Macromolecular Radical Crossover Reaction of Disulfide-Containing Polyester Triggered by Free-Radical Generators

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The macromolecular radical crossover reaction of disulfide-containing polyester triggered by free-radical generators was successfully carried out in solution. IR, NMR, and gel permeation chromatographic (GPC) measurements revealed that the macromolecular crossover reaction between the main chains of disulfide-containing polymers occurred only in the presence of free-radical generators such as benzoyl peroxide (BPO) and 2,2'-azobis(isobutyronitrile) (AIBN). The fractionated polymer with narrow molecular weight distribution reorganized to the polydispersed polymer due to the chain transfer reaction, but no decomposition of repeating units was observed during the reaction. The number average molecular weight slightly decreased after the reaction because catalytic amount of free-radical generators gave terminal groups of the polymer chains. The generated free-radicals initiated the chain transfer-type crossover reaction to give the scrambled polymers.

Key words: polymer reaction, disulfide, dynamic covalent bond, polyester

1. INTRODUCTION

Reorganization of polymer main chains by external stimulation is an attractive method to control the molecular weight and composition of polymer library by combinatorial scrambling. Not only the use of supramolecular chemistry but also the introduction of dynamic covalent chemistry[1] opened the door to the facile reorganization of polymer main chains.[2] Dynamic covalent bond can dissociate and associate reversibly under thermodynamic control by a particular external stimulation such as heating, catalyst, and so on. Very recently, the authors reported that the thermally exchangeable polyalkoxyamines, in which the initiator units for nitroxide mediated radical polymerization are incorporated, can reorganize upon heating without the formation of any monomeric or oligomeric compounds during the scrambling process.[3]

On the other hand, disulfide bonds are one of the simplest dynamic covalent bonds, and also exist in nature: the thiol-disulfide interchange reaction is widely acknowledged to be important in stabilizing protein structures. Disulfide bonds are tolerant for many functional groups except for thiol group,[4] the cleavage of sulfur-sulfur bonds is known to occur either homolytically or heterolytically: (a) short-lived sulfenyl radicals are generated by homolytic scission via photolysis,[5] oxidation,[6] or heating;[7] and (b) ionic scission generates mercaptides (XS⁻) under basic/nucleophilic conditions[8] or sulfenium cation (XS⁺) under acidic/electrophilic conditions.[9,10] The generated sulfur radical, anion, or cation then reacts with another disulfide, resulting in exchange reactions (Fig. 1).[11] Because of having such a character, the compounds with disulfide groups have been the subject of many studies.[12] Takata et al. have recently reported a new synthetic method for rotaxanes based on the concept of dynamic covalent chemistry, which involves the thermodynamic control of the thiol-catalyzed reversible cleavage of a
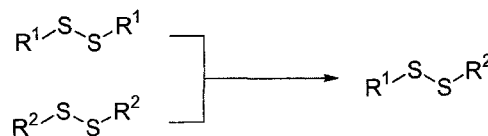

Fig. 1 Exchange reaction of the disulfide compounds.

disulfide linkage.[13] An interesting application of disulfide polymers is the formation of copolymers with vinyl monomers under irradiation of UV light, which occurs via the cleavage of the disulfide group.[14] In this paper, the authors report the macromolecular radical crossover reaction between the main chains of disulfide-containing polyester triggered by free-radical generators.

2. EXPERIMENTAL SECTION

2.1 Measurement

^1H and ^{13}C NMR spectroscopic measurements were carried out with a JEOL JNM-EX400 spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform-*d* (CDCl₃). IR spectra were obtained with a Perkin Elmer Spectrum One infrared spectrometer as thin films on NaCl or neat. Analytical thin layer chromatography (TLC) was performed on commercial Merck plates coated with silica gel (0.25 mm thick). Number and weight average molecular weights (M_n and M_w, respectively) and molecular weight distribution (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a TOSOH system equipped with a refractive index (RI) detector using THF as an eluent at a flow rate of 0.8 mL·min⁻¹, calibrated with polystyrene standards. Fractionation was conducted on a JAI LC-908 HPLC system equipped with two mixed polystyrene gel columns [JAIGEL-2H, JAIGEL-3H (600 × 20 mm)]. Chloroform was used as an eluent at a flow

rate of 3.8 mL·min⁻¹.

2.2 Preparation of disulfide-containing polymer

Adipoyl chloride (4.1 mL, 28 mmol) was added to the solution of 2-hydroxyethyl disulfide (HEDS) (4.3 g, 28 mmol) and pyridine (4.9 mL, 60 mmol) in dichloromethane (28 mL). The reaction mixture was stirred at room temperature under nitrogen for 72 h. After the addition of methanol (2.5 mL), dichloromethane was added to the reaction mixture and washed with 0.1 mol/L HCl aqueous solution. Then, the organic layer was washed with water three times, dried with anhydrous magnesium sulfate, and evaporated to dryness. The residue was purified by reprecipitation with chloroform/hexane and dried in vacuo to give the polymer as a white powder. $M_n = 28400$, $M_w/M_n = 1.82$; ^{1}H NMR: δ / ppm 1.67 (m, 4H), 2.36 (m, 4H), 2.92 (t, J = 7 Hz, 4H), 4.34 (t, J = 7 Hz, 4H); ^{13}C NMR: δ / ppm 24.31, 33.76, 37.23, 62.16, 172.86; FT-IR (NaCl, cm⁻¹): 2947, 2871, 1734, 1453, 1385, 1244, 1166, 1077, 992, 749.
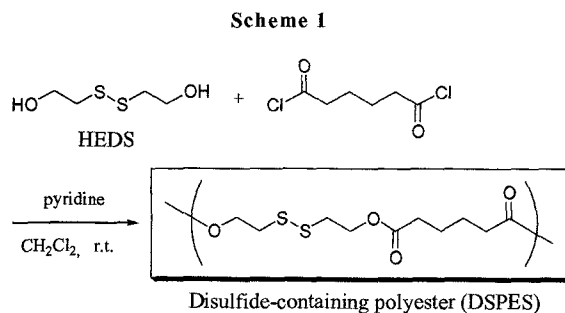
2.3 Polymer reaction

Typical example: A mixture of disulfide-containing polyesters ($M_n = 102700$, $M_w/M_n = 1.13$ as high molecular weight species and $M_n = 21800$, $M_w/M_n = 1.20$ as low molecular weight species) was dissolved in anisole (total concentration of disulfide unit: 0.2 M), added benzoyl peroxide (BPO) as free-radical generator, sealed, and heated at 353 K for 24 h.

3. RESULTS AND DISCUSSION

3.1 Synthesis of disulfide-containing polyester

Disulfide-containing polyester (DSPES) was synthesized by polycondensation from HEDS and adipoyl chloride in CH₂Cl₂ in the presence of pyridine at room temperature. Chemical structure of synthesized DSPES is shown in Scheme 1. The corresponding DSPES with $M_n = 28400$, $M_w/M_n = 1.82$ was obtained in 89% yield after purification. The structure of DSPES was confirmed by IR and NMR measurements. Fig. 2 shows the ^{1}H-NMR spectrum of DSPES in CDCl₃. The methylene protons derived from HEDS were observed at 4.34 and 2.92 ppm and those of adipate were observed at 2.36 and 1.67 ppm. ^{13}C NMR and IR spectra revealed the signals of carbonyl group at 172.86 ppm and 1734 cm⁻¹, respectively.

Scheme 1

HO⌒⌒S·S⌒⌒OH + Cl⌒(O)⌒⌒⌒(O)Cl

HEDS

pyridine / CH₂Cl₂, r.t.

Disulfide-containing polyester (DSPES)

3.2 Influence of free-radical generators

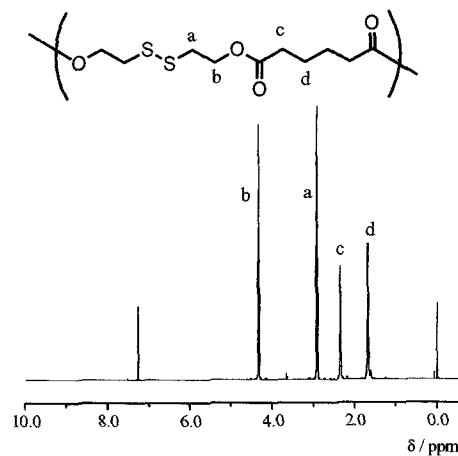To follow the macromolecular radical crossover reaction of DSPES, the reaction behavior of fractionated reaction of DSPES, the reaction behavior of fractionated

Fig. 2 ^{1}H NMR spectrum of DSPES (400 MHz, CDCl₃).

DSPES 1 ($M_n = 41300$, $M_w/M_n = 1.24$) in the presence of free-radical generator (BPO) was investigated. The macromolecular radical crossover reaction of 1 was carried out by heating with 1 mol% of BPO in anisole at 353 K. 1 ([disulfide unit = 0.2 M]) was dissolved in anisole, added BPO as free-radical generator, sealed, and heated at 333 K or 353 K for 24 h. 1 was also heated in anisole without BPO at 353 K for 24 h. The GPC profiles of the resulted polymers are shown in Fig. 3. In the absence of BPO, no significant change in the GPC profile was observed. On the other hand, M_w/M_n of the resulted polymers increased from 1.24 to 1.59 in the presence of BPO at 353 K, which indicates that the radical crossover reaction between the main chains in
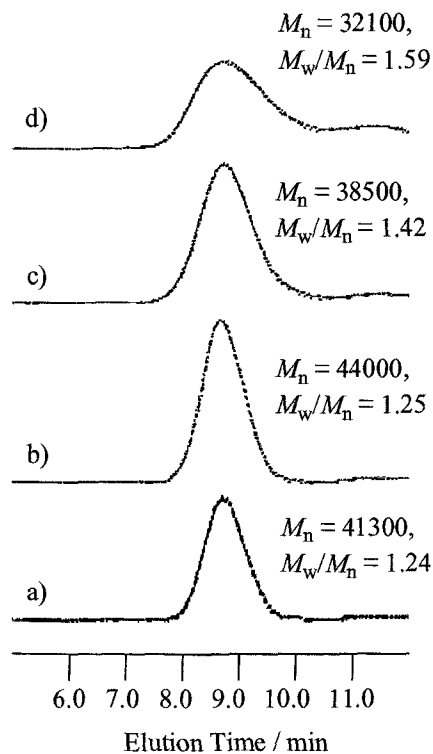

Fig. 3 GPC profiles of DSPES a) before heating, b) after heating without BPO at 353 K and after heating with 1 mol% of BPO at c) 333 K and d) 353 K in anisole for 24 h.

disulfide-containing polymers occurred due to the radical chain transfer reaction of disulfide units. M_n slightly decreased from 41300 to 32100 and the moiety of low molecular weights produced after the reaction. This is probably due to the introduction of the polymer chain end derived from BPO of free-radical generator. In the case of the addition of AIBN instead of BPO as free-radical generator, similar reaction phenomena were observed.

3.3 Influence of reaction time

In order to investigate the influence of reaction time on the macromolecular radical crossover reaction of DSPES, the reaction of fractionated DSPES 2 (M_n = 52700, M_w/M_n = 1.18) was carried out by heating with 1 mol% of BPO in anisole at 353 K. 2 was dissolved in anisole ([disulfide unit = 0.2 M]), added BPO as free-radical generator, sealed, and heated at 353 K. The M_n vs. reaction time and the M_w/M_n vs. reaction time plots are shown in Fig. 4. As the reaction proceeded, M_w/M_n increased to 1.64 and M_n became constant after 6 h, which indicates the radical crossover reaction between the main chains in disulfide-containing polymers occurred and reached to the equilibrium.
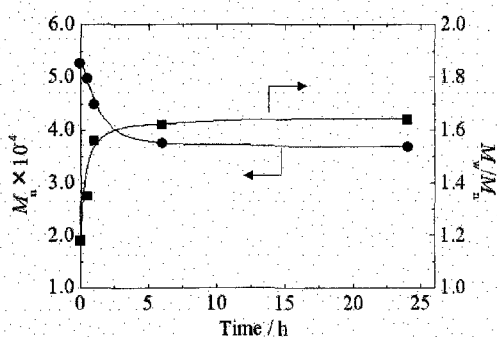

Fig. 4 The M_n and M_w/M_n vs. reaction time plots of 2 (M_n = 52700, M_w/M_n = 1.18) with 1 mol% of BPO in anisole ([disulfide unit = 0.2 M]) at 353 K.

By careful fractionation of DSPES using preparative HPLC, two polymers with narrow molecular weight distribution, DSPES 3 (M_n = 102700, M_w/M_n = 1.13) and DSPES 4 (M_n = 21800, M_w/M_n = 1.20), were successfully isolated. The mixture of 3 and 4 showed two apparent peaks in the GPC profile as shown in Fig. 5a. Equal amounts of 3 and 4 were mixed in anisole (total concentration of disulfide units: 0.2 M), sealed, and heated at 353 K. The reaction was carried out in the presence or absence of free-radical generators.

The GPC profiles of the resulted polymers are also shown in Fig. 5b-f. In the presence of 1 mol% BPO as a free-radical generator, as the reaction proceeded, the peaks derived from 3 and 4 gradually fused into a unimodal peak. In contrast, no significant change in GPC profiles was observed in the absence of free-radical generators (Fig. 5f). Therefore, the phenomenon can undoubtedly be attributed to the radical crossover reaction of disulfide units between the main chains triggered by free-radical generators.

3.4 Mechanism of the reaction
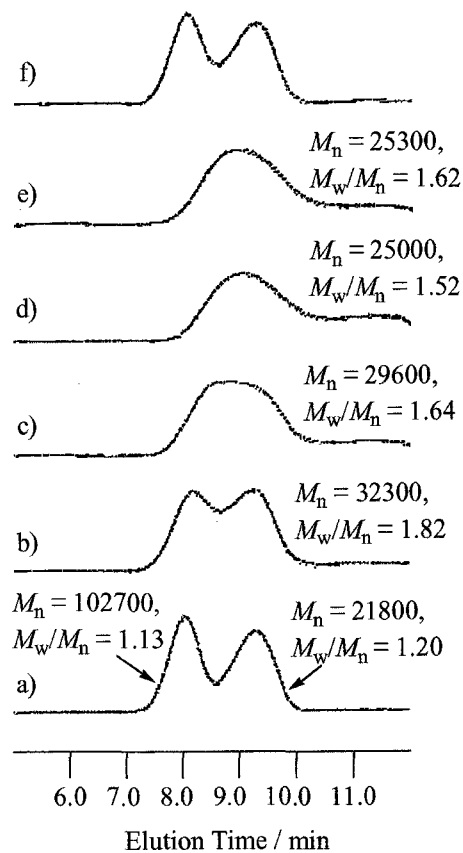
The structure of the resulted polymers was

Fig. 5 GPC profiles of the mixture of DSPESs with different molecular weight a) before heating and after heating for b) 0.5 h, c) 1 h, d) 6 h and e) 24 h with 1 mol% of BPO and f) after heating for 24 h without BPO in anisole (total concentration of disulfide units: 0.2 M) at 353 K.

characterized by NMR measurements. Decomposition of repeating units and generation of byproducts were not confirmed because no significant change was observed in ^1H and ^{13}C NMR spectra before and after the reaction. Although the possibility of the formation of ring compounds was presumed, by NMR measurements the end group analysis of the prepolymer and the obtained polymer at present concentration gave no significant information whether any cyclic compounds were formed or not.

The predictable mechanism of this scrambling reaction was shown in Fig. 6. Disulfide bond cannot dissociate at 353 K. However, in the presence of free-radical generators, the generated radicals attack the disulfide bond and consequently thiyl radicals generate like chain transfer reaction in radical polymerization. The generated thiyl radicals attack the other disulfide bond to generate new thiyl radicals. These repeated reactions are originally triggered by catalytic amount of free-radical generator molecules but attain the macromolecular crossover reaction in total. These findings showed strongly that the disulfide–containing polymers are reorganizable and can dissociate and associate reversibly in the main chain like polyalkoxyamine when triggered by free-radical generator as external stimulation.
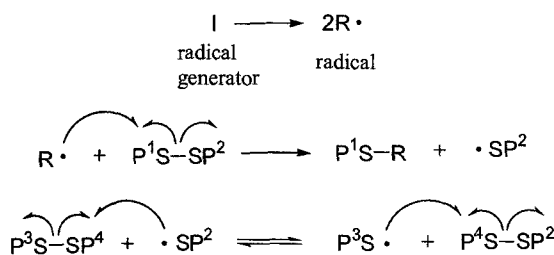
I ⟶ 2R•
radical   radical
generator

R• + P^{1}S–SP^2 ⟶ P^{1}S–R + •SP^2

P^{3}S–SP^4 + •SP^2 ⇌ P^{3}S• + P^{4}S–SP^2

Fig. 6 The predictable mechanism of the scrambling reaction of disulfide-containing polymer in the presence of free-radical generator.

4. CONCLUSION

In summary, the present study demonstrated the possibility of free-radical induced polymer scrambling reaction by incorporating dynamic covalent disulfide bonds into the polymer main chain. The simple and facile polymer reactions based on sulfur-containing dynamic covalent bonds can be applicable to the other types of external stimulation such as catalyst, light, and redox-type radical generating reactions.

5. ACKNOWLEDGEMENT

6. REFERENCES AND NOTES

[1] S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem. Int. Ed.*, **41**, 898-952 (2002).

[2] W. G. Skene and J.-M. Lehn, *Proc. Natl. Acad. Sci. USA*, **101**, 8270-8275 (2004).

[3] H. Otsuka, K. Aotani, Y. Higaki and A. Takahara, *Chem. Commun.*, 2838-2839 (2002); H. Otsuka, K. Aotani, Y. Higaki and A. Takahara, *J. Am. Chem. Soc.*, **125**, 4064-4065 (2003).

[4] W. J. Lees and G. M. Whitesides, *J. Org. Chem.*, **58**, 642-647 (1993).

[5] Kj. Rosengren, *Acta Chem. Scand.*, **16**, 1401-1417 (1962); B. Milligan, D. E. Rivett and W. E. Savige, *Aust. J. Chem.*, **16**, 1020-1029 (1963); K. Sayamol and A. R. Knight, *Can. J. Chem.*, **46**, 999-1003 (1968).

[6] B. Nelander and S. Sunner, *J. Am. Chem. Soc.*, **94**, 3576-3577 (1972); T. Nagano, K. Arakane and M. Hirobe, *Tetrahedron Lett.*, **21**, 5021-5024 (1980); Q. T. Do, D. Elothmani, G. L. Guillanton and J. Simonet, *Tetrahedron Lett.*, **38**, 3383-3384 (1997); Exchange reaction of alkyl disulfide in solution using NO-O$_2$ is reported. T. Itoh, N. Tsutsumi and A. Ohsawa, *Bioorg. Med. Chem. Lett.*, **9**, 2161-2166 (1999).

[7] G. Leandri and A. Tundo, *Ric. Sci.*, **23**, 1646-1648 (1953); *Chem. Abstr.*, **48**, 12699t (1954).

[8] D. T. McAllan, T. V. Cullum, R. A. Dean and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627-3632 (1951); A. J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071-3075 (1960); L. Haraldson, C. J. Olander, S.

Sunner and E. Varde, *Acta Chem. Scand.*, **14**, 1509-1514 (1960); G. Dalman, J. McDermed and G. Gorin, *J. Org.Chem.*, **29**, 1480-1484 (1964); D. N. Harpp and R. A. Smith, *J. Am. Chem. Soc.*, **104**, 6045-6053 (1982).

[9] F. Sanger, *Nature*, **171**, 1025-1026 (1953); I. M. Kolthoff, W. Stricks and R. C. Kapoor, *J. Am. Chem. Soc.*, **77**, 4733-4739 (1955); R. E. Benesch and R. Benesch, *J. Am. Chem. Soc.*, **80**, 1666-1669 (1958); A. P. Ryle, F. Sanger, L. F. Smith and R. Kitai, *Biochem. J.*, **60**, 541-556 (1955); J. L. Kice and G. E. Ekman, *J. Org. Chem.*, **40**, 711-716 (1975).

[10] Disulfide-thiol exchange reaction was reported. For example, G. Dalman, J. McDermed and G. Gorin, *J. Org. Chem.*, **29**, 1480-1484 (1964); L. Eldjarn and A. Pihl, *J. Am. Chem. Soc.*, **79**, 4589-4593 (1957).

[11] L. Field, "Organic Chemistry of Sulfur", Ed. by S. Oae, Plenum Press, New York (1977) Chap. 7.

[12] W. H. Stockmayer, R. O. Howard and J. T. Clarke, *J. Am. Chem. Soc.*, **75**, 1756-1757 (1953); A. V. Tobolsky and B. Baysal, *J. Am. Chem. Soc.*, **75**, 1757 (1953); K. Endo, K. Murata and T. Otsu, *Macromolecules*, **25**, 5554-5556 (1992); T. Suzuki, Y. Nambu and T. Endo, *Macromolecules*, **23**, 1579-1582 (1990); K. Endo, T. Shiroi, N. Murata, G. Kojima and T. Yamanaka, *Macromolecules*, **37**, 3143-3150 (2004); N. V. Tsarevsky and K. Matyjaszewski, *Macromolecules*, **35**, 9009-9014 (2002); G. M. Whitesides, J. Houk and M. A. K. Patterson, *J. Org. Chem.*, **48**, 112-115 (1983); M. Arisawa and M. Yamaguchi, *J. Am. Chem. Soc.*, **125**, 6624-6625 (2003); S.-W. Tam-Chang, J. S. Stehouwer and J. Hao, *J. Org. Chem.*, **64**, 334-335 (1999); S. Otto, R. L. E. Furlan and J. K. M. Sanders, *J. Am. Chem. Soc.*, **122**, 12063-12064 (2000); S. Otto, R. L. E. Furlan and J. K. M. Sanders, *Science*, **297**, 590-593 (2002).

[13] Y. Furusho, T. Hasegawa, A. Tsuboi, N. Kihara and T. Takata, *Chem. Lett.*, 18-19 (2000); Y. Furusho, T. Oku, T. Hasegawa, A. Tsuboi, N. Kihara and T. Takata, *Chem. Eur. J.*, **9**, 2895-2903 (2003); T. Oku, Y. Furusho and T. Takata, *J. Polym. Sci. Part A: Polym. Chem.*, **41**, 119-123 (2003); T. Oku, Y. Furusho and T. Takata, *Angew. Chem. Int. Ed.*, **43**, 966-969 (2004).

[14] F. J. T. Fildes and A. V. Tobolsky, *J. Polym. Sci.: Part A-1*, **10**, 151-161 (1972); K. Endo, K. Murata and T. Otsu, *Polymer*, **33**, 3976-3977 (1992).