(14) Ishigaki, I.; Morita, Y.; Nishimura, K.; Ito, A. *J. Appl. Polym. Sci.* **1974**, *18*, 1927.
(15) Collins, G. L.; Greene, R. K.; Berardinelli, F. M.; Garruto, W. V. *J. Polym. Sci., Polym. Lett. Ed.* **1979**, *17*, 667.
(16) Chien et al. also reported trimodal GPC curves for the ring-opening cationic polymerization of 1,3,6-trioxocane and 2-butyl-1,3,6-trioxocane.[21] They assumed that the fraction eluted with the smallest retention volume corresponded to the linear high molecular weight polymer and the fractions at higher retention volumes were probably the macrocycles.
(17) Okamura, S.; Hayashi, K.; Kitanishi, Y. *J. Polym. Sci.* **1962**, *58*, 925.
(18) This rearrangement, as proposed by the Freiburg group,[9] makes progress at the Ostwald-Ripening mechanism supported by the vaporization-condensation theory of Lifshitz-Slyozov:[22] small particles with a high vapor pressure have a tendency to redissolve and depolymerize into the monomer and large particles further grow by a chain-propagation reaction in order to minimize the excess interfacial free energy of the whole system.
(19) Wunderlich, B. *Fortschr. Hochpolym.-Forsch.* **1968**, *5*, 568.
(20) *Polymer Handbook*, 2nd ed.; Wiley: New York, 1975; p V-63.
(21) Xu, B.; Lillya, P.; Chien, J. *Macromolecules* **1987**, *20*, 1445.
(22) Lifshitz, I. M.; Slyozov, V. V. *J. Phys. Chem. Solids* **1961**, *19*, 35.
(23) Chen, S. H. Catherine; Edwardo, A. D. *Adv. Chem. Ser.* **1969**, *No. 91*, 359.

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Reversible Gelation of Polyoxazoline by Means of Diels-Alder Reaction[1]

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ABSTRACT: Polyoxazoline hydrogel was prepared by means of intermolecular Diels-Alder reaction between furan-modified poly(*N*-acetylethylenimine) (PAEI) and maleimide-modified PAEI, which were synthesized from the partially hydrolyzed PAEIs by the reaction with furan- or maleimidecarboxylic acid, respectively, in the presence of dicyclohexylcarbodiimide. A film was prepared by casting a methanol solution of these two functionalized PAEIs onto a glass slide. After reaction in bulk film in the dark at room temperature for 1 week, the polyoxazoline gel was obtained in a good yield. The film was much swollen in water and stable enough at ambient temperature to be handled. A series of the PAEIs having varying amounts of the functional groups were prepared and subjected to the cross-linking reaction. The swelling degree depended on the content of the functional groups in the prepolymer. These gels were gradually dissolved by heating to regenerate a pair of the starting polymers by the so-called retro-Diels-Alder reaction. This observation shows that the gelation system via Diels-Alder reaction between maleimide moiety and furan moiety in the polymer pendant is thermally reversible. It is the first example of a thermally reversible hydrogel through the covalent bond.

Introduction

Hydrogels are known to be one of the most interesting polymeric materials and have been used in the various fields for several years. The commercially available polymeric hydrogels are usually based on the cross-linked polyelectrolytes such as poly(acrylic acid) salt. A large volume change of the gels with temperature or with solvent has been successfully explained by the phase transition of the cross-linked ionic gel. The generality of these phenomena has been under investigation extensively by Tanaka's group.[2] In aqueous salts, the swelling degrees of these ionic hydrogels are known to be diminished largely in comparison with those of nonionic hydrogels made from poly(oxyethylene)[3] or poly(acrylamide).[4-7] However, less varieties of nonionic hydrogels were prepared than those of ionic hydrogels so far.[8-13]

A thermally reversible hydrogel system prepared from poly(*N*-alkylacrylamide) was also studied for the utilization as a drug delivery system.[14-17] The reversible change of the swelling volume or sol-gel transition with temperature was caused by the change of the physical cross-linking, i.e., the change of the solubility in water. However, very little has been known about the thermally reversible systems through covalent bonds. Only a few examples were demonstrated by using the thermal equilibrium of Diels-Alder reaction.[18-20] However, these covalent cross-linked polymers were studied in view of the polymer processing for thermosetting or thermoplastic properties. Accordingly, they are based on the thermoplastic elastomers such as polyisobutylene[18] or polyphosphazene.[20] No study on the thermally reversible cross-linked polymer system through covalent bonds has been carried out using the hydrophilic polymers. This system may offer a thermally reversible hydrogel through the covalent cross-linkings.

We have been studying the ring-opening polymerization of 2-methyl-2-oxazoline (1) for several years.[21] The resulting poly(*N*-acetylethylenimine) (PAEI) (polyoxazoline) has high hydrophilicity and high compatibility with several commodity polymers.[22] Very recently, we reported the preparation of polyoxazoline gels by two independent methods, i.e., partial hydrolysis cross-linking[23] and copolymerization.[24] They have characteristic properties as a nonionic hydrogel, i.e., a large swelling degree both in water and in aqueous salts.

In this article, we describe a novel method for the preparation of polyoxazoline hydrogels by means of Diels-Alder reaction between the maleimide-modified PAEI and

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furan-modified polymer. The reversible interconversion between hydrogel and the linear soluble polymer by a change in temperature was also achieved using this system.

Experimental Section

General Procedures. IR spectra were recorded on a Hitachi 260-50 grating spectrophotometer. ^{1}H NMR spectra were obtained on a Hitachi R-600 (60 MHz) or a JEOL JNM-JX-400 (400 MHz) spectrometer. All NMR spectra were recorded in deuterated solvent relative to the internal standard tetramethylsilane. GPC analysis was carried out on a Toso CCPD (TSK gel, G4000) after calibration with standard polystyrene samples.

Materials. All solvents and reagents were used as supplied except the following cases. *N,N*-Dimethylformamide (DMF) was distilled from BaO under reduced pressure. Nitromethane or 1,2-dichloroethane was distilled from P_2O_5 under nitrogen. Acetonitrile was distilled from calcium hydride. Acetic anhydride was kept with P_2O_5 overnight and distilled under nitrogen. Thionyl chloride was distilled from triphenyl phosphite. Methyl *p*-toluenesulfonate (**2**) was distilled under reduced pressure. 2-Methyl-2-oxazoline (**1**) or diethylamine was distilled from potassium hydroxide. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ under nitrogen atmosphere. β-Furylacrylic acid (**9**) was synthesized from furfural and malonic acid according to a literature.[25]

3-(2,5-Dioxo-1*H*-pyrrolyl)propanoic Acid (7). To a solution of maleic anhydride (**5**) (23.2 g, 0.236 mol) in 100 mL of dry THF was added 20.06 g (0.225 mol) of β-alanine with vigorous stirring. The resulting slurry was stirred for 1 week under nitrogen at room temperature. The white precipitate was collected by filtration, washed with several portions of THF, and dried in vacuo. *N*-(Carboxyethyl)maleamic acid (**6**) (42 g) was obtained (99%) and used without further purification: ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ 2.54 (t, 2 H, *J* = 7 Hz), 3.52 (dt, 2 H, *J* = 7 Hz), 6.33 (d, 1 H, *J* = 11 Hz), 6.48 (d, 1 H, *J* = 11 Hz), 9.27 (br s, 1 H), 13.29 (br s, 2 H); MS 184 (M^+); IR (KBr) 3320, 3040, 1700, 1680, 1620, 1560, 1400, 1220, 1200, 1150 cm^{-1}; mp 151–153 °C.

A mixture of maleamic acid (**6**) (10.85 g, 58.0 mmol) and sodium acetate (9.5 g, 115.8 mmol) was added to 120 mL of acetic anhydride and heated at 70 °C for 3.5 h. After cooling to room temperature, acetic anhydride was removed by vacuum distillation. The dark brown residue was dissolved in 40 mL of water and acidified by concentrated hydrochloric acid at 0 °C. An aqueous mixture was extracted with several portions of ethyl acetate (400 mL and 100 mL × 4). The combined organic layer was washed with distilled water, dried over sodium sulfate, and concentrated in vacuo to give a black oily solid. The resulting solid was recrystallized from dichloromethane to yield 1.3 g (13%) of 3-(2,5-dioxo-1*H*-pyrrolyl)propanoic acid (**7**): ^{1}H NMR δ 2.71 (t, 2 H, *J* = 7 Hz), 3.86 (t, 2 H, *J* = 7 Hz), 6.69 (s, 2 H), 9.30 (br s, 1 H); MS 169 (M^+), 151 ($M^+ - H_2O$), 123 (M^+ – COOH, H), 110 ($M^+ - CH_2COOH$); IR (KBr) 3430, 3080, 2930, 1700, 1450, 1410, 1245, 1145, 940, 825 cm^{-1}; mp 104–108 °C.

***N,N*-Diethyl-3-(2,5-dioxo-1*H*-pyrrolyl)propanamide (12).** 3-(2,5-Dioxo-1*H*-pyrrolyl)propanoic acid (**7**) (1.44 g, 8.52 mmol) was dissolved in 5 mL of thionyl chloride under nitrogen atmosphere. After the mixture was stirred for 5 h at room temperature, excess thionyl chloride was removed under reduced pressure to yield an acid chloride as a brown solid: IR 1780 cm^{-1}.

The resulting residue was dissolved in 10 mL of freshly distilled 1,2-dichloroethane, and the solution was transferred to a dropping funnel. To the solution of diethylamine (1.43 g, 19.5 mmol) in 15 mL of 1,2-dichloroethane was added the solution of acid chloride dropwise at 0 °C, and the resulting reaction mixture was allowed to stand at room temperature with stirring. Diethylamine hydrochloride was removed by filtration, and the solvent was evaporated under reduced pressure. The brown residue was purified by column chromatography (eluent, ethyl acetate) to yield a yellow solid. After recrystallization from light petroleum ether and chloroform, *N',N'*-diethylamide **12** was obtained in a yield of 0.902 g (47%): ^{1}H NMR δ 1.09 (t, 3 H, *J* = 7 Hz), 1.16 (t, 3 H, *J* = 7 Hz), 2.50 (t, 2 H, *J* = 7 Hz), 3.25 (q, 2 H, *J* = 7 Hz), 3.35 (q, 2 H, *J* = 7 Hz), 3.99 (t, 2 H, *J* = 7 Hz), 6.70 (s, 2 H); MS 224 (M^+), 152 ($M^+ - Et_2N$), 110 ($M^+ - CH_2CONEt_2$); IR (KBr) 3080, 2950, 1700, 1605, 1580, 1440, 1400, 1360, 1290, 1160, 1065, 817 cm^{-1}; mp 57–58 °C.

3-(2-Furyl)propanoic Acid (10). 3-(2-Furyl)propanoic acid (**10**) was prepared by the catalytic hydrogenation of 3-furylacrylic acid (**9**) according to a literature.[26] Yield was 88.5%: ^{1}H NMR δ 2.70 (dt, 2 H, *J* = 8 Hz, *J* = 0.6 Hz), 2.97 (t, 2 H, *J* = 8 Hz), 6.03 (dd, 1 H, *J* = 0.6 Hz, *J* = 4 Hz), 6.30 (dd, 1 H, *J* = 4 Hz, *J* = 2 Hz), 7.31 (d, 1 H, *J* = 2 Hz); mp 54–55 °C (lit.[26] mp 57–58 °C).

***N,N*-Diethyl-3-(2-furyl)propanamide (13).** To a solution of 3-(2-furyl)propanoic acid (**10**) (1.5 g, 10.7 mmol) in 20 mL of dry acetonitrile was added 2.25 g (10.9 mmol) of dicyclohexylcarbodiimide (DCC) at 0 °C. After the mixture was stirred for 10 min in an ice bath, diethylamine (0.78 g, 10.7 mmol) was added to the resulting white suspension. After dicyclohexylurea was removed by filtration, the solvent was evaporated under reduced pressure. The brown oil was diluted with 5 mL of ethyl acetate and stored in a refrigerator (4 °C). The white precipitate generated was removed by filtration. After the solution was concentrated in vacuo, the oil was subjected to silica gel chromatography (3 cm × 15 cm; eluent, ethyl acetate/*n*-hexane = 1/2). *N,N*-Diethylamide derivative **13** was obtained as a light yellow oil. Yield was 0.767 g (36.7%): ^{1}H NMR δ 1.11 (t, 6 H, *J* = 7 Hz), 2.46–2.73 (m, 2 H), 2.97–3.11 (m, 2 H), 3.27 (q, 2 H, *J* = 7 Hz), 3.39 (q, 2 H, *J* = 7 Hz), 6.02 (d, 1 H, *J* = 4 Hz), 6.26 (dd, 1 H, *J* = 4 Hz, *J* = 2 Hz), 7.28 (d, 1 H, *J* = 2 Hz); MS 195 (M^+); IR (KBr) 3080, 2950, 1640, 1600, 1420, 1380, 1240, 1135, 1080, 1005, 720 cm^{-1}.

Poly(*N*-acetylethylenimine) (PAEI) (3).[23] To a solution of 2-methyl-2-oxazoline (**1**) (30.7 g, 361 mmol) in 60 mL of acetonitrile was added methyl *p*-toluenesulfonate (**2**) (0.354 g, 1.9 mmol; [monomer]/[initiator] = 190) at room temperature under nitrogen. The reaction mixture was heated at 60 °C for 125 h. The resulting orange-yellow solution was diluted with 300 mL of chloroform. This polymer solution was poured into ca. 1500 mL of diethyl ether to precipitate the polymeric product. The white precipitate was collected by filtration and redissolved in 200 mL of dichloromethane. After evaporation of the solvent and freeze-drying with 10 mL of benzene, PAEI (**3**) was isolated in a yield of 28.25 g (90%). The molecular weight of this polymer was estimated by GPC analysis: M_n = 15 800, M_w = 22 500, M_w/M_n = 1.44 (polystyrene standard; eluent, DMF with 0.4% triethylamine).

Partially Hydrolyzed PAEI [Poly(ethylenimine)–Poly(*N*-acetylethylenimine) Random Copolymer] (4).[23] A typical procedure of the partial hydrolysis of PAEI (**3**) is as follows. A mixture of PAEI (**3**) (5.46 g, 64.2 mmol, equivalent NH) and sodium hydroxide (0.43 g, 1.08 mmol) was dissolved in 20 mL of distilled water. This solution was heated under reflux for 92 h. After cooling to room temperature, the polymer solution was dialyzed with distilled water (ca. 200 mL × 2), methanol/water = 1/1 (v/v) (ca. 200 mL × 2), and methanol (ca. 200 mL × 2) to remove salts. The solvent was removed in vacuo, and the polymeric residue was extracted with dichloromethane. After filtration to remove insoluble parts, the solvent was removed under reduced pressure. After freeze-drying with benzene, 3.69 g (72%) of partially hydrolyzed PAEI (**4**) was obtained. From the results of titration with perchloric acid in acetic acid and of ^{1}H NMR spectrum, the degree of hydrolysis was determined (12.8% hydrolyzed).

Maleimide-Modified PAEI (8). In a typical procedure, 12.8% hydrolyzed PAEI (**4**) (0.512 g, 0.826 mmol, NH equivalent) and 3-(2,5-dioxo-1*H*-pyrrolyl)propanoic acid (**7**) (0.296 g, 1.73 mmol) were mixed and freeze-dried with benzene (ca. 5 mL). After dry nitrogen was introduced, the mixture was dissolved in 30 mL of dry acetonitrile and cooled to 0 °C. To this solution was added dicyclohexylcarbodiimide (DCC) (0.215 g, 1.04 mmol). A white precipitate was separated immediately, and the white suspension was stirred overnight. After dicyclohexylurea (DCU) was removed by filtration, the solution was concentrated. The residue was exctracted with 15 mL of methanol and precipitated into ca. 150 mL of diethyl ether. The white polymer was collected and washed well with diethyl ether. The polymer was redissolved in dichloromethane, and the insoluble part was fil-

tered off. After reprecipitation with diethyl ether and drying in vacuo, maleimide-modified PAEI (8) was obtained (0.533 g, 83%). The degree of substitution was determined by ^{1}H NMR (in the text).

Furan-Modified PAEI (11). A typical procedure is as follows. Partially hydrolyzed PAEI (4) (12.8% hydrolyzed, 0.468 g, 0.754 mmol, NH equivalent) and 3-(2-furyl)propanoic acid (10) (0.184 g, 1.31 mmol) were mixed and freeze-dried with benzene (ca. 5 mL). After dry nitrogen was introduced, the mixture was dissolved in 30 mL of dry acetonitrile and cooled to 0 °C. To this solution was added DCC (0.184 g, 0.89 mmol) and the resulting white suspension was stirred overnight. After DCU was removed by filtration, acetonitrile was evaporated under reduced pressure. Reprecipitating twice with diethyl ether and drying in vacuo produced furan-modified PAEI (11) (0.414 g, 74%). The degree of substitution was determined by ^{1}H NMR (in the text).

Model for Diels–Alder Reaction. A model reaction was carried out both in $CDCl_3$ in an NMR tube at room temperature as well as in bulk. In the bulk reaction, *N*,*N*-diethyl derivatives of 3-(2,5-dioxo-1*H*-pyrrolyl)propanoic acid (12) (0.159 g, 0.71 mmol) and that of 3-(2-furyl)propanoic acid (13) (0.136 g, 0.70 mmol) were mixed at room temperature without any solvents. The mixture was stirred in the dark for 7 days. Then, the yellow oil was dissolved in a small amount of dichloromethane. The Diels–Alder adduct (14) (164 mg, 56%) was isolated by silica gel column chromatography (eluent, ethyl acetate–ethanol). The isomer ratio (endo/exo isomer) was about 4.6/1. ^{1}H NMR ($CDCl_3$): endo isomer, (14a), δ 1.17 (m, 4 H), 2.46–3.72 (m, 14 H), 5.14 (br s, 1 H), 6.45 (br s, 2 H); exo isomer (14b), δ 1.10 (m, 6 H), 2.50 (m, 4 H), 3.10–3.53 (m, 6 H), 5.24 (d, 1 H, J = 5 Hz), 6.30 (br s, 2 H).

Gelation by Diels–Alder Reaction. A mixture of maleimide-modified PAEI (8) (55.8 mg, 12.8% functionalized) and furan-modified PAEI (11) (55.8 mg, 12.8% functionalized) was dissolved in 0.5 mL of methanol in a Petri dish (3-cm diameter) by shaking gently and kept for 6 h in the dark. The resulting film was placed in the dark at room temperature for 1 week to complete the cross-linking reaction. The formed gel was immersed in methanol, washed well, and collected. After the mixture was dried in vacuo, 0.108 g (96.8%) of polyoxazoline gel (15) was obtained.

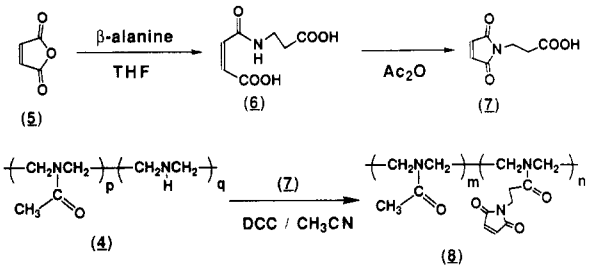
Swelling Properties. The equilibrium swelling properties in water were examined as follows. The carefully dried and weighed gel 15 (0.108 g) was immersed in ca. 100 mL of deionized water (the resistance was more than 12 MΩ) for 24 h at room temperature. The weight of the swollen gel was measured (0.222 g) after filtration by a 1G4 glass filter under reduced pressure (ca. 17 mmHg, 2 min). The swelling degree was calculated by the following equation: $\{W_g(s) - W_g(d)\}/W_g(d)$, where $W_g(s)$ is weight of the swollen gel and $W_g(d)$ is weight of the dry gel. The swelling degree was proved to be 1.05.

Cleavage of the Gel by Retro-Diels–Alder Reaction. The polyoxazoline hydrogen (15) (10 mg) prepared from 5.3% maleimide-modified polymer (8) and 4.8% furan-modified PAEI (11) by Diels–Alder reaction in bulk film was swollen in CD_3NO_2 or in aqueous methanol. After the reaction mixture was heated for several hours, the solvent was removed in vacuo. The resulting polymer was obtained quantitatively and was easily dissolved in chloroform, in methanol, and in water. The ^{1}H NMR spectrum of the obtained polymer is shown in the text.

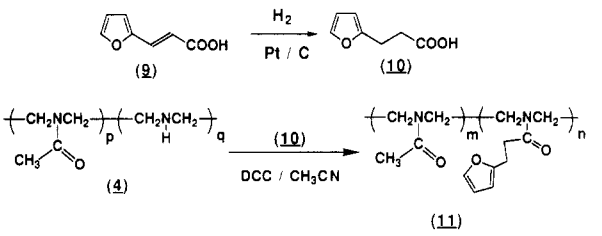
Change of the Swelling Properties by Retro-Diels–Alder Reaction with Heating. The gel 15 (20 mg) was swollen in 30 mL of methanol/water = 1/1 (v/v) and heated for 1 h. The suspension was cooled to room temperature by an external ice bath and kept for 40 h. The weight of the swollen gel (0.162 g) was measured as described above. The dried weight (13 mg, 65%) was also measured after drying the gels in vacuo. The swelling degree was calculated from these values as mentioned above (swelling degree = 11.5).

Regelation of the Product by Retro-Diels–Alder Reaction. The gel 15 (20 mg) was swollen in 5 mL of nitromethane and heated for 24 h. After the gel was dissolved, the solvent was removed in vacuo. The resulting polymer film was redissolved in a small amount of methanol and cast upon a clean glass slide. The film was placed in dark under air at room temperature for 1 week. The formed gel was washed repeatedly with several portions of methanol and dried in vacuo. Yield of polyoxazoline gel was 16 mg (65%).

Scheme I



Scheme II



Results and Discussion

Syntheses of Maleimide-Modified PAEI (8) and Furan-Modified PAEI (11). The preparations of maleimide-modified PAEI (8) and furan-modified PAEI (11) are outlined in Schemes I and II, respectively. A series of partially hydrolyzed PAEI (4) with various degrees of hydrolysis were prepared by the slightly modified method from the previous report.[23] The degree of hydrolysis could be successfully controlled by the amount of alkaline.

These polymers with various degrees of hydrolysis were treated with 3-(2,5-dioxo-1*H*-pyrrolyl)propanoic acid (7) or with 3-(2-furyl)propanoic acid (10) in the presence of a few equivalents of dicyclohexylcarbodiimide (DCC) as a condensing agent. Figure 1 illustrates ^{1}H NMR spectra of furan- and maleimide-modified PAEIs (8 and 11). The peak of the methylene protons adjacent to the secondary amino groups disappeared completely. This result is taken to support the quantitative introduction of a maleimide or furan group in PAEI. The substitution degrees of furan or maleimide groups could be calculated by the integral ratio of olefin (in the case of dienophile) or of ring (in diene) protons to acetyl protons. Table I summarizes the results of the preparation of maleimide-containing PAEIs (8), and Table II shows those of furan-containing polymers (11).

The substitution degrees were in good agreement with the hydrolysis degrees in the starting partially hydrolyzed PAEI (4). In the case of lower functionalization of the hydrolyzed polymer (2.5%), the peak of furan or maleimide in ^{1}H NMR was too small to estimate the substitution degree. The titration of the secondary amino groups in the resulting polymer showed no remaining amino group could be detected within an experimental error. The results of the swelling properties of the resulting gels were also comparable with the degrees of the substitution (vide infra). These results strongly support the complete introduction of functional groups to the starting polymer. In other words, the functionality of the furan or maleimide PAEIs could be easily controlled by the degree of hydrolysis in the starting polymers.

No significant change of the molecular weights of these functionalized PAEIs (8 and 11) was recognized in comparison with those of the parent polymers (PAEI, 3). The

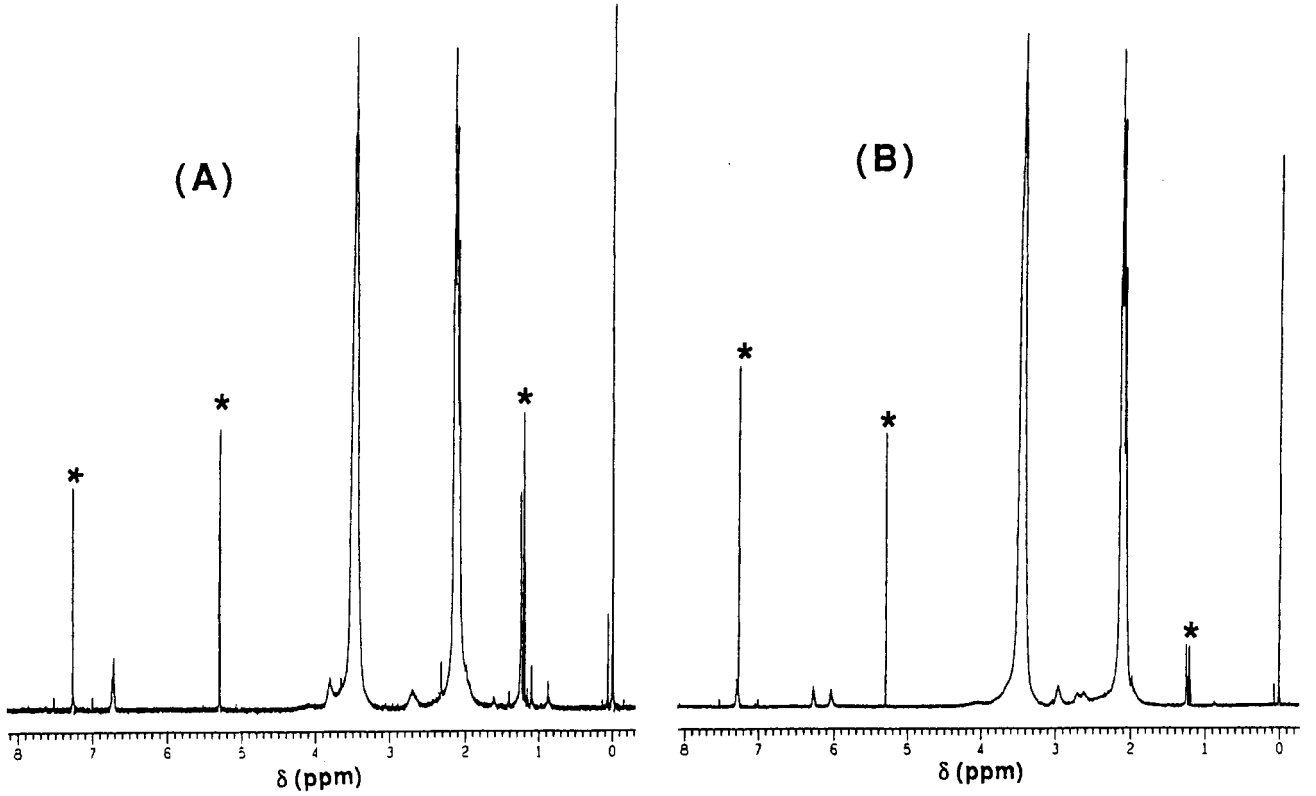


Figure 1. ^{1}H NMR (400-MHz) spectra of (A) maleimide-modified (8) (4.1%) and (B) furan-modified (11) (4.0%) poly(*N*-acetylethylenimine)s. Asterisks show the peaks due to solvents.

Table I
Synthesis of Maleimide-Modified PAEI (8)

	4		8	
run	$\bar{M}_n$[a]	$q/(p+q)$[b]	yield, %	$n/(m+n)$[c]
1	15 800	0.025	79	
2	15 800	0.051	92	0.041
3	15 800	0.068	81	0.053
4	15 800	0.128	83	0.131
5	15 800	0.234	89	0.219

[a] Determined by GPC (PSt standard). [b] Degree of hydrolysis (p,q in Scheme I) was determined by titration. [c] Degree of substitution (m,n in Scheme I) was determined by ^{1}H NMR.

Table II
Synthesis of Furan-Modified PAEI (11)

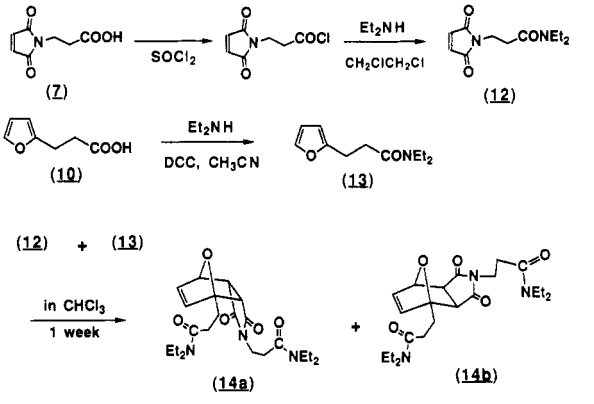
	4		11	
run	$\bar{M}_n$[a]	$q/(p+q)$[b]	yield, %	$n/(m+n)$[c]
1	15 800	0.025	72	
2	15 800	0.051	74	0.040
3	15 800	0.068	79	0.048
4	15 800	0.128	74	0.138
5	15 800	0.234	80	0.213

[a] Determined by GPC (PSt standard). [b] Degree of hydrolysis (p,q in Scheme II) was determined by titration. [c] Degree of substitution (m,n in Scheme II) was determined by ^{1}H NMR.

molecular weight distributions ($M_w/M_n = 1.5$) of the resulting polymers were also similar to those of the starting polymers. These data indicate that no significant chain degradation and cross-linking occurred during the condensation reaction for the preparation of these functionalized PAEIs.

Model Reaction. As shown in Scheme III, *N*,*N*-diethyl derivatives **12** and **13** were prepared from the corresponding carboxylic acids and subjected to the Diels–Alder reaction. The adduct **14** was isolated by silica gel column chromatography in 60% yield. The stereoisomers of the Diels–Alder adduct are characterized by the

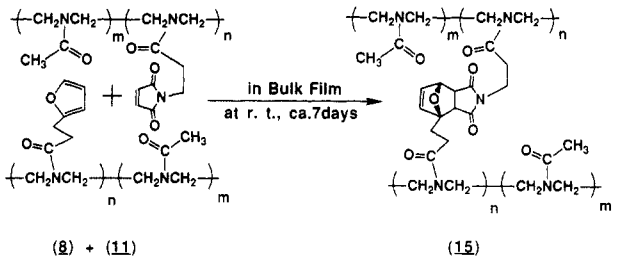
Scheme III



multiplicity of the bridgehead proton (at C_4) in their ^{1}H NMR spectra.[27] That is, an endo isomer (**14a**) shows a singlet peak at δ 5.14, while an exo isomer (**14b**) shows a doublet (J = 5 Hz) peak at δ 5.24 due to the coupling with the proton at C_5. Thus, the ratio between endo and exo isomers was about 4.6/1 calculated from the values of their isolated yields. Kinetic study at room temperature in $CDCl_3$ also showed that the peaks due to the Diels–Alder adduct in ^{1}H NMR increased to a constant level. After 3 days of reaction, the conversion of Diels–Alder reaction was estimated about 50–60% from the integral ratio between the olefinic protons (C_2, C_3)[27] of the Diels–Alder adduct and those of maleimide. Isolated yield of the Diels–Alder adduct was also 50–60%. As a result, the Diels–Alder reaction between maleimide and furan derivatives was not quantitative under the present condition and about half of them reacted within a few days.

Gelation by Diels–Alder Reaction. The intermolecular Diels–Alder reaction was carried out in bulk film in dark place at room temperature as represented in Scheme IV. A mixture of dienophile- and diene-PAEIs (8 and

Scheme IV



Scheme V

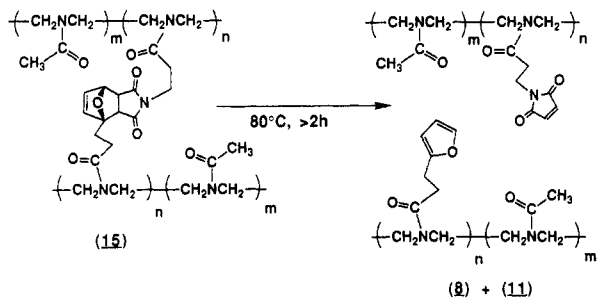


Table III
Gelation by Diels–Alder Reaction[a]

run	prepolymers[b] 8	11	15: yield, %	swelling degree[c] in H_2O
1	4.1	0	0	
2	0	4.0	0	
3	4.1	4.0	70	14.8
4[d]	4.1	4.0	89	11.8

[a] 3 days, at room temperature, in bulk film, in dark. [b] Mole percent of maleimide (8) and furan (11) ($n/(m+n)$). [c] Grams of H_2O per grams of dry gel. [d] 7 days.

Table IV
Gelation by Diels–Alder Reaction[a]

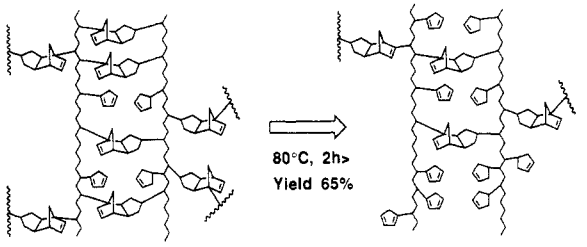
run	prepolymers[b] 8	11	15: yield, %	swelling degree[c] in H_2O
1	2.5	2.5	0[d]	
2	4.1	4.0	89	11.8
3	4.8	5.3	88	5.6
4	13.8	13.1	97	2.0
5	21.3	21.9	95	1.1

[a] 7 days, at room temperature, in bulk film, in dark. [b] Mole percent of diene and dienophile. [c] Grams of H_2O per grams of dry gel. [d] No gel products.

11) were cast onto a glass slide to form a transparent film without phase separation. The results of the Diels–Alder gelations between furan and maleimide polymers (substitution degree, ca. 4%) are summarized in Table III. The obtained gel **15** was insoluble in water, methanol, and other organic solvents. The film made from the furan- or maleimide-modified PAEI alone, respectively, gave no gel under the same reaction conditions, which were soluble in methanol. This result shows that the crosslinking to form a stable gel was caused by the intermolecular Diels–Alder reaction between the furan- and maleimide-modified PAEIs.

Swelling Property in Water. Table IV shows the results of the Diels–Alder gelation between furan- and maleimide-modified PAEIs with various substitution degrees and the swelling degrees of the obtained polyoxazoline gels. The transparent gel films were obtained in good yields in all cases where the contents of each functional groups were higher than 2.5%. The obtained gels swelled in water and showed characteristic properties as

Scheme VI



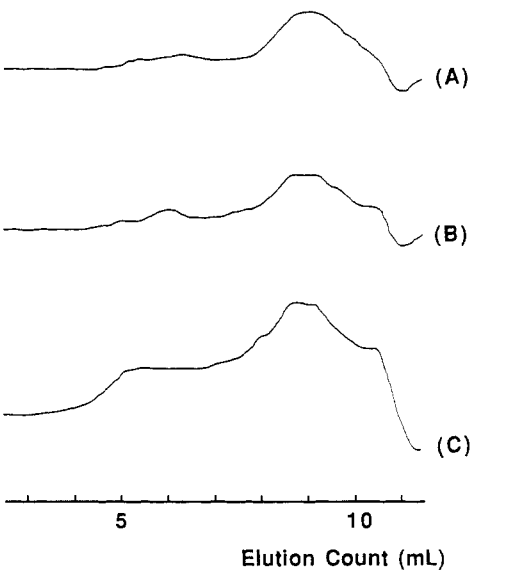


Figure 2. GPC traces of (A) 4.0% furan-modified (11) and (B) 4.1% maleimide-modified (8) PAEIs and (C) regenerated polymer after retro-Diels–Alder reaction.

a hydrogel, which had enough strength and stability to be handled in water. A pair of low-substitution polymers (run 1) gave no gel because of insufficient crosslinking points. The equilibrium swelling degrees in water increased with the decrease of substitution degrees of each polymer. This means that the swelling property can be controlled by the substitution degrees and consequently, the hydrolysis degrees of the starting PAEIs.

Reversibility of the Diels–Alder Reaction. Within a few hours, the gel product **15** after Diels–Alder reaction was redissolved into hot solvent (methanol/water or nitromethane). This solubility change can be explained by the retro-Diels–Alder reaction, which cleaves the crosslinking bonds by heating (Scheme V). The GPC chart of the regenerated polymer is illustrated together with those of the starting diene and dienophile polymers in Figure 2. No apparent increase of the molecular weight was recognized after one-cycle conversion of polymer–gel–polymer. Without heating, the Diels–Alder gel was only swollen in the same solvent for a longer reaction time (vide infra). The ^1H NMR spectrum of the resulting soluble polymer is shown in Figure 3. Both the olefinic protons of the maleimide moiety (δ 6.9) and the ring protons (δ 6.3–7.0) of the furan moiety are observed in this spectrum. The integral ratio between these peaks and acetyl protons in the polymer backbone was in good agreement with that calculated from the substitution degrees of the initial polymers. Thus, the Diels–Alder gel turned out to be soluble by heating reversibly. It should be noted that the present diene- and dienophile–PAEI systems are the first examples of a thermally reversible

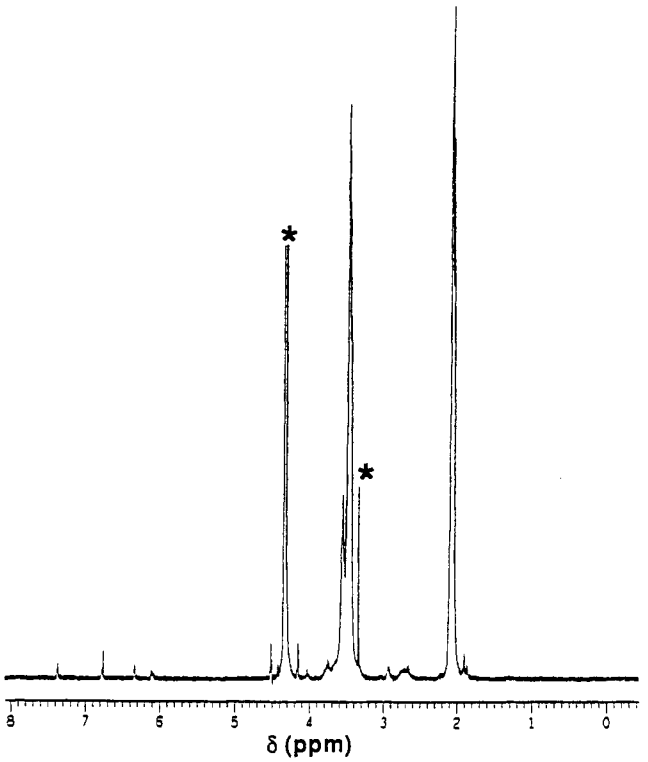
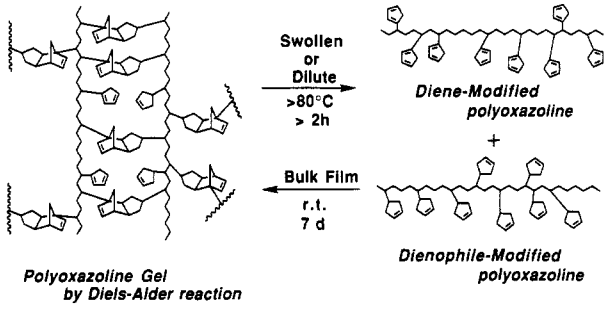


Figure 3. ^{1}H NMR (400-MHz) spectrum of regenerated polymer after retro-Diels–Alder reaction. Asterisks show the peaks due to solvents.

Scheme VII



hydrogel through the covalently cross-linking points via the Diels–Alder reaction.

Change of the Swelling Properties by Heating. The partial cleavage of the Diels–Alder gel **15** was carried out in methanol/water = 1/1 for a few hours (Scheme VI). The gel was swollen in this mixed solvent more and more by heating at 80 °C. After 1 h, the resulting gel showed a swelling degree about 2 times as large as that of its original gel. The retro-Diels–Alder reaction occurred by heating, and a part of the cross-linking points was cleaved to increase the swelling degree.

Recycle of the Diels–Alder Gel. The soluble polymer prepared by the retro-Diels–Alder reaction described above gave the gel product **15** again under the same condition as that of the previous Diels–Alder gelation reaction (1 week, in bulk film, in the dark). The resulting gel was also swollen in water to form a stable hydrogel. The swelling degree was almost the same as that of the original Diels–Alder gel. In conclusion, the present gelation system proved to be a complete thermally reversible hydrogel system through the covalent cross-linking points by means of the Diels–Alder reaction (Scheme VII).

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References and Notes

(1) A Novel Nonionic Hydrogel from 2-Methyl-2-oxazoline. 4. Parts 1–3: see refs 23, 24, and 28, respectively.
(2) Hirose, Y.; Amiya, T.; Hirokawa, Y.; Tanaka, T. *Macromolecules* **1987**, *20*, 1342 and references cited therein.
(3) Gnanou, Y.; Hild, G.; Rempp, P. *Macromolecules* **1984**, *17*, 945.
(4) Nieto, J. L.; Baselga, J.; Hernandez-Fuentes, I.; Llorente, M. A.; Pierola, I. F. *Eur. Polym. J.* **1987**, *23*, 551.
(5) Baselga, J.; Llorente, M. A.; Nieto, J. L.; Hernandez-Fuentes, I.; Pierola, I. F. *Eur. Polym. J.* **1988**, *24*, 161.
(6) Baselga, J.; Llorente, M. A.; Nieto, J. L.; Hernandez-Fuentes, I.; Pierola, I. F. *Eur. Polym. J.* **1989**, *25*, 471.
(7) Baselga, J.; Llorente, M. A.; Nieto, J. L.; Hernandez-Fuentes, I.; Pierola, I. F. *Eur. Polym. J.* **1989**, *25*, 477.
(8) Davis, T. P.; Huglin, M. B. *Polym. Commun.* **1987**, *28*, 218.
(9) Davis, T. P.; Huglin, M. B. *Makromol. Chem., Rapid Commun.* **1988**, *9*, 39.
(10) Yamashita, S.; Shibutani, K.; Takakura, K.; Imai, S. *Kobunshi Ronbunshu* **1982**, *39*, 187.
(11) Tsukahara, Y.; Tsai, H.-C.; Yamashita, Y.; Muroga, Y. *Polym. J.* **1987**, 19, 1033.
(12) Davis, T. P.; Huglin, M. B.; Yip, C. F. *Polymer* **1988**, *29*, 701.
(13) Chapiro, A.; Legris, C. *Eur. Polym. J.* **1989**, *25*, 305.
(14) Hoffman, A. S.; Afrassiabi, A.; Dong, L. C. *J. Controlled Release* **1986**, *4*, 213.
(15) Dong, L. C.; Hoffman, A. S. *J. Controlled Release* **1986**, *4*, 223.
(16) Afrassiabi, A.; Hoffmann, A. S.; Cadwell, L. A. *J. Membr. Sci.* **1987**, *33*, 191.
(17) Bae, Y. H.; Okano, T.; Hsu, R.; Kim, S. W. *Makromol. Chem., Rapid Commun.* **1987**, *8*, 481.
(18) Kennedy, J. P.; Castner, K. F. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 2055.
(19) Stevens, M. P.; Jenkins, A. D. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 3675.
(20) Salamone, J. C.; Chung, Y.; Clough, S. B.; Watterson, A. C. *J. Polym. Sci., Polym. Chem. Ed.* **1988**, *26*, 2923.
(21) Reviews of the polymerization of cyclic imino ethers: (a) Kobayashi, S.; Saegusa, T. In *Ring-opening Polymerization*; Ivin, K. J., Saegusa, T., Eds.; Elsevier Applied Science Publishers: Essex, U.K., 1984; Vol. 2, p 761. (b) Saegusa, T.; Kobayashi, S. *Encyclopedia of Polymer Science and Technology*; Wiley: New York, 1976; Supplemental Vol. 1, p 220. (c) Saegusa, T.; Kobayashi, S. In *Macromolecular Science, International Review of Science, Physical Chemistry Series 2*; Butterworth: London, 1975; Vol. 8, Chapter 4.
(22) Kobayashi, S.; Kaku, M.; Saegusa, T. *Macromolecules* **1988**, *21*, 334.
(23) Chujo, Y.; Yoshifuji, Y.; Sada, K.; Saegusa, T. *Macromolecules* **1989**, *22*, 1074.
(24) Chujo, Y.; Sada, K.; Matsumoto, K.; Saegusa, T. *Macromolecules* **1990**, *23* (5), 1234.
(25) Rajagopalan, S.; Raman, P. V. A. *Org. Synth.* **1945**, *25*, 51.
(26) Rallings, R. J.; Smith, J. C. *J. Chem. Soc.* **1953**, 618.
(27) For the Diels–Alder reaction of *N*-methylmaleimide and furan, see: Anderson, W. K.; Milowsky, A. S. *J. Org. Chem.* **1985**, *508*, 5423.
(28) Chujo, Y.; Sada, K.; Saegusa, T. *Macromolecules*, in press.