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# Crystal structures of cyclomaltoheptaose (β-cyclodextrin) complexed with ethylene glycol · $8.0H_2O$ and glycerol · $7.2H_2O$ *

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## ABSTRACT

Single-crystal X-ray diffraction studies were carried out for the title compounds at room temperature. The crystal packings are of the cage-type and isomorphous to that of β-cyclodextrin (βCD) hydrate. In both crystal structures, disorder and extensive thermal vibrations of the complexed guest molecules are observed. In βCD–ethylene glycol·$8H_2O$, one ethylene glycol molecule (disordered over two discrete sites) and three water molecules (four discrete sites) are included in the βCD cavity. Within the βCD cavity, *all* oxygen sites (ordered and disordered) are in positions occupied by water molecules in βCD·$12H_2O$; this is only possible because the ethylene glycol molecule adopts the low-energy conformation with the O–C–C–O torsion angle ~60° and an O · · · O separation of 2.9 Å, in which its hydroxyl groups can directly substitute for two hydrogen-bonding water molecules. In βCD–glycerol·$7.2H_2O$, one glycerol molecule (disordered over two discrete sites) and two water molecules (two fully occupied sites) are included in the βCD cavity. The general situation in both compounds parallels that found earlier in βCD–ethanol·$8H_2O$. It is assumed that the disorder is dynamic, i.e., associated with jumps between the partially occupied molecular sites.

## INTRODUCTION

The macrocyclic cyclodextrins (CDs, cyclomaltooligosaccharides) consist of six (αCD) to nine (δCD) α-D-glucose residues connected by (1 → 4) bonds. Because the surface of the central cavity is formed by H atoms bonded to C and by glycosidic O atoms, it is of hydrophobic nature. The three hydroxyl groups per glucose residue are placed at the rims of the CD molecule. The CDs form inclusion complexes with molecules of suitable size[1,2]. Many of these complexes crystallize form aqueous solution, and the crystals always contain several water molecules per CD.

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* Topography of Cyclodextrin Inclusion Complexes, Part 31. For Part 30, see ref 7.

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In our laboratory, we use crystalline cyclodextrin complexes as model systems to investigate structural and dynamic characteristics of extended hydrogen-bond (H-bond) networks, and of host–guest interactions[3,4]. The present contribution is part of a study where various hydrophilic molecules are included in the hydrophobic cavity of βCD[4–9]. To permit direct comparison of the different crystal structures, only those complexes are selected that crystallize with a molecular packing isomorphous to the pure hydrate $\beta$CD · 12$H_2O$[5]. Small molecules such as ethanol[4], water[5–7], and $H_2O_2$[8] tend to be disordered over several partially occupied sites; this disorder is highly dynamic, as was shown by incoherent neutron scattering[10] and solid-state NMR[11] studies. The larger 1,4-butanediol molecule was found in a single position that is fixed by hydrogen bonding of the terminal hydroxyl groups, whereas the $(-CH_2-)_4$ chain shows extensive vibrations[9].

In contrast to the structural fluctuations and rearrangements of the guest molecules in the solid state, the conformation of the βCD host is fixed in the crystal lattice; in solution, the cyclodextrin conformation is also flexible as shown by molecular dynamics simulations of αCD complexes[12]. To generalise these findings, we further varied the guest molecules, and report here the crystal structures of βCD complexed with ethylene glycol and glycerol.

## EXPERIMENTAL

*Crystallisation.*—To obtain single crystals, concentrated solutions of βCD in 1:2 ethylene glycol–$H_2O$ and glycerol–$H_2O$, respectively, were cooled from ~ 70°C in a Dewar flask. Crystals of the size ~ $0.5 \times 0.3 \times 0.2$ mm$^3$ were used for the diffraction experiments.

*X-ray diffraction experiments.*—For both complexes, X-ray diffraction data sets were collected on crystals that were mounted in glass capillaries together with some mother liquor (Enraf–Nonius Turbo-CAD 4 diffractometer, Ni-filtered Cu$K\alpha$-radiation from a rotating-anode generator, $\lambda = 1.542$ Å, $\omega/2\theta$-scan mode, $2\theta_{max} = 120°$, nominal resolution $\lambda/2 \sin \theta_{max} = 0.89$ Å, $\psi$-scan absorption correction[13], T ~ 20°C). Crystal data are given in Table I.

*Determination and refinement of the structures.*—The atomic coordinates of the βCD molecule in the isomorphous structure βCD–1,4-butanediol · 6.25$H_2O$[9] were used for initial phasing (space group $P2_1$). Consecutive cycles of least-squares refinement and difference Fourier analyses gradually revealed the positions of the alcohol and water molecules (program SHELX76[14], function minimized $\Sigma\omega(|F_o| - |F_c|)^2$ with $w = 1.0$ for all reflections, guided by frequent inspection of electron density maps with the computer graphics program FRODO[15,16], version[17] E4.4). In the final stages of anisotropic refinement, H atoms bonded to C were placed in their calculated positions. Hydroxyl H atoms were not located. Final $R$-values are given in Table I.

Refinement of the βCD molecules proceeded smoothly. For disordered primary (O-6) hydroxyl groups, the sum of oxygen occupation factors was fixed at one.

TABLE I

Crystallographic data [a,b] for the βCD inclusion complexes with ethylene glycol and glycerol

| | Ethylene glycol | Glycerol |
|---|---|---|
| $a$ (Å) | 21.212(1) | 21.322(6) |
| $b$ (Å) | 10.021(3) | 9.954(1) |
| $c$ (Å) | 15.208(1) | 15.251(6) |
| $\beta$ (°) | 111.47(3) | 111.20(1) |
| $V$ (Å$^3$) | 3008(3) | 3018(1) |
| No. of unique reflections | 4934 | 4642 |
| Reflections with $F_o > 2\sigma(F_o)$ | 3778 | 4378 |
| $R$ value [c] | 0.070 | 0.066 |

[a] Space group $P2_1$, $Z = 2$. [b] Standard deviations are given in parentheses. [c] $R = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$ for $F_o > 2\sigma(F_o)$.

For the cocrystallized solvent molecules, refinement was complicated due to disorder. In the complex of βCD with ethylene glycol, two of the five interstitial water molecules were found disordered over two and three sites, respectively. In the βCD cavity, three water sites were located, one of which is partially occupied (W8, occupancy ~ 0.70), and one (W7) exhibits an elongated electron-density distribution. The latter is indicative of disorder with alternative positions closer than the crystallographic resolution ~ 0.9 Å. One ethylene glycol molecule is included in each βCD cavity. This guest molecule shows positional disorder: a well-defined major site (occupancy 0.67) and a minor site (occupancy 0.33) are identified. As these sites overlap partially, they could not be refined individually; their covalent geometries had to be fixed to ideal values, and the sum of occupancy of both sites was fixed at 1.0. One oxygen atom of the major site has an occupancy of 1.0. This suggests that a water molecule takes its place (W9), if the ethylene glycol molecule occupies its minor site.

In the refinement of the βCD–glycerol crystal structure, similar problems arose. Two interstitial water molecules are three-fold disordered. The βCD cavity contains one glycerol and two water molecules. The glycerol molecule is disordered in a similar way as the ethylene glycol molecule discussed above: a well-defined major site is easily recognized (occupancy 0.62), and an overlapping minor site (occupancy 0.38) is more difficult to trace. Both sites had to be refined with stereochemical restraints (only torsion angles allowed to vary).

For both crystal structures, the disorder of the guest molecules is resolved with only limited reliability: the major sites of the ethylene glycol and glycerol molecules are well determined, but the overlapping minor sites are refined at a much lower level of accuracy. Positional disorder of water molecules is indicated by irregular shapes of their electron density distributions, but could not be resolved. This suggests that the actual situation in the crystals might be more complex than discussed in the simple two-site models presented below.

## RESULTS

*General.*—Fractional atomic coordinates and equivalent isotropic temperature factors are listed in Tables II and III. Anisotropic displacement parameters and further structural data have been deposited *. Atom labelling is as in our previous contributions[5,9], where superscripts in atom designations indicate the glucose residues, e.g., C-$2^4$ means atom C-2 of glucose residue 4 of the βCD molecule.

*Crystal packing.*—For both compounds, the βCD molecules are arranged in a herring-bone fashion as in the isomorphous complex $\beta CD \cdot 12H_2O$[5]. In this packing mode, the βCD cavities are closed on both ends by neighbouring βCD molecules, so that a molecular 'cage' is formed. This packing, however, is not tight enough to prevent water molecules from travelling through the crystal lattice, as was shown by dehydration of $\beta CD \cdot 12H_2O$[7]. The general packing mode is illustrated in Figs. 1A and 1B for βCD complexed with ethylene glycol and glycerol, respectively.

*The βCD molecule.*—The conformation of the βCD molecule in this crystal packing is comparable to that described for $\beta CD \cdot 12H_2O$[5]. The only conformational difference of βCD in the isomorphous structures is the disorder of primary hydroxyl groups C-6–O-6, which may point 'away' from the molecular axis, or 'inside'. The C-$6^1$–O-$6^1$ and C-$6^2$–O-$6^2$ groups are disordered (Figs. 2 and 3), and for C-$6^2$–O-$6^2$, the 'inward' orientations are only weakly populated with occupancies ~ 0.1, i.e., at the limit of crystallographic detectability (Tables II and III).

*Crystal composition.*—In both crystal structures, each βCD cavity contains one ethylene glycol or glycerol molecule. Due to disorder, the total number of cocrystallized water molecules is less clear and can only be determined with accuracies around ±0.3. If the occupancies of alternative water sites which are mutually exclusive are set so that they sum up to 1.0 (W-3A/W-3B and W-5A/W-5B/W-5C in Tables II and III), the total water contents are 8.0 for the complex βCD–ethylene glycol, and 7.2 for βCD–glycerol. As the disorder is not satisfactorily well resolved for all water molecules, however, it is not always clear whether two sites are mutually exclusive or not, and the possibility of a slightly higher content of water remains (up to ~ 8.3 for βCD–ethylene glycol and 7.6 for βCD–glycerol).

*Interstitial water molecules.*—In all isomorphous complexes of βCD, interstitial water molecules were found in equivalent positions. These are also observed in the title compounds, and labelled the same way as in $\beta CD\text{–}1,4\text{-butanediol} \cdot 6.25H_2O$[9] (W-1 to W-5), and drawn as open spheres in Figs. 2 and 3. W-1, W-2, and W-4 are ordered, and W-3 and W-5 are disordered in both crystal structures. Due to resolution problems in refinement, it is not definitely clear whether the alternative sites of W-5 are mutually exclusive or not. The large sum of occupancies (*Σocc.*

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* Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

TABLE II

Fractional atomic coordinates [a], equivalent isotropic temperature factors $U_{eq}$ [b] of the nonhydrogen atoms in β-cyclodextrin–ethylene glycol·8$H_2O$. Occupancies are given if < 1.0

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ | Occ. |
|---|---|---|---|---|---|
| C-1$^1$ | 0.5482(5) | 0.5330(–) | 0.0997(6) | 0.047(6) | |
| C-2$^1$ | 0.4783(5) | 0.507(1) | 0.0256(6) | 0.044(6) | |
| C-3$^1$ | 0.4836(4) | 0.420(1) | −0.0540(6) | 0.037(6) | |
| C-4$^1$ | 0.5350(5) | 0.4778(9) | −0.0906(7) | 0.043(6) | |
| C-5$^1$ | 0.6022(4) | 0.501(1) | −0.0131(6) | 0.045(6) | |
| C-6$^1$ | 0.6542(5) | 0.564(1) | −0.0443(8) | 0.072(7) | |
| O-2$^1$ | 0.4353(3) | 0.4493(8) | 0.0683(4) | 0.055(5) | |
| O-3$^1$ | 0.4197(3) | 0.4115(9) | −0.1290(5) | 0.059(5) | |
| O-4$^1$ | 0.5426(3) | 0.3819(7) | −0.1563(4) | 0.046(5) | |
| O-5$^1$ | 0.5922(3) | 0.5860(7) | 0.0577(4) | 0.049(5) | |
| O-6$^1$A | 0.6377(6) | 0.689(1) | −0.0823(8) | 0.088(7) | 0.70 |
| O-6$^1$B | 0.7120(8) | 0.602(2) | 0.030(1) | 0.078(8) | 0.30 |
| C-1$^2$ | 0.6813(5) | 0.285(1) | 0.4181(7) | 0.048(6) | |
| C-2$^2$ | 0.6051(5) | 0.276(1) | 0.3842(6) | 0.050(6) | |
| C-3$^2$ | 0.5738(4) | 0.288(1) | 0.2763(6) | 0.048(6) | |
| C-4$^2$ | 0.6021(4) | 0.409(1) | 0.2453(6) | 0.040(6) | |
| C-5$^2$ | 0.6792(5) | 0.404(1) | 0.2797(6) | 0.045(6) | |
| C-6$^2$ | 0.7166(5) | 0.511(1) | 0.2514(8) | 0.057(6) | |
| O-2$^2$ | 0.5863(3) | 0.1527(8) | 0.4159(5) | 0.057(5) | |
| O-3$^2$ | 0.5019(3) | 0.2944(9) | 0.2455(5) | 0.070(6) | |
| O-4$^2$ | 0.5732(3) | 0.4102(7) | 0.1444(4) | 0.043(5) | |
| O-5$^2$ | 0.7029(3) | 0.3982(7) | 0.3828(4) | 0.046(5) | |
| O-6$^2$A | 0.7009(4) | 0.6390(8) | 0.2713(6) | 0.063(6) | 0.91 |
| O-6$^2$B | 0.7864(9) | 0.493(3) | 0.287(3) | 0.056(4) | 0.09 |
| C-1$^3$ | 0.8577(5) | −0.113(1) | 0.5004(6) | 0.042(6) | |
| C-2$^3$ | 0.7875(5) | −0.151(1) | 0.4959(7) | 0.056(6) | |
| C-3$^3$ | 0.7339(4) | −0.056(1) | 0.4318(7) | 0.042(6) | |
| C-4$^3$ | 0.7537(4) | 0.087(1) | 0.4627(6) | 0.038(6) | |
| C-5$^3$ | 0.8257(5) | 0.116(1) | 0.4702(7) | 0.047(6) | |
| C-6$^3$ | 0.8516(6) | 0.250(1) | 0.5117(8) | 0.058(7) | |
| O-2$^3$ | 0.7726(3) | −0.2870(7) | 0.4619(5) | 0.056(5) | |
| O-3$^3$ | 0.6694(3) | −0.0813(8) | 0.4374(5) | 0.053(5) | |
| O-4$^3$ | 0.7068(3) | 0.1667(7) | 0.3902(4) | 0.040(5) | |
| O-5$^3$ | 0.8720(3) | 0.0203(7) | 0.5300(4) | 0.044(5) | |
| O-6$^3$ | 0.8459(4) | 0.2593(9) | 0.6053(5) | 0.070(6) | |
| C-1$^4$ | 0.9702(4) | −0.276(1) | 0.2605(7) | 0.046(6) | |
| C-2$^4$ | 0.9496(5) | −0.380(1) | 0.3188(7) | 0.044(6) | |
| C-3$^4$ | 0.8946(4) | −0.319(1) | 0.3494(7) | 0.044(6) | |
| C-4$^4$ | 0.9176(4) | −0.191(1) | 0.3998(6) | 0.039(6) | |
| C-5$^4$ | 0.9449(5) | −0.091(1) | 0.3426(6) | 0.044(6) | |
| C-6$^4$ | 0.9818(6) | 0.025(1) | 0.4002(8) | 0.065(7) | |
| O-2$^4$ | 0.9255(3) | −0.4968(7) | 0.2652(5) | 0.053(5) | |
| O-3$^4$ | 0.8786(3) | −0.4141(7) | 0.4099(5) | 0.053(5) | |
| O-4$^4$ | 0.8593(3) | −0.1289(7) | 0.4089(4) | 0.041(5) | |
| O-5$^4$ | 0.9953(3) | −0.1604(7) | 0.3160(4) | 0.045(5) | |
| O-6$^4$ | 0.9984(6) | 0.1205(9) | 0.3455(7) | 0.107(7) | |
| C-1$^5$ | 0.8645(4) | −0.232(1) | −0.1089(6) | 0.044(6) | |

TABLE II (continued)

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ | Occ. |
|---|---|---|---|---|---|
| C-2$^{5}$ | 0.8576(5) | −0.367(1) | −0.0668(6) | 0.045(6) | |
| C-3$^{5}$ | 0.8570(4) | −0.3472(9) | 0.0328(6) | 0.038(6) | |
| C-4$^{5}$ | 0.9169(5) | −0.267(1) | 0.0886(6) | 0.042(6) | |
| C-5$^{5}$ | 0.9191(5) | −0.134(1) | 0.0436(6) | 0.043(6) | |
| C-6$^{5}$ | 0.9789(5) | −0.050(1) | 0.0935(8) | 0.059(6) | |
| O-2$^{5}$ | 0.8011(4) | −0.4377(7) | −0.1267(5) | 0.057(5) | |
| O-3$^{5}$ | 0.8544(3) | −0.4741(7) | 0.0738(5) | 0.056(5) | |
| O-4$^{5}$ | 0.9131(3) | −0.2468(7) | 0.1801(4) | 0.043(5) | |
| O-5$^{5}$ | 0.9199(3) | −0.1607(8) | −0.0502(4) | 0.051(5) | |
| O-6$^{5}$ | 1.0410(3) | −0.1206(9) | 0.1193(5) | 0.070(6) | |
| C-1$^{6}$ | 0.6613(5) | 0.043(1) | −0.3484(6) | 0.044(6) | |
| C-2$^{6}$ | 0.6512(4) | −0.1040(9) | −0.3433(7) | 0.042(6) | |
| C-3$^{6}$ | 0.6923(4) | −0.1546(9) | −0.2431(6) | 0.039(6) | |
| C-4$^{6}$ | 0.7658(4) | −0.118(1) | −0.2211(6) | 0.039(6) | |
| C-5$^{6}$ | 0.7718(5) | 0.033(1) | −0.2281(6) | 0.043(6) | |
| C-6$^{6}$ | 0.8427(5) | 0.082(1) | −0.2106(8) | 0.062(6) | |
| O-2$^{6}$ | 0.5803(3) | −0.1334(8) | −0.3707(5) | 0.055(5) | |
| O-3$^{6}$ | 0.6856(4) | −0.2978(7) | −0.2401(6) | 0.060(6) | |
| O-4$^{6}$ | 0.8024(3) | −0.1617(6) | −0.1265(4) | 0.038(5) | |
| O-5$^{6}$ | 0.7312(3) | 0.0749(7) | −0.3222(4) | 0.043(5) | |
| O-6$^{6}$ | 0.8716(3) | 0.0279(9) | −0.2722(5) | 0.073(6) | |
| C-1$^{7}$ | 0.5238(5) | 0.423(1) | −0.2529(6) | 0.042(6) | |
| C-2$^{7}$ | 0.4827(4) | 0.312(1) | −0.3122(6) | 0.044(6) | |
| C-3$^{7}$ | 0.5266(4) | 0.185(1) | −0.2991(6) | 0.043(6) | |
| C-4$^{7}$ | 0.5910(4) | 0.2205(9) | −0.3174(6) | 0.034(6) | |
| C-5$^{7}$ | 0.6284(5) | 0.3396(9) | −0.2626(7) | 0.045(6) | |
| C-6$^{7}$ | 0.6808(5) | 0.388(1) | −0.2984(7) | 0.050(6) | |
| O-2$^{7}$ | 0.4243(3) | 0.2854(8) | −0.2922(5) | 0.054(5) | |
| O-3$^{7}$ | 0.4910(3) | 0.0809(7) | −0.3613(4) | 0.049(5) | |
| O-4$^{7}$ | 0.6347(3) | 0.1046(6) | −0.2847(4) | 0.042(5) | |
| O-5$^{7}$ | 0.5822(3) | 0.4505(7) | −0.2733(4) | 0.049(5) | |
| O-6$^{7}$ | 0.6512(3) | 0.4318(8) | −0.3940(5) | 0.060(5) | |
| W-1 | 0.4617(3) | 0.1273(8) | 0.4494(5) | 0.061(6) | 1.00 |
| W-2 | 0.9748(4) | −0.1484(9) | −0.2358(6) | 0.085(6) | 1.00 |
| W-3A | 0.7564(7) | 0.601(1) | −0.391(1) | 0.099(7) | 0.71 |
| W-3B | 0.772(1) | 0.531(2) | −0.410(2) | 0.090(8) | 0.31 |
| W-4 | 0.9317(5) | 0.312(1) | 0.0373(7) | 0.102(7) | 1.00 |
| W-5A | 0.8873(6) | 0.502(1) | −0.2918(9) | 0.085(7) | 0.69 |
| W-5B | 0.901(2) | 0.615(3) | −0.294(3) | 0.234(8) | 0.44 |
| W-5C | 0.856(2) | 0.448(3) | −0.259(3) | 0.083(4) | 0.19 |
| W-6 | 0.8681(7) | 0.251(1) | 0.278(1) | 0.205(7) | 1.0 |
| W-7 | 0.7801(8) | 0.288(1) | −0.061(1) | 0.210(7) | 0.97 |
| W-8 | 0.763(1) | 0.283(2) | 0.111(2) | 0.269(7) | 0.71 |
| W-9 | at the position of O-1$^{EG}$A | | | | 0.33 |
| O-1$^{EG}$A | 0.6987(5) | −0.1844(8) | 0.1257(7) | 0.105(6) | 0.67 |
| C-1$^{EG}$A | 0.7487(7) | −0.087(2) | 0.149(1) | 0.088(7) | 0.67 |
| C-2$^{EG}$A | 0.751(1) | −0.011(2) | 0.067(2) | 0.219(7) | 0.67 |
| O-2$^{EG}$A | 0.6904(8) | 0.066(2) | 0.024(2) | 0.223(7) | 0.67 |
| O-1$^{EG}$B | 0.739(2) | 0.060(3) | 0.186(2) | 0.201(7) | 0.33 |

TABLE II (continued)

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ | Occ. |
|---|---|---|---|---|---|
| C-$1^{EG}$B | 0.781(2) | 0.098(3) | 0.135(2) | 0.201(8) | 0.33 |
| C-$2^{EG}$B | 0.750(2) | 0.053(3) | 0.033(2) | 0.197(8) | 0.33 |
| O-$2^{EG}$B | 0.690(2) | 0.124(3) | −0.016(2) | 0.222(8) | 0.33 |

[a] Standard deviations are given in parentheses. [b] $U_{eq}$ in Å$^2$, for $P2_1$: $U_{eq} = \frac{1}{3}\cdot[U_{22} + 1/\sin^2\beta\cdot(U_{11} + U_{33} + 2U_{13}\cos\beta)]$.

W-5 = 1.4 for βCD–glycerol, Table III) might be a refinement artefact, but might also indicate that at least two of the alternative sites can be occupied simultaneously (as is actually observed in a recent well-resolved X-ray crystal structure of $\beta CD \cdot 12H_2O$[18]).

*The guest molecules in βCD–ethylene glycol · $8H_2O$.*—In the βCD–ethylene glycol inclusion complex (Figs. 1A and 2), the βCD cavity contains one alcohol and three water molecules. The ethylene glycol molecule is found in two alternative discrete positions with occupancies of 0.67 and 0.33, respectively. These sites overlap partially; consequently, the 'major' site is well refined, whereas the 'minor' site could be determined only with limited accuracy. For both sites of the ethylene glycol molecule, the hydrogen-bond network formed by the guest molecules can be clearly described. (Figs. 4A and 4B).

In its major site (EG-A, occupancy 0.67), the ethylene glycol molecule is placed at the wider end of the βCD cavity. The O–C–C–O torsion angle is 65(2)°, i.e., in one of the two equivalent low-energy conformations ±60°. Both hydroxyl groups are oriented towards the cavity opening, and form hydrogen bonds with neighboring βCD molecules. The hydrophobic $-(CH_2)_2-$ moiety is oriented towards the cavity center (Fig. 1A, top). One hydroxyl group, O-$1^{EG}$A, forms hydrogen bonds *only* with hydroxyl groups of neighboring βCD molecules. The other hydroxyl group, O-$2^{EG}$A, forms hydrogen bonds with a neighboring βCD molecule and a water molecule that is also enclosed in the βCD cavity (Figs. 1A and 4A).

If the ethylene glycol molecule is in its major site, the three water molecules in the βCD cavity are placed at the narrow end of the cavity and form a hydrogen-bonded chain W-6 · · · W-8 · · · W-7 (Figs. 1A, 2A, and 4A). They also form several hydrogen bonds to the outside of the cavity, but only one bond with the ethylene glycol molecule.

In its minor site (EG-B, occupancy 0.33), the ethylene glycol molecule has the same conformation as in the major site [O–C–C–O torsion angle 68(4)°]. It is placed in the central part of the βCD cavity, and both hydroxyl groups form hydrogen bonds in the directions of the wider as well as the narrower cavity opening (Fig. 1A, bottom). Hydroxyl group O-$1^{EG}$ of the major site is replaced by a water molecule (W-9, occupancy 0.33), which is in hydrogen-bond distance to O-$1^{EG}$ of the minor site (Fig. 4B). The second hydroxyl group, O-$2^{EG}$B, is shifted by 0.85 Å with respect to the major position, and forms a hydrogen bond to a different water site than O-$2^{EG}$A. The three water molecules in the cavity are not

TABLE III

Fractional atomic coordinates [a], equivalent isotropic temperature factors $U_{eq}$ [b] of the nonhydrogen atoms in β-cyclodextrin–glycerol·7.6$H_2O$. Occupancies are given if $<1.0$

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ | Occ. |
|---|---|---|---|---|---|
| C-1$^1$ | 0.5492(4) | 0.5330(0) | 0.1018(5) | 0.04(1) | |
| C-2$^1$ | 0.4793(4) | 0.5092(9) | 0.0284(5) | 0.04(1) | |
| C-3$^1$ | 0.4850(3) | 0.4200(9) | −0.0515(5) | 0.03(1) | |
| C-4$^1$ | 0.5356(4) | 0.4790(8) | −0.0896(5) | 0.04(1) | |
| C-5$^1$ | 0.6030(4) | 0.5030(9) | −0.0109(6) | 0.04(1) | |
| C-6$^1$ | 0.6536(5) | 0.574(1) | −0.0432(7) | 0.07(1) | |
| O-2$^1$ | 0.4367(3) | 0.4484(7) | 0.0704(4) | 0.05(1) | |
| O-3$^1$ | 0.4211(3) | 0.4126(7) | −0.1269(4) | 0.05(1) | |
| O-4$^1$ | 0.5437(2) | 0.3829(6) | −0.1541(3) | 0.04(1) | |
| O-5$^1$ | 0.5921(3) | 0.5903(6) | 0.0587(4) | 0.05(1) | |
| O-6$^1$A | 0.6313(6) | 0.693(1) | −0.0899(7) | 0.09(1) | 0.73 |
| O-6$^1$A | 0.7126(8) | 0.605(2) | 0.030(1) | 0.06(1) | 0.27 |
| C-1$^2$ | 0.6840(4) | 0.282(1) | 0.4190(6) | 0.05(1) | |
| C-2$^2$ | 0.6064(4) | 0.269(1) | 0.3871(6) | 0.05(1) | |
| C-3$^2$ | 0.5755(4) | 0.286(1) | 0.2783(6) | 0.05(1) | |
| C-4$^2$ | 0.6044(4) | 0.410(1) | 0.2467(5) | 0.04(1) | |
| C-5$^2$ | 0.6803(4) | 0.3996(9) | 0.2796(5) | 0.04(1) | |
| C-6$^2$ | 0.7171(4) | 0.509(1) | 0.2497(7) | 0.05(1) | |
| O-2$^2$ | 0.5884(3) | 0.1472(7) | 0.4169(4) | 0.06(1) | |
| O-3$^2$ | 0.5035(3) | 0.2931(9) | 0.2504(5) | 0.07(1) | |
| O-4$^2$ | 0.5746(3) | 0.4098(6) | 0.1457(3) | 0.04(1) | |
| O-5$^2$ | 0.7050(3) | 0.3967(6) | 0.3829(4) | 0.04(1) | |
| O-6$^2$A | 0.7025(4) | 0.6395(7) | 0.2733(5) | 0.06(1) | 0.91 |
| O-6$^2$B | 0.785(1) | 0.476(4) | 0.270(4) | 0.05(1) | 0.09 |
| C-1$^3$ | 0.8579(4) | −0.1195(9) | 0.5012(6) | 0.04(1) | |
| C-2$^3$ | 0.7874(4) | −0.161(1) | 0.4965(6) | 0.05(1) | |
| C-3$^3$ | 0.7348(4) | −0.0639(9) | 0.4309(6) | 0.04(1) | |
| C-4$^3$ | 0.7548(4) | 0.0812(9) | 0.4626(5) | 0.04(1) | |
| C-5$^3$ | 0.8273(4) | 0.1136(9) | 0.4707(6) | 0.04(1) | |
| C-6$^3$ | 0.8524(4) | 0.246(1) | 0.5119(7) | 0.05(1) | |
| O-2$^3$ | 0.7732(3) | −0.2962(7) | 0.4614(5) | 0.06(1) | |
| O-3$^3$ | 0.6702(3) | −0.0877(7) | 0.4371(4) | 0.05(1) | |
| O-4$^3$ | 0.7081(3) | 0.1629(6) | 0.3900(4) | 0.04(1) | |
| O-5$^3$ | 0.8724(3) | 0.0129(6) | 0.5310(4) | 0.04(1) | |
| O-6$^3$ | 0.8460(3) | 0.2540(8) | 0.6053(5) | 0.06(1) | |
| C-1$^4$ | 0.9711(4) | −0.2805(9) | 0.2619(6) | 0.04(1) | |
| C-2$^4$ | 0.9505(4) | −0.3858(9) | 0.3179(6) | 0.04(1) | |
| C-3$^4$ | 0.8949(4) | −0.3275(9) | 0.3479(5) | 0.04(1) | |
| C-4$^4$ | 0.9183(3) | −0.1971(9) | 0.4005(5) | 0.03(1) | |
| C-5$^4$ | 0.9463(4) | −0.100(1) | 0.3461(6) | 0.04(1) | |
| C-6$^4$ | 0.9840(5) | 0.018(1) | 0.4087(7) | 0.05(1) | |
| O-2$^4$ | 0.9264(3) | −0.5056(6) | 0.2634(4) | 0.04(1) | |
| O-3$^4$ | 0.8781(3) | −0.4238(7) | 0.4069(4) | 0.05(1) | |
| O-4$^4$ | 0.8594(3) | −0.1364(6) | 0.4088(3) | 0.04(1) | |
| O-5$^4$ | 0.9950(3) | −0.1664(6) | 0.3160(4) | 0.04(1) | |
| O-6$^4$ | 1.0023(4) | 0.1155(8) | 0.3573(6) | 0.09(1) | |

TABLE III (continued)

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ | Occ. |
|---|---|---|---|---|---|
| C-1$^5$ | 0.8628(4) | −0.239(1) | −0.1101(6) | 0.04(1) | |
| C-2$^5$ | 0.8565(4) | −0.3709(9) | −0.0669(5) | 0.04(1) | |
| C-3$^5$ | 0.8564(4) | −0.3522(9) | 0.0316(5) | 0.04(1) | |
| C-4$^5$ | 0.9164(4) | −0.2714(9) | 0.0885(5) | 0.04(1) | |
| C-5$^5$ | 0.9164(4) | −0.1357(9) | 0.0412(5) | 0.04(1) | |
| C-6$^5$ | 0.9770(5) | −0.048(1) | 0.0927(7) | 0.06(1) | |
| O-2$^5$ | 0.7998(3) | −0.4447(6) | −0.1251(4) | 0.05(1) | |
| O-3$^5$ | 0.8552(3) | −0.4804(7) | 0.0737(4) | 0.05(1) | |
| O-4$^5$ | 0.9132(2) | −0.2486(6) | 0.1803(3) | 0.04(1) | |
| O-5$^5$ | 0.9176(3) | −0.1650(7) | −0.0514(4) | 0.05(1) | |
| O-6$^5$ | 1.0386(3) | −0.1193(9) | 0.1202(5) | 0.07(1) | |
| C-1$^6$ | 0.6619(4) | 0.0428(9) | −0.3477(5) | 0.04(1) | |
| C-2$^6$ | 0.6518(4) | −0.1081(9) | −0.3454(6) | 0.04(1) | |
| C-3$^6$ | 0.6915(4) | −0.1581(8) | −0.2447(6) | 0.04(1) | |
| C-4$^6$ | 0.7645(4) | −0.1210(9) | −0.2208(5) | 0.03(1) | |
| C-5$^6$ | 0.7712(4) | 0.0319(9) | −0.2260(6) | 0.04(1) | |
| C-6$^6$ | 0.8414(4) | 0.085(1) | −0.2088(6) | 0.05(1) | |
| O-2$^6$ | 0.5809(3) | −0.1358(7) | −0.3718(4) | 0.05(1) | |
| O-3$^6$ | 0.6851(3) | −0.3021(6) | −0.2404(5) | 0.05(1) | |
| O-4$^6$ | 0.8009(3) | −0.1658(6) | −0.1265(3) | 0.04(1) | |
| O-5$^6$ | 0.7303(2) | 0.0739(6) | −0.3220(3) | 0.04(1) | |
| O-6$^6$ | 0.8701(3) | 0.0268(8) | −0.2711(5) | 0.07(1) | |
| C-1$^7$ | 0.5259(4) | 0.4231(9) | −0.2501(5) | 0.04(1) | |
| C-2$^7$ | 0.4846(4) | 0.3102(9) | −0.3122(6) | 0.04(1) | |
| C-3$^7$ | 0.5270(4) | 0.1842(8) | −0.2976(6) | 0.04(1) | |
| C-4$^7$ | 0.5910(4) | 0.2164(8) | −0.3164(5) | 0.03(1) | |
| C-5$^7$ | 0.6282(4) | 0.3386(8) | −0.2614(6) | 0.04(1) | |
| C-6$^7$ | 0.6820(4) | 0.3874(9) | −0.2958(6) | 0.05(1) | |
| O-2$^7$ | 0.4253(3) | 0.2846(7) | −0.2895(4) | 0.05(1) | |
| O-3$^7$ | 0.4900(3) | 0.0810(6) | −0.3602(4) | 0.05(1) | |
| O-4$^7$ | 0.6336(3) | 0.1017(5) | −0.2849(3) | 0.03(1) | |
| O-5$^7$ | 0.5839(3) | 0.4500(6) | −0.2710(4) | 0.04(1) | |
| O-6$^7$ | 0.6522(3) | 0.4301(7) | −0.3928(4) | 0.06(1) | |
| OW1 | 0.4646(3) | 0.1235(7) | 0.4490(4) | 0.06(1) | 1.0 |
| OW2 | 0.9725(3) | −0.1511(8) | −0.2335(5) | 0.08(1) | 1.0 |
| OW3A | 0.7582(8) | 0.595(2) | −0.388(1) | 0.08(1) | 0.54 |
| OW3B | 0.778(1) | 0.518(2) | −0.404(1) | 0.10(1) | 0.49 |
| OW3C | 0.658(2) | 0.623(5) | −0.507(3) | 0.12(1) | 0.18 |
| OW4 | 0.9332(4) | 0.3080(9) | 0.0361(6) | 0.09(1) | 1.0 |
| OW5A | 0.8874(8) | 0.495(2) | −0.291(1) | 0.10(1) | 0.59 |
| OW5B | 0.9044(9) | 0.592(2) | −0.278(2) | 0.16(1) | 0.62 |
| OW5C | 0.851(2) | 0.434(4) | −0.259(2) | 0.08(1) | 0.22 |
| OW6 | 0.8774(6) | 0.245(1) | 0.2944(9) | 0.15(1) | 1.0 |
| OW7 | 0.7675(6) | 0.283(1) | −0.043(1) | 0.19(1) | 1.0 |
| O-1$^{GA}$ | 0.7085(8) | −0.172(2) | 0.153(1) | 0.10(1) | 0.62 |
| O-2$^{GA}$ | 0.8110(8) | 0.112(2) | 0.125(2) | 0.18(1) | 0.62 |
| O-3$^{GA}$ | 0.6755(8) | 0.124(2) | −0.007(1) | 0.15(1) | 0.62 |
| C-1$^{GA}$ | 0.753(1) | −0.100(2) | 0.120(2) | 0.23(1) | 0.62 |
| C-2$^{GA}$ | 0.7572(8) | 0.049(1) | 0.144(1) | 0.17(1) | 0.62 |
| C-3$^{GA}$ | 0.6906(8) | 0.121(2) | 0.092(2) | 0.17(1) | 0.62 |

TABLE III (continued)

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ | Occ. |
|---|---|---|---|---|---|
| O-$1^{GB}$ | 0.780(2) | 0.158(2) | 0.152(3) | 0.26(1) | 0.38 |
| O-$2^{GB}$ | 0.6957(9) | −0.168(2) | 0.117(1) | 0.05(1) | 0.38 |
| O-$3^{GB}$ | 0.689(2) | 0.067(3) | −0.017(2) | 0.19(1) | 0.38 |
| C-$1^{GB}$ | 0.748(2) | 0.048(3) | 0.180(2) | 0.18(1) | 0.38 |
| C-$2^{GB}$ | 0.746(1) | −0.076(2) | 0.119(1) | 0.10(1) | 0.38 |
| C-$3^{GB}$ | 0.740(1) | −0.029(2) | 0.021(2) | 0.12(1) | 0.38 |

[a] Standard deviations are given in parentheses. [b] $U_{eq}$ in Å$^2$, for $P2_1$: $U_{eq} = \frac{1}{3} \cdot [U_{22} + 1/\sin^2\beta \cdot (U_{11} + U_{33} + 2U_{13}\cos\beta)]$.

arranged in a chain, but isolated from each other: W-6 and W-7 are (roughly) in the same places as before (total occupancy 1.0), but the site W-8 is not occupied due to spatial interference with the ethylene glycol minor site (the W-8 ··· C-$1^{EG}$B distance would be 1.91 Å).

As the guest molecules form a hydrogen-bonded cluster in which all molecules are in some way associated with each other, it is expected that the disorder of the ethylene glycol molecule also leads to some disorder of the fully occupied water sites W-6 and W-7. This is actually indicated by an irregular electron-density distribution of W-7. With the present resolution, however, this presumed disorder could not be resolved.

It is remarkable that *all* oxygen atoms of the guest molecules are in positions that are equivalent to those occupied by water molecules in $\beta$CD · $12H_2O$[5], and form similar hydrogen-bond patterns: W-6 is at the position of W-14 ($\beta$CD · $12H_2O$), W-7 is in a similar position as W-10 ($\beta$CD · $12H_2O$), and W-8 is close to the position of W-12 ($\beta$CD · $12H_2O$). As the ethylene glycol molecule has a conformation with an intramolecular O ··· O distance ~ 2.9 Å in both sites, its hydroxyl groups can directly substitute for two water molecules that are in hydrogen-bonding contact: in the major site, O-$1^{EG}$A is exactly in the place of W-4 ($\beta$CD · $12H_2O$), and O-$2^{EG}$A is in a similar place as W-6 ($\beta$CD · $12H_2O$). In the minor site, O-$1^{EG}$B is close to the place of W-8 ($\beta$CD · $12H_2O$), and O-$2^{EG}$B is close to W-6 ($\beta$CD · $12H_2O$). The close relation of the hydrogen-bond pattern with that in $\beta$CD · $12H_2O$ (and also in $\beta$CD–glycerol, see below, and $\beta$CD–ethanol octahydrate[4]) shows that variation of guest molecules may result in only small variations of the hydrogen-bond configuration if the functional O–H groups can be placed in equivalent positions.

In CD inclusion complexes, hydrophilic guest molecules may or may not form O–H ··· O hydrogen bonds with the CD host. In $\beta$CD–ethylene glycol · $8H_2O$, W-6 is in hydrogen-bond distance with two primary hydroxyl groups (O-$6^2$B and O-$6^4$) of the $\beta$CD host (Fig. 2). The shortest contact to an O-4 atom of the cavity wall is O-$1^{EG}$B ··· O-$4^3$, 3.59 Å, a distance that can only with difficulty be interpreted as a hydrogen bond.

*Displacement parameters of the guest molecules in $\beta$CD–ethylene glycol octahydrate.*—The guest molecules have very high displacement parameters: for the

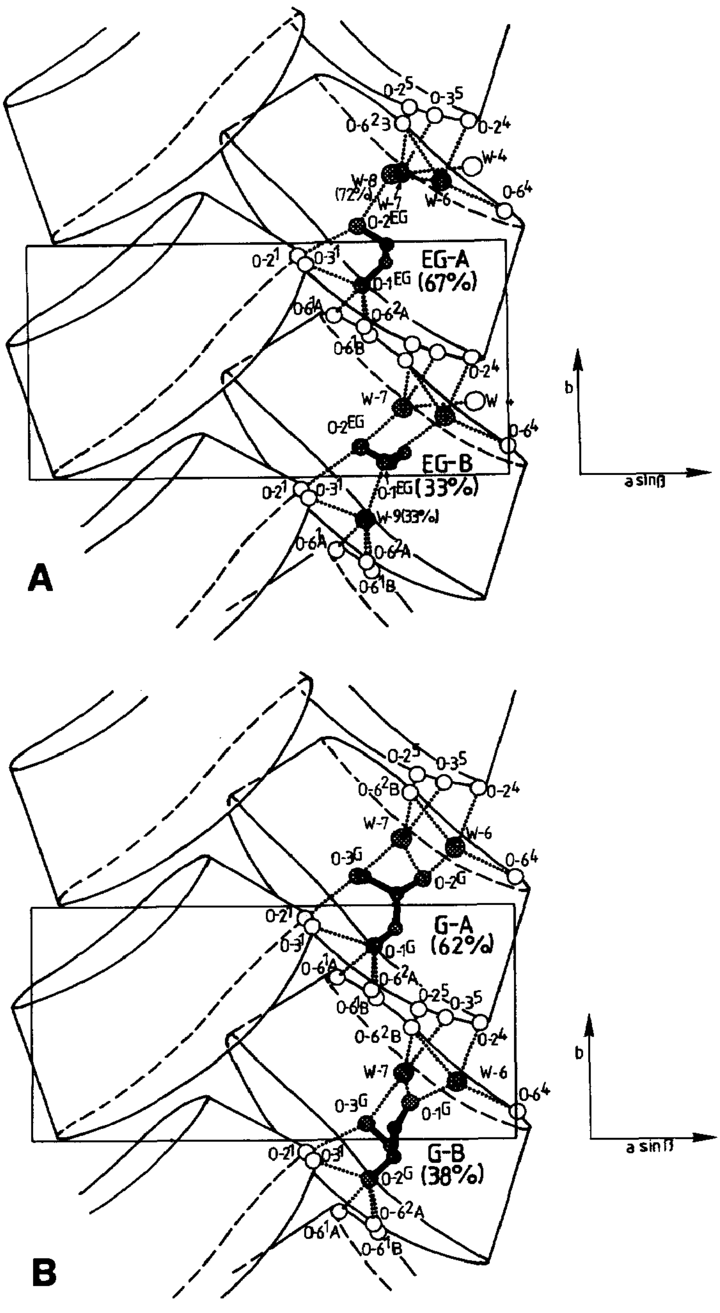

Fig. 1. Crystal packing arrangement of the title compounds, and hydrogen-bond network of the guest molecules enclosed in the $\beta$CD cavities; $\beta$CD molecules are drawn schematically. Molecules enclosed in the $\beta$CD cavities are shaded, occupancies are given in parentheses. Projection is along the *c*-axis. **A**, $\beta$CD–ethylene glycol·$8H_2O$; the ethylene glycol major site is drawn in the top cavity, the minor site is drawn in the bottom cavity. **B**, $\beta$CD–glycerol·$7.2H_2O$; the glycerol major site is drawn in the top cavity, the minor site is drawn in the bottom cavity.

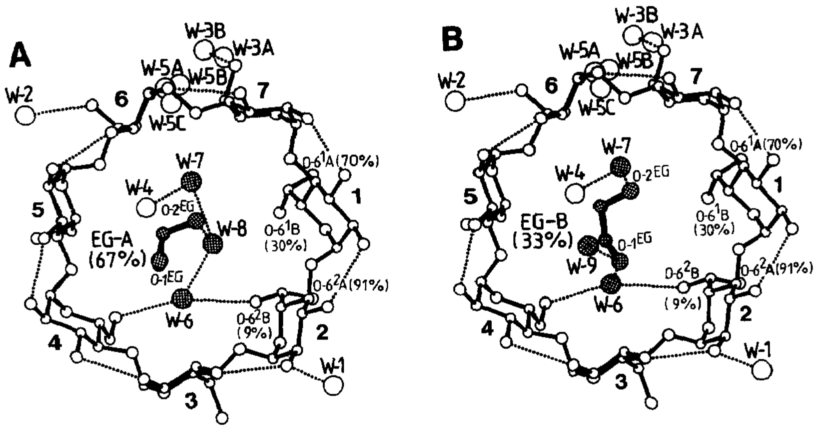

Fig. 2. One crystal asymmetric unit of βCD–ethylene glycol·$8H_2O$ in projection along the βCD molecular axis. Shaded molecules are included in the βCD cavities; occupancies are given in parentheses; water molecule W-4 is placed 'below' the O-6 rim outside the βCD cavity. Dotted lines: O···O contacts < 3.2 Å suggestive of hydrogen bonds. A, Configuration of ethylene glycol major site. B, Configuration of ethylene glycol minor site.

ethylene glycol molecule, the mean $U_{eq}$ is 0.16 and 0.21 Å$^2$ for the major and minor site, respectively; for the enclosed water molecules W-6, W-7, W-8, it is 0.17 Å$^2$ (compared to 0.063 for βCD hydroxyl groups and 0.11 for the interstitial water molecules). Similar mean temperature factors for host and disordered guest molecules were earlier observed in the isomorphous βCD hydrate and βCD–

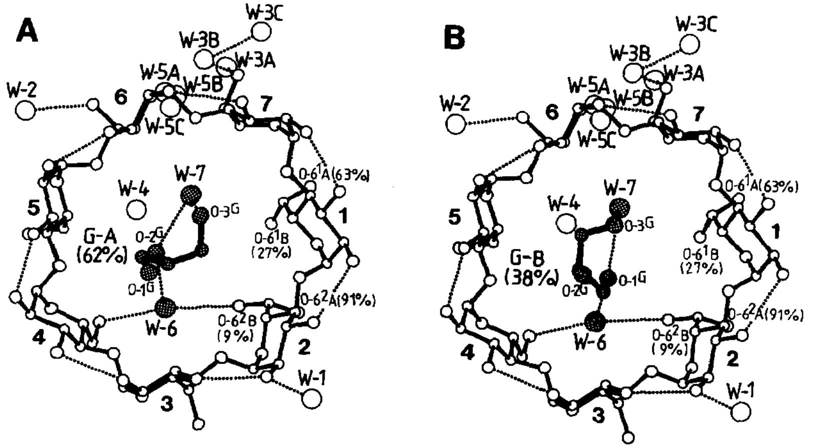

Fig. 3. One crystal asymmetric unit of βCD–glycerol·$7.2H_2O$, symbols as Fig. 2. A, Configuration of glycerol major site. B, Configuration of glycerol minor site. Note that both glycerol sites have the same global configuration, and are rotated by ~180° with respect to each other. Torsion angles of the glycerol molecule: major site [minor site] O-$1^G$–C-$1^G$–C-$2^G$–O-$2^G$ = 169(2)° [−157(3)°], O-$1^G$–C-$1^G$–C-$2^G$–C-$3^G$ = −67(2)° [−32(3)°], O-$2^G$–C-$2^G$–C-$3^G$–O-$3^G$ = 58(2)° [78(3)°], C-$1^G$–C-$2^G$–C-$3^G$–O-$3^G$ = −67(2)° [−48(3)°].

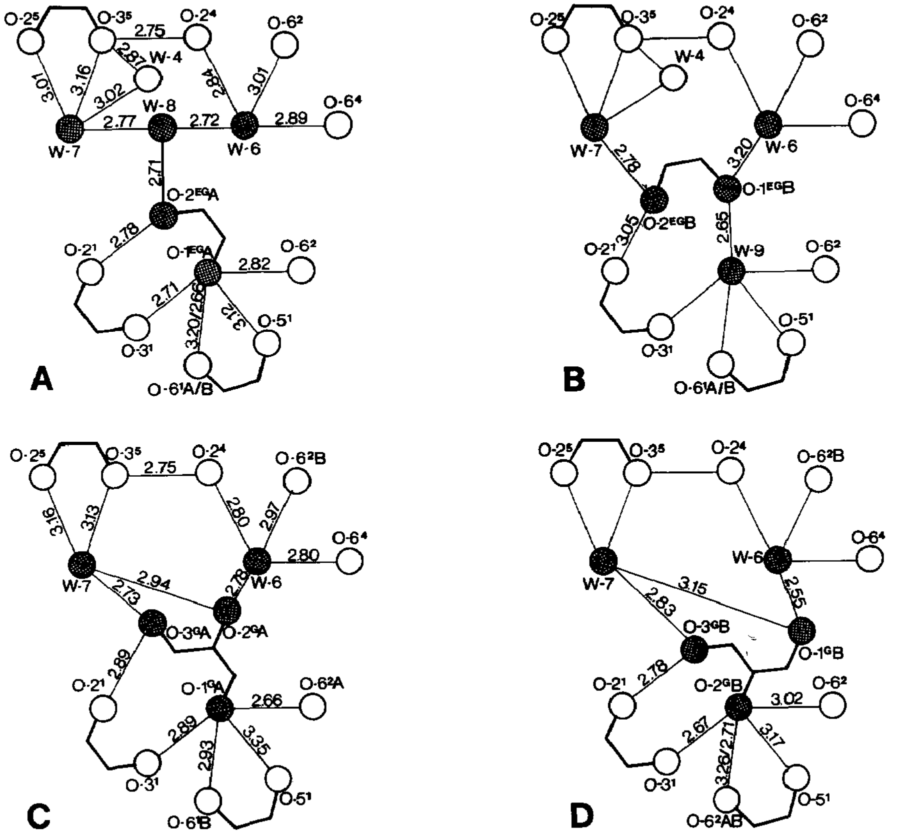

Fig. 4. Schematic representation of the hydrogen bonding within and around the clusters of guest molecules; shaded molecules are included in the $\beta$CD cavities. Shown are O ··· O distances < 3.2 Å. **A**, $\beta$CD–ethylene glycol·$8H_2O$, ethylene glycol major site; **B**, $\beta$CD–ethylene glycol·$8H_2O$, ethylene glycol minor site; **C**, $\beta$CD–glycerol·$7.2H_2O$, glyercol major site; **D**, $\beta$CD–glycerol·$7.2H_2O$, glyercol minor site.

ethanol·$8H_2O$[11]. The parallel behaviour of both the positional disorder and the displacement parameters suggests that the dynamic properties of the guest molecule disorder are also comparable, i.e., that the enclosed molecules frequently rearrange by jumping between their alternative sites[10].

*The guest molecules in $\beta$CD–glycerol·$7.2H_2O$.*—Two alternative discrete sites are observed for the glycerol molecule (occupancies 0.62 and 0.38, respectively) (Figs. 1B and 3). Whereas the major site is well refined, the minor site is even less accurately determined (due to overlap with the major site) than for the ethylene glycol molecule discussed above. For both sites, surprisingly similar hydrogen-bond patterns are formed (Figs. 4C and 4D).

In the major site, the glycerol molecule adopts an almost ideal low-energy conformation with all torsion angles around 180° or ±60° (tabulated in legend to

Fig. 3). It is oriented in such a way that two hydroxyl groups, O-1$^G$A and O-3$^G$A, are placed at the wider end, and the third one, O-2$^G$, in the central part of the $\beta$CD cavity (Fig. 1B, top). O-1$^G$ and O-3$^G$ are in positions very similar to those of the two hydroxyl groups O-1$^{EG}$A and O-2$^{EG}$A in the $\beta$CD–ethylene glycol complex (and water molecules W-4 and W-6 in $\beta$CD $\cdot$ 12$H_2O$[5]), and form an equivalent hydrogen-bond network (Figs. 1 and 4). The geometry of O-1$^G$A/O-3$^G$A, however, is not identical to O-1$^{EG}$A/O-2$^{EG}$A, as the oxygen atoms are separated by four covalent bonds compared to three for O-1$^{EG}$/O-2$^{EG}$, and consequently have a larger O $\cdots$ O distance. The hydroxyl group O-2$^G$ does not have a direct equivalent in $\beta$CD–ethylene glycol $\cdot$ 8$H_2O$ or in $\beta$CD $\cdot$ 12$H_2O$.

In its minor site, the glycerol molecule is in a similar conformation as in the major site, but rotated by ~ 180° (Fig. 3). The torsion angles deviate from the ideal low-energy values (legend to Fig. 3), but this is presumably due to the poor

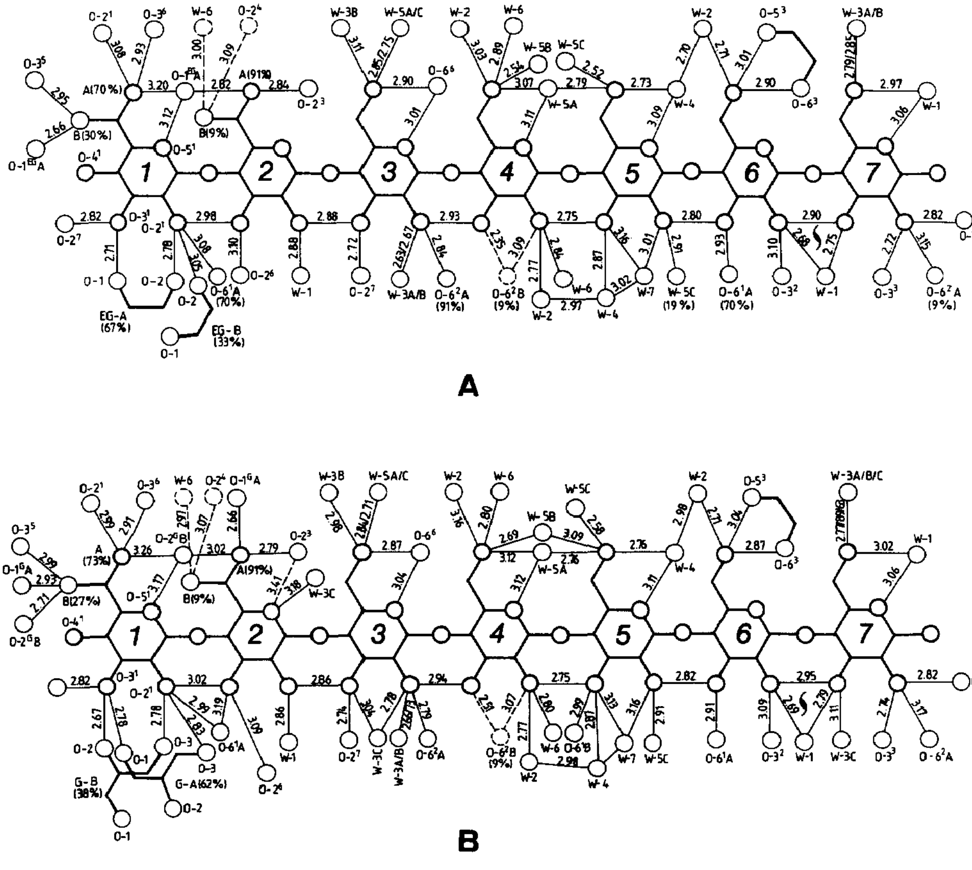

Fig. 5. Schematic representation of the hydrogen bonding around the $\beta$CD molecules: **A**, $\beta$CD–ethylene glycol$\cdot$8$H_2O$; and **B**, $\beta$CD–glycerol$\cdot$7.2$H_2O$. Symbols as in Fig. 4. For simultaneous contacts[4] to O-5 and O-6, all distances < 3.5 Å are shown.

refinement. The most significant difference between the two sites is the position of C-$3^G$ (Fig. 3), whereas the hydroxyl groups are in similar positions and are engaged in a functionally identical hydrogen-bond network (Figs. 4C and 4D) (the separations between the O positions are: O-$1^G$A $\cdots$ O-$2^G$B ~ 0.5 Å, O-$2^G$A $\cdots$ O-$1^G$B ~ 1.0 Å, O-$3^G$A $\cdots$ O-$3^G$B ~ 0.7 Å).

Two water molecules are included in the $\beta$CD cavity, W-6 and W-7. They are in similar positions as W-6 and W-7 in $\beta$CD–ethylene glycol $\cdot$ $8H_2O$, and are engaged in a similar hydrogen-bond network (Fig. 4). These water molecules have no direct hydrogen-bond contact to each other, but are bridged by the glycerol hydroxyl group O-$2^G$A (or O-$1^G$B). We expect that the disorder of the glycerol molecule leads to some disorder of these water molecules, which cannot be resolved at the given resolution.

No hydrogen bonds of guest molecules with O-4 atoms of the cavity wall are observed. As in $\beta$CD–ethylene glycol $\cdot$ $8H_2O$, the displacement parameters of the guest molecules are larger by a factor of ~ 3 than those of the host: mean $U_{eq}$ ~ 0.17 for the major and the minor sites of the glycerol molecule, and for the water sites W-6 and W-7, compared to 0.06 for the $\beta$CD hydroxyl groups and 0.09 for the interstitial water molecules.

*The hydrogen-bond network.*—The hydrogen-bond network around the clusters of guest molecules, and around the $\beta$CD molecule, is schematically shown in Figs. 4 and 5 in the same way as in previous reports[4,9]. As expected, the hydrogen-bond

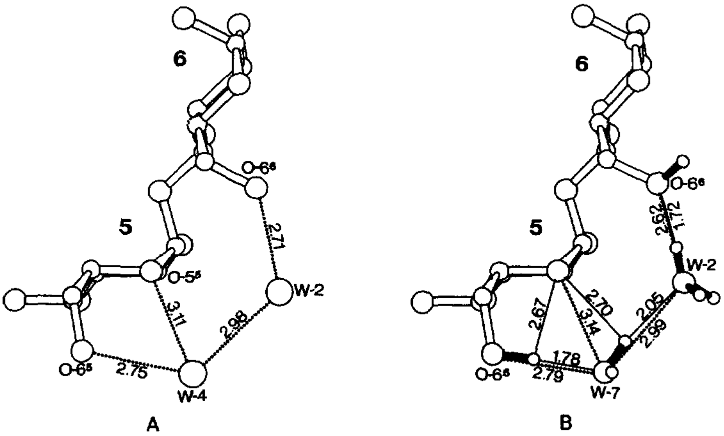

Fig. 6. Typical example of three-centre hydrogen bonding: A, the water bridge O-$6^5$ $\cdots$ W-4 $\cdots$ W-2 $\cdots$ O-$6^6$ in $\beta$CD–glycerol $\cdot$ $7.2H_2O$. W-4 is in short contact with O-$6^5$ *and* O-$5^5$, which is suggestive of a three-centre hydrogen bond[4]; **B**, in the isomorphous complex $\beta$CD–ethanol $\cdot$ $8H_2O$[4], an equivalent arrangement with very similar O $\cdots$ O separations is observed: O-$6^5$ donates a three-centre bond to W-7 and O-$5^5$, and W-7 donates a three-centre bond to W-2 and O-$5^5$ (one H atom of W-2 is two-fold disordered). Due to the similarity of the O $\cdots$ O distances, a related system of three-centre bonds is probable in both title compounds (Figs. 6A and 6B); only the *orientation* of the hydrogen-bond chain may be reversed (or disordered).

schemes are very similar in the isomorphous complexes; in some details, however, variations are observed. The similarity of the hydrogen-bond arrangement within the βCD cavity is remarkable.

*Three-center hydrogen bonds.*—A typical feature of hydrogen bonding in cyclodextrins[4] (and carbohydrates in general) is three-center hydrogen bonding, i.e., an interaction of an O–H donor with *two* acceptor atoms[19]. Proper description of such arrangements requires the experimentally determined H positions, which are not available for the present X-ray structures. In special cases, however, they can also be identified from the O positions[4]. Examples are the numerous chelated arrangements, where a water or hydroxyl O atom *simultaneously* has short contacts < 3.5 Å with O-6 and O-5 of a glucose residue (Figs. 6A and 6B). In most cases, these arrangements represent three-center hydrogen bonds[4]; the *orientation* of these bonds, however, cannot be specified if the H atom is not located.

Several examples of three-center hydrogen bonds in CD-complexes have been shown previously[4,9]. As a representative example of the present structures, the hydrogen-bond geometry of the water bridge between the primary hydroxyl groups O-$6^5$ and O-$6^6$ in βCD–glycerol · $7.2H_2O$ is shown in Fig. 6A (hydrogen-bond chain O-$6^5$ ··· W-4 ··· W-2 ··· O-$6^6$). For comparison, the neutron-determined hydrogen-bond network in the isomorphous complex βCD–ethanol · $8H_2O$ is shown in Fig. 6B (the location of these interstitial water molecules is conserved in all isomorphous structures).

## SUMMARY AND DISCUSSION

X-ray crystal structures were determined for the crystalline complexes of βCD with ethylene glycol · $8H_2O$ and glycerol · $7.2H_2O$. For both compounds, the arrangement and conformation of the βCD molecules and the positions of the 5 interstitial water molecules (per βCD) are as in βCD · $12H_2O$[5].

In βCD–ethylene glycol · $8H_2O$, one ethylene glycol molecule and three water molecules are included in the βCD cavity. These molecules show positional disorder over several discrete, partially occupied sites: for the alcohol molecule, two sites (occupancies 0.67 and 0.33), and for the water molecules, four sites (occupancies 1.0, 1.0, 0.72 and 0.33) are located. Both sites of the ethylene glycol molecule exclude the population of one water site each.

The ethylene glycol molecule in both sites has a low-energy conformation with the torsion angle O–C–C–O close to 60° and an O ··· O separation of ~ 2.9 Å. Geometrically, the two hydroxyl groups can substitute for two water molecules that are in hydrogen-bonding distance. Actually, for both sites, the hydroxyl groups are found in positions similar to those of water molecules in the complex βCD · $12H_2O$.

In βCD–glycerol · $7.2H_2O$, one glycerol and two water molecules are included in the βCD cavity. The glycerol molecule is disordered over two discrete sites (occupancies 0.62 and 0.38), which both have the same position in the βCD cavity, but are rotated by ~ 180° with respect to each other. Both water sites are fully occupied. For both orientations of the glycerol molecule, a functionally identical system of hydrogen bonds is formed. The glycerol molecule is in a low-energy conformation in both sites.

In the complex βCD–ethylene glycol · $8H_2O$, *all* oxygen sites (ordered as well as disordered) are in positions occupied by water molecules in βCD · $12H_2O$. This completely parallels the situation in βCD–ethanol · $8H_2O$[4], where all O atoms in the βCD cavity are also found in positions that are occupied by water molecules in βCD · $12H_2O$. In the complex βCD–glycerol · $7.2H_2O$, one glycerol hydroxyl group (O-$2^G$A or O-$1^G$B) has no structural equivalent in βCD · $12H_2O$.

In both title compounds, and for all sites of the disordered alcohol molecules, all the guest molecules are interconnected by hydrogen bonds. This is not a necessity: in βCD–ethanol · $8H_2O$ (one ethanol and three water molecules in the βCD cavity; ethanol disordered over two discrete sites), the ethanol molecule in its major site forms *no* hydrogen bonds with water molecules, and one of the enclosed three water molecules is isolated from the other two.

The clusters of guest molecules form very similar hydrogen bonds to O-$6^2$ and O-$6^4$ of the cavity and with neighboring molecules. The only major difference between the compounds is that water molecule W-7 forms a hydrogen bond to the interstitial water molecule W-4 in βCD–ethylene glycol · $8H_2O$, but not in βCD–glycerol · $7.2H_2O$.

The global features of the hydrogen-bond network are as in the isomorphous complexes βCD · $12H_2O$ and βCD–ethanol · $8H_2O$[4] (e.g., 'chelated' arrangements at O-5/O-6 of numerous glucose residues that represent three-center hydrogen bonds, and water bridges between O-6 atoms of adjacent glucose residues; Fig. 6).

In both compounds (and for all alternative sites), the guest molecules display average displacement factors that are larger by a factor of 1.5 compared to interstitial water molecules, and by a factor of 3 compared to the βCD hydroxyl groups.

The structural situation of the guest molecules is comparable to that found in the complexes βCD · $12H_2O$ and βCD–ethanol · $8H_2O$: the molecules are disordered over partially occupied discrete sites, they form hydrogen-bond networks in each alternative position, and they exhibit large displacement parameters. This suggests (though not rigorously proves) that the dynamic properties are also similar, i.e., that the disorder is not static, but dynamic, and associated with jumps between the different alternative site. The *time scale* on which this disorder occurs, however, i.e., the frequency of the reorientation jumps, may be very different for different compounds. It is on a $10^{-11}$-s scale in βCD · $12H_2O$[10,20] and presumably slower in βCD–ethanol · $8H_2O$[11]. It is expected that molecules become less mobile with increasing size, and with increasing numbers of hydrogen bonds in which they are involved.

The essential conclusion is that the general behaviour of the guest molecules is similar for all inclusion complexes of βCD with small hydrophilic molecules studied so far. If the complexed molecule is too small to fill the cavity, several water molecules are also included, thereby forming a cluster of hydrogen-bonded guest molecules. This cluster is dynamically disordered: the molecules are mobile, and perform jumps between different alternative (*but discrete*) sites. In solution, such rearrangements certainly occur in an even more pronounced way than in the crystalline solid state.

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