homologue of butamben. Comparison is limited, however, owing to the very different structural motifs arising with the hosts β-CD and TRIMEB. The β-CD·benzocaine complex is a dimeric species (space group *C*2) in which the two halves of the dimer are related by the diad. Owing to channel-stacking of the complex units, guest disorder is common in this arrangement and benzocaine is no exception. One parallel between β-CD·benzocaine and TRIMEB·butamben, however, is the presence of a single water molecule in the host cavity. In the former structure, the water molecule links guest ester moieties by hydrogen bonding to their carbonyl oxygen atoms. In addition, statistical disorder leads to two modes of guest(NH_2) hydrogen bonding: the $-NH_2$ group of one guest molecule hydrogen bonds directly to a primary –OH group of the host β-CD, while that of the other is hydrogen-bonded *via* a water molecule to a different host primary –OH group. Interestingly, in the structure of the TRIMEB·butamben complex, both types of hydrogen bonding [$-NH_A\cdots$O(host), $-NH_B\cdots$O(water)···O(host)] are manifested simultaneously by the ordered $-NH_2$ group (Figure 6). The importance of water molecules as a possible determinant of guest orientation in CD inclusion complexes was stressed earlier [18]. In the complex TRIMEB·clofibric acid, hydrogen bonding mediated by water molecules allows the polar carboxyl group of the guest to be located inside the hydrophobic host cavity.

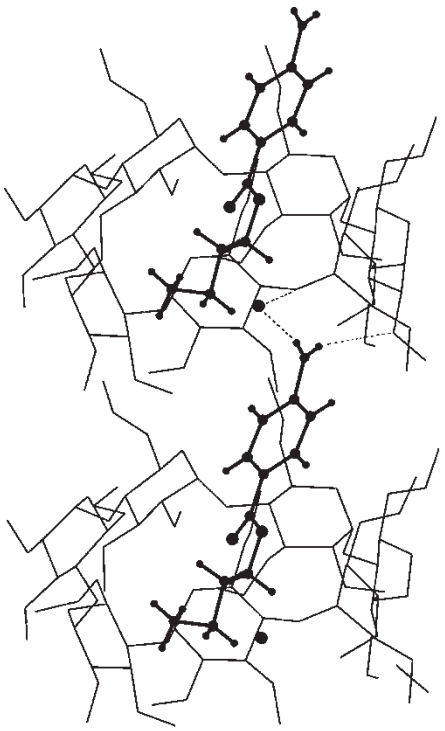

FIGURE 6 Two TRIMEB·butamben complex units related by translation along the *a*-axis and host–guest hydrogen bonds (dotted lines). The water molecule is represented by a filled circle.

The channel-like packing arrangement (space group $P2_1$) is shown in Fig. 7. The presence of 2_1-axes

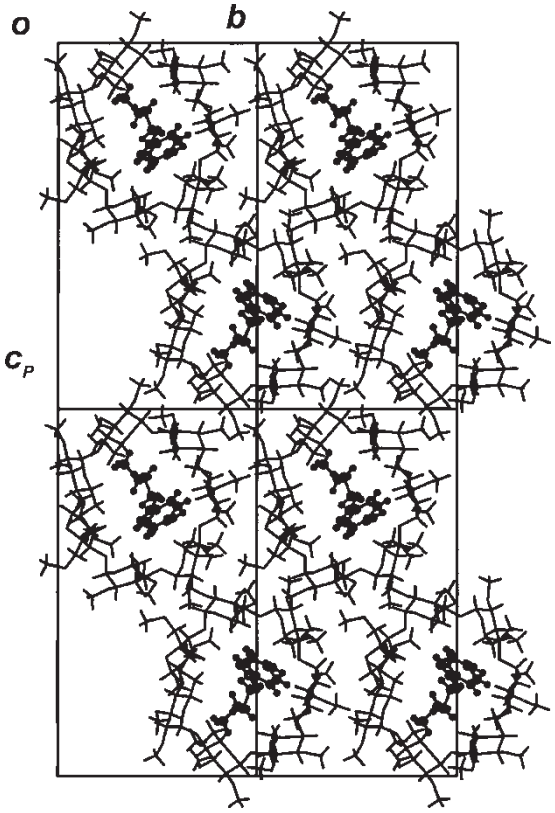

FIGURE 7 [1 0 0] Projection of the crystal packing in the TRIMEB·butamben complex.

parallel to only one direction (the unique axis) yields a structure in which successive layers of complex units parallel to *b* have alternating polarities. This is unusual for TRIMEB complexes, which typically crystallize in the space group $P2_12_12_1$, consistent with modulated channel-packing motifs [5]. Consequently, the PXRD pattern of the TRIMEB·butamben complex differs significantly from that of known TRIMEB inclusion complexes, having no isostructural counterpart. From the computed PXRD pattern based on CuKα X-rays, the most intense peak for this phase comprises contributions from the reflections (1 0 0) and (1 0 $-$ 1) with $2\theta = 8.23°$ and 8.33° respectively.

Conclusion

Ample evidence for the formation of inclusion complexes between the local anesthetic butamben and various CDs has been presented in this report. Powder X-ray diffraction was invaluable in proving the formation of complexes of butamben with the native hosts β- and γ-CD, while single crystal X-ray analysis revealed an unusual mode of inclusion of the drug in permethylated β-CD, associated with a novel crystal packing arrangement. The interaction between CDs and related compounds with anesthetic properties is currently under investigation in this laboratory.

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