Synthesis of Highly Polymerizable 1,3-Benzoxazine Assisted by Phenyl Thio Ether and Hydroxyl Moieties

Asei W. Kawaguchi, Atsushi Sudo, Takeshi Endo

Molecular Engineering Institute, Kinki University, Kayanomori, Iizuka, Fukuoka 820-8555, Japan
Correspondence to: T. Endo (E-mail: tendo@moleng.fuk.kindai.ac.jp)

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INTRODUCTION Benzoxazines have received considerable attention because their ring-opening polymerization provides the corresponding polymers possessing excellent properties such as mechanical strength,[1] thermal stability,[2] and durability under humid environment.[3] Recently, such advantageous features have prompted researchers to develop new approaches to multifunctional benzoxazines involving polymers bearing benzoxazine moieties in main chains,[4–23] side chains,[24–32] and chain ends.[33–35] These approaches have been enabled by preparation of some benzoxazines bearing reactive groups and the selective utilization of the reactive groups orthogonally to the ring-opening reaction of benzoxazine.

Herein, we disclose a new benzoxazine **1** bearing thiol moiety. The reason why we designed this compound was that we expected the highly nucleophilic thiol moiety would react smoothly with various electrophiles to afford the corresponding molecules bearing benzoxazine moieties (Scheme 1). To the best of our knowledge, this article is the first report on synthesis and utilization of benzoxazine bearing thiol group. In this work, epoxide was used as an electrophile that readily accepted the nucleophilic attack of thiol. Thermally induced ring-opening polymerization of the resultant benzoxazine bearing sulfide and hydroxyl moieties is also reported herein.

RESULTS AND DISCUSSION

Scheme 2 illustrates the present approach to a thiol-functionalized 1,3-benzoxazine **1**. The key step in this approach was the selective reduction of disulfide linkage of a bifunctional benzoxazine **2**. We expected that the thiol group of **1** would be efficiently used as a highly nucleophilic anchor that allows introduction of the benzoxazine moiety into various molecules through the nucleophilic reaction of thiol with epoxides.

The precursor **2** was easily synthesized from 4,4′-dihydroxydiphenyldisulfide (DHPDS), which was obtained by oxidative coupling reaction of 4-hydroxythiophenol (Supporting Information Scheme S-1). For transforming DHPDS into **2**, we exploited a method relying on utilization of 1,3,5-triphenyl-1,3,5-triazine (TPTA), which is a cyclocondensate of aniline and formaldehyde (Supporting Information Scheme S-2). The advantage of this method is that one can minimize formation of by-products involving oligomers of benzoxazines and aminomethyl phenols formed by hydrolysis of benzoxazines.[36,37] By heating DHPDS, TPTA, and an equimolar amount of paraformaldehyde, **2** was obtained successfully. As only a negligible amount of by-products contaminated **2**, it was easily purified by recrystallization, leading to the successful confirmation of its purity by elemental analysis. The ^{1}H NMR spectrum of **2** is shown in Figure 1(A). All the signals, which involve two singlet ones at 4.6 and 5.4 ppm for the two methylene groups in the benzoxazine ring, were successfully assigned. The ^{13}C NMR spectrum also supported the chemical structure of **2** (Supporting Information Fig. S-3).

The obtained bifunctional benzoxazine **2** was treated with a combination of triphenylphosphine and water as a reducing agent and a proton source, respectively, for the purpose of cleaving disulfide linkage to afford a novel 1,3-benzoxazine **1** bearing thiol moiety. This reductive cleavage of disulfide was performed in the presence of glycidyl phenyl ether (GPE), based on the expectation that the electrophilic GPE would react with the formed thiol immediately and undergo the ring-opening reaction irreversibly to afford the corresponding adduct **3a**. The reaction was monitored by ^{1}H NMR, leading to the confirmation of the complete consumption of GPE. Analysis of the reaction mixture by thin-layer chromatography also confirmed the complete consumption of GPE, as well as formation of a new product considered as the adduct **3a**. Then, **3a** was successfully isolated by silica gel column chromatography. Figure 1(B) shows the ^{1}H NMR spectrum of

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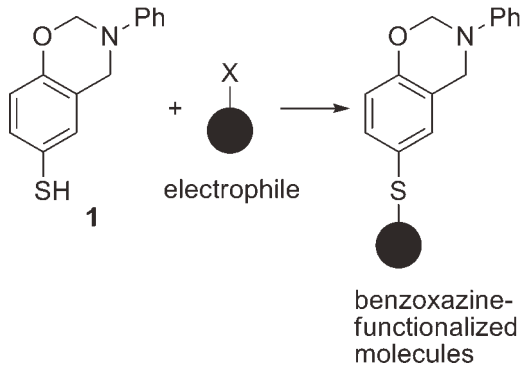
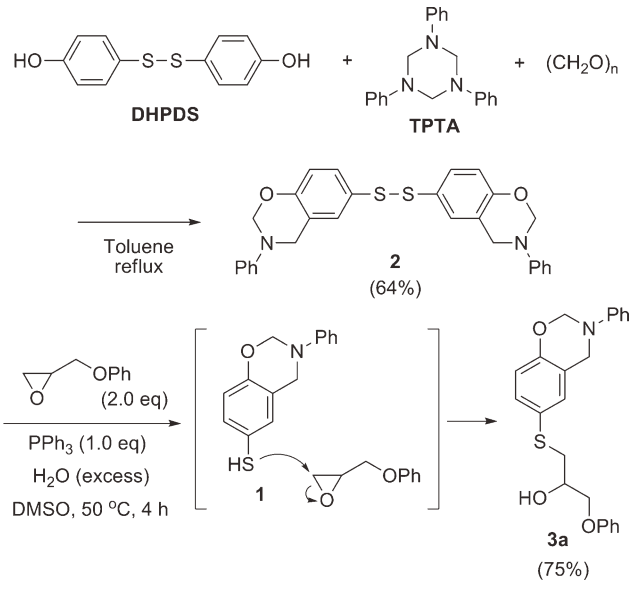


SCHEME 1 New approach to benzoxazine-containing molecules.

3a: All the signals, which involve two singlet ones at 4.6 and 5.3 ppm for the two methylene groups in the benzoxazine ring were successfully assigned. The mutiplet signal at 3.1 ppm was assigned for the methylene group connected to the sulfur atom. The ^{13}C NMR spectrum also supported the chemical structure of **3a** (Supporting Information Fig. S-4).

Thermally induced polymerization of **3a** was carried out at 150 and 180 °C (Supporting Information Scheme S-4). As referential experiments, thermally induced polymerization of *N*-phenylbenzoxazine **3b** bearing methylthio group and that of *p*-cresol-derived *N*-phenylbenzoxazine **3c** were performed under the same conditions. By heating **3a** at 150 °C, 95% of it was consumed within 2 h, showing that the reactivity of **3a** was outstandingly high [Fig. 2(A)]. In comparison, **3b** and **3c** did not convert to the corresponding polymers at 150 °C. At 180 °C, the polymerization of **3a** proceeded much faster, leading to its complete consumption within 1 h [Fig. 2(B)]. Compounds **3b** and **3c** underwent the polymerizations smoothly at this elevated temperature; however, **3a** exhibited much higher polymerizability than these referential benzoxazines. It is noteworthy that **3b** was more reactive than **3c**, to suggest that the sulfide moiety contributed to the accelerated polymerization.



SCHEME 2 Synthesis and utilization of thiol-functionalized benzoxazine **1**.

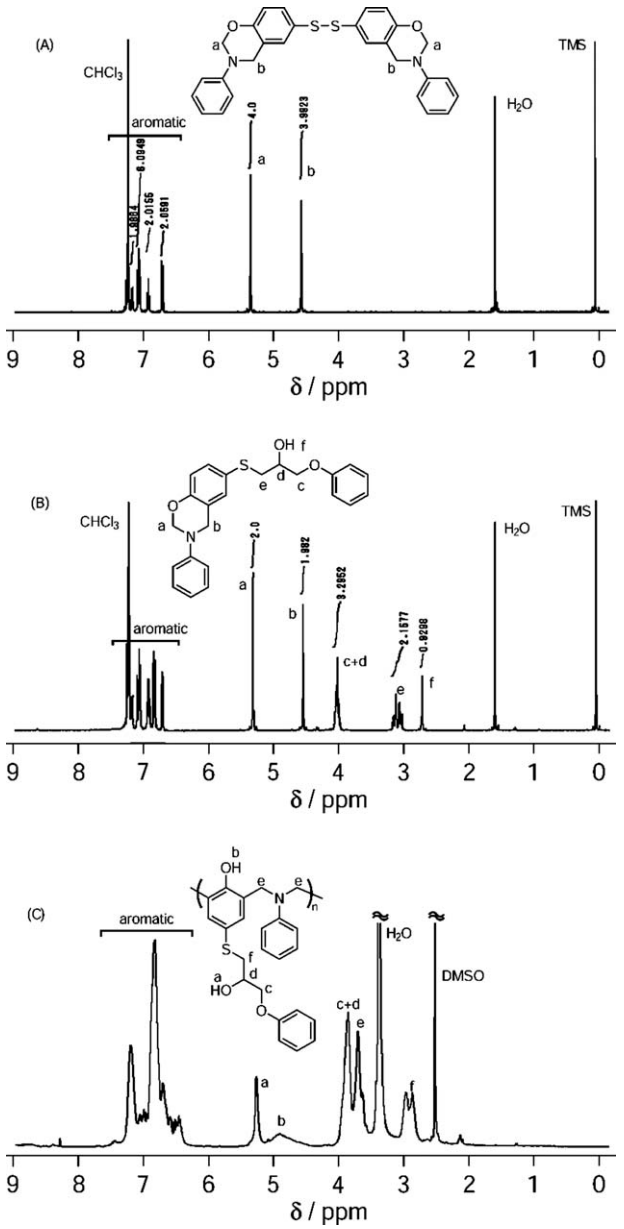


FIGURE 1 ^1H NMR spectra of benzoxazines **2** (A), **3a** (B), and polymer **4a** obtained after heating for 2 h at 180 °C (C).

The remarkably high polymerizability of **3a** could be arisen from two factors of a certain electronic effect of sulfide group and the intramolecular hydrogen bond as described below. A hypothetical role of sulfide group is depicted in Scheme 3. So far, it has been postulated that one of the mechanisms for the ring-opening polymerization of benzoxazines would involve heterolysis of the N,O-acetal ring into the corresponding zwitter ionic intermediate A bearing phenoxide and iminium moieties. This postulation gives us another postulation that one of effective ways to promote the polymerization of benzoxazines can be promoting the

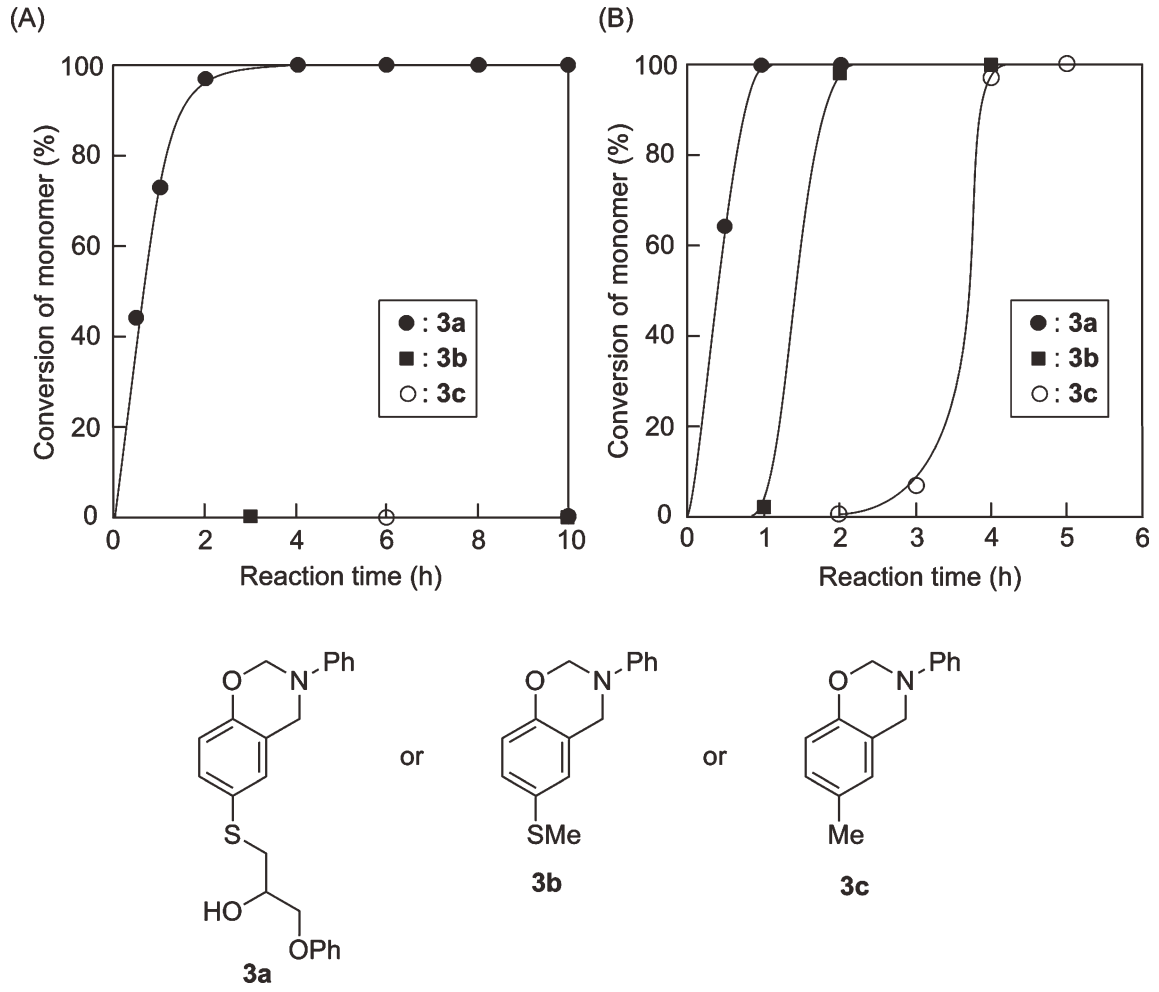
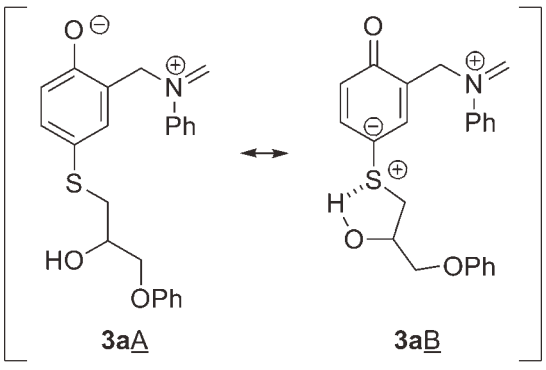


FIGURE 2 Time-conversion plots for the thermally induced polymerizations of benzoxazines: (A) at 150 °C; (B) at 180 °C.

formation of this zwitter ionic intermediate by stabilizing it somehow. In general, sulfur atom can stabilize its adjacent carbanion because the negative charge can be delocalized by the vacant d-orbital of sulfur.[38,39] In one of the mesomeric forms of the zwitter ion B, a negative charge can be located adjacent to the sulfur atom, so that the sulfur atom can contribute to the stabilization of the zwitter ionic intermediate.



SCHEME 3 Plausible acceleration mechanism for polymerization of **3a**.

Particularly in the case of the ring-opening reaction of **3a**, intramolecular hydrogen bonding between the sulfur atom and the hydroxyl group can increase the electron negativity of the sulfur atom to enhance its ability to stabilize the zwitter ionic intermediate.

Figure 1(C) shows the ^{1}H NMR spectrum of polymer **4a** obtained by the polymerization of **3a** at 180 °C for 2 h. At 3.7 ppm, a broad signal that can be assigned for the methylene group between an aromatic ring and nitrogen atom was observed, implying that **4a** was a typical Mannich-type polymer. The spectrum also confirmed that the sulfide moiety bearing hydroxyl group of the monomer was successfully inherited by the polymer as its side chain.

EXPERIMENTAL

Materials

All reagents and solvents were used as received. *p*-Mercaptophenol (90.0%), iodine (99.0%), aniline (99.0%), paraformaldehyde (94.0%), 4-(methylthio)phenol (99.0%), triphenylphosphine (99%), and the other solvents were purchased from Wako Pure Chemical Industries. GPE (99.0%) was obtained from Tokyo Chemical Industry. Synthesis procedures

and ^{1}H and ^{13}C NMR spectra of DHPDS, TPTA, and **3b** are described in the Supporting Information, respectively. Thermally induced polymerization of **3a**, molecular weight, and M_w/M_n of **4a** are also described in the Supporting Information.

Measurements

NMR spectra (400 MHz for ^{1}H, δ_{CHCl3} =7.26 ppm, $\delta_{DMSO\text{-}d_6}$ = 2.40 ppm; 100.6 MHz for ^{13}C, δ_{CHCl3} = 77.00 ppm) were obtained on a Varian NMR spectrometer model Unity INOVA. Chemical shift δ and is given in ppm. Number average molecular weight (M_n) and weight average molecular weight (M_w) were estimated from size exclusion chromatography, performed on a Tosoh chromatograph model HLC-8120GPC equipped with Tosoh TSK gel-Super HM-H styrogel columns (ϕ6.0 mm × 15 cm), using THF as an eluent at the flow rate of 0.6 mL/min after calibration with polystyrene standards.

Synthesis of 2

A mixture of DHPDS (7.50 g, 30 mmol), TPTA (6.3 g, 20 mmol), paraformaldehyde (1.8 g, 60 mmol), and toluene (60 mL) was heated with refluxing for 4 h. The reaction mixture was cooled to room temperature and left overnight at 0–5 °C in a refrigerator (Scheme 1). The resulting precipitate was collected with suction, washed with *n*-hexane, and recrystallized from dichloromethane and *n*-hexane (volume ratio = 2:1) to obtained **1** (9.36 g, 19.4 mmol, 64%) as a white crystal: Melting point = 136–137 °C.

^{1}H NMR (in $CDCl_3$) δ 7.3–6.7 (16H, aromatic), 5.4 (4H, O-CH_2-N), 4.6 (4H, Ar-CH_2-N); ^{13}C NMR (in $CDCl_3$) δ 154.7–117.7 (Aromatic), 154.7 (*C*-O—CH_2), 148.0 (*C*-N(CH_2)CH_2), 128.3 (*C*-S), 79.7 (O-*C*H_2-N), 50.3 (Ar-*C*H_2-N). Elem. Anal. of **1**: $C_{28}H_{24}N_2O_2S_2$: C, 69.39%; H, 4.99%; N, 5.78%, S, 13.23%. Found: C, 69.10%; H, 4.89%; N, 5.74%, S, 12.98%. The spectra are shown in Figure 1 and Supporting Information Figure S-3.

Synthesis of 3a

In a 100-mL round bottom flask, **1** (4.5 g, 10 mmol), triphenylphosphine (2.6 g, 10 mmol), GPE (3.0 g, 20 mmol), water (0.5 mL), and DMF (5 mL) were added. The resulting solution was heated at 50 °C for 4 h under nitrogen. Then, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (120 mL), and washed with brine (200 mL) four times. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was fractionated by flash column chromatography (eluent; ethyl acetate:*n*-hexane = 1:4) to isolate **3a** (5.93 g, 15.1 mmol, and 75%) as a white solid. Compound **3a** (Scheme 1) was further purified by recrystallization from dichloromethane and *n*-hexane (volume ratio = 1:2): Melting point = 100–101 °C.

^{1}H NMR (in $CDCl_3$) δ 7.3–6.7 (13H, aromatic), 5.3 (2H, O—CH_2—N), 4.6 (2H, Ar-CH_2-N), 4.0 (3H, PhO—CH_2—C*H*—OH), 3.1 (2H, S-CH_2), 2.7 (1H, CH_2—O*H*); ^{13}C NMR (in $CDCl_3$) δ 158.4–114.6 (Aromatic), 158.7 (*C*—O—CH_2—CH) 154.1 (*C*—O—CH_2), 148.1 (*C*—N(CH_2)CH_2), 125.5 (*C*—S—CH_2—CH), 79.5 (O—*C*H_2—N), 70.0 (O—*C*H_2—CH), 68.6 (*C*H—OH), 50.2 (Ar—*C*H_2—N). 39.4 (S—*C*H_2—CH). Elem. Anal.: Calcd for $C_{23}H_{23}N_2O_3S$: C, 70.20%; H, 5.89%; N, 3.56%, S, 8.15%. Found: C, 70.08%; H, 5.60%; N, 3.55%, S, 7.90%. The ^{1}H and ^{13}C NMR spectra were shown in Figure 1 and Supporting Information Figure S-4.

CONCLUSIONS

A new strategy for functionalization of 1,3-benzoxazine has been developed based on preparation and usage of a novel 1,3-benzoxazine **1** bearing thiol moiety. The thiol moiety on benzoxazine **1** was generated by reductive scission of disulfide linkage of a bifunctional benzoxazine **2** and was conveniently used for the addition reaction with GPE, to prove the feasibility of our concept that **1** would be an useful building block for synthesizing various benzoxazine-containing molecules based on the high nucleophilicity of thiol that allows its highly efficient reactions with various electrophiles. Another advantage of this strategy is the high polymerization ability of benzoxazine **3a** formed by the reaction of **1** and epoxide, to which the sulfide group located at the para position to the oxygen atom of the benzoxazine would have been contributing to some extent. Further investigation for applying the present strategy based on utilization of the thiol-functionalized benzoxazine **1** to development of various benzoxazine-containing materials is ongoing.

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