

## Cleavage and Coupling of Bis(4-vinylbenzyl)disulfide as a Novel Cross-linker for Reversible Solubilizing Polystyrene Supports

SHIMOMURA Osamu<sup>a</sup>, ISHINO Yosuke<sup>a</sup>, OHTAKA Atsushi<sup>a</sup> and NOMURA Ryôki<sup>a,b</sup>

<sup>a</sup>Department of Applied Chemistry, and <sup>b</sup>NMRC, Osaka Institute of Technology,

Ô-miya, Asahi-ku, Osaka 535-8585,

Fax: 81-6-6954-4269, e-mail: shimomura@chem.oit.ac.jp

A polystyrene cross-linked with disulfide moiety was prepared from copolymerization of styrene with bis(4-vinylbenzyl)disulfide (**1**) under suspension conditions. The obtained copolymer was treated with tributylphosphine in THF at rt and the resulting linear copolymer dissolved completely in THF by reduction of disulfides into thiols. Then, acetyl capping was done for the thiol resin to maintain its solubility by avoiding the coupling of thiols. Further this resin was turned insoluble again by consecutive uncapping of thioester to thiol using NaBH<sub>4</sub> in EtOH/THF at rt, and recoupling of thiol by treating with I<sub>2</sub> in toluene at rt. The reaction conditions of cleavage and recouple of disulfide bond were thoroughly investigated.

**Key words:** reversible cross-linkage / solubilization / insolubilization / cross-linked polystyrene / disulfide

### 1. INTRODUCTION

Generally a cross-linked polymer has high mechanical strength and high stability against various chemicals, which are the main advantage to use cross-linked polymers. Whereas the high performance of these polymers, such the properties hindered from their recycling. Consequently, an introduction of reversible cross-linking is necessary to recycling. Some examples are known for using reversible cross-linking, 1) applications of Diels-Alder reaction as a thermal reversible reaction [1], 2) thiol-disulfide interconversion reaction under redox conditions [2-4], and so on. In order to synthesize polymer beads having variable solubility, we thought that an introduction of disulfide linkage within cross-linker was promising. In 1990, Tesoro prepared the thermosetting polymer from EPON 828 as an epoxide oligomer and 4,4'-dithiodianiline (DTDA) as a curing agent. The cleavage and recoupling of DTDA was reported [3,4]. In 1978, Wulff reported that the cross-linked polymer was prepared from styrene, bis(4-vinylbenzyl)disulfide (**1**), and divinyl benzene, and the redox properties of the thiol groups was discussed in the polystyrene networks [5]. In the later case, the cross-linked polymer prepared from **1** with styrene could not be dissolved in solvents under reduction conditions. Disulfides were known as chain transfer agent. The order of chain transfer constants was as following, diphenyl disulfide > dibenzyl disulfide > dibutyl disulfide [6]. In addition, the order of the reactivity from thiol to disulfide under oxidation conditions is benzenethiol > phenylmethanethiol > butanethiol [7]. Therefore, we prepared copolymers of **1** with styrene by suspension polymerization and the nature of the copolymers for solubilizing and insolubilizing was studied.

### 2. EXPERIMENTAL SECTION

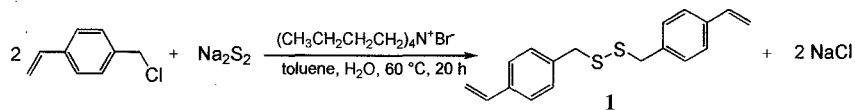
#### 2.1. Measurements.

<sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded in CDCl<sub>3</sub> with a Varian Unity-300 spectrometer using tetramethylsilane (TMS) as an internal standard. Gas chromatography-mass spectrometry (GC-MS) analyses were carried out on Shimadzu GC-17A gas chromatography instrument using J&W GC Column (30 m × 0.250mm × 0.25 μm) and Shimadzu QP-5000 mass spectrometer. Gel permeation chromatographic analyses (GPC) were carried out on a TOSOH HLC-8020 (TSK-GEL® α, α-2500 and α-3000 column, DMF as an eluent) calibrated with polystyrene standards.

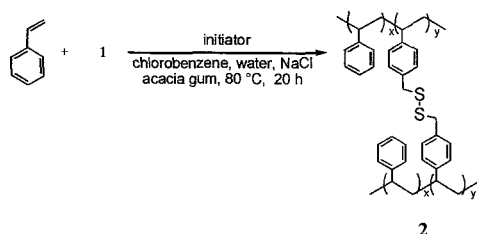
#### 2.2. Preparation of bis(4-vinylbenzyl)disulfide (**1**) as a reversible cross-linker.

The cross-linker **1** was prepared by a slight modification of a reported method [8]. A mixture of sodium sulfide pentahydrate 11.7 g (68 mmol) and sulfur powder 2.24 g (68 mmol) in 125 mL of water were stirred at 100 °C for 1 h. The mixture was cooled to ca. 40 °C. Toluene (250 mL) and Tetrabutylammonium bromide (TBAB, 2.21 g, 6.8 mmol) was added, and then 20.3 g of 4-vinylbenzyl chloride (120 mmol) was added dropwise to the solution. After stirring at 60 °C for 20 h, the mixture was cooled to rt. The organic layer was washed with cold water (200 mL×3). After evaporation of the solvent, the residue was dissolved in ether, and hexane was added to the solution and cooled to -78 °C. The precipitates were then filtered off, washed with cold hexane. The obtained **1** was crystallized twice in a similar way, and dried under vacuum. Since this product gradually decomposed, **1** was recrystallized before use. An ether solution of **1** was filtered off by Celite 521 and the filtrate was recrystallized in a similar way. This brilliant white solid was dried under vacuum. Yield: 11.4 g (64 %)

## Scheme I. Preparation of cross-linker



## Scheme II. Suspension Polymerization



$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.61 (s, 4H), 5.24 (d, 2H,  $J=12$  Hz), 5.74 (d, 2H,  $J=18$  Hz), 6.70 (dd, 1H,  $J=11$  Hz, 18 Hz), 7.19 (d, 4H,  $J=8$  Hz), 7.35 (d, 4H,  $J=8$  Hz);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  43.0, 113.9, 126.3, 129.6, 136.4, 136.8, 136.9; GC-MS ( $m/z$ ): 298( $\text{M}^+$ ); mp 72-74 °C.

## 2.3. Suspension polymerization of 1 with styrene.

The conditions of suspension polymerization of reported method [9] were applied. A mixture of 1 (0.746 g, 2.50 mmol, 2.5 mol% for overall monomers), styrene (10.4 g, 99.5 mmol), and AIBN (83.3 mg, 0.51 mmol) was dissolved in chlorobenzene (10.9 g). Aqueous phase was prepared by the following procedure. A solution of 25 g of NaCl and 40.1 g of acacia gum in 1 L of water was stirred until acacia gum dissolved, and the solution was filtered off by Celite 545. The organic solution was added dropwise to aqueous phase (210 mL) under  $\text{N}_2$  at 80 °C in the dark. After 20 h, the reaction mixture was filtered off and the recovered polymer beads 2 were washed with hot water. The obtained polymer was washed further with THF in a Soxhlet extractor for 20 h. The recovered polymer was filtered off and was washed with ether and hexane, and dried under vacuum for 24 h. Yield: 8.02 g (72%).

Table I. Relationship between yield of resin and initiator

Initiator	Temp. / °C	Initiator (mol%)	Yield of resin (wt%)
BPO	80	0.50	0
AIBN	80	0.50	72

Table II. Concentration of initiator and yield of resin

AIBN (mol%)	Temp. / °C	Yield of resin (wt%)
0.5	80	72
1.0	80	72
1.5	80	72

## 2.4. Reduction of disulfide for solubilizing resins and protection of thiol.

Reduction for solubilizing of resins and protection of thiol was carried out followed by reported method [10]. The resin 2 (4.35 g), 100 mL of THF, 0.900 g of purified water (50 mmol) and 10.9 g of tributylphosphine (50 mmol) were placed in a 200 mL flask. The mixture was stirred under  $\text{N}_2$  at rt. After 24 h, acetic anhydride (10.3 g, 100 mmol) was added to the solution, and was stirred for 24 h. The reaction mixture was added to 560 mL of EtOAc. The organic layer was washed with 1 mol  $\text{L}^{-1}$  aqueous HCl (200 mL $\times$ 3) and brine (200 mL $\times$ 2), dried over  $\text{MgSO}_4$ . The filtrate was roughly evaporated and the solution was added to methanol. The white precipitate 3 was filtered off and washed with methanol, and was dried under vacuum. Yield: 3.75 g (85%).

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.9-1.0, 1.1-1.2, 1.2-1.7, 1.7-2.0, 2.0-2.1, 2.1-2.3, 2.3-2.40, 3.9-4.2, 6.1-6.8, 6.8-7.2.

## 2.5 Measurement of swelling volumes [11].

The resin 2 (150-212  $\mu\text{m}$ ) was placed in a 1 mL syringe with filter and various types of solvents (0.8 mL) was added respectively. The syringe was placed on a shaker for 1 h and the volume of the resin was measured.

## 2.6 Deprotection of mercapto groups [12].

$\text{NaBH}_4$  (61.1 mg, 1.49 mmol) was added to a solution of 4 (0.306 g, content of thiol ester: 0.477 mmol/g) in 15 mL of THF/EtOH (2:1). The solution was stirred at rt for 24 h under  $\text{N}_2$ . The mixture was then quenched with 50 mL of 5 wt% citric acid and was extracted with EtOAc (70 mL $\times$ 3). The organic layer was washed with brine (70 mL $\times$ 2) and was dried over  $\text{MgSO}_4$ . The filtrate was roughly evaporated and was added to methanol. The white precipitate 5 was filtered off, washed with methanol, dried under vacuum. Yield: 0.252 g (84%).

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.9-1.0, 1.1-1.2, 1.2-1.6, 1.7-2.0, 2.0-2.1, 2.1-2.4, 3.4-3.8, 6.1-6.8, 6.8-7.2.

## 2.7 Recoupling thiol to disulfide for insolubilizing [5].

A mixture of 5 (0.210 g) and 0.05 mol  $\text{L}^{-1}$  iodine-toluene solution (4 mL) was placed in a test tube, which was agitated on shaker in the dark. After 24 h, the solution was added to 0.05 mol  $\text{L}^{-1}$  aqueous solution of sodium

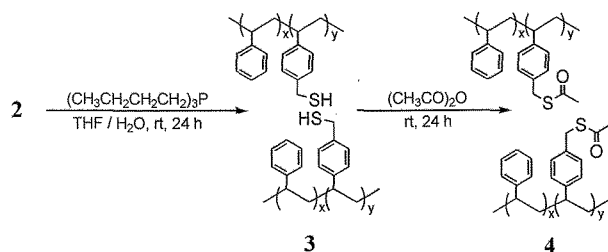
Table III. Yield of resin under various polymerization temp.

Temp. / °C	AIBN (mol%)	Yield of resin (wt%)
60	0.5	74
70	0.5	73
80	0.5	72

Table IV. Swollen volume (mL/g) of **2**

hexane	Et <sub>2</sub> O	toluene	THF	EtOAc	CHCl <sub>3</sub>	DMF	EtOH	DMSO	MeOH
2	3	7	7	4	6	5	2	2	2

Scheme III. Solubilization of resin and protection of thiol

Figure I. Solubilization of resin from **2** to **3**

sulfite (100 mL). After stirring for 2 h, the colored polymer by iodine was completely disappeared. The polymer **6** was filtered off, washed with THF, ether, and hexane. The obtained polymer was dried under vacuum. Yield: 0.176 g (84%)

### 3. RESULTS AND DISCUSSION

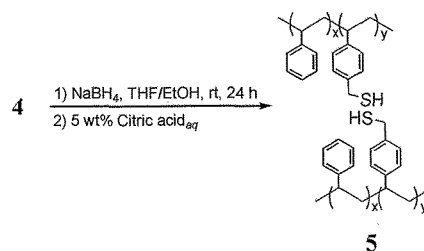
#### 3.1 Suspension polymerization

To prepare a polystyrene resin having cleavable cross-linker **1** (as shown in **Scheme I**), styrene and **1** (2.5 mol%) was copolymerized with benzoyl peroxide (BPO, 0.50 mol%) as an initiator at 80 °C under suspension polymerization conditions, as shown in **Scheme II**. No resin beads were prepared under the conditions. Therefore, the initiator was changed to 2,2'-azobisisobutyronitrile (AIBN). The results are shown in **Table I**. In the case of AIBN as an initiator, the copolymerization reaction proceeded preferably. The yield of copolymer resin **2** was 72%. The effectiveness of the concentration of initiator for the yield of resin, the ratio of the AIBN changed from 0.5 mol% to 1.5 mol% for monomer as shown in **Table II**. The yields of the resins were almost the same for the concentration of AIBN. The relationships between the reaction temperature and the yields were shown in **Table III**. The polymer **2** in the following section was used by the preparation with AIBN (0.5 mol%) as an initiator at 80 °C.

#### 3.2 Degree of swelling.

The swell ability of the resins in solvents is needed to use as polymer supports. The resin **2** was immersed in various solvents, and after 1 h, the volume of **2** was measured as shown in **Table IV**. The resin prepared showed good swelling in toluene, THF and chloroform.

Scheme IV. Deprotection of acetyl group



#### 3.3 Solubilization of resin **2** and protection of thiol.

Solubilization conditions of **2** were modified to the reported method [10]. The disulfide bond of **2** was reduced using tributylphosphine and water in THF at rt, as shown in **Scheme III**. The excess amount of tributylphosphine was used to dissolve **2**. After 24 h, **2** was completely dissolved as shown in **Figure I**. After the reaction, the thiol was protected completely by acetyl group to avoid the coupling to disulfide structure and the polymer **5** was recovered in 85% yield. In addition, the cross-linking ratio (2.6 mol%) was estimated from integral value of benzyl protons at  $\delta$  3.9-4.2 and aryl protons at  $\delta$  6.1-6.8 of **4** by <sup>1</sup>H-NMR analysis. The molecular weight ( $M_n$ ) and molecular weight distribution of **4** were 56000 and 3.7 respectively determined by GPC analysis as shown in **Table V**.

#### 3.4 Deprotection of mercapto groups.

Deprotection of **4** was applied to the reported method [12]. To deprotect the acetyl group of **4**, **4** was treated with NaBH<sub>4</sub> in THF/EtOH (2/1; v/v) at rt for 24 h (**Scheme IV**). <sup>1</sup>H-NMR spectra of **4** and **5** were shown in **Figure II**. The benzyl proton of **4** at  $\delta$  4.1 completely disappeared and the benzyl proton of **5** appeared at  $\delta$  3.6. Therefore, the complete deprotection of acetylthio group to thiol was confirmed by <sup>1</sup>H-NMR.

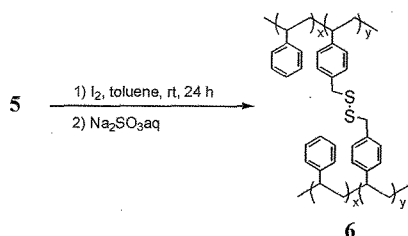
#### 3.5 Cross-linking.

To regenerate an insoluble resin from **5**, the thiol was oxidized to disulfide again. The polymer **5** was cross-linked in 0.05 mol L<sup>-1</sup> iodine – toluene solution for

Table V.  $M_n$  and  $M_w / M_n$  of **4**

cross-linked ratio <sup>1)</sup> (mol%)	Conv. <sup>1)</sup> (mol%)	$M_n$ <sup>2)</sup>	$M_w / M_n$ <sup>2)</sup>	Yield (wt%)
2.6	>99	56000	3.7	85

<sup>1)</sup> determined by <sup>1</sup>H-NMR <sup>2)</sup>determined by GPC ( PSt standards )

Scheme V. Cross-linking of **5**

24 h. After the reaction, the toluene phase was added to aqueous solution of sodium sulfite. After 2 h at rt, the mixture was filtered off to recover the polymer (**Scheme V**). The obtained polymer **6** was insoluble in THF. The cross-linking reaction of **5** was confirmed by the insolubilization in solvents. Therefore the cross-linked polymer by disulfide linkage had the properties of the reversible insolubilizing at rt under redox conditions.

## 4. Summary

A polystyrene cross-linked with disulfide moiety was prepared from copolymerization of styrene with bis(4-vinylbenzyl)disulfide under suspension conditions. The obtained copolymer was solubilized by reduction of disulfides to thiols. The resulting copolymer was soluble in THF. Further this resin was turned insoluble again by oxidation of thiols to disulfides. The reaction conditions of solubilization and insolubilization for the polystyrene cross-linked with disulfide moiety would be investigated further.

## Acknowledgment

We are grateful to NMRC of OIT for financial and instrumental supports.

## Reference and Notes

- [1] Y. Chujo, K. Sada, A. Naka, R. Nomura and T. Saegusa, *Macromolecules*, **23**, 2636 (1990).
- [2] Y. Chujo, K. Sada, A. Naka, R. Nomura, and T. Saegusa, *Macromolecules*, **26**, 883 (1993).
- [3] G. C. Tesoro and V. Sastri, *J. Appl Polym. Sci.*, **39**, 1425 (1990).
- [4] V. Sastri and G. C. Tesoro, *J. Appl Polym. Sci.*, **39**, 1439 (1990).
- [5] G. Wulff and I. Schulze, *Israel J. Chem.*, **17**, 291-297 (1978).
- [6] J. Brandrup, E. H. Immergut, and E. A. Grulke, "Polymer Handbook", 4 th Ed., vol II, A John Wiley, (1999) pp.155-6.
- [7] T. J. Wallance, *J. Am. Chem. Soc.*, **86**, 2018-2021 (1963).
- [8] T. Tachihara, K. Inaba, T. Kawanobe, JP Patent 2001039947 (2001).
- [9] P. H. Toy, K. D. Janda, *Tetrahedron Lett.*, **40**, 6329-6332 (1999).
- [10] J. T. Ayers and S. R. Anderson, *Synth. Comms.*, **29**(3), 351-358 (1999).
- [11] O. Shimomura, B. S. Lee, S. Meth, H. Suzuki, S. Mahajan, R. Nomura and K. D. Janda, *Tetrahedron*, **61**, 12160-12167 (2005).
- [12] C. Cox, H. Wack and T. Lectka, *J. Am. Chem. Soc.*, **121**, 7963-7964 (1999).

(Received December 20, 2007 ; Accepted February 21, 2008)

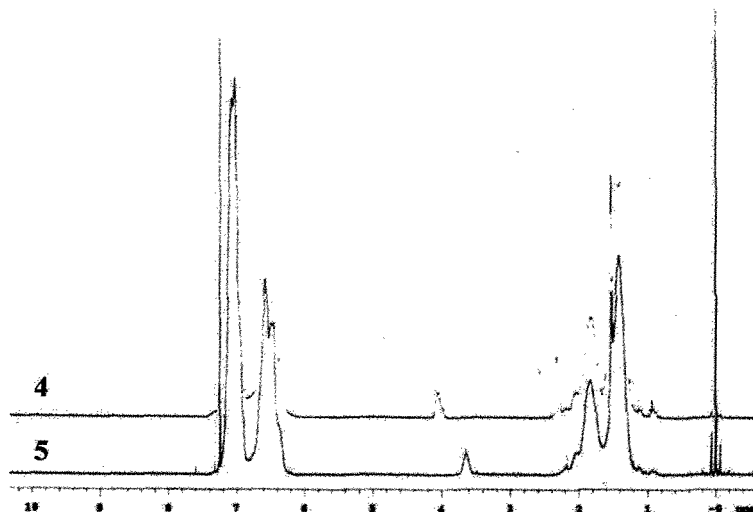


Figure II. <sup>1</sup>H-NMR spectra of **4** and **5**