

SHORT COMMUNICATIONS

Synthesis of Thermo-Sensitive Poly(*N*-isopropylacrylamide) Gel by Amidation of Poly(acrylic acid) Gel

Takashi IIZAWA,[†] Naoki MATSUNO, Masashi TAKEUCHI, and Fumihiko MATSUDA

Department of Chemical Engineering, Faculty of Engineering, Hiroshima University,
Kagamiyama, Higashi-Hiroshima, 739-8527, Japan

(Received May 6, 1999)

KEY WORDS Gel Capsule / 1,8-Diazabicyclo-[5,4,0]-7-undecene / Amidation / Poly(acrylic acid) Gel / Poly(*N*-isopropylacrylamide) Gel / Thermo-Sensitive /

Poly(*N*-isopropylacrylamide) has been studied widely as a thermo-sensitive polymer for many applications such as drug carriers¹ because it has lower critical solution temperature (LCST) in the vicinity of 32°C.² However, this polymer has not been prepared except by radical polymerization of *N*-isopropylacrylamide. Recently, direct polycondensation using activating agents has been developed.³ Higashi^{3a} reported the synthesis of polyamide with high molecular weight by direct polycondensation of dicarboxylic acid with aromatic diamine using triphenylphosphite (TPP) and pyridine system. Yamazaki and Higashi⁴ studied peptide synthesis using TPP and pyridine system. This synthetic method is applicable to the synthesis of poly(*N*-alkylacrylamide)s from poly(acrylic acid). However, the reaction of carboxylic acid with aliphatic amine shows lower selectivity than that with aromatic amine using this system.

In previous papers,⁵ we investigated heterogeneous esterification of 1,8-diazabicyclo-[5,4,0]-7-undecene (DBU) salt (DAA) of poly(acrylic acid) gel with alkyl halide. The reaction occurred from the surface into the interior gradually. Quantitative esterification gave the corresponding poly(alkyl acrylate) gel through a new amphiphilic core-shell typed gel “gel capsule” consisting of a hydrophilic core gel covered and bound chemically with hydrophobic shell. This reaction system may be applicable to amidation of DAA.

This communication reports the synthesis of poly(*N*-isopropylacrylamide) gel from amidation of DAA with isopropylamine (IPA) in the presence of TPP as an activating agent, and characterizes the resulting gel from the IR spectrum and LCST.

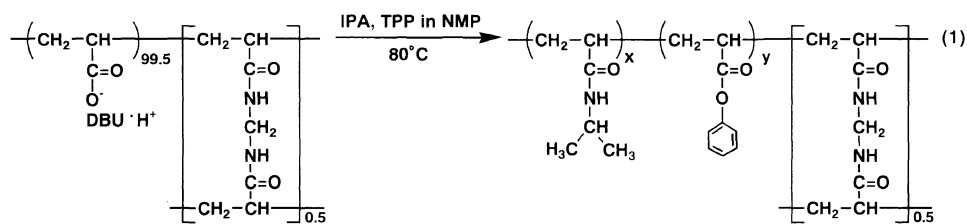
Cylindrical DAA (length and diameter; 5 mm) was prepared in two-steps; copolymerization of acrylic acid with 0.5 mol% of *N,N'*-methylenebisacrylamide in Teflon tubes (internal diameter; 6 mm) and neutralization of the resulting gel with excess DBU in methanol according to previous papers.^{5a,c} Poly(*N*-isopropylacrylamide) gels containing small amounts of acrylic acid or phenyl acrylate unit and *N,N'*-methylenebisacrylamide unit were synthesized by similar polymerization as above. The samples were sufficiently washed with methanol by a Soxhlet extractor, and dried *in vacuo* at 60°C until constant weight. A typical amidation of DAA is as

follows. A mixed solution (50 mL) of IPA (1.0 mol L⁻¹) and TPP (1.0 mol L⁻¹) in *N*-methyl-2-pyrrolidone (NMP) was charged into a 50 mL cylindrical cell in a water bath at 80°C. Cylindrical DAA was dipped in the solution. R_t and r_t of the sample, radii of shell and core after t min, respectively, were periodically observed by a digital video camera (Sony, DCR-VX1000). After the disappearance of the core, unreacted substances and by-products were washed away with methanol and acetonitrile by a Soxhlet extractor. The gel was dried carefully and slowly, and finally dried *in vacuo* at 110°C until constant weight. The degree of amidation was 92.5%, calculated from $A_{\text{ester}}/A_{\text{amide}}$, where A_{ester} and A_{amide} , absorptions at 1755 and 1650 cm⁻¹, respectively. Equilibrium swelling ratio was measured according the method reported^{1b} and is defined as $(W_s + W_p)/W_p$, where W_s and W_p are weights of absorbed water and dried polymer, respectively.

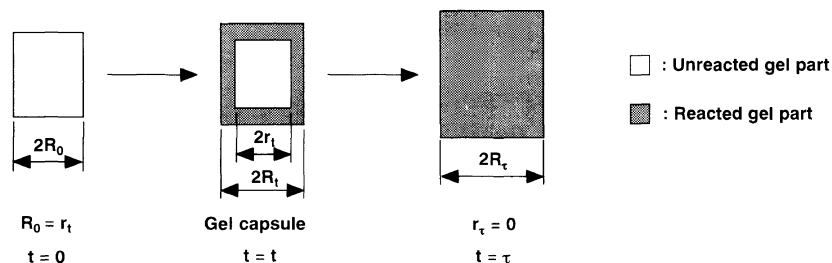
RESULTS AND DISCUSSION

Amidation of cylindrical DAA (length same as diameter; 5 mm) with various concentrations of IPA solution was carried out in NMP using TPP at 80°C. When DAA was placed in NMP containing excess IPA and TPP, swelling occurred and the gel was divided into a swollen shell and unswollen cylindrical core (Scheme 1). The shell expanded with decreasing core size during reaction. At the end of the reaction, the core disappeared. This reaction is similar to esterification of DAA with alkyl bromide.^{5a,b} Surprisingly, the reaction proceeded smoothly without IPA and was independent of the concentration of IPA, although dependent on the concentration of TPP (Figure 1). Complete reaction with various concentrations (1.0, 0.05, and 0 mol L⁻¹) of IPA solution gave gels **I**, **II**, and **III** in the presence of TPP (1.0 mol L⁻¹), respectively. Gel **I** swelled in many solvents such as water, methanol, acetone, benzene, and NMP. Gel **III** hardly swelled in protic solvents such as water and methanol. The IR spectra of the gels are shown in Figure 2. The spectrum of gel **I** showed strong absorptions at 1650, 1545 (amide I and amide II), and 3300 cm⁻¹ (N–H, stretching) and was different from that of poly(acrylic acid) but almost the same as that of poly(*N*-isopropylacrylamide). The spectrum of gel **III** showed strong absorption at 1755 cm⁻¹ (C=O of ester, stretching), which is consistent with that of poly(phenyl

[†] To whom all correspondence should be addressed.



DAA



Scheme 1. Reaction of DAA with IPA using TPP as an activating agent.

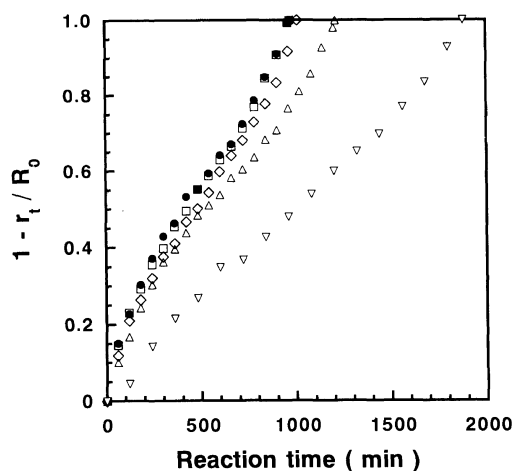


Figure 1. Amidation of DAA with various concentrations of IPA in the presence of TPP in NMP at 80°C. (●) $[\text{IPA}]_0 = 1.0 \text{ mol L}^{-1}$, $[\text{TPP}]_0 = 1.0 \text{ mol L}^{-1}$; (◇) $[\text{IPA}]_0 = 0.05 \text{ mol L}^{-1}$, $[\text{TPP}]_0 = 1.0 \text{ mol L}^{-1}$; (□) $[\text{IPA}]_0 = 0 \text{ mol L}^{-1}$, $[\text{TPP}]_0 = 1.0 \text{ mol L}^{-1}$; (△) $[\text{IPA}]_0 = 1.0 \text{ mol L}^{-1}$, $[\text{TPP}]_0 = 0.5 \text{ mol L}^{-1}$; (▽) $[\text{IPA}]_0 = 1.0 \text{ mol L}^{-1}$, $[\text{TPP}]_0 = 0.3 \text{ mol L}^{-1}$.

acrylate). The content of phenyl acrylate unit in gel **III**, regarded as a copolymer of phenyl acrylate and acrylic acid with 0.5 mol% of *N,N'*-methylenebisacrylamide, was 98.1 mol%, calculated from back-titration using triethylamine solution in tetrahydrofuran (THF) (10 mmol L^{-1})– 10 mmol L^{-1} aqueous HCl solution according to the reported procedure.^{5b} Quantitative esterification of DAA with TPP thus occurs to yield the poly(phenyl acrylate) gel under these conditions. The spectrum of gel **II** showed mixed absorptions based on poly(*N*-isopropylacrylamide) and poly(phenyl acrylate). Absorptions of mixture films of poly(*N*-isopropylacrylamide) at 1650 cm^{-1} (A_{amide}) and poly(phenyl acrylate) at 1755 cm^{-1} (A_{ester}) were measured, and a proportional relation between $A_{\text{ester}}/A_{\text{amide}}$ and molar ratio of phenyl acrylate unit (y) to *N*-isopropylacrylamide unit (x) in the mixtures was obtained. The contents of *N*-isopropylacrylamide units of gel **I** and **II** were 96.1 and 32.0 mol%, respectively, calculated from this relation. These results suggested that the amidation of DAA with IPA takes

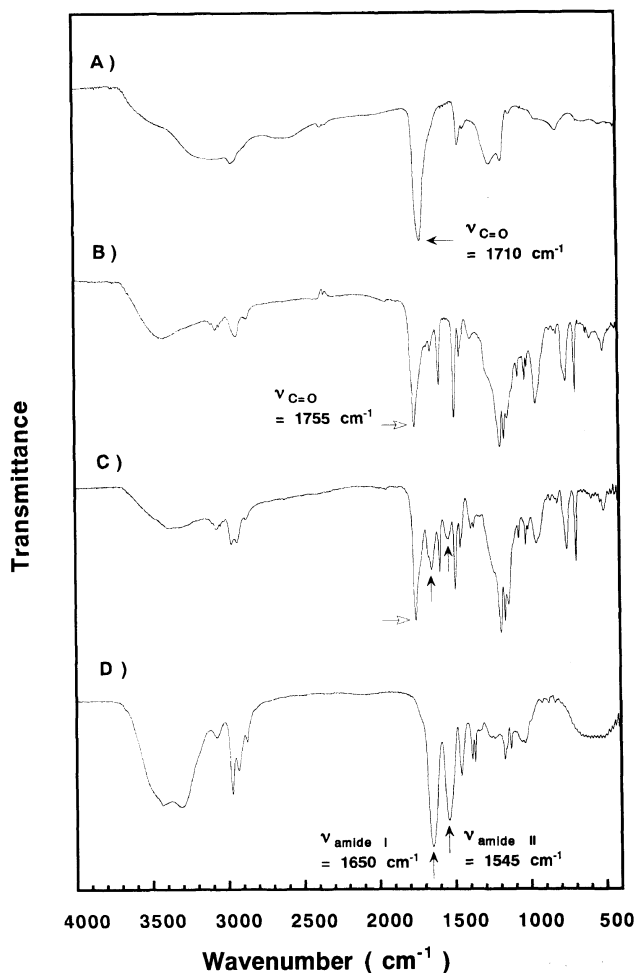
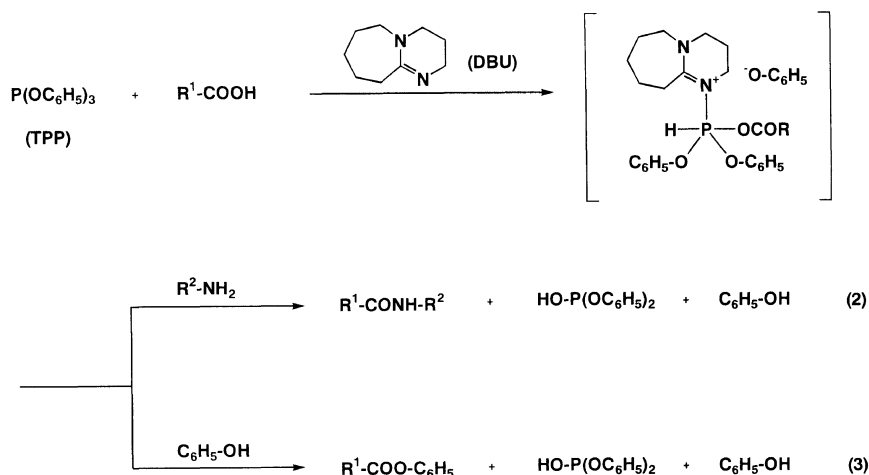


Figure 2. IR spectra (KBr) of A) poly(acrylic acid) gel, B) gel **III**, C) gel **II**, and D) gel **I**.

place preferentially when high concentration ($\geq 1.0 \text{ mol L}^{-1}$) of IPA solution is used. Yamazaki and Higashi⁴ investigated reaction of carboxylic acid with amine using pyridine–TPP or diphenyl phosphite system, and proposed a reaction mechanism through acyloxy *N*-phosphonium salt of pyridine. The reaction of carboxylic



Scheme 2. Reaction mechanism of carboxylic acid with amine using the TPP-DBU system.

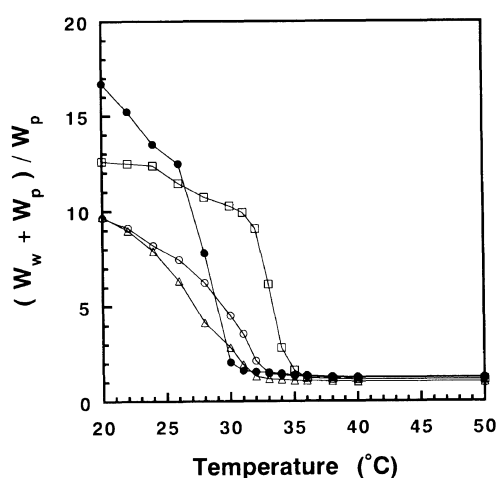


Figure 3. Equilibrium swelling ratio of poly(*N*-isopropylacrylamide) gels in water as a function of temperature; (○) poly(*N*-isopropylacrylamide) gel; (□) poly(*N*-isopropylacrylamide) gel containing 1 mol% acrylic acid unit; (△) poly(*N*-isopropylacrylamide) gel containing 4.8 mol% phenyl acrylate unit; (●) gel I.

acid-DBU salt with IPA in the presence of TPP can be explained similarly as that using TPP-pyridine system as shown in Scheme 2. The formation of intermediate is important for smooth reaction, and may be attributed to balance between basicities of IPA and tertiary amine such as pyridine or DBU. When a weaker base such as pyridine than IPA was used, it was difficult to form the acyloxy *N*-phosphonium salt. However, IPA did not inhibit the formation of intermediate of DBU, because DBU ($\text{p}K_a = 11.5$) is stronger base than IPA and pyridine ($\text{p}K_a = 5.25$). The intermediate can react with IPA and phenol resulting as a by-product to give the corresponding amide and phenyl ester, respectively. Under homogeneous conditions, aminolysis proceeded preferentially, since IPA shows much higher nucleophilicity than phenol. When the intrinsic amidation rate was much faster than diffusion rate of IPA and phenol through the swollen part in the reaction of gel, the concentration of the resulting phenol was high and the concentration of IPA was very low in the reaction zone. Under these conditions, esterification took place in competition with amidation to give the copolymer of *N*-isopropyl-

acrylamide with phenyl acrylate.

Equilibrium swelling ratio of gel I was measured in water at wide range of temperature (Figure 3). LCST of copolymer of *N*-isopropylacrylamide is very sensitive to the content and hydrophilicity of the comonomer unit.^{1b,c} Poly(*N*-isopropylacrylamide) gels containing 0 or 1.0 mol% hydrophilic acrylic acid and 0.5 mol% of *N,N'*-methylenebisacrylamide units show LCST around 32°C and 35°C, respectively. When the obtained gel contained small amounts of unreacted DBU salt or free carboxylic acid, LCST was higher than 32°C. Gel I showed almost the same LCST at about 30°C as copolymer gels (content of phenyl acrylate unit: 4.8 mol%, LCST: about 31°C) obtained from copolymerization of *N*-isopropylacrylamide with 10 mol% of phenyl acrylate in the presence of 3.0 mol% of *N,N'*-methylenebisacrylamide in dimethylformamide. This indicates that the reaction of DAA with excess IPA and TPP proceeds quantitatively to give poly(*N*-isopropylacrylamide) gel with small amount of phenyl acrylate unit.

The amidation of DAA with IPA thus proceeds smoothly in the presence of TPP to afford a copolymer of *N*-isopropylacrylamide with phenyl acrylate. The content of *N*-isopropylacrylamide unit increased with IPA concentration, although the apparent reaction was not affected by IPA concentration. When the concentration was high, amidation occurred preferentially. A gel capsule has been synthesized by selective esterification of external DAA with alkyl halide⁵ and selective thermal acid-catalyzed deesterification of internal poly(*t*-butyl methacrylate) gel in a solvent.⁶ This reaction gives a new gel capsule consisting of a hydrophilic unreacted core and thermo-sensitive shell. Further studies on the amidation of poly(acrylic acid) gel and characteristics of the resulting gel capsule are now in progress.

REFERENCES

- a) Y. Okahata, H. Noguchi, and T. Seki, *Macromolecules*, **19**, 493 (1986); b) T. Okano, Y. H. Bae, H. Jacobs, and S. W. Kim, *J. Controlled Release*, **11**, 255 (1990); c) L. Dong and A. S. Hoffman, *J. Controlled Release*, **15**, 141 (1990); d) R. Yoshida, Y. Haneko, K. Sakurai, T. Okano, Y. Sakura, Y. H. Bae, and S. W. Kim, *J. Controlled Release*, **32**, 97 (1994); e) A. D'Emanuele and R. Dinarvand, *J. Controlled Release*, **36**, 221

- (1995).
2. a) M. Heskins and J. E. Guillet, *J. Macromol. Sci. Chem.*, **A2**, 1441 (1968); b) S. Hirotsu, Y. Hirokawa, and T. Tanaka, *J. Chem. Phys.*, **87**, 1392 (1987); c) S. Fujishige K. Kubota, and I. Ando, *J. Phys. Chem.*, **93**, 3311 (1989).
 3. a) F. Higashi, *J. Synth. Org. Chem. Jpn.*, **47**, 995 (1989); b) M. Ueda, *J. Synth. Org. Chem. Jpn.*, **48**, 144 (1990).
 4. a) N. Yamazaki and F. Higashi, *Tetrahedron Lett.*, **49**, 5047 (1972); b) N. Yamazaki and F. Higashi, *Tetrahedron*, **30**, 1323 (1974).
 5. a) T. Iizawa and F. Matsuda, *Polym. J.*, **30**, 155 (1998); b) F. Matsuda, S. Miyamoto, and T. Iizawa, *Polym. J.*, **31**, 435 (1999); c) F. Matsuda, N. Matsuno, and T. Iizawa, *Kobunshi Ronbunshu*, **55**, 439 (1998).
 6. a) T. Iizawa, T. Fujimoto, and F. Matsuda, *Polym. J.*, **29**, 784 (1997); b) T. Iizawa and T. Fujimoto, *Kobunshi Ronbunshu*, **55**, 490 (1998); c) F. Matsuda, T. Fujimoto, and T. Iizawa, *Kobunshi Ronbunshu*, **55**, 697 (1998).