Synthesis and Evaluation of Thiol Polymers

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SYNTHESIS AND EVALUATION OF THIOL POLYMERS

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ABSTRACT

Thiol polymer, which is known as a reactive and functional polymer, is synthesized and evaluated quantitatively by the modified Ellman method. The synthesis was accomplished by 1) hydrolysis of an isothiouronium salt that is the adduct of 4-chloromethylstyrene (CMS) homopolymer or CMS-styrene (St) copolymer with thiourea; 2) hydrolysis of a precursor copolymer made from 4-vinylbenzyl N-ethyldithiocarbamate (VBEC) and St or N-vinyl-2-pyrrolidone (NVP); 3) solvolysis of an iminium salt polymer obtained from the reaction of CMS-NVP copolymer with N,N-dimethylthioformamide (TDMF). When a higher thiol content is desired, more severe hydrolysis conditions are required which however, also increase the loss of thiol. Hence, it is clear that the best synthesis of thiol polymers is Method 3. A quantitative yield of functional thiol polymer is obtained by this method, and the product is soluble in DMSO, DMF, and $CHCl_3$.

INTRODUCTION

Since the oxidation-reduction potential of thiol is low, thiol is used as the mild redox system for biochemical systems. Thiol also works as the active site of hydrolysis enzymes due to its high nucleophilicity. Therefore, thiol polymers have been employed as models of redox systems or catalysts for hydrolysis [1, 2]. Moreover, thiol polymers have been used as protecting

reagents in the organic syntheses [3] and as binding sites for heavy metals [4]. Consequently, it is very important to establish an effective synthesis for thiol polymers, but it is impossible to polymerize thiol monomer directly because the thiol group has a highly acidic proton and strong chain-transfer activity. As a result, the only successful methods to synthesize thiol polymer have been the polymerization of thiol-protected monomer [5] and the polymer reaction of suitable functional groups [6-8].

Furthermore, thiol transforms easily into disulfide by oxidative coupling. As the thiol group is more concentrated in polymers than in low molecular weight analogs, it is oxidized rapidly to form insoluble crosslinked polymers. Frecht et al. synthesized crosslinked thiol polymer by hydrolysis of isothio-uronium salt polymers in the presence of a phase-transfer catalyst. They stressed that the generation of disulfide was effectively depressed under an-aerobic conditions, but they did not investigate the reaction quantitatively [9]. The disulfide linkage is, of course, reduced back to thiol by a reducing agent, such as another thiol or sodium sulfite. However, soluble thiol poly-mer could not be obtained by this method.

As a result, there is no report of an effective synthetic method and the quantitative evaluation of polymeric thiols. However, in order to use thiol polymer as a functional polymer or a polymer catalyst, these problems are of fundamental importance. In this paper we report efficient methods for the synthesis of thiol polymers, the determination of their composition, and the quantitative determination of the thiol group.

EXPERIMENTAL

Materials

4-Chloromethylstyrene (CMS) [10] and N,N-dimethylthioformamide (TDMF) [11] were prepared by the reported methods. The monomers styrene (St) and N-vinyl-2-pyrrolidone (NVP) were purified and distilled just before polymerization. 2,2′-Azobisisobutyronitrile (AIBN) was recrys-tallized twice from methanol (MeOH). The solvents were purified by the cus-tomary methods. Sodium N-ethyldithiocarbamate was obtained from Ouchi-Shinko Co., and 2,2′-azobis(2,4-dimethylvarelonitrile (V-65) was obtained from Wako Pure Chemical Industries Co. Other reagents were obtained com-mercially and used without further purification.

Instruments

^{1}H-NMR spectra were recorded on a 60-MHz Hitachi R-600 spectrometer with tetramethylsilane as the internal standard in CDCl$_3$. IR spectra were recorded on a JASCO IRA-2 spectrophotometer. UV and visible spectra were obtained from a Hitachi-124 spectrophotometer.

Synthesis of 4-Vinylbenzyl-N-ethyldithiocarbamate (VBEC)

VBEC was synthesized by the reaction of CMS and sodium N-ethyldithio-carbamate. In a 300-mL three-necked flask equipped with a magnetic stirrer and a dropping funnel, 20.7 g (0.16 mol) sodium N-ethyldithiocarbamate and 250 mL ethanol (EtOH) were placed. CMS (22.9 g, 0.15 mol) was added dropwise for 3 h. The flask was screened from sunlight to avoid decomposition of the dithiocarbamoyl group produced. The reaction was carried out at room temperature for 8 h under nitrogen. Then the mixture was poured into water and extracted with dichloromethane (CH$_2$Cl$_2$) (3 × 50 mL). The extract was washed with water and dried over anhydrous sodium sulfate overnight. The solvent was removed under reduced pressure, and the residual yellow oil was recrystallized twice, once from petroleum ether and once from MeOH/H$_2$O.

Yield, 14.2 g (40%); mp, 48.5-50.0°C; IR(KBr) 990, 910, 1630 cm^{-1} (–CH=CH$_2$), 1515 cm^{-1} (–C(=S)N), 3280 cm^{-1} (–NH–); ^{1}H NMR(CDCl$_3$) δ: 1.37 (d, 3H, –CH$_3$), 3.65 (broad, 2H, N–CH$_2$–), 4.52 (s, 2H, –C$_6$H$_4$–CH$_2$–), 5.00-6.00 (m, 2H, –CH=CH$_2$), 6.40-7.05 (m, 1H, –CH=CH$_2$), 7.32 (s, 4H, benzene ring).

Sulfur analysis. Calculated: 27.02%. Found: 26.91%.

Synthesis of Precursor Polymer

In a Pyrex tube were placed monomer, initiator, and solvent as shown in Table 1. The solution was degassed by the conventional freezing and thawing technique, it was sealed off under vacuum, and that was followed by heating at 60°C for the required time. The content of the tube was poured into a large amount of a poor solvent for the particular polymer. The copolymers were purified by reprecipitation, and the compositions were determined by elemental analysis for S or Cl.

TABLE 1. Copolymerization of CMS with St or NVP[a]

Monomer				Copolymer	
[CMS], mol/L	[2nd], mol/L	Conversion, %	Cl, %	[CMS], mol%	[2nd], mol%
Styrene[b]					
7.20	—	35.8	23.94	100	0
5.64	1.89	17.9	20.14	81.7	18.3
3.95	3.95	22.6	16.32	61.7	38.3
2.08	6.21	12.5	11.62	40.6	59.4
N-Vinyl-2-pyrrolidone[c]					
1.25	3.75	29.6	18.99	76.5	23.5
0.65	4.35	22.3	15.08	57.4	42.6
0.50	4.50	29.5	10.20	36.3	63.7
0.25	4.75	56.1	1.87	6.0	94.0

[a][AIBN] 10 mmol/L.
[b]Polymerized at 60°C for 4 h in bulk.
[c]Polymerized at 60°C for 15 h in benzene.

Synthesis of Thiol Polymer via Isothiouronium Salt Polymer

Synthesis of Isothiouronium Salt Polymer

A mixture of 0.50 g CMS homopolymer or CMS-St copolymer and thiourea (1.30 mol equiv to CMS unit) in 15 mL dioxane and 14 mL acetone was stirred for 2 h under reflux. After the required time, the precipitated iso-thiouronium salt polymers obtained from CMS homopolymer or CMS-St (82/18) copolymer were purified by twice reprecipitating from the MeOH-EtOH system. The copolymers that contained much St were purified twice with the MeOH/acetone-petroleum ether system.

Hydrolysis of Isothiouronium Salt Polymer

The isothiouronium salt polymers were suspended in 10 mL deionized water and dissolved by heating. To the polymer solutions were added 20 mL of 2.5 N aqueous sodium hydroxide under nitrogen, and then the mixtures were stirred for 1.5 h at 100°C. After cooling, the solution was neutralized with 1 N aqueous HCl and washed with H_2O, EtOH, and diethyl ether. The compositions of the resulting thiol polymers, which had been dried in vacuum, were determined by elemental analyses for S, C, and N, and by quantitative analysis of the thiol group by Ellman's method [12].

Synthesis of Thiol Polymer by Hydrolysis of VBEC Polymer

Hydrolysis of VBEC-St Copolymer

A suspension of 0.20 g VBEC-St copolymer, 4.2 mL aqueous sodium hydroxide (10 N), and 3.3 mL tetrahydrofuran (THF) in a Pyrex tube was degassed by the freezing and thawing technique. The tube was sealed in vacuo and shaken at 60°C for 12 h. After the reaction the content was neutralized by 1 N HCl and washed successively with H_2O, EtOH, and ether. The obtained thiol polymer was dried in vacuum overnight. The polymer composition was determined by elemental analysis for S and by quantitative analysis of the thiol group.

Hydrolysis of VBEC-NVP Copolymer

The hydrolysis of VBEC-NVP copolymer was carried out under mild conditions in a sealed tube. The copolymer ([VBEC] 0.05 M) was suspended in a 1:1 mixture of THF and aqueous 1.25 N NaOH and heated at 50°C for 3 h. The hydrolyzed polymer was neutralized with 1 N HCl, washed with H_2O, and purified by reprecipitation with the THF/n-hexane system.

Synthesis of Thiol Polymer by TDMF Method

A typical procedure for the synthesis of thiol polymer by the TDMF method was as follows: In a 30-mL round-bottom flask was placed 0.15 g CMS-NVP (77/23) copolymer (0.84 mmol CMS units) and 7.2 g TDMF (100 equiv). The solution was heated at 80°C with magnetic stirring for 3 h under nitrogen followed by methanolysis at 60°C for 1 h. The generated thiol polymer was purified by reprecipitation with the EtOH/CHCl$_3$-ether system, or washing with

ether, and dried *in vacuo* for 4 h. The composition of the resulting copolymer was determined by elemental analysis for 5 and Cl, and quantitative analysis of the thiol group.

## Quantitative Analysis of the Thiol Group in the Polymers

The thiol group in the polymers was determined by the modified Ellman method [8, 12], as shown in Scheme 1. That is, in the presence of triethylamine the thiol polymer was reacted with 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) in DMF, and the resulting 2-nitro-4-thiobenzoate dianion was detected by its absorbance at 501 nm (ϵ_{501} 24 400). The details were as follows: 3 mg of finely divided thiol polymer was suspended in 15 mL dry DMF under nitrogen at 25°C for 1 h, followed by the addition of DTNB and Et_3N ([SH + SS]/[DTNB]/[Et_3N] = 1/5/100). The absorbance of thiophenolate anion increased as soon as the DTNB and base were added.

RESULTS AND DISCUSSIONS

Synthesis of the Precursor Polymers

Since thiol polymer cannot be synthesized directly by polymerization of thiol monomer (because of the high chain transfer ability of the thiol group and its acidic proton), it is usually made by reaction of a precursor polymer.

In this article we report the preparation of thiol polymer by the following three methods. 1) Hydrolysis of an isothiouronium salt polymer that is the adduct of CMS polymer and thiourea [6, 9]. 2) Hydrolysis of VBEC polymer [13]. 3) Solvolysis of an iminium salt polymer that is the adduct of
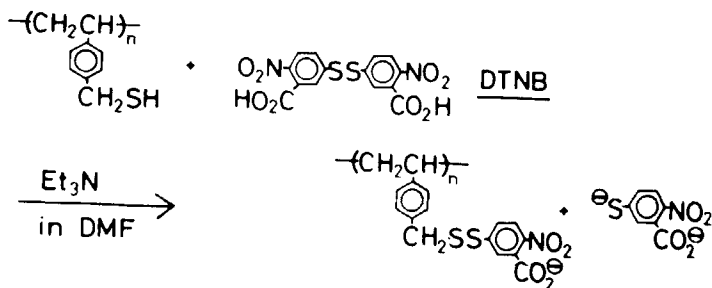
SCHEME 1.

TABLE 2. Copolymerization of VBEC with St or NVP[a]

Monomer				Copolymer	
[VBEC], mol/L	[2nd], mol/L	Conversion, %	S, %	[VBEC], mol%	[2nd], mol%
Styrene					
1.00	—	55.7	26.50	100	0
0.75	0.25	50.5	22.20	66.7	33.3
0.50	0.50	41.0	19.67	54.0	46.0
0.25	0.75	39.0	13.46	30.3	69.7
N-Vinyl-2-pyrrolidone					
1.50	0.50	77.9	25.79	90.8	9.2
0.30	1.70	24.7	20.91	61.6	38.4
0.65	4.35	32.7	17.90	47.9	52.1

[a]V-65 (2,2'-azobis(2,4-dimethylvaleronitrile)) 10 mmol/L; 50°C; 20 h; in benzene.

CMS polymer and TDMF [11]. These precursor copolymers are obtained by radical polymerization of their corresponding monomers with AIBN initiator. The compositions of the presursor copolymers are determined by elemental analyses for S and Cl, as shown in Tables 1 and 2.

Method 1: Synthesis of Thiol Polymer via Isothiouronium Salt Polymer

Thiol polymer is synthesized from CMS-St copolymer and thiourea by Method 1, and the results are shown in Table 3. Here, "salt yield" means the conversion of chloromethyl groups into the isothiouronium salt group. "Residual SH" (SH/(SH + SS)) is the mol% of thiol groups in the hydrolyzed isothiouronium salt. The "SH yield" signifies the transformation of chloromethyl groups to thiol groups, and this value indicates the efficiency of the thiol polymer synthesis.

This hydrolyzed polymer precipitates as the reaction proceeds, and it is not

TABLE 3. Synthesis Method 1: Hydrolysis of Isothiouronium Salt Polymer[a]

Prepolymer CMS/St	Salt[b] yield, %	Hydrolysis[c] yield, %	Residual SH[d] %	SH[e] yield, %
100/0	93.3	91.8	63.2	54.1
82/18	91.5	93.6	59.0	50.4
62/38	74.2	95.4	56.8	40.2
41/59	63.7	93.6	59.1	35.3

[a]Reaction condition. Synthesis of isothiouronium salt: $[(NH_2)_2CS]/$ $[CMS] = 1.3$ in dioxane/acetone = 9/10 (v/v), refluxed for 2 h. Hydrolysis of isothiouronium salt: $1.7\ N$ aqueous NaOH at $100°C$ for 1.5 h under N_2.
[b]Isothiouronium salt unit/CMS unit.
[c]Hydrolyzed unit/isothiouronium salt unit.
[d]SH/(SH + SS), SH unit/hydrolyzed unit.
[e]SH unit/CMS unit.

soluble in any solvent. Since the reaction conditions are severe, the thiol groups are converted to disulfide by oxidative coupling. Therefore, low residual SH values and low SH yields are attained for any polymer composition.

Method 2: Synthesis of Thiol Polymer via VBEC Polymer

Since Okawara et al. [13] reported the synthesis of benzyl mercaptan by the hydrolysis of benzyl N-ethyldithiocarbamate, thiol polymer has also been synthesized by that method (Table 4). In this case the amount of residual SH increases with increasing styrene units in the VBEC-St copolymer, and very high residual SH is obtained in the copolymer VBEC-St (30/70). This result means that the styrene unit acts as a diluent of the SH group, which is concentrated near the main chain. Therefore, the possibility of oxidative coupling decreases, and the residual SH increases.

Since this polymer is hydrophobic due to its high styrene content, it does not dissolve in the hydrolysis solvent. Unfortunately, therefore, the hydrolysis yield and SH yield (SH unit/VBEC unit) are less than 80 and 75%, respectively.

In order to overcome the solubility problem, we tried VBEC/NVP copolymer as the precursor (Table 4b). Because of the hydrophilicity of NVP, the

TABLE 4. Synthesis Method 2: Hydrolysis of VBEC/St, and VBEC/NVP Polymers

Prepolymer composition, VBEC/2nd	Hydrolysis[c] yield, %	Residual SH,[d] %	SH yield,[e] %
a. VBEC/St[a]			
100/0	100	41.4	41.4
67/33	87.6	73.5	64.4
54/46	88.2	82.2	72.5
30/70	78.8	94.6	74.5
b. VBEC/NVP[b]			
91/9	97.7	66.4	64.9
62/38	100	69.4	69.4
48/52	99.1	73.7	73.0

[a]10 N NaOH/THF; 60°C; 12 h.
[b]1.25 N NaOH/THF; 50°C; 3 h.
[c]Hydrolyzed unit/VBEC unit.
[d]SH/(SH + SS) SH unit/hydrolyzed unit.
[e]SH unit/VBEC unit.

hydrolysis proceeds under mild conditions, and a quantitative yield of thiol is attained. The loss of thiol groups decreases with increasing NVP content, as in the case of VBEC-St. The resulting thiol polymer is soluble in THF, dioxane, DMSO, and DMF, with little insoluble residue. However, after purification and/or drying of this polymer, it does not dissolve in most solvents.

Effect of Hydrolysis Conditions on Residual SH

As mentioned above, the amount of residual SH is widely affected by hydrolysis conditions. The amount of residual SH decreases gradually with time, while the hydrolysis reaches its maximum in the early stages, as shown in Fig. 1.

Figure 2 shows that the residual SH falls to two-thirds when the catalyst concentration increases from 1.25 to 10 N. Thus, the hydrolysis of precursor polymer must be done under mild conditions for a limited time.
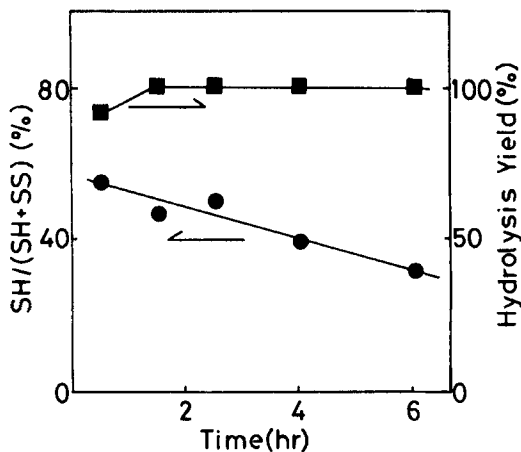
FIG. 1. Effect of hydrolysis time on residual SH (●) and hydrolysis yield
(■). Conditions: 1.7 N aqueous NaOH, 60°C, under N_2. Isothiouronium
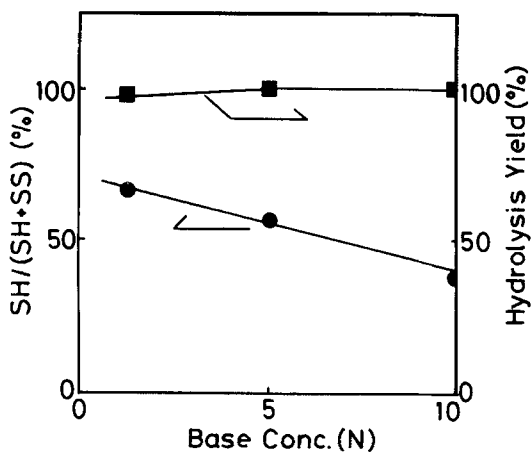salt polymer [CMS/St = 82/18].

FIG. 2 Effect of base concentration on residual SH (●) and hydrolysis
yield (■). Conditions: Aqueous NaOH/THF, 50°C, 3 h. Polymer: VBEC/
NVP = 91/9.

**Method 3: Synthesis of Thiol Polymer through Iminium Salt
Polymer Prepared from Poly-CMS and TDMF**

Recently, Itabashi et al. [11] reported a valuable thiol synthesis method, the methanolysis of the adduct of an alkyl halide and TDMF. This synthetic method can be carried out under mild conditions, and the purification of product is performed easily. Therefore, we used this method with the procedure outlined in Scheme 2.

The results are shown in Table 5. The reactions proceeded homogeneously and quantitatively. Moreover, the residual SH increases with increasing NVP content in the copolymer. The best result is obtained for CMS-NVP copolymer (6/94) when the residual SH is 96.5%.

The solubility of the resulting thiol polymers is summarized in Table 6. Soluble thiol polymer is not obtained from low-NVP copolymer, but high-NVP copolymer leads to thiol polymer that is soluble in DMSO, DMF, and $CHCl_3$ with little insoluble fraction and swells in benzene, THF, and dioxane just after solvolysis. However, this polymer is not soluble any longer after purification by reprecipitation or drying. The SH yield of these insoluble thiol polymers decreases from 80.5 to 65.5%, and from 96.5 to 80.5%, respectively (Table 5). These results clearly indicate that the thiol group in the polymer is easily transformed into disulfide by oxidative coupling.
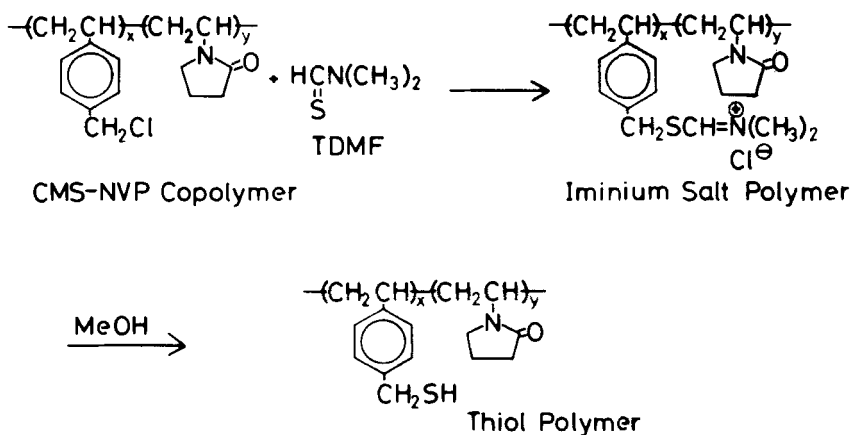
SCHEME 2.

TABLE 5. Synthesis Method 3: Solvolysis of Iminium Salt[a]

Prepolymer CMS/NVP	Salt[b] yield, %	Solvolysis[c] yield, %	Residual SH,[d] %	SH[e] yield, %
77/23	95.6	100	28.3	27.1
57/43	99.1	99.6	68.7	67.1
36/64	100	100	80.5	80.5
36/64[f]	100	100	65.5	65.5
6/94	100	100	96.5	96.5
6/94[f]	100	100	80.5	80.5

[a]Reaction condition. Synthesis of iminium salt: [CMS]/[TDMF] = 1/100; 80°C; 1.5 h; under N_2. Solvolysis of iminium salt: [CMS]/[MeOH] = 1/500; 60°C; 1 h, under N_2.
[b]Iminium salt unit/CMS unit.
[c]Solvolyzed unit/iminium salt unit.
[d]SH unit/solvolyzed unit.
[e]SH unit/CMS unit.
[f]Reprecipitated polymer.

TABLE 6. Solubility[a] of Thiol Polymer Made by Synthesis Method 3

Prepolymer, CMS/NVP	DMSO, DMF	CHCl$_3$	Benzene	THF, Dioxane
77/23	△	△	△	△
57/43	△	△	△	△
36/64	●	●	○	△
36/64[b]	△	○	○	△
6/94	●	●	○	△
6/94[b]	△	○	△	△

[a]●: Soluble. ○: Soluble with insoluble fraction. △: Swelling only.
[b]Reprecipitated polymer.

In conclusion, the synthesis of thiol polymer requires mild solvolysis conditions to prevent loss of thiol. Moreover, the thiol groups which are concentrated around the main chain should be separated from each other by the copolymerization method.

It is necessary to pay attention to the loss of free thiol in the synthesis of useful and reactive thiol polymers and the application of such functional polymers. We are now investigating how to make use of thiol polymer as polymeric nucleophilic reagents with attention to these considerations.

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