Polymer−Cyclodextrin Inclusion Compounds: Toward New Aspects of Their Inclusion Mechanism

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ABSTRACT: α-Cyclodextrin inclusion compounds were prepared in the presence of a polymer and a small molecule model for the polymer repeat unit. By means of this technique, we are able to demonstrate that α-cyclodextrin prefers the inclusion of the longer molecular chain guest. Comparison of the cyclodextrin inclusion compounds formed with poly(ϵ-caprolactone) and hexanoic acid, separately and from solution containing both poly(ϵ-caprolactone) and hexanoic acid in varying amounts, enables us to draw certain conclusions concerning both the thermodynamic and kinetic aspects of poly(ϵ-caprolactone)−α-cyclodextrin inclusion compound formation. Differential scanning calorimetry, Fourier transform infrared, and wide-angle X-ray diffraction have been used to verify the formation and successfully characterize all inclusion compounds.

Introduction

Cyclodextrins (CDs) are well-known in supramolecular chemistry as molecular hosts capable of including with a degree of selectivity a range of guest molecules via noncovalent interactions in their hydrophobic cavities. Cyclodextrins, cyclic starch oligomers, are represented as shallow truncated cones consisting of 6, 7, and 8 glucose units and named α-, *β*-, and *γ*-CD, respectively (Figure 1). Packing of the CD molecules in the crystal lattices of their inclusion compounds (ICs) occurs in one of two distinct modes, described as cage and channel structures (Figure 2).[1]

Much attention was given in recent years to these supramolecular complexes of cycloamyloses due to their significance for understanding noncovalent binding forces, the selectivity and molecular recognition of the guest molecules, and for their industrial importance, particularly with respect to drug encapsulation and targeting.[2] For instance, our group has successfully focused on the fabrication of unique polymer−polymer composites and blends, including intimate blends of normally incompatible polymers, as well as the delivery of additives to polymers by means of embedding polymer− or additive−CD ICs into carrier polymer films and fibers, followed by coalescence of the IC guest, or by coalescence of two polymers or a polymer and additive from their common CD IC crystals.[3−5] The possibility of obtaining unique polymer materials via fabrication with CD ICs has therefore been demonstrated.

In many cyclodextrin complex forming reactions the correlation between structure (both of guest and host) and selectivity is a decisive factor. Molecular recognition is based on the selectivity−structure correlation, which in CD chemistry means those interactions between CDs and reacting partners (solvent and guest), not only guests. In most cases, the CDs form their ICs in the presence of water, i.e., from a multicomponent system, where correlation between structure and selectivity is a decisive facter. Consequently, from this point of view it is important to understand the factors responsible for the preferential inclusion of certain guests when forming CD ICs in the presence of a mixture of guests, such as hexanoic acid (HA) and poly(ϵ-caprolactone) (PCL) in this study, to begin to establish the mechanisms of organization of soluble CD ICs into solid CD IC crystals.

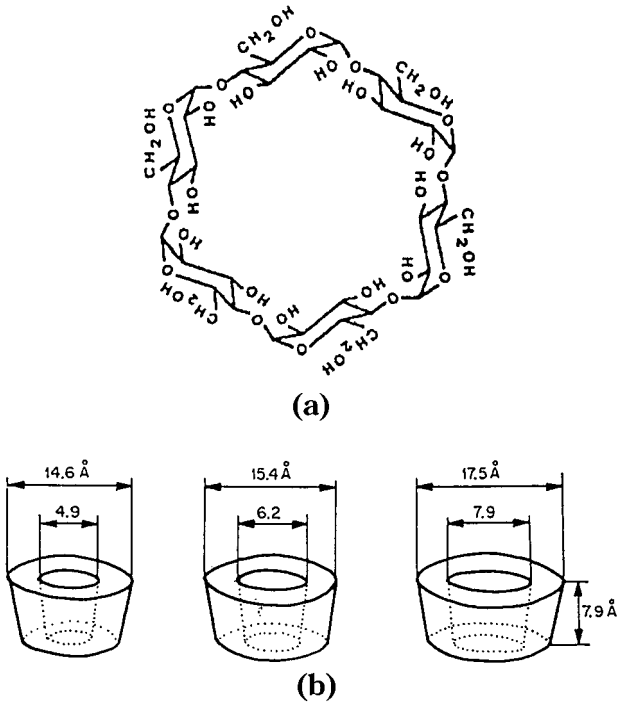

Figure 1. Chemical structure of α-cyclodextrin (a) and molecular dimensions of (left to right) α-, *β*-, and *γ*-cyclodextrins (b).

In a previous investigation,[6] we looked at the separation of polymers by molecular weight through inclusion compound formation with urea and α-CD hosts. Both urea and α-CD exhibit molecular weight selective polymer inclusion in the complexation process. Unlike α-CD, the urea host exclusively complexes the polymer

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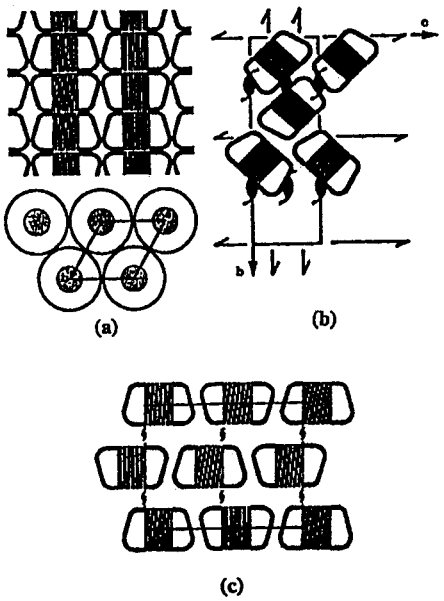

Figure 2. Schematic description of channel type (a), cage herringbone type (b), and cage brick type (c) crystal structures formed by crystalline cyclodextrin inclusion complexes. Note that only the host CD lattices are shown.

having the higher molecular weight in order to form a more thermodynamically stable IC, while α-CD exhibits a similar, though not exclusive, preference for the high molecular weight polymer, poly(ethylene glycol) in that case. We have observed a general discrimination between polymers with distinct molecular weights, between polymers with distinct chemical microstructures, and between a polymer and a model compound of its repeat unit.

In the work presented here, crystalline α-CD ICs have been prepared in the presence of PCL and HA, a model compound for the PCL repeat unit. By varying the relative amounts of both guests and the CD host and comparison with the formation of their individual crystalline CD ICs, we have begun to formulate certain conclusions concerning the thermodynamic and kinetic aspects of guest inclusion in the α-CD IC channels during crystallization.

Experimental Section

Samples. Hexanoic acid (HA) and poly(ϵ-caprolactone) (PCL) (M_w = 65 000) were obtained from Aldrich Chemical Co., and α-cyclodextrin (α-CD) was purchased from Cerestar Co.

α-CD ICs were prepared via a cocrystallization method. PCL and HA were dissolved together (1:1 molar ratio) in 100 mL of acetone while continuously heating (60 °C) and stirring. The heated solution was then slowly added to aqueous solutions saturated with α-CD (a 25 mL solution containing 3.625 g of α-CD and a 50 mL solution containing 7.25 g of α-CD) also held at 60 °C. The two combined solutions contained 1:1:1 and 1:1:2 PCL:HA:CD molar ratios. After 3 h of stirring at 60 °C, these solution were allowed to cool to room temperature while continuously stirring for another 2 days. A white powder was collected by filtration and then washed with water and acetone to remove uncomplexed α-CD and free guests, respectively. Finally, the powder was dried in the vacuum oven at 50 °C for another 24 h.

DSC Measurements. Differential scanning calorimetry was carried out on 3−10 mg samples with a Perkin-Elmer DSC-7 thermal analyzer equipped with a cooler system. A heating rate of 10 °C/min was employed, and an indium standard was used for calibration.

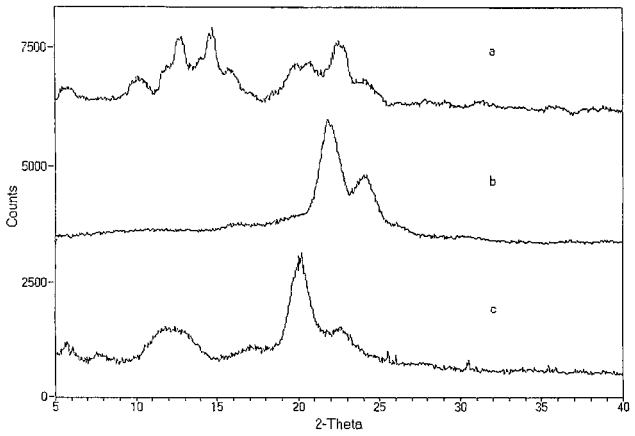

Figure 3. X-ray diffractograms of α-CD (a), pure PCL (b), and PCL−α-CD IC.

Wide-Angle X-ray Diffraction. A Siemens type-F X-ray diffractometer with a nickel-filtered Cu Kα radiation source (wavelength = 1.54 Å) and voltage and current set to 30 kV and 20 mA, respectively, was operated at a scan rate of 2θ = 1 °/min, between 2θ = 5° and 40°, to obtain the powder diffractograms.

FTIR Spectroscopy. Absorbance Fourier transform infrared spectra were recorded on a Nicolet 510p FTIR spectrometer with OMNIC software at frequencies from 400 to 4000 cm^{-1}, gain = 1, and scans = 128. Samples were thoroughly mixed with KBr and pressed into pellet form.

Results and Discussion

IC Yields. On the basis of the anticipated 1:1 HA or PCL repeat unit:CD stoichiometry, we found HA−, PCL−, and HA/PCL(1:1:2)−α-CD and HA/PCL(1:1:1)−α-CD IC yields of 85 ± 1%.

DSC. The DSC technique was employed to determine whether the inclusion compounds obtained contain free guests. As long as the involved guests are included in the CD ICs channels, they do not show any endothermic peaks in the DSC thermograms. Since cyclodextrins and their ICs decompose while melting, we tested them below their decomposition temperature (>270 °C), which in the present case is higher than the guests' melting points (60 °C for PCL and −3 °C for HA). The DSC thermograms recorded for HA−α-CD IC, PCL−α-CD IC, and HA/PCL−α-CD IC show no endothermic peaks corresponding to the melting of PCL and/or HA. This fact indicates that there is no free guest in our samples. Since pure PCL and HA can form inclusion compounds with α-CD,[7] we expect the guests to be included together or separately in the channels of the host CD lattice. Moreover, the TGA thermograms of all α-CD ICs, which are not presented here, show a higher decomposition temperature (>320 °C) than that of pure α-CD (298 °C). This may imply that the guests included inside the CD channels can improve the thermal stability of α-CD.

X-ray Diffraction. The X-ray diffractograms of α-CD, PCL, and PCL−α-CD IC are presented in Figure 3, where their comparison clearly reveals that our PCL−α-CD IC sample is not simply a mixture of free cyclodextrin host and PCL guest but that a crystalline IC has been formed between the two. Major peaks at 9.6°, 12.03°, 19.5°, and 21.8° were observed for pure α-CD. PCL showed two strong reflections at 2θ = 22.0° and 23.8°. The most prominent peak for PCL−α-CD IC is at approximately 20.0° (2θ) and indicates that the inclusion compound has formed with PCL included inside the CD channels. Like the PCL−α-CD IC dif-

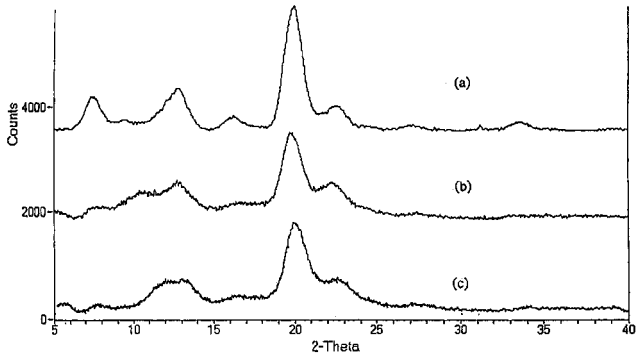

Figure 4. X-ray diffractograms of HA−α-CD IC (a), HA/PCL−α-CD (1:1:1) (b), and HA/PCL−α-CD IC (1:1:2).

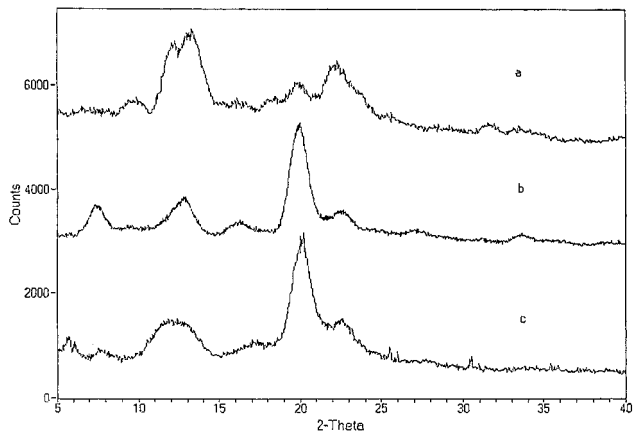

Figure 5. X-ray diffractograms of propionic acid−α-CD IC (a), valeric acid−α-CD IC (b), and PCL−α-CD IC (c).

fractogram, those of HA−α-CD IC and HA/PCL−α-CD ICs (1:1:1 and 1:1:2, molar ratios of HA:PCL:α-CD used in their formation) also show the characteristic diffraction pattern of a channel α-CD IC (see Figure 4). By comparing any of the above IC diffractograms, for instance PCL−α-CD IC, with the X-ray diffraction patterns of valeric acid-α-CD IC and propionic acid−α-CD IC, whose inclusion structures are already known from single-crystal X-ray diffraction studies to be channel and cage types, respectively,[8,9] we observe the PCL−α-CD IC pattern is much more similar to that of valeric acid−α-CD IC (see Figure 5). This is very strong evidence that PCL−α-CD IC, HA−α-CD IC, and HA/PCL−α-CD ICs (1:1:1 and 1:1:2) are obtained and have a channel type structure. It is also interesting that the X-ray diffraction patterns of all ICs mentioned above are similar, having a characteristic strong peak at about $2\theta = 20°$.[10] In addition, diffraction peaks from free PCL expected at 2 Å = 22.0° and 23.8° are absent.

FTIR Spectroscopy. It has been demonstrated that FTIR is a very useful tool to prove the presence of both guest and host components in IC samples. The FTIR spectra of pure HA (a), PCL (b), and α-CD (c) in the region from 400 to 4000 cm^{-1} are presented in Figure 6. The α-CD spectrum shows bands at 3371 cm^{-1} due to the symmetric and antisymmetric O−H stretching mode, at 2931 cm^{-1} due to the C−H stretching mode, and several peaks in the 1500−1200 cm^{-1} region which are assigned to C−H, CH_2, and O−H bending modes.[11] Positions and relative intensities of a few bands due to both the host and the guests are affected by the formation of the inclusion compound. Thus, the broad band at 3371 cm^{-1} is shifted to higher frequency at 3391 cm^{-1} in the HA−α-CD IC spectrum (Figure 7a) and at 3397 cm^{-1} in the PCL−α-CD IC spectrum (Figure 7b). This shift may be accounted for by comparison with α-CD bridged systems[12] and also can be observed for HA/PCL−α-CD ICs (1:1:1 and 1:1:2 molar ratio) (Figure 7c,d). The most distinctive bands in the IC spectra appear in the 1700−1800 cm^{-1} region, and they are assigned to the C═O stretching bands for PCL and HA, respectively. Therefore, the new bands at 1736 and 1710 cm^{-1} in the PCL−α-CD IC and HA−α-CD IC spectra are absent in the pure CD spectrum. According to the DSC and X-ray measurements, the entire amounts of PCL or HA guests are included inside of the α-CD IC channels; consequently, these new bands are due to the included guests.

Comparison of the intensities of PCL and HA carbonyl bands at 1734 and 1714 cm^{-1}, respectively, illustrates that the amounts of both components in the common α-CD IC can be controlled by the stoichiometry of the starting guest and host solutions. In the α-CD IC formed with a 1:1:1 molar ratio of PCL:HA:α-CD (Figure 7c), the included guest is found to be predominantly PCL, while for a 1:1:2 ratio with sufficient α-CD to include both guests, we do in fact see comparable amounts of PCL and HA included (Figure 7d). Figure 8 presents an expansion of the carbonyl stretching region of these FTIR spectra which clearly establish the preference for PCL inclusion compared with its repeat unit model compound HA, an observation similar to that reported previously for PEG oligomer and polymer.[6] Though not definitive, this observation suggests that PCL inclusion in α-CD IC may be favored by kinetic rather than thermodynamic factors over HA inclusion, because both guests have demonstrated the ability to form thermodynamically stable ICs when in the presence of sufficient quantities of CD to include both guests. It is only when the amount of CD used in IC formation is sufficient for complexing either all of one or half of each guest that we observe a predominant preference for PCL inclusion, thereby suggesting that IC formation is dominated by the kinetics of the process.

Because each PCL repeat unit included in the interior of an α-CD is connected to neighboring repeat units in the same PCL chain, the decomplexation of all but the last CD complexed PCL repeat unit is hindered by the complexation of neighboring PCL repeat units. Thus, in both solution and the crystal it might be expected that once a PCL repeat unit is inserted and complexed into the central CD core its removal and resolubilization is hindered by the necessarily cooperative dissruption of the CD complexes formed by its neighboring, connected repeat units. Even a PCL repeat unit that is a terminal member of a PCL fragment, at least some of whose repeat units are CD-complexed, should find it more difficult to decomplex, because of the necessity for its bound CD to completely dethread from the PCL chain. Complete CD removal requires its unthreading and must involve a series of decomplexation and complexation steps as the threaded CD traverses the PCL chain during the unthreading process. Though the inherent thermodynamic stabilities of a CD-complexed PCl repeat unit and a CD-complexed HA molecule may be comparable, the complexation/dissolution, which must accompany crystallization/decomplexation of the connected and CD-complexed repeat units of PCL chains included in the α-CD crystalline channels, is likely biased toward formation of crystalline PCL−α-CD IC, because their complexation with CD and incorporation

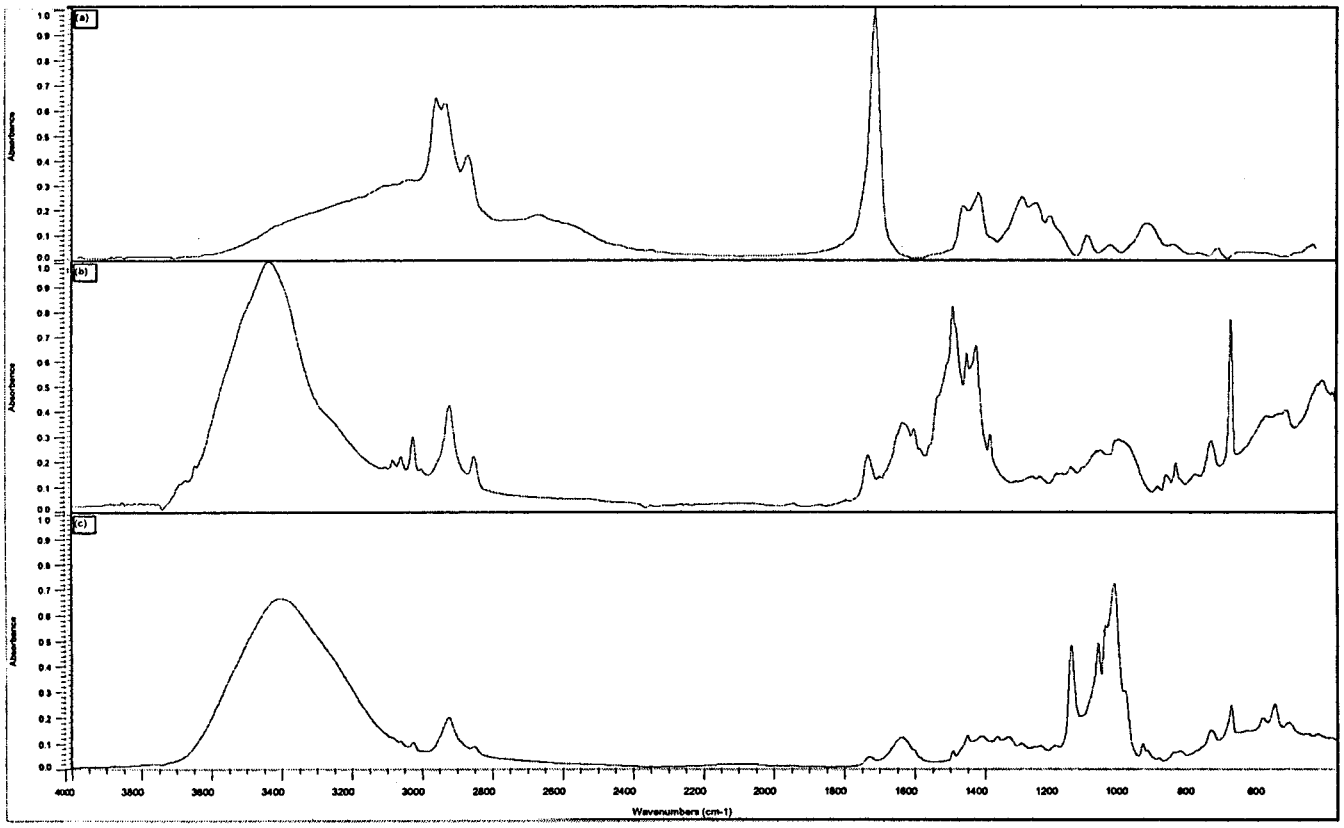

Figure 6. FTIR spectra of pure HA (a), PCL (b), and α-CD (c).

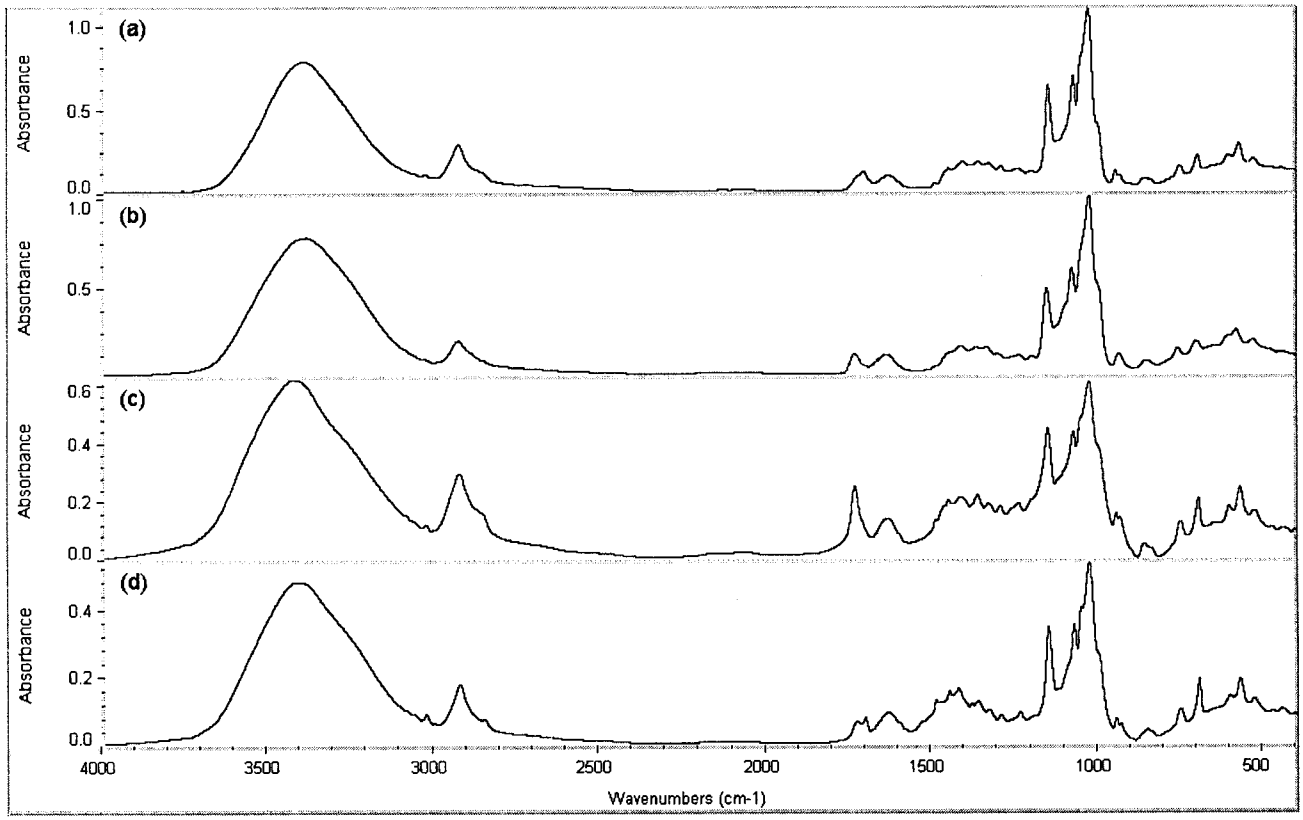

Figure 7. FTIR spectra of HA−α-CD IC (a), PCL−α-CD IC (b), HA/PCL−α-CD IC (1:1:1) (c), and HA/PCL−α-CD IC (1:1:2) (d).

into the crystalline IC lattice may be enhanced by their connectivity.

For example, let us envision the formation of crystals of PCL− and HA−CD ICs from solutions containing the host CD and either guest. At any instant in time in the HA/CD solution a certain fraction of HA molecules are complexed in the interiors of their CD hosts.[13] Judging from the equilibrium constant characterizing their

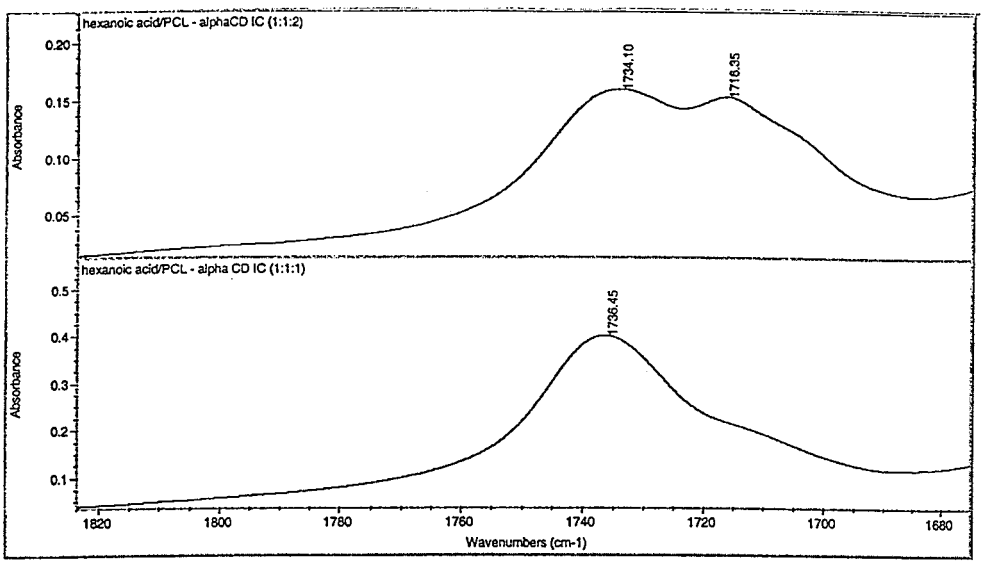

Figure 8. Expansions of the carbonyl stretching regions of the FTIR spectra shown in Figure 7c,d.

complexation,[13] the rate of HA inclusion into CD far exceeds that for HA removal, and a similar behavior might at first glance be expected for the terminal repeat unit of a PCL chain. However, because CD may thread further along the PCL chain toward its interior and because the terminal PCL unit is necessarily anchored to the PCL chain, thereby slowing its separation from the CD, it would be reasonable to expect that the rate of decomplexation of a PCL repeat unit from inclusion in CD would be significantly retarded compared with the decomplexation of HA and CD. Thus, it might be expected during the cocrystallization of CD-complexed PCL and HA that once a crystal of PCL−α-CD IC is nucleated, its growth by attachment of HA−α-CD IC complexes would be made difficult by the fact that unthreaded, uncomplexed portions of the PCL chains in the crystal nucleus would prevent attachment of HA−α-CD complexes. Of course the identical argument could be invoked concerning a crystal nucleus made up of HA−α-CD complexes, and so this would suggest that PCL−α-CD IC likely nucleates the growth of CD IC crystals faster than HA−α-CD IC.

The faster nucleation of CD-IC crystals suggested for PCL−α-CD IC is also consistent with a difference in water solubility of PCL− and HA−α-CD ICs. The hydrogen bonding between −OH groups on both sides of the truncated cones of neighboring CDs threaded on the PCL chain, which is not possible for HA−α-CD IC, would be expected to reduce the solubility of PCL−α-CD IC more than HA−α-CD IC when compared to the solubility of free CD in water.

Knowing that the urea (U) host has discriminating complexing properties as well,[6] we have therefore attempted to form HA/PCL−U IC, using the same molar ratios as above. Unfortunately, all our attempts have failed. However, we also used γ-CD as a host to obtain HA/PCL−γ-CD IC. Since the γ-CD cavity is large enough to include both guests in a side-by-side arrangement, even at a 1:1:1 molar ratio of PCL:HA: γ-CD, the IC obtained was observed to contain comparable amounts of included PCL and HA.

Further studies concerning guest−host and/or guest−guest interactions in these CD ICs by a variety of solid-state NMR spectroscopic techniques[14,15] are now in progress, with the eventual hope of delineating the mechanism(s) of polymer−CD IC formation and understanding their stabilities more completely. For example, these solid-state NMR observations should be able to distinguish between side-by-side occupation of PCL−HA in the same γ-CD channel or segregation of side-by-side PCL−PCL and side-by-side HA−HA in different γ-CD channels.

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