

Double stimuli-responsive behavior of aliphatic poly(urethane-amine)s derived from supercritical carbon dioxide†

Osamu Ihata,^a Yoshihito Kayaki*^a and Takao Ikariya*^b

Received (in Cambridge, UK) 16th December 2004, Accepted 1st March 2005

First published as an Advance Article on the web 10th March 2005

DOI: 10.1039/b418850k

Copolymeric products from 2-methylaziridine and carbon dioxide showed sharp and rapid phase transitions in response to both temperature and pH; the responsive property can be controlled by varying the reaction conditions whilst maintaining the supercritical state.

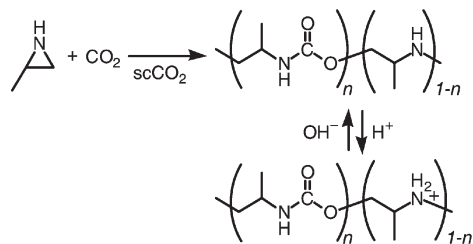
Phase transition behavior of water-soluble polymers in response to external stimuli induced by changes in temperature,¹ pH,² light illumination,³ and electric field,⁴ has attracted a great deal of interest. Among them, thermoresponsive materials exhibiting a lower critical solution temperature (LCST) have been widely investigated as intelligent materials for drug delivery systems,⁵ micro actuators,⁶ sensors⁷ and gene transfection agents.⁸ To develop more sophisticated molecular devices relevant to biomedical applications, by combining responses to plural stimuli, a number of copolymers^{9–12} and interpenetrated polymeric networks¹³ (IPNs) have been designed from components particularly sensitive to temperature and pH.

We have recently synthesized thermoresponsive polymers from aziridines and carbon dioxide (CO₂) under supercritical conditions without catalysts.¹⁴ The reaction of the aziridines with CO₂ proceeds competitively with homo-polymerization of the aziridines, leading to copolymers containing aliphatic urethane and amine units as shown in Scheme 1.¹⁵ A decrease in the amine content of the polymers obtained under supercritical conditions, caused a marked decrease in their LCSTs in water because of the decrease in the hydrophilicity of the polymers. We have explored potential uses of the CO₂-aziridine copolymers and found that, in aqueous solutions, the copolymers show a remarkable phase transition in response to temperature and pH. We now report the

first example of a double stimuli-responsive material derived from CO₂.¹⁶

Table 1 summarizes experimental results in the preparation of the copolymers 1–5, bearing various urethane contents, from 2-methylaziridine and CO₂. LCSTs for 1–5 were estimated from temperature-dependent solution transmittance changes monitored with a UV-vis spectrometer. It should be noted that the LCST of an aqueous solution of a product was strongly influenced by its concentration. As shown in Table 2, when the concentration of 5 increased from 0.10 to 0.80 wt%, the LCST decreased from 69 to 45 °C. It turns out that the pH values of the solutions of 5 increased with their concentrations, ranging from pH 9.2 for 0.10 wt% to pH 9.7 for the 0.80 wt% solution, possibly because the copolymer bears basic amine units. These results imply that phase transition behavior of the solution of 5 could be controlled by a change in pH. In fact, when a solution containing the product 5 was adjusted to pH 10.0 by use of a standard solution of NaHCO₃–Na₂CO₃ (0.025 M:0.025 M), no significant change in the thermoresponsive properties of the solutions was observed, even with a large change in the concentration of 5; the LCST being in the range of 30–32 °C when the concentration was varied from 0.10 to 0.80 wt%.

A sharp stimuli-responsive behavior was observed with a change in the pH value of solutions containing 5 by addition of dilute NaOH and HCl as shown in Fig. 1. The LCST value of the



Scheme 1 Thermo- and pH-responsive poly(urethane-amine) product.

† Electronic supplementary information (ESI) available: experimental details and spectroscopic data for 5 (PDF). See <http://www.rsc.org/suppdata/cc/b4/b418850k/>

*ykayaki@o.cc.titech.ac.jp (Yoshihito Kayaki)
tikariya@apc.titech.ac.jp (Takao Ikariya)

Table 1 Properties of the copolymeric products from 2-methylaziridine^a

| Product | CO ₂ (MPa) | Yield (%) ^c | Urethane content (%) | LCST (°C) |
|---------|-----------------------|------------------------|----------------------|-----------|
| 1 | 3.0 ^b | 25 | 33 | 64 |
| 2 | 8.0 | 19 | 34 | 41 |
| 3 | 12 | 29 | 42 | 37 |
| 4 | 16 | 26 | 54 | 35 |
| 5 | 22 | 35 | 62 | 34 |

^a Conditions: 2-methylaziridine = 8.8 mmol, 100 °C, 24 h. ^b Under subcritical conditions. ^c After re-precipitation.

Table 2 Effect of concentration on LCSTs of the product 5

| Concentration (wt%) | pH ^a | LCST (°C) ^a | LCST (°C) ^b |
|---------------------|-----------------|------------------------|------------------------|
| 0.10 | 9.2 | 69 | 32 |
| 0.20 | 9.4 | 62 | 31 |
| 0.40 | 9.6 | 50 | 31 |
| 0.80 | 9.7 | 45 | 30 |

^a For the solutions prepared by addition of deionized water (see Fig. S3 in ESI). ^b For the solutions adjusted to pH 10.0 by NaHCO₃–Na₂CO₃ standard solution (see Fig. S4 in ESI).

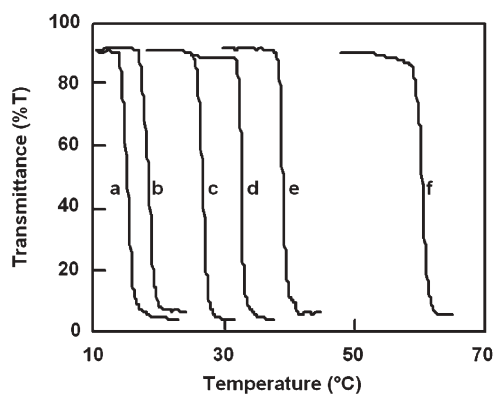


Fig. 1 Light transmittances of 0.80 wt% solutions of **5** adjusted to various pH conditions of (a) pH 12.3, (b) pH 11.7, (c) pH 10.6, (d) pH 10.0, (e) pH 9.5 and (f) pH 9.0.

solution was gradually lowered with an increase of pH, indicating that the thermoresponsive property of the solution was tunable within a wide temperature range, from 15 °C to 60 °C, depending on its pH condition. The phase behavior was not observed in the acidic region below pH 8.

The present multi-stimuli-responsive copolymers are more appealing from the synthetic point of view because the urethane content of the copolymers can be easily tuned just by changes in the reaction conditions. Under similar pH conditions, the LCSTs of the aqueous solutions of **1–5**, with different urethane contents, varied from 64 to 34 °C (Table 1).¹⁷ By changing the pH conditions, the LCSTs of **1–5** proved to be greatly shifted. As shown in Fig. 2, the thermoresponsive behavior of each product was clearly observed in the range of pH 9–13, and the LCSTs increased with increasing urethane content of the products under identical pH conditions. In each case, decreasing pH resulted in the increase of the LCST.

Although the origin of the double stimuli-responsive properties in the CO₂ copolymers is not yet clear, the phase transition behavior suggests that the copolymer chains might undergo the coil-to-globule transition with desorption of water molecules from the chain and hydrophobic aggregation of the colloidal particles.^{1c} Since the amino function in the copolymers would influence the hydrophilicity through an equilibrium between the amine and ammonium forms, an increase in the acidity of the solution should result in an increase in the solubility of the polymer in water, as

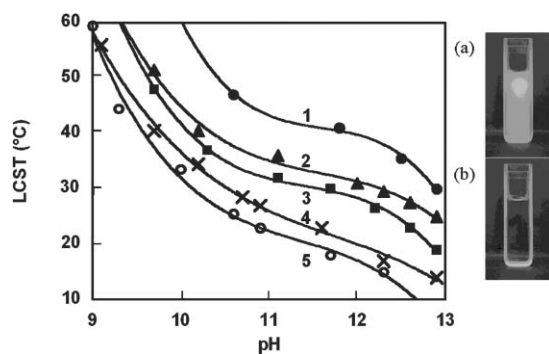


Fig. 2 pH-Dependence of the LCSTs for the products **1–5** and images of the product solution (a) above LCST and (b) below LCST.

observed in other pH-responsive polymers containing amine moieties.^{9a,9b,18}

In conclusion, we have successfully synthesized a new family of smart polymers from 2-methylaziridine and CO₂ under supercritical conditions, which showed sharp and rapid phase transition behaviors, responsive to both temperature and pH. Thanks to pressure- and temperature-tunable physical properties of supercritical CO₂,¹⁹ an appropriate hydrophilic–hydrophobic balance in the structures of the copolymer was achieved. The advantages of scCO₂ as a reaction medium and a reactant offer a sustainable synthetic route to the bifunctional material and permit control of the performance in a wide temperature or pH range due to variable urethane contents.

This work was financially supported by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan (No 14078209) and in part by the 21st Century COE Program.

Osamu Ihata,^a Yoshihito Kayaki^{*a} and Takao Ikariya^{*b}

^a*PRESTO, Japan Science and Technology Agency, 2-12-1, O-okayama, Meguro-ku, Tokyo 152-8552, Japan. E-mail: ykayaki@o.cc.titech.ac.jp; Fax: +81-3-5734-2637*

^b*Graduate School of Science and Engineering and Frontier Collaborative Research Center, Tokyo Institute of Technology, 2-12-1, O-okayama, Meguro-ku, Tokyo 152-8552, Japan. E-mail: tikariya@apc.titech.ac.jp*

Notes and references

‡ CAUTION: operators of high-pressure equipment should take proper precautions to minimize the risk of personal injury.

§ Synthesis of copolymers **1–5**: to an autoclave filled with argon gas, 2-methylaziridine (8.8 mmol) and CO₂ were introduced and then stirred at 100 °C under a pressure of 3.0–22 MPa for 24 h. After re-precipitation, by addition of a methanol solution of the crude product to diethyl ether, the product was obtained as a white powder. The molecular weights of these products were in the range of $M_w = 10^4$ – 10^5 .

- (a) M. Heskins and J. E. Guillet, *J. Macromol. Sci.*, 1968, **A2**, 1441–1455; (b) P. S. Stayton, T. Shimoboji, C. Long, A. Chilkoti, G. H. Chen, J. M. Harris and A. S. Hoffman, *Nature*, 1995, **378**, 472–474; (c) S. Sugihara, S. Kanaoka and S. Aoshima, *Macromolecules*, 2004, **37**, 1711–1719.
- O. E. Philippova, D. Hourdet, R. Audebert and A. R. Khokhlov, *Macromolecules*, 1997, **32**, 8278–8285.
- A. Suzuki and T. Tanaka, *Nature*, 1990, **346**, 345–347.
- Y. Osada, H. Okuzaki and H. Hori, *Nature*, 1992, **355**, 242–244.
- J. Kost and R. Langer, *Adv. Drug Delivery Rev.*, 2001, **46**, 125–148.
- M. E. Harmon, M. Tang and C. W. Frank, *Polymer*, 2003, **44**, 4547–4556.
- T. Miyata, N. Asami and T. Uragami, *Nature*, 1999, **399**, 766–769.
- N. Takeda, E. Nakamura, M. Yokoyama and T. Okano, *J. Controlled Release*, 2004, **95**, 343–355.
- Random copolymers: (a) K. Yamamoto, T. Serizawa, Y. Muraoka and M. Akashi, *Macromolecules*, 2001, **34**, 8014–8020; (b) L. H. Gan, Y. Y. Gan and G. R. Deen, *Macromolecules*, 2000, **33**, 7893–7897; (c) S. Uchiyama, N. Kawai, A. P. de Silva and K. Iwai, *J. Am. Chem. Soc.*, 2004, **126**, 3032–3033.
- Block copolymers: (a) S. Dinçer, A. Tuncel and E. Piskin, *Macromol. Chem. Phys.*, 2002, **203**, 1460–1465; (b) C. M. Schilli, M. Zhang, E. Rizzardo, S. H. Thang, B. Y. K. Chong, K. Edwards, G. Karlsson and A. H. E. Müller, *Macromolecules*, 2004, **37**, 7861–7866.
- Graft copolymers: (a) G. H. Chen and A. S. Hoffman, *Nature*, 1995, **373**, 49–52; (b) S. B. Lee, D. I. Ha, S. K. Cho, S. J. Kim and Y. M. Lee, *J. Appl. Polym. Sci.*, 2004, **92**, 2612–2620.
- Post treatment on a base polymer: Y. Tachibana, M. Kurisawa, H. Uyama and S. Kobayashi, *Biomacromolecules*, 2003, **4**, 1132–1134.
- (a) D. Dhara, C. K. Nisha and P. R. Chatterji, *Macromol. Chem. Phys.*, 2001, **202**, 3617–3623; (b) H. Chen and Y.-L. Hsieh, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 3293–3301.
- O. Ihata, Y. Kayaki and T. Ikariya, *Angew. Chem. Int. Ed.*, 2004, **43**, 717–719.

-
- 15 K. Soga, W. Y. Chiang and S. Ikeda, *J. Polym. Sci., Polym. Chem. Ed.*, 1974, **12**, 121–131.
- 16 E. J. Beckman, *Science*, 1999, **283**, 946–947.
- 17 The LCSTs in Table 1 were measured at unadjusted pH conditions.
- 18 (a) K. Kataoka, H. Koyo and T. Tsuruta, *Macromolecules.*, 1995, **28**, 3336–3341; (b) Y. Haba, A. Harada, T. Takagishi and K. Kono, *J. Am. Chem. Soc.*, 2004, **126**, 12760–12761.
- 19 (a) P. G. Jessop, T. Ikariya and R. Noyori, *Science*, 1995, **269**, 1065–1069; (b) P. G. Jessop, T. Ikariya and R. Noyori, *Chem. Rev.*, 1999, **99**, 475–494; (c) *Green Chemistry Using Liquid and Supercritical Carbon Dioxide*, ed. J. M. DeSimone and W. Tumas, Oxford University Press, New York, 2003; (d) *Chemical Synthesis Using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999; (e) E. J. Beckman, *J. Supercrit. Fluids*, 2004, **28**, 121–191.