-Cyclodextrin: Hydration Properties and Hydrogen Bonding

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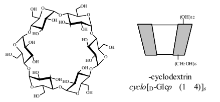
Molecular Dynamics of -Cyclodextrin in Water

Introduction

The torus-like shape of cyclodextrins (CDs) allows for the formation of inclusion complexes with a large variety of small organic guest molecules on the basis of hydrophobic interactions[1].



-cyclodextrin
cyclo[D-Glc*p* (1 4)]$_6$

In extension of our studies on the hydrophobic characteristics of CDs[2], their inclusion complexes[3], and various non-glucose cyclooligosaccharides[4], we have analyzed the hydration properties of -CD in aqueous solution by means of molecular dynamics (MD) simulations with explicit incorporation of the solvent[5].

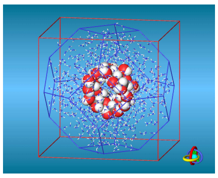


Fig. 1. MD simulation box of -CD in aqueous solution (periodic boundary conditions of the truncated octahedron; boxsize 32 Å including 609 water molecules, CHARMM[6] force-field[7]).

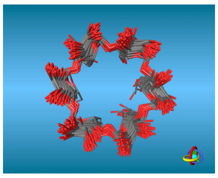


Fig. 2. Superimposition of 60 -CD snapshot geometries taken in 10 ps intervals from a 600 ps MD simulation (hydrogen atoms and water molecules left off for clarity).

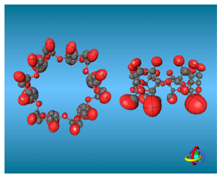


Fig. 3. Mean geometry and anisotropic thermal ellipsoids of -CD (least-squares 3D-fitting of 11939 MD configurations); on the left, the 2/3-OH groups face the viewer, whereas the right model is rotated by 90° around a horizontal axis.

Hydration and Hydrogen-Bonding of -Cyclodextrin

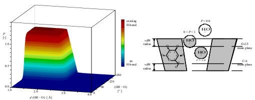


Fig. 4. Definition of the 2D-Fermi-Dirac type hydrogen bonding "*quality*" function (left) and cavity dimensions (right) used to analyze the MD simulations of -CD. H-Bonds persist for hydrogen ··· acceptor distances (OH ··· O) < 2.4 Å and O-H ··· O-angles > 100°. The mean-planes of the 2/3-oxygens and C-6 atoms, and the corresponding vdW-radii were used to define the "*upper*" and "*lower*" limiting boundaries of the CD cavity, water molecules were counted according to their volume fraction located inside cavity.

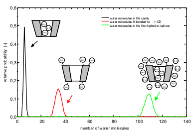


Fig. 5. Probability distributions for the number of water molecules inside the cavity (black), hydrogen bonded to -CD (red), and within the first hydration sphere (green).

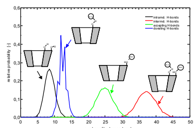
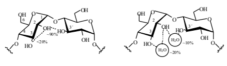


Fig. 6. MD derived distributions of the number of intra- (black) and intermolecular hydrogen bonds for -CD (blue: CD as donor, green: CD as acceptor, red: total).

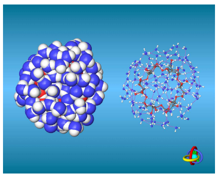
Table 1. Summary of the hydration parameters of -CD as derived from the MD simulations in aqueous solution.

hydration properties	-cyclodextrin
number of water molecules	
first hydration sphere	105 - 115
hydrogen bonded	34.2 ± 2.5
in the cavity	6.2 ± 0.7
intramolecular H-bonds	8.7 ± 1.5
intermolecular H-bonds	
total solute-solvent	37.3 ± 2.8
solute-O ··· H-OH	24.9 ± 2.4
solute-O-H ··· OH_2	12.4 ± 1.1

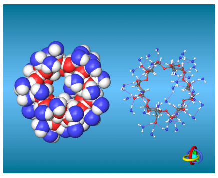


Typical hydrogen-bonding patterns of high significance

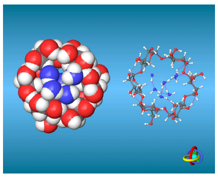
First hydration sphere



Hydrogen-bonded water



Cavity water



Diffusion trajectories of water

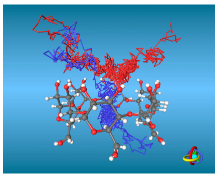
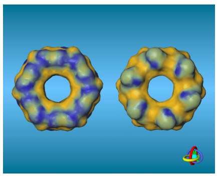
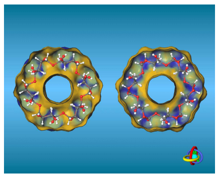


Fig. 7. Typical MD snapshot configurations for the first hydration shell of -CD (top left), the water molecules hydrogen bonded (top right), and the water inside of the cavity of the solute (lower left). In each case, a space-filling CPK-type model as well as a ball-and-stick model are shown; water molecules are colored blue, thin pink lines indicate hydrogen-bonds. The lower right picture displays partial diffusion trajectories (time series of water oxygen atomic positions taken in 0.2 ps intervals) of two individual water molecules, superimposed to an averaged mean-geometry of -CD: the blue trajectory corresponds to a water molecule entering the CD cavity from the (upper) 2/3-OH side and leaving at the opposite (bottom) torus rim (6-CH_2OH side, approx. 120 ps in total), the red path visualizes a water dipping into the cavity only (approx. 180 ps).

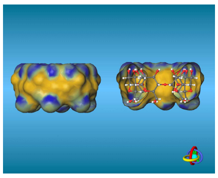
Solute-solvent hydrogen-bonding probabilities



2/3-OH side **6-CH_2OH side**



2/3-OH side **6-CH_2OH side**



method of mapping hydrogen bonding vectors onto the solute surface:

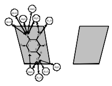


Table 2. Average number of intermolecular (solute-solvent) hydrogen bonds formed by each -CD solute oxygen atom (values are symmetry averaged, root-mean-square deviations in parenthesis).

H-bond donor/acceptor (solute oxygens)	total (solute-O ··· OH_2)	accepting (solute-O ··· HOH)	donating (solute-OH ··· OH_2)
O-1	0.03(16)	0.03(16)	-
O-2	1.70(66)	1.12(72)	0.58(51)
O-3	1.62(65)	1.11(67)	0.58(51)
O-5	0.28(43)	0.28(43)	-
O-6	2.59(60)	1.61(55)	0.98(22)

Fig. 8. Color-coded mapping of the intermolecular solute-solvent (-CD ··· H_2O) hydrogen-bond vectors onto the solvent-accessible (contact) surface of the -CD mean-geometry: the mapped surface quality correlates to the probability density of hydrogen-bond vectors (cf. bottom right schematic plot), with blue/green colors corresponding to intense H-bond interactions, whereas yellow colors indicate the absence of solute-solvent H-bonds. The top two pictures show the -CD macrocycle from the 2/3-OH and 6-CH_2OH side each, with the surface in closed and bisected form (ball-and-stick model inserted), respectively. The lower left picture provides an side-view on the -CD torus (2/3-OH groups pointing upward, 6-CH_2OH groups downward). Due to the absence of H-bond donors and acceptors inside the cavity of -CD, water molecules trapped in the cavity are not able to form H-bonds with the solute. This "*hydrophobic*" character of the central cavity enables cyclodextrins to form inclusion complexes with a large variety of guest molecules. In Table 2 (bottom right), the average numbers of H-bonds formed per -CD oxygen (total number and -CD as donor or acceptor) are summarized.

Pair Distribution Functions, Water Densities, and Solvent Structuring

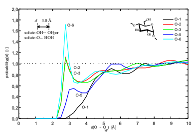
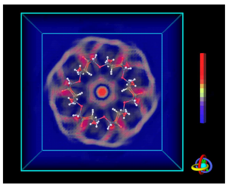


Fig. 9. MD derived radial pair distribution functions[8] of water oxygen atoms around -CD, i.e. the spherically averaged probability to find a water molecule around the pyranose oxygens (distributions are symmetry averaged). The sharp peaks at around 3.0 Å (hydrogen-bonding distance between solute and solvent) indicate a well defined first hydration shell around the 2-, 3-, and 6-OH groups, whereas the O-1 and O-5 oxygen atoms are less hydrated. Small fluctuations of the pair distribution functions at larger distances (4.5 - 6.0 Å) indicate a weak second hydration sphere; at distances > 6.0 Å the relative water densities reach the standard value of 1.0 for the bulk phase.



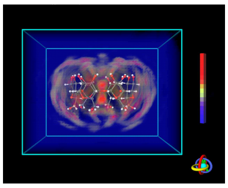


Fig. 10. Front- (left) and side-views (right) of the three-dimensional water probability densities around -CD; opaque red to orange-yellow colors indicate increased water densities around the solute in relation to the bulk phase water (transparent blue colors). The contours were obtained from 3D-fitting and superimposition of all MD snapshot geometries of -CD (incl. solvent; a total of 11939 configurations were used), and analyzing the relative water densities on an orthogonal grid (bulk water density = 1.0). The orange-red spatial regions correlate with the well-defined first hydration shell of -CD around the 2-, 3-, and 6-OH groups (compare to Fig. 9). The center red spots correspond to trapped water molecules of decreased mobility inside the cavity.

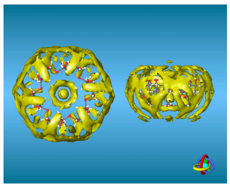


Fig. 11. 3D-Water densities displayed as solid iso-contour surfaces; the contour level encloses spatial regions of increased water density of about 20% above the bulk phase average. The modes of viewing correspond to Fig. 9.

References

[1] See for example: W. Saenger: Cyclodextrin inclusion compounds in research and industry. *Angew. Chem.* **1980**, *92*, 343-361; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344-362. (b) W. Saenger: Structural aspects of cyclodextrins and their inclusion complexes. In: Inclusion Compounds (J.L. Atwood, J.E.D. Davies, and D.D. MacNicol, Eds.), Acad. Press, London, Vol. 2, **1984**, pp. 231-259. (c) R.J. Clarke, J.H. Coates, and S.F. Lincoln: Inclusion complexes of the cyclodextrins. *Adv. Carbohydr. Chem. Biochem.* **1988**, *46*, 205-249. (d) G. Wenz: Cyclodextrins as building blocks for supramolecular structures and functional units. *Angew. Chem.* **1994**, *106*, 851-870; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803-822.

[2] F.W. Lichtenthaler and S. Immel: On the hydrophobic characteristics of CDs: computer-aided visualization of molecular lipophilicity patterns. *Liebigs Ann. Chem.* **1996**, 27-37.

[3] F.W. Lichtenthaler and S. Immel: Towards understanding formation and stability of cyclodextrin inclusion complexes: the lipophilicity patterns of some typical examples. *Starch/Stärke* **1996**, *48*, 145-154.

[4] (a) F.W. Lichtenthaler and S. Immel: Cyclodextrins, cyclomannins, and cyclogalactins with five and six (1 4)-linked sugar units: a comparative assessment of their conformations and hydrophobicity potential profiles. *Tetrahedron: Asymmetry* **1994**, *5*, 2045-2060. (b) F.W. Lichtenthaler and S. Immel, The lipophilicity patterns of cyclodextrins and non-glucose cyclooligosaccharides. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1996**, *25*, 3-16. (c) Y. Nogami, K. Nasu, T. Koga, K. Ohta, K. Fujita, S. Immel, H.J. Lindner, G.E. Schmitt, and F.W. Lichtenthaler: Synthesis, structure, and conformational features of -cycloaltrin: a cyclooligosaccharide with alternating $^4C_1/^1C_4$ pyranoid chairs. *Angew. Chem.* **1997**, *109*, 1987-1991; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1899-1902.

[5] The 3D-structures can be viewed at "http://caramel.oc.chemie.tu-darmstadt.de/immel/3Dstructures.html", MOLCAD graphics are available at "http://caramel.oc.chemie.tu-darmstadt.de/immel/molcad/Gallery.html".

[6] B.R. Brooks, R.E. Bruccoleri, B.D. Olafson, D.J. States, S. Swaminathan, and M. Karplus: CHARMM: a program for macromolecular energy, minimization, and dynamics. *J. Comp. Chem.* **1983**, *4*, 187-217.

[7] S. Reiling, M. Schlenkrich, and J. Brickmann: Force-field parameters for carbohydrates, *J. Comp. Chem.* **1996**, *17*, 450-468.

[8] M.P. Allen and D.J. Tildesley, Computer Simulation of Liquids, **1996**, Clarendon Press, Oxford.