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Crystallization on heating and complex phase behavior of α-cyclodextrin solutions

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Solutions composed of α-cyclodextrin (α-CD), water, and various methylpyridines, in particular, 4-methylpyridine (4MP), undergo reversible liquid-solid transitions upon heating, the crystalline solid phases undergoing further phase transformations at higher temperatures. This unusual behavior has been characterized by an ensemble of measurements, including solubility, differential scanning calorimetry, quasielastic neutron scattering, as well as x-ray powder diffraction. For the α-CD/4MP system five crystalline phases have been identified. The unit cell parameters and corresponding changes with temperature indicate a scenario for the crystallization process. A simple model is proposed that mimics the observed disorder-order transition. © *2006 American Institute of Physics*. [DOI: 10.1063/1.2346680]

I. INTRODUCTION

We have recently reported a reversible liquid-solid transition upon heating a simple solution composed of α-cyclodextrin (α-CD), water, and 4-methylpyridine (4MP).[1] These solutions are homogeneous and transparent at ambient temperature and form a milky white solid when heated to temperatures between 45 and 75 °C. This process is fully reversible, on cooling the solid melts and the original, homogeneous solution is recovered. Neutron diffraction measurements had shown that the solid phase is crystalline, and, even though only a fraction of the solvent molecules is incorporated in the crystal phase, the overall aspect of the samples is a solid gel. The observed solidification phenomenon is, in fact, due to an extraordinarily strong negative temperature coefficient of the solubility of α-CD in 4MP with a sudden drop of solubility above a critical temperature of about 70 °C. This solidification with increasing temperature depends crucially on the presence of small amounts of water, indicating the establishment of intermolecular hydrogen bonds, via water molecules, between α-CD and leading to a fairly open regular structure of the α-CD molecules. The remaining space is filled with 4MP molecules, which remain partially mobile, as shown by quasielastic neutron scattering.

In this Communication we report a series of measurements (x-ray diffraction, differential scanning calorimetry, thermal expansion, and solubility) aimed at a better physical characterization of this and related systems, which exhibit an analogous strong negative temperature coefficient of the solubility. These observations lead to a scenario of crystallization, in which α-CD molecules arrange in sheets separated

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by the 4MP solvent. A simple theoretical model is presented, which mimics the observed disorder-order (liquid to crystal) transition as temperature increases.

II. EXPERIMENT

Materials. α-CD (Sigma-Aldrich) was dried in primary vacuum over P_2O_5 for about one day. The solvents (pyridine, 2-methylpyridine, 3-methylpyridine, 4MP and, 3,4-dimethylpyridine were distilled and stored over a 3 Å molecular sieve to remove water. Determinations of the water content of solutions of 200–300 mg of α-CD in 1 ml of 4MP showed that there remains an average of six molecules of water per α-CD corresponding to the value determined in x-ray studies for α-CD hydrate modifications.[2–4] Deuterated α-CD (α-CD$-D_{18}H_{42}$) was prepared by multiple exchanges with D_2O.

Sample preparation. In order to minimize in the measurements the contribution of solvent not incorporated in the crystal phase, solutions with the highest possible concentrations were prepared. The maximum concentration of liquid samples at room temperature that could be prepared was 450 mg of α-CD hydrate per milliliter of 4MP solvent. These optically homogeneous and transparent solutions, obtained after prolonged mixing on a roller stirrer, are highly viscous. Addition of water (40 mg/ml of 4MP) produces lumps of a white precipitate. By mixing this solution, a pastelike sample was obtained that was still sufficiently fluid to be loaded in a Lindeman tube using a Pasteur pipette. These samples never returned to a homogeneous transparent state and remained at least partially solid. Using anhydrous α-CD, homogeneous solutions of higher concentrations, containing more than 750 mg of anhydrous α-CD per milliliter of 4MP, could be prepared, but these syruplike samples are unstable in time and crystallize over prolonged periods of weeks to months. In solvents with 10–20 mg of water per milliliter added, homogeneous solutions of 300 mg/ml could be prepared at room temperature and these solutions returned fully to this state after solidification by heating. Solutions with solvents other than 4MP were prepared in an analogous fashion, but were not studied as systematically.

Thermal expansion. ca. 2 ml glass bulbs were fused to a 1 mm inner diameter tube of ca. 10 cm length. Two of these containers were filled with pure 4MP and a 300 mg/ml solution of α-CD in 4MP, respectively, and heated from room temperature to about 85 °C in a bath of ethyl glycol. The measurement was repeated with the containers for the two samples exchanged. To within the experimental accuracy of about 8%, the thermal expansion coefficient for the two samples was the same and equal to 9.2×10^{-4} K^{-1} ±8% over this temperature range: no anomaly could be detected at the liquid-solid phase transition of the α-CD solution.

Powder x-ray diffraction. Samples were loaded in 0.7 mm Lindeman tubes. Overview measurements were made using a Siemens M18XHF-SRA generator ($\lambda = 1.541\,79$ Å), a MAR345 image plate, and running AUTOMAR software. The sample temperature was controlled by an Oxford Cryosystems Cryostream cooler (80–375 K, stability ±0.1 K). Higher resolution powder diffraction measurements were made at the ESRF beamlines BM1 and BM8.[5,6] Beamline BM8 (GILDA) uses a translating imaging plate recording continuously slices of the diffraction patterns while the temperature of the sample is changed by a cryostream gas blower, $\lambda = 0.858\,640$ Å, resolution in $2\theta < 0.1°$. The highest resolution diffraction patterns were recorded at beamline BM1, which uses an array of six Na–I scintillation counters mounted on a rotating axis to detect diffraction patterns at an angular resolution of 0.01° full width at half maximum (FWHM), $\lambda = 0.799\,89$ Å, and the temperature of the sample being again controlled to within 0.2 °C by a nitrogen gas blower.

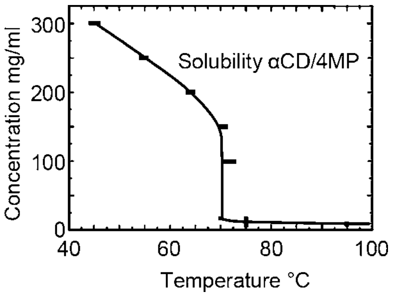

FIG. 1. Solubility of α-CD in solutions of 4MP containing ca. 2% in weight H_2O.

DSC measurements. A differential scanning calorimeter, TA Instruments Model Q10, providing 1 mW sensitivity over a temperature range from −180 to +725 °C was used. The samples were 300 mg/ml solutions of α-CD in 4MP with ca. 10 mg of H_2O added. After equilibration at 30 °C, the samples (encapsulated in an aluminum can) were heated at a rate of +5 °C/min.

Solubility measurements. The solubility of α-CD was determined by noting the limit of precipitation upon heating for solutions of given concentrations. At higher temperatures, when the solubility becomes smaller, solutions of smaller initial concentration were used. These solutions do not completely solidify, but a precipitate forms upon heating. Samples of the solution from above the precipitate were then taken at different temperatures and the solid residue, after evaporating the solvent, of these samples was weighed. Error bars associated with these measurement procedures were much smaller than uncertainties due to retardation of crystallization (supersaturation), speed of heating, as well as the dependence on the water content. In addition, in all experiments reported below a considerable hysteresis between heating and cooling is observed: the data plotted in Fig. 1 correspond to measurements made during heating only and to solutions to which 10–20 mg of water per milliliter of solution had been added.

III. RESULTS AND DISCUSSION

Solubility. Figure 1 shows the variation of the solubility of α-CD in 4MP as a function of temperature. Even though the precision of these data is limited by the factors indicated above as well as the existence of five different crystal phases, the near vertical drop of solubility near 75 °C is reproduced in all measurements.

TABLE I. Cell parameters of the five phases of α-CD/4MP/H_2O.

Phase	Volume	$a=b$ (Å)	c (Å)	Remarks
I	8253	13.690	50.85	Metastable
II	7461	13.691	45.964	<55 °C
III	7254	13.699	44.632	55 °C<79 °C
IV	7621	23.597	15.804	79 °C<89 °C, same as V, with some extra peaks
V	7621	23.597	15.804	>89 °C

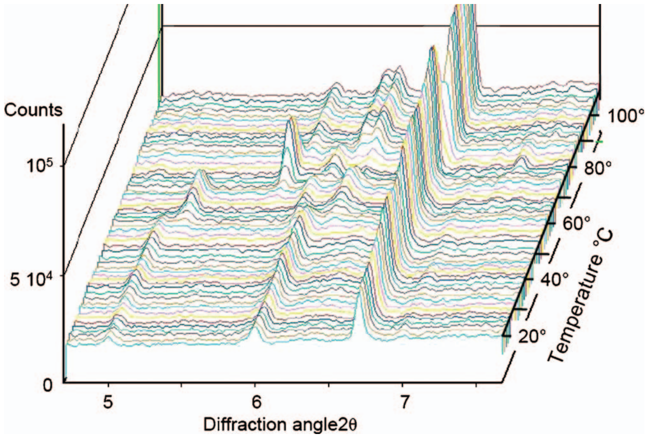

FIG. 2. (Color) Detail of a diffraction pattern of a 450 mg/ml sample of α-CD in a 4MP/H_2O solution recorded at beamline BM8 (GILDA) with a temperature ramp of 0.5625 °C/min illustrating the transitions between phases II and V.

A decrease of solubility in water with increasing temperature (negative solubility coefficient) has been reported for a number of methylated β-cyclodextrins and was attributed to a progressive destruction of the hydration shells around the methyl groups.[7,8] The solubility of heptakis (2,6-di-O-methyl)-β-cyclodextrin, for example, drops from 60 mg/ml at room temperature to <1 mg/ml above 70 °C. This behavior is in contrast with unmodified cyclodextrins with positive solubility coefficients. In the present case, water was shown to be essential for the crystallization. The high solubility of α-CD in water-free 4MP certainly involves hydrogen bonds between α-CD and 4MP. We suggest that a solvation shell of 4MP molecules around α-CD prevents the crystallization at lower temperatures, while at higher temperatures this structure is destabilized and, in the presence of water, an ordered α-CD–H_2O network is formed.

Phase behavior, diffraction. For solutions with concentrations above about 150 mg/ml α-CD in 4MP and containing the necessary minimal amount of water, the overall aspect of the sample at higher temperatures becomes that of a solid, even though a large amount (ca. 75% by weight in a 150 mg/ml sample) of solvent still surrounds the microcrystals. The temperature of this "solidification" increases from 45 to 70 °C as the concentration decreases from 300 to 150 mg/ml. Once solidified, the fraction of crystalline material in the sample increases further upon heating as the solubility of α-CD continues to decrease. More interesting, the solid samples were observed to undergo four phase transitions upon heating, the first of which is irreversible, the other transitions being reversible with considerable hysteresis. All diffraction patterns could be indexed within hexagonal cells. The unit cell parameters of the five different crystal structures are given in Table I. The diffraction patterns of phases II and III as well as of phases IV and V are very similar, the differences being hard to detect in low resolution diffractograms.

Starting from homogeneous liquid solutions at room temperature, the first crystal phase (I), which is formed upon heating, is metastable and converts spontaneously to phase II over a time interval that decreases with increasing temperature (1–3 h at 50 °C). Upon cooling, the reverse transformation from phase II to phase I was never observed, the samples returning directly to the liquid state. Samples with higher concentrations of 450 mg/ml are already solid at room temperature and are in phase II. All further phase transitions are reversible. Transition from II to III occurs around 66 °C, III to IV at about 79 °C, and IV to V at ca. 89 °C. With a ramp of 0.563 °C/min the transformations take 7–10 min and are spread out over ca. 5 °C but eventually lead to pure phases, as is illustrated in Fig. 2, for the transitions from phases II–V in a 450 mg/ml sample measured at beamline GILDA. The reverse transitions occur over much longer times. When a 450 mg/ml sample, having reached phase V, was cooled to room temperature, phase IV was formed over several hours and phase III over tens of hours, while phase II was never completely reached over the time of the measurements. Using much slower temperature ramps becomes impractical. An increase of intensity of the diffraction peaks between 20 and 60 °C is clearly visible in Fig. 2 and reflects the decrease in solubility and the corresponding increase of the crystalline fraction of the sample.

All hexagonal unit cells (see Table I) can be built in an approximate fashion from a (near hexagonal) unit cell of $a=b=13.7$ Å and $c=15$ Å. An example of the successful indexing is shown in Fig. 3 for a high resolution diffractogram of phase V recorded at beamline BM1 with $\lambda=0.799\,89$ Å. The strong 030 reflection together with the absence of the 010 and 020 reflections can be rationalized by the fact that, in the a,b plane, the unit cell can approximately be decomposed into the three near hexagonal cells mentioned above.

Polymorphism of α-CD hydrates and inclusion complexes is a common observation, as is illustrated by the four

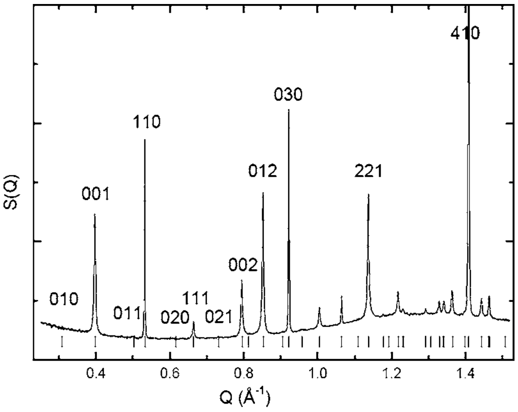

FIG. 3. High resolution diffractogram of phase V, recorded at beamline BM1, example of indexing.

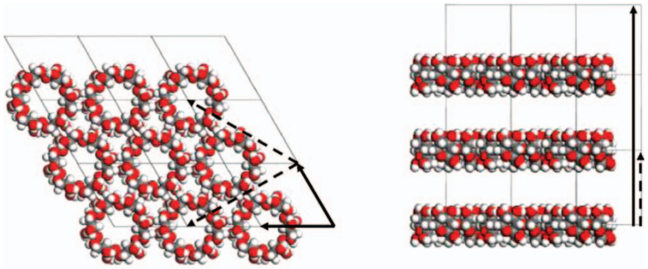

FIG. 4. (Color) Schematic drawing of the proposed hexagonal crystal structures with projections along the c axis (left) and a axis (right). Only α-CD is shown and 4MP molecules are omitted for clarity. The unit cell vectors of phases I–III and IV and V are indicated by full and dashed arrows, respectively.

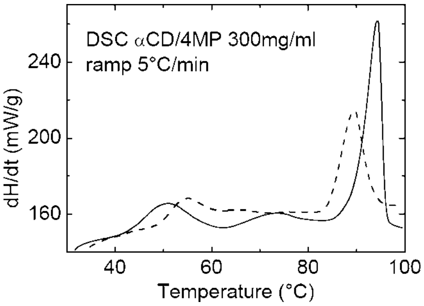

FIG. 5. Differential scanning calorimetry scans of two samples of 300 mg/ml α-CD in $4MP/H_2O$.

hydrate polymorphs that have been reported. In these systems, the exact water content is different and varies between 6 and 11 H_2O per α-CD.[2–4] What is remarkable in the present systems is the fact that the different phases interconvert as a function of temperature. The structural information, given in Table I, suggests a scenario, described below, which accounts for the observed phase changes and accompanying changes of cell parameters and volumes.

The density of conventional α-CD inclusion complexes with one guest molecule with a size comparable to 4MP is around 1.5, the density of 4MP is 0.96, and the densities of the present compounds, which contain significantly more solvent, are taken to be about 1.2, a weighted average of these two numbers. The cell parameters of phases I–III and the transition to phases IV and V indicate that α-CD lies in the a,b plane and that there are three α-CD molecules per unit cell. The overall structure of these crystals is shown schematically in Fig. 4 and is composed of sheets of hydrogen bonded (including H_2O bridges) α-CD molecules, arranged in an exact or approximate hexagonal structure with 4MP solvent molecules (not shown) separating these sheets. In phases I–III the repeat length is three of these sheets, going to a single sheet in the transition to IV and V accompanied by a tripling of the unit cell base in the a,b plane $(a_{\text{new}}=(a+b)_{\text{old}}, b_{\text{new}}=(2b-a)_{\text{old}})$. The irreversible transition from phase I to phase II is accompanied by an expulsion of several (four to six) 4MP molecules, while the composition of the crystals during the other transitions remains approximately the same, but not necessarily stoichiometric, with about eight 4MP molecules per α-CD. The presence of extra peaks in the diffractogram of phase IV as compared to phase V may indicate that the transition from II to IV/V first leads to a near hexagonal phase IV, which then stabilizes to phase V. In these structures, α-CD makes up only about 50% of the weight of the crystal, and the volume per α-CD is more than twice that of the corresponding volume in α-CD hydrates. This is the least compact α-CD structure known to date.

DSC. The phase transitions observed in diffraction are also partially resolved in differential scanning calorimetry (DSC) measurements made for 300 mg/ml α-CD/4MP samples. Figure 5 shows DSC scans with a temperature ramp of +5 °C/min, where several endothermic peaks are resolved. The two traces correspond to two different samples containing each 300 mg of α-CD per milliliter of 4MP and slightly different amounts of added water. The different behaviors of the two samples and the difference with the diffraction measurements reflect the sensitivity to exact sample composition and heating rate, as already mentioned above. Lack of resolution and smaller enthalpies prevent a complete resolution of all transitions. Detailed calorimetric measurements on a 100 mg/ml α-CD/4MP sample, using temperature ramps of 0.2 °C/min, have been reported recently[9] and differ significantly from the measurements shown in Fig. 5. Because of the lower concentration, solidification occurs around 75 °C and gives rise to a broad endothermic peak, but no further phase changes are resolved, while the significant broadening of the transition (between 65 and 45 °C), observed in measurements with decreasing temperature, certainly reflects these phase transitions. When corrected for the difference in concentration, the sum of the enthalpies of the transitions deduced from the present measurements is higher (but of the same order of magnitude) as compared to the enthalpy corresponding to the single peak reported in Ref. 9.

Other solvents. Measurements with solutions of α-CD in different, related solvents [pyridine, 2-methylpyridine (2MP), 3-methylpyridine (3MP), and 3,4-dimethylpyridine] expose a behavior similar to the one observed for 4MP and also show additional phase transitions in the solid phase. With increasing number of methyl groups, the solubility of α-CD in these solvents increases, while the decrease of solubility with increasing temperature is smaller. For the highest concentration samples (300 mg/ml) of 3,4-dimethylpyridine some precipitation but not a complete solidification is observed upon heating. For pyridine at the highest concentration of 150 mg/ml, the solidification upon heating is much more pronounced, but not complete, due to the lower initial concentration. For both 2MP and 3MP, the observed behavior is rather similar to 4MP. α-CD could be dissolved up to 300 mg/ml in these two solvents and solidification of the samples upon heating was observed. Both samples undergo phase transitions, the diffraction patterns of the phases resembling phase II/III and phase IV/V of the 4MP samples, respectively. With a ramp of 0.5 °C/min the transitions are observed at 89 °C for the 2MP sample and for the 3MP sample at 78 °C with a ramp of 0.75 °C/min.

IV. A MODEL OF THE DISORDER-ORDER TRANSITION AT SOLIDIFICATION

The solidification observed for the different α-CD solutions reflects a disorder-order transition, which is rather un-

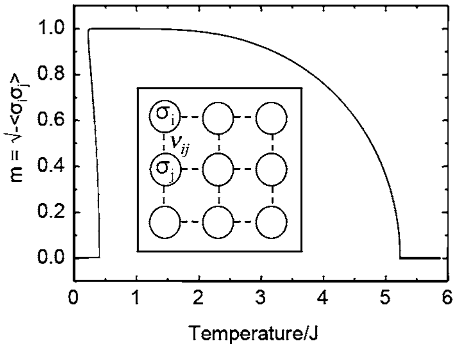

FIG. 6. Numerical solution of the model for the values of the parameters $z=6$, $k=10$, and $\Delta=2$. Inset: illustration of the model used to mimic the disorder-order transition observed for the α-CD/4MP/H_2O system.

usual, since entropy must increase with increasing temperature. In the following it is shown that the ordering with increasing temperature can be mimicked in a model, illustrated in Fig. 5, in which the lowest energy configuration of α-CD is unique while a larger number of higher energy configurations enable intermolecular hydrogen bonds via water molecules. Analogous models have recently been explored to rationalize in more general terms this unusual and counterintuitive phenomenon, also called "inverse freezing."[10,11]

The α-CD molecule can be in two states, $\sigma_i=\pm 1$. By definition, crystal structure is associated with an "antiferromagnetic order."

The variable $\nu_{ij}=0,1,2,3,\ldots,k$ corresponds to the different configurations of α-CD. $\nu_{ij}=0$ corresponds to the unique lowest energy form of α-CD, which does not allow hydrogen bonds between α-CD molecules. The excited states $\nu_{ij}=1,2,\ldots,k$ with an energy Δ above the ground state establish intermolecular hydrogen bonds between α-CD molecules.

The Hamiltonian of such a system is

$$H=-\Delta\sum_{\langle i,j\rangle}\delta_{\nu_{ij},0}+J\sum_{\langle i,j\rangle}\sigma_i\sigma_j(1-\delta_{\nu_{ij},0}), \tag{1}$$

where Δ is the stabilization of the unique lowest energy configuration with respect to the k, higher energy configurations, and J is the energy of an intermolecular hydrogen bond via water molecules. In the limit of all $\nu_{ij}=0$ the system is disordered and H goes to $-\frac{1}{2}zN\Delta$, while in the limit of all $\nu_{ij}\neq 0$, $\sigma_i\sigma_j=-1$, the system is ordered, and H goes to $-\frac{1}{2}zNJ$. The requirement that the lowest energy state is disordered imposes $\Delta>J$. The mean value $m=\sqrt{-\langle\sigma_i\sigma_j\rangle}$ for i and j on different sublattices and $i-j\rightarrow\infty$ defines the degree of order: $m=1$ is equivalent to complete order.

For this model Hamiltonian, the molecular field approximation yields the equation

$$\frac{e^{\Delta/T}+ke^{m^2/T}}{ke^{m^2/T}}=\frac{zm/T}{\operatorname{arctanh}(m)}, \tag{2}$$

which can be solved for $m(T)$. Here z is the number of neighbors to which bonds can be established, and $J=1$ is used as scale for energy and temperature T. Figure 6 shows a numerical solution for $z=6$, $k=10$, and $\Delta=2$. The model is ordered for $T=T_c<z$, but for much lower temperatures, order breaks down as T reaches the value of $T_d=\Delta/\ln(kz)$. The back bending of $m(T)$ signals a sudden drop of the order parameter, i.e., a discontinuous transition from the ordered (crystalline) to the disordered (liquid) state. Analogous behavior is observed for other values of the parameters within ranges that are reasonable for this model and, regarding Δ and J, lie within the range of energies involved in hydrogen bond rearrangements as indicated by numerical calculations.

V. CONCLUSIONS

The structural information obtained in the present work is sufficient to clearly establish key features of the crystallites formed in the high temperature solid. There are three α-CD molecules in a unit cell and there are about eight 4MP molecules per α-CD in the stable crystal phases (II–V). The structures are composed of layers of α-CD and 4MP, the former being stabilized by hydrogen-bonding water molecules.

Extensive quasielastic neutron scattering (QENS) measurements have been made and will be reported separately.[12] These measurements indicate that complexes comprised of α-CD and 4 ± 2 4MP molecules have dynamics in the range of 10–100 ps in the liquid phase, being further slowed down to >100 ps upon solidification. The dynamics of the remaining 4MP molecules is faster and occurs on a time scale comparable to the one measured in pure 4MP. These findings support the proposition made above that, already in the liquid phase, α-CD is contained in a solvent shell of 4MP molecules. Even though the precision of the data is limited, the difference between the number of eight 4MP molecules contained in the unit cell and the number of molecules determined to slow down in QENS measurements indicates that some 4MP molecules retain significant mobility in the crystal and that the composition of the crystal unit cell may not be strictly stoichiometric.

The more complex behavior of α-CD solutions, as born out in the present measurements and in the QENS data, suggests that the rearrangement of hydrogen bonds involves complexes of α-CD solvated in a shell of 4MP due to opening of intramolecular hydrogen bonds of α-CD as proposed previously.[1] The essential role that water molecules play in this process is fully confirmed by the present measurements.

If one excludes a flip of α-CD by 180° during the phase transitions, the unit cell dimensions and their transformations imply that all α-CD molecules are oriented the same way: the resulting structures would be polar. Such a packing of α-CD molecules is rather novel as compared to structures commonly observed for other cyclodextrine compounds[13,14] and differs also significantly from the structure reported for the β-CD-pyridine-water compound,[15] which resembles otherwise most closely in composition the present system.

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