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Inclusion of Ibuprofen by Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin: An X-ray Diffraction and Thermal Analysis Study

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Abstract. Inclusion of the non-steroidal anti-inflammatory drug ibuprofen by permethylated β-cyclodextrin (TRIMEB) was investigated by thermal analysis and X-ray diffraction. Reaction between racemic ibuprofen and TRIMEB yielded a mixture of isomorphous crystals of TRIMEB – (*R*)-ibuprofen and TRIMEB – (*S*)-ibuprofen. The single crystal chosen for X-ray analysis was found to contain the (*S*)-isomer of the drug. The crystal is orthorhombic, space group $P2_12_12_1$, with a = 15. 232(7) Å, b = 21.327(7) Å, c = 27.597(7) Å and Z = 4. The structure was solved using the coordinates for the rigid portion of the cyclodextrin molecule of the isomorphous complex with (*S*)-naproxen. Refinement by full-matrix least-squares techniques gave a final R factor of 0.079 for 7473 unique observed reflections. The isobutyl group of (*S*)-ibuprofen is included in the cyclodextrin cavity through hydrophobic forces, with the propionic acid group protruding from the *O*(2), *O*(3) face. The lack of chiral discrimination of the host TRIMEB towards ibuprofen as guest was confirmed by a combination of X-ray diffraction methods, thermal analysis and polarimetry.

Key words: Permethylated β-cyclodextrin, ibuprofen, inclusion complex, X-ray crystal structure, thermal analysis.

1. Introduction

As part of a systematic study of the inclusion of non-steroidal anti-inflammatory drugs (NSAIDs) by cyclodextrins (CDs), we have investigated the inclusion of ibuprofen (2-(4-isobutylphenyl) propionic acid) by permethylated β-CD (heptakis (2,3,6-tri-*O*-methyl)-β-CD, or TRIMEB). Ibuprofen is a widely used anti-inflammatory agent which is effective in the treatment of rheumatoid arthritis and primary dysmenorrhea. It belongs to the arylpropionic acid derivative class of NSAIDs, which includes fenoprofen, flurbiprofen, ketoprofen and naproxen [1]. Because of the generally low aqueous solubilities of compounds in this class, several studies have been carried out aimed at improving their bioavailability by CD-inclusion [2]. Solubility enhancement factors at 25 °C for ibuprofen in

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10% aqueous solutions of β-CD, DIMEB (heptakis(2,6-di-*O*-methyl)-β-CD) and TRIMEB have been reported as 2.1, 28.0 and 1.9, respectively [3]. It has further been demonstrated that the β-CD complex of ibuprofen is less irritating to mucous membranes relative to the free drug [4] and that both the undesirable taste [4] and smell [5] of ibuprofen are masked by CD-inclusion.

Our interest lies in the nature of host–guest interactions in complexes of this type. We recently reported the thermal analysis and X-ray crystal structure of the 1 : 1 complex between (*S*)-naproxen and TRIMEB [6]. Crystal structures of TRIMEB complexes with (*R*)- and (*S*)-flurbiprofen have also been reported [7, 8]. Here we present the preparation, thermal analysis and X-ray powder diffraction data for the TRIMEB complex with ibuprofen and we describe the mode of inclusion of the (*S*)-isomer of the drug molecule in the cavity of the TRIMEB molecule in the solid state as determined by single crystal X-ray analysis. The results of experiments involving complex formation between (*S*)-ibuprofen and TRIMEB, and between racemic ibuprofen and TRIMEB are also discussed with reference to the question of chiral discrimination.

2. Experimental

2.1. Materials

Racemic ibuprofen (m.p. 75–77 °C) and (*S*)-ibuprofen (m.p. 50–54 °C) were obtained from The Boots Company, Nottingham, U.K., and TRIMEB from Cyclolab, Budapest, Hungary.

2.2. Complex preparation

Equimolar amounts of TRIMEB and racemic ibuprofen were dissolved in distilled water at room temperature and the resultant solution was incubated at 50 °C for 48 h. Large, colourless prismatic crystals were obtained. In separate experiments, microcrystalline complexes of TRIMEB with both racemic and (*S*)-ibuprofen were prepared by stirring equimolar aqueous solutions for 24 h and filtering the insoluble powders that formed in each case.

2.3. Thermal analysis

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were performed on a Perkin–Elmer PC-7 series thermal analysis system at a scanning rate of 5 °C/min under N_2. Traces were recorded over a temperature range of 30–200 °C. Sample masses were 7–11 mg. Samples for DSC were placed in vented pans.

2.4. CRYSTAL STRUCTURE SOLUTION

A single crystal, selected from those prepared by using racemic ibuprofen and TRIMEB, was mounted on an Enraf–Nonius CAD4 diffractometer and intensity data were collected at 253 K using graphite-monochromated MoK_α radiation (λ = 0.71069 Å). Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections in the range $16° < \theta < 17°$. The ω-scan technique was used and, to ensure accurate measurement of weak reflections, a pre-scan acceptance parameter of zero was chosen to force the final intensity scans up to a maximum of 100 s per reflection. Data were collected to $(\sin \theta/\lambda)_{max}$ = 0.595 Å^{-1}. Three standard reflections (3 15 8; 3 2 21; 5 15 6), which were monitored every hour, showed only a 2.5% decrease in intensity over the period of the data collection. Orientation control was performed every 200 reflections. Data were corrected for Lp effects. Crystal data collection and refinement details are given in Table I.

The structure was solved using coordinates for the non-hydrogen atoms (excluding O(6), C(7), C(8) and C(9) for each methylglucose residue) of the isomorphous TRIMEB(−)(*S*)-naproxen complex [6]. After refinement of these atoms by full-matrix least-squares techniques (minimisation of $\sum w(|F_0| - |kF_c|)^2$ using SHELX-76 [9]), successive difference Fourier syntheses revealed all remaining non-hydrogen atoms. One molecule of ibuprofen, in the (*S*)-configuration, was found to be included in the TRIMEB molecule. All atoms were assigned anisotropic temperature factors. Hydrogen atoms attached to carbon atoms on both host and guest were inserted at idealised positions (C—H = 1.00 Å), with methyl hydrogen atoms on the cyclodextrin and guest being assigned a common variable isotropic temperature. Other hydrogen atoms on each methylglucose moiety and the guest were allocated common variable isotropic temperature factors. Due to abnormally long bond lengths and large bond angles for atoms of the guest isobutyl group, the position of H(13) was not idealised and was instead obtained from a difference Fourier synthesis, and allowed to refine with distance constraints to atoms C(12), C(13) and C(14). The final fractional coordinates obtained for the non-hydrogen atoms of the complex are listed in Table II. Molecular diagrams were drawn with PLUTO [10] and molecular parameters were calculated using program PARST [11].

2.5. X-RAY POWDER DIFFRACTION (XRD)

XRD traces were recorded in the 2θ range of 6–40° on a Philips PW1050/80 vertical goniometer with Ni-filtered CuK_α radiation (λ = 1.5418 Å). Samples were mounted in aluminium holders and step scans (0.1°2θ, 1s counts) were carried out using automatic receiving and divergence slits.

A simulated XRD pattern for the TRIMEB – (*S*)-ibuprofen complex was calculated with the program LAZY PULVERIX [12] using refined crystal data as input.

Table I. Crystal data, experimental and refinement parameters for TRIMEB – (*S*)-ibuprofen complex.

Molecular formula	$C_{63}H_{112}O_{35}\cdot C_{13}H_{18}O_2$
M_r/g mol^{-1}	1635.8
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z	4
a (Å)	15.232 (7)
b (Å)	21.327 (7)
c (Å)	27.597 (7)
V (Å^3)	8965 (5)
D_x (g cm^{-3})	1.211
Crystal dimensions (mm)	0.3 × 0.4 × 0.5
T/K	253
Range scanned θ °	$1 \leq \theta \leq 25$
Index range	h: 0, 18; k: 0, 25; l: 0, 32
Scan width (°)	0.8 + 0.35 tan θ
Aperture width (mm)	1.12 + 1.05 tan θ
No. reflections collected	8619
No. unique reflections	7473
No. reflections with $I > 2\sigma(I)$	4888
No. L.S. parameters	1112
R	0.079
w	$[\sigma^2(F_0)]^{-1}$
R_w	0.066
S	4.029
Shift/e.s.d. max., ave.	0.921, 0.040
$(\Delta\rho)_{max}$ final (e Å^{-3})	0.15
$(\Delta\rho)_{min}$ final (e Å^{-3})	−0.11

3. Results and Discussion

3.1. Thermal analysis

The TGA and DSC traces for the crystals obtained by reacting racemic ibuprofen and TRIMEB are shown in Figure 1, (i) and (ii), respectively. Thermogravimetric analysis (TGA) showed a negligible mass loss (0.5%) over the temperature range. This may be attributed to loss of surface water. It was concluded that no molecules of water of crystallisation were present in the complex. This was supported by no apparent cracking of the crystal surfaces under the hot stage microscope and confirmed by the X-ray analysis. The melting endotherm for the complex occurs at 186.3 °C, a significantly higher temperature than that corresponding to fusion of TRIMEB, 159.1 °C (Figure 1(iii)). These melting temperatures were confirmed by hot stage microscopy.

Table II. Final fractional atomic coordinates ($\times 10^4$) and displacement parameters ($Å^2 \times 10^3$) with estimated standard deviations in parentheses for TRIMEB–(*S*)-ibuprofen complex.

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i * a_j * a_i \cdot a_j$$

Atom	x/a	y/b	z/c	U_{eq}
C(1G1)	8631(6)	4637(5)	4754(4)	42(4)
C(2G1)	7917(6)	4164(4)	4917(3)	38(4)
C(3G1)	7372(6)	3943(4)	4486(3)	35(3)
C(4G1)	6980(6)	4528(4)	4251(3)	36(4)
C(5G1)	7712(6)	4970(4)	4093(3)	38(4)
C(6G1)	7403(7)	5569(5)	3869(4)	51(4)
C(7G1)	8547(7)	3736(5)	5633(4)	59(4)
C(8G1)	6664(7)	2952(5)	4435(4)	70(5)
C(9G1)	6354(9)	6358(5)	3941(4)	94(7)
O(2G1)	8282(4)	3619(3)	5147(2)	45(3)
O(3G1)	6696(5)	3547(3)	4660(2)	49(3)
O(4G1)	6473(4)	4316(3)	3846(2)	39(2)
O(5G1)	8220(4)	5141(3)	4516(2)	39(2)
O(6G1)	6731(5)	5825(3)	4154(3)	63(3)
C(1G2)	11802(6)	4178(5)	4041(3)	47(4)
C(2G2)	11517(6)	3738(5)	4457(4)	41(4)
C(3G2)	10508(6)	3725(5)	4492(3)	37(4)
C(4G2)	10141(6)	4389(5)	4517(4)	43(4)
C(5G2)	10530(6)	4805(5)	4123(4)	43(4)
C(6G2)	10304(7)	5498(5)	4184(4)	60(5)
C(7G2)	12676(8)	2992(6)	4478(5)	105(6)
C(8G2)	9856(7)	2804(5)	4826(4)	61(5)
C(9G2)	10303(11)	6451(6)	3786(6)	137(9)
O(2G2)	11765(5)	3096(4)	4387(3)	63(3)
O(3G2)	10273(4)	3389(3)	4913(2)	44(3)
O(4G2)	9205(4)	4306(3)	4435(2)	40(3)
O(5G2)	11468(5)	4765(3)	4141(2)	51(3)
O(6G2)	10506(6)	5804(4)	3749(3)	89(4)
C(1G3)	12454(7)	3908(5)	2177(3)	43(4)
C(2G3)	12454(7)	3283(5)	2437(3)	46(4)
C(3G3)	11917(7)	3332(5)	2904(4)	50(4)
C(4G3)	12162(6)	3907(5)	3201(3)	43(4)
C(5G3)	12126(6)	4495(5)	2891(3)	45(4)
C(6G3)	12355(7)	5098(5)	3134(4)	53(4)
C(7G3)	12527(15)	2280(7)	2137(6)	212(14)
C(8G3)	11266(9)	2467(6)	3304(5)	96(7)
C(9G3)	13455(8)	5616(6)	3562(5)	101(6)
O(2G3)	12162(6)	2812(4)	2134(3)	82(4)
O(3G3)	12041(5)	2768(3)	3172(3)	63(3)
O(4G3)	11528(4)	3929(3)	3594(2)	41(2)
O(5G3)	12702(4)	4402(3)	2488(2)	42(3)

Table II. Continued

$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i * a_j * a_i \cdot a_j$

Atom	x/a	y/b	z/c	U_{eq}
O(6G3)	13194(5)	5037(3)	3360(3)	61(3)
C(1G4)	10512(6)	4540(5)	696(3)	48(4)
C(2G4)	11366(6)	4166(6)	628(4)	60(5)
C(3G4)	11644(6)	3877(5)	1102(3)	48(4)
C(4G4)	11627(6)	4341(5)	1522(3)	39(4)
C(5G4)	10813(6)	4733(5)	1537(3)	43(4)
C(6G4)	10890(7)	5286(5)	1877(4)	57(5)
C(7G4)	11272(10)	3863(7)	−194(4)	122(8)
C(8G4)	12646(9)	3037(5)	913(5)	83(6)
C(9G4)	10153(9)	6043(6)	2336(5)	102(6)
O(2G4)	11284(5)	3695(4)	289(3)	75(4)
O(3G4)	12527(4)	3666(4)	1073(2)	56(3)
O(4G4)	11628(4)	4013(3)	1972(2)	43(3)
O(5G4)	10646(4)	5011(3)	1061(2)	49(2)
O(6G4)	10085(5)	5557(4)	1972(3)	78(3)
C(1G5)	7105(7)	4029(5)	610(4)	42(4)
C(2G5)	7690(6)	3657(5)	268(4)	47(4)
C(3G5)	8614(6)	3602(5)	454(4)	41(4)
C(4G5)	8975(6)	4233(5)	591(4)	44(4)
C(5G5)	8353(6)	4572(5)	928(3)	42(4)
C(6G5)	8615(7)	5210(5)	1063(3)	47(4)
C(7G5)	6600(8)	3043(6)	−121(4)	82(6)
C(8G5)	9436(9)	2731(6)	166(5)	101(7)
C(9G5)	9136(8)	6166(6)	732(4)	76(6)
O(2G5)	7350(5)	3058(3)	179(3)	59(3)
O(3G5)	9163(5)	3358(3)	81(3)	58(3)
O(4G5)	9822(4)	4146(3)	818(2)	41(2)
O(5G5)	7504(4)	4633(3)	710(2)	37(3)
O(6G5)	8851(5)	5563(3)	638(2)	52(3)
C(1G6)	5017(7)	3582(5)	2061(4)	44(4)
C(2G6)	5333(7)	2975(5)	1840(4)	50(4)
C(3G6)	6186(7)	3065(5)	1574(4)	50(5)
C(4G6)	6125(6)	3592(5)	1222(4)	42(4)
C(5G6)	5733(7)	4177(5)	1451(4)	43(4)
C(6G6)	5536(7)	4703(5)	1108(4)	57(5)
C(7G6)	5123(9)	1944 (5)	2107(4)	92(6)
C(8G6)	7293(8)	2325(5)	1341(5)	91(6)
C(9G6)	4195(7)	4436(7)	710(4)	84(6)
O(2G6)	5426(5)	2529(3)	2227(3)	62(3)
O(3G6)	6408(5)	2492(4)	1346(3)	62(3)
O(4G6)	6998(4)	3707(3)	1055(2)	48(3)
O(5G6)	4929(4)	4039(3)	1697(2)	47(3)
O(6G6)	5109(5)	4541(4)	675(3)	64(3)

Table II. Continued

$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i * a_j * a_i \cdot a_j$

Atom	x/a	y/b	z/c	U_{eq}
C(1G7)	5654(6)	4630(5)	3765(4)	51(4)
C(2G7)	4937(7)	4143(5)	3703(3)	43(4)
C(3G7)	5090(7)	3739(5)	3255(4)	47(4)
C(4G7)	5222(7)	4147(5)	2819(3)	45(4)
C(5G7)	5835(7)	4693(5)	2920(4)	51(5)
C(6G7)	5778(9)	5187(6)	2525(4)	68(6)
C(7G7)	4579(8)	4069(6)	4549(4)	70(6)
C(8G7)	4423(7)	2731(6)	3335(4)	68(5)
C(9G7)	6758(14)	5805(10)	2168(7)	243(15)
O(2G7)	4838(4)	3731(3)	4117(2)	52(3)
O(3G7)	4347(4)	3344(3)	3166(2)	47(3)
O(4G7)	5585(4)	3779(3)	2438(2)	45(3)
O(5G7)	5662(5)	5012(3)	3361(2)	50(3)
O(6G7)	6510(9)	5563(6)	2551(4)	148(6)
C(1)	7340(7)	1749(6)	3431(4)	54(4)
C(2)	6930(8)	2164(7)	3120(4)	74(5)
C(3)	7311(10)	2750(7)	3014(5)	83(6)
C(4)	8102(11)	2922(7)	3212(4)	81(7)
C(5)	8526(8)	2491(7)	3501(4)	74(6)
C(6)	8148(8)	1907(6)	3613(4)	70(5)
C(7)	6896(8)	1097(6)	3553(4)	77(5)
C(8)	6190(9)	1270(6)	3923(7)	93(7)
O(9)	5435(7)	1339(5)	3782(4)	120(5)
O(10)	6397(6)	1331(4)	4350(3)	98(4)
C(11)	6564(9)	735(6)	3122(4)	85(6)
C(12)	8551(10)	3550(6)	3102(5)	109(7)
C(13)	8762(15)	3696(10)	2615(7)	208(15)
C(14)	9040(12)	3328(9)	2267(5)	195(13)
C(15)	9092(14)	4383(8)	2625(7)	265(15)

When racemic ibuprofen and TRIMEB were reacted in a 1 : 1 molar ratio, residual traces of uncomplexed racemic ibuprofen in the product crystals were sometimes detected as a very small endothermic peak at 77 °C in DSC curves of different batches of the complex. This result, together with the absence of a fusion peak for (*R*)- or (*S*)-ibuprofen in the range 50–54 °C is evidence for the lack of enantioselectivity of TRIMEB towards the drug under the conditions employed. Further confirmation was obtained by measurements of optical rotation. Thus, the crystals isolated from the preparation using racemic ibuprofen and TRIMEB gave $[\alpha]_D = 132 \pm 3°$ in 40 : 60 EtOH : H_2O while the mother liquor diluted with EtOH to give the same solvent composition yielded $[\alpha]_D = 130 \pm 3°$. A control solution

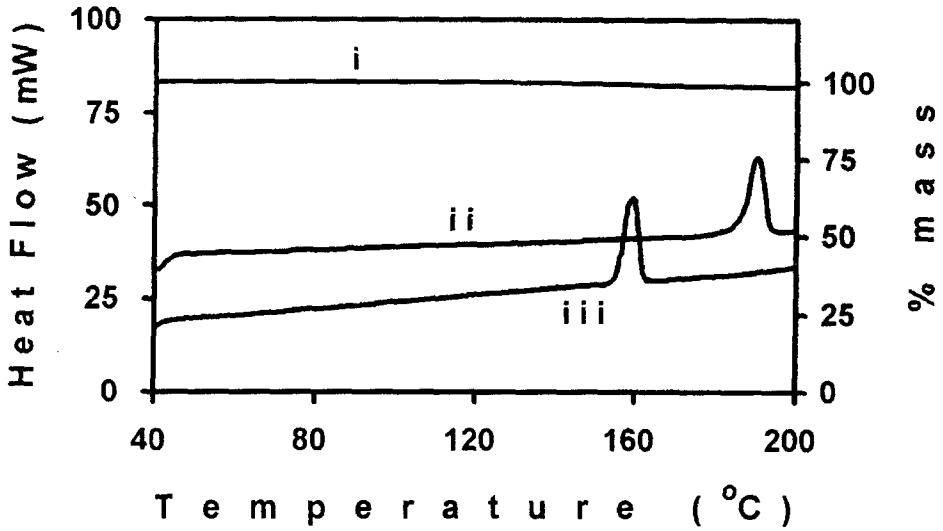

Figure 1. Thermal analysis: (i) TGA trace for the complex; (ii) and (iii) DSC traces for the complex and TRIMEB, respectively.

of mother liquor from a crystallization using (*S*)-ibuprofen and TRIMEB, yielded a significantly different rotation of $[\alpha]_D = 118 \pm 3°$.

3.2. CRYSTAL AND MOLECULAR STRUCTURE

The structure of the complex and the numbering scheme used for atoms of the host are given in Figure 2. The conformation of the guest molecule is shown in Figure 3. The isobutyl group of (*S*)-ibuprofen is inserted in the cavity of the TRIMEB molecule. All methylglucose residues of the TRIMEB molecule are in the $^4C_1$ chair conformation. The O(2)—C(7) bonds of the host are directed away from the cavity and the O(3)—C(8) bonds are directed inward. The C(6)—O(6) bonds of residues G2, G4 and G7 are directed toward the cavity in the (+)-*gauche* conformation, while those in residues G1, G3, G5 and G6 are directed away, in the (−)-*gauche* conformation. All O(6)—C(9) bonds are *trans* to the respective C(5)—C(6) bonds on each residue, except in G6 where the bond lies *gauche*. Geometrical data describing the conformation of the TRIMEB molecule in the title complex appear in Table III. To assess the effect of inclusion of different guests on the conformation of the TRIMEB molecule, we compared the O(4)···O(4′) distances, the radii of the O(4) heptagon and the residue tilt angles with analogous data for the isomorphous complexes with (*S*)-naproxen [6] and flurbiprofen [7] as guests. Our data for TRIMEB in the title complex are in excellent agreement with those reported for the TRIMEB complex with (*S*)-naproxen. The ranges for the O(4)···O(4′) distances and the heptagon radii are 4.21–4.48 Å and 4.71–5.17 Å, respectively, in the title complex, and 4.25–4.54 Å and 4.61–5.21 Å, respectively,

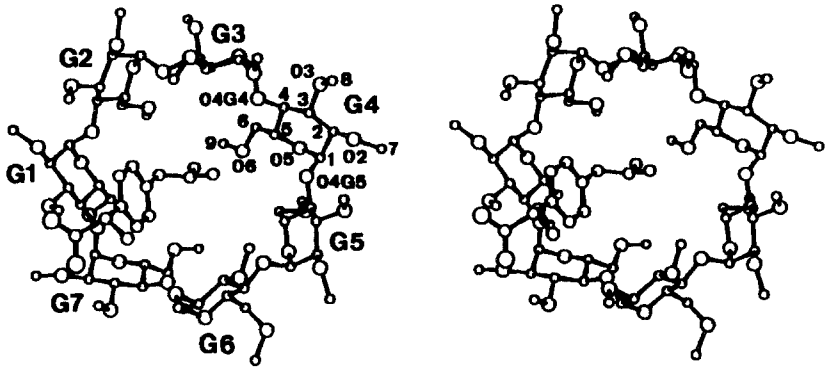

Figure 2. Stereodiagram of the TRIMEB–(*S*)-ibuprofen complex showing the numbering scheme for TRIMEB. C atoms are labelled with numerals only.

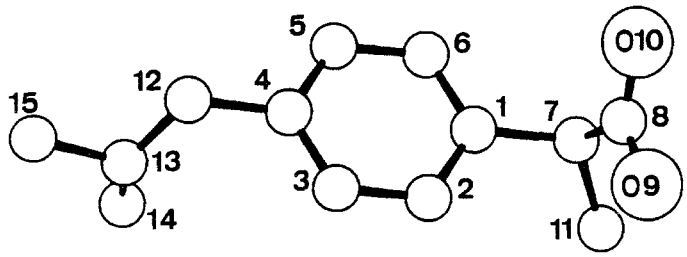

Figure 3. Conformation of (*S*)-ibuprofen in the complex. C atoms are labelled with numerals only.

in the (*S*)-naproxen complex. Remarkably, corresponding residue tilt angles agree to within 2° in the two complexes. These conformational parameters are also in close agreement with those reported for TRIMEB in the (*S*)-flurbiprofen complex [7] where the O(4)···O(4′) distance range is 4.22–4.55 Å and the heptagon radii range is 4.70–5.23 Å. Again, no tilt angle differs by more than 2° when compared with the corresponding one in the title complex. Thus, the distorted conformation of the TRIMEB molecule in its complexes with the (*S*)-enantiomers of ibuprofen, flurbiprofen and naproxen is practically invariant. Harata et al. [7] found that the tilt angle of the G7 residue of the TRIMEB complex with (*R*)-flurbiprofen is greater by 5.6° than the corresponding angle in the complex with (*S*)-flurbiprofen, a difference which they attributed to steric effects.

The conformation of the complexed TRIMEB molecule, described above, differs markedly from that of the 'free' TRIMEB molecule. We previously reported that in the crystal structure of TRIMEB monohydrate [13], the host assumes a severely collapsed conformation in which six of the glucose residues adopt the $^4C_1$ conformation and one adopts the $^1C_4$ conformation, a unique occurrence in cyclodextrin

Table III. Geometrical data for TRIMEB.

Residue	Tilt angle[a]	Deviation[b]	Torsion angle index[c]	Glycosidic oxygen angle[d]	Radius of heptagon[e]
G1	28.3	0.446(6)	116.0	128.7	4.93
G2	18.7	0.208(6)	139.8	124.8	5.16
G3	−11.3	−0.511(6)	116.3	124.0	5.06
G4	41.9	−0.013(6)	139.7	137.3	4.71
G5	33.3	0.566(6)	118.4	120.4	5.17
G6	−14.1	−0.312(6)	128.6	126.5	5.06
G7	36.3	−0.383(6)	138.1	130.2	4.87
			Average	127.4	4.99

[a] The tilt angle is the angle (°) between the O(4) plane and the plane through C(1), C(4), O(4) and O(4′).
[b] The deviation (Å) of O(4) atoms from the least-squares plane through all O(4) atoms.
[c] The torsion-angle index is defined as $|\psi(C1—C2)| + |\psi(C2—C3)| - |\psi(C3—C4)| - |\psi(C4—C5)| + |\psi(C5—O5)| + |\psi(O5—C1)|$, where $\psi(C1—C2)$ is the torsion angle O(5)—C(1)—C(2)—C(3).
[d] The glycosidic oxygen angle is the O(4) ... O(4′) ... O(4″) angle (°) subtended at the O(4′) atom.
[e] The radius of heptagon (Å) is the average value of the distance of each O(4) atom from the centre of gravity of seven O(4) atoms.

crystal structures. This distorted conformation minimises the hydrophobic cavity in the absence of a hydrophobic guest. As for other reported TRIMEB structures, two of the residues have a negative tilt angle, namely G3 and G6. The positive tilt angles of the remaining residues give the TRIMEB molecule a cup-shaped appearance, with the primary face being almost entirely sealed off by the C(6)—O(6)—C(9) groups. A series of intramolecular hydrogen bonds maintain the conformation of the host TRIMEB molecule. These interactions are comparable to those reported for other TRIMEB species [6, 13]. Five C6(G_n)—H···O5(G_{n-1}) bonds stabilise residues G1, G2, G4, G5 and G7, while two C—H···O interactions, namely C(1G3)—H···O(3G4) and C(1G5)—H···O(6G6), maintain the negative tilt angles of G3 and G6. The C···O distance range for these interactions is 3.09(1)–3.39(1) Å. The existence of intramolecular C—H···O hydrogen bonds in cyclodextrins has been documented by Steiner and Saenger [14] and we have confirmed their presence in other crystals containing TRIMEB [6, 13].

Figure 4 is a stereoscopic view of the complex unit showing the extent of penetration of the guest in the host cavity. The isobutyl group of (*S*)-ibuprofen is stabilised by hydrophobic forces within the cavity of TRIMEB, with the propionic acid group protruding from the O(2), O(3) face. This is analogous to what is found in the complexes of TRIMEB with other profen anti-inflammatories such as flurbiprofen and naproxen [6, 7] and with 4-biphenylacetic acid, a structurally similar compound [15]. The angle between the least-squares plane of the phenyl

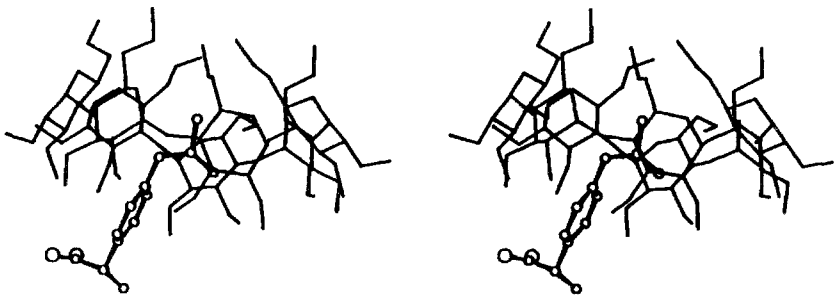

Figure 4. Stereodiagram of the title complex showing the extent of guest penetration.

Table IV. Torsion angles (°) for ibuprofen in (a) racemic ibuprofen, (b) (*S*)-(+)-ibuprofen and (c) TRIMEB – (*S*)-ibuprofen complex.

Atoms	*a*	*b*(i)	*b*(ii)	*c*
τ_1 C(2)—C(1)—C(7)—C(11)	42(1)	40(1)	28(1)	48(2)
τ_2 C(2)—C(1)—C(7)—C(8)	−81(1)	−85(1)	−95(1)	−78(1)
τ_3 C(1)—C(7)—C(8)—O(9)	−88(1)	−81(1)	83(1)	−83(1)
τ_4 C(3)—C(4)—C(12)—C(13)	−102(1)	−92(1)	−79(1)	−59(2)
τ_5 C(4)—C(12)—C(13)—C(14)	−170(1)	−170(1)	171(1)	−37(3)
τ_6 C(4)—C(12)—C(13)—C(15)	67(1)	66(1)	−64(1)	173(1)

group of ibuprofen and the normal to the least-squares plane of the O(4) atoms of the cyclodextrin, is 20.9°. The corresponding angle in the TRIMEB–(*S*)-naproxen structure is 23.3°. The conformation of the propionic acid group is defined by the torsion angles τ_1, τ_2 and τ_3, and that of the isobutyl substituent by τ_4, τ_5 and τ_6, defined in Table IV, where these parameters are compared for (*S*)-ibuprofen as it occurs in the complex and in free ibuprofen (both as the racemate and the pure (*S*)-isomer). (*S*)-Ibuprofen crystallises with two molecules in the asymmetric unit, and torsion angles for both molecules are tabulated for comparison [16, 17]. From the values of τ_1–τ_3, the conformation of the propionic acid residue and its orientation with respect to the phenyl ring of (*S*)-ibuprofen in the TRIMEB complex are very similar to what is observed in racemic ibuprofen. In the case of the TRIMEB complex, the combination of τ_4–τ_5 values brings the isobutyl group of the (*S*)-ibuprofen guest nearly normal to the phenyl ring plane (Figures 2–4). The conformational flexibility of the isobutyl group in ibuprofen, as indicated by the range of values in Table IV, has been noted previously [17].

Comparing the TRIMEB – (*S*)-ibuprofen complex structure with that of TRIMEB – (*S*)-naproxen [6], we note the remarkable similarity in the positions occupied by the phenyl and propionic acid moieties relative to the host TRIMEB, despite significant structural differences in the remaining guest residues which are buried in the respective host cavities. The relationship is clear from a comparison

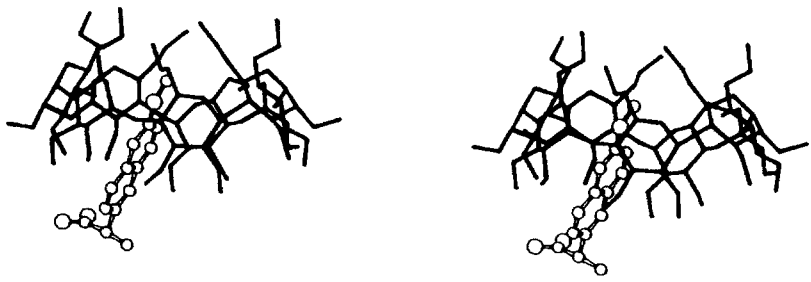

Figure 5. Stereodiagram of the TRIMEB–(*S*)-naproxen complex. (Reproduced with permission from Ref. 6).

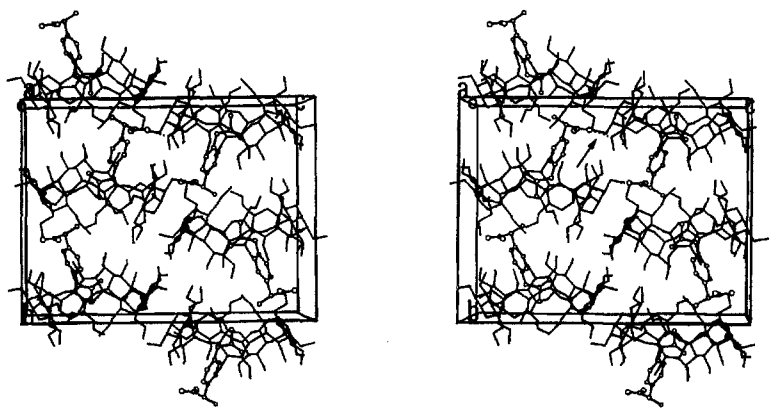

Figure 6. Stereo packing diagram showing the complex viewed down [100]. The arrow indicates the intermolecular O—H···O hydrogen bond, represented by the dotted line.

of Figures 4 and 5, the latter being an analogous stereoview of the TRIMEB–(*S*)-naproxen complex [6]. This emphasises the non-specific nature of guest recognition by the TRIMEB molecule. In both structures, the carboxylic acid group is appropriately situated and orientated to form an intermolecular hydrogen bond with a methoxy group O atom of a symmetry-related TRIMEB molecule; this strong interaction evidently also contributes in determining the extent of guest penetration in the host cavity. Details of this hydrogen bond are as follows: O(10)–H···O(3G2)^I ($I = x + 1/2, -y + 1/2, -z + 1$) with O···O 2.72(1) Å. The same intermolecular hydrogen bond occurs in other reported complexes of TRIMEB with the (*S*)-isomers of profens.

A stereoview of the packing arrangement is shown in Figure 6. Complex molecule units are packed head-to-tail in a screw channel mode, positioned with their axes almost parallel to the *b* axis. This arrangement is isomorphous with those of almost all other TRIMEB complex structures that have been reported to date, with the exception of the complex with *m*-iodophenol [15].

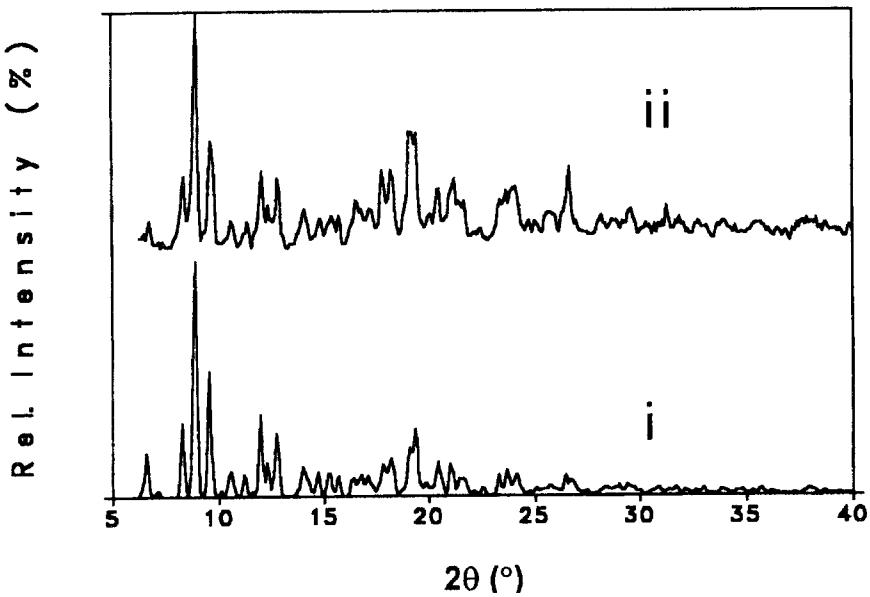

Figure 7. (i) XRD pattern for the TRIMEB–(*S*)-ibuprofen complex calculated from the single crystal data; (ii) Experimental XRD pattern for the complex prepared using racemic ibuprofen.

3.3. XRD

Unit cell data, atomic coordinates and thermal parameters for the TRIMEB–(*S*)-ibuprofen complex were used to generate the representative XRD pattern shown in Figure 7(i). This pattern was found to match the experimental pattern obtained from the powder prepared by reaction of (*S*)-ibuprofen and TRIMEB.

Figure 7(ii) shows the experimental XRD pattern for the powder obtained by reacting racemic ibuprofen and TRIMEB. Since thermal analysis indicated that this sample contained crystals of both TRIMEB – (*R*)-ibuprofen and TRIMEB – (*S*)-ibuprofen, the overall correspondence between the traces in Figure 7 is evidence of isomorphism of the two crystals. The detailed nature of the inclusion of (*R*)-ibuprofen in TRIMEB cannot, however, be deduced from these data since it has been shown by single crystal X-ray diffraction that the modes of inclusion of e.g. (*R*)- and (*S*)-flurbiprofen in TRIMEB are somewhat different, even though the crystals of the two complexes are isomorphous [7].

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