Preparation and Characterization of Inclusion Complexes of Biodegradable Amphiphilic Poly(ethylene oxide)−Poly[(*R*)-3-hydroxybutyrate]−Poly(ethylene oxide) Triblock Copolymers with Cyclodextrins

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ABSTRACT: Inclusion complexes (ICs) of biodegradable amphiphilic poly(ethylene oxide)−poly[(*R*)-3-hydroxybutyrate]−poly(ethylene oxide) triblock copolymers with α-cyclodextrin (α-CD) or γ-cyclodextrin (γ-CD) were prepared from aqueous medium. The ICs were characterized by XRD, DSC, ^{13}C CP/MAS NMR, ^{1}H NMR, FTIR, and TGA. The results of XRD and ^{13}C CP/MAS NMR indicated that the ICs formed channel structure, and the α-CD or γ-CD molecules in the ICs adopted a more symmetric conformation compared with their uncomplexed states. As to the triblock copolymers, while the poly(ethylene oxide) blocks were included in the channel structure, the poly[(*R*)-3-hydroxybutyrate] block was partially threaded by α-CD or γ-CD, which was confirmed by the results of XRD, DSC, ^{1}H NMR, and FTIR. The formation of ICs led to an increase in the thermal stability of both cyclodextrins and the triblock copolymers.

Introduction

Cyclodextrins (CDs) are cyclic molecules consisting of six to eight glucose units joined by α-1,4-glycosidic linkages and are named α-, *β*-, and γ-CD, respectively. With doughnut-shaped geometry that gives a hydrophobic cavity, CDs were widely used in preparation of inclusion complexes (ICs) with low molecular weight compounds.[1,2] Recently, they have been extensively studied in supramolecular chemistry as host molecules capable of including polymers. The first example of stoichiometric inclusion complexes between CD and polymers is the inclusion complex between α-CD and poly(ethylene glycol) (PEG).[3] Until now, a large number of reports have been published on formation of ICs between CD and various polymers with necklace-like supramolecular structures.[4] Although the depth of the hydrophobic cavity of CDs is the same (ca. 7.0 Å), the internal diameters of the cavities are different, being ca. 4.5 Å for α-, ca. 7.0 Å for *β*-, and ca. 8.5 Å for γ-CD.[1] It has been found that the correlation between the cross-sectional areas of the polymer chains and the cavity sizes of CDs plays an important role in the IC formation.[4]

However, there were few reports on the ICs formed between CDs and block copolymers,[5,6] especially on biodegradable block copolymers.[6] Because of the preferential inclusion, CDs can be threaded onto specific blocks of the copolymers, which may affect the morphology of the remaining blocks. It is well-known that the morphology of biodegradable polymers plays an important role in determining their material performances and properties such as degradability and permeability.[7,8] Recently, an example was reported to regulate the biodegradability of poly(ϵ-caprolactone)−poly(L-lactide) diblock copolymers upon formation of ICs with CDs.[6b]

The optically active poly[(*R*)-3-hydroxybutyrate] (PHB), synthesized and accumulated by a variety of bacteria as a energy and carbon storage material, has attracted much attention lately, because of its potential environmental, pharmaceutical, and biomedical applications.[9−11] Its excellent biodegradability and biocompatibility in various environments are remarkable characteristics of PHB. Some attempts have been made to improve its physical properties by means of blending or copolymerization.[12−14] Recently, we have synthesized new amphiphilic poly(ethylene oxide)−poly[(*R*)-3-hydroxybutyrate]−poly(ethylene oxide) (PEHE) triblock copolymers.[15] It is of great interest to study the IC formation between CDs and the new copolymers and how the complexation affects the morphology of the triblock copolymers. Here we report the preparation and characterization of ICs of PEHE with CDs. We have found that both α-CD and γ-CD preferentially include the PEO block, while the middle PHB block is only partially covered by CD molecules.

Experimental Section

Materials. Natural source poly[(*R*)-3-hydroxybutyrate] (PHB) was purchased from Fluka. PHB was purified by dissolving in chloroform followed by precipitation in petroleum ether before use. The methoxy-poly(ethylene oxide) (M-PEO) with molecular weight of 2000 was purchased from Sigma. Diglyme [bis(2-methoxyethyl)ether], ethylene glycol, dibutyltin dilaurate, 1,3-*N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), succinic anhydride, and triethylamine were obtained from Aldrich. α-CD, *β*-CD, and γ-CD were supplied by Tokyo Kasei, Tokyo. Diglyme was dried with molecular sieves (4 Å). Methylene chloride was distilled over CaH_2 before use.

Telechelic hydroxylated PHB (PHB-diol) prepolymers with various molecular weights were prepared by a transesterification procedure from the natural PHB and diethylene glycol with dibutyltin dilaurate as catalyst in diglyme as reported

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Table 1. Molecular Characteristics of the PEO−PHB−PEO Triblock Copolymers

				block length (M_n)		T_m (°C)[c]	
copolymer	M_n[a]	M_w[a]	M_w/M_n	PEO[a]	PHB[b]	PEO	PHB
PEHE(20−39−20)	7290	8000	1.10	1820	3910	25.4	142.3
PEHE(20−52−20)	8120	9260	1.14	1820	5230	23.3	153.6
PEHE(20−68−20)	9690	11770	1.21	1820	6840	25.3	155.2

[a] Determined by GPC. [b] Determined by combination of ^{1}H NMR and GPC results. [c] Determined in DSC second heating run.

previously.[16] M-PEO-monocarboxylic acid (M-PEO-A) prepolymer with M_n of 1820 was prepared by reaction of M-PEO with succinic anhydride in the presence of DMAP and triethylamine in 1,4-dioxane as reported previously.[17]

Polymer Synthesis. The synthesis and characterization of PEHE were reported previously.[15] Typically, in a 250 mL two-neck round-bottomed flask, 2.00 g (1.1 mmol) of M-PEO-A (M_n 1820), 1.54 g (0.4 mmol) of PHB-diol (M_n 3850), and 0.04 g (0.33 mmol) of DMAP were added and dried in a high vacuum overnight at 60 °C. Then, 30 mL of anhydrous methylene chloride was added to the flask and distilled off 20 mL of methylene chloride to remove any trace water in the system. After cooling to room temperature, 3 mL of DCC in anhydrous methylene chloride (1 M) was added and stirred overnight at room temperature under dried nitrogen. The precipitated dicyclohexylurea was filtered off. The filtrate was precipitated in cold diethyl ether (4 °C). The desired triblock copolymer was collected by filtration and fractionated in methanol and diethyl ether mixture to remove remaining M-PEO-A. Yield: 1.6 g, 53%. Three triblock copolymers were prepared, and their number-average molecular weight, weight-average molecular weight, and polydispersity are given in Table 1.

Preparation of Inclusion Complexes. PEHE triblock polymer (20 mg) was soaked with 0.06 mL of H_2O and left to stand overnight at room temperature. Then, 3.0 mL of saturated aqueous solution of CDs was added, and the mixture was sonicated in a water bath for 10 min, followed by standing 2 days at room temperature. The precipitated product was collected by centrifugation and washed with water and acetone alternately. Finally, it was dried in a vacuum at 70 °C for 2 weeks. For comparison, ICs of α-CD with PEO and γ-CD with poly(propylene oxide) (PPO) were prepared according to previous reports.[3,4c]

Measurements. X-ray diffraction (XRD) measurements were carried out using a Siemens D5005 diffractometer using Ni-filtered Cu Kα (1.542 Å) radiation (40 kV, 40 mA). Powder samples were mounted on a sample holder and scanned in 0.01° steps from 5° to 35° (in 2θ) with 1 s per step.

Differential scanning calorimetry (DSC) measurements were performed using a TA Instruments 2920 differential scanning calorimeter equipped with an auto-cool accessory and calibrated using indium. The following protocol was used for each sample: heating from room temperature to 200 °C at 20 °C min^{-1}, holding at 200 °C for 2 min, cooling from 200 °C to −30 °C at 5 °C min^{-1}, and finally reheating from −30 °C to 200 °C at 5 °C min^{-1}. Data were collected during the second heating run. Transition temperatures were taken as peak maxima. Thermogravimetric analysis (TGA) was made using a TA Instrument SDT 2960. Samples were heated at 20 °C min^{-1} from room temperature to 800 °C in a dynamic nitrogen atmosphere (flow rate = 70 mL min^{-1}).

^{1}H NMR spectra of the complexes in DMSO were recorded at 400 MHz on a Bruker DPX-400 NMR spectrometer. Chemical shifts of the complexes were referenced to δ = 2.50 ppm for DMSO. ^{13}C CP/MAS NMR spectra were acquired on a Bruker DPX-400 NMR spectrometer with a sample spinning rate of 8.0 kHz at room temperature. The spectra were acquired with a 2.75 μs proton 90° pulse, a 3 ms contact time, and a 3 s repetition time.

Fourier transform infrared (FTIR) spectra were recorded on a Bio-Rad 165 FTIR spectrophotometer; 64 scans were signal-averaged with a resolution of 2 cm^{-1} at room temperature. Samples were prepared by dispersing the complexes in KBr and compressing the mixtures to form disks.

Table 2. Yields and the Ratios of PEO Repeat Unit CH_2CH_2O to CD of the α-CD−PEHE and γ-CD−PEHE ICs

	yield[a] (mg)		CH_2CH_2O/CD[b]	
copolymer	α	γ	α	γ
PEHE(20−39−20)	75.0	60.6	1.2	2.1
PEHE(20−52−20)	67.9	56.3	1.4	2.6
PEHE(20−68−20)	65.8	60.0	1.1	2.3

[a] Complexes were formed from 20 mg of the triblock polymers and 3.0 mL of saturated aqueous solutions of CDs. [b] Determined from ^{1}H NMR results.

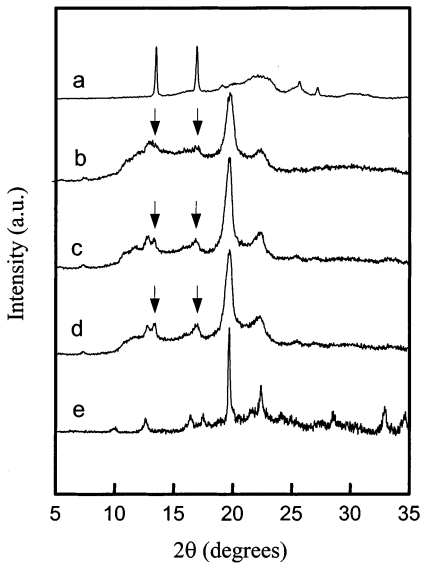

Figure 1. XRD results of pure PEHE(20−52−20) (a), α-CD−PEHE(20−39−20) IC (b), α-CD−PEHE(20−52−20) IC (c), α-CD−PEHE(20−68−20) IC (d), and α-CD−PEO IC (e). The arrows show the characteristic peaks of crystalline PHB.

Results and Discussion

When an aqueous solution of α-CD or γ-CD was added to the PEHE triblock copolymer soaked with water and sonicated for 10 min, complexes were formed as crystalline precipitates. The appearance of precipitates was an indication of the formation of crystalline ICs between the copolymers and CDs.[3] In comparison, there was no precipitate formed in the mixture of β-CD and the PEHE triblock copolymer solution even after standing 2 weeks. This observation indicates that the PEHE triblock polymers can form ICs with α-CD and γ-CD, but not with β-CD. The yields of the IC formation are shown in Table 2.

The formation of CD-PEHE ICs was strongly supported by X-ray diffraction (XRD) studies. Figure 1 shows the XRD patterns of pure PEHE(20−52−20) and ICs of α-CD with all three PEHE triblock copolymers in comparison with IC formed by α-CD and PEO (M_n 2000). In Figure 1e, a number of sharp reflections with two prominent peaks at 2θ = 19.4° and 22.1° represent the channel-type structure of crystalline necklace-like complex of α-CD and PEO.[3,18] The observation of similar

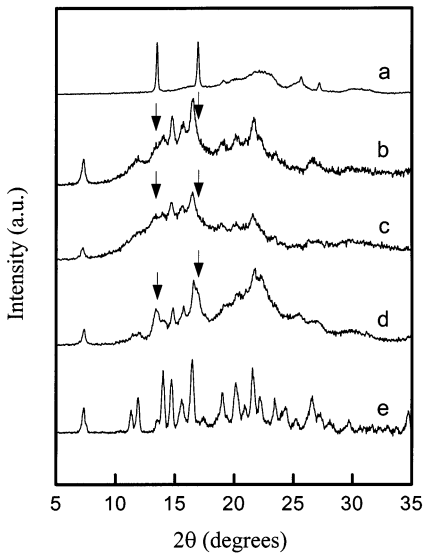

Figure 2. XRD results of pure PEHE(20−52−20) (a), γ-CD−PEHE(20−39−20) IC (b), γ-CD−PEHE(20−52−20) IC (c), γ-CD−PEHE(20−68−20) IC (d), and γ-CD−PPO IC (e). The arrows show the characteristic peaks of crystalline PHB.

diffraction patterns for α-CD-PEHE ICs (Figure 1b−d) indicates the α-CD-PEHE ICs assume the channel-type structure like that of α-CD-PEO IC. When compared with α-CD-PEO IC, two extra small peaks at $2\theta = 13.6°$ and 17.0° appear in the patterns of α-CD-PEHE ICs (shown with arrows). The relative intensity of the two peaks increases with increasing the ratio of PHB to PEO in PEHE. With pure PEHE, as shown in Figure 1a, the peaks at 13.6° and 17.0° are a characteristic of crystalline PHB. Thus, the presence of the two peaks indicates that parts of the PHB block aggregate to form crystalline phase, which coexists with the IC crystals.

The XRD patterns of γ-CD-PEHE ICs are shown in Figure 2, as compared with those of pure PEHE and γ-CD-PPO IC. Although relative intensities of each peak are different, the XRD patterns of γ-CD-PEHE ICs are very similar to each other and are also similar to that of γ-CD-PPO IC, in which a channel-type structure has been established. Furthermore, the characteristic peak at 7.6° is observed, which is the key feature serving as a fingerprint for the channel-type structure of γ-CD-polymer ICs.[19] Therefore, γ-CD-PEHE ICs assume a channel-type structure. The two peaks at $2\theta = 13.6°$ and 17.0° (shown with arrows in Figure 2) attributed to the crystalline PHB block are also observed in the XRD patterns of γ-CD-PEHE ICs as in α-CD-PEHE ICs. The broadening XRD patterns for α-CD-PEHE and γ-CD-PEHE ICs compared with the stoichiometric α-CD-PEO and γ-CD-PPO ICs (Figures 1e and 2e) are due to the lower crystallinity of the ICs most likely caused by the uncovered PHB segments that "break up" and shorten the channels in the ICs.

The DSC curves of pure PEHE(20−52−20) and α-CD-PEHE ICs are shown in Figure 3. As shown in Figure 3a, there are two endothermic peaks at 23.3 and 153.6 °C in the DSC curve of pure PEHE(20−52−20), corresponding to crystal fusion of PEO and PHB blocks, respectively. Upon formation of ICs, the endothermic peak corresponding to PEO block is absent in Figure 3b−d. This is because the PEO block is included separately in the channels of the host α-CD lattice and then cannot aggregate to form the crystalline phase. However, the endothermic peak corresponding to PHB

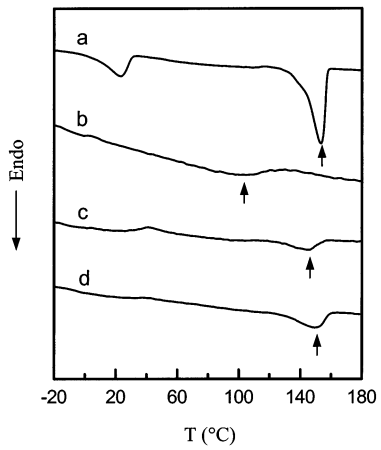

Figure 3. DSC curves of pure PEHE(20−52−20) (a), α-CD−PEHE(20−39−20) IC (b), α-CD−PEHE(20−52−20) IC (c), and α-CD−PEHE(20−68−20) IC (d). The arrows indicate the endothermic peaks for the PHB block.

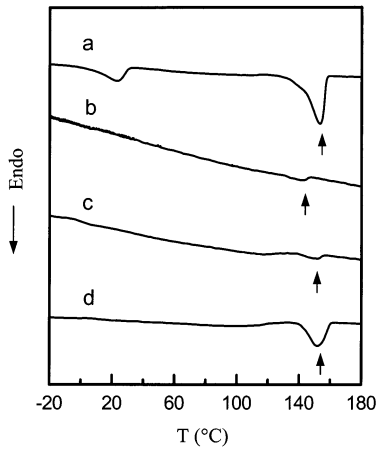

Figure 4. DSC curves of pure PEHE(20−52−20) (a), γ-CD−PEHE(20−39−20) IC (b), γ-CD−PEHE(20−52−20) IC (c), and γ-CD−PEHE(20−68−20) IC (d). The arrows indicate the endothermic peaks for the PHB block.

block is still observable (Figure 3b−d). But the fusion temperatures move to lower range, and the enthalpy changes decrease dramatically with the formation of α-CD-PEHE ICs. The results indicate that each PHB block is partially covered by α-CD, and most likely the middle portion of the PHB block is uncomplexed by α-CD. The decreases in fusion temperature and the enthalpy change are due to the perturbation of crystallization resulting from the partial inclusion of the PHB block. In the α-CD-PEHE ICs, there is a trend that both fusion temperature and enthalpy change increase with an increase in the chain length of the middle PHB block. This is in accordance with the fact that the α-CD-PEHE ICs with longer PHB block have longer uncomplexed portion of PHB chain. Figure 4 shows the DSC curves of pure PEHE(20−52−20) and γ-CD-PEHE ICs. Similar results as those from Figure 3 can be obtained. All the DSC results for both α-CD-PEHE and γ-CD-PEHE ICs indicate that the PEO block is fully covered by CDs, while the middle PHB block is partially covered, which is consistent with the XRD results. Shuai et al.[20] reported the formation of IC between poly[(*R*)-3-hydroxybutyrate] and α-CD in DMSO. Their results showed that a PHB chain is only partially included by α-CD. For our system, threading of α-CD onto PHB block is still thwarted by the hydrophobicity of PHB,

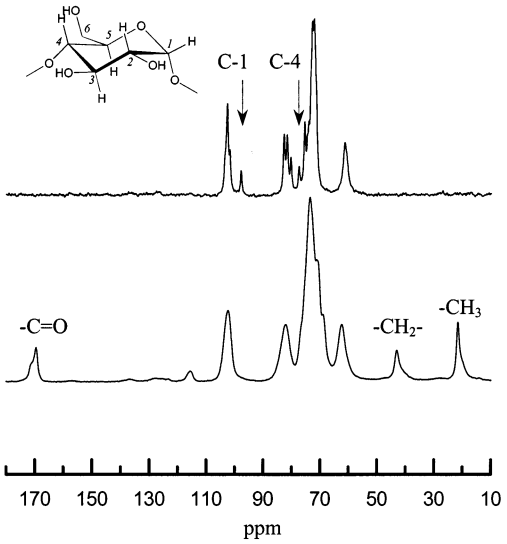

Figure 5. ^{13}C CP/MAS NMR spectra of uncomplexed α-CD (a) and α-CD-PEHE(20−52−20) IC (b). The arrows show the resolved resonances for C-1 and C-4 adjacent to a single conformationally strained glycosidic linkage.

although the CD threading onto the PEO block can further slide onto the middle PHB block. In another study on IC formation between poly(ϵ-caprolactone)−poly(propylene glycol)−poly(ϵ-caprolactone) (PCL−PPG−PCL) triblock copolymers and α- or γ-CD,[6c] it was found that only PCL blocks are included in the IC of α-CD, while both PCL and PPG blocks are included in the IC of γ-CD. The PEHE−CD system differs in that the middle PHB segments are rigid and highly crystalline, while the PPG segments are flexible and amorphous. Therefore, the middle PHB block is only partially included even in the γ-CD−PEHE ICs.

Figure 5 shows the ^{13}C CP/MAS NMR spectra of α-CD and α-CD−PEHE(20−52−20) IC. The spectrum of α-CD in the uncomplexed state shows multiple resolved resonances for C_1 and C_4. Especially, resonances for C_1 and C_4 adjacent to a single conformationally strained glycosidic linkage are observed in the spectrum. The results indicate that the α-CD assumes a less symmetrical conformation in the crystalline uncomplexed state. On the contrary, for α-CD−PEHE(20−52−20) IC, all C_1−C_6 of CD shows single unresolved resonance, indicating that α-CD adopts a more symmetric conformation, and each glucose unit of α-CD is in a similar environment in the IC. Similar observations, which are believed to support the formation of ICs between CDs and polymers, have been previously observed in the solid-state ^{13}C CP/MAS NMR spectra of various crystalline ICs.[3−6] In addition, the resonances for the PHB block are also clearly observed at 21.6, 43.0, and 168.6 ppm for the methyl, methylene, and carbonyl carbons, respectively, while that for the methine carbons is found to overlap with those of the CD carbons at the region of 66−75 ppm. The results strongly suggest the existence of the PEHE triblock copolymers in the ICs.

The partial coverage of the middle PHB block by α-CD or γ-CD was also demonstrated by the ^1H NMR spectra of the CD−PEHE ICs. Figure 6 shows the ^1H NMR spectrum of α-CD−PEHE(20−52−20) in DMSO-d_6. As shown in Figure 6, all proton signals belonging to both α-CD and PEHE(20−52−20) are confirmed. By comparing the integral of the peaks, the ratio of the ingredients in the crystalline IC can be determined. As reported

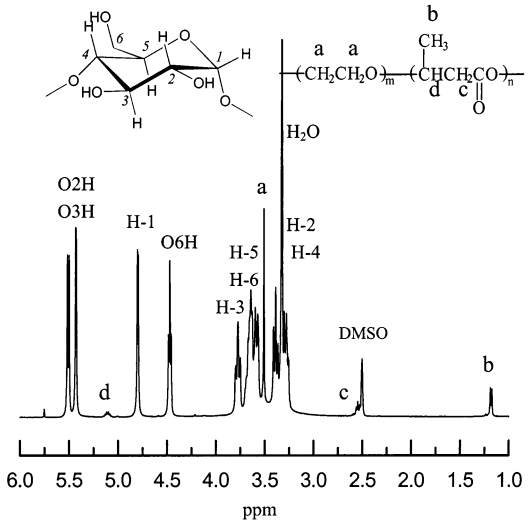

Figure 6. The 400 MHz ^1H NMR spectrum of α-CD−PEHE-(20−52−20) IC in DMSO-d_6.

previously, PEO can form inclusion complex with α-CD and γ-CD with the ratio of PEO repeat unit to CD being 2 and 4, respectively.[3,4a] However, the ratio of PEO repeat unit to α-CD obtained from Figure 6 for α-CD−PEHE(20−52−20) IC is 1.4, indicating more α-CD molecules have been contained in the α-CD−PEHE(20−52−20) IC than forming a stoichiometric complex of α-CD and the PEO blocks. On the other hand, the solid-state ^{13}C CP/MAS NMR measurement shows all α-CD in the IC has been threaded on polymer chain and adopt the channel structure. Thus, some α-CD must slide onto the middle PHB block. The ratios of PEO repeat unit to CD for all CD−PEHE ICs are summarized in Table 2. In the cases of ICs with γ-CD, the ratios are between 2.1 and 2.6, similarly, which indicates some γ-CD molecules also slide onto the middle PHB block. These results further support the hypothesis that the PEO block is fully covered by α-CD or γ-CD, while the middle PHB block is partially covered in the CD−PEHE ICs.

FTIR has been a useful tool to prove the presence of both guest and host components in ICs.[21] The FTIR spectra of the α-CD−PEHE or γ-CD−PEHE ICs were studied compared with the pure PEHE(20−52−20) and α-CD. The spectrum for α-CD shows a broad band at 3360 cm^{-1} due to the symmetric and antisymmetric O−H stretching mode. Upon formation of ICs, the broad hydroxyl band shifts to higher frequency at 3390 cm^{-1} in the spectra of the ICs, most probably due to formation hydrogen bonding between the hydroxyl groups of CDs in channel structure. An intensive carbonyl stretching band at 1723 cm^{-1} characterizes the FTIR spectrum of pure PEHE(20−52−20), which is ascribed to the PHB part in PEHE(20−52−20). The carbonyl stretching band is resolved into an intensive band at 1723 cm^{-1} and a weak shoulder at 1736 cm^{-1}, corresponding to the carbonyl stretching band of the crystalline PHB phase and that of the amorphous PHB regions, respectively.[22] Figure 7 shows the expansion of the carbonyl stretching region of these FTIR spectra. As compared with the pure PEHE(20−52−20), the peak at 1723 cm^{-1} decreases sharply while the shoulder at 1736 cm^{-1} increases sharply in the spectra of α-CD−PEHE(20−52−20) and γ-CD−PEHE(20−52−20). When ICs are formed, some of the PHB segments are located individually in the IC channels and thus are not able to aggregate to form PHB crystals. The existence of the peak at 1723 cm^{-1}

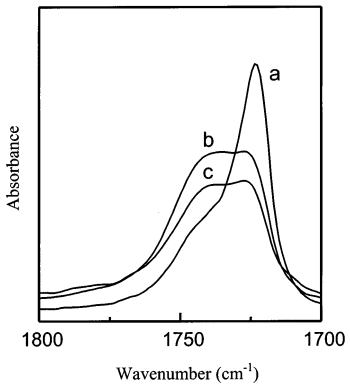

Figure 7. Expansions of the FTIR spectra of pure PEHE-(20−52−20) (a), α-CD−PEHE(20−52−20) IC (b), and γ-CD−PEHE(20−52−20) IC (c).

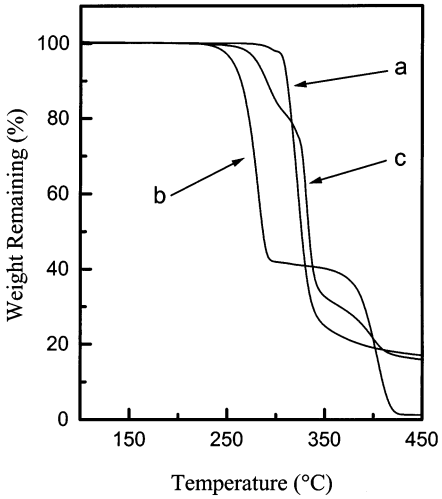

Figure 8. TGA curves of pure α-CD (a), pure PEHE(20−52−20) (b), and α-CD−PEHE(20−52−20) IC (c).

indicates only a portion of the PHB block has been covered by CD, and the remaining PHB segments still can aggregate to form a crystalline phase. This is in agreement with the XRD and the DSC results as discussed above.

Figure 8 shows the results of the thermogravimetric analysis (TGA) scans for α-CD, pure PEHE(20−52−20), and their IC up to 450 °C. As shown in Figure 8, α-CD starts to decompose at 279.2 °C, and pure PEHE(20−52−20) shows an initial weight loss of 58.7% and second weight loss of 39.3% on heating with onset of thermal decomposition at 222.4 and 343.8 °C, respectively. We attribute the first weight loss to decomposition of the PHB block and the second weight loss to the decomposition of PEO blocks. However, the onsets of the decomposition of PHB block, the PEO blocks, and α-CD in the α-CD-PEHE IC are observed at 247.2, 309.3, and 365.8 °C, respectively. They all are higher than those of the PHB and PEO blocks in PEHE(20−52−20) and the pure α-CD, respectively. The higher decomposition temperatures of α-CD−PEHE ICs are due to the contribution of complex formation to thermal stability of both α-CD and PEHE. Similar results have been also observed for γ-CD−PEHE ICs.

Conclusions

Amphiphilic PEHE triblock copolymers were found to form ICs with α-CD and γ-CD from aqueous medium. The XRD studies showed that all the α-CD−PEHE and γ-CD−PEHE ICs assume a channel-type structure. Both XRD and DSC results suggested that a portion of the middle PHB block of PEHE is not covered by CD molecules in the ICs. The ^{1}H NMR results revealed that the ratios of PEO repeat unit to α-CD or γ-CD in the α-CD−PEHE or γ-CD−PEHE ICs are lower than 2:1 or 4:1 stoichiometries for the previously reported α-CD−PEO or γ-CD−PEO ICs, respectively, suggesting the existence of extra complexed CDs besides a close inclusion of the PEO blocks in the α-CD−PEHE or γ-CD−PEHE ICs. The results strongly supported the hypothesis that the PEO block is fully complexed by α-CD or γ-CD, while the middle PHB block is also partially complexed. The formation of α-CD−PEHE and γ-CD−PEHE ICs was further confirmed by solid-state ^{13}C NMR and FTIR spectroscopic studies. Finally, TGA results showed that α-CD, γ-CD, and the PEHE triblock copolymers in the ICs have better thermal stability than their respective free counterparts.

This study has provided new understanding of the IC formation between CDs and biodegradable amphiphilic triblock copolymers. We believe that the formation of CD−PEHE ICs may lead to a novel way to modulate the morphology and the bulky properties of the new amphiphilic triblock copolymers. Now such studies are underway in this lab. In the meantime, the studies on formation of ICs between CDs and the PEHE triblock copolymers in nonaqueous media and how it will affect the complex structures are also ongoing.

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Supporting Information Available: FTIR analysis of ICs formed between PEHE triblock copolymers and α- or γ-CD and FTIR spectra of pure PEHE(20−52−20), α-CD−PEHE-(20−52−20) IC, γ-CD−PEHE(20−52−20) IC, and pure α-CD. This material is available free of charge via the Internet at http://pubs.acs.org.

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