Synthesis of Eight-Membered Lactone Having Tertiary Amine Moiety by Ring-Expansion Reaction of 1,3-Benzoxazine and Its Anionic Ring-Opening Polymerization Behavior

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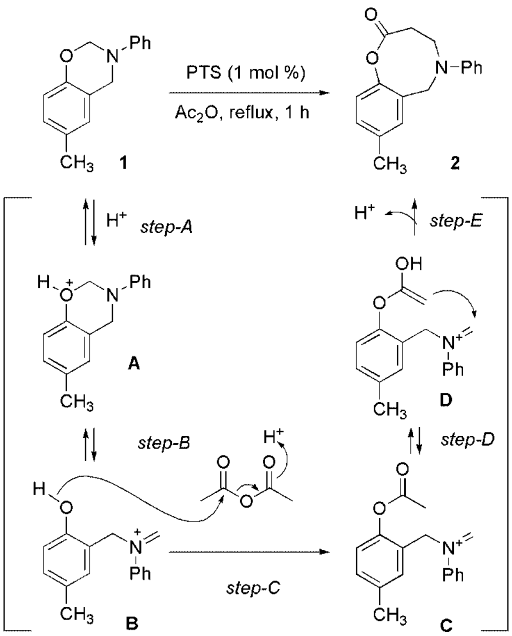
Introduction. 1,3-Benzoxazines are an intriguing class of cyclic compounds, which have attracted considerable attention as cyclic monomers so far. Their ring-opening polymerizations afford corresponding polymers having excellent properties such as high mechanical strength,[1] thermal stability,[2] and durability under humid environment.[3] They can be easily synthesized from various phenolic compounds, amines, and formaldehyde,[4] and their availability in a wide range is the origin of the structural diversity of 1,3-benzoxazines that has allowed the tailored molecular designs for specific applications.[5−15]

Herein, we report another interesting aspect of 1,3-benzoxazine as a new starting material for organic synthesis. As was reported by Donagh and Smith, protonated 3,4-dihydro-2*H*-1,3-benzoxazine is in an equilibrium with the corresponding acyclic species via the reversible heterolytic bond scission of the cyclic *N*,*O*-acetal moiety.[16,17] The acyclic species has a phenol and an imminium moiety, which are potentially a nucleophile and an electrophile, respectively. We focused our attention on this chemical feature of 1,3-benzoxazine that can afford a potentially versatile building block having both nucleophilicity and electrophilicity, of which selective reactions would allow diverse transformations of benzoxazine into a wide variety of functional monomers. In this Communication, a new ring-expansion reaction of benzoxazine **1** is reported. The reaction afforded a new 8-membered lactone **2** having tertiary amine group inside ring (Scheme 1): **1** acted as a precursor for the species B, of which the phenol moiety reacted with electrophilic acetic anhydride. This reaction was followed by an unexpected ring-closure step to give **2**, which underwent the anionic ring-opening polymerization to afford a new polyester having tertiary amine group in the main chain (Scheme 2). To our best knowledge, this is the first example of utilization of 1,3-benzoxazine as a precursor for a new cyclic monomer.

Ring-Expansion Reaction of Benzoxazine. First, a solution of **1** in acetic anhydride was heated at 140 °C; however, GC analysis of the mixture revealed that **1** was not consumed at all even though the reaction time was prolonged to 8 h (Table 1, entry 1). On the other hand, addition of a catalytic amount of *p*-toluenesulfonic acid (PTS) remarkably accelerated the consumption of **1** (entry 2). GC analysis of the reaction mixture indicated formation a small amount of a new compound, which was successfully isolated by silica gel column chromatography. The spectroscopic features of this compound strongly supported that it was an 8-membered lactone **2**: In the ^{1}H NMR spectrum, two triplet signals appeared at 2.78 and 3.75 ppm, which were assigned to the adjoining two methylene groups (c and d) in the lactone ring (Figure 1a). The presence of the ester linkage in the molecule was confirmed by the ^{13}C NMR signal at 172.5 ppm and the IR absorption peak at 1750 cm^{-1}. In addition, the mass/charge ratio (*m*/*z*) observed in the GC/MS analysis was 267, which was same as the calculated mass number of **2**.

Scheme 1



Scheme 2

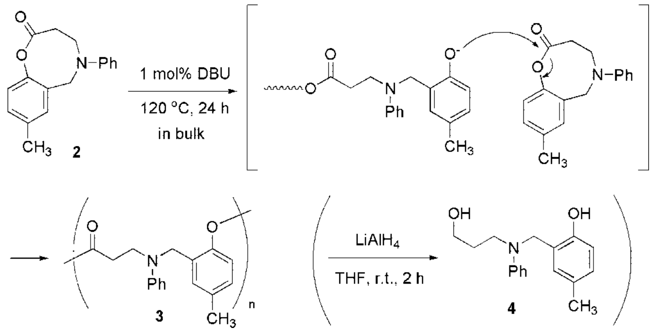


Table 1. Synthesis of Monomer 2

run	[**1**]$_0$/M	temp/°C	time/h	conv/%^{a}	yield **2**/%^{a}
1^b	0.5	140	8	0	0
2	0.5	140	1	56	15
3	0.5	140	8	90	12
4	0.025	140	1	78	28
5	0.5	reflux^c	1	90	70

^{a} Determined by GC. ^{b} The reaction was performed in the absence of PTS. ^{c} The temperature outside of the vessel was set to 150 °C.

Encouraged by this successful isolation of a new lactone, more suitable reaction conditions were surveyed. When the reaction time was prolonged to 8 h at 140 °C (entry 3), consumption of **1** increased but yield of **2** was not improved, presumably due to a competition between the thermodynamically disfavored cyclization into the 8-membered ring and other reactions involving oligomerization of **1**. Therefore, in entry 4, the initial concentration of **1** was lowered on the assumption that such a lower concentration would be favored by the intramolecular reaction. As a result, the yield was improved indeed but was not satisfactory yet. Finally, the temperature

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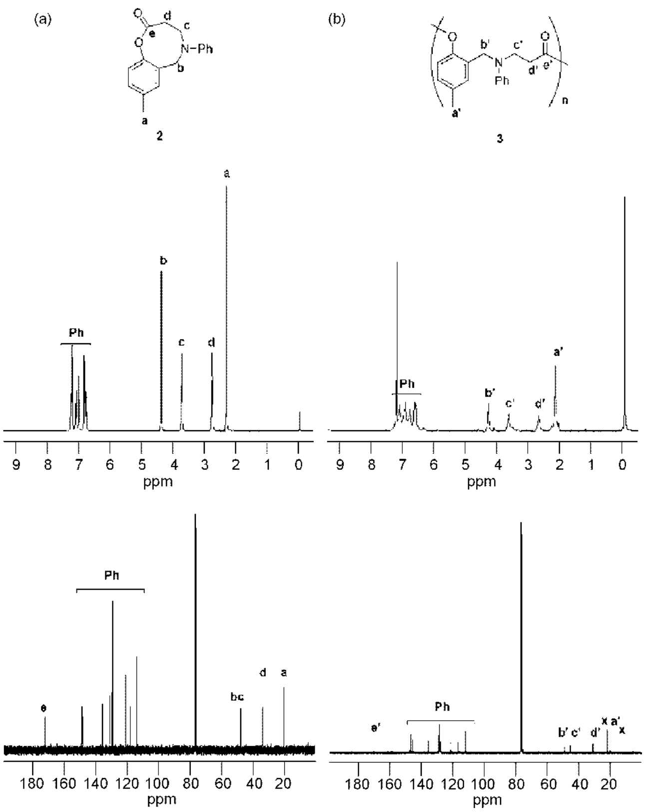

Figure 1. ^{1}H and ^{13}C NMR spectra of (a) lactone **2** and (b) polymer **3**.

outside of the vessel was raised to 150 °C so that the solution kept refluxing. 90% of **1** was consumed within 1 h, and at the same time, the yield of **2** increased remarkably.

Possible reaction pathways involved in this ring-expansion reaction are shown in Scheme 1. The initial step is protonation of **1** at the oxygen atom. The protonated benzoxazine **A** can undergo a ring-opening reaction to afford the corresponding species **B** having a phenol and an imminium moiety. The phenol group should be enough nucleophilic to react with acetic anhydride to give the adduct **C**, of which the acetyl moiety would be in a tautomerism with the enol moiety in the species **D**. The final step is a cyclization reaction of **D** into the lactone **2** through an intramolecular nuclophilic reaction of the enol to the imminium moiety.

Anionic Ring-Opening Polymerization of Lactone 2. Ring-opening polymerization of cyclic monomers having heteroatoms as constituents is a highly reliable method to deliver those heteroatoms into the main chain of the resulting polymers. Wang et al. have reported the ring-opening polymerization of *p*-dioxanone, and Albertsson et al. have reported the ring-opening polymerization of 1,5-dioxepan-2-one.[18,19] These polymerizations afforded the corresponding polyesters, of which main chains inherited the ether moiety from the monomers. Lactone **2**, which was obtained by the ring-expansion reaction of benzoxazine **1**, is a new class of monomer that possesses a nitrogen atom as a constituent of the ring structure, and thus its ring-opening polymerization would afford a polyester having tertiary amine moiety in the main chain.

Anionic polymerization of **2** was carried out with using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as an anionic initiator (Scheme 2). A mixture in bulk was heated at 120 °C with tracking the consumption of **2** by GC analysis of the mixture. Figure S1 in the Supporting Information shows the resulting time−conversion relationship, which revealed 90% of **2** was consumed within 4 h. From the mixture, the formed polymer **3** was separated as a hexane-insoluble fraction in 73% yield and was analyzed by size exclusion chromatography (SEC). Number- and weight-average molecular weights (M_n and M_w) of **3** were estimated to be 1600 and 3900, respectively. The relatively low molecular weight of **3** would be due to serious backbiting reaction under the polymerization conditions. We attempted to determine the polymer terminal structure by MALDI-Tof mass spectroscopy; however, the polymer was not successfully ionized. The obtained polymer was a polyester, of which structure was confirmed by NMR spectroscopic analyses (Figure 1b). All signals in the ^{1}H NMR spectrum were assigned to the corresponding protons in the structure of **3**. In the ^{13}C NMR spectrum, a signal at 170.5 ppm was assigned to the carbonyl carbon of the acyclic ester group ($C_{e'}$). Besides these spectroscopic analyses, we examined a reductive scission of the main chain of the polyester **3** with $LiAlH_4$, with expecting the selective formation of the corresponding diol **4**. Indeed, the ester bonds were completely reduced to give diol **4** in 90% yield, and its chemical structure was confirmed by NMR (Figure S2 in the Supporting Information) and IR analyses.

The thermal stability of the polyester **3** was evaluated by TG analysis. The temperatures of 5% and 10% weight loss (T_{d5} and T_{d10}) of the obtained polymer were 234 and 249 °C, respectively, and its DSC analysis revealed that its glass transition temperature (T_g) was 55 °C.

To our best knowledge, the present polymerization would be the first example of homopolymerization of aromatic lactone, whose oxygen atom is directly attached onto aromatic ring, in other words, which has a masked phenol by acylation.[20] Because of this structural feature of the monomer, the propagating species of the polymerization would be a phenoxide-type one. The propagation reaction involves a nucleophilic reaction of this phenoxide-type propagating end to the lactone to induce its ring-opening reaction, leading to the formation of a phenoxide at the chain end again. This “nucleophilic attack of a phenoxide to release a phenoxide” is generally not accompanied by any enthalpy change; however, the increase in entropy by the transformation of the 8-membered ring into the acyclic structure can promote the propagation reaction.

Summary. A reaction of benzoxazine **1** with acetic anhydride was carried out to obtain a new 8-membered lactone monomer, which structure was conformed by spectroscopic analyses. The DBU-initiated anionic ring-opening polymerization of the lactone gave corresponding polyester, which structure was conformed by spectroscopic analyses and reductive cleavage of the polymer.

Experimental Section. *Materials.* Benzoxazine **1** was synthesized according to the reported procedure. *p*-Toluenesulfonic acid, acetic anhydride, phosphate buffer powder (pH = 7.4), $LiAlH_4$, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Wako Pure Chemical Industries and used as received.

Measurements. ^{1}H NMR and ^{13}C NMR spectra were recorded in chloroform-*d* ($CDCl_3$) on a JEOL EX-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer, with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded with a JASCO FT/IR-460 Plus, and the values were given in cm^{-1}. Number- and weight-average molecular weights (M_n and M_w) and polydispersity index (M_w/M_n) were estimated by size exclusion column chromatography (SEC) on a Tosoh HPLC HLC-8120 system, equipped with two consecutive polystyrene gel columns

(G2500HXL, and G5000HXL) and refractive index (RI) and ultraviolet (UV, 254 nm) detectors, using THF as an eluent (flow rate 1.0 mL/min), calibrated with polystyrene standards. Gas chromatography analyses were carried out on a Shimadzu GC-2014. GC/MS chromatography analyses were carried out on a Shimadzu GCMS-QP5050.

Synthesis of Lactone **2**. A solution of **1** (2.25 g, 10.0 mmol) and *p*-toluenesulfonic acid (0.0190 g, 0.100 mmol) in acetic anhydride (20 mL) were refluxed for 1 h. After the reaction, the resulting mixture was dissolved in CH_2Cl_2 (200 mL) and washed with aqueous $NaHCO_3$ solution (500 mL) and distilled water (500 mL). The CH_2Cl_2 layer was dried over magnesium sulfate overnight, filtered, and concentrated under reduced pressure. GC analysis of the crude mixture indicated **2** was given in 70% yield. The residue was fractionated by silica gel column chromatography, and the obtained solid was purified by recrystallized form *n*-hexane to isolate **2** (1.10 g, 1.12 mmol, 40%). ^{1}H NMR (in $CDCl_3$, at 20 °C): 2.33 (s, 3H, CH_3-), 2.78 (t, 2H, $J = 2$, $-CH_2-$), 3.75(t, $J = 2$, $-CH_2-$), 4.40(s, 2H, $-CH_2-$), 6.27−7.27(8H, Ph). ^{13}C NMR (in $CDCl_3$, at 20 °C): 20.83, 33.92, 48.31, 52.63, 114.12, 118.47,121.59, 129.27, 129.89, 130.31, 131.44, 136.16, 148.24, 149.09, 172.46. IR (KBr): 1756 ($-C(=O)-O-$), 744, 687 (Ph) cm^{-1}. GC-MS (*m*/*z*) [M$^+$] 267 (calcd 267.32). Elem Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38%; H, 6.41%; N, 5.24%. Found: C, 76.58%; H, 6.45%; N, 5.25%.

Anionic Ring-Opening Polymerization of **2**. DBU (7.61 mg, 0.050 mmol) and **2** (1.34 g, 5.00 mmol) were mixed in a test tube, and the resulting mixture was heated at 120 °C for 24 h under argon. After the reaction, the crude product was dissolved in THF, and the solution was poured into *n*-hexane. The resulting precipitate was collected by filtration and was dried in vacuo to give polymer **3** ($M_n = 1600$, $M_w = 3900$, 978 mg, 73%). ^{1}H NMR (in $CDCl_3$, at 20 °C): 2.05−2.45 (br, 3H), 2.58−2.86 (br, 2H), 3.45−3.85 (br, $-CH_2-$), 4.15−4.24 (br, 2H), 6.50−7.24 (8H, Ph). ^{13}C NMR (in $CDCl_3$, at 20 °C): 22.62, 31.81, 46.12, 49.76, 112.60, 117.19, 122.03, 128.57, 128.72, 129.43, 129.67, 136.03, 136.24, 147.52, 170.54. IR (KBr): 1753 ($-C(=O)-O-$), 749, 694 (Ph) cm^{-1}. FAB-MS (*m*/*e*) [M + H]$^+$: 272.1656 (calcd 272.1651).

Reductive Cleavage of Polymer **3** *with* $LiAlH_4$. To a suspension of $LiAlH_4$ (0.562 g, 14.8 mmol) in THF (10 mL) was added a solution of **3** (0.978 g) in THF (20 mL) at 0 °C, and the resulting mixture was stirred at room temperature. After 16 h, the solution was carefully poured into a phosphate buffer solution (400 mL, pH = 7.4) at 0 °C. The mixture was extracted with (500 mL), and the organic layer was washed by distilled water, dried over magnesium sulfate, filtered, and was dried in vacuo to give **4** (0.880 g, 3.25 mmol, 90%). ^{1}H NMR (in $CDCl_3$, at 20 °C): 1.70 (quint, 2H, $J = 2$, $-CH_2-$), 2.33 (s, 3H, CH_3-), 3.26(t, 2H, $J = 2$, $-CH_2-$), 3.56 (t, 2H, $J = 2$, $-CH_2-$), 4.30 (s, 2H, $-CH_2-$), 6.70−7.30 (8H, Ph). ^{13}C NMR (in $CDCl_3$, at 20 °C): 20.45, 28.88, 49.42, 56.92, 60.37, 115.82, 120.17, 121.86, 122.59, 128.82, 129.06, 129.15, 129.25, 148.90, 154.41. IR (KBr): 3448, 3156 ($-OH$), 1203 ($-Ph-OH$), 1047 ($-CH_2-OH$), 748, 690 (Ph) cm^{-1}.

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Supporting Information Available: Time−conversion relationship of **2** (Figure S1); NMR and IR spectra of diol **4** (Figure S2).This material is available free of charge via the Internet at http://pubs.acs.org.

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