Morphology-Controlled Self-Assembly and Synthesis of Biopolyimide Particles from 4-Amino-L-phenylalanine

Thawinda Hirayama,†‡ Amit Kumar,† Kenji Takada,† and Tatsuo Kaneko*,†‡

‡Graduated School of Advanced Science and Technology, Japan Advanced Institute of Science and Technology, 1-1 Asahidai, Nomi, Ishikawa 923-1292, Japan
†Department of Chemistry, Faculty of Science, Chulalongkorn University, 254 Phayathai Road, Pathumwan, Bangkok 10330, Thailand

Supporting Information

ABSTRACT: Self-assembling polyimides (PIs) having diketopiperazine (DKP) components were synthesized by polycondensation of a 4-amino-L-phenylalanine (4APhe) dimer, an aromatic diamine newly designed in this study. The amino acid-derived PIs showed high thermal resistance, with a 10% weight loss temperature (T$_{10}$) of 432 °C at the maximum, and did not show any glass transition below the thermal decomposition temperature. The poly(amic acid) (PAA) precursors formed nanospheres upon reprecipitation over dimethylacetamide into water. The nanospheres were then added to solvents with different polarities and sonicated to induce deformation of the spherical forms into spiky balls, flakes, or rods. The PAA particle morphologies were retained in the PIs after the two-step imidization. Finally, the PI particles with self-assembling DKP moieties were formed, and their morphologies were fine-tuned using different mixed solvents.

INTRODUCTION

The development of biobased polymers is essential for establishing a sustainable green society. Conventional biobased aliphatic polymers such as polyesters and polycarbonates have unsatisfactory thermal and mechanical properties, although several attempts have been made to improve these properties. One of the most effective strategies in this regard is to incorporate an aromatic component into the polymer backbone.

Polyimides (PIs), a class of super-high-performance plastics, are widely used in electronic devices and in aerospace applications because of their outstanding mechanical durability and high thermal and chemical stabilities, which enable them to tolerate harsh environments. PIs were initially synthesized from petrochemical-based monomers, but there have been a few recent attempts to synthesize them from biobased monomers. In particular, attempts have been made to prepare partially or completely biobased PIs using a biobased aromatic diamine, 4,4′-diaminotrichlorilic acid (4ATA), and various dihydrides. 4ATA was synthesized by photodimerization of the biobased 4-aminoiminic acid (4ACA), an aromatic amino acid obtained by the bioconversion of 4-aminophenylalanine (4APhe) using phenylalanine ammonia lyase (PAL), and a genetically engineered microorganism. With regard to molecular design, we found that the alicyclic structure sandwiched between two aromatic rings imparted rigidity to produce thermally resistant PIs with a T$_{g}$ of 425 °C, while retaining important functions, such as optical transparency, in the case of 4ATA. Despite the outstanding thermal stability, the low efficiency of the bioconversion step involving PAL reduced the yield of 4ACA significantly. This motivated us to use 4APhe in the present study in order to eliminate the inefficient bioconversion step involving PAL. If 4APhe is dimerized, another aromatic diamine biomonomer can be synthesized.

In order to synthesize a structure in which heterocyclic compounds are sandwiched by two aromatic rings, we carried out the dimerization of 4APhe and obtained a 2,5-diketopiperazine (2,5-DKP) derivative. The core structure of several drugs contains central 2,5-DKP rings, but 2,5-DKP has not been extensively used as a building block to synthesize functional polymeric materials. In the present study, we have designed a monomer containing a centrosymmetric amide functionality in the 2,5-DKP ring, apart from two aromatic rings that can induce self-assembly of the corresponding polymer chains through hydrogen bonding and π–π interactions. Particle formation can be expected as a result of the chain self-assembly, rendering these PIs suitable for applications such as fillers, heat resistant superhydrophobic coatings, and ultralow-dielectric-constant films.

Received: October 1, 2019
Accepted: November 25, 2019
Published: February 3, 2020
Here, we report the synthesis of the biobased aromatic diamine 3,6-di(4-aminophenylmethyl)-2,5-DKP (DKP-4APhe) from 4-Amino-L-phenylalanine (4APhe) through a simple coupling of stepwise protection and deprotection. The corresponding PIs having the 2,5-DKP heterocyclic structure in the backbone are prepared by polycondensation with commercially available aromatic dianhydrides. The present study investigates the particle formation ability of the PIs and attempts to control their morphology starting from a spherical form into various nonspherical shapes.

**RESULTS AND DISCUSSION**

**Monomer Syntheses.** A biobased aromatic diamine including a 2,5-DKP central core, DKP-4APhe, was synthesized by stepwise 4APhe dimerization (see Scheme 1). First, the aromatic amine group in 4APhe was protected by benzyl chloroformate (z-) to obtain 4APhe-z. Successive protections of the carboxylic acid and α-amine groups were separately carried out by methanol (methyl-) in the presence of trimethylsilyl chloride (TMSCl) and by di-tert-butyl dicarbonate (Boc-) to obtain methyl-4APhe-z and Boc-4APhe-z, respectively. The linear dipeptide was then synthesized by amidation coupling of methyl-4APhe-z and Boc-4APhe-z in the presence of condensation reagents. In the last step, Boc was deprotected from the α-amine group, which was successively cyclized by a reaction with methyl ester to form the central 2,5-DKP ring (total yield; 29 wt %). It should be noted here that two other methods for cyclodimerization had been tried. Cyclodimerization of 4APhe with z-protection at aromatic amine was tried by heating at 170 °C in ethylene glycol, but the reaction did not proceed. By cyclodimerization using PCl5, 4APhe with z-protection at aromatic amine was refluxed for 4 h in tetrahydrofuran (THF) and PCl5. Although the reaction was carried out successfully, the purity of the obtained product was not satisfactory enough to be used for polymerization. As the polymerization requires high purity of monomers, an alternative approach was applied for the synthesis of the DKP monomer.

The structure of the aromatic diamine was confirmed by 1H nuclear magnetic resonance (NMR), 13C NMR, Fourier-transform infrared (FTIR), and electrospray ionization-mass spectrometry (ESI-MS) analyses and was identical to the expected structure.
As a result of cyclization, the $^1$H NMR signals of the $\beta$-carbons of the 4APhe moieties (see Figure S1) shifted from 2.76–3.08 to 2.08 ppm, which coupled with the proton signals of 2,5-DKP at 7.63 (–NH–) and 3.80 ppm (–CH–). The proton signal at 4.89 ppm was attributed to the aromatic amine groups. The FTIR spectrum (Figure S2) showed N–H stretching, C=O stretching, and N–H bending bands of the amide group at 3570–3310, 1656, and 1459 cm$^{-1}$, respectively. C=C and C–H stretching peaks of the aromatic ring manifested at 1516 and 3030–2870 cm$^{-1}$, respectively. The formation of DPK-4APh was also confirmed by $^{13}$C NMR (see Figure S3) and FT-ion cyclotron resonance (ICR)-MS (ESI) (see Figure S4). The observed signal at $m/z$ 347.147642 for the species [M + Na]$^+$.

**Polymer Syntheses.** Poly(amic acids) (PAAs), the precursors of PIs, were prepared by polycondensation of the prepared diamine, DPK-4APh, with stoichiometric amounts of the dianhydrides, PMDA, BTDA, OPDA, BPA, and DHCDA, as shown in Table 1. The $^1$H NMR spectra of the PAAs, the chain main proton signals for the carboxylic acid, amide, cyclic amide groups of DPK, and the aromatic diamine group appeared at $\delta$ 12.2–13.2, 10.4–9.8, 8.1–7.9, and 7.5–7.0 ppm, respectively. PAAs derived from the aromatic dianhydrides, PMDA, BTDA, OPDA, BDA, and DHCDA, showed proton signals at $\delta$ 8.3–7.1 ppm in addition to the abovementioned peaks. On the other hand, PAAs derived from the aliphatic dianhydrides, CBDA and DHCDA, showed signals corresponding to cyclobutane and methylcyclohexene at $\delta$ 3.9–3.4 and 3.0–1.7 ppm, respectively. The proton signal at 5.5 ppm was assigned to the double bond in DHCDA.

The dimethylacetamide (DMAc) solution of the PAAs was prepared diamine, DKP-4APhe, with stoichiometric amounts of the dianhydrides, PMDA, BTDA, OPDA, BPA, and DHCDA. The PI derived from PMDA showed the weight-average molecular weight ($M_w$), number-average molecular weight ($M_n$), and polydispersity index (PDI) were determined using the PAAs (see Table 1). The PAAs had $M_w$ and $M_n$ values in the ranges of 16.8–33.2 and 24.9–14.7 $\times$ 10$^3$ kDa, respectively, while the PDI values ranged from 1.1 to 1.4. Note that only the dissolved fraction in LiBr/DMF was measured, in order to decrease the molecular weight and make the distribution narrower.

**Table 1. Molecular Weights of PAAs Derived from Biobased Aromatic Diamine, DKP-4APhe**

| dianhydrides | PMDA | BTDA | CBDA | DSDA | OPDA | BPDA | DHCDA |
|--------------|------|------|------|------|------|------|-------|
| $M_w$ (kDa)$^a$ | 20.3 | 24.9 | 21.2 | 27.0 | 19.1 | 18.8 | 14.7  |
| $M_n$ (kDa)$^a$ | 24.5 | 33.2 | 29.4 | 22.5 | 23.5 | 23.4 | 16.8  |
| PDI$^a$ | 1.2  | 1.3  | 1.4  | 1.2  | 1.3  | 1.2  | 1.1   |

$^a$Weight-average molecular weight, $M_w$, number-average molecular weight, $M_n$, and PDI of the dissolved PAA fraction in LiBr/DMF were measured by gel permeation chromatography (GPC).

**Table 2. Thermal Degradation Temperatures of Biopolyimides Derived from DPK-4APh**

| $T_d$ (°C)$^a$ | PMDA | BTDA | CBDA | DSDA | OPDA | BPDA | DHCDA |
|----------------|------|------|------|------|------|------|-------|
| $T_d5$ | 420  | 411  | 392  | 383  | 398  | 401  | 365   |
| $T_d10$ | 432  | 427  | 415  | 397  | 414  | 414  | 388   |

$^a$5 and 10% weight loss temperatures, $T_d5$ and $T_d10$, were obtained from TGA curves scanned at a heating rate of 10 °C/min under a nitrogen atmosphere.

**Thermal Properties.** Thermogravimetric analysis (TGA) was used in order to study the thermal degradation of the PIs in a nitrogen atmosphere, using a heating rate of 10 °C/min. The 5 and 10% weight-loss temperatures, $T_d5$ and $T_d10$, were evaluated in each case. As shown in Table 2, all of the PIs exhibited $T_d10$ values in the range 388–432 °C and $T_d5$ values in the range 365–420 °C, which indicated a high degree of resistance toward thermal degradation. The PI derived from PMDA showed the highest $T_d10$ value of 432 °C. In contrast, PI–DHCDA showed the lowest $T_d10$ value, presumably because of the presence of fewer aromatic rings than the others, leading to more susceptible chain scission at elevated temperatures. From our previous research, the biopolyimides derived from 4AT4A and PMDA,
both showed a $T_{\text{dil}}$ value of 425 °C,\(^\text{19}\) which is lower compared to the values for the PIs in the present study. The higher thermal resistance observed for the PIs in this study can be attributed to the intermolecular forces from the DKP moieties.

The thermal transition behavior of the PIs was investigated by differential scanning calorimetry (DSC) under a nitrogen atmosphere. There were no distinct peaks or points of inflections below the thermal degradation temperatures for all the PIs investigated here, presumably because of high glass transition temperatures. The hydrogen bonding interactions between the imide group and DKP ring or between DKP moieties could contribute to the high thermal stability of these compounds.

**Particulation.** The self-assembly behavior of the synthesized polymers was investigated. The polymers synthesized in this study have a DKP six-membered ring with two amide groups and other sites such as the amide and acid groups and the aromatic ring, all of which can trigger various noncovalent interchain interactions.

Here, the PAA nanoparticles with narrow size distribution (see Table S1 and Figure S8) were formulated according to the solvent displacement technique with surfactant-assisted cooperative self-assembly.\(^\text{39,40}\) The PAs derived from DKP-4APhe diamine with a series of dianhydrides, PMDA, BTDA, DSDA, and CBDA were taken for self-assembly (PAA−PMDA, PAA−BTDA, PAA−DSDA, and PAA−CBDA, respectively).

Typically, a preformed PAA polymer solved in DMAc, a water-miscible solvent, was slowly introduced drop by drop to an aqueous phase containing Triton X-100 as the emulsifier under vigorous magnetic stirring. After adding the organic phase into the watery phase, a slight turbidity could be observed. The PAA surfactant in water formed aggregated structures with a hydrophilic exterior and a hydrophobic interior. Subsequent self-assembly was initiated by the fast diffusion of the organic solvent (DMAc) into the aqueous medium, which progressively enriched the concentration of the polymers in emulsion droplets. To counteract the loss of the configurational entropy, cooperative noncovalent interactions of PAA chains and polymer self-assembly were induced within surfactant aggregates giving rise to uniform nanoparticles.\(^\text{41}\) The zeta potentials of the prepared PAA particles, as measured by dynamic light scattering (DLS), indicate that the surfaces of all particles were negatively charged, irrespective of the nature of the dianhydride (see Table S2). This result suggests that the carboxyl groups in each PAA are self-arranged on the exterior surface of particles, which would help stabilize the dispersion in the aqueous colloidal system.

**Figure 1** shows changes in the hydrodynamic diameter, $D_h$, of PAA−BTDA particles as a function of PAA concentration and Triton X-100 concentration. The PAA particles with the smallest hydrodynamic size of 110 nm were formed at a PAA concentration of 0.5 wt %, allowing for an increased particle size, as confirmed by dynamic light scattering (DLS) (see Figure 2, Table S1). The morphology of PI−PMDA in the SEM image was not as clear as that of the other samples because of particle agglomeration and the formation of irregular particle clusters [but DLS indicates a $D_h$ of 780 nm (Table S1)]. Because of imide formation, no net repulsion is expected between PI particles, allowing for an increased particle size, as confirmed by DLS (see Table S1).

**Figure 3** shows the results of TGA measurements for the PI nanoparticles. The data demonstrate that the thermal behavior of the two-step imidized PI nanoparticles is comparable to that of...
PIs with a 5% weight loss approximately at 400 °C in most cases (see Table 2), indicating a high thermal resistance.

**Morphology Control.** Particle morphologies of DKP-based PIs were controlled by external stimuli, namely, variation of the solvent polarity. After collecting the PAA microspheres from aqueous medium by centrifugation, they were redispersed in three solvent systems, acetone/water mixture, methanol/water mixture, and cyclohexane, followed by sonication for 5 h. Figure 4 shows SEM images of the PAA−BTDA particles after treatment by different solvents, clearly revealing morphology changes. When 20% acetone/80% water mixture was used, microparticles such as spiky balls were formed (8.6 ± 1.0 μm) (see Figure 4a). The spiky ball can be regarded as consisting of secondary aggregates, with needles on their surface. We propose that the needles could be formed as a result of interchain self-assembly via DKP interactions. When the proportion of acetone was changed in the mixed solvent, the secondary aggregates were formed but needles were formed to some extent only at two compositions, with 10 and 50% acetone (see Figure S10a2,a3, respectively). The introduction of PAA nanospheres into a less polar solvent, such as acetone/water mixed solvent, seemed to induce polymer aggregation, with a consequent increase in the particle size. Under sonication, the polymers could rearrange themselves into more highly ordered structures. It is possible that the solvent polarity may be finely-tuned to cause the formation of needle-like structures on the secondary aggregate surfaces. When a 40% methanol/60% water mixture was used, rod-like microparticles, whose lengths ranged from 10 to 60 μm (with aspect ratios ranging from 1 to 6), were formed. The volumes of the rods were much higher than those of the pretreated spheres, and this is attributed to efficient self-assembly by using the mixed solvent (methanol/water) of the right polarity. The rod content in a SEM image seemed to be related to the proportion of methanol in the mixed solvent (see Figure S10b1,b2). This suggests that when PAA spheres were plasticized by an appropriate composition of methanol/water, the PAA chains were able to self-assemble efficiently to form the rods.

When cyclohexane was used as a solvent, flake-like microparticles were formed. If the PAA was partially dissolved in cyclohexane under ultrasonication, the brittle and thin film formed was cast over cyclohexane solution and appeared to be flake-like particles. After the two-step imidization, the PAA particle morphologies were still maintained in the corresponding PIs (see Figure 4a2,b2,c2). The morphology of the PI particles was then finely-tuned by the use of mixed solvents of different polarities.

The self-assembly was investigated in terms of hydrogen bonding by FTIR techniques. Figure 5b shows the FTIR spectrum of the PI−BTDA spherical particles obtained by solvent displacement and subsequent imidization, showing five specific vibrations at 1780, 1718, 1667, 1516, and 1375 cm⁻¹, which were assigned to C=O of benzophenone, C=O of the imide ring (imide I), C=O stretching of DKP (amide I), N−H bending of DKP (amide II), and C−N of imide (imide II), respectively. The FTIR peaks of the spiky balls were not very different from those of the spheres (see Figure 5c), although the C=O of the imide ring showed a slight shift toward higher wavenumbers. The absence of any significant change of the

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**Figure 2.** SEM images of PI particles derived from DKP−4APhe with various dianhydrides (a) BTDA, (b) CBDA, (c) DSDA, and (d) PMDA.

**Figure 3.** Thermogravimetric curves of PI particles prepared from DKP−4APhe with various dianhydrides (a) BTDA, (b) CBDA, (c) DSDA, and (d) PMDA, recorded under a nitrogen atmosphere.

**Figure 4.** SEM images of PAA−BTDA obtained by redispersion of PAA spheres into (a1) 20% acetone/water, (b1) 40% methanol/water, and (c1) cyclohexane, following sonication and conversion to PI by two-step imidization as given in (a2,b2,c2), respectively.
FTIR spectrum suggests that there is no distinct change in the hydrogen bonding patterns during the morphology conversion from spheres to spiky balls. Although the transformation from a smooth to a spiky surface could have resulted from an enhancement in hydrogen bonding, the percentage change was too small. On the other hand, rods formed by the methanol/water stimulus showed the broadening of amide I, as well as the red shifts of amide II, C=O of benzophenone, and imide II peaks, clearly indicating the enhanced hydrogen bonding in stacked polymer chains via DKP interactions, even after imidization (see Figure S1d). Regarding the flats formed by the cyclohexane stimulus, the blue shifts of amide I and amide II were observed (see Figure S5a), which implied that the hydrogen bonds became weaker after drying over cyclohexane. The IR analyses support the notion of solvent casting of particles to be film-like structures.

The solvent effects for the previously reported PAA–BTDA particles, derived from 4ATA dimethyl ester, were investigated for comparison. 4ATA dimethyl ester is a diamine monomer having a central cyclobutane ring sandwiched by aromatic rings similar to DKP-4APhe monomers, but having no amide linkage which makes it different from DKP. The particle morphologies were observed by SEM (see Figure S11). Although spherical particles (605 ± 157 nm) were obtained by the solvent displacement method (Figure S11a), particles were broken into diffuse shapes after redispersion into solvent mixtures of 20% acetone/80% water, 40% methanol/60% water, and cyclohexane, following sonication (Figure S11b–d, respectively). This suggests that DKP units could play a key role in the solvent-assisted morphological change in the present PAA and PI systems. Thus, the thermoresistant biopolymamide particles have the ability to transform into different shapes by the external stimuli of solvent exchange, and the morphology change can help to add to their functionality. This could in turn increase the number of possible applications for such molecules, for example, as fillers reinforcing a polymer matrix.

**CONCLUSIONS**

We synthesized the aromatic diamine, 3,6-di(4-aminophenylmethyl)-2,5-DKP (DKP-4APhe), by cyclic dipeptide formation of a functionalized α-amino acid, 4APhe, where the 2,5-DKP ring can induce self-assembly because of its centrosymmetric cyclic amide groups. DKP-4APhe was polymerized with various dianhydrides to obtain biobased PAA, which were converted into PIs with high thermal resistance. Among all the PI molecules in the present study, the PI from PMDA showed the highest T<sub>dlm</sub> of 432 °C. In addition, its T<sub>g</sub> value could not be estimated, presumably because it is higher than the temperature at which the PI decomposes. Using the simple solvent displacement method from DMAc into water, PAA and PI spheres having smooth surfaces were formed. The PAA spheres underwent morphological changes into spiky ball-, rod-, or flake-like particles upon varying the solvent polarity using an acetone/water mixture, methanol/water mixture, or cyclohexane, respectively. The morphology observed at the PAA stage was retained in the PI particles, even after the two-step imidization. FTIR analyses indicated that hydrogen bonding was enhanced in the rod-like particles, presumably because of the self-assembly of the DKP moiety. To summarize, biobased PI particles with high thermal resistance were prepared, which can be potentially used as fillers for reinforcing aromatic polymer matrices. Indeed, nonspherical particle morphologies may enhance filler–matrix interactions.

**EXPERIMENTAL SECTION**

**Materials.** 4-Amino-1-phenylalanine (4APhe: from Watanabe chemical), benzyl chlorofluorurate (CBrCl: >96.0% from TCI), TMSCl (TMSCl: from Shin-etsu Chemical), methanol (>99.8% from Kanto Chemical), di-tert-butyl dicarbonate (Boc<sub>2</sub>O: >95.0% from TCI), sodium hydroxide (NaOH, >97.0% from Kanto Chemical), N,N'-dicyclohexylycarbodiimide (DCC: >98.0% from TCI), hydroxybenzotriazole (HOBt: anhydrous from Dojindo), formic acid (>98.0%, from Kanto Chemical), trimethylamine (>99.5% from Aldrich), hydrogen bromide solution, 33 wt% in acetic acid (33% HBr/ACOH: from Sigma-Aldrich), and NH<sub>4</sub> solution (conc 28.0–30.0% from Kanto Chemical) were used for monomer syntheses as received. Dianhydrides used as counter monomers such as OPDA (>98.0%), PMDA (>98.0%), BPDA (>98.0%), and DHCDA (>98.0%) were purchased from Tokyo Chemical Industry Co., Ltd (TCI) and were purified by sublimation at 160 °C under reduced pressure and annealing at 110 °C under vacuum just before use. Other dianhydrides such as CBDA (purified by sublimation >98.0% from TCI), BTDA (purified by sublimation >98.0% from TCI), and DSDA (purified by sublimation >98.0% from TCI) were used as received. Acetic anhydride (>95.0% from Kanto Chemical) and pyridine (anhydrous >99.5% from Kanto Chemical) were used for chemical imidization as received. A surfactant used for particle formation, Triton X-100 (from Acros), was used as received. Solvents such as 2-butanol (>99.0% from Kanto Chemical), acetic acid (AcOH: >99.7% from Kanto Chemical), N,N-DMAC (DMAC: >99.8% anhydrous from Kanto Chemical), 1,4-dioxane (>99.5% from Kanto Chemical), THF (>99.5% from Kanto Chemical), and toluene (>99.0% from Kanto Chemical) were used without further purification after received.

**Measurements.** <sup>1</sup>H NMR and <sup>13</sup>C NMR were performed on a Bruker BioSpin AG 400 MHz spectrometer using DMSO-d<sub>6</sub> as a solvent at 23.1 °C with 16 accumulation scans, using the proton resonance of residual nondeuterated DMSO as an internal standard (2.55 ppm). The FTIR spectra were recorded with a PerkinElmer Spectrum One spectrometer between 4000 and 400 cm<sup>−1</sup> using a diamond-attenuated total reflection (ATR) accessory. The number-average molecular weight (M<sub>n</sub>), weight-average molecular weight (M<sub>w</sub>) and the molecular weight distribution (PDI, M<sub>w</sub>/M<sub>n</sub>) were determined by gel permeation chromatography (GPC; Shodex GPC-101, concen-
Instruments SII, X-DSC7000T, respectively, at a heating rate of were carried out by Seiko Instruments SII, SSC/5200 and Seiko ° and absorbed moisture in polymer samples were removed at 250 μ (5 SEM). To prepare a sample, a droplet of the dispersion liquid temperature; the glass slide was

operating in the nebulizer-assisted ESI mode used in the positive FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a concentration 0.7 g/L, 10 mM LiBr/DMF eluent) equipped with a JASCO RI-2031 Plus Intelligent RI detector and JASCO UV- 2075 Plus Intelligent UV/Vis detector after calibration with poly styrene. Experiments were performed using a Shimadzu JASCO RI-2031 Plus Intelligent RI detector and JASCO UV-2075 Plus Intelligent UV/Vis detector. The eluent was filtered and washed with water. The spectrometer was equipped with a Nanospray source (Zetasizer Nano ZS90). The calculation of size distribution from light scattering measurements is based on the assumption that the particles are spherical. Ultrasonic sonication bath (AS ONE Corporation, AS12GTU) with an oscillation frequency at 35 kHz, 60 W was used in the particulation control study.

Monomer Synthesis. The schematic representation of the synthesis of the biobased aromatic DKP diamine from 4APhe is shown in Scheme 1.

(a) Synthesis of 4APhe-z: a solution of 4APhe (10.0 g, 0.040 mol) dissolved in 10% AcOH (340 mL) was added drop by drop with 5 M NaOH to raise pH to 3. A solution of CbzCl (6 mL, 0.040 mol) in 1,4-dioxane (340 mL) was then slowly added, and the mixture was stirred overnight at room temperature. The mixture was brought to pH 7 by 5 M NaOH before filtration and washed with water. The expected product was obtained as white shiny powder with 82% yield. The speciation was as follows. 1H NMR (400 MHz, DMSO-d6, δ ppm): 2.76 (dd, 1H, J = 8.8, 14.0 Hz), 3.08 (dd, 1H, J = 3.4, 14.0 Hz), 3.60 (t, 1H, J = 3.4 Hz), 5.15 (s, 2H), 7.18 (d, 2H, J = 8.4 Hz), 7.40 (m, 7H), 9.72 (s, 1H).

(b) Synthesis of methyl-4APhe-z: the milky mixture of 4APhe-z (5.0 g, 0.016 mol) in MeOH (80 mL) was added with TMSCl (8.5 mL, 0.067 mol). The mixture was stirred overnight at room temperature. The solvent was evaporated, and the crude sample was further recrystallized from MeOH and diethyl ether to obtain the expected product with 96% yield. The speciation was as follows. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.15 (dd, 1H, J = 5.2, 14.0 Hz), 3.65 (s, 3H), 4.17 (t, 1H, J = 5.2 Hz), 5.14 (s, 2H), 7.14 (d, 2H, J = 8.8 Hz), 7.40 (m, 7H), 8.47 (s, 3H), 9.82 (s, 1H).

(c) Synthesis of Boc-4APhe-z: a stirred solution of 4APhe-z (4.5 g, 0.014 mol) in THF/H2O (11:1, 62 mL) was added with NaOH (1.3 g, 0.033 mol) at room temperature followed by the addition of Boc2O (3.5 g, 0.016 mol). The reaction mixture was stirred at room temperature overnight. THF was then removed by evaporation, and 1 M HCl was added to bring pH to 4 and followed by filtration to obtain the product with 98% yield. The specification was as follows. 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.35 (s, 9H), 2.92 (d, 2H, J = 7.0 Hz), 3.59 (dd, 1H, J = 7.0, 14.0 Hz), 5.13 (s, 2H), 5.71 (d, 1H, J = 6.1 Hz), 6.99 (d, 2H, J = 12.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 7.41 (m, 5H).

(d) Synthesis of linear dipeptide-4APhe-z: to a 0 ºC solution of Boc-4APhe-z (8.5 g, 0.021 mol) in dichloromethane (DCM) (120 mL), HOBt (3.05 g, 0.022 mol) was added followed by the addition of DCC (5.08 g, 0.025 mol). The reaction mixture was stirred for 1 h and allowed it to cool to room temperature. Then, a solution of methyl-4APhe-z (8.25 g, 0.023 mol) in DCM (23 mL) was added followed by the addition of trimethylamine (3.4 mL, 0.024 mol). The reaction was stirred further at room temperature overnight. To work up, the precipitated dicyclohexylurea was filtered off and washed with little DCM. The filtrate was concentrated by evaporation and its pH was adjusted to 2–3 by adding 1H NCl under ice condition. The crude product was obtained by filtration with 70% yield. The specification was as follows. 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.29 (s, 9H), 1.68 (d, 2H, J = 22.0 Hz), 2.89 (d, 2H, J = 21.0 Hz), 3.58 (s, 3H), 4.12 (dd, 1H, J = 7.0, 14.0 Hz), 4.46 (dd, 1H, J = 7.2, 14.0 Hz), 5.14 (s, 4H), 6.81 (d, 1H, J = 9.0 Hz), 7.12 (d, 4H, J = 8.0 Hz), 7.38 (m, 14H), 8.20 (d, 1H, J = 8.1 Hz), 9.68 (s, 1H), 9.70 (s, 1H).

(e) Synthesis of cyclic dipeptide 4APhe-z: to remove the Boc group, linear dipeptide-APhe-z (7.77 g, 0.011 mol) was charged with 98% formic acid (466 mL), followed by stirring for 5 h at room temperature. Excess formic acid was then removed in vacuum (temperature less than 30 ºC was maintained). The obtained crude was refluxed in the mixture of 310 mL of 2-butanol and 155 mL of toluene at 110 ºC for 5 h, followed by the filtration and drying under vacuum to obtain the expected product with 58% yield. The specification was as follows. 1H NMR (400 MHz, DMSO-d6, δ ppm): 2.14 (dd, 2H, J = 6.4, 13.6 Hz), 3.92 (dd, 2H, J = 4.4, 13.6 Hz), 5.12 (s, 4H), 6.94 (d, 4H, J = 8.4 Hz), 7.35 (m, 14H), 7.89 (s, 2H), 9.75 (s, 2H).

(f) Synthesis of DKP-4APhe: 33% HBr/AcOH solution (38.5 mL) was added to cyclic dipeptide 4APhe-z (3.85 g, 0.0065 mol). The mixture was stirred at room temperature for 3.5 h. Diethyl ether was added and decanted several times. The procedure was repeated several times to remove excess acid. The crude compound was dried under vacuum. After drying, the compound was dissolved in water followed by the addition of NH3 solution drop by drop till the pH became 12 while stirring. The precipitate was collected by filtration to obtain the expected product with 98% yield. The specifications were as follows. 1H NMR (400 MHz, DMSO-d6, δ ppm): 2.08 (dd, 4H, J = 6.8, 13.6 Hz), 3.80 (t, 1H, J = 6.0 Hz), 5.34 (s, 2H), 7.14 (d, 2H, J = 8.8 Hz), 7.40 (m, 7H), 8.47 (s, 3H), 9.82 (s, 1H).

PAA and PI Syntheses. A typical procedure for the synthesis of PAA is shown in Scheme 2. A diamine of DKP-4APhe (0.20 g, 0.62 mmol) mixed with an equimolar of dianhydrides such as CBDA (0.12 g, 0.62 mmol), BTDA (0.20 g, 0.62 mmol), and LiBr/DMF eluent) equipped with a JASCO RI-2031 Plus Intelligent RI detector and JASCO UV-2075 Plus Intelligent UV/Vis detector after calibration with poly styrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standards. The mass spectra were measured using a FT-ICR MS (Solarix) equipped with a Nanospray source polystyrene standard...
0.62 mmol), PMDA (0.14 g, 0.62 mmol), DSDA (0.22 g, 0.62 mmol), OPDA (0.19 g, 0.62 mmol), BPDA (0.18 g, 0.62 mmol), and DHCDA (0.16 g, 0.62 mmol) was dissolved in DMAC (1 mL, 0.6 M) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 48 h to yield a viscous PAA solution. The PAA solution was added into a 1:1 mixture of water and methanol and precipitated to obtain the respective PAA polymers in quantitative yields (PAA—BTDA: yield 93%, PAA—CBDA: yield 91%, PAA—PMDA: yield 90%, PAA—DSDA: yield 93%, PAA—OPDA: yield 90%, PAA—BPDA: yield 92% and PAA—DHCDA: yield 89%). PI was obtained by thermal imidization of the PAA in an oven under vacuum by stepwise heating at 100, 150, and 200 °C for 1 h and 250 °C for 3 h at each step.

**Preparation of PAA and PI Particles.** In a typical solvent displacement method, a PAA solution in DMAC (4% w/v, 100 μL) was dropped into an aqueous solution of Triton X-100 (1% w/v, 10 mL) and magnetically stirred vigorously as a poor solvent at room temperature to obtain PAA particles. Collecting PAA by centrifugation, the two-step imidization was subsequently performed to convert PAA to PI. First, PAA was chemically imidized using a mixture of pyridine and acetic anhydride (1:1 M ratio, 100 °C for 3 h, resulting in yellowish powder of PI particles.

To study the particulation control of PIs, PAA particles collected by centrifugation were dispersed in different solvent systems such as acetone/water mixture, methanol/water mixture, and cyclohexane and further sonicated for 5 h. After that, subsequent imidization to convert PAA to PI was carried out by the chemical procedure and thermal treatment. The morphology of dispersed particles of PAA and PI was determined using SEM, as illustrated in Figure 6. Here, PI—BTDA was chosen as an example for study.

**Particle Morphology Control.** Various factors during particle formation could govern the properties of fabricated particles (e.g., particle size). The effect of formulation variables (polymer concentration: 0.5, 1, 2, 4, and 6% (w/v); surfactant concentration: 0.1, 0.5, 1, and 3% (w/v); polymer structure with various dianhydrides: BTDA, CBDA, DSDA, and PMDA) on the particle size was studied.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03231.

1H NMR spectra, FT-IR spectra, 13C NMR spectrum, mass spectrum, SEM images, particle size and size distribution of PAA and PI particles, and zeta potential of PAA particles dispersed in water (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail: kaneko@jaist.ac.jp.*

**ORCID**

Thawinda Hirayama: 0000-0001-5690-1359

Kenji Takada: 0000-0001-9306-6639

Tatsuo Kaneko: 0000-0001-9794-083X

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work has been financially supported by JST-ALCA project (JPMJAL1010) and Cross-ministerial Strategic Innovation Promotion Program (SIP2), “Smart-bio” (Bio-oriented Technology Research Advancement Institution, NARO).

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