Photo-Cross-Linking and Cleavage Induced Reversible Size Change of Bio-Based Nanoparticles

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Received March 24, 2008; Revised Manuscript Received August 19, 2008

ABSTRACT: Reversible size changes in degradable nanoparticles composed of bio-based cinnamate derivative copolymers, poly(3,4-dihydroxycinnamic acid-*co*-4-hydroxycinnamic acid) [P(3,4DHCA-*co*-4HCA)], were observed for the first time. The 860 nm diameter decreased to almost one-half (420 nm) during UV irradiation over 280 nm and rapidly recovered to 620 nm upon subsequent irradiation at 254 nm. Results from UV−vis and ^{1}H NMR spectra suggested that diameter-changing phenomena corresponded to [2 + 2] cycloaddition formation and cleavage of the cinnamate groups. This significant diameter change was reproduced for at least three cycles, and the reason for this significant size change seemed to be due to the fact that all units of the copolymer contained photochromic groups. Furthermore, these photo-cross-linked bio-based nanoparticles showed various size change behaviors during hydrolytic degradation depending on the degree of cross-linking. Photosensitive degradable nanoparticles may be useful as novel, size-controllable carriers for environmental and biomedical fields.

Introduction

Light-induced responses have attracted much attention since they represent one of the most desirable methods for easy, rapid, and efficient control of material properties by tuning light parameters such as wavelength, time, and energy.[1,2] Photosensitive materials have great potential applications in shape-memory systems,[3] as recording and switching sensors,[4] and for microstructuring and patterning of surfaces.[5] Therefore, photosensitive, nanoscaled materials such as nanoparticles, nanofibers, and nanofilms are expected to have applications not only in nanotechnologies but also in biomedical fields. In general, azide groups,[6] diazo groups,[7] and cinnamate groups[8,9] are widely used as photochromic groups for photosensitivity. Cinnamic acid and its derivates exist in plant cell walls as an intermediate metabolite in the biosynthetic pathway of lignin and other biological materials[10] and show several photoreactions such as [2 + 2] cycloaddition and trans/cis isomerization, which lead to the transformation of the photoactive yellow protein in photosynthetic bacteria.[11] Therefore, materials containing cinnamate groups can be useful for developing photosensitive nanoscaled materials for biomedical and environmental applications. Although many researchers have reported photosensitive materials based on cinnamate moieties,[3,8,9,12−14] there are few reports on the use of the cinnamate group as a chromophore for nanoscaled materials. Schartl et al. reported poly(organosiloxane) nanospheres with photolabeled coumarin as dye molecules conjugated onto particle surfaces and investigated the aggregation and disaggregation of these clusters induced by UV irradiation.[15] Zhao et al. studied polymer micelles with coumarin moiety side chains for the stabilization of micelles by UV-induced cross-linking.[16]However, conventional photosensitive nanoscaled materials do not show a large or significant morphological or size changes because they only contain a few photochromic groups. We speculated that biocompatible and degradable nanomaterials consisting of whole cinnamate groups would be useful as novel, more pliable photosensitive nanomaterials for environmental and biomedical fields.

In previous studies, we reported the development of a novel cinnamic acid and its derivative homopolymers and copolymers.[12,17−19] The bio-based copolymer P(3,4DHCA-*co*-4HCA), which has photosensitivity, cell adhesion, and strong mechanical properties, was prepared from cinnamic acid derivative phytomonomers, 3,4-dihydroxycinnamic acid (3,4DHCA) and 4-hydroxycinnamic acid (4HCA).[17] Herein, the “bio-based copolymer” is defined as a “naturally resourceable copolymer”. Furthermore, nanoparticles self-organized by mixing two homogeneous P(3,4DHCA-*co*-4HCA) copolymer solutions in *N*,*N*-dimethylformamide (DMF) and trifluoroacetic acid (TFA).[20] Many researchers have reported the preparation of nanoparticles composed of well-known, degradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-carprolactone) (PCL), and polyanhydride and investigated their degradation behaviors.[21]However, an important limitation in the use of these polyesters for biomedical and environmental applications is their lack of reactive functional groups in response to environmental conditions, such as light responsiveness. Photosensitive nanoparticles consisting of P(3,4DHCA-*co*-4HCA) are expected to show large property changes following photoreactions, such as size, morphology, and degradation behavior, because all of the nanoparticle components are cinnamate derivatives.

In this study, we found that nanoparticle diameter underwent significant changes and rapid recoveries following photo-cross-linking and photocleavage reactions of cinnamate groups (Scheme 1). Moreover, nanoparticles with various cross-linking degrees could be hydrolyzed in buffer solutions and showed interesting size change behaviors during their hydrolytic degradation depending on the degree of cross-linking. To the best of our knowledge, this is the first example of a size-controllable, nanoscaled, and degradable biomaterial composed of complete cinnamate derivatives.

Experimental Section

Materials. The monomers 4-hydroxycinnamic acid (4HCA, Tokyo Chemical Industry (TCI)) and 3,4-dihydroxycinnamic acid (3,4DHCA, Wako Pure Chemical Industries, Ltd.) were used as received. *N*,*N*-Dimethylformamide (DMF), trifluoroacetic acid (TFA), dichloromethane (DCM), tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and 1,4-dioxane were purchased from Wako

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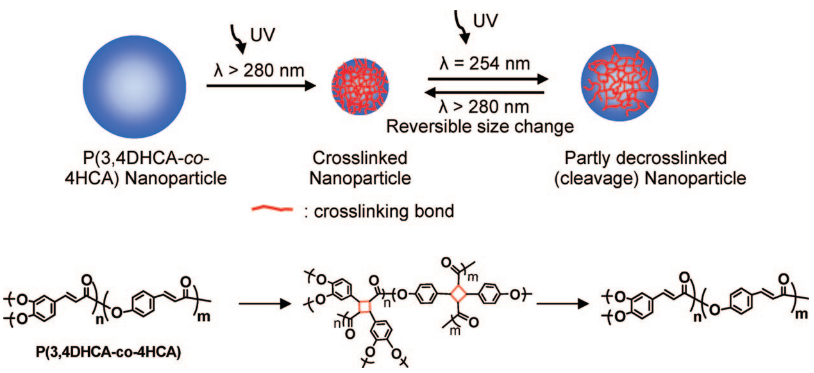
10.1021/ma800648e CCC: $40.75

Scheme 1. Schematic Representation of Size Change Behavior of P(3,4DHCA-*co*-4HCA) Nanoparticles with UV Irradiation; Chemical Structure of UV-Induced [2 + 2] Cycloaddition Formation (Cross-Linking) and Deformation (Cleavage)



Pure Chemical Industries Ltd. and were used without further purification.

Preparation of P(3,4DHCA-*co*-4HCA) Nanoparticles. Bio-based copolymer P(3,4DHCA-*co*-4HCA) (50/50, mol/mol) was prepared from the 3,4DHCA and 4HCA monomers by thermal polycondensation at 200 °C for 6 h, according to the method previously reported.[17−19] The copolymer was then dissolved in DMF and TFA at the same concentration of 10 mg/mL to form transparent solutions. The two solutions were then mixed with the same volume ratio under stirring to immediately create the suspension. The mixture was centrifuged to remove the supernatant and was washed with distilled water three times. The nanoparticles were obtained by lyophilization.[20]

Photo-Cross-Linking and Photocleavage of Nanoparticles. The nanoparticles prepared from the bio-based copolymer P(3,4DHCA-*co*-4HCA) were dispersed in an organic solvent (THF, 1,4-dioxane, or DMSO) to a concentration of 0.04 mg/mL. A quartz UV cell was filled with that nanoparticle solution and was inserted into a UV reactor with a focused UV beam from a 350 W high-pressure mercury lamp. The distance between the solution and the lamp was ∼5 cm. The photo-cross-linking of the cinnamate groups was first performed by UV irradiation at $\lambda > 280$ nm (80 mW/cm^2) until the cinnamate groups were almost completely reacted. After exchanging with a 254 nm UV pass filter (0.6 mW/cm^2), the above solution was subsequently irradiated at $\lambda = 254$ nm. The photo-cross-linking and photocleavage cycles were repeated several times to evaluate their reversibility. The diameters of all samples were measured before and after cross-linking or cleavage over three cycles by dynamic light scattering (DLS, Malvern Zeta-sizer Nano ZS Instruments). Scanning electron microscopy (SEM, JEOL JSM-6700F) was used to observe the size and morphology of the nanoparticles after casting the sample solutions onto a stage and subsequent drying in vacuo overnight. The UV−vis absorbance change of the nanoparticle in THF at a concentration of 0.04 mg/mL was measured during UV irradiation at $\lambda > 280$ nm for 30 min and during subsequent irradiation at $\lambda = 254$ nm for 30 s to evaluate the photo-cross-linking and photocleavage with a UV−vis spectrophotometer (Hitachi, U3010 spectrometer). ^{1}H NMR (JEOL JNM-GSX400, 400 MHz spectrometer) measurements in trifluoroacetic acid (TFA)-d_1/dichloromethane (DCM)-d_2 (1/5, v/v) mixed solvent were performed to confirm the structural change of the nanoparticles following the UV-induced cross-linking and cleavage of the cinnamate groups. The nanoparticles in their dried state were cross-linked by UV irradiation at $\lambda > 280$ nm for 4 or 8 h and subsequently cleaved by UV irradiation at $\lambda = 254$ nm for 30 min. Fourier transform infrared spectroscopy (FT-IR) spectra were recorded to evaluate the photo-cross-linking and photocleavage of the cinnamate groups after UV irradiation in dried state using the attenuated total reflection (ATR) method with a FT-IR spectrometer (Spectrum 100, Perkin-Elmer).

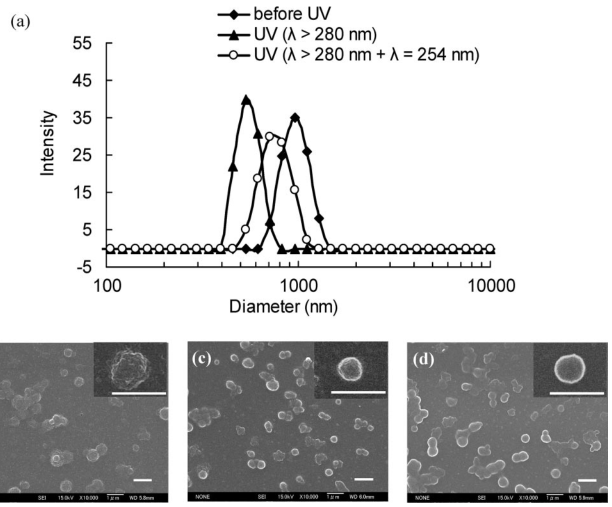


Figure 1. (a) Size distributions of the nanoparticles in THF at a concentration of 0.04 mg/mL before and after UV irradiation at $\lambda >$ 280 nm for 30 min and subsequent irradiation at $\lambda = 254$ nm for 30 s by DLS measurements.SEM images of the nanoparticles before UV irradiation (b), after UV irradiation at $\lambda > 280$ nm for 30 min (c), and after subsequent irradiation at $\lambda = 254$ nm for 30 s (d) are shown. The scale bars are 1 μm.

Calculation of the Cross-Linking Degree of Nanoparticles with UV Irradiation. The cross-linking degree (CD) was calculated from the FT-IR spectrum by comparing the peak areas between the double carbon ($\nu_{C=C}$) assigned to the cinnamate group and the benzene group by the following equation:

$$\mathrm{CD}\ (\%) = \frac{A_{C_T}/A_{B_T}}{A_{C_0}/A_{B_0}} \qquad (1)$$

Here, A_C and A_B are the peak area of the double carbon ($\nu_{C=C}$) assigned to the cinnamate group and the benzene group. T and 0 represent the "T" time of irradiation and before irradiation, respectively.

Hydrolytic Degradation of Nanoparticles with or without Cross-Linking. The photo-cross-linking of the nanoparticles was performed using the same process as mentioned above in the dried state. The cross-linking degree was then calculated from the FT-IR spectra. 25 mg of the nanoparticles with various cross-linking degrees was placed in sample tubes, and 50 mL of alkaline buffer solution (NaOH/NaHCO$_3$) at pH = 12 was added into each tube and then incubated with mild agitation at 37 °C for the predetermined time. After hydrolysis, the remaining nanoparticles were obtained by centrifugation, washing with distilled water for neutralization and subsequently drying by lyophilization for 3 days. The diameters of the obtained nanoparticles in THF were then measured by DLS.

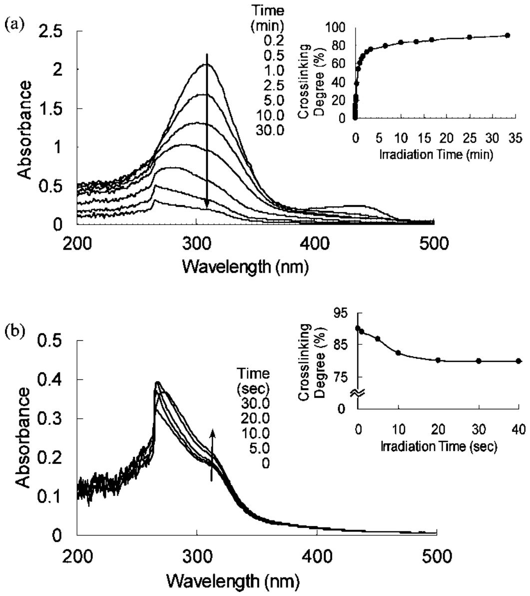


Figure 2. UV−vis absorbance of the nanoparticles in THF at a concentration of 0.04 mg/mL during UV irradiation at $\lambda > 280$ nm for 30 min (a) and subsequent irradiation at $\lambda = 254$ nm for 30 s (b). The insets in (a) and (b) show the cross-linking degree of cinnamate groups during UV irradiation, as determined by their UV−vis absorbance at 310 nm.

Results and Discussion

Photoreactions of Nanoparticles in Solution. Bio-based P(3,4DHCA-*co*-4HCA) nanoparticles self-organized by mixing two homogeneous solutions in DMF and TFA,[20] and the diameters approximated 860 nm after dispersion in THF. Figure 1a shows diameter changes of these nanoparticles upon irradiation at $\lambda > 280$ nm and subsequent irradiation at $\lambda = 254$ nm by DLS measurements. When the nanoparticle solution was irradiated at $\lambda > 280$ nm, surprisingly, the diameter decreased significantly to almost one-half, from 860 to 420 nm after irradiation for 30 min. The coefficients of variation (CV % = standard deviation/mean diameter) of the nanoparticles slightly increased from 15 to 18% after photo-cross-linking. SEM observations also showed a diameter decrement of the nanoparticles after UV irradiation at $\lambda > 280$ nm, the same as DLS measurements (Figure 1b,c). Furthermore, subsequent UV irradiation at $\lambda = 254$ nm induced a rapid recovery of the diameter within only 30 s by DLS measurements, and a slight increase of CV to 20% was observed. The photoreactions seemed to lead to slight incremental CV changes; however, the nanoparticles still maintained monodispersibility (Figure 1a). SEM observations also indicated a recovery of the nanoparticle diameter (Figure 1d) after subsequent UV irradiation at $\lambda = 254$ nm for 30 s. Although the diameters were not completely restored to their original sizes, from 420 to 620 nm, a significant diameter decrease and a recovery of a bio-based nanoparticle was observed for the first time.

We hypothesized that these diameter-changing phenomena were caused by photoreactions consisting of inter- and intramolecular [2 + 2] cycloaddition formation (cross-linking) and deformation (cleavage) of cinnamate groups, and therefore the UV−vis absorbance of these nanoparticles was determined in detail. Figure 2 shows the UV−vis absorbance of these nanoparticles during UV irradiation at $\lambda > 280$ nm (a) and subsequent irradiation at $\lambda = 254$ nm (b). The absorbance of the cinnamate groups at 310 nm gradually decreased with increasing irradiation time, and the value equilibrated after 30 min (Figure 2a). Many researchers have reported the same decrease in UV absorbance of the cinnamate groups with UV irradiation time due to formation of cyclobutane bonds.[8,9,15−17]The inset in Figure 2a shows the increase in the cross-linking degree as estimated from the change in absorbance at 310 nm. The cross-linking degree was saturated after 30 min of irradiation, and about 90% of the cinnamate groups in the nanoparticles were cross-linked by UV irradiation at $\lambda > 280$ nm. The photo-cross-linking speed of the nanoparticles was almost the same as that of polymer micelles containing coumarin moieties.[16]^{1}H NMR measurements of P(3,4DHCA-*co*-4HCA) in TFA-d_1/DCM-d_2 (1/5, v/v) were evaluated to investigate the [2 + 2] cycloaddition formation after UV irradiation at $\lambda > 280$ nm for 30 min (Figure 3a,b). Peaks at $\lambda = 6.8$ and 7.9 ppm were assigned to double carbon bonds in the cinnamate groups, and these areas decreased after UV irradiation at $\lambda > 280$ nm, as shown in Figure 3b. New peaks at $\lambda = 3.8−4.5$ ppm were assigned to cyclobutane bonds after cross-linking (Figure 3b). From these results, the driving force for the large diameter decrease after UV irradiation at $\lambda > 280$ nm seemed to be the [2 + 2] cycloaddition, the cross-linking of the cinnamate groups in the nanoparticles. When the nanoparticle solution was subsequently irradiated at $\lambda = 254$ nm, the absorbance of the cinnamate groups at 310 nm quickly recovered and saturated within 30 s, and the cross-linking degree decreased from 90 to 79% (Figure 2b). Peak areas of the cyclobutane bonds at 3.8−4.5 ppm decreased by about 16%, and peak areas of the double carbon bonds of the cinnamate groups at 6.8 and 7.9 ppm recovered partially by about 12% after the subsequent irradiation at $\lambda = 254$ nm for 30 s from ^{1}H NMR spectra (Figure 3c). However, recoveries of these peaks were not as high as same as results from UV−vis spectra (Figure 2b). During irradiation at 254 nm, not only photocleavage but also photo-cross-linking takes place.[8,9] Furthermore, the UV reactor power was not high at 254 nm (0.6 mW/cm^2), and thus cyclobutane cleavage reactions may have been incomplete (only 10%). However, surprisingly, DLS results indicated that only 10% of the photocleaved cinnamate groups were sufficient to quickly induce the recovery of the diameter from 420 to 620 nm (Figure 1a). This may be due to the fact that the cleaved parts of the nanoparticles may have swelled in THF solvent, and this swelling behavior led to the increments in diameters.

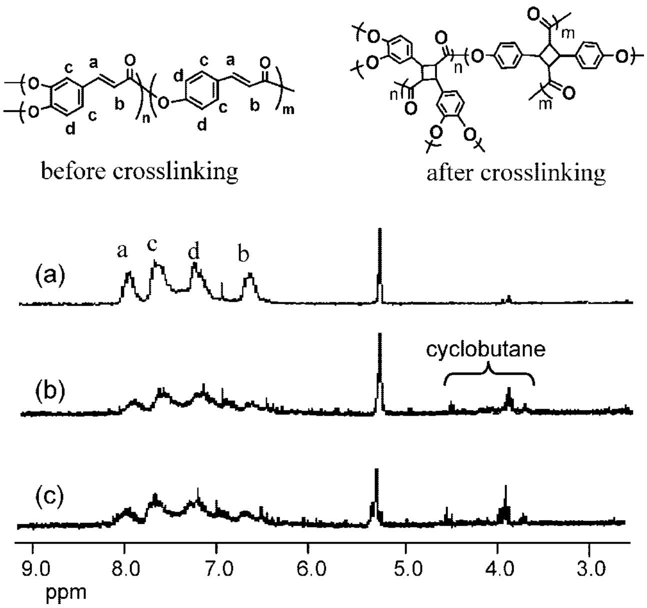


Figure 3. ^{1}H NMR spectra of the nanoparticles before UV irradiation (a), after UV irradiation with $\lambda > 280$ nm for 30 min (b), and after subsequent UV irradiation at 254 nm for 30 s (c) in a TFA-d_1/DCM-d_2 (1/5, v/v) mixed solvent.

Figure 4a shows diameter changes of the nanoparticles at

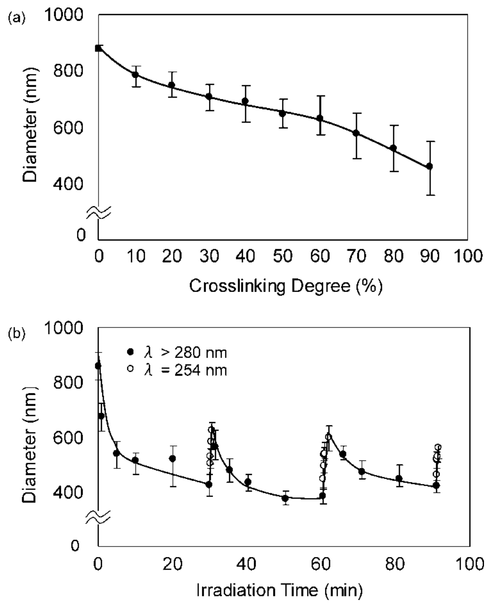


Figure 4. (a) Diameter changes of the nanoparticles at increment of each 10% during photo-cross-linking upon UV irradiation at $\lambda > 280$ nm. (b) Diameter change of the nanoparticles in THF at a concentration of 0.04 mg/mL during UV irradiation at $\lambda > 280$ nm (close circle) and $\lambda = 254$ nm (open circle) by DLS measurements ($n = 3$).

increment of each 10% during photo-cross-linking. The diameter of the nanoparticles gradually decreased with increasing of cross-linking degree by UV irradiation at $\lambda > 280$ nm. At the initial 10% and final 20% (70−90%) of photo-cross-linking, the size largely decreased about 100 nm, but the detailed reason was not understood. Although, the photocleavage of the cinnamate dimers appeared to be incomplete (Figure 2b), reversible photocontrol of the diameters could be achieved to a certain degree, as shown in Figure 4b. When the nanoparticle solutions were repeatedly exposed to alternating UV light for three cycles at $\lambda > 280$ nm for 30 min and $\lambda = 254$ nm for 30 s, reversible changes in the diameters could be observed. Whereas, the photoreactive efficiencies decreased slightly during repeating processes, the size reversible phenomena of the nanoparticles were observed continuously for at least three cycles. The CV value of the nanoparticles increased from 15 to 30% after three cycles of photo-cross-linking and photocleavage, and the nanoparticles maintained monodispersibility during three photoreaction cycles. It is well-known that the photo-cross-linking and cleavage reactions of cinnamic acid derivatives occurred at equilibrium during UV irradiation at both $\lambda > 280$ and $\lambda = 254$ nm.[3,8,9,16] Accordingly, CV values of the nanoparticles might increase with increasing the cycle numbers of the photoreactions. This reversible experiment suggested that the P(3,4DHCA-*co*-4HCA) nanoparticle would be useful as degradable and biocompatible photoreactive nanoparticles for various applications.

These nanoparticles also dispersed in various organic solvents such as 1,4-dioxane and DMSO, and diameters were 830 and 665 nm, respectively, as shown in Figure 5.The diameter decreased with increasing solvent polarity due to different swelling capabilities of the nanoparticles.We evaluated UV-induced size changes of the nanoparticles in THF, dioxane, and DMSO under the same conditions. In all solvents, the diameter decreased to about one-half after UV irradiation at $\lambda > 280$ nm for 30 min and then recovered to ~70% after subsequent irradiation at $\lambda = 254$ nm for 30 s.The magnitude of the size change of the nanoparticles with photoreactions was independent of the solvent polarity, suggesting the photoreactivity of the nanoparticles in various solvents.

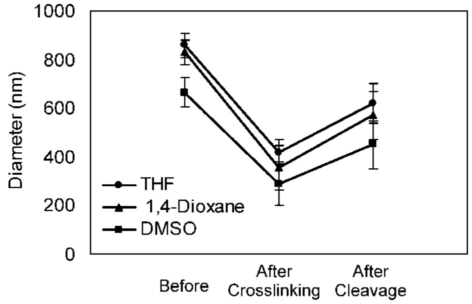


Figure 5. Diameter changes of the nanoparticles after cross-linking with UV irradiation at $\lambda > 280$ nm and after cleavage with UV irradiation $\lambda = 254$ nm by DLS measurements. THF, 1,4-dioxane, and DMSO were used as solvents at nanoparticle concentrations of 0.04 mg/mL.

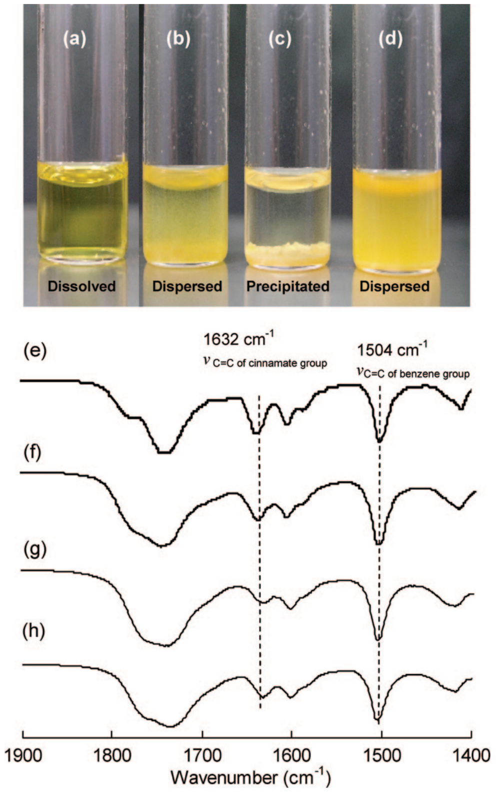


Figure 6. Solubility tests of the nanoparticles following photoreaction in DMF (a−d) and the FT-IR spectra of the nanoparticles following photoreaction (e−h). Nanoparticles before UV irradiation (a, e), after UV irradiation for 4 h at $\lambda > 280$ nm (b, f), after UV irradiation for 8 h at $\lambda > 280$ nm (c, g), and after subsequent UV irradiation at $\lambda = 254$ nm for 30 min to the nanoparticle irradiated for 8 h (d, h) in the dried state.

Photoreactions of Nanoparticles in Dry State. When nanoparticles were irradiated with UV light in dry state, the nanoparticles showed solubility changes following UV irradiation (Figure 6a−d). Nanoparticles were completely dissolved in DMF before UV irradiation (Figure 6a), but dispersions and precipitates were observed after the nanoparticles were irradiated in dry state at $\lambda > 280$ nm for 4 and 8 h, respectively, due to photo-cross-linking (Figure 6b,c). Interestingly, after subsequent irradiation at $\lambda = 254$ nm for 30 min to the nanoparticles irradiated for 8 h, the obtained nanoparticles could be dispersed in DMF again, as shown in Figure 6d. The aforementioned indicated that the recovery of the double carbon bond of the cinnamate groups caused the swelling in DMF. The cross-linking degrees (CD) of the above four samples in dry state were

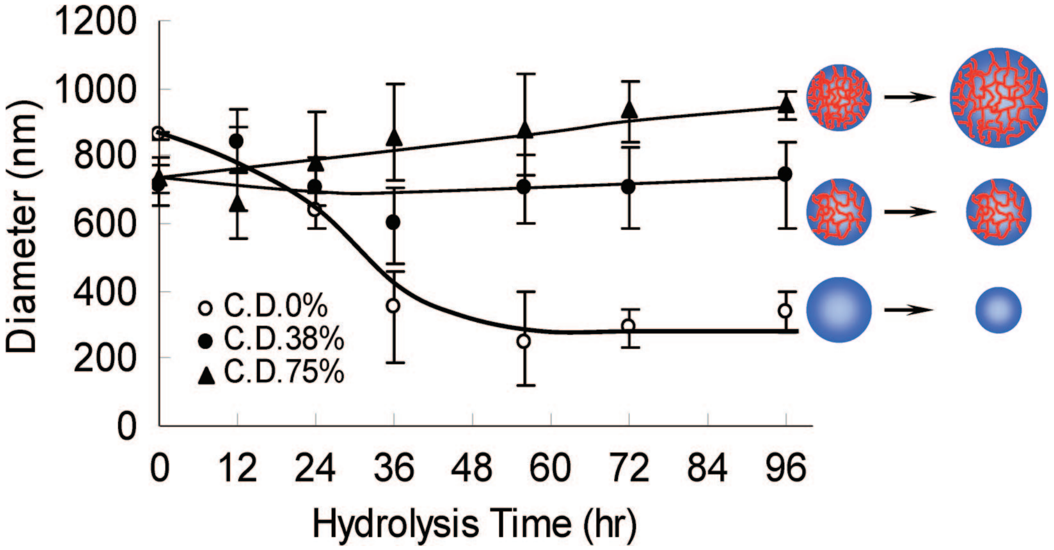


Figure 7. Diameter changes of the remaining nanoparticles with different cross-linking degrees during hydrolysis in alkaline buffer solution (NaOH/$NaHCO_3$) at pH = 12 at 37 °C for predetermined times by DLS measurements. CD means the cross-linking degree. The remaining nanoparticles were dispersed in THF to a concentration of 0.04 mg/mL after collecting them with centrifugation, washing with pure water, and subsequent lyophilization for 3 days.

calculated from their FT-IR spectra by comparing peak areas between double carbon bonds ($\nu_{C=C}$) assigned to cinnamate groups at 1632 cm^{-1} and double carbon bonds ($\nu_{C=C}$) assigned to benzene groups at 1504 cm^{-1} (Figure 6e−h) because the peak area $\nu_{C=C}$ assigned to the benzene group did not changed with UV irradiation. The peak area $\nu_{C=C}$ from the cinnamate group decreased with increasing UV irradiation time ($\lambda > 280$ nm), and the cross-linking degrees after irradiation for 4 and 8 h were 38 and 75%, respectively (Figure 6f,g). After subsequent irradiation at $\lambda = 254$ nm for 30 min to the sample in Figure 6g, the peak area at 1632 cm^{-1} increased and the cross-linking degree decreased to 60% (Figure 6h) due to cleavage of the cyclobutane groups.These results indicated that the photo-cross-linking and photocleavage of the P(3,4DHCA-*co*-4HCA) nanoparticles also occurred in dry state with UV irradiation, but the photoreaction velocities in dry state were much slower than those in solution.

Hydrolytic Degradation of Nanoparticles with or without Cross-Linking. Hydrolytic degradation behaviors of nanoparticles with different cross-linking degrees were investigated in an alkaline buffer (NaOH/$NaHCO_3$) at pH = 12 at 37 °C as an acceleration test. Three kinds of nanoparticles with CD values of 0, 38, and 75% were used to evaluate the effect of photo-cross-linking on hydrolysis. All samples were obtained with centrifugation and redispersion in THF to a concentration of 0.04 mg/mL to measure the diameters. Figure 7 shows the diameter change of the remaining nanoparticles with various cross-linking degrees during hydrolysis. The diameter of the nanoparticles with CD 0% significantly decreased from 850 to 300 nm after hydrolysis for 96 h. Interestingly, the diameter of the nanoparticles with CD 38% showed no change at about 700 nm for all hydrolysis times. To our surprise, an interesting phenomenon of nanoparticles with higher CD values of 75% was found during hydrolysis. The diameter of the nanoparticle did not decrease, but slightly increased from 700 to 950 nm during hydrolysis, and these size change behaviors might be caused by swelling properties of the photo-cross-linked nanoparticles. The un-cross-linked polymer chain easily hydrolyzed, and the hydrolyzed chain could dissolve in buffer solution during the hydrolysis process, while the cross-linked networks could not dissolve in buffer solutions. Accordingly, the terminal hydrolyzed groups, such as carboxyl anion or hydroxyl groups, remained in cross-linked networks after hydrolysis; thus, these hydrophilic groups might lead swelling properties. The swelling properties of the bio-based nanoparticles are characteristic because the swelling properties increase upon increasing the photo-cross-linking degree, although the swelling properties of general hydrogels or cross-linked nanoparticles decrease when increasing the cross-linking degree. The diameters of both cross-linked nanoparticles (CD 38 and 75%) were larger as compared to those of un-cross-linked nanoparticles after hydrolysis, and swelling diameters depended on the photo-cross-linking degree. Although the CD 38% seemed to stabilize at about 700 nm, the nanoparticle surely swelled considering the size decrease of un-cross-linked sample. Detailed experiments on this hydrolytic degradation behavior are now in progress. To our best knowledge, this is the first report that controls the diameter of degradable nanoparticles during hydrolysis. It is expected that drug release behavior from these nanoparticles during hydrolysis can be controlled by altering the degree of photo-cross-linking.

Conclusions

We found significant and reversible size changes in photosensitive, bio-based nanoparticle with photosensitivity following UV irradiation. The diameter of the nanoparticles decreased to almost one-half and rapidly recovered following the UV-induced cross-linking and cleavage of the cinnamate groups. This diameter-changing phenomenon was reproducible for at least three cycles, and the reason for this significant size change seems to be the fact that these nanoparticles were wholly composed of photochromic groups. The particle diameter was dependent on the solvent polarity, but the magnitude of the size change was independent of the polarity. Furthermore, these photo-cross-linked bio-based nanoparticles showed various size change behaviors during hydrolytic degradation dependent on the degree of photo-cross-linking. Detailed hydrolysis experiments of nanoparticles with different cross-linking degrees are now in progress, and we will report the results in the next paper. These rapidly photoresponsive and degradable nanoparticles composed of bio-based copolymers, P(3,4DHCA-*co*-4HCA), could be used as a novel functional nanocarriers with potential applications in drug delivery systems and in environmental fields.

Acknowledgment. This research was supported by 21st Century COE Program "Center for Integrated Cell and Tissue Regulation", Osaka University, Japan.

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MA800648E