Carbohydrate Research, 247 (1993) 83–98
Elsevier Science Publishers B.V., Amsterdam

Crystal structure of 6-*O*-[(*R*)-2-hydroxypropyl]cyclomaltoheptaose and 6-*O*-[(*S*)-2-hydroxypropyl]cyclomaltoheptaose

Kazuaki Harata [a,*], C. Trinadha Rao [b] and Josef Pitha [b]

[a] *Research Institute for Polymers and Textiles, 1-1-4 Higashi, Tsukuba, Ibaraki 305 (Japan)*
[b] *National Institutes of Health, NIA / GRC, Baltimore, MD 21224 (USA)*

(Received October 27th, 1992; accepted March 15th, 1993)

ABSTRACT

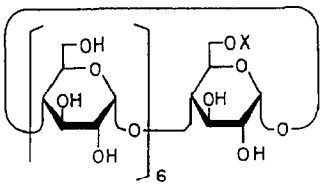
Crystal structures of 6-*O*-[(*R*)-2-hydroxypropyl]- and 6-*O*-[(*S*)-2-hydroxypropyl]-cyclomaltoheptaose were determined by X-ray analysis. In both structures, the 2-hydroxypropyl group is inserted into the macrocyclic cavity of the next molecule related by the two-fold screw axis, and a helically extended polymeric structure is formed by repetition of the intermolecular inclusion. The hydroxyl group of the substituent group penetrates through the macrocyclic ring from the secondary hydroxyl side and is linked to an HO-6 group by a hydrogen bond. Comparison of intermolecular contacts of the substituent group indicates that the (*S*)-2-hydroxypropyl group is better fitted to the cavity than the (*R*)-2-hydroxypropyl group.

INTRODUCTION

Cyclomaltoheptaose (β-cyclodextrin, βCD) is a macrocyclic oligosaccharide consisting of seven D-glucose residues. Alkylated βCDs, including hydroxypropyl derivatives, are of industrial interest because of their markedly high solubility in water[1]. Recently, interest has been focused on pharmaceutical applications since hydroxypropyl-βCDs have been found to be non-toxic, with biological compatibility[2–4]. Hydroxypropyl-βCDs have been investigated as potential drug carriers, and as solubilising additives for sparingly soluble pharmaceuticals[5–9]. However, in these studies, the hydroxypropyl derivatives have usually been in the form of mixtures of compounds with several degrees of substitution, regioisomers, or

* Corresponding author. Present address: Biomolecules Department, National Institute of Bioscience and Human-Technology, 1-1 Higashi, Tsukuba, Ibaraki 305, Japan.

optical isomers, and the physicochemical properties of each individual isomer have not been elucidated. Rao et al. have synthesised and purified several hydroxyalkyl derivatives of βCD[10,11]. The solubility of βCD is decreased by the introduction of the substituent at the 2-*O* position but markedly increased by substitution at the 6-*O* position. In a previous paper[12], we reported the structure of 2-*O*-[(*S*)-2-hydroxypropyl]-βCD and suggested that the low solubility can be ascribed to the polymeric structure in the crystal where the substituent group is included in the macrocyclic cavity of the adjacent molecule. This paper deals with the structures of 6-[*O*-[(*R*)-2-hydroxypropyl]- and 6-*O*-[(*S*)-2-hydroxypropyl]-βCD (**1** and **2**, respectively).



1 X = (*R*)-2-hydroxypropyl
2 X = (*S*)-2-hydroxypropyl

EXPERIMENTAL

Crystallisation and X-ray measurements.—Synthesis and purification of **1** and **2** were carried out according to the procedure previously reported[10]. Crystals of these βCD derivatives were obtained by the slow evaporation of an aqueous solution at room temperature. X-ray diffraction experiments were carried out on an Enraf–Nonius CAD4 diffractometer with a GX21 generator (40 kV, 60 mA, focal spot size of 0.3 × 3 mm) for graphite-monochromated Cu*Kα* radiation. The crystal, which rapidly breaks up in air, was sealed in a glass capillary. The unit-cell parameters were refined with 25 reflections in the 2*θ* range of 40–44°. Reflection data were collected up to 140° in 2*θ*. Using the *θ*–2*θ* scan mode, 7250 and 7219 reflections were measured using crystals of 0.3 × 0.4 × 0.5 mm for **1** and 0.2 × 0.3 × 0.6 mm for **2**, respectively. An empirical absorption correction was made by using the program incorporated in the CAD4 structure determination package. The reflections with $|F_o| > 3\sigma(F)$, 5750 (79%) and 5255 (73%) for **1** and **2**, respectively, were considered as observed, and used for structure determination and refinement.

Crystal data.—(*1*) Compound **1**: $C_{45}H_{76}O_{36} \cdot 10.3H_2O$, mol wt 1379.0, orthorhombic, space group $P2_12_12_1$, $z = 4$, $a = 13.164(1)$, $b = 19.335(1)$, $c = 27.261(2)$ Å, $V = 6938(1)$ Å^3, $D_c = 1.320$ g cm^{-3}, $\mu = 11.86$ cm^{-1}. (*2*) Compound **2**: $C_{45}H_{76}O_{36} \cdot 12.0H_2O$, mol wt 1410.0, orthorhombic, space group $P2_12_12_1$, $z = 4$, $a = 12.939(2)$, $b = 19.528(2)$, $c = 27.303(2)$ Å, $V = 6899(1)$ Å^3, $D_c = 1.358$ g cm^{-3}, $\mu = 12.26$ cm^{-1}.

Structure determination and refinement.—The orientation of the βCD ring was roughly estimated from the Patterson map of **1**. The rotation around the pseudo

TABLE I

Atomic coordinates ($\times 10^4$) and temperature factors (Å^2)

Residue	Atom	Occupancy	x	y	z	B_{eq} [a]
I. 6-*O*-[(*R*)-2-Hydroxypropyl]cyclomaltoheptaose						
G-1	C-1	1.0	1479(8)	2237(4)	2415(3)	5.42
	C-2	1.0	416(8)	2406(5)	2566(3)	5.81
	C-3	1.0	3(7)	3026(4)	2308(3)	4.98
	C-4	1.0	740(7)	3634(4)	2346(3)	4.99
	C-5	1.0	1809(8)	3440(4)	2212(4)	5.85
	C-6	1.0	2562(9)	4001(5)	2324(5)	8.51
	O-2	1.0	−172(6)	1796(3)	2476(2)	6.05
	O-3	1.0	−956(5)	3199(3)	2500(2)	6.25
	O-4	1.0	380(5)	4167(3)	2031(2)	4.80
	O-5	1.0	2130(5)	2839(3)	2481(2)	6.08
	O-6	1.0	3563(6)	3839(4)	2145(4)	11.96
G-2	C-1	1.0	2740(8)	566(5)	1009(3)	5.62
	C-2	1.0	1775(8)	342(4)	1308(3)	5.51
	C-3	1.0	1245(7)	978(4)	1515(3)	4.35
	C-4	1.0	2008(7)	1427(4)	1778(3)	4.94
	C-5	1.0	2913(7)	1617(5)	1445(4)	6.09
	C-6	1.0	3761(9)	2032(6)	1694(5)	9.01
	O-2	1.0	1101(5)	−59(3)	1011(2)	5.80
	O-3	1.0	478(5)	749(3)	1845(2)	5.36
	O-4	1.0	1489(5)	2049(3)	1917(2)	4.77
	O-5	1.0	3398(5)	980(3)	1282(2)	5.80
	O-6	1.0	4126(7)	1668(5)	2092(4)	12.61
G-3	C-1	1.0	2693(9)	1160(5)	−896(3)	6.78
	C-2	1.0	1746(10)	760(5)	−727(4)	7.52
	C-3	1.0	1553(8)	847(5)	−164(4)	6.62
	C-4	1.0	2562(7)	737(5)	112(3)	5.79
	C-5	1.0	3436(8)	1183(4)	−102(3)	5.59
	C-6	1.0	4409(8)	1053(6)	134(4)	7.73
	C-7	1.0	6073(13)	1487(11)	197(6)	14.91
	C-8	1.0	6676(17)	1118(19)	−222(9)	27.12
	C-9	1.0	6864(18)	1645(22)	−630(10)	34.93
	O-2	1.0	839(7)	975(5)	−1001(3)	9.82
	O-3	1.0	836(6)	368(4)	12(3)	9.09
	O-4	1.0	2334(5)	955(3)	601(2)	5.73
	O-5	1.0	3541(5)	1024(3)	−619(2)	6.06
	O-6	1.0	5109(6)	1601(5)	−4(3)	9.46
	O-7	1.0	7720(16)	1141(13)	−91(6)	30.44
G-4	C-1	1.0	2695(8)	3604(5)	−1770(4)	6.53
	C-2	1.0	2140(8)	2958(5)	−2000(3)	6.19
	C-3	1.0	1830(8)	2467(5)	−1599(3)	5.89
	C-4	1.0	2769(9)	2277(5)	−1292(4)	6.35
	C-5	1.0	3278(8)	2922(5)	−1090(3)	6.14
	C-6	1.0	4257(10)	2803(6)	−822(4)	8.35
	O-2	1.0	1309(6)	3180(4)	−2292(3)	7.75
	O-3	1.0	1416(6)	1854(4)	−1822(3)	7.35
	O-4	1.0	2409(5)	1869(3)	−883(2)	5.69
	O-5	1.0	3507(5)	3383(3)	−1491(2)	6.26
	O-6	0.55	4571(14)	3340(8)	−569(6)	11.39
	O-6′	0.45	5048(20)	2418(14)	−1096(11)	15.36

TABLE I (continued)

Residue	Atom	Occupancy	x	y	z	B_{eq} [a]
G-5	C-1	1.0	1128(8)	5944(4)	−1115(3)	5.66
	C-2	1.0	489(8)	5594(5)	−1499(3)	6.18
	C-3	1.0	695(7)	4815(5)	−1513(3)	5.71
	C-4	1.0	1836(8)	4676(5)	−1531(3)	5.99
	C-5	1.0	2424(10)	5044(4)	−1107(3)	6.33
	C-6	1.0	3544(8)	4969(5)	−1097(4)	6.33
	O-2	1.0	−562(5)	5723(4)	−1416(2)	6.95
	O-3	1.0	204(6)	4520(4)	−1932(3)	8.63
	O-4	1.0	1928(6)	3940(3)	−1487(2)	6.62
	O-5	1.0	2167(5)	5774(3)	−1158(2)	5.81
	O-6	1.0	3940(6)	5170(4)	−1543(3)	7.33
G-6	C-1	1.0	43(10)	6507(5)	719(4)	7.42
	C-2	1.0	−778(10)	6537(6)	334(4)	8.19
	C-3	1.0	−508(8)	6069(5)	−100(4)	6.78
	C-4	1.0	537(8)	6246(5)	−279(3)	6.13
	C-5	1.0	1290(10)	6213(5)	127(4)	7.52
	C-6	1.0	2329(12)	6473(10)	−31(5)	12.71
	O-2	1.0	−1697(7)	6368(5)	547(3)	9.35
	O-3	1.0	−1227(6)	6150(5)	−476(3)	8.79
	O-4	1.0	740(5)	5722(3)	−644(2)	5.88
	O-5	1.0	1010(7)	6673(3)	510(3)	8.84
	O-6	0.55	3088(16)	6398(12)	302(7)	14.56
	O-6′	0.45	2317(24)	7077(13)	−183(9)	16.39
G-7	C-1	1.0	108(8)	4822(4)	2243(3)	5.25
	C-2	1.0	−926(7)	5024(5)	2050(3)	5.47
	C-3	1.0	−858(7)	5203(5)	1507(3)	5.43
	C-4	1.0	−41(8)	5721(4)	1437(3)	5.46
	C-5	1.0	951(8)	5475(4)	1630(3)	5.81
	C-6	1.0	1823(9)	5985(5)	1593(4)	7.41
	O-2	1.0	−1625(5)	4471(3)	2126(2)	6.44
	O-3	1.0	−1804(5)	5465(4)	1350(2)	6.75
	O-4	1.0	36(6)	5822(3)	905(2)	6.04
	O-5	1.0	829(5)	5320(3)	2156(2)	5.48
	O-6	1.0	1529(6)	6644(3)	1800(3)	7.87
Water	O-W1	1.0	−552(15)	2125(7)	−542(5)	20.56
	O-W2	1.0	−2319(16)	7448(7)	1230(7)	24.77
	O-W3	1.0	4172(13)	6697(7)	−1263(5)	19.60
	O-W4	0.71	6017(17)	6444(7)	−1309(12)	25.23
	O-W5	0.65	−3467(13)	4902(12)	2451(9)	19.87
	O-W6	0.35	−3444(24)	3796(22)	2850(10)	16.25
	O-W7	0.42	−945(46)	6672(16)	−2214(12)	33.29
	O-W8	0.71	−3315(15)	6121(17)	1859(7)	27.27
	O-W9	0.58	4476(19)	2887(14)	2769(12)	31.96
	O-W10	0.43	4549(29)	4815(19)	1453(14)	22.17
	O-W11	0.63	8723(20)	40(11)	−414(10)	21.92
	O-W12	0.46	−3602(19)	6165(14)	31(11)	16.83
	O-W13	0.33	−1370(39)	7717(23)	−1746(12)	21.52
	O-W14	0.31	7348(54)	7155(19)	−1579(20)	30.96
	O-W15	0.22	4428(34)	5403(62)	2054(17)	37.63
	O-W16	0.25	−1000(40)	7666(17)	−884(13)	13.31
	O-W17	0.18	−3363(59)	6922(24)	−505(29)	17.30

TABLE I (continued)

Residue	Atom	Occupancy	x	y	z	B_{eq} [a]
	O-W18	0.21	7602(44)	7212(23)	−754(16)	15.39
	O-W19	0.21	243(48)	8003(28)	−833(15)	13.58
	O-W20	0.18	−5119(34)	6688(26)	−233(25)	12.82
	O-W21	0.19	−4369(78)	6543(42)	−564(29)	26.56
	O-W22	0.32	919(41)	7711(25)	−1533(32)	35.00
II. 6-*O*-[(*S*)-2-Hydroxypropyl]cyclomaltoheptaose						
G-1	C-1	1.0	1507(7)	2222(4)	2440(3)	4.56
	C-2	1.0	407(7)	2374(4)	2588(3)	4.96
	C-3	1.0	−16(7)	2981(4)	2332(3)	4.21
	C-4	1.0	714(6)	3599(4)	2378(3)	4.36
	C-5	1.0	1803(7)	3403(4)	2238(3)	4.80
	C-6	1.0	2561(8)	3963(5)	2376(4)	7.30
	O-2	1.0	−180(5)	1755(3)	2495(2)	5.35
	O-3	1.0	−991(5)	3147(3)	2531(2)	5.87
	O-4	1.0	338(4)	4104(2)	2053(2)	4.17
	O-5	1.0	2140(5)	2803(3)	2509(2)	5.18
	O-6	1.0	3590(6)	3807(4)	2191(4)	10.25
G-2	C-1	1.0	2769(7)	615(4)	985(3)	5.04
	C-2	1.0	1854(7)	366(4)	1310(3)	4.69
	C-3	1.0	1288(6)	969(4)	1531(3)	3.86
	C-4	1.0	2054(6)	1431(4)	1793(3)	4.03
	C-5	1.0	2936(7)	1641(4)	1454(3)	5.01
	C-6	1.0	3819(8)	2051(5)	1709(4)	6.73
	O-2	1.0	1175(5)	−38(3)	1013(2)	5.27
	O-3	1.0	529(4)	724(3)	1862(2)	4.53
	O-4	1.0	1504(4)	2027(2)	1937(2)	3.99
	O-5	1.0	3442(4)	1022(3)	1270(2)	4.95
	O-6	1.0	4196(6)	1685(4)	2114(3)	8.69
G-3	C-1	1.0	2621(7)	1223(4)	−897(3)	4.75
	C-2	1.0	1671(7)	841(4)	−709(3)	5.09
	C-3	1.0	1531(7)	952(5)	−164(3)	5.04
	C-4	1.0	2531(7)	805(4)	111(3)	4.46
	C-5	1.0	3418(6)	1230(4)	−114(3)	4.37
	C-6	1.0	4452(7)	1068(5)	117(4)	6.31
	C-7	1.0	6201(8)	1347(7)	47(5)	9.66
	C-8	1.0	6861(9)	1761(11)	−334(6)	14.79
	C-9	1.0	6686(13)	1469(11)	−830(4)	15.72
	O-2	1.0	757(5)	1093(3)	−974(2)	6.25
	O-3	1.0	739(5)	497(4)	24(2)	7.23
	O-4	1.0	2345(4)	1009(3)	610(2)	4.63
	O-5	1.0	3497(4)	1067(3)	−625(2)	4.48
	O-6	1.0	5184(5)	1568(3)	−43(3)	6.55
	O-7	1.0	7925(9)	1582(8)	−160(4)	18.04
G-4	C-1	1.0	2712(8)	3625(4)	−1776(3)	5.91
	C-2	1.0	2200(7)	3008(5)	−2009(3)	5.43
	C-3	1.0	1848(7)	2502(5)	−1610(3)	5.13
	C-4	1.0	2773(7)	2333(4)	−1296(3)	5.08
	C-5	1.0	3303(7)	2973(4)	−1092(3)	4.70
	C-6	1.0	4292(8)	2829(5)	−817(4)	6.37
	O-2	1.0	1351(5)	3217(4)	−2319(2)	6.89
	O-3	1.0	1430(5)	1907(3)	−1836(2)	5.99

TABLE I (continued)

Residue	Atom	Occupancy	x	y	z	B_{eq} [a]
	O-4	1.0	2385(5)	1941(3)	−882(2)	4.56
	O-5	1.0	3549(5)	3418(3)	−1484(2)	5.27
	O-6	0.55	4553(11)	3376(6)	−545(5)	8.09
	O-6′	0.45	5116(15)	2448(10)	−1092(7)	9.91
G-5	C-1	1.0	1098(7)	5938(4)	−1091(3)	5.22
	C-2	1.0	471(7)	5603(4)	−1497(3)	5.27
	C-3	1.0	655(7)	4826(4)	−1520(3)	5.35
	C-4	1.0	1828(7)	4697(4)	−1533(3)	5.14
	C-5	1.0	2372(7)	5056(4)	−1114(3)	5.01
	C-6	1.0	3549(8)	4990(5)	−1099(3)	6.00
	O-2	1.0	−620(5)	5736(3)	−1417(2)	6.25
	O-3	1.0	189(6)	4570(4)	−1956(2)	7.25
	O-4	1.0	1919(5)	3970(3)	−1496(2)	5.86
	O-5	1.0	2156(5)	5773(3)	−1142(2)	5.08
	O-6	1.0	3976(5)	5196(3)	−1545(2)	6.53
G-6	C-1	1.0	−25(10)	6408(4)	727(3)	7.08
	C-2	1.0	−862(9)	6470(5)	344(3)	6.88
	C-3	1.0	−571(8)	6024(5)	−89(3)	5.82
	C-4	1.0	480(8)	6203(4)	−263(3)	5.80
	C-5	1.0	1246(8)	6173(5)	135(3)	6.25
	C-6	1.0	2295(11)	6443(9)	−16(5)	11.89
	O-2	1.0	−1820(6)	6271(4)	553(2)	8.42
	O-3	1.0	−1316(6)	6108(4)	−476(2)	8.05
	O-4	1.0	709(5)	5704(3)	−638(2)	4.93
	O-5	1.0	938(6)	6602(3)	530(2)	7.29
	O-6	0.65	2271(14)	7069(7)	−162(5)	13.44
	O-6′	0.35	3068(28)	6258(22)	333(12)	19.85
G-7	C-1	1.0	59(7)	4742(4)	2254(3)	4.52
	C-2	1.0	−1001(7)	4944(4)	2056(3)	4.64
	C-3	1.0	−937(7)	5115(4)	1518(3)	4.74
	C-4	1.0	−114(7)	5647(4)	1437(3)	4.50
	C-5	1.0	909(7)	5389(4)	1634(3)	5.28
	C-6	1.0	1813(8)	5887(5)	1584(4)	6.35
	O-2	1.0	−1697(5)	4393(3)	2143(2)	5.74
	O-3	1.0	−1902(5)	5360(3)	1349(2)	5.95
	O-4	1.0	−38(5)	5749(3)	911(2)	5.13
	O-5	1.0	794(4)	5250(3)	2159(2)	4.52
	O-6	1.0	1512(6)	6550(3)	1775(3)	7.12
Water	O-W1	0.44	5021(32)	7039(19)	886(20)	29.05
	O-W2	1.0	4587(8)	2789(4)	569(3)	10.80
	O-W3	1.0	4106(10)	6737(6)	−1219(5)	15.91
	O-W4	1.0	4435(14)	4724(9)	1499(9)	30.71
	O-W5	0.34	3946(26)	2373(18)	3307(14)	15.78
	O-W6	0.90	−1065(16)	3573(7)	3619(8)	23.44
	O-W7	0.76	−3601(11)	4794(11)	2451(7)	20.02
	O-W8	0.88	−1334(16)	217(10)	−310(8)	24.84
	O-W9	0.40	−1404(18)	6641(10)	−2099(6)	9.39
	O-W10	1.0	−3363(11)	6114(9)	1877(5)	20.83
	O-W11	0.96	2600(15)	7572(7)	−1179(6)	20.95
	O-W12	0.28	−3612(45)	6491(39)	−98(28)	33.69

TABLE I (continued)

Residue	Atom	Occupancy	x	y	z	E_{eq} [a]
	O-W13	0.35	2384(31)	7844(16)	687(15)	19.20
	O-W14	0.24	4632(23)	2893(15)	2721(10)	7.50
	O-W15	0.22	4445(25)	5859(39)	1901(18)	24.23
	O-W16	0.18	−5011(62)	5964(52)	350(60)	35.14
	O-W17	0.20	4215(24)	2716(17)	2912(13)	6.94
	O-W18	0.21	4181(48)	7332(17)	804(12)	12.82
	O-W19	0.26	−3707(26)	5980(15)	108(15)	12.04
	O-W20	0.56	−1622(27)	7684(16)	−1700(11)	27.19
	O-W21	0.22	−2240(49)	2744(25)	3513(25)	22.25
	O-W22	0.21	1524(97)	8065(27)	604(16)	30.42
	O-W23	0.26	−5075(27)	6810(16)	−291(16)	11.99
	O-W24	0.17	5135(28)	3268(22)	2605(11)	6.61

[a] $B_{eq} = 4/3\Sigma a_i \mathbf{a}_j B_{ij}$, where $\mathbf{a}_i$ and $\mathbf{a}_j$ are lattice parameters and B_{ij} is the anisotropic temperature factor.

symmetry axis of the βCD ring and the position of the molecule in the unit cell were determined by the *R*-map method combined with the rigid-body least-squares refinement for each D-glucose residue. Since crystals of **1** and **2** were isomorphous, a set of βCD coordinates of **1** was used as an initial model for the structure determination of **2**. 2-Hydroxypropyl groups and water molecules were found on Fourier and difference Fourier maps. The structure was refined by the block-diagonal least-squares method that minimised $\Sigma w(|F_o| - |F_c|)^2$ with anisotropic temperature factors and unit weight for all reflections. In the final stage, the positions of hydrogen atoms of methine and methylene groups of the βCD moiety were calculated and included in the refinement with isotropic temperature factors of bonded heavy atoms. The refinement converged at the *R*-value of 0.092 for **1** and 0.077 for **2**. The maximum and minimum values of residual electron density were 0.30 and −0.21 e Å^{-3}, respectively, for **1**; and 0.23 and −0.19 e Å^{-3}, respectively, for **2**. Final atomic coordinates are given in Table I *.

DESCRIPTION OF THE STRUCTURE

The structures of **1** and **2** are shown in Figs. 1(a) and 1(b), respectively. Parameters that describe the macrocyclic conformation of βCD are given in Fig. 2. In both structures, all D-glucose residues are in the $^4C_1$ chair conformation. The primary hydroxyl groups, HO-6, show two types of conformation, *gauche–gauche* (to the O-5–C-5 bond and C-4–C-5 bond, respectively) and *gauche–trans*. The C-6–O-6 bond in the G-2, G-5, and G-7 residues shows the former conformation, while the latter conformation is found in the G-1 and G-3 residues. The C-6–O-6

* Observed and calculated structure factors, bond distances, angles, torsion angles, and atomic coordinates of hydrogen atoms are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, Netherlands. Reference should be made to No. BBA/DD/534/Carbohydr. Res., 247 (1993) 83–98.

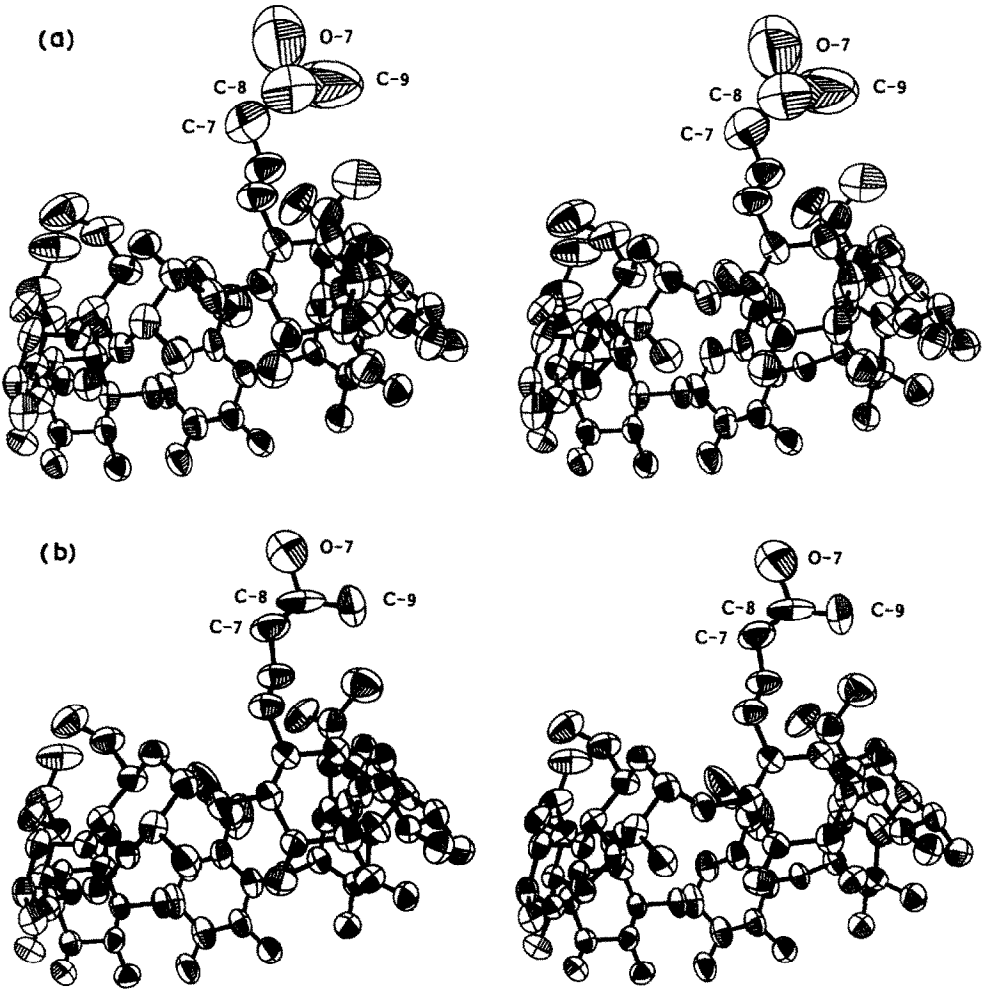


Fig. 1. Stereo-drawings of the structures **1** (a) and **2** (b).

bond in the G-4 and G-6 residues is disordered and both conformers are statistically distributed. The (*R*)- and (*S*)-2-hydroxypropyl groups are attached to the G-3 residue. The O-6–C-7 bond is *trans* in both **1** and **2**. However, the C-7–C-8 bond shows different conformations. The *trans* conformation is observed in **1**, while the C-7–C-8 bond in **2** is in the *gauche* conformation to the C-6–O-6 bond.

The seven glycosidic oxygen atoms form a distorted heptagon. The O-4 angle is distributed in the range 115–119° in both structures, with the average value of 118° (Table II). These O-4 atoms are nearly coplanar within the deviation of 0.13 Å in **1** and 0.17 Å in **2**, and the respective rms deviations are 0.09 and 0.11 Å. The pyranoid ring of each D-glucose residue is not perpendicular to the O-4 plane but inclines as indicated by the tilt angle (Table II). The G-3 residue slightly inclines

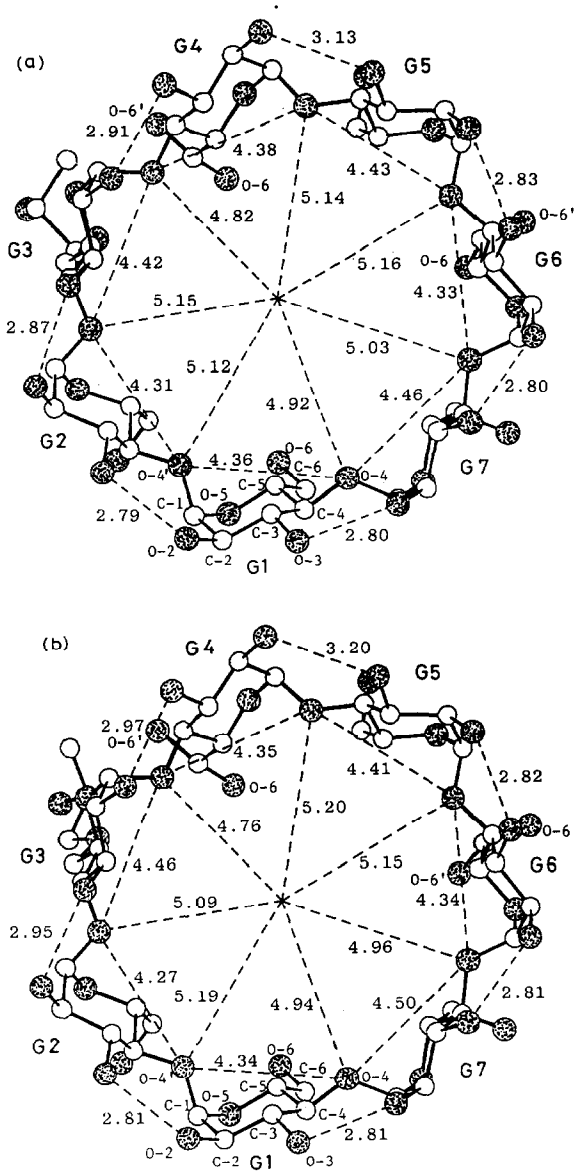


Fig. 2. Radius and side length (Å) of the heptagon consisting of O-4 atoms and the distance (Å) between O-2 and O-3 of the adjacent residue for **1** (a) and **2** (b).

with its secondary hydroxyl side towards the inside of the macrocycle. The other residues incline in the opposite direction. The geometry of the O-4 heptagon is a good estimate of the macrocyclic conformation. The radius of the heptagon is in the ranges 4.82–5.16 Å in **1** and 4.76–5.20 Å in **2** with the respective average value of 5.05 and 5.04 Å. The side length of the heptagon is distributed in the ranges 4.31–4.46 Å in **1** and 4.27–4.50 Å in **2**, and the average value is 4.38 Å for both

TABLE II

Parameters describing the macrocyclic conformation

Residue	O-4 angle (°)		Torsion-angle index (°) [a]		Tilt angle (°) [b]		Deviation of O-4 atom (Å) [c]	
	1	2	1	2	1	2	1	2
G-1	119	117	121	120	15.6	16.5	0.036	0.039
G-2	118	119	111	124	18.7	19.4	−0.134	−0.148
G-3	119	119	110	115	−2.8	−6.1	0.046	0.036
G-4	115	115	118	121	28.2	27.8	0.132	0.166
G-5	118	119	112	117	16.3	17.2	−0.127	−0.134
G-6	118	118	117	124	13.3	12.9	0.023	−0.056
G-7	119	119	111	113	5.3	5.3	0.070	0.096
Average	118	118	114	119	13.5	13.3		
esd	1	1	4	4	9.9	10.9	0.093 [d]	0.109

[a] The torsion-angle index is defined as $|\phi(\text{C-1-C-2})| + |\phi(\text{C-2-C-3})| - |\phi(\text{C-3-C-4})| - |\phi(\text{C-4-C-5})| + |\phi(\text{C-5-O-5})| + |\phi(\text{O-5-C-1})|$, where ϕ(C-1-C-2) is the torsion angle of O-5-C-1-C-2-C-3. [b] The tilt angle is defined as an angle made by the O-4 plane and the plane through C-1, C-4, O-4, and O-4′. [c] The deviation of each O-4 atom from the plane through seven O-4 atoms. [d] The rmsd value.

structures. The HO-2 groups are hydrogen-bonded to the HO-3 group of an adjacent D-glucose residue. The O-2 · · · O-3′ distance varies in the ranges 2.79–3.13 Å in **1** and 2.81–3.20 Å in **2**. The O-2 · · · O-3′ distance is highly correlated with the tilt angle of donor and acceptor residues, and increased by the inclination of these residues with the O-6 side towards the inside of the macrocycle. Therefore, the largest O-2 · · · O-3′ distance, 3.13 Å in **1** and 3.20 Å in **2**, occurs between the G-4 and G-5 residues that have a large tilt angle.

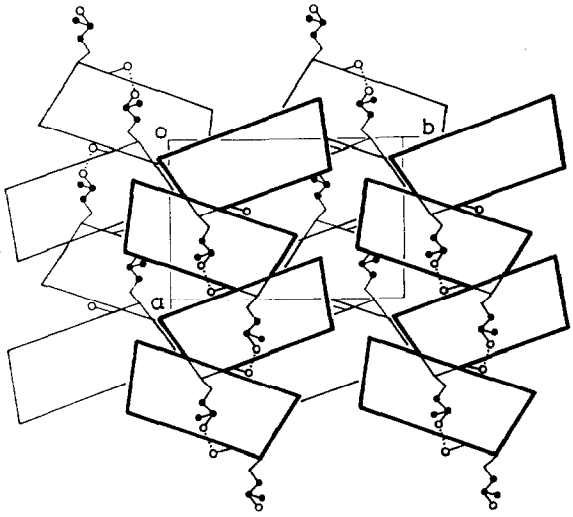


Fig. 3. A schematic drawing of the packing in the crystal viewed along the *c*-axis.

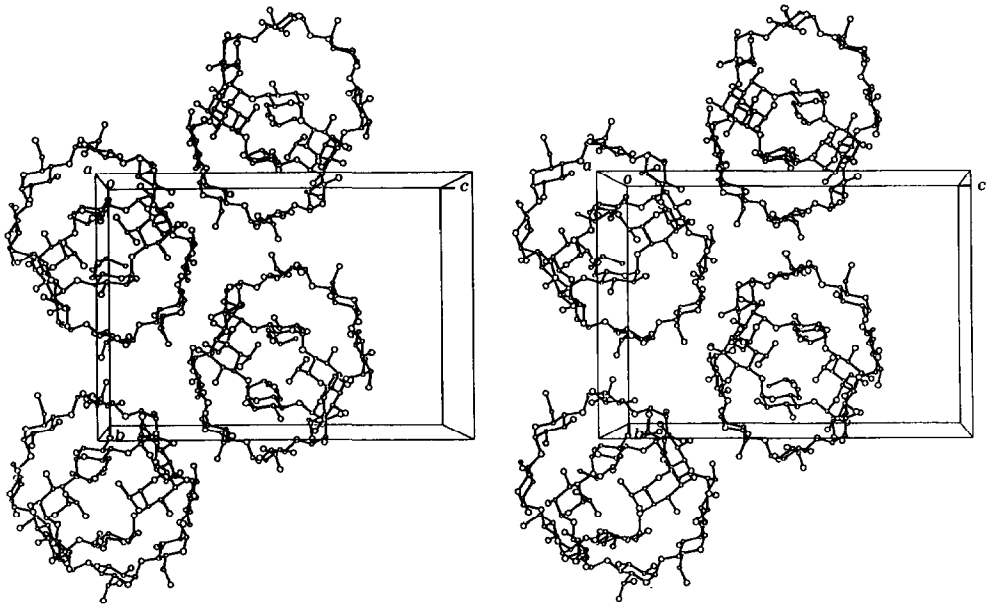


Fig. 4. A stereo-drawing of the crystal structure viewed along the *a* axis. Water molecules are not drawn for reasons of clarity.

Crystals of **1** and **2** are isomorphous and the molecules are located along the two-fold screw axis parallel to the *a* axis in both structures (Figs. 3 and 4). The (*R*)- and (*S*)-2-hydroxypropyl groups are inserted into the βCD ring of the next molecule. The molecular plane is not perpendicular to the *a* axis but makes an angle of ~ 70°. Since the center of the molecule is laterally shifted from the screw axis, the molecules are in a helical arrangement along the screw axis. The 2-hydroxypropyl group that is included in the adjacent molecule acts as a guest in the crystal (Fig. 5). The interaction of the 2-hydroxypropyl groups within the cavity of the macrocycle is different in the crystals of **1** and **2** because of the difference in the absolute configuration. The HO-7 group of **1** forms hydrogen bonds with the HO-6 group of the G-4 residue and a water molecule (W11). On the other hand, the (*S*)-2-hydroxypropyl group forms hydrogen bonds with the HO-6 group and two water molecules (W2 and W8). In both structures, methyl and methylene groups of the substituent are in van der Waals contact with O-4 atoms and HC-5 methine groups located on the inside wall of the host cavity. The (*R*)-2-hydroxypropyl group that is located near the G-4 and G-5 residues has contacts mostly with these residues. On the other hand, the (*S*)-2-hydroxypropyl group is found at the center of the cavity and is in contact with the G-1 and G-4 residues. The 2-hydroxypropyl group penetrates through the cavity of the macrocycle and is linked to the O-6 end of the cavity by a hydrogen bond. Therefore, the molecules form a polymeric structure with a helical arrangement parallel to the *a* axis. The

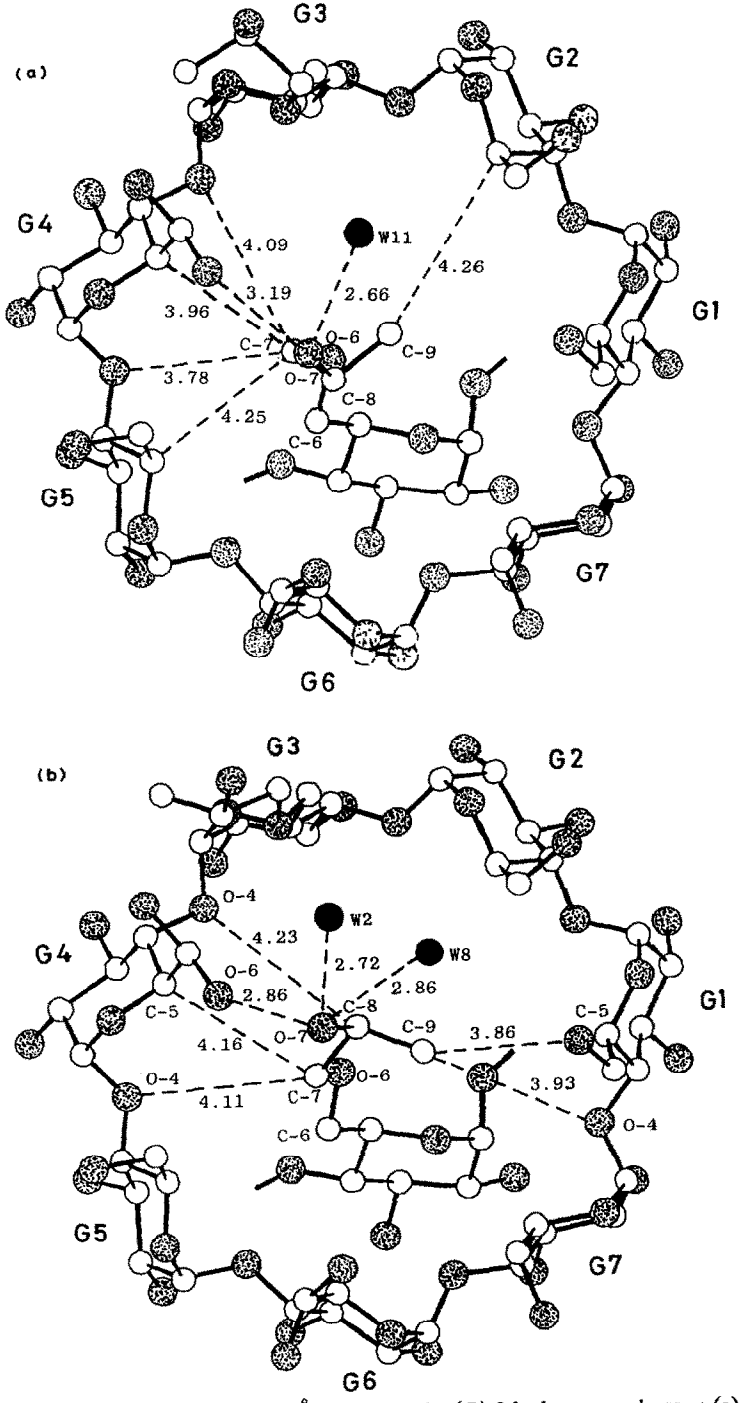


Fig. 5. Interatomic contacts (Å) involving the (*R*)-2-hydroxypropyl group (a) and the (*S*)-2-hydroxypropyl group (b).

asymmetric unit contains 10–12 water molecules. Most of these water molecules are found in intermolecular space and form hydrogen-bond networks.

DISCUSSION

Crystal structures of **1** and **2** confirmed that the 2-hydroxypropyl group is attached to an O-6 atom. The 2-hydroxypropyl groups are included in the cavity of an adjacent molecule to form a polymeric structure. A similar structure has been observed in other 6-*O*-monosubstituted βCD derivatives. Kamitori et al.[13] have reported the structure of phenylthio- and phenylsulphinyl-βCDs, in which the phenyl group is inserted into the βCD ring from the secondary hydroxyl side. In the structure of 6-*O*-α-D-glucopyranosyl-αCD[14], the primary hydroxyl group of the substituent glucosyl group penetrates into the macrocycle. In contrast, we have shown[12] that 2-*O*-[(*S*)-2-hydroxypropyl]-βCD forms the same packing structure as that observed in the crystal of unsubstituted βCD[15]; the (*S*)-2-hydroxypropyl group is inserted into the cavity of the adjacent molecule from the secondary hydroxyl side and is linked to a primary hydroxyl group by a water-mediated hydrogen-bond bridge. Therefore, the inclusion of the substituent group is a common characteristic in the crystal structure of monosubstituted βCDs. The inclusion of the substituent seems to be energetically more favorable than the inclusion of water molecules. In the crystal of unsubstituted βCD, the macrocyclic cavity is filled with water molecules, which have been considered to be in a high energy state because they cannot form full hydrogen bonds in the hydrophobic environment[15]. The inclusion of the 2-hydroxypropyl group excludes these water molecules. The alkyl group is more favorably accommodated in the hydrophobic cavity, and the hydroxyl group forms hydrogen bonds with water molecules and/or a primary hydroxyl group of the host βCD ring. In solution, 2-*O*- and 6-*O*-(2-hydroxypropyl)-βCD form complexes with guest molecules. However, no crystalline complexes were ever obtained with 2-*O*-derivatives, whereas 6-*O*-(2-hydroxypropyl)-βCD easily formed insoluble, presumably crystalline, complexes with toluene[10]. In the course of crystallisation, competition may occur between the substituent group and the guest molecule, to occupy the host cavity.

The monosubstitution of an HO-6 position does not much affect the macrocyclic conformation of βCD. The average values for the radius and side length of the O-4 heptagon and the O-2 $\cdots$ O-3′ distances are nearly the same as those observed in native βCD. The tilt angles, 13.5° in **1** and 13.3° in **2**, are also in good agreement with that (12.5°) of βCD. The residue carrying the 2-hydroxypropyl group gives a negative value of the tilt angle while positive values are observed in the other residue. The inclination of the G-3 residue is so restrained that the 2-hydroxypropyl group can be included in the adjacent βCD ring. A similar effect has been observed in the 2-*O*-(*S*)-2-hydroxypropyl derivative, in which the substituted residue inclines much more with the primary hydroxyl side towards the inside of the macrocycle. Except for the G-3 residue, the difference of the tilt angle of

TABLE III

Intermolecular distances < 3.2 Å

Atom–Atom	Distance (Å)	Atom–Atom	Distance (Å)
I. 6-*O*-[(*R*)-2-Hydroxypropyl]cyclomaltoheptaose			
O-2(G-1)–O-5(G-7)	3.15(k) [a]	O-2(G-5)–W6	2.57(p)
–O-6(G-7)	2.68(k)	–W7	2.89
O-3(G-1)–W14	3.18(m)	O-3(G-5)–W5	3.05(p)
O-5(G-1)–W9	3.19	–W15	2.81(o)
O-6(G-1)–W9	2.78	O-6(G-5)–W3	3.06
O-6(G-1)–W10	2.97	O-2(G-6)–W2	2.92
O-2(G-2)–W4	2.80(f)	–W12	2.90
O-3(G-2)–O-6(G-5)	2.82(f)	O-3(G-6)–W16	3.15
O-4(G-2)–O-6′(G-4)	3.11(f)	–W17	3.18
O-5(G-2)–O-3(G-5)	3.12(c)	–W18	2.68(b)
O-6(G-2)–O-2(G-4)	2.94(c)	O-5(G-6)–W17	2.84(e)
–O-3(G-5)	2.74(c)	–W18	3.08(h)
–W9	3.03	O-6(G-6)–W11	2.92(f)
O-2(G-3)–W1	3.14	–W16	2.69(c)
–W10	2.60(f)	–W18	3.03(h)
O-3(G-3)–W11	3.08(b)	–W20	2.83(a)
–W12	3.06(c)	O-6′(G-6)–W2	3.03(e)
O-6(G-3)–W1	3.01(c)	–W17	2.84(e)
O-7(G-3)–O-6(G-4)	3.19(c)	–W18	2.93(h)
–W11	2.66	O-2(G-7)–W5	2.71
O-2(G-4)–W13	2.77(1)	O-3(G-7)–W8	2.74
O-3(G-4)–W6	3.08(c)	O-6(G-7)–W13	3.03(e)
–W7	2.72(1)	–W14	2.63(h)
O-6(G-4)–W1	3.17(c)		
II. 6-*O*-[(*S*)-2-Hydroxypropyl]cyclomaltoheptaose			
O-2(G-1)–O-6(G-7)	2.67(k)	O-2(G-4)–W15	2.97(o)
O-3(G-1)–W6	3.09	–W20	2.89(1)
O-5(G-1)–W17	2.91	O-3(G-4)–W9	2.96(1)
O-6(G-1)–W4	2.82	–W24	2.71(g)
–W14	2.66	O-2(G-5)–W9	2.76
–W17	3.01	O-3(G-5)–W7	2.90(p)
–W24	2.53	O-5(G-5)–W3	3.16
O-2(G-2)–O-5(G-7)	3.19(k)	O-6(G-5)–W3	3.14
–W6	2.90(k)	O-2(G-6)–W11	2.93(h)
O-3(G-2)–O-6(G-5)	2.83(g)	–W12	2.95
O-4(G-2)–O-6′(G-4)	3.10(g)	–W19	2.79
O-6(G-2)–O-2(G-4)	2.85(c)	O-3(G-6)–W13	2.71(h)
–O-3(G-5)	2.80(c)	O-5(G-6)–W13	3.09
–W10	3.16(k)	–W22	2.96
–W14	2.94	O-6(G-6)–W11	2.98
–W17	2.97	–W13	2.77
O-2(G-3)–W2	2.88(g)	–W-22	3.01
–W4	2.74(g)	O-6′(G-6)–W8	2.98(c)
O-3(G-3)–O-6(G-4)	3.04(g)	–W16	2.55(a)
–W8	2.89	–W18	2.85
–W16	3.18(c)	–W24	3.14(a)
–W19	2.99(c)	O-2(G-7)–W7	2.72

Table III (continued)

Atom–Atom	Distance (Å)	Atom–Atom	Distance (Å)
O-6(G-3)–W2	3.01	O-3(G-7)–W10	2.80
O-7(G-3)–O-6(G-4)	2.86(c)	O-6(G-7)–W20	2.85(d)
–W2	2.72(c)	–W21	2.63(i)
–W8	2.86(a)		

[a] Symmetry operator:

None	x,	y,	z	i	$-x$,	$1/2+y$,	$1/2-z$
a	$1+x$,	y,	z	j	$1-x$,	$1/2+y$,	$1/2-z$
b	$-1+x$,	y,	z	k	$-x$,	$-1/2+y$,	$1/2-z$
c	$1/2+x$,	$1/2-y$,	$-z$	l	$-x$,	$-1/2+y$,	$-1/2-z$
d	$1/2+x$,	$1/2-y$,	$1-z$	m	$1/2-x$,	$1-y$,	$1/2+z$
e	$1/2+x$,	$3/2-y$,	$-z$	n	$-1/2-x$,	$1-y$,	$1/2+z$
f	$-1/2+x$,	$1/2-y$,	$-z$	o	$-1/2-x$,	$1-y$,	$-1/2+z$
g	$-1/2+x$,	$1/2-y$,	$1-z$	p	$-1/2-x$,	$1-y$,	$-1/2+z$
h	$-1/2+x$,	$3/2-y$,	$-z$				

each residue between **1** and **2** is less than 1°. The difference for the G-3 residue, 3.3°, is considered to be due to the difference in the interaction of the (*R*)- and (*S*)-2-hydroxypropyl groups with the βCD ring. In both structures, the HO-7 group of the G-3 residue forms a hydrogen bond with the HO-6 group of the G-4 residue. However, the O-7 ··· O-6 distance in **1**, 3.19 Å (Table III), indicates that the hydrogen bond in **1** is weaker than that (2.86 Å) in **2**. The comparison of intermolecular contacts of methyl and methylene groups suggests that the (*S*)-2-hydroxypropyl group is better fitted to the cavity than the (*R*)-2-hydroxypropyl group. Cyclomalto-oligosaccharides are optically active compounds and structural evidence for chiral recognition has been shown in several inclusion complexes[16–19]. The present structures provide another example of the interaction of the βCD cavity with chiral groups.

The temperature factor of the (*S*)-2-hydroxypropyl group is lower than for the (*R*)-2-hydroxypropyl group. The difference in the absolute configuration of the substituent group affects the thermal vibration of the whole molecule in the crystalline state. The average temperature factor of each D-glucose residue in **1** is ~ 1 Å^2 larger than that of the corresponding residue in **2** (Table IV). The largest difference of 1.9 Å^2 is observed for the G-3 residue. The larger temperature factor of **1** may be responsible for the higher solubility. The solubility of the (*R*)-2-hydroxypropyl derivative in water is twice that of the (*S*)-2-hydroxypropyl derivative although the ability for complex formation with phenolphthalein does not change[10]. The (*R*)-2-hydroxypropyl group is more loosely bound to the next molecule as is indicated by the weaker hydrogen bond and larger temperature factors. Therefore, the polymeric structure of **1** may be more easily dissociated in solution.

The solubility of βCDs is increased by the introduction of a 2-hydroxypropyl group to a 6-*O* position but decreased by 2-*O* substitution. 2-*O*-[(*S*)-Hydroxypropyl]-βCD has the same packing mode as that found in unsubstituted βCD, which

TABLE IV

Average temperature factors for each glucose residue (Å^2)

Residue	Temperature factor	
	1	2
G-1	6.4(2.1) [a]	5.6(1.8)
G-2	6.4(2.3)	5.2(1.4)
G-3	7.3(1.5) [b]	5.4(1.0) [b]
G-4	7.2(2.0)	5.8(1.2)
G-5	6.5(0.8)	5.7(0.7)
G-6	8.8(2.7)	8.0(3.2)
G-7	6.1(0.9)	5.3(0.9)

[a] The value in parentheses is the standard deviation. [b] The 2-hydroxypropyl group is not included in the calculation.

is made even more advantageous by the intermolecular host–guest complexation of substituents[12]. Consequently, the solubility of the 2-*O*-derivative is even lower than that of βCD. Attachment of 2-hydroxypropyl substituents to the primary hydroxyl side prevents compounds assuming the packing mode of βCD. The difference in the crystal packing seems to be responsible for the higher solubility of the 6-*O*-derivatives. The volume for one molecule in the crystal of 6-*O*-derivatives is 13% larger than that of 2-*O*-derivatives. The intermolecular complexation of substituents is nevertheless sustained even in this series and its energetics determine the relative solubilities of the (*R*) and (*S*) diastereomers.

REFERENCES

1 L. Szente and C.E. Strattan, in D. Duchêne (Ed.), *New Trends in Cyclodextrins and Derivatives*, Editions de Santè, Paris, 1991, pp 55–96.
2 J. Pitha and J. Pitha, *J. Pharm. Sci.*, 74 (1985) 987–990.
3 A. Yoshida, H. Arima, K. Uekama, and J. Pitha, *Int. J. Pharm.*, 46 (1988) 217–222.
4 C.E. Strattan, *Pharm. Tech.*, (1992) 52–58.
5 B.W. Müllar and U. Brauns, *Int. J. Pharm.*, 26 (1985) 77–88.
6 J. Pitha, J. Miłecki, H. Fales, L. Pannell, and K. Uekama, *Int. J. Pharm.*, 29 (1986) 73–82.
7 A. Yoshida, M. Yamamoto, T. Irie, F. Hirayama, and K. Uekama, *Chem. Pharm. Bull.*, 37 (1989) 1059–1063.
8 J. Pitha, T. Hoshino, J. Torres-Labandeira, and T. Irie, *Int. J. Pharm.*, 80 (1992) 253–258.
9 B.W. Müllar and E. Albers, *Int. J. Pharm.*, 79 (1992) 273–288.
10 C.T. Rao, B. Lindberg, J. Lindberg, and J. Pitha, *J. Org. Chem.*, 56 (1991) 1327–1329.
11 B. Lindberg, J. Lindberg, J. Pitha, C.T. Rao, and K. Harata, *Carbohydr. Res.*, 222 (1991) 113–119.
12 K. Harata, C.T. Rao, J. Pitha, K. Fukunaga, and K. Uekama, *Carbohydr. Res.*, 222 (1991) 37–45.
13 S. Kamitori, K. Hirotsu, and T. Higuchi, *J. Chem. Soc., Perkin Trans. 2*, (1987) 7–14.
14 T. Fujiwara, N. Tanaka, K. Hamada, and S. Kobayashi, *Chem. Lett.*, (1989) 1131–1134.
15 K. Lindner and W. Saenger, *Carbohydr. Res.*, 99 (1982) 103–115.
16 K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *J. Incl. Phenom.*, 2 (1984) 583–594.
17 G. Le Bas, C.B. Rango, N. Rysanek, and G. Tsoucaris, *J. Incl. Phenom.*, 2 (1984) 861–867.
18 K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *Bull. Chem. Soc. Jpn.*, 60 (1987) 497–502.
19 J.A. Hamilton and L. Chen, *J. Am. Chem. Soc.*, 110 (1988) 4379–4391.