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Carbohydrate Research 340 (2005) 1631–1637

Carbohydrate
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# Structure and stability of columnar cyclomaltooctaose (γ-cyclodextrin) hydrate

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Received 10 January 2005; accepted 16 March 2005

**Abstract**—Rapid recrystallization of cyclomaltooctaose (γ-cyclodextrin, γ-CD) from aqueous solution resulted in formation of a columnar structure with only water as the guest molecule. Upon vacuum drying at 90 °C for 15 h, γ-CD, which was initially in the columnar structure, became amorphous. Complementary water vapor sorption and wide-angle X-ray diffractometry experiments were performed on columnar γ-CD in its vacuum dried and as-precipitated states to elucidate its stability in humid environments and the crystal structure present at varying sorption levels. These experiments show that both types of γ-CD transform to the cage crystal structure upon exposure to water vapor at 40 °C and with an activity of 1.0. Sorption equilibrium is reached long before the crystal structure transformation is complete, indicating that a significant amount of molecular mobility exists in the various hydrated γ-CD crystal structures.

*Keywords:* γ-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. γ-CD can exist in two classes of crystal structures called cage and columnar.[1] In the cage structure (Fig. 1a), the CD cavities are not aligned, whereas they stack on top of each other in the columnar structure (Fig. 1b) to form long cylindrical channels in which, for example, guest polymer molecules can reside.[2–9]

The as-received γ-CD cage structure has a 'herringbone' arrangement (Fig. 1a) in which the cavity of each molecule is blocked by neighboring molecules. It is obtained upon recrystallization of γ-CD from water. Harata[10] assigned the γ-CD hydrate unit cell to the monoclinic space group $P2_1$. He reports that 14.1 water molecules are distributed over 23 sites per γ-CD molecule while 7.1 of those water molecules are located inside the γ-CD cavity. Only the water molecules outside the cavity are involved in hydrogen bonding with γ-CD.

Nakai et al.[11] characterized γ-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 seven water molecules per γ-CD molecule that forms from $a = 0.3$ to 0.5, where $a$ represents the water vapor activity. Another hydrate containing almost 17 water molecules per γ-CD molecule was characterized at $a = 0.93$. Using the same sorption technique, Tanada et al.[12] also report that γ-CD forms two hydrates at intermediate and high activities.

The γ-CD inclusion compounds (ICs) form the columnar structure in which the cavity of each molecule

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doi:10.1016/j.carres.2005.03.021

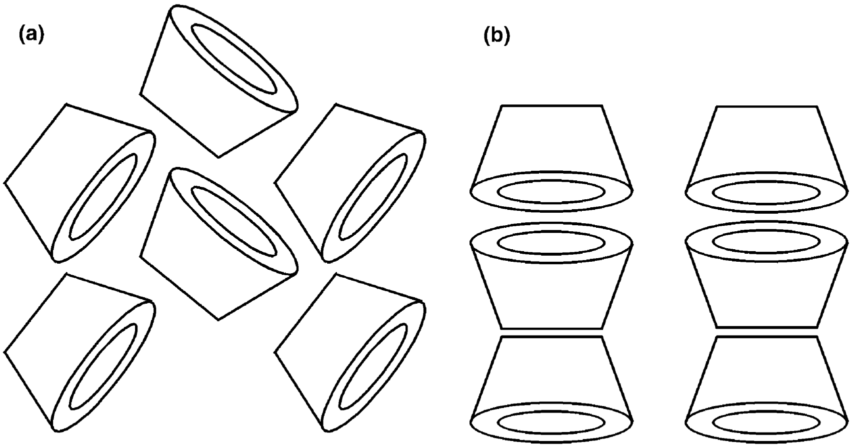

**Figure 1.** Schematic representation of the packing of γ-CD molecules in the cage (a) and columnar (b) crystal structures.

is aligned in a columnar fashion. For example, Kamitori et al.[13] assigned the γ-CD·12-crown-4-LiSCN inclusion compound unit cell to the tetragonal space group $P42_12$. They report that 14.1 water molecules are distributed over 23 sites per γ-CD molecule, while 7.1 of those water molecules are located inside the γ-CD cavity. The orientation of γ-CD in the columns is head–head:tail–head, resulting in a 3-molecule repeating unit (Fig. 1b). Rusa et al.[14] first prepared γ-CD in the columnar structure with only water as the guest molecule. This was done by rapidly precipitating γ-CD from an aqueous solution using acetone. In the same publication, Rusa et al. also reported preparation of columnar α-CD in a similar way by rapid precipitation from water using chloroform.

Miyake et al.[15] have recently reported that CD molecules in the columnar structure with a polymer guest are arranged in both head-to-head and head-to-tail configurations in a ratio of 2:1, respectively. In contrast, Becheri et al.[16] suggest that polymer–CD IC crystal precipitation is preceded by the formation of wormlike aggregates of CD in aqueous solution, which are most likely oriented in a head-to-head fashion. This explains how CD in the columnar structure with no guest molecule other than water can be obtained from rapid precipitation.

In a previous paper,[17] we characterized the structure and stability of rapidly precipitated columnar α-CD, using water vapor sorption and complementary WAXD measurements. In this paper, we report similar measurements for the rapidly precipitated columnar structure of γ-CD. It is found that γ-CD undergoes a crystal structure transformation from the columnar to the cage structure at elevated water vapor activities. Vacuum-drying the as-precipitated columnar structure transforms it to an amorphous phase, which also undergoes a crystal structure transformation at elevated water activities.

## 2. Experimental

### 2.1. Materials

The γ-CD was purchased from Cerestar in powder form. Acetone was obtained from Aldrich Chemical Co. and used without further purification. Deionized water used for all recrystallizations was purified with a US Filter system.

### 2.2. Preparation of γ-CD columnar structure

A solution containing 11.6 g of γ-CD in 50 mL of deionized water was stirred continuously at 50 °C for 2 h. The clear solution was then poured into 250 mL of stirred acetone at room temperature. The precipitate was immediately vacuum filtered and is henceforth referred to as 'as-precipitated'.[14] As-precipitated γ-CD columnar structure which was then vacuum dried at 90 °C for 15 h is referred to as 'vacuum dried'.

### 2.3. Thermogravimetric measurements

Thermogravimetric analysis (TGA) was carried out with a Perkin–Elmer Pyris 1 Thermogravimetric Analyzer on samples weighing 5 mg. Samples were placed in an open platinum pan that was hung in the furnace. The weight percentage of the remaining material in the pan was recorded during heating from 25 to 600 °C at a heating rate of 10 °C/min. Nitrogen was used as the purge gas.

### 2.4. Water vapor sorption isotherms

A custom-built gravimetric balance was used to measure the sorption of water vapor in dehydrated γ-CD. Samples weighing 0.2–0.5 g were first vacuum dried at 90 °C and then vacuum dried in the balance chamber at 40 °C to remove any water adsorbed after removal from the vacuum oven. The samples were then tested at 40 °C and water activities ranged from 0.1 to 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 re-established. 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 these experiments are plotted as sorption/desorption isotherms at 40 °C. Approximately 16 h were required to establish sorption equilibrium at each water activity, and approximately one week was required to collect a complete sorption or desorption isotherm.

Sorption kinetics experiments were also conducted to determine the time dependence of the γ-CD phase transformation from the columnar to the cage structure. Approximately 0.3 g of as-precipitated or vacuum-dried γ-CD was placed in the balance chamber at 40 °C and $a = 1.0$ ($a$ = water vapor activity). Here, water uptake was measured as a function of time.

### 2.5. Wide-angle X-ray diffraction

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 scanning rate of ($2\theta = 3°$)/min unless otherwise specified.

Time-dependent WAXD experiments designed to track the phase transformation of γ-CD and to complement the sorption kinetics experiments were conducted with γ-CD stored at 40 °C in water vapor at $a = 1.0$. The sample was removed from the humidity chamber several times during the experiment and placed in the diffractometer to collect diffractograms as a function of time. The characteristic peaks for cage γ-CD occur at approximately $2\theta = 12.4°$, 16.5°, 18.8°, and 23.4°. Columnar γ-CD has one major peak at $2\theta = 7.5°$ with minor reflections at $2\theta = 16.7°$ and 21.8°. To minimize time spent outside of the humidity chamber, time-dependent diffractograms were only collected from $2\theta = 5°$ to 25° which includes all of the aforementioned reflections.

## 3. Results and discussion

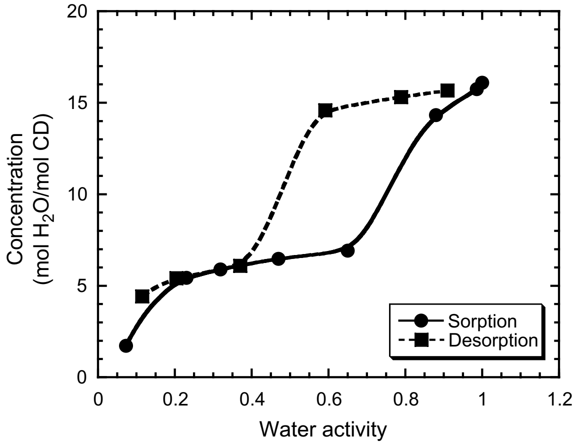

**Figure 2.** Sorption isotherm for water vapor in as-received cage γ-CD at 40 °C.

Figure 2 shows the sorption and desorption isotherms for water vapor in as-received γ-CD, which has the cage structure. The sorption stage exhibits a plateau between $a = 0.3$ and 0.6 corresponding to a hydrate of approximately six molecules of water per molecule of γ-CD. At activities beyond 0.6, the sorbed concentration rises rapidly, reaching a final sorption level of more than 16 molecules of water per molecule of γ-CD. The desorption stage exhibits the same trend as the sorption stage, but the transition in water concentration is shifted to lower activities, indicating a strong affinity for water by γ-CD.

It has been shown that γ-CD in the columnar structure is destabilized by the removal of water under vacuum at 90 °C, resulting in an amorphous structure.[14] The large interstitial sites between the CD columns is where a portion of the crystal water resides in the fully hydrated structure. When this water is removed, structure destabilization is likely since the interstitial water is loosely bound. This would suggest that water residing in interstitial sites between γ-CD columns and between γ-CD molecules within a column stabilizes the structure through primary CD–water and possibly secondary CD–water–water–CD hydrogen bonds. Unlike γ-CD, the α-CD cage structure is stable upon vacuum drying, indicating that CD–CD hydrogen bonds are present in this crystal structure.[14] It is possible that γ-CD molecules in the columns tilt in a random fashion upon water removal in an attempt to adopt the more stable cage structure. This randomness is evident by the absence of reflections in the WAXD pattern of (amorphous) vacuum-dried columnar γ-CD shown in Figure 3c, which compares WAXD patterns of various γ-CD samples.

The equilibrium water vapor sorption experiment first requires vacuum drying of the sample, which produces an amorphous structure in the case of γ-CD as described by Rusa et al.[14] The starting material in such an experiment is therefore expected to be amorphous γ-CD. As a result, the sorption isotherm of vacuum-dried γ-CD

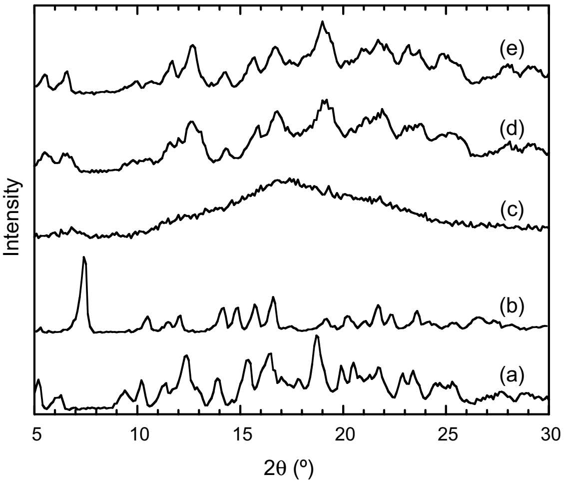

**Figure 3.** WAXD patterns of as-received cage γ-CD (a), as-precipitated columnar γ-CD (b), vacuum-dried columnar γ-CD (c), vacuum-dried columnar γ-CD after equilibrium sorption and desorption of water at $a = 1$ and 40 °C (d) and vacuum-dried columnar γ-CD after sorption of water at $a = 1.0$ and 40 °C (e).

(Fig. 4) exhibits different behavior than the cage polymorph in that no stable hydrate is observed at intermediate water activities. Instead, an almost linear increase in water uptake versus water activity occurs. This was also observed by Nakai et al.[18] in which γ-CD was ground in a tungsten carbide vibrational mill to create amorphous γ-CD. The resulting sorption isotherm at 40 °C is linear with no intermediate hydrate present and is similar to the sorption behavior of amorphous γ-CD shown in Figure 4.

The maximum sorption level at $a = 1.0$ in Figure 4 is approximately 17 moles of water per mole of γ-CD, which is comparable to the maximum sorption level of cage γ-CD (Fig. 2). This suggests that amorphous γ-CD transforms to the cage structure during the sorption experiment. The desorption stage is nearly identical to cage structure desorption with a stable hydrate of approximately six moles of water per mole of γ-CD forming between $a = 0.25$ and 0.35, which further indicates that an amorphous-to-cage crystal structure transformation occurs during sorption. WAXD performed at the end of the desorption stage confirms the presence of the cage structure (Fig. 3d).

A sorption kinetics experiment for vacuum-dried columnar γ-CD is shown in Figure 5. The maximum sorption level of 18 moles of water per mole of γ-CD is reached after approximately 2 h. This sorption level could be attributed to the hydrate of vacuum-dried γ-CD if the amorphous structure contains more free volume than the cage structure. The sorption maximum is followed by the expulsion of approximately three moles of water, which lowers the sorbed concentration to 15 moles per mole of γ-CD, which is close to the sorption level of cage γ-CD at the same water activity as seen in Figure 2. The WAXD pattern for vacuum-dried columnar γ-CD (Fig. 3e), collected approximately 24 h after completion of the sorption kinetics experiment of Figure 5, shows a complete transformation to the cage structure. This sample was stored in a sealed vial under ambient laboratory conditions during the intervening 24-h period.

TGA was used to measure the water content of as-precipitated columnar γ-CD (Fig. 6). The TGA scan shows two major regions of weight loss. The first one is a dehydration step that occurs between 25 °C and 160 °C. The dehydration step accounts for approximately 24 wt % loss, which corresponds to 22.4 moles of water per mole of γ-CD. The dehydration step occurs over a range of 135 °C, suggesting multiple binding energies for water. The broadness of the transition could result from water molecules in different environments (e.g., water inside vs water outside the γ-CD cavity) exiting the crystal at different temperatures. The second weight loss region occurs between 310 °C and 420 °C, which is associated with the decomposition of γ-CD.

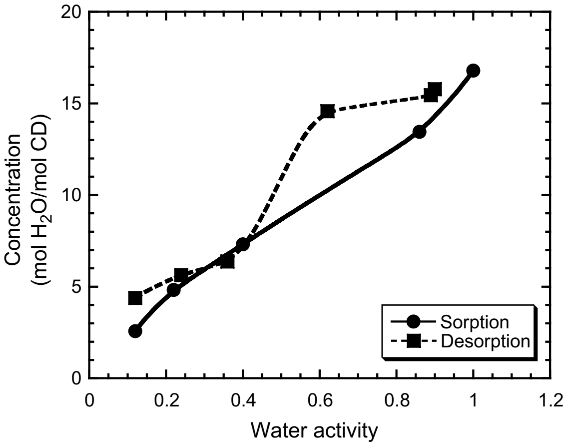

**Figure 4.** Sorption isotherm for water vapor in vacuum-dried columnar γ-CD at 40 °C.

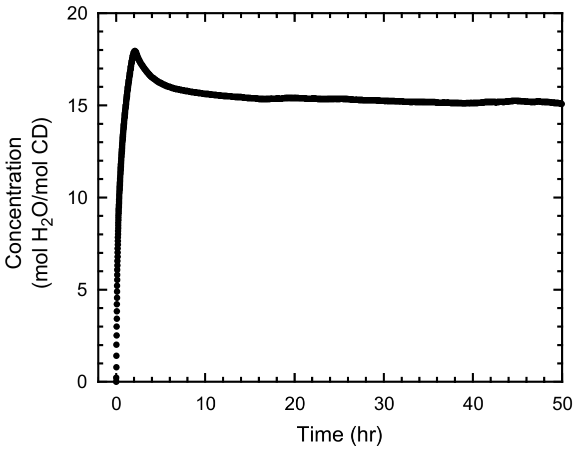

**Figure 5.** Water vapor sorption kinetics for vacuum-dried columnar γ-CD at $a = 1.0$ and 40 °C.

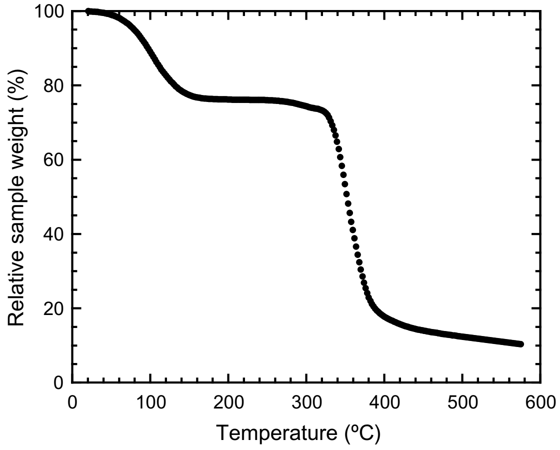

**Figure 6.** Thermogravimetric analysis at 10 °C/min. for as-precipitated columnar γ-CD initially containing 24 wt % water or 22.4 moles of water per mole of γ-CD.

A sorption kinetics experiment was also performed with as-precipitated columnar γ-CD at 40 °C and $a = 1.0$ (Fig. 7). At approximately 20 min, the sample sorbed a maximum of 24.5 moles of water per mole of γ-CD, followed by a loss of 7.9 moles after approximately 7 h. The final water vapor sorption level of 16.6 moles is close to that of the γ-CD cage structure, which contains 16.1 moles of water per mole of γ-CD (Fig. 2), suggesting a columnar-to-cage phase transformation occurs under these conditions. These results may be compared with similar results for columnar α-CD from our laboratory.[17] Columnar α-CD reaches a maximum sorption level of 5.5 moles of water per mole of α-CD after 15 min at 40 °C and $a = 1.0$. This is followed by a loss of 2.3 moles of water per mole of α-CD over a 2-h period as the columnar α-CD begins transforming to the cage structure. WAXD shows that complete conversion of α-CD to the cage structure requires approximately 100 h at 40 °C and $a = 1.0$.

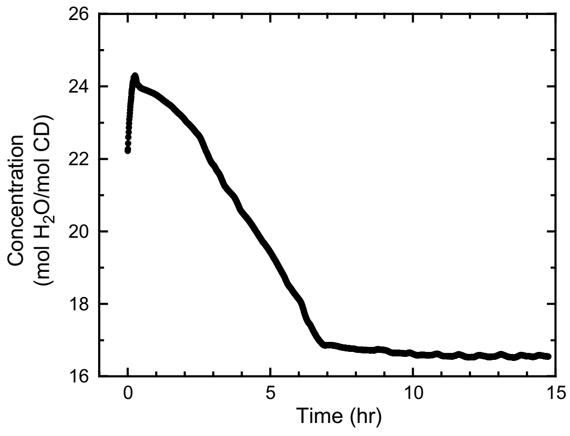

**Figure 7.** Water vapor sorption kinetics for as-precipitated columnar γ-CD at $a = 1.0$ and 40 °C.

The crystal structure of columnar γ-CD has not been completely characterized due to the method by which it is obtained. Rapid precipitation from the solution with a nonsolvent produces crystals that are too small for traditional single-crystal X-ray diffractometry studies. For this work, the crystal structure of columnar γ-CD is presumed isomorphous with the tetragonal $P42_12$ crystal of γ-CD·12-crown-4-LiSCN IC.[13] This assignment is based on the close match of the *d*-spacings (Table 1) derived from the as-precipitated columnar γ-CD hydrate WAXD pattern (shown in Fig. 3b) to the *d*-spacings calculated for the structure of γ-CD·12-crown-4-LiSCN IC proposed by Kamitori et al.[13] This lattice contains 7.7 molecules of water per molecule of γ-CD, all located outside the γ-CD cavities because of the included crown ether guest molecules.

To further understand the kinetics of the phase transformation in vacuum-dried columnar γ-CD suggested in Figures 4 and 5, time-dependent WAXD patterns were collected for samples stored at $a = 1.0$ and 40 °C. These patterns (Fig. 8) show no significant changes on the time scale of the sorption data for the same sample studied in

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

| $2\theta$ (obs) (deg) | *d* (obs) (Å) | *d* (calcd)[a] (Å) | (*hkl*) |
|---|---|---|---|
| 5.30 | 16.7 | 16.5 | (011) |
| 7.45 | 11.9 | 11.9 | (200) |
| 10.5 | 8.42 | 8.25 | (202) |
| 11.6 | 7.66 | 7.64 | (003) |
| 12.1 | 7.31 | 7.27 | (013) |
| 14.2 | 6.25 | 6.43 | (023) |
| 14.9 | 5.94 | — | — |
| 15.8 | 5.62 | 5.50 | (033) |
| 16.7 | 5.32 | 5.44 | (331) |

[a] Calculated assuming a tetragonal unit cell with $a = b = 23.75$ Å, $c = 22.92$ (Ref. 13).

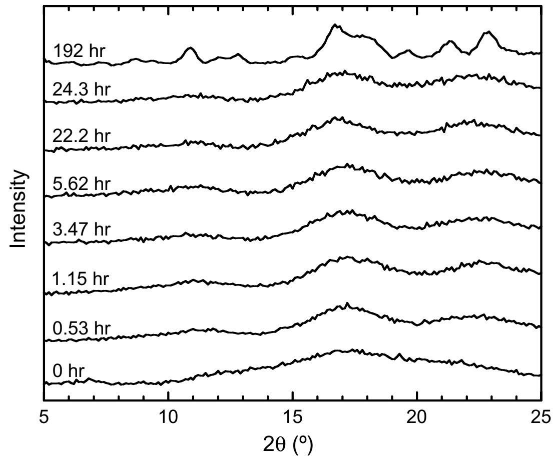

**Figure 8.** WAXD patterns of vacuum-dried columnar γ-CD exposed for various times to water vapor at $a = 1.0$ and 40 °C.

Figure 5. Therefore, the expulsion of three moles of water per mole of γ-CD after 2 h at $a = 1.0$ and 40 °C does not signify the end of the phase transformation. The phase transformation occurs over a much longer time period, as evidenced by the preliminary appearance of cage γ-CD reflections sometime between 24 and 192 h (8 days). A complete transformation to the cage structure apparently would require more than 192 h under these conditions. A similar vacuum-dried sample of columnar γ-CD exposed to ambient laboratory conditions ($a = 0.58$ at 21 °C; data not shown) for 26 h also showed no change from its amorphous X-ray pattern.

In contrast, a similar sample subjected to the sorption kinetics experiment of Figure 5, then stored under ambient laboratory conditions for 24 h, underwent a more rapid transformation to the cage structure (Fig. 3e). This sample endured a total of 50 h of exposure to water vapor at 40 °C and $a = 1.0$. The larger number of reflections for the X-ray pattern in Figure 3e compared to Figure 8 could be due to exposure of the sample to ambient conditions for 24 h after the conclusion of the experiment in Figure 5 and before the collection of the WAXD pattern in Figure 3e. During this time, the sample loses water and cools slightly. This suggests that the phase transformation is accelerated by a reduction in either water activity or temperature. Loss of water from the sample could increase the interactions between γ-CD molecules, allowing the cage structure to develop more rapidly.

The WAXD patterns collected as a function of time for as-precipitated columnar γ-CD stored at $a = 1.0$ and 40 °C (Fig. 9) show a gradual reduction in the intensity of the characteristic columnar structure peak centered at $2\theta = 7.5°$. New peaks at $2\theta = 12.4°$, 15.2°, 16.5°, and 18.8° begin to appear after 164 h. These new reflections match well with those for cage γ-CD as shown in Figure 3a, again confirming the occurrence of a crystal structure transformation as suggested by the corresponding water vapor sorption kinetics experiment (Fig. 7). However, the time at which the apparent transformation occurs in the sorption kinetics experiment again is much shorter than the time required for the phase transformation seen in the WAXD patterns of Figure 9. The equilibrium sorption level for water vapor in the γ-CD columnar structure is reached before the crystal structure transformation to the cage structure is complete. Similar behavior has been noted for the columnar-to-cage transformation in α-CD.[17] After sorption equilibrium is reached, the α and γ-CD molecules undergo a slow rearrangement to the cage structure at constant water content. This indicates that a significant amount of molecular mobility exists in the various hydrated α and γ-CD crystal structures.

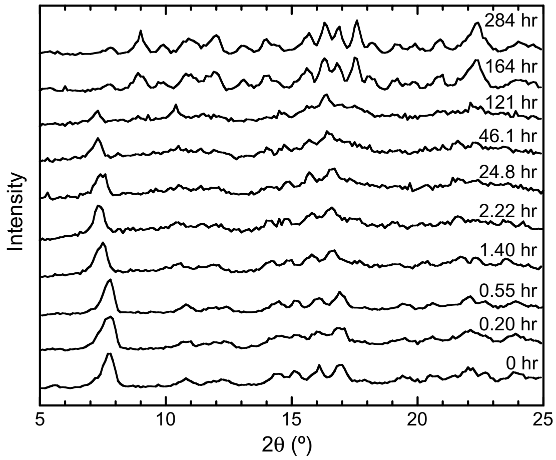

**Figure 9.** WAXD patterns of as-precipitated columnar γ-CD exposed for various times to water vapor at $a = 1.0$ and 40 °C.

## 4. Conclusions

Rapid recrystallization of γ-CD from the aqueous solution results in formation of the columnar crystal structure with only water as the guest molecule. The columnar structure transforms to an amorphous phase upon vacuum drying at 90 °C for 15 h. After equilibrium water vapor sorption at 40 °C and an activity of 1.0, amorphous γ-CD transforms to the cage structure, as suggested by the desorption isotherm, which is nearly identical to the desorption isotherm of as-received cage γ-CD. This is confirmed by WAXD performed at the end of the equilibrium water vapor sorption experiment. However, time-dependent WAXD experiments conducted with amorphous γ-CD stored at 40 °C and $a = 1.0$ reveal that the phase transformation requires more than 192 h (8 days) for completion under these conditions. As-precipitated columnar γ-CD also exhibits an extended transformation to the cage structure at 40 °C and $a = 1.0$ that requires 164 h. In both cases, sorption equilibrium is reached long before the crystal structure transformation to the cage structure is complete. Similar behavior has been noted for the columnar-to-cage transformation in α-CD.[17] After reaching sorption equilibrium, the CD molecules apparently undergo a slow rearrangement to the cage structure at constant water content. This indicates that a significant amount of molecular mobility exists in the various hydrated α- and γ-CD crystal structures. Water content clearly plays an integral role in the crystal structures adopted by γ-CD, and it is likely that water content is also important in determining the crystal structures of polymer–CD ICs as well.

## Acknowledgments

The authors appreciate funding from the state of North Carolina and the National Textile Center (Grant #M02-

NS01). Tamer Uyar assisted in sample preparation, L. Catherine Heath assisted in sorption data collection and Justin D. Fox assisted in WAXD data collection.

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