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Synthesis of Vinyl Polymer—Poly (α-Amino Acid) Block Copolymers by End-Reactive Oligomers

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ABSTRACT

In order to synthesize block copolymers consisting of segments having dissimilar properties, vinyl polymer - poly(α-amino acid) block copolymers were synthesized by two different methods. In the first method, the terminal amino groups of polysarcosine, poly(γ-benzyl L-glutamate), and poly(ε-benzyloxycarbonyl-L-lysine) were haloacetylated. The mixture of the terminally haloacetylated poly(α-amino acid) and styrene or methyl methacrylate was photoirradiated in the presence of $Mn_2(CO)_{10}$, or heated with $Mo(CO)_6$, yielding A-B-A-type block copolymers consisting of poly(α-amino cid)(the A component) and vinyl polymer(the B component). The characterization of block copolymers revealed that the thermally initiated polymerization of vinyl compounds by the trichloroacetyl poly(α-amino acid)/$Mo(CO)_6$ system was most suitable for the synthesis of vinyl polymer - poly(α-amino acid) block copolymers. In the second method, poly(methyl methacrylate) and polystyrene having a terminal amino group were synthesized by the radical polymerization in the presence of 2-mercaptoethylammonium chloride. Using these polymers having a terminal amino group as an initiator, the block polymerizations of γ-benzyl L-glutamate NCA and ε-benzyloxycarbonyl-L-lysine NCA were carried out, yielding A-B-type block copolymer. By eliminating the protecting groups of the side chains of poly(α-amino acid) segment, block copolymers such as poly(methyl methacrylate) with poly(L-glutamic acid) or poly(L-lysine) and polystyrene with poly(L-glutamic acid) and poly(L-lysine) were successfully synthesized.

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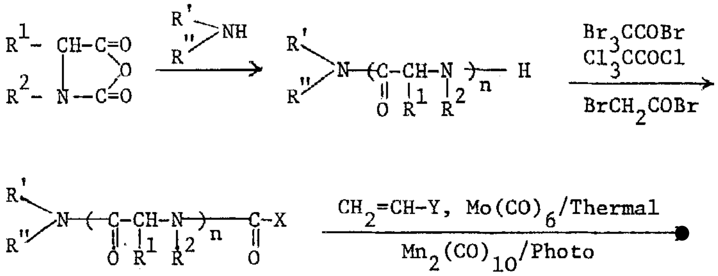
INTRODUCTION

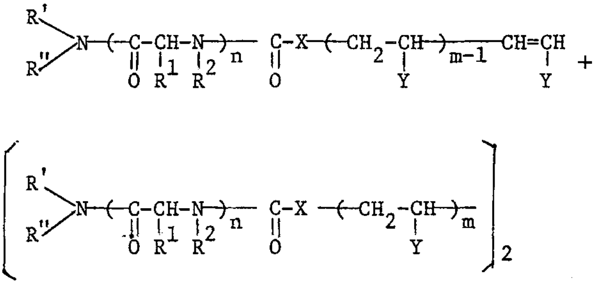
Block copolymers consisting of segments having dissimilar properties undergo a microphase separation in the solid phase and lead to the development of a domain structure [1]. Synthetic polymers having a biocompatibility, especially a blood compatibility, have been interested in recently. Among them, segmented polyetherurethanes, which have a suitable repetition of soft and hard segments, have attracted much attention as antithrombogenic elastic materials [2]. We have been interested in block copolymers consisting of α-amino acid and vinyl compound. It is expected that this type of block copolymer, which possesses the segments of dissimilar properties, may form a domain structure after the microphase separation and consequently have an antithrombogenicity. In order to investigate basic problems concerning the relationship between the structure of block copolymer and the antithrombogenicity, the nature of the α-amino acid and vinyl compound should be widely changed, and the degree of polymerization(DP) and its distribution of each segment should be regulated. For these purposes, we prepared vinyl polymer - poly(α-amino acid) block copolymers by two different mechanisms and characterized the resultant block copolymers.

BLOCK COPOLYMERIZATION OF VINYL COMPOUNDS BY THE TERMINAL-GROUP ACTIVATION OF POLY(α-AMINO ACID)S

General Scheme for the Synthesis of Block Copolymer

The synthetic scheme of block copolymers by the present method is described below.

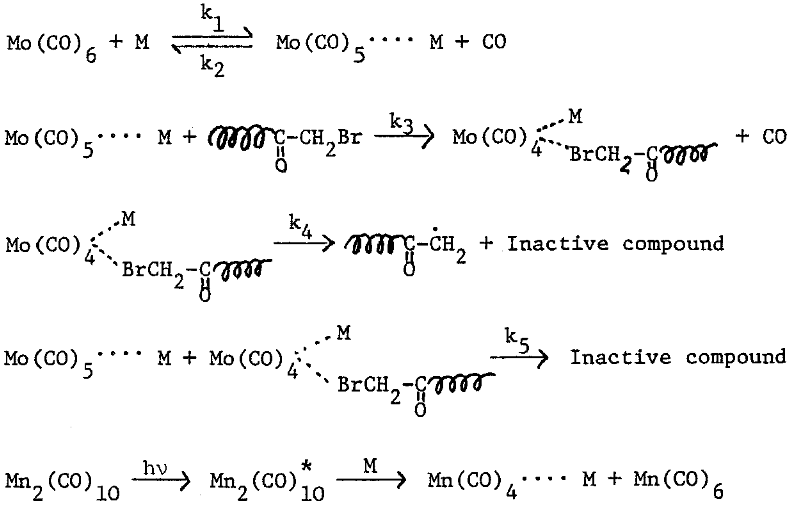




$$R'R''N\!\left(C(=O)-CH(R^1)-N(R^2)\right)_n-C(=O)-X\!\left(CH_2-CH(Y)\right)_{m-1}CH=CH(Y) \;+$$

$$\left[R'R''N\!\left(C(=O)-CH(R^1)-N(R^2)\right)_n-C(=O)-X\left(CH_2-CH(Y)\right)_m\right]_2$$

The N-carboxyanhydrides(NCA) of sarcosine(Sar), γ-benzyl L-glutamate[Glu(OBzl)], and ε-benzyloxycarbonyl-L-lysine[Lys(Z)] were polymerized by primary or secondary amine as an initiator. The terminal amino groups of these poly(α-amino acid)s were haloacetylated by bromoacetyl bromide, trichloroacetyl chloride, or tribromoacetyl bromide. The mixture of the terminally haloacetylated poly(α-amino acid) and styrene(ST) or methyl methacrylate(MMA) was photoirradiated in the presence of $Mn_2(CO)_{10}$, or heated with $Mo(CO)_6$. By this procedure a carbon radical is produced at the terminal of a poly(α-amino acid) chain, which initiates a radical polymerization of vinyl compound. The reaction mechanism is illustrated below [3]. A-B-A- or A-B-type block copolymer consisting of poly(α-amino acid) (the A component) and vinyl polymer(the B component) is produced according to the mechanism of termination reaction.



$$Mo(CO)_6 + M \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Mo(CO)_5\cdots M + CO$$

$$Mo(CO)_5\cdots M + \sim\sim C(=O)-CH_2Br \xrightarrow{k_3} Mo(CO)_4\begin{smallmatrix}\cdot\cdot M\\ \cdot\cdot BrCH_2-C(=O)\sim\sim\end{smallmatrix} + CO$$

$$Mo(CO)_4\begin{smallmatrix}\cdot\cdot M\\ \cdot\cdot BrCH_2-C(=O)\sim\sim\end{smallmatrix} \xrightarrow{k_4} \sim\sim C(=O)-\dot{C}H_2 + \text{Inactive compound}$$

$$Mo(CO)_5\cdots M + Mo(CO)_4\begin{smallmatrix}\cdot\cdot M\\ \cdot\cdot BrCH_2-C(=O)\sim\sim\end{smallmatrix} \xrightarrow{k_5} \text{Inactive compound}$$

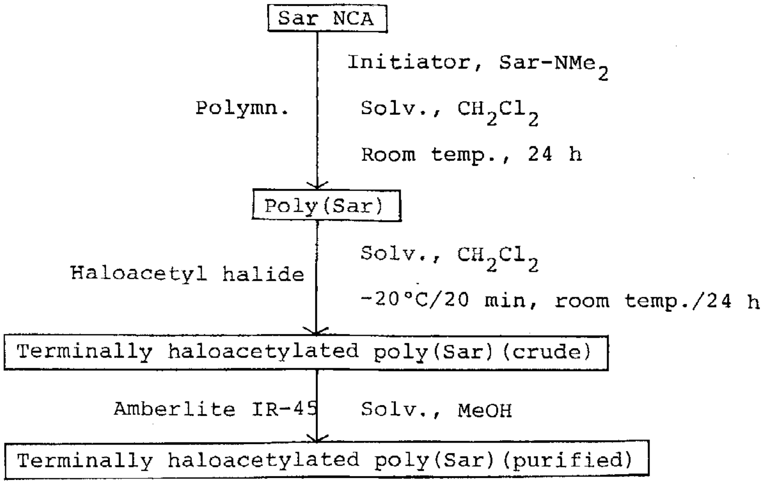
$$Mn_2(CO)_{10} \xrightarrow{h\nu} Mn_2(CO)_{10}^{*} \xrightarrow{M} Mn(CO)_4\cdots M + Mn(CO)_6$$

Synthesis of Terminally Haloaceytlated Poly(Sar)

The terminal amino groups of poly(Sar)s having different DPs were haloacetylated. The experimental procedure is described in SCHEME 1.

Poly(Sar)s having the number-average DP 10, 30, and 87 were bromoacetylated. The bromine content of the bromoacetyl poly(Sar) $[BrCH_2CO\text{-(}Sar)_n]$ was analyzed. For n = 10; 8.43%(calcd.), 8.38%(found): for n = 30; 3.37%(calcd.), 3.00%(found): for n = 87; 1.24%(calcd.), 1.86%(found). $BrCH_2CO\text{-(}Sar)_n$ having n 10 and 30 contained nearly the theoretical amount of bromine. However, that with n 87 contained more bromines than the theoretical amount. This disagreement may be explained partly by an incorrect estimation of DP and partly by a loss of high DP portions during the ion exchange.

Poly(Sar)s were also trihaloacetylated by the same procedures as in SCHEME 1. The halogen contents of the products were analyzed. The Cl content of $Cl_3CCO\text{-(}Sar)_n$: for n = 10; 11.16%(calcd.), 7.71% (found); for n = 32; 4.15%(calcd.), 3.37%(found); for n = 72; 1.97% (calcd.); 1.59%(found). The Br content of $Br_3CCO\text{-(}Sar)_n$: for n = 10;



SCHEME 1 Synthetic Procedure for Terminally Haloacetylated Polysarcosine

22.30%(calcd.), 14.06%(found); for n = 28; 10.21%(calcd.); 8.01%(found);for n = 74; 4.25%(calcd.), 3.06%(found). The content of terminal haloacetyl group was 60 - 80% of the theoretical value.

Synthesis of Terminally Haloacetylated Poly[Glu(OBzl)]

In a similar method as SCHEME 1, terminally trihaloacetylated poly[Glu(OBzl)]s were prepared. Sometimes, the reaction product was purified by reprecipitation with MeOH instead of ion exchange.

When Glu(OBzl) NCA was polymerized by n-$C_6H_{13}NH_2$ in CH_2Cl_2, the resultant poly[Glu(OBzl)]s had two peaks in the distribution curve of DP. The terminally trihaloacetylated poly[Glu(OBzl)]s were therefore double-peaked in the DP distribution. The halogen contents of the products were analyzed. The Cl content of Cl_3CCO+Glu-(OBzl)$]_n$: for n = 10; 3.80%(calcd.), 2.01%(found); for n = 30; 1.72%(calcd.), 0.86%(found); for n = 100; 1.11%(calcd.), 0.42%(found). The Br content of Br_3CCO+Glu(OBzl)$]_{100}$: 2.63%(calcd.) 0.87% (found). The content of terminal haloacetyl group was 30 - 50% of the theroetical value. It was lower than the case of poly(Sar) and decreased with increasing DP of poly[Glu(OBzl)].

When Glu(OBzl) NCA was polymerized by n-$C_6H_{13}NH_2$ in $AcNMe_2$, the resultant poly[Glu(OBzl)]s had a unimodal distribution of DP. These polymers were trichloroacetylated and the chlorine contents of the products Cl_3CCO+Glu(OBzl)$]_n$ were analyzed: for n = 10; 2.32% (calcd.), 0.96%(found); for n = 30, 1.46%(calcd.), 0.59%(found); for n = 100; 0.92%(calcd.), 0.29%(found). The content of terminal trichloroacetyl group was 30 - 40% of the theoretical value, which is not much different from those of double-peaked poly[Glu(OBzl)].

Synthesis of Terminally Trichloroacetylated Poly[Lys(Z)]

In a similar way as SCHEME 1, terminally trichloroacetylated poly[Lys(Z)]s were prepared. The polymerization of Lys(Z) NCA was carried out in $AcNMe_2$ by n-$C_6H_{13}NH_2$ or $H_2N(CH_2)_2NH_2$ as an initiator. In the former case, poly[Lys(Z)] carrying one trichloroacetyl group at one end may be produced, whereas in the latter case, poly[Lys(Z)] carrying two trichloroacetyl groups at both ends may be produced. The reaction product was purified by reprecipitation with water.

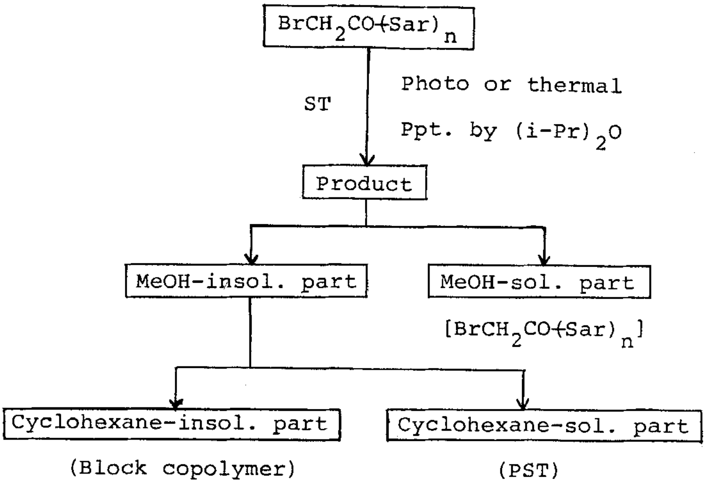
The chlorine contents of $Cl_3CCO\text{+}Lys(Z)]_n$ were anlyzed: for n = 10; 3.72%(calcd.), 1.47%(found); for n = 30; 1.31%(calcd.), 0.79% (found); for n = 100; 0.90%(calcd.), 0.28%(found). The chlorine contents of $Cl_3CCO\text{+}Lys(Z)]_nCOCCl_3$ were analyzed: for n = 20; 3.81%(calcd.), 1.77%(found); for n = 60; 1.33%(calcd.), 0.76%(found); for n = 100; 0.80%(calcd.), 0.50%(found). The content of terminal trichloroacetyl group was 40 - 70% of the theoretical value, which is intermediate between poly(Sar) and poly[Glu(OBzl)].

Synthesis of Poly(Sar)/PST Block Copolymer

Terminally haloacetylated poly(Sar) and metal carbonyls were used as initiators for the block copolymerizations by photoirradiation or heating. The experimental procedures using $BrCH_2CO\text{(}Sar)_n$ as an initiator are described in SCHEME 2.

The molecular weight(MW) of the block copolymer produced was determined by gel-permeation chromatography(g.p.c.) or calculated from the intrinsic viscosity [η], which was measured on the 2-butanone solution at 25°C, by using an equation [4], $[\eta] = 3.9\times10^{-4}\ MW^{0.58}$. The MW of poly(Sar) segment in the block copolymer was calculated from the MW and the nitrogen content of block copolymer, and compared with the MW of poly(Sar) initiator to determine which of A-B-A- or A-B-type block copolymer was formed. The experimental results showed as a whole the formation of A-B-A-type block copolymer. Therefore, the termination reaction in the radical block copolymerization of ST took place almost exclusively by the recombination mechanism. Chain-transfer reactions of primary radicals or growing radicals to $BrCH_2CO\text{(}Sar)_n$, which should produce block copolymers, were shown not to be important.

The weight fraction of poly(Sar) initiator incorporated in the block copolymer was calculated from the nitrogen content of the block copolymer. The initiator efficiency of $BrCH_2CO\text{(}Sar)_n$ was calculated from the weight fraction of poly(Sar) initiator in the block



Photoinitiated polymn.: $Mn_2(CO)_{10}$, 30°C, 10 h, $AcNMe_2$, 500W Hg-lamp

Thermally initiated polymn.: $Mo(CO)_6$, 80°C, 8 h, $AcNMe_2$, dark

SCHEME 2 Procedures for Synthesis and Purification of Poly(Sar) - PST Block Copolymer

copolymer. The initiator efficiency of $BrCH_2CO\!\leftarrow\!Sar)_n$ was higher in photoinitiated polymerization(3.2 - 6.2%) than in thermally initiated polymerization(1.3 - 2.2%). This relationship is in agreement with the experimental results reported by Bamford et al. [5,6].

In the block copolymerization using $BrCH_2CO\!\leftarrow\!Sar)_n$ as active halogen compound, the initiator efficiency was below 10% either in the photoinitiated or in the thermally initiated polymerization. To overcome these difficulties, much more reactive halogenated poly(α-amino acid) should be used as the initiator. Therefore, block copolymerizations initiated by $Cl_3CCO\!\leftarrow\!Sar)_n$ and $Br_3CCO\!\leftarrow\!Sar)_n$ were investigated. The experimental results of the thermally initiated block copolymerization of ST are summarized in TABLE 1.

The initiator efficiency was determined to be 40 - 60% in the case of $Cl_3CCO\!\leftarrow\!Sar)_n$ and 20 - 30% in the case of $Br_3CCO\!\leftarrow\!Sar)_n$, which

TABLE 1

Thermally Initiated Block Copolymerization of ST by Trihaloacetyl Poly-(Sar) and Characterization of Block Copolymers

Run no.	Active halogen compound		$Mo(CO)_6$	ST	Conversion of ST, %		$X_3CCO\text{+Sar)}_n$ used in copolymn., %		MW of copolymer[b]	MW of A segment		
	Structure	mM	mM	M	Total	Block copolymer	Elemental analysis	I.r.		Calcd.	Elemental analysis	I.r.
1	$Cl_3CCO\text{+Sar)}_{10}$	15	5	4.35	27.5	15.3	52.1	46.3	27×10^3	920	—	1700
2	$Cl_3CCO\text{+Sar)}_{32}$	10	5	2.89	22.9	15.5	44.3	43.7	23×10^3	2500	2300	2200
3	$Cl_3CCO\text{+Sar)}_{72}$	5	5	2.89	21.4	15.4	42.6	43.9	54×10^3	5400	5000	5400
4	$Br_3CCO\text{+Sar)}_{10}$	15	5	4.35	22.7	15.0	23.6	31.9	43×10^3	1000	1100	1500
5	$Br_3CCO\text{+Sar)}_{28}$	10	5	2.89	17.2	9.3	25.4	29.3	30×10^3	2800	2500	2800
6	$Br_3CCO\text{+Sar)}_{74}$	5	5	2.89	13.4	10.3	15.1	26.4	147×10^3	5600	8500	15000
7	$Cl_3CCO\text{+Sar)}_{10}$	15	0	4.35	2.8	0	—	—	—	—	—	—
8	$Cl_3CCO\text{+Sar)}_{72}$	5	10[a]	2.89	36.1	1.7	—	13.3	—	—	—	—
9	$Cl_3CCO\text{+Sar)}_{72}$	5	5[a]	2.89	32.7	0.7	—	5.3	—	—	—	—
10	$Br_3CCO\text{+Sar)}_{28}$	5	10[a]	2.89	45.0	7.3	—	48.8	28×10^3	2800	—	2900
11	$Br_3CCO\text{+Sar)}_{28}$	5	5[a]	2.89	34.2	9.1	—	44.9	32×10^3	2800	—	2600

a Initiator AIBN

b Calculated from [η]

are considerably higher than that with $BrCH_2CO\!\leftarrow\!\!Sar)_n$. The formation of block copolymer from purely thermal initiation was shown to be neglegible(compare run 1 with 7).

The MW of block copolymer was calculated from [η], which was determined on $CHCl_3$ solution at 25°C, by using an equation [7], $[\eta] = 1.12\times10^{-4}\ MW^{0.73}$. The calculated MW value of poly(Sar)(A) segment agreed well with the observed value, which was determined on the assumption of A-B-A-type block copolymer. A disagreement was observed with a block copolymer produced by $Br_3CCO\!\leftarrow\!\!Sar)_{74}$ as an initiator. The reason for the disagreenent could be the formation of branched polymers due to chain transfer reactions to the dibromoacetyl group in the preformed polymers. A small amount of block copolymer was formed by the initiation with AIBN without $Mo(CO)_6$(compare run 3 with 8 or 9, and run 5 with 10 or 11). This could be due to the initiation of block copolymerization by the chain-transfer reaction of growing radicals with possibly low DP to trichaloacetyl poly(Sar). Judged from the amounts of block copolymers formed, $Br_3CCO\!\leftarrow\!\!Sar)_n$ is more susceptible to the chain-transfer reaction than $Cl_3CCO\!\leftarrow\!\!Sar)_n$. These experimental findings suggest a frequent chain-transfer reactions to dibromoacetyl group in the preformed polymers. This idea is supported by the considerably higher MW of this block copolymer than usual. Apart from these problems, the recombination termination seems to be operating in the thermally initiated polymerizations, yielding A-B-A-type block copolymers.

The photoinitiated block copolymerization was carried out in $HCONMe_2$. A remarkable point in this polymerization system is that the gelation occurred in 1.5 h in the polymerization by $Br_3CCO\!\leftarrow\!\!Sar)_n$. The crosslinking reaction due to chain-transfer reactions, in which dibromoacetyl groups in preformed polymers participate, should be a reason for the gelation.

The efficiency of $Cl_3CCO\!\leftarrow\!\!Sar)_n$ in the block copolymerization was about 20%, which is lower than that in the thermally initiated polymerization. The initiator efficiency of $Br_3CCO\!\leftarrow\!\!Sar)_n$ in the block copolymerization was not determined accurately because of the gelation.

With block copolymers produced from $Cl_3CCO\!\!+\!\!Sar)_n$, the observed MW of poly(Sar) segment in the block copolymer, which was calculate on the assumption of the recombination termination of the radical block copolymerization of ST, was considerably higher than the MW of poly(Sar) initiator. The disagreement could have arizen from the chain branching formed by the chain-transfer reaction to dichloroacetyl groups in the preformed polymers.

To sum up, for the synthesis of poly(Sar)/PST block copolymers, a thermally initiated polymerization at 80°C using $Cl_3CCO\!\!+\!\!Sar)_n/Mo(CO)_6$ should be most suitable.

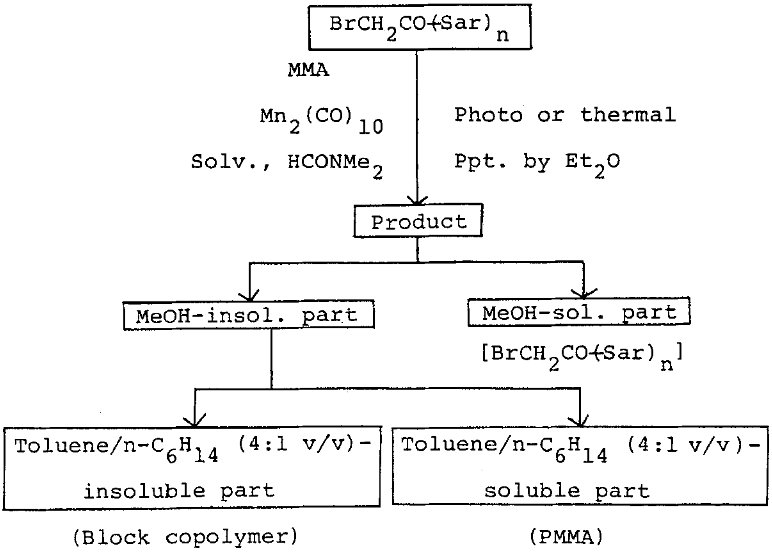
Synthesis of Poly(Sar)/PMMA Block Copolymer

Photoinitiated or thermally initiated block copolymerizations of MMA by using terminally haloacetylated poly(Sar)/$Mn_2(CO)_{10}$ initiator system were investigated. The experimental procedures for the block copolymerization are described in SCHEME 3.

The experimental results of block copolymerizations of MMA by $BrCH_2CO\!\!+\!\!Sar)_n/Mn_2(CO)_{10}$ are shown in TABLE 2.

The thermally initiated block copolymerization of MMA with $Mn_2(CO)_{10}$ was faster and produced polymers with higher MW as compared with the thermally initiated block copolymerization of ST with $Mo(CO)_6$. According to Bamford et al. [8], for the thermal initiation at 80°C, $Mo(CO)_6$ is more reactive than $Mn_2(CO)_{10}$. Therefore, the fast block copolymerization of MMA by $Mn_2(CO)_{10}$ should be due to the high reactivity of MMA. Consequently, the content of poly(Sar) initiator in the block copolymer was extremely low. The determination of poly(Sar) initiator in the block copolymer was possible only when a high MW initiator $BrCH_2CO\!\!+\!\!Sar)_{80}$ was used in the photoinitiated block copolymerization with $Mn_2(CO)_{10}$. The content of poly(Sar) initiator was very low, and the use of reactive haloacetyl poly(Sar) is desired to increase the initiator efficiency.

The MW of block copolymer was determined from [η], which was measured on $CHCl_3$ solution at 20°C, by using an equation [9], $[\eta] = 0.485\times10^{-4}\ MW^{0.80}$. The MW of poly(Sar) segment in the block copoly-



Photoinitiated polymn.: 500 W Hg-lamp,
UV-39 filter (435.8 nm), d=11.5 cm, 30°C, 10 h
Thermally initiated polymn.: 80°C, 3 h, dark

SCHEME 3 Procedures for Synthesis and Purification of Poly(Sar) - PMMA Block Copolymer

mer was obtained from the content of poly(Sar) segment in the block copolymer and the observed MW of block copolymer, assuming the formation of A-B-A-type block copolymers. The MW agreed well with the MW of poly(Sar) initiator used, indicating a purely recombinative termination reaction. On the other hand, it is well-known that in the radical polymerization of MMA only 30 - 40% of the termination reactions occur by the recombination mechanism. The reason for the discrepancy is not clear, because the much higher MW of PMMA segment than the poly(Sar) segment disturb the quantitative discussion.

Synthesis of Poly[Glu(OBzl)]/PST Block Copolymer

Using terminally haloacetylated poly[Glu(OBzl)] and metal carbonyls, photo- or thermally initiated block copolymerization of ST

TABLE 2

Photo- and Thermally Initiated Block Copolymerization of MMA by Bromoacetyl Poly(Sar) and Characterization of Block Copolymers

Active halogen compound		Polymn.	$Mn_2(CO)_{10}$	MMA	Conversion of MMA, %		$BrCH_2CO{+}Sar)_n$ used in copolymn., %		MW of	MW of A segment		
Structure	mM	method	mM	M	Total	Block copolymer	Elemental analysis	I.r.	copolymer[a]	Calcd.	Elemental analysis	I.r.
$BrCH_2CO{+}Sar)_{10}$	15	Photo	2	4.67	34.7	30.9	—	—	30.2×10^4	—	—	—
$BrCH_2CO{+}Sar)_{10}$	15	Photo	5	4.67	30.0	25.4	—	—	24.4×10^4	—	—	—
$BrCH_2CO{+}Sar)_{10}$	15	Photo	8	4.67	29.0	25.1	—	—	23.9×10^4	—	—	—
$BrCH_2CO{+}Sar)_{30}$	10	Thermal	10	3.12	19.3	17.6	—	—	57.3×10^4	—	—	—
$BrCH_2CO{+}Sar)_{80}$	5	Photo	5	1.87	9.8	9.5	1.6	1.5	34.5×10^4	5800	5900	5500
$BrCH_2CO{+}Sar)_{80}$	5	Photo	5	3.12	8.5	6.9	2.3	2.4	25.3×10^4	5800	5000	5100
$BrCH_2CO{+}Sar)_{80}$	5	Thermal	5	3.51	12.7	12.3	—	—	99.8×10^4	—	—	—

a Calculated from [η]

was carried out. The experimental procedures were nearly the same as those described in SCHEME 2, but the cyclohexane-insoluble part was further extracted with trifluoroacetic acid to remove the soluble poly[Glu(OBzl)] initiator from the insoluble block copolymers. The experimental results of the block copolymerization initiated by terminally haloacetylated poly[Glu(OBzl)]s having bimodal DP distribution are shown in TABLE 3.

In the thermally initiated polymerization by $Cl_3CCO{+}Glu(OBzl)]_n$, and $Mo(CO)_6$ the conversion of ST was relatively high, but a considerable amount of PST was produced by the initiation from $Cl_3CCOOH/Mo(CO)_6$ system, Cl_3CCOOH being contaminated in $Cl_3CCO{+}Glu(OBzl)]_n$. The MW of the poly[Glu(OBzl)] segment in a hypothetical A-B-

TABLE 3

Photo- and Thermally Initiated Block Copolymerization of Styrene by Trihaloacetyl Poly[Glu(OBzl)] with Bimodal Distribution of Molecular Weight and Characterization of Block Copolymers

Active halogen compound		Polymn.	$Mo(CO)_6$	$Mn_2(CO)_{10}$	ST	Conversion of ST, %		$X_3CCO{-}[Glu(OBzl)]_n$	MW of	MW of A segment	
Structure	mM	method	mM	mM	M	Total	Block copolymer	used in copolymn.[a], %	copolymer[b]	Calcd.	Found
$Cl_3CCO{-}[Glu(OBzl)]_{10}$	10	Thermal	5	—	4.35	30.8	7.5	51.0	12.4×10^3	2500	1660
$Cl_3CCO{-}[Glu(OBzl)]_{30}$	5	Thermal	5	—	4.35	24.2	3.7	34.1	19.3×10^3	6200	3960
$Cl_3CCO{-}[Glu(OBzl)]_{100}$	3	Thermal	3	—	4.35	17.5	3.7	17.0	42.0×10^3	9600	7730
$Br_3CCO{-}[Glu(OBzl)]_{100}$	3	Thermal	3	—	4.35	9.9	8.6	8.3	150×10^3	9100	9350
$Cl_3CCO{-}[Glu(OBzl)]_{10}$	10	Photo	—	5	4.35	3.2	2.9	24.2	16.7×10^3	2800	2590
$Cl_3CCO{-}[Glu(OBzl)]_{30}$	5	Photo	—	5	4.35	1.7	1.6	19.0	22.4×10^3	6200	5110
$Br_3CCO{-}[Glu(OBzl)]_{100}$	3	Photo	—	3	4.35	2.0	1.7	7.7	45×10^3	9100	9120

[a] Determined by nitrogen content

[b] Determined by g.p.c.

A-type block copolymer was considerably lower than the MW of poly-[Glu(OBzl)] initiator used. This could be due to the formation of A-B-type block copolymers that have arizen from the recombination of growing chains initiated by $Cl_3CCO{-}[Glu(OBzl)]_n$ and by Cl_3CCOOH. On the other hand, in the photoinitiated polymerization by $Cl_3CCO{-}[Glu(OBzl)]_n$ and $Mn_2(CO)_{10}$, the main product was A-B-A-type block copolymer. Neither PST nor A-B-type block copolymer was formed.

The initiator efficiency of $Cl_3CCO{-}[Glu(OBzl)]_n$ in the thermally initiated polymerization was higher than that of $Cl_3CCO{-}(Sar)_n$ and that in the photoinitiated block copolymerization. The initiator efficiency of $Cl_3CCO{-}[Glu(OBzl)]_n$ in both types of initiation reactions were higher with decreasing DP of poly[Glu(OBzl)]. The initiator efficiency of $\mathrm{Br_3CCO{+}Glu(OBzl)]_{100}}$ was much lower than $\mathrm{Cl_3CCO{-}[Glu(OBzl)]_n}$ either in thermally initiated or in photoinitiated block copolymerization. In the photoinitiated polymerization by $\mathrm{Br_3{-}CCO{+}Glu(OBzl)]_{100}/Mn_2(CO)_{10}}$ system, no gelation occurred.

The block copolymerization of ST thermally initiated by poly[Glu(OBzl)] having a unimodal distribution of DP was not much different from that initiated by poly[Glu(OBzl)] having a bimodal distribution of DP.

To sum up, for the synthesis of block copolymers of ST, a thermally initiated polymerization by $\mathrm{Cl_3CCO{+}Glu(OBzl)]_n/Mo(CO)_6}$ is most suitable.

Synthesis of Poly[Lys(Z)]/PST Block Copolymer

Poly[Lys(Z)] having a trichloroacetyl group at one or both ends of a chain was used in combination with $\mathrm{Mo(CO)_6}$ for the thermally initiated block copolymerization of ST. The experimental procedures are the same as those in the case of trihaloacetyl poly[Glu(OBzl)]. The experimental results are summarized in TABLE 4.

In the thermally initiated polymerization of ST by monofuctional $\mathrm{Cl_3CCO{+}Lys(Z)]_n}$, the incorporation of the initiator poly(α-amino acid) into the block copolymer was as low as 10%. In the case of difunctional $\mathrm{Cl_3CCO{+}Glu(OBzl){+}_n COCCl_3}$, the incorporation increased up to 27 - 28%, which could have arizen from a start of block copolymerization from either terminal of an initiator chain. Since the MWs of the block copolymers obtained by the difunctional initiators were nearly the same as those by the monofunctional initiators, the possibility for a simultaneous initiation from both terminals of an initiator chain is denied.

The MWs of poly[Lys(Z)] segments in the block copolymers were calculated on the assumption of the formation of A-B-A-type block copolymer, and not in agreement with the MWs of the initiators used. However, A-B-A-type block copolymers are likely to be the main product.

TABLE 4

Thermally Initiated Block Copolymerization of ST by Mono- or Difunctional Trichloroacetyl Poly[Lys(Z)] and Characterization of Block Copolymers

Active halogen compound		$Mo(CO)_6$	ST	Conversion of ST, %	
Structure	mM	mM	M	Total	Block copolymer
$Cl_3CCO\text{-}[Lys(Z)]_{10}$	10	5	4.35	12.2	1.6
$Cl_3CCO\text{-}[Lys(Z)]_{30}$	5	5	4.35	10.0	1.3
$Cl_3CCO\text{-}[Lys(Z)]_{10}\text{-}COCCl_3$	5	5	4.35	11.8	3.7
$Cl_3CCO\text{-}[Lys(Z)]_{30}\text{-}COCCl_3$	2.5	5	4.35	9.9	4.4

Active halogen compound used in copolymn.[a], %	MW of copolymer[b]	MW of A segment	
		Calcd.	Found
11.1	29.0×10^3	2870	4350
8.0	65.0×10^3	8120	11570
27.1	29.0×10^3	5600	4550
28.0	48.0×10^3	16090	8808

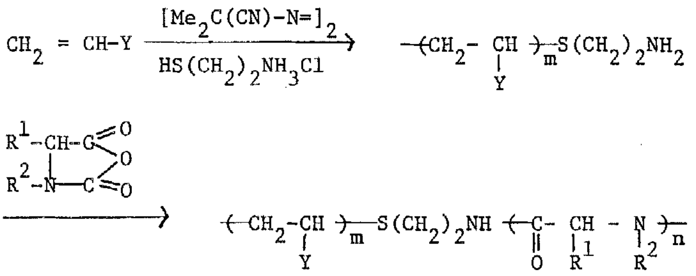
[a] Determined by nitrogen content

[b] Determined by g.p.c.

BLOCK COPOLYMERIZATION OF α-AMINO ACID NCA INITIATED BY VINYL POLYMERS HAVING A TERMINAL AMINO GROUP

General Scheme for the Synthesis of Block Copolymer

The synthetic scheme of block copolymers by the present method is described below.



The radical polymerizations of MMA and ST were carried out in the presence of a chain-transfer reagent, 2-mercaptoethylammonium chloride [10]. Frequent chain-transfer reactions may produce PMMA or PST bearing a primary amino terminal group. Terminally aminated PMMA or PST was used to initiate the block copolymerization of Glu(OBzl) and Lys(Z) NCA, yielding A-B-type block copolymer.

Synthesis of PMMA Having a Terminal Amino Group

PMMA having a terminal amino group was synthesized under the experimental conditions described in TABLE 5. The resultant PMMA was titrated with N/100 $HClO_4$/dioxane in PhOMe/EtOH(5:1 v/v) mixture. The number-average MW of polymer was determined by v.p.o. on a benzene solution and g.p.c. on a $CHCl_3$ solution. The experimental results are summarized in TABLE 5.

The MWs determined by two independent methods were different from each other by 2 - 3 times, and the content of amino group per a chain of PMMA ranged between 0.5 and 1.3. It could be concluded that PMMAs produced under the present conditions contain nearly one amino group per a chain.

TABLE 5

Radical Polymerization[a] of MMA in the Presence of 2-Mercaptoethylammonium Chloride

$HS-(CH_2)_2-NH_3Cl$		Polymer yield		Amine content	M.W. calcd[b] (A)	M.W. v.p.o. (B)	$\frac{(A)}{(B)}$	M.W. g.p.c. (C)	$\frac{(A)}{(C)}$
g	M	g	%	meq/g					
0.213	0.234	1.20	32.1	0.079	1.26×10^4	7.33×10^3	1.72	1.6×10^4	0.79
0.141	0.155	1.50	40.1	0.066	1.52×10^4	6.65×10^3	2.29	1.9×10^4	0.80
0.107	0.118	1.57	42.0	0.059	1.09×10^4	7.62×10^3	2.22	2.4×10^4	0.70

[a] [MMA] = 4.67 M(4 ml); [AIBN] = 2.78 mM(3.65 mg): solv., $HCONME_2$ (4 ml); temp., 60°C; time, 8 h

[b] MW calculated assuming one amino group per polymer chain

Synthesis of PST Having a Terminal Amino Group

PST having a terminal amino group was synthesized by the same method as employed for PMMA. The experimental results are summarized in TABLE 6.

The MWs determined by g.p.c. were about five times as large as those determined by v.p.o., and the numbers of amino group per a chain of PST scattered in a relatively wide range between 0.5 and 2.5.

Block Copolymerization of Glu(OBzl) NCA by PMMA Having a Terminal Amino Group and the Debenzylation of Block Copolymer

The experimental procedure is shown in SCHEME 4.

No suitable mathod to separate poly[Glu(OBzl)] from PMMA-poly-[Glu(OBzl)] block copolymer is available. Therefore, the AcOEt/n-C_6H_{14}(3:1 v/v)-insoluble part was subjected to the debenzylation and poly(Glu) was extracted by MeOH. The yield of poly[Glu(OBzl)] was

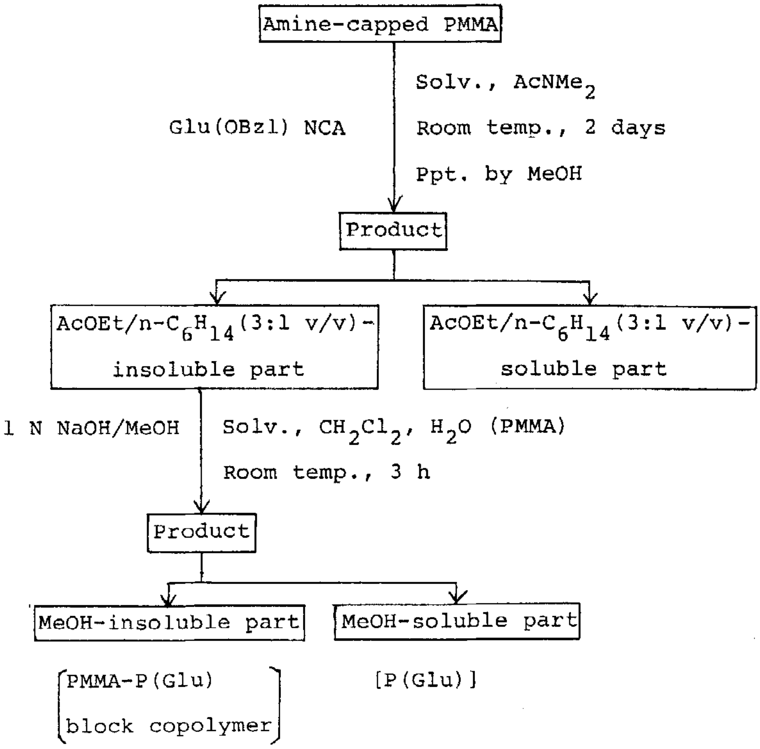
TABLE 6

Radical Polymerization[a] of ST in the Presence of 2-Mercaptoethylammonium Chloride

$HS-(CH_2)_2-NH_3Cl$		Polymer yield		Amine content	M.W. calcd[b]	M.W. v.p.o.	$\frac{(A)}{(B)}$	M.W. g.p.c.	$\frac{(A)}{(C)}$
g	M	g	%	meq/g	(A)	(B)		(C)	
0.212	0.233	0.834	23.1	0.125	8.00×10^3	4.42×10^3	1.81	1.9×10^4	0.42
0.141	0.155	0.924	25.6	0.106	9.43×10^3	4.64×10^3	2.03	2.6×10^4	0.38
0.107	0.118	0.955	26.5	0.094	1.06×10^4	5.19×10^3	2.04	2.6×10^4	0.41

[a] [ST] = 4.34 M(4 ml); [AIBN] = 5.56 mM(7.31 mg); solv., $HCONMe_2$ (4 ml); temp., 70°C; time, 8 h

[b] MW calculated assuming one amino group per polymer chain



SCHEME 4 Procedures for Synthesis and Debenzylation of PMMA - poly[Glu(OBzl)] Block Copolymer

thus determined and the yield of block copolymer was calculated. The experimental results are described in TABLE 7.

About 90% of PMMA initiator and about 70% of Glu(OBzl) NCA used in the copolymerization were found in the block copolymer. The production of homopolymer was low. The DP of poly[Glu(OBzl)] segment in the block copolymer was 1.1 - 1.6 times as large as the [NCA]/[Amine] molar ratio in the block copolymerization. From these results it was concluded that the block copolymerization was initiated by the nucleophilic addition of the terminal amino group of PMMA initiator to the 5-carbonyl group of Glu(OBzl) NCA [11], yielding A-B-type block copolymers.

Block Copolymerization of Lys(Z) NCA by PMMA Having a Terminal Amino Group and the Debenzyloxycarbonylation of Block Copolymer

The experimental procedure is shown in SCHEME 5.

The copolymerization product was subjected to debenzyloxycarbonylation without pre-extraction, and the debenzyloxycarbonylated product was extracted by solvents to remove homopolymers from the block copolymer. The experimental results are described in TABLE 8.

The DPs of poly[Lys(Z)] segment in the block copolymers were calculated on the basis of the content of basic amino group in the PMMA - poly[Lys(Z)] block copolymers, and are very close to the [NCA] /[Amine] molar ratios in the block copolymerization. This experimental result shows that the terminal amino group of PMMA initiator underwent a nucleophilic addition reaction to the 5-carbonyl group of Lys(Z) NCA to initiate the block copolymerization.

Block Copolymerization of Glu(OBzl) NCA by PST Having a Terminal Amino Group and the Debenzylation of Block Copolymer

The experimental procedure is shown in SCHEME 6.

To separate poly[Glu(OBzl)] from PST - poly[Glu(OBzl)] block copolymer, the cyclohexane-insoluble part was extracted by trifluoroacetic acid. Poly[Glu(OBzl)] and block copolymers having higher content of poly[Glu(OBzl)] segments were soluble in trifluoroacetic

TABLE 7

Polymerization[a] of Glu(OBzl) NCA by PMMA with Terminal Amino Group

Block copolymer[b]	PMMA-NH$_2$ $\bar{P}$	PMMA-NH$_2$ g	[NCA]/[Amine][c]	Polymer yield g	Polymer yield %	PMMA recovered[d], g	P[Glu(OBzl)] recovered[e], g	Block copolymer Yield[f], g	Block copolymer N[g], %	Efficiency of block copolymn. PMMA[h], %	Efficiency of block copolymn. Glu(OBzl)NCA[i], %	P[Glu(OBzl)] in copolymer wt%[j]	P[Glu(OBzl)] in copolymer $\bar{P}$[k]
PMMA(274)-P[Glu(OBzl)](86)	274	2.26	86	4.38	96.1	0.19	0.83(0.49)	3.36	2.91(3.57)	84.3(91.3)	69.2(62.4)	45.5(32.9)	104
PMMA(329)-P[Glu(OBzl)](67)	329	3.31	67	5.36	95.5	0.44	0.30(0.18)	4.62	2.30(2.70)	93.5(86.1)	75.7(86.3)	36.0(24.9)	84
PMMA(374)-P[Glu(OBzl)](95)	374	2.73	95	4.87	96.8	0.37	0.50(0.29)	4.00	2.84(3.48)	84.0(86.0)	79.9(77.5)	44.5(32.1)	137

a [Glu(OBzl)NCA]=0.3M(2.76g); solv,AcNMe$_2$(35ml); temp,room temp; time, 2days.

b Numerical values in parentheses represent $\bar{P}$ of each segment. $\bar{P}$ of PMMA block is the observed value . $\bar{P}$ of P[Glu(OBzl)] block is the [NCA]/[Amine] ratio.

c Determined by titration.

d AcOEt/n-C_6H_{14} (3:1 v/v)-soluble part.

e Calculated on the basis of the amount of MeOH-soluble P(Glu) after the debenzylation which is given in the parenthesis.

f Polymer yield-(PMMA recovered + P[Glu(OBzl)] recovered).

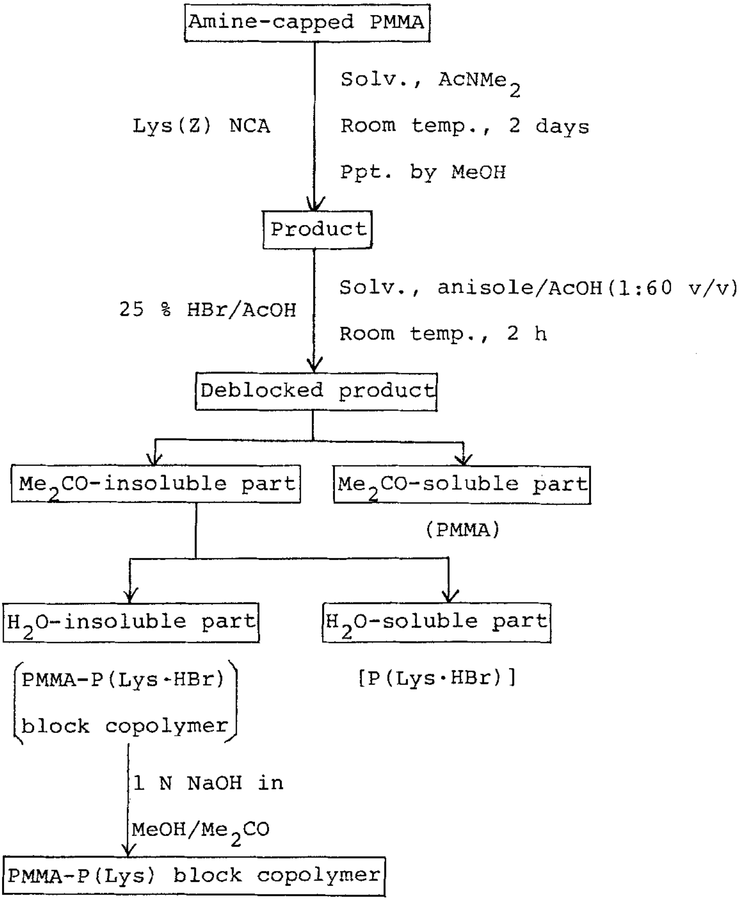
g Calculated from P[Glu(OBzl)] wt% in the block copolymer. Values shown in parentheses are the nitrogen content of PMMA-P(Glu) block copolymer after the debenzylation.

h Based on the PMMA wt% in the block copolymer. Values shown in parentheses were calculated on the basis of the difference between the amount of initiator PST used and the amount of PST recovered.

i Based on the P[Glu(OBzl)] wt% in the block copolymer. Values shown in parentheses were calculated on the basis of the difference between the theoretical amount of P[Glu(OBzl)] formed and the amount of P[Glu(OBzl)] recovered.

j Calculated on the basis of the P(Glu) wt% in the MeOH-insoluble block copolymer after the debenzylation, which is given in the parenthesis.

k Calculated from the molecular weight of PMMA initiator and the P[Glu(OBzl)] wt% in the block copolymer.



SCHEME 5 Procedures for Synthesis and Debenzyloxycarbonylatioon of PMMA - Poly[Lys(Z)] Block Copolymer

acid. An alternative way to separate them from each other was the debenzylation of the cyclohexane-insoluble part and the extraction of poly(Glu) with MeOH. The yield of poly[Glu(OBzl)] was thus determined and the yield of block copolymer was calculated. The experimental results are summarized in TABLE 9.

70 - 80% of PST initiator and 60 - 90% of Glu(OBzl) NCA used in the copolymerization were found in the block copolymer. The eff-

TABLE 8

Polymerization[a] of Lys(Z) NCA by PMMA with Terminal Amino Group

Block copolymer[b]	PMMA-NH$_2$		Lys(Z)NCA	AcNMe$_2$	[NCA]/[Amine][c]	Polymer yield		PMMA-P(Lys) block copolymer[d]		P[Lys(Z)] in copolymer	
	$\bar{P}$	g	g	ml		g	%	Yield,g	Basic N[e],%	wt%[f]	$\bar{P}$[g]
PMMA(295)-P[Lys(Z)](123)	295	1.80	2.30	25	123	3.50	92.8				
PMMA(286)-P[Lys(Z)](120)	286	3.00	3.82	42	120	5.68	90.6	2.60	3.17	45.5(29.0)	91
PMMA(261)-P[Lys(Z)](68)	261	2.90	2.30	25	68	4.38	89.9	1.77	2.70	40.2(24.7)	67
PMMA(261)-P[Lys(Z)](117)	261	2.90	4.00	42	117	5.73	90.5				

[a] Temp, room temperature; time, 4 days.

[b] Numerical values in parentheses represent $\bar{P}$ of each segment. $\bar{P}$ of PMMA block is the observed value(Table2). $\bar{P}$ of P[Lys(Z)] is the [NCA]/[Amine] ratio.

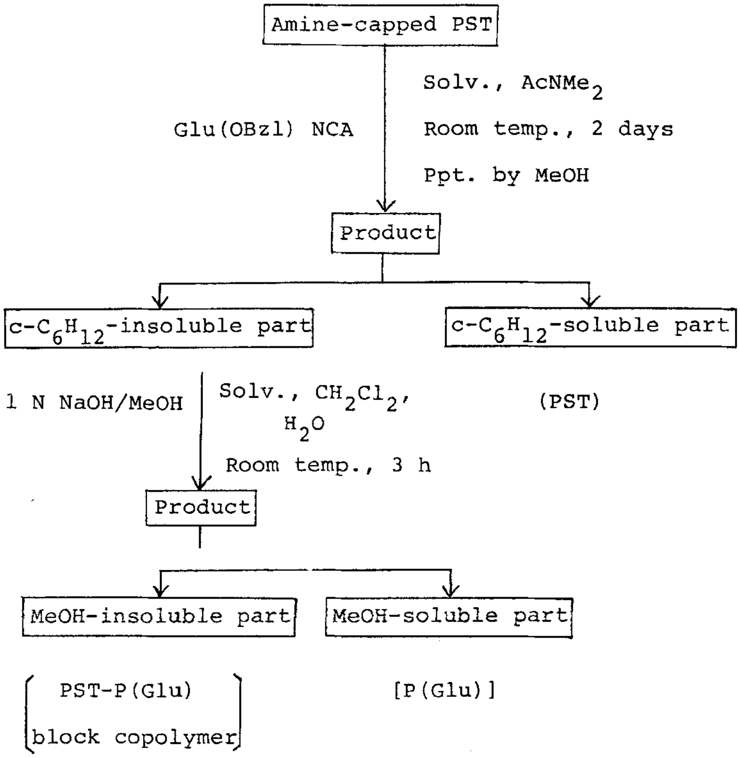
[c] Calculated by assuming one amino group per chain of PMMA initiator.

[d] Acetone- and water-insoluble part after the debenzyloxycarbonylation.

[e] Determined by titration.

[f] Weight % of P[Lys(Z)] segment in the PMMA-P[Lys(Z)] block copolymer was calculated from $\bar{P}$ of PMMA initiator and $\bar{P}$ of P[Lys(Z)] segment in the block copolymer. Values shown in the parentheses are the weight % of P(Lys) segment in the PMMA-P(Lys) block copolymer, which was calculated from the basic nitrogen content in the PMMA-P(Lys) block copolymer.

[g] Calculated from the weight % of P(Lys) segment in the PMMA-P(Lys) block copolymer and $\bar{P}$ of PMMA initiator.



SCHEME 6 Procedures for Synthesis and Debenzylation of PST - Poly-[Glu(OBzl)] Block Copolymer

iciency of block copolymerization is very high, if one takes into account that a part of block copolymers is extracted by solvent together with homopolymers to lower the apparent yield of block copolymer. The DP of poly[Glu(OBzl)] segment in the block copolymer was 1.3 - 2.0 times as large as the [NCA]/[Amine] molar ratio in the block copolymerization. From these results it was concluded that the block copolymerization was initiated mainly by the nucleophilic addition reaction of the terminal amino group of PST initiator to Glu(OBzl) NCA [11].

TABLE 9
Polymerization[a] of Glu(OBzl) NCA by PST with Terminal Amino Group

Block copolymer[b]	PST-NH_2		$\frac{[NCA]}{[Amine]}$[c]
	$\overline{P}$	g	
PST(108)-P[Glu(OBzl)](70)	108	0.76	70
PST(150)-P[Glu(OBzl)](50)	150	1.61	50
PST(174)-P[Glu(OBzl)](60)	174	1.72	60

Polymer yield		PST	P[Glu(OBzl)]	Block copolymer	
g	%	recovered[d],g	recovered[e],g	Yield[g],g	N[i],%
2.85	93.1	0.13	0.12(0.075)	2.60	4.58(6.50)
3.81	97.4	0.40	0.25(0.17)	3.16	3.04(3.79)
3.87	96.3	0.50	0.94[f]	2.44[h]	3.79[j]

Efficiency of block copolymn.		P[Glu(OBzl)] in copolymer	
PST[k],%	Glu(OBzl)NCA[l],%	wt%[m]	$\overline{P}$[o]
104(81.6)	87.1(94.4)	71.7(59.9)	130
106(74.5)	67.1(88.8)	47.6(34.9)	65
60(69.8)	65.3(57.6)	59.3[n]	120

[a] [Glu(OBzl)]=0.3M(2.76g); solv, CH_2Cl_2(35ml); temp, room temp; time, 2days.

[b] Numerical values in parentheses represent $\overline{P}$ of each segment. $\overline{P}$ of PST block is the observed value. $\overline{P}$ of P[Glu(OBzl)] block is the [NCA]/[Amine] ratio.

[c] Determined by titration.

[d] Cyclohexane-soluble part.

[e] Calculated on the basis of the amount of MeOH-soluble P(Glu) after the debenzylation which is given in the parenthesis.

[f] TFA-soluble part,containing a small amount of block copolymer.

[g] Polymer yield - (PST recovered + P[Glu(OBzl)] recovered).

[h] TFA-insoluble part.

[i] Calculated from P[Glu(OBzl)] wt% in the block copolymer. Values shown in parentheses are the nitrogen content of PST-P(Glu) block copolymer after the debenzylation.

[j] Elemental analysis of TFA-insoluble part.

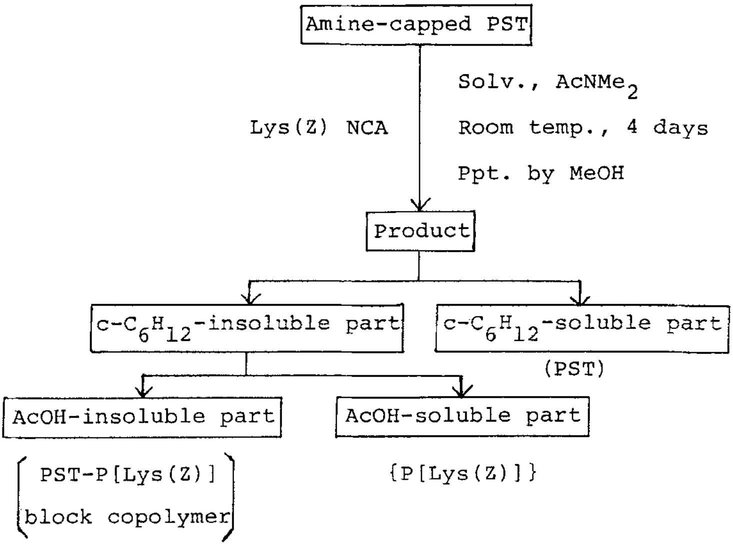
[k] Based on the difference between the amount of initiator PST and the PST recovered.

[l] Based on the P[Glu(OBzl)] wt% in the block copolymer. Values shown in parentheses were calculated on the basis of the difference between the theoretical amount of P[Glu(OBzl)] formed and the amount of P[Glu(OBzl)] recovered.

[m] Calculated on the basis of the P(Glu) wt% in the MeOH-insoluble block copolymer after the debenzylation,which is given in the parenthesis.

[n] Calculated from the nitrogen contnet of TFA-insoluble block copolymer.

[o] Calculated from the molecular weight of PST initiator and the P[Glu(OBzl)] wt% in the block copolymer.



SCHEME 7 Procedures for Synthesis and Purification of PST - Poly-[Lys(Z)] Block Copolymer

Block Copolymerization of Lys(Z) NCA by PST Having a Terminal Amino Group

The experimental procedure is shown in SCHEME 7.

Homopolymers were removed from the block copolymer by the solvent extraction. The experimental results are summarized in TABLE 10.

70 - 90% of PST initiator and 60 - 80% of Lys(Z) NCA used in the block copolymerization were found in the block copolymer. The efficiency of block copolymerization is fairly high. On the other hand, the DP of poly[Lys(Z)] segment in the block copolymer was 1.6 - 2.0 times as large as the [NCA]/[Amine] molar ratio in the block copolymerization. If the block copolymerization is initiated by the nucleophilic addition reaction of the terminal amino group of PST initiator to Lys(Z) NCA, the high DP of poly[Lys(Z)] segment should be explained by the formation of A-B-A-type block copolymer. This explanation puts forward the presence of two amino groups at both terminals of a PST chain. However, for a PST chain to have two amino

TABLE 10

Polymerization of Lys(Z) NCA by PST with Terminal Amino Group

Block copolymer[b]	PST-NH_2		Lys(Z)NCA	$AcNMe_2$	[NCA] / [Amine][c]
	$\bar{P}$	g	g	ml	
PST(108)-P[Lys(Z)](70)	108	0.76	3.22	35	70
PST(150)-P[Lys(Z)](50)	150	1.61	3.22	35	50
PST(174)-P[Lys(Z)](40)	174	2.57	3.22	35	40

Polymer yield		PST recovered[d]	P[Lys(Z)] recovered[e]	Block copolymer	
g	%	g	g	Yield[f],g	N[g],%
2.73	77.1	0.03	0.74	1.83	7.76
3.59	81.8	0.23	0.63	2.67	6.42
4.97	92.9	0.66	0.50	3.70	5.72

Efficiency of block copolymn.		P[Lys(Z)] in copolymer	
PST[h],%	Lys(Z)NCA[i],%	wt%[j]	$\bar{P}$[k]
85.3(94.9)	62.1(65.5)	72.7	114
80.9(82.5)	70.6(72.3)	60.1	90
71.9(72.4)	76.8(80.6)	53.6	80

[a] Temp, room temp; time, 4days.

[b] Numerical values in parentheses represent $\bar{P}$ of each segment. $\bar{P}$ of PSt block is the observed value. $\bar{P}$ of P[Lys(Z)] block is the [NCA]/[Amine] ratio.

[c] Determined by titration.

[d] Cyclohexane-soluble part.

[e] AcOH-soluble part.

[f] AcOH-insoluble part.

[g] Elemental analysis.

[h] Based on the P[Lys(Z)] wt% in the block copolymer. Values shown in parentheses were calculated on the basis of the difference between the amount of initiator PST used and the amount of PST recovered.

[i] Based on the P[Lys(Z)] wt% in the block copolymer. Values shown in parentheses were calculated on the basis of the difference between the theoretical amount of P[Lys(Z)] formed and the amount of P[Lys(Z)] recovered.

[j] Calculated from the nitrogen content of the block copolymer.

[k] Calculated from the molecular weight of PST initiator and the P[Lys(Z)] wt% in the block copolymer.

groups, the radical polymerization of ST in the presence of 2-mercaptoethylammonium chloride should be terminated by the recombination reaction, which is extremely difficult to consider.

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