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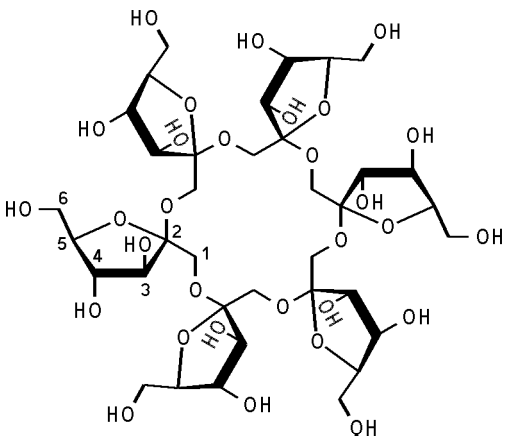
Cyclofructohexaoside : Molecular Electrostatic and Lipophilic Potential Profiles

Abstract: On the basis of the color-coded visualization of molecular electrostatic potential (MEP's) profiles and lipophilicity patterns (MLP's), the structural differences and analogies of cycloinulohexaose (≡ *cyclo*[D-Fru*f*β(1→2)]$_6$, "α-cyclofructin") with its backbone-derived 18-crown-6 ether and cyclodextrins are derived. α-Cyclofructin exhibits no central cave like the corresponding α-cyclodextrin to form inclusion complexes, but a similar "front-" / "backside" differentiation of hydrophobic and hydrophilic surface regions. In agreement with experimental observations, the electrostatic potential profile reflects the crown ether-analog properties of α-cyclofructin being suitable for metal cation complexation and indicate a distinct regioselectivity for incorporation of the cations.

Following the routes for the generation of cyclodextrins[305-308], the enzymatic degradation of inulin yields a new type of cyclooligosaccharides, cycloinulins ("cyclofructins"), which consist out of six to eight β(1→2)-fructofuranose residues[447,448].

α-Cyclofructin (≡*cyclo*[Fru*f*β(1→2)]$_6$) as the most readily accessible compound out of this series, possesses a unique 18-crown-6 ether-like backbone, carrying the *spiro*-anellated furanosyl ring systems in a "propeller"-analog fashion. In the sequel it should be pointed out inasmuch these structural features affect the physico-chemical properties of the cyclofructins in relation to cyclodextrins, and how their properties can be related to the crown ether-type skeleton.



Solid state structural analysis of α-cyclofructin[257] revealed a molecular geometry with C_3-symmetry. The two different furanose rings adopt $E_3 \leftrightarrow {}^4T_3$ conformations (Cremer-Pople ring puckering parameters[122,123] $q = 0.383$ Å / $\phi = 259.6°$ and $q = 0.416$ Å / $\phi = 261.7°$), respectively, which are typical for β-D-fructofuranosyl residues (Chapter 5). The propeller-type anellation requires the exocyclic 6-CH_2OH groups to be located on one side of the macrocycle pointing to its outside, while the

3-OH hydroxyls cap the other side, with three out of the six hydroxyls forming a cycle of cooperative hydrogen bonds. The 18-crown-6 ether skeleton exhibits a rather unique conformation, which is not common to the unsubstituted crown ether and its complexes[257,465,466]. The MOLCAD-program[48] generated contact surfaces[46] of the crystal structure geometry of α-cyclofructin[257] and the PIMM91 force field[45] optimized 18-crown-6 backbone derived therefrom (Fig. 10-1) exhibit no central cavity similar to the corresponding α-cyclodextrin, but a rather small and shallow surface groove only. The apparent molar volume of α-cyclofructin is calculated to be approximately 980 – 985 $Å^3$ (≈ 590 – 595 cm^3/mol).

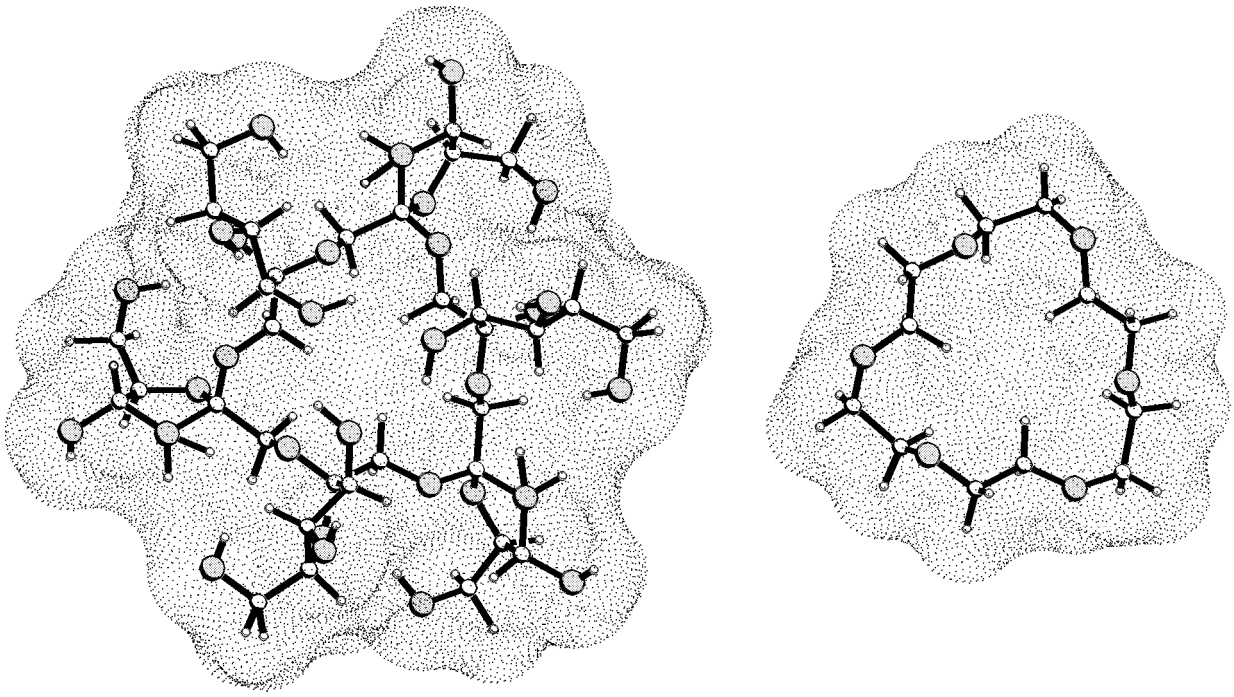


Fig. 10-1. Ball and stick model representation of the solid state structure of cycloinulohexaose (α-cyclofructin)[257] (*left* side) and the 18-crown-6 skeleton derived therefrom (*right* side) including their contact surfaces in dotted form.

The cross section contours of those contact surfaces with a rotating plane perpendicular to the cyclooligosaccharide mean plane and through its geometrical center (step size of rotation 10°) are shown in Fig. 10-2, they directly display the effective molecular dimensions. Despite the close correspondence of the α-cyclofructin diameter of approx. 14.3 Å and the torus height of ≈ 8.0 Å with the size parameters of α-cyclodextrin (Chapter 6), these contours illustrate the absence of a center cave (for the crown ether this holds only true for the conformation derived from the cycloinulin) that could lead to the formation of inclusion complexes of the cyclodextrin-type.

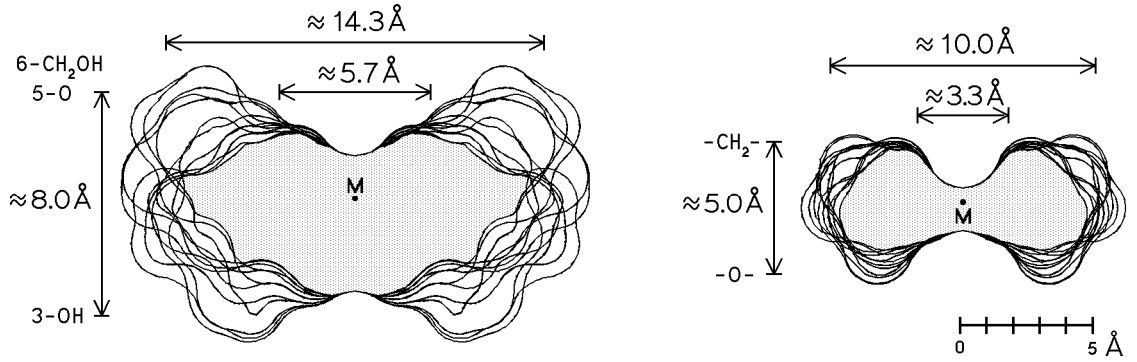


Fig. 10-2. Cross section plots (cf. Fig. 6-7) through the contact surfaces (cf. Fig. 10-1) of cycloinulohexaose (*left* side) and the 18-crown-6 ether derived from this structure (*right* side). The structural fragments related to the top and bottom sides are indicated on the *left* side each (*M*: center of geometry).

Molecular Lipophilicity Patterns

Color-coded visualization of the **m**olecular **l**ipophilicity **p**attern (**MLP**)[58] of α-cyclofructin by using the MOLCAD-program[48,59] (Fig. 10-3) indicates a distinct hydrophilic / hydrophobic differentiation between the "front-" and "backside" of this compound: due to the location of the hydroxyl groups in position 3 and 4 of each fructofuranosyl moiety and the O-1 oxygen atoms involved in the intersaccharidic linkages on the same molecular side ("frontside" in Fig. 10-3), this surface region becomes highly hydrophilic. The opposite side located areas are associated with the 1- and 6-methylene groupings and the O_5-C_5-H_5 fragments, contributing to an obviously more hydrophobic surface. The very same trend is observed for the isolated 18-crown-6 unit with the analogous conformation. The striking correspondence of opposite side located hydrophilic and hydrophobic regions is caused by the spatial separation of the surface parts associated with the ring oxygens – which correlate with the O-1 atoms of α-cyclofructin – and the -CH_2-CH_2-units (≡ 1-CH_2 and C-2 of α-cyclofructin).

For α-cyclofructin as well as for the crown ether skeleton, the hydrophilic molecular parts should be more affected by solvation and hydrogen bonding interactions in aqueous solution than the opposite water-repellent (hydrophobic) sides. Despite the fact, that hydrophobic interactions[116,117] are generally not very strong, the separation of hydrophilic and lipophilic molecular parts represents a factor which may determine molecular orientations in anisotropic environments, such as crystal structures.

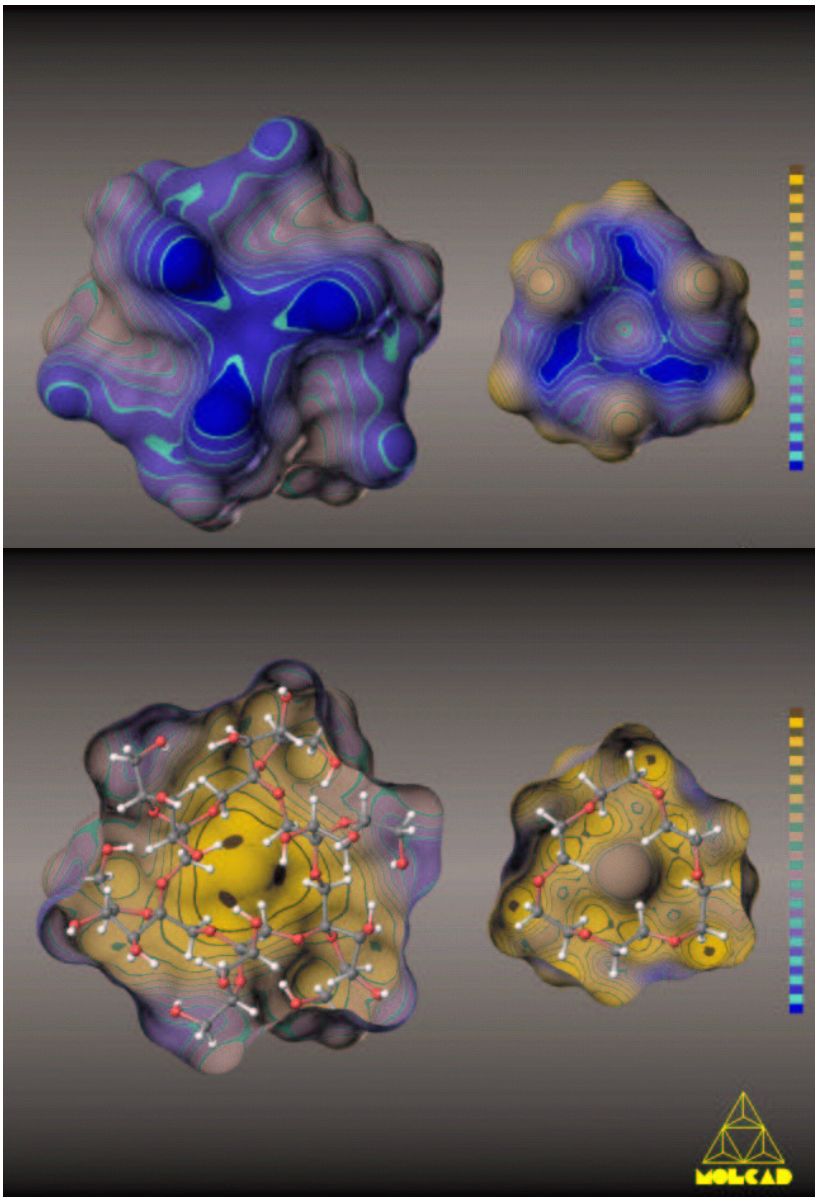


Fig. 10-3. MOLCAD-program generated molecular hydrophobicity patterns of α-cyclofructin (*left* side each) and 18-crown-6 with similar back-bone conformations; yellow-brown colors correspond to hydrophobic surface areas, blue regions indicate hydrophilic molecular parts. The half-opened models illustrate the molecular orientation and the backside surface properties.

Molecular Electrostatic Potential Profiles

Crown ethers are well known for their ability to complex a large variety of metal cations by chelat coordination via their ether-type oxygen atoms[465]. Since the stability of these complexes can be attributed mainly to strong electrostatic interactions between their C-O-bond dipoles and the cation[465], the **m**olecular **e**lectrostatic

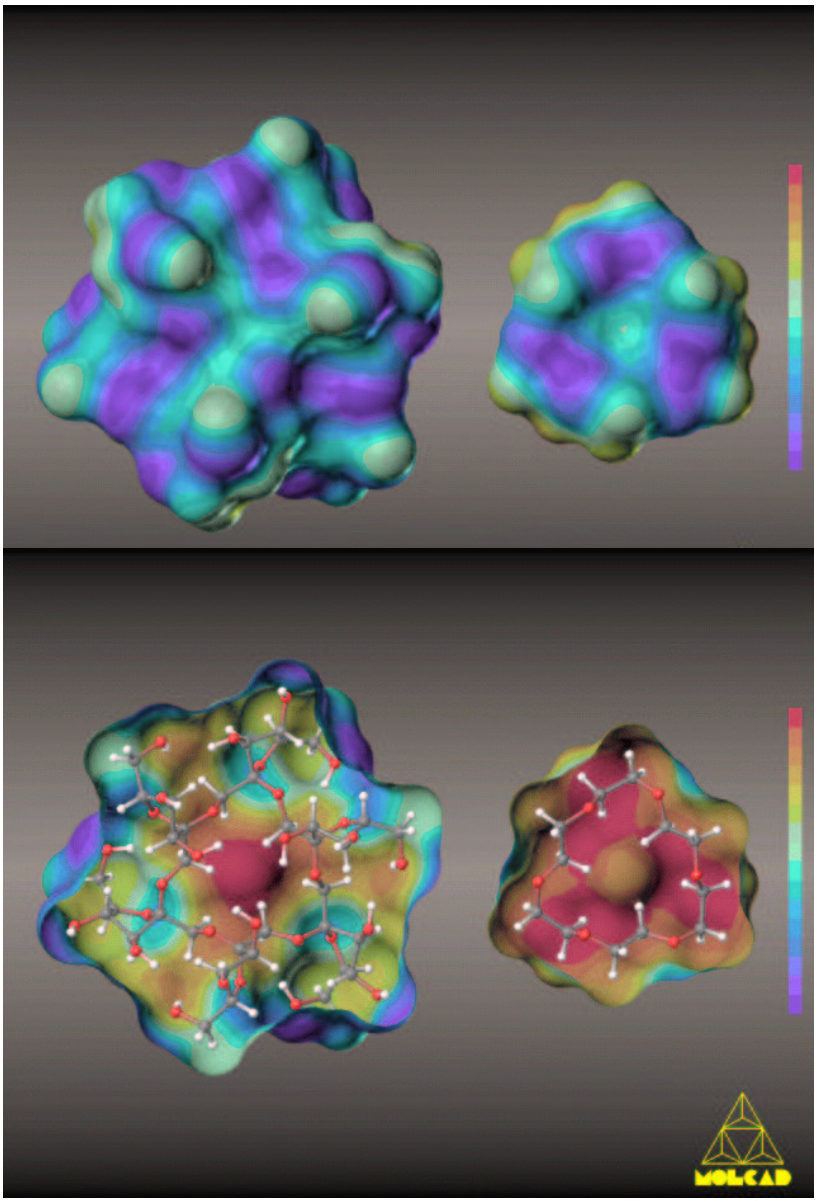


Fig. 10-4. Molecular electrostatic potential (MEP's) profiles on the contact surface of α-cyclofructin (*left column*) and 18-crown-6 ether (*right side* each). Red colors correspond to electropositive surface areas, while violet coloring is used to indicate negative electrostatic potentials.

potential (**MEP**'s) profiles[49] of α-cyclofructin should be more relevant for assessment of its chemical properties than the MLP's are. The MEP's of α-cyclofructin and 18-crown-6 were calculated from the PIMM91[45] partial atomic charges of the fully optimized geometries (Fig. 10-4). They reveal even further similarities between both compounds: due to the accumulation of the negatively charged O-1, O-3, and O-4 atoms of α-cyclofructin and the ring oxygens of the crown ether on the hydrophilic (*vide supra*) molecular sides, highly negative electrostatic potentials (≈ -15 – -25 kcal/mol) are computed on these surfaces regions. Moreover, the opposite

side located areas made up by the CH_2-groups pointing towards the center surface dent are characterized by high positive potentials. The striking analogies between both structures lead to the reasonable assumption that at least their physico-chemical properties based on electrostatic interactions should closely correspond each other.

Indeed, there is overwhelming NMR-experimental evidence for the complexation of metal cations by cycloinulohexaose and its permethylated derivative in aqueous solution as well as in organic solvents[467-470]. Albeit the fact, that the association constants for α-cyclofructin are approximately two orders of magnitude smaller than those measured for the corresponding 18-crown-6[469,470], the effects observed suggest strong binding of the cations Pb^{2+}, Ba^{2+}, K^+, Rb^+, and Cs^+, for example, while Li^+, Na^+, and Ca^{2+} interact only very weakly with α-cyclofructin[467-470]. On the basis of induced-shift differences in the ^{1}H-NMR spectra of the K^+ and Ba^{2+} complexes – both cations having approx. the same size, but different charge, and thus, should level off the effect of conformational changes of the host – it becomes obvious that the oxygen atoms O-1 and, in particular, O-3 are involved in capturing cations[469,470]. However, in a strict sense these considerations are only valid if both complexes exhibit identical or almost similar conformations. Since low-temperature NMR revealed different types of symmetry for both geometries (C_2 symmetry for Ba^{2+} and C_3 symmetry for K^+), considerations derived from the charge induced-shifts might be misleading[470].

Nevertheless, the MEP profiles of α-cyclofructin (Fig. 10-4) strongly support the proposed regioselectivity of metal cation incorporation: the highly negative electrostatic potentials around the O-1, O-3, and O-4 atoms act as a trap for the cations. The side specificity is even more enhanced by the repulsive positive potentials on the opposite molecular side. Direct proof for these models was obtained from solid state structure analysis of the permethylated α-cyclofructin · $Ba(SCN)_2$ complex, indicating 10-fold coordination of the Ba^{2+}-ion by all O-1 atoms and four out of six of the 3-OMe groups (long range interaction with the SCN^- anion might even increase the coordination number to 11)[470]. The results point out one probable mechanism for the complex formation: simultaneous or successive rotation of the *spiro*-anellated fructofuranosyl residues – in the sense of the 3-OMe groups moving from the center towards the outside of the molecule – opens a center pocket of high electronegative character. Trapping and inclusion of the cation by long-ranged strong electrostatic forces lead to the constitution of the complex, whereby the resulting symmetry of the adduct depends on the strength of the Coulomb interactions (i.e. the charge of the cations)[470] and the type of preferred coordination. Albeit not discussed here, the degree of conformational freedom should also affect the relative stability of complexes: in accord with experimental findings[468,470], the certainly increased

flexibility of higher cyclofructins (e.g. β-cyclofructin and γ-cyclofructin) represents an at least unfavorable entropic factor, and thus must lead to a decrease of the corresponding association constants.

Conclusions

Both the MLP's and the MEP's illustrate the crown ether-analog properties of cycloinulins. The results obtained are in agreement with experimental data, in particular the functional groups of α-cyclofructin involved in metal cation complexation are unequivocally identified. In relation to the inclusion complex formation of cyclodextrins – which is determined mainly by hydrophobic interactions – the cycloinulins represent interesting complements to study electrostatic interactions of carbohydrates with metal cations, for example. Further studies are required to reveal how far these interactions are related to the ability of carbohydrates to adopt alternative (high energy) conformations in an "induced-fit" fashion while forming molecular complexes.

Along this vein, the interplay of different interactions and driving forces for the complex formation of cyclodextrins and cyclofructins may be investigated by co-crystalization of cyclodextrins, cycloinulins, and metal salts with large, hydrophobic anions. Cycloinulin mediated masking of suitable cations in cyclodextrin-polyiodide complexes analogous to $\alpha\text{-}CD_2 \cdot Cd_{0.5}I_5 \cdot 27H_2O$, and $\alpha\text{-}CD_2 \cdot LiI_3 \cdot I_2 \cdot 8H_2O$[405], or $\beta\text{-}CD_2 \cdot KI_3(I_2)_2 \cdot 9H_2O$)[414] may yield valuable information on the effect of cation / anion separation.