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Note

Solubility and primary nucleation of cyclomaltoheptaose

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Cyclomaltoheptaose, (β-cyclodextrin, βCD) is composed of seven glucose units linked α-(1 → 4) in a cyclic structure. It is produced industrially from the enzymatic reaction of corn or potato starch. The unique structure of this compound, with the hydroxyl groups oriented on the outside of the ring, gives the molecule both polar and nonpolar sections and facilitates an ability to form inclusion complexes in the hydrophobic cavity. Many applications, particularly in the food and pharmaceutical industries, have been proposed for cyclodextrins. A review of many of these applications and other aspects of cyclodextrin technology is given by Szejtli [1,2].

The purpose of the present work was to determine the solubility and primary nucleation characteristics of βCD in water. Two types of samples were examined: (*i*) a refined material which may be considered relatively pure; (*ii*) a spray-dried sample that contained small, undefined amounts of impurities. Solubility measurements were performed between 14.7 and 85.1°C, and the nucleation experiments were performed for βCD concentrations between 25.4 and 185.9 mg of βCD/g H_2O for the refined sample and between 38.5 and 241.5 mg βCD/g H_2O for the spray-dried sample.

The results of the solubility measurements for the refined βCD are presented in Table 1. In general, the reproducibility was within ±0.6%. Fig. 1 shows that the new data are in good agreement with the measurements by Wiedenhof and Lammers [3] and Jozwiakowski and Connors [4]. French et al. [5] also report a room-temperature solubility of βCD in water to be 1.85 g/100 mL solution, which is in close agreement

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Table 1
Solubility of refined β-cyclodextrin in water

Temperature (°C)	βCD Solubility (mg/g H_2O)	Number of samples	Reproducibility (standard deviation)
14.7	13.18	3	0.013
20.0	15.35	3	0.050
26.1	19.90	3	0.075
35.0	28.28	2	0.158
40.0	35.33	3	0.079
44.8	43.86	3	0.041
50.4	58.47	3	0.214
54.8	72.15	3	0.843
60.7	95.52	3	0.269
64.9	118.4	3	0.132
70.3	154.2	3	0.292
75.0	195.6	3	0.441
80.0	251.3	3	0.863
84.8	315.7	3	1.595

to an interpolated value obtained from the data of the present work. However, since French et al. did not report a specific temperature, their value is not presented in Fig. 1. No previously published data are known to exist for temperatures above 48°C.

The solubility data were fit with an exponential equation which showed that solubility is given by

$$c^* = 5.91 \exp(0.046T) \quad (1)$$

where c^* is the equilibrium concentration of βCD expressed in mg/g H_2O, and T is temperature in °C. Given the form of this relationship, subsequent plots involving the equilibrium behavior are logarithmic.

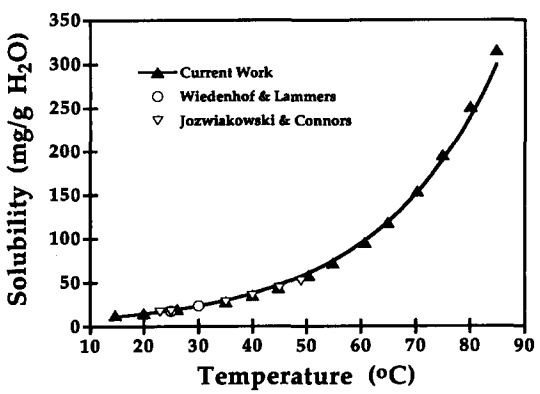

Fig. 1. Solubility of refined βCD in water.

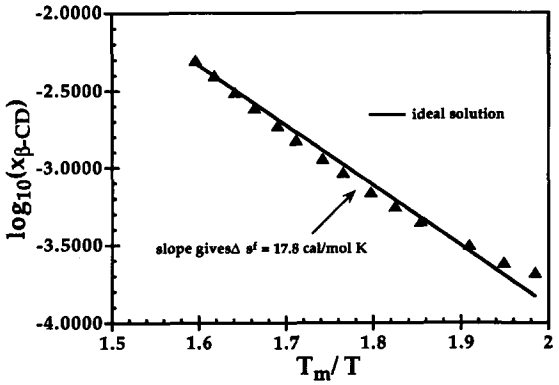

Fig. 2. Plot of solubility data using the ideal solution approximation ($\log_{10} x_{\beta CD} \rightarrow 0$ as $T_m / T \rightarrow 1$).

The data could also be treated as an ideal solution as described by Prausnitz [6]. Assuming ideal solution behavior

$$\ln \frac{1}{x_{\beta CD}} = \frac{\Delta h^f}{RT}[1 - T/T_m] \tag{2}$$

where $x_{\beta CD}$ is the mole fraction of βCD, Δh^f is the enthalpy of fusion of βCD, and T_m is the melting point of βCD. Through procedures described by Prausnitz, eq. (2) can be modified to

$$\ln x_{\beta CD} = -\frac{\Delta s^f}{R}\left[\frac{T_m}{T} - 1\right] \tag{3}$$

where Δs^f is the entropy of fusion. Fig. 2 shows the solubility measurements plotted using 298°C (571 K) as the melting temperature of βCD. The slope gave a value of $\Delta s^f = 17.8$ cal/mol K. Similarly, the heat of fusion was determined to be 10,200 cal/mol.

The results of the solubility measurements for the spray-dried βCD are presented in Table 2. The reproducibility for the spray-dried sample solubility measuments was generally within 1.5%. Comparisons between the refined and spray-dried βCD are shown in Fig. 3. The presence of cyclomaltohexaose (α-cyclodextrin), cyclomaltooctaose (γ-cyclodextrin), or acyclic sugar impurities in the spray-dried sample could account for the higher solubility, since all these compounds have higher solubilities in water than βCD. However, the material used to obtain these data was from a proprietary sample, and no analytical data were available to confirm the presence of these impurities.

Metastable limits were difficult to determine because of the difficulty in distinguishing the first crystals from exogenous insoluble particles that may have been present in the system. As a consequence, the nucleation temperatures reported here may be slightly low; however, they are thought to be within 1.5°C of the point of nucleation.

Table 2
Solubility of the spray-dried βCD sample

Temperature (°C)	βCD Solubility (mg/g H_2O)	Number of samples	Reproducibility (standard deviation)
15.0	18.69	2	0.025
20.1	22.20	3	0.501
25.0	24.07	3	0.271
30.0	28.25	3	0.148
35.0	35.34	3	0.137
40.0	46.60	3	0.218
45.0	56.79	3	0.508
50.2	71.68	3	0.162
54.7	90.88	3	1.013
59.9	113.9	2	0.497
64.9	142.2	3	2.517
70.7	188.6	3	0.580
74.9	230.8	3	0.400
80.1	298.0	3	0.511
85.1	388.7	3	4.677

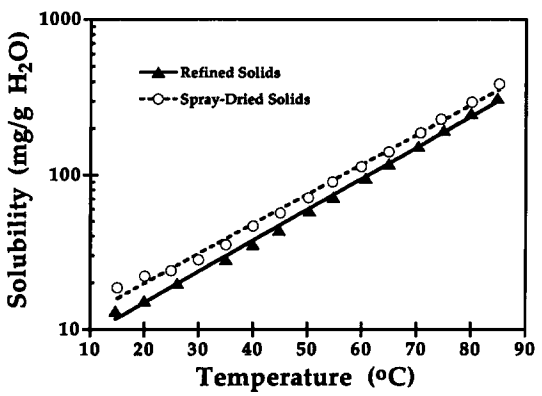

Fig. 3. Comparison of the solubilities of the βCD samples.

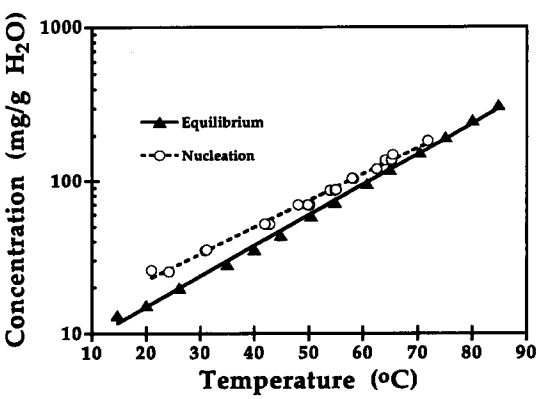

Fig. 4. Nucleation temperatures of refined βCD in water.

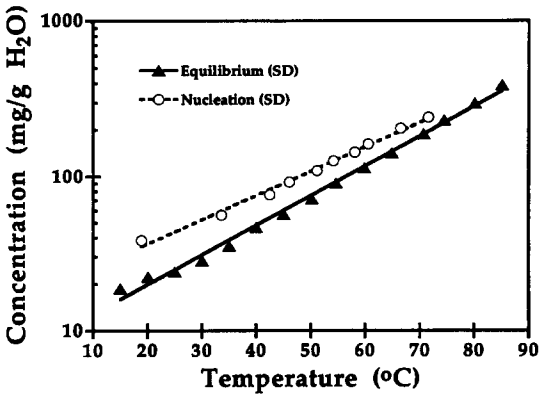

Fig. 5. Nucleation temperatures of spray-dried βCD in water.

The results of the refined βCD nucleation experiments are shown in Fig. 4. As expected, the metastable limit (the difference between the solubility and nucleation curves) is larger at lower solution concentrations, with the metastable nucleation temperature becoming very close to the solubility temperature at βCD concentrations above 150 mg βCD/g H_2O.

The results of the spray-dried βCD nucleation experiments are shown in Fig. 5. Like the refined material, these results show expected larger metastable limits at lower solution concentrations. However, the metastable region for the spray-dried βCD sample is larger over the entire composition range than for the refined sample.

The results of the experiments on nucleation demonstrate that the degree of subcooling that can be supported by solutions of βCD depend upon the solution concentration. Concentrations of the order of 25 mg βCD/g H_2O will support as much as a 9°C subcooling without nucleation, while concentrations in the order of 200 mg βCD/g H_2O will support no more than about 1°C subcooling. It should be noted, however, that these values are for the given cooling rate and may vary with the crystallizer.

A second conclusion that can be drawn from these results is that impurities typically found in processing βCD tend to inhibit nucleation. Solutions comprised of spray-dried βCD can support subcoolings of almost twice those of refined material.

1. Experimental

Solubility.—Approximately 80 mL of distilled water and excess solute (βCD) were added to a cylindrical jacketed mixing vessel constructed of glass. The solution was mixed with a Teflon-coated stirring bar on the bottom of the mixing vessel. The mixing vessel was approximately 100 mL in volume and contained three baffles to aid mixing. The top of the mixing vessel was covered to prevent contamination and evaporation.

The temperature of the mixing vessel was measured by a calibrated mercury thermometer and controlled by circulating water from a bath through the jacket. Mixing was continued for at least 3 h prior to sampling the solution. This was found to be

adequate for establishing equilibrium; that is, experiments were performed to determine that the solution had achieved a constant βCD concentration after 3 h.

The vessel contents were sampled by extracting an aliquot of approximately 5 to 10 mL with a syringe and filtering the aliquot through a syringe filter assembly equipped with a 0.45-μm nylon filter. The filtered aliquot was collected in a 50-mL beaker and covered to prevent evaporation. The weight of the aliquot was determined, the water evaporated, and the remaining βCD weighed. Where appropriate, the syringe and filter assembly were heated to prevent crystallization during sampling and filtering. Whether the syringe and filter assembly were heated and the amount of heating depended on the solution temperature. In general, three samples at each temperature were taken. The solubility was determined from an average of the samples. For the lower temperature measurements (40°C and lower), some of the samples were taken at the same time; however, for the higher temperature measurements, each sample was taken in approximately 30- to 40-min intervals.

Distilled water was used in the experiments. The βCD samples were supplied by the American Maize-Products Company. The refined and spray-dried samples contained an estimated 12.4 and 9.5% water, respectively.

Metastable limits.—Solutions of βCD and water were prepared by adding a specified mass of βCD and a given volume of water into the jacketed mixing vessel previously described. The solutions were held for at least an hour at approximately 10°C or more above the solubility conditions. Then the solution was filtered through a 0.45-μm nylon filter into another jacketed mixing vessel. Despite filtration, a few small insoluble particles (presumably starch) still remained. It should be added, however, that these particles were often only readily noticeable with the aid of illumination directly behind the mixing vessel (light scattering). After filtration, the solution temperature was held constant for at least an additional hour. The temperature was then lowered at a rate of 6°C/h until crystallization occurred, as determined visually with the aid of light scattering. The temperature at nucleation is referred to as the metastable limit at the given conditions (solution composition and cooling rate).

Acknowledgement

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