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Synthesis and Polymerization of (S)-4-Methyl-2-N,N-dimethylaminopentyl Methacrylate

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ABSTRACT

(S)-4-Methyl-2-N,N-dimethylaminopentyl methacrylate (DMAPM) was synthesized from the reaction of N,N-dimethyl-L-leucinol with methacryl chloride, and its radical polymerization was investigated. It was found that DMAPM readily polymerized by α,α' -azobisisobutyronitrile (AIBN) as an initiator to give poly-DMAPM. The copolymerization of DMAPM(M_1) with styrene(M_2) was also studied in various solvents with AIBN as an initiator at 60°C. From the result obtained in benzene, Q and e values of DMAPM were determined to be 0.64 and -0.04, respectively. Specific rotations of the copolymers of DMAPM with styrene were not proportional to the weight percent of the DMAPM unit incorporated, but the observed relation gave a downward curve. The copolymerizations of DMAPM with α,β -disubstituted monomers such as maleic acid, maleimide, and N-phenylmaleimide were carried out in order to induce asymmetric center in the polymer chain. After hydrolysis of the copolymers obtained, the hydrolyzed polymers were found

to be optically active, suggesting an induction of asymmetric center into the polymer chain.

INTRODUCTION

Many studies have been reported on synthesis and reaction of optically active polymers derived from amino acids. The amino group in most of such polymers was protected by acylation. If the amino group is contained without acylation in polymer, such a polymer is expected to interact with many compounds through hydrogen bonding or charge transfer, and hence interestingly, to catalyze various reactions. From these viewpoints, synthesis of (S)-4-methyl-2-N,N-dimethylaminopentyl methacrylate (DMAPM) was attempted. Similar optically active methacrylates containing L-ephedrine [1] and quinine [2] were synthesized and homopolymerized by other workers.

The present paper deals with radical polymerization of DMAPM and induction of an asymmetric center into the polymer chain of copolymers from copolymerization of DMAPM with α,β -disubstituted monomers.

EXPERIMENTAL

Synthesis of DMAPM

N,N-Dimethylamino-L-leucine was synthesized according to the method of Ikutani [3]. The required amounts of L-leucine, silk-palladium catalyst [4], 37% aqueous formaldehyde, and water were placed in an autoclave which was then filled with hydrogen. The mixture was reacted at about 50°C until no more hydrogen was absorbed. N,N-Dimethylamino-L-leucine was obtained in 70% yield.

A 23-g portion of N,N-dimethylamino-L-leucine was added at 0°C to 100 ml tetrahydrofuran containing a dispersion of 6.2 g lithium aluminum hydride (LiAlH_4) with stirring. This process was exothermic. After cooling, this solution was further heated at about 50°C for 3 hr and then cooled to room temperature. To consume unreacted LiAlH_4 , a large amount of diethyl ether containing a small quantity of water was added in the solution. After filtration of this solution, the filtrate was evaporated and then distilled under reduced pressure. A yield of 20.2 g of N,N-dimethylamino-L-leucinol was obtained (96%); bp 62°C/2.5 Torr; $[\alpha]_D = +49.0^\circ$ ($c = 2.68$, chloroform), 24.1° ($c = 3.69$, benzene).

A solution of methacryl chloride (7 ml) in 10 ml of chloroform

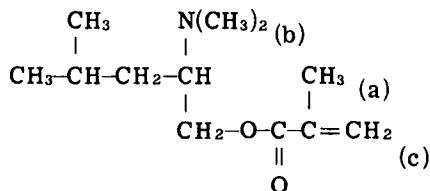
was added dropwise to a stirred solution of 10.1 g of *N,N*-dimethyl-amino-*L*-leucinol in 20 ml of chloroform at 0°C. This mixture was allowed to stand overnight in the dark. After reaction, the salt of DMAPM with hydrochloric acid was neutralized by adding slowly a saturated aqueous solution of sodium bicarbonate. The chloroform phase of this mixture was separated and dried over sodium sulfate. After filtration, the filtrate was evaporated and distilled under reduced pressure, yielding 9.5 g of free DMAPM (64%); bp 84°C/1.5 Torr; $n_D^{20} = 1.4482$; $[\alpha]_D = +10.7^\circ$ ($c = 2.79$, methanol), $+6.9^\circ$ ($c = 2.69$, ethanol), -2.1° ($c = 4.48$, benzene), -5.0° ($c = 2.95$, dioxane), -2.8° ($c = 2.76$, acetonitrile).

ANALYSIS. Calcd for DMAPM ($C_{12}H_{23}NO_2$): C, 67.57%; H, 10.87%; N, 6.57%. Found: C, 66.86%; H, 10.89%; N, 6.50%.

The picrate of DMAPM was also prepared and recrystallized three times from ethanol; mp 109.5°C.

ANALYSIS. Calcd for DMAPM picrate ($C_{18}H_{26}N_4O_9$): C, 48.87%; H, 5.92%; N, 12.66%. Found: C, 48.79%; H, 5.85%; N, 12.60%.

DMAPM obtained was also identified from IR and NMR spectra. The IR showed bands of 1720 cm^{-1} (C=O), 1630 cm^{-1} (C=C). NMR (CCl_4) showed H_a 2.0 ppm, H_b 2.3 ppm, H_c 5.5-6.1 ppm.



DMAPM

Other Materials

Vinyl monomers used as comonomers were purified by ordinary methods. The other reagents were used after purification.

Polymerizations

All polymerizations and copolymerizations were carried out at 60°C in sealed tubes which were degassed by the usual freezing and thawing technique.

Radical polymerization of DMAPM was carried out in benzene and in dioxane with α, α' -azobisisobutyronitrile (AIBN) as an initiator.

The resulting polymer was isolated by pouring the reaction mixture into a large amount of water-methanol mixture. Then the polymer obtained was purified by reprecipitation from methanol-water. The thermal polymerization was also carried out in bulk, in benzene, and in ethanol.

Copolymerizations of DMAPM with maleic acid or citraconic acid were carried out in acetone or in ethanol with AIBN. After polymerization, the copolymers formed were isolated by pouring the polymerization mixture into a large amount of acetone. Copolymerizations of DMAPM with maleimide and *N*-phenylmaleimide were also carried out in dioxane with AIBN. After a given time the copolymers were obtained by pouring the reaction mixture into diethyl ether. The copolymers were then purified by precipitation from the methanol-diethyl ether system.

Hydrolysis of Polymers

Hydrolysis was performed by dissolving the polymers in concentrated H_2SO_4 for two weeks at room temperature. Thereafter the solution was added to a large quantity of ice water to isolate the hydrolyzed polymers. The purification of the polymer was done by pouring its methanol solution into a large amount of diethyl ether.

Characterization of Polymers

The composition of resulting copolymers was determined from their nitrogen or carbon elemental analyses. The specific rotation ($[\alpha]_D$) of the copolymers was measured by using a JASCO-DIP-4 polarimeter at room temperature.

RESULTS AND DISCUSSION

Homopolymerization of DMAPM

The homopolymerization of DMAPM was carried out under various conditions. The results observed are shown in Table 1, from which homopolymer of DMAPM was found to be obtained in good yields under these conditions.

There has been interest in the reactivity of dimethylaminoethyl methacrylate (DMAEM) in which the dimethylamino group may interact with the double bond or carbonyl group. Shalati found that the polymerization of DMAEM is thermally initiated at a moderate rate in the

From this, the thermal polymerization of DMAPM was also attempted at 60°C. As can be seen from Table 1, polymer was obtained in 4.6% yield in bulk in 15 hr and 6.6% yield in benzene in 10 hr, but only a trace of polymer was obtained in ethanol. The IR spectrum of the resulting poly-DMAPM showed no absorption due to the vinyl group.

The specific rotation of poly-DMAPM formed was measured in various solvents. The result obtained in benzene is given in Table 1. The values of $[\alpha]_D$ of polymer 1 in other solvents were: +6.0 ($c = 1.03$, in acetic acid), -3.5 ($c = 1.36$, in dioxane), +2.2 ($c = 1.06$, in benzene), -3.9 ($c = 0.88$, tetrahydrofuran), -0.7 ($c = 0.84$, in chloroform).

Thus the value of the specific rotation was found to depend on the solvent used. A large positive value observed in acetic acid, a protic solvent, is considered to be derived from the hydrogen bonding between the dimethylamino group of the polymer and the carboxyl group of the acid. It is interesting that the specific rotation varied greatly even in two aprotic solvents, benzene and dioxane.

Thus the variation in the specific rotation of poly-DMAPM was investigated in benzene-dioxane mixture solvent. Figure 1 shows the results obtained. An inflection point was observed at 55 vol % of dioxane. The cause for the variation of the specific rotation in benzene-dioxane mixture solvent may be transformation in conformation of poly-DMAPM or to change in electrostatic interaction of poly-DMAPM with solvents. As stated later, the former cause seems to be more reasonable.

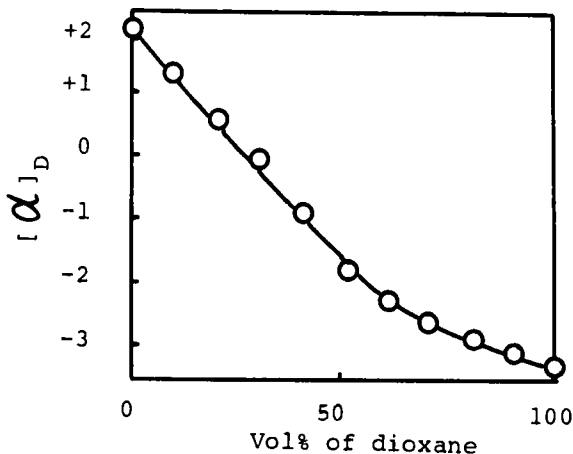


FIG. 1. Solvent effect on $[\alpha]_D$ of poly-DMAPM at room temperature.

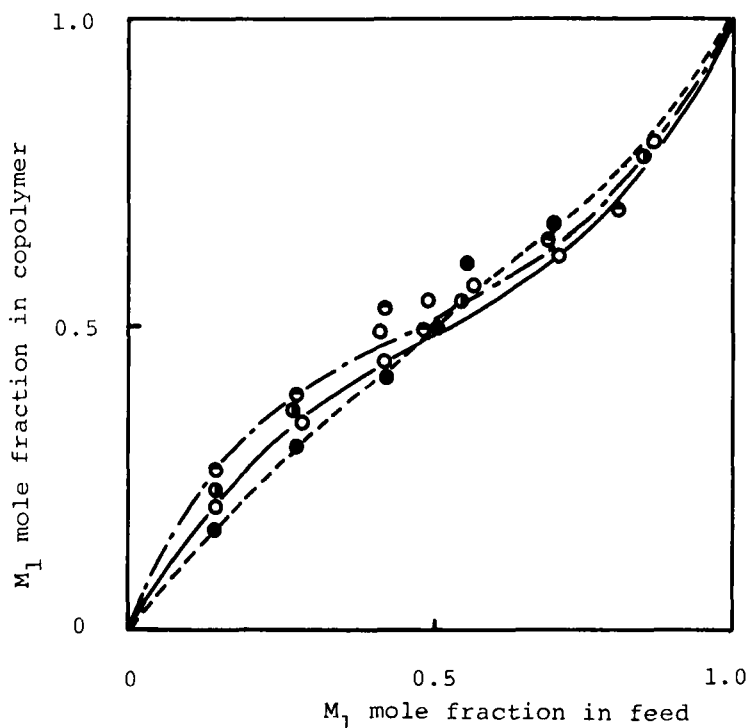


FIG. 2. Copolymerization of DMAPM (M_1) with styrene (M_2) with AIBN at 60°C in various solvents: (○) dioxane; (◐) ethanol; (○) acetonitrile; (●) benzene.

Copolymerization of DMAPM with Styrene

Since the optical activities of the monomer and its polymer were found to change with the solvent used, it is expected that the reactivities of the monomer and the polymer radical may depend on the solvents. Thus, the effect of solvent on the reactivity of the monomer was investigated by copolymerization with styrene in various solvents.

The copolymerization of DMAPM(M_1) with styrene(M_2) was carried out in benzene, dioxane, acetonitrile, and ethanol with AIBN as an initiator at 60°C . The composition of copolymer was determined from carbon content by elementary analysis. The resulting composition curves are shown in Fig. 2, from which the monomer reactivity ratio was determined as shown in Table 2. Moreover, Q_1 and e_1

TABLE 2. Copolymerization Parameters for Radical Copolymerization of DMAPM(M_1) with Styrene(M_2)

Solvent	r_1	r_2	Q_1	e_1
Benzene	0.70	0.80	0.68	-0.04
Dioxane	0.44	0.53	0.72	0.41
Ethanol	0.50	0.40	0.93	0.47
Acetonitrile	0.40	0.40	0.85	0.55
MMA (benzene)	0.46	0.52	0.74	0.40

values are also shown in Table 2, together with those for methyl methacrylate (MMA) in benzene for comparison.

It is clear that the reactivity of DMAPM toward the polystyryl radical depends on the solvents used. Q_1 and e_1 values in dioxane are similar to those of MMA and are somewhat smaller than those in ethanol and in acetonitrile.

It is noted that the e_1 value observed in benzene is much less than that of MMA. As pointed out above, the dimethylamino group in DMAPM can interact with a vinyl or carbonyl group in the monomer and its polymer radical. This interaction might cause the DMAPM to show a different copolymerization behavior from MMA, especially in benzene, an aprotic nonpolar solvent, in which this interaction may operate more strongly.

Chow [6] has reported a considerably lower e value of 0.25 for 2-(1-aziridinyl)ethyl methacrylate from copolymerization with styrene (St) in benzene, which has a very similar structure to DMAPM.

Furthermore, the specific rotations of DMAPM-St copolymer formed in various solvents were measured in benzene. The results obtained are shown in Fig. 3. It is well known that the specific rotation of copolymer of an optically active monomer with a monosubstituted monomer such as St is nearly proportional to the content of the optically active monomer incorporated [7]. As shown in Fig. 3, it was found that the optical activity of DMAPM-St copolymer was not proportional to the content of the DMAPM unit in copolymer, but the observed relation showed downward curves. Further, the curves shown in Fig. 4 were obtained when $[\alpha]_D$ values per DMAPM unit were plotted against weight percent of DMAPM in copolymer. From the observed relation, where $[\alpha]_D$ values per DMAPM unit decreased with decreasing DMAPM content, extrapolated values of $[\alpha]_D$ per DMAPM unit were obtained as -6 to -9°.

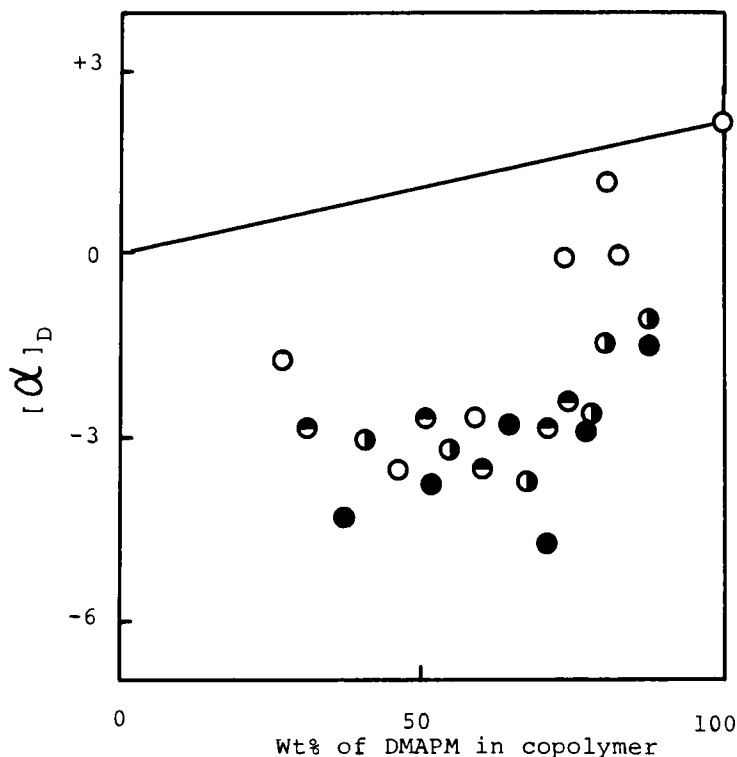


FIG. 3. $[\alpha]_D$ of DMAPM-styrene copolymer in benzene at room temperature: (○) benzene; (◐) ethanol; (◑) dioxane; (●) acetonitrile.

On the other hand, model compounds I and II were synthesized, and the specific rotations of these compounds in benzene were determined. In all cases, R is $-\text{CH}_2\text{CH}(\text{CH}_3)_2$.

The specific rotations of these model compounds are considerably different from that of poly-DMAPM. This difference might be due to the asymmetry of the conformation of poly-DMAPM. Further, the specific rotation of model compound II is near the extrapolated values obtained from Fig. 4. These results may be interpreted by considering that as the content of St in copolymer increases, the contribution of the polymer conformation to the specific rotation decreases due to isolation of the DMAPM unit.

Moreover, as shown in Fig. 4, the contribution from the conformation in DMAPM-St copolymer obtained in benzene to the specific

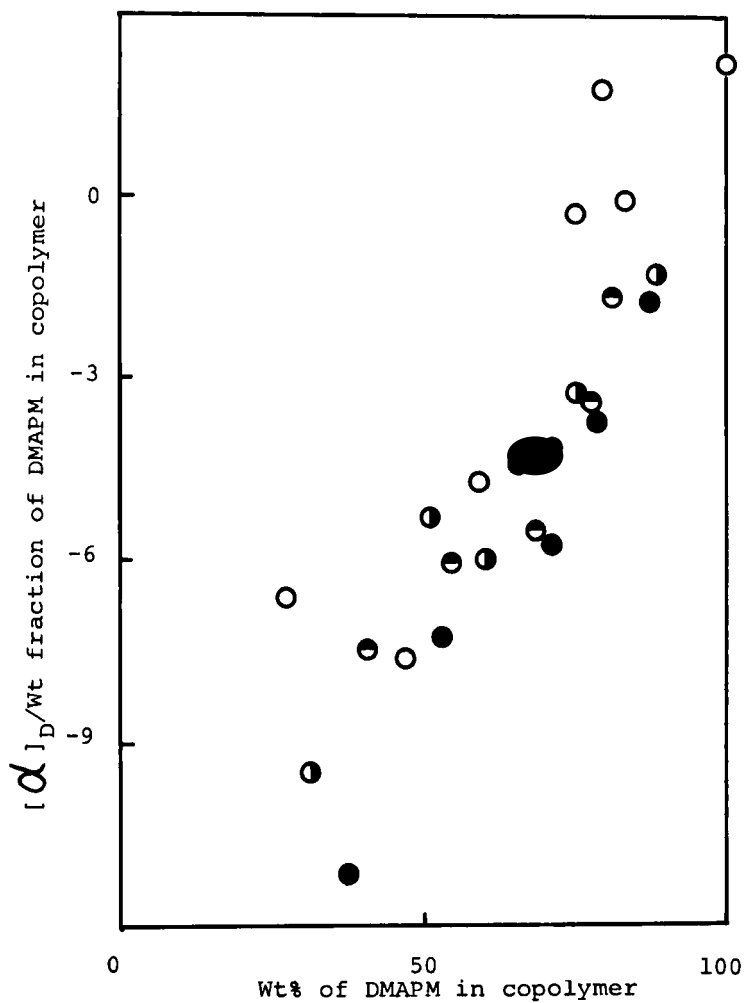
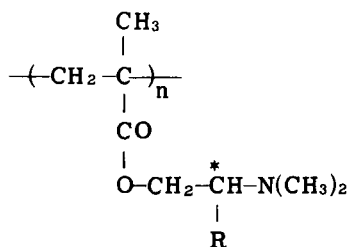
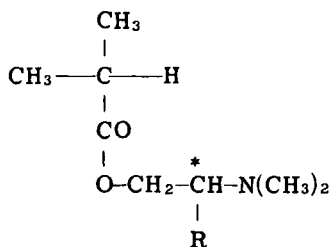


FIG. 4. Relationship between $[\alpha]_D$ per DMAPM unit and wt % of DMAPM in DMAPM-styrene copolymer: (○) benzene; (◐) ethanol; (◑) dioxane; (●) acetonitrile.



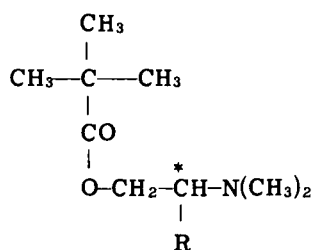
poly-DMAPM

$$[\alpha]_D = +2.2^\circ \quad (c = 1.06)$$



model I

$$[\alpha]_D = -2.1^\circ \quad (c = 5.35)$$



model II

$$[\alpha]_D = -7.1 \quad (c = 2.95)$$

rotation seems larger than that obtained in the other solvents. This is compatible with the solvent effect on the copolymerization of DMAPM with St.

Copolymerization of DMAPM with α, β -Disubstituted Monomer and Hydrolysis of the Resulting Copolymer

When copolymerizations of DMAPM with α, β -disubstituted monomers, which can interact with the dimethylamino group bonding to the asymmetric center, are carried out, an asymmetric center is expected to be induced in the polymer chain formed.

Since the dimethylamino group can interact with the carboxyl group through a hydrogen bond, the copolymerization of DMAPM with maleic acid (MA) or citraconic acid (CA) was attempted. DMAPM was also copolymerized with maleimide (MIm) and N-phenylmaleimide (NPMIm), strong electron-accepting monomers.

To clarify the interaction of DMAPM with MA, the effect of MA on

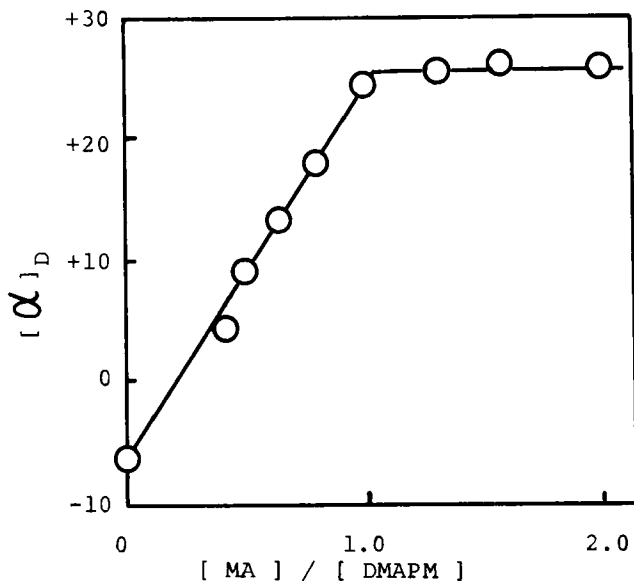
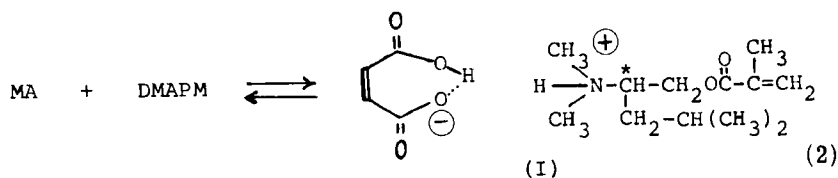


FIG. 5. Effect of maleic acid (MA) on $[\alpha]_D$ of DMAPM ($c = 2.01$ g/dl) in acetone at room temperature.

the specific rotation of DMAPM was investigated in acetone. Figure 5 shows the result observed. As the content of MA in the solution of DMAPM increased, the specific rotation increased linearly. However, the specific rotation varied no more when the molar ratio of MA to DMAPM became greater than unity, probably indicating the formation of their 1:1 salt [Eq. (2)].



It is considered that the equilibrium of Eq. (2) tends largely to the formation of the salt.

When DMAPM was added to the solution of MA or CA in acetone, a white precipitate formed rapidly and then dissolved gradually on shaking, which indicates also the formation of the salt.

TABLE 3. Copolymerization of DMAPM(M_1) with Maleic Acid or Citraconic Acid (M_2) at 60°C

Solvent	$M_1:M_2$ in feed	[AIBN] 10^2 (mole/ liter)	Time (hr)	Conversion (%)	$M_1:M_2$ in copolymer
Acetone	1:1	1.52	10	90.5	1:1.6
Acetone	1:1.5	1.71	11	82.5	1:1.9
Acetone	1:2	1.64	17	50.6	1:1.7
Acetone	2:1	1.61	10	79.0	1:1.9
Ethanol	1:2	1.50	10	67.0	1:1.8
Water	1:1.5	7.31 ^a	17	45.5	-
Acetone ^b	1:1	2.50	10	43.0	1:2.0

^aInitiator: KPS.

^bCitraconic acid was used.

Table 3 shows the results obtained in the copolymerization of DMAPM with MA and CA with AIBN at 60°C. In the copolymerization of DMAPM with MA, copolymer formed precipitated from the polymerization system when the concentration of DMAPM was higher than that of MA. The copolymerization of DMAPM with CA proceeded in a similar manner.

As stated above, DMAPM was easily homopolymerized with AIBN, while MA or CA does not undergo homopolymerization. It was found, however, that the molar ratios of MA or CA to DMAPM in copolymers were somewhat more than unity in all cases. This seems to come from a difficulty in elementary analysis of the low molecular weight polymer carrying many carboxyl groups and also from copolymerization of the salt with MA or CA, in which the acid of the salt remains as a pendant without reaction.

Hydrolysis of copolymers obtained was attempted to ascertain whether an asymmetric center in the polymer chain was induced. Results obtained are listed in Table 4.

The specific rotation of poly-DMAPM was +6.0° ($c = 1.03$, in acetic acid) before hydrolysis and 0° ($c = 0.68$, in methanol) after hydrolysis. The nitrogen content of the hydrolyzed poly-DMAPM was very small, though not zero. This is considered to result from a small amount of the unreacted side chain or unhydrolyzed fragments of AIBN in the polymer. Moreover, the IR spectrum of poly-MMA formed by methylation of the

TABLE 4. Hydrolysis of DMAPM-Maleic Acid and DMAPM-Citraconic Acid Copolymers

Solvent	M ₁ :M ₂ in feed	Before hydrolysis		After hydrolysis		
		$[\alpha]_D^a$	c (g/dl)	$[\alpha]_D^b$	c (g/dl)	Nitrogen content (%)
Acetone	1:1	+16.2	1.02	+3.2	0.63	0.53
Acetone	1:1.5	+15.3	0.93	+4.4	1.13	0.84
Acetone	1:2	+15.1	1.33	+2.1	0.93	0.41
Acetone	2:1	+15.8	0.95	+3.5	1.11	0.72
Ethanol	1:2	+14.0	1.14	+4.1	0.82	0.53
Water	1:1.5	-	-	+1.6	0.88	0.46
Acetone ^c	1:1	+9.2	1.22	0	0.27	0.18
Benzene ^d	-	+6.0	1.03	0	0.68	0.67

^aDetermined in acetic acid.

^bDetermined in methanol.

^cDMAPM-citraconic acid copolymer.

^dPoly-DMAPM.

hydrolyzed polymer with diazomethane was the same as that of ordinary poly-MMA. These results indicate that hydrolysis of polymer proceeded almost completely.

DMAPM-MA copolymers obtained under various conditions were found to show specific rotations in acetic acid positively greater than that of poly-DMAPM, suggesting that induction of an asymmetric center occurred in the chain of these copolymers. In fact, the specific rotations of the hydrolyzed copolymers showed positive values in methanol, indicating that these copolymers contain an asymmetric center in the polymer chain.

On the other hand, the specific rotation of DMAPM-CA copolymer in acetic acid was not so large as that of DMAPM-MA copolymer, and it became zero in methanol after hydrolysis.

The copolymerizations of DMAPM with MIm and NPIM were carried out. Table 5 shows the results obtained.

The polymerization mixture of DMAPM with MIm in dioxane was initially pale yellow and turned red as the polymerization proceeded. A portion of copolymer precipitated from the system. The

TABLE 5. Copolymerization of DMAPM(M_1) with Maleimide or N-Phenylmaleimide (M_2) in Dioxane at 60°C for 10 hr

M_1 ^a	$M_1:M_2$ in feed	[AIBN] $\times 10^2$ (mole/liter)	Conversion (%)	$[\alpha]_D$	
				Before hydrolysis	After hydrolysis
MIm	1:1	1.00	76	+12.8 ^b	+5.0 ^b
NPMIm	1:1	5.08	73	-	+9.7 ^c

^a Monomers: MIm = maleimide; NPMIm = N-phenylmaleimide.

^b In methanol.

^c In a 1:1 acetone-methanol mixture.

specific rotation of DMAPM-MIm copolymer obtained was +12.8° ($c = 0.85$, in methanol) before hydrolysis and +5.0 ($c = 0.76$, in methanol) after hydrolysis. From this result, it is expected that an asymmetric center was also induced in this copolymer chain.

In the copolymerization of DMAPM with NPMIm in dioxane, the polymerization mixture initially showed a yellow color due to NPMIm, and then it changed to a red color. As the polymerization proceeded, DMAPM-NPMIm copolymer precipitated. Although the specific rotation of copolymer could not be measured owing to its strong red coloration, the hydrolyzed copolymer showed a specific rotation of +9.7 ($c = 0.83$) in a 1:1 acetone-methanol mixed solution, suggesting asymmetric induction into this copolymer. However, since the imide groups in these copolymers were difficult to hydrolyze, complete hydrolysis of the asymmetric side group of DMAPM could not be judged from nitrogen content of the hydrolyzed copolymers.

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