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Pseudopolymorphism in Tetradeca-2,6-*O*-methyl-*β*-cyclodextrin: The Crystal Structures for Two New Hydrates—Conformational Variability in the Alkylated *β*-Cyclodextrin Molecule

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Abstract: Tetradeca-2,6-*O*-methyl-*β*-cyclodextrin, per-2,6-OMe-*β*-CD, is an unusual *β*-cyclodextrin, *β*-CD, derivative because it has a negative thermal solubility coefficient in aqueous solution. This report describes two new crystal structures for hydrates of per-2,6-OMe-*β*-CD crystallized at different temperatures: per-2,6-OMe-*β*-CD•1.08H_2O crystallized at 50 °C and per-2,6-OMe-*β*-CD•14.7H_2O crystallized at 4 °C. The crystal structure for per-2,6-OMe-*β*-CD•1.08H_2O reveals conformational flexibility in the methylated *β*-CD molecule; two adjacent glucose residues are disordered as a result of their adopting different tilts with respect to the O_4 plane characterizing the molecule. When one conformation is present there is a water molecule in the lattice (0.5 population parameter); said water is displaced by the methyl of a methoxy substituent when the other conformer is present.

Introduction

There is a long history of interest in the properties of cyclodextrins, ranging from early studies by Villiers, Schardinger, Freudenberg, French, and Cramer, among others. Szejtli[1] has recently reviewed the impact of their studies in a special issue of *Chemical Reviews*.[2] As demonstrated by the articles in the special issue of *Chemical Reviews*, the range of interest in cyclodextrins is very broad indeed, such as the following: solution studies by NMR,[3] structural studies and their interpretation,[4,5] a search for new derivatives,[6] catalysis by cyclodextrins and their derivatives,[7] reaction mediation,[8] industrial applications,[9] and potential pharmaceutical applications.[10]

Tetradeca-2,6-*O*-methyl-*β*-cyclodextrin, per-2,6-OMe-*β*-CD, is a cyclodextrin derivative that differs from the parent natural product *β*-cyclodextrin, *β*-CD, in two important physical properties: (a) surprisingly, the alkylated derivative is much more water soluble at room temperature than the parent and (b) in contrast to *β*-CD, per-2,6-OMe-*β*-CD has a negative thermal solubility coefficient. Per-2,6-OMe-*β*-CD is one of a number of cyclodextrin derivatives that have more desirable properties as drug carriers and delivery agents than *β*-CD.[10] The ability of per-2,6-OMe-*β*-CD to form well-defined inclusion complexes was demonstrated several years ago by a crystal structure determination for a complex with adamantanol.[11]

A thorough understanding of the interactions of per-2,6-OMe-*β*-CD in aqueous environments and its behavior upon crystallization from aqueous solution is important for the design of experiments for drug preparation. The observation of pseudopolymorphic per-2,6-OMe-*β*-CD hydrates was communicated in 1984.[12] Crystal structure determinations for anhydrous[13] per-2,6-OMe-*β*-CD and for a dihydrate[14] have been reported, also. We report the preparation of two additional crystalline hydrates, per-2,6-OMe-*β*-CD•1.08H_2O and per-2,6-OMe-*β*-CD•14.7H_2O, and crystal structure determinations for them. Pseudopolymorphic hydrates have also been reported for the inclusion complex of *n*-propanol with *β*-cyclodextrin.[15]

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Table 1. Lattice Parameters, Unit Cell Volumes, and Chemical Compositions for the Known Pseudopolymorphs of Per-2,6-OMe-β-CD

crystallization temp T (°C)	4	18	50	60
space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a, Å	13.976(7)	15.2415(5)	13.328(7)	13.821(2)
b, Å	20.763(7)	10.6391(4)	17.410(7)	17.424(6)
c, Å	28.807(8)	23.3239(8)	29.760(8)	29.610(7)
α, deg	90	90	90	90
β, deg	90	101.798(1)	90	90
γ, deg	90	90	90	90
V, Å^3	8359	3702	6905	7131
chemical formula	$C_{56}H_{98}O_{35}\cdot 14.7H_2O$	$C_{56}H_{98}O_{35}\cdot 2H_2O$	$C_{56}H_{98}O_{35}\cdot 1.08H_2O$	$C_{56}H_{98}O_{35}$
crystal temp, K	∼100	∼300	∼100	∼300

Table 2. Summary of Selected Crystallographic Data[a]

	per-2,6-OMe-β-CD$\cdot 14.7H_2O$	per-2,6-OMe-β-CD$\cdot 1.08H_2O$
chemical composition	$C_{56}H_{98}O_{35}\cdot 14.7H_2O$	$C_{56}H_{98}O_{35}\cdot 1.08H_2O$
formula weight	1565.54	1348.61
D_x, kg m^{-1}	1.273	1.315
no. of unique reflcns	9273	7577
no reflcns $I > 3\sigma(I)$	4786	3934
no. of contributing reflcns/no. variables	6295/987	4980/1040
R-factors (obsd data): R/wR	0.083/0.142	0.070/0.116
R-factors (all data): R/wR	0.129/0.157	0.117/0.153
goodness of fit		1.154
shift/error (ave/max)	0.001/0.036	0.002/0.040
residual electron density (min/max)	−0.56/0.77	−0.364/0.461
nominal data set resoln	0.71 Å	0.77 Å

[a] Table 1 contains additional data. A CIF file has been deposited as Supporting Information.

Experimental Section

Per-2,6-OMe-β-CD was prepared according to Takeo[16] and purified by recrystallization at 50 °C. Crystals of per-2,6-OMe-β-CD$\cdot 1.08H_2O$ were harvested directly from the purification step. Their morphology was that of long needles with typical dimensions 0.2 × 0.2 × 2+ mm^3, where the + symbol indicates that much longer needles were obtained. A crystal for X-ray diffraction intensity data collection, measuring ∼0.2 × 0.2 × 0.2 mm^3, was simply cut from a long needle. The space group and lattice parameters for a crystal at ∼100 K are presented in Table 1.

Crystals for per-2,6-OMe-β-CD$\cdot 14.7H_2O$ were grown by slow evaporation of an aqueous solution at 4 °C in a two-step process. An initial sample was allowed to form a glass by evaporation from a solution in a 50 mL beaker tipped at about a 45° angle. When said glass had “dried” sufficiently to show numerous cracks, a large single drop of water was placed at one edge of the glass formed at the interface of the beaker bottom and side; the beaker was covered with parafilm and maintained at 4 °C. After a number of weeks a very small number of large crystals formed in the drop: typical dimensions ∼0.4 × 0.4 × 0.6 mm^3. The space group and lattice parameters for a crystal at ∼100 K are contained in Table 1.

X-ray diffraction data were collected for each pseudopolymorph from an appropriate crystal maintained at ∼100 K by using an automated four-circle diffractometer (monochromated Mo Kα radiation) operating in a ω-scan technique to a resolution of ∼0.77 Å. Intensity data were corrected for Lorentz and polarization effects and background radiation, but not for absorption. The data sets and crystal structure determination are characterized in Table 2.

The initial models for the crystal structures were determined by direct methods with SHELXS; the models were developed by difference Fourier techniques by using the XTAL program library (versions 3.2 to 3.7) in combination with the graphics display program INSIGHT-II for analysis of difference electron density maps generated by a locally written program that prepared grid maps at 0.3 Å resolution. Two of the glucose residues in the crystal structure of per-2,6-OMe-β-CD$\cdot 1.08H_2O$ are disordered, Figure 1; their population parameters were estimated to be ∼50% based on a statistical average of refined population parameters of individual carbon and oxygen atoms in the two residues. A number of methoxy substituents were also disordered. Except where disorder imposed limitations, all non-hydrogen atoms were refined with anisotropic temperature factors. Hydrogen atom positions were calculated where possible from consideration of known geometry and included with isotropic temperature factors without refinement in the structure factor calculations.

Results and Discussion

Crystal Structures. The crystal structures are presented in stereoscopic projections for per-2,6-OMe-β-CD$\cdot 14.7H_2O$ in Figure 2a and for per-2,6-OMe-β-CD$\cdot 1.08H_2O$ in Figure 2b, respectively. The hydration differences are readily apparent in Figure 2 and will be discussed in more detail below. The molecular structures, with the refined atomic displacement parameters, are illustrated in Figure 3.

Molecular Conformations. The molecular conformations for the crystal structures reported here are characterized in Table 3 and illustrated in Figure 3. All glucose residues, including the disordered glucose residues G4 and G5 in the crystals of per-2,6-OMe-β-CD$\cdot 1.08H_2O$, are in the usual $^4C_1$ chair conformation; the disorder in the orientations of G4 and G5 is sufficient to merit describing two molecular conformations (molecules A and B) in this structure. The angles between the plane normal of plane fit to the O4 atoms of each molecule and the normals of the planes fit to the “seat” of the chair for each glucose residue are presented in Figure 3; the respective average values are 78.7°, 78.6°, and 76.9°. A number of observations can be made from this figure: (a) with the exception of a small number of 6-methoxy groups, the conformations of the per-2,6-OMe-β-CD molecules in the four crystal structures are similar (see Figure 4); (b) as indicated by the range of tilt angles (Figure 3), the conformation is not a particularly close approximation to a regular truncated cone; and (c) in each molecule there are

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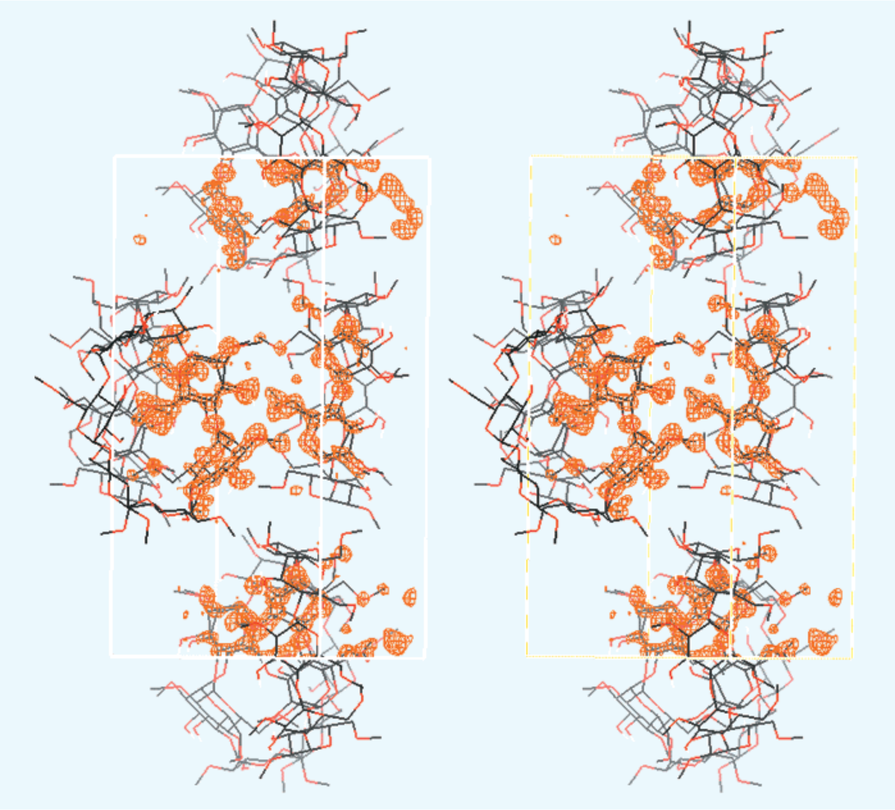


Figure 1. A stereoscopic projection of a difference electron density map illustrating the disorder found for two glucose residues, G4 and G5, in the crystal structure of per-2,6-OMe-β-cyclodextrin·1.08H_2O. Note the disordered glucose residues display intermolecular interactions as illustrated by the two molecules in the center of the diagram.

Table 3. Geometrical Properties of Individual Glucose Residues in the Crystal Structures of **Per-2,6-OMe-β-CD·14.6H_2O** and **Per-2,6-OMe-β-CD·1.08H_2O**, Molecules A and B

	residue G*n*						
	G1	G2	G3	G4	G5	G6	G7
per-2,6-OMe-β-CD·14.6H_2O							
d_p(C1,C4)	(−0.63, 0.67)	(0.65, −0.62)	(0.66, −0.62)	(0.65, −0.67)	(0.63, −0.66)	(−0.65, 0.65)	(−0.67, 0.73)
$\Delta d_p(C_2,C_3,C_5,O_5)$	0.02	0.01	0.02	0.03	0.04	0.02	0.04
$\angle P_{O4},P_{Gn}$	81.0(3)	80.1(2)	78.9(2)	77.1(3)	87.5(3)	75.1(3)	71.1(3)
$\phi(O_5C_1O_{4'}C_{4'})$	107.0(9)	109.1(9)	112.5(10)	100.1(10)	111.1(10)	107.0(10)	96.1(9)
$\psi(C_1O_{4'}C_{4'}C_{3'})$	127.9(8)	128.0(9)	129.0(10)	114.8(9)	134.2(9)	134.4(9)	121.4(9)
tilt angle	12.0(5)	11.4(5)	13.6(5)	18.8(6)	2.1(4)	16.9(5)	25.6(5)
O_4 deviation	−0.09	0.05	0.14	−0.14	−0.06	0.20	−0.08
$d\{O_4-O_{4'}\}$	4.307(8)	4.354(9)	4.452(8)	4.377(9)	4.287(9)	4.464(9)	4.421(8)
$d\{O_3-O_{2'}\}$	2.82(1)	3.01(1)	2.76(1)	2.80(1)	2.93(1)	2.85(1)	2.98(1)
per-2,6-OMe-β-CD·1.08H_2O: Molecule A							
d_p(C1,C4)	(0.69, −0.68)	(0.65, −0.65)	(0.70, −0.68)	(−0.66, 0.82)	(−0.69, 0.64)	(−0.71, 0.65)	(0.66, −0.73)
$\Delta d_p(C_2,C_3,C_5,O_5)$	0.00	0.04	0.01	0.01	0.02	0.01	0.03
$\angle P_{O4},P_{Gn}$	83.2(2)	74.5(2)	80.7(2)	78.9(12)	89.9(7)	78.2(8)	64.8(2)
$\phi(O_5C_1O_{4'}C_{4'})$	97.0(7)	108.7(7)	104.1(6)	124(1)	99(3)	115(2)	111.7(8)
$\psi(C_1O_{4'}C_{4'}C_{3'})$	135.0(6)	124.0(7)	121(2)	150(3)	120(2)	140.5(7)	115.9(7)
tilt angle	10.1(4)	17.3(3)	12.1(4)	15(1)	20(1)	7.2(7)	31.0(4)
O_4 deviation	0.04	−0.03	−0.05	0.59	0.11	−0.02	−0.03
$d\{O_4-O_{4'}\}$	4.311	4.375	4.342	4.551	4.410	4.103	4.497
$d\{O_3-O_{2'}\}$	2.90(1)	2.89(1)	2.77 (1)	2.84(3)	2.74(3)	2.99(1)	2.91(1)
per-2,6-OMe-β-CD·1.08H_2O: Molecule B							
d_p(C1,C4)	(0.69, −0.68)	(0.65, −0.65)	(0.69, −0.67)	(−0.66, 0.82)	(−0.69, 0.64)	(−0.71, 0.65)	(0.66, −0.72)
$\Delta d_p(C_2,C_3,C_5,O_5)$	0.00	0.04	0.01	0.02	0.01	0.01	0.03
$\angle P_{O4},P_{Gn}$	83.0(2)	74.4(2)	80.9(2)	73.6(7)	84.1(8)	78.1(2)	64.5(2)
$\psi(C_1O_{4'}C_{4'}C_{3'})$	124.0	148.5	77.9	144.3	140.5	115.8	135.2
tilt angle	31.2(4)	10.4(4)	17.5(3)	12.1(4)	31(1)	22(1)	16.5(7)
O_4 deviation	0.03	−0.02	−0.02	0.04	0.60	−0.01	−0.04
$d\{O_4-O_{4'}\}$	4.378	4.342	4.447	4.230	4.466	4.497	4.311
$d\{O_3-O_{2'}\}$	2.90(1)	2.89(1)	2.95(2)	2.75(4)	2.97(3)	2.99(1)	2.91(1)

three primary hydroxyl groups turned in over the torus (Figure 3) in a manner reported earlier for the molecule in the anhydrous crystals,[13] but not in the dihydrate[14]—the resultant structure is essentially closed on the primary side, Figure 5.

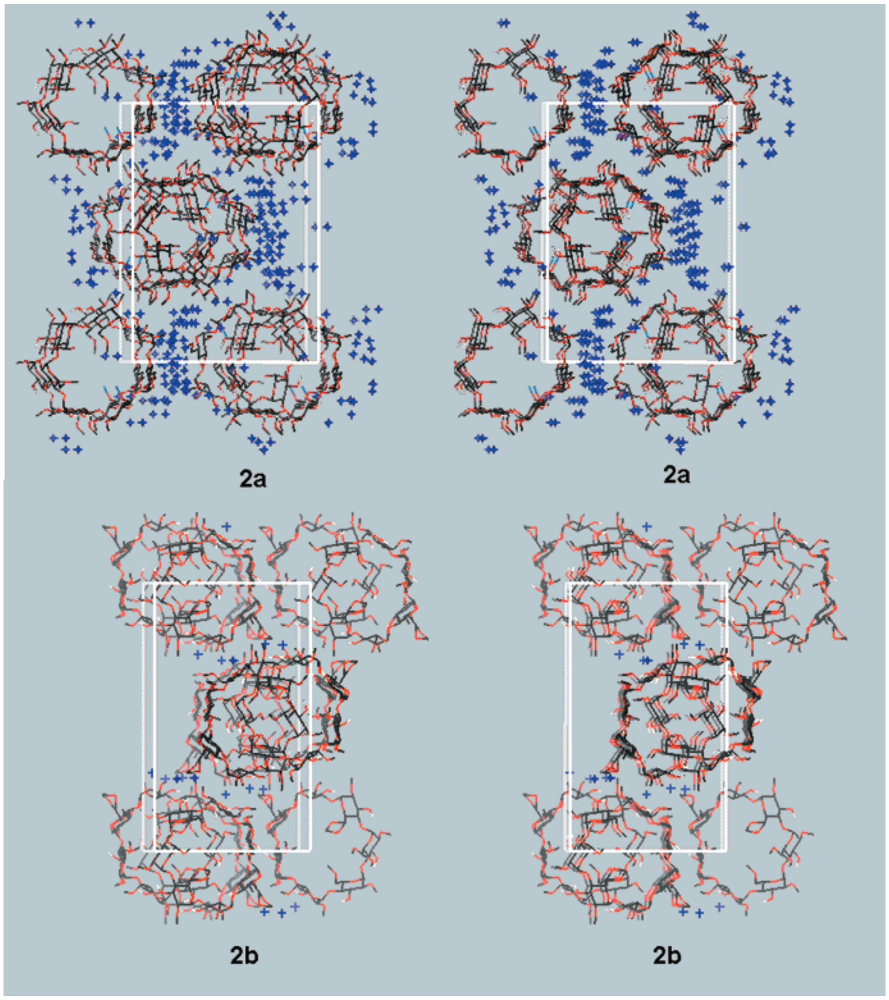


Figure 2. Stereoscopic projections on the *bc*-plane for the crystal structure models of (a) per-2,6-OMe-β-CD$\cdot$14.7H_2O and (b) per-2,6-OMe-β-CD$\cdot$1.08H_2O. Oxygen atoms of the water molecules are blue.

Crystal Packing and Molecular Conformations. The influence of crystal packing on the conformation is difficult to assess fully; however, some correlations are apparent. These involve similarities in stacks of per-2,6-OMe-β-CD molecules in per-2,6-OMe-β-CD$\cdot$14.7H_2O (crystals grown at 4 °C), in per-2,6-OMe-β-CD$\cdot$1.08H_2O (crystals grown at 50 °C), and in anhydrous per-2,6-OMe-β-CD (crystals grown at 60 °C). Both crystals reported here consist of stacks of per-2,6-OMe-β-CD molecules related by a 2_1-symmetry axis (parallel to the **a**-axis of the unit cell), the structure of the stacks being very similar to that reported for the anhydrous crystals. In each case the primary methoxy moiety of residue G1 penetrates the secondary side of the torus of the molecule “below” it. In per-2,6-OMe-β-CD$\cdot$14.7H_2O and per-2,6-OMe-β-CD$\cdot$1.08H_2O this methoxy substituent is disordered in the same manner as in the anhydrous crystals. In contrast, the crystal packing in per-2,6-OMe-β-CD$\cdot$2H_2O is reported to have a water molecule in the torus;[14] thus the packing mechanism is different.

In the per-2,6-OMe-β-CD$\cdot$1.08H_2O crystals, the intermolecular interactions that involve the two disordered glucose molecules can be viewed in Figure 2. In the more highly hydrated per-2,6-OMe-β-CD$\cdot$14.7H_2O crystals, there are columns of water molecules running parallel to the **a**-axis (view axis). The columns are the width of a per-2,6-OMe-β-CD molecule and serve to separate adjacent stacks in the **b**-axis direction. Figure 2b indicates that these stacks of methylated-β-CD molecules are in contact in the less hydrated crystals. Disordered glucose residues G4 and G5 make these contacts. Therefore crystal packing appears to play an important role in influencing the minor conformational differences of Molecules A and B.

Upon methylation, the primary (C6) hydroxyl groups take on considerable conformational flexibility. The methyl groups may be oriented over the torus, extended essentially parallel to the side of the cyclodextrin, or oriented outward from the molecule. Table 4 displays the conformations observed for the primary methoxy groups in the four known crystal structures. Examination of the table indicates that multiple conformers are present in each molecule.

Hydrogen Bonding and Waters of Crystallization. There are no apparent intermolecular hydrogen bonds involving only per-2,6-OMe-β-CD molecules in either of the structures reported here. All free hydroxyl hydrogen donors appear to be involved in intramolecular H bonds in the manner discussed earlier by Steiner and Saenger for the anhydrous crystal structure.[13]

The Per-2,6-OMe-β-CD$\cdot$14.7H_2O Structure. Figure 2 illustrates the extensive interactions between water molecules and per-2,6-OMe-β-CD molecules and between water molecules in the crystal structure of per-2,6-OMe-β-CD$\cdot$14.7H_2O. The interactions, too numerous to display graphically, are presented in Table 5. A few of the observed interactions merit comment.

Water/Per-2,6-OMe-β-CD Molecule Interactions. Water molecules O03W, O05W, and the disordered O15a,bW are in hydrogen bond contact distances to atom pairs [O5G3,O6G3], [O5G5,O6G5], and [O5G6,O6G6], respectively. This observa-

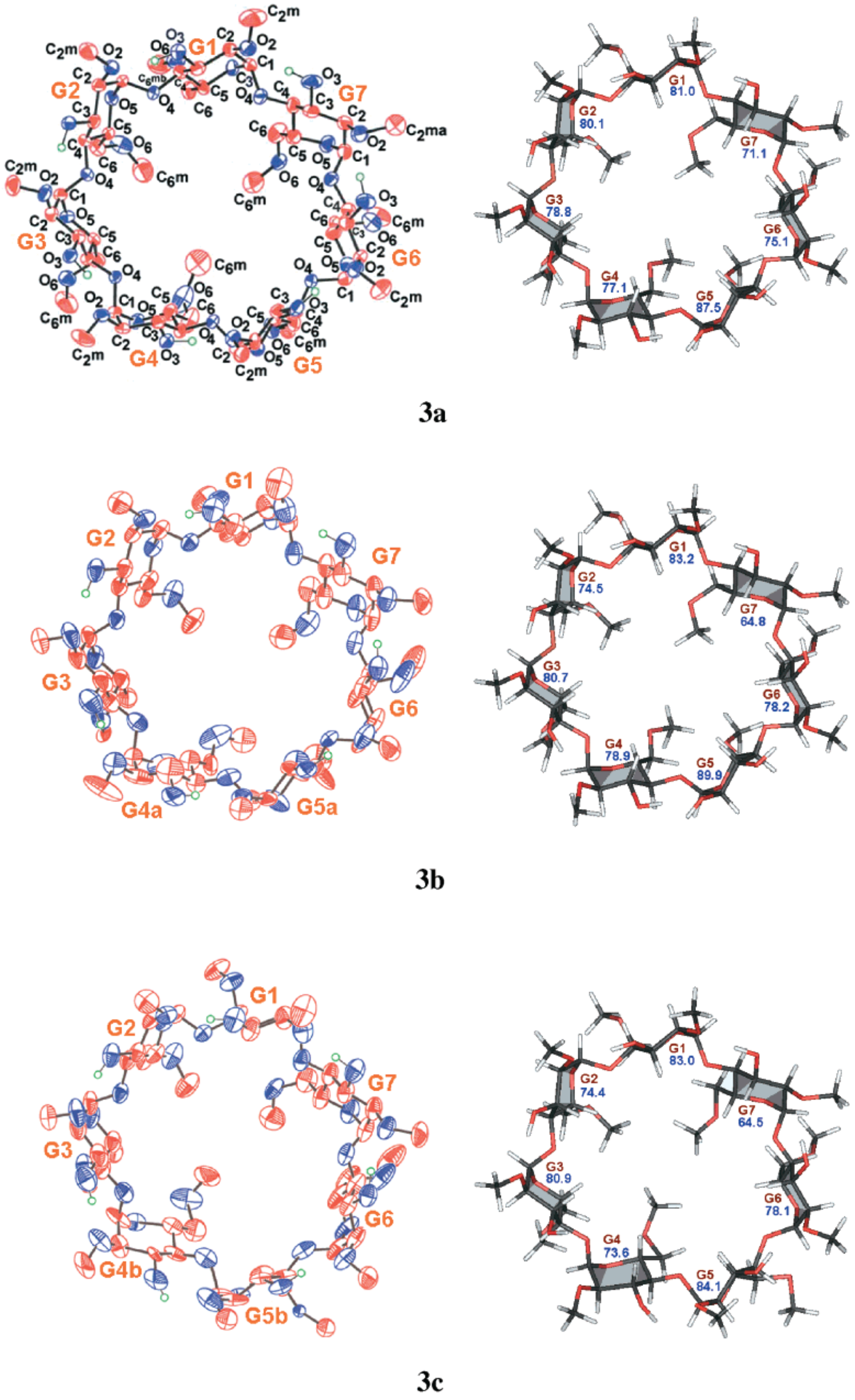


Figure 3. The 2,6-per-*O*-methyl-*b*-cyclodextrin molecular models from the crystal structure refinements. The three examples are drawn in the same orientation. Individual atom labels are indicated in the top left image. The sequence is (a) per-2,6-OMe-*β*-CD•14.7H_2O, (b) per-2,6-OMe-*β*-cyclodextrin•1.08H_2O molecule a, and (c) per-2,6-OMe-*β*-cyclodextrin•1.08H_2O molecule b. Glucose residues G1-G3 and G6-G7 are common in parts b and c. The left images illustrate refined atomic displacement parameters for carbon (red) and oxygen atoms (blue) drawn at the 50% probability level. The angles between the plane fit to atoms C2, C3, O5, and C5 and the plane of the seven O4 atoms are presented in the images on the right.

tion indicates a probable presence of three bifurcated hydrogen bonds in which the H-bond donor from the water molecules interacts with both possible acceptors in the three glucose residues. The remaining interactions involve water molecules O01W, O02W, O04W, O06W, O08W, O12W, and O13W, each of which interacts, almost certainly, as a H-bond donor to an

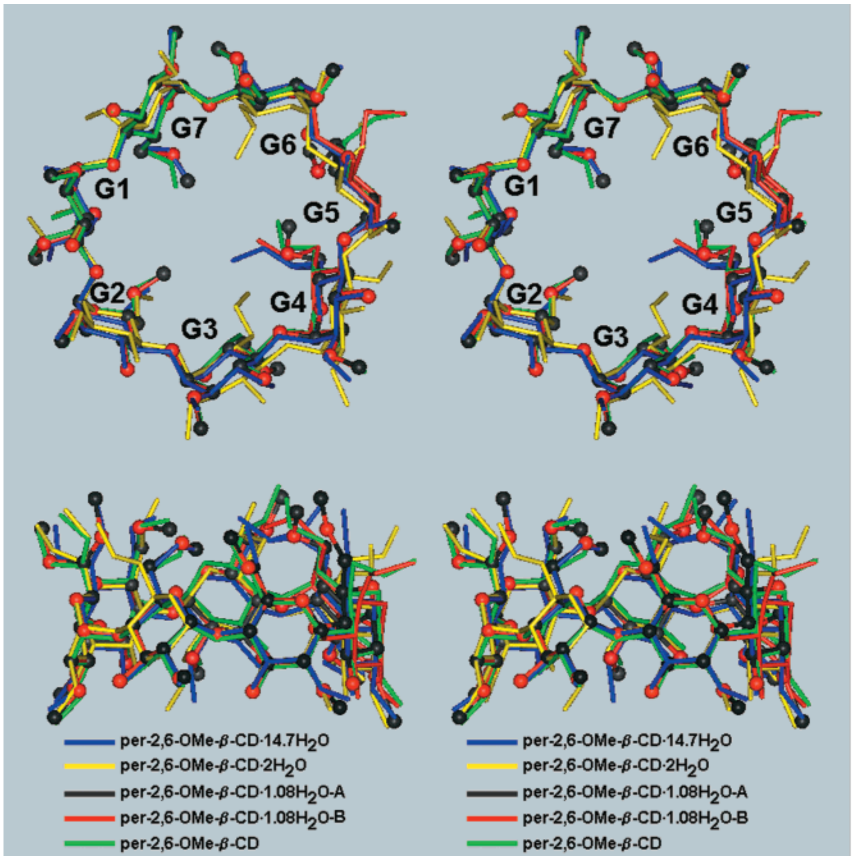


Figure 4. A stereoscopic superposition diagram of the per-2,6-OMe-*b*-cyclodextrin molecules in the four hydrate pseudopolymorphs.

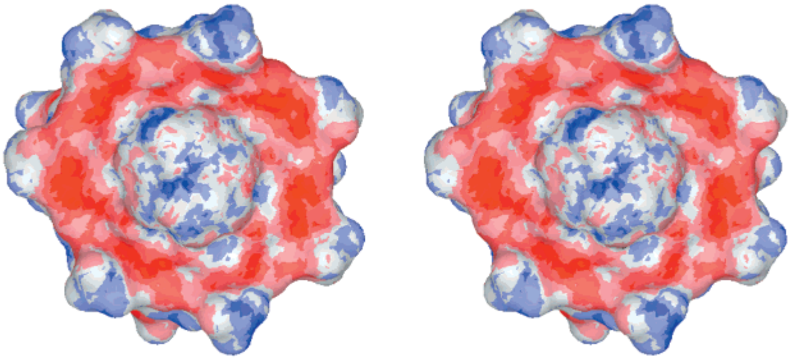


Figure 5. A stereoscopic projection of an electrostatic potential surface plot for an example of a per-2,6-OMe-*β*-CD molecule. The image was created with Chime. The red color represents negative potential, blue positive potential, and gray neutral potential.

individual O3 of a glucose: that is each O3 of glucose residues 1−7 is involved with a single water molecule as an acceptor in an H-bond interaction.

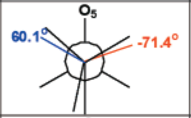
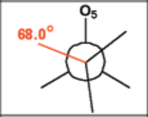
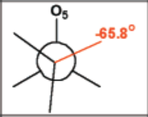
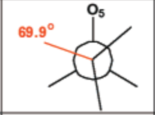
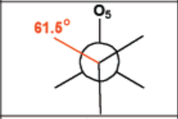
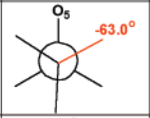
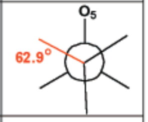
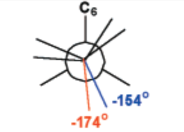
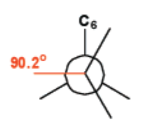
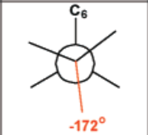
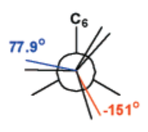
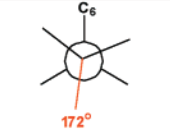
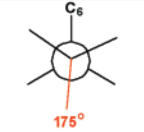
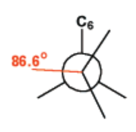
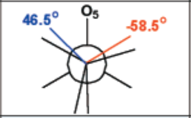
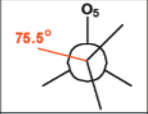
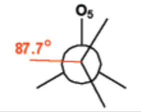
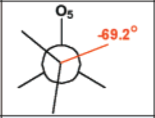
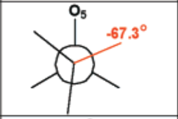
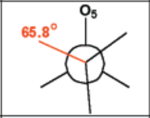
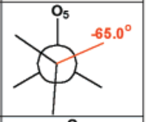
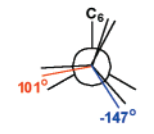
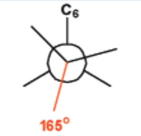
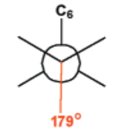
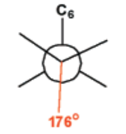
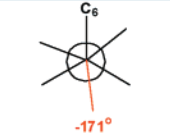
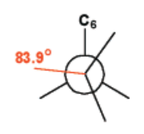
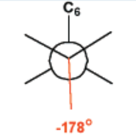
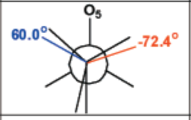
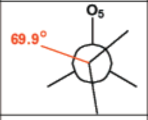
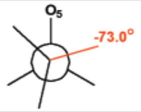
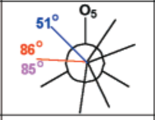
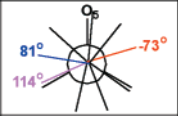
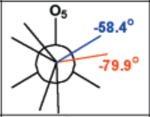
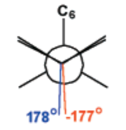
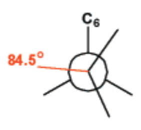
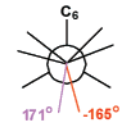
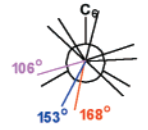
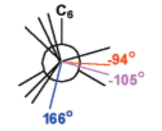
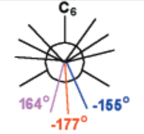
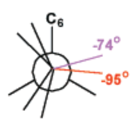
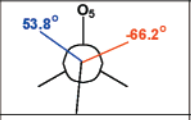
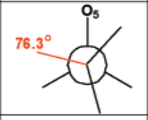
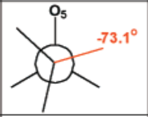
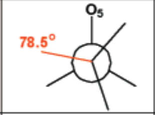
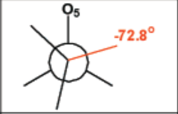
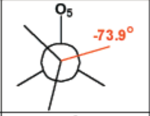
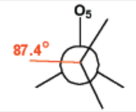
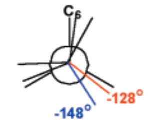
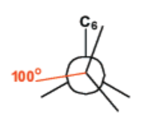
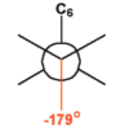
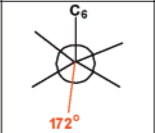
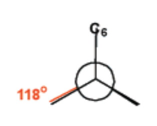
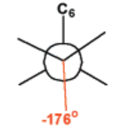
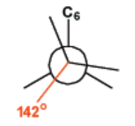
Water/Water Interactions. As tabulated in Table 4, there are extensive O···O contact distances indicative of H-bond interactions. Of the 14.7 water of crystallization molecules, four (O07W, O09W, O11W, and O15W) are disordered over two nearby sites. Each appears to fill a void in the lattice, taking advantage of suitable H-bond interactions.

Why 14.7H$_2$O? Of the 15 unique water molecule sites found in the asymmetric unit, one, O12W, has been estimated to have a population parameter equal to 50% based on the observation that this water oxygen atom has a contact distance of 1.81 Å to a disordered methoxy carbon atom, C6Mb_G4 (estimated population parameter 30%); these two atoms cannot be present simultaneously.

Hydrogen Bonding in Per-2,6-OMe-*β*-CD·1.08H$_2$O. The hydrogen bonding interactions in per-2,6-OMe-*β*-CD·1.08H$_2$O are illustrated as a stereoscopic projection in Figure 6. There are three partially occupied sites for water molecules in the lattice that were easily recognized in difference electron density maps as the model for the crystal structure was developed. Their refined occupancy factors are O01W 35%, O02W 41%, and O03W 32%, giving rise to the 1.08 hydration number.

The steric factors in the lattice determining these occupancy factors are not entirely clear. For example, there are no interatomic contact distances to O01W that would preclude its being fully occupied. However, setting the occupancy to 100% leads to unacceptably large values for the refined anisotropic atomic displacement parameters. The disorder in the conformation of the per-2,6-OMe-*β*-CD does play a role in the occupancy for the other two water molecules. There is a relatively close contact distance between O02W and C2MG4A (3.38 Å). Further, there are no H-bond interactions involving disordered glucose residues G4A and G5A, but there are two favorable H-bond interactions of O02W with the disordered O6 atoms of

Table 4. The Conformations of the Primary Methoxy Substituents in the Four Crystal Structures[a]

Crystal Temp.	Torsion	Residue G1	Residue G2	Residue G3	Residue G4	Residue G5	Residue G6	Residue G7
4 °C	$O_5C_5C_6O_6$							
	$C_5C_6O_6C_{6M}$							
18 °C	$O_5C_5C_6O_6$							
	$C_5C_6O_6C_{6M}$							
50 °C	$O_5C_5C_6O_6$							
	$C_5C_6O_6C_{6M}$							
60 °C	$O_5C_5C_6O_6$							
	$C_5C_6O_6C_{6M}$							

[a] Where more than one conformation is observed the one presented in red has the highest population followed by the blue one, then the magenta one.

G5B, Table 5. Water O03W cannot be present simultaneously with O6aG5B (contact distance 1.79 Å).

On the basis of the refined occupancy factors for O6aG5B (21%) and O6bG5B (29%) it would not be unreasonable to estimate the occupancy factors for O01W, O02W, and O03W to be 50%, 50%, and 29%, respectively. While such values are not all that different from the refined occupancy factors, experience refining occupancy factors in other crystal structure models suggests that the idealized values are outside the usual variance typically encountered.

Finally, it should be noted that the water molecules in the crystals grown at 50 °C are in similar but significantly different positions than those in the crystals grown at 4 °C. Using a cyclodextrin molecule stack as a reference in a superposition calculation, the closest approach for water molecules in the two crystal structures reported here ranges from 0.52 to 1.66 Å.

Crystal Structure Comparison. Per-2,6-OMe-β-CD·1.08H_2O and anhydrous per-2,6-OMe-β-CD crystallize with the same space group symmetry, Table 1. As indicated in the table, the respective crystals were grown at 50 and 60 °C. Considering the similarities in lattice parameters and the modest difference in temperature at which the crystals were grown, one might question whether the crystal structures are really different. While Steiner and Saenger do not totally preclude the presence of water molecules in the crystals grown at 60 °C, they observe that there is no indication for their presence in their final difference electron density map. In view of the importance of accurate characterization pseudopolymorphism to the pharmaceutical industry, it is appropriate to examine the similarities and differences in the crystal structure models developed in these two studies.

The crystal structures are at least apparently isomorphous. Glucose residue G1 in the current model corresponds to the 5th residue in the model reported by Steiner and Saenger. The 6-methoxy group of this residue displays similar conformational disorder in both crystal structure models; however, the population parameters differ. The population parameter for the major component (O6aG1−C6MaG1) in the current model refined to 87% compared with 80% in the anhydrous model. No other disorder is reported in the model for the anhydrous crystals. The conformational disorder in glucose residues G4 and G5 in the current model was mentioned above and illustrated in Figures 1 and 3. In addition to that disorder, the 6-methoxy-oxygen atom of residue G5B is 2-fold disordered (O6aG5B 21% and O6bG5B 29%); similar disorder has been found for glucose G7 (O6aG7 45% and O6bG7 55%), Figure 6.

The differences in the refined crystal structure models for per-2,6-OMe-β-CD·1.08H_2O and anhydrous per-2,6-OMe-β-CD are significant; however, it is difficult to unequivocally assign

Table 5. Intermolecular O···O Distances for H Bonds

Per-2,6-OMe-*β*-CD·14.7H_2O			**Per-2,6-OMe-*β*-CD·1.08H_2O**		
		β-CD to water distances			
O3_G1	O12W	2.84(2)	O3_G2	O02W	2.73(2)
O6b_G1	O1H∸x	3.04(5)	O3_G3	O01W	3.12(2)
O3_G2	O01W	2.78(2)	O6a_G5B	O02W	2.73(2)
O3_G3	O13W	2.81(1)	O6b_G5B	O02W	2.70(2)
O5_G3	O03W	3.06(1)	O3_G6	O03W	2.87(2)
O6_G3	O03W	2.92(1)	O3_G7	O01W	2.54(2)
O3_G4	O04W	2.83(1)			
O3_G5	O06W	2.81(2)			
O5_G5	O05W	2.97(1)			
O6_G5	O05W	2.96(1)			
O3_G6	O02W	2.74(1)			
O5_G6	O15Wa	2.94(2)			
O6_G6	O15Wa	3.19(2)			
O5_G6	O15Wb	2.85(3)			
O6_G6	O15Wb	3.11(4)			
O3_G7	O08W	2.85(1)			
		water−water distances			
O01W	O02W	2.75(1)	O01W	O02W	2.89(2)
O01W	O07Wa	2.76(2)	O02W	O03W	2.76(2)
O01W	O07Wb	2.67(3)			
O02W	O04W	2.76(1)			
O03W	O04W	2.79(1)			
O03W	O09Wa	2.74(2)			
O03W	O09Wb	2.95(4)			
O03W	O14W	2.79(2)			
O05W	O07Wa	2.95(2)			
O05W	O07Wb	2.57(3)			
O05W	O08W	2.74(2)			
O05W	O13W	2.78(2)			
O06W	O07Wa	3.07(3)			
O06W	O11Wa	2.83(2)			
O06W	O11Wb	2.83(5)			
O06W	O15Wa	2.70(2)			
O06W	O15Wb	2.99(4)			
O07Wa	O10W	2.60(2)			
O07Wb	O10W	2.99(3)			
O08W	O09Wa	2.83(2)			
O08W	O09Wb	2.60(4)			
O09Wa	O11Wa	3.03(2)			
O09Wa	O11Wb	2.64(4)			
O09Wa	O12W	2.88(2)			
O09Wb	O11Wa	2.74(4)			
O09Wb	O11Wb	2.30(5)			
O10W	O11Wa	2.61(2)			
O10W	O15Wa	2.76(2)			
O11Wb	O15Wb	2.89(6)			
O13W	O14W	2.86(2)			
O14W	O15Wa	2.94(2)			
O14W	O15Wb	2.49(4)			

them to differences in the crystal structures. They may reflect either truly different crystal structures produced by growing the crystals at different temperature or the effects of cooling the crystal on resolution in the resultant model. On the basis of the isotropic equivalent temperature factors reported for the anhydrous crystal structure and our experience in determining the current crystal structure, we believe the differences to be real rather than a reflection of artifacts in the data.

Conclusion

Crystal structures have been determined for two new hydrate pseudopolymorphs of tetradeca-2,6-*O*-methyl-*β*-cyclodextrin. Crystals grown at 50 °C have been found to contain 3 partially occupied water molecule sites to give crystals with the composition $C_{56}H_{98}O_{35}\cdot 1.08H_2O$ while those grown at 4 °C have the composition $C_{56}H_{98}O_{35}\cdot 14.7H_2O$. In the latter crystals there are several water molecules that are disordered, but with the exception of one site, the sum of their occupancies is 100%; the remaining site is shared with a methoxy methyl group.

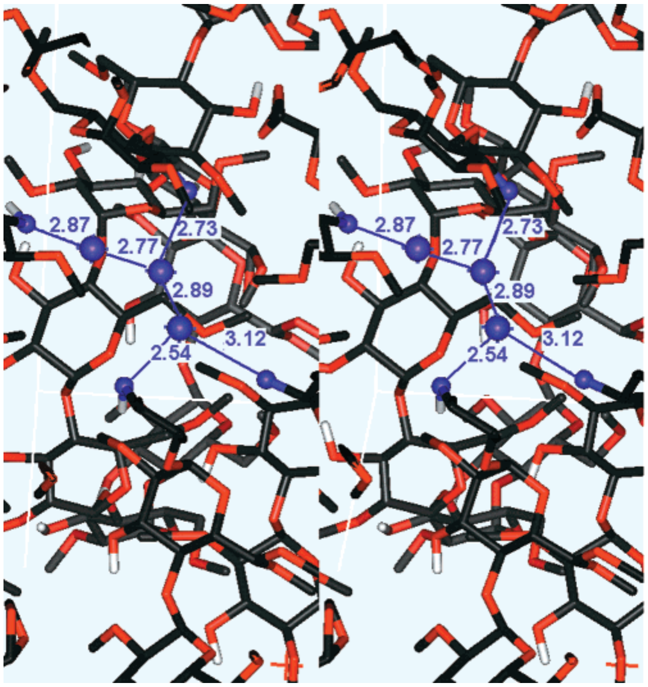


Figure 6. A stereoscopic projection illustrating the hydrogen bonding interactions in the per-2,6-OMe-*β*-CD·1.08H_2O crystal structure. Note, the illustrated water molecules are not present at 100% occupancy. See the text for details.

The tetradeca-2,6-*O*-methyl-*β*-cyclodextrin molecules stack in similar “herringbone” stacks in both structures. There is contact between the stacks in the less hydrated crystals and the glucose residues in the contact region show conformational disorder. In the more hydrated crystals, the stacks are separated by a water layer that displays extensive hydrogen bond interactions. While there are clearly significant conformational differences in the molecular conformations of the alkylated cyclodextrin molecules, a superposition diagram indicates that the differences are relatively minor.

Results to date demonstrate that there are at least four hydrate polymorphs of crystalline tetradeca-2,6-*O*-methyl-*β*-cyclodextrin. Each has been grown from pure aqueous solution at temperatures ranging from 4 to 60 °C. The observed differences in the crystal structures determined for crystals grown at 50 and 60 °C indicate that a careful structural study of crystals grown over a temperature range, probably from ∼ 40 to 70 °C, could be particularly interesting with respect to better understanding kinetically controlled crystal growth. Further, in view of the potential of this cyclodextrin derivative to serve as a drug delivery aid, possibly due to host−guest complex formation, there are expected to be practical benefits that can be gained from continued efforts to characterize pseudopolymorphs. The crystal structures reported here are not likely to be those obtained with complexes of pharmaceutical agents; however, understanding the conditions under which they have been grown and the nature of the differences in crystal packing are important considerations in designing manufacturing processes.

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Supporting Information Available: CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

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