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Structure and stability of columnar cyclomaltohexaose (α-cyclodextrin) hydrate

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Abstract—Rapid recrystallization of cyclomaltohexaose (α-cyclodextrin, α-CD) from aqueous solution resulted in formation of the columnar crystal structure of α-CD containing only water as the guest molecule. Complementary water vapor sorption and wide-angle X-ray diffractometry (WAXD) experiments were performed on the α-CD columnar structure to elucidate the crystal structure present at varying sorption levels. Equilibrium isothermal water vapor sorption experiments at 40 °C revealed that the α-CD columnar structure is unstable above a water activity of approximately 0.67. This was confirmed by WAXD diffractograms collected over time, which further revealed that α-CD columnar structure undergoes a phase transformation to the cage structure after approximately 0.25 h at 40 °C and a water activity of 1.0.

Keywords: Cyclomaltohexaose; α-Cyclodextrin; Water vapor sorption; Wide-angle X-ray diffraction; Phase transformation

1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are cyclic oligosaccharides capable of forming inclusion complexes with small molecules and macromolecules due to their hollow, truncated cone structure. CD molecules may be composed of 6, 7, or 8 glucose units, which correspond to α-, β-, and γ-CD, respectively. These molecules have a hydrophilic surface and a hydrophobic cavity in which the guest molecule resides. CDs can exist in three classes of crystal structures called cage, layer, and columnar.[1] In the cage and layer structures (Fig. 1a and b), the CD cavities are not aligned, whereas they stack on top of each other in the columnar structure (Fig. 1c) to form long cylindrical channels in which, for example, guest polymer molecules can reside.[3–10]

The α-CD cage structure has a 'herring-bone' arrangement in which the cavity of each molecule is blocked by neighboring molecules. It is obtained upon recrystallization of α-CD from water. Manor and Saenger[11] assigned the α-CD hexahydrate unit cell to the orthorhombic space group $P2_12_12_1$. They report that two water molecules are located inside the α-CD cavity, and the other four are outside. Both water types are involved in hydrogen bonding with α-CD. Nakai et al.[12] characterized α-CD in the cage structure by isothermal water vapor sorption experiments at 40 °C and complementary wide-angle X-ray diffractometry (WAXD) to determine the effect of water content on the WAXD pattern. They confirm the existence of a hydrate containing six water molecules per α-CD molecule that forms from $a = 0.2$ to 1.0 (a = activity of water vapor). Using the same sorption technique, Tanada et al.[13] also report that α-CD forms a hexahydrate between $a = 0.2$ and 1.0 at 20 °C.

Another structure similar to the cage structure, in the sense that the cavities are unaligned, is the layer structure (Fig. 1b).[1] Here, α-CD molecules are arranged

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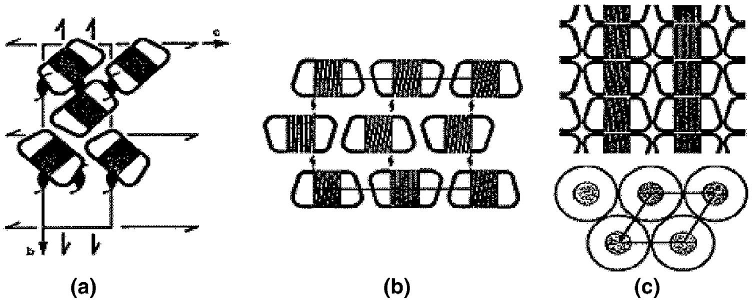

Figure 1. Schematic representation of the packing of CD molecules within their crystal lattices: cage (a), layer (b), and head-to-head columnar (c) structure. From Ref. 2.

almost parallel to the ring plane to form layers that are shifted half a molecule with respect to adjacent layers. The layer structure forms when the guest molecule is larger than the cavity of α-CD. It has been assigned two possible space groups: $P2_1$[14] or $P2_12_12_1$[15] depending on the guest molecule included.

Four crystal structures have been reported for α-CD inclusion compounds (ICs) in the columnar structure: two are classified as the head-to-head[16] (Fig. 1c) arrangement, while the other two are head-to-tail.[17,18] These differences are due, in part, to the influence of the guest molecule type on the conformation and, thus, the packing of α-CD. The head-to-head configuration can exist in either the triclinic $P1$ or tetragonal $P4_22_12$ space groups with 4 and 13.5 mol of water per mole of α-CD, respectively. The head-to-tail configuration can exist in the monoclinic $P2_1$[16] or orthorhombic $P2_12_12$[17] space groups with 6 and 9.7 mol of water per mole of α-CD, respectively.

Topchieva et al.[19] first prepared α-CD in the columnar structure containing only water by first preparing a polymer-CD IC, then removing the polymer. Recently, Rusa et al.[20] directly prepared α-CD in the columnar structure with only water as the guest molecule by rapid precipitation of α-CD from its aqueous solution using chloroform. X-ray analysis confirmed the presence of the columnar structure, while thermal analyses revealed that water occupies three distinct sites based on different binding energies.

Miyake et al.[21] recently reported that CD molecules in the columnar structure with a polymer guest are arranged in both head-to-head and head-to-tail conformations in a ratio of 2–1, respectively. In contrast, Becheri et al.[22] suggest that polymer-CD IC crystal precipitation is preceded by the formation of worm-like aggregates of CD in aqueous solution, which are most likely oriented in a head-to-head fashion. This explains how columnar α-CD with no guest molecule other than water can be obtained.

The water sorption behavior of columnar α-CD has not been investigated. The purpose of this work is to study the water vapor sorption of columnar α-CD (as prepared by Rusa et al.[20]) and to study its stability to water vapor. It is found that α-CD undergoes a crystal structure transformation from the columnar to the cage structure at a particular water vapor activity. Complementary WAXD is used to follow the crystal structure phase transformation. The sorption behavior of α-CD columnar structure is also compared to the cage structure.

2. Experimental

2.1. Materials

The α-CD was purchased from Cerestar in powder form. Chloroform was obtained from Aldrich Chemical Co. and used without further purification.

2.2. Precipitation of α-CD columnar structure

A solution containing 1.825 g of α-CD in 12.5 mL of deionized water was stirred continuously at 50 °C for 1 h. The clear solution was then quickly poured into 50 mL of stirred chloroform at room temperature, and the precipitate was immediately vacuum-filtered and allowed to dry overnight under a vacuum draft.[20]

2.3. Water vapor sorption isotherms

A custom-built gravimetric balance was used to measure the sorption of water vapor in dehydrated α-CD. Samples weighing 0.2–0.5 g were first vacuum-dried at 40 °C in the balance chamber until no weight loss was recorded, then were tested at 40 °C and water activities ranging from 0.1–1.0. Using flow meters for regulation, dry nitrogen gas was mixed with nitrogen gas bubbled through a water-containing reservoir to achieve the desired water activity. The humid gas was then passed through the sample chamber at a constant flow rate. Samples were allowed to sorb water until equilibrium weight gain was achieved at each water activity. After reaching a constant weight, the water activity was increased by approximately 0.2 and equilibrium was reestablished. This was repeated up to the saturation concentration of water vapor in nitrogen gas. A desorption isotherm was also collected by decreasing the water activity in increments of −0.2, down to a water activity of approximately 0.1. The results of this experiment are plotted as sorption/desorption isotherms at 40 °C.

A sorption kinetics experiment was also conducted to determine the kinetics of the phase transformation from the α-CD columnar structure to the cage structure. Approximately 0.3 g of vacuum-dried α-CD columnar structure was placed in the gravimetric balance chamber at 40 °C and $a = 1.0$. Here, water uptake was measured as a function of time.

2.4. Wide-angle X-ray diffraction (WAXD)

WAXD measurements were performed using a Siemens type-F X-ray diffractometer with Ni-filtered Cu Kα radiation ($\lambda = 1.54$ Å). The supplied voltage and current were 30 kV and 20 mA, respectively. The diffraction intensities were measured every 0.1° from $2\theta = 5°$ to 30° at a rate of ($2\theta = 3°$)/min unless otherwise specified.

WAXD experiments designed to track the phase transformation of α-CD and to complement the sorption kinetics experiment were conducted with the sample holder containing CD stored at 40 °C in water vapor at $a = 1.0$. The sample was removed from the humidity chamber periodically and placed in the diffractometer to collect diffractograms as a function of time. To minimize time spent outside of the humidity chamber, WAXD diffractograms for α-CD were only collected from $2\theta = 10°$ to 25°.

3. Results and discussion

Figure 2 shows the water vapor sorption isotherm of the "as-received" α-CD cage structure, which forms a stable hydrate at $a = 0.2$ containing approximately 6 mol of water per mole of α-CD as evidenced by little additional sorption for $a > 0.2$. The desorption stage exhibits the same trend as the sorption stage, but with slightly higher sorption levels from $a = 0.2$–0.8. Water vapor sorption of the α-CD columnar structure exhibited different behavior compared to the cage structure (Fig. 3). After drying, the α-CD columnar structure exhibits steadily increasing water sorption up to a water activity of approximately 0.67. At this point water is dramatically expelled from the CD to form a trihydrate, which contains half the amount of water as the stable hydrate of the as-received cage structure.

The mechanism for the loss of water in the sorption isotherm of the α-CD columnar structure is not well understood. However, it is well known that an extensive network of hydrogen bonds exists in the cage structure.[16] If a similar hydrogen-bonding network exists in the columnar structure, disruption of these intermolecular α-CD hydrogen bonds and formation of adsorbed water/α-CD hydrogen bonds would give rise to increased α-CD mobility. This would result in destabilization of the columnar structure and reorganization to form the preferred α-CD cage structure hydrate. WAXD (Fig. 4c) performed on α-CD columnar structure after sorption to $a = 1.0$ confirms that a phase transformation from columnar to cage structure occurs based on the presence of the α-CD cage structure peak at approximately $2\theta = 12°$,[20] which represents the (1 2 0) planes of the α-CD cage crystal structure. Also of interest is the sorption maximum for the α-CD columnar structure, which is approximately 5.3 mol of water per mole of

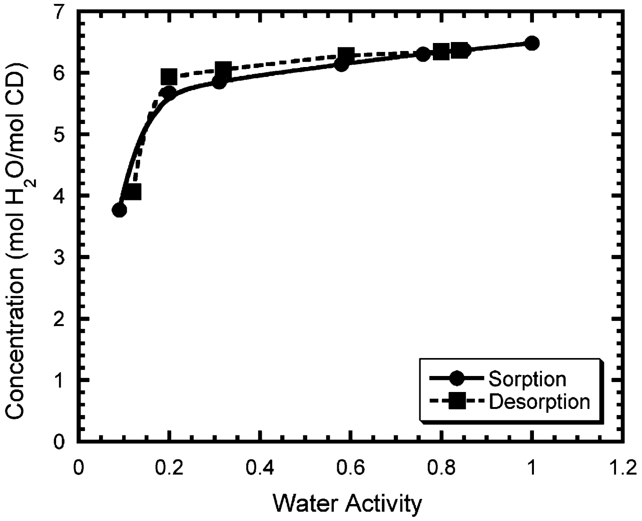

Figure 2. Sorption isotherm of vapor water in "as-received" α-CD at 40 °C.

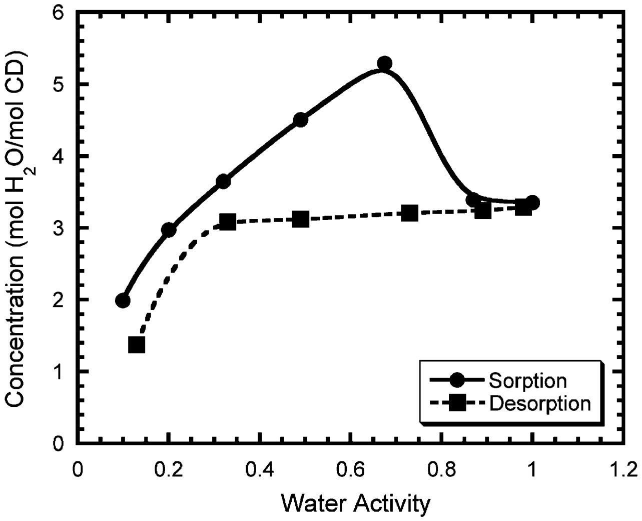

Figure 3. Sorption isotherm of water vapor in the α-CD columnar structure at 40 °C.

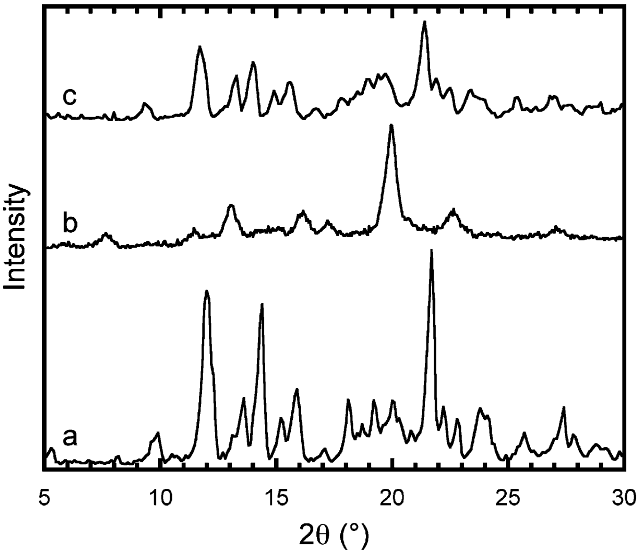

Figure 4. WAXD diffractograms of "as-received" cage α-CD (a) and vacuum-dried α-CD columnar structure before (b) and after (c) sorption to *a* = 1.0.

α-CD. This is close to the maximum water vapor sorption for the cage structure, suggesting that the α-CD columnar structure might reach the same hydration level excluding any effects of the aforementioned phase transformation.

The desorption stage of the experiment in Figure 3 reveals that the α-CD trihydrate formed during the sorption stage is stable from approximately *a* = 1.0 to 0.35. Since α-CD in the cage form contains approximately 6 mol of water at the same water activities, this would suggest that a new trihydrate crystal is formed after exposing the α-CD columnar structure to a water activity above 0.67 at 40 °C. After completion of the desorption isotherm, the WAXD diffractogram of α-CD trihydrate also showed a strong peak for the cage crystal at $2\theta = 12°$.[20]

The sorption kinetics experiment performed on the α-CD columnar structure (Fig. 5) also showed evidence of the phase transformation to the cage structure. After approximately 15 min, the sample sorbed its maximum of 5.5 mol of water per mole of α-CD columnar structure. This was followed by a loss of approximately 2.3 mol of water per mole of α-CD, which is attributed to the phase transformation to the cage structure. The amount of water lost during the transformation compares well with the two moles of water lost in the sorption isotherm of the α-CD columnar structure (Fig. 3).

The "as-received" α-CD cage structure has many WAXD reflections, but there are three salient peaks associated with its crystal structure occurring at $2\theta = 12.0°$, 14.4°, and 21.7° (Fig. 4a). The α-CD columnar structure has significantly fewer reflections with two salient peaks centered at $2\theta = 13.2°$ and 20.0° (Fig. 4b). The reason for fewer reflections in the α-CD columnar structure is probably due to small and/or imperfect crystals relative to the cage structure. Since formation of the α-CD columnar structure occurs rapidly, the molecules do not have sufficient time to order completely, possibly resulting in amorphous regions.

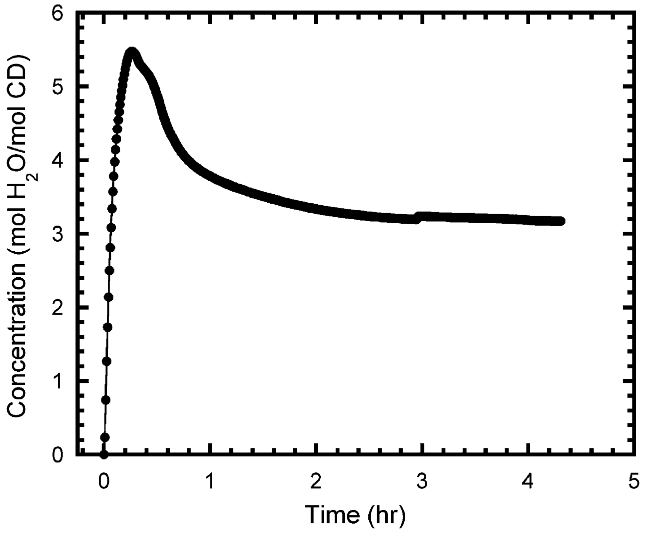

Figure 5. Water vapor sorption kinetics of the α-CD columnar structure at *a* = 1.0 and 40 °C.

The crystal structure of the α-CD columnar structure has not been directly identified due to the method in which it is obtained. Because it is precipitated rapidly from solution by a nonsolvent, the crystals formed are too small for traditional single-crystal X-ray diffractometry studies. For this work, the crystal structure of columnar α-CD is presumed isomorphous with the triclinic *P*1 crystal of LiI_3/I_2-α-CD IC.[16] This assignment is based on the close match of the *d*-spacings (Table 1) derived from the "as-precipitated" α-CD columnar structure hydrate WAXD diffractogram shown in Figure 4b to the *d*-spacings calculated for the LiI_3/I_2-α-CD IC proposed by Noltemeyer and Saenger.[16] The reflection at $2\theta = 11.5°$ could not be assigned to this lattice possibly because it belongs to the α-CD cage structure, which exhibits a reflection near $2\theta = 12°$.[23]

Table 1. Crystallographic spacings for the columnar α-CD crystal structure

2θ(obsd) (deg)	*d*(obsd) (Å)	*d*(calcd)[a] (Å)	*hkl*
7.65	11.6	11.6	100
11.5	7.72	—	—
13.1	6.78	6.82	110
16.2	5.48	5.45	021
17.2	5.15	4.86	003
20.0	4.45	4.50	120
20.8	4.28	4.22	211
22.7	3.92	3.86	300
27.1	3.29	3.24	310

[a] Calculated assuming a triclinic unit cell with *a* = 13.38 Å, *b* = 13.88 Å, *c* = 15.69 Å, $\alpha = 94.1°$, $\beta = 87.8°$, and $\gamma = 120°$ (Ref. 16).

LiI_3/I_2-α-CD IC contains four moles of water per mole of α-CD that are located outside the α-CD cavities because of the included iodine guest molecules.[16] Since α-CD in the cage crystal contains two molecules of water per α-CD cavity,[11] the corresponding columnar structure should also contain two molecules of water per α-CD cavity. LiI_3/I_2-α-CD IC would then contain six molecules of water per molecule of α-CD if no iodine was present. Therefore, the maximum water content of the α-CD columnar structure (Fig. 3) matches well with the triclinic crystal reported by Noltemeyer and Saenger.[16]

To quantify the stability of the α-CD columnar structure, WAXD was performed over time under the same environmental conditions as the sorption kinetics experiment in Figure 5. Time-dependent WAXD patterns are shown in Figure 6. The $2\theta = 12.9°$ peak, which represents the (1 1 0) plane in the α-CD columnar structure, disappears after 0.42 h. This could correlate with the peak at 0.25 h in the sorption kinetics experiment as shown in Figure 5. Shortly afterward, a significant buildup of the α-CD cage peak at $2\theta = 12.2°$ occurs.

Without further analysis, it would appear that the columnar-to-cage phase transformation occurs in less than an hour. However, the columnar α-CD peak at $2\theta = 19.8°$ persists while the $2\theta = 12.2°$ peak area continues to increase after 100 h (Fig. 6), suggesting that columnar α-CD transforms to some intermediate structure containing reflections for both columnar and cage crystals due to the heterogeneous nature of the phase transition. The surfaces of the crystals probably transform first because of their direct exposure to water vapor, while the molecules in the bulk require a longer time due to fewer degrees of freedom. This result also suggests that the sorption equilibrium is reached long before the columnar to cage phase transformation is complete. Further elucidation of this transition would require single-crystal X-ray diffraction studies.

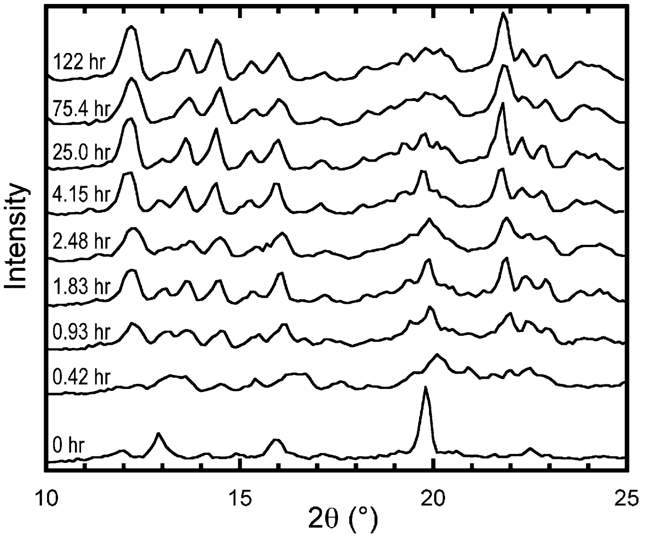

Figure 6. Time-dependent WAXD diffractograms of α-CD columnar structure at $a = 1.0$ and 40 °C.

4. Conclusions

Rapid recrystallization of α-CD from aqueous solution resulted in formation of the columnar crystal structure containing only water as the guest molecule. Isothermal sorption experiments at 40 °C revealed that the α-CD columnar structure is stable up to a water activity of 0.67, at which point a phase transformation occurs resulting in the formation of a stable α-CD trihydrate. This was confirmed by continuous WAXD experiments, which further revealed that the α-CD columnar structure undergoes a heterogeneous phase transformation from columnar to a mixture of cage and columnar crystal structures after approximately 0.5 hour at 40 °C and $a = 1.0$. Complete transformation to the cage structure occurs on the order of 100 h. Sorption equilibrium is reached long before the columnar-to-cage phase transformation is complete. This indicates that water content plays an integral role in the structures and analyses of α-CD and its inclusion compounds.

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