Solid-State Complexation of Poly(Ethylene Glycol) with α−Cyclodextrin

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ABSTRACT: Low-molecular-weight liquid poly(ethylene glycol) (PEG) spontaneously forms an inclusion compound (IC) when combined with α-cyclodextrin (α-CD) powder at room temperature. This process can be followed with wide-angle X-ray diffraction (WAXD). The WAXD data shows that the α-CD crystals undergo a solid-state crystal−crystal transformation from the cage to the channel crystal structure upon IC formation over a period of about 8 h. The time dependence of the $2\theta = 20°$ α-CD channel structure X-ray peak can be described by a simple first-order kinetic model. The effects of changing the temperature, PEG:α-CD molar ratio, PEG molecular weight, and vacuum-drying the CD have been studied. The barrier opposing the PEG inclusion-induced solid-state transformation of α-CD from the cage to the channel crystal structure appears to be dominated by changes in the packing/interactions of α-CDs, rather than the loss in the conformational entropy experienced by the PEG chains during the inclusion process.

Introduction

Cyclodextrins (CDs) are torus-shaped cyclic starch molecules containing 6, 7, or 8 glucoside rings and are referred to as α-, *β*-, and *γ*-CD, respectively (Figure 1). They were first isolated from starch by Villiers in 1891[1] and have since been of increasing interest due to their unique ability to form crystalline inclusion compounds (ICs) with both small molecules[2] and polymers.[3−8] The included (guest) polymer chains in polymer/CD-ICs are isolated and highly extended because they are confined to occupy narrow channels in the crystalline matrix formed by the CD host (Figure 2). When guest polymers are coalesced from their CD-IC crystals by disruption of the IC and removal of CD with a solvent that is good for the CD, but which is a nonsolvent for the polymer, the resultant consolidated guest polymer chains may retain some degree of their extended, unentangled nature. As a consequence of the unique environment provided by CD-ICs for their guest polymers, it might be expected that consolidation of guest polymers from their CD-ICs could yield bulk polymer samples with structures and morphologies that are significantly altered from those normally achieved from their disordered solutions and melts.

The effects produced by coalescing polymers from their CD-IC crystals may be generally summarized in the following ways:[9−11] (i) crystallizable homopolymers can evidence increased levels of crystallinity, different polymorphs, and higher melting and decomposition temperatures than samples consolidated from their disordered solutions and melts, (ii) molecularly mixed, intimate blends of two or more polymers that are normally believed to be immiscible can be achieved by coalescence from their common CD-IC crystals, (iii) the phase segregation of incompatible blocks can be greatly suppressed when block copolymers are coalesced from their CD-IC crystals, and (iv) the thermal and temporal stabilities of the well-mixed homopolymer blends and block copolymers obtained by coalescence from their CD-ICs appear to be substantial, thereby suggesting retention of their as-coalesced structures and morphologies under normal thermal processing conditions.

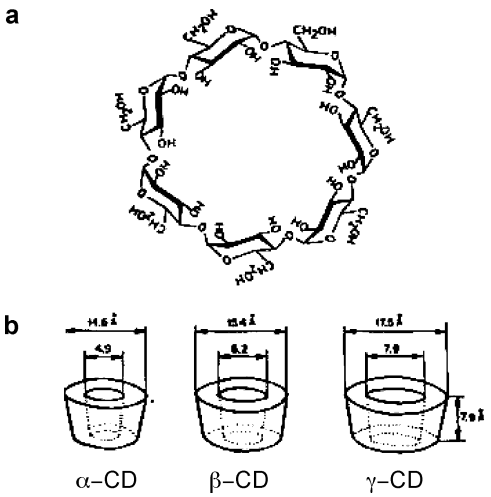

Figure 1. The chemical structure of *β*-CD (a) and the dimensions of α-, *β*-, and *γ*-CD (b).

The specific inclusion compound formed between α-CD and poly(ethylene glycol) (PEG) was first studied by Harada and Kamachi.[3] These inclusion compounds were prepared by adding aqueous solutions of PEG to saturated aqueous solutions of α-CD, which resulted in formation of the crystalline IC as a precipitate. It was found that the PEG CD-IC contains two PEG repeat units per α-CD molecule (described as a 2:1 molar ratio hereafter) and that PEG did not form an IC with *β*-CD. The rate at which the ICs were formed was determined by following the development of turbidity in these solutions with time. A maximum in the rate of turbidity development was found for PEG of molecular weight 1000 g/mol. Horsky[12] studied the formation of solvated ICs between PEG and 2-hydroxypropyl-α-CD using reduced viscosity measurements and also found that PEG formed an IC with α-CD but not with *β*-CD.

Many methods have been used to confirm the formation of polymer−CD ICs after the fact, including NMR,

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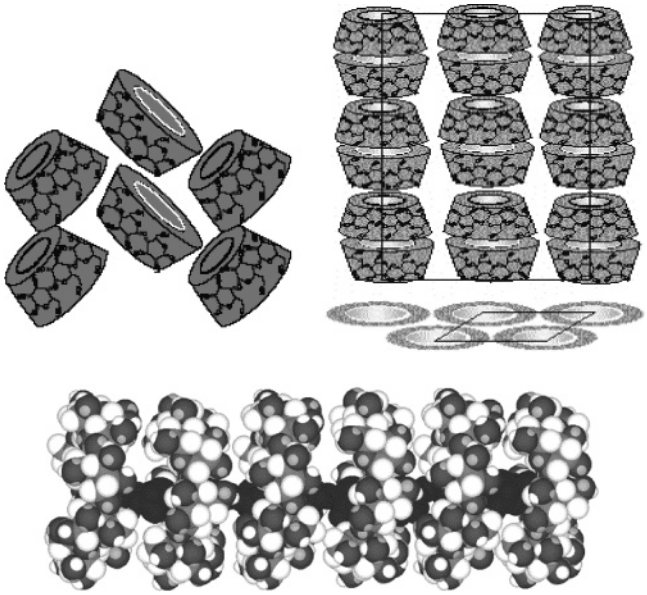

Figure 2. Cage and columnar CD crystal structures (upper) and a polymer chain isolated in the channel of its CD-IC (lower).

DSC, FTIR, reduced viscosity measurements, and wide-angle X-ray diffraction (WAXD).[3−16] In general, these methods have not been used to follow the kinetics of the inclusion process. The most accepted and direct of these methods has been WAXD, as it can clearly differentiate between the cage and channel structures of CD (see Figure 2), the latter being indicative of an inclusion compound.[5,13,17] The channel structure for α-CD is characterized by a strong reflection around $2\theta = 20°$ and contains α-CD molecules stacked on top of each other in the crystal lattice to form long, cylindrical channels in which the guest molecules reside. The cage structure for α-CD does not have continuous channels and is characterized by a strong reflection around $2\theta = 12°$.

In this paper, we report the formation of inclusion compounds between low-molecular-weight PEG and α-CD simply by mixing the liquid PEG with α-CD powder. During IC formation, the α-CD undergoes a solid-state crystal structure transformation from the cage to the channel structure, which allow the kinetics of this process to be followed with WAXD. The effects of varying the temperature and PEG molecular weight on the inclusion kinetics are also presented.

Experimental Section

PEG having molecular weights of 200 and 400 g/mol (PEG200 and PEG400, respectively) was obtained from Aldrich Chemical, and α-CD was obtained from Cavitron. WAXD patterns were collected on a Siemens type-F X-ray diffractometer from $2\theta = 5°$ to 40° using a nickel-filtered Cu−Kα radiation source (wavelength = 1.54 Å) operating at a voltage of 30 kV and a current of 20 mA.

It has been established that the molar ratio of PEG repeat units to α-CD molecules is 2:1 when the PEG molecule is fully threaded by α-CD in an inclusion compound.[18] Samples for X-ray analysis were prepared by mixing PEG with α-CD and stirring by hand. Most samples were prepared at a PEG/α-CD molar ratio of 3:1, while a few samples were prepared at ratios of 5:1 and 2:1 for comparison. The resulting slurry was then placed in a standard X-ray pan inside the diffractometer. Scans were obtained once per hour up to 8 h, and then a few scans were taken at 24 h and later to ensure that the complexation process was finished and no further changes occurred. Over this time, the sample consistency changed from a wet slurry to a dry paste. For the room-temperature experiments ($T = 20$ °C), samples remained in the diffractometer during the entire time period studied. For the higher-temperature experiments, samples were placed in an oven at the desired temperature and removed at the time intervals mentioned above for X-ray analyses at room temperature.

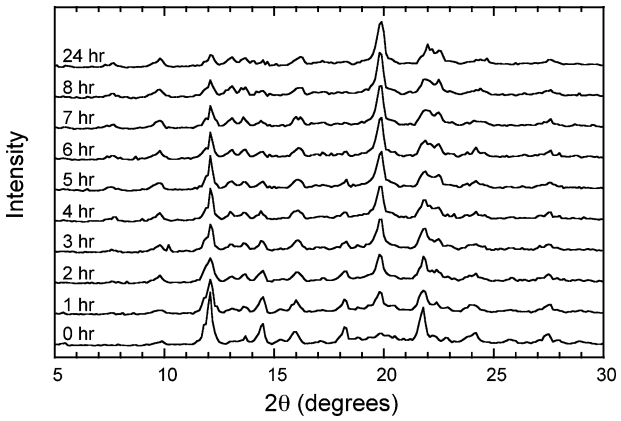

Figure 3. Time-dependent diffractometer scans for a 2:1 mixture of AR PEG200/α-CD obtained at 20 °C.

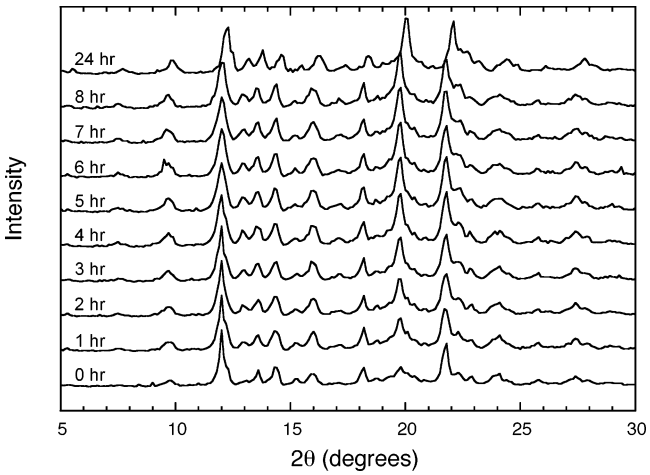

Figure 4. Time-dependent diffractometer scans for a 3:1 mixture of AR PEG200/α-CD obtained at 20 °C.

Results and Discussion

A typical set of time-dependent diffractometer scans recorded after mixing as-received PEG200 with α-CD are shown in Figure 3. The molar ratio of PEG repeat units to α-CD was 2:1 for these experiments. These patterns clearly show the disappearance of the cage structure which is associated with the reduction in intensity of the 12° peak. This reduction correlates with an increase in intensity of the peak at 20° associated with the channel structure, which indicates that α-CD undergoes a solid-state phase transformation as it forms an inclusion compound with PEG. The size of the 20° peak is about the same for the 8 and 24 h scans, indicating that the phase transformation has stopped after 8 h.

Similar results were obtained for as-received PEG200/α-CD ICs formed at temperatures of 20, 40, and 60 °C using a 3:1 molar ratio of PEG repeat units to α-CD, and these are displayed in Figures 4, 5, and 6, respectively. The integrated intensities of the peak at $2\theta = 20°$ are plotted vs time in Figure 7 for all the X-ray patterns in Figures 3−6. For each series of diffraction

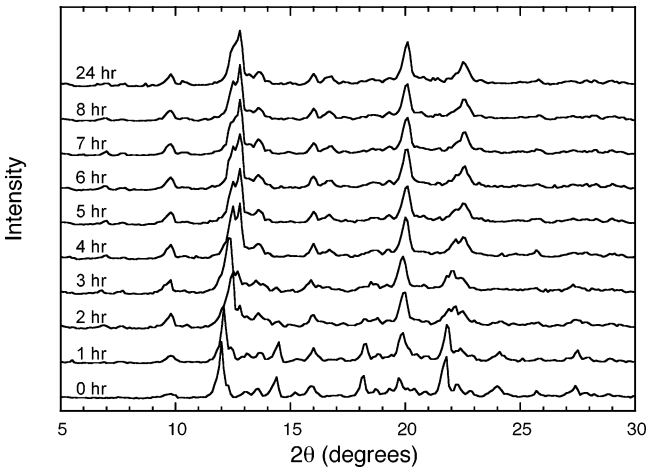

Figure 5. Time-dependent diffractometer scans for a 3:1 mixture of AR PEG200/α-CD obtained at 40 °C.

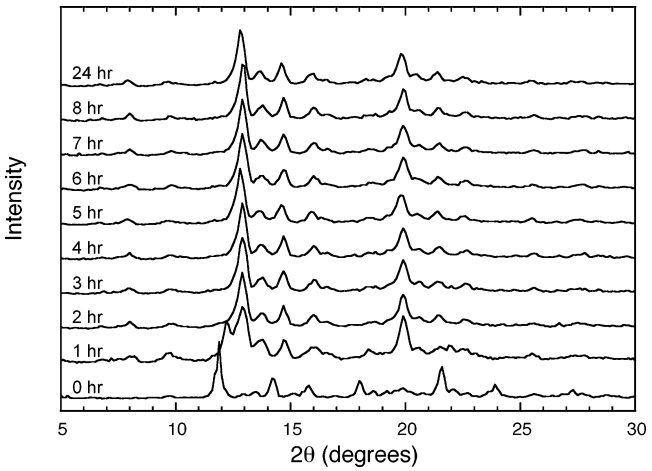

Figure 6. Time-dependent diffractometer scans for a 3:1 mixture of AR PEG200/α-CD obtained at 60 °C.

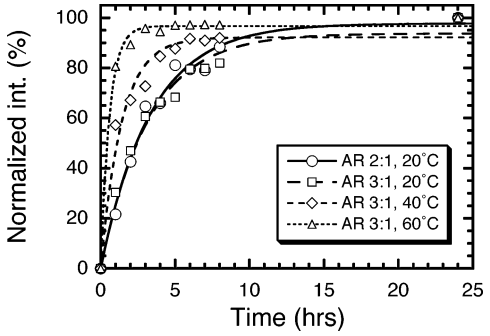

Figure 7. Dependence of the normalized integrated X-ray intensities for the $2\theta = 20°$ channel structure peak with time for AR 3:1 PEG200 at various temperatures and stoichiometric ratios of PEG/α-CD. The lines are fits of the first-order kinetic model to the data.

patterns, intensities were normalized to 0 for the $t = 0$ scan and 100 for the final scan at 24 h to facilitate comparison. The two data sets at 20 °C differ slightly in the PEG/CD molar ratio, yet they still demonstrate good reproducibility. The inclusion kinetics and associated CD crystal structure transformation occurs more rapidly as temperature is increased.

The data in Figure 7 were fit by a first-order kinetic model which assumes that the rate at which the intensity (I) of the 20° channel structure peak increases is proportional to the amount of cage structure remaining ($I_\infty - I$), where I_∞ is the intensity of the 20° peak when the transformation is complete. This is expressed in eq 1:

$$\frac{dI}{dt} = k(I_\infty - I) \tag{1}$$

where k is the rate constant and t is time. The solution to eq 1 is

$$I = I_\infty(1 - e^{-kt}) \tag{2}$$

The solid lines in Figure 7 represent fits of eq 2 to the data, with k and I_∞ as adjustable parameters. The parameter values are collected in Table 1, rounded to two significant figures. The uncertainties in the parameter values derived from the curve-fitting routine are listed as "±" values in Table 1. This model fits the data reasonably well at each temperature. The rate constants for the runs at 20 °C are very similar, again indicating good reproducibility between these two data sets. An Arrhenius plot showing the temperature dependence of the rate constants for the PEG200 as-received samples is displayed in Figure 8. The plot is linear and yields an activation energy of 8.3 ± 0.3 kcal/mol of α-CD. This number may be compared with a free energy change of 2.5 kcal/mol of α-CD (or 2 mol of PEG repeat units), which has been calculated by Tonelli[19] for PEG when it transforms from a randomly coiled molecule to an extended conformation upon complexation with α-CD. This suggests that most of the energy required to induce formation of a PEG/α-CD IC is not associated with the conformational restriction of the included polymer. Rather, the free energy change associated with the α-CD crystal structure transformation induced by PEG inclusion is dominated by differences in the packings and interactions between α-CDs in the channel and cage structures.

Table 1. Parameters for First-Order Kinetic Model

sample[a]	k (s^{-1})	I_∞ (%)
PEG200, AR 2:1, 20 °C	0.30 ± 0.03[b]	98 ± 4[b]
PEG200, AR 3:1, 20 °C	0.31 ± 0.03	94 ± 3
PEG200, AR 3:1, 40 °C	0.71 ± 0.10	92 ± 3
PEG200, AR 3:1, 60 °C	1.7 ± 0.1	97 ± 1
PEG200, VD 3:1, 20 °C	0.31 ± 0.03	97 ± 3
PEG200, VD 5:1, 20 °C	0.47 ± 0.04	100 ± 2
PEG400, AR 2:1, 20 °C	0.077 ± 0.019	120 ± 20

[a] AR = as received; VD = vacuum-dried; 3:1 = PEG repeat unit/α−CD molar ratio. [b] Uncertainties in the parameters from the curve-fitting process.

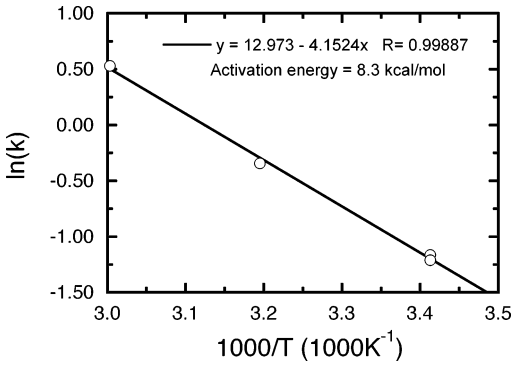

Figure 8. Arrhenius plot for AR 3:1 PEG200/α-CD inclusion compound formation.

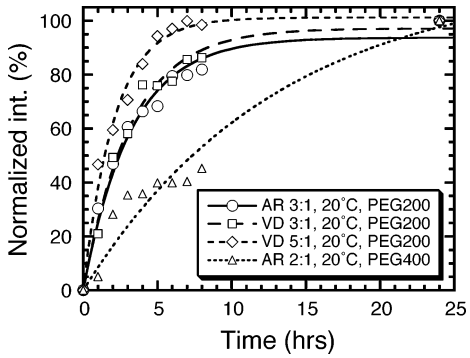

Figure 9. Dependence of the normalized integrated X-ray intensities for the $2\theta = 20°$ channel structure peak with time for various PEG/α-CD molar ratios and PEG molecular weights at room temperature. AR, as-received; VD, vacuum-dried. The lines are fits of the first-order kinetic model (eq 2) to the data.

The effects of increasing the PEG repeat unit/α-CD molar ratio, vacuum-drying the α-CD prior to complexation, and increasing the PEG molecular weight were also considered. Shown in Figure 9 are the time-dependent integrated X-ray intensities for the $2\theta = 20°$ channel structure peak acquired at 20 °C for: (i) a sample consisting of a 5:1 molar ratio of PEG200 repeat units to α-CD, (ii) a 3:1 sample for which the α-CD was initially vacuum-dried at 80 °C for one week, and (iii) a 2:1 sample prepared using PEG400. These are compared with the 3:1 PEG200/α-CD as-received sample (the same data as the squares in Figure 7). After extended vacuum-drying, it was found that the α-CD still contained 1.2 mol of water per mole of α-CD. It is likely that this remaining water is entrapped in the interstitial cavities of α-CD, where it is strongly hydrogen-bonded with the hydroxyl groups on the outside of the α-CD molecules. Water contained within the hydrophobic α-CD cavities is not strongly bound and would be expelled after extended vacuum-drying at 80 °C. Comparison of the vacuum-dried sample with the as-received sample shows a negligible effect on the complexation kinetics, suggesting that the water inside the α-CD cavities in the as-received sample does not affect the complexation kinetics. Increasing the amount of PEG in the sample to a 5:1 molar ratio (well beyond the stoichiometric limit of 2:1 for the PEG/α-CD-IC) speeds the complexation process considerably, while increasing the molecular weight of PEG from 200 to 400 g/mol slows the complexation process.

These results, as well as the effect of temperature on the complexation kinetics, can all be explained by changes in the mobility or diffusivity of the PEG molecules. The sample begins as a suspension of α-CD particles in liquid PEG which has the consistency of a slurry. The PEG mobility in this suspension will increase with increasing temperature, increasing PEG concentration, and decreasing PEG molecular weight. Higher PEG mobility should result in increased complexation rates, which is exactly what is observed. An additional factor that may contribute to the lower complexation rates observed for PEG400 is the reduction in the number of chain ends compared to PEG200. Interaction of PEG chain ends with α-CD molecules is required for the complexation process to occur; thus, a reduction in the number of chain ends might be expected to reduce the rate of complexation. However, this was not observed during the inclusion of poly(*N*-acylethylenimine)s (PNAIs) of different molecular weight from their solutions into suspended α-CD crystals[20] (see below for description of this technique), where a PNAI with a higher molecular weight was included faster than one with a lower molecular weight. Harada[3] has also noted that the complexation rate for PEG with α-CD, when both components are initially dissolved in water, increases with PEG molecular weight up to 1000 g/mole and decreases thereafter.

The rate constants obtained from fits of the kinetic model to the data in Figure 9 are also listed in Table 1 and reflect the trends noted above. However, the kinetic model is a poor fit to the PEG400 data. For this sample, the intensity of the $2\theta = 20°$ X-ray peak at 24 h is much higher than expected on the basis of the trend established by the shorter-time data. The reason for this behavior is currently not known. The 24 h data points in the other data sets shown in Figures 7 and 9 exhibit similar behavior, although the offset in those cases is much less pronounced. This causes most of the I_∞ values in Table 1 to fall systematically below the expected value of 100%.

In preliminary work, we have also monitored the solid-state complexion of PEG oligomers with α-CD by differential scanning calorimetry (DSC). This is made possible by observing the time-dependent reduction in the melting endotherm of unincluded crystalline PEG chains before they penetrate the cage α-CD and form the channel structure PEG/α-CD-IC. Though not presented here, the DSC observations confirm the results obtained by X-ray diffraction, i.e. PEG inclusion is complete after 8−10 h, the rate of inclusion decreases with an increase in the molecular weight of PEG, and the inclusion proceeds more rapidly at higher temperatures.

We have also begun to observe the inclusion of PEG from solution into cage-structure α-CD particles suspended in PEG/acetone solutions, as monitored by ^{1}H NMR. Because only the dissolved and unincluded PEG is observable by solution ^{1}H NMR, we may observe the disappearance of dissolved PEG chains as they penetrate cage-structure α-CD and convert it to PEG/α-CD-IC. For a 1% PEG200/acetone solution at room temperature containing suspended-cage α-CD at a PEG/α-CD molar ratio of 2:1, we observe the inclusion to be essentially complete in slightly over 1 h. This is an order of magnitude faster than the inclusion of neat PEG200 (see Figures 3 and 7). The mobility of PEG in solution greatly exceeds its neat mobility, but the concentration of PEG in solution is only 1% of the neat PEG. The former factor apparently dominates the latter, because the inclusion of PEG into solid-cage α-CD proceeds much faster from solution than from its bulk liquid.

These preliminary studies of the inclusion of neat and dissolved PEG oligomers by the alternative DSC and ^{1}H NMR methods, respectively, have also been performed using α-CD that already exists in the columnar channel structure (α-CD$_{col}$, see Figure 2) but only contains the water of hydration as a guest.[21] X-ray diffraction cannot be used to monitor the inclusion of PEGs into α-CD$_{col}$ because there is no change in crystal structure as hydration water is replaced by the PEG chains that are included. These alternative techniques show that the inclusion of both neat and dissolved PEG oligomers in α-CD$_{col}$ is much faster than for cage-structure α-CD, which was exclusively used here. Since no alteration of the packing and hydrogen-bonding between α-CDs occurs when PEG is included in α-CD$_{col}$, ie., there is no accompanying cage-to-columnar solid−

solid phase transition involved, it is not surprising that PEG inclusion occurs more rapidly in α-CD_{col} than in cage α-CD. As a consequence, the eventual analysis of the temperature-dependent kinetics of PEG oligomer inclusion in α-CD_{col} should permit an experimental assessment of the free energy change experienced by randomly coiling PEG oligomers as they are extended, confined, and included in α-CD_{col}.

Conclusions

α-CD spontaneously forms an inclusion compound upon mixing with neat liquid PEG at room temperature and concurrently undergoes a solid-state phase transformation from the cage to the channel structure (see Figure 2). Penetration and threading of α-CD packed in the cage structure by PEG induces the solid-state phase transition of α-CD to the channel structure. The kinetics of the phase transformation have been followed with time-dependent X-ray diffractometry. The effects of changing the temperature, PEG/α-CD molar ratio, PEG molecular weight, and vacuum-drying the α-CD have been studied. Increasing the temperature or the amount of PEG in the mixture increase the complexation rate, while increasing the PEG molecular weight decreases the complexation rate. These results can be attributed to changes in the PEG molecular mobility. Vacuum-drying the α-CD prior to complexation has no effect, which suggests that water included in the α-CD cage crystal structure does not play a role in the complexation process. The time-dependent changes in the intensity of the channel structure X-ray peak at $2\theta = 20°$ can in most cases be well-described by a simple first-order kinetic model. An Arrhenius plot of the rate constants derived from this model yield an activation energy of 8.3 ± 0.3 kcal/mol. This number can be compared to the value (2.5 kcal/mol) calculated[15] for the conformational change occurring in PEG when it transforms from its unincluded randomly coiled state to an extended conformation upon inclusion in the IC. This suggests that the free energy barrier accompanying the α-CD crystal structure transformation during IC formation is not dominated by the increased free energy of the included PEG chains, which is mainly due to the loss of conformational entropy for the highly extended and constrained included chains. Rather, the energy barrier resisting the solid-state cage-to-channel transformation of the α-CD crystal structure induced by PEG inclusion appears to be dominated by changes in the packing and interactions between α-CDs.

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