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ScienceDirect

Polymer 49 (2008) 985–991

polymer

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The effect of water and guest hydrophobicity on the complexation of oligomers with solid α-cyclodextrin

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Received 20 August 2007; received in revised form 2 January 2008; accepted 5 January 2008

Abstract

α-Cyclodextrin (α-CD), a cyclic oligosaccharide, can form inclusion complexes (ICs) with polymer molecules in which α-CD molecules stack in the columnar crystal to form a molecular tube. Physical mixtures of α-CD powder and oligomeric liquids such as poly(ethylene glycol) (PEG) have been shown to spontaneously form an IC, which is accompanied by a solid-state α-CD phase transformation from the cage to the columnar crystal structure. In this paper, the phase transformation is tracked with wide-angle X-ray diffraction as a function of temperature, atmospheric water vapor content and the type of guest molecule. A first-order kinetic model is used to describe the kinetics of complexation. The time required to completely complex PEG200 (200 g/mol) at low water activities is greater than 300 h, whereas only a few hours are necessary at high water activities. Solid-state complexation of α-CD with a hydrophobic guest molecule (hexatriacontane, HTC), is also reported here for the first time. Slower complexation kinetics are observed for α-CD with HTC compared to PEG600 (600 g/mol).

Keywords: α-Cyclodextrin; Inclusion complex; Phase transformation

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes (ICs) with small molecules and macromolecules due to their hollow, truncated cone structure. CDs are most commonly composed of 6, 7, or 8 glucopyranose units, which correspond to α-, β-, and γ-CD, respectively. These molecules have a hydrophilic surface and a hydrophobic cavity in which various guest molecules can reside. CDs can exist in two general classes of crystal structures called cage and columnar [1]. In the cage structure (Fig. 1a), the CD cavities are not aligned but can still complex with small molecules such as methanol [2] and water [3]. In the columnar crystal (Fig. 1b), CDs stack on top of each other to form long cylindrical columns in which various chain-like guest molecules can be complexed [4–7].

Polymer/CD ICs are typically made by mixing CD solutions with solutions of low or high molecular weight polymers [4,5]. However, polymer/CD ICs have recently been made with CD in the undissolved state. Rusa et al. [8] suspended solid cage and columnar γ-CD particles in deuterated acetone solutions of poly(*N*-acylethylenimine) (PNAI). Using solution ^{1}H NMR spectroscopy, a reduction in proton peaks of the polymer molecules was observed over time as the polymer came out of solution and formed an IC with the γ-CD in the particles. A simultaneous build-up of water peaks in acetone was observed as a result of expulsion of water initially included inside the γ-CD cavities. They observed that PNAI with a higher molecular weight complexed to a greater degree than PNAI with lower molecular weight, though both were included with very similar kinetics. Particles of γ-CD in the cage structure must undergo a solid-state phase transformation to the columnar structure upon formation of the IC. Faster

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doi:10.1016/j.polymer.2008.01.007

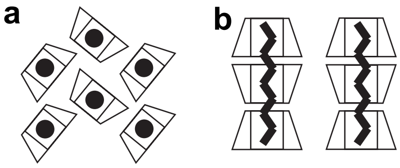

Fig. 1. Schematic representation of the packing of CD ICs within their crystal lattices: cage (a) and head-to-head columnar (b) structure.

complexation kinetics were observed when the suspended particles contained columnar γ-CD, since no solid-state phase transformation was necessary in that case.

Peet et al. [9] were able to obtain ICs of PEG and CD without any solvent. Liquid PEG having molecular weights of 200 or 400 g/mol was physically mixed with cage α-CD in a 2:1 ratio based on PEG repeat units per CD. During the complexation process α-CD transforms from the cage crystal to the columnar crystal to accommodate the PEG molecules. This conversion allowed X-ray diffractometry to be used to measure the complexation kinetics of PEG in α-CD. Similar work was reported by Harada et al. [10] which also showed that no change in α-CD particle morphology occured upon complexation.

Although Peet et al. [9] probed the temperature and molecular weight dependence of the PEG/α-CD phase transformation kinetics, they did not study the effect of water in the CD crystal. Water (i.e. relative humidity) is expected to be important in the complexation kinetics since it is a good solvent for both α-CD and PEG. In this paper, we report the effect of atmospheric water vapor on the PEG/α-CD complexation process. Parallel experiments were also carried out on hexatriacontane (HTC)/α-CD mixtures to understand the effect of guest hydrophobicity on complexation.

2. Experimental

2.1. Materials

The α-CD was purchased from Cerestar in powder form. HTC, PEG200 (200 g/mol) and PEG600 (600 g/mol) were purchased from Aldrich and used without further purification. PEGs and α-CD were vacuum-dried overnight at 50 °C to remove any absorbed water before use. Water was deionized with a Millipore Milli-DI system.

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

WAXD measurements were performed using a Siemens type-F X-ray diffractometer with a Ni-filtered Cu-Kα radiation source ($\lambda = 1.54$ Å). The supplied voltage and current were 30 kV and 20 mA, respectively. The diffraction intensities were measured at every 0.1° from $2\theta = 10$–$25°$ at a rate of $(2\theta = 3°)$/min. The WAXD scans were obtained at room temperature, whereas the complexation experiments were conducted at 30 or 90 °C. To minimize the time spent outside of the humidity- and temperature-controlled environment, diffractograms were collected from $2\theta = 10$–$25°$, which includes all the peaks of interest. This yields a 5-min scan time which is very short compared to the time necessary for the complexation to finish (several hours at least).

Time-dependent experiments designed to track the phase transformation of α-CD were conducted at 30 °C with PEG200 and PEG600 mixed with α-CD in a 3:1 molar ratio (3 repeat units/α-CD molecule) and stored at various water activities (a). Samples were prepared by gently mixing liquid oligomer and solid CD in a mortar and pestle for approximately 1 min. A WAXD pattern was collected for this initial mixture which is defined as the start of the experiment ($t = 0$ h). The constant humidity chambers consisted of jars containing either pure deionized water ($a = 1$), dessicant ($a = 0$), or a saturated aqueous salt solution ($0 < a < 1$). The samples were removed from the humidity chambers at various times during the experiment and placed in the diffractometer to collect diffractograms as a function of time. The characteristic peaks for cage α-CD are centered at $2\theta = 12.0$ and 21.7°, which correspond, respectively, to the (031) and (331) planes with $d = 7.4$ and 4.1 Å [3]. Columnar α-CD has characteristic peaks at $2\theta = 13.0$ and 20.0°, which correspond to the (110) and (120) planes with $d = 6.8$ and 4.4 Å [6]. None of these d-spacings correspond in a simple way to the dimensions of an α-CD molecule. It should be mentioned that the peak assignments for the columnar structure are based on the analysis of an IC formed between α-CD and LiI_3/I_2 [6]. Although these peaks are commonly observed for other columnar α-CD ICs, a complete crystal structure determination has not been performed for the ICs studied in this paper since it is difficult to prepare large single crystals of the ICs. Thus, the same indexing assignments may not apply here.

For the HTC samples, α-CD and HTC powders were placed in a mortar and heated to 90 °C to ensure complete melting of HTC ($T_{melt} = 75$ °C). The components were then mixed in the hot mortar with a pestle also heated to 90 °C for approximately 1 min. A WAXD pattern was collected for this initial mixture which is defined as the start of the experiment ($t = 0$ h). The HTC/α-CD mixtures were removed from the humidity chambers at various times during the experiment and placed in the diffractometer to collect diffractograms as a function of time. To compare the results for HTC to PEG at the same temperature, similar experiments were conducted at 90 °C for PEG600/α-CD mixtures.

3. Results

Fig. 2 shows time-dependent X-ray diffraction patterns of a 3:1 (mol PEG repeat units/mol α-CD) mixture of PEG200 and α-CD which was complexed at a water activity of 1.0 and 30 °C. This ratio is 50 mol% in excess of the stoichiometric ratio [10] of 2:1 PEG repeat units per α-CD and corresponds to 13.6 wt% PEG. α-CD cage peaks are eliminated within 20 h while a gradual build-up of the columnar structure peak at $2\theta = 20°$ occurs. This provides clear evidence of a transformation from cage-to-columnar structure. The only mechanism by which cage α-CD converts to the columnar structure is through complexation/inclusion of PEG chains with/into α-CD cavities.