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ROMP of Norbornene Monomers Carrying Nonprotected Amino Groups with Ruthenium Catalyst

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ABSTRACT: Amino acid-derived novel norbornene monomers (**1a**-**2b**) having nonprotected amino groups, together with *tert*-butoxycarbonyl (Boc) protected ones (**1a-Boc**-**2b-Boc**) were synthesized and polymerized by ring-opening metathesis polymerization using the Grubbs second generation ruthenium catalyst. The L-alanine-derived *endo,endo*-monomer **1a** with amino groups gave no polymer, while the *exo,exo*-isomer **1b** gave a polymer by raising the catalyst concentration. *N*-Methyl-L-alanine-derived **2a** and **2b** carrying secondary amino groups gave polymers in yields higher than **1a** and **1b**. On the other hand, Boc-protected **1a-Boc**-**2b-Boc** gave the polymers in almost quantitative yields irrespective of the stereo structure (*endo, exo*) as well as the absence and presence of methyl group at the nitrogen atom. ^{1}H−^{1}H COSY NMR spectroscopic analysis and molecular mechanics calculation indicated that the polymers were syndiotactic.

Introduction

Ring-opening metathesis polymerization (ROMP) of norbornene derivatives generate polymers with diverse features, which can be tailored by the functional groups substituted at the backbone.[1] Development of ruthenium complexes tolerant to polar groups has made it possible to synthesize biological polymers carrying amino acids, peptides, and saccharides by ROMP.[2] These polymers are applicable to controlled drug delivery systems, cell-adhesive materials, and chiral recognition materials.[3,4] Thus far, norbornene derivatives substituted with polar groups including amide, ester, and hydroxy groups have been successfully polymerized by ruthenium complexes,[5,6] due to the high functional group tolerance compared with the other metathesis catalysts such as titanium-, tungsten-, and molybdenum-based ones. However, ruthenium catalysts were commonly limited by incompatibility with nitriles and amines.[7−9] Recently, it has been reported that some nitrile-containing norbornene monomers undergo ROMP with the Grubbs ruthenium catalysts when the nitrile group is positioned far from the norbornene skeleton,[10,11] or directly connected to the norbornene.[12,13] These examples suggest that sophisticated molecular design enables norbornene monomers to undergo ruthenium-based ROMP, even though the monomers contain basic groups that retard the catalytic activity.

A few studies have been reported regarding the ROMP of amino group-containing norbornene monomers, such as ROMP of 2-aminomethyl norbornene derivatives[14] and a cyclic alkene containing a tertiary nitrogen atom in the 2-position of norbornene skeleton[15] with tungsten/aluminum-based catalysts. However, ROMP of a norbornene monomer substituted with a nonprotected amino group was observed to be unsuccessful with a ruthenium catalyst.[16] The incompatibility of amines with ruthenium has also been proved by the fact that protection of amino group is necessary in the acyclic diene metathesis polycondensation of amines with ruthenium catalysts.[17] Very recently, it has been reported that a 7-oxanorbornene substituted with dimethylamino groups undergoes ROMP with the Grubbs third generation catalyst,[18] but no examples of monomers with primary and secondary amino groups have been demonstrated.

We previously reported that amino acid-bifunctionalized norbornene derivatives efficiently undergo ROMP to give polymers with fairly high molecular weights in good yields.[19] The polymerization proceeds in a living fashion to some extent (polydispersity index: 1.10−1.40) The polymerizability of the monomers largely depends on the substituents, stereo structure (*endo*- and *exo*-), solvents, and catalysts. In the course of our study on the ROMP of amino acid-derived norbornene monomers, we found that L-leucine-derived ones having nonprotected carboxy groups successfully undergo ROMP with the Grubbs second generation ruthenium catalyst, during which the carboxy groups need no protection.[19] It seems that the amino acid spacers between the norbornene and carboxy groups are effective to enhance the polymerizability. Namely, the spacers possibly prevent the carboxy groups from interacting with the ruthenium center of the catalyst coordinated at the double bond in the metathesis intermediate.

Similarly, it may become possible to achieve ROMP of norbornene monomers having nonprotected amino groups by employing an amino acid moiety as a spacer. Although there are some reports regarding the ROMP of amino acid-derived norbornenes with protected amino groups as described above,[4,19] there is no successful report regarding the ROMP of amino acid-derived norbornenes carrying nonprotected primary or secondary amino group to the best of our knowledge. The present article deals with the synthesis and ROMP of amino acid-derived novel norbornene monomers (**1a**-**2b**) having nonprotected amino groups, together with *tert*-butoxycarbonyl (Boc)-protected ones (**1a-Boc**-**2b-Boc**) as illustrated in Scheme 1.

Experimental Section

Measurements. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using tetramethylsilane (TMS) as an internal standard in CDCl$_3$ or DMSO-d_6 on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FTIR-4100. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Elemental analysis was done at the Microanalytical Center of Kyoto Univer-

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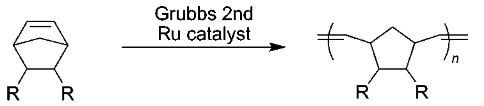
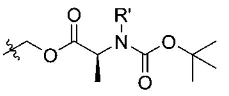
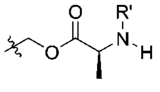
Scheme 1. ROMP of Amino Acid-Derived Norbornene Monomers



monomer	R	R'	stereostructure
1a-Boc		H	*endo,endo-*
1b-Boc		H	*exo,exo-*
2a-Boc		CH_3	*endo,endo-*
2b-Boc		CH_3	*exo,exo-*
1a		H	*endo,endo-*
1b		H	*exo,exo-*
2a		CH_3	*endo,endo-*
2b		CH_3	*exo,exo-*

sity. Specific rotations ([α]$_D$) were measured on a JASCO DIP-1000 digital polarimeter with a sodium lamp as a light source. Number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) on a JASCO Gulliver system (PU-980, CO-965, RI-930, and UV-1570) equipped with polystyrene gel columns (Shodex column KF805L, bead size 10 μm; exclusion limit 4 × 10^6) using tetrahydrofuran (THF) as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C or on TSK gel α-M (bead size 13 μm; exclusion limit 1 × 10^7) and TSK gel GMH$_{XL}$ (bead size 9 μm; exclusion limit 4 × 10^8) 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.

Materials. Bis[*N*-(*tert*-butoxycarbonyl)-L-alanine] 5-norbornene-2,3-*endo,endo*-dimethyl ester (**1a-Boc**) and bis[*N*-(*tert*-butoxycarbonyl)-L-alanine] 5-norbornene-2,3-*exo,exo*-dimethyl ester (**1b-Boc**) were prepared according to the reported method.[19b] 5-Norbornene-2,3-*endo,endo*-dimethanol (TCI), 5-norbornene-2,3-*exo,exo*-dimethanol (TCI), *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-alanine (Watanabe Chemical Industries), *N*-(*tert*-butoxycarbonyl)-L-alanine (Watanabe Chemical Industries), *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (EDC•HCl; EIWEISS Chemical), and 4-(dimethylamino)pyridine (DMAP; Wako Pure Chemical Industries), the Grubbs second generation catalyst (Materia) were used without purification. DMF and CH_2Cl_2 used for polymerization were distilled over CaH_2 under nitrogen prior to use.

Synthesis of Bis(L-alanine) 5-Norbornene-2,3-*endo,endo*-dimethyl Ester (1a). 1a-Boc (2.43 g, 4.9 mmol) was dissolved in CH_2Cl_2 (30 mL). Trifluoroacetic acid (TFA, 5 mL, 0.067 mol) was added to the solution at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction progress was monitored by TLC. The solvent and TFA were removed under reduced pressure to obtain bis(L-alanine−trifluoroacetate) 5-norbornene-2,3-*endo,endo*-dimethyl ester as sticky liquid (2.1 g, 90%). A saturated $NaHCO_3$ aq. solution (10 mL) was added to bis(L-alanine−trifluoroacetate) 5-norbornene-2,3-*endo,endo*-dimethyl ester (2.1 g, 4.0 mmol). The resulting mixture was extracted with CH_2Cl_2 three times. The organic phase was dried over $MgSO_4$. It was concentrated on a rotary evaporator to obtain **1a** as sticky liquid. Yield: 0.84 g (40%). [α]$_D$ = +10.2° (c = 0.1 g/dL in $CHCl_3$, room temperature). IR (KBr): 3373 (N−H), 3303 (N−H), 3058 (C═C−H), 2973 (C−H), 2872 (C−H), 1733 (C═O), 1602, 1455 (C−H), 1374 (C−H), 1325 (═CH), 1185 (C−N), 1142, 1066, 974 (C−C), 913, 746 (C═C−H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.35 (d, J = 6.8 Hz, 6H, 2 × CH_3), 1.54−1.63 (m, 6H, 2 × NH_2, norbornene C*H*$_2$), 2.46 (s, 2H, norbornene C*H*), 2.92 (s, 2H, bridge position), 3.53−3.58 (m, 2H, 2 × >C*H*CH$_3$), 3.72−3.84, 3.89−3.96 (m, 4H, 2 × C*H*$_2$), 6.18 (s, 2H, −C*H*═C*H*−). ^{13}C NMR ($CDCl_3$): δ 20.65 (CH*C*H$_3$), 40.51 (*C*HCH$_2$), 45.31 (*C*H, bridge position), 48.94 (norbornene *C*H$_2$), 49.97 (*C*HNH$_2$), 64.82 (*C*H$_2$O), 64.89 (*C*H$_2$O), 135.33 (H*C*═*C*H), 176.31 (CH*C*OO). HRMS (EI): calcd for $C_{15}H_{24}N_2O_4$, 296.1736; found, 296.1740.

Synthesis of Bis(L-alanine) 5-Norbornene-2,3-*exo,exo*-dimethyl Ester (1b). The title compound was synthesized from **1b-Boc** in a manner similar to **1a**. Yield: 43%. [α]$_D$ = +20.7° (c = 0.1 g/dL in THF, room temperature). IR (KBr): 3374 (N−H), 3307 (N−H), 3060 (C═C−H), 2972 (C−H), 1734 (C═O), 1603, 1456 (C−H), 1374 (C−H), 1326 (═CH), 1186 (C−N), 1143, 1066, 962 (C−C), 903, 755 (C═C−H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.36 (d, J = 5.9 Hz, 6H, 2 × CH_3), 1.52−1.58 (m, 6H, 2 × NH_2, norbornene C*H*$_2$), 1.89 (s, 2H, norbornene C*H*), 2.74 (s, 2H, bridge position), 3.55−3.60 (m, 2H, 2 × >C*H*CH$_3$), 4.08 (s, 2H, C*H*$_2$), 4.28−4.30 (m, 2H, C*H*$_2$), 6.19 (s, 2H, −C*H*═C*H*−). ^{13}C NMR ($CDCl_3$): δ 20.66 (CH*C*H$_3$), 39.71 (*C*HCH$_2$), 42.60 (*C*H, bridge position), 44.68 (norbornene *C*H$_2$), 50.05 (*C*HNH$_2$), 65.78 (*C*H$_2$O), 65.82 (*C*H$_2$O), 137.22 (H*C*═*C*H), 176.45 (CH*C*OO). HRMS (EI): calcd for $C_{15}H_{24}N_2O_4$, 296.1736; found, 296.1735.

Synthesis of Bis[*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-alanine] 5-Norbornene-2,3-*endo,endo*-dimethyl Ester (2a-Boc). The title compound was synthesized from 5-norbornene-2,3-*endo,endo*-dimethanol and *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-alanine in a manner similar to **1a-Boc**.[19b] Yield: 83%. [α]$_D$ = −44.99° (c = 0.1 g/dL in $CHCl_3$, room temperature). IR (KBr): 3461 (N−H), 3058, 2976 (C−H), 2937 (C−H), 1742 (C═O), 1696 (C═C), 1479, 1455 (C−H), 1390, 1367 (C−H), 1324 (═CH), 1253, 1207 (C−N), 1155, 1094, 1047, 995 (C−C), 871, 774 (C═C−H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 125−1.51 [m, 26H, 2 × (C*H*$_3$)$_3$, 2 × CHC*H*$_3$, norbornene C*H*$_2$], 2.52 (s, 2H, 2 × C*H*), 2.84 (d, J = 20 Hz, 6H, −NC*H*$_3$), 2.91 (s, 2H, norbornene bridge position), 3.75−3.80 (m, 2H, C*H*$_2$O), 3.93 s, 2H, C*H*$_2$O), 4.91 (s, 1H, C*H*CH$_3$), 4.81 (s, 1H, C*H*CH$_3$), 6.15 (s, 2H, −C*H*═C*H*−). ^{13}C NMR ($CDCl_3$): δ 14.72 (CH*C*H$_3$), 15.15 (CH*C*H$_3$), 28.13, 28.21, 28.30, 28.38 (6C, *C*H$_3$), 30.41 (N*C*H$_3$), 30.78 (N*C*H$_3$), 40.42 (*C*HCH$_2$), 45.28 (*C*H bridge position), 48.79 (norbornene *C*H$_2$), 53.50 (*C*HCH$_3$), 54.82 (*C*HCH$_3$), 64.84 (*C*H$_2$O), 79.86 (*C*CH$_3$), 80.11 (*C*CH$_3$), 135.35 (H*C*═*C*H), 155.80 (*C*OOC(CH$_3$)$_3$), 172.03 (CH$_2$*C*OO). HRMS (EI): calcd for $C_{27}H_{44}N_2O_8$, 524.3098; found, 524.3095.

Synthesis of Bis[*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-alanine] 5-Norbornene-2,3-*exo,exo*-dimethyl Ester (2b-Boc). The title compound was synthesized from 5-norbornene-2,3-*exo,exo*-dimethanol instead of 5-norbornene-2,3-*endo,endo*-dimethanol in a manner similar to **2a**. Yield 91%. [α]$_D$ = −68.6° (c = 0.1 g/dL in $CHCl_3$, room temperature). IR (KBr): 3479 (N−H), 3060, 2975 (C−H), 1742 (C═O), 1695, 1479 (C−H), 1390, 1367 (C−H), 1325 (═CH), 1209 (C−N), 1154, 1094, 1047, 956 (C−C), 870, 774 (C═C−H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 141−1.52 [m, 26H, 2 × (C*H*$_3$)$_3$, 2 × CHC*H*$_3$, norbornene C*H*$_2$], 1.85 (s, 2H, 2 × C*H*), 2.72 (s, 2H, bridge position), 2.84 (d, J = 19.3 Hz, 2 × −NC*H*$_3$), 4.05−4.07 (m, 2H, C*H*$_2$O), 4.26−4.29 (m, 2H, C*H*$_2$O), 4.49−4.50 (m, 1H, >C*H*CH$_3$), 4.83−4.84 (m. 1H, >C*H*CH$_3$), 6.15 (s, 2H, −C*H*═C*H*−). ^{13}C NMR ($CDCl_3$): δ 14.67 (CH*C*H$_3$), 15.18 (CH*C*H$_3$), 28.18 (6C, *C*H$_3$), 30.35 (N*C*H$_3$), 39.61, 39.70 (*C*HCH$_2$), 42.51 (*C*H bridge position), 44.58, 44.64 (norbornene *C*H$_2$), 53.42 (*C*HCH$_3$), 54.96 (*C*HCH$_3$), 65.70 (*C*H$_2$O), 65.85 (*C*H$_2$O), 80.14 (*C*CH$_3$), 137.21 (H*C*═*C*H), 155.79 [*C*OOC(CH$_3$)$_3$], 172.13 (CH$_2$*C*OO). Anal. Calcd for $C_{27}H_{44}N_2O_8$: C, 61.81; H, 8.45; N, 5.34. Found: C, 61.52; H, 8.29; N, 5.29.

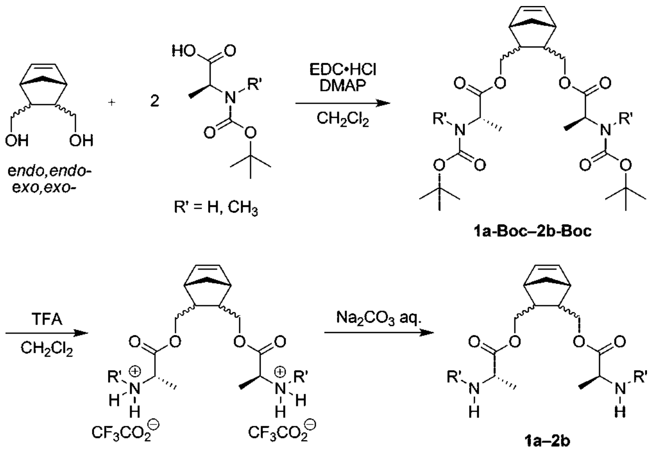
Synthesis of Bis(*N*-methyl-L-alanine) 5-Norbornene-2,3-*endo,endo*-dimethyl ester (2a). The title compound was synthesized from **2a-Boc** in a manner similar to **1a**. Yield: 35%. [α]$_D$ = −29.7° (c = 0.1 g/dL in THF, room temperature). IR (KBr): 3331 (N−H), 3057, 2974 (C−H), 2872 (C−H), 1735 (C═O), 1689, 1455 (C−H), 1373 (C−H), 1334 (═CH), 1178, 1131, 1072, 972 (C−C), 798 (C═C−H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.35−1.60 (m, 8H, 2 × CH_3, norbornene C*H*$_2$), 2.49 (s, 6H, >NHC*H*$_3$), 2.55 (s, 2H, norbornene C*H*), 2.92 (s, 2H, bridge position), 3.38−3.47 (m, 2H, 2 × >C*H*CH$_3$), 3.83−3.89 (m, 2H, C*H*$_2$), 3.94−3.98 (m, 2H, C*H*$_2$), 5.08 (s, 2H, 2 × −N*H*), 6.18 (s, 2H, −C*H*═C*H*−). ^{13}C NMR ($CDCl_3$): δ 17.40 (CH*C*H$_3$), 33.37 (NH*C*H$_3$), 40.55 (*C*HCH$_2$), 45.43 (*C*H bridge position), 48.99 (norbornene *C*H$_2$), 57.61 (*C*HCH$_3$), 57.68 ($CHCH_3$), 65.16 (CH_2O), 135.39 (HC=CH), 173.53 (CH_2COO). HRMS (EI): calcd for $C_{17}H_{28}N_2O_4$, 324.2049; found, 324.2051.

Synthesis of Bis(*N*-methyl-L-alanine) 5-Norbornene-2,3-*exo*,*exo*-dimethyl Ester (2b). The title compound was synthesized from **2b-Boc** in a manner similar to **1a**. Yield: 42%. $[\alpha]_D = -23.0°$ ($c = 0.1$ g/dL in THF, room temperature). IR (KBr): 3326 (N−H), 2973 (C−H), 2801, 1737 (C=O), 1685, 1456 (C−H), 1327 (=CH), 1201 (C−N), 1131, 1073, 1019, 830, 799 (C=C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38−1.59 (m, 8H, 2 × CH_3, norbornene CH_2), 1.89 (s, 2H, norbornene CH), 2.50−2.68 (m, 6H, $>NHCH_3$), 2.73 (s, 2H, bridge position), 3.47−3.53 (m, 2H, 2 × $>CHCH_3$), 4.05−4.14 (m, 2H, CH_2), 4.27−4.34 (m, 2H, CH_2), 5.28 (s, 2H, 2 × −NH), 6.18 (s, 2H, −CH=CH−). ^{13}C NMR ($CDCl_3$): δ 17.07 ($CHCH_3$), 33.16 ($NHCH_3$), 39.71 ($CHCH_2$), 42.70 (CH bridge position), 44.72 (norbornene CH_2), 57.49 ($CHCH_3$), 66.22 (CH_2O), 137.22 (2C, HC=CH), 173.28 (CH_2COO). HRMS (EI): calcd for $C_{17}H_{28}N_2O_4$, 324.2049; found, 324.2050.

Polymerization: Typical Procedure. Polymerizations were carried out in a glass tube equipped with a three-way stopcock under nitrogen. Monomer **1a** (183 mg, 0.42 mmol) and the Grubbs second generation ruthenium catalyst (3.6 mg, 4.2×10^{-3} mmol) were dissolved in CH_2Cl_2 (0.5 mL) separately. The catalyst solution was added to the monomer solution and the resulting mixture was vigorously stirred. It was kept in a water bath at 30 °C for 20 h. A sticky mass precipitated during the reaction. Then, ethyl vinyl ether (0.2 mL, 2.1 mmol) was added to the mixture to quench the reaction. The reaction mixture was poured into a large amount of hexane. The mass was separated from the solvent by decantation, and dried under reduced pressure.

Spectroscopic Data of the Polymers. The data poly(**1a-Boc**) and poly(**1b-Boc**) are reported in the literature.[19b] **Poly(2a-Boc)**. IR (KBr): 3369 (N−H), 2972 (C−H), 2979 (C−H), 1739 (ester C=O), 1688, 1457 (C−H), 1384 (C−H), 1317 (=CH), 1155, 1095, 1047, 992 (C−C), 870, 775 (C=C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26−1.64 [m, 26H, 2 × $(CH_3)_3$, 2 × $CHCH_3$, norbornene CH_2], 2.46 (broad, 2H, 2 × CH), 2.82 (d, $J = 15.4$ Hz, 8H, 2 × $-NCH_3$, norbornene bridge position), 4.11 (s, 4H, 2 × CH_2O), 4.44 (s, 1H, $CHCH_3$), 4.75 (s, 1H, $CHCH_3$), 5.35 (s, 2H, −HC=CH−). **Poly(2b-Boc)**. IR (KBr): 3467 (N−H), 2925 (C−H), 1734 (C=O), 1683, 1456 (C−H), 1384 (C−H), 1180 (C−N), 1022, 747 (C=C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 126−1.65 (m, 26H, 2 × $(CH_3)_3$, 2 × $CHCH_3$, norbornene CH_2), 2.10 (broad, 2H, 2 × CH), 2.25−2.61 (broad, 2H, bridge position), 2.81 (d, $J = 15.8$ Hz, 6H, 2 × $-NCH_3$),, 4.13 (s, 4H, 2 × CH_2O), 4.46 (s, 1H, $CHCH_3$), 4.78 (s, 1H, $CHCH_3$), 5.22 (s, 1H, −HC=CH−), 5.33 (s, 1H, −HC=CH−). **Poly(1b).** IR (KBr): 3315 (NH_2), 3086 (C=C−H), 2960 (C−H), 2603, 1731 (ester C=O), 1593, 1455 (C−H), 1356 (C−H), 1307, 1209 (C−N), 1151, 1114, 1038, 969 (C−C), 851, 770, 707 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.29−1.33 (m, 6H, 2 × CH_3), 1.45 (d, $J = 9.3$ Hz, 2H, norbornene CH_2), 1.61 (s, broad, 4H, 2 × NH_2), 1.82 (s, 2H, norbornene CH), 2.54 (broad, 2H, norbornene bridge position), 3.47−3.51 (m, 2H, 2 × $>CHCH_3$), 4.00−4.23 (m, 4H, CH_2), 5.19 (s, 1H, −CH=CH−), 5.26 (s, 1H, −CH=CH−). **Poly(2a).** IR (KBr): 3439 (N−H), 2964 (C−H), 1743 (C=O), 1686, 1458 (C−H), 1201 (C−N), 1127, 1073, 970 (C−C), 832, 798, 721 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.31−1.44 (m, 8H, 2 × CH_3, norbornene CH_2), 2.43−2.50 (m, 8H, 2 × −CH, $>NHCH_3$), 2.79 (broad, 2H, bridge position), 3.54 (broad, 4H, 2 × $>CHCH_3$, 2 × −NH), 4.14 (broad, 4H, 2 × $-CH_2$), 5.36 (broad, 2H, −CH=CH−). **Poly(2b).** IR (KBr): 3463 (N−H), 2853, 1748 (C=O), 1559, 1457 (C−H), 1384 (C−H), 1201 (C−N), 1018, 970, 721 (C=C−H) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.35 (broad, 8H, 2 × CH_3, norbornene CH_2), 2.13 (s, 2H, norbornene CH), 2.58−2.66 (broad, 8H, $>NHCH_3$, bridge position), 3.79 (s, 2H, 2 × $>CHCH_3$), 4.17 (broad, 6H, 2 CH_2, −NH), 5.25 (s, 1H, −CH=CH−), 5.37 (s, 1H, −CH=CH−).

Scheme 2. Synthesis of Amino Acid-Derived Norbornene Monomers



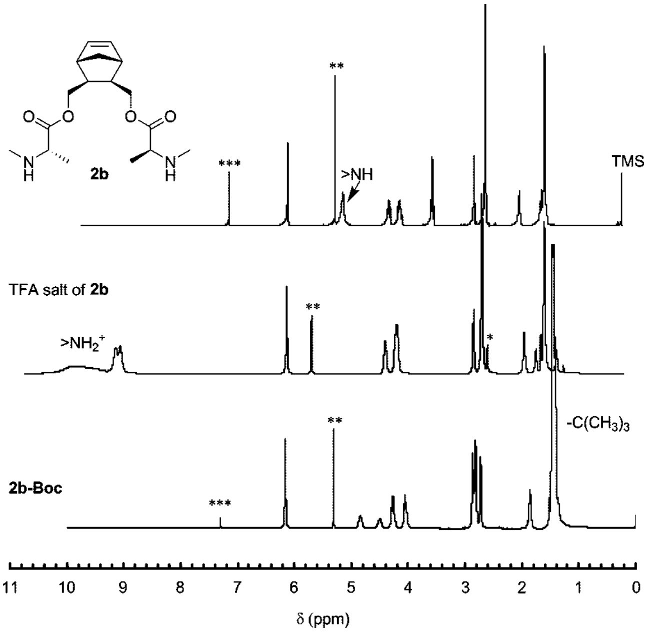


Figure 1. ^1H NMR spectra (400 MHz) of **2b**, TFA salt of **2b**, and **2b-Boc**: *: DMSO; **, CH_2Cl_2; ***, $CHCl_3$.

Results and Discussions

Monomer Synthesis. The L-alanine- and *N*-methylalanine-derived *exo,exo*- and *endo,endo*-monomers, **1a-2b** with non-protected amino groups were synthesized from the *N*-Boc-protected precursors, **1a-Boc-2b-Boc** by deprotection using TFA, followed by neutralization with a base as illustrated in Scheme 2. The structures of the monomers were determined by IR, ^1H NMR, and ^{13}C NMR spectroscopies, besides either elemental analysis or high resolution mass spectrometry. The ^1H NMR spectra in Figure 1 indicate the successful transformation from **2b-Boc** into the TFA salt, and **2b** with amino groups. Figure 2 depicts the IR spectra of **1b** and **2b**, in which the difference of absorption peaks between primary and secondary amino groups of monomers **1b** and **2b** was clearly observed. Namely, **1b** exhibited absorption peaks due to symmetric and asymmetric stretchings at 3307 and 3374 cm^{-1}, respectively. On the other hand, **2b** exhibited an absorption peak due to asymmetric stretching around 3326 cm^{-1}.

All the norbornene monomers carrying nonprotected amino groups were colorless viscous liquid absorbing moisture easily. It was necessary to keep them in a refrigerator at −25 °C for avoiding moisture absorption. This is also considered to be effective to suppress the ester-amide exchange reaction of the monomers leading to degradation. We always checked the purity of the monomer samples by ^1H NMR spectroscopy just before polymerization.

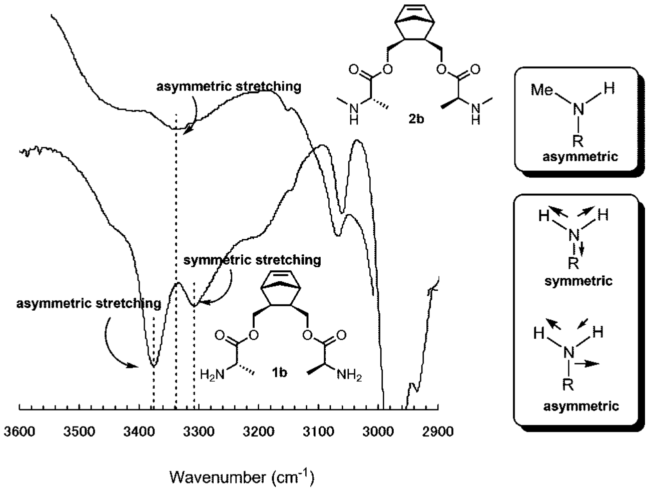


Figure 2. IR spectra of the monomers carrying primary amino groups (**1b**) and secondary amino groups (**2b**).

Polymerization. The polymerization was carried out with the Grubbs second generation ruthenium catalyst in CH_2Cl_2 and DMF. Table 1 lists the conditions and results of ROMP of **1a-2b** together with the Boc-protected counterparts, **1a-Boc-2b-Boc** for comparison. Boc-protected **1a-Boc-2b-Boc** satisfactorily gave the polymers with M_n's of 176 000−364 000 in 85%-quantitative yields by the polymerization in CH_2Cl_2, irrespective of the stereo structure (*endo-*, *exo-*) as well as the absence and presence of methyl group at the nitrogen atom (runs 1−4). Meanwhile, *endo,endo*-monomer **1a** with nonprotected amino groups gave no polymer, even when the polymerization time was extended from 1 to 20 h (run 5). *exo,exo*-Monomer **1b** with nonprotected amino groups slightly gave a polymer at $[M]_0/[Ru] = 100$ by the polymerization in CH_2Cl_2 (run 8). Interestingly, the polymer yield increased to 14% by changing the solvent from CH_2Cl_2 into DMF (run 9). DMF may strongly interact with the amino groups of the monomer, leading to the decrease of deactivation of the ruthenium catalyst by the amino groups. Moreover, the increase of catalyst concentration ($[M]_0/[Ru] = 50$, 20) enhanced the yields of poly(**1b**) (runs 10 and 11). However, **1a** did not give a polymer even by raising the catalyst concentration in DMF (runs 6 and 7).

On the other hand, *N*-methyl-L-alanine-derived **2a** and **2b** carrying secondary amino groups gave polymers (runs 12 and 13) in yields higher than L-alanine-derived **1a** and **1b** carrying primary amino groups (runs 5−11) under the same conditions. *N*-Methylamino group is more basic than nonmethylated one due to the electron-donating ability of methyl group, but the former is more bulky than the latter. Consequently, the degree of deactivation of the catalyst by the *N*-methylamino groups of **2a** and **2b** seems to be smaller than the amino group of **1a** and **1b**, resulting in the higher polymerizability of the former two monomers in ROMP. The M_n's of the polymers carrying nonprotected amino groups were lower than those of the polymers carrying Boc-protected amino groups. The monomers carrying nonprotected amino groups gave polymers with molecular weight distributions (1.29−1.49, runs 8−13) narrower than the ones carrying protected amino groups (1.83−3.10, runs 1−4). The living character is possibly due to the coordination of the amino groups to the ruthenium center, leading to slow propagation of these monomers. Back-biting reactions leading to broadening of molecular weight distributions[20] seem to be also suppressed.

The cis/trans ratios of the double bond at the polymer main chain were determined by the integration ratios of the ^1H NMR signals of the olefinic protons at 5.1−5.4 ppm. The polymer yields of *exo,exo*-monomers **1b** and **2b** were higher than those of the *endo,endo*-counterparts in all cases. It is likely that the amino groups at the norbornene *endo*-positions hinder the coordination of the double bond to the ruthenium center of the catalyst, leading to the deactivation of catalyst.[16,19,21−24]

As described in the Introduction, most of metathesis catalysts are inactivated by compounds substituted with nonprotected amino groups,[15−17] and ruthenium complexes have not been able to polymerize norbornene derivatives with primary and/or secondary amino groups thus far. The ROMP of *endo,exo*-2,3-bis(ethoxycarbonyl)norbornene with the Grubbs second generation catalyst is retarded by the addition of 150−300 equivalents of diethylamine, but it still gives a polymer in 80% yield.[10] It seems that the amino group connected to the norbornene largely suppresses the ROMP judging from the unsatisfactory data of

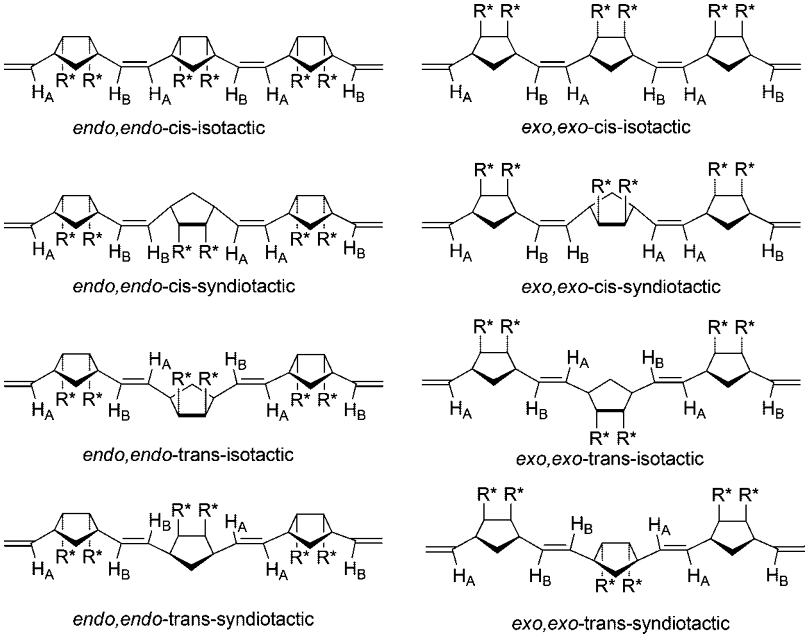


Figure 3. Possible regular structures of poly(*endo,endo*-2,3-disubstituted norbornene) (left) and poly(*exo,exo*-2,3-disubstituted norbornene) (right): R*, chiral group; H_A and H_B, two sets of inequivalent olefinic protons distinguishable by ^1H NMR spectroscopy.

Table 1. Polymerization of **1a-Boc-2b-Boc** and **1a-2b**[a]

					polymer			
run	monomer	$[M]_0/[Ru]$	solvent	time (h)	yield[b] (%)	M_n[c]	M_w/M_n[c]	cis content [d] (%)
1	**1a-Boc**	100	CH_2Cl_2	1	85	210 000	2.00	51
2	**1b-Boc**	100	CH_2Cl_2	1	93	261 000	3.10	43
3	**2a-Boc**	100	CH_2Cl_2	1	quant	176 000	1.83	*e*
4	**2b-Boc**	100	CH_2Cl_2	1	quant	364 000	1.89	50
5	**1a**	100	CH_2Cl_2	20	0			
6	**1a**	50	DMF	20	0			
7	**1a**	20	DMF	20	0			
8	**1b**	100	CH_2Cl_2	20	trace	8300	1.32	*e*
9	**1b**	100	DMF	20	14	9900	1.37	*e*
10	**1b**	50	CH_2Cl_2	20	11	7600	1.39	48
11	**1b**	20	CH_2Cl_2	20	68	5000	1.49	*e*
12	**2a**	50	CH_2Cl_2	20	20	14 000	1.36	*e*
13	**2b**	50	CH_2Cl_2	20	81	12 500	1.29	50

[a] Conditions: $[M]_0 = 0.42$ M with the Grubbs second generation ruthenium catalyst at 30 °C. [b] Hexane-insoluble part. [c] Determined by GPC eluted with THF (runs 1 and 2) or DMF (LiBr 10 mM solution, runs 3, 4, and 8−13). [d] Determined by ^1H NMR. [e] Not determined due to the overlap of signals.

1a (runs 5−7 in Table 1). From the overall obtained results, it is considered that the amino groups of the present study are nicely positioned except **1a**, where they do not intramolecularly interact with the ruthenium coordinated to the olefin moiety so much, especially in the cases of *exo,exo*-monomers **1b** and **2b**. Another possibility is N−H---O intramolecular hydrogen bonding that forms a pseudo five-membered ring. It is also likely to prevent interaction between the ruthenium and amino groups. *N*-Methyl substitution was effective to enhance the polymerizability, presumably because the methyl groups suppress the interaction between the amino groups and ruthenium center.

Tacticity of the Polymers. Furthermore, the polymer microstructure was investigated. Figure 3 illustrates the possible regular structures of polymers of *endo,endo*- and *exo,exo*-norbornenes substituted with optically active groups (R*). The olefinic protons H_A and H_B are distinguishable from each other due to the unsymmetry based on the chiral arrangement of R*. When the ^1H NMR olefinic proton signals can be resolved, it is possible to determine the tacticity of the polymers; inequivalent olefinic proton signals that are coupled imply isotacticity, while inequivalent olefinic protons that are not coupled imply syndiotacticity.[25]

Figure 4 shows the $^1H-^1H$ COSY NMR spectra of poly(**1b**), poly(**2a**), and poly(**2b**). Poly(**1b**) and poly(**2b**) clearly exhibited two proton signals around 5.1−5.4 ppm. The two signals are assignable to *cis* and *trans* olefinic protons judging from the differences between the chemical shift of the two signals (0.13 ppm).[26] On the other hand, poly(**2a**) exhibited a slightly split signal around 5.4 ppm. It is considered that the splitting originates from syndiotactic H_A and H_B as illustrated in Figure 3, because the chemical shift difference between the split peak tops is small (ca. 0.05 ppm) compared to that of cis and trans (0.13 ppm), and no coupling between the signal tops.[25] However, there is a possibility that the splitting of the olefinic proton of poly(**2a**) is brought about by the existence of cis and trans structures, and it is not deniable. In the cases of poly(**1b**) and poly(**2b**), the splitting based on H_A and H_B in each cis or trans proton is not clear compared with that of poly(**2a**), but they also look like syndiotactic. We also measured the ^{13}C NMR spectra of the polymers but could not obtain clear information on the microstructure (See Supporting Information).

To obtain further information on the tacticity of the polymers, we estimated the steric energies of metallacyclobutane intermediates to give the eight stereo structures by the molecular mechanics calculation. To save the CPU time, bromine atom was used as the substituents at 2,3-positions of norbornene. An ethylidene group was chosen as a chain initiator instead of benzylidene unit resulting from the use of the Grubbs second generation catalyst, and hydrogen was used as the ligands of ruthenium for this purpose as well. The metallacyclobutane moiety was constructed at the *exo*-face of norbornene. This is

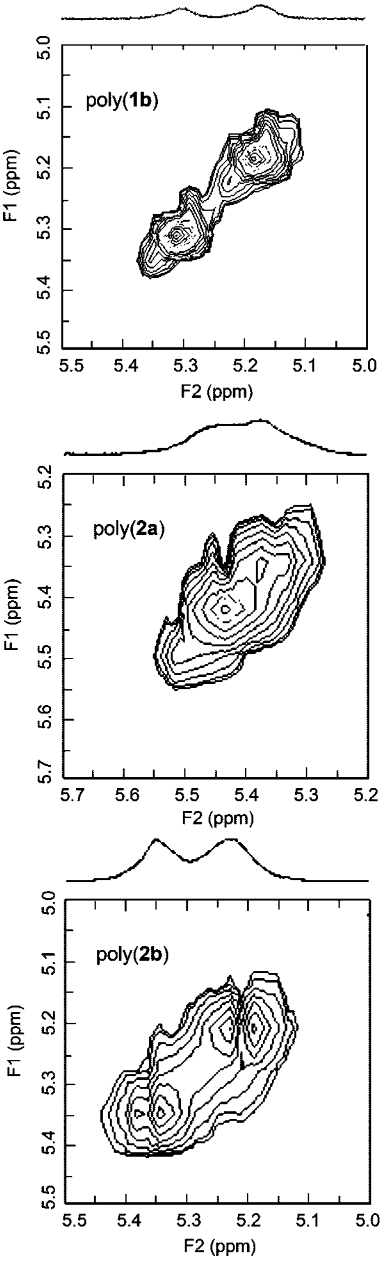


Figure 4. Olefinic proton region of the $^1H-^1H$ COSY NMR spectra of poly(**1b**), poly(**2a**), and poly(**2b**) measured in DMSO-d_6 at 35 °C.

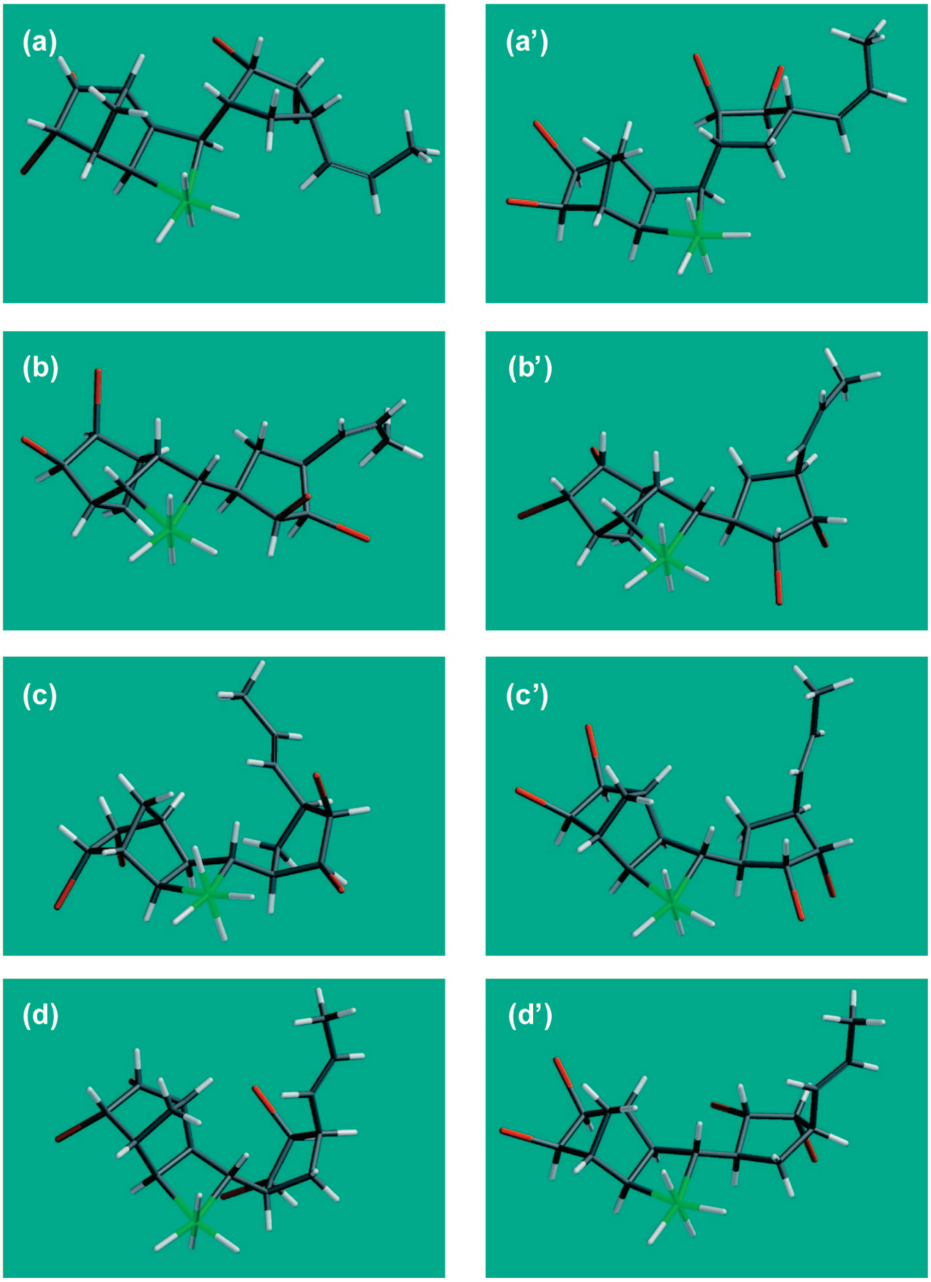


Figure 5. Models of metallacyclobutane intermediates that give possible regular structures of poly(*endo,endo*-2,3-disubstituted norbornene) and poly(*exo,exo*-2,3-disubstituted norbornene): (**a**−**d**) *endo,endo*-; (**a′**−**d′**) *exo,exo*-; (**a**, **a′**) *cis*-isotactic; (**b**, **b′**) *cis*-syndiotactic, (**c**, **c′**) *trans*-isotactic; (**d**, **d′**) *trans*-syndiotactic. Hydrogen atoms are used as the ligands of the ruthenium (green) catalyst, and bromine (orange) atoms are used as the substituents of norbornene for simplification. The geometries are optimized by the molecular mechanics method.

Table 2. Surface Areas and Steric Energies of the Metallacyclobutane Intermediates and Trimers

			steric energy[d] (kcal/mol)	
metallacyclobutane intermediate[a]	stereostructure that forms from the intermediate [b]	surface area[c] (Å^2)	metallacyclobutane intermediate[a]	trimer[e]
a	*endo,endo-cis*-isotactic	389.2	91.5	76.1
b	*endo,endo-cis*-syndiotactic	391.1	85.2	75.5
c	*endo,endo-trans*-isotactic	390.9	87.6	71.1
d	*endo,endo-trans*-syndiotactic	391.2	92.8	66.2
a′	*exo,exo-cis*-isotactic	393.7	83.5	67.9
b′	*exo,exo-cis*-syndiotactic	393.8	84.6	63.7
c′	*exo,exo-trans*-isotactic	397.2	81.6	62.5
d′	*exo,exo-trans*-syndiotactic	396.6	79.7	64.1

[a] See Figure 5. [b] See Figure 3. [c] Calculated with Wavefunction Inc. Spartan ‘06 Windows. [d] Calculated with CambridgeSoft Chem3D Pro 11.0. [e] See Figure 3. The end olefin moieties are terminated with hydrogen.

based on the report that the *exo*-face of norbornene preferably reacts with a metal carbene double bond compared to the *endo*-face.[23] Figure 5 shows the optimized structures of the intermediates. Table 2 summarizes the steric energies of the metallacyclobutane intermediates that give the possible regular structures illustrated in Figure 3. It was confirmed that the *exo,exo*-

intermediates had steric energies 0.6−13.1 kcal/mol lower than the *endo,endo*-counterparts. This result well explains the fact that *exo,exo*-norbornene monomers including the present study are more active in ROMP.[19,21−24] The reason why the *exo,exo*-intermediates are more stable than the *endo,endo*-ones is attributable to the steric repulsion between the substituents at the 2,3-positions. For example, intermediate **d**, which gives an *endo,endo-trans*-syndiotactic structure, positions the four substituents on the same side of the molecule. On the other hand, intermediate **d′**, which gives an *exo,exo-trans*-syndiotactic structure, positions the two substituents on the opposite side of the other two substituents. Furthermore, the molecular shape of intermediate **d** is compact, while that of **d′** is extended. This is also understood from the surface area of intermediate **d′** (396.6 Å^2) larger than that of **d** (391.2 Å^2) as listed in Table 2. Consequently, intermediate **d′** is sterically more favorable than **d**. This tendency was observed in all cases between *endo,endo*- and *exo,exo*-ones. The average surface areas of intermediates **a**−**d** and **a′**−**d′** were 390.6 and 395.3 Å^2, respectively. Judging from the steric energy of intermediates **a**−**d** together with the ^{1}H−^{1}H COSY NMR spectroscopic data, it is likely that poly(**2a**) is *cis*-syndiotactic.[27] This is compatible with the literature reporting that large alkyl substituents raise the proportion of *cis*-syndiotactic double bonds.[23]

We also calculated the steric energies of trimers of the stereoisomers illustrated in Figure 3, wherein bromine was used as R* and the chain end olefin moieties were terminated with methylidene to save the CPU time. The steric energies of the *endo,endo*- and *exo,exo*-trimers were in the ranges of 66.2−76.1 kcal/mol (average 72.2 kcal/mol) and 62.5−67.9 kcal/mol (average 64.6 kcal/mol), respectively, as listed in Table 2. It is considered that *exo,exo*-polymers favorably form as compared with *endo,endo*-ones from the viewpoint of thermodynamic stability as well.

Conclusion

In the present study, we have achieved the ROMP of norbornene monomers carrying nonprotected amino groups using a ruthenium catalyst. *N*-Methyl substitution was effective to enhance the polymerizability. As far as we know, the present norbornene monomers are the first ones carrying amino groups without protection that undergo ROMP with a ruthenium catalyst satisfactorily. The key importance should be the presence of amino acid spacers between the amino groups and norbornene skeleton, and possibly the intramolecular hydrogen bonding between the amino and carbonyl groups. We have also examined the tacticities of the polymers by ^{1}H−^{1}H COSY NMR spectroscopy and molecular mechanics calculation to find that the polymers are syndiotactic. It has been proved that the molecular design of norbornene monomers carrying nonprotected amino groups makes them active in ROMP with a ruthenium catalyst. We believe that the achievement in the present study contributes to the development of ROMP chemistry, and extends the possibility of application of ROMP-based polymers to biocompatible and pH responsive materials.

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Supporting Information Available: ^{13}C NMR spectra of poly(**2a**) and poly(**2b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) In the cases of poly(**1b**) and poly(**2b**), *trans*-syndiotactic is the most preferable, and the second one is not cis-syndiotactic but trans-isotactic based on the results of calculation for metallacyclobutane intermediates. The reason for this discordance is not clear. If we could appropriately estimate the steric energies of monomer-coordinated ruthenium alkylidene intermediates and activation energies for the stereostructures, this point might become clearer. However, it was very difficult to construct reliable molecular models of these intermediates and activated complexes.

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