Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **20:** 277–290, 1995.

X-Ray Structure and Thermal Analysis of a 1 : 1 Complex between (*S*)-Naproxen and Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin

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(Received: 2 November 1994; in final form: 24 January 1995)

Abstract. An inclusion complex between TRIMEB and (*S*)-naproxen has been crystallised and characterised by physicochemical methods including X-ray analysis. The complex crystallises in the orthorhombic crystal system, space group $P2_12_12_1$, with $a = 15.179(4)$, $b = 21.407(5)$, $c = 27.67(1)$ Å and $Z = 4$. The structure was solved using published coordinates for the skeleton atoms of TRIMEB in an isomorphous complex. Refinement by full-matrix least-squares analysis yielded $R = 0.0571$ for 6573 unique observed reflections. Hydrophobic forces are responsible for the inclusion of the drug, which has its methoxy group buried in the cavity of the host and its propionic acid moiety protruding from the O(2), O(3) side of the TRIMEB molecule. Both host and guest undergo conformational changes on complexation relative to their conformations observed in the TRIMEB monohydrate and naproxen crystal structures respectively. Complex units pack in a screw-channel mode in a head-to-tail fashion with their axes almost parallel to the *b*-axis.

Key words: Permethylated β-cyclodextrin, (*S*)-naproxen, inclusion complex, X-ray crystal structure.

1. Introduction

The cyclodextrins and their derivatives are finding increasing application in the pharmaceutical industry as carrier molecules for many drugs, as complexation can result in improved physical characteristics such as increased aqueous solubility [1]. The interaction between the non-steroidal anti-inflammatory drug, naproxen ((*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid), and β-cyclodextrin has been investigated in solution and in the solid state [2–7]. Molecular modelling and NMR studies have generated proposals on the mode of inclusion of the drug by β-cyclodextrin [2, 5–7] and stability constants for the complex have been estimated by phase solubility, NMR, fluorescence, circular dichroism and U.V. techniques [2, 5–7]. The ^{13}C-NMR study by Bettinetti *et al.* [2] also includes the

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calculation of stability constants in solution of naproxen complexes with some β-cyclodextrin derivatives, amongst which is a partially methylated β-cyclodextrin. However, there are no data available on the interaction between naproxen and permethylated β-cyclodextrin ((2,3,6-tri-*O*-methyl)-β-cyclodextrin, or TRIMEB). Permethylation of β-cyclodextrin renders it many times more soluble and, as such, potentially more useful in the pharmaceutical industry [8]. We report here the preparation, thermal analysis and crystal structure of a naproxen–TRIMEB complex.

2. Experimental

2.1. MATERIALS

TRIMEB (Cyclolab, Hungary) and (*S*)-naproxen (Syntex, U.S.A.) were used as received.

2.2. THERMOGRAVIMETRIC ANALYSIS AND DIFFERENTIAL SCANNING CALORIMETRY

Thermogravimetric (TGA) and differential scanning calorimetric (DSC) traces were recorded on a Perkin–Elmer PC7-Series Thermal Analysis System in the range 30–180 °C at a scanning rate of 5 °C/min under N_2 gas-purge. Sample masses were 7–8 mg. Samples were placed in vented pans.

2.3. PREPARATION OF THE NAPROXEN–TRIMEB COMPLEX

Crystals of the complex, which are colourless and prismatic, were grown at approximately 50 °C from an aqueous solution prepared by mixing equimolar amounts of (*S*)-naproxen and TRIMEB in distilled water at room temperature and then filtering off the undissolved naproxen.

2.4. CRYSTAL STRUCTURE SOLUTION

In order to optimise diffraction data quality, reflection intensities were measured from a crystal of dimensions 0.50 × 0.50 × 0.50 mm cooled to −15 °C (258 K) on an Enraf–Nonius CAD-4 diffractometer using graphite-monochromated MoKα radiation ($\lambda = 0.71069$ Å). Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections in the range $16 \leq \theta \leq 17°$. Intensity data were collected by the ω-scan technique. To ensure accurate measurement of weak reflections, a pre-scan acceptance parameter of zero was chosen to force their final intensity scans up to a maximum time of 100 s per reflection. Data were collected to $(\sin\theta/\lambda)_{max} = 0.595$ Å^{-1}. Three standard reflections (2 13 15; 2 16 8; 10 3 13), which were monitored every hour, showed a 4% decrease in intensity during data collection. Orientation control was performed every 150 reflections. Data were corrected for Lp effects. Crystal data collection and refinement details

are listed in Table I. The structure was solved using published coordinates for the non-hydrogen cyclodextrin atoms (excluding the O(6), C(7), C(8) and C(9) atoms of each methylglucose residue – see Figure 2 for numbering scheme) of the isomorphous *p*-iodophenol–TRIMEB tetrahydrate complex [9]. A difference Fourier synthesis after refinement by full-matrix least-squares techniques (minimisation of $[\sum(w(F_0^2 - F_c^2)^2)/\sum(w(F_0^2)^2]^{1/2}$) [10] revealed all the non-hydrogen atoms of the guest and many of the remaining non-hydrogen atoms of the host. Once all non-hydrogen atoms had been located from subsequent difference Fourier syntheses, all the cyclodextrin hydrogen atoms linked to carbon atoms were inserted at idealised positions with C—H = 1.00 Å. All the methyl hydrogen atoms were assigned a common variable isotropic temperature factor and the remaining hydrogen atoms of each methylglucose moiety were assigned common variable isotropic temperature factors. All non-hydrogen atoms were assigned anisotropic temperature factors, except for C(7G3), which was disordered, and C(l), C(5), C(9) and C(10) of the naproxen molecule, which, in addition, were refined subject to the following distance constraints, on account of abnormally long bond distances for C(1)—C(9) and C(5)—C(10): C(1)—C(2), C(1)—C(9), C(5)—C(6) and C(5)—C(10) with C—C = 1.42 Å, σ = 0.005 Å. The hydrogen atoms attached to the carbon atoms of the guest were also inserted at idealised positions with C—H = 1.00 Å and assigned a common isotropic temperature factor. The carboxyl hydrogen atom of the guest was located in a difference Fourier synthesis and allowed to refine subject to a distance constraint (O—H = 1.00 Å, σ = 0.05 Å). Final fractional coordinates for non-hydrogen atoms are given in Table II.

3. Results and Discussion

3.1. THERMOGRAVIMETRIC ANALYSIS AND DIFFERENTIAL SCANNING CALORIMETRY

TGA and DSC traces are given in Figure 1. TGA of the complex showed a loss of 0.4 weight percent from 30 to 150 °C. This is negligible and probably represents surface water. There was no evidence for any water molecules in the structure solution and crystals of the complex showed no signs of cracking in this temperature range on a hot-stage microscope. It was therefore concluded that the complex contains no water molecules of crystallisation. The DSC trace confirmed this as it was featureless except for an endotherm corresponding to fusion of the complex at 165.7 °C (onset melting temperature).

3.2. CRYSTAL STRUCTURE SOLUTION

Numbering schemes for the host and guest are given in Figure 2, which shows the host and guest molecules separately. Figure 3 shows a stereodiagram of the (*S*)-naproxen–TRIMEB complex. The naproxen molecule is inserted in the host cavity, with the propionic acid moiety protruding from the O(2), O(3) face. The mode of

TABLE I. Crystal data, experimental and refinement parameters for the title compound.

Molecular formula	$C_{63}H_{112}O_{35}\cdot C_{14}H_{14}O_3$
M_r/g mol^{-1}	1659.8
Crystal system	Orthorhombic
Space Group	$P2_12_12_1$
Z	4
a (Å)	15.179(4)
b (Å)	21.407(5)
c (Å	27.67(1)
V (Å^3)	8991(5)
D_x	1.226 g cm^{-3}
Crystal dimensions (mm)	0.5 × 0.5 × 0.5
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. of reflections collected	8655
No. of unique reflections	8613
No. of reflections with $I > 2\sigma(I)$	6573
No. of L.S. parameters	1050
$R1$ ($I > 2\sigma(I)$)	0.0571
$wR2$ (F^2)	0.1456
w	$[\sigma^2(F_0)^2 + (0.0859 \times P)^2 + (1.79 \times P)]^{-1}$ $P = (\max(F_0^2, 0 + F_c^2)/3$
S	1.120
Shift/e.s.d. max., average	0.362, 0.006
$(\Delta\rho)_{max}$ final (e Å^{-3})	0.56
$(\Delta\rho)_{min}$ final (e Å^{-3})	−0.27

inclusion will be discussed in more detail once the conformation of the host has been described. All seven methylglucose moieties of the TRIMEB molecule are in the $^4C_1$ chair conformation. Average bond lengths and angles for the host are within the standard deviations of those reported for other TRIMEB complexes [9, 12]. Atom C(7G3) is disordered over three sites with site occupancies of 0.56, 0.22 and 0.22. As is normally the case for TRIMEB, the O(2)—C(7) bonds are directed away from the cavity and the O(3)—C(8) bonds are directed towards the cavity [9, 11–14]. The C(6)—O(6) bonds of residues G1, G3, G5, and G6 are directed away from the cavity in the (−)-*gauche* conformation [15], while those of G2, G4 and G7 point towards the cavity in the (+)-*gauche* conformation. The O(6)—C(9) bonds of all glucose residues are *trans* to the corresponding C(5)—C(6) bonds except in G6, where the relationship is *gauche*. Table III lists values for the O(4)···O(4′)···O(4″) angles of the O(4) heptagon, radii of the O(4) heptagon, O(4)···O(4′) distances,

TABLE II. Final fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for the naproxen–TRIMEB complex.

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

	x	y	z	U_{eq}/U_{iso}^*
C(1G1)	8639(3)	4589(2)	4730(2)	41(1)
C(2G1)	7926(3)	4129(2)	4883(2)	42(1)
C(3G1)	7392(3)	3910(2)	4447(2)	40(1)
C(4G1)	7014(3)	4495(2)	4210(2)	41(1)
C(5G1)	7758(3)	4930(2)	4063(2)	45(1)
C(6G1)	7449(4)	5522(2)	3830(2)	55(1)
C(7G1)	8543(4)	3703(3)	5595(2)	63(2)
C(8G1)	6683(4)	2936(3)	4350(3)	75(2)
C(9G1)	6413(6)	6332(3)	3897(3)	90(2)
O(2G1)	8277(2)	3590(2)	5113(1)	50(1)
O(3G1)	6718(2)	3507(2)	4602(1)	49(1)
O(4G1)	6497(2)	4310(2)	3802(1)	46(1)
O(5G1)	8250(2)	5104(1)	4488(1)	45(1)
O(6G1)	6787(3)	5800(2)	4118(1)	65(1)
C(1G2)	11859(3)	4139(2)	4046(2)	46(1)
C(2G2)	11565(3)	3720(2)	4468(2)	47(1)
C(3G2)	10566(3)	3716(2)	4504(2)	42(1)
C(4G2)	10166(3)	4360(2)	4507(2)	43(1)
C(5G2)	10558(3)	4774(2)	4109(2)	45(1)
C(6G2)	10313(4)	5447(2)	4164(2)	62(1)
C(7G2)	12721(4)	2985(4)	4536(3)	101(3)
C(8G2)	9928(4)	2798(2)	4869(2)	61(1)
C(9G2)	10344(8)	6406(3)	3761(4)	132(4)
O(2G2)	11823(2)	3093(2)	4421(1)	63(1)
O(3G2)	10311(2)	3402(2)	4941(1)	49(1)
O(4G2)	9244(2)	4278(2)	4426(1)	42(1)
O(5G2)	11506(2)	4742(2)	4129(1)	51(1)
O(6G2)	10517(3)	5770(2)	3734(2)	86(1)
C(1G3)	12446(3)	3881(2)	2176(2)	47(1)
C(2G3)	12445(4)	3270(2)	2451(2)	52(1)
C(3G3)	11927(4)	3293(2)	2916(2)	51(1)
C(4G3)	12174(3)	3863(2)	3213(2)	44(1)
C(5G3)	12090(3)	4441(2)	2896(2)	45(1)
C(6G3)	12316(3)	5058(2)	3125(2)	52(1)
C(7G3)[a]	12736(15)	2269(9)	2151(7)	120(6)*
C(73A)[b]	11511(21)	2504(15)	2076(11)	70(7)*
C(73B)[b]	12292(19)	2177(12)	2185(9)	51(6)*
C(8G3)	11382(6)	2412(3)	3354(3)	100(3)
C(9G3)	13409(6)	5602(3)	3528(3)	97(2)

TABLE II. Continued.

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

	x	y	z	U_{eq}/U_{iso}^*
O(2G3)	12147(4)	2784(2)	2143(2)	83(1)
O(3G3)	12114(3)	2734(2)	3171(2)	70(1)
O(4G3)	11556(2)	3883(2)	3611(1)	46(1)
O(5G3)	12666(2)	4373(2)	2486(1)	47(1)
O(6G3)	13166(2)	5023(2)	3335(2)	66(1)
C(1G4)	10507(3)	4571(3)	694(2)	51(1)
C(2G4)	11356(3)	4194(3)	629(2)	54(1)
C(3G4)	11621(3)	3882(3)	1103(2)	48(1)
C(4G4)	11599(3)	4326(2)	1529(2)	46(1)
C(5G4)	10780(3)	4737(2)	1537(2)	45(1)
C(6G4)	10898(4)	5279(2)	1885(2)	55(1)
C(7G4)	11266(7)	3915(5)	−199(2)	119(3)
C(8G4)	12619(5)	3027(3)	932(3)	85(2)
C(9G4)	10188(6)	6099(3)	2277(3)	88(2)
O(2G4)	11284(3)	3719(2)	279(1)	72(1)
O(3G4)	12506(2)	3659(2)	1073(1)	57(1)
O(4G4)	11602(2)	3972(2)	1970(1)	46(1)
O(5G4)	10642(2)	5012(2)	1068(1)	50(1)
O(6G4)	10102(3)	5596(2)	1949(1)	70(1)
C(1G5)	7095(3)	4077(2)	582(2)	43(1)
C(2G5)	7682(3)	3709(2)	240(2)	46(1)
C(3G5)	8598(3)	3632(2)	425(2)	46(1)
C(4G5)	8973(3)	4267(2)	570(2)	41(1)
C(5G5)	8344(3)	4614(2)	904(2)	43(1)
C(6G5)	8624(3)	5270(2)	1028(2)	50(1)
C(7G5)	6571(4)	3108(3)	−147(3)	89(2)
C(8G5)	9431(6)	2766(3)	147(4)	108(3)
C(9G5)	9147(5)	6203(3)	697(2)	76(2)
O(2G5)	7330(3)	3105(2)	149(1)	64(1)
O(3G5)	9149(2)	3380(2)	62(1)	64(1)
O(4G5)	9803(2)	4160(2)	801(1)	46(1)
O(5G5)	7492(2)	4660(1)	677(1)	43(1)
O(6G5)	8859(2)	5586(2)	603(1)	52(1)
C(1G6)	4987(3)	3627(2)	2040(2)	47(1)
C(2G6)	5313(4)	3014(2)	1820(2)	53(1)
C(3G6)	6160(4)	3105(2)	1545(2)	49(1)
C(4G6)	6093(3)	3640(2)	1180(2)	46(1)
C(5G6)	5713(3)	4223(2)	1418(2)	44(1)
C(6G6)	5508(4)	4756(2)	1079(2)	54(1)

TABLE II. Continued.

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

	x	y	z	U_{eq}/U_{iso}^*
C(7G6)	5099(7)	1973(3)	2090(3)	110(3)
C(8G6)	7263(5)	2354(3)	1317(4)	105(3)
C(9G6)	4171(4)	4480(4)	690(2)	85(2)
O(2G6)	5414(3)	2572(2)	2190(1)	68(1)
O(3G6)	6364(3)	2532(2)	1301(2)	69(1)
O(4G6)	6974(2)	3741(2)	1015(1)	49(1)
O(5G6)	4906(2)	4077(2)	1669(1)	49(1)
O(6G6)	5083(2)	4587(2)	643(1)	64(1)
C(1G7)	5679(3)	4617(2)	3742(2)	49(1)
C(2G7)	4940(3)	4140(2)	3678(2)	51(1)
C(3G7)	5108(3)	3746(2)	3227(2)	46(1)
C(4G7)	5211(3)	4172(2)	2791(2)	47(1)
C(5G7)	5856(4)	4703(2)	2884(2)	52(1)
C(6G7)	5811(5)	5198(3)	2506(2)	64(2)
C(7G7)	4609(4)	4033(4)	4515(2)	79(2)
C(8G7)	4485(4)	2727(3)	3322(2)	68(2)
C(9G7)	6695(9)	5907(5)	2086(4)	149(5)
O(2G7)	4854(2)	3729(2)	4078(1)	60(1)
O(3G7)	4382(2)	3345(2)	3134(1)	54(1)
O(4G7)	5576(2)	3817(2)	2397(1)	45(1)
O(5G7)	5683(2)	5013(2)	3335(1)	51(1)
O(6G7)	6626(4)	5506(3)	2471(2)	128(2)
C(1)	7191(5)	2085(3)	3160(2)	84(2)*
C(2)	7441(4)	1610(3)	3475(2)	74(2)
C(3)	8235(5)	1686(4)	3732(3)	95(2)
C(4)	8770(6)	2194(4)	3688(3)	98(2)
C(5)	9057(5)	3213(3)	3331(3)	99(2)*
C(6)	8774(5)	3693(3)	3017(3)	81(2)
C(7)	8000(5)	3605(4)	2781(3)	88(2)
C(8)	7496(6)	3090(4)	2816(3)	100(2)
C(9)	7738(4)	2628(3)	3109(2)	70(2)*
C(10)	8503(4)	2670(3)	3372(2)	68(2)*
C(11)	6876(4)	1044(3)	3558(2)	60(1)
C(12)	6524(5)	716(4)	3114(3)	81(2)
C(13)	6139(4)	1240(3)	3897(2)	64(2)
O(14)	5401(3)	1354(3)	3765(2)	93(2)
O(15)	6385(3)	1272(3)	4342(2)	85(1)
O(16)	9278(5)	4230(3)	2989(3)	129(2)
C(17)	8939(12)	4725(6)	2712(6)	181(6)

[a]Site occupancy 0.56.
[b]Site occupancy 0.22.

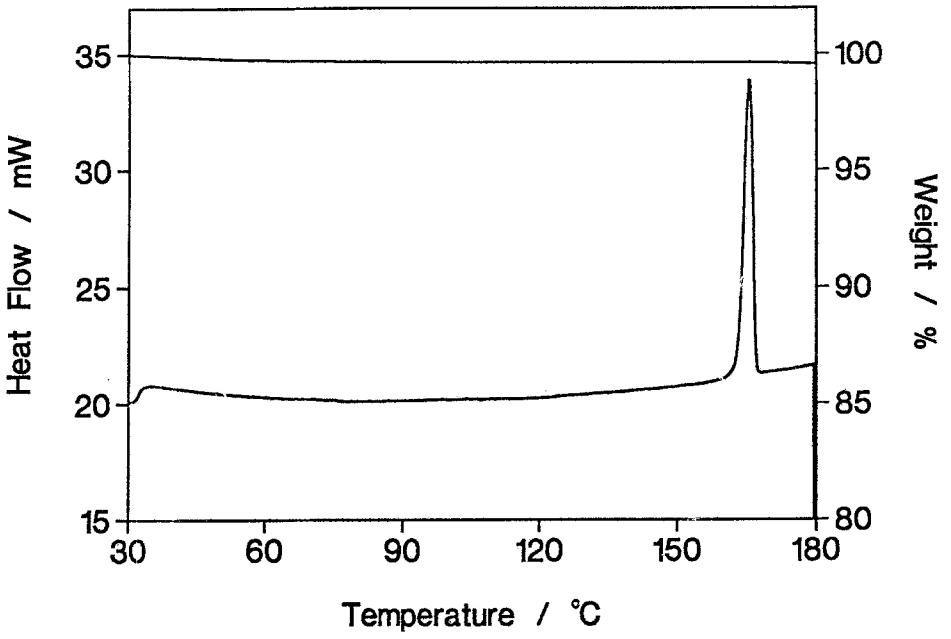

Fig. 1. TGA and DSC traces for the title compound.

tilt angles and deviations of the O(4) atoms from their least-squares plane. The values calculated for these parameters are comparable with those found for other TRIMEB complexes [9, 11–14] and, as usual, two glucose moieties have negative tilt angles (in this case G3 and G6), while all the others have positive tilt angles [11]. The TRIMEB molecule is cup-shaped with the C(6)—O(6)—C(9) groups of G1, G2, G4, G5 and G7 almost closing off the O(6) side of the TRIMEB cavity.

The distorted conformation of the TRIMEB molecule relative to the conformation observed for the parent β-cyclodextrin molecule is stabilised by numerous intramolecular C—H···O interactions, a common interaction found in carbohydrate crystal structures [16]. We have found that in the crystal strucure of TRIMEB monohydrate [17] the conformation of TRIMEB is stabilised by four intramolecular C(6G$_n$)—H···O(5G$_{n-1}$) hydrogen bonds. Furthermore, we have noted 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 [17]. These hydrogen bonds are also present in the naproxen–TRIMEB crystal structure. In addition, there are two C—H···O interactions stabilising the negative tilt angles of G3 and G6, namely C(1G3)—H···O(3G4) and C(1G5)—H···O(6G6). Table IV lists C—H···O hydrogen bonding parameters.

Figure 3 is a stereoview of the title complex. The naproxen molecule is held in the TRIMEB cavity by hydrophobic forces and is inserted from the O(2), O(3) side of the cyclodextrin molecule with the methoxy group buried in the cavity near the

TABLE III. Geometrical data for TRIMEB.

i. Glycosidic oxygen angle (°) and radius (Å) of the O(4) heptagon (measured from the centre of gravity of seven O(4) atoms to each O(4) atom).			
O(4G7)···O(4G1)···O(4G2)	130.4	G1	4.86
O(4G1)···O(4G2)···O(4G3)	124.2	G2	5.21
O(4G2)···O(4G3)···O(4G4)	122.2	G3	5.14
O(4G3)···O(4G4)···O(4G5)	139.0	G4	4.64
O(4G4)···O(4G5)···O(4G6)	120.1	G5	5.17
O(4G5)···O(4G6)···O(4G7)	125.5	G6	5.12
O(4G6)···O(4G7)···O(4G1)	130.2	G7	4.86
Average	127.4	Average	5.00
ii. O(4)···O(4′) distance (Å)			
O(4G1)···O(4G2)	4.513	O(4G5)···O(4G6)	4.425
O(4G2)···O(4G3)	4.256	O(4G6)···O(4G7)	4.377
O(4G3)···O(4G4)	4.543	O(4G7)···O(4G1)	4.265
O(4G4)···O(4G5)	4.251	Average	4.376

iii. Tilt angle (°) and deviation (Å) of each O(4) atom from the least-squares plane through the seven O(4) atoms.

Residue	Tilt-angle	O(4) atom	Deviation
G1	27.0	O(4G1)	0.430(3)
G2	20.8	O(4G2)	0.225(2)
G3	−9.4	O(4G3)	−0.504(3)
G4	44.3	O(4G4)	−0.037(3)
G5	34.3	O(4G5)	0.581(3)
G6	−14.4	O(4G6)	−0.317(3)
G7	34.4	O(4G7)	−0.377(3)

TABLE IV. Intramolecular C—H···O hydrogen bonds.

			Distance (Å)			Angle (°)
C	H	O	C···O	C—H	H···O	C—H···O
C(6G1)—H(261)		O(5G7)	3.201(7)	0.97	2.54	125.5
C(6G2)—H(162)		O(5G1)	3.341(7)	0.97	2.44	155.1
C(6G3)—H(263)		O(5G2)	3.114(6)	0.97	2.35	134.9
C(6G5)—H(265)		O(5G4)	3.112(6)	0.97	2.42	128.5
C(6G6)—H(266)		O(5G5)	3.216(6)	0.97	2.45	136.2
C(1G3)—H(1G3)		O(3G4)	3.090(6)	0.98	2.44	123.5
C(1G5)—H(1G5)		O(6G6)	3.247(6)	0.98	2.45	138.1

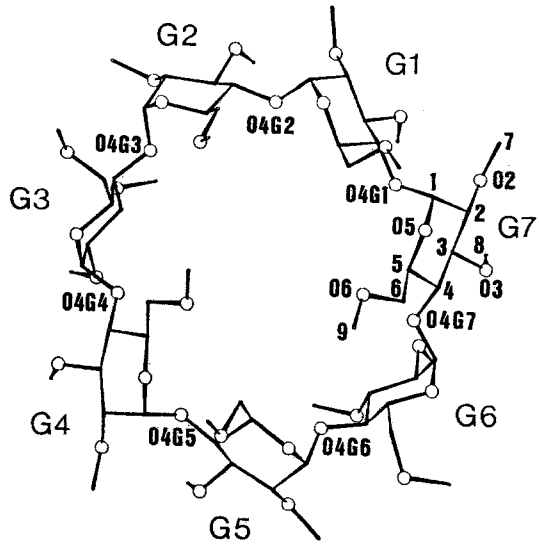

Fig. 2a. Numbering scheme for the host. C atoms are labelled with numerals only.

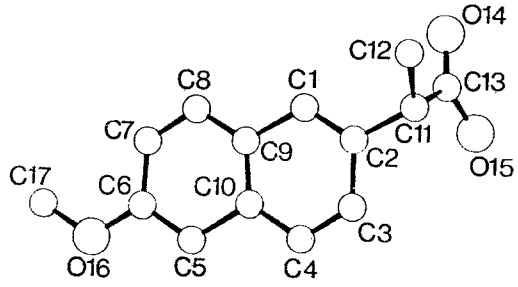

Fig. 2b. Numbering scheme for the guest.

O(6) side and the propionic acid group protruding from the O(2), O(3) side. Bond lengths and bond angles for the naproxen molecule are listed in Table V. The way in which the naproxen molecule is included by TRIMEB in the solid state is similar

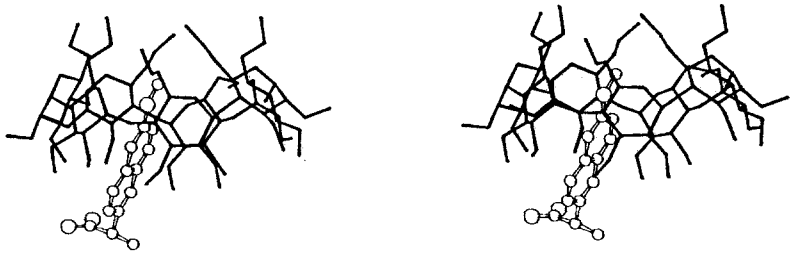

Fig. 3. Stereodiagram of the title compound.

TABLE V. Bond lengths (Å) and angles (°) for naproxen.

C(1)—C(2)	1.392(5)	C(2)—C(1)—C(9)	119.7(6)
C(1)—C(9)	1.435(5)	C(1)—C(2)—C(3)	117.7(7)
C(2)—C(3)	1.41(1)	C(l)—C(2)—C(11)	122.0(6)
C(2)—C(11)	1.502(9)	C(3)—C(2)—C(11)	120.3(6)
C(3)—C(4)	1.36(1)	C(4)—C(3)—C(2)	123.8(8)
C(4)—C(10)	1.40(1)	C(3)—C(4)—C(10)	117.6(7)
C(5)—C(6)	1.412(5)	C(6)—C(5)—C(10)	117.3(6)
C(5)—C(10)	1.440(5)	C(7)—C(6)—C(5)	117.2(7)
C(6)—C(7)	1.36 (1)	C(7)—C(6)—O(16)	124.6(7)
C(6)—O(16)	1.383(8)	C(5)—C(6)—O(16)	118.1(7)
C(7)—C(8)	1.34(1)	C(8)—C(7)—C(6)	124.8(8)
C(8)—C(9)	1.33(1)	C(9)—C(8)—C(7)	119.8(8)
C(9)—C(10)	1.374(9)	C(8)—C(9)—C(10)	120.4(6)
C(11)—C(12)	1.513(9)	C(8)—C(9)—C(1)	120.2(6)
C(11)—C(13)	1.519(8)	C(10)—C(9)—C(1)	119.4(6)
C(13)—O(14)	1.204(7)	C(9)—C(10)—C(4)	121.8(6)
C(13)—O(15)	1.286(7)	C(9)—C(10)—C(5)	120.4(6)
O(16)—C(17)	1.40(2)	C(4)—C(10)—C(5)	117.8(6)
		C(12)—C(11)—C(2)	116.8(5)
		C(12)—C(11)—C(13)	111.7(5)
		C(2)—C(11)—C(13)	107.0(5)
		O(14)—C(13)—O(15)	123.3 (6)
		O(14)—C(13)—C(11)	123.7(6)
		O(15)—C(13)—C(11)	113.0(6)
		C(17)—O(16)—C(6)	117.1(9)

to the modes of inclusion of naproxen by β-cyclodextrin proposed by Bettinetti *et al.* [2], Otero-Espinar *et al.* [5] and Ganza-Gonzalez *et al.* [7] on the basis of their NMR and/or molecular modelling studies. The guest is not as fully included in the TRIMEB molecule on account of the host's cup-like shape as opposed to the toroidal shape of β-cyclodextrin. However, the mode of inclusion proposed by Wang and Warner [6] for naproxen and β-cyclodextrin, where the methoxy group is near the secondary hydroxyl side and the carboxyl group near the primary hydroxyl side, cannot be ruled out by the results of the present study as it has been noted by Harata that for some guests an 'upside-down relationship is found between cyclodextrin complexes and methyl-cyclodextrin complexes' [11].

As we reported earlier [17], the uncomplexed TRIMEB molecule has a somewhat collapsed structure, partially attributed to its attempt to minimise the hydrophobic cavity size in the absence of a hydrophobic guest, thereby facilitating more efficient packing and simultaneously avoiding accommodation of water molecules in a relatively hydrophobic environment. On complexation with the (*S*)-naproxen molecule, the ellipticity of the TRIMEB molecule is significantly reduced. We not-

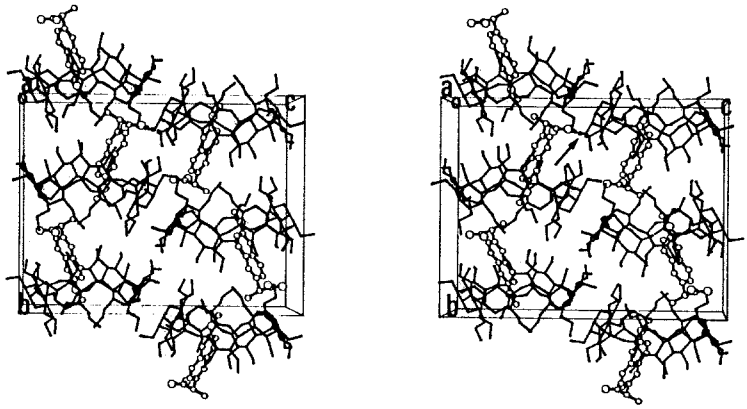

Fig. 4. Stereo packing diagram of the title compound viewed down the a-axis. The O—H···O hydrogen bond is indicated by the dashed line.

ed that one of the seven methylglucose residues in uncomplexed TRIMEB adopts the unusual $^1C_4$ conformation [17] in the crystal while the title complex and other TRIMEB complexes contain only residues of $^4C_1$ conformation. Since the most stable conformation of uncomplexed TRIMEB in solution may not coincide with that observed in the crystal, inclusion of guests by TRIMEB is not necessarily accompanied by the $^1C_4$ to $^4C_1$ conformational change. We intend to use molecular mechanics and NMR techniques to investigate the dynamics of complexation in solution.

The conformation of the methoxy group in naproxen with respect to the naphthalene ring is defined by the torsion angle $\tau 1$ C(5)—C(6)—O(16)—C(17) and that of the propionic acid substituent by $\tau 2$ C(1)—C(2)—C(11)—C(12), $\tau 3$ C(1)—C(2)—C(11)—C(13) and $\tau 4$ C(2)—C(11)—C(13)—O(15). The values for these torsion angles are −173.9(9), 48.1(8), −77.9(7), and −78.4(7)°, respectively. The values for the corresponding torsion angles in the crystal structure of naproxen have been calculated for the (*S*)-isomer using the published coordinates [18] and are −2, −129, 112 and −90° (e.s.d.s $\leq 1°$) respectively. The methoxy group, while still coplanar with the naphthalene ring has C(17) *anti*-periplanar to C(5) as opposed to a *syn*-periplanar relationship in the naproxen crystal structure. The former conformation is favoured for inclusion as it reduces the width of the naproxen molecule. The propionic acid substituent itself is in much the same conformation as that in the naproxen crystal structure, but, like the methoxy group, is rotated by approximately 180° with respect to the naphthalene ring (i.e. around C(2)—C(11)). The dihedral angle between the least-squares planes of the two rings of the naphthalene moiety is only 1.4(5)° compared with a value of 5.2(2)° in the naproxen crystal structure [18].

Calculation of the propionic acid group torsion angles in (*S*)-flurbiprofen using published coordinates for the crystal structures of flurbiprofen [19] and the (*S*)-

flurbiprofen–TRIMEB complex [12] reveal similar conformations for the propionic acid substituent as in the (*S*)-naproxen–TRIMEB complex. The values for the torsion angles corresponding to $\tau 2$, $\tau 3$ and $\tau 4$ are 52, -70 and $-102°$ respectively (e.s.d.s $\leq 1°$) in uncomplexed (*S*)-flurbiprofen and 39, -87 and $-88°$ respectively (e.s.d.s $\leq 1.6°$) in the (*S*)-flurbiprofen–TRIMEB complex. This means that this residue of the (*S*)-flurbiprofen molecule undergoes little change in conformation on complexation with TRIMEB, in contrast to what is reported here for the complexation of naproxen by TRIMEB.

An intermolecular hydrogen bond between the carboxyl group of naproxen and a methoxy oxygen atom of a symmetry-related TRIMEB molecule, namely O(15)—H···O(3G2)^{I} (I = $x-1/2, -y+1/2, -z+1$ with O···O 2.661(6), H···O 1.80(8) Å and O—H···O 141(12)°), stabilises the packing arrangement of the complex. This interaction is also present in the (*S*)-flurbiprofen–TRIMEB crystal structure [12] as may have been expected, given the similar way in which this guest molecule interacts with the host compound. Figure 4 shows a stereo packing diagram for the naproxen–TRIMEB complex. Complex units pack in screw-channel mode in a head-to-tail fashion with their axes almost parallel to the *b*-axis. This is a common type of packing arrangement for TRIMEB complexes and has been observed in all the TRIMEB complex structures published to date [11–14], with the exception of the *m*-iodophenol–TRIMEB complex [13].

Acknowledgements

Financial assistance from the Foundation for Research Development (Pretoria), the University of Cape Town and South African Druggists is gratefully acknowledged.

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