

Novel Use of Cross-Linked Poly(*N*-isopropylacrylamide) Gel for Organic Reactions in Aqueous Media

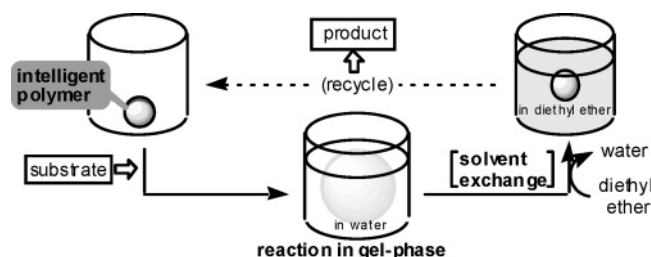
Hiromi Hamamoto, Masahiro Kudoh, Hideyo Takahashi, and Shiro Ikegami*

School of Pharmaceutical Sciences, Teikyo University, Sagamiko,
Kanagawa 199-0195, Japan

somc@pharm.teikyo-u.ac.jp

Received June 26, 2006

ABSTRACT



A poly(*N*-isopropylacrylamide) (PNIPAAm) gel cross-linked with quaternized aminoalkyls was designed. A novel recyclable system based on the external solvent-responsive oil-absorption/elution transition ability of the PNIPAAm gel matrix was then developed.

The study of polymer gels and their response to the external environment such as temperature, solvent, pH, etc. is of special interest¹ because of their potential as drug delivery systems, actuators, and separation devices.² A frequently

studied polymer gel is based on poly-*N*-isopropylacrylamide (PNIPAAm).³ When un-cross-linked PNIPAAm polymers are dissolved in an aqueous solution, the turbidity of the solution varies due to dissolution and precipitation of the polymer. When the polymer chains are cross-linked, the conformational changes lead to macroscopic mechanical change in the polymer network. Such a conformational change in the polymer chain induces a swelling/deswelling transition with the change in external solvent, which allows control of the absorbency of organic substrates.

Utilization of the stimuli-responsive ability of intelligent materials is an important strategy in the creation of efficient reagent or catalyst recycling systems.^{4–8} Previously, the utilization of the temperature-responsive nature of PNIPAAm

(1) (a) Duske, K.; Patterson, D. *J. Polym. Sci. 2-A, Polym. Phys.* **1968**, *6*, 1209–1216. (b) Tanaka, T. *Phys. Rev. Lett.* **1978**, *40*, 820–823. (c) Tanaka, T.; Fillmore, D.; Sun, S.-T.; Nishio, I.; Swislow, G.; Shah, A. *Phys. Rev. Lett.* **1980**, *45*, 1636–1639. (d) Ilavsky, M. *Macromolecules* **1982**, *15*, 782–788. (e) Ohmine, I.; Tanaka, T. *J. Chem. Phys.* **1982**, *77*, 5725–5729. (f) Hirokawa, Y.; Tanaka, T. *J. Chem. Phys.* **1984**, *81*, 6379–6380. (g) Siegel, R. A.; Firestone, B. A. *Macromolecules* **1988**, *21*, 3254–3259. (h) Ilmain, F.; Tanaka, T.; Kokufuta, E. *Nature (London)* **1991**, *349*, 400–401. (i) Annaka, M.; Tanaka, T. *Nature (London)* **1992**, *355*, 430–432. (j) Zhang, Y.-Q.; Tanaka, T.; Shibayama, M. *Nature (London)* **1992**, *360*, 142–144. (k) Chen, G.; Hoffman, A. S. *Nature (London)* **1995**, *373*, 49–52. (l) Yoshida, R.; Uchida, K.; Kaneko, Y.; Sakai, K.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Nature (London)* **1995**, *374*, 240–242.

(2) (a) Hoffman, A. S. *J. Controlled Release* **1987**, *6*, 297–305. (b) Peppas, N. A.; Langer, R. *Science* **1994**, *263*, 1715–1720. (c) Hu, Z.; Zhang, X.; Li, Y. *Science* **1995**, *269*, 525–527. (d) Stayton, P. S.; Shimoboji, T.; Long, C.; Chilkoti, A.; Chen, G.; Harris, J. M.; Hoffman, A. S. *Nature (London)* **1995**, *378*, 472–474. (e) Kanazawa, H.; Yamamoto, K.; Matsushima, Y.; Takai, N.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Anal. Chem.* **1996**, *68*, 100–105. (f) Jeong, B.; Bae, Y.; Lee, H. D. S.; Kim, S. W. *Nature (London)* **1997**, *388*, 860–862. (g) Holtz, J. H.; Asher, S. A. *Nature (London)* **1997**, *389*, 829–832. (h) Park, T. G. *Biomaterials* **1999**, *20*, 517–521. (i) Langer, R.; Tirrell, D. A. *Nature (London)* **2004**, *428*, 487–492. Kim, J.; Nayak, S.; Lyon, L. A. *J. Am. Chem. Soc.* **2005**, *127*, 9588–9592.

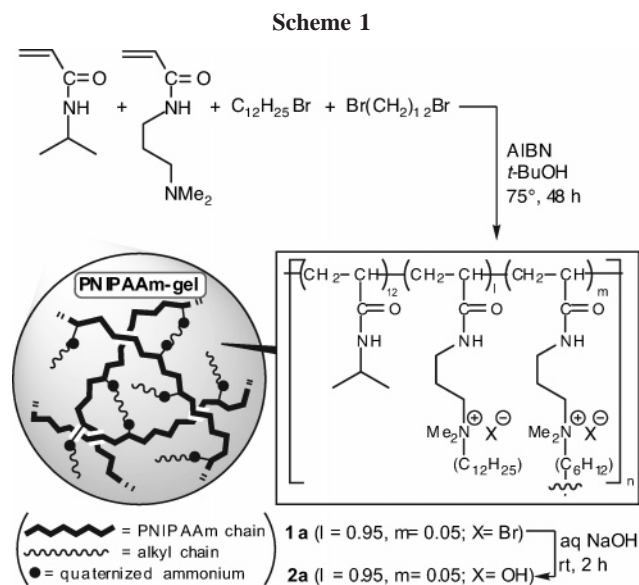
(3) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163–249.

(4) (a) Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319–1324. (b) Kragl, U.; Dwars, T. *Biotechnology* **2001**, *19*, 442–449. (c) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215–3216. (d) Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702–1706.

(5) (a) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174–1196. (b) Hovath, I. T. *Acc. Chem. Res.* **1998**, *31*, 641–650. (c) Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823–3825. (d) Tzschucke, C. C.; Market, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964–4000.

networked by the inorganic species in a catalyst recycling system was achieved.^{9b} Here, we describe the preparation of a new cross-linked PNIPAAm gel and application of its solvent-responsive swelling/deswelling transition ability to design a new recyclable catalytic system.

Previously, un-cross-linked PNIPAAm grafted with quaternized aminoalkyl chains was synthesized in the preparation process of a networked PNIPAAm–tungsten catalyst.⁹ Scheme 1 shows the novel design of a cross-linked PNIPAAm



gel based on a modification of the previous synthesis. Cross-linked PNIPAAm gel (**1a**), which is cross-linked or grafted with quaternized aminoalkyl chains, was prepared by radical polymerization of *N*-isopropyl acrylamide and *N,N*-dimethylaminopropyl acrylamide with the addition of dibromododecane and bromododecane via in situ formation of ammonium salt. The insoluble polymer gel **1a** obtained was treated with aqueous sodium hydroxide to afford PNIPAAm gel with hydroxide form **2a** (Scheme 1).¹⁰

(6) (a) Wang, Y.; Jiang, J.; Zhang, R.; Liu, X.; Jin, Z. *J. Mol. Catal. A* **2000**, *157*, 111–115. (b) Ishihara, K.; Kondo, K.; Yamamoto, H. *Synlett* **2001**, 1371–1374. (c) Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490–11491. (d) Xiang, J. N.; Orita, A.; Otera, J. *Adv. Synth. Catal.* **2002**, *344*, 84–90. (e) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1299–1301. (f) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861–5872.

(7) (a) Zuwei, X.; Ning, Z.; Yu, S.; Li, K. *Science* **2001**, *292*, 1139–1141. (b) Dioumaev, V. K.; Bullock, R. M. *Nature (London)* **2003**, *424*, 530–533.

(8) Selected lead references: (a) Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053–6062. (b) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058–9064. (c) Bergbreiter, D. E.; Hughes, R.; Besinaiz, J.; Li, C.; Osburn, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 8244–8249.

(9) (a) Yamada, Y.; Tabata, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2004**, *60*, 4087–4096. (b) Hamamoto, H.; Suzuki, Y.; Yamada, Y.; Tabata, H.; Takahashi, H.; Ikegami, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4536–4538.

(10) Experimental procedure for the synthesis of cross-linked PNIPAAm gel (**2a**) and characterization data are cited in Supporting Information.

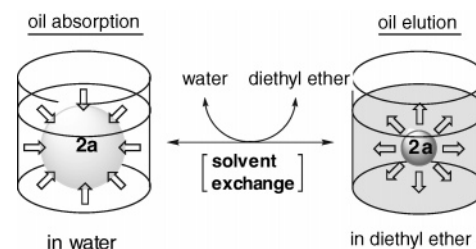


Figure 1. Schematic illustration of the oil absorption/elution transition of PNIPAAm gel (**2a**).

The resulting PNIPAAm gel **2a** showed an interesting absorbency of organic materials responsive to the external solvent (Figure 1 and Table 1). When 2-octanol and **1a** were

Table 1. Recovery of Oil via the Absorption/Elution Process

sample	resin	oil	oil/resin (wt %)	recovery (%) ^a
A	2a	2-octanol (3)	200	95
B	2a	2-octanol (3)	400	97
C	2a	2-octanol (3)	800	96
D	2a	benzaldehyde (4)	400	93
E	2a	acetophenone (5)	400	94
F	Amberlite IRA-900	2-octanol (3)	200	– ^b
G	Amberlyst A-26	2-octanol (3)	200	– ^b

^a Recovery of oil from the ethereal phase. ^b Absorption was not detected.

submerged in water, 2-octanol was absorbed into **1a** (Figure 2A and 2B). The hydrophobic graft chain and cross-linker

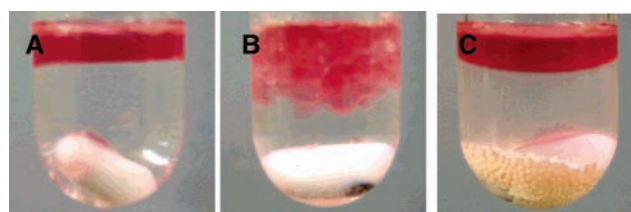


Figure 2. Photographs of a mixture of 2-octanol and water (A) in the absence of a polymer; (B) in the presence of **1a**; and (C) in the presence of Amberlite IRA-900. The oil phase was colored with oil red O dye.

of **1a** result in this notable absorbency in water. Remarkably, the retained oil was released by changing the external solvent to diethyl ether. The recovery rate of 2-octanol in this process was 97%. On the other hand, a similar absorbency was not observed in the presence of commercially available polystyrene-divinylbenzene resin with a quaternized amine unit (Figure 2C and Table 1, samples F and G).

The reaction utilizing an amphiphilic molecule based on the hydrophobic effect in water is an attractive alternative

to achieve an organic solvent-free reaction, although the difficulty in the removal of surfactants often diminishes its utility.^{11–13} Therefore, the use of a recyclable polymeric agent would be advantageous. Because the specific PNIPAAm gel phase in water appears to be an interesting reaction medium, utilization of cross-linked PNIPAAm gel in a new recyclable system utilizing the external solvent-dependent absorption and elution process was examined (Figure 3).

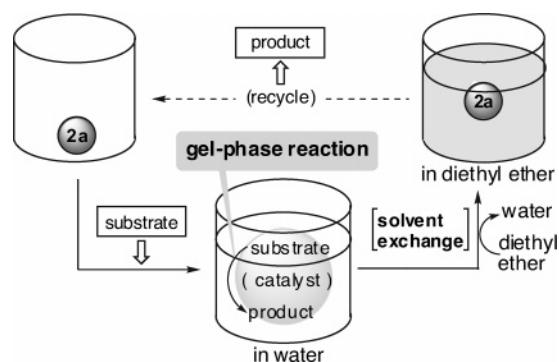


Figure 3. Simplified representation of a novel recyclable catalytic system utilizing **2a**.

In the **2a**-catalyzed Claisen–Schmidt reaction of benzaldehyde (**4**) and acetophenone (**5**), a similar initial absorption of organic materials occurs in water.¹⁴ After replacement of the solution with diethyl ether, chalcon (**6**) was obtained in good yield from the ethereal phase and no extraction process was needed (Table 2, entry 2). Alternatively, the un-cross-linked PNIPAAm catalyst **2b** showed similar reactivity, but this method required extraction with a large amount of diethyl ether because **2b** was soluble in an aqueous solution (Table 2, entry 7). In contrast, cross-linked PNIPAAm gel without a graft-quaternized aminoalkyl chain **2c** showed poor absorbency and moderate catalytic activity. It should be noted that the catalytic activity of **2a** was much greater than that of the quaternary ammonium resin of commercially available polystyrene-divinylbenzene (Table 2, entries 9 and 10), indicating that the novel hydrophobic effect of PNIPAAm gel due to the absorption of organic substrates is responsible for the activity of **2a** in water.

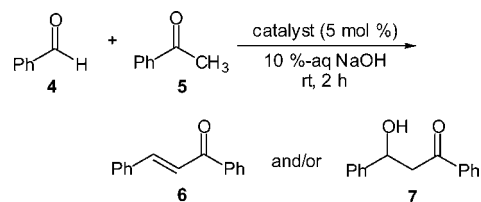
(11) (a) Schwuger, M.-J.; Stickdorn, K.; Schomäcker, R. *Chem. Rev.* **1995**, *95*, 849–864. (b) Tascioglu, S. *Tetrahedron* **1996**, *52*, 11113–11152. (c) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772.

(12) (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074. (b) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169.

(13) (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boulet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234. (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (c) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578–1591. (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

(14) (a) Fuentes, A.; Marinas, J. M.; Sinisterra, J. V. *Tetrahedron Lett.* **1987**, *28*, 4541–4544. (b) Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207–3209. (c) Fringuelli, F.; Pani, G.; Piermatti, O.; Pizzo, F. *Tetrahedron* **1994**, *50*, 1149–11508. (d) Kad, G. L.; Kaur, K. P.; Singh, V.; Singh, J. *Synth. Commun.* **1999**, *29*, 2583–2585. (e) Shimizu, S.; Shirakawa, S.; Suzuki, T.; Sasaki, Y. *Tetrahedron* **2001**, *57*, 6169–6173. (f) Fringuelli, F.; Pizzo, F.; Vittorini, C.; Vaccaro, L. *Chem. Commun.* **2004**, 2756–2757.

Table 2. Organic Solvent-Free Claisen–Schmidt Reaction



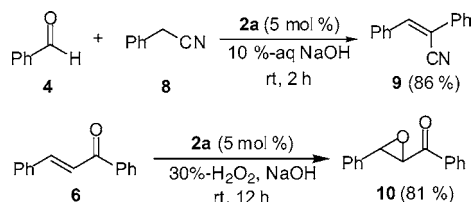
entry	catalyst	yield (%) ^a	
		6	7
1	(none)	8	18
2	2a	89	(<5 ^b)
3	2a (2nd use)	88	(<5 ^b)
4	2a (3rd use)	90	(<5 ^b)
5	2a (4th use)	88	(<5 ^b)
6	2a (5th use)	89	(<5 ^b)
7	2b (<i>l</i> = 1, <i>m</i> = 0)	88	(<5 ^b)
8	2c (<i>l</i> = 0, <i>m</i> = 1)	66	8
9	Amberlite IRA-900	5	21
10	Amberlyst A-26	35	29

^a Yield of isolated product. ^b In gas chromatographic or ¹H NMR analysis.

The catalyst is easily recovered and can be used for consecutive reactions without any significant loss of catalytic efficacy (Table 2, entries 3–6). A typical experimental procedure is as follows: A mixture of benzaldehyde (2 mmol), acetophenone (2 mmol), and **2a** (0.17 g, 0.1 mmol) in 10% aqueous NaOH (2 mL) was stirred for 2 h. After removal of the aqueous phase and washing with distilled water, diethyl ether (4 mL) was added to the gel and stirred for 20 min. Recovered **2a**, which was filtered and washed with diethyl ether (2 mL × 3), was reused for subsequent catalytic experiments. The ethereal phase was dried over MgSO₄. Purification of the residue on column chromatography with silica gel gave chalcon.

The applications of the present system to other reactions were also successful. Similar efficiency was also observed in the nitrile aldol reaction and epoxidation of α,β -enones,¹⁵ and the desired products were obtained in good yields (Scheme 2).

Scheme 2



In conclusion, we have designed a novel cross-linked PNIPAAm gel. The gel can control the absorbency of organic

(15) (a) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (b) Banfi, S.; Colonna, S.; Molinary, H.; Julia, S.; Guixer, J. *Tetrahedron* **1984**, *24*, 5207–5211. (c) Anand, R. V.; Singh, V. K. *Synlett* **2000**, 807–808.

substrates due to external solvent changes. In the development of a new recyclable reaction system, the unique absorbency resulted in an enhancement of catalyst reactivity, simple isolation of organic products, and easy catalyst recycling. The results described herein highlight the potential use of PNIPAAm in the field of organic synthesis. More detailed investigations into the physical properties of **2a** and efforts to extend this system to other types of reactions are currently ongoing.

Acknowledgment. This work was partially supported by a Grant-in-Aid from the Ministry of Education, Culture,

Sport, Science, and Technology, Japan. We thank Ms. J. Shimode and Ms. A. Tonoki (Teikyo University) for performing spectroscopic measurements.

Supporting Information Available: Experimental procedure for the synthesis of cross-linked PNIPAAm gel and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL061562B