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STRUCTURE OF INCLUSION COMPLEXES OF CYCLOMALTOHEPTAOSE (CYCLOHEPTAAMYLOSE): CRYSTAL STRUCTURE OF THE 1-ADAMANTANEMETHANOL ADDUCT

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ABSTRACT

Cyclomaltoheptaose (cycloheptaamylose) has been crystallized with 1-adamantanemethanol as the guest molecule. The complex crystallized in space group $C222_1$, with unit-cell dimensions a = 19.162 (13), b = 23.965 (17), and c = 32.597 (27) Å. The structure was solved by rotation–translation search-methods. The cyclomaltoheptaose exists as a dimer in the crystal by means of extensive hydrogen-bonding across the secondary hydroxyl ends of two cyclomaltoheptaose molecules. The two halves of the dimer are related by a crystallographic two-fold axis. The primary hydroxyl ends of two adjacent cyclomaltoheptaose molecules are also related by a crystallographic two-fold axis, but do not directly hydrogen bond to one another. Instead, they are held in place by a strong hydrogen bond from the hydroxyl group of the 1-adamantanemethanol to a primary hydroxyl group on an adjacent cyclomaltoheptaose molecule. Other stabilizing hydrogen bonds are formed *via* three water molecules which are situated at the primary hydroxyl interface, and others that form parallel columns stabilizing the crystal structure. A unique feature of this complex is the presence of trapped water in the cavity at the secondary hydroxyl interface. This water is distributed over 3 disordered sites. Its presence blocks one possible site for the 1-adamantanemethanol, which, instead, binds near the primary hydroxyl end, with its hydroxyl group and part of the adamantane moiety protruding from the cyclomaltoheptaose.

INTRODUCTION

The cyclomaltaoses (cycloamyloses, cyclodextrins) are cyclic oligosaccharides containing 6 to 12 D-glucopyranosyl residues linked α-(1→4). They have attracted attention as models for such enzymes as the serine acylase enzymes, in particular chymotrypsin[1,2]. Cyclomaltohexaose (cyclohexaamylose, α-cyclodextrin), cyclomaltoheptaose (cycloheptaamylose, β-cyclodextrin), and, to a lesser extent, cyclomalto-octaose (cyclo-octaamylose, γ-cyclodextrin) have been studied, in order to examine the mode of binding of organic molecules in their cavities. This

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complexation process is the basis for all of the wide variety of phenomena produced by the cyclomaltaoses, including drug stabilization and solubilization and the catalysis of ester hydrolysis. These phenomena, and other applications of the cyclomaltaoses in research and industry, have recently been reviewed by Saenger[3].

Because a thorough appreciation of the interactions between cyclomaltaoses and substrate molecules can only be achieved when the structural properties of the host system and its complexes are understood, we have been examining, by crystal-structure analysis, some of the key complexes of cyclomaltoheptaose. Recently, we completed the crystal-structure determination of cyclomaltoheptaose with 1-adamantanecarboxylic acid, which binds well in the cavity and is a competitive inhibitor of phenyl ester hydrolysis by cyclomaltoheptaose[1,4,5].

The best ratio of catalyzed *vs.* uncatalyzed reaction found by Bender and Komiyama[2] for acetyl transfer to cyclomaltoheptaose was only 250 for the substrate *tert*-butylphenyl acetate. However, as pointed out by Breslow and co-workers[6], true enzymes often achieve ratios of 10^5–10^{10}, or greater. They suggested, on the basis of model building, that such substrates as *tert*-butylphenyl acetate can bind fully in the cavity in the complex, but they are pulled up partly out of the cavity by formation of the tetrahedral intermediate. They proposed several types of new substrates, selected to retain as much binding as possible while proceeding from the bound substrate to the bound transition-state to the bound, tetrahedral intermediate to the product. One particular class of these new substrates is based on the adamantane framework. In view of this work, and the fact that the 1-adamantanecarboxylic acid study showed two distinct binding-sites for the adamantane moiety in the cavity, the present study was undertaken to provide additional information on the binding and depth of penetration of the adamantane moiety in the cyclomaltoheptaose cavity.

EXPERIMENTAL

Crystals for the complex of cyclomaltoheptaose with 1-adamantanemethanol were prepared as previously described[7]. The crystals are orthorhombic, space group $C222_1$, with unit-cell dimensions $a = 19.162$ (13), $b = 23.965$ (17), and $c = 32.597$ (27) Å. X-Ray-intensity data were collected at $-160°$.

The cell parameters were determined, and refined, on a Picker four-circle, automated diffractometer at $-160°$. The intensity data, 5335 reflections (4824 with $F_0 > 1\sigma$ (F)) were also measured at $-160°$ on the Picker four-circle, automated diffractometer. Small crystals and MoKα radiation were used to minimize absorption. No absorption corrections were applied. The 5335 measured reflections corresponded to 99% of the possible reflections in the 0.9-Å sphere of resolution.

Structure determination and refinement

The structure was solved by using rotation–translation search methods[8–10]. Refinement of the rough atomic coordinates produced by the rotation–translation

search has always been the most difficult part of applying this method. In this instance, the rough positional parameters did not yield to refinement by rigid-body, least-squares methods, despite attempts to start with low-resolution data and to increase the resolution gradually. Similarly, attempts to improve the phases by using tangent refinement were not successful. Because of this, the rotation–translation search-methods were continued, with smaller and smaller intervals of the translation and rotational parameters and increasing resolution of the data. Because this procedure involves varying a minimum of 6 parameters simultaneously, the amount of CPU time needed, even on a large, fast computer, was enormous. However, the extra effort did result, for the cyclomaltoheptaose skeleton, in a set of positional parameters that could then be refined by individual-atom, least-squares methods. It is difficult to see why the rigid-body refinement was unable to deal with the problem, especially in view of the fact that the maximum error in positional parameter between the set which refined and that which did not was only 0.5 Å.

The positions of the 1-adamantanemethanol, the water molecules, and the primary hydroxyl groups were found by using difference Fourier synthesis. The quantity minimized in the least-squares refinement was $\Sigma w(|F_o| - |F_c|)^2$, where $w = 1/\sigma^2(F_o)$. The final R for the 5335 measured reflections (those with $F_o < \sigma(F_o)$ coded unobserved) was 0.125. The weighted R value was 0.115. This value is rather high, and reflects the effect, on the observed data, of disordering of the water. The data were collected as monoclinic, the presence of the C-centering having been confirmed by collection of a shell of high-order reflections. Initially, the structure was solved as C2 with two molecules in the asymmetric unit. The space group $C222_1$ was assigned after scrutiny of the equivalent reflections. There is no disorder of the guest, but only of a few water molecules. As the host and guest molecules often follow different symmetry in these complexes, we usually make a point of collecting redundant data. Scattering factors were taken from International Tables for X-Ray Crystallography and computer programs from the XRAY 76 system. Anisotropic thermal parameters were used for all atoms. Partial occupancy for the disordered water molecules was estimated from difference-Fourier maps, and was refined by least-squares methods, except where the occupancy value was small.

RESULTS AND DISCUSSION

The final atomic coordinates are given in Table I. The numbering scheme is shown in Fig. 1. The corresponding bond lengths and angles are listed in Table II. Tables III and IV list the intra- and inter-molecular hydrogen-bond data. A diagram showing the hydrogen bonding and close contacts of the cyclomaltoheptaose dimer is given in Fig. 2a, and a diagram of the hydrogen bonding involving the guests, in* Fig. 2b.

*Tables containing positions of calculated C–H hydrogen atoms, and anisotropic temperature factors of C and O atoms and structure amplitudes 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/313/*Carbohydr. Res.*, 142 (1985) 21–37.

TABLE I

FRACTIONAL COORDINATES ($\times 10^4$) OF NON-HYDROGEN ATOMS

Molecule	*Atom*[a]	*x*	*y*	*z*
Cyclomaltoheptaose				
	C-11	7679(9)	2565(7)	1089(5)
	C-12	7709(8)	2931(7)	1474(5)
	C-13	7015(9)	3114(7)	1572(5)
	C-14	6721(8)	3428(7)	1209(5)
	C-15	6731(8)	3083(7)	822(5)
	C-16	6555(9)	3398(8)	451(5)
	O-12	8052(6)	2615(5)	1802(4)
	O-13	7035(6)	3458(5)	1933(4)
	O-14	6014(6)	3556(5)	1306(4)
	O-15	7412(5)	2867(5)	749(3)
	O-16	6984(6)	3881(5)	398(4)[b]
	C-21	5801(10)	4116(8)	1258(6)
	C-22	5541(10)	4333(7)	1665(6)
	C-23	4871(8)	4027(7)	1798(5)
	C-24	4324(9)	4056(7)	1442(5)
	C-25	4650(9)	3860(7)	1031(5)
	C-26	4143(10)	3957(8)	691(5)
	O-22	6055(6)	4319(5)	1985(4)
	O-23	4566(6)	4235(5)	2152(3)
	O-24	3753(5)	3704(4)	1547(3)
	O-25	5281(6)	4170(5)	957(4)
	O-26	3888(7)	4528(5)	684(4)[b]
	C-31	3088(9)	3968(6)	1531(5)
	C-32	2760(8)	3852(7)	1944(5)
	C-33	2646(9)	3237(8)	2001(6)
	C-34	2219(9)	3014(7)	1644(6)
	C-35	2518(9)	3186(7)	1223(5)
	C-36	2062(9)	3042(8)	875(5)
	O-32	3152(7)	4080(5)	2275(4)
	O-33	2282(6)	3109(5)	2385(4)
	O-34	2220(6)	2422(5)	1672(4)
	O-35	2663(6)	3758(4)	1214(4)
	O-36	1406(5)	3290(5)	903(3)[b]
	C-41	1577(9)	2147(8)	1670(6)
	C-42	1506(9)	1784(7)	2052(5)
	C-43	2084(7)	1325(7)	2055(5)
	C-44	2015(7)	1010(8)	1654(5)
	C-45	1997(10)	1354(8)	1279(5)
	C-46	1863(14)	1072(11)	890(8)
	O-42	1553(6)	2106(5)	2411(3)
	O-43	1990(6)	972(4)	2398(3)
	O-44	2557(5)	590(4)	1634(3)
	O-45	1508(6)	1791(5)	1309(4)
	O-46	1188(9)	789(6)	914(4)[b]
	C-51	2411(8)	13(7)	1610(6)
	C-52	2752(7)	−278(6)	1950(5)
	C-53	3529(8)	−236(7)	1913(6)
	C-54	3741(7)	−441(6)	1487(5)
	C-55	3347(8)	−179(6)	1146(5)
	C-56	3472(9)	−435(7)	730(5)

TABLE I *(continued)*

Molecule	*Atom*[a]	*x*	*y*	*z*
	O-52	2502(5)	−82(4)	2334(3)
	O-53	3858(5)	−525(5)	2229(3)
	O-54	4478(5)	−325(4)	1426(3)
	O-55	2612(5)	−196(5)	1221(4)
	O-56	3298(5)	−1024(4)	749(3)
	C-61	4954(8)	−805(7)	1357(6)
	C-62	5515(9)	−776(6)	1681(5)
	C-63	5916(8)	−227(7)	1668(5)
	C-64	6234(7)	−185(6)	1257(5)
	C-65	5676(7)	−227(7)	915(5)
	C-66	5993(8)	−278(8)	506(5)
	O-62	5200(6)	−870(5)	2073(3)
	O-63	6439(6)	−232(5)	1989(4)
	O-64	6578(5)	349(4)	1235(3)
	O-65	5275(5)	−711(4)	966(3)
	O-66	6439(6)	−749(5)	462(3)
	C-71	7283(9)	375(7)	1096(5)
	C-72	7752(7)	595(6)	1427(5)
	C-73	7530(8)	1218(8)	1513(6)
	C-74	7569(7)	1542(7)	1110(5)
	C-75	7154(7)	1276(7)	776(5)
	C-76	7233(9)	1532(7)	352(5)
	O-72	7702(5)	276(5)	1783(3)
	O-73	8000(6)	1453(5)	1813(3)
	O-74	7283(5)	2080(4)	1175(3)
	O-75	7319(5)	691(5)	731(3)
	O-76	7915(6)	1431(5)	187(3)
1-Adamantanemethanol				
	C-1	4215(10)	1933(8)	159(5)
	C-2	4096(10)	1301(9)	221(7)
	C-3	4454(9)	1078(7)	576(6)
	C-4	5250(10)	1233(8)	547(6)
	C-5	5371(10)	1465(8)	526(6)
	C-6	5035(10)	2120(10)	926(7)
	C-7	4212(13)	1984(10)	925(6)
	C-8	3873(10)	2228(9)	555(6)
	C-9	4172(11)	1337(11)	936(6)
	C-10	5003(11)	2097(9)	150(7)
	C-11	3833(12)	2151(10)	−200(7)
	O-1	4114(6)	1936(5)	−603(4)
	W-1	7739(5)	9525(5)	235(3)
	W-2	9277(8)	11246(7)	412(6)
	W-3	11208(7)	9817(6)	398(4)
	W-4	9791(10)	10197(10)	341(8)
	W-5	5206(7)	7727(5)	1055(4)
	W-6	10039(10)	11554(7)	1067(5)
	W-7	14435(8)	7879(7)	1764(5)
	W-8	5813(7)	8241(6)	2418(4)
	W-9	10782(12)	10392(11)	2248(12)[b]
	W-10	9481(10)	11437(10)	1915(7)[b]
	W-11	9069(27)	10289(18)	1934(16)
	W-12	10000(0)	12066(13)	2500(0)
	W-13	14372(25)	11955(17)	2555(26)[b]

TABLE I *(continued)*

Molecule	*Atom*[a]	*x*	*y*	*z*
	W-14	5035(65)	12373(24)	2237(21)[b]
	W-15	4825(51)	11507(20)	2279(24)[b]
	W-16	9167(35)	10400(26)	2272(23)[b]

[a]The numbering of atoms is defined as A(m,n) where A is the atom type, m is the residue number, and n is the atom number within a residue (see also, Fig. 1). W denotes a water molecule. [b]This indicates that these molecules have population parameters of <1. W-4 is 0.75, W-9 is 0.5, W-10 is 0.75, W-13 is 0.33, W-14 is 0.33, W-15 is 0.30, and W-16 is 0.3.

TABLE II

BOND LENGTHS (Å) AND ANGLES (DEGREES) OF THE CYCLOMALTOHEPTAOSE COMPLEX

Bond	*G1*	*G2*	*G3*	*G4*	*G5*	*G6*	*G7*	*Mean*	*σ*
Cyclomaltoheptaose									
C-1–C-2	1.53(2)	1.51(3)	1.51(2)	1.52(3)	1.46(2)	1.51(2)	1.50(2)	1.51	0.02
C-1–O-4	1.42(2)	1.41(2)	1.42(2)	1.40(2)	1.41(2)	1.49(2)	1.43(2)	1.42	0.03
C-2–C-3	1.44(2)	1.54(2)	1.50(3)	1.56(2)	1.50(2)	1.52(2)	1.58(2)	1.52	0.05
C-2–O-2	1.47(2)	1.44(2)	1.42(2)	1.41(2)	1.42(2)	1.43(2)	1.39(2)	1.43	0.03
C-3–C-4	1.51(2)	1.57(2)	1.52(3)	1.52(3)	1.53(2)	1.48(2)	1.53(2)	1.52	0.03
C-3–O-3	1.44(2)	1.39(2)	1.47(2)	1.41(2)	1.39(2)	1.45(2)	1.44(2)	1.43	0.03
C-4–C-5	1.51(2)	1.55(3)	1.54(3)	1.47(3)	1.48(2)	1.55(2)	1.49(2)	1.51	0 03
C-4–O-4	1.43(2)	1.42(2)	1.42(2)	1.45(2)	1.45(2)	1.44(2)	1.42(2)	1.43	0.01
C-5–O-5	1.42(2)	1.44(2)	1.40(2)	1.41(2)	1.43(2)	1.40(2)	1.45(2)	1.42	0.02
C-5–C-6	1.47(2)	1.49(3)	1.47(2)	1.46(3)	1.51(2)	1.47(2)	1.52(2)	1.48	0.02
C-6–O-6	1.43(2)	1.45(2)	1.39(2)	1.46(3)	1.45(2)	1.43(2)	1.43(2)	1.43	0.02
C-1–O-5	1.42(2)	1.40(2)	1.41(2)	1.46(2)	1.42(2)	1.43(2)	1.41(2)	1.42	0.02
1-Adamantanemethanol									
C-1–C-2			1.55(3)			C-4–C-5			1.53(3)
C-1–C-8			1.61(3)			C-5–C-6			1.58(3)
C-1–C-10			1.56(3)			C-5–C-10			1.52(3)
C-1–C-11			1.47(3)			C-6–C-7			1.61(3)
C-2–C-3			1.45(3)			C-7–C-8			1.49(3)
C-3–C-4			1.57(3)			C-7–C-9			1 55(3)
C-3–C-9			1 43(3)			C-11–O-1			1.51(3)
Bond angles (degrees)	*G1*	*G2*	*G3*	*G4*	*G5*	*G6*	*G7*	*Mean*	*σ*
Cyclomaltoheptaose									
C-1–C-2–C-3	109(1)	111(2)	111(1)	110(1)	111(2)	112(1)	107(1)	110	1.7
C-1–C-2–O-2	109(1)	114(2)	113(1)	111(1)	111(1)	109(2)	111(1)	111	1.9
O-2–C-2–C-3	114(1)	111(1)	111(1)	110(1)	113(1)	112(1)	111(1)	112	1.4
C-2–C-3–C-4	109(1)	109(1)	109(1)	107(1)	108(1)	107(1)	108(1)	108	0.9
C-2–C-3–O-3	110(1)	115(1)	112(1)	110(1)	111(1)	109(1)	109(1)	111	2.3
O-3–C-3–C-4	111(1)	109(1)	109(1)	112(1)	113(1)	112(1)	111(1)	111	1.5
C-3–C-4–C-5	112(1)	111(1)	113(2)	116(2)	114(1)	111(1)	113(1)	113	1.8
C-3–C-4–O-4	107(1)	108(1)	107(2)	109(1)	109(1)	107(1)	108(1)	108	0.9

TABLE II *(continued)*

Bond angles (degrees)	*G1*	*G2*	*G3*	*G4*	*G5*	*G6*	*G7*	*Mean*	*σ*
O-4–C-4–C-5	109(1)	110(1)	109(1)	112(1)	108(1)	110(1)	107(1)	109	1.6
C-4–C-5–O-5	111(1)	109(1)	111(1)	112(1)	111(1)	110(1)	112(1)	111	1.1
C-4–C-5–C-6	114(2)	110(2)	114(2)	118(2)	115(1)	112(1)	116(1)	114	2.6
O-5–C-5–C-6	105(1)	110(1)	109(1)	107(2)	107(1)	105(1)	106(1)	107	1.9
C-5–C-6–O-6	113(1)	112(1)	113(1)	109(2)	109(1)	114(1)	111(1)	112	2.0
C-5–O-5–C-1	113(1)	116(1)	117(1)	115(1)	114(1)	118(1)	115(1)	115	1.7
O-5–C-1–C-2	111(1)	110(1)	110(1)	109(2)	113(1)	108(1)	113(1)	111	1.9
C-1–O-4–C-4	117(1)	115(1)	118(1)	123(1)	118(1)	119(1)	121(1)	119	2.6
C-2–C-1–O-4	109(1)	109(1)	105(1)	110(1)	110(1)	107(1)	111(1)	109	2.1
O-5–C-1–O-4	112(1)	112(1)	113(1)	111(1)	110(1)	106(1)	110(1)	111	2.3

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C-2–C-1–C-10	113(2)	C-4–C-5–C-10	109(2)
C-2–C-1–C-8	105(2)	C-6–C-5–C-10	110(2)
C-2–C-1–C11	112(2)	C-5–C-6–C-7	109(2)
C-8–C-1–C-10	107(2)	C-6–C-7–C-8	111(2)
C-10–C-1–C-11	112(2)	C-6–C-7–C-9	104(2)
C-1–C-2–C-3	113(2)	C-8–C-7–C-9	113(2)
C-2–C-3–C-4	109(2)	C-7–C-8–C-1	107(2)
C-2–C-3–C-9	108(2)	C-7–C-9–C-3	113(2)
C-4–C-3–C-9	108(2)	C-1–C-10–C-5	110(2)
C-3–C-4–C-5	113(2)	C-1–C-11–O-1	113(2)
C-4–C-5–C-6	106(2)		

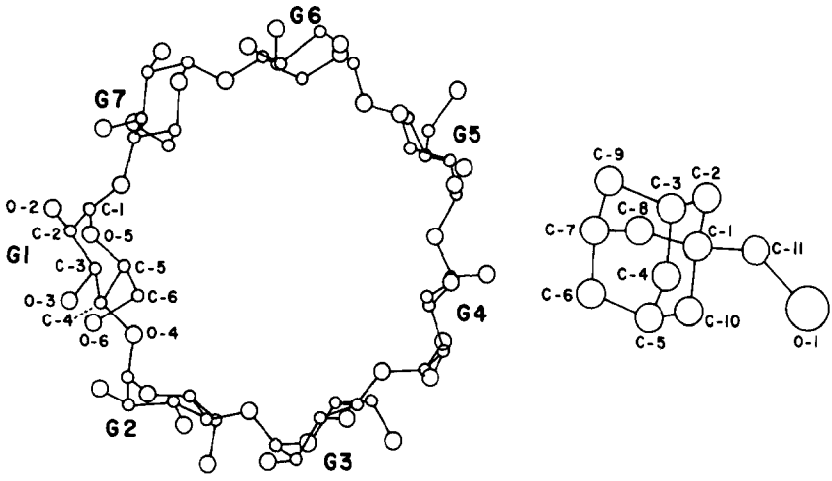

Fig. 1. Numbering scheme for the cyclomaltoheptaose and 1-adamantanemethanol molecules.

TABLE III

INTRAMOLECULAR HYDROGEN-BOND LENGTHS AND ANGLES[a]

Hydrogen bond	*Distance (Å)*	*Hydrogen bond*	*Angle (degrees)*
O-12–O-73	2.79	C-12–O-12–O-73	121
O-22–O-13	2.79	C-22–O-22–O-13	116
O-32–O-23	2.76	C-32–O-32–O-23	117
O-42–O-33	2.78	C-42–O-42–O-33	119
O-52–O-43	2.72	C-52–O-52–O-43	120
O-62–O-53	2.75	C-62–O-62–O-53	121
O-72–O-63	2.79	C-72–O-72–O-63	120
		C-13–O-13–O-22	117
		C-23–O-23–O-32	119
		C-33–O-33–O-42	117
		C-43–O-43–O-52	117
		C-53–O-53–O-62	116
		C-63–O-63–O-72	115
		C-73–O-73–O-12	114

[a]The standard deviation in bond length is 0.01Å, and in angle is 1°.

The seven D-glucopyranosyl residues were all in the $^4C_1$(D) conformation. Table II lists the bond lengths and angles for all seven independent residues. Comparison of the average values of these bond lengths and angles with those published for cyclomaltohexaose[12], cyclomaltoheptaose dodecahydrate[11], cyclomaltoheptaose–1-adamantanecarboxylic acid[13], cyclomaltoheptaose benzocaine[14], cyclomaltoheptaose–propanol[15], and cyclomaltoheptaose–1,4-diazabicyclo[2.2.2]octane[16] indicated that the only significant difference between the D-glucosyl residues in cyclomaltoheptaose and cyclomaltohexaose is the D-glucosidic angle (C-4–O-4–C-1). As shown in Table V, the average values for the cyclomaltoheptaose are smaller. The average for six independent cyclomaltohexaose molecules is 119.0 ±0.3°, and for eight cyclomaltoheptaose molecules, 117.4 ±1.0°. In his discussion of cyclomaltoheptaose dodecahydrate, Saenger[12] suggested that this might be the case, but, at that time, insufficient cyclomaltoheptaose structures were available for comparison.

The torsion angles were, in general, consistent over the cyclomaltoheptaose structures listed in Table V, and did not differ from those found for cyclomaltohexaose structures[12,13]. In general, the C-6–O-6 bonds point outwards (*gauche-gauche*) from the cyclomaltoheptaose cavity, so that the primary hydroxyl groups can hydrogen-bond to water in the water channel. Exceptions occurred when the primary hydroxyl group hydrogen-bonded to the guest or to water in the cavity[12,14,16]. In this case, the C-6–O-6 bond pointed inwards to the cyclomaltoheptaose cavity, or was sometimes disordered, having both *gauche-gauche* and *trans-gauche* orientations. In the cyclomaltoheptaose–benzocaine structure[14], the primary hydroxyl group of residue G6 was equally disordered over three positions, two of which were simultaneously involved in hydrogen bonding to the amino

TABLE IV

INTERMOLECULAR HYDROGEN-BOND LENGTHS AND ANGLES

Hydrogen bonds involving primary and secondary hydroxyl groups

Bond	*Distance (Å)*	*Angle (degrees)*
C-12–O-12–W-7 I	2.73	106
C-12–O-12–O-33 II	2.97	110
C-13–O-13–O-33 II	2.71	120
C-22–O-22–W-9 I	2.76	94
C-23–O-23–W-11 I	2.79	105
C-23–O-23–W-16 I	2.92	125
C-23–O-23–O-23 II	2.81	115
C-32–O-32–O-52 III	2.69	114
C-32–O-32–O-13 II	3.00	113
C-33–O-33–O-13 II	2.71	114
C-42–O-42–W-8 I	3.07	118
C-43–O-43–O-73 II	2.82	119
C-43–O-43–W-9 V	2.74	106
C-52–O-52–O-63 II	3.02	112
C-52–O-52–O-32 VI	2.69	109
C-53–O-53–O-63 II	2.70	118
C-62–O-62–O-53 II	3.02	112
C-62–O-62–W-8 VII	2.68	108
C-72–O-72–W-16 VII	3.24	108
C-73–O-73–O-43 II	2.82	118
C-16–O-16–W-3 I	2.69	111
C-16–O-16–O-56 VIII	2.78	123
C-26–O-26–W-1 I	2.64	107
C-26–O-26–W-4 I	2.61	111
C-36–O-36–O-66 IX	2.72	108
C-36–O-36–W-5 I	2.71	124
C-46–O-46–W-3 V	2.87	110
C-46–O-46–W-6 V	2.91	113
C-56–O-56–O-16 I	2.78	106
C-56–O-56–AO-1 X	2.73	130
C-66–O-66–W-1 VII	2.68	113
C-66–O-66–O-36 XI	2.72	127
C-76–O-76–W-1 XIV	2.69	103
C-76–O-76–W-2 VII	2.75	143

Hydrogen bonds involving water molecules

Bonds	*Distances*		*Angle*
O-66–W-1 VII–W-1 XIII	2.68	2.75	111
O-66–W-1 VII–O-26 XI	2.68	2.64	129
O-66–W-1 VII–O-76 XII	2.68	2.69	93
W-1 VII–O-76 XII–W-2 XIV	2.69	2.75	97
O-76 XII–W-2 XIV–W-6 XIV	2.75	2.69	133
O-76 XII–W-2 XIV–W-4 XIV	2.75	2.71	118
W-4 XIV–W-2 XIV–W-6 XIV	2.71	2.69	97
W-2 XIV–W-4 XIV–W-3 XIV	2.71	2.87	129
W-2 XIV–W-4 XIV–O-26 XV	2.71	2.61	107
W-2 XIV–W-4 XIV–W-4 XVI	2.71	2.42	116
W-4 VII–W-3 VII–O-46 XVII	2.87	2.87	113
W-4 VII–W-3 VII–O-16 XI	2.87	2.69	114

TABLE IV *(continued)*

Bonds	*Distances*		*Angle*
W-3 VII–O-16 XIV–O-56 XVII	2.69	2.78	116
O-16 XI–O-56 XVII–AO-1 XVIII	2.78	2.73	113
O-56 XVII–AO-1 XVIII–W-5 XIX	2.73	2.68	126
W-2 VII–W-6 VII–W-5 XIV	2.69	2.83	109
W-10 VII–W-6 VII–W-5 XI	2.98	2.83	99
W-2 VII–W-6 VII–O-46 XVII	2.69	2.91	96
O-46 XVII–W-6 VII–W-5 XI	2.91	2.83	123
W-2 VII–W-6 VII–W-10 VII	2.69	2.98	121
O-46 XVII–W-6 VII–W-10 VII	2.91	2.98	112
W-6 VII–O-46 XVII–W-3 VII	2.91	2.87	128
W-6 VII–W-5 XI–O-36 XVII	2.83	2.71	126
W-6 VII–W-5 XI–AO-1 XV	2.83	2.68	103
W-6 VII–W-10 VII–W-11 VII	2.98	2.86	102
W-6 VII–W-10 VII–W-12 VII	2.98	2.63	119
W-6 VII–W-10 VII–O-73	2.98	2.86	104
W-10 VII–W-11 VII–O-72	2.86	2.67	106
W-10 VII–W-11 VII–O-23 XI	2.86	2.79	141
O-72–W-11 VII–O-23 XI	2.67	2.79	112
W-10 VII–W-12 VII–W-10 XIV	2.63	2.63	110
W-10 VII–W-12 VII–O-42 XVI	2.63	2.99	109
W-10 VIV–W-12 VII–O-42 XVI	2.63	2.99	73
W-6 VII–W-5 XI–W-7 XI	2.83	2.77	93
W-7 XI–W-5 XI–AO-1 XV	2.77	2.68	90
O-36 XVII–W-5 XI–AO-1 XV	2.71	2.68	114
O-36 XVII–W-5 XI–W-7 XI	2.71	2.77	123
W-5 XI–W-7 XI–O-12	2.77	2.73	122
O-62–W-8 VII–O-33 XI	2.68	2.83	121
W-5 XI–W-7 XI–W-12 VII	2.77	3.28	111
W-10 XIV–W-12 VII–W-7 XI	2.63	3.28	72
O-22–W-9 I–W-11 XX	2.76	2.69	102

Equivalent positions

I x − 1/2, y − 1/2, z
II − x + 1, y, − z + 1/2
III − x + 1/2, y + 1/2, − z + 1/2
IV − x + 1, y − 1, − z + 1/2
V x − 1, y − 1, z
VI 1/2 − x, y − 1/2, − z + 1/2
VII x, y − 1, z
VIII x + 1/2, y + 1/2, z
IX x − 1/2, y + 1/2, z
X x, − y, − z
XI x + 1/2, y − 1/2, z
XII x, − y + 1, − z
XIII x, − y + 3, − z
XIV x, − y + 1, − z
XV x + 1/2, − y + 1 1/2, − z
XVI x, y + 1, z
XVII x + 1, y, z
XVIII x + 1, − y, − z
XIX x + 1, y + 1, z
XX − z + 2 1/2, y − 1/2, 1/2 − z
XXI x − 1, y, z

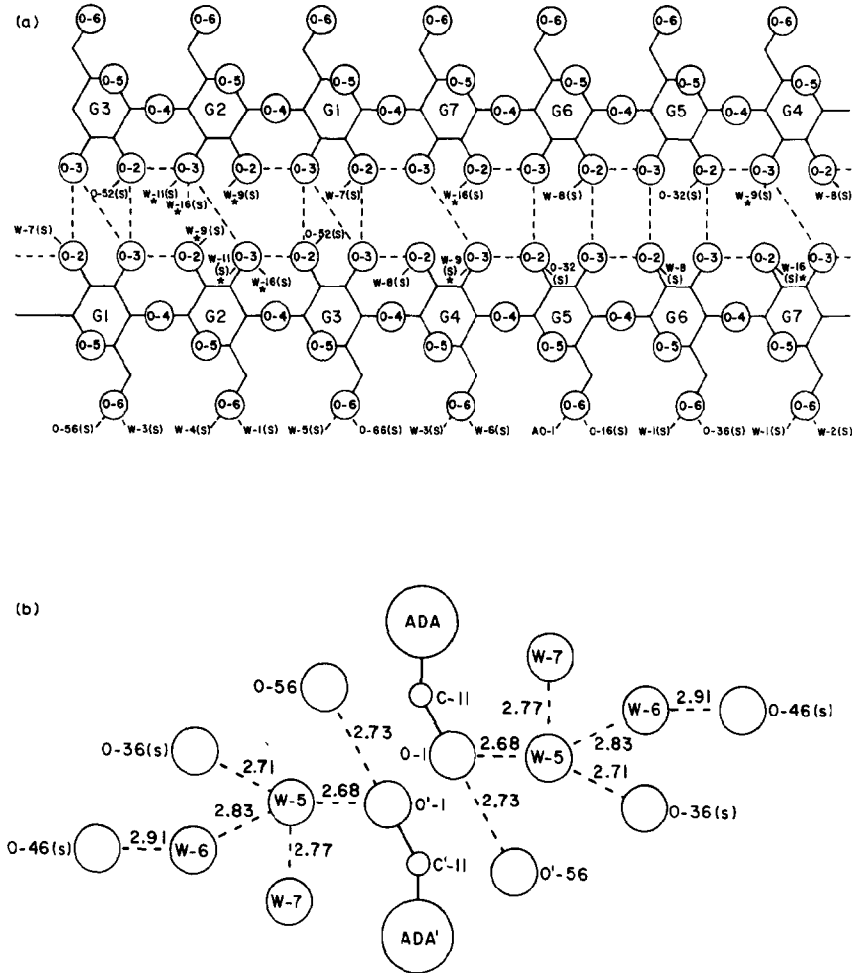

Fig. 2. Hydrogen-bonding scheme for (a) the cyclomaltoheptaose dimer, and (b) the two 1-adamantanemethanol molecules.

group of the benzocaine guest. In general, the C-6–O-6 bonds show the widest spread in bond length of any of the cyclomaltoheptaose bonds.

The cyclomaltoheptaose macrocycle is in the shape of a truncated cone, with the seven-fold symmetry being very well maintained. If the ring atoms of the D-glucosyl residues and the D-glucosidic oxygen atoms are considered as a series of circles (the seven symmetry-related atoms of each type forming a circle), and if the centroids of these circles are plotted, they fall on a straight line. This regular, molecular symmetry is also apparent in the heptagon formed by the seven O-4 atoms. The sides of the heptagon show a mean length of 4.362 ±0.057 Å for the monomer form, and 4.367 ±0.065 Å for the dimer form, using those complexes listed in Table V. The average for the angles O-4–O-4–O-4 is 128.2 ±2.85° for the

TABLE V

AVERAGE VALUES OF THE D-GLUCOSIDIC ANGLE (DEGREES)

Compound	*Average value over 7 D-glucosyl residues*
Cyclomaltoheptaose dodecahydrate	117.7 ±1.0
Cyclomaltoheptaose–1,4-diazabicyclo[2.2.2]octane	117.4 ±1.0
Cyclomaltohexaose	119.0 ±0.3
(averaged over a number of compounds)	
Cyclomaltoheptaose–benzocaine	115 ±0.9
Cyclomaltoheptaose–1-adamantanecarboxylic acid	116.6 ±1.0
(2 crystallographically independent molecules)	117.9 ±1.0
Cyclomaltoheptaose–1-propanol	117.9 ±0.6
(2 different crystal structures)	117.6 ±0.6
Cyclomaltoheptaose–1-adamantanemethanol	119.2 ±1.0

monomer form, and 128.6 ±2.85° for the dimer form. The average angle for all of the structures compares well with that of 128.6° for an ideal heptagon. It is important to note that all of these structures, except the dodecahydrate and the 1,4-diazabicyclo[2.2.2]octane complex, contain the cyclomaltoheptaose dimer as the basal unit. Dimerization by hydrogen bonding of the secondary hydroxyl groups of adjacent molecules does not appear to affect the molecular symmetry.

The conformation of the macrocycle is stabilized by a ring of hydrogen bonds between the secondary hydroxyl groups (O-2–O-3) on adjacent D-glucosyl residues (see Tables III and VI). Comparison of the average values for the structures listed in Table VI suggests that the lengths of these intramolecular hydrogen bonds are slightly shorter for those cyclomaltoheptaose molecules involved in dimer formation. Lindner and Saenger[11] were unable to locate the hydrogen atoms in these bonds in the X-ray crystal-structure determination of cyclomaltoheptaose dodecahydrate, and, in a subsequent paper describing a neutron-diffraction study[17] of this complex, showed that intramolecular "flip-flop" bridges are formed between all 2- and 3-hydroxyl groups of adjacent D-glucosyl residues. This means that the hydrogen bonds are disordered, interactions of the type O-H–H-O being observed; *i.e.*, H atoms are 1 Å apart, with occupation parameters of 0.5 average. In the X-ray studies, only the average state is seen. The hydroxyl groups not participating in the "flip-flop" bonds do participate in hydrogen bonding to external hydroxyl groups. It is difficult to predict the effect that dimerization of the cyclomaltoheptaose *via* the 2- and 3-hydroxyl groups will have on the "flip-flop" arrangement. However, it seems probable that it will have some effect, perhaps causing localization of the hydrogen atoms and fixing the direction of the intramolecular hydrogen bonds. The number of intra-dimer hydrogen bonds possible is 14. On the basis of O–O distances and C-O–O angles we have observed, on the average, 14 likely intra-dimer hydrogen bonds[13,14] (see Fig. 2a). These have get to be confirmed by location of the hydrogen atoms involved. Stezowski and Jogun[18] have completed refinement of two, very similar, cyclomaltoheptaose–1-propanol

TABLE VI

COMPARISON OF INTRAMOLECULAR HYDROGEN BONDS

Bond (Å)	*Compound*[a]	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*Mean*	*σ*
O-2*n*–O-3*n* +1	Cyclomaltoheptaose dodecahydrate	2.955(9)	2.861(9)	2.855(10)	2.768(7)	2.780(7)	2.904(8)	2.876(9)	2.857	0.066
O-2*n*–O-3*n* +1	Cyclomaltoheptaose–1,4-diazabicyclo[2.2.2]octane	2.691(5)	2.860(6)	2.881(8)	2.853(6)	2.788(5)	2.822(7)	2.860(6)	2.822	0.065
O-2*n*–O-3*n* +1	Cyclomaltoheptaose–benzocaine*	2.75(3)	2.71(4)	2.82(3)	2.92(3)	2.78(3)	2.75(3)	2.82(3)	2.79	0.07
O-2*n*–O-3*n* +1	Cyclomaltoheptaose–1-adamantanecarboxylic acid*[b]	2.77(2)	2.76(2)	2.82(2)	2.79(2)	2.82(2)	2.79(2)	2.67(2)	2.77	0.05
		2.72(2)	2.81(2)	2.74(2)	2.78(2)	2.74(2)	2.74(2)	2.70(2)	2.75	0.04
O-2*n*–O-3*n* +1	Cyclomaltoheptaose–1-propanol*[c]	2.771(8)	2.769(9)	2.807(7)	2.825(7)	2.814(7)	2.806(7)	2.683(7)	2.782	0.049
		2.732(8)	2.779(7)	2.807(8)	2.818(7)	2.765(7)	2.832(7)	2.734(8)	2.781	0.040
		2.793(7)	2.732(9)	2.763(10)	2.716(9)	2.855(7)	2.955(9)	2.751(8)	2.795	0.084
		2.742(8)	2.751(9)	2.775(9)	2.754(8)	2.761(8)	2.852(9)	2.820(7)	2.779	0.041
O-2*n*–O-3*n* +1	Cyclomaltoheptaose–1-adamantanemethanol*	2.79(1)	2.79(1)	2.76(1)	2.78(1)	2.72(1)	2.75(1)	2.79(1)	2.77	0.03

[a]The asterisk indicates that these molecules are involved in dimer formation. [b]Two crystallographically independent molecules. [c]Two structure determinations, each with two crystallographically independent molecules.

complexes; these are by far the most accurate cyclomaltoheptaose structures determined by X-ray diffraction. They tried to locate the hydrogen atoms involved in the intramolecular and intra-dimer hydrogen bonds. On this basis, they suggest that only 7 or 8 intra-dimer bonds are actually present. It seems to us, however, unlikely that hydroxyl groups having the capability of hydrogen bonding, *i.e.*, situated at the correct distance and angle, would not do so. Clarification of this aspect must await the results of a neutron-diffraction study.

In the cyclomaltoheptaose–1-adamantanecarboxylic acid structure[13], the adamantane moiety shows a different site for binding to the cyclomaltoheptaose cavity in the two crystallographically independent complexes. In each case, the widest part of the adamantane ring avoids constrictions in the cavity in the vicinity of the H-5 and O-4 atoms. Both guests are oriented with their carboxylic acid group at the primary hydroxyl end of the cyclomaltoheptaose, so that maximum hydration and hydrogen-bonding can occur. It was anticipated that the 1-adamantanemethanol molecule would be located with the adamantane ring in one of the two positions found in the 1-adamantanecarboxylic acid structure. In fact, its position does correspond approximately to one of the previous binding-sites, but the adamantane ring protrudes even farther from the cyclomaltoheptaose cavity (see Fig. 3). The 1-adamantanemethanol hydroxyl group is oriented towards the primary hydroxyl end of the host and, of course, also protrudes from the cavity. It hydrogen-bonds directly to the primary hydroxyl group on residues G5 of the adajacent cyclomaltoheptaose molecule (see Figs. 2b and 4); this stabilizes the crystal packing. Channeling of the cyclomaltoheptaose dimer is not as good in this structure as in the C2 crystal forms[10,14]. In fact, the 1-adamantanemethanol faces the water channel (see Fig. 4). Parallel stacks of cyclomaltoheptaose dimers are held together by channels of water molecules.

One of the most interesting results of the present study is the reason for the extra distance that the adamantane guest protrudes from the cyclomaltoheptaose cavity. Water is trapped in three disordered sites at the dimer interface (see Fig. 5). This water prohibits the binding of the adamantane ring at the interface of the dimer, as observed for one of the 1-adamantanecarboxylic acid molecules. The 1-adamantanemethanol therefore binds in the second of the favored binding-sites, but is farther out of the cavity. It is difficult at present to decide whether the trapped water is a cause, or a consequence, of this and the hydrogen bonding from the methanol hydroxyl group to the primary end of an adajacent host molecule. Trapped water has been observed in only one other dimer complex, namely, cyclomaltoheptaose–benzocaine[14]. Here, one molecule of water was found in 1 site and was hydrogen-bonded to the ester group of the benzocaine. In the present structure, there appears to be hydrogen bonding between the three sites, but no hydrogen bonding to the complex. The water simply occupies space at the dimer interface.

A complete explanation of the sequence of events leading to the trapping of the water molecule awaits more information. The cyclomaltoheptaose complex

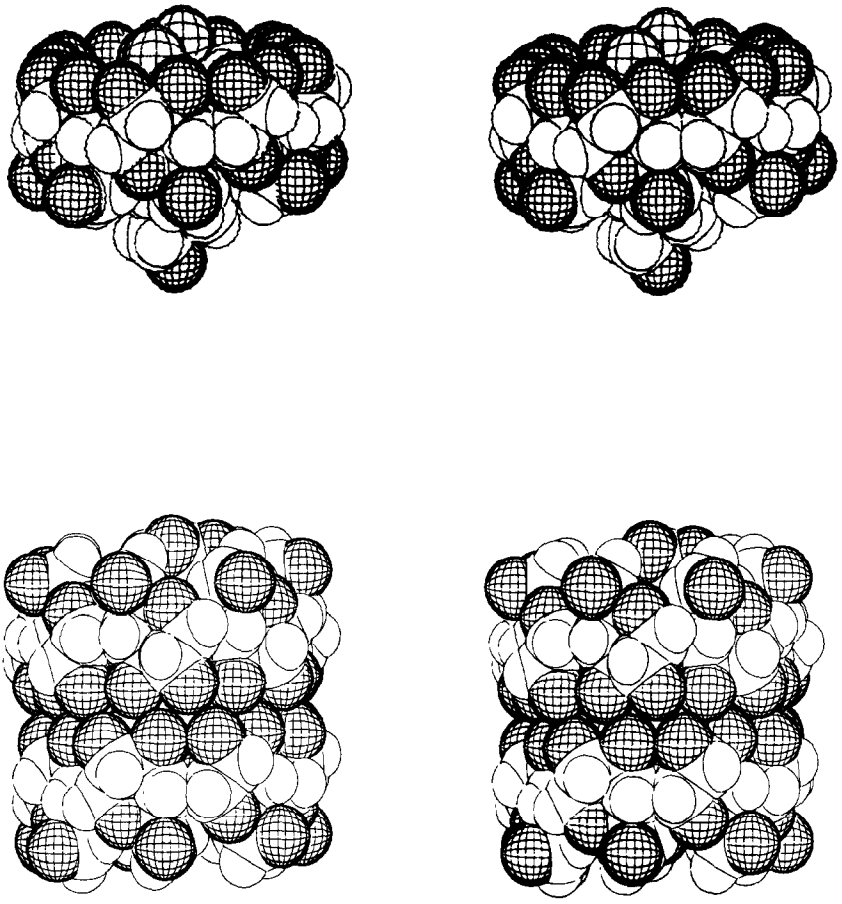

Fig. 3. Stereoview of the space-filling model of a cyclomaltoheptaose monomer unit complexed with 1-adamantanemethanol. For comparison, the cyclomaltoheptaose complex with 1-adamantanecarboxylic acid is also shown.

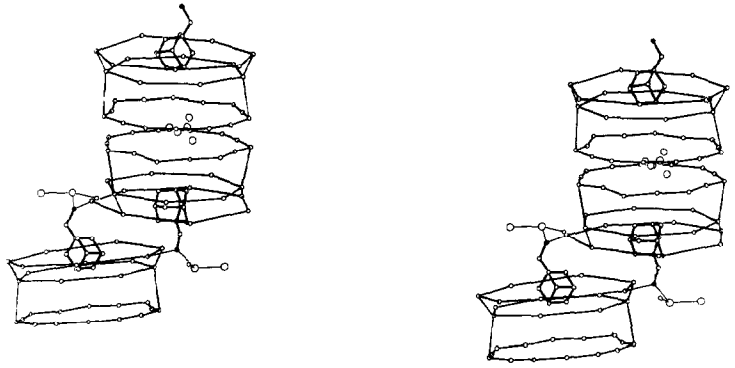

Fig. 4. Stereoview of the dimer plus an additional complex unit related by symmetry. The cyclomaltoheptaose molecules are represented by their primary and secondary hydroxyl groups, and glycosidic oxygen atoms. These are joined to form rings. The larger, open circles represent water molecules.

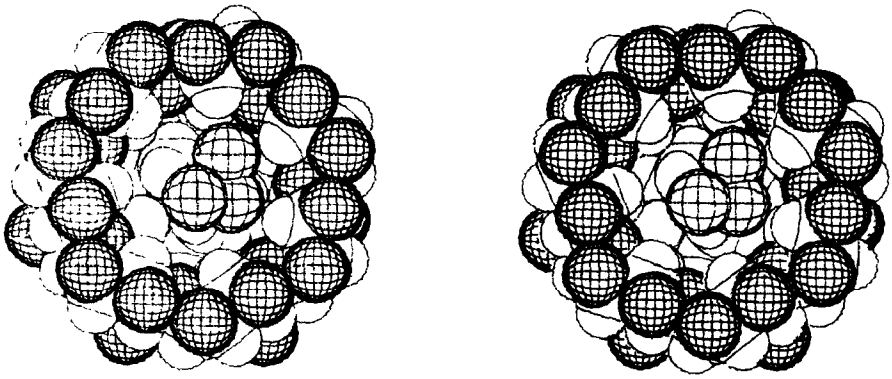

Fig. 5. Stereoview of the space-filling model of the cyclomaltoheptaose–1-adamantanemethanol complex. [Seen from the secondary hydroxyl end, to show the three disordered sites of the trapped water molecule.]

with 1-adamantane-ethanol has been crystallized, and it appears to be isomorphous with the present structure. It seems likely that the adamantane moiety may be more included in the cyclomaltoheptaose cavity in the 1-adamantane-ethanol complex, with elimination of the trapped water. In any event, comparison of results for the two structures should help explain the complexation sequence.

In conclusion, this structural analysis confirms one of the two binding sites possible for an adamantane moiety inside the cyclomaltoheptaose dimer. These sites are determined by the need for the broadest part of the adamantane ring to avoid the constriction in the cyclomaltoheptaose cavity in the vicinity of the H-5 atoms. The orientation of the guest in the cavity is determined by the need to solvate the hydrophilic group[10,13,14]. This is at the primary hydroxyl end of the cyclomaltoheptaose, as access of water at the secondary hydroxyl end is prevented by dimer formation.

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