ADMET Polycondensation of Diketopiperazine-Based Dienes. Polymerization Behavior and Effect of Diketopiperazine on the Properties of the Formed Polymers

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ABSTRACT: L-Glutamic acid diketopiperazine ω-alkenyl esters were synthesized and polymerized via acyclic diene metathesis polycondensation chemistry using ruthenium catalysts. The polycondensation of L-glutamic acid diketopiperazine ω-allyl ester (**1**) was unsuccessful, while the polycondensation of L-glutamic acid diketopiperazine ω-homoallyl ester (**2**), -pentenyl ester (**3**), and -hexenyl ester (**4**) with Grubbs second-generation catalyst and Grubbs−Hoveyda catalyst satisfactorily proceeded to give the corresponding polymers. They exhibited melting temperatures around 150 °C, and possessed crystalline structures similar to that of polyethylene. Dynamic light scattering and differential scanning calorimetric measurements suggested that the polymers formed aggregates in *N*,*N*-dimethylformamide, presumably based on hydrogen bonding between diketopiperazine moieties.

Introduction

Functional macromolecular materials using biological chiral resources such as amino acids have been gathering much interest due to their biocompatibility and biodegradability easing the environmental burden.[1] Diketopiperazine (DKP), a cyclic amino acid dimer, is a typical byproduct in peptide synthesis. It has recently attracted much attention as a bioactive and enzyme−inhibitory compound.[2] DKP has two s-*cis* secondary amide groups, which can hydrogen bond horizontally along the ring plane. In fact, some DKPs form aggregates based on tandem hydrogen bonding between the amide groups in the solid state. The structure of aggregates depends on the amino acid components of DKPs. For instance, a glycine-based DKP adopts a linear tape orientation, while an alanine-based one forms a layer-type structure.[3] The solubility of DKP is commonly low due to the lack of flexibility of the ring bearing amide groups; *N*-alkylation of one amide group effectively enhances the solubility, resulting in a change of association state.[4] This type of DKP constructs supramolecular architectures utilizing noncovalent bonding such as hydrophobic and electrostatic interactions in addition to hydrogen bonding between the amide groups. Such aggregates show liquid crystallinity[5] and form microcapsules.[6] Phenylalanine-, aspartic-, and glutamic acid-based DKPs serve as oil gelators,[7] wherein intermolecular hydrogen bonding plays a key role to form molecular networks. Unsymmetrical DKPs consisting of phenylalanine together with histidine or arginine are used as an organocatalyst for asymmetric hydrocyanation.[8]

As described above, DKP derivatives have several interesting features, but only a few approaches to the synthesis of polymers carrying DKPs have been implemented, and the molecular weights and the detail of the properties of the resultant polymers have not been well determined.[9] We have recently performed the polycondensation of aspartic and glutamic acid DKPs with various diamines and dibromoxylenes to obtain polymers with weight-average molecular weights ranging from 1200 to 4100.[10] Due to the low solubility and degree of polymerization of the polymers, their properties have not been thoroughly examined.

Among various polycondensation methods, acyclic diene metathesis (ADMET) polycondensation is useful in the synthesis of polymers with precise arrangement of substituents along the polymer's main chain.[11] The recent progresses in the development of ruthenium catalysts has enabled polymerization of polar monomers possessing ether, ester, amide, alcohol, and carboxylic acid moieties, as well as allowing for the use of polar solvents, owing to their excellent tolerance toward polar functional groups.[12] These catalysts allow amino acid- and peptide-containing monomers to undergo polymerization, leading to development of novel biocompatible polymeric materials.[13] It is also expected that these polymers form secondary structures like peptides, and are applicable to drug delivery systems, chiral recognition stationary phases, and asymmetric catalysts.[14] The ADMET polycondensation of amino acid- and peptide-based dienes gives polyolefins that form strong films possessing moduli of up to 220 MPa with up to 260% elongation and showing high melting temperatures, which are attractive in biomedical applications.[15] The crystallinity of the polymers largely depends on the amino acid and peptide functionalities. It is expected that incorporation of DKP moieties, which can strongly form hydrogen bonding, will also lead to development of polymers with unique properties. This article deals with polycondensation of novel glutamic acid diketopiperazine ω-alkenyl esters using ADMET chemistry.

Experimental Section

Measurements. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FT/IR-4100 spectrophotometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-100 digital

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polarimeter with a sodium lamp as a light source. The number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) on TSK gel α-M and TSK gel GMH_{XL}, using a solution of LiBr (10 mM) in *N*,*N*-dimethylformamide (DMF) as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C. Dynamic light scattering (DLS) measurements were performed on a Viscotek 802DLS equipped with a 50 mW fiber coupled diode laser (830 nm), using omniSIZE 3.0 software. Differential scanning calorimetric (DSC) analyses were performed under a nitrogen atmosphere using a Perkin-Elmer PYRIS Diamond DSC. Temperature-modulated differential scanning calorimetric (MDSC) analyses were performed on a TA Instruments Q1000 equipped with a liquid nitrogen cooling accessory calibrated using sapphire and high-purity indium metal. Modulated experiments were scanned at 3 °C/min with a modulation amplitude of 0.4 °C and period of 80 s. XRD measurements were done using a Philips X'Pert MRD system using grazing incidence ($\omega = 3°$). Thermogravimetric analyses (TGA) were conducted in air with a Perkin-Elmer TGA7 thermal analyzer.

Materials. All the reagents for monomer synthesis were used as purchased without purification. *cyclo*-(L-Pyroglutaminyl-L-pyroglutaminyl) was prepared from pyroglutamic acid as described in the literature.[16] DMF and DMSO were distilled over calcium hydride.

Monomer Synthesis. *cyclo*-(*O*-Allyl-L-glutaminyl-*O*-allyl-L-glutaminyl) (1). *cyclo*(L-Pyroglutaminyl-L-pyroglutaminyl) (3.35 g, 15.1 mmol) and sulfuric acid (6 drops) were added into a solution of allyl alcohol (4.42 g, 76.1 mmol) in benzene (45 mL). The reaction mixture was refluxed for 6 h until the DKP dissolved, and then concentrated. The residue was dissolved in $CHCl_3$, and washed with saturated aqueous $NaHCO_3$ and NaCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. It was purified by column chromatography eluted with $CHCl_3$ and recrystallization from ethanol to obtain **1** as a colorless solid in 61% yield: Mp 142−143 °C; $[\alpha]_D$ −67° ($c = 0.10$ g/dL in $CHCl_3$ at room temperature). ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.87−2.05 [m, 4H, >CHCH_2−], 2.38−2.47 [m, 4H, −CH_2COO−], 3.91 [t, $J = 5.0$ Hz, 2H, >CHCH_2−], 4.54 [d, $J = 5.2$ Hz, 4H, −COOCH_2−], 5.21 [d, $J = 10.4$ Hz, 2H, −CH=CH_2], 5.30 [d, $J = 17.6$ Hz, 2H, −CH=CH_2], 5.87−5.97 [m, 2H, −CH=CH_2], 8.23 [s, 2H, −CONH−]. ^{13}C NMR (100 Hz, DMSO-d_6): δ 27.94 [>CHCH_2−], 29.16 [−CH$_2$COO−], 53.10 [−NHCHCO−], 64.43 [−COOCH$_2$−], 117.69 [−CH=CH$_2$], 132.72 [−CH=CH_2], 167.77 [>CHCONH−], 171.99 [−CH_2COO−]. IR (cm^{-1}, KBr): 3321 (NH), 3205 (NH), 3093 (=CH), 2951 (CH), 2877 (CH), 1732 (C=O), 1678 (NHCO), 1446, 1180, 991, 926. HRMS: calcd for $C_{16}H_{22}N_2O_6$ (*m*/*z*), 338.1478; found, 338.1476.

***cyclo*-(*O*-Butenyl-L-glutaminyl-*O*-butenyl-L-glutaminyl) (2).** The title compound was synthesized from *cyclo*(L-pyroglutaminyl-L-pyroglutaminyl) and 3-buten-1-ol in a manner similar to **1**. Yield: 30%. Mp: 153−154 °C. $[\alpha]_D$ −62° ($c = 0.10$ g/dL in $CHCl_3$ at room temperature). ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.85−2.03 [m, 4H, >CHCH_2−], 2.31−2.46 [m, 8H, −CH_2COO−, −COOCH_2CH_2−], 3.89 [t, $J = 5.0$ Hz, 2H, >CHCH_2−], 4.07 [t, $J = 6.6$ Hz, 4H, −COOCH_2−], 5.05 [d, $J = 10.4$ Hz, 2H, −CH=CH_2], 5.11 [d, $J = 17.6$ Hz, 2H, −CH=CH_2], 5.73−5.84 [m, 2H, −CH=CH_2], 8.21 [s, 2H, −CONH−]. ^{13}C NMR (100 Hz, DMSO-d_6): δ 28.01 [>CHCH$_2$−], 29.26 [−CH$_2$COO−], 32.57 [−CH$_2$CH=CH_2], 53.13 [−NHCHCO−], 62.91 [−COOCH$_2$−], 117.13 [−CH=CH$_2$], 134.53 [−CH=CH_2], 167.74 [>CHCONH−], 172.28 [−CH_2COO−]. IR (cm^{-1}, KBr): 3321 (NH), 3205 (NH), 3089 (=CH), 2978 (CH), 2873 (CH), 1732 (C=O), 1682 (NHCO), 1446, 1184, 991, 914. HRMS: calcd for $C_{18}H_{26}N_2O_6$ (*m*/*z*), 366.1791; found, 366.1797.

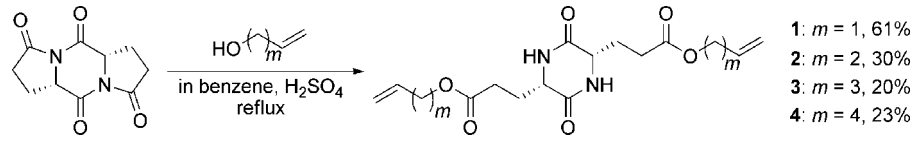
***cyclo*-(*O*-Pentenyl-L-glutaminyl-*O*-pentenyl-L-glutaminyl) (3).** The title compound was synthesized from *cyclo*(L-pyroglutaminyl-L-pyroglutaminyl) and 4-penten-1-ol in a manner similar to **1**. Yield: 20%. Mp: 143−145 °C. $[\alpha]_D$ −64° ($c = 0.10$ g/dL in $CHCl_3$ at room temperature). ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.63−1.70 [m, 4H, −CH_2CH_2CH_2−], 1.86−2.10 [m, 8H, >CHCH_2−, −CH_2CH=CH_2], 2.33−2.47 [m, 4H, −CH_2COO−], 3.90 [t, $J = 5.0$ Hz, 2H, >CHCH_2−], 4.01 [t, $J = 6.6$ Hz, 4H, −COOCH_2−], 4.98 [d, $J = 10.4$ Hz, 2H, −CH=CH_2], 5.04 [d, $J = 17.2$ Hz, 2H, −CH=CH_2], 5.76−5.86 [m, 2H, −CH=CH_2], 8.21 [s, 2H, −CONH−]. ^{13}C NMR (100 Hz, DMSO-d_6): δ 27.23 [−CH_2CH$_2$CH$_2$−], 28.01 [>CHCH$_2$−], 29.24 [−CH$_2$COO−], 29.51 [−CH$_2$CH=CH_2], 53.14 [−NHCHCO−], 63.30 [−COOCH$_2$−], 115.25 [−CH=CH$_2$], 137.74 [−CH=CH_2], 167.74 [>CHCONH−], 172.33 [−CH_2COO−]. IR (cm^{-1}, KBr): 3321 (NH), 3205 (NH), 3085 (=CH), 2970 (CH), 1728 (C=O), 1678 (NHCO), 1446, 1188, 991, 910. HRMS: calcd for $C_{20}H_{30}N_2O_6$ (*m*/*z*), 394.2104; found, 394.2105.

***cyclo*-(*O*-Hexenyl-L-glutaminyl-*O*-hexenyl-L-glutaminyl) (4).** The title compound was synthesized from *cyclo*(L-pyroglutaminyl-L-pyroglutaminyl) and 5-hexen-1-ol in a manner similar to **1**. Yield: 23%. Mp: 146−147 °C. $[\alpha]_D$ −60° ($c = 0.10$ g/dL in $CHCl_3$ at room temperature). ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.34−1.42 [m, 4H, −CH$_2$CH$_2$CH=CH_2], 1.52−1.59 [m, 4H, −COOCH_2CH_2−], 1.84−2.05 [m, 8H, >CHCH_2−, −CH_2CH=CH_2], 2.31−2.45 [m, 4H, −CH_2COO−], 3.88 [t, $J = 5.0$ Hz, 2H, >CHCH_2−], 4.00 [t, $J = 6.4$ Hz, 4H, −COOCH_2−], 4.93 [d, $J = 10.0$ Hz, 2H, −CH=CH_2], 4.99 [d, $J = 17.2$ Hz, 2H, −CH=CH_2], 5.72−5.82 [m, 2H, −CH=CH_2], 8.19 [s, 2H, −CONH−]. ^{13}C NMR (100 Hz, DMSO-d_6): δ 24.63 [−COOCH$_2C$H$_2$CH$_2$−], 27.60 [−COOCH$_2$CH$_2C$H$_2$−], 28.04 [>CHCH$_2$−], 29.26 [−CH$_2$COO−], 32.74 [−CH$_2$CH=CH_2], 53.16 [−NHCHCO−], 63.74 [−COOCH$_2$−], 114.94 [−CH=CH$_2$], 138.40 [−CH=CH_2], 167.76 [>CHCONH−], 172.35 [−CH_2COO−]. IR (cm^{-1}, KBr): 3321 (NH), 3209 (NH), 3086 (=CH), 2931 (CH), 1732 (C=O), 1678 (NHCO), 1446, 1184, 995, 910. HRMS: calcd for $C_{22}H_{34}N_2O_6$ (*m*/*z*), 422.2417; found, 422.2423.

Polymerization. The polymerization was carried out in a glass tube equipped with a three-way stopcock under nitrogen. A ruthenium catalyst was added to a solution of a monomer (0.25 mmol) in DMF (0.25 mL), and the resulting mixture was kept stirring in a water bath at 60 °C for 24 h under reduced pressure (100 mmHg). The polymerization was quenched by adding ethyl vinyl ether (0.1 mL). The resulting mixture was concentrated with a vacuum pump and the residual mass was washed with MeOH to isolate a polymer. It was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Spectroscopic Data of the Polymers. Poly(2): ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.74−2.07 [m, 4H, >CHCH_2−], 2.18−2.48 [m, 8H, −CH_2COO−, −CH_2CH=CH_2], 3.87 [s, 2H, >CHCH_2−], 3.94−4.16 [m, 4H, −COOCH_2−], 5.02 [d, $J = 10.4$ Hz, −CH=CH_2 of external olefins], 5.09 [d, $J = 17.2$ Hz, −CH=CH_2 of external olefins], 5.39−5.54 [m, 2H, −CH=CH_2−], 5.78−5.84 [m, 2H, −CH=CH_2 of external olefins], 8.20 [s, 2H, −CONH−]. IR (cm^{-1}, KBr): 3317 (NH), 3201 (NH), 3089 (=CH), 2962 (CH), 2893 (CH), 1732 (C=O), 1678 (NHCO), 1450, 1180, 976. **Poly(3)**: ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.53−1.67 [m, 4H, −CH_2CH$_2$CH$_2$−], 1.83−2.21 [m, 8H, >CHCH_2−, −CH_2CH=CH_2], 2.30−2.46 [m, 4H, −CH_2COO−], 3.89 [s, 2H, >CHCH_2−], 3.99 [t, $J = 6.2$ Hz, 4H, −COOCH_2−], 4.97 [d, $J = 10.0$ Hz, −CH=CH_2 of external olefins], 5.02 [d, $J = 16.8$ Hz, −CH=CH_2 of external olefins], 5.35−5.54 [m, 2H, −CH=CH_2−], 5.77−5.81 [m, 2H, −CH=CH_2 of external olefins], 8.20 [s, 2H, −CONH−]. IR (cm^{-1}, KBr): 3205 (NH), 3093 (=CH), 2958 (CH), 2900 (CH), 1732 (C=O), 1678 (NHCO), 1450, 1176, 968. **Poly(4)**: ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.24−1.46 [m, 4H, −CH$_2$CH$_2$CH=CH_2], 1.46−1.75 [m, 4H, −COOCH_2CH_2−], 1.81−2.22 [m, 8H, >CHCH_2−, −CH_2CH=CH_2], 2.30−2.48 [m, 4H, −CH_2COO−], 3.89 [s, 2H, >CHCH_2−], 4.00 [s, 4H, −COOCH_2−], 4.95 [d, $J = 9.6$ Hz, −CH=CH_2 of external olefins], 5.01 [d, $J = 16.8$ Hz, −CH=CH_2 of external olefins], 5.39 [m, 2H, −CH=CH−], 5.72−5.90 [m, 2H, −CH=CH_2 of external olefins], 8.20 [s, 2H, −CONH−]. IR (cm^{-1}, KBr): 3316 (NH), 3201 (NH), 3093 (=CH), 2938 (CH), 2862 (CH), 1732 (C=O), 1678 (NHCO), 1450, 1176, 968.

Scheme 1



Scheme 2

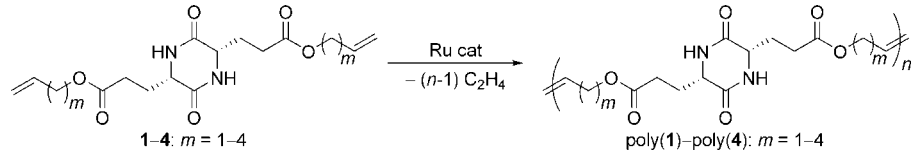
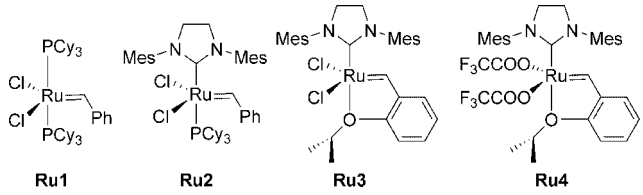


Chart 1. Catalysts for ADMET Polycondensation



Results and Discussion

Monomer Synthesis. We first tried to synthesize DKP monomers **1**−**4** by condensation of glutamic acid DKP with the corresponding alcohols using a condensation agent, but failed presumably due to intramolecular condensation forming pyroglutamic acid DKP. Instead, **1**−**4** were synthesized by acid-catalyzed addition of alcohols to pyroglutamic acid DKP as illustrated in Scheme 1 and were purified by column chromatography and subsequent recrystallization. The structures were determined by ^{1}H NMR, ^{13}C NMR, and IR spectroscopies as well as high resolution mass spectrometry (HRMS). No impurities were detected in any case.

ADMET Polycondensation. The ADMET polycondensation of **1**−**4** (Scheme 2) was performed with Grubbs and Grubbs-Hoveyda ruthenium complexes **Ru1**−**Ru4** shown in Chart 1 as catalysts under reduced pressure to remove ethylene gas evolving during the metathesis reaction. At first, the polycondensation of **1**−**4** was carried out with **Ru1** and **Ru2** at 45 °C. However, neither of these catalysts yielded polymers, and unreacted monomers were recovered. Therefore, the polycondensation temperature was raised to 60 °C in order to promote the metathesis reaction. **Ru3** was also employed as a catalyst in addition to **Ru1** and **Ru2**, because it has been reported to retain stability and activity even at elevated temperatures.[17] Moreover, we employed **Ru4**, which catalyzes the metathesis reaction of acetylene derivatives as well as olefins.[18]

Table 1 lists the results of the ADMET polycondensation. No polymer was obtained and the monomer was recovered in all the cases of the polycondensation of **1** (runs 1−4). This lack of reactivity is described later. The polycondensation of **2** and **3** with **Ru1** was also unsatisfactory (runs 5 and 10). This catalyst seemed to be unstable and decomposed in DMF at 60 °C, which was indicated by the fact that the brown reaction mixture turned green. In the case of **4**, a polymer with an M_w of 5 300 was obtained with **Ru1**, although the yield was low (run 16).[19] It is considered that **4** is reactive enough to undergo polymerization to some extent before catalyst decomposition by heating. In contrast, the polycondensation mixtures of **2**-**4** with **Ru2** gradually increased the viscosity to give polymers with M_w's of 4 500−5 300 (runs 6, 11, and 17).

The polycondensation of **2** with **Ru3** proceeded in a fashion similar to that with **Ru2** to give a polymer with an M_w of 4000 (run 7). In the polycondensation of **3**, a light brown mass precipitated accompanying the viscosity increase (run 12). In the polycondensation of **4** using **Ru3**, a light brown mass immediately precipitated just after the reaction was initiated (run 18). These masses seem to be high-molecular-weight polymers that do not dissolve in DMF. The polycondensation of **3** and **4** was also carried out in DMSO, but little polymer was isolated in either case (runs 14 and 20). When the $[M]_0/[Ru]$ ratio was changed from 50 to 200, the polymer yield largely decreased in the polycondensation of **2** and **3** (runs 8 and 13). At this $[M]_0/[Ru]$ ratio, only the polycondensation mixture of **4** increased the viscosity to give a polymer with an M_w of 4 300 (run 19). **Ru4** was not effective for the ADMET polycondensation of the present DKP monomers. **Ru4** is as active as **Ru1**, and less active than **Ru2** in the ring-closing metathesis of diethyl diallylmalonate.[18a] Therefore, it seems reasonable that **Ru1** and **Ru4** are not effective in the ADMET polycondensation of the present monomers, but the concrete reason of the inactivity is unclear. Polymers obtained could not form self-standing films, presumably due to the relatively low molecular weight and high crystallinity.

Table 1. ADMET Polycondensation of 1−4 [a]

			polymer			
run	monomer	catalyst	yield[d] (%)	M_w[e]	M_w/M_n[e]	$[\alpha]_D$[f] (deg)
1	**1**	**Ru1**	0			
2	**1**	**Ru2**	0			
3	**1**	**Ru3**	0			
4	**1**	**Ru4**	0			
5	**2**	**Ru1**	0			
6	**2**	**Ru2**	15	4600	1.27	
7	**2**	**Ru3**	42	4000	1.20	
8[b]	**2**	**Ru3**	2			
9	**2**	**Ru4**	4			
10	**3**	**Ru1**	0			
11	**3**	**Ru2**	31	4500	1.42	−39
12	**3**	**Ru3**	80	12000	2.12	
13[b]	**3**	**Ru3**	0			
14[c]	**3**	**Ru3**	13			
15	**3**	**Ru4**	3			
16	**4**	**Ru1**	5	5300	1.50	
17	**4**	**Ru2**	46	5300	1.31	−29
18	**4**	**Ru3**	84	15200	2.66	
19[b]	**4**	**Ru3**	50	4300	1.43	
20[c]	**4**	**Ru3**	14			
21	**4**	**Ru4**	0			

[a] Conditions: $[M]_0$ = 1.0 M, $[M]_0/[Ru]$ = 50, in DMF, 60 °C, under 100 mmHg, 24 h. [b] $[M]_0/[Ru]$ = 200. [c] In DMSO. [d] MeOH-insoluble part. [e] Estimated by GPC based on polystyrene standards, eluent; LiBr solution in DMF (10 mM). [f] Measured by polarimetry at room temperature, c = 0.10 g/dL in DMF. $[\alpha]_D$ of monomers: **1**, −22°; **2**, −44°; **3**, −39°; **4**, −29°.

Characterization of the Polymers. Poly(**3**) and poly(**4**) obtained by the polymerization with **Ru2** were soluble in DMF and DMSO, but insoluble in $CHCl_3$. Meanwhile, the **Ru3**-based polymers were hardly soluble in DMF and partly soluble in

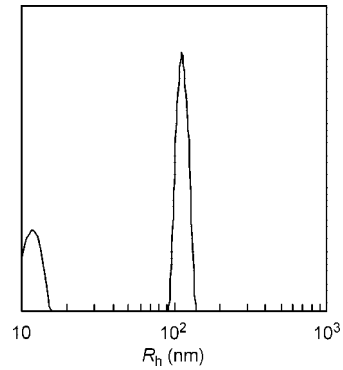


Figure 1. Histogram analysis of DLS of poly(**4**) measured in DMF (c = 0.5 wt%) at 80 °C.

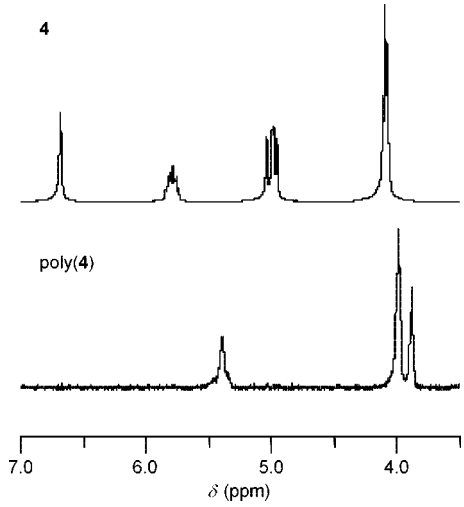


Figure 2. Partial ^{1}H NMR (400 MHz) spectra of **4** and poly(**4**) measured in DMSO-d_6.

DMSO. The difference in solubility is attributable to the molecular weight difference. When a small amount of trifluoroacetic acid (TFA) was added to suspensions of poly(**3**) and poly(**4**) in $CHCl_3$, they became transparent. Judging from a report regarding the formation of a 2:1 cocrystal of TFA and a DKP,[4] TFA molecules cap the amide moieties disrupting the association of DKPs. This result suggests that the low solubility of the DKP polymers is caused by self-assembling based on hydrogen bonding between the amide groups of the DKP. Meanwhile, the polymers showed $[\alpha]_D$ values similar to those of the monomers in DMF, and no CD signal. These facts indicate that they did not take a chiral secondary structure in the solvent.

Figure 1 shows the DLS histogram of **Ru3**-based poly(**4**) measured in DMF at 80 °C. The peaks around 12 and 113 nm are assignable to unimeric and aggregated polymers, respectively. It was confirmed that the polymer molecules were partially assembled, presumably based on hydrogen bonding between the amide groups of the DKP in DMF.

Figure 2 shows the partial ^{1}H NMR spectra of **4** and poly(**4**) obtained by the polymerization with **Ru3**. Poly(**4**) exhibited an internal olefin proton signal at 5.4 ppm. The *trans*/*cis* ratio of the double bonds at the main chain could not be determined by ^{1}H NMR spectroscopy, because the *trans*- and *cis*-olefin proton signals overlapped each other. It was estimated to be 9/1 by ^{13}C NMR spectroscopy instead (*trans*- and *cis*-olefin carbon signals: 130.0 and 129.3 ppm). Poly(**2**) and poly(**3**) exhibited almost the same *trans*/*cis* ratio as that of poly(**4**). The internal olefins of polymers obtained via ADMET chemistry are

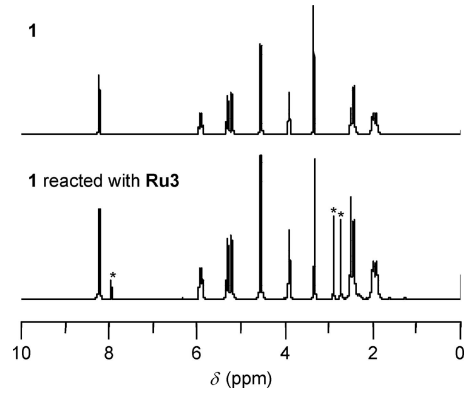
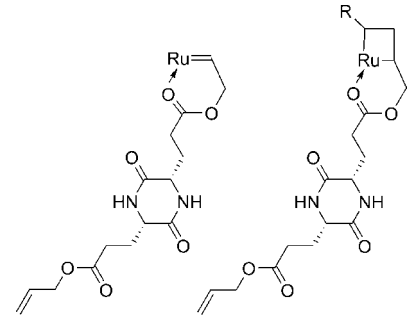


Figure 3. ^{1}H NMR (400 MHz) spectra of **1** and **1** reacted with **Ru3** measured in DMSO-d_6. Asterisks represent the signals of DMF.

Chart 2. Negative Neighboring Group Effect



generally *trans*-rich and the results in this paper are in good agreement with previous work.[20]

There are two possible reasons why no polymer was obtained from allylic ester monomer **1**. One is isomerization of allylic ester into 1-propenyl ester. Ruthenium complexes are well-known to catalyze olefin migration in *O*-allyl systems.[21] We measured the ^{1}H NMR spectra of **1** and a reaction mixture of **1** with **Ru3** to check the possibility. As shown in Figure 3, the two spectra were nearly identical each other, indicating that **1** did not isomerize during the reaction with **Ru3**. No isomerization was confirmed in the polycondensation of **1** with the other ruthenium catalysts, either. Consequently, we consider another reason for no polycondensation of **1**, so-called negative neighboring group effect.[22] As illustrated in Chart 2, the oxygen atom possibly coordinates to the ruthenium center to form a six-membered structure, which stabilizes the ruthenium catalyst, resulting in no catalytic activity for ADMET polycondensation. At the same time, the polarization of olefin induced by the ester hinders coordination of olefins and formation of metallocycles. Actually, the negative charge of terminal olefinic carbon atoms of **1** was the smallest among those of the monomers (see Supporting Information). Considering the fact that allyl esters tend to isomerize into 1-propenyl esters under metathesis conditions,[21] this behavior of **1** is somewhat strange. The DKP moiety may also participate in the intramolecular coordination to assist the deactivation of the ruthenium catalysts.

Thermal Properties of the Polymers. The thermal properties of poly(**3**) and poly(**4**) were examined by DSC under nitrogen (Figure 4). They exhibited melting temperatures (T_m) at 153 and 159 °C upon heating, and crystallized at 106 and 121 °C upon cooling, respectively. Moreover, we measured the DSC of poly(**4**) in the presence of 0.1−2.0 equiv of $C_{13}F_{27}COOH$ and 100 equiv of DMSO. As shown in Figure 4, the addition of $C_{13}F_{27}COOH$ led to disappearance of the exothermic peak at 121 °C derived from crystallization of poly(**4**). On the other

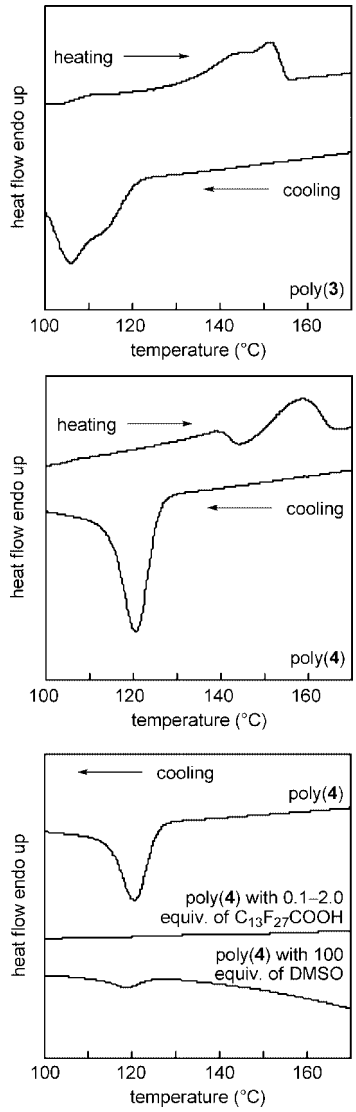
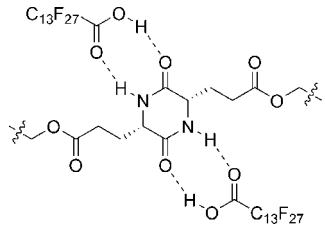


Figure 4. DSC curves of poly(**3**) and poly(**4**) (samples: runs 12 and 18 in Table 1) in the absence and presence of 0.1−2.0 equiv of $C_{13}F_{27}COOH$ and 100 equiv of DMSO measured in N_2.

Chart 3. Complex of DKP and $C_{13}F_{27}COOH$



hand, the peak still remained upon the addition of as much as 100 equiv. of DMSO. It suggests that the crystallinity of poly(**4**) was based on hydrogen bonding between the amide groups of the DKP moieties of the polymer, and $C_{13}F_{27}COOH$ prohibited the crystallization. We have previously examined the intermolecular interaction of L-aspartic acid DKP cyclohexyl ester by ^1H NMR spectroscopy.[10] The chemical shift of the amide NH proton showed a downfield shift with an increase in concentration and decrease in temperature. It indicates the formation of intermolecular hydrogen bonding between the amide groups of DKP moieties. In a similar fashion, the monomeric units in the present study presumably form hydrogen bonding between the amide groups as well, leading to crystallization of the polymers.

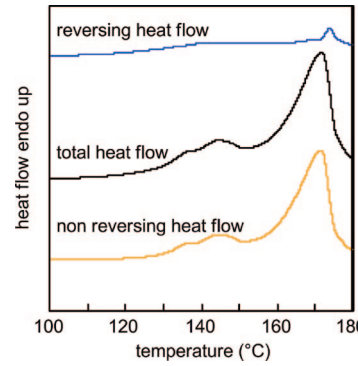


Figure 5. Modulated DSC of poly(**4**) (sample: run 18 in Table 1).

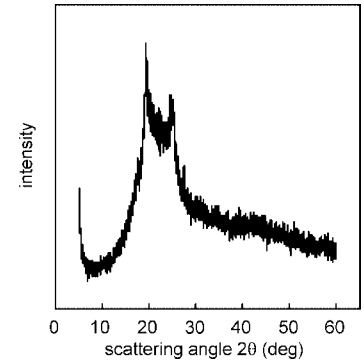


Figure 6. X-ray diffraction pattern for poly(**4**) (sample: run 18 in Table 1).

As described above, DKP forms a complex with TFA based on hydrogen bonding of the amide groups.[4] In the same way, it is possible for DKP to form hydrogen bonds with $C_{13}F_{27}COOH$ (Chart 3). Consequently, the association of DKP moieties between the polymer chains is disturbed, disrupting the ability of the material to crystallize. Meanwhile, DMSO did not interrupt this association and the polymers can crystallize in this solvent.

We further investigated the thermal properties of poly(**4**) by MDSC (Figure 5). MDSC has the advantage of increased sensitivity over traditional DSC as well as the ability to separate transitions that are reversible or irreversible over the scanning conditions.[23] The data shows that the majority of the total heat flow is attributed to the nonreversing heat flow part and that the contribution from the reversing heat flow is negligible; meaning that the melting transitions witnessed are largely irreversible for these scanning conditions. Taking both the standard DSC (loss of melting behavior when $C_{13}F_{27}COOH$ is introduced) and MDSC (melting transition largely irreversible) together provides strong evidence that the crystallization is predominated by aggregates formed in solution, which are not reversible when cooling from the melt.

We also examined the crystalline structure of poly(**4**) by XRD. As shown in Figure 6, XRD peaks were observed at 19.5° and 25.0°, corresponding to the surface distances of 4.55 Å and 3.56 Å, respectively. The former is attributable to the length between the main chains and the latter is attributable to the length between the DKP rings aligned in the horizontal direction. It is considered that the crystalline structure of poly(**4**) is supplemented by hydrogen bonding between the DKP moieties.

Figure 7 depicts the TGA curves of poly(**3**) and poly(**4**) obtained with **Ru3**. The onset temperatures of weight loss (T_0) of the polymers were around 200 °C in air, independent of m length and the molecular weights. The polymers decomposed in two steps. It is likely that the ester groups of the polymers

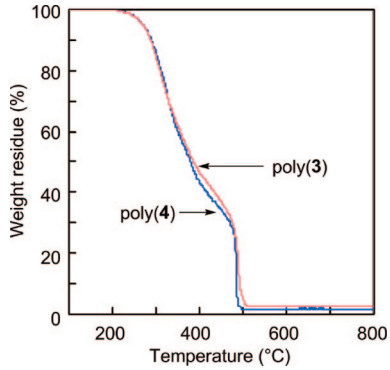


Figure 7. TGA curves of poly(**3**) and poly(**4**) (samples: runs 12 and 18 in Table 1) measured in air at a heating rate of 10 °C/min.

were cleaved in the first step. Judging from the unit molecular weights, it is considered that glutamic acid DKPs remained after cleavage of ester groups at the weight residue around 50%.

Conclusions

In this article, we have demonstrated the ADMET polycondensation of novel glutamic acid diketopiperazine ω-alkenyl esters **1**-**4** with ruthenium catalysts **Ru1**−**Ru4**. The polycondensation of **1** was unsuccessful, while the polycondensation of **2**−**4** with **Ru2** and **Ru3** satisfactorily proceeded to give the corresponding polymers [poly(**2**)−poly(**4**)]. XRD and DSC analyses indicated that the backbones of the polymers crystallized, wherein hydrogen bonding between the DKP moieties possibly assisted the crystallization. In fact, the addition of $C_{13}F_{27}COOH$ caused disappearance of a crystal-based DSC peak of the polymer. DLS measurement of the polymer confirmed that the polymer formed aggregates, presumably based on hydrogen bonding between the DKP moieties. It is expected that the modification of length and structure of the spacer between the DKP and olefin moieties leads to a precise control over thermal and crystalline properties of the polymers.

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Supporting Information Available: Expanded ^{1}H NMR spectrum of poly(**4**) (Figure S1), and net atomic charges of the olefin terminal carbon atoms of the monomers and their analogues (Table S1). This material is available free of charge via the Internet at http://pubs.acs.org.

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