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Radical polymerization and antibacterial activity of copolymers based on *N*-1-adamantylmaleimide

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Summary

New copolymers were prepared by radical polymerization starting from N-1-adamantylmaleimide (AMI) and styrene (ST). The copolymerization of AMI with ST proceeded easily to give medium molecular weight of copolymers ($\overline{Mn} > 10^4$) in high yield. The poly(AMI-co-ST)s had high Tg (205-236 °C) and good thermal stability. Moreover, the poly(AMI-co-ST)s exhibited activity against the staphlococcus aureus ATCC 25923. The monomer reactivity ratios(r_1,r_2) in the copolymerizations of AMI with ST, and Alfrey-Price Q, e values for AMI were determined.

Introduction

N-Substituted maleimides(RMI) is an important reagent to improve the thermal stability of common vinyl polymers and resins (1). Thus, the copolymerization of RMI was described in many papers (2-7). These thermally stable polymaleimides are expected to be applied to various fields such as a deep-UV resistor (8), a thermoplastic matrix composite (9), controllable thermoplastic coatings (10), and electrodeposition coatings (11). However,there have been no reports on antibacterial activity related to the composition of the copolymer for RMI.

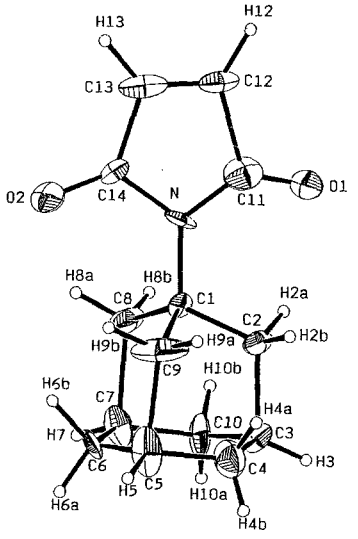

Figure 1. ORTEP diagram of AMI.

Many studies on the bactericidal and fungicidal actions of N-substituted maleimides have been reported (12,13). On the other hand, as the retention of drugs in the body can be increased by the use of macromolecular controls, some interest has been paid recently to the synthesis of pharmacologically active macromolecular compounds that are capable of a slow, controlled release of a drug by enzymatic degradation or hydrolysis (14,15). Incorporation of adamantyl groups into polyacrylate, polyester, polycarbonate, and polyurethane polymers has been reported to result in increased thermal stability and glass transition temperatures (16). Very recently, we

found radical polymerization of N-1-adamantylmaleimide (AMI) showed relatively slower than those for the other maleimides (17). The poly(N-1-adamantylmaleimide) (P(AMI)) showed good thermal stability and biological activities (17). In this article we describe the radical copolymerization of AMI with styrene (ST). The characteristic copolymerization behavior of AMI is discussed. In addition, the solubility, thermal properties, and antibacterial activities of the polymers were also investigated.

Experimental

Materials and copolymerization

AMI was synthesized by the reaction of maleic anhydride with 1-aminoadamantane, followed by dehydration with acetic anhydride and sodium acetate (17), as shown in Figure 1. The properties were as follows: mp:136-138 ℃ ; IR(KBr) 3050(=C-H), 1696(C=O), 1644(C=C), 700, 1360, 1746(imide) cm^{-1}; EIMS m/z(%) 231(M^+,100); ^1H NMR (300MHz,CD_3OD) δ 1.73(6H,d,H-4,6,10), 2.08(6H,m,H-3,5,7), 2.38(6H,d,H-2,8,9), 6.57(2H,s,CH=CH); ^{13}C NMR (75MHz,CD_3OD) δ 31.21(C-3,5,7), 37.28(C-4,6,10), 41.30(C-2,8,9), 60.49(C-1), 135.0(CH=CH), 173.82(C=O); Anal. Calcd for $C_{14}H_{17}NO_2$: C,72.73; H,7.36; N,6.06. Found: C,72.39; H,7.62; N,5.95. Crystal data:$C_{14}H_{17}NO_2$, colorless crystal, 0.10 × 0.38 × 0.50 mm, Orthorhombic C 2221 with a=7.065(3), b=10.905(3), c=30.956(8) Å with Dc=1.288 gcm^{-3} for Z=8, V=2385.1(14) Å, T=298 K, λ =0.7107 Å, μ =0.802 cm^{-1}, F(000)=992, intensity variation < 4%. 1-Aminoadamantane and maleic anhydride were purified by vacuum sublimation. 2,2'-Azobisisobutyronitrile(AIBN) was recrystallized three times from methanol and dried in vacuum. The ST and benzene were purified by the usual methods just before use.

The radical copolymerizations were done with AIBN as an initiator in benzene in a sealed glass tube at 60℃. After the required amounts of AMI monomer, comonomer(ST), AIBN, and benzene were placed in the tube, the tube was degassed under vacuum. The copolymerizations were accomplished while shaking this mixture, with the thermostat set at 60℃. After a certain period of time, the contents were poured from the tube into a large amount of methanol so as to precipitate to copolymer. The composition of the copolymer obtained was determined by nitrogen analysis.

Characterization

A Perkin-Elmer 240C elemental analyzer was used for elemental analysis. Qualitative solubility was determined using 0.01g of polymer in 1 ml of solvent. A Du Pont 9900 differential scanning calorimeter (DSC) and a Du Pont 9900 thermogravimetric analysis (TG) were employed to study the transition data and the thermal decomposition temperature. The wide-angle X-ray diffraction (WAXD) measurements were performed on a Philips PW 1730-10 X-ray diffractometer using CuKα radiation. Number-average molecular weight ($\overline{Mn}$) and Weight-average molecular weight ($\overline{Mw}$) were determined by gel permeation chromatography (GPC) on the basis of polystyrene calibration on an Applied Biosystem apparatus (eluent: THF). Light scattering measurements as well as differential refractometry measurments were performed at 25℃ and λ_0=633nm using an He-Ne ion laser (Photal Otsuka Model DLS-7000HL,DRM-1021).

Antibacterial activity test

Antibacterial activity was tested by agar diffusion method for three species of microorganisms. All the test materials were dissolved in dimethyl foramide (DMF) for the

Table 1. Copolymerization of AMI(M_1) with ST(M_2) in THF at 60°C[a]

Copolymer[b]	M_1 in monomer (mol %)	Polym.time (hours)	Yield[c] (%)	N[d] (%)	M_1 in copolymer (mol %)	$\overline{Mn}$[e] $\times 10^{-4}$	$\overline{Mw}/\overline{Mn}$
PAS-1	75.0	3	31.1	4.26	51.6	4.08	2.1
PAS-2	62.5	6	68.1	4.21	50.6	6.57	2.2
PAS-3	50.0	6	73.7	4.07	47.9	6.74	2.2
PAS-4	37.5	4	55.9	3.86	44.1	5.85	2.0
PAS-5	25.0	4	41.3	3.60	39.7	4.31	2.1
PAS-6	12.5	2	15.2	3.25	34.3	3.45	1.9

[a] [AIBN]=5×10^{-3} mol;[M_1]+[M_2]=1.0 mol l^{-1}. [b] Symbol of copolymer. [c] Yield of the copolymer insoluble in methanol. [d] Elemental analysis of copolymers. [e] By GPC.

staphylococcus aureus ATCC 25923 or escherichia coli ATCC 25922 test, and they were dissolved in dimethyl sulfoxide (DMSO) for the pseudomonas aeruginosa ATCC 9027 test. An agar plate containing each microorganism, on which lied a 8 mm paper disc (Toyo Roshi Kaisha,Ltd.) containing 30 μ g of samples was incubated for 18 hours at 37°C. The antibacterial activity was determined by the diameter of inhibitory zone. The paper disc was incubated with the corresponding solvent(DMF or DMSO) to provide a negative control, and ampicillin paper disc (10 μ g) was incubated to provide a positive control.

Result and Discussion

Radical Copolymerization

The copolymerizations of AMI (M_1) with ST (M_2) were performed in benzene at 60°C by using AIBN as the initiator. The polymeriations were homogeneous throughout. The results of the polymerizations are shown in Table 1. Although the homopolymerization of AMI was low conversion and $\overline{Mn}$ (For example, conversion of homopolymerization was 15.4 % with $\overline{Mn}=7.8 \times 10^3$ when [AMI]=1.0M in benzene at 60°C for 12 hours) (17), the copolymerization of AMI with ST proceeded rapidly as shown in Table 1. This reason for high reactivity of copolymerization for AMI may be due to the formation a charge transfer (CT) complex. Moreover, the $\overline{Mn}$ of copolymers were approximatly 10 times larger than that of homopolymer (Poly(AMI)). It is known that the copolymerization of RMI with ST is a practically alternating one (6). But, in the copolymerization of AMI with ST, the alternating character decreased. Table 1 also reveals that at low concentrations of AMI in the feed, the copolymers contain relatively more stryene. However, at above or equal 50 mol% of AMI in the feed the copolymer compositions are very nearly equilmolar, too. It is also seen from the data in Table 1 that the departure from equimolarity in the copolymers is more pronounced at low concentrations of AMI in the feed. This may be due to the fact that the reactivity of ST in radical polymerization is higher than that of AMI. This could be observed in the polymerization of N-(4-carboxyphenyl) maleimide (CPMI) with ST (5).

Composition of the copolymer obtained was calculated by nitrogen analysis as shown in Table 1. Monomer reactivity ratios, r_1 and r_2, calculated from the high-conversion method reported by Kelen et al. (18) as shown in Figure 2, and Alfrey-Price (19) Q-e values were as follows:r_1=0.014, r_2=0.1384, Q_1=0.98, e_1=1.70 in the AMI(M_1)-ST(M_2) system.

Considering that copolymer (Poly(AMI-co-ST)) containing a bulky and rigid adamantyl group, the backbone seems to have an appreciable rigid conformation. In order to estimate

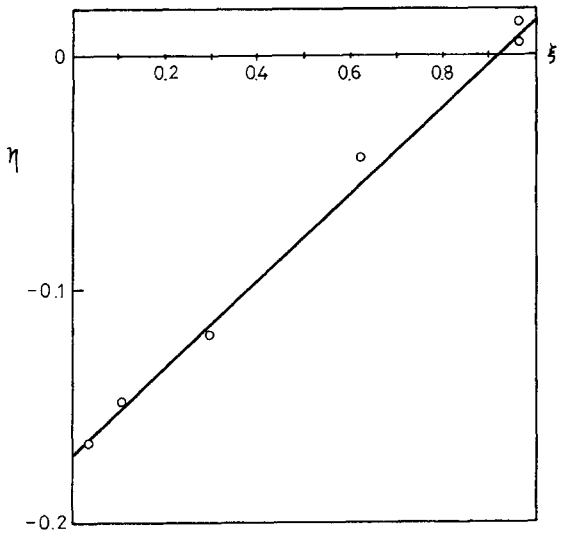

Figure 2. Kelen-Tüdös diagram for calculation of r_1(N-1-adamantylmaleimide) and r_2 (styrene), with $\alpha=(F_{min} \cdot F_{max})^{0.5}=0.814$.

the flexibility of the copolymer chain in solution, light scattering measurements were carried out. From a Zimm plot, as shown in Figure 3, we can determine the weight-average molecular weight ($\overline{M}w$), the second virial coefficient (A_2), and the Z-average root-mean-square radius of gyration (Rg). The results are listed in Table 2, in which the results reported about poly(tBMI) (20) and polystyrene (21) as typical semifexible and flexible polymers, respectively, are also contained. Table 2 indicated that the Rg of PAS-4 is larger than a random coil of polystyrene in benzene as a good solvent. It indicates directly the expanded configuration of less-flexible PAS-4 in solution. Table 2 also indicated that the Rg of PAS-4 is smaller than a less-flexible poly(tBMI) in THF. This may be expected due to the fact that PAS-4 contained flexible styrene comonomer.

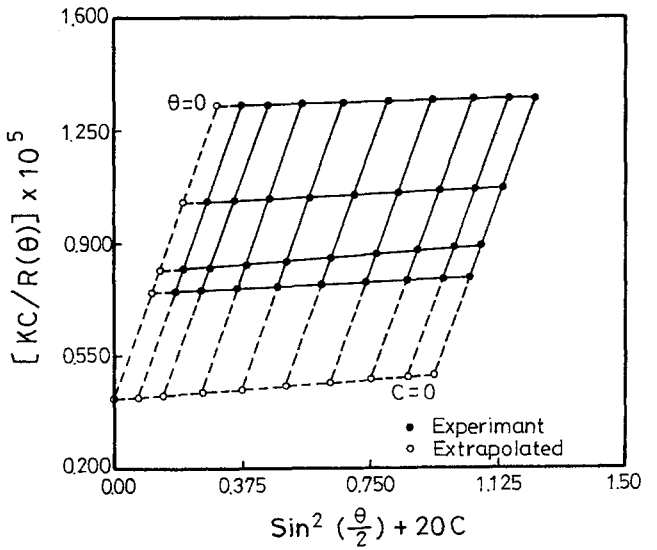

Figure 3. Zimm plot of PAS-4 in THF at 25°C with $(\partial n/\partial c)_T=0.152$ ml/g at 633 nm; K is the optical constant of the system, $R(\theta)$ is the Rayleigh ratio(θ), n is the refractive index of the solvent, and λ is the wavelength of incident light.

Table 2. Results for light scattering of PAS-4

Polymer	$\overline{Mw} \times 10^{-5}$	$A_2 \times 10^4$ (mL/g^2)	Rg (nm)	Reference
PAS-4	2.40	3.02	27.2	this paper
Poly(tBMI)[a]	2.92	2.44	34.5	25
Polystyrene[b]	3.42	4.12	24.0	26

[a] Poly(N-tert-Butylmaleimide) in tetrahydrofuran (THF). [b] in benzene at 30°C

Table 3. Sensitivity of Staphylococcus aureus ATCC 25923 to polymers[a]

	PS[b]	P(AMI)[c]	PAS-1	PAS-2	PAS-3	PAS-4	PAS-5	PAS-6
Zone diameter (mm)	0	11	11	11	11	11	11	11

[a] An agar plate containing Staphylococus aureus ATCC 25923 on which 8 mm paper disc containing 30 μg of samples was incubated for 18 hours at 37°C. [b] Polystyrene. [c] Poly(N-1-adamantylmaleimide).

Comparisons of weight-average molecular weight obtained by GPC and light scattering, namely, $\overline{Mw}$, agreement is not as good as desirable. This result is found in other literature (20).

Antibacterial Activity

The antibacterial activity was determined by the diameter of inhibitory zone for staphylococcus aureus ATCC 25923, as shown in Table 3. Table 3 indicated that Poly(N-1-adamantylmaleimide) and Poly(AMI-co-ST)s had similar activity against staphylococcus aureus ATCC 25923. Moreover, the poly(AMI-co-ST)s had a similar activity against staphylococcus aureus ATCC 25923. This may be attributed to the fact that the poly(AMI-co-ST)s had similar chemical structures. However, all of the test materials were

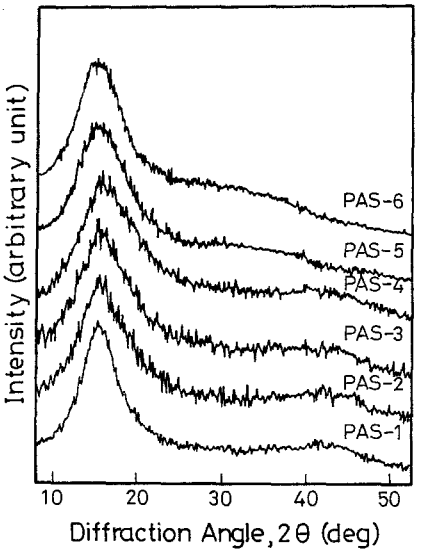

Figure 4. Wide-angle X-ray diffraction curves of poly(AMI-co-ST)s.

almost inactive in vitro against pseudomonas aeruginosa ATCC 9027 and escherichis coli ATCC 25922.

Characterization

All of poly(AMI-co-ST)s were colorless powder, soluble in benzene, toluene, chloroform, pyridine, nitrobenzene, 1,3-dioxane, and THF, and insoluble in methanol and acetone. Transparent and brittle films of poly(AMI-so-ST)s could be obtained by the casting of their benzene solution. An approach for structural characterization has been made by the X-ray method with the "as prepared" powders. The poly(AMI-co-ST)s had almost the same semicrystalline patterns, exhibiting crystalline peaks(2θ) at around 16°, as shown in Figure 4. In poly(AMI-co-ST)s had a less tendency to form crystal with increasing in ST content. The thermal behaviors of these polymers were evaluated by means of TG and DSC, and those results are summarized in Table 4. The representative DSC and TG curves for these polymers are shown in Figure 5. Table 4 indicates that the copolymers had high Tg and good thermal stability. Their temperatures at 5% weight loss range from 365 to 389°C in nitrogen. The glass-transition temperatures of the copolymers were found to be 205-236°C by DSC. In copolymers the glass transition temperature increases markedly with increasing in AMI content.

Table 4. Thermal properties of copolymers

Polymer	Tg[a] (°C)	T5[b] (°C)	Tmax[c] (°C)	Residue at 600°C (%)
PAS-1	—[d]	389	476	2.5
PAS-2	236	386	471	2.5
PAS-3	236	387	473	2.5
PAS-4	214	376	472	2.5
PAS-5	210	373	470	2.0
PAS-6	205	365	463	1.5

[a] Glass transition temperatures measured by DSC at a heating rate of 20°C/min.

[b] Temperatures at which 5% weight loss recorded by TG at a heating of 20°C/min.

[c] Maximum decomposition temperatures recorded by TG. [d] not be found.

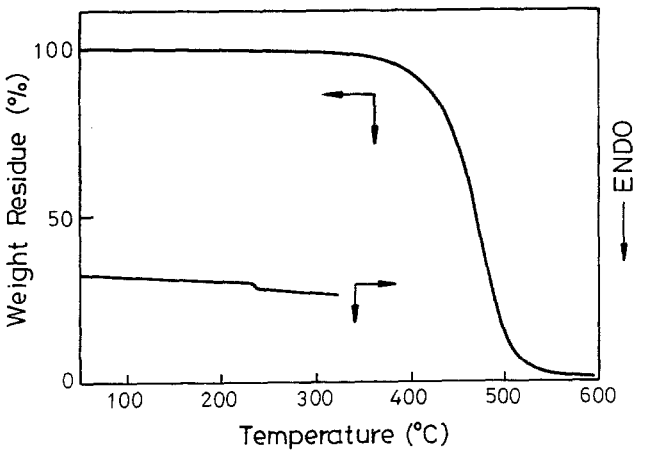

Figure 5. DSC and TG curves for PAS-2 at a heating rate of 20°C /min in nitrogen.

Conclusion

The copolymerization of AMI with ST proceeded easily to give medium molecular weight copolymer ($\overline{Mn} > 10^4$) in high yields. The poly(AMI-co-ST)s had high Tg (205-236°C) and good thermal stability. Moreover, the poly(AMI-co-ST)s had similar activity against staphlococcus aureus ATCC 25923. The results from the light scattering measurement indicate that the expanded configuration of poly(AMI-co-ST)s showed in THF solvent. At above or equal 50 mol% of AMI in the feed the copolymer compositions are very nearly equimolar. However, the departure from equimolarity in the copolymers is more pronounced at low concentrations of AMI in the feed. The monomer reactivity ratios (r_1,r_2) in the polymerization of AMI(M_1) with ST(M_2) and Alfrey-Price Q,e values were determined as r_1=0.014, r_2=0.1384, Q_1=0.98, e_1=1.70.

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