Synthesis of polymer microspheres with mercapto groups by polycondensation of $\alpha,\omega$-alkanedithiol and $\alpha,\omega$-dibromoalkane in the presence of a poly[styrene-$N$-(hydroxymethyl)acrylamide] latex

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Introduction

Polymer microspheres with narrow size distribution have been generally prepared by soap-free emulsion polymerization, dispersion polymerization, or precipitation polymerization. These methods have been utilized complementarily depending on the particle size. The control of functional group density and diameter is important for the properties of polymer microspheres. However, independent control of particle size and functional group density cannot be achieved by one-step polymerization. So far two-step polymerization methods such as two-stage shot growth process\(^1\) or seeded polymerization\(^2\) have been employed to control both the particle size and the functional group density.

The mercapto group has specific reactivities such as strong nucleophilicity, radical capture properties, and strong binding with noble metal ions\(^3\). However it is difficult to directly introduce the mercapto group into polymer microspheres because of its high radical chain transfer activity. Thus, the microspheres having mercapto groups have been prepared by two preparation steps, i.e., the introduction of functional groups such as isothiouronium salts\(^4,\,5\), epoxides\(^6\), or thioacetates\(^7\) into polymer particles, and their subsequent conversion to mercapto groups on the polymer surface.

Recently, we have reported a novel method for preparing polymer microspheres having mercapto groups, by means of the polycondensation of $\alpha,\omega$-alkanedithiol and $\alpha,\omega$-dibromoalkane in the presence of polystyrene latex\(^8,\,9\). The condensation reaction proceeds in the polystyrene latex, and the end groups of the polysulfide, i.e., mercapto groups, are immobilized directly onto the poly-
mer particle. Both particle size and mercapto group density can be regulated merely by changing the monomer ratio and the seed particle size. However, some drawbacks to this method exist such as the necessity of a nonionic surfactant for the polycondensation and the formation of polydispersity polymer microspheres. To overcome these problems, we employed poly[styrene-N-(hydroxy-

methyl)acrylamide] latex (PS-HMAm) as a seed particle. There are some reasons that we chose PS-HMAm latex. First, it is highly stable against coagulation with the aid of nonionic segments of HMAm. In the previous report, ionic surfactants (sodium dodecyl sulfate or cetyltrimethylammonium chloride) could not stabilize the PS latex sufficiently to disperse during the polycondensation. Only a nonionic surfactant could disperse the particles into water effectively. Nonionic segments of HMAm could stabilize the particle in this system. Second, we can examine the influence of particle size on the mercapto group content, because the particle sizes of PS-HMAm were reported to be easily regulated. Third, the amide linkages of HMAm are not cleaved readily under the polycondensation conditions, i.e., in diluted alkaline media at high temperature.

In this paper, the polycondensations of dithiols and dibromoalkanes with various alkylene chain lengths were conducted in the presence of PS-HMAm particles and the immobilization of mercapto groups was studied.

**Experimental part**

**Measurements**

Diameters of polymer microspheres were determined by means of a scanning electron microscope (JEOL JSM-588) or a transmission electron microscope (Hitachi H-9000NAR). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 2000 spectrophotometer.

**Materials**

All reagents were obtained commercially and used as received. Poly[styrene-N-(hydroxyethyl)acrylamide] latexes (PS-HMAm) with different diameters were prepared by the reported method.

**Polycondensations**

Into a 100-mL flask equipped with a condenser, 1,6-dibromohexane (0.488 g; 2.0 mmol), and PS-HMAm latex (1.0 g) dispersed in deionized water (30 mL) were placed and stirred for 30 min at room temperature. Into the mixture, 1,3-propanediol (0.271 g; 2.50 mmol) in 1.0 M potassium hydroxide (5.0 mL; 5.0 mmol) was added. The polycondensation was carried out at 100 °C for 24 h in a nitrogen atmosphere. After cooling, the coagulated polymer was removed by filtration and the microspheres were centrifuged three times with deionized water (18500 g).

**Mercapto group and sulfur content of the polymer microspheres**

The mercapto group content of the microspheres was determined by the Ellman method using either ethanol-water (vol. ratio 1/1) or N,N-dimethylformamide (DMF) solvent following the literature methods. Because the mercapto groups on the microspheres were generally not stable, we usually determined their content within 24 h after the polycondensations. The determination of sulfur content in the particle was performed by means of the combustion of the polymer under an oxygen atmosphere followed by measurement of the liberated sulfate ions by ion chromatography.

**Size-exclusion chromatography (SEC) measurement**

Because the PS-HMAm was not completely soluble, the soluble polymer was extracted with chloroform using a Soxhlet extractor for 5 h. The molecular weight of the soluble polymer was determined by SEC measurement on a TOSOH HLC 8020 instrument equipped with a refractive index detector using tetrahydrofuran as an eluent at 40 °C. The column was calibrated with 5 polystyrene standards.

**Results and discussion**

**Preparation of PS-HMAm latices as seed particles**

In this study, PS-HMAm latices were employed as seed particles. To investigate particle size effect on the immobilization of mercapto groups, we prepared three sizes of seed particles initiated with K,S,S04 according to the reported method as shown in Tab. 1. The particle sizes were controlled by just changing the amount of HMAm or mode of monomer charge. The large particles were prepared by the aqueous prepolymerization of HMAm for 1 h, followed by addition and polymerization of St. The hydroxy group density of the particles was determined by elemental analysis and the diameter based on the assumption that all the hydroxy groups were located on the surface (Tab. 1). Since hydrophilic hydroxymethylamide groups stabilized the particle in water, the particles hav-

<table>
<thead>
<tr>
<th>Tab. 1. Preparation of PS-HMAm latex as a seed particle&lt;br&gt;</th>
<th>Seed</th>
<th>Amount of S</th>
<th>Amount of HMAm</th>
<th>Diameter</th>
<th>OH density</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>20.0</td>
<td>5.00</td>
<td>0.127 ± 0.007</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>20.0</td>
<td>3.16</td>
<td>0.324 ± 0.006</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>19.0</td>
<td>1.00</td>
<td>0.456 ± 0.027</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>18.0</td>
<td>2.00</td>
<td>0.283 ± 0.014</td>
<td>14.8</td>
<td></td>
</tr>
</tbody>
</table>

a) 0.1 M phosphate buffer (pH 9.0); 160 mL, K,S,S04: 0.529 mmol, condition: 70 °C, 20 h. 
b) Hydroxymethylamide group density on the particle surface determined from elemental analysis and diameter. 
c) S was added after the prepolymerization of HMAm for 1 h. 
d) V-50 was used as an initiator.
ing high OH group density, i.e., the small particles were dispersed stably in water. The positively charged PS-HMAm particles were also prepared with cationic 2,2'-azobis(2-amidinopropane) dihydrochloride (V-50) as an initiator (Seed C).

**Polycondensation of 1,6-dibromohexane and 1,3-propanedithiol in the presence of PS-HMAm**

The microspheres having mercapto groups were prepared by the polycondensations of 1,6-dibromohexane and 1,3-propanedithiol in the presence of polymer latices as seed particles. On the use of PS latices, it was necessary to use a nonionic surfactant, triton® X-405 and to elevate polymerization temperature gradually (at 60°C for 2h, at 80°C for 2h, and at 100°C for 20 h). When the polycondensation was conducted without a nonionic surfactant or the temperature was rapidly elevated to 100°C, all polymer was coagulated in the initial stage of the polycondensation. Furthermore, the size distributions of particles became broader upon polycondensation.

Polycondensations of 1,3-propanedithiol and 1,6-dibromohexane were performed in the presence of PS-HMAm (Seed M; see Tab. 1) instead of PS latex as seed particles. The results are listed in Tab. 2. When the polymerization was carried out in the absence of nonionic surfactant at 100°C, HS(CH₂)ₙSH + Br(CH₂)ₓBr KOH → H+·S(CH₂)ₙS(CH₂)ₓ±·SH polymer microspheres with mercapto groups were obtained in quantitative yields. Their diameters corresponded with the seed particle diameters and monodisperse particles were obtained, as can be seen in Fig. 1. Although a high concentration of electrolyte (KOH) existed in aqueous media, the hydroxymethylamide groups of HMAm enhanced the particle stability to enable formation of monodisperse microspheres. In any case, the sulfur content of the microsphere was consistent with that calculated with the feed ratio of dithiol to PS-HMAm, indicating that polysulfide was incorporated into the particle quantitatively. The polysulfide chains might be entangled with PS-HMAm chains and be stably immobilized in the particles. The mercapto group contents were strongly influenced by the molar ratio of dithiol to dibromide. No mercapto groups were detected in the polymer microspheres obtained by equimolar or a little excess amount of dithiol to dibromide (run no. 1 and 2). A high molar ratio of dithiol against dibromide afforded the formation of microspheres with a high mercapto group content (run no. 4 and 5). Although particles were exposed to the alkaline solution at 100°C, the amide carbonyl band (1671 cm⁻¹) in infrared spectrum was not changed and no carbonyl band corresponding to aliphatic carboxylic acid (1700–1730 cm⁻¹) appeared, suggesting that amide linkages were not cleaved in the course of the condensation reaction. The microspheres were also recovered quantitatively without any coagulated polymer after the polycondensations at low temperature (60 or 80°C), however, no mercapto groups were incorporated in the particles.

### Tab. 2. Polycondensation of propanedithiol and dibromohexane in the presence of PS-HMAm latex

<table>
<thead>
<tr>
<th>Run no.</th>
<th>Amount of dithiol in mmol</th>
<th>Yield in %</th>
<th>Diameter in μm</th>
<th>SH content in μmol/g</th>
<th>Sulfur content in mmol/g calc.</th>
<th>found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>96</td>
<td>–</td>
<td>0</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>97</td>
<td>–</td>
<td>0</td>
<td>3.2</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>96</td>
<td>0.333 ± 0.009</td>
<td>12</td>
<td>3.6</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>2.7</td>
<td>94</td>
<td>0.332 ± 0.009</td>
<td>20</td>
<td>3.9</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>96</td>
<td>0.332 ± 0.005</td>
<td>123</td>
<td>4.3</td>
<td>4.1</td>
</tr>
</tbody>
</table>

a) PS-HMAm: 1.0 g (Seed M; see Tab. 1), dibromide: 2.0 mmol, KOH: 5.0 mmol, H₂O: 35 mL; condition: 100°C, 24 h.

b) SH content of polymer microsphere determined by Ellman method in a mixture of ethanol and water (v/v = 1/1).

c) Sulfur content of polymer microsphere calculated from feed ratio assuming that all monomer was incorporated in the particle.

d) Sulfur content of polymer microsphere.

![Fig. 1. Transmission electron micrographs of PS-HMAm latex, seed M (a), polymer microsphere with mercapto groups; run no. 3 (b). Scale bars indicate 1.0 μm](image-url)
Synthesis of polymer microspheres with mercapto groups by polycondensation of...

Polycondensation of dibromoalkane and alkanedithiol having various alkylene chain lengths

The results of the polycondensations with alkanedithiols and dibromoalkanes with various alkylene chain lengths are summarized in Tab. 3. Although microspheres prepared with an excess dithiol had generally large amounts of mercapto groups (runs no. 5, 8, and 10), the most hydrophilic dithiol, ethanedithiol, gave the microspheres with a low mercapto group content (run no. 6). Hydrophobic dithiols \((n = 3 \text{ or } 4)\) increased the mercapto group contents. Dibromoalkane also had an influence on the mercapto group content. The polycondensation using a hydrophilic dibromide \((m = 3)\) and an excess of dithiol afforded particles with a very high mercapto group content (run no. 10; 221 \(\mu\)mol/g).

We carried out the measurement of mercapto group contents by the Ellman method using both ethanol/water \((v/v = 1/1)\) and DMF as solvents. In ethanol/water, only mercapto groups near the surface are detected, because the Ellman reagent \((5,5'\text{-dithiobi}-2\text{-nitrobenzoic})\) acid) can not reach the inside of particle due to the poor solubility of the polymer. In contrast, the polymer is soluble or highly swelled in DMF and all mercapto groups are detectable. The mercapto group contents measured in DMF were much higher than those in EtOH-H\(_2\)O, except run no. 10. These suggest that a considerable amount of mercapto groups are located inside the particles. Hydrophilic hydroxymethylamid groups are on the water-polymer interface and cover the mercapto groups. In contrast, mercapto group contents for only the particles of run no. 10 were nearly identical measured in both solvents. The polysulfide having many mercapto groups and short alkylene chains i.e., prepared with dibromopropane and propanedithiol (run no. 10), was more hydrophilic, and hence the mercapto groups attached with the polysulfide were located near the surface.

Fig. 2 illustrates the SEC charts of PS-HMAm latex, seed M (a), and polymer microsphere with mercapto groups, run no. 3 (b).

Tab. 3. Polycondensation of alkanedithiol and dibromoalkane in the presence of PS-HMAm latex\(^a\)

<table>
<thead>
<tr>
<th>Run no.</th>
<th>Seed(^b)</th>
<th>Dithiol (n) (in mmol)</th>
<th>Dibromide (m)</th>
<th>Yield in %</th>
<th>Coagulated polymer in %</th>
<th>SH content in (\mu)mol/g</th>
<th>(M_n)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>M</td>
<td>2 (3,0)</td>
<td>6</td>
<td>85</td>
<td>0</td>
<td>13</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>3 (2,5)</td>
<td>6</td>
<td>99</td>
<td>0</td>
<td>12</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>3 (3,0)</td>
<td>6</td>
<td>96</td>
<td>0</td>
<td>123</td>
<td>371</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
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<td>6</td>
<td>93</td>
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<td>74</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>4 (3,0)</td>
<td>6</td>
<td>80</td>
<td>0</td>
<td>84</td>
<td>161</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>3 (2,5)</td>
<td>3</td>
<td>99</td>
<td>0</td>
<td>22</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>3 (3,0)</td>
<td>3</td>
<td>87</td>
<td>0</td>
<td>221</td>
<td>259</td>
</tr>
<tr>
<td>11</td>
<td>C</td>
<td>3 (2,5)</td>
<td>6</td>
<td>90</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>C</td>
<td>3 (3,0)</td>
<td>6</td>
<td>85</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>C</td>
<td>3 (3,0)</td>
<td>6</td>
<td>0</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) PS-HMAm: 1.0 g, dibromide: 2.0 mmol, KOH: 5.0 mmol, H\(_2\)O: 35 mL; condition: 100 °C, 24 h.

\(^b\) See Tab. 1.

\(^c\) Number-average molecular weight of polysulfide determined by SEC.

\(^d\) SH content of polymer microsphere determined by Ellman method in a mixture of ethanol and water \((v/v = 1/1)\).

\(^e\) SH content of polymer microsphere determined by Ellman method in DMF.
1000–3000. At first, we had anticipated that increase of dithiol against dibromide decreased molecular weight, affording the particle with high SH content, however, there was little correlation between molecular weight and SH content. This indicated that all of the end groups were not mercapto groups despite an excess dithiol used. For example, when the molecular weight of the polysulfide was 1290 (run no. 8), the mercapto group content should be about 540 μmol/g based on the assumption that all of the end groups were mercapto groups. The observed mercapto groups of run no. 8 in DMF was only 161 μmol/g.

When the polycondensation of propanedithiol and dibromohexane \((n = 3, m = 6)\) was carried out with the PS latex \((D_w = 0.69 \, \mu m)\), the molecular weights were much higher (38000 and 16300, molar ratios of dithiol to dibromide were 1.25 and 1.50, respectively) than those with PS-HMAm. This might be attributed to the distribution of polysulfides in particles. Using hydrophobic seed particles (PS latex), the more hydrophilic polysulfide polymers might be located near the surface and its bromo group reacted more easily with dithiol monomer than the hydrophobic dibromide monomer. Hence high molecular weight polysulfides were obtained. However, in contrast, polysulfides and dibromide monomer in PS-HMAm particle were equally distributed, because the polysulfide was not hydrophilic compared with the particle surface. The bromo group of polysulfide was consumed similarly to the dibromo monomer, yielding the low molecular weight polysulfide.

**Polycondensation of dibromoalkane and alkanedithiol using positively charged PS-HMAm as a seed particle**

We also employed PS-HMAm latex initiated with cationic initiator (V-50) as a seed particle, however, the reproducibility of the polycondensation was poor (Tab. 3). In run no. 12, the polymer microspheres were dispersed stably in the course of the polycondensation. However, all polymer was coagulated in run no. 13, despite the polycondensation being conducted under the same conditions as run no. 12. Positively charged particles (seed C) were not dispersed stably because of the low hydroxy group density, compared with the negatively charged seed M (Tab. 1). Additionally, the positive charge on the PS-HMAm was neutralized with the mercaptide anion during the polycondensation, followed by the particle coagulation. Hydroxymethylamidine groups stabilize particles effectively; however, the charges on the surface also play an important role to disperse particles. Negative charge on the surface must act as an electrostatic repulsive barrier against the other particles and prevent the polymer coagulation. The obtained particles (run no. 11, 12) did not have any mercapto groups and the molecular weights of polysulfides were much higher than those using negatively charged PS-HMAm (run no. 3, 5). Due to the high molecular weight of polysulfide, the amount of the end groups (mercapto or bromo group) per weight decreased, so that no mercapto groups were incorporated in the particle.

Why was high molecular weight polysulfide formed using the positively charged seed particles? We assume that mercaptide monomer reacted with the bromo groups of polysulfides dominantly compared with dibromide monomer. The polysulfide with mercaptide anion was expected to be formed on the surface due to its hydrophilicity. The mercaptide mainly reacted with the bromo groups of polysulfides, not dibromide monomer, so that high molecular weight polymers were obtained. While, since dibromide monomer and polysulfide were distributed homogeneously in the negatively charged seed particle, low molecular weight polysulfide was formed to yield the particle with high SH content.

**Polycondensation of dibromopropane and propanedithiol in the presence of different diameter particles of PS-HMAm**

Three seed particles with different diameters \((0.456, 0.324, \text{and } 0.127 \, \mu m)\) were employed in the polycondensation with propanedithiol and dibromopropane. In all cases, microspheres with mercapto groups were obtained in quantitative yields. However, for large particles, their size distributions were broader and some nonspherical particles were included after the polycondensations. Since the density of hydroxymethylamidine group for large particles was low (Tab. 1), particles were not dispersed stably and some of them fused together in the course of polycondensation. The mercapto group contents measured in EtOH-water are listed in Fig. 3. In any particle, the mercapto group contents increased with the molar ratio of dithiol to dibromide. Use of large particles \((0.456 \, \mu m)\) reduced the mercapto group content. The polycondensation with small seed particles \((0.127 \, \mu m)\) produced microspheres with high mercapto group contents. The similar particle size effect was observed in the polycondensation using PS seed particles\(^9\). When the molar ratio of dithiol to dibromide was 1.5 and the small or medium
particle was used, the mercapto group densities were 5.3 and 16.8 (μmol/m²), respectively. The highest SH density particle was obtained using the medium seed particle.

This kind of polycondensation is a sort of two-phase polycondensation which is generally carried out using a phase-transfer catalyst. Dithiol and potassium hydroxide form potassium mercaptide in the aqueous medium, while dibromoalkane is in the polymer particles. The mercaptide enters into the polymer particles and then reacts with dibromide. Since the polymer particle has a large aqueous-organic interfacial area, the mercaptide moves into the particle and the condensation reaction proceeds smoothly without any phase-transfer catalyst. In the initial polycondensation stage, an excess of dibromide exists in the reaction locus and the slow penetration of the mercaptide into the particle makes polysulfide with bromo end groups. This leads to the low mercapto group content in the microsphere. The hydrophobic dithiol can penetrate into the particle easily and most of the chain that using more hydrophilic propane dithiol (run no. 5) could permeate into the particle easily and most of the chain that using more hydrophilic propane dithiol (run no. 5) could be penetrated into the particle. Consequently, the mercapto group content of particles using the hydrophobic dithiol (run no. 8) decreased.

Mercapto group stability of the microsphere

Mercapto groups are known to be easily oxidized to disulphides or to higher oxidation products depending on the reaction conditions. By using PS latex as a seed particle, the mercapto group content decreased drastically after a storage for 5 weeks probably due to the oxidation with air (from 71 to 12 μmol/g). Surprisingly, the mercapto group content in the PS-HMAm particle was hardly changed after 5 weeks (from 88 to 83 μmol/g). The hydrophilic hydroxymethylamidine groups on the surface might restrict the mobility of mercapto groups, resulting in their high stability.

In conclusion, we prepared polymer microspheres with mercapto groups by the polycondensations of α,ω-alkanediol and α,ω-dibromoalkane in the presence of PS-HMAm seed particles. Monodisperse particles were obtained in quantitative yields without any surfactant by using PS-HMAm in place of PS latex. Mercapto group contents were controllable by changing the molar ratio of dithiol to dibromide and the seed particle size. The mercapto groups immobilized into PS-HMAm particle showed remarkable stability against the oxidation with air. Further studies on the reactivity and the stability of mercapto groups in the particles are now under investigation.