

Crystal structure of 2-*O*-[(*S*)-2-hydroxypropyl]cyclomaltoheptaose

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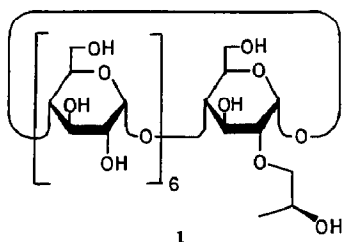
ABSTRACT

2-*O*-[(*S*)-2-Hydroxylpropyl]cyclomaltoheptaose crystallises in the monoclinic space group $P2_1$ with unit-cell dimensions $a = 15.072(1)$, $b = 10.409(1)$, $c = 20.623(2)$ Å, and $\beta = 108.52(1)^\circ$. The structure was solved by X-ray diffraction and refined to an R -value of 0.096. The macrocyclic ring of the cyclomaltoheptaose moiety is less symmetrical than that in cyclomaltoheptaose. The glucose residue that carries the hydroxypropyl group inclines much more with its primary hydroxyl side towards the inside of the macrocycle than the other glucose residues. The molecules are arranged in a herring-bone fashion to form a cage-type packing structure. The hydroxypropyl group is inserted into the cavity of an adjacent molecule related by a two-fold screw axis, and the hydroxyl group is linked to an HO-6 via $\text{OH}\cdots\text{water}\cdots\text{OH}$ hydrogen bonds. The crystal contains 8.5 water molecules which occupy 11 sites. Two water molecules are included at the primary hydroxyl side of the cyclomaltoheptaose cavity.

INTRODUCTION

Cyclomalto-oligosaccharides (cyclodextrins, CDs) are effective agents for solubilising sparingly soluble substances in water¹. However, their solubilising power is limited by their own solubility. For example, cyclomaltoheptaose dissolves to an extent of only 1.8% in water at room temperature. Several attempts have been made to improve some of the useful properties of CDs by chemical modification^{2,3}, including hydroxypropylation. HydroxypropylCDs, which are highly soluble in water, have been used to solubilise lipophilic drugs and as drug carriers because of their non-toxicity^{4,5}. The hydroxypropylCDs used were mixtures of compounds with different d.s., and the physicochemical properties of each component have not been defined. We have prepared and purified 2- and 6-*O*-monohydroxypropylcyclomaltoheptaose⁶. The solubility of the 2-*O*-substituted isomer was less than that of cyclomaltoheptaose, but increased

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markedly in the presence of guest compounds. The structure of 2-*O*-[(*S*)-2-hydroxypropyl]cyclomaltoheptaose (**1**) has now been investigated by X-ray diffraction.

EXPERIMENTAL

X-Ray measurements. — Slow evaporation of the solvent from a solution of **1** in aqueous 70% 1-propanol gave fine needles which slowly broke up in air. An Enraf-Nonius CAD4 diffractometer was used with an Elliott GX21 generator (40 kV, 60 mA, focal spot size 0.3×3 mm) and graphite-monochromated CuK_α radiation. The crystal was sealed in a glass capillary with a small amount of the mother liquor. Lattice dimensions were refined by using 25 reflections in a 2θ range of $35\text{--}45^\circ$. By using the $\theta\text{--}2\theta$ scan mode, 6194 reflections were collected up to 140° in 2θ , and 3749 reflections with $|F_o| \geq 3\sigma(F)$ were considered as observed and used for determination of the structure and refinement.

Crystal data. — Compound **1**: $\text{C}_{45}\text{H}_{76}\text{O}_{36} \cdot 8.5\text{H}_2\text{O}$, mol. wt. 1346.2, monoclinic, space group $P2_1$, $Z = 2$, $a = 15.072(1)$, $b = 10.409(1)$, $c = 20.623(2)$ Å, $\beta = 108.52(1)^\circ$, $V = 3068(7)$ Å³, $D_c = 1.457$ g.cm^{−3}.

Determination of the structure and refinement. — The unit-cell parameters of the crystal were similar to those of the cyclomaltoheptaose complex with nicotinamide⁷, which indicated similar molecular packing. The atomic co-ordinates for cyclomaltoheptaose in the nicotinamide complex were used as an initial model without considering the hydroxypropyl group. The position and orientation of the molecule were corrected by the rigid-body least-squares method. The structure was determined and refined by the block-diagonal least-squares procedure, which minimised $\sum w(|F_o| - |F_c|)^2$ with anisotropic temperature factors and unit weight for all reflections, combined with Fourier and difference-Fourier syntheses. In the final stage, the positions of the hydrogen atoms attached to methine and methylene groups of cyclomaltoheptaose were calculated and included in the refinement with isotropic temperature factors of the bonded heavy atoms. The refinement converged at an *R*-value of 0.096. The atomic co-ordinates are listed in Table I*.

* Observed and calculated structure factors, anisotropic temperature factors, bond distances, angles, torsion angles, co-ordinates of hydrogen atoms, and the Figure of the crystal structure are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/476/*Carbohydr. Res.*, 222 (1991) 37–45.

TABLE I

Atomic co-ordinates ($\times 10^3$) and temperature factors (\AA^2)

Atom		Occupancy	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}^a
G-1	C-1		−135(1)	81(2)	360(1)	4.06
	C-2		−205(1)	40(2)	290(1)	4.82
	C-3		−188(1)	130(2)	236(1)	5.01
	C-4		−204(1)	270(2)	255(1)	3.66
	C-5		−138(1)	302(2)	325(1)	4.27
	C-6		−164(1)	432(2)	349(1)	5.09
	O-2		−189(1)	−90(1)	277(1)	5.06
	O-3		−256(1)	99(1)	171(1)	4.81
	O-4		−179(1)	348(−)	203(1)	3.06
	O-5		−154(1)	213(1)	373(1)	4.34
	O-6		−262(1)	434(1)	344(1)	6.15
G-2	C-1		207(1)	−93(2)	471(1)	4.50
	C-2		129(1)	−185(2)	448(1)	3.77
	C-3		46(1)	−120(2)	393(1)	3.60
	C-4		20(1)	5(2)	418(1)	3.68
	C-5		104(1)	89(2)	446(1)	4.26
	C-6		83(1)	209(2)	482(1)	7.26
	O-2		156(1)	−302(1)	425(1)	4.61
	O-3		−33(1)	−206(1)	371(1)	4.27
	O-4		−45(1)	63(1)	360(1)	3.27
	O-5		179(1)	23(1)	495(1)	3.47
	O-6		159(1)	291(2)	501(1)	11.60
G-3	C-1		482(1)	−66(2)	363(1)	3.76
	C-2		429(1)	−193(2)	356(1)	4.36
	C-3		331(1)	−169(1)	356(1)	3.81
	C-4		332(1)	−90(1)	418(1)	2.89
	C-5		383(1)	30(2)	421(1)	4.10
	C-6		393(1)	114(2)	483(1)	5.17
	O-2		429(1)	−262(1)	296(1)	5.90
	O-3		284(1)	−287(1)	354(1)	5.53
	O-4		237(1)	−62(1)	414(1)	3.82
	O-5		477(1)	3(1)	422(1)	4.44
	O-6		432(1)	42(1)	545(1)	6.60
G-4	C-1		516(1)	219(2)	160(1)	3.67
	C-2		517(1)	73(2)	151(1)	4.41
	C-3		458(1)	15(1)	193(1)	3.62
	C-4		502(1)	61(2)	269(1)	3.65
	C-5		499(1)	204(2)	269(1)	4.04
	C-6		549(1)	258(2)	344(1)	5.10
	O-2		475(1)	45(1)	79(1)	4.54
	O-3		465(1)	−123(1)	189(1)	5.28
	O-4		439(1)	9(1)	302(1)	3.14
	O-5		555(1)	253(1)	230(1)	3.42
	O-6		640(1)	219(2)	371(1)	6.47
G-5	C-1		279(1)	568(1)	15(1)	3.42
	C-2		304(1)	452(2)	−26(1)	3.70
	C-3		333(1)	339(2)	21(1)	3.81

(contd.)

Atom	Occupancy	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}^a
C-4		412(1)	377(1)	84(1)	3.11
C-5		388(1)	495(1)	120(1)	3.74
C-6		472(1)	543(2)	177(1)	4.46
O-2		221(1)	423(1)	−83(1)	4.12
O-3		362(1)	237(1)	−14(1)	4.18
O-4		425(1)	266(1)	130(1)	3.07
O-5		357(1)	597(1)	71(1)	3.68
O-6		545(1)	578(1)	150(1)	5.67
G-6					
C-1		−48(1)	699(2)	36(1)	4.11
C-2		−39(1)	667(2)	−36(1)	4.17
C-3		41(1)	581(2)	−27(1)	4.12
C-4		131(1)	631(2)	24(1)	4.01
C-5		114(1)	665(2)	92(1)	4.29
C-6		198(1)	727(2)	144(1)	8.15
C-7		−184(1)	704(3)	−133(1)	7.87
C-8		−160(1)	689(4)	−203(1)	13.97
C-9		−148(4)	541(4)	−218(2)	26.84
O-2		−123(1)	618(1)	−78(1)	4.81
O-3		57(1)	567(1)	−93(1)	5.10
O-4		201(1)	538(1)	34(1)	3.58
O-5		36(1)	747(1)	80(1)	4.63
O-6	0.47	174(2)	736(5)	210(1)	13.28
O-6'	0.53	215(2)	847(4)	113(2)	11.47
O-7		−66(1)	748(2)	−191(1)	12.95
G-7					
C-1		−238(1)	456(2)	177(1)	4.54
C-2		−279(1)	441(2)	99(1)	4.39
C-3		−202(1)	461(2)	65(1)	4.12
C-4		−152(1)	578(2)	88(1)	4.12
C-5		−107(1)	579(2)	169(1)	4.24
C-6		−55(1)	697(2)	202(1)	6.07
O-2		−321(1)	316(1)	84(1)	4.85
O-3		−249(1)	468(2)	−7(1)	8.11
O-4		−73(1)	581(1)	62(1)	3.79
O-5		−188(1)	569(1)	195(1)	4.51
O-6		3(1)	668(2)	268(1)	10.35
Water					
O-W1		615(1)	−10(2)	568(1)	12.30
O-W2		287(1)	549(2)	527(1)	9.35
O-W3		685(3)	−12(3)	730(2)	25.65
O-W4		−119(2)	−44(3)	723(1)	24.36
O-W5	0.50	381(2)	133(2)	648(1)	5.99
O-W6	0.50	320(2)	167(3)	619(1)	6.23
O-W7		533(1)	291(1)	−37(1)	4.50
O-W8		348(1)	271(2)	−223(2)	21.95
O-W9	0.50	275(2)	325(3)	−384(2)	9.83
O-W10	0.50	234(3)	339(4)	384(2)	14.11
O-W11	0.50	75(4)	466(4)	405(3)	20.64

^a $B_{eq} = 4/3 \sum a_i a_j B_{ij}$, where a_i and a_j are lattice parameters and B_{ij} is the anisotropic temperature factor.

DISCUSSION

The X-ray structure presented confirms that the hydroxypropyl group is attached to an O-2 of cyclomaltoheptaose (Fig. 1). The average bond distances, angles, and their deviations are normal, and the introduction of the hydroxypropyl group does not significantly affect the structure of each glucose residue. The hydroxypropyl group points away from the centre of the macrocycle. The torsion angles C-1-C-2-O-2-C-7 and C-3-C-2-O-2-C-7 are 106° and -132° , respectively, which are similar to those (94° and -147°) of methyl groups found in methylated cyclomaltoheptaose¹¹. The C-7-C-8 bond is *gauche* to the C-2-O-2 bond, and both the C-8-C-9 and C-8-O-7 bonds are *gauche* to the O-2-C-7 bond. The conformation of the hydroxypropyl group is stabilised by the hydrogen bond with O-3 of the G-6 unit. The interaction of adjacent molecules may also affect the conformation. The C-6-O-6 bonds in the G-2, G-3, G-4, and G-5 units are in *gauche-gauche* conformations to the C-5-O-5 and C-4-C-5 bonds, respectively, whereas the G-1 and G-7 units show a *gauche-trans* conformation of the C-6-O-6 bond. Disorder is found in the orientation of the C-6-O-6 bond of the G-6 unit and the two conformers are distributed statistically in the crystal.

The torsion-angle index (Table II) is in the range 108 – 129° as in cyclomaltoheptaose⁸. This index is sensitive to a small change in conformation of the pyranose ring.

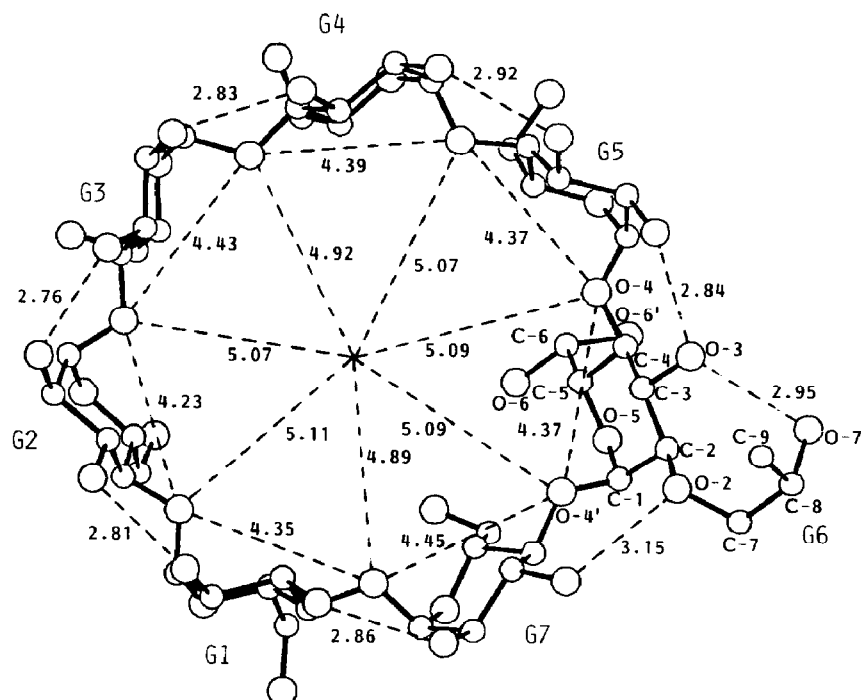


Fig. 1. Radius and side length of the O-4 heptagon and distances between O-2 and O-3 of the adjacent glucose residue. The radius of the heptagon is the distance from the centre of gravity of seven O-4 atoms to each O-4 atom.

TABLE II

Some parameters that describe the conformation of the macrocycle

Glucose residue	$\varphi(^{\circ})^a$	$\Phi(^{\circ})^b$	Tilt angle ($^{\circ}$) ^c	Deviation (\AA) ^d
G-1	115	129	3.4	0.183
G-2	119	122	18.8	0.116
G-3	119	112	10.7	-0.271
G-4	116	125	10.0	0.058
G-5	117	125	10.7	0.219
G-6	118	120	27.7	-0.130
G-7	120	108	13.4	-0.132

^a Glycosidic oxygen angle. ^b Torsion-angle index defined as $|\varphi(\text{C-1-C-2})| + |\varphi(\text{C-2-C-3})| + |\varphi(\text{C-5-O-5})| + |\varphi(\text{O-5-C-1})| - |\varphi(\text{C-3-C-4})| - |\varphi(\text{C-4-C-5})|$, where $\varphi(\text{C-1-C-2})$ is the torsion angle of O-5-C-1-C-2-C-3.

^c Defined as the angle made by the O-4 plane and the plane through C-1, C-4, O-4, and O-4'. ^d Deviation of the O-4 atoms from the least-squares plane through six O-4 atoms.

However, comparison of the indexes for the various glucose residues indicates that the pyranose ring of the G-6 residue is not affected significantly by the introduction of the hydroxypropyl group.

Some parameters that describe the macrocyclic conformation of **1** are shown in Fig. 1. Seven O-4 atoms are almost coplanar within 0.27 Å from their least-squares plane (Table II), and form a heptagon with a mean radius of 5.03 Å and mean side-length of 4.37 Å. The respective standard deviations of 0.09 and 0.07 Å indicate that the O-4 heptagon is more distorted than that found in cyclomaltoheptaose⁹. The distance between O-2 and O-3 of adjacent units is in the usual range of O-H...O hydrogen bonds, except the O-2(G-6)...O-3(G-7) distance of 3.15 Å which indicates a weak hydrogen bond. The relatively large O-2-O-3 distance between the G-6 and G-7 units is caused by the inclination of the G-6 unit with its O-6 side towards the inside of the macrocycle. The tilt angle of the G-6 unit is 27.7°, which is considerably larger than those (3.4–18.8°) of the other units.

The molecule is stacked along the two-fold screw axis. The hydroxypropyl group is inserted into the cavity of an adjacent molecule from the secondary hydroxyl side, *i.e.*, the cyclomaltoheptaose moiety is the host for an adjacent hydroxypropyl group. A similar host-guest interaction has been observed for 6-*O*-monosubstituted cyclomaltoheptaoses¹⁰, heptakis(2,6-di-*O*-methyl)cyclomaltoheptaose¹¹, and 6-*O*-D-glucosylcyclomaltohexaose¹².

Since the hydroxypropyl group is enclosed fully within the cavity in **1**, the cyclomaltoheptaose moiety can adopt the packing mode found for cyclomaltoheptaose, which includes water molecules instead of the hydroxypropyl group. Intermolecular contacts of the included hydroxypropyl group with the adjacent cyclomaltoheptaose ring are shown in Fig. 2. The C-7 methylene group and the C-9 methyl group are in weak van der Waals contact with the inside wall of the macrocyclic cavity. HO-7 is hydrogen-bonded to the O-W4 water molecule which forms a hydrogen bond with HO-6 of the host macrocycle. Therefore, the hydroxypropyl group is pulled into the cavity of **1** by the O-7...water...O-6 hydrogen bond.

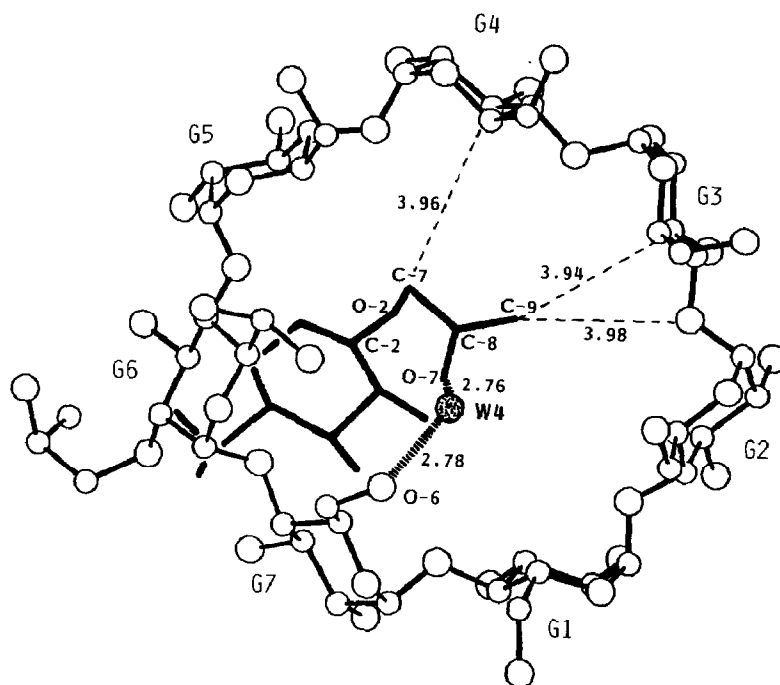


Fig. 2. Intermolecular contacts of the hydroxypropyl group included within the cavity of the adjacent molecule.

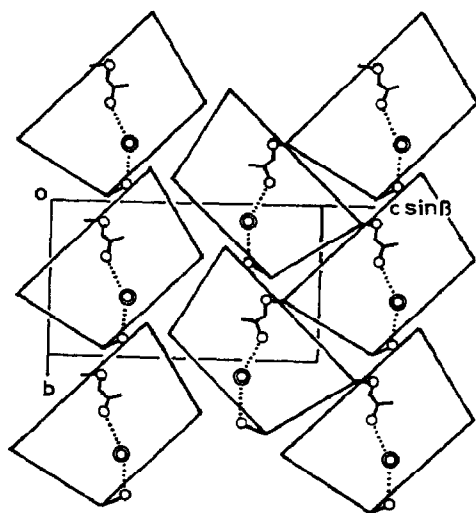


Fig. 3. Packing structure of the crystal. Hydrogen bonds involving the hydroxypropyl group are shown by dotted lines.

TABLE III

Intermolecular distances (Å) < 3.2 Å

Atom-Atom	Distance	Atom-Atom	Distance
O-2(G-1)-O-W8	2.71(i) ^a	O-2(G-4)-O-W7	2.75(k)
O-2(G-1)-O-W9	3.02(i)	O-3(G-4)-O-W8	2.91(k)
O-3(G-1)-O-2(G-5)	2.75(i)	O-6(G-4)-O-W2	2.70(l)
O-5(G-1)-O-6(G-4)	3.09(c)	O-3(G-5)-O-W7	2.82
O-6(G-1)-O-6(G-4)	2.83(c)	O-5(G-5)-O-W7	2.87(g)
O-6(G-1)-O-W5	2.78(h)	O-6(G-5)-O-W7	3.18(g)
-O-W6	2.78(h)	-O-W8	2.71(g)
O-2(G-2)-O-W2	2.84(d)	O-2(G-6)-O-6'(G-6)	3.12(i)
-O-W11	2.69(d)	O-2(G-6)-O-W9	2.49(b)
O-3(G-2)-O-6(G-7)	2.69(d)	O-6'(G-6)-O-3(G-7)	2.70(f)
O-5(G-2)-O-W6	3.14	O-2(G-7)-O-W7	2.76(c)
O-6(G-2)-O-W6	3.12	O-6(G-7)-O-W4	2.78(h)
-O-W11	2.69	O-7(G-6)-O-W4	2.76(e)
O-2(G-3)-O-W3	3.07(l)	O-W1-O-W2	2.86(i)
-O-W5	2.94(l)	-O-W10	2.69(l)
O-3(G-3)-O-6(G-6)	2.92(d)	O-W2-O-W9	3.02(b)
-O-W1	2.96(l)	O-W3-O-W4	3.02(a)
-O-W3	3.04(l)	O-W4-O-W10	2.65(j)
O-3(G-5)-O-W1	3.07	-O-W11	2.93(j)
O-6(G-3)-O-W1	2.71	O-W5-O-W9	2.51(b)
-O-W5	2.65	O-W8-O-W9	3.19
-O-W6	2.91	O-W10-O-W11	2.89

^a Symmetry operator:

None	x,	y,	z	g	1-x	1/2 + y,	-z
a	1 + x,	y	z	h	-x,	1/2 + y,	1-z
b	x,	y,	1 + z	i	-x	-1/2 + y,	-z
c	1 + x,	y,	z				
d	x,	-1 + y,	z	j	-x,	-1/2 + y,	1-z
e	x,	1 + y,	-1 + z	k	1-x,	-1/2 + y,	-z
f	-x,	1/2 + y,	-z	l	1-x,	-1/2 + y,	1-z

The molecular packing, illustrated in Fig. 3, shows a typical cage-type herring-bone structure⁹. The hydroxypropyl group is enclosed within the "cage" that is formed by the blocking of both ends with adjacent molecules. Two molecules of **1**, related by the two-fold screw axis, are connected by three hydrogen bonds, O-3(G-1)⋯O-2(G-5), O-2(G-6)⋯O-6'(G-6), and O-3(G-7)⋯O-6'(G-6). Two water molecules, O-W3 and O-W4, are included at the O-6 side of the cavity of **1**, whereas the other water molecules are distributed in intermolecular space and form a hydrogen-bond network. Intermolecular distances which involve water molecules and hydroxyl groups are given in Table III. Eight water molecules are linked by hydrogen bonds to form a chain with the sequence O-W5, O-W9, O-W2, O-W1, O-W10, O-W4, and O-W3. The other three water molecules, O-W6, O-W7, and O-W8, are isolated and form hydrogen bonds with surrounding hydroxyl groups of molecules of **1**.

The crystal structure suggests that the molecules of **1** could also associate in solution with the inclusion of the hydroxypropyl group. When a guest compound is

added to the solution, it may form a complex more soluble than **1** by competing with the hydroxypropyl group, which may be the reason for the increase of the apparent solubility of **1**. In spite of the crystallisation from aqueous 70% 1-propanol, the crystal of **1** contained only water molecules. It is possible that **1** forms an inclusion complex with 1-propanol which, during crystallisation, is expelled by the hydroxypropyl group of another molecule of **1**.

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