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Article / Book Information

題目(和文)	システイン由来の新規ポリマーの合成と反応
Title(English)	Synthesis and reactions of novel polymers derived from cysteine
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Author(English)	
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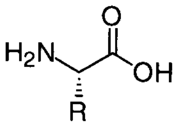
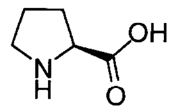
Chapter 1

General Introduction

General Introduction

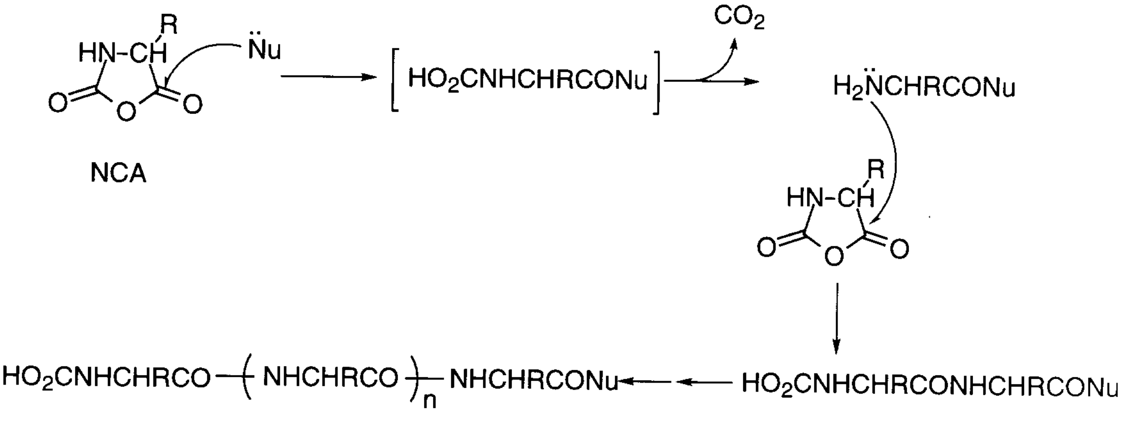
Amino acids exist in living organisms both as free forms and amide linkages in peptides and proteins, which are assembled under nucleic acid control according to a menu comprising amino acids. Table 1 summarizes naturally occurring twenty α-amino acids.

Table 1.

Amino acid		- R
 α-amino acid	Alanine	$-CH_3$
	Arginine	$-(CH_2)_3NHC(=NH)NH_2$
	Asparagine	$-CH_2CONH_2$
	Asparatic acid	$-CH_2CO_2H$
	Cysteine	$-CH_2SH$
	Glutamine	$-(CH_2)_2CONH_2$
	Glutamic acid	$-(CH_2)_2CO_2H$
	Glycine	-H
	Histidine	$-CH_2$ (4-imidazoyl)
	Isoleucine	$-CH(CH_3)CH_2CH_3$
	Leucine	$-CH_2CH(CH_3)_2$
	Lysine	$-(CH_2)_4NH_2$
	Methionine	$-(CH_2)_2SCH_3$
	Phenylalanine	$-CH_2Ph$
	Serine	$-CH_2OH$
	Threonine	$-CH(CH_3)OH$
	Tryptophan	$-CH_2$(3-indolyl)
	Tyrosine	$-CH_2$ (4-hydroxyphenyl)
	Valine	$-CH(CH_3)_2$
 imino acid	Proline	

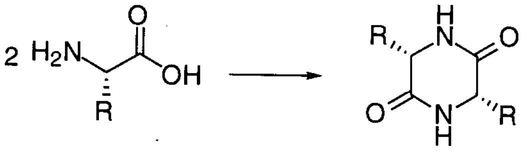
The chemistry of amino acids and peptides has been developed directing structual elucidation and synthesis of peptides of useful biological function.[1] Due to the contribution of recent remarkable improvements in fermentation and organic synthetic technology, we can now obtain optically pure amino acids with low prices. Consequently, amino acid and some oligo peptides are now widely used for drugs, food, and chiral sources in organic synthesis. Amino acid-based polymers and peptides are expected not only as biocompatible materials but also chemically functional materials. Peptides are commonly synthesized by ring opening polymerization of Leuch's anhydrides, NCAs.[2] Scheme 1 illustrates a plausible mechanism of NCA polymerization. First, an initiator attacks the carbonyl carbon of NCA to form a carbamic acid derivative, followed by decarboxylation affording an amine. Successive addition of the amino group to the monomer and decarboxylation result in a poly(amino acid).

Scheme 1:



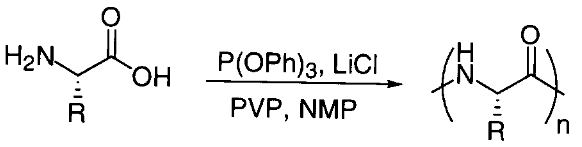
Commonly, direct condensation of an amino acid is unsatisfactory to obtain a peptide, where a thermodynamically stable 2,5-piperazinedione is formed (Scheme 2).

Scheme 2.



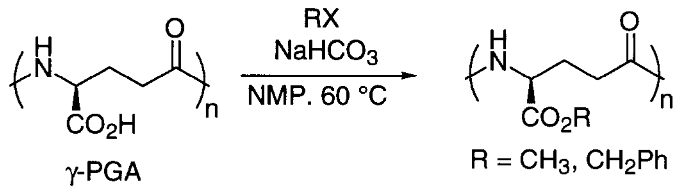
However, Higashi et al. have reported that a peptide can be directly synthesized from an amino acid using P(OPh)3 as condensation reagent in *N*-methyl pyrrolidinone (NMP) in the presence of poly(vinyl pyrrolidinone) (PVP) as a polymer matrix (Scheme 3).[3] Poly(amino acid)s tend to be insoluble in common organic solvents and decompose in the molten state. [4]

Scheme 3:



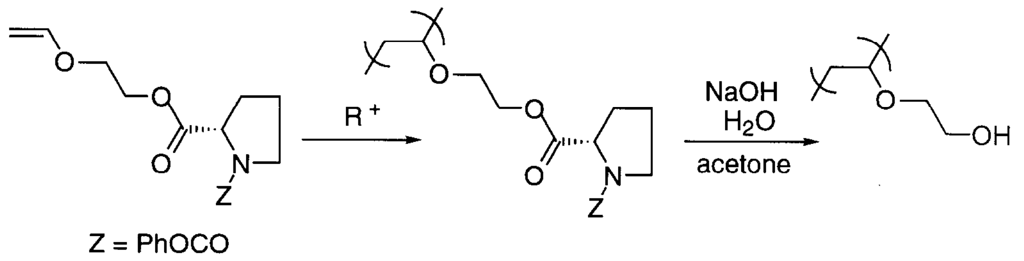
Meanwhile, several attempts have been made to synthesize amino acid-based non-peptide polymers. Endo et al. have developed this kind of polymer synthesis based on amino acids and peptides, where wide variety of polymerization methods are employed such as fermentation, polycondensation, polyaddition, ring-opening polymerization, cationic, anionic, and radical polymerizations.[5] Followings are examples accomplished by them. Poly(γ-glutamic acid) (γ-PGA) is a biosynthesized polymer derived from glutamic acid consisting of a nylon-4 structure with pendant α-carboxyl groups. The esterification of the α-carboxyl group of γ-PGA with alkyl halides affords the corresponding γ-PGA α-esters, which can form fibers showing similar mechanical strength as nylons (Scheme 4).[6]

Scheme 4:



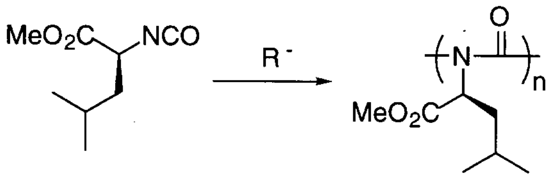
Cationic polymerization of a proline-derived vinyl ether affords the corresponding poly(vinyl ether). Alkaline hydrolysis of the polymer affords poly(hydroxyethyl vinyl ether) releasing *N*-benzyloxycarbonyl proline (Scheme 5).[7]

Scheme 5:



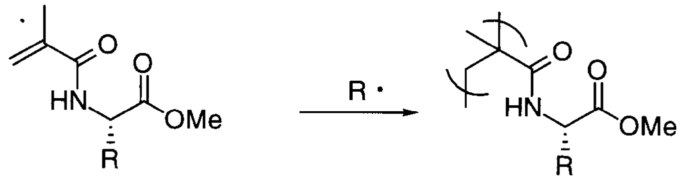
An L-leucine-derived isocyanate undergoes anionic polymerization to afford an optically active "nylon-1" polymer having L-leucine moiety in the side chain (Scheme 6).[8]

Scheme 6:



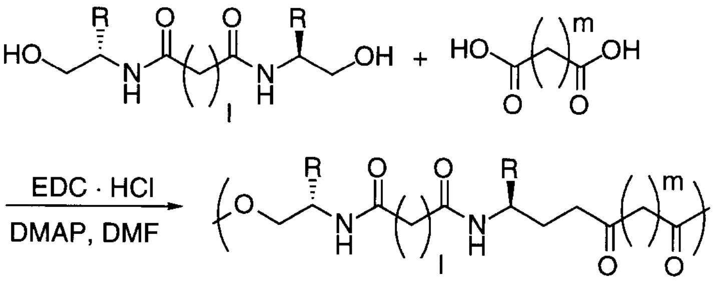
The radical polymerization of amino acid-derived methacrylamides affords the corresponding polymethacryamides, some of which show several functions and reactivities such as polyelectrolyte,[9] oxidation,[10] and α-helix matrix[11] (Scheme 7).

Scheme 7:



Amino alcohols are easily obtained by reduction of amino acids. They are widely used as chiral building blocks in organic synthesis. Endo et al. have also developed polymer synthesis based on amino acid-derived amino alcohols. Polycondensation of dicarboxylic acids with diols derived from amino alcohols affords the corresponding poly(ester-amide)s, which show an even-odd effect in the relationship between the methylene chain length and the glass transition temperatures (Scheme 8).[12]

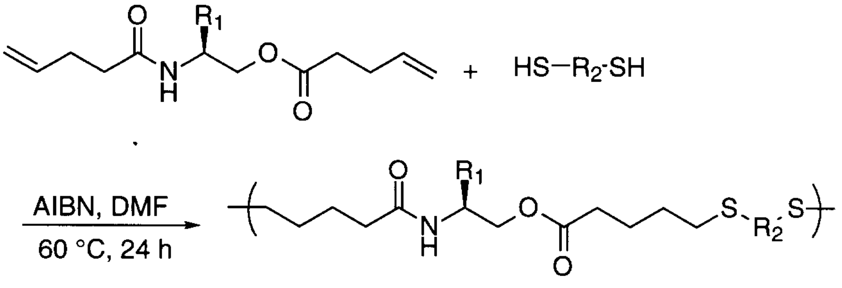
Scheme 8:



$R = CH_2Ph, CH_2CH(CH_3)_2$
$l = 2,4,\ m = 2 \sim 8$

Radical polyaddition with dithiols with amino alcohol derived diolefin affords polysulfides, which are degraded with enzymes (Scheme 9).[13]

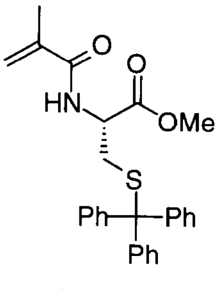
Scheme 9:



R_1 = CH_2Ph, $CH_2CH(CH_3)_2$, CH_2Ph
R_2 = $(CH_2)n$ ($n = 2 - 6$), 1,4-CH_2-Ph-CH_2

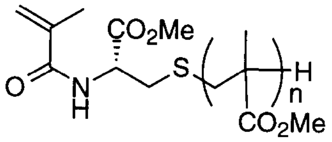
As described above, we can find various kinds of works concerning synthesis and polymerization of the optically active monomers derived from amino acids. Amino acid-based polymers have attracted much attention as chemically functional optically active biocompatible materials. In this thesis, I present synthesis and polymerization of several monomers derived from cysteine, and reactions of the obtained polymers. Cysteine is characterized by its thiol group, which can show variety of functions such as capturing heavy metals,[14] serving as chain transfer reagents,[15] and catalysts for hydrolysis of formamides.[16] Therefore, it is expected that the polymers derived from cysteine show various functions and reactivities.

Chapter 2 describes synthesis and radical polymerization of *N*-methacryloyl-*S*-trityl-L-cysteine methyl ester [MA-C(Trt)-M], along with the specific rotations of the monomer, polymers, and copolymers with several comonomers. In addition, it describes deprotection of trityl group from poly[MA-C(Trt)-M].



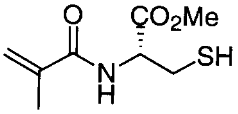
MA-C(Trt)-M

Chapter 3 describes synthesis and radical polymerization of cysteine-based macromonomers and the thermal properties of the macromonomers and the graftpolymers.

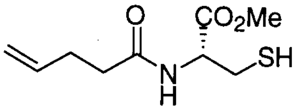


Macromonomer

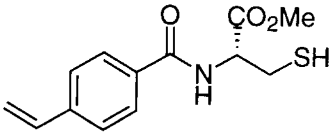
Chapter 4 describes synthesis and radical self-polyaddition of *N*-methacryloyl-L-cysteine methyl ester (MA-C-M), *N*-4-pentenoyl-L-cysteine methyl ester (P-C-M), and *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M). Furthermore, it discusses the conformational aspects of poly(V-C-M) based on the measurement of the specific rotation and CD spectroscopic analysis.



MA-C-M

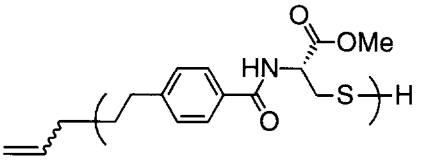


P-C-M



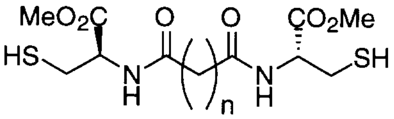
V-C-M

Chapter 5 describes radical polymerization of MMA and TrtMA in the presence of poly(V-C-M) to obtain block copolymers along with oxidation and hydrolysis of poly(V-C-M).



Poly[V-C-M]

Chapter 6 describes synthesis and oxidation polymerization of novel optically active dithiol monomers having dithiol groups derived from cysteine. It also discusses the differences of the specific rotation and Cotton effect between the monomers and corresponding polymers.



1a : n = 6
1b : n = 5
1c : n = 4
1d : n =3

Chapter 7 summarizes the results of Chapters 2 ~ 6.

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Chapter 2

Synthesis and Radical Polymerization of an Optically Active Monomer Derived from Cysteine

Abstract

Synthesis and radical polymerization of *N*-methacryloyl-*S*-trityl-L-cysteine methyl ester [MA-C(Trt)-M] derived from cysteine were examined. Its radical polymerization was carried out at 60 °C for 20 h in the presence of AIBN in benzene, PhCl, and DMF to afford the corresponding polymer with M_ns in the range of 13200-130000 in good yields. In the radical copolymerizations of MA-C(Trt)-M with methyl methacrylate and trityl methacrylate, the specific rotations of the copolymers showed the maximum values with the MA-C(Trt)-M content of 60 and 80%, respectively. The polymers were treated with HBr/CH_3CO_2H (30 wt %) to afford the trityl group-free polymers, which were insoluble in solvents due to the oxidative crosslinking reaction between the thiol groups.

2.1. Introduction

The synthesis and radical polymerization of the various mathacrylamides derived from amino acids have been reported, and much attention has been paid to their unique polymerization behavior, structure, and properties based on chirality. Morcellet et al. synthesized polymethacryamides derived from alanine, glutamic acid, asparartic acid, asparagine and lysine in the side chain, and examined complexing properties toward divalent metal ions[1]. Sakota, et al. studied photocopolymerization of *N*-methacryloyl valine methyl ester with maleic anhydride, and suggested the induction of assymmetric center into the polymer main chain.[2] Endo et al. reported the synthesis and radical polymerization of methacryloyl and acrylamides having amino acids and peptide moieties, and noted large polymerizability in spite of the bulky substituents, probably due to hydrogen bonding[3]. Furthermore, cysteine is characterized by its thiol group, which can show variety of functions such as capturing heavy metals,[4] serving as chain transfer reagents,[5] and catalysts for hydrolysis of formamides.[6] Therefore, it is expected that the polymers derived from cysteine show various functions and reactivities. Although there have been many reports on the synthesis of polymers bearing thiol groups,[7] polymers derived from cysteine have been hardly reported.[8] In this chapter, I describe the synthesis and radical polymerization behavior of a methacrylamide derived from cysteine, and the reaction of the obtained polymer.

2.2. Experimental

2.2.1. *Measurements*

^{1}H and ^{13}C-NMR spectra were recorded on a JEOL JNM EX-400 spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). IR spectra were obtained with a JASCO FTIR-5300 spectrometer. Melting points (mp) were measured by a YANACO micro melting point apparatus. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimater using a sodium lamp as a light source. Circular dichroism (CD) spectra were measured on a JASCO J-720 spectropolarimeter. Molecular weights (M_n) and polydispersity ratios (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC HLC-8020 system, equipped with consecutive three polystyrene gel columns (TSK-gels G5000H, G4000H, and G2500H), using *N,N*-dimethylformamide (DMF, 5.8 mM lithium bromide solution) as an eluent at a flow rate of 1.0 mL/min, polystyrene calibration, and refractive index (RI) and ultraviolet (UV) detectors. Thermal analyses were performed on Seiko instruments TG/DTA 220 and DSC 220C. Glass transition temperatures (T_g) were taken as an inflection point on a trace at a heating rate of 10 °C/min by differential scanning calorimetry (DSC). Temperatures (T_{d10}) with 10 % weight loss were determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under nitrogen atmosphere.

2.2.2. *Materials*

L-Cysteine and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl) were obtained from Ajinomoto Co. and Eiweiss Chemical Co., respectively. Triphenylmethyl methacrylate (TrtMA) was synthesized according to the reported method.[9] Initiator 2,2'-azobis(isobutyronitrile) (AIBN) was purchased from Tokyo Kasei Kogyo

Co. Chlorobenzene, benzene, DMF, methyl methacrylate, and styrene were distilled over calcium hydride before use.

2.2.3. *Synthesis of N-methacryloyl-S-trityl-L-cysteine methyl ester (MA-C(Trt)-M)*

L-Cysteine methyl ester hydrochloride

Thionyl chloride (78 mL, 0.9 mol) was added dropwise to methanol (300 mL) at -10 °C, and the mixture was stirred for 10 min. L-Cysteine (36.35 g, 300 mmol) was added to the mixture, followed by stirring for 15 h at room temperature. The reaction mixture was concentrated by a rotary evaporator and the residual mass was washed with ethyl ether (300 mL) several times to obtain powdery L-cysteine methyl ester hydrochloride, which was used for the next step without further purification. Yield 46.3 g (90 %). ^{1}H-NMR (DMSO-*d*$_6$, 400 MHz): δ = 2.96-3.09 (m, 2H, -CH$_2$-S-), 3.75 (s, 3H, -CO$_2$CH$_3$), 4.19-4.37 (m, 1H, -CH<), 6.35 (br s, 3H, HCl·NH$_2$-), 3.34 (m, 1H, -SH) ppm. ^{13}C-NMR (DMSO-*d*$_6$, 400 MHz): δ = 24.15, 52.96, 53.93, 169.18 ppm.

S-Trityl-L-cysteine methyl ester hydrochloride (HCl-C(Trt)-M)

BF_3OEt_2 (3.8 mL, 28 mmol) was added to a solution of triphenylmethanol (7.0 g, 27 mmol) and crude L-cysteine methyl ester hydrochloride (4.6 g, 27 mmol) in glacial acetic acid (27 mL). The mixture was stirred at 60 °C for 30 min, and kept at room temperature for 45 min, followed by the addition of methanol (40 mL) and water (13.5 mL). The resulting mixture was concentrated by a rotary evaporator and the residual mass was washed with ethyl ether (100 mL) several times to obtain powdery, *S*-trityl-L-cysteine methyl ester hydrochloride (HCl-C(Trt)-M), which was used for the next step without further purification. Yield 10.7 g (96 %). ^{1}H-NMR (DMSO-*d*$_6$, 400 MHz): δ = 2.53-2.62 (m, 2H, -CH_2-S-), 3.71 (s, 3H, -CO_2CH_3), 3.84-3.86 (m, 1H, -CH<), 8.40 (br s, 3H, HCl·NH_2-), 7.10-7.39 (m, 15H, -$C(C_6H_5)_3$) ppm. ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 31.39, 51.06, 53.03, 66.64, 127.08, 128.23, 128.97, 143.47, 168.21 ppm.

N-Methacryloyl-S-trityl-L-cysteine methyl ester (MA-C(Trt)-M)

Methacrylic acid (10.9 mL, 127.9 mmol) was added to a solution of EDC·HCl (24.5 g, 127.9 mmol) in CH_2Cl_2 (500 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Crude HCl-C(Trt)-M (48.1 g, 116.3 mmol) and triethylamine (17.8 mL, 127.9 mmol) were added to the resulting mixture, and it was stirred at 0 °C for 2 h and then at room temperature over night. The resulting mixture was concentrated by a rotary evaporator. After that, ethyl acetate (300 mL) was added to the residual mass and the resulting suspension was washed with water, saturated aqueous sodium hydrogen carbonate, 1N hydrogen chloride solution, and water. The organic phase was dried over $MgSO_4$ and concentrated by a rotary evaporator. The residue was purified by silica gel column chromatography eluted with ethyl acetate/*n*-hexane (volume ratio 1/1), followed by recrystallization from ethyl acetate to obtain colorless solid (MA-C(Trt)-M). Yield 34.2 g (66 %), mp = 126-127 °C, $[\alpha]_D^{30}$= 25° (*c*=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.96 (s, 3H, =C(CH_3)-), 2.68 (d, *J*=4.9 Hz, 2H, -CH_2-S-), 3.72 (s, 3H, -CO_2CH_3), 4.63-4.68 (m, 1H, -CH<), 5.38-5.73 (m, 2H, CH_2=), 6.36 (d, *J*=7.3 Hz, 1H, -C(O)-NH-), 7.19-7.39 (m, 15H, -$C(C_6H_5)_3$) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 18.48, 33.96, 51.17, 52.70, 66.88, 120.43, 128.02, 129.50, 139.40, 144.31, 167.74, 171.01 ppm. IR (KBr): 3333, 1743, 1657, 1612, 1442, 1205, 745, 702 cm^{-1}. Anal. Calcd. for $C_{27}H_{27}NO_3S$ Calcd C 72.78 H 6.11 N 3.14 S 7.20.

Found C 72.85 H 6.17 N 3.02 S 7.41.

2.2.4. *Synthesis of N-Pivaloyl-S-trityl-L-cysteine methyl ester (PA-C(Trt)-M)*

PA-C(Trt)-M was synthesized from pivalic acid (2.92 g, 28.6 mmol) and crude L-cysteine methyl ester hydrochloride (11.7 g, 27 mmol) in the similar way as MA-C(Trt)-M as mentioned above, and purified by silica gel column chromatography eluted with ethyl acetate/*n*-hexane (volume ratio 1/1), followed by recrystallization from ethyl acetate to obtain coroless solid (PA-C(Trt)-M). Yield 6.9 g (56 %), mp 143-144 °C $[\alpha]_D^{30}$= 23 ° (*c*=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.18 (s, 9H, $(CH_3)_3C$-), 2.55-2.27 (m, 2H, -CH_2-S-), 3.70 (s, 3H, -CO_2CH_3), 4.57-4.61 (m, 1H, -CH_2-S-), 5.38-5.73 (m, 2H, =C(CH_3)-), 6.24 (d, *J* = 7.3Hz, 1H, -C(O)-NH-), 7.20-7.43 (m, 15H, -C(C_6H_5)$_3$) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 27.37, 33.92, 38.72, 50.91, 52.58, 66.61, 126.86, 127.93, 128.20, 129.46, 144.29, 171.18, 178.09 ppm. IR (KBr): 3340, 2969, 1744, 1667, 1491, 1443, 748, 705 cm^{-1}. Anal. Calcd for $C_{28}H_{31}NO_3S$ Calcd C 72.85 H 6.77 N 3.04 S 6.95.

Found C 72.78 H 6.82 N 3.08 S 7.14.

2.2.5. *Radical polymerization*

Typical procedure : To a monomer (3.00 mmol) in a polymerization tube was introduced AIBN (15 mg, 0.09 mmol), and subsequently a dry solvent (3 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. The conversion of the monomer was determined by ^{1}H NMR spectroscopy. The reaction mixture was poured into ethyl ether or *n*-hexane to precipitate a polymer. The ethyl ether- or *n*-hexane-insoluble polymer was isolated by filtration with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried in vacuo at 60 °C for 12 h.

2.2.6. *Deprotection of trityl group*

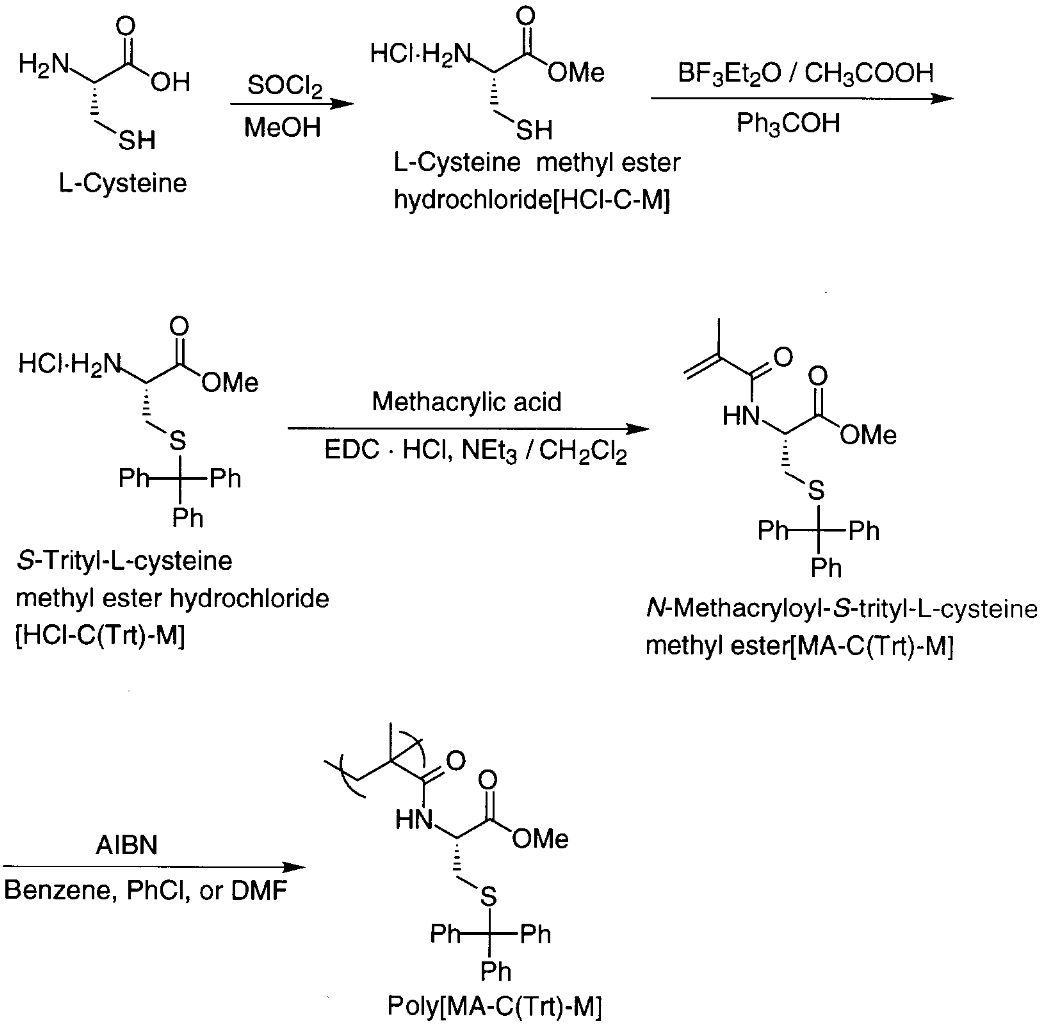
To an ice-cooled suspension of poly[MA-C(Trt)-M] (0.445 g) in acetic acid (3.0 mL) was added dropwise HBr/CH3COOH (30 wt %, 1.0 mL), and the mixture was stirred at room temperature under an atmosphere of nitrogen. The reaction mixture changed into clear after 5 minutes. The resulting mixture was poured into ether (150 mL) to precipitate a polymer. The ethyl ether-insoluble polymer was filtered with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried in vacuo at 60 °C for 12 h. The resulting polymer was insoluble in common organic solvents.

2.3. Results and Discussion

2.3.1. *Monomer synthesis*

The monomer, *N*-methacryloyl-*S*-trityl-L-cysteine methyl ester [MA-C(Trt)-M] was synthesized by condensation of *S*-trityl-L-cysteine methyl ester hydrochloride with methacrylic acid using EDC·HCl in a satisfactory yield. The structure of the monomer was confirmed by ^{1}H, ^{13}C-NMR, and IR spectroscopy, besides elemental analysis. Trityl group was employed as the protecting group of the thiol moiety because of its appropriate protecting ability.[10]

Scheme 1 :



2.3.2. *Radical polymerization*

Radical polymerization of MA-C(Trt)-M was carried out at 60 °C for 20 h in the presence of AIBN (3 mol %) in benzene, chlorobenzene and DMF to afford the corresponding polymer, poly[MA-C(Trt)-M] with M_ns 47800~61400 in 81~88% yields, as summarized in Table 1.

Table 1. Radical polymerization of MA-C(Trt)-M[a)]

Run.	Solv.	Conv.[b)] (%)	Yield [c)] (%)	M_n (M_w / M_n)[d)]	[α] D[e)] (°)
1	benzene	98	88	49800 (2.12)	25
2	PhCl	85	84	47800 (2.23)	23
3	DMF	93	81	61400 (2.23)	26

a) Conditions: monomer conc. 1 mol/L, initiator AIBN 3 mol %, 60 °C, 20 h. b) Determined by ^{1}H-NMR. c) Ether-insoluble part. d) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). e) Measured by a polarimater at 30 °C (*c*=1.00, $CHCl_3$).

2.3.3. *Radical copolymerization*

Radical copolymerization of MA-C(Trt)-M with MMA was examined with various feed monomer molar ratios. The copolymers were isolated by precipitation with ethyl ether or *n*-hexane in 65-92% yields as summarized in Table 2. The copolymer compositions corresponded to the feed molar ratios. The M_ns of the polymers obtained in the polymerization in DMF were larger than those in benzene and chlorobenzene. It is noteworthy that some copolymers showed larger specific rotation values compared with the homopolymer, poly[MA-C(Trt)-M]. As shown in Figure 1, no linear relationship was observed between the monomer compositions and the specific rotations of the copolymers. The maximum specific rotation was achieved by the copolymers with the MA-C(Trt)-M unit ratio of around 70/30 independent of the solvent used in the copolymerization.

Table 2. Radical copolymerization of MA-C(Trt)-M with MMA[a]

Feed Molar Ratio MA-C-(Trt)-M / MMA	Solv.	Conv.[b] (%)	Yield[c] (%)	Copolymer Composition[b] MA-C-(Trt)-M / MMA	M_n (M_w / M_n)[d]	$[\alpha]_D$[e] (°)
0 / 100	none	—	86[f]	0 / 100	130000 (2.69)	0
30 / 70	benzene	92	92[f]	17 / 83	13400 (1.72)	27
30 / 70	PhCl	88	86[f]	27 / 73	21400 (2.16)	28
30 / 70	DMF	72	70[f]	18 / 82	31300 (1.61)	20
50 / 50	benzene	95	90	45 / 55	16400 (2.06)	35
50 / 50	PhCl	91	89	47 / 53	28400 (1.59)	33
50 / 50	DMF	74	65	35 / 65	32000 (1.62)	28
70 / 30	benzene	96	90	60 / 40	33000 (1.72)	39
70 / 30	PhCl	91	83	69 / 31	23000 (2.26)	35
70 / 30	DMF	90	81	62 / 38	64000 (2.12)	35
100 / 0	benzene	98	88	100 / 0	49800 (2.12)	25
100 / 0	PhCl	85	84	100 / 0	47800 (2.23)	23
100 / 0	DMF	93	81	100 / 0	61400 (2.23)	26

a) Conditions: total monomer conc. 1 mol/L, initiator AIBN 3 mol %, 60 °C, 20 h. b) Determined by ^{1}H-NMR. c) Ether-insoluble part. d) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). e) Measured by a polarimater at 30 °C (c=1.00, $CHCl_3$). f) n-Hexane-insoluble part.

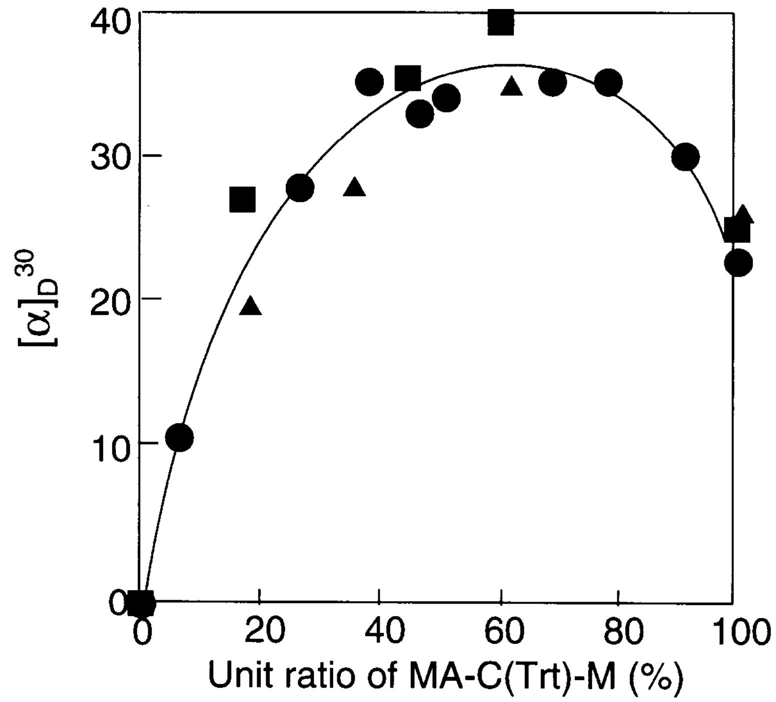


Figure 1. Relationship between the monomer unit ratio and the specific rotation (c =1.00, $CHCl_3$) of poly[MA-C(Trt)-M-*co*-MMA] obtained by the polymerization in benzene (■), chlorobenzene (●), and DMF (▲).

Possible reasons for this interesting result may be followings. One may be asymmetric induction from the L-cysteine moiety into the polymer main chain. Another reason may be due to higher order structures of the polymer such as a helix structure. Similar nonlinear effects of specific rotation have been reported in the cases of the copolymers obtained by radical polymerization of chiral styrene derivatives with achiral monomers, styrene, vinylnaphthalene, and methacrylates, where the specific rotation curves depend on the comonomers.[11] It has been reported that methacrylates with bulky ester substituents such as triphenylmethyl methacrylate (TrtMA) afford helical polymers by anionic polymerization initiated with chiral initiators.[12] Bulky ester groups are effective to induce the helical structure, which results in a large specific rotation value of the polymer. Further, it has been reported that in the radical copolymerization of optically active phenyl-2-pyridyl-*o*-tolylmethyl methacrylate with TrtMA, highly isotactic copolymers are obtained, and the optically active methacrylate induces a helical conformation, while in the copolymerization with MMA, atactic polymers are obtained with much smaller optically activity than the copolymers with TrtMA.[13] Employed TrtMA as the comonomer instead of MMA in the radical copolymerization of MA-C(Trt)-M in this work, a different relationship may be observed between the copolymer composition and the specific rotation. Table 3 summarizes the conditions and results of the copolymerization of MA-C(Trt)-M with TrtMA. The M_ns of the copolymers were lower compared with those of the copolymers of MA-C(Trt)-M with MMA. The maximum specific rotation could not be observed for poly[MA-C(Trt)-M] but for poly[MA-C(Trt)-M$_{81}$-*co*-TrtMA$_{19}$] as shown in Figure 2. The unit ratio-$[\alpha]_D$ curve of poly[MA-C(Trt)-M-*co*-TrtMA] showed the maximum with the MA-C(Trt)-M content somewhat larger compared with that of poly[MA-C(Trt)-M-*co*-MMA].

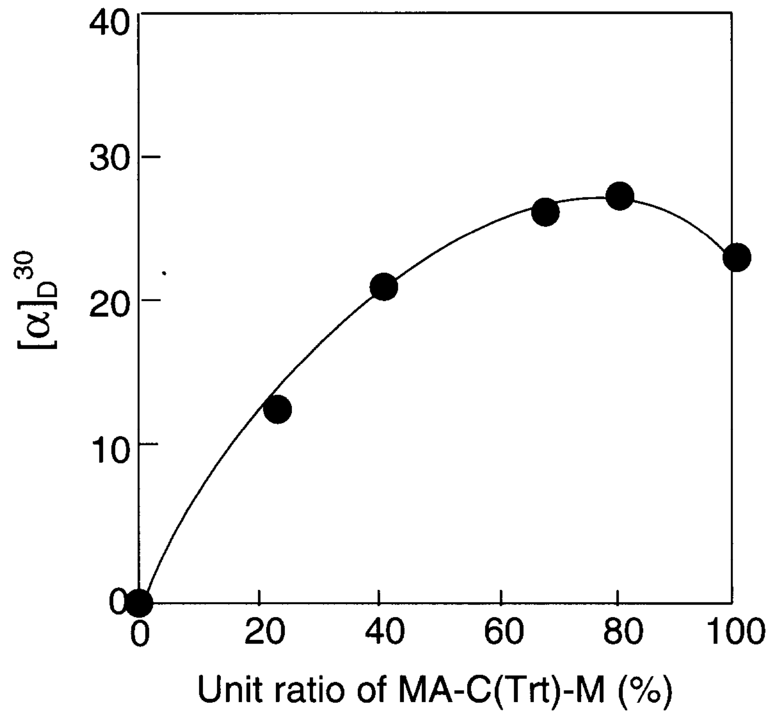


Figure 2. Relationship between the monomer unit ratio and the specific rotation (c =1.00, $CHCl_3$) of poly[MA-C(Trt)-M-*co*-TrtMA].

Table 3. Radical copolymerization of MA-C(Trt)-M with TrtMA[a)]

Feed Molar Ratio MA-C-(Trt)-M / TrtMA	Conv.[b)] (%)	Yield [c)] (%)	Copolymer Composition[b)] MA-C-(Trt)-M / TrtMA	M_n (M_w / M_n)[d)]	$[\alpha]_D$[e)] (°)
30 / 70	76	75[f)]	23 / 77	13200 (2.13)	13
50 / 50	75	74	41 / 59	13500 (1.97)	21
70 / 30	86	82	68 / 32	17200 (2.35)	26
80 / 20	88	88	81 / 19	24200 (2.13)	27

a) Conditions: total monomer conc. 1 mol/L, initiator AIBN 3 mol %, 60 °C, 20 h in chlorobenzene (1 M). b) Determined by ^1H-NMR. c) Ether-insoluble part. d) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). e) Measured by a polarimater at 30 °C (c=1.00, $CHCl_3$). f) *n*-Hexane-insoluble part.

The triad tacticity of poly[MA-C(Trt)-M] was determined as syndio (rr) : hetero (rm) : iso (mm) = 53 : 11 : 36 by the integration ratio of the carbonyl carbon signals (168 - 174 ppm) of ^{13}C-NMR as shown in Figure 3.[14] No significant difference could be observed in the tacticity between homopoly[MA-C(Trt)-M] and the copolymers with MMA and TrtMA.

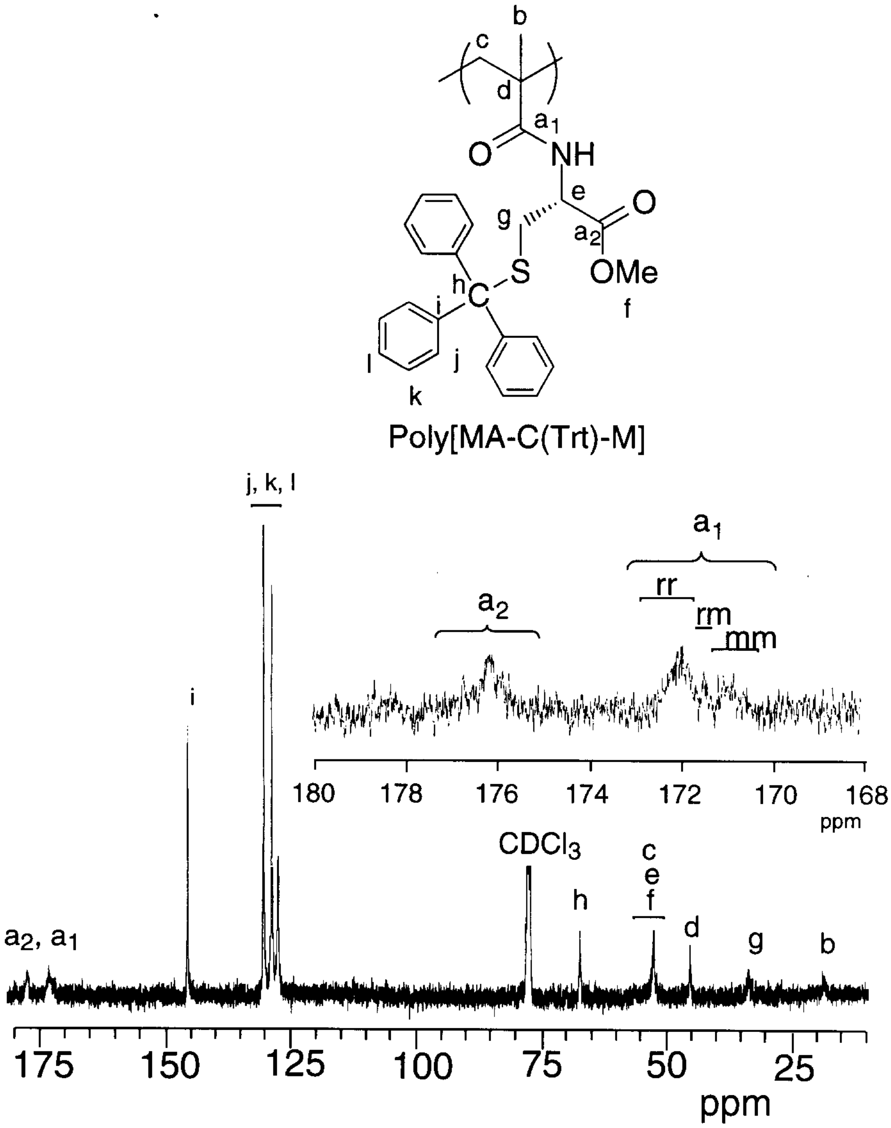


Figure 3. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of poly[MA-C(Trt)-M] obtained in the polymerization with AIBN (3 mol %) in chlorobenzene at 60 °C for 20 h (run 2 in Table 1).

Figure 4 illustrates the CD spectra of poly[MA-C(Trt)-M-*co*-MMA], poly[MA-C(Trt)-M-*co*-TrtMA], and a model compound of the polymer unit, *N*-pivaloyl-*S*-trityl-L-cysteine methyl ester [PA-C(Trt)-M]. All of the polymers showed negative and positive cotton effects around 260 and 240 nm, respectively. The absolute values of the specific ellipticity [ψ] at λmax of the polymers were larger than those of the model compound, and increased as the composition of the chiral monomer increased in the copolymer. The CD and specific rotation results suggest that the copolymers of MMA and TrtMA may not have a regurated higher order structure such a helical conformation.

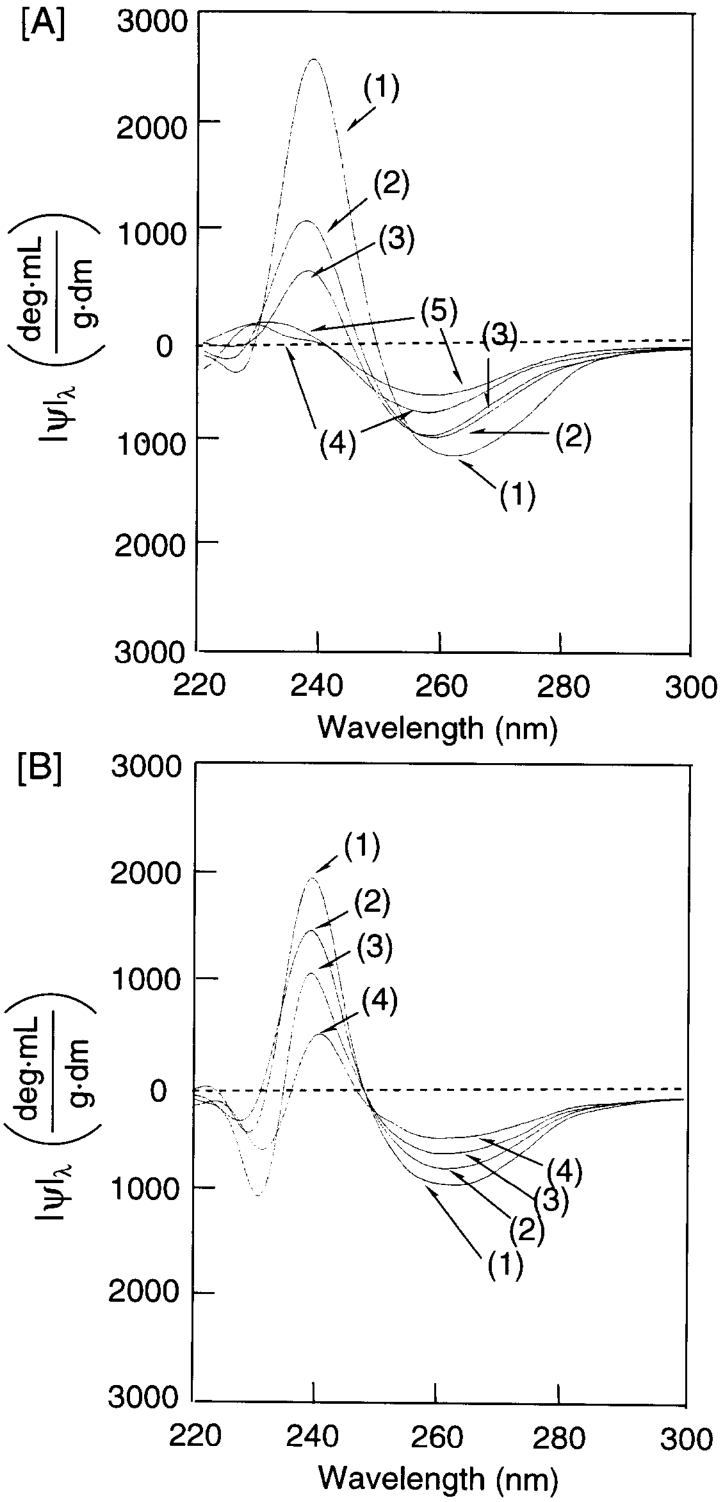


Figure 4. CD (c 0.01 g/dL, $CHCl_3$) spectra of the polymers obtained in chlorobenzene, and a model compound. [A] Poly[MA-C(Trt)-M-*co*-MMA] and PA-C(Trt)-M. (1) Poly[MA-C(Trt)-M], (2) Poly[MA-C(Trt)-M_{78}-*co*-MMA_{22}], (3) Poly[MA-C(Trt)-M_{51}-*co*-MMA_{49}], (4) Poly[MA-C(Trt)-M_{27}-*co*-MMA_{73}], (5) PA-C(Trt)-M. [B] Poly[MA-C(Trt)-M-*co*-TrtMA]. (1) Poly[MA-C(Trt)-M_{81}-*co*-$TrtMA_{19}$], (2) Poly[MA-C(Trt)-M_{68}-*co*-$TrtMA_{32}$], (3) Poly[MA-C(Trt)-M_{41}-*co*-$TrtMA_{59}$], (4) Poly[MA-C(Trt)-M_{23}-*co*-$TrtMA_{77}$].

Table 4 summarizes the radical copolymerization of MA-C(Trt)-M with styrene (ST). The specific rotation of poly[MA-C(Trt)-M-*co*-ST] was constant independent of the copolymer composition exept for the copolymer with 21% of MA-C(Trt)-M ratio. No apparent Tg was observed up to 200 °C in the cases of the homopolymer of MA-C(Trt)-M and the copolymers with MMA, TrtMA and ST. Td_{10}s were observed in the range of 258~280 °C.

Table 4. Radical copolymerization of MA-C(Trt)-M with ST[a)]

Feed Molar Ratio			Copolymer Composition[b)]		
MA-C-(Trt)-M / ST	Conv.[b)] (%)	Yield[c)] (%)	MA-C-(Trt)-M / ST	M_n (M_w / M_n)[d)]	$[\alpha]_D$[e)] (°)
20 / 80	55	40[f)]	21 / 79	13300 (1.21)	4
50 / 50	88	86	27 / 83	13600 (1.43)	21
70 / 30	100	99	60 / 40	13700 (1.45)	22
80 / 20	77	68	72 / 28	24200 (1.61)	22

a) Conditions: total monomer conc. 1 mol/L, initiator AIBN 3 mol %, 60 °C, 20 h in chlorobenzene (1 M). b) Determined by ^{1}H-NMR. c) Ether-insoluble part. d) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8mM). e) Measured by a polarimater at 30 °C (c= 1.00, $CHCl_3$). f) *n*-Hexane insoluble part.

2.3.4. *Deprotection of trityl group from poly[MA-C(Trt)-M]*

As described in the introduction, poly[MA-C(Trt)-M] can be expected as a reactive polymer utilizing its thiol group. The obtained poly[MA-C(Trt)-M] was treated with HBr in acetic acid to deprotect the trityl group. A polymer insoluble in common organic solvents was obtained quantitatively. When poly[MA-C(Trt)-M] was treated with HBr/CH_3CO_2H in acetic anhydride, the obtained polymer was partially soluble in common organic solvents. Figure 5 depicts the IR spectra of the poly[MA-C(Trt)-M] and solvent-insoluble polymers obtained by the reaction in acetic acid and acetic anhydride. The IR spectrum of poly[MA-C(Trt)-M] showed absorption peaks based on the phenyl group at

702 and 743 cm^{-1} [Figure 5, (a)], while those of acid-treated solvent-insoluble polymers did not [Figure 5, (b) and (c)]. Figure 5, (b) showed an absorption peak at 2559 cm^{-1} assignable to a thiol group, which was not observed in Figure 1, (a) and (c). In Figure 1, (c), an absorption peak assignable to a thioester unit (-S-C(O)-) was observed at 1132 cm^{-1}. Figure 6 depicts the ^{1}H-NMR spectrum of the solvent-soluble polymer obtained by the reaction with acetic anhydride, which showed no signals assignable to the trityl group but *S*-acetyl group.

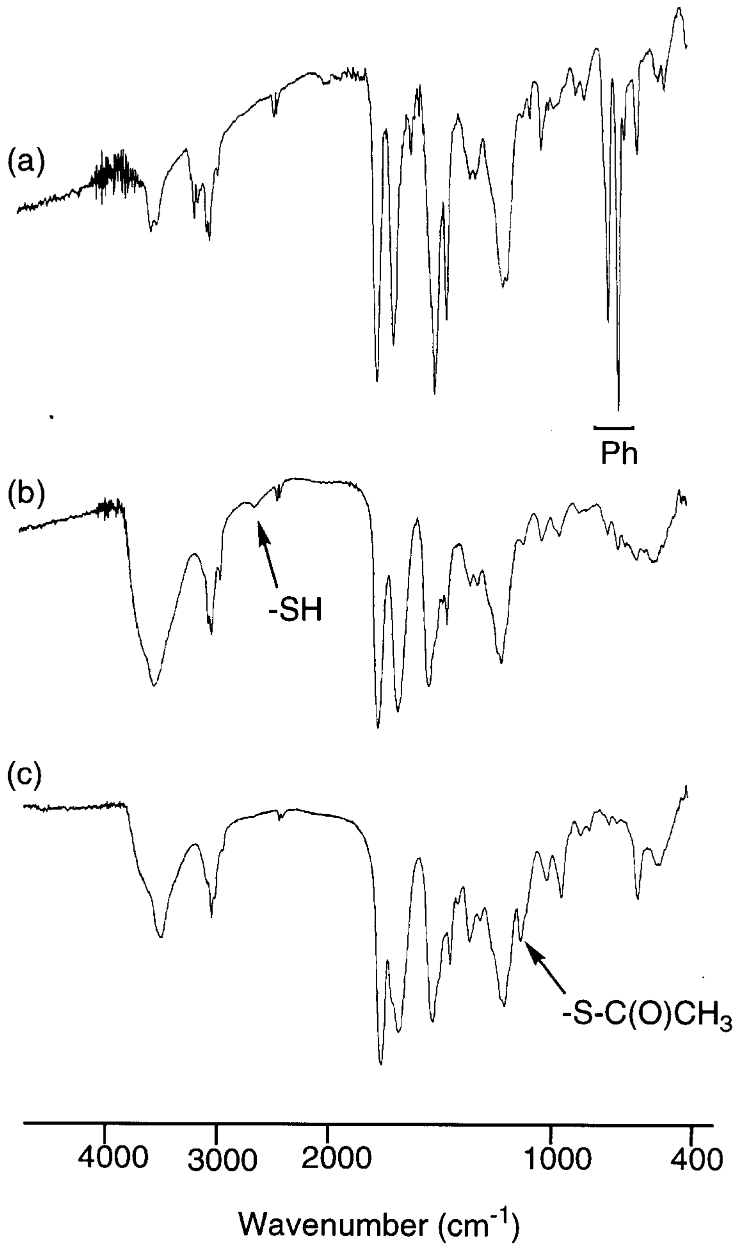
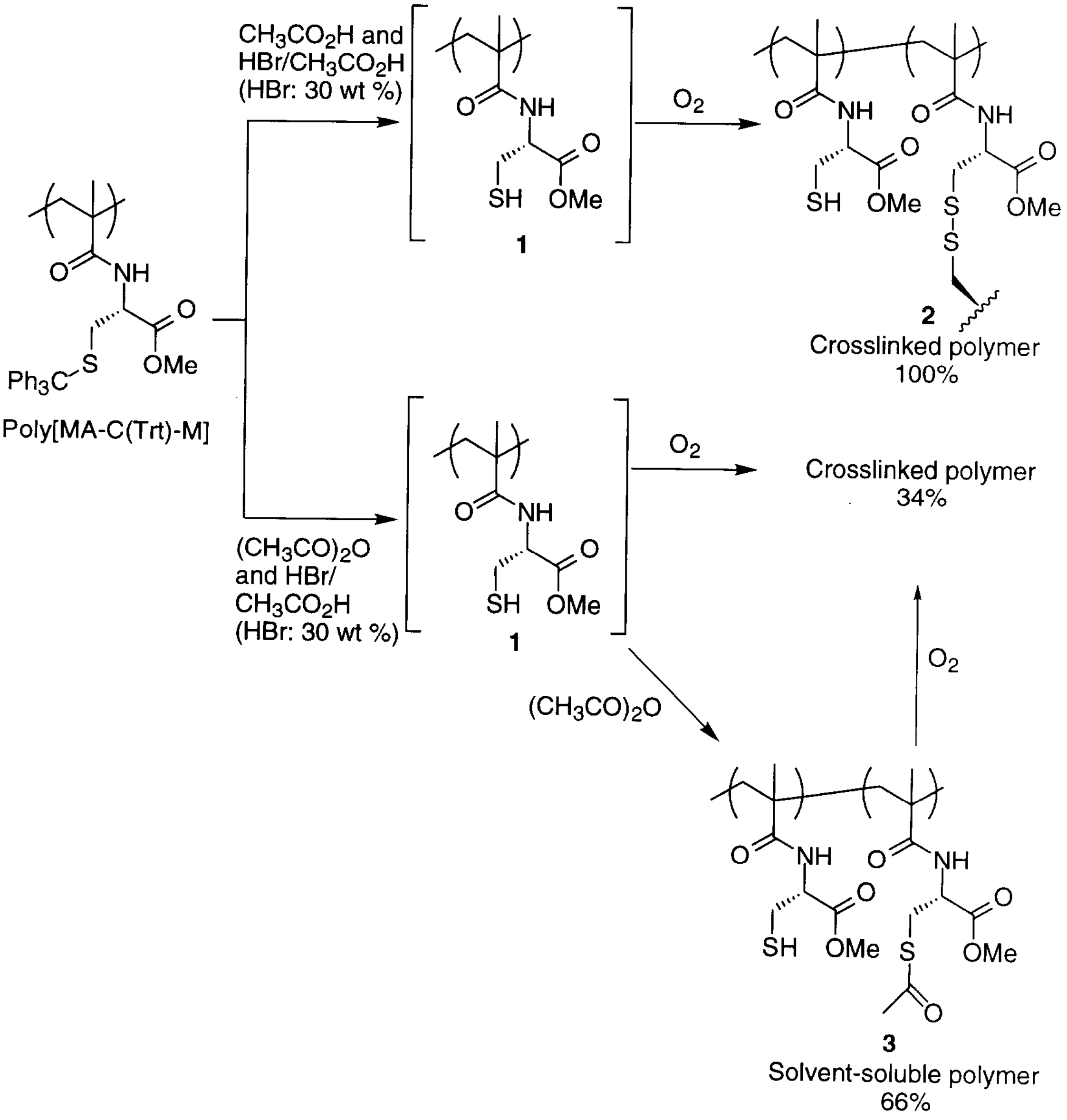


Figure 5. IR spectra (KBr) of (a) poly[MA-C(Trt)-M], (b) solvent-insoluble polymer obtained by the detritylation in CH_3CO_2H-HBr/CH_3CO_2H, and (c) solvent-insoluble polymer obtained by the detritylation in $(CH_3CO)_2O$-HBr/CH_3CO_2H.

From these spectroscopic data along with the solubility of the polymers, the deprotection of the trityl group can be summarized as shown in scheme 2. When CH_3CO_2H-HBr/CH_3CO_2H was used, the trityl group was completely cloven to afford the thiol substituted polymer (**1**), followed by auto-oxidation resulting in the crosslinked polymer (**2**) with a disulfide linkage. When $(CH_3CO)_2O$-HBr-CH_3CO_2H was used, the thiol group was partially acetylated to afford the acetylthioxy group substituted polymer (**3**), which should be less-oxidizable compared with **1**. The degree of acetylation of the solvent-soluble polymer was 38%, which could be estimated by the ^{1}H-NMR integration ratio of signals f and d, j at 2.18 and 2.38 ppm, respectively (Figure 6).

Scheme 2 :



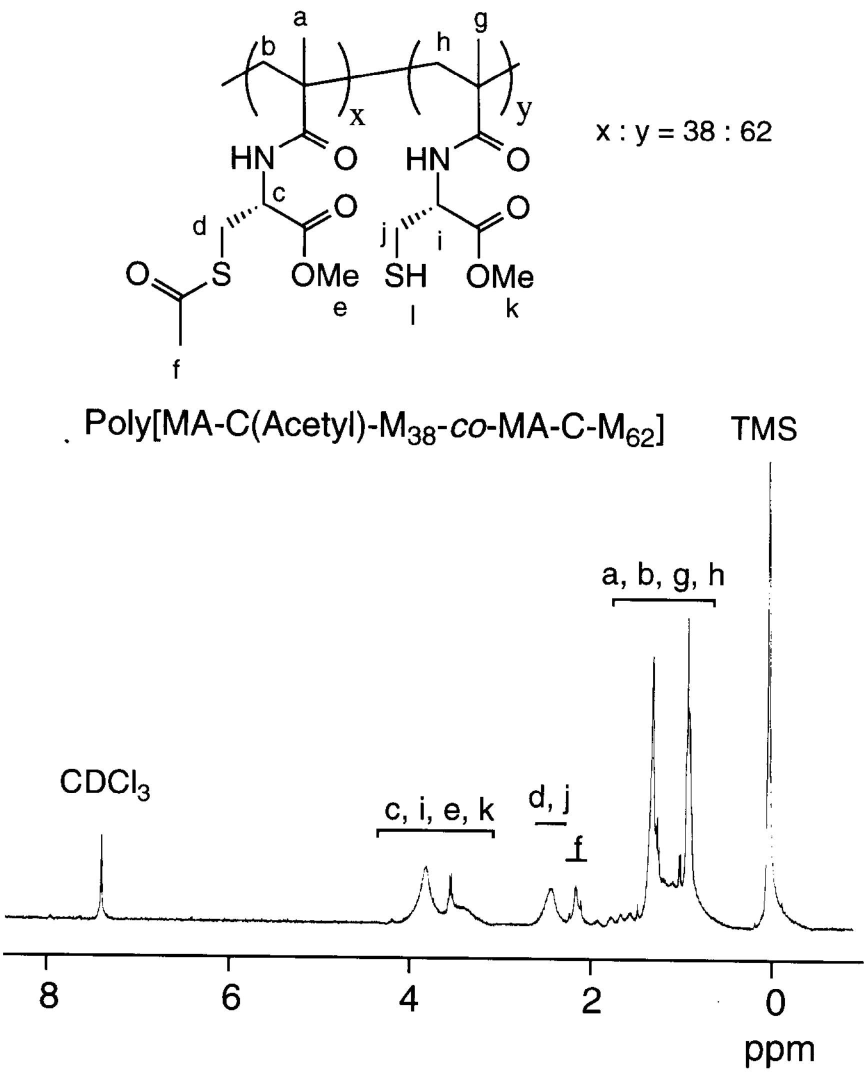


Figure 6. ^{1}H-NMR spectrum of poly[MA-C(Acetyl)-M-*co*-MA-C-M] obtained by the detritylation with $(CH_3CO_2)O$-HBr/CH_3CO_2H (HBr: 30 wt %).

2.4. Summary

In this chapter, a novel cysteine based methacrylamide, MA-C(Trt)-M was synthesized, and its radical homopolymerization and copolymerization with MMA, TrtMA, and ST were examined. The copolymers showed nonlinear relationships between the monomer composition and the specific rotation. Quantitative deprotection of the thiol group of the polymer could be achieved by the acid treatment.

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Chapter 3

Synthesis and Radical Polymerization of Cysteine-Based Macromonomers

Abstract

Synthesis and radical polymerization of cysteine-based macromonomers were examined. The macromonomers were synthesized by the radical oligomerization of methyl methacrylate (MMA) in the presence of cysteine methyl ester hydrochloride (HCl·CM) as a chain transfer agent with AIBN (3 mol %) as an initiator in DMF at 60 °C for 20 h, followed by the reaction of the obtained oligomers with methacryloyl chloride in the presence of NEt_3 in CH_2Cl_2. The degrees of polymerization of the macromonomers were evaluated on the basis of the end methacryloyl group by ^{1}H-NMR spectroscopy. The macromonomers afforded the corresponding graft polymers by radical polymerization and copolymerization with MMA and styrene.

3.1. Introduction

Amino acids are expected not only as biocompatible materials but also as sources of chemically functional materials. Endo et al. has developed polymers based on amino acids and peptides as biocompatible materials as well as optical and chemically functional materials.[1] Cysteine is characterized by its mercapto group, which can serve as chain transfer agent.[2] Radical chain transfer reaction is the most convenient and widely employed method to synthesize macromonomers.[3] A large variety of macromonomers has been synthesized by radical,[4] anionic,[5] and cationic polymerization,[6] as the precursors of graft polymers, which are applicable to coatings, adhesives, compativilizers and emulsifiers. However, no research has been reported concerning the macromonomer and graft polymer synthesis utilizing cysteine as far as I know. In this chapter, I describe the synthesis and radical polymerization of novel macromonomers using cysteine as a chain-transfer agent.

3.2. Experiments

3.2.1. *Measurements*

^1H and ^{13}C-NMR spectra were recorded on a JEOL JNM EX-400 spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). IR spectra were measured with a JASCO FTIR-5300 spectrometer. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter using a sodium lamp as a light source. Molecular weights (M_n) and polydispersity ratios (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC, HLC-8020 system, equipped with three consecutive polystyrene gel columns (TSK-gels, G5000H, G4000H, and G2500H), using *N,N*-dimethylformamide (DMF, 5.8 mM lithium bromide solution) as an eluent at a flow rate of 1.0 mL/min, polystyrene calibration, and refractive index and ultraviolet detectors. Thermal analyses were performed on Seiko instruments TG/DTA 220 and DSC 220C. Glass transition temperatures (T_g) were taken as an inflection point on a trace at a heating rate of 10 °C/min by differential scanning calorimetry (DSC). Temperatures with 10 % weight loss (T_{d10}) were determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under nitrogen atmosphere.

3.2.2. *Materials*

L-Cysteine was obtained from Ajinomoto Co. Initiator 2, 2'-azobis(isobutyronitrile) (AIBN), methyl methacrylate (MMA), and styrene (ST) were purchased from Tokyo Kasei Kogyo Co. Dichloromethane and DMF were distilled over calcium hydride before use.

L-Cysteine methyl ester hydrochloride (HCl·CM)

Thionyl chloride (78 mL, 0.9 mol) was added to methanol (300 mL) dropwise at -10 °C, and the mixture was stirred for 10 min. L-Cysteine (36.35 g, 300 mmol) was added to the mixture, and it was stirred for 15 h at room temperature under nitrogen. The reaction mixture was concentrated by a rotary evaporator and the residual mass was washed with ethyl ether (300 mL) several times to obtain white powder, which was purified by recrystallization from methanol twice to obtain colorless solid, L-cysteine methyl ester hydrochloride (HCl·CM). Yield 27.8 g (54%). Mp = 140-141 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 2.96-3.09 (m, 2H, -CH_2-S-), 3.34 (m, 1H, -SH), 3.75 (s, 3H, -$COOCH_3$), 4.19-4.37 (m, 1H, >CH-), 6.35-6.36 (broad, 3H, HCl·NH_2-) ppm. ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 24.15, 52.96, 53.93, 169.18 ppm. IR (KBr): 3326, 2955, 1755, 1655, 1618, 1520, 1435, 1200, 932, 631 cm^{-1}. Anal. Calcd for $C_4H_{10}NO_2SCl$: C 27.98, H 5.87, N 8.16, S 18.68, Cl 20.68. Found. C 27.95, H 6.01, N 8.41, S 18.42, Cl 20.71.

3.2.3. *Polymerization of MMA in the presence of HCl·CM (Synthesis of Premacromonomers)*

Typical Procedure: To MMA (3.00 g, 30 mmol) in a polymerization tube were introduced HCl·CM (0.258 g, 1.5 mmol) and AIBN (0.15 g, 0.9 mmol), and subsequently DMF (3.15 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. The reaction mixture was poured into ethyl ether/*n*-hexane (volume ratio 1/1, 200 mL) to precipitate an oligomer. It was filtered with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried *in vacuo* at 40 °C for 12 h to obtain the premacromonomer. Yield 3.03 g (93%). M_n = 14600, M_w/M_n = 1.41. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.84-1.27 (broad m, 70.5H, CH_3-, polyMMA), 1.71-1.94 (broad m, 43H,

-CH_2-, polyMMA), 2.74-2.78 (m, 5H, -CH_2-S-CH_2-, -CH, polymer end), 3.76 (broad s, 70.5H, -OCH_3, polyMMA), 3.85 (s, 3H, -OCH_3, cysteine in the polymer end), 8.93-9.34 (broad m, 3H, HCl·NH_2-, polymer end) ppm. IR (KBr): 3409, 2955, 1740, 1655, 1657, 1522, 1439, 1213, 1024, 978, 542 cm^{-1} (run 7 in Table 1).

3.2.4. Synthesis of *macromonomer*

Typical procedure: To a solution of the premacromonomer synthesized above (3.07 g) in dichloromethane (31 mL) were added triethylamine (2.1 mL, 15 mmol), and then a solution of methacryloyl chloride (0.73 g, 7.5 mmol) in dichloromethane (5.0 mL) slowly at 0 °C under nitrogen. The mixture was stirred at room temperature for 2 days. The resulting mixture was concentrated by a rotary evaporator, and the residual mass was washed with *n*-hexane to remove unreacted methacryloyl chloride and triethylamine. The mass was purified by silica gel column chromatography using $CHCl_3$ as an eluent, and then by preparative HPLC (Nihon Bunseki Kogyo), equipped with two polystyrene gel columns (JAI-GELs H1 and H2), using $CHCl_3$ as an eluent, and further precipitation with *n*-hexane to obtain white powder. It was filtered with a membrane filter and then dried *in vacuo* at 40 °C for 12 h. Yield 1.87 g (61%). M_n = 14000 (M_w/M_n = 1.41). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.84-1.43 (broad m, 82.5H, CH_3-, polyMMA, cysteine in the polymer end), 1.53-2.07 (broad m, 53H, -CH_2-, polyMMA), 2.74-3.00 (m, 5H, -CH_2-S-CH_2-, -CH, polymer end), 3.60 (broad s, 70.5H, -OCH_3, polyMMA), 3.78 (s, 3H, -OCH_3, cysteine in the polymer end), 5.43-5.81 (m, 2H, CH_2=C<, polymer end), 6.58-6.78 (m, 1H, -NH-, polymer end) ppm. IR (KBr): 3450, 2998, 2952, 1732, 1437, 1194, 1150, 990 cm^{-1} (run 7 in Table 1).

3.2.5. *Radical polymerization of macromonomer*

Typical procedure: To the macromonomer (0.1 g) synthesized above in a polymerization tube were introduced AIBN (0.25 mg, 0.25 wt%), and subsequently DMF (1 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. $CHCl_3$ (2 mL) was added to the reaction mixture and the resulting mixture was poured into *n*-hexane to precipitate a white powdery polymer. The *n*-hexane-insoluble polymer was filtered with a membrane filter and then dried *in vacuo* at 40 °C for 12 h. Yield 0.095 g (95%). $M_n = 15200$ ($M_w/M_n = 1.21$) (run 3 in Table 2).

3.3. Results and Discussion

3. 3. 1. *Premacromonomer synthesis*

The radical oligomerization of MMA was carried out with AIBN (3 mol %) as an initiator in DMF at 60 °C for 20 h in the presence of HCl·CM as a chain transfer agent to afford the corresponding oligomer, premacromonomer (Scheme 1). Table 1 summarizes the M_n estimated by GPC and the degree of polymerization (DP_n) calculated by the ^{1}H-NMR integration ratio between the methyl ester signals of HCl·CM and poly methyl methacrylate (polyMMA) at 3.85 and 3.76 ppm, respectively.

Scheme1:

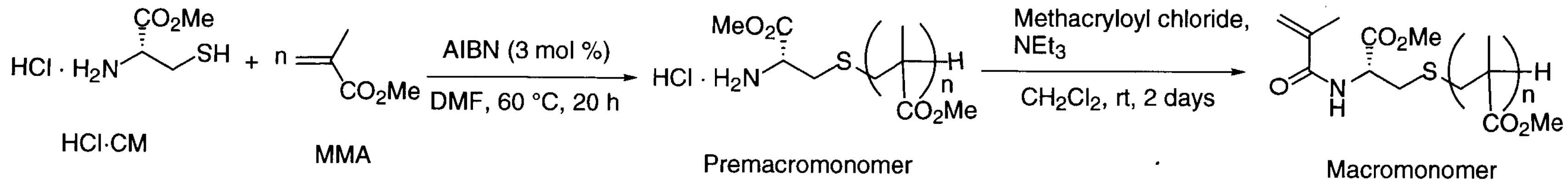

Table 1. Radical oligomerization of MMA in the presence of HCl·CM [a], and reaction with methacryloyl chloride of the obtained oligomers[b]

Run	Feed Molar Ratio	Premacromonomer			Macromonomer		
	HCl·CM / MMA	Yield [c] (%)	M_n (M_w / M_n) [d]	DP_n [e]	Yield [f] (%)	M_n (M_w / M_n) [d]	DP_n [e]
1	1 / 1	quant.	3400 (1.04)	1.7	-	-	-
2	1 / 1.25	94	5000 (1.10)	1.7	-	-	-
3	1 / 1.67	94	5600 (1.10)	2.4	-	-	-
4	1 / 2.5	99	6700 (1.17)	3.6	-	-	-
5	1 / 5	quant.	8600 (1.21)	6.3	quant.	9100 (1.29)	7.3
6	1 / 10	85	10600 (1.23)	11.4	85	11000 (1.11)	11.5
7	1 / 20	93	14600 (1.41)	23.5	61	14000 (1.41)	26.5
8	1 / 30	90	24500 (1.24)	- [g]	74	23800 (1.65)	- [g]

a) Conditions: MMA 30 mmol in DMF 3.15 mL, initiator AIBN (3 mol %), 60 °C, 20 h. b) In CH_2Cl_2 in the presence of NEt_3 at room temperature for 2 days. c) Ethyl ether/n-hexane (1/1)-insoluble part. d) Estimated by GPC based on polystyrene standard samples; LiBr solution in DMF (5.8 mM). e) Calculated by ^{1}H-NMR. f) *n*-Hexane-insoluble part. g) Not determined.

The M_n and $1/DP_n$ of the oligomers increased as the feed molar ratio of HCl·CM decreased. The oligomers obtained in runs 1 ~ 7 in Table 1 showed ^{1}H-NMR signals assignable to amino and methyl ester groups of L-cysteine methyl ester, but the oligomer in run 8 did not. As shown in Figure 1, a linear relationship was observed between the feed molar ratio of HCl·CM/MMA and DP_n calculated by ^{1}H-NMR. HCl·CM served as an efficient chain transfer agent to be incorporated into the polymer end. Yamashita et al. have determined C_s of thioglycolic acid as 0.50 - 0.75 in the radical polymerization of MMA.[7] In this work, C_s of HCl·CM in the radical polymerization of MMA was calculated as 0.61 from Figure 1.[8]

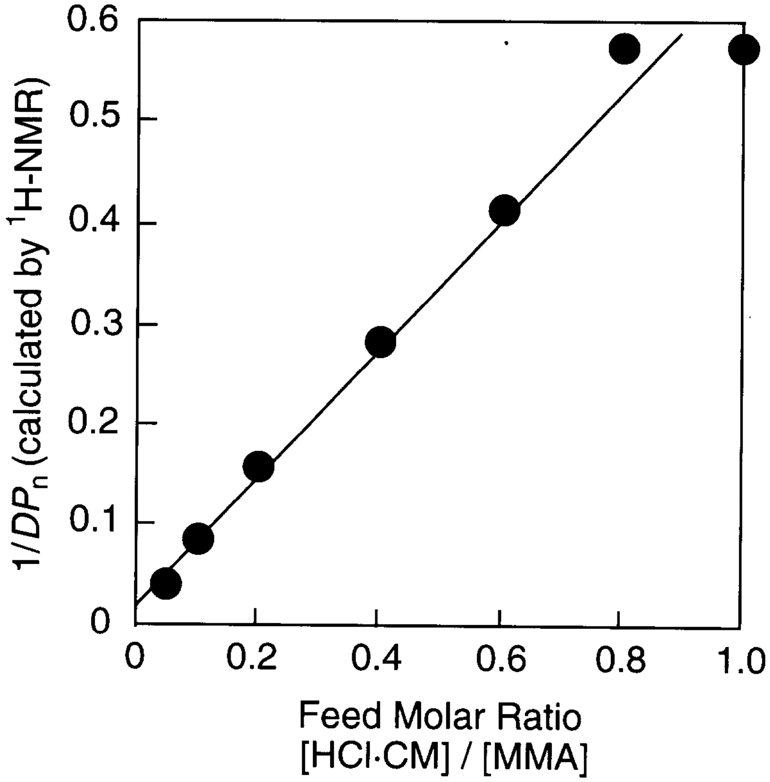

Figure 1. Relationship between [HCl·CM] / [MMA] and 1/DPn, in the radical polymerization of MMA in the presence of HCl·CM. Conditions: MMA 30 mmol, DMF 31.5 mL, initiator AIBN (3 mol%), 60 °C, 20 h.

3.3.2. *Macromonomer synthesis*

The premacromonomers were converted into the corresponding macromonomers by the reaction with methacryloyl chloride in the presence of NEt_3 in CH_2Cl_2 (Scheme 1, Table 1). The macromonomers were obtained in good yields, which showed almost the same M_n and DP_n as the corresponding premacromonomers. Figure 2 illustrates the ^{1}H-NMR spectrum of the macromonomer obtained by the oligomerization of MMA in the presence of 1/20 equivalent of HCl·CM, followed by the reaction with methacryloyl chloride (run 7 in Table 1). The incorporation of methacryloyl group was confirmed by the presence of the corresponding signals *a* and *e* at 5.43-5.81 and 3.79 ppm, whose integration ratio to that of polyMMA methyl ester signals at 3.60 ppm showed the DP_n = 26.5. This value agreed well with that of the corresponding premacromonomer (23.5).

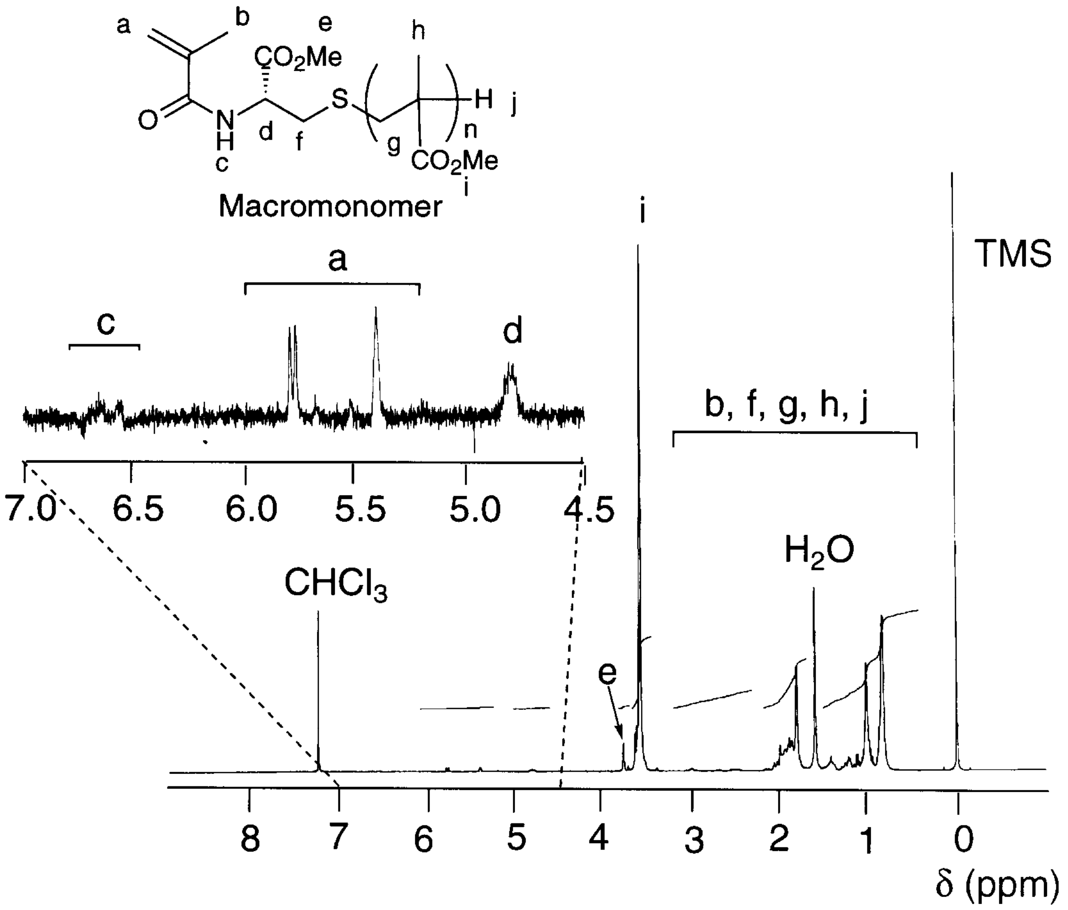

Figure 2. ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of the macromonomer (M_n 14000, M_w/M_n 1.41, $DP_n = 26.5$) obtained in run 7 in Table 1.

3.3.3. *Radical polymerization of macromonomers*

The radical polymerization of the macromonomers was carried out at 60 °C for 20 h in the presence of AIBN (0.25 wt %) in DMF to afford the corresponding graft polymers in good yields, which showed no residual olefin proton signals in the ^{1}H-NMR spectra (Scheme 2). The macromonomer with the M_n of 9100 afforded the higher molecular weight polymer with the M_n of 69600 (run 1 in Table 2). The M_w/M_n became wider from 1.29 to 4.58 after polymerization. Meanwhile, the macromonomers with the M_ns of 11000 and 14000 showed slight M_n increase under the similar polymerization conditions (runs 2 and 3 in Table 2), probably due to the lower concentration of the methacryloyl group. The resulting graft polymers also showed no residual olefin proton signals in the ^{1}H-NMR spectra. Further, radical copolymerization of the macromonomer (M_n 14000, M_w/M_n 1.41) with MMA and ST was examined with various feed ratios (Table 3). The copolymers with ST were purified by HPLC, followed by precipitation with *n*-hexane, because the resulting copolymers were contaminated with oligoST.

Scheme 2:

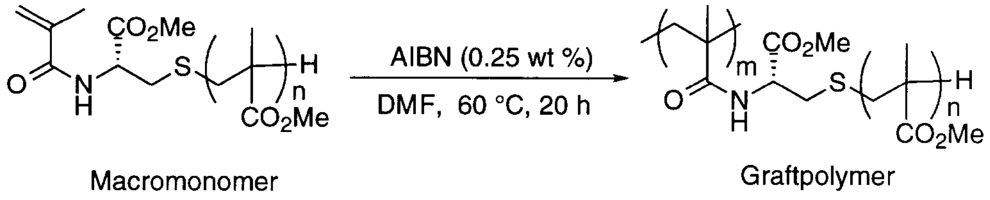

Table 2. Radical polymerization of the macromonomers [a)]

Run	Macromonomer		Graft polymer	
	M_n (M_w / M_n)	DP_n	Yield [b)] (%)	M_n (M_w / M_n) [c)]
1	9100 (1.29)	7.3	quant.	69600 (4.58)
2	11000 (1.11)	11.5	94	14800 (1.48)
3	14000 (1.41)	26.5	95	15200 (1.21)

a) Conditions: macromonomer 0.1 g in DMF 0.1 mL, initiator AIBN 0.25 wt %, 60 °C, 20 h. b) n-Hexane-insoluble part. c) Estimated by GPC based on polystyrene standard samples; LiBr solution in DMF (5.8 mM).

Table 3. Radical copolymerization of the macromonomers with MMA and ST [a)]

Run	Macromonomer	Comonomer	Feed Ratio (wt %)	Yield [b)] (%)	M_n [C)] (M_w / M_n)	Tg [e)] (°C)
	M_n (M_w / M_n)		Macromonomer / Comonomer			
1	11000 (1.11)	-	100 / 0	81	14800 (1.48)	- [f)]
2	11000 (1.11)	MMA	75 / 25	76	16000 (1.50)	- [f)]
3	11000 (1.11)	MMA	50 / 50	80	17600 (1.60)	- [f)]
4	11000 (1.11)	MMA	25 / 75	95	21000 (1.62)	- [f)]
5	11000 (1.11)	ST	75 / 25	65 [d)]	17000 (1.30)	- [f)]
6	11000 (1.11)	ST	50 / 50	40 [d)]	16500 (1.22)	- [f)]
7	11000 (1.11)	ST	25 / 75	34 [d)]	19500 (1.33)	- [f)]
8	14000 (1.41)	-	100 / 0	quant.	15200 (1.21)	83
9	14000 (1.41)	MMA	75 / 25	quant.	14500 (1.51)	82
10	14000 (1.41)	MMA	50 / 50	85	19500 (1.33)	81
11	14000 (1.41)	MMA	25 / 75	95	22000 (1.859	79
12	14000 (1.41)	ST	75 / 25	50 [d)]	16700 (1.24)	82
13	14000 (1.41)	ST	50 / 50	35 [d)]	16000 (1.30)	83
14	14000 (1.41)	ST	25 / 75	28 [d)]	20000 (1.27)	85

a) Conditions: total monomer 0.1 g in DMF (0.1 mL), initiator AIBN (0.25 wt %), 60 °C, 20 h. b) n-Hexane-insoluble part. c) Estimated by GPC based on polystyrene standard samples; LiBr solution in DMF (5.8 mM). d) Separated by HPLC in $CHCl_3$. e) Determined by DSC. f) Not observed.

Figure 3 illustrates the GPC profiles of the macromonomer (M_n 14000, M_w/M_n 1.41) and the polymers obtained by the polymerization and copolymerization with MMA and ST. The peak top of the GPC curve of the macromonomer shifted to the higher molecular weight region after polymerization. The copolymerization with MMA and ST [(C), (D)] showed larger shift than the homopolymerization [(B)] as commonly reported in the macromonomer polymerization.[9] The GPC-curve shift and unimodal GPC profiles suggested that the polymerization and copolymerization of the macromonomer proceeded satisfactorily.

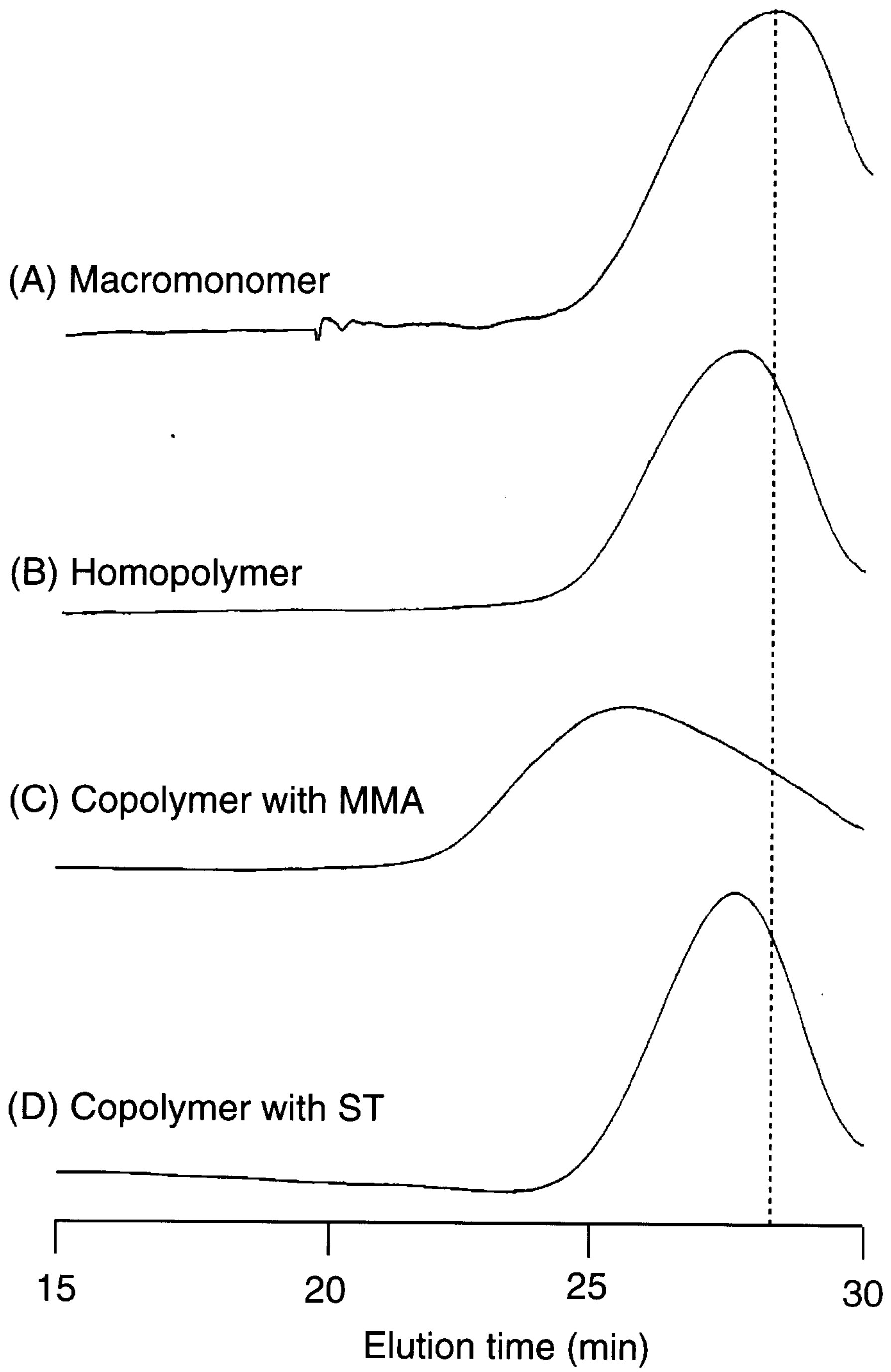

Figure 3. GPC profiles (RI detector) of the macromonomer and graftpolymers obtained by the radical polymerization. (A) macromonomer (M_n 14000, M_w/M_n 1.41, run 7 in Table 1), (B) homopolymer of the macromonomer (M_n 15200, M_w/M_n 1.21, run 3 in Table 2), (C) copolymer of the macromonomer and MMA with the feed weight ratio of 50 : 50 (M_n 19500, M_w/M_n 1.73, run 10 in Table 3), (D) copolymer of the macromonomer and ST with the feed weight ratio of 50 : 50 (M_n 16000, M_w/M_n 1.30, run 13 in Table 3).

3.3.4. *Thermal property of the graft polymer*

Figure 4 illustrates the TGA profiles of the macromonomer (M_n 9100, M_w/M_n 1.29) and the corresponding graft polymer (M_n 69600, M_w/M_n 4.58). It was notable that the graftpolymer was thermally more stable than the macromonomer. The similar tendency was also observed in the copolymers with MMA and ST.

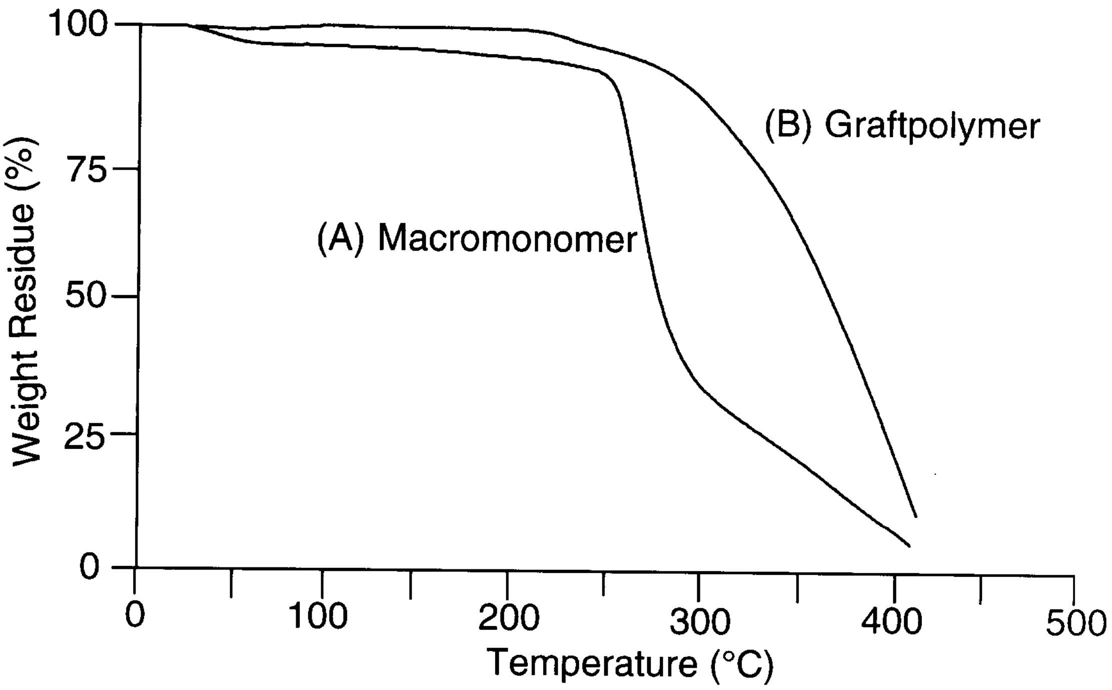

Figure 4. TGA profiles of the macromonomer and the corresponding graftpolymer. (A) macromonomer (M_n 9100, M_w/M_n 1.29, run 5 in Table 1). (B) homopolymer of macromonomer (M_n 69600, M_w/M_n 4.58, run 1 in Table 2).

The Tgs of the macromonomers and graftpolymers were determined by DSC. All of the macromonomer of run 7 in Table 1 (M_n 14000, M_w/M_n 1.41), its polymer, and copolymers with MMA and ST (runs 8 ~ 14 in Table 3) showed the Tgs around 80 °C, which might be based on the side chain, but the other macromonomers and the polymers showed no apparent T_g up to 200 °C. The specific rotation of the macromonomers and graftpolymers were measured, but the absolute values were in the range of 0.3 ~ 0.5, too small to discuss the difference.

3.4. Summary

In this chapter, I synthesized the cysteine-based macromonomers by the radical oligomerization of MMA in the presence of HCl·CM as a chain transfer agent, followed by *N*-methacrylation of the obatined oligomers. The macromonomers afforded the graftpolymers by the radical polymerization and copolymerization with MMA and ST. The obtained graftpolymers showed higher thermal stability than the macromonomers.

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(8) The C_{S} value was calculated by the following equation.

$$\frac{1}{DP_{\mathrm{n}}} = \left(\frac{1}{DP_{\mathrm{n}}}\right)_0 + C_{\mathrm{s}} \frac{[\mathrm{HCl{\cdot}CM}]}{[\mathrm{MMA}]}$$

where $(1/DP\mathrm{n})0$ is the value of 1/DPn in the absence of HCl·CM, Reference: Mayo, F. R. *J. Am. Chem. Soc.* **1943,** 65, 2324.

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Chapter 4

Synthesis and Radical Self-Polyaddition of Optically Active Monomers Derived from Cysteine

Abstract

Synthesis and radical polyaddition behavior of *N*-methacryloyl-L-cysteine methyl ester (MA-C-M), *N*-4-pentenoyl-L-cysteine methyl ester (P-C-M), *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M), were examined. Although MA-C-M afforded a crosslinked polymer and P-C-M did not polymerize at 60 °C, V-C-M polymerized satisfactorily to afford the corresponding polysulfide with M_ns in the range of 7000 - 23000 in good yields. The molecular weight of poly(V-C-M) increased after post polymerization, indicating the telechelic structure with mercapto and olefin moieties at the polymer ends. The specific rotation and CD spectrospecific analysis suggested that poly(V-C-M) had some higher order structures.

4.1. Introduction

L-cysteine is characterized by its mercapto group and forms parts of molecular frameworks of peptides through disulfide formation. Thiyl radicals are important species in redox processes and serve as intermediates in an electron or hydrogen donating reaction, the so called " repair " reaction of thiols toward the targeted carbon centered radicals.[1] Glutathione is the most abundant among thiols serving as reducing agents in biological systems.[2] Other sulfur-containing polymers such as polysulfides, polysulfoxides, and polysulfones attract much attention due to the excellent thermal stability and optical properties.[3] There are many reports concerning the synthesis of polysulfides containing sulfur in the main chains by ring-opening polymerization,[4] polycondensation,[5] and polyaddition.[6] The addition reaction of thiols to unsaturated compounds can be promoted by radical initiators or UV light irradiation.[7] In this chapter, I describe the synthesis and radical self-polyaddition behavior of cysteine-based monomers having mercapto and olefin groups.

4.2. Experiments

4.2.1. *Measurements*

^1H and ^{13}C-NMR spectra were recorded on a JEOL JNM EX-400 spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). IR spectra were measured with a JASCO FTIR-5300 spectrometer. Melting points (mp) were measured on a YANACO micro melting point apparatus. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter using a sodium lamp as a light source. Circular dichroism (CD) spectra were measured on a JASCO J-720 spectropolarimeter. Molecular weights (M_n) and polydispersity ratios (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC, HLC-8020 system, equipped with three consecutive polystyrene gel columns (TSK-gels, G5000H, G4000H, and G2500H), using *N,N*-dimethylformamide (DMF, 5.8 mM lithium bromide solution) as an eluent at a flow rate of 1.0 mL/min, polystyrene calibration, and refractive index (RI) and ultraviolet (UV) detectors. Thermal analyses were performed on Seiko instruments TG/DTA 220 and DSC 220C. Glass transition temperatures (T_g) were taken as an inflection point on a trace at a heating rate of 10 °C/min by differential scanning calorimetry (DSC). 10% weight loss temperatures (T_{d10}) were determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under nitrogen atmosphere.

4.2.2. *Materials*

L-Cysteine was obtained from Ajinomoto Co. Initiators, 2,2'-azobis(isobutyronitrile) (AIBN) and di-*tert*-butyl peroxide (DTBP) were purchased from Tokyo Kasei Kogyo Co. and Nakarai Tesque Co., respectively. Dichloromethane, chlorobenzene, DMF, DMSO, and methacryloyl chloride were distilled over calcium hydride before use. 4-vinylbenzoyl chloride was synthesized according to the previous report.[8]

4.2.3. *Synthesis of monomers: MA-C-M, P-C-M, V-C-M*

L-Cysteine methyl ester hydrochloride

Thionyl chloride (78 mL, 0.9 mol) was added to methanol (300 mL) dropwise at -10 °C, and the mixture was stirred for 10 min. L-Cysteine (36.35 g, 300 mmol) was added to the mixture, and it was stirred for 15 h at room temperature. The reaction mixture was concentrated by a rotary evaporator and the residual mass was washed with ethyl ether (300 mL) several times to obtain powdery L-cysteine methyl ester hydrochloride, which was used to the next step without further purification. Yield 46.3 g (90%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 2.96-3.09 (m, 2H, -CH_2-S-), 3.34 (m, 1H, -SH), 3.75 (s, 3H, -$COOCH_3$), 4.19-4.37 (m, 1H, >CH-), 6.35-6.36 (broad, 3H, HCl·NH_2-) ppm. ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 24.15, 52.96, 53.93, 169.18 ppm.

N-Methacryloyl-L-cysteine methyl ester hydrochloride (MA-C-M)

To a suspension of L-cysteine methyl ester hydrochloride (4.28 g, 25 mmol) in dichloromethane (75 mL) was added triethylamine (7.30 mL, 52.4 mmol) slowly at 0 °C under nitrogen, and then a solution of methacryloyl chloride (2.61 g, 25 mmol) in dichloromethane (25 mL) slowly at 0 °C. The mixture was stirred at 0 °C for 30 min, then at room temperature overnight. The resulting mixture was concentrated by a rotary evaporator and the residual mass was washed with ethyl acetate (200 mL). It was filtered to remove triethylamine hydrochloride, and the filtrate was concentrated by a rotary evaporator again, followed by recrystallization by ethyl acetate/*n*-hexane (2 / 1, volume ratio) twice to obtain colorless solid, *N*-methacryloyl-L-cysteine methyl ester (MA-C-M). Yield 4.16 g (86%). Mp = 92-93 °C. $[\alpha]_D^{25}$ = -25 ° (*c* = 1 g/dL, DMF). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.99 (s, 3H, $-CH_3$), 3.21-3.26 (m, 2H, $-CH_2$-S), 3.43 (t, *J* = 2.40 Hz, 1H, -SH), 3.78 (s, 3H, $-OCH_3$), 4.89-4.98 (m, 1H, >CH-), 5.42-5.81 (m, 2H, CH_2=), 6.73-6.81 (m, 1H, -NH-) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 18.45, 40.64, 51.89, 52.81, 120.83, 139.15, 167.94, 170.88 ppm. IR (KBr): 3326, 2955, 1755, 1655, 1618, 1520, 1435, 1200, 932, 631 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_3S$: C 49.74, H 6.96, N 6.45, S 14.26. Found. C 49.70, H 6.73, N 6.49, S 15.04.

4-Pentenoyl chloride

To thionyl chloride (71.38 g, 0.6 mol) was added 4-pentenoic acid (19.62 g, 0.2 mol) at room temperature. The reaction mixture was stirred at 80 °C for 3 h. After that, residual thionyl chloride was removed from the mixture, followed by distillation to obtain 4-pentenoyl chloride. Bp = 40 °C / 9 mmHg. Yield 16.8 g (71%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.39 - 2.48 (m, 2H, $-CH_2$-), 3.00 (t, *J* = 7.32 Hz, 2H, $-CH_2$-C(O)-), 5.07-5.14 (m, 2H, CH_2=), 5.74-5.84 (m, 1H, =CH-) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 28.91, 46.23, 116.92, 134.69, 173.15 ppm.

N-4-Pentenoyl-L-cysteine methyl ester (P-C-M)

P-C-M was synthesized from L-cysteine methyl ester hydrochloride (4.28 g, 25 mmol) and 4-pentenoyl chloride (2.97 g, 25 mmol) in the similar fashion with MA-C-M as mentioned above, and purified by recrystallization from ethyl acetate. Yield 4.08 g (75%). Mp = 93-94 °C. $[\alpha]_D^{25}$= -11.4 ° (*c* =1 g/dL, DMF). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.35 (t, *J* = 7.33 Hz, -SH), 2.05-2.43 (m, 4H, $-C_2H_4$-), 3.15-3.25 (m, 2H, $-CH_2-S-$), 3.77 (s, 3H, $-C(O)OCH_3$), 4.85-4.90 (m, 1H, >CH-), 5.01-5.89 (m, 3H, $CH_2=CH-$), 6.58 (d, $J = 7.2$ Hz, 1H, -C(O)-NH-) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz): $\delta = 29.20, 35.29, 40.52, 51.49, 52.62, 115.57, 136.67, 170.82, 172.23$ ppm. IR (KBr): 3333, 1743, 1657, 1612, 1442, 1205, 745, 702 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_3S$: C 47.30, H 6.45, N 6.89, S 15.78. Found. C 47.25, H 6.35, N 6.62, S 16.15.

N-4-Vinyl benzoyl-L-cysteine methyl ester (V-C-M)

V-C-M was synthesized from L-cysteine methyl ester hydrochloride (4.28 g, 25 mmol) and 4-vinylbenzoyl chloride (4.17 g, 25 mmol) in the similar fashion with MA-C-M and P-C-M as mentioned above. Yield 4.16 g (86%). Mp = 105-106 °C. $[\alpha]_D^{25} = -9.8$ ° ($c = 1$ g/dL, DMF). $[\alpha]_D^{25} = -2.4$ ° ($c = 1$ g/dL, acetone). $[\alpha]_D^{25} = -2.9$ ° ($c = 1$ g/dL, CH_2Cl_2). $[\alpha]_D^{25} = -5.2$ ° ($c = 1$ g/dL, $CHCl_3$). ^1H-NMR ($CDCl_3$, 400 MHz): $\delta = 1.41$ (t, $J = 9.2$ Hz, 1H, -SH), 3.12-3.16 (m, 2H, $-CH_2-$), 3.80 (s, 3H, $-OCH_3$), 5.07-5.10 (m, 1H, -CH<), 5.36-6.79 (m, 3H, $CH_2=CH-$), 7.08 (d, $J = 6.4$ Hz, 1H, -C(O)-NH-), 7.40-7.86 (m, 4H, $-C_6H_4-$) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz): $\delta = 27.01, 52.96, 53.93, 116.29, 126.43, 127.49, 132.55, 135.88, 141.20, 166.55, 170.74$ ppm. IR (KBr): 3297, 2575, 1736, 1644, 1535, 1333, 1221, 1188, 996, 924, 858, 779, 694 cm^{-1}. Anal. Calcd for $C_{13}H_{15}O_3NS$: C 58.84, H 5.70, N 5.28, S 12.09. Found. C 59.06, H 5.77, N 5.15, S 11.83.

4.2.4. *Radical Polyaddition*

Typical procedure: To a monomer (0.5 mmol) in a polymerization tube was introduced AIBN (2.5 mg, 0.015 mmol), and subsequently a dry solvent (1 mL or 0.5 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. The reaction mixture was poured into ethyl ether to precipitate the polymer. The ethyl ether-insoluble polymer was filtered with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried *in vacuo* at 40 °C for 12 h.

Poly(MA-C-M). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 0.80-1.63 (broad m, 3H, CH_3-), 1.99 (s, 3H, CH_3-, polymer end), 1.71-2.46 (broad m, 3H, -CH_2-CH<), 2.83-3.60 (broad m, 4H, -CH_2-S-CH_2-), 3.45-3.51 (d, *J* = 13.8 Hz, 2H, -CH_2-S, polymer end), 3.78 (broad s, 3H, -OCH_3), 4.90 (broad s, 1H, -CH<), 5.38-5.70 (m, 2H, CH_2=, polymer end), 7.90-8.52 (broad s, 1H, -NH-) ppm. IR (KBr): 3409, 2955, 1740, 1655, 1657, 1522, 1439, 1213, 1024, 978, 542 cm^{-1} (run 3 in Table 1).

Poly(P-C-M). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.35-2.53 (m, 6H, -C_3H_6-), 2.98-3.00 (m, 4H, -CH_2-S-CH_2-), 3.77 (s, 3H, -C(O)OCH_3), 4.82-4.89 (m, 1H, >CH-), 5.83-5.85 (m, 3H, CH_2=CH-, polymer end), 6.41-6.83 (m, 1H,-NH-) ppm. IR (KBr): 3332, 1745, 1655, 1612, 1442, 1206, 744, 701 cm^{-1}.

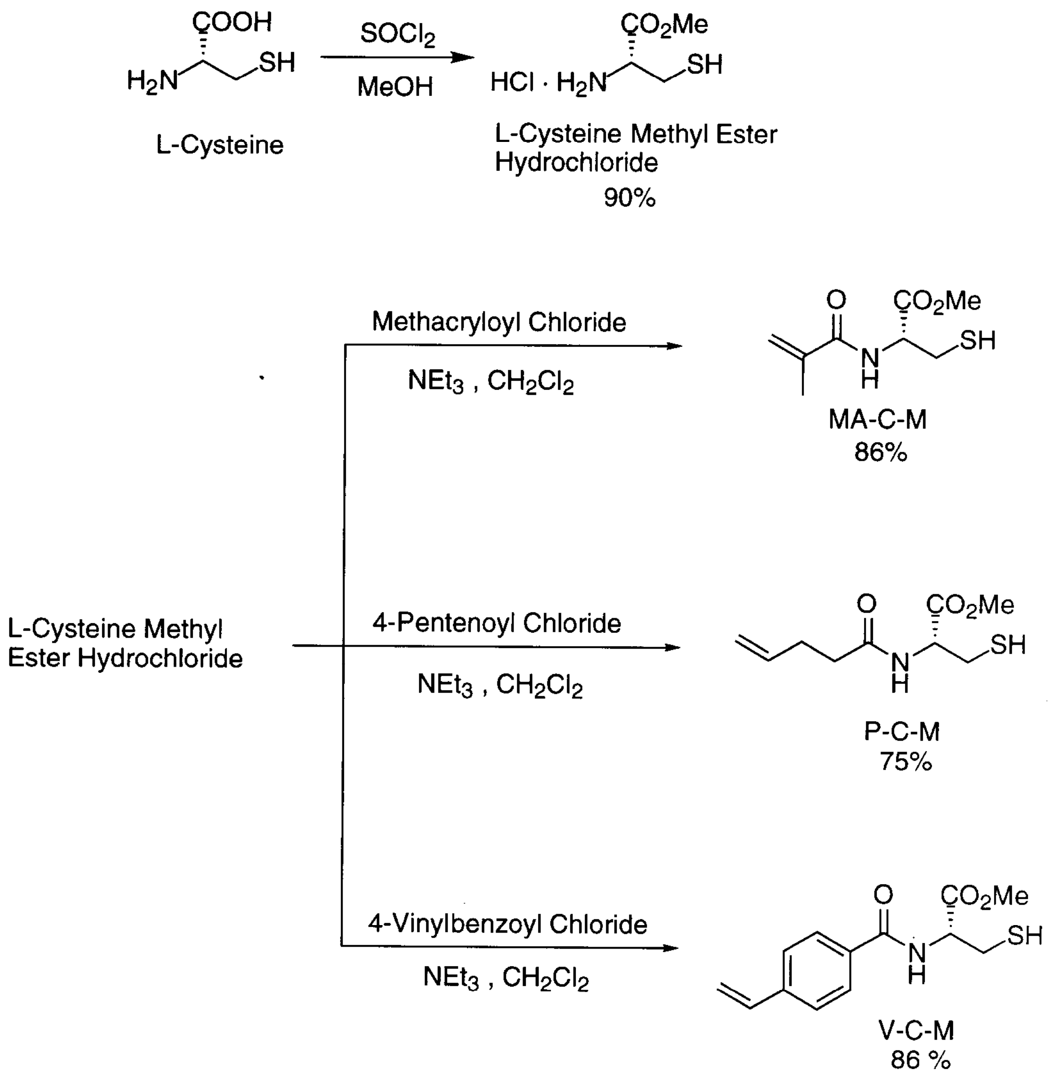
Poly(V-C-M). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.42 (broad s, 1H, -SH, polymer end), 1.91-2.44 (m, 2H, -CH_2-Ph), 2.81-3.33 (m, 4H, -CH_2-S-CH_2-), 3.78 (s, 3H, -C(O)OCH_3), 5.05 (broad s, 1H, >CH-), 5.33-6.78 (m, 3H, CH_2=CH-, polymer end), 7.11-7.71 (broad m, 5H, -C_6H_4-, -NH-) ppm. IR (KBr): 3366, 2951, 1742, 1649, 1611, 1535, 1499, 1310, 1215, 1019, 858, 855, 710 cm^{-1} (run 1 in Table 2).

4.3. Results and Discussion

4.3.1. *Monomer synthesis*

The monomers, *N*-methacryloyl-L-cysteine methyl ester (MA-C-M), *N*-4-pentenoyl-L-cysteine methyl ester (P-C-M), and *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M) were synthesized in satisfactory yields by the reaction of L-cysteine methyl ester hydrochloride with methacryloyl chloride, 4-pentenoyl chloride, 4-vinylbenzoyl chloride, in the presence of triethylamine in CH_2Cl_2, respectively (Scheme 1). The structures of the monomers were confirmed by ^1H, ^{13}C-NMR, and IR spectroscopy, besides elemental analysis. I can expect that the monomers easily and efficiently undergo radical polyaddition, because the unit ratio of the two functional groups is automatically equal in the polyaddition. Nuyken et al. have reported that mercaptostyrenes spontaneously undergo self-polyaddition, but the polymerization has not been fully characterized, because the monomers cannot be isolated due to the unstability.[9] In this work, the novel mercapto-olefin monomers could be isolated by recrystallization, were stable at room temperature and easy to handle.

Scheme 1:



4.3.2. *Radical polyaddition*

Radical polyaddition of MA-C-M was carried out at 60 °C for 20 h in the presence of AIBN (3 mol %) in chlorobenzene, DMF, and DMSO to afford the polymers as summarized in Scheme 2 and Table 1. The polymers were isolated by precipitation with ether. The polymerization in chlorobenzene (0.5 M) afforded the DMF-soluble polymer in 85% yield along with a small amount of DMF-insoluble polymer (run 1 in Table 1). Increase of the monomer concentration resulted in the insolubility of the obtained polymer both in the polymerization in chlorobenzene and DMF (runs 2 and 4 in Table 1). The DMF-soluble polymers obtained by polymerization in DMF (1 M) and DMSO (1 M) showed large polydispersity ratios (4.28 - 4.45) (runs 3 and 5 in Table 1). These results suggest that the produced polymers contained branched and partially crosslinked structures, formed by vinyl polymerization of the methacryloyl group of MA-C-M along with the polyaddition.

Scheme 2:

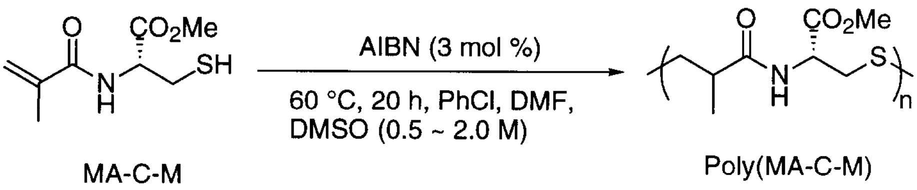


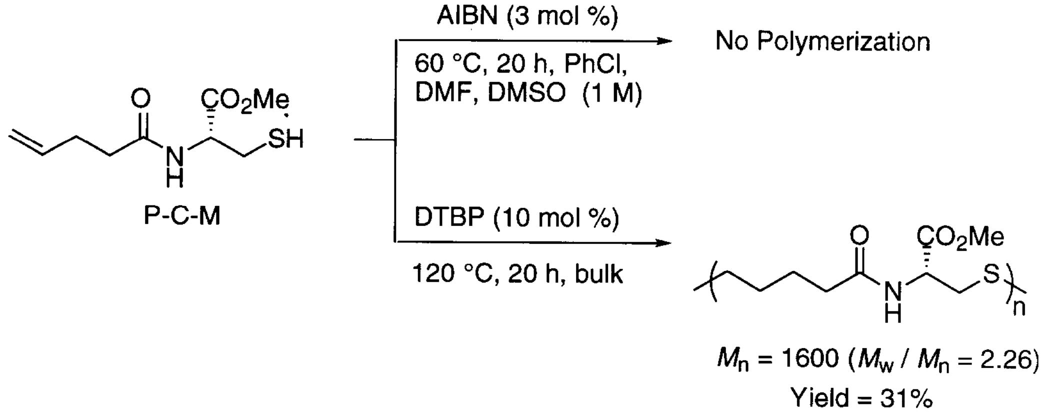
Table 1. Radical self-polyaddition of MA-C-M [a)]

run	solvent (M)	conv [b)] (%)	yield [c)] (%)	M_n (M_w / M_n) [d)]	$[M]_D$ [e)] (degree)
1	Ph-Cl (0.5 M)	- [h)]	85	16800 (2.27) / 2900 (1.03) [g)]	- [h)]
2	Ph-Cl (1.0 M)	- [f)]	qunat	- [h)]	- [f)]
3	DMF (1.0 M)	quant.	87	46000 (4.45)	- 144.8
4	DMF (2.0 M)	- [f)]	quant.	- [h)]	- [h)]
5	DMSO (2.0 M)	quant.	quant.	43200 (4.28)	- 61.1

a) Conditions: initiator AIBN (3 mol %), 60 °C, 20 h. b) Determined by ^{1}H-NMR. c) Ether-insoluble part. d) Estimated by GPC based on polystyrene standards; eluent: LiBr solution (5.8 mM) in DMF. e) $[M]_D = [\alpha]_D \cdot MW / 100$, where MW represents the formula weight of the polymer repeating unit, $[\alpha]_D$ was measured by a polarimeter at 25 °C (c = 1.00 g/dL, DMF). f) Not determined, solvent-insoluble polymer was obtained. g) Bimodal peak, yield of the low molecular-weight part 18%. h) Not measured.

Next, I examined the radical polyaddition of P-C-M in the presence of AIBN and DTBP at 60 and 120 °C (Scheme 3). I expected to obtain the polymer *via* selective polyaddition because the olefin group of P-C-M is less reactive compared with the methacryloyl group of MA-C-M[11]. However, P-C-M afforded no polymer in the polyaddition in chlorobenzene, DMF, and DMSO at 60 °C. However, a low molecular weight oligomer with the M_n of 1600 was obtained in 31% yield in the presence of DTBP (10 mol %) in the bulk at 120 °C for 20 h.

Scheme 3:



The radical polyaddition of V-C-M was carried out in the presence of AIBN (3 mol %) in DMF, MeOH, chlorobenzene, and CH_2Cl_2 (1 M) at 60 °C for 20 h as summarized in Scheme 4 and Table 2. Polyaddition with monomer concentration of 1.0 M (runs 5 ~ 8 in Table 2) afforded polymer with M_n of 10000 ~ 17000 in quantitative yield. This was higher than the polymer obtained in the polymerization with the monomer concentration of 0.5 M (runs 1 ~ 4 in Table 2). Polymers obtained by polymerization in MeOH, CH_2Cl_2, and chlorobenzene were partially insoluble in DMF (runs 6, 7, and 8 in Table 2), which would result in the absolute values of the specific rotations smaller than that obtained in DMF (run 5 in Table 2).[11]

Scheme 4:

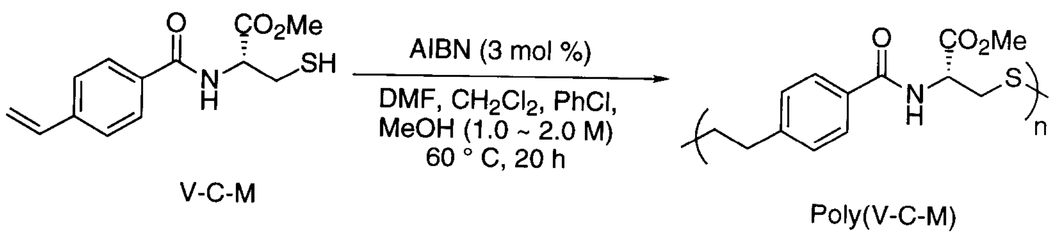


Table 2. Radical self-polyaddition of V-C-M in several solvents [a)]

run	monomer conc (M)	solvent	yield [b)] (%)	M_n (M_w / Mn) [c)]	$[M]_D$ [d)] (degree)
1	0.5	DMF	85	7100 (1.21)	- 25.2
2	0.5	MeOH	62	7300 (1.50)	- 21.2
3	0.5	CH_2Cl_2	88	7000 (1.45)	- 25.2
4	0.5	PhCl	91	6900 (1.43)	- 27.3
5	1.0	DMF	quant.	14000 (1.95)	- 9.3 [g)]
6	1.0	MeOH	quant.	10000 (1.44)	- 14.3 [g)]
7	1.0	CH_2Cl_2	95	17000 (2.07)	- 14.3 [g)]
8	1.0	PhCl	quant.	16000 (2.15)	- 9.6 [g)]

a) Conditions: V-C-M (0.5 mmol), initiator AIBN (3 mol %), 60 °C, 20 h. b) Ether-insoluble part. c) Estimated by GPC based on polystyrene standards; eluent: LiBr solution (5.8 mM) in DMF. d) $[M]_D = [\alpha]_D \cdot MW / 100$, where MW represents the formula weight of the polymer repeating unit, $[\alpha]_D$ was measured by a polarimeter at 25 °C (c = 1.00 g/dL, DMF). e) Became heterogeneous after 3 h. f) Became heterogeneous after 12 h. g) The obtained polymer was partially insoluble in DMF.

Figure 1 illustrates the ^1H-NMR spectrum of poly(V-C-M) along with that of V-C-M. The figure shows signals assignable to vinyl and mercapto groups of the polymer ends at 5.35, 5.82 ppm, and 1.42 ppm as well as the signals assignable to the polysulfide unit. Poly(V-C-M) seems to be a telechelic polymer. The degree of polymerization is calculated to be 12 by ^1H-NMR integration of the signal for the olefin protons, of the polymer ends at 5.35 ppm and the methyl ester protons at 3.78 ppm.

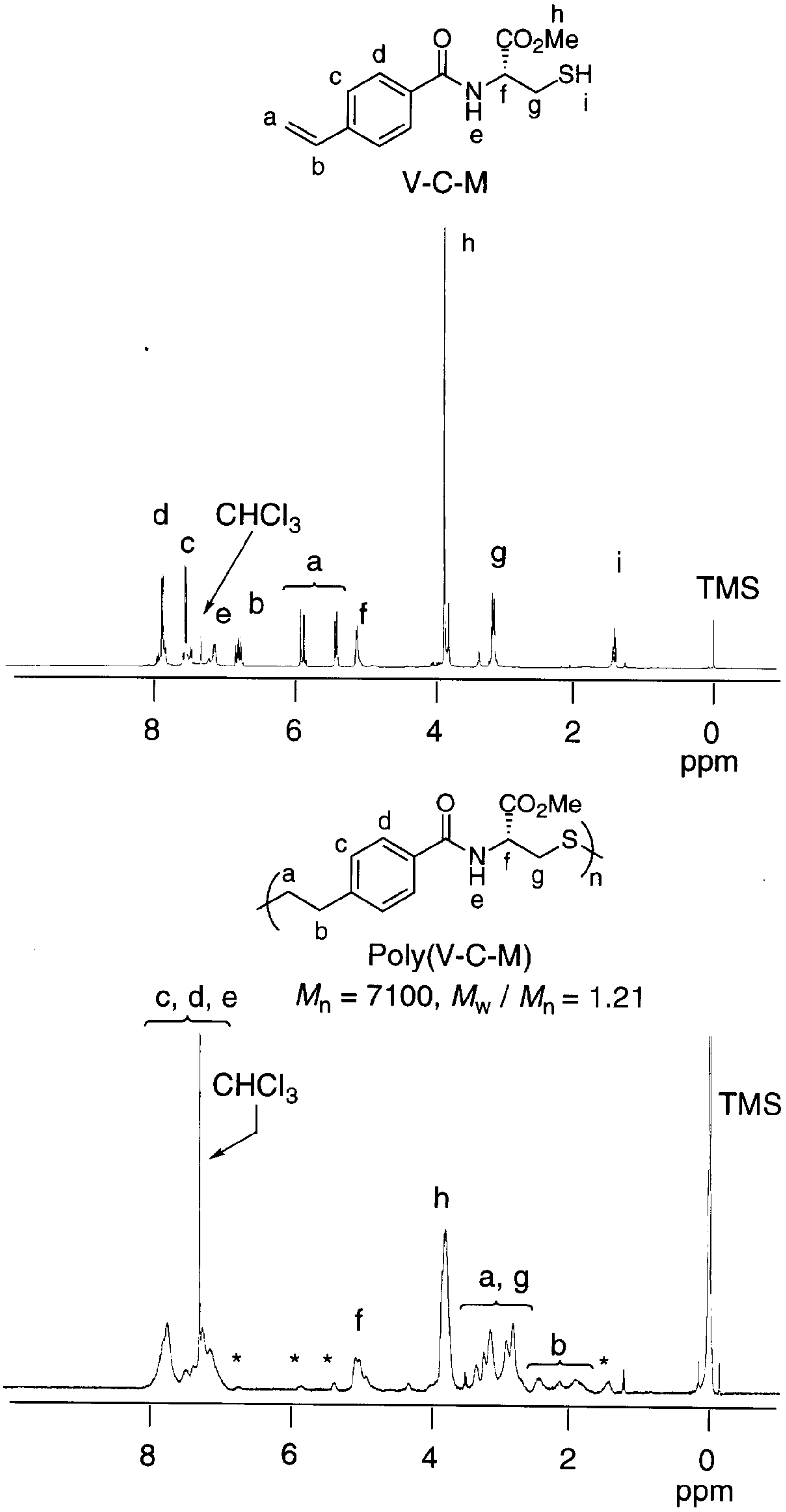


Figure 1. ^{1}H-NMR spectra (400 MHz, $CDCl_3$) of V-C-M and poly(V-C-M) obtained in the radical polyaddition with AIBN (3 mol %) in DMF (0.5 M) at 60 °C for 20 h (run 1 in Table 2). * : signal derived from the polymer end.

To confirm the telechelic structure of the polymer, post reaction was carried out in the presence of AIBN (10 mol %) in DMF (1 M) at 60 °C for 20 h. Figure 2 illustrates the GPC profiles before and after the post radical polyaddition, showing the increase of the M_n from 7100 to 15700. This result indicates that the original telechelic polymer has been converted into a higher molecular weight polymer.

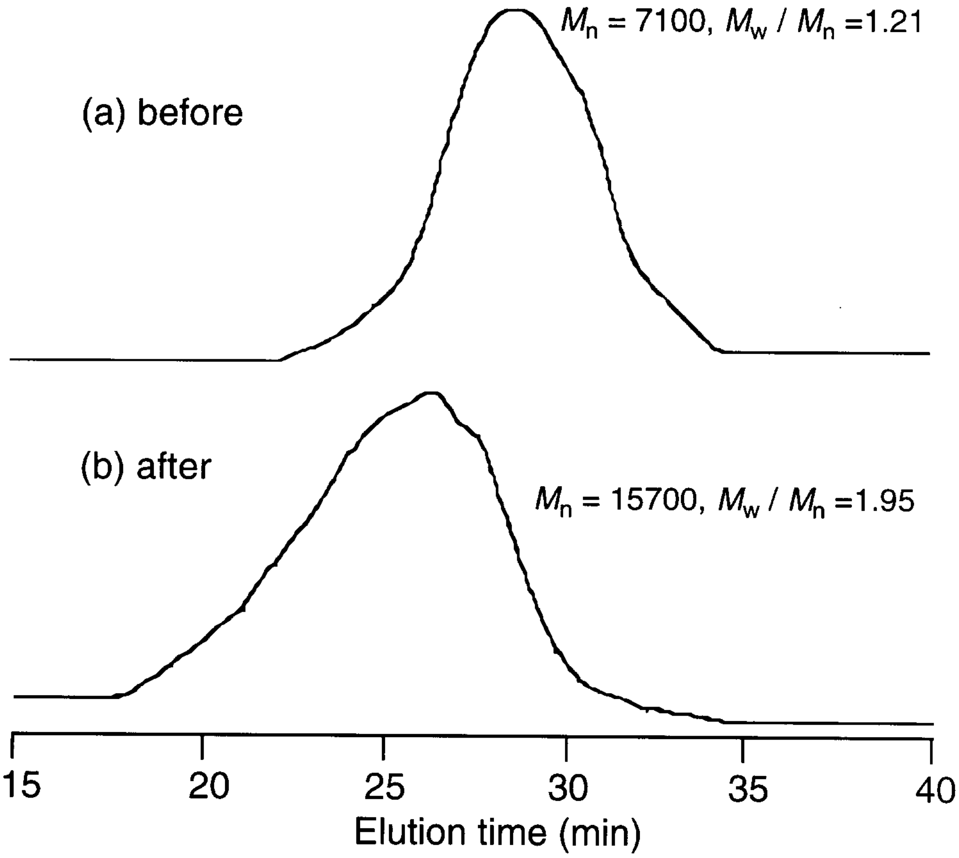


Figure 2. GPC profiles [eluent: LiBr (5.8 mM) in DMF] before and after the post radical polyaddition of poly(V-C-M) obtained in the radical polyaddition with AIBN (3 mol %) in DMF (0.5 M) at 60 °C for 20 h (run1 in Table 2). (a) Before post radical polyaddition of poly(V-C-M). $M_n = 7100, M_w / M_n = 1.21$. (b) After post radical polyaddition of poly(V-C-M). $M_n = 15700, M_w / M_n = 1.95$.

The radical polyaddition of V-C-M was carried out in the presence of AIBN ranging from 1 to 30 mol % as summarized in Table 3. The polymer yield and M_n increased with the amount of AIBN in most cases. The absolute value of $[M]_D$ slightly increased with the M_n.

Table 3. Radical self-polyaddition of V-C-M in the presence of AIBN[a)]

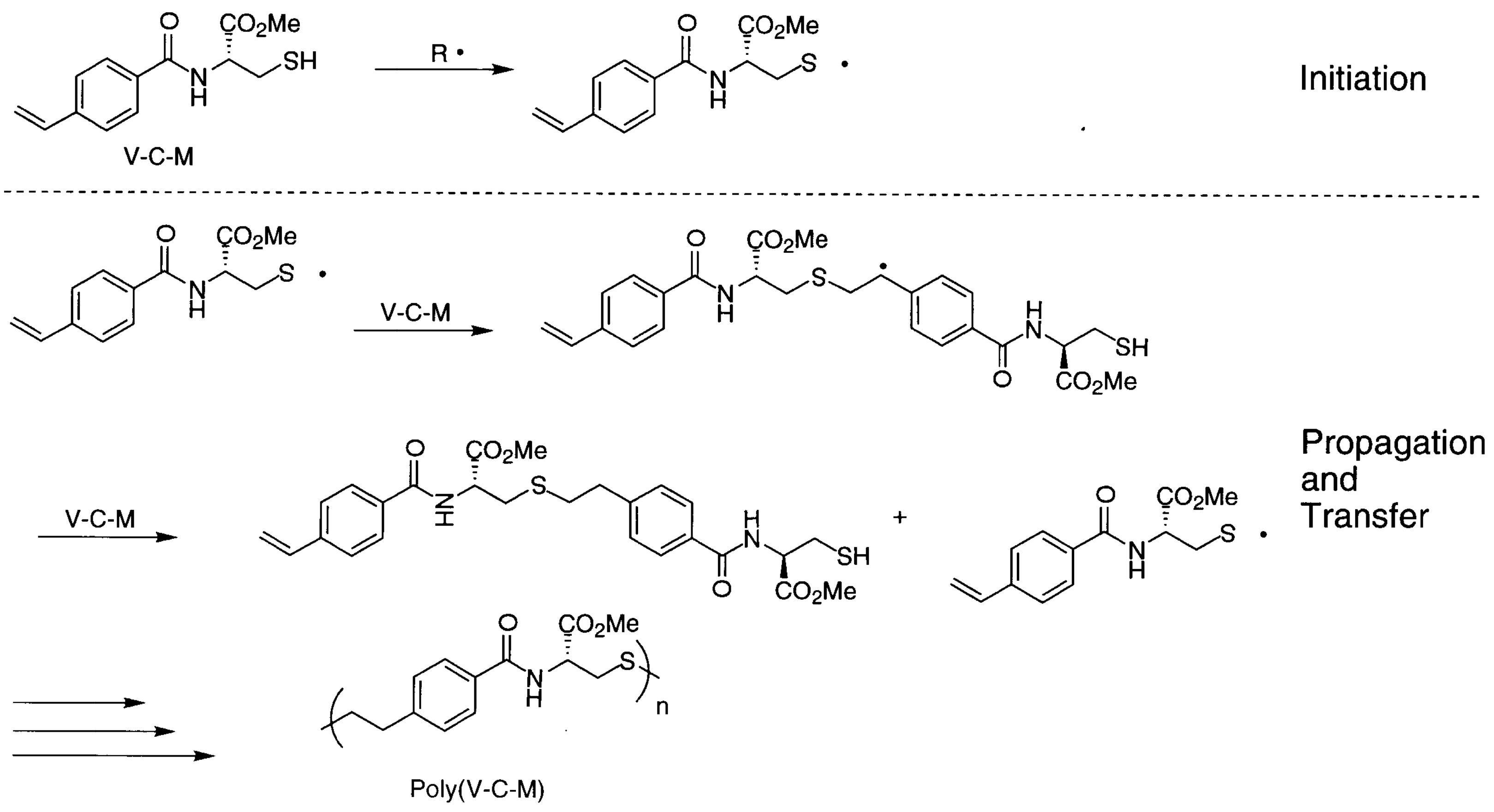
run	amount of AIBN (mol %)	yield[b)] (%)	M_n (M_w / M_n)[c)]	$[M]_D$[d)] (degree)
1	1	62	8900 (1.38)	- 24.4
2	3	76	7100 (1.21)	- 25.2
3	5	83	18000 (1.76)	- 30.8
4	10	88	23000 (1.43)	- 32.9
5	30	97	19000 (1.95)	- 32.1

a) Conditions: V-C-M (0.5 mmol), initiator AIBN (3 mol %), 60 °C, 20 h in DMF (1.0 mL). b) Ether-insoluble part. c) Estimated by GPC based on polystyrene standards; eluent: LiBr solution (5.8 mM) in DMF. d) $[M]_D = [\alpha]_D \cdot MW / 100$, where MW represents the formula weight of the polymer repeating unit, $[a]_D$ was measured by a polarimeter at 25 °C (c = 1.00 g/dL, DMF).

4.3.3. *Mechanism of radical polyaddition of V-C-M*

Scheme 5 illustrates a plausible mechanism of the radical polyaddition of V-C-M. In the initiation step, the radical initiator abstracts the thiol hydrogen atom of V-C-M to produce a thiyl radical species. Second step is the addition of the thiyl radical to another monomer followed by the chain transfer, i.e., abstraction of hydrogen from another mercapto group. Consequently, radical polyaddition proceeds to afford the polysulfide.

Scheme 5:


V-C-M
R •
Initiation
V-C-M
V-C-M
+
Propagation
and
Transfer
Poly(V-C-M)
CO2Me
SH
S
NH
O
n

4.3.4. *Specific rotations of V-C-M and poly(V-C-M)*

Figure 3 illustrates the relationships between the specific rotations of V-C-M and poly(V-C-M), and DMF content of the measuring mixed solvent of DMF and $CHCl_3$. Poly(V-C-M) was insoluble in the mixed solvent whose DMF-content was less than 50%. The specific rotation of V-C-M and DMF-content showed a linear relationship as shown in Figure 3, while that of poly(V-C-M) showed a minimum at the DMF content of 86% independent of M_n. The polymer with M_n of 18000 showed smaller $[M]_D$ than that with M_n of 7100. Endo et al. have reported that the solvent effect on the specific rotation of *N*-pivaloyl-L-leucine methyl ester to find it decreased as the relative dielectric constant of the measuring solvent increased.[12] From the conformational analysis of *N*-pivaloyl-L-leucine methyl ester by molecular orbital calculation, it was suggested that the compound changed its conformation according to the solvent resulting in the change of $[M]_D$. The similar conformational change of V-C-M appeared to cause the change of $[M]_D$ of V-C-M according to the measuring solvent content. Possible reason for these interesting results concerning specific rotations is a higher order structure of the polymer constructed by hydrogen bonding between the carbonyl groups and amide hydrogen. Lotz et al. have reported that a polysulfide with asymmetric carbons in the main chain, poly(*tert*-butylethylene sulfide) is one of several isotactic polymers and forms one-handed helices of one hand.[13] Poly(V-C-M) seems to take some helical structures due to its asymmetric carbons.

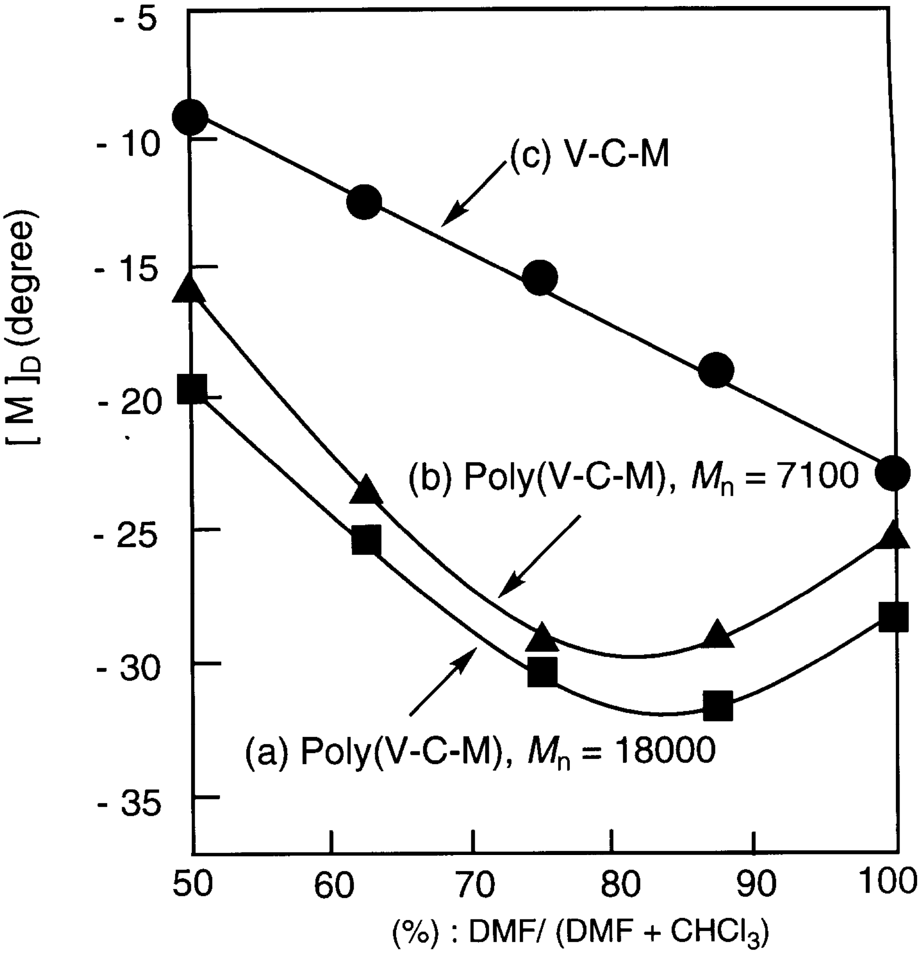


Figure 3. Specific rotation ([M]D) of V-C-M and poly(V-C-M) vs DMF content of the mixed solvent of DMF and $CHCl_3$. [M]D = [α]D · MW / 100 where MW represents the formula weight of the polymer repeating unit, [α]D was measured by a polarimeter at 25 °C (c = 1.00 g/dL, DMF/$CHCl_3$). (a) Poly(V-C-M) (M_n = 18000, Mw / M_n = 1.76) obtained in the radical polyaddition with AIBN (5 mol %) in DMF (0.5 M) at 60 °C for 20 h (run 3 in Table 3). (b) Poly(V-C-M) (M_n = 7100, M_w / M_n = 1.21) obtained in the radical polyaddition with AIBN (3 mol %) in DMF (0.5 M) (run 1 in Table 2). (c) V-C-M.

4.3.5. *Circular dichroism (CD) spectra of V-C-M and poly(V-C-M)*

Figure 4 illustrates the CD spectra of poly(V-C-M) with M_n of 7100 and V-C-M measured in chloroform (0.01 g/mL). The polymer with M_n of 18000 was insoluble in chloroform. The Cotton effect of poly(V-C-M) at 245 nm much larger than that of V-C-M and the results of specific rotations suggested that poly(V-C-M) had some regulated higher order structures such as a helical conformation to some extent. Poly(V-C-M) did not show an apparent Tg up to 200 °C, and showed T_{d10}s in the range of 264 - 275 °C.

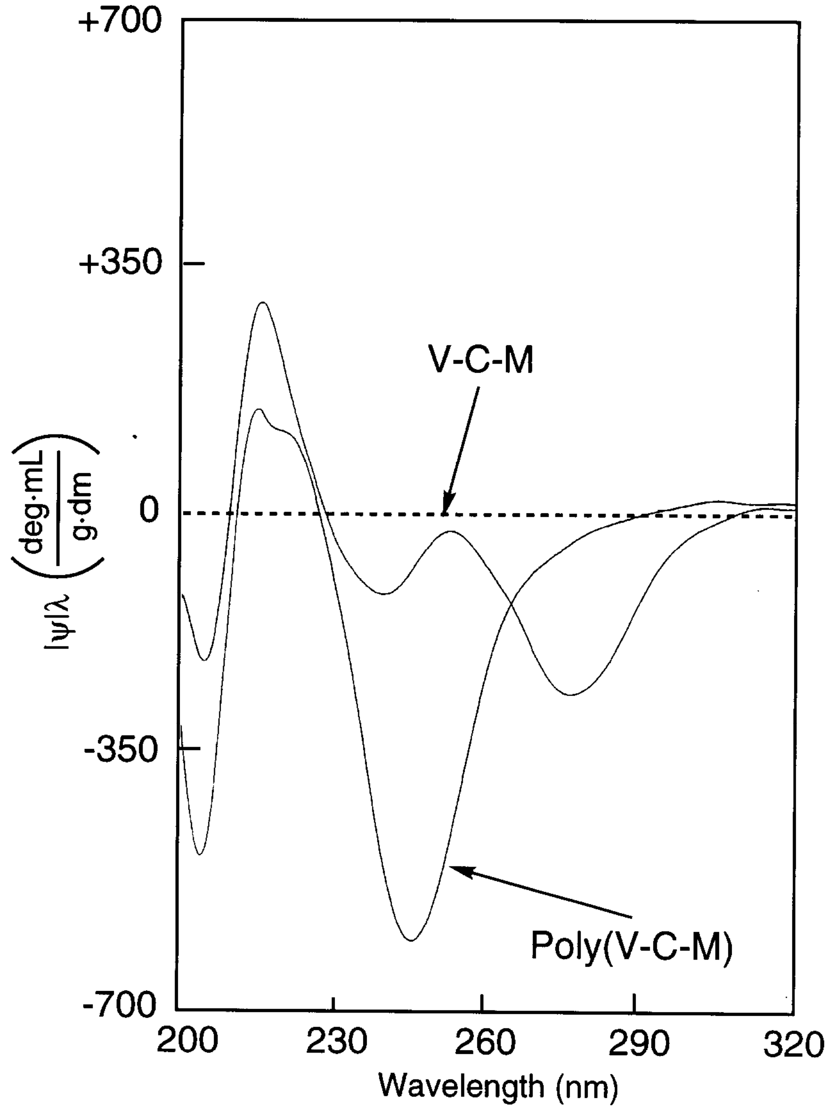


Figure 4. CD spectra (c = 0.01 g/dL, $CHCl_3$) of V-C-M and poly(V-C-M). Poly(V-C-M) (M_n = 7100, M_w / M_n = 1.21) wa obtained in the radical polyaddition with AIBN (3 mol %) in DMF (0.5 M) (run 1 in Table 2).

4.4. Summary

In this chapter, I examined the synthesis and radical polyaddition of the novel three monomers having olefin and mercapto groups derived from cysteine. The radical polyaddition of *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M) proceeded satisfactorily to afford the corresponding polysulfide with M_n in the range of 7000 ~ 23000 in good yields. The specific rotation and CD spectrospecific analysis suggested that poly(V-C-M) had some higher order structures. It is expected that poly(V-C-M) shows interesting functions, because it has wide variety of functional groups, i.e., amide and sulfide moieties, and asymmetric carbons in the main chain, besides ester groups in the side chain as well as olefin and mercapto groups in the polymer ends.

4.5. References and Notes

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(11) This means that the real reagent concentrations of the solutions in runs 6-8 in Table 2 were smaller than $c = 1$ g/dL. Possible reasons of formation of the DMF-insoluble part is incorporation of crosslinked

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Chapter 5

Reactions of Telechelic Polymers Having Olefin and Thiol Moieties

Abstract

Radical self-polyaddition of *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M) was carried out in the presence of AIBN (3 mol %) as an initiator in DMF (0.5 and 1.0 M) at 60 °C for 20 h under nitrogen atmosphere to afford the corresponding polymers[poly(V-C-M)] with M_ns 5300 and 18000 in 76 and 95% yields. The obtained polymers had a heterotelechelic structure with thiol and olefin end moieties. Radical polymerization of MMA and TrtMA was carried out in the presence of poly(V-C-M) with AIBN (3 mol %) as an initiator in DMF at 60 °C for 20 h to afford block copolymers with M_ns in the rang of 13000~26800 in good yields. Oxidation and hydrolysis of poly(V-C-M) were examined. Poly(V-C-M) was oxidized with H_2O_2 to the polymer having the sulfoxide and sulfone groups in the main chain, and hydrolyzed with NaOH aq. to the polymer having carboxyl groups in the side chain.

5.1. Introduction

Telechelic polymers with functional groups at the ends are useful as reactive polymers,[1] which can be submitted for coupling reaction to afford block copolymers and network polymers.[2] Heterotelechelic polymers with two different functional groups at the ends have been synthesized by free radical addition fragmentation chain transfer reaction.[3] In chapter 4, I described the synthesis and radical self-polyaddition of *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M). The obtained polymer, poly(V-C-M) had a heterotelechelic structure with thiol and olefin groups, besides ester groups in the side chain, amide, sulfide moieties and asymmetric carbons in the main chain. It is expected that poly(V-C-M) shows wide variety of functions and reactivities. In this chapter, I describe the synthesis of block copolymers consisting of poly(V-C-M) and methacrylates along with hydrolysis and oxidation of poly(V-C-M).

5.2. Experimental

5.2.1. *Measurements*

^{1}H and ^{13}C-NMR spectra were recorded on a JEOL JNM EX-400 spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). IR spectra were obtained with a JASCO FTIR-5300 spectrometer. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimater using a sodium lamp as a light source. Circular dichroism (CD) spectra were measured on a JASCO J-720 spectropolarimeter. Molecular weights (M_n) and polydispersity ratios (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC HLC-8020 system, equipped with consecutive three polystyrene gel columns (TSK-gels G5000H, G4000H, and G2500H), using *N,N*-dimethylformamide (DMF, 5.8 mM lithium bromide solution) as an eluent at a flow rate of 1.0 mL/min, polystyrene calibration, and refractive index (RI) and ultraviolet (UV) detectors. Thermal analyses were performed on Seiko instruments TG/DTA 220 and DSC 220C. Glass transition temperatures (T_g) were taken as an inflection point on a trace at a heating rate of 10 °C/min by differential scanning calorimetry (DSC). Temperatures (T_{d10}) with 10 % weight loss were determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under nitrogen atmosphere.

5.2.2. *Materials*

Initiator 2,2'-azobis(isobutyronitrile) (AIBN), methyl methacrylate and *m*-chloroperoxybenzoic acid (*m*-CPBA) were purchased from Tokyo Kasei Kogyo Co. Triphenylmethyl methacrylate (TrtMA) was synthesized according to the reported method.[4] DMF and methyl methacrylate were distilled over calcium hydride before use.

5.2.3. *Radical polyaddition of V-C-M*

Typical procedure: To a monomer (1.33 g, 5.0 mmol) in a flask was introduced AIBN (25 mg, 0.15 mmol), and subsequently a dry solvent (10 mL). The flask was cooled, degassed, and heated at 60 °C for 20 h under nitrogen atmosphere. The reaction mixture was poured into ethyl ether to precipitate a polymer. The ethyl ether-insoluble polymer was filtered with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried *in vacuo* at 45 °C for 12 h. Yield = 1.22 g (92%). M_n = 5300 , M_w/M_n = 1.61. $[\alpha]_D^{25}$ = - 9.0 ° (c = 1 g/dL, DMF). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.44 (broad s, 1H, -SH, polymer end), 1.93-2.45 (m, 2H, -CH_2-Ph), 2.81-3.33 (m, 4H, -CH_2-S-CH_2-), 3.78 (s, 3H, -C(O)OCH_3), 5.05 (broad s, 1H, >CH-), 5.33-6.78 (m, 3H, CH_2=CH-, polymer end), 7.11-7.71 (broad m, 5H, -C_6H_4-, -NH-) ppm. IR (KBr): 3366, 2951, 1742, 1649, 1611, 1535, 1499, 1310, 1215, 1019, 858, 855, 710 cm^{-1}.

5.2.4. *Polymerization MMA and TrtMA in the presence of poly(V-C-M)*

Typical procedure: To MMA (50 mg, 0.5 mmol) and poly(V-C-M) (M_n 5300, M_w/M_n 1.61) (66.3 mg, 0.25 mmol) into a polymerization tube was introduced AIBN (1.2 mg, 0.0075 mmol), and subsequently a dry DMF (0.5 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. The reaction mixture was poured into ethyl ether or methanol to precipitate a polymer. The ethyl ether- or methanol-insoluble polymer was isolated by filtration with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried in vacuo at 45 °C for 12 h. Yield = 101.2 mg (87 %). M_n = 17000, M_w/M_n = 2.10.

5.2.5. *Hydrolysis of poly(V-C-M)*

The suspension of poly(V-C-M) (M_n 18000, M_w/M_n 1.61) (65 mg, 0.25 mM) in sodium hydroxide aqueous solution (NaOH 40 mg, 1.0 mmol, H_2O 1.0 mL) was stirred at room temperature under an atmosphere of nitrogen. The reaction mixture changed into clear after 5 h. Conc. HCl was added to the solution until the pH became 2.0, and the resulted mixture was extracted three times with CH_2Cl_2 (10 mL), and the combined extract was dried over anhydrous magnesium sulfate. It was concentrated by a rotary evaporator. The residue was poured into a large amount of ethyl ether to precipitate a polymer, which was filtered with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried in vacuo at 45 °C for 12 h. Yield = 0.051 g. M_n = 17300, M_w/M_n = 1.88. $[\alpha]_D^{25}$ = - 10.0 ° (c = 1 g/dL, DMF). ^{1}H-NMR (DMSO, 400 MHz): δ = 2.31-2.52 (m, 2H, $-CH_2-C_6H_4-$), 2.66-3.23 (m, 4H, $-CH_2-S-CH_2-$), 3.61-3.63 (broad s, 3H, $-C(O)OCH_3$), 4.58-4.69 (broad m, -CH<), 7.11-7.94 (broad m, 4H, $-C_6H_4$), 8.30-8.43 (broad m, 1H, -NH-), 12.87-12.89 (broad s, 1H, -COOH) ppm. IR (KBr): 3287, 2938, 1732, 1643, 1537, 1501, 1191, 1019, 857 cm^{-1}.

5.2.6. *Oxidation of poly(V-C-M)*

To a solution of poly(V-C-M) (6.65 mg, 0.25 mmol) in CH_2Cl_2 (1.0 mL) was added aqueous 31% H_2O_2 (109.7 mg, 1.0 mmol), and the mixture was vigorously stirred at 25 °C for 24 h. The solvent and residual H_2O_2 were evaporated from the reaction mixture, and DMF (0.5 mL) was added to the residue. The resulting solution was poured into a large amount of ethyl ether to precipitate a polymer, which was filtered with a membrane filter (Millipore LAWPO 4700 pore size 0.45 μm) and then dried in vacuo at 45 °C for 12 h. Yield = 0.445 g (72%). M_n = 19500, M_w/M_n = 1.80 $[\alpha]_D^{25}$ = -5.1° (c = 1 g/dL, DMF). ^{1}H-NMR (DMSO, 400 MHz): δ = 1.94-2.53 (m, 2H, $-CH_2-C_6H_4-$), 2.75-2.97 (m, 4H, $-CH_2-$

S-CH_2- and -CH_2-$S(O)$-CH_2-), 3.31-3.74 (broad m, 3H, -$C(O)OCH_3$), 4.50-4.98 (broad m, -CH<), 8.80-9.02 (broad m, 1H, -NH-) ppm. IR (KBr): 3402, 1736, 1648, 1539, 1502, 1297, 1228, 1125, 1042, 1024, 860, 670 cm^{-1}.

5.3. Results and discussion

5.3.1. *Heterotelechelic polymer synthesis*

Radical self-polyaddition of *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M) was carried out in the presence of AIBN (3 mol %) as an initiator in DMF (0.5 and 1.0 M) at 60 °C for 20 h under nitrogen atmosphere to afford the corresponding polymer[poly(V-C-M)] with M_ns 5300 and 18000 in 76 and 95% yields, respectively (Table 1). The obtained polymer had a heterotelechelic structure with thiol and olefin groups, as described in chapter 4.[5]

Scheme 1:

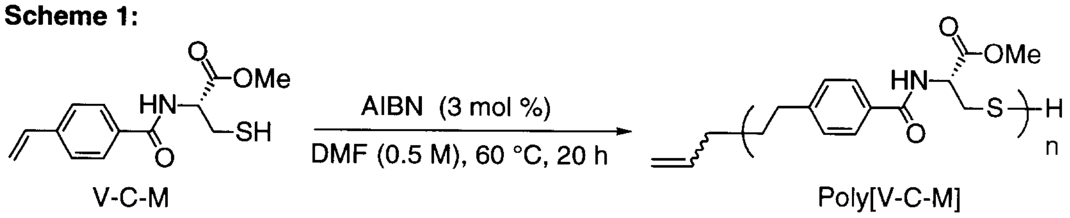


Table 1. Radical self-polyaddition of V-C-M [a]

Run	Monomer conc. (M)	Yield [b] (%)	$M_n(M_w/M_n)$ [c]	$[\alpha]_D^{25}$ [d] (degree)	T_g [e] (°C)	Td_{10} [f] (°C)
1	0.5	76	5300 (1.61)	- 9.0	- [g]	251
2	1.0	95	18000 (1.56)	-10.5	- [g]	256

a) Conditions : V-C-M (5 mmol), AIBN (3 mol %), 60 °C, 20 h, under nitrogen atmosphere in DMF. b) Ether-insoluble part. c) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). d) Measured by a polarimeter at 25 °C (c = 1.00, DMF). e) Determined by DSC. f) Determined by TG. g) Not observed up to 200°C.

5.3.2. *Radical polymerization of MMA and TrtMA in the presence of poly(V-C-M)*

Okaya et al. have reported a block copolymerization of poly(vinyl alcohol-*co*-vinyl acetate) having a thiol group at the one end with some vinyl monomers such as acrylic acid and acrylamide,[6] whose initiation is the redox reaction of the thiol group of the polymer end and an oxidant such as potassium bromate. In this work, radical polymerization of MMA and TrtMA was carried out in the presence of poly(V-C-M) having olefin and thiol ends with AIBN as an initiator in DMF at 60 °C for 20 h to obtain the corresponding copolymers with M_ns in the rang of 17000-26800 in 87-95% yields as summarized in Table 2. The polymer obtained by the polymerization of TrtMA in the presence of poly(V-C-M) (M_n 18000, M_w/M_n 1.56) was insoluble in common organic solvents (run 4 in Table 2).

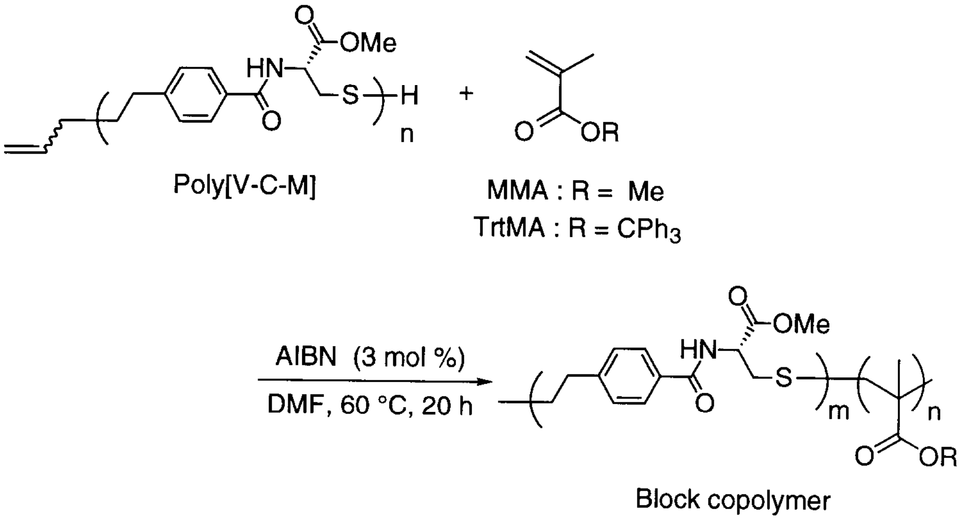
Table 2 : Radical polymerization of MMA and TrtMA in the presence of poly(V-C-M) [a)]

Run	Monomer	Poly(V-C-M) M_n (M_w / M_n)	Yield (%)	Copolymer Composition Monomer / V-C-M	M_n(M_w/M_n)[b)]	$[\alpha]_D^{25}$ [c)] (degree)	Td_{10} [d)] (°C)
1	MMA	5300 (1.61)	87 [e)]	20 / 13	17000 (2.10)	-1.7	288
2	TrtMA	5300 (1.61)	95 [f)]	20 / 11	13000 (1.28)	2.0	237
3	MMA	18000 (1.56)	90 [e)]	20 / 12	26800 (1.98)	1.1	298
4	TrtMA	18000 (1.56)	91 [f)]	- [g)]	- [g)]	- [g)]	244

a) Conditions: monomer (50 mg, 0.5 mmol), poly(V-C-M) (66.3 mg), feed molar ratio: Monomer/V-C-M (the polymer repeating unit) = 20 / 10, AIBN (3 mol % vs monomer), 60 °C, 20 h. b) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). c) Measured by a polarimeter at 25 °C (c = 1.00, DMF). d) Determined by TG. e) Ethyl ether-insoluble part. f) Methanol-insoluble part. g) Not determined.

Figure 1 illustrates the GPC profiles of poly(V-C-M) (M_n 5300, M_w/M_n 1.61) and the polymer (M_n 17000, M_w/M_n 2.10) obtained by the polymerization of MMA in the presence of poly(V-C-M). The latter showed a larger M_n than the former, and no absorption corresponding to the original poly(V-C-M). The ^{1}H-NMR spectrum of the obtained polymer (Figure 2 [B]) showed both signals based on poly(V-C-M) and poly(MMA) units. These results strongly indicates the formation of a block copolymer of V-C-M and MMA. The unit ratio of V-C-M and MMA was calculated to be 20 : 13 from the integration ratio of the methine proton signal of V-C-M unit at 4.98 ppm and methyl proton signal of MMA unit at 0.84 - 1.22 ppm. The copolymer of V-C-M and TrtMA was obtained in the similar way, whose unit ratio was calculated by the integration ratio of the methine proton signal of V-C-M unit and methyl proton signal of TrtMA at 0.84-1.22 ppm. The copolymers showed nearly the same unit ratios as expected from the feed ratios. While the copolymers were insoluble in ethyl ether nor methanol. The homopolymers of MMA and TrtMA were soluble in ethyl ether and methanol, respectively, which also supported the formation of block copolymers (Scheme 2). Poly(V-C-M) and the block copolymers showed no apparent T_g up to 200 °C.

Scheme 2:



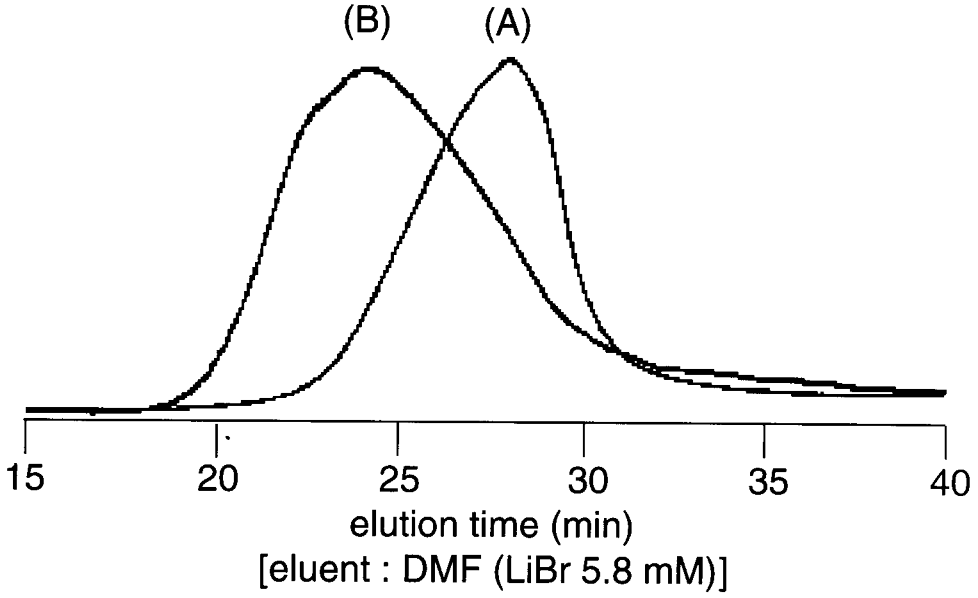


Figure 1. GPC profiles (UV detector). (A) Poly(V-C-M), M_n = 5300, M_w/M_n = 1.61, (run 1 in Table 1). (B) Polymer obtained by the polymerization of MMA in the presence of poly(V-C-M) (A), M_n = 17000, M_w / M_n = 2.10, (run 1 in Table 2).

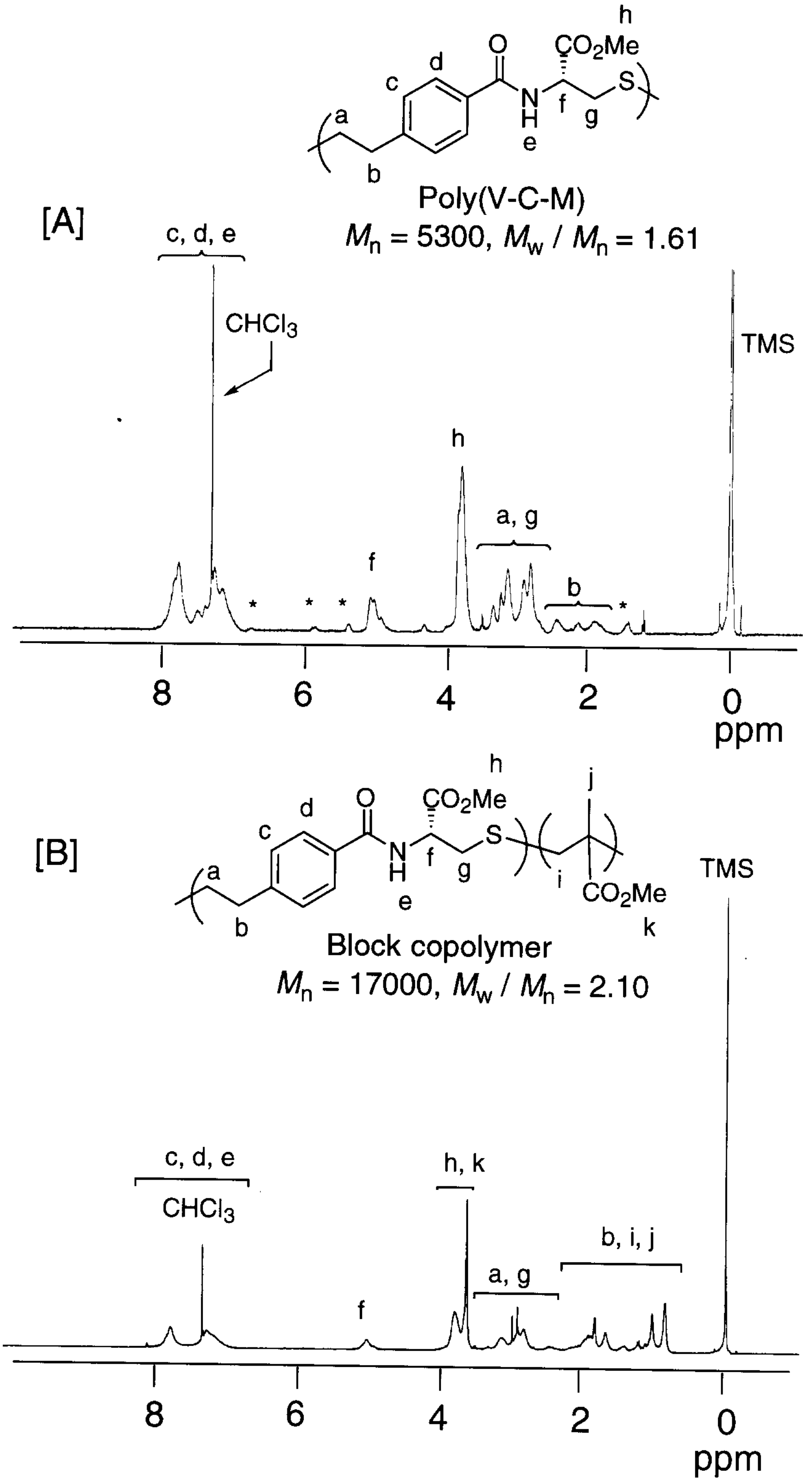


Figure 2. ^{1}H-NMR spectra (400 MHz, $CDCl_3$) of [A]: poly(V-C-M), M_n = 5300, M_w/M_n = 1.61 (run 1 in Table 1), and [B]: copolymer of poly(V-C-M) with MMA, M_n = 17000, M_w/M_n = 2.10 (run 1 in Table 2). * : signal derived from the polymer end vinyl and mercapto groups.

5.3.3. *Thermal property of the block polymer*

Figures 3 and 4 illustrate the TGA profiles of poly(V-C-M) (M_n 5300, M_w/M_n 1.61) and the corresponding block copolymers with MMA (M_n 17000, M_w/M_n 2.10) and TrtMA (M_n 13000, M_w/M_n 1.28). The block copolymer with MMA was thermally stabler than poly(MMA) and poly(V-C-M), while the block copolymer with TrtMA was thermally less stable than poly(TrtMA) and poly(V-C-M).

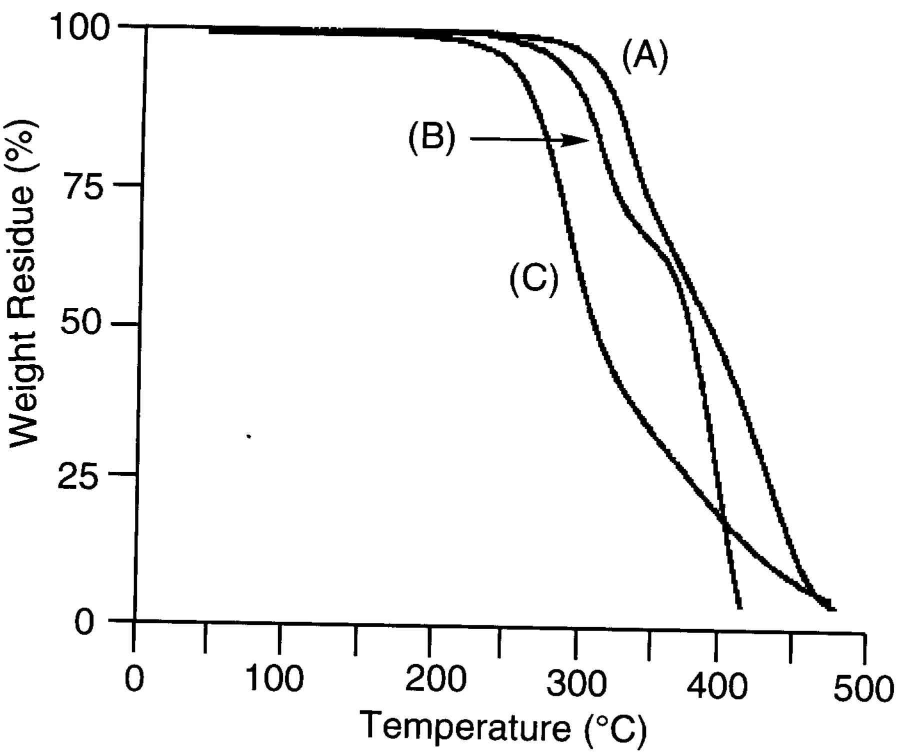


Figure 3. TGA profiles of poly(V-C-M), and the corresponding block polymer with MMA. (A) block polymer with MMA (M_n 17000, M_w/M_n 2.10), (run 1 in Table 2). (B) poly(MMA) (M_n 47000, M_w/M_n 1.78) obtained in the presence of AIBN (3 mol %) in DMF (0.5 M) at 60 °C for 20 h. (C) poly(V-C-M) (M_n 5300, M_w/M_n 1.61), (run 1 in Table 1).

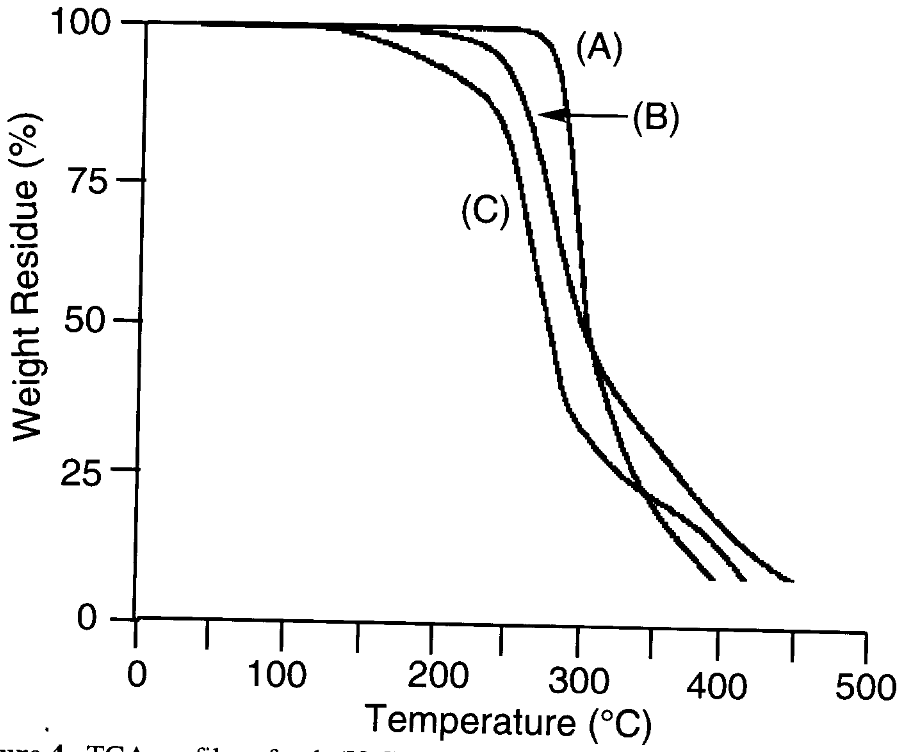
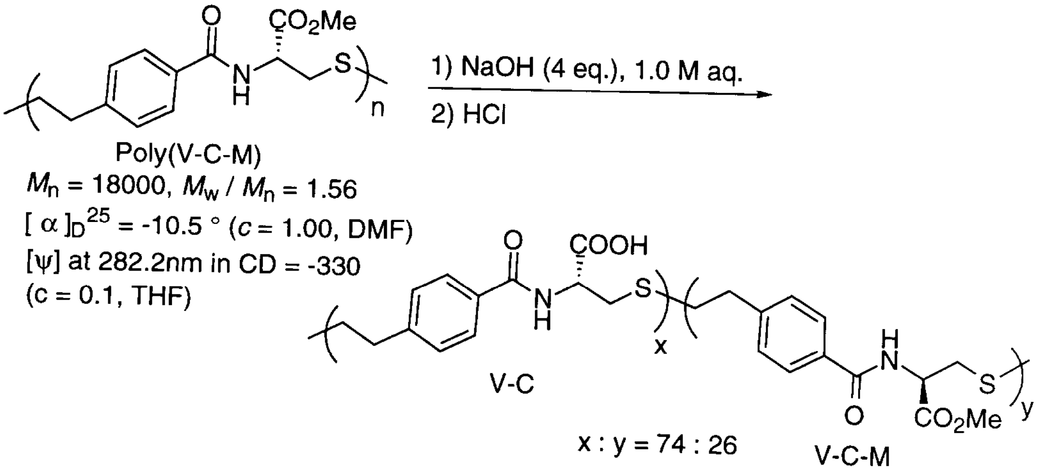


Figure 4. TGA profiles of poly(V-C-M), and the corresponding block polymer with TrtMA. (A) block polymer with TrtMA (M_n 13000, M_w/M_n 1.28), (run 2 in Table 2). (B) poly(TrtMA) (M_n 7100, M_w/M_n 1.80) obtained in the presence of AIBN (3 mol %) in DMF (0.5 M) at 60 °C for 20 h. (C) poly(V-C-M) (M_n 5300, M_w/M_n 1.61), (run 1 in Table 1).

5.3.4. *Hydrolysis of poly(V-C-M)*

Poly(carboxylic acid)s have specific features owing to the hydrophilic carboxyl groups, which are applicable to electrolytes, detergents, flocculants, and absorbents.[7] Poly(V-C-M) (M_n 18000, M_w/M_n 1.56) was treated with 4 equiv. of NaOH aq. (1.0 M) to afford a partially hydrolyzed polymer (poly[$(V\text{-}C)_{74}$-*co*- $(V\text{-}C\text{-}M)_{26}$] having carboxyl groups with M_n 17300, M_w/M_n = 1.88 in 95% yield (Scheme 3). The M_n, $[\alpha]_D^{25}$, and $[\psi]$ at 285.5 nm in CD of the obtained polymer showed nearly the same values as the polymer before hydrolysis. Figure 5 illustrates the ^{1}H-NMR spectra of the polymers before and after hydrolysis. The integration ratio of the methyl ester signal decreased to 26% and a carboxyl proton signal appeared at 12.8 ppm after hydrolysis. The IR spectrum (Figure 6) of the hydrolyzed polymer showed characteristic absorption based on carboxylic acid at 2900 ~ 3400 cm^{-1}.

Scheme 3:



Poly(V-C-M)
M_n = 18000, M_w / M_n = 1.56
$[\alpha]_D^{25}$ = -10.5 ° (c = 1.00, DMF)
$[\psi]$ at 282.2nm in CD = -330
(c = 0.1, THF)

x : y = 74 : 26

Poly[$(V\text{-}C)_{74}$-*co*-$(V\text{-}C\text{-}M)_{26}$]
Yield = 95 %
M_n = 17300, M_w / M_n = 1.88
$[\alpha]_D^{25}$ = -10.0 ° (c = 1.00, DMF)
$[\psi]$ at 285.5 nm in CD = - 360
(c = 0.1, THF)

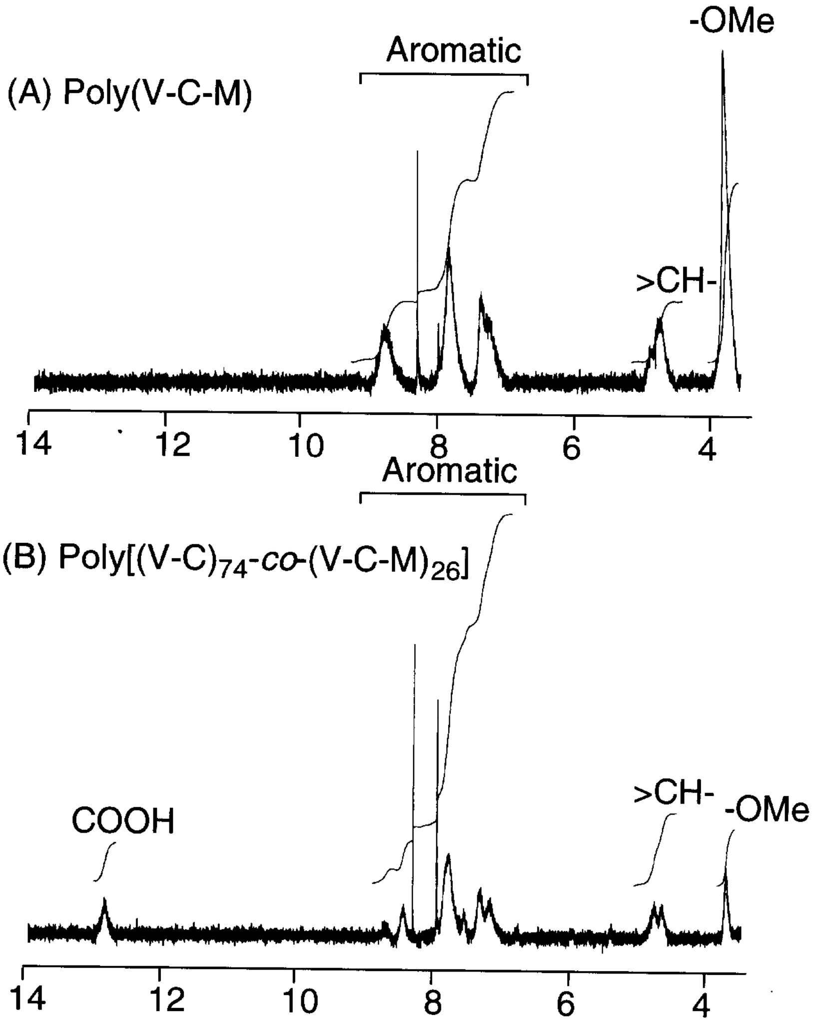


Figure 5. ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of before and after hydrolysis with NaOH aq. (A) Poly(V-C-M). (B) Poly[(V-C)$_{74}$-*co*-(V-C-M)$_{26}$].

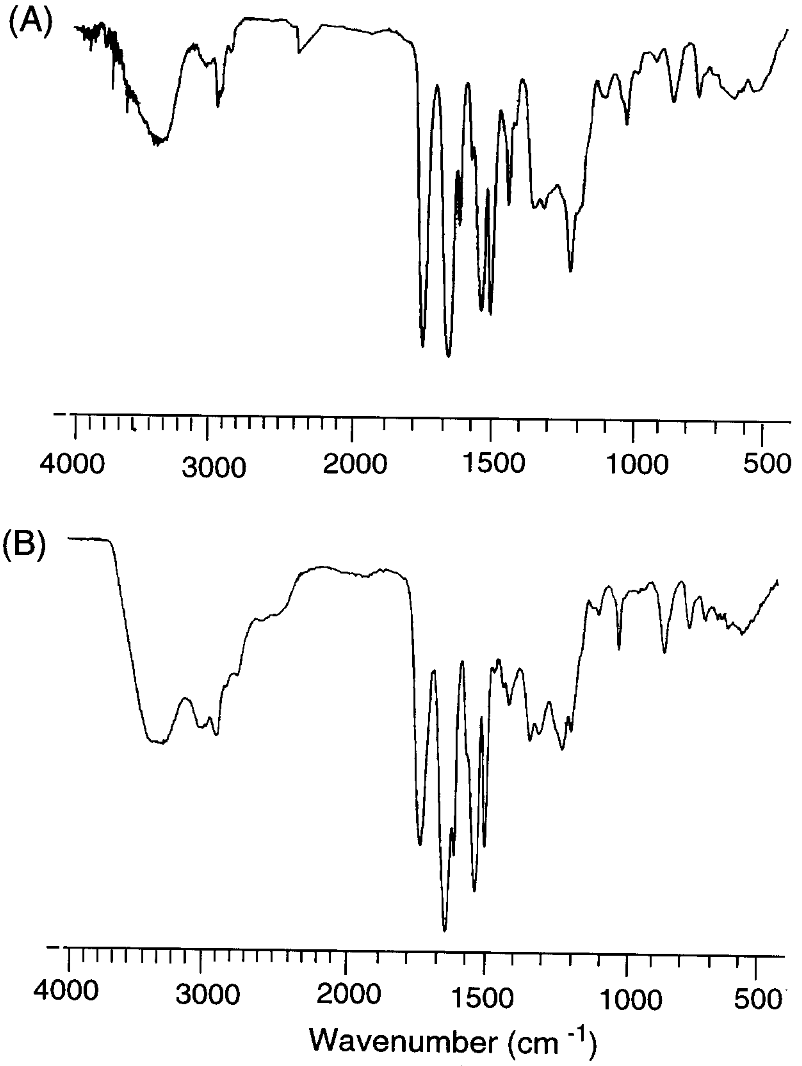
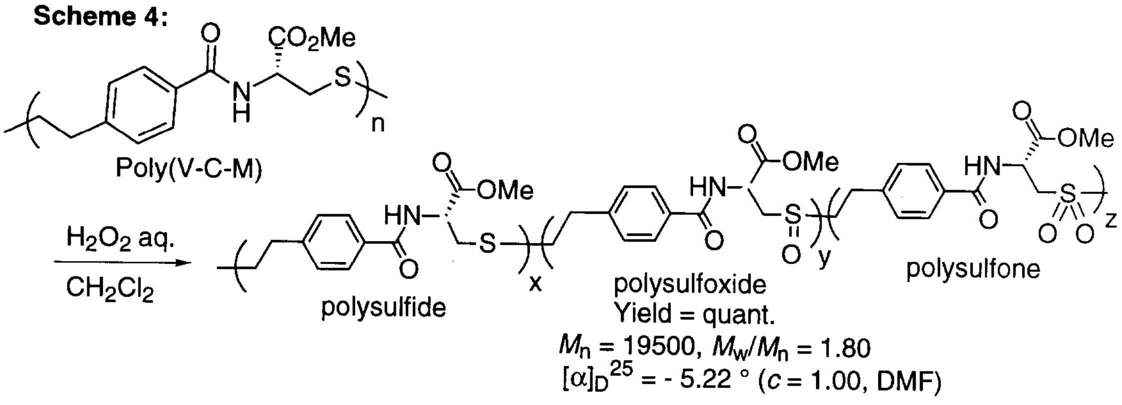


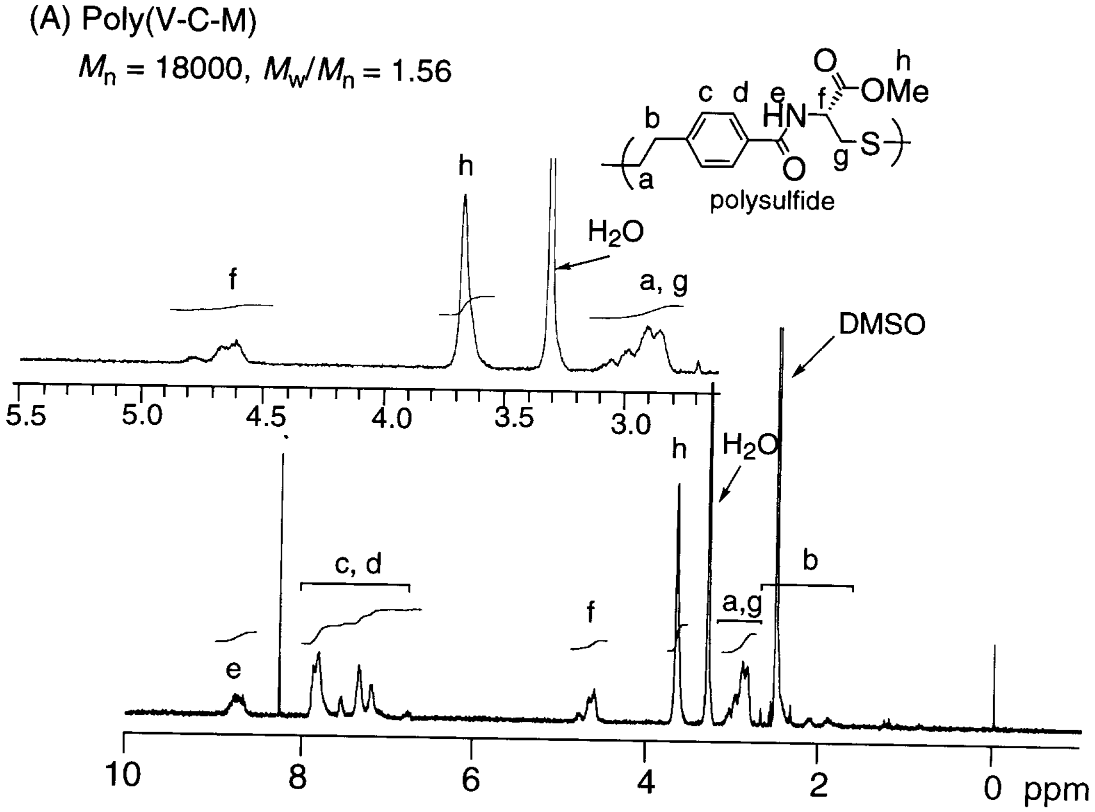
Figure 6. IR spectra (KBr) of before and after hydrolyzed polymer. (A) poly(V-C-M) (M_n 18000, M_w/M_n 1.56). (B) (poly[(V-C)$_{74}$-*co*- (V-C-M)$_{26}$] having carboxylic acid with M_n = 17300, M_w/M_n = 1.88.

5.3.5. *Oxidation of poly(V-C-M)*

Polysulfoxides are useful as polymeric oxidants and permeation membranes for isolation of SO_2.[8] In this work, poly(V-C-M) was oxidized to poly(sulfoxide) with 4 equivalent of H_2O_2 per sulfide unit in CH_2Cl_2 (1.0 M) for 20 h (Scheme 4). The molecular weight of the oxidized polymer was almost the same as the one before oxidation, indicating that no polymer chain was cleaved during oxidation. The structure of the oxidized polymer was confirmed by ^{1}H-NMR and IR spectroscopy. Figure 7 illustrates the ^{1}H-NMR spectra of polymers before and after oxidation. The α-methylene proton of the sulfide group and methine proton were observed at 2.75-2.97 and 4.50-4.58 ppm, respectively (Figure 5, (A)). Those of sulfoxide and sulfone were observed at 3.05-3.16 and 4.79-4.98 ppm, respectively (Figure 5, (B)). Figure 8 depicts the IR spectroscopy of the oxidized polymer along with that of poly(V-C-M). The characteristic absorption of peaks based on sulfoxide and sulfone groups were observed at 1042 and 1297, 1125 cm^{-1}, respectively. The ratio of sulfide, sulfoxide and sulfone moieties in oxidized polymers were 20, 48 and 32%, respectively. The $[\alpha]_D^{25}$ of oxidized polymer was -5.22, which was different from that of poly(V-C-M) ($[\alpha]_D^{25}$ = -10.1). The T_{d10} of the oxidative polymer was 147 °C measured by TGA, indicated that the oxidized polymer was not thermally stable.

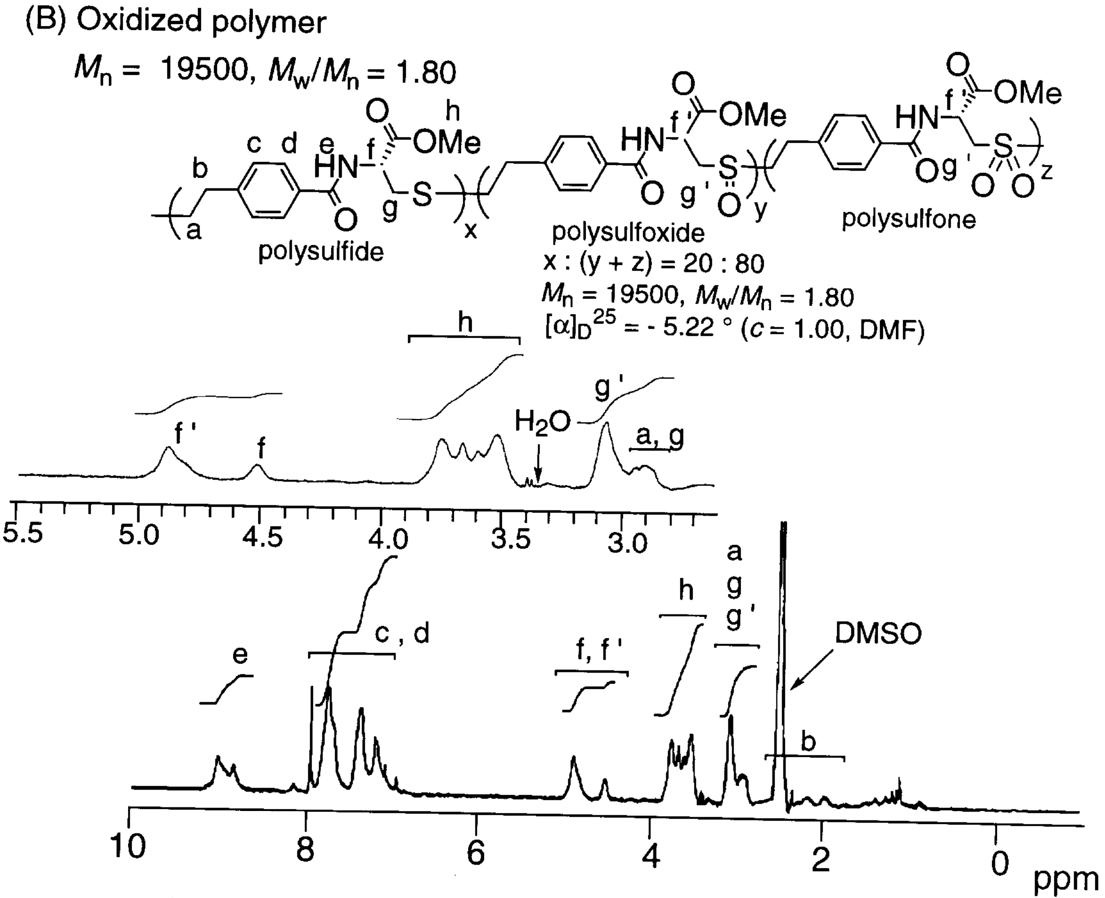
Scheme 4:





(A) Poly(V-C-M)

M_n = 18000, M_w/M_n = 1.56



(B) Oxidized polymer

M_n = 19500, M_w/M_n = 1.80

Figure 7. ^{1}H-NMR spectra (400 MHz, DMSO-d_6) of poly(V-C-M) (M_n 18000, M_w/M_n 1.56) and the polymer oxidized with H_2O_2 (M_n 19500, M_w/M_n 1.80).

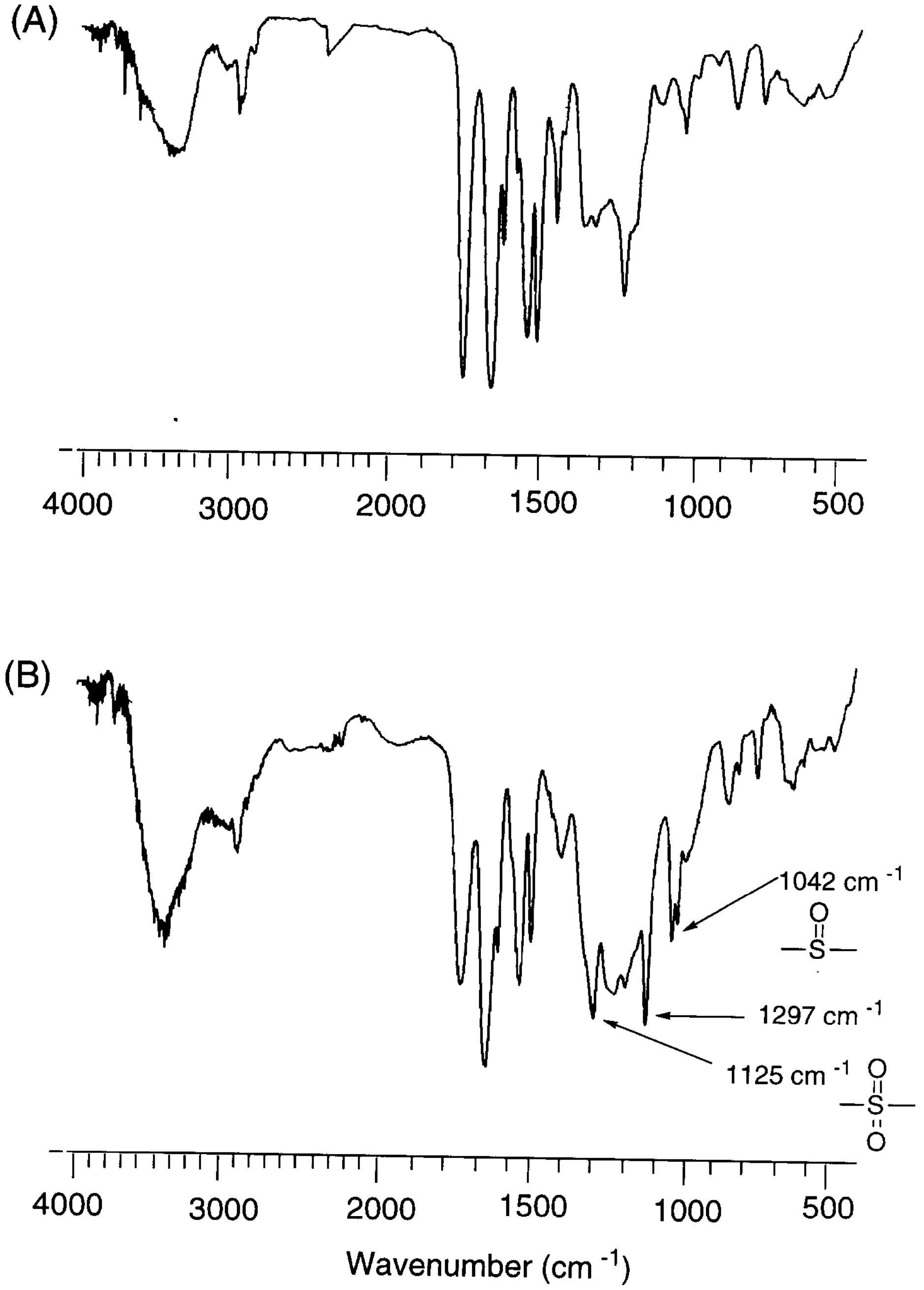


Figure 8. IR spectra (KBr) of (A) poly(V-C-M) (M_n 18000, M_w/M_n 1.56) and (B) the polymer oxidized with H_2O_2 (M_n 19500, M_w/M_n 1.80).

5.4. Summary

In this chapter, I examined that the reactions of a thiol-olefin heterotelechelic polymer, poly(V-C-M). Radical polymerization of MMA and TrtMA was carried out in the presence of poly(V-C-M) with AIBN as an initiator in DMF to afford the corresponding block copolymers. Poly(V-C-M) was oxidized with H_2O_2 to the polymer having sulfoxide and sulfone groups in the main chain , and was hydrolyzed with NaOH to the polymer having carboxyl groups in the side chain.

5.5. References and Notes

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(5) The ^{1}H-NMR spectrum of the polymer showed signals assignable to mercapto and olefin groups at the polymer ends at 1.42 and 5.33-6.78 ppm, respectively, as shown in Figure 1 in chapter 4. Furthermore, the post polymerization of the poly(V-C-M) with M_n 7100 using AIBN (10 mol %) in DMF at 60 °C for 20 h afforded a higher polymer weight (M_n 15700). These results indicated that the poly(V-C-M) was a heteroterechelic polymer.

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Chapter 6

Synthesis and Oxidation Polymerization of Cysteine-Based Dithiols

Abstract

Synthesis and oxidation polymerization of novel optically active dithiol monomers, **1a**, **1b**, **1c** and **1d**, having dithiol groups derived from cysteine were carried out in the presence of triethylamine in DMF and DMSO under oxygen atmosphere. At 60 °C, the corresponding polydisulfides with M_ns of 3900 ~ 7200 were obtained in 78 ~ 90% yields, while at 25 °C, cyclic dimers were obtained quantitatively. The specific rotation and Cotton effect of poly**1b** were drastically different from those of **1b**, suggesting the presence of higher order structures.

6.1 Introduction

Thiols are easily oxidized into disulfides by oxygen even at room temperature under atmospheric pressure.[1] Various oxidizing agents such as nitric acid, hydrogen peroxide, potassium ferricyanide and iodide have been employed along with oxygen for the conversion of thiols to disulfide.[2] Some researchers have developed oxidation polymerization of dithiols to obtain polydisulfides utilizing the high reactivity of thiols.[3] However, oxidation polymerization is not common because of high cost and bad smell of commercially available dithiols. Recently, Endo et al. have synthesized some optically active sulfur-containing polymers from cysteine,[4] whose mercapto group plays an important role such as chain transfer applicable to macromonomer synthesis.[5] In this chapter, I describe the synthesis and oxidation polymerization of cysteine-based dithiol monomers.

6.2. Experiment

6.2.1. *Measurements*

^1H and ^{13}C-NMR spectra were recorded on a JEOL JNM EX-400 spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). FAB mass spectra were recorded on a JEOL JMS-700 instrument with *p*-nitrobenzyl alcohol as the matrix. IR spectra were measured with a JASCO FTIR-5300 spectrometer. Melting points (mp) were measured on a YANACO micro melting point apparatus. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter using a sodium lamp as a light source. Circular dichroism (CD) spectra were measured on a JASCO J-720 spectropolarimeter. Molecular weights (M_n) and polydispersity ratios (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC, HLC-8020 system, equipped with three consecutive polystyrene gel columns (TSK-gels, G5000H, G4000H, and G2500H), using *N,N*-dimethylformamide (DMF, 5.8 mM lithium bromide solution) as an eluent at a flow rate of 1.0 mL/min, polystyrene calibration, and refractive index (RI) and ultraviolet (UV) detectors.

6.2.2. *Materials*

L-Cysteine was obtained from Ajinomoto Co. Suberoylchloride, pimeroylchloride, adipoylchloride and glutarylchloride were purchased from Tokyo Kasei Kogyo Co. DMF and DMSO were distilled over calcium hydride before use.

6.2.3. *Synthesis of cysteine-based dithiol monomers*

Synthesis of **1a**: To a suspension of L-cysteine methyl ester hydrochloride (4.28 g, 25 mmol) in dichloromethane (75 mL) was added triethylamine

(7.30 mL, 52.4 mmol) slowly at 0 °C under nitrogen, and then a solution of suberoyl chloride (2.64 g, 2.25 mL, 12.5 mmol) in dichloromethane (12.5 mL) slowly at 0 °C. The mixture was stirred at 0 °C for 30 min, then at room temperature overnight. The resulting mixture was concentrated by a rotary evaporator and the residual mass was washed with ethyl acetate (200 mL). It was filtered to remove triethylamine hydrochloride, and the filtrate was concentrated by a rotary evaporator again, followed by recrystallization twice by ethyl acetate under nitrogen to obtain colorless solid, (**1a**). Yield 3.98 g (73%). Mp = 60-61 °C. $[\alpha]_D^{25}$ = 85.6 ° (*c* = 0.1 g/dL, $CHCl_3$), 90.4 ° (*c* = 0.1 g/dL, DMSO). ^1H-NMR ($CDCl_3$, 400 MHz): δ = 1.36-1.41 (m, 6H, -SH, $-CH_2-CH_2-$), 1.67 (s, 4H, $-CH_2-CH_2-$), 2.25-2.30 (m, 4H, $-CH_2-C(O)-$), 2.96-3.20 (m, 4H, $-CH_2-S$), 3.77-3.87 (m, 6H, $-OCH_3$), 4.87-4.93 (m, 2H, >CH-), 6.46-6.64 (m, 2H, -NH-) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 25.21, 25.26, 26.85, 28.48, 28.52, 36.02, 36.11, 52.80, 53.37, 170.78, 172.85 ppm. IR (KBr): 3313, 2937, 2860, 2560, 1745, 1645, 1535, 1436, 1350, 1216, 1176, 1137, 1041, 980, 675, 586 cm^{-1}. Anal. Calcd for $C_{16}H_{28}N_2O_6S_2$: C 47.04, H 6.91, N 6.86, S 15.70. Found. C 47.32, H 6.90, N 6.88, S 15.61.

Synthesis of **1b**: **1b** was synthesized from L-cysteine methyl ester hydrochloride and pimeroylchloride in the similar manner with **1a**. Yield 82%. Mp = 57-58 °C. $[\alpha]_D^{25}$ = 68.1 ° (*c* = 1 g/dL, $CHCl_3$), -22.8 ° (*c* = 0.1 g/dL, DMSO). ^1H-NMR ($CDCl_3$, 400 MHz): δ = 1.35-1.45 (m, 4H, $-CH_2-$, -SH), 1.66-1.73 (m, 4H, $-CH_2-$), 2.23-2.58 (m, 4H, $-C(O)-CH_2-$), 2.58-3.02 (m, 4H, $-CH_2-S$), 3.77 (s, 6H, $-OCH_3$), 4.88-4.92 (m, 2H, >CH-), 6.46 (d, *J* = 7.59 Hz, 2H, -NH-) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 24.97, 26.85, 28.54, 36.07, 52.79, 53.39, 170.71, 172.70 ppm. IR (KBr): 3325, 2951, 2862, 2563, 1738, 1640, 1535, 1438, 1321, 1216, 1177, 1142, 1054, 980, 678, 589 cm^{-1}. Anal. Calcd for $C_{15}H_{26}N_2O_6S_2$: C 45.67, H 6.64, N 7.10, S 16.25. Found. C 45.44, H 6.68, N 6.90, S 16.51.

Synthesis of **1c**: **1c** was synthesized from L-cysteine methyl ester hydrochloride and adipoylchloride in the similar manner with **1a**. Yield 80%. Mp = 54-55 °C. $[\alpha]_D^{25}$ = 67.1 ° (*c* = 1 g/dL, $CHCl_3$), - 27.6 ° (*c* = 0.1 g/dL, DMSO). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.41 (t, *J* = 8.9, 2H, -SH), 1.73 (s, 4H, $-CH_2-CH_2-$), 2.32 (s, 4H, $-CH_2-C(O)-$), 3.00-3.05 (m, 4H, $-CH_2-S$), 3.80 (s, 6H, $-OCH_3$), 4.87-4.91 (m, 2H, >CH-), 6.51 (d, *J* = 6.79, 2H, -NH-) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 24.71, 26.78, 35.82, 52.81, 53.48, 170.69, 172.48 ppm. IR (KBr): 3310, 2952, 2868, 2570, 1742, 1645, 1537, 1438, 1341, 1223, 1179, 1148, 1041, 952, 634, 586 cm^{-1}. Anal. Calcd for $C_{14}H_{24}N_2O_6S_2$: C 44.20, H 6.36, N 7.36, S 16.85. Found. C 44.15, H 6.22, N 7.60, S 16.61.

Synthesis of **1d**: **1d** was synthesized from L-cysteine methyl ester hydrochloride and glutarylchloride in the similar manner with **1a**. Yield 75%. Mp = 96-97 °C. $[\alpha]_D^{25}$ = 43.0 ° (*c* = 1 g/dL, $CHCl_3$), - 41.8 ° (*c* = 0.1 g/dL, DMSO). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.59 (t, *J* = 8.8 Hz, 2H, -SH), 2.05-2.09 (m, 2H, $-CH_2-$), 2.25-2.37 (m, 4H, $-C(O)-CH_2-$), 2.95-3.04 (m, 4H, $-CH_2-S$), 3.80 (s, 6H, $-OCH_3$), 4.97-5.01 (m, 2H, >CH-), 7.59 (d, *J* = 8.39 Hz, 2H, -NH-) ppm. ^{13}C-NMR ($CDCl_3$, 400 MHz): δ = 22.22, 26.26, 34.06, 52.70, 54.06, 172.73, 173.36 ppm. IR (KBr): 3334, 2953, 2566, 1748, 1737, 1636, 1529, 1439, 1318, 1231, 1050, 622, 590 cm^{-1}. Anal. Calcd for $C_{13}H_{22}N_2O_6S_2$: C 42.61, H 6.05, N 7.64, S 17.50. Found. C 42.66, H 6.18, N 7.76, S 17.53.

6.2.4. *Oxidation of 1a ~ 1d*

Typical procedure at 60 °C: To **1a** (101.5 mg, 0.25 mmol) in a polymerization tube was introduced NEt_3 (0.07 mL, 0.5 mmol), and subsequently dry DMF (0.75 mL). The tube was cooled, degassed, and the reaction mixture was stirred at 60 °C under oxygen atmosphere for 24 h. The reaction mixture was homogeneous consistently. The resulting homogeneous mixture was poured into water (50 mL) and extracted three times with CH_2Cl_2 (10 mL), and the combined extract was dried over anhydrous magnesium sulfate. The resulting mixture was concentrated by a rotary evaporator. The residual mass was purified by preparative HPLC (Nihon Bunseki Kogyo), equipped with two polystyrene gel columns (JAL-GELs H_1 and H_2), using $CHCl_3$ as an eluent, and then dried *in vacuo* at 50 °C for 12 h to obtain poly**1a**. Yield 81.3 mg (80%). M_n = 4800, M_w/M_n = 1.31. $[\alpha]_D^{25}$ = 24 ° (c = 0.1 g/dL, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.25 (broad, s, 4H, -CH_2-CH_2-), 1.66 (broad, s, 4H, -CH_2-), 2.27 (broad, s, 4H, -CH_2-C(O)-), 2.89-3.19 (broad, m, 4H, -CH_2-S-), 3.48-3.96 (m, 6H, -OCH_3), 4.80 (broad, 2H, >CH-), 6.60-8.20 (m, 2H, -NH-) ppm. IR (KBr): 3325, 2951, 2862, 1735, 16450, 1536, 1438, 1325, 1215, 1187, 1142, 1054, 980, 678, 589 cm^{-1}.

poly**1b**. Yield 73%. M_n = 4100, M_w/M_n = 1.14. $[\alpha]_D^{25}$ = -1039 ° (c = 0.1 g/dL, $CHCl_3$), - 31.1 ° (c = 0.1 g/dL, DMSO). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.25 (broad s, 4H, -CH_2-CH_2-), 1.66 (broad s, 4H, -CH_2-), 2.27 (broad s, 4H, -CH_2-C(O)-), 2.89-3.19 (broad m, 4H, -CH_2-S-), 3.48-3.96 (m, 6H, -OCH_3), 4.80 (broad s, 2H, >CH-), 6.60-8.20 (m, 2H, -NH-) ppm. IR (KBr): 3325, 2951, 28612, 1737, 1640, 1534, 1439, 1320, 1215, 1176, 1144, 1051, 985, 587 cm^{-1}.

poly**1c**. Yield 73%. M_n = 3900, M_w/M_n = 1.16. $[\alpha]_D^{25}$ = 5.2 ° (c = 0.1 g/dL, $CHCl_3$), - 58.0 ° (c = 0.1 g/dL, DMSO). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.72 (broad s, 4H, -CH_2-CH_2-), 2.32 (broad s, 4H, -C(O)-CH_2-), 3.22 (broad s, 4H, -S-CH_2), 3.76-3.85 (m, 6H, -OCH_3), 4.85 (broad s, 2H, >CH-), 6.58-7.86 (broad m, 2H, -NH-) ppm. IR (KBr):

3330, 2951, 2862, 1737, 1640, 1534, 14409, 1320, 1216, 1176, 1144, 1050, 985, 676, 587 cm^{-1}.

poly**1d**. Yield 90%. M_n = 3900, M_w/M_n = 1.14. $[\alpha]_D^{25}$ = 43 ° (*c* = 0.1 g/dL, $CHCl_3$), - 42.0 ° (*c* = 0.1 g/dL, DMSO). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.03 (broad, s, 2H, -CH_2-), 2.27-2.43 (broad, m, 4H, -C(O)-CH_2-), 2.96-3.26 (broad, m, 4H, -S-CH_2), 3.74-3.84 (broad m, 6H, -OCH_3), 4.87-4.97 (broad, m, 2H, >CH-), 6.58-7.86 (broad, m, 2H, -NH-) ppm. IR (KBr): 3334, 2952, 2563, 1745, 1735, 1637, 1531, 1441, 1322, 1231, 1051, 623, 591 cm^{-1}.

Typical procedure at 25 °C: To **1a** (101.5 mg, 0.25 mmol) in a polymerization tube was introduced NEt_3 (0.07 mL, 0.5 mmol), and subsequently a dry DMF (0.75 mL). The tube was cooled, degassed, and stirred at 25 °C in oxygen atmosphere for 24 h. The reaction mixture became heterogeneous 6 h after the reaction had been started. The resulting mixture was poured into a large amount of ethyl ether. The ethyl ether-insoluble part was filtered off and then dried *in vacuo* at 50 °C for 12 h to obtain colorless solid (**2a**). (**2a**): Yield = 94.7 mg (100%). Mp = 207-208 °C. $[\alpha]_D^{25}$ = - 64.6 ° (*c* = 0.1 g/dL, DMSO). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 1.15 (s, 8H, -CH_2-CH_2-), 1.46 (s, 8H, -CH_2-CH_2-), 2.08 (s, 8H, -CH_2-C(O)-), 2.82-3.11 (m, 8H, -CH_2-S-), 3.63 (s, 12H, -OCH_3), 4.53-4.58 (m, 4H, >CH-), 8.31 (d, *J* = 7.6, 2H, -NH-) ppm. ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 18.45, 40.64, 51.89, 52.81, 120.83, 139.15, 167.94, 170.88 ppm. IR (KBr): 3330, 2955, 2862, 1738, 1641, 15365, 1439, 1321, 1216, 1178, 1142, 1054, 980, 678, 589 cm^{-1}. Anal. Calcd for $C_{32}H_{52}N_4O_{12}S_4$: C 47.27; H 6.45; N 6.89, S 15.77. Found. C 47.31, H 6.50, N 6.85, S 15.79. HRFAB-MS: $(M + H)^+$ Calcd for $C_{15}H_{27}N_2O_6S_2$: 813.02. Found: 813.04

2b: Yield 100%. Mp = 220-222 °C. $[\alpha]_D^{25}$ = 73.9 ° (*c* = 1 g/dL, DMF). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ = 1.35 (s, 4H, $-CH_2-$), 1.65 (s, 8H, $-CH_2-$), 2.26 (s, 8H, $-C(O)-CH_2-$), 3.18-3.22 (m, 8H, $-CH_2-S-$), 3.78 (s, 12H, $-OCH_3$), 4.86-4.87 (m, 4H, >CH-), 6.77-6.95 (m, 4H, -NH-) ppm. ^{13}C-NMR (DMSO-*d*6, 400 MHz): δ = 18.45, 40.64, 51.89, 52.81, 120.83, 139.15, 167.94, 170.88 ppm. IR (KBr): 3325, 2951, 2862, 1738, 1641, 1534, 1439, 1320, 1215, 1175, 1143, 1054, 980, 679, 587 cm^{-1}. Anal. Calcd for $C_{30}H_{48}N_4O_{12}S_4$: C 45.90, H 6.16, N 7.10, S 16.34. Found. C 45.44, H 6.68, N 6.90, S 16.51. HRFAB-MS: $(M + H)^+$ Calcd for $C_{30}H_{49}N_4O_{12}S_4$: 785.22. Found: 785.3

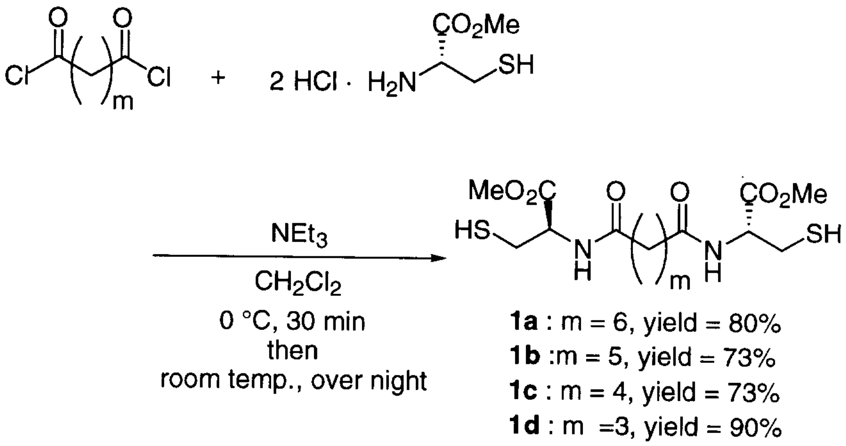
2c: Yield 100%. Mp = 243-244 °C. $[\alpha]_D^{25}$ = - 19.32 ° (*c* = 0.1 g/dL, DMSO). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ = 1.46 (s, 8H, $-CH_2-CH_2-$), 2.11 (s, 8H, $-C(O)-CH_2-$), 2.93-3.41 (m, 8H, $-CH_2-S-$), 3.64 (s, 12H, $-OCH_3$), 4.55-4.61 (m, 4H, >CH-), 8.36 (d, *J* = 7.99 Hz, 4H, -NH-) ppm. ^{13}C-NMR (DMSO-*d*6, 400 MHz): δ = 24.56, 34.71, 45.66, 52.05, 64.88, 169.94, 172.14 ppm. IR (KBr): 3320, 2950, 2865, 1742, 1646, 1531, 1439, 1340, 1222, 1179, 1148, 1041, 951, 635, 585 cm^{-1}. Anal. Calcd for $C_{28}H_{44}N_4O_{12}S_4$: C 44.43, H 5.86, N 7.40, S 16.94. Found. C 47.44, H 6.18, N 6.60, S 15.61. HRFAB-MS: $(M + H)^+$ Calcd for $C_{28}H_{45}N_4O_{12}S_4$: 757.18. Found: 757.6

6.3. Results and Discussion

6.3.1. *Monomer synthesis*

The monomers, **1a**, **1b**, **1c** and **1d**, were obtained as solid in satisfactory yields by the reaction of L-cysteine methyl ester hydrochloride with suberoylchloride, pimeroylchloride, adipoylchloride and glutarylchloride, respectively in the presence of triethylamine in CH_2Cl_2, in nitrogen atmosphere (Scheme 1). The structure of the monomer was confirmed by ^1H, ^{13}C-NMR, and IR spectroscopy, besides elemental analysis.

Scheme 1 :



6.3.2. *Oxidation polymerization of 1a, 1b, 1c and 1d.*

Oxidation polymerization of **1a**, **1b**, **1c** and **1d** was carried out in the presence of NEt3 in DMF and DMSO at 25 and 60 °C for 24 h under oxygen atmosphere (Scheme 2).

Scheme 2 :

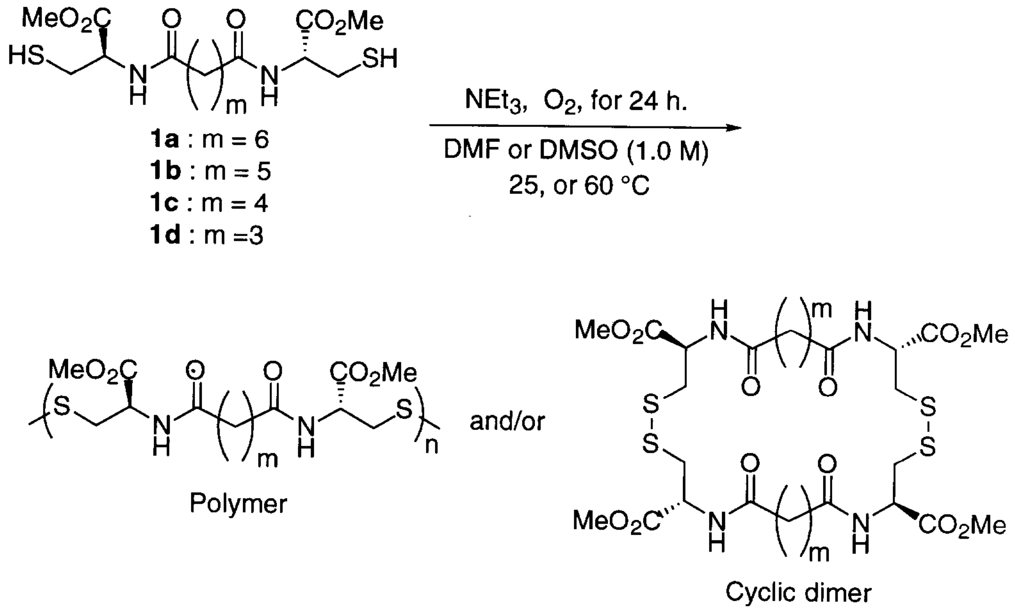


Table 1 summarizes the conditions and results of the oxidation polymerization of the monomers **1a**, **1b**, **1c** and **1d**. Figure 1 illustrates the ^{1}H-NMR spectra of **1a** and the polymer obtained by the reaction in DMF at 60 °C (run 3 in Table 1). All the protons of the polymer appeared as broad signals at the same positions as the monomer, indicating the polymer was formed by oxidation coupling of the thiol groups. Figure 2 illustrates the 1H-NMR spectrum of the product (**2a**) obtained by the reaction in DMF (run 1 in Table 1). The product **2a** showed no IR absorption assignable to a thiol group at 2563 cm^{-1}, and showed a FAB mass parent peak at 813.4 (Figure 3). Poly**1a** was soluble in $CHCl_3$, CH_2Cl_2, DMF and DMSO, while **2a** was only soluble in DMSO. From these results, it was concluded that **2a** was a cyclic dimer. Cyclic dimers, **2b** and **2c** were also obtained quantitatively in the oxidation of **1b** and **1c** in DMF and DMSO at 25 °C (runs 5, 6, 9 and 10 in Table 1). At 60 °C, poly**1b** and poly**1c** were obtained in the oxidation in DMF and DMSO with M_ns in the range of 4800 ~ 7200 (runs 7, 8, 11, and 12 in Table 1). On the other hand, no cyclic dimer was obtained in the oxidation of **1d** at 25 and 60 °C but the polymer (poly**1d**) with M_ns in the range of 3300 ~ 6500 in 85 ~ 95% yields (runs 13 ~ 16 in Table 1). It was surprising that the cyclic dimers and polymers were formed with complete selectivity according to the reaction temperature. The precipitation of the dimers during the reaction at 25 °C should efficiently shift the equilibrium between the dimers and polymers to the dimer side. From the view point of macrocycle synthesis, this result is quite interesting and useful, because the large-memberd cyclic dimers were obtained quantitatively. Karle et al. have reported of the synthesized nanotubes consisting of aromatic-bridged cystine cyclic peptides (cystinophanes), but the yields are only 4 ~ 51%.[6] Cysteine-based cyclic peptides are expected as artificial proteins[7] and peptidomimetic drugs.[8]

Table 1. Oxidation polymerization and dimerization of **1a**, **1b**, **1c** and **1d** [a]

Run	Monomer	Reaction Temperature (°C)	Solvent	Yield (%)	M_n (M_w / M_n) [b]	$[M]_D^{25}$ [c] (degree)	$[M]_D^{25}$ [d] (degree)
1	**1a**	25	DMF	quant.[e]	Cyclic dimer (**2a**)	- [g]	-528.5
2	**1a**	25	DMSO	90 [f]	4500 (1.27)	89.4	- 20.1
3	**1a**	60	DMF	80 [f]	4800 (1.31)	97.6	- 19.3
4	**1a**	60	DMSO	78 [f]	5000 (1.25)	93.5	- 22.7
5	**1b**	25	DMF	quant. [e]	Cyclic dimer (**2b**)	- [g]	580.9
6	**1b**	25	DMSO	quant. [e]	Cyclic dimer (**2b**)	- [g]	580.9
7	**1b**	60	DMF	73 [f]	4100 (1.14)	- 4098.9	- 135.3
8	**1b**	60	DMSO	80 [f]	7200 (1.43)	- 4457.9	-122.1
9	**1c**	25	DMF	quant.[e]	Cyclic dimer (**2c**)	- [g]	- 146.1
10	**1c**	25	DMSO	quant.[e]	Cyclic dimer (**2c**)	- [g]	- 146.1
11	**1c**	60	DMF	80 [e]	3900 (1.16)	19.7	- 221.5
12	**1c**	60	DMSO	82 [e]	5500 (1.43)	20.8	- 220.3
13	**1d**	25	DMF	95 [e]	3300 (1.14)	164.0	- 384.7
14	**1d**	25	DMSO	92 [e]	3200 (1.14)	156.7	- 380.1
15	**1d**	60	DMF	90 [e]	3900 (1.14)	156.7	- 340.0
16	**1d**	60	DMSO	88 [e]	6500 (1.53)	156.7	- 355.8

a) Conditions : monomer 1.0 mmol, NEt_3 2.2 mmol, solvent 3.0 ml, reaction for 24 h in O_2. b) Estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). c) $[M]_D = [\alpha]_D \times MW/100$, where MW represents the formula weight of the polymer repeating unit, $[\alpha]_D$ was measured by a polarimeter at 25 °C (c = 0.1 g/dL, $CHCl_3$). $[M]_D^{25}$ of the monomers, **1a**: 350 °, **1b**: 269 °, **1c**: 255 °, **1d**: 157.6 °. d) $[\alpha]_D$ was measured by a polarimeter at 25 °C (c = 0.1 g/dL, DMSO). $[M]_D^{25}$ of the monomers, **1a**: 369.3 °, **1b**: - 89.9 °, **1c**: - 104.9 °, **1d**: - 153.2 °. e) Ethyl-ether insoluble part, obtained as the white poweder. f) Separated by HPLC (eluent: $CHCl_3$). g) Not measured, cyclic dimers were insoluble in $CHCl_3$.

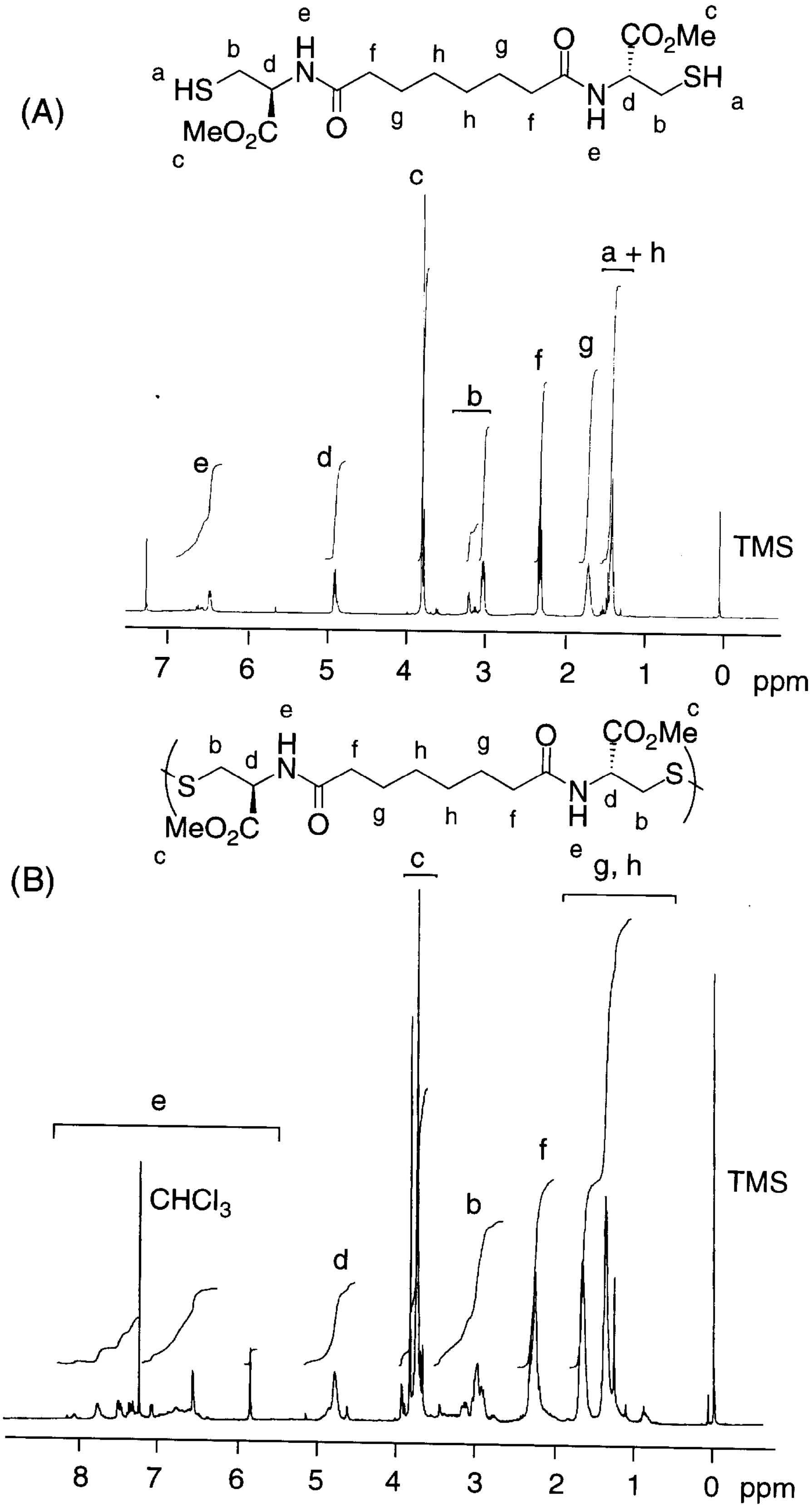


Figure 1. ^{1}H-NMR (400 MHz, CDCl$_3$) spectra of (A) monomer **1a** and (B) polymer (M_n = 4800, M_w/M_n = 1.31) obtained by the oxidation polymerizatior in DMF in the presence of NEt$_3$ at 60 °C for 24 h (run 3 in Table 1).

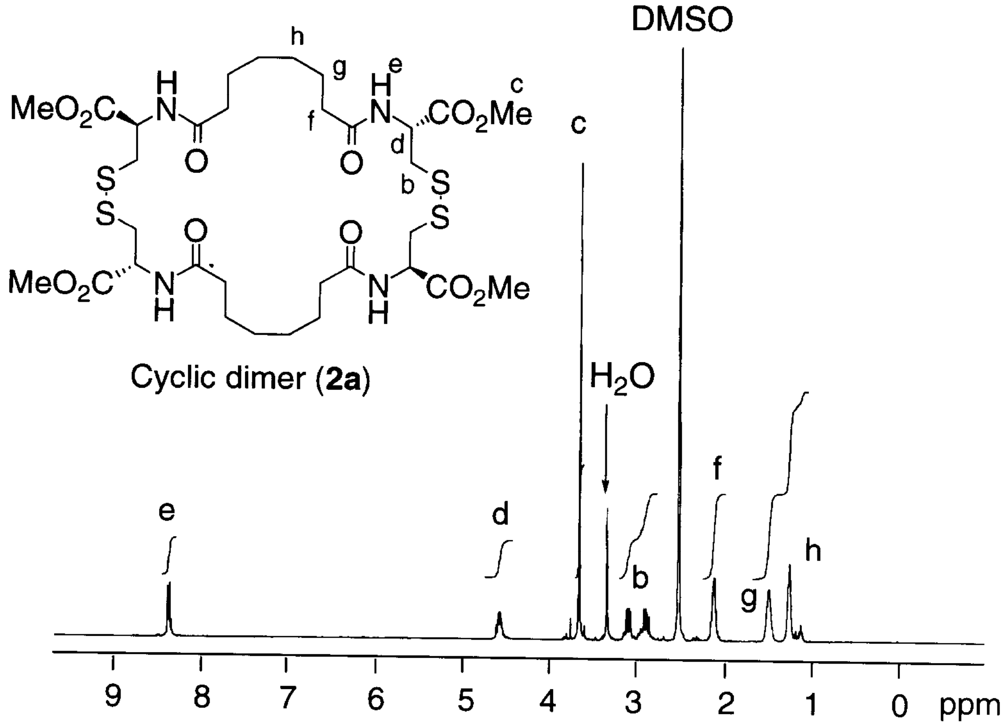


Figure 2. ^{1}H-NMR spectrum (400MHz, DMSO-d_6) of cyclic dimer (**2a**) obtained in oxidation of **1a** in DMF at 25 °C for 24 h.

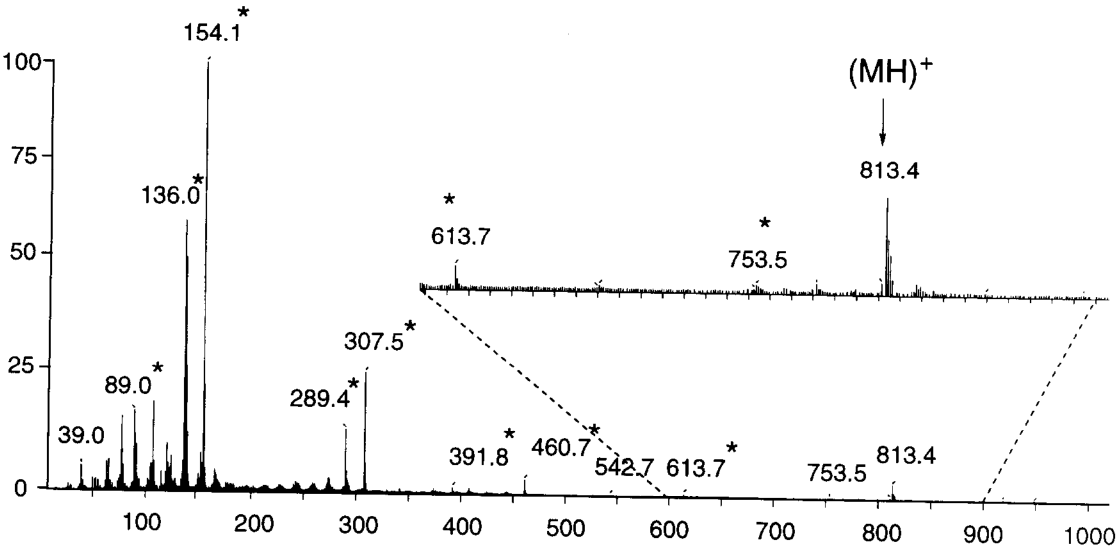


Figure 3. FAB mass spectrum of **2a**. * peaks derived from a matrix, nitrobenzyl alcohol .

6.3.3. *Optical properties*

Table 1 also summarizes the specific rotations of the monomers, cyclic dimers, and polymers. The completely different $[M]_D$ (c = 0.1 g/dL, $CHCl_3$) of the polymers and the corresponding monomers suggests the presence of some higher order structures, especially in the case of poly**1b**. The $[M]_D$ (c = 0.1 g/dL, DMSO) difference between the cyclic dimers and the polymers would be another evidence for the formation of the dimers. Poly**1a**, poly**1c** and poly**1d** showed nearly the same values as the monomer, **1a**, **1c**, and **1d** showed similar cotton effects to the corresponding monomers at 230 nm, while poly**1b** showed much larger than **1b** as shown in Figure 4. The result also suggests that the poly**1b** has some regulated higher order structures such as a helix.

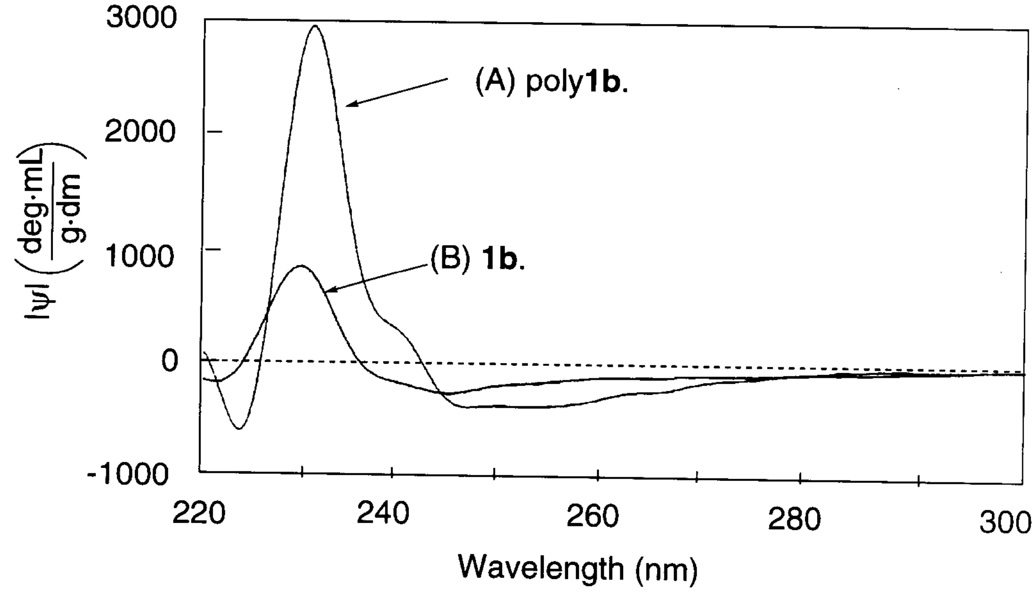


Figure 4. CD spectra (c = 0.1 g/dL, $CHCl_3$) of poly**1b** and the monomer (**1b**). (A) poly**1b** obtained in oxidation polymerization of **1b** in DMF in the presence of NEt_3 at 60 °C for 24 h under O_2, M_n = 4100, M_w/M_n = 1.14 (run 7 in Table 1). (B) monomer **1b**.

6.4. Summary

In this chapter, I examined the synthesis and oxidation polymerization of cysteine-based novel optically active monomers, **1a**, **1b**, **1c** and **1d**, having dithiol groups. At 60 °C, polydisulfides with M_ns in the range of 3200 ~ 7200 were obtained in good yields. At 25 °C, no polymer was formed but cyclic dimers were obtained quantitatively. The drastic difference of the specific rotation between **1b** and poly**1b** suggested the presence of some regulated higher order structures such as a helix.

6.5. References and Notes

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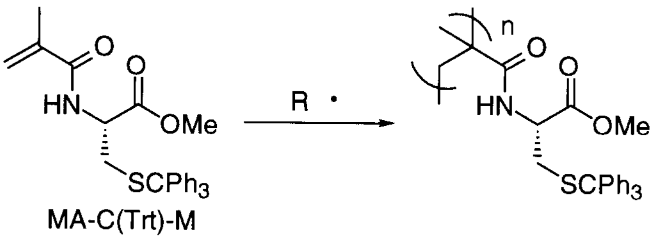
Chapter 7

Summary

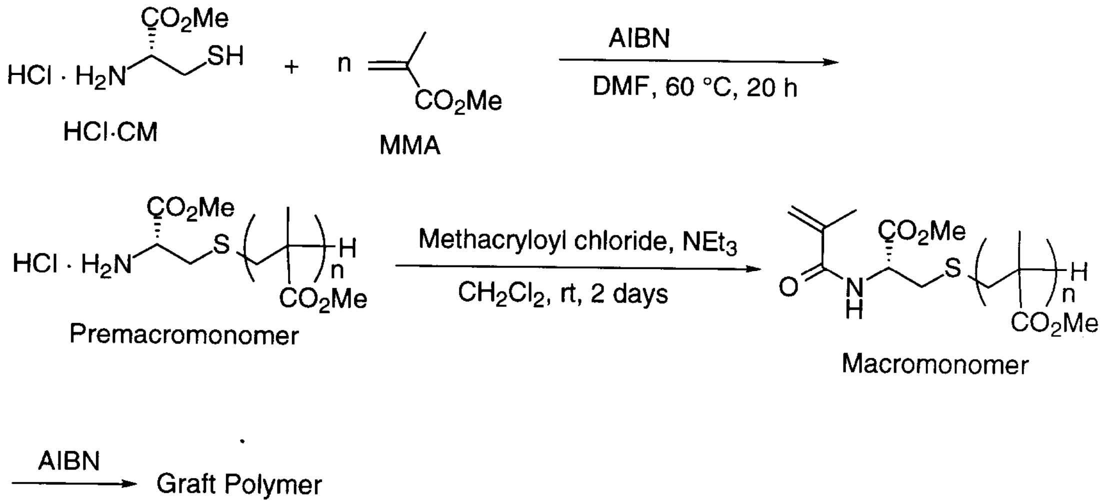
Summary

In this thesis, I investigated the synthesis and reactions of novel polymers derived from cysteine.

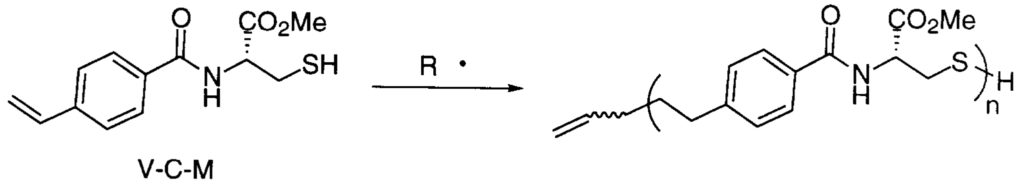
In **Chapter 2**, I examined the synthesis and radical polymerization of *N*-methacryloyl-*S*-trityl-L-cysteine methyl ester [MA-C(Trt)-M] derived from cysteine. Its radical polymerization was carried out at 60 °C for 20 h in the presence of AIBN in benzene, PhCl, and DMF to afford the corresponding polymer with M_ns in the range of 13200-130000 in good yields. In the radical copolymerizations of MA-C(Trt)-M with methyl methacrylate and trityl methacrylate, the specific rotations of the copolymers showed the maximum values with the MA-C(Trt)-M content of 60 and 80%, respectively. The polymers were treated with HBr/CH_3CO_2H (30 wt %) to afford the trityl group-free polymers, which were insoluble in solvents due to the oxidative crosslinking reaction between the thiol groups.



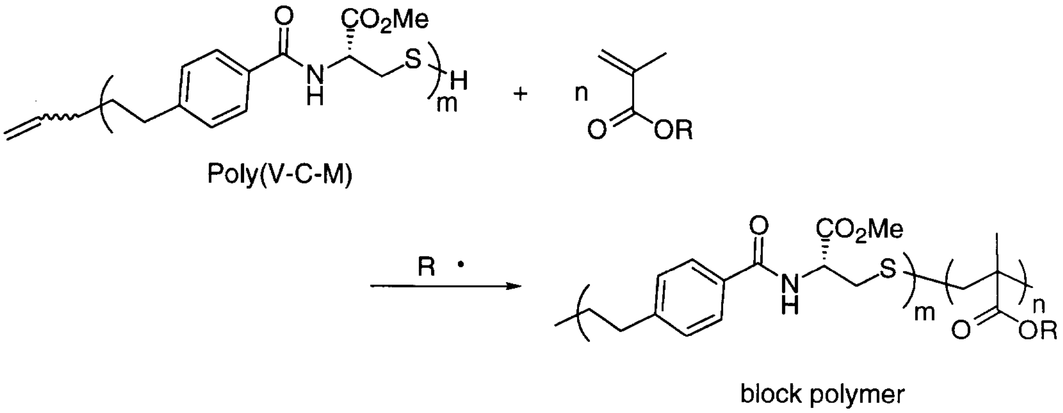
In **Chapter 3**, I synthesized the cysteine-based macromonomers by the radical oligomerization of MMA in the presence of HCl·CM as a chain transfer agent, followed by *N*-methacrylation of the obtained oligomers. The macromonomers afforded the graftpolymers by the radical polymerization and copolymerization with MMA and ST. The obtained graftpolymers showed higher thermal stability than the macromonomers.



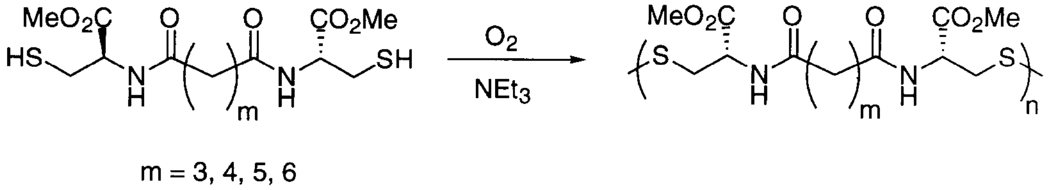
In **Chapter 4**, I examined the synthesis and radical self-polyaddition of the novel three monomers having olefin and mercapto groups derived from cysteine. The radical polyaddition of *N*-4-vinylbenzoyl-L-cysteine methyl ester (V-C-M) proceeded satisfactorily to afford the corresponding polysulfide with M_ns in the range of 7000 ~ 23000 in good yields. The specific rotation and CD spectrospecific analysis suggested that poly(V-C-M) had some higher order structures.



In **Chapter 5**, I examined that the reactions of a thiol-olefin heterotelechelic polymer, poly(V-C-M). Radical polymerization of MMA and TrtMA was carried out in the presence of poly(V-C-M) with AIBN as an initiator in DMF to afford the corresponding block copolymers. Poly(V-C-M) was oxidized with H_2O_2 to the polymer having sulfoxide and sulfone groups in the main chain, and was hydrolyzed with NaOH to the polymer having carboxyl groups in the side chain.



In **Chapter 6**, I examined the synthesis and oxidation polymerization of cysteine-based novel optically active monomers, **1a**, **1b**, **1c** and **1d**, having dithiol groups. At 60 °C, polydisulfides with M_ns in the range of 3200 ~ 7200 were obtained in good yields. At 25 °C, no polymer was formed but cyclic dimers were obtained quantitatively. The drastic difference of the specific rotation between **1b** and poly**1b** suggested the presence of some regulated higher order structures such as a helix.



As summarized above, this thesis dealt with the synthesis of cysteine-based polymers, by radical polymerization, radical polyaddition, chain transfer reaction and oxidation. Furthermore, it examined the reactions of the obtained polymers such as oxidation and hydrolysis. I hope that the work achieved in this thesis will become one of the bases on the development of novel functional materials based on cysteine.

List of Publications

Chapter 2. Synthesis and Radical Polymerization of Optically Active Monomer Derived from Cysteine

Kudo, H.; Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 1232

Chapter 3. Synthesis and Radical Polymerization of Cysteine-Based Macromonomer

Kudo, H.; Sanda, F.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* submitted

Chapter 4. Synthesis and Radical Polyaddition of Optically Active Monomer Derived from Cysteine

Kudo, H.; Sanda, F.; Endo, T. *Macromolecules* **1999**, *32*, 8370.

Chapter 5. Reaction of Telechelic Polymers Having Olefin and Thiol

Kudo, H.; Sanda, F.; Endo, T. in preparation

Chapter 6. Synthesis and Oxidation Polymerization of Cysteine-Based Dithiols

Kudo, H.; Sanda, F.; Endo, T. in preparation.

List of Presentations

1. Synthesis and Radical Polymerization of *N*-Methacryloyl-*S*-trityl-L-cysteine methyl ester. Kudo, H.; Sanda, F.; Endo, T. *The 74 th Annual Meeting of Chem. Soc. Jpn., (Abstr.),* Kyoto, Japan, March 1998, I F541.

2. Synthesis and Radical Polyaddition of Olefin with Thiol Derived from Cysteine. Kudo, H.; Sanda, F.; Endo, T. *Polym. Prepr. Jpn.*, Kyoto, Japan, May 1998, II -5-20.

3. Synthesis and Radical Polymerization of Methacrylamide Derived from Cysteine. Kudo, H.; Sanda, F.; Endo, T. *Polym. Prepr. Jpn., Nagoya, Japan*, October 1998, II Pb024.

4. Synthesis and Self Radical Polyaddition of Cysteine-Based Monomers. Kudo, H.; Sanda, F.; Endo, T. *Polym. Prepr. Jpn.,* Nagoya, Japan, October 1998, II Pc033.

5. Synthesis and Self Radical Polyaddition of *N*-4-vinyl-benzoyl-L-cysteine methyl ester. Kudo, H.; Sanda, F.; Endo, T. *The 75 th Annual Meeting of Chem. Soc. Jpn., (Abstr.),* Kanagawa, Japan, March 1999, III H104.

6. Synthesis Macromonomers using Cysteine as a Chain-Transfer Reagent and the Radical polymerization. Kudo, H.; Sanda, F.; Endo, T. *Polym. Prepr. Jpn.,* Kyoto, Japan, May 1999, III Pd03.

7. Synthesis of Optically active Polymer derived from cysteine. Kudo, H.; Sanda, F.; Endo, T. *The 37 th Annual Meeting of the Adhesion Society of Japan.* 1999, P-31-A.

8. Synthesis of Graft Polymers Using Cysteine. Kudo, H.; Sanda, F.; Endo, T. *Polym. Prepr. Jpn.,* Niigata, Japan, October 1999, I Pd022.

9. Synthesis and Reaction of Telechelic Polymers Having Thiol and Olefin Groups at the Ends. Kudo, H.; Sanda, F.; Endo, T. *Polym. Prepr. Jpn.,* Niigata, Japan, October 1999, III Pd024.

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