The Hydrophobic Topographies of Cyclodextrins and Some Non-Glucose Cyclooligosaccharides and Their Properties in Aqueous Solution

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Molecular dynamics simulations of α-cyclodextrin (**1**) in water were used to analyze hydrogen-bonding, hydration properties, and water exchange phenomena in detail (Fig. 1 and 2). Of the approx. 105 - 115 water molecules contained in the first hydration sphere of α-CD, an average of 34.2 ± 2.5 are engaged into 37.3 ± 2.8 hydrogen bonding interactions with the solute; the cavity itself is filled with an average of 6.2 H_2O molecules.

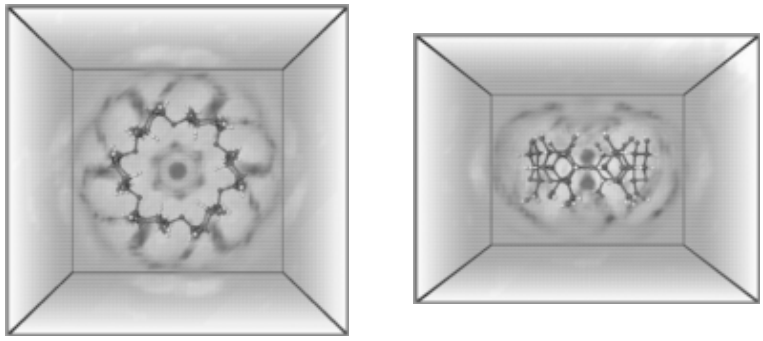
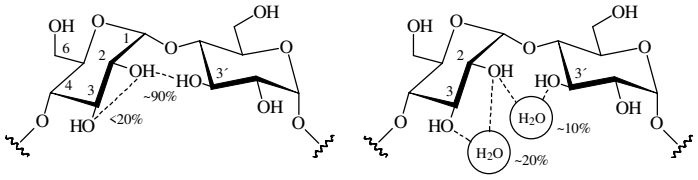


Fig. 1: MD-derived relative water densities around α-CD in solution: dark shading indicates enhanced water probabilities, whereas light areas correspond to low or bulk phase water densities (*left*: front view perpendicular to the CD macrocycle, *right*: side view)

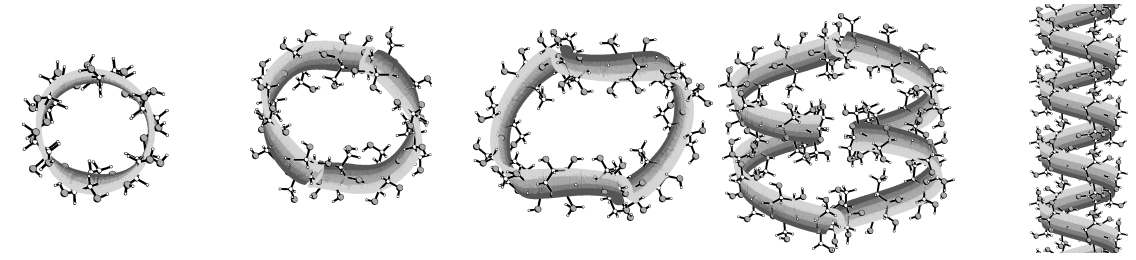
Fig. 2: 120 ps partial MD trajectory of the diffusion of a single water molecule through the CD cavity.

All hydroxyl groups are engaged in extensive H-bonding interactions with the surrounding solvent. Preferred are interresidue interactions of the 2-O ··· O-3' type between adjacent glucose units, but water-mediated hydrogen bond bridges (i.e. water molecules H-bonded to two hydroxyl groups simultaneously, cf. Fig. 3) were also found to persist with high significance.

Fig. 3: In α-CD interresidue hydrogen bonds of the 2-O ··· O-3' type occur with high probability and long life-spans of around 30 ps, whereas the intra-residue interaction is disfavored. Water-mediated H-bond bridges are observed with probabilities of around 10 - 20 %.

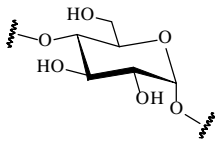


The hydrophobic characteristics of small- and large-ring CDs (cf. ribbon models shown below) were studied by molecular modeling and color-coded projection of the molecular lipophilicity patterns onto the solvent-accessible surfaces of the cyclodextrins[1].

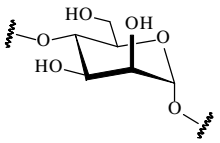


CD_6 (α-CD, **1**) CD_{10} CD_{14} CD_{26} V_H-amylose

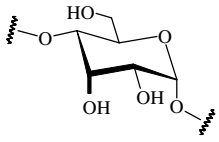
Non-Glucose Cyclooligosaccharides



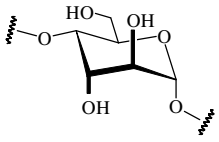
cyclodextrins
cyclo[D-Glc*p* α(1→4)]$_n$



cyclomannins
cyclo[D-Man*p* α(1→4)]$_n$



cycloallins
cyclo[D-All*p* α(1→4)]$_n$

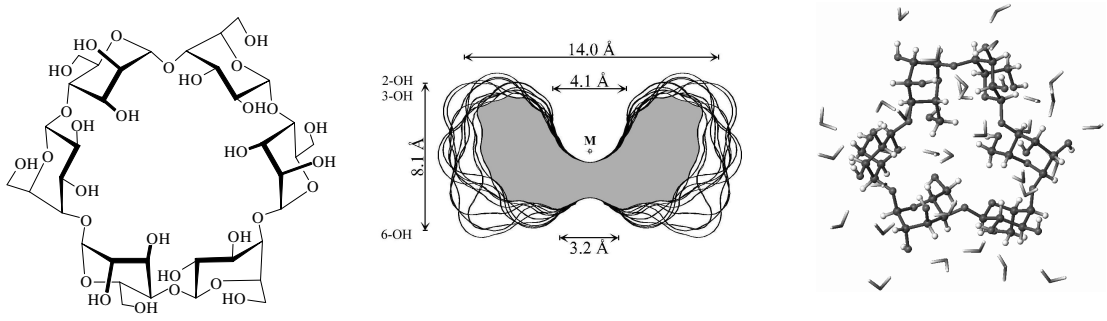


cycloaltrins
cyclo[D-Alt*p* α(1→4)]$_n$

Out of the large number of cyclooligosaccharides consisting of other sugar units than glucose, the cyclomannins, cycloallins, and in particular the cycloaltrins appear most interesting. In α-cycloaltrin (α-CA **2**, i.e. *cyclo*[D-Alt*p* α(1→4)]$_6$), inversion of the configuration at C-2 and C-3 is likely not only to introduce additional strain into the macrocycle, but it also renders the monosaccharide units with considerable flexibility.

α-CA (**2**) adopts in the solid-state[2] a unique C_3 symmetrical conformation with nearly perfect $^4C_1$ and $^1C_4$ chairs in an alternating sequence (**2a**, cf. Fig. 4). ^{1}H and ^{13}C NMR data in D_2O at 30°C and 4°C indicate a dynamic conformational equilibrium of at least two different altrose geometries with almost equal energies in the macrocycle. Unlike the conformation **2a** (Fig. 4) which features side-on indentations only, the intermediate all-$^OS_2$ structure **2b** in the $^4C_1 \rightleftharpoons {}^OS_2 \rightleftharpoons {}^1C_4$ equilibrium has a "through-going" central cavity (Fig. 4). We have investigated the dynamic processes in **2** by means of molecular dynamics (MD) simulations in aqueous solution.

2a



2b

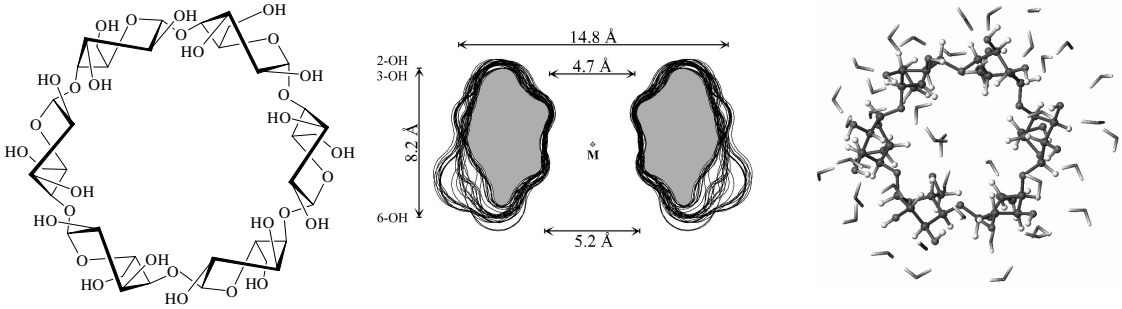


Fig. 4: Superimposed surface cross section cuts (center) of the alternating $^4C_1$ / $^1C_4$ (**2a**) and all-$^OS_2$ conformation (**2b**) of α-cycloaltrin with approximate molecular dimensions in Å. On the right, typical MD derived snap-shot geometries of the first hydration shell of both geometries with 31 and 41 water molecules hydrogen bonded to **2a** and **2b** are displayed.

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

[2] Y. Nogami, K. Nasu, T. Kog