Synthesis of Polymers with Adamantane Amino Derivatives as Pendant Groups

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ABSTRACT: Radical polymerizations of *N*-(tricyclo[3.3.1.1^{3,7}]decane-1-yl)4-vinylbenzylamine (Ad0) and *N*-(tricyclo[3.3.1.1^{3,7}]decane-1-yl-methyl)4-vinylbenzylamine (Ad1) were conducted in bulk under nitrogen. The polymerizations of Ad0 and Ad1 proceeded at the vinyl groups to give polymers with adamantane amino derivatives as pendant groups. The polymerization of Ad0 gave the polymers without any crosslinked product, although a partially or completely crosslinked polymer was obtained from the polymerization of Ad1 at high temperature. Thermal stability of poly(Ad0) and poly(Ad1) was excellent, and the stability of poly(Ad1) was much higher than that of poly(Ad0). The copolymerizations of Ad0 and Ad1 with styrene and methyl methacrylate (MMA) were also performed by 2,2'-azobis(isobutyronitrile) (AIBN) at 80°C. The copolymers had similar feed ratios of monomers to styrene or MMA.

KEY WORDS Adamantane Amino Derivatives / Styrene / Methyl Methacrylate / Radical Polymerization / Random Copolymers / Thermal Stability /

Adamantane, discovered in petroleum, has attracted considerable attention because its derivatives show various bioactivities. The derivatives with amino and with amide groups have greater antiviral activity than those with other functional groups. These activities are, for instance, fungicidal, repellent, and herbicidal for *N,N*-alkyl-adamantanecarboxamide.¹ Clinical investigators have found prophylactic effects of 1-adamantanamine and its hydrochloride salt toward influenza A virus strains,² and therapeutic effects in patients suffering from Parkinson's disease.³ Inhibition of rubella,⁴ Rous sarcoma,^{5,6} and Esh sarcoma viruses has also been reported. Some publications have already been released on the immobilization of the amino and amide adamantane derivatives in polymers, for obtaining polymeric drugs with controlled release. These publications concern radical polymerizations of methacrylate and methacrylamide derivatives of adamantanamine.⁷ It is expected that monomers with bulky pendant groups such as adamantyl show low reactivity for polymerizing, because the groups prevent the growing polymer chain end from reacting with the monomers. Steric hindrance of the bulky group causes formation of oligomers and polymers with low molecular weights. In this study, we prepared two monomers of vinyl benzylamino derivatives from 1-adamantanamine and from 1-adamantanemethylamine. Benzylamino derivatives of adamantane have the greatest antiviral activities among other amino derivatives with adamantane moiety.⁸ This paper describes the synthesis of polymers with adamantane benzylamine derivatives as pendant groups through the radical polymerizations of the two monomers, *N*-(tricyclo[3.3.1.1^{3,7}]decane-1-yl)4-vinylbenzylamine (Ad0) and *N*-(tricyclo[3.3.1.1^{3,7}]decane-1-yl-methyl)4-vinylbenzylamine (Ad1). The reactivity and thermal stability of the resulting polymers are described.

EXPERIMENTAL

Measurements

IR spectra were recorded with a JASCO FT/IR-5300 Fourier transfer infrared spectrometer. ¹H NMR spectra were obtained with a Bruker ARX-500 NMR spectrometer and ultraviolet (UV) spectra were also obtained with a Shimadzu UV-2500PC UV-VIS recording spectrophotometer. Differential scanning calorimetry (DSC) spectra were obtained with a Mac Science DSC-3100. Thermogravimetric analyses (TGA) spectra were recorded with a Shimadzu thermal analyzer DT-30. Gas chromatography (GC) was performed with a Shimadzu GC-6A. Gel permeation chromatography (GPC) was performed with a Tosoh HLC-802A instrument equipped with a Tosoh CP-8000 chromatoprocessor. Two polystyrene gel columns of Tosoh TSK gel G4000H₈ and G2000H₈ were used with tetrahydrofuran (THF) as the eluent at 42°C.

Materials

4-Vinylbenzaldehyde was prepared as previously reported.⁹ Benzene was purified by refluxing on sodium for several hours and distilled over sodium. Ether was purified by refluxing on sodium for several hours and distilled over sodium just before use. Commercial grade styrene was washed with aqueous alkaline solution and water, and distilled over calcium hydride. Methyl methacrylate (MMA) was distilled over calcium hydride. 2,2'-Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol. 1,1'-Azobis(cyclohexanecarbonitrile) was recrystallized from ethanol. 1-Adamantanamine, 1-adamantanemethylamine, *t*-butylcatechol, and di-*t*-butyl peroxide were used without further purification. Extrapure grade lithium aluminum hydride and anhydrous magnesium sulfate were used without further purification.

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N-(Tricyclo[3.3.1.1^{3,7}]decane-1-yl)4-vinylbenzylamine (Ad0)

A solution of 4-vinylbenzaldehyde (6.57 g, 49.7 mmol), 1-adamantanamine (8.28 g, 54.7 mmol), *t*-butylcatechol (5 mg), and anhydrous magnesium sulfate (18.0 g, 0.149 mol) in benzene (120 mL) was heated for 24 h under reflux with azeotropic removal of water. After the solution was cooled, it was washed with water, evaporated under reduced pressure and dried *in vacuo* for several hours to give the product of 11.2 g. A solution of this product of 11.2 g in ether (80 mL) was added dropwise at room temperature over 30 min under nitrogen, to ether (30 mL) suspended with lithium aluminum hydride (1.61 g, 42.3 mmol). The solution was heated at 50°C for 4 h. The solution was washed with water, evaporated under reduced pressure and dried *in vacuo* for several hours to give 10.3 g of Ad0 as white crystals. The product was purified by repeated flush column chromatography. Ad0: ¹H NMR (CDCl₃) δ 1.66 (6H, dd, *J* = 14, 25 Hz adamantyl CH₂), 1.73 (6H, s, adamantyl CH₂), 2.09 (3H, s, adamantyl CH), 3.75 (2H, s, CH₂-NH), 5.20, 5.72 (2H, d, *J* = 11, 18 Hz, vinyl CH₂), 6.70 (1H, dd, *J* = 11, 18 Hz, vinyl CH), 7.31 (2H, d, *J* = 8 Hz, Ar CH (C-2, 6)), 7.36 (2H, d, *J* = 8 Hz, Ar CH (C-3, 5)). ¹³C NMR (CDCl₃) δ 29.6 (adamantyl C-3, 5, 7), 36.9 (adamantyl C-4, 6, 10), 42.9 (adamantyl C-1, 2, 8, 9), 44.9 (CH₂-NH), 113.4 (CH₂=CH), 126.3 (Ar C-3, 5), 128.6 (Ar C-2, 6), 136.2 (CH₂=CH), 136.8 (Ar, C-1, 4). IR (KBr, cm⁻¹) 3260, 3084, 3019, 2899, 2845, 1628, 1564, 1510, 1451, 1150, 992. *m/z* = 267.20. mp = 44.0°C.

N-(Tricyclo[3.3.1.1^{3,7}]decane-1-yl-methyl)4-vinylbenzylamine (Ad1)

The monomer of Ad1 was prepared in the same way as Ad0. A solution of 4-vinylbenzaldehyde (0.582 g, 4.405 mmol), 1-adamantanamine (0.800 g, 4.84 mmol), *t*-butylcatechol (1 mg), and anhydrous magnesium sulfate (1.59 g, 13.2 mmol) in benzene (15 mL) was heated for 24 h under reflux with azeotropic removal of water. After being cooled, the solution was washed with water, evaporated under reduced pressure and dried *in vacuo* for several hours to give the product of 1.16 g. A solution of this product of 1.16 g in ether (5 mL) was added dropwise at room temperature over 30 min under nitrogen, to ether (6 mL) suspended with lithium aluminum hydride (0.150 g, 3.96 mmol). The solution was heated at 45°C for 4 h. The solution was washed with water, evaporated under reduced pressure and dried *in vacuo* for several hours to give 0.93 g of Ad1 as white crystals. The product was purified by repeated flush column chromatography. Ad1: ¹H NMR (CDCl₃) δ 1.53 (6H, s, adamantyl CH₂), 1.67 (6H, dd, *J* = 12, 38 Hz, adamantyl CH₂), 1.96 (3H, s, adamantyl CH), 2.25 (2H, s, NH-CH₂-adamantyl), 3.80 (2H, s, Ar-CH₂-NH), 5.22, 5.73 (2H, d, *J* = 11, 18 Hz, vinyl CH₂), 6.71 (1H, dd, *J* = 11, 18 Hz, vinyl CH), 7.30 (2H, d, *J* = 8 Hz, Ar CH (C-2, 6)), 7.38 (2H, d, *J* = 8 Hz, Ar CH (C-3, 5)). ¹³C NMR (CDCl₃) δ 28.6 (adamantyl C-3, 5, 7), 37.3 (adamantyl C-4, 6, 10), 41.0 (adamantyl C-1, 2, 8, 9), 54.3 (NH-CH₂-adamantyl), 61.8 (Ar-CH₂-NH), 113.5 (CH₂=CH), 126.4 (Ar C-3, 5), 128.4 (Ar C-2, 6), 136.4 (CH₂=CH), 136.8 (Ar, C-1, 4). IR (KBr, cm⁻¹) 3068, 3038, 3016, 2901, 2849, 1630, 1510, 1456, 1360, 1140,

Table I. Radical polymerization of Ad0 and Ad1^a

Monomer	Initiator	Temperature	Conversion ^b	[η] ^c
		°C	%	
Ad0	AIBN	60	58	0.309
Ad0	AIBN	80	73	0.276
Ad0	ACHCN ^d	120	89	0.173
Ad0	<i>t</i> -BP ^e	120	88	0.095
Ad1	AIBN	60	0	—
Ad1	AIBN	80	74	0.287
Ad1	ACHCN	120	92 ^f	—
Ad1	<i>t</i> -BP	120	— ^g	—

^a Polymerized in bulk for 24 h under N₂. [I]₀ = 3 mol%. ^b Estimated by ¹H NMR. ^c Intrinsic viscosity. Solvent: benzene, at 25°C.

^d 1,1'-Azobis(cyclohexanecarbonitrile). ^e Di-*t*-butyl peroxide. ^f Partially gelled. ^g Crosslinked polymer.

1100, 895, 856, 826. *m/z* = 281.21. mp = 31.5°C.

Radical Polymerization of Ad0 by AIBN

Ad0 (300 mg, 1.12 mmol) and AIBN (5.5 mg, 0.0337 mmol) were placed in 10 mL flask with a three-way stopcock and degassed. Polymerization was carried out at a specified temperature under nitrogen atmosphere. The product was dissolved in 2 mL benzene, purified by repeated precipitations from benzene into methanol, and finally freeze-dried with benzene to give the product polymer.

The radical polymerization of Ad1 and copolymerization with styrene and with MMA was carried out the same as for the polymerization of Ad0.

RESULTS AND DISCUSSION

The radical polymerization of Ad0 and of Ad1 was performed by AIBN as an initiator, in bulk for 24 h under nitrogen. The results are shown in Table I. The polymerization was carried out at 60°C to give a white polymer from Ad0, although no polymer was obtained from Ad1. When polymerization was performed at 80°C, the polymers were obtained from both monomers. These polymers were soluble in common organic solvents except for hexane and alcohols. The resulting polymers were isolated and purified by repeated reprecipitation, to investigate the structures of the polymers. The IR spectra of poly(Ad0) and poly(Ad1) showed no absorption at 1630 cm⁻¹ from the vinyl groups. The absence of vinyl groups was also confirmed in ¹H NMR spectra of the polymers. Figures 1 and 2 show ¹H NMR spectra of Ad0, Ad1, and their polymers. Signals of the vinyl group were observed at 5.2, 5.7, and 6.7 ppm in the spectra of the monomers. These signals were not observed in the spectra of the polymers. In the spectra of poly(Ad0) and poly(Ad1), broad signals were observed at 0.6–2.3 ppm. These broad signals were attributed to methylene and methine protons of the polymer main chains. Signals were noted at 6.1–7.2, 3.5–3.8, and 1.7–2.1 ppm, due to aromatic, benzyl, and methylene and methine protons of the adamantane moiety. Conversion was estimated from the relative intensity of the benzyl protons based on the polymers and monomers. The benzyl protons of the monomers appeared as a sharp singlet signal at 3.8 ppm. Observation of the signals of the methylene

Figure 1. ^1H NMR spectra of Ad0 (upper) and poly(Ad0) (lower) (solvent: CDCl_3).

Figure 2. ^1H NMR spectra of Ad1 (upper) and poly(Ad1) (lower) (solvent: CDCl_3).

attached to the adamantyl moiety was made at 2.3 ppm, in the spectra of Ad1 and poly(Ad1). It was assumed that the polymerization proceeded at the vinyl group, and the relative integral intensity of the respective signals

Scheme 1.

Figure 3. TGA spectra of the poly(Ad0) (a) and the poly(Ad1) (b) obtained by polymerization at 80°C .

was in a good agreement with the theoretical one. It can be deduced that the adamantyl moieties did not participate the polymerization at all, and that the synthesis of the polymers with adamantane amino derivatives as pendant groups was attained (Scheme 1). When the polymerization was performed at 120°C by 1,1'-azobis(cyclohexane carbonitrile) as the initiator, a benzene-soluble polymer was obtained from Ad0, while a partially crosslinked polymer was generated from Ad1. The polymerization of Ad1 was carried out using di-*t*-butyl peroxide at 120°C to give a completely crosslinked polymer. This indicates that the crosslinking reaction more easily occurs in the polymerization of Ad1 than in that of Ad0. This can be accounted for by the fact that the methylene spacer attached to the adamantyl group diminishes steric hindrance of this group, at the benzyl position, so that crosslinkage easily occurs by coupling between benzyl radicals. Molecular weights and polydispersities of the resulting polymers could not be calculated by GPC, because the polymers were adsorbed in the polystyrene gel columns used with THF as an eluent. Therefore, the intrinsic viscosity of the polymers was determined with benzene as the solvent. It is clear that steric hindrance of the adamantyl group prevents the polymerization from proceeding. This is because poly(4-aminomethylstyrene) and poly(4-aminoethylstyrene) obtained by radical polymerization in bulk at 80°C had much higher viscosity than that of poly(Ad0) and poly(Ad1).¹⁰

The thermal stability of poly(Ad0) and poly(Ad1) was excellent based on TGA analysis. As seen in Figure 3, poly(Ad0) shows a 10% weight loss at 380°C , while

Figure 4. Time-conversion plots in the polymerization of Ad0 (●) and of Ad1 (▲). Polymerized in bulk at 80°C under N₂. [AIBN]₀ = 3 mol%.

Table II. Copolymerization of Ad and styrene^a

Monomer	Feed ratio		Conversion/%		Ratio in copolymer ^b		[η] ^d
	Ad	St	Ad ^b	St ^c	Ad	St	
Ad0	0.10	0.90	97	97	0.11	0.89	0.402
Ad0	0.20	0.80	94	95	0.20	0.82	0.446
Ad0	0.33	0.67	95	89	0.31	0.69	0.424
Ad0	0.50	0.50	77	91	0.45	0.55	0.395
Ad0	0.67	0.33	88	87	0.60	0.40	0.394
Ad0	0.80	0.20	93	88	0.77	0.23	0.295
Ad0	0.90	0.10	84	82	0.81	0.19	0.366
Ad1	0.10	0.90	98	97	0.08	0.92	0.421
Ad1	0.20	0.80	99	95	0.18	0.82	0.401
Ad1	0.33	0.67	96	90	0.28	0.72	0.434
Ad1	0.50	0.50	98	90	0.51	0.49	0.381
Ad1	0.67	0.33	88	79	0.41	0.59	0.323
Ad1	0.80	0.20	93	88	0.70	0.30	0.319
Ad1	0.90	0.10	86	80	0.79	0.21	0.263

^a Polymerized in bulk by AIBN at 80°C for 48 h. [AIBN]₀ = 3 mol%. ^b Estimated by ¹H NMR. ^c Calculated by GC. ^d Intrinsic viscosity. Solvent: benzene, at 25°C.

poly(Ad1) shows that at 420°C. It is clear that this high stability of poly(Ad1) is caused by the presence of the methylene group attached to the adamantyl moiety. This can be accounted for by the fact that the methylene spacer has the potential to reduce interactions between adamantyl moieties in the polymer.

Time-conversion plots in the polymerization of Ad0 and of Ad1 are shown in Figure 4. The polymerization was carried out by AIBN at 80°C. The conversion reached ca. 60% in 6 h, and then leveled off in both cases. The reactivity of Ad0 and Ad1 was thus not so high, and that this low reactivity is caused by the steric hindrance between the adamantyl groups attached to the growing chain end and to the monomer. One reason for the low reactivity may also be that the polymers have low solubility in monomers. This is because the polymers precipitated during the polymerization over ca. 50% of the conversion. It is expected that the conversions increase in the copolymerization with monomers in which poly(Ad0) and poly(Ad1) easily dissolved. The copolymerizations of Ad0 and of Ad1 with styrene were performed by AIBN in bulk at 80°C for 48 h. The results are summarized in Table II. As expected, the conversions of the monomers reached over 80% in all cases. The viscosity of the copolymer decreased as a result of increase in the monomer. The ratios of Ad0 and Ad1 to styrene units in the copolymers were estimated by ¹H

Figure 5. DSC spectra of the poly(Ad0-styrene) (a, Ad0/styrene = 45/55) and the poly(Ad1-styrene) (b, Ad1/St = 51/49).

Figure 6. ¹H NMR spectrum of the poly(Ad0-MMA) (solvent: CDCl₃).

NMR, and were in a good agreement with the feed ratios of the monomers. The random copolymers were obtained, because DSC analysis demonstrated that the copolymers had only one *T_g* between those of the homopolymers (Figure 5). The copolymer in which the ratio of Ad0 to styrene units was 45/55 showed *T_g* at 147°C, while the homopolymer of Ad0 had that at 165°C. The poly(Ad1-styrene) (Ad1/styrene = 51/49) also had one *T_g* at 119°C, and poly(Ad1) showed this at 125°C. Polystyrene obtained by polymerization with AIBN at 80°C showed *T_g* at 90°C. We deduced that the random copolymers were obtained.

The copolymerizations of monomers with MMA were carried out at feed ratios of the monomers to MMA of 10/90. The polymerization was performed by AIBN at 80°C for 1 h to give white polymers. The copolymers of Ad0 and of Ad1 had molecular weights of 7500 and 16200, and polydispersities of 1.77 and 2.36, respectively. These molecular weights and polydispersities were estimated by GPC calibrated with polystyrene standards. The copolymers obtained showed signals originating from the monomers and MMA, in the ¹H NMR spectra (Figure 6). The ratios of the monomers to MMA units in the copolymers were estimated as 14/86 for poly(Ad0-MMA), and to be 22/78 for poly(Ad1-MMA), based on the relative intensity of the aromatic protons of Ad0 and Ad1, to the protons observed at 3.4–3.9 ppm. These protons originate from the methylene of Ad0 and

Ad1 units and methoxy protons of MMA units. The DSC spectra demonstrated that the random copolymers were obtained, because the copolymers each had one T_g at 127°C for poly(Ad0-MMA), and at 118°C for poly(Ad1-MMA).

Study on bioactivity of poly(Ad0), poly(Ad1), and their copolymers is in progress.

CONCLUSION

The radical polymerization of Ad0 and of Ad1 proceeded at vinyl groups to give polymers with adamantane amino derivatives as pendant groups. The reactivity of the monomers was not so high. The polymerization of Ad0 gave polymers without cross-linked products, and the copolymers were completely soluble in several organic solvents. Remarkable effect of temperature was observed on the polymerization of Ad1. In particular, the polymerization of Ad1 at 120°C produced a crosslinked polymer. This indicates that crosslinking occurs more easily in the polymerization of Ad1 than Ad0, because the methylene spacer diminishes steric hindrance of the adamantyl group, at the benzyl position. This methylene spacer contributed to the thermal stability of poly(Ad1). The conversions of Ad0

and Ad1 leveled off in the polymerization in bulk at 80°C, due to low solubility of the polymers in the monomers. The conversions reached over 80% in copolymerization with styrene. The copolymerization gave the corresponding random copolymers in which the ratios of the monomers to styrene units were essentially the same as the feed ratios.

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