<Original Paper>

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Synthesis of Reversibly Soluble–Insoluble Polystyrene Supports with Disulfide Cross-Linkage

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Abstract

Copolymerization of styrene with 2.5 mol% of bis(4-vinylbenzyl)disulfide (1) under radical suspension polymerization conditions gave an insoluble cross-linked polystyrene (2) in 72% yield. Polystyrene 2 was treated with tributylphosphine (TBP) and water in THF to give soluble copolymer 3 possessing free thiol groups, which were successively protected by acetylation to give soluble copolymer (4). To regenerate an insoluble cross-linked polystyrene, the thiol groups were deprotected by NaBH_4 and the generated thiols were oxidized to disulfide again by iodine to obtain the insoluble polymer with spherical shapes.

Key words : crosslinking, polystyrene, supports, reversible solubilization, recycling

1. Introduction

Cross-linked polymers have been used habitually as durable materials based on their mechanical and chemical stabilities. Among them, cross-linked polystyrene was generally used for solid phase organic synthesis (SPOS) as supports¹⁾. In our continuous studies, the syntheses of novel tailor-made polymer supports for SPOS was attempted^{2–3)}. The target polymer supports were, however, insoluble to the reaction media, so the status of successive reaction steps during the multi-step solid phase syntheses could not be monitored by solution analyses such as standard NMR techniques. Thus, we noticed that altering the solubility of the cross-linked polymer supports during the process is necessary to monitor the reaction quantitatively and qualitatively.

Meanwhile, some attempts were done to solubilize

cross-linked polymers using connect-disconnect reversible cross-linking in order to recover, to recycle, and to reuse them in the field of materials chemistry. Some examples have been reported for thiol-disulfide interconversion reaction under redox conditions etc^{4–7)}. Tesoro and Sastri 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 were reported^{5–6)}. Wulff and Schulze 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 were discussed in the polystyrene networks⁸⁾. Attempts to solubilize the disulfide cross-linked polystyrene with reduction of S-S linkage by $\text{NaBH}_4/\text{AlCl}_3$ was, however, failed.

On the other hand, some trials for syntheses and application of polymers with disulfide linkage in the backbone were studied in recent years. Tsarevsky and Matyjaszewski reported that bis(2-hydroxyethyl) disulfide bis(2-bromopropionate) as an initiator was used for the ATRP of styrene and the disulfide containing polymers were prepared⁹⁾. The internal disulfide was

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cleaved and coupled by redox conditions. Takahara and coworkers reported the metathesis reaction of disulfide-containing polyester (DSPES) by photoirradiation¹⁰⁾. Chujo and coworkers reported about the polymerization of diethynyl disulfide derivative¹¹⁾ and molecular release using disulfide linked water soluble polyhedral oligomeric silsesquioxane (POSS)¹²⁾.

Consequently, we tried to synthesize novel reversible solubilization of disulfide cross-linked polystyrene supports. We prepared copolymers of **1** with styrene by suspension polymerization and the nature of the copolymers for solubilizing and insolubilizing was studied¹³⁾.

2. Results and Discussion

A cleavable cross-linker, **1** was prepared as shown in Scheme 1. A mixture of sodium disulfide and TBAB (tetra-*n*-butylammonium bromide) in toluene/H₂O, 4-vinylbenzyl chloride was added to the solution to give **1** in 57% yield. To prepare the cross-linked polystyrene, styrene and **1** (2.5 mol%) was copolymerized with 2,2'-azobisisobutyronitrile (AIBN, 0.5 mol%) as an initiator at 80°C under suspension polymerization conditions as shown in Scheme 2. The yield of cross-linked polystyrene **2** was 72%.

Generally, good supports possess good swelling ability in certain solvents which are employed as reaction media. Thus, cross-linked polystyrene **2** was immersed in various solvents, and after 1 h, the volume of **2** was measured. Those results were summarized in Table 1. The resin prepared here showed good swelling in tolu-

Scheme 1 Preparation of bis(4-vinylbenzyl)disulfide **1**.

Scheme 2 Suspension polymerization of **1** with styrene.

ene, THF, and chloroform.

To solubilize **2**, the reduction of the disulfide bond of **2** was tried using tributylphosphine (TBP) and water in THF at rt, as shown in Scheme 3. After 24 h, **2** was completely dissolved to form polymer **3** as shown in Fig. 1(c). Similarly, the reduction of **2** with ZrCl₄/NaBH₄¹⁴⁾, LiCl/NaBH₄¹⁵⁾, and Ph₃P¹⁶⁾ was also carried out but no solubilization of **2** was observed under those conditions.

After the solubilization of **2**, the thiols of **3** were protected completely by acetylation to avoid the coupling to disulfide and the polymer **4** was recovered in 85% yield. The benzyl protons of **3** at δ 3.6 was completely disappeared and the benzyl protons of **4** was appeared at δ 4.1 confirmed by ¹H-NMR analyses. In addition, the actual cross-linking ratio was then estimated to be 2.6 mol% from integral ratio of benzyl protons at δ 4.1 and that of aryl protons at δ 6.1–6.8 (Fig. 2). The ratio was good agreement with the starting monomer ratio (2.5 mol%), side reactions, such as cleaving of disulfide bond hardly occurred under the polymerization conditions. The molecular weight ($10^{-4} \times M_n$) and molecular weight distribution (*Mw*) of **4** were 5.6 and 3.7 respectively determined by GPC analysis.

To deprotect the thiol groups of **4**, **4** was treated with NaBH₄ in THF/EtOH (2/1; v/v) at rt for 24 h (Scheme 4). After the reaction, the polymer was treated

Scheme 3 Solubilization of **2** and protection of thiol.

(a) 0 h (b) 1 h (c) 24 h

Fig. 1 Solubilization of **2** to **3**.

Table 1 Swollen volume (mL/g) of **2**.

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

Fig. 2 ^1H -NMR spectrum of 4.

Scheme 4 Deprotection of thiol of 4.

Fig. 3 ^1H -NMR spectrum of 3'.

with aqueous solution of 5wt% citric acid to obtain 3' in 84% yield. The benzyl protons of 4 at δ 4.1 completely disappeared and the benzyl protons of 3' appeared at δ 3.6 confirmed by ^1H -NMR (Fig. 3). Therefore, the complete deprotection of acetylthio groups to thiols was detected.

To regenerate an insoluble cross-linked spherical polymer from 3', the thiols were oxidized to disulfide

Scheme 5 Recross-linking of 3' under suspension condition.

Fig. 4 Optical micrographs of 2 and 2' (X150).

again. A solution of 3' in toluene was added to the aqueous phase with stirring. After the addition, iodine in toluene was added to the solution. After 24h at rt, the cross-linked polymer precipitated was obtained in 76% yield (Scheme 5). The polymer 2' obtained was insoluble in solvents such as THF. The cross-linking reaction of 3' 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. Optical micrographs of 2 after the sieve separation from 355 to 500 μm and 2' were shown in Fig. 4. The spherical shapes of milky polymer 2' were observed as shown in Fig. 4 (b). The regeneration of insoluble cross-linked polymer using connect-disconnect reversible cross-linking by disulfide linkage was accomplished.

3. Experimental

3.1 Measurements

^1H - and ^{13}C -NMR spectra were recorded in CDCl_3 with a Varian Unity-300 spectrometer using tetramethylsilane (TMS) as an internal standard. FT-IR spectra were obtained with a Shimadzu IR-8100 infrared spectrometer. Gas chromatography-mass spectrometry (GC-MS) analyses were carried out on Shimadzu GC-17A gas chromatography instrument using J&W GC Column (30 m $\times$ 0.25mm $\times$ 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.

Preparation of bis(4-vinylbenzyl)disulfide (1) as a reversible cross-linker. The cross-linker **1** was prepared by a modification of the preparation of bis(phenylacetyl) disulfide¹⁷⁾. A mixture of sodium sulfide pentahydrate (11.7 g, 69 mmol) and sulfur powder (2.24 g, 70 mmol) in water (125 mL) 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 4-vinylbenzyl chloride (20.3 g, 133 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 $\times$ 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. 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 (57 %). Since this product gradually decomposed, **1** was recrystallized before use.

¹H-NMR (300 MHz, CDCl₃) δ 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); ¹³C-NMR (75 MHz CDCl₃) δ 43.0, 113.9, 126.3, 129.6, 136.4, 136.8, 136.9; IR (KBr) 3084, 3049, 2932, 2976, 2930, 1915, 1822, 1626, 1508, 1404, 1229, 1122, 1097, 991, 904, 847, 829, 764, 698, 484 cm⁻¹, GC-MS (m/z): 298 (M⁺); mp 73-74°C (Ref: 87-88°C)¹⁸⁾.

Suspension polymerization of 1 with styrene. The conditions of suspension polymerization were applied for reported method¹⁹⁾. 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 NaCl (25 g) and gum arabic (40.1 g) in water (1 L) was stirred until gum arabic dissolved, and the solution was filtered off by Celite 545. The organic solution was added dropwise to aqueous phase (210 mL) under N₂ at 80°C in the dark. After 20 h, insoluble beads of **2** were

filtered off from the reaction mixture, and successively washed with hot water. Then **2** was thoroughly washed with THF in a soxhlet extractor for 20 h. Additionally, **2** was washed with ether and hexane, and dried under vacuum for 24 h. Yield: 8.02 g (72%).

Measurement of swelling volumes²⁾. The beads of **2** were then sieved off (212 – 355 μ m) and placed in 1 mL syringes with filter and various types of solvents (0.8 mL) respectively. The syringes were set on a shaker for 1 h and the volume of the resin was measured.

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 method²⁰⁾. The resin **2** (4.35 g), THF (100 mL), purified water (0.900 g, 50 mmol) and TBP (10.9 g, 50 mmol) were placed in a 200 mL flask. The mixture was stirred under N₂ 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 EtOAc (560 mL). The organic layer was washed with 1 mol L⁻¹ aqueous HCl (200 mL $\times$ 3) and brine (200 mL $\times$ 2), dried over MgSO₄. 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%).

¹H-NMR (300 MHz, CDCl₃) δ 0.9-1.0 (br, -C(CH₃)CN), 1.2-1.7 (br, -CH(Ar)-CH₂-), 1.7-2.2 (br, -CH(Ar)-CH₂-), 2.3-2.4 (br, -CH₂-S-COCH₃), 3.9-4.2 (br, Ar-CH₂-S-), 6.1-6.8 (br, *m*-Ar), 6.8-7.2 (br, *o*, *p*-Ar)

Reduction of disulfide for solubilizing resins with ZrCl₄/NaBH₄. The method described for reduction of dibenzyl disulfide with ZrCl₄/NaBH₄ was applied for the polymer reaction¹⁴⁾. The resin **2** (0.300g), ZrCl₄ (0.16 g, 0.69 mmol), and NaBH₄ (0.11g, 2.75 mmol, 92% purity), and THF (5 mL) were placed in a pyrex tube. The mixture was stirred under N₂ at rt for 10 days.

Reduction of disulfide for solubilizing resins with LiCl/NaBH₄. The method described for reduction of dibenzyl disulfide with LiCl/NaBH₄ was applied for the polymer reaction¹⁵⁾. The resin **2** (0.300g), LiCl (29.5 mg, 0.69 mmol), and NaBH₄ (28.5 mg, 0.69 mmol, 92% purity), and THF (5 mL) were placed in a pyrex tube. The mixture was stirred under N₂ at rt for 10 days.

Reduction of disulfide for solubilizing resins with

Ph_3P . Herewith Ph_3P was used instead of TBP described above. Into the mixture of THF (7 mL), purified water (0.062 mL, 3.4 mmol) and triphenylphosphine (0.932 g, 3.5 mmol) in a pyrex tube, were added **2** (0.300 g). The mixture was stirred under N_2 at rt for 7 days.

*Deprotection of acetyl groups*²¹⁾. $NaBH_4$ (61.1 mg, 1.62 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 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 $MgSO_4$. The filtrate was roughly evaporated and was added to methanol. The white precipitate **3'** was filtered off, washed with methanol, dried under vacuum. Yield: 0.252 g (84%)

¹H-NMR (300 MHz, $CDCl_3$); δ 0.9-1.0 (br, $-C(CH_3)CN$), 1.2-1.6 (br, $-CH(Ar)-CH_2-$), 1.7-2.3 (br, $-CH(Ar)-CH_2-$), 3.4-3.8 (br, $Ar-CH_2-SH$), 6.1-6.8 (br, *m*-Ar), 6.8-7.2 (br, *o*, *p*-Ar).

Recoupling thiol to disulfide for insolubilizing. A solution of **3'** (0.201 g) in toluene (1 mL) was added to the aqueous phase (50 mL) prepared from the same recipe using suspension polymerization with stirring. After the addition, iodine in toluene (1 mL, 1 mol L^{-1}) was added to the solution. After 24h at rt, the resin was filtered off and washed with hot water. The resin **2'** was transferred to plastic syringe (10 mL) and was washed with THF to disappear the brown color of iodine. The resin obtained was succeedingly washed with 3 times of diethyl ether and hexane and was dried *in vacuo*. Yield: 0.153 g (76%).

4. Conclusion

In 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 the reduction of disulfides to thiols using TBP. The resulting copolymer was soluble in solvents such as THF. Further this resin was turned insoluble again by oxidation of thiols to disulfides using iodine. The reaction conditions of solubilization and insolubilization for the polystyrene cross-linked with disulfide moiety would be investigated further. These results would

help to develop connect-disconnect reversible cross-linking resins and adhesives.

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<研究論文>

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可逆的可溶化–不溶化が可能なジスルフィド架橋
ポリスチレン担体の合成

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要 旨

懸濁重合条件下、スチレンとビス(4-ビニルベンジル)ジスルフィド(1)との共重合反応により不溶性の架橋ポリスチレン(2)を収率70%で得た。ポリスチレン2はTHF中、トリブチルホスフィン–水で処理することによりチオール基を持つ可溶性共重合体3となり、続いてアセチル化による保護により可溶性共重合体(4)を得た。不溶性の架橋ポリスチレンを再生するためにNaBH₄によりチオール基を脱保護した後、生じたチオールをヨウ素により酸化することにより球状の不溶性高分子を再生した。

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