

CHAPTER 4

CONCLUSIONS

Two different techniques, X-ray crystallography and neutron scattering, have shed light on the extraordinary solubility of methylated CDs.

4.1 X-ray Crystallographic Study

Methylated CDs are well soluble in cold water and only slightly soluble in hot water where they are normally crystallized as can be seen from a number of crystal structures reported so far [74]. Since water molecules must play a crucial role in stabilizing the methylated CDs in the cold aqueous solution, the “helper gas” (H_2S) might be a suitable candidate to stabilize the water molecules in the crystallization process of methylated CDs from cold water. However, it was found that with or without H_2S , crystals could be grown by very slow evaporation of water (at least two months). To shorten the crystallization time, saturated (or extremely concentrated) solutions of methylated CD were prepared in cold water (around 273 K) and allowed to stay at higher temperature (say 291 K) to reduce their solubilities. With this method, crystals of highly hydrated CDs can be grown within two weeks. The methylated CD crystals which could be obtained from cold water at 291 K and were characterized crystallographically are as the following: $\text{DIMEB}\cdot 2\text{H}_2\text{O}$, $\text{DIMEB}\cdot 15\text{H}_2\text{O}$, $(4\text{TRIMEG})\cdot 19.3\text{H}_2\text{O}$, and $\text{TRIMEG}\cdot 4.5\text{H}_2\text{O}$.

1. *DIMEB·2H₂O* is the first crystal structure of a water inclusion complex of the methylated β -CD. The DIMEB macrocycle adopts an open “cylinder” form sta-

bilized by systematic intramolecular, interglucose $O3(n)-H \cdots O2(n+1)$ hydrogen bonds. Both ends of the cavity are closed by adjacent molecules which are related by a characteristic “cage type” crystal packing. One water molecule is included in the hydrophobic cavity of the torus and has very high thermal vibration due to lack of hydrogen bonding interactions to DIMEB, while the other one is located in the interstices between DIMEB macrocycles and forms hydrogen bonds to O3 and O6 oxygen atoms.

- DIMEB·15H₂O is the most thermostable and largest clathrate hydrate.* The DIMEB macrocycle of DIMEB·15H₂O is very similar to that of DIMEB·2H₂O except that the cavity at the O6-end is closed by “inward” rotation of three O6-CH₃ groups yielding a “bowl” rather than a cone shape and the central cavity is filled by a twofold disordered O6-CH₃ group of a symmetry related DIMEB molecule (“self-inclusion”). The sites of the 15 water molecules are fully occupied and form a regular hydrogen bonding network encapsulating the DIMEB guest molecule in a channel clathrate hydrate host structure with the seven O3-H groups of DIMEB systematically hydrogen bonded to water molecules. This gives rise to high thermal stability of the crystal with a phase transition at 110°C and decomposition at 280°C.
- (4TRIMEG)·19.3H₂O is the largest crystal structure of CDs with more than 450 non-hydrogen atoms in the asymmetric unit.* The four molecules of TRIMEG are similar with O4 atoms nearly coplanar and pseudo-twofold rotation axes passing through the centers of the macrocycles. The glucoses are oriented *syn* except for the diametrically opposed glucose units 1 and 5 which are flipped by $\approx 180^\circ$ (*anti*), their C5-C6-O6-C9 chains being rotated toward the center and closing the cavity from one side giving rise to bowl-shaped molecules; the O6 atoms of these chains are hydrogen bonded to water molecules located on the pseudo-twofold axes. The 19.3 water molecules are distributed over 27 sites hydrogen bonded in different patterns to the four TRIMEG molecules.
- TRIMEG·4.5H₂O is an evidence for conformational flexibility of permethylated CDs.* Because all O-H groups are methylated and no intramolecular, interglucose $O3(n)-H \cdots O2(n+1)$ hydrogen bonds can be formed the permethylated CDs are much more flexible than their parents. This can be directly seen with

TRIMEG which does not exist exclusively in the “elliptical” form found in $(4\text{TRIMEG})\cdot 19.3\text{H}_2\text{O}$ and $\text{TRIMEG}\cdot 2\text{H}_2\text{O}$, but it can also adopt the “round” form with all glucose units oriented *syn*. The $\text{TRIMEG}\cdot 4.5\text{H}_2\text{O}$ molecules are stacked to form infinite cylinders with the central cavities aligned into channels filled for each TRIMEG by 4.5 water molecules distributed over 15 partially occupied sites.

5. *Hydration–dehydration process is a probable reason for the unusual solubility behavior of methylated CDs.* Methylated CD crystals grown from cold water have much higher water content when compared to those grown from hot water which have no or only few water of hydration molecules. This suggests that methylated CDs are extremely soluble in water at low temperature probably because they are strongly hydrated. As the temperature rises, the hydration breaks down, the hydrophobic methylated CDs aggregate and crystallize. To trace a route from high solubility in cold water (hydration) to low solubility in hot water (dehydration), the neutron scattering has been employed to monitor the hydration dynamics of methylated CDs.

4.2 Neutron Scattering Study

As the hydration should be a key to disclose the anomalous solubility (negative solubility coefficient in water) of methylated CDs, the neutron scattering experiments have been performed which allow to observe directly the dynamics of CD and its hydration water. This study has not yet been completed so far, due to difficulties in analysing the data. However, the obtained dynamical parameters of CD solutions reported here are probably close to the final values as indicated by good fitting of theoretical curves to the measured data. Neutron scattering technique gives a picture for hydration dynamics of methylated CDs which leads to an explanation for their negative solubility coefficient in water.

1. At low temperature, DIMEB and TRIMEG are very well soluble in water because they are massively hydrated by hydration numbers of *ca.* 52 and 37 water molecules (7 and 4 molecules per one glucose residue), respectively (at 287 K). This is evidenced by a broad quasielastic peak which shows the diffusive motion

of liquid state. The CD macrocycle and its hydration water diffuse together with the same D_{trans} and D_{rot} of $0.68\text{--}1.07 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ and $0.002\text{--}0.004 \text{ meV}$ for DIMEB, $0.65\text{--}0.96 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ and $0.001\text{--}0.003 \text{ meV}$ for TRIMEG (at 287–305 K).

2. When the temperature increases, the water molecules in the hydration shell become more mobile and displace to the bulk region, consequently CD and its remaining hydration water diffuse faster. As the temperature reaches the crystallizing point, the hydration is disrupted, the hydrophobic methylated CDs aggregate and crystallize as indicated by a sharp elastic peak of DIMEB at 323 K which is an indication of very slow motion of solid state. At 323 K the hydration number decreases dramatically to *ca.* 17 and 27 molecules for DIMEB and TRIMEG, respectively. TRIMEG persists to be hydrated by a sufficient number of water molecules; this explains why TRIMEG is still soluble at this condition. If the TRIMEG solution is further heated up to its crystallization temperature at 353 K, similar behavior is observed as in case of DIMEB.
3. By contrast, γ -CD has a positive solubility coefficient in water, i.e., the solubility is proportional to the temperature. It shows similar dynamics behavior to DIMEB and TRIMEG at the ambient temperature as its hydration number decreases and D_{trans} increases with increasing temperature. As the temperature rises to 323 K the hydration number of γ -CD remains constant at *ca.* 29 water molecules but those of DIMEB and TRIMEG are diminished continuously. The certain hydration number of γ -CD explain why it is still soluble at higher temperature.