Fabrication of Inclusion Compounds with Solid Host γ-Cyclodextrins and Water-Soluble Guest Polymers: Inclusion of Poly(*N*-acylethylenimine)s in γ-Cyclodextrin Channels As Monitored by Solution ^{1}H NMR

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ABSTRACT: We successfully report the formation of poly(*N*-acylethylenimine)−γ-cyclodextrin inclusion compounds (PNAI-γ-CD ICs). The PNAI-γ-CD ICs were obtained by three techniques: (a) the precipitation of γ-CD in the polymer solution and (b) and (c) the suspension of as-received cage structure γ-CD and γ-CD_{CS}, with a preformed channel structure, respectively, in the polymer solutions. The PNAI-γ-CD ICs were characterized by solid-state FTIR, X-ray, NMR, DSC, and TGA observations. A ^{1}H NMR study was performed in order to follow the kinetics of the inclusion process in solution. The time-dependent inclusion of PNAIs with different molecular weights by suspension of either as-received cage structure γ-CD or channel structure γ-CD_{CS} in the PNAI solutions was monitored with ^{1}H NMR. Acetone, a nonsolvent for γ-CD, was used as the solvent for the PNAI solutions. Some aspects regarding the role water plays in the polymer inclusion process are revealed from our temporal observations of the inclusion of PNAI guests into solid host γ-CDs.

Introduction

Much recent research has been focused on the design of nanoscale architectures for polymers having unique structures (double-helical polymers,[1] dendrimers, etc.) and functionalities. Both poly(ethylenimine)s and cyclodextrin derivatives have been extensively exploited in the design of nanometer-scale ordered structures for biomedical applications.

Cyclodextrins (CDs) are cyclic compounds consisting of six to eight glucose units and are well-known to form inclusion complexes (ICs) with various low- and high-molecular-weight compounds. CD IC guests range from nonpolar to polar, from aliphatic to aromatic, and from hydrophilic to hydrophobic molecules, resulting in interesting architectures or potential components for molecular-based machines.[2] Hydrophilic cyclodextrins also possess biocompatibility and can act as solubilizers and stabilizers, as artificial chaperones, as absorption enhancers, and as sustained-release carriers.[3]

Poly(*N*-acylethylenimine) (PNAI) possesses several special characteristics: high hydrophilicity and water solubility as required for most biological applications; good miscibility with a wide range of organic polymers; extremely low toxicity; desirable biocompatibility; easy preparation by living cationic polymerization, enabling effective control of molecular parameters and introduction of functional end groups that can moderate surface properties; and sufficient chemical versatility to permit a range of subsequent chemical reactions that allow them to fill various structural and/or functional roles within the final material.

Although significant advances have been made in the assembly of such structures,[4] the challenge to design and prepare inclusion complexes of versatile polymers with cyclodextrins and the control of the inclusion process remain important goals. The mechanism and kinetics of the inclusion process, especially in the case of hydrophilic guests, have not yet been completely elucidated. Normally polymer−CD ICs are formed in solution, often by mixing solutions of the guest polymer with aqueous solutions of the host CDs, followed by precipitation of the polymer−CD IC, wherein the host CDs are crystallized into stacked columns and the guest polymer chains are included in the narrow channels (∼0.5−1.0 nm in diameter) of the CD stacks. Thus, the net process of forming polymer−CD ICs involves the removal of randomly coiling guest polymer chains from solution by threading them with CD, during which time they become isolated and are highly extended. At the same time the host CDs are also removed from solution as they thread the guest polymers and form stacks that pack together and crystallize into polymer−CD ICs.

It is not surprising that the process of threading a polymer through CDs to form a polymer−CD IC is enthalpically driven, and its kinetics depend strongly on choice of reactants, concentration, solvent nature, addition of cosolutes, and temperature. Hydrogen and ionic bonding, hydrophobic and van der Waals interactions, and molecular recognition (guest/host shapes and sizes) are generally accepted as playing roles in the inclusion process,[5] but their relative importance, as related to the structures of the host CDs and the guest polymers, is not yet completely elucidated or understood: nor are the effects on the inclusion process of guest polymer molecular weights, temperature, and solvent. Recently,[6] we have prepared columnar CDs, CD_{CS}, that contain no included guests aside from water of hydration and found CD_{CS} to be able to include guest polymers when suspended in guest polymer solutions. Because this method of forming polymer−CD ICs does not alter the organization and structure of the columnar

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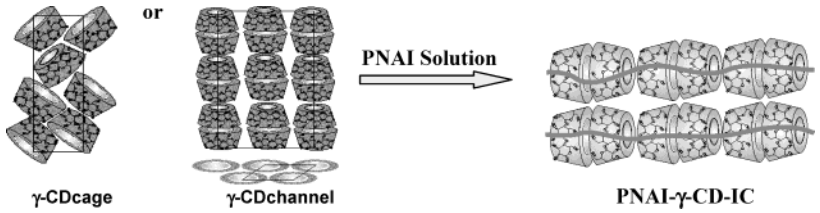
Chart 1. Suspension of As-Received Cage or Precipitated Columnar γ-CDs in PNAI Solutions To Form PNAI−γ-CD ICs



host CD crystalline lattice, but only the penetration and inclusion of guest polymer chains in and removal of water of hydration from the CD channels, we hope to utilize this approach to gain a better understanding of the inclusion process.

Seeking new synthetic methodologies for the formation of inclusion compounds and a better control of the process, we report here the extension of this new preparative route to CD ICs. This involves the suspension of cyclodextrin with a preformed channel structure, CD_{CS}, in the solution of the polymer made with a nonsolvent for CDs. To better quantify and understand the driving forces and environmental parameters influencing the inclusion of polymers into CDs, we develop and present in this paper a new technique based on ^{1}H NMR observations made in solution during complexation. A study of the inclusion process by solution ^{1}H NMR is presented for the first time, several observations pertaining to the mechanism and the kinetics of inclusion into solid γ-CDs are made for PNAIs, and some aspects regarding the role of water in the inclusion process are briefly addressed.

Experimental Section

Chemicals. Chloroform ($CHCl_3$), methanol (MeOH), and ethanol were distilled under dry N_2 and stored over molecular sieves (4 Å). 2-Ethyl-2-oxazoline (EOZO) was purified by heating to reflux for 2 h over KOH and subsequently distilling under dry N_2 before being stored over molecular sieves. γ-Cyclodextrin (γ-CD) was obtained from Cerestar (Hammond, IN), and the water used in this study was deionized (DI-H_2O). Other reagents (deuterated solvents, methyl iodide, K_2CO_3) were used as received.

Synthesis of Poly(*N*-acylethylenimine). Poly(*N*-acylethylenimine) (PNAI) samples were prepared according to a published procedure.[7] Under dry N_2, 0.02 mol of 2-ethyl-2-oxazoline was added to a solution of 0.001 mol of initiator (methyl iodide) in 4 mL of $CHCl_3$ at 0 °C using syringes. The reaction vessel was sealed and allowed to react under reflux. A terminal OH group was introduced by adding a slight excess of aqueous K_2CO_3. This sample, PNAI1, had a $M_w = 3200$ (∼30 repeat units) as determined by GPC using polystyrene standards. Another sample of PNAI (PNAI2), with a higher molecular weight, $M_w = 9000$ (∼90 repeat units), was prepared by the same procedure.

CD IC Formation. *Classical Method*: To a solution of polymer in acetone (0.1 g PNAI in 20 mL of acetone) vigorously stirred at 50 °C, an aqueous solution of γ-CD (1 g in 4.4 mL of H_2O) was added dropwise. The mixture was kept at 50 °C for 3 h, and subsequently under moderate stirring at room temperature for 3 days, after which the white precipitate was collected by filtration, briefly washed with 10 mL of acetone to remove any unincluded polymer, and then characterized.

New Method: To a solution of polymer in acetone (0.1 g of PNAI in 10 mL of acetone) at room temperature, 0.65 g of as-received, cage structure γ-CD or γ-CD with a preformed channel structure,[6] γ-CD_{CS}, was added, and the mixture was moderately stirred for 2 days and allowed to stand overnight (see Chart 1). The white precipitate was collected by filtration, briefly washed with 10 mL of acetone to remove any unincluded polymer, and then characterized.

The same procedure was used in the kinetic studies by ^{1}H NMR: γ-CDs were suspended in solutions of the PNAIs dissolved in deuterated acetone. [Also, see the related α-CD/poly(ethylene oxide) study.[8]]

Characterization. a. Gel Permeation Chromatography (GPC) (Size Exclusion). Molecular weights and their distributions were measured via GPC using a Jasco PU-1580 pump and a Jasco RI-1530 refractive index detector under a flow rate of 1 mL/min at room temperature on two PL-Gel mixed C columns. Chloroform was the mobile phase. Molecular weights are reported relative to narrow molecular weight polystyrene standards (Pressure Chemical, Inc.).

b. ^{1}H Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR). ^{1}H NMR spectra of polymers were recorded on a Mercury 300 spectrometer in $CDCl_3$ [using tetramethylsilane (TMS) as the internal standard], in DMSO-d_6, or in deuterated acetone. The kinetic study was performed by suspending as-received, cage crystalline γ-CD or channel crystalline structure γ-CD_{CS} in solutions of polymer in deuterated acetone and following the decrease in intensity of polymer peaks and the increase in intensity of the H_2O peak, as polymer displaces H_2O from the γ-CD channels during polymer inclusion and complexation. The insoluble γ-CDs settled on the bottom of the NMR tubes, where the polymer is removed from the solution during the inclusion process and is transparent to solution ^{1}H NMR, as are included PNAI and water.

The same technique has been used to observe the release of water from the cavities of the γ-CD's in two different solvents (acetone and chloroform). To quantify the amount of water released in these experiments, a calibration was done by measuring the increase of the water proton peak for a known amount of added water.

c. Solid-State ^{13}C Nuclear Magnetic Resonance Spectroscopy. High-resolution solid-state ^{13}C NMR experiments were carried out at 50.1 MHz on a Chemagnetics CMX200 spectrometer using cross-polarization and magic angle spinning (CP/MAS) with high-power proton dipolar decoupling (DD). The spinning speed ranged from 4 to 4.2 kHz. The ^{13}C chemical shifts were referenced relative to TMS. The spectra were obtained with 1000 transients, 1.0 ms contact time, and 3.0 s pulse delay. The spectral width was 15 kHz with 2K data points, which were zero-filled to 8K before Fourier transformation.

d. Wide-Angle X-ray Diffraction. Wide-angle X-ray diffraction (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 diffraction intensities were measured every 0.1° from $2\theta = 5°$ to 30° at a rate of $2\theta = 3°$/min. The supplied voltage and current were 30 kV and 20 mA, respectively.

e. Fourier Transform Infrared Spectroscopy. Transmission FTIR spectra were recorded using a Nicolet 510P FT-IR spectrometer on pressed thin transparent disks of the samples mixed with KBr. Spectra were obtained by collecting and averaging 200 scans, at a resolution of 2 cm^{-1}.

f. Differential Scanning Calorimetry (DSC). DSC experiments were performed with a Perkin-Elmer DSC7 under nitrogen purge gas. Indium was used as a standard for calibration. All samples studied in this work were subjected to heating and cooling cycles (unless otherwise specified), consisting of 1.0 min hold at 0 °C, ramp to 150 °C at 20 °C/

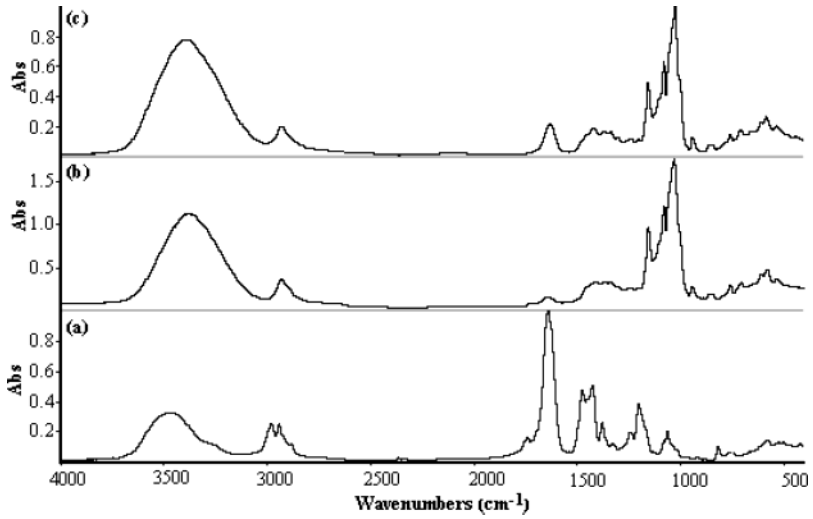
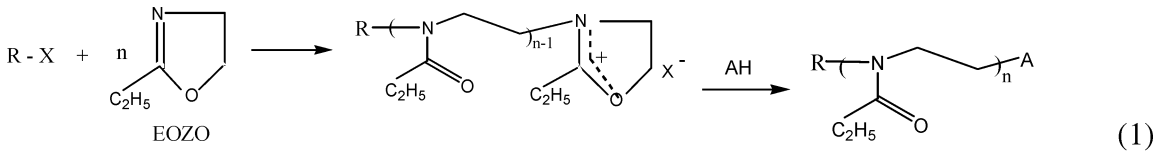


Figure 1. FTIR spectra of pure PNAI (a), pure γ-CD (b), and PNAI−γ-CD ICs (c) from bottom to top, respectively.

Scheme 1



(1)

min, hold at 150 °C for 1 min, and ramping to 0 °C at −200 °C/min. Samples were subjected to a second cycle to investigate any changes in thermal behavior following the first heat.

g. Thermogravimetric Analysis (TGA). Thermal analyses of the samples were performed with a Perkin-Elmer Pyris 1 thermogravimetric analyzer (TGA). Thermal decomposition of the samples was recorded between 22 and 600 °C. The heating rate was 20 °C/min, and nitrogen was used as a purge gas.

Results and Discussion

The unique features of PNAI prompted us to examine its possible use in the controlled syntheses of polymer inclusion compounds formed with γ-CD. Living cationic ring-opening polymerization of 2-substituted 2-oxazolines was chosen as a synthetic route to a defined, flexible hydrophilic/hydrophobic (depending on substituent) polymer.[9] We chose an alkyl halide (R−X) as the initiating group on the basis of previous work and on its ability to initiate the polymerization of 2-oxazolines (Scheme 1), thus providing routes to macromolecules with a considerable range of molecular weights and very low polydispersities.[10]

The preparation of polymer−CD ICs can be achieved by multiple methods, the most frequently used being the addition of a saturated solution of CD in water or DMSO to a stirred solution of polymer. The ICs of PNAI with γ-CD were obtained by several procedures, including addition of aqueous solution of γ-CD to the solution of the polymer in acetone (nonsolvent for γ-CD), addition of polymer in powder form to the aqueous solution of γ-CD (synthesis in a common solvent), and suspension of γ-CD, with as-received, cage or preformed, channel structures, in the solution of polymer dissolved in acetone (see Chart 1). Successful preparation of the PNAI−γ-CD ICs was confirmed by FTIR and NMR spectroscopy (^{1}H NMR in solution and solid-state ^{13}C NMR), and the resulting products were further characterized by X-ray, DSC, and TGA. For example, spectral features characteristic of the polymer—the appearance of the strong amide band (1640 cm^{-1}), the characteristic stretching vibrational modes of the methylene groups in the polymer backbone, and the propionyl side chain around 2979 and 2941 cm^{-1}—are detected in the FTIR spectra of the PNAI−γ-CD ICs (see Figure 1). Though not presented, ^{1}H NMR spectra of the PNAI−γ-CD ICs dissolved in DMSO show resonances characteristic for the polymer at 3.46 ppm (N−CH_2−CH_2−, 4H), 2.3 ppm (CO−CH_2−CH_3, 2H), and 1.1 ppm (CH_2−CH_3, 3H).

Solid-state X-ray, ^{13}C NMR, DSC, and TGA observations (not shown) of the PNAI−γ-CD ICs and a physical mixture of PNAI and γ-CD reveal that the γ-CDs are packed in the columnar structure and that the polymer is included in the channels of the γ-CD ICs. For example, while the DSC scan of the physical mixture showed a melting endotherm for the free PNAI, the DSC scans for PNAI−γ-CD ICs did not, indicating that all PNAI chains were included in the host γ-CD channels. We also quantified gravimetrically the amount of polymer that was not included, but remained in solution, and we observed that best results were obtained by adding γ-CD_{CS} (60% yield vs 30% yield for suspended cage γ-CD) with preformed channel structure to the polymer solutions in acetone, which is a nonsolvent for γ-CD (see Chart 1).

It seems remarkable that suspension of as-received, cage structure γ-CD in acetone solutions of PNAIs results in the formation of PNAI−γ-CD ICs because this requires a solid-state crystal−crystal transition for the γ-CD lattice from the cage to the channel structure. Somehow the PNAI chains penetrate the γ-CD cage structure crystals, thread the γ-CDs, and convert them to γ-CD channel structure crystals, where the PNAI are included (see Chart 1). Similar observations were made[8] in the case where crystals of cage α-CD were suspended in liquid poly(ethylene glycol) (PEG) oligomers, and the

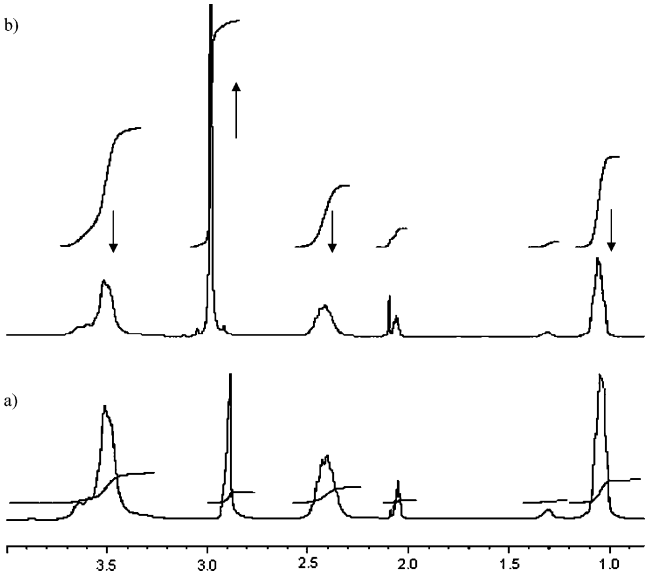


Figure 2. Time-dependent ^{1}H NMR spectra of PNAI-1 in acetone solution containing settled, initially cage structure γ-CD: (a) initial; (b) after 90 h. ↓, ↑ = PNAI, H_2O peaks.

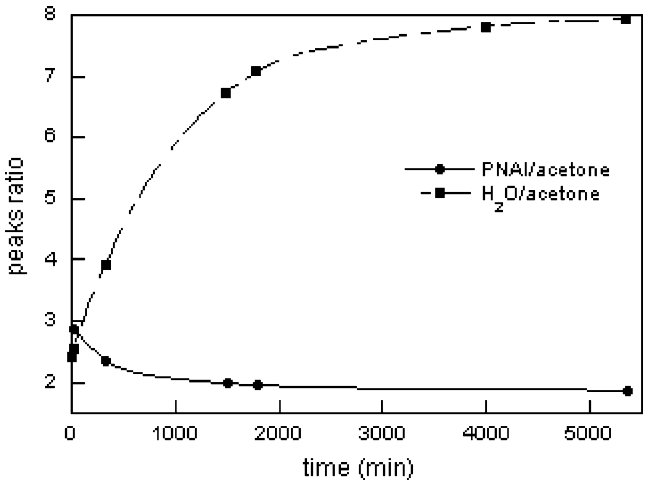


Figure 3. Variation of polymer and water ^{1}H NMR peak intensities relative to the intensity of the solvent (acetone) peak, as PNAI1 in solution is included in as-received, cage structure γ-CD.

solid-state transition from cage to channel structure crystalline structure was monitored by X-ray diffraction, DSC, and rheological observations.

We used the same approach for a kinetic study by ^{1}H NMR and are able to report for the first time a facile method for quantifying the inclusion process. Observation of the decrease in polymer proton peak intensities (↓), as a result of inclusion in the suspended as-received, cage structure γ-CD settled on the bottom of the NMR tube, and the increase of the water peak intensity (↑), as a result of its release from the γ-CD cavities as PNAI chains are included to produce a channel structure PNAI-γ-CD-IC, are evident in Figures 2 and 3. [Note that IC-included polymer or water and suspended γ-CD (free or in the IC) are transparent to solution ^{1}H NMR.] Similar observations were made for α-CD/PEG[8] and γ-CD/styrene monomer.[11] At no time during the inclusion of PNAI into the suspended solid γ-CDs did we observe proton resonances characteristic of γ-CD, which strongly indicates the absence of any dissolution of the suspended γ-CDs, either cage or columnar, during the inclusion process.

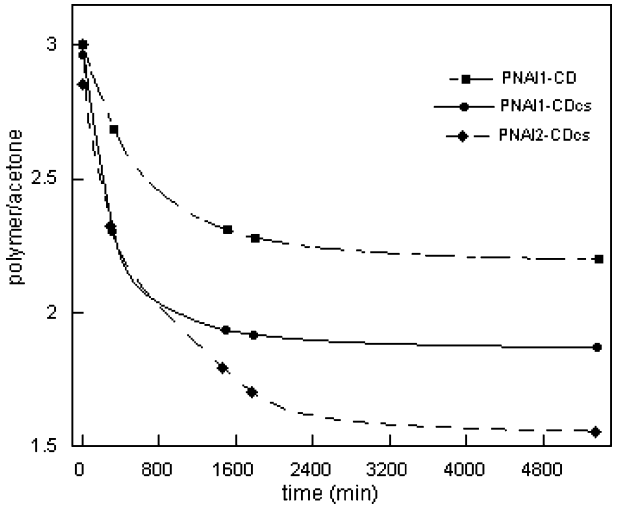


Figure 4. Decrease of polymer peak intensities with time as a result of inclusion in cage γ-CD or in columnar γ-CD_{CS}. PNAI2 has a higher molecular weight than PNAI1.

These results prompted us to make comparative studies for the cases where as-received cage structure γ-CD or preformed channel structure γ-CD_{CS} are suspended or when PNAIs with different molecular weights were included. In agreement with our gravimetric quantifications, a higher quantity of polymer disappears faster from solution to form an IC with the γ-CD_{CS} compared with as-received, cage γ-CD. The rate and amount of PNAI included by suspended γ-CD_{CS} are both greater than for suspended cage γ-CD. The faster kinetics are not surprising because in the case of PNAI inclusion by cage γ-CD, a solid−solid, crystal−crystal transition must accompany the inclusion of PNAI chains. Also, in accord with our previous experiments[12] with other polymers, we observed a greater ability to form a CD IC with the PNAI having a higher molecular weight (PNAI2; see Figure 4). Though the amount of PNAI2 (MW = 9000) included in suspended γ-CD_{CS} is greater than the amount of PNAI1 (MW = 3200) included, the kinetics of their inclusions appear nearly the same over the first several hours. Thus, unlike our previous observations[12] of the solution inclusion of PEOs with different molecular weights and of poly(ϵ-caprolactone) and hexanoic acid in α-CD, which suggested a kinetic preference for inclusion of higher molecular weight guests, apparently thermodynamics favors the inclusion of the higher MW PNAI2 over the lower MW PNAI1 in the suspended solid columnar lattice provided by γ-CD_{CS}.

The method developed here is appropriate for systems where the solvent for the guest is a nonsolvent for CD. For polymers soluble only in the same solvents as CD, such as poly(vinyl alcohol),[13] the modification of ^{1}H NMR peak areas with time was not practically observable, so supplementary studies by UV−vis spectroscopy were necessary. The evolution of turbidity with time during the formation of the threaded structures supported, however, the observations made by ^{1}H NMR. For water-soluble polymers, the process is not readily quantifiable since the coalescence of the final product from its IC is not possible, and very often IC remains in solution and/or only small amounts precipitate. For these cases, the NMR technique can only be used as a supplementary tool in the observation and elucidation of the inclusion process.

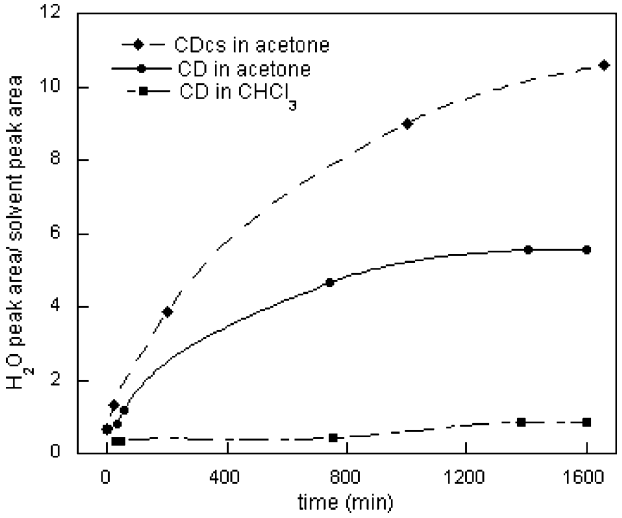


Figure 5. Water release from cage γ-CD and channel γ-CD_{CS} suspended in acetone and cage γ-CD suspended in $CDCl_3$.

It is known that, although the penetration of a long polymer chain into host CD cavities should lead to a significant lowering of its conformational entropy,[14] the water molecules that are released to the external environment during the threading process may largely compensate this entropic loss.[5] To understand better the role of water, while retaining our focus on the ability to predict what happens during the inclusion process, we also followed the release of water by the same ^{1}H NMR method described above. In Figure 5 we present the release of water from the γ-CD cavities only under the action of solvent. These experiments allowed us to determine whether there are any differences between cage structure γ-CD and γ-CD_{CS} from this point of view and also whether the nature of the solvent influences the release of water.

If the release of water is accepted as a driving force for the inclusion process, it appears that CD with a preformed channel structure and a solvent easily miscible with water are more favorable for the formation of γ-CD-ICs (see Figure 5). The first hypothesis was confirmed by our experimental data because a more pronounced decrease of PNAI peaks was observed as it was included in γ-CD_{CS} compared with cage γ-CD. Both the rate and amount of water released from γ-CD_{CS} suspended in acetone are greater than observed for suspension in chloroform. The second hypothesis was confirmed as well, as illustrated in Figure 6: no decrease of the polymer peaks was observed when chloroform was used as solvent. Apparently, the reluctance of water to leave the γ-CD_{CS} channels and enter the chloroform solution prevents the PNAI chains from threading their ways into the γ-CD_{CS} channels to form PNAI−γ-CD IC.

Recent and related X-ray experiments performed by Topchieva et al.,[15] which indicate that the formation of channel structure α-CD in chloroform occurs only at high temperatures, support our observations. The effect of temperature can be related to the water release—at room temperature the water may not migrate from the cavities, while higher temperature could facilitate the release. Further studies examining the second hypothesis—that inclusion is favored in solvents easily miscible with water and is eventually aided by the concomitant removal of water from the system in the case of hydrophilic solvents—are being pursued in our laboratory.

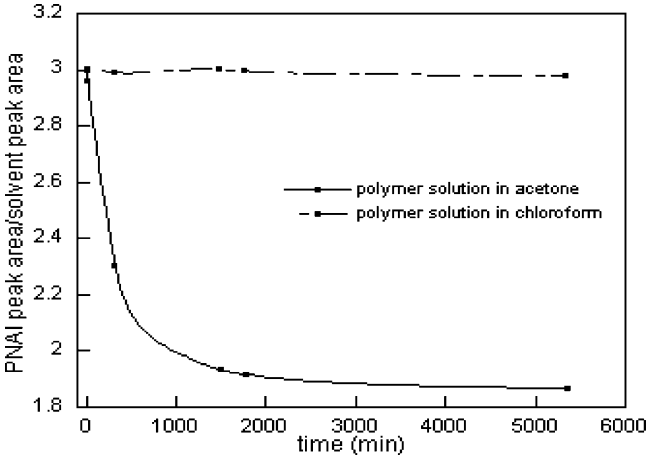


Figure 6. Decrease of polymer ^{1}H NMR peak intensity with time as a result of inclusion from polymer solutions into the channels of suspended γ-CD_{CS}.

All these observations suggest that release of the water of hydration, possibly along with hydrogen-bonding interactions between CDs,[8] likely dominates the process of including guests in crystalline CDs to form channel structure CD ICs. This is certainly the case for inclusion of guests in suspended CD_{CS}, where hydrogen-bonding interactions between CDs are not altered during inclusion.

On the basis of estimates[14] of the changes in conformational energies and reduction in conformational entropies expected for polymer chains upon inclusion in the narrow channels of polymer−CD ICs ($-T\Delta S \sim +2$ kcal/mol of γ-CD), the release of water of hydration from the γ-CD channels as they are replaced by the inclusion of guests, must be accompanied by a lowering of their free energy that approximates −2 kcal/mol of γ-CD. Approximately six H_2O/CD reside in the channels of γ-CD_{CS},[6] but calibration by solution NMR—to quantify how many H_2O molecules correspond to the observed increase of the water peak—indicated the release of only two molecules of water/γ-CD_{CS} at room temperature. Thus, the water that is displaced from the γ-CD_{CS} channels by including polymer or small-molecule guests likely experience a free energy reduction of ∼−2 kcal/mol of γ-CD or −1 kcal/mol of H_2O. More importantly, apparently most of the water residing in the channels of γ-CD_{CS} remains after threading and inclusion of the PNAI chains to form PNAI−γ-CD_{CS} ICs.

Conclusions

Our studies have demonstrated that poly(*N*-acylethylenimine) can form an IC with γ-CD. Two synthetic routes give PNAI/γ-CD ICs in high yield: addition of an aqueous solution of γ-CD to the solution of the polymer in acetone (∼50%) and suspension of γ-CD_{CS} with preformed channel structure in the acetone solution of polymer (∼60%). We have developed an alternative method to monitor the temporal evolution of the inclusion process using solution ^{1}H NMR. This method proved to be a facile and proficient means to observe the inclusion of guest polymers into γ-CDs to form crystalline polymer−γ-CD ICs, especially in the case of water-soluble polymers, where the information obtained from classical characterization techniques is limited. These observations have permitted us to suggest that the release of the water of hydration associated with γ-CDs dominates the process of including guests in

crystalline γ-CDs to form channel structure γ-CD ICs and may also be important to the formation of crystalline guest−CD ICs from solution(s) containing both the guest and host CD. This despite the apparent retention of a majority of water molecules in the solid γ-CD channels after inclusion of the guest PNAI chains to form PNAI−γ-CD ICs.

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