Macromolecules **2005,** *38,* 6429−6434

Aliphatic Poly(urethane−amine)s Synthesized by Copolymerization of Aziridines and Supercritical Carbon Dioxide

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Received March 15, 2005; Revised Manuscript Received May 12, 2005

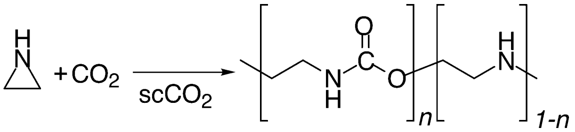
ABSTRACT: A reaction of aziridines and carbon dioxide (CO_2) proceeds under supercritical conditions to give random copolymers containing urethane and amine moieties. The ratio of urethane and amine linkages in the product can be controlled by reaction conditions including temperature and pressure as well as addition of *N*,*N*-dimethylacetamide as a cosolvent. An aqueous solution of the copolymer obtained from 2-methylaziridine and CO_2 undergoes a thermally induced phase transition at a lower critical solution temperature (LCST). The critical temperature is highly sensitive to changes in the primary structure of the products. The use of supercritical CO_2 ($scCO_2$) allows us to construct a functional material through the effective chemical fixation of CO_2.

Introduction

There has been extensive interest in supercritical fluids (SCFs) as alternatives to hazardous organic solvents.[1] The use of SCFs as reaction media potentially leads to higher rates and/or higher product selectivity based on their high gas miscibilities, high diffusivities of solutes, and tunable solvent properties. In particular, CO_2 has been utilized as one of the most suitable media for organic reactions because of its low cost, nontoxicity, nonflammability, and moderate critical point (31.1 °C, 7.38 MPa).[2]

Utilization of CO_2 as a reactant in synthetic processes has been extensively investigated in the past decade. However, few studies of copolymerization using CO_2 as a monomer under supercritical condition have been carried out[3] other than synthesis of aliphatic polycarbonates from epoxides and CO_2 using metal catalysts.[4] Since the early works were reported by Stevens in 1966 and Inoue and Tsuruta in 1969,[5] a significant improvement in the activity and selectivity of the copolymerization has been achieved using well-defined molecular catalysts.[6] On the other hand, distorted three-membered cyclic amines (secondary aziridines) were reported to react with CO_2 to give polymeric products consisting of urethane and amine units even in the absence of a metal catalyst (Scheme 1).[7] The chain growth reaction, involving a successive ring-opening reaction of the aziridines to form polyamines in preference to the copolymerization with CO_2, led to products with insufficient content of the urethane linkage. We have recently reported that the copolymerization of aziridines and CO_2 under supercritical conditions efficiently proceeded to give the corresponding poly(urethane−amine), which exhibited a thermally induced reversible transition property in the aqueous solution around the lower critical solution temperature (LCST),[8] as observed in typical thermoresponsive polymers such as poly(*N*-isopropylacrylamide) (PNIPAAm). This important class of materials has attracted a great deal of interest for potential applications in drug delivery systems,[9] microactuators,[10] and gene-transfection agents.[11] In this paper, we describe details of the copolymerization of aziridines and CO_2 and the influence of the reaction conditions on the structure of the products and the thermoresponsive properties.

Scheme 1. Copolymerization of Aziridine and CO_2



Experimental Section

Materials. 2-Methylaziridine was purchased from Tokyo Kasei Co. and purified by distillation under reduced pressure; other aziridines were synthesized by dehydration of the corresponding amino alcohols with H_2SO_4.[12] These aziridines were stored over sodium hydroxide before use. Liquefied carbon dioxide (99.999%) was purchased from Showa Tansan.

Typical Procedure for Copolymerization. *Caution: since high gas pressures are involved, safety precautions must be taken at all stages of studies*. The reaction was carried out in a 50 mL stainless steel autoclave. To the autoclave filled with argon gas, 2-methylaziridine (8.8 mmol) was introduced with a syringe. Then CO_2 was charged through a cooling apparatus with an HPLC pump. After stirring at 100 °C for 24 h, the reaction was stopped by cooling the autoclave in a dry ice−methanol bath. The autoclave was slowly cooled in the ice bath, followed by the slow release of CO_2. The polymeric product was purified by reprecipitation from methanol/ether to remove low-molecular-weight products, and finally, the product was dried in vacuo.

Measurements. All NMR experiments were performed on a JEOL Lambda 300 spectrometer. The experimental procedures for high-pressure NMR studies have previously been described in detail.[13] C, H, and N elemental analyses were performed on a Perkin-Elmer 2400 analyzer. Urethane con-

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10.1021/ma050549o CCC: $30.25

Table 1. Copolymerization of Aziridines and CO$_2$[a]

aziridine	temp, °C	CO$_2$, MPa	yield, %	urethane content, %
2-methylaziridine	100	22	35	62
2-ethylaziridine	100	10	10	54
2-ethylaziridine	100	22	18	62
cyclohexeneimine	100	10	6	73
2,2-dimethylaziridine	140	22	8	52

[a] Conditions: 50 mL autoclave, aziridine = 8.8 mmol, 24 h.

Table 2. Pressure Effect on the Copolymerization of 1 and CO$_2$[a]

CO$_2$, MPa	yield, %	urethane content, %	LCST, °C	M_w
3	14	32	85	7.0×10^3
10	18	47	64	1.5×10^5
16	22	53	41	1.4×10^5
22	35	62	34	2.7×10^4

[a] Conditions: 50 mL autoclave, **1** = 8.8 mmol, 100 °C, 24 h.

Table 3. Temperature Effect on the Copolymerization of 1 and CO$_2$[a]

temp, °C	yield, %	urethane content, %	LCST, °C
60	0		
80	8	58	67
100	35	62	34
120	18	52	24
140	11	47	28

[a] Conditions: 50 mL autoclave, **1** = 8.8 mmol, CO$_2$ = 22 MPa, 24 h.

tents in Tables 1−3 were calculated from the elemental analyses of the copolymerization products containing urethane and amine moieties. GC-MS analyses were carried out using a Shimadzu QP-5000 spectrometer. Infrared spectra of KBr pellet samples were recorded with a JASCO FTIR-610 spectrometer.

The molar mass distributions of the products were determined by SEC using a dual-detector system consisting of a MALLS device (DAWN-EOS Model, Wyatt Technology) and a refractive index detector set in the direction of the flow. All samples were filtered through Millipore Millex-LG (0.20 μm) before the analyses. SEC-MALLS measurements were carried out at 35.0 °C using Shodex OHpak SB-804HQ and SB-806MHQ columns at the polymer concentration of 10 mg/mL. Eluent was an aqueous solution of 0.2 M NaNO$_3$/0.5 M CH$_3$COOH at a flow rate of 0.5 mL/min. The LCST for the product was measured by monitoring the transparency at 500 nm of a 2.0 wt % of aqueous solution at a rate of heating of 1 °C/min with a temperature-variable UV−vis spectrometer Shimadzu UV-1600PC. The LCST was defined as the onset point in the absorbance curve of the polymer solution during the heating process.

Results and Discussion

Copolymerization of Aziridines and CO$_2$. A reaction of 2-methylaziridine (**1**) with CO$_2$ at 22 MPa and 100 °C in a 50 mL stainless steel autoclave proceeded smoothly without any additives to give viscous crude products. As shown in Figure 1, the ^{1}H NMR spectra of the reaction products revealed the formation of the desired polyurethanes in addition to the lower molecular weight cyclic urethanes, 4-methyl-2-oxazolidinone and 5-methyl-2-oxazolidinone, which are possibly formed by ring expansion of the monomer[14] or by degradation (backbiting)[15] of the product polyurethane. Formation of the five-membered cyclic urethanes was also confirmed by GC-MS analyses of the crude products. Notably, monomer **1** was totally recovered after being heated to 100 °C in the absence of CO$_2$. The polymeric product was purified by reprecipitation from a methanol solution of the crude product into diethyl ether to give a white powder in 35% yield. Size exclusion chromatography coupled with multiangle laser light scattering (SEC-MALLS) analysis indicated that the isolated product was indeed a high molecular weight material ($M_w = 2.7 \times 10^4$). The urethane content in the product can be estimated to be 62% by elemental analysis.

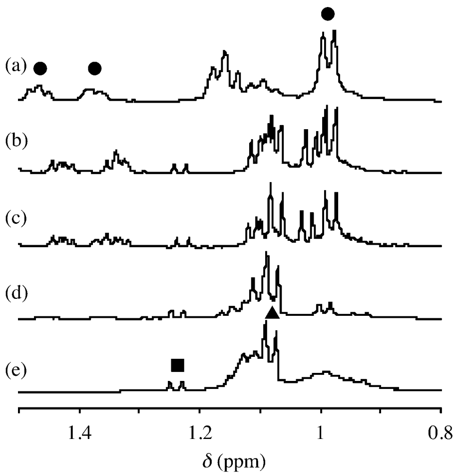


Figure 1. ^{1}H NMR spectra of the crude product prepared from **1** and scCO$_2$ (22 MPa) with various reaction times in D$_2$O as the NMR solvent: (a) 1.0 h, (b) 2.0 h, (c) 4.0 h, (d) 12 h, and (e) 24 h (●, **1**; ▲, 4-methyl-2-oxazolidinone; ■, 5-methyl-2-oxazolidinone).

In a similar manner, 2-ethylaziridine, cyclohexeneimine, and 2,2-dimethylaziridine (**2**) reacted with scCO$_2$ to give copolymerization products. The results of the copolymers obtained at 100 or 140 °C are summarized in Table 1. The reaction of cyclohexeneimine under a pressure of 10 MPa provided a polymeric product with relatively high urethane content (73% urethane linkages).

Notably, the CO$_2$ pressure was found to affect the outcome of the copolymerization. The representative results in the copolymerization of **1** are summarized in Table 2. An increase in the reaction pressure caused the enhancement of CO$_2$ incorporation into the products derived from **1** or 2-ethylaziridine, the urethane content of the product reaching up to 62%. The reaction with subcritical CO$_2$ (3.0 MPa) provided unsatisfactory results in terms of the isolated yields, the urethane content, and the M_w.

The reaction temperature also affected the outcome of the copolymerization as shown in Table 3. When the reaction was conducted at 60 °C for 24 h, the aziridine was mostly consumed, but no solid products were obtained after the reprecipitation. Copolymer with high molecular weight was isolated in 8% yield after the reaction at 80 °C. The maximum yield and urethane content were obtained from the reaction at 100 °C.

Phase Behavior for the Copolymerization under Supercritical Conditions. The outcome of the copolymerization was found to be significantly dependent upon reaction conditions, especially the CO$_2$ pressure, suggesting that the phase behavior of the copolymerization in scCO$_2$ might be varied by the change in the CO$_2$ pressure or the reaction temperature. In fact, as depicted in Figure 2, a high-pressure NMR spectrum of the reaction mixture in scCO$_2$ (40 °C, 8.0 MPa) showed sharp signals due to the monomer **1**, where **1** dissolved in the CO$_2$ medium to form a homogeneous

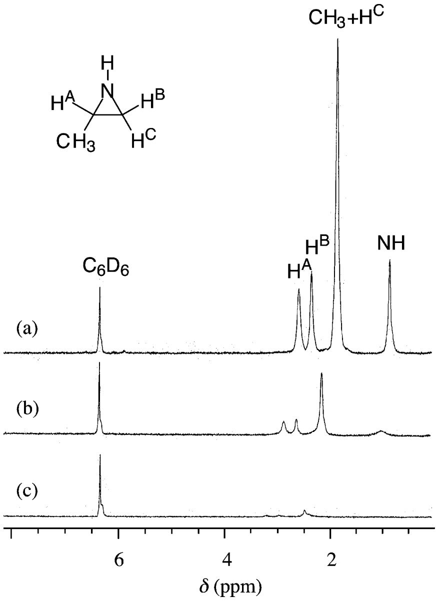


Figure 2. ^{1}H NMR spectra of **1** in $scCO_2$ (40 °C, 8.0 MPa): (a) 0, (b) 1.5, and (c) 17 h.

single phase. These signals became weaker as the reaction progressed, implying that CO_2-insoluble substances might be precipitated from the $scCO_2$ phase during the reaction.

Visual inspection of the reaction phase behavior using a 50 mL high-pressure reactor equipped with sapphire windows revealed that the homogeneous phase containing **1** (8.8 mmol) was observed at the initial stage of the reaction at 100 °C and 22 MPa of CO_2, and the subsequent phase separation by precipitation of the polymeric products from CO_2 phase appeared after 2 h of reaction, as shown in Figure 3a.

To overcome the phase separation due to the lower solubility of the product, we examined the effect of a cosolvent, *N*,*N*-dimethylacetamide (DMAc), which may have a marked affinity to both the hydrophilic polymers and the CO_2 medium.[16] An addition of DMAc to the reaction mixture could cause a marked enhancement of the solubility of the products into CO_2 to provide a homogeneous reaction phase, leading to facilitating chain elongation by introducing CO_2 molecules. In fact, the copolymerization of **1** in $scCO_2$ containing DMAc (1.0 mL) under appropriate conditions gave the polymeric product with a urethane content of up to 74%. These results strongly imply that the supercritical homogeneous phase is a crucial factor for attaining well-controlled copolymerization with CO_2.

Spectral Analysis of Copolymer. Figure 4 illustrates the ^{1}H NMR spectra of the copolymeric products from the monomer **1** and CO_2 at 3.0−22 MPa. The signals due to methyl protons in the products are observed at 0.7−1.2 ppm in each spectrum. The signals assigned to both methylene and methine protons bound to heteroatoms of the amine and urethane linkages should appear in the region from 2.0 to 4.3 ppm. The comparable integral values calculated for the signals at 0.7−1.2 and 2.0−4.3 ppm are in agreement with the structure of the polymeric products, as shown in Scheme 1. Formation of urethane units by incorporation of CO_2 molecules into the polymer can be confirmed with the signals at 3.6−4.3 ppm attributable to protons on the carbon adjacent to the urethane's oxygen. As shown in Figure 4, an increase in the urethane content of the copolymeric products by increasing the reaction pressure resulted in a marked increase in the signals due to urethane units. These NMR data are consistent with the results of elemental analysis listed in Table 2.

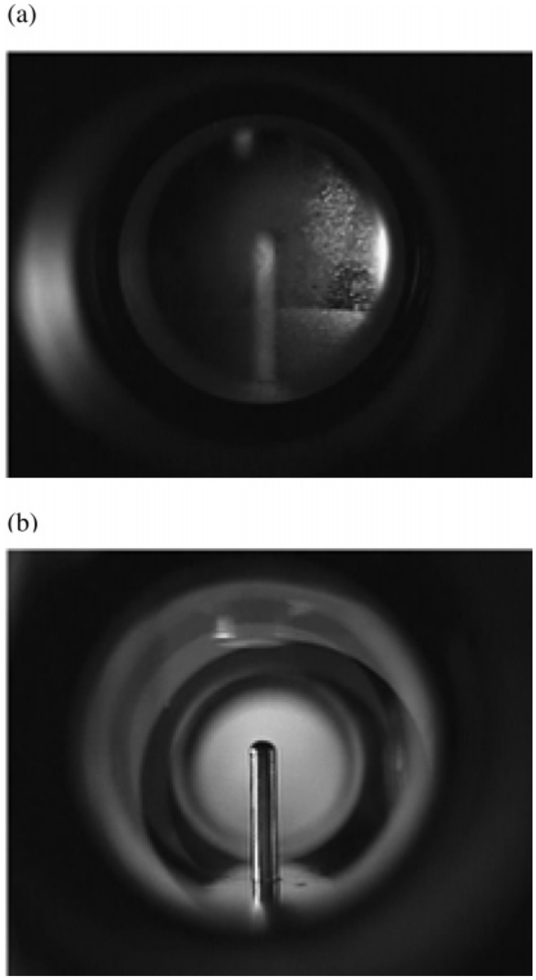


Figure 3. Photographs of the internal of the reaction autoclave after 2 h of polymerization with **1** in $scCO_2$ (22 MPa) (a) without cosolvent and (b) with DMAc *N*,*N*-dimethylacetamide (1 mL).

In contrast to the spectra of the polymers obtained from **1**, the products from 2,2-dimethylaziridine (**2**) gave simple NMR spectra, as shown in Figure 5a. The ^{1}H NMR spectrum of the copolymer prepared from **2** at 100 °C exhibited signals due to the methylene protons adjacent to the urethane oxygen and the amine nitrogen at $\delta = 3.8{-}4.2$ and 2.3−2.6 ppm, respectively. No strong signals assigned to the methylene group bound to the nitrogen atom in the urethane linkage were observed at around 3 ppm, suggesting that the monomer **2** reacts regioselectively. As shown in Figure 5b,c, the ^{1}H NMR spectra markedly changed with the reaction temperature. In particular, the signals due to the methylene group bound to amine moiety were weakened, and the signals at $\delta = 3.0{-}3.6$ ppm assignable to the methylene protons adjacent to urethane nitrogen appeared with increasing reaction temperature.

Figure 6 displays the IR spectra of the products synthesized from **1** and $scCO_2$ at 100 °C. The urethane moiety in the polymer provided sharp peaks at 1710 and 1540 cm^{-1} for carbonyl groups, in addition to the peaks at 1250 and 1080 cm^{-1} due to urethane C−O−C symmetric and asymmetric bending vibrations. Under higher CO_2 pressure, the intensities of these peaks

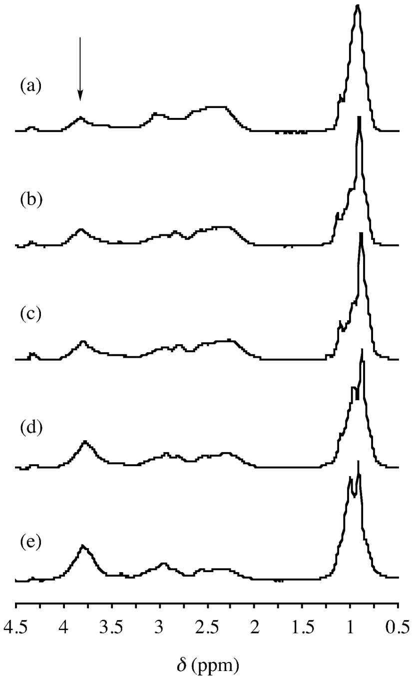


Figure 4. ^{1}H NMR spectra of the polymeric products prepared from **1** and CO_2 at (a) 3.0, (b) 8.0, (c) 12, (d) 16, and (e) 22 MPa.

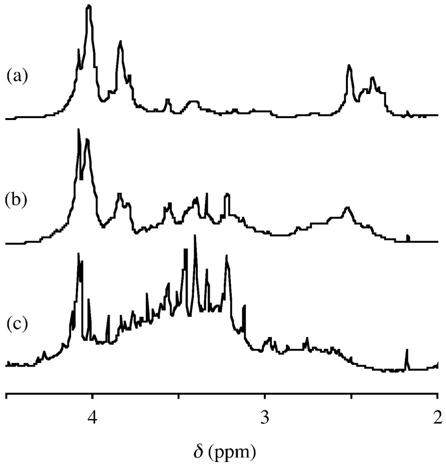


Figure 5. ^{1}H NMR spectra of the products prepared from **2** in $scCO_2$ (22 MPa) at (a) 140, (b) 120, and (c) 100 °C.

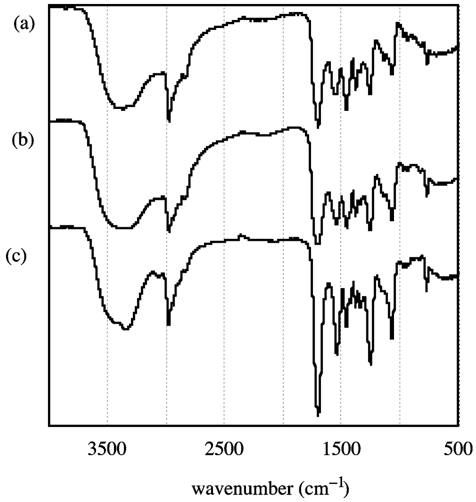


Figure 6. IR spectra of the polymeric products prepared from **1** and CO_2 at (a) 3.0, (b) 12, and (c) 22 MPa.

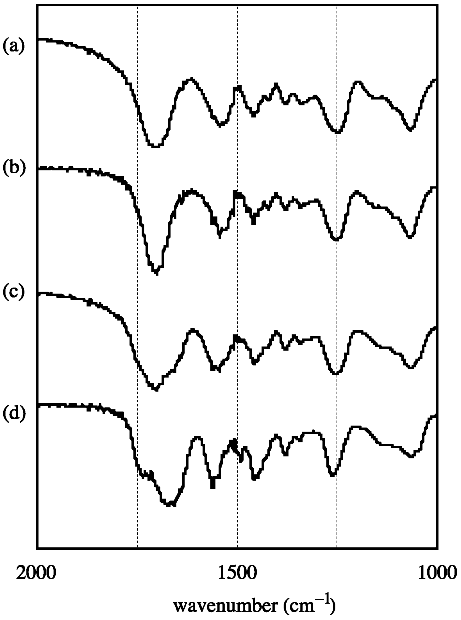
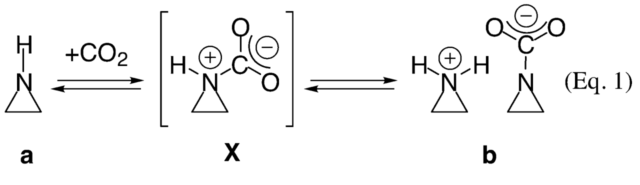


Figure 7. IR spectra of the polymeric products prepared from **1** in $scCO_2$ (22 MPa) at (a) 80, (b) 100, (c) 120, and (d) 140 °C.

increased relatively with increasing urethane content in the product polymer.

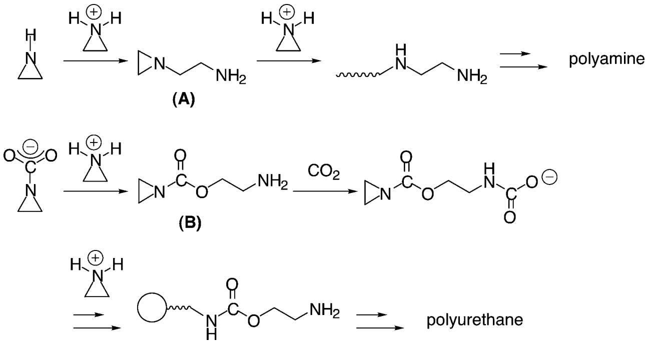
The temperature-dependent change in the IR spectra of polymers was observed, as shown in Figure 7. At higher reaction temperatures, a new peak at 1670 cm^{-1} due to the carbonyl groups in the polymers was observed in addition to the band at 1710 cm^{-1}. Furthermore, a peak at 1540 cm^{-1} related to hydrogen bonding at the urethane's nitrogen decreased in absorbance. These changes in the IR spectra are consistent with the change in the ^{1}H NMR spectra of the product by reaction temperature as shown in Figure 5b,c, indicating that an increase in the reaction temperature caused the side reaction of the secondary amine units in the polymer main chain, leading to formation of the N,N-disubstituted urethane structure as will be discussed later.[17]

Mechanism of Copolymerization. As many primary and secondary amines have been known to reversibly generate the corresponding carbamic acid derivatives by uptaking of CO_2, the monomer cyclic amine (**a**) should exist in an equilibrium with the corresponding ammonium carbamate (**b**) under copolymerization conditions (eq 1).[18] It seems likely that nucleophilic attack of the carbamate anion on an aziridinium cation is favored to a neutral aziridine molecule. Since any transformation of the monomer **1** was not observed under otherwise identical conditions to the copolymerization except for the absence of CO_2, the CO_2-assisted reversible formation of the aziridinium cation might be an essential step for the ring-opening reaction. A plausible mechanism of the copolymerization of aziridine and CO_2 is outlined in Scheme 2.

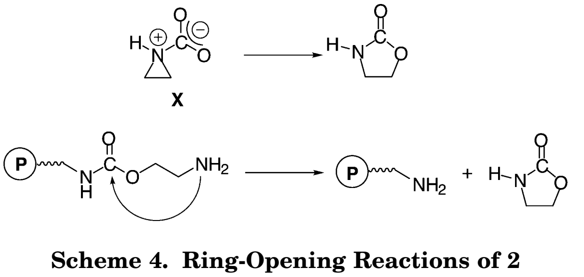


The nucleophilic attack of the aziridine molecule or the carbamate anion on the carbon atom of the aziri-

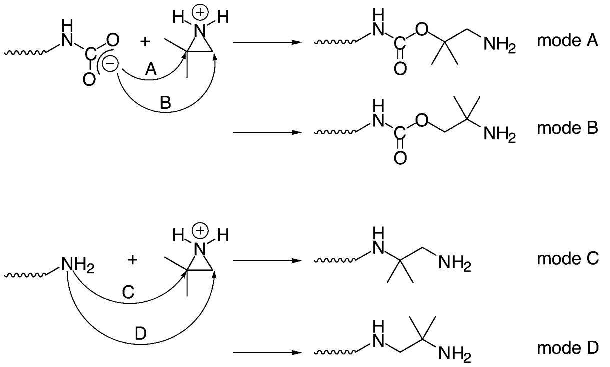
Scheme 2. Plausible Copolymerization Routes of Aziridines and CO_2



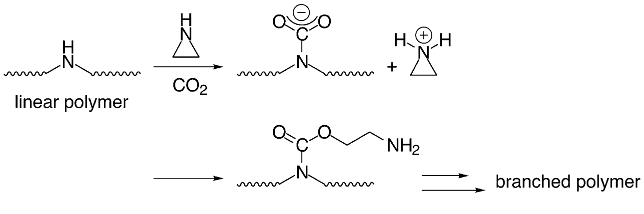
Scheme 3. Possible Mechanisms for the Formation of Cyclic Urethanes



Scheme 4. Ring-Opening Reactions of 2



Scheme 5. Formation of the Branched Structure in the Copolymerization of Aziridines and CO_2



dinium cation provides ring-opening intermediates **A** or **B**, respectively, which will repeatedly react to form the polymeric products, as shown in Scheme 2. The molar ratio of **A** and **B** intermediates might be determined by the concentration of the carbamate anion in the reaction system. The shift to ammonium carbamate in the equilibrium in eq 1 under higher pressure CO_2[19] would result in the preferential formation of the urethane linkages in the copolymerization of aziridines. In fact, the urethane content of the product from **1** was up to 62% under supercritical conditions, whereas the product obtained at 3.0 MPa of CO_2 had only 33% of urethane linkages. The formation of byproducts, such as cyclic urethanes, might be explained either by a rearrangement of the twitter ionic intermediate **X** or by backbiting [15] from the intermediate **B**, as shown in Scheme 3.

Further information on the copolymerization mechanism was obtained with separate experiments. When the substituted aziridine **2** is used as a monomer, there are two possible ring-opening modes in terms of the regioselectivity in the formation of the urethane, as illustrated in Scheme 4. If the carbon−nitrogen bond cleavage in the aziridinium cation occurred on the sterically hindered side (mode A), the resulting urethane nitrogen would be attached to the methylene group, while the ring-opening at the less hindered carbon atom should give the products bearing the methylene units bound to a urethane oxygen atom (mode B). These methylene proton signals might be distinguishable by the chemical shifts in the ^1H NMR spectrum. As shown in Figure 5a, the ^1H NMR spectrum of the reaction products of **2** and CO_2 shows the typical signals for the methylene group bound to the urethane's oxygen at $\delta = 3.8-4.3$ ppm, indicating that the ring-opening takes place via the attack of the carbamate oxygen on the less hindered carbon and the methylene carbon−nitrogen scission (mode B). In a similar way, the formation of amine moieties in either mode C or D provides products with a methylene group in the α-position to the amino group. The ^1H NMR spectrum in Figure 5a shows the signals due to these methylene protons at around 2.5 ppm. Notably, when the reaction temperature was increased up 140 °C, IR and NMR spectra of the reaction products dramatically changed, as discussed in the previous section (see Figures 5b,c and 7). These can be explained as a result of the side reaction caused by the secondary amine in the polymer main chain to give branched polymers containing the N,N-disubstituted urethane structure, as shown in Scheme 5.

Thermoresponsive Properties. The product copolymers were soluble in aqueous solutions but underwent a phase transition in response to thermal stimulus. Figure 8 shows the UV−vis light transmittance measurements ($\lambda = 500$ nm) of 1 wt % solutions of the copolymers of **1** determined at temperatures ranging from 20 to 90 °C. The transmittance of the solution of product prepared at 3.0 MPa of CO_2 decreased gradually above 80 °C, while the products obtained under supercritical conditions showed quick and reversible phase transition behaviors around the LCST. The LCST of copolymer was strongly affected by the polymerization conditions. As seen from Table 2, an increased in the pressure of CO_2 from 3.0 to 22 MPa caused a significant drop of the LCST of the product from 85 to 34 °C. When the reaction temperature was increased from 80 to 120

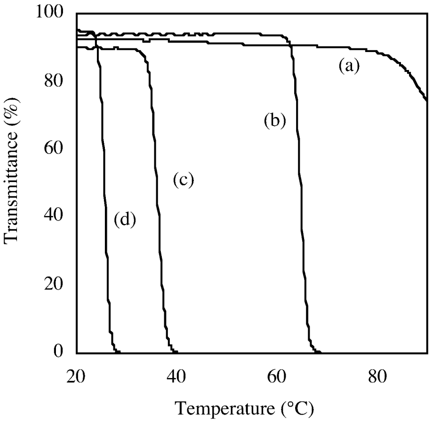


Figure 8. Light transmittances of 2.0 wt % aqueous solutions of the copolymeric products from **1** at (a) 100 °C, $CO_2 = 3.0$ MPa, (b) 100 °C, $CO_2 = 10$ MPa, (c) 100 °C, $CO_2 = 22$ MPa, and (d) 120 °C, $CO_2 = 22$ MPa.

°C, the LCST was decreased from 67 to 24 °C, as listed in Table 3.

Controlling Factors for Determining the Thermoresponsive Properties of the Copolymers. Since the thermally induced phase transition behavior in the aqueous solution is attributed to the dehydration and hydrophobic aggregation of the polymers, a suitable balance of the both hydrophilic and hydrophobic moieties in the polymer structures should determine the thermoresponsive properties.[20] It has been reported that control of the LCST of PNIPAAm copolymers can be attained by employing hydrophilic and hydrophobic monomers.[21] The influence of CO_2 pressure on the LCST of the copolymeric product from **1** as shown in Figure 8 can be simply explained by the fact that the unit ratio of the hydrophilic amine moiety in the polymer chain to the relatively hydrophobic urethane moiety was precisely controlled by the reaction pressure and temperature. The increase in the urethane content in the copolymers obtained under higher pressure could have led to a lowering of the LCST with a decrease in the hydrophilicity of the polymers (Table 2). However, on the other hand, the reaction temperature proved to be the dominant factor in determining the LCST rather than the urethane content in the copolymer, especially for the products obtained at 120 and 140 °C as discussed above (Table 3). The formation of branched structures might cause a loss in the NH protons in the polymer chains, leading to lowering of the hydrophilicity of the whole copolymer[22] and a drop in the LCST, even if the ratio of urethane and amine linkages were not altered.

Conclusions

We have demonstrated that copolymerization of aziridines with CO_2 proceeded smoothly without any catalysts under $scCO_2$ to give the polymeric products having a thermoresponsive functionality covering a wide temperature range. Since their primary structures and physical properties have proven to be strongly influenced by external polymerization conditions, the thermoresponsive properties can be simply tuned by reaction conditions, in particular the CO_2 pressure. Current efforts involve the exploration of other properties, the analysis of this copolymerization mechanism, and the use of other aziridine families as monomers.

Acknowledgment. This work was financially supported by a Grant-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan (No. 14078209). A part of this study was supported by the 21st Century COE Program. The authors thank Dr. Y. Sato and Professor A. Maruyama of Kyushu University for performing temperature-controlled UV−vis spectroscopy.

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MA050549O