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Iron(II) Bipyridyl-Branched Polyoxazoline Complex as a Thermally Reversible Hydrogel

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ABSTRACT: An intermolecular cross-linked metal complex between bipyridyl-branched polyoxazoline and ferrous ion was prepared, in which the thermally reversible nature was observed. The red complex gels were much swollen in water and stable enough at ambient temperature for a few days, while they turned soluble in hot water within 30 min. The resulting red solution was concentrated slowly to dryness under atmospheric pressure to give a red gel again in quantitative yield. This reversible interconversion between the gel and the soluble polymer was caused by the ligand exchange reaction. The initial intermolecular complex gel was converted to the entropically favorable intramolecular one (soluble polymer) by swelling in water. The thermal reversibility of this hydrogel was caused by the thermal acceleration of the ligand exchange reaction. From the results of the swelling behavior and the kinetics of the thermal cleavage reaction of the coordination gel at 40 °C, it was found that the swelling equilibrium in water was the rate determining step at the first stage, then the rapid cleavage reaction took place, and simultaneously, the water content of the gel increased rapidly. A series of poly(*N*-acetylethylenimine)s (PAEIs) having varying amounts of the functional groups were prepared and subjected to a cross-linking reaction. The degree of swelling and the stability of the gel in water depended on the content of the functional groups in the prepolymer. In the case of less substituted polymer, e.g., 3.3% bipyridyl-branched PAEI, the water uptake was up to 56 multiples of its own weight in the dry state. This gel was completely dissolved into water rapidly. This interconversion from a hydrogel to a soluble polymer by heating can be regarded as a novel thermally reversible hydrogel system by means of kinetic control of the ligand exchange reaction.

Introduction

Various thermally reversible hydrogel systems have been studied for use as a drug delivery system.[3-7] 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 of the water-soluble polymers such as poly(*N*-alkylacrylamide),[8,9] poly(vinyl alcohol),[10]) or polypeptide.[11] Previously, we reported a novel thermally reversible hydrogel system through covalent bonds by means of a Diels–Alder reaction based on nonionic and hydrophilic poly(*N*-acetylethylenimine) (PAEI).[12] We also studied the reversible hydrogels based on polyoxazoline using a photoreaction[13] or redoxinterconversion.[14]

Very recently, we have explored the preparation of bipyridyl-branched PAEI and its gelation by the metal coordination.[15] The stability of these networks prepared by metal coordination was dependent both on their thermodynamic stability constants and on the kinetic inertness of tris(bipyridyl) complexes. Although the metal ions such as iron(II), cobalt(II), ruthenium(III), and copper(II) are known to have large stability constants with bipyridyl derivatives, the intermolecular cross-linkings in some cases were changed to the entropically favorable intramolecular cross-linkings by the rapid ligand exchange reaction between the polymer ligands upon dilution or swelling in water. As a result, the kinetically labile metal complexes gave no stable networks. Thus, the swelling property and the stability of the gels could be successfully controlled by the kinetic inertness of the model complexes.

In this paper, the thermal behavior of these complex gels based on bipyridyl-branched PAEIs is described. Among various metal ions, the iron(II) complex gel, the medium inert complex gel, was found to have the unique property of swelling equilibrium and stability. By thermal activation of the ligand exchange reaction, the lifetime of the network was varied from 5 min to 9 h. This large dependence of the stability of gels on the temperature provided us the "kinetically controlled" thermally reversible hydrogels.

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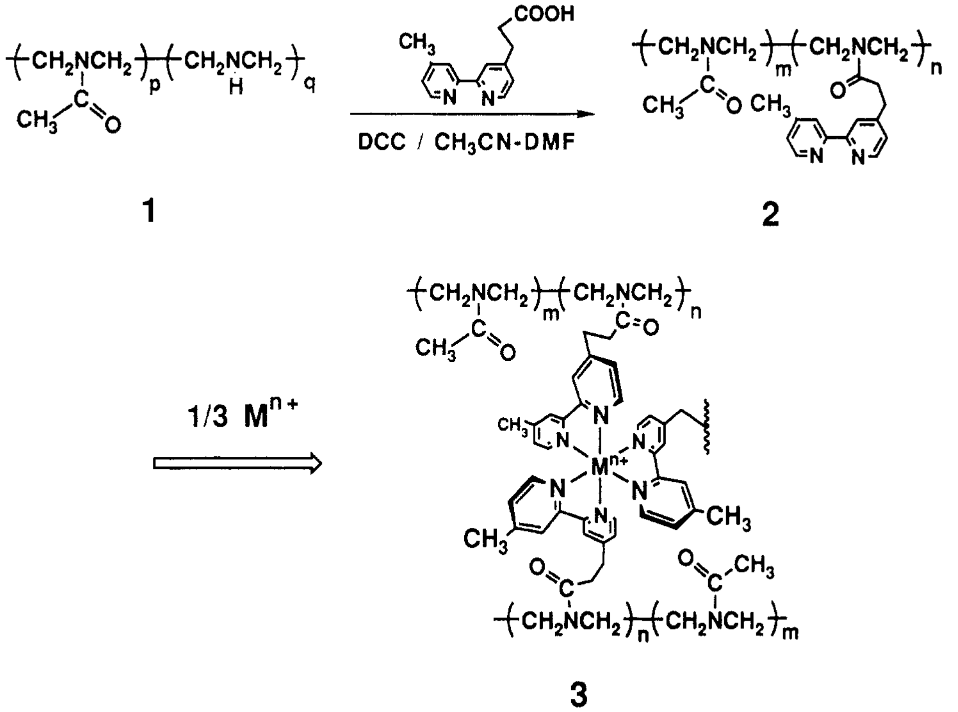
Scheme I.



Experimental Section

General Procedure. UV–visible spectra were recorded on a Hitachi 200 UV–vis spectrophotometer. GPC analysis was carried out on a Tosoh CCPD (TSK gel G4000) after calibration with the standard polystyrene samples.

Materials. All solvents and reagents were used as supplied except the following materials. *N,N*-Dimethylformamide (DMF) was distilled from barium oxide and then from calcium hydride under reduced pressure. Nitromethane was distilled from phosphorus pentoxide under nitrogen. Acetonitrile was distilled from calcium hydride and then distilled again from phosphorus pentoxide under nitrogen. Methyl *p*-toluenesulfonate was distilled under reduced pressure. 2-Methyl-2-oxazoline was distilled from potassium hydroxide.

Poly(*N*-acetylethylenimine) (PAEI) was prepared by the ring-opening polymerization of 2-methyl-2-oxazoline in the presence of methyl *p*-toluenesulfonate as an initiator and was partially hydrolyzed by treatment with aqueous sodium hydroxide.[12] The degree of hydrolysis, i.e., the amount of secondary amino groups in the polymer, was calculated from the results of titration in acetic acid with perchloric acid. The introduction of bipyridyl groups to PAEI was carried out as described before.[15] The molecular weight of the modified PAEI was determined by gel permeation chromatography based on polystyrene standard samples (eluent: DMF with 0.4% triethylamine). The degree of substitution (bipyridyl moiety) was estimated from the absorption spectrum (λ_{max} = 284 nm, ϵ = 15 500). The metal-induced gelation of the bipyridyl-branched PAEI was carried out according to the previous report.[15] The degree of swelling of the hydrogel was measured by the conventional filtration method.[16-18]

Kinetic Measurements. The kinetics of the cleavage reaction and the change of the swelling property of iron coordination gel were typically measured as follows. The Fe(II) bipyridyl complex gel (7.2% modified, ca. 9 mg) was placed in a 10-mL glass vial. After ca. 10 mL of water was added, the tightly capped glass vial containing the gel suspension was incubated in a thermostated bath shaking at a rate of 160 strokes/min. After incubation for a designated time, the gel was filtered by a 1G4 glass frit using a suction pump for 2 min. The UV spectrum of the filtrate was measured after dilution with 25 mL of distilled water. The degree of swelling was calculated from the following equation; [W_s- W_d]/W_d, (W_d, the weight of dried gel; W_s, the weight of swollen gel). The wet weight (W_s) of the PAEI hydrogel was measured directly after filtration of the swollen gel. The dried weight (W_d) was also determined directly by the removal of water from the swollen gel under vacuum or was estimated from the initial weight of the gel in the dry state and the calculated weight of the soluble part from its absorption spectra (λ_{max} = 299 nm, ϵ = 18 400, M_n = 1440 per iron(II) tris(bipyridyl) complex dichloride)[15] from the filtrate.

Lifetime of the Coordination Gel. The lifetime of the iron coordination gel under various conditions was determined by the analogous method for kinetic measurement except as follows. The heating and shaking were continued until no insoluble gel was observed. The complete dissolving of the gel was confirmed by no more change of the absorption spectrum.

Thermal Reversibility. The red solution of the iron–bipyridyl complex gel (7.2 mol % modified) for the kinetic measurement was collected, and the solvent was removed under reduced pressure at room temperature. After drying in vacuo, the soluble iron(II) bipyridyl-branched PAEI complex (20 mg) was recovered. This red polymer was redissolved in 2 mL of distilled water, and then the solution was concentrated under atmospheric pressure by heating slowly to dryness. To the resulting red film was added 10 mL of water to extract the unreacted polymer. The stable gel film was collected by a glass frit (1G4) and washed well with a large amount of water and then with methanol. After drying in vacuo, the gel was obtained (19-mg yield).

Results and Discussion

Synthesis and Characterization of Metal Tris(Bipyridyl-Branched PAEI) Complex Gel 3. The bipyridyl group was introduced to PAEI by the reaction of partially hydrolyzed polymer 1 with 3-{4-(4′-methyl-2,2′-bipyridyl)}propanoic acid in the presence of dicyclohexylcarbodiimide (DCC) (Scheme I).[15]

The content of the bipyridyl group in the polymer was easily determined by the UV spectrum. The degree of substitution could be controlled by the degree of hydrolysis in the prepolymer (1). The molecular weights of the modified PAEIs and their molecular weight distributions were not changed during the condensation reaction. This result indicates that no cross-linking and no degradation reaction of the polymer backbone occurred.

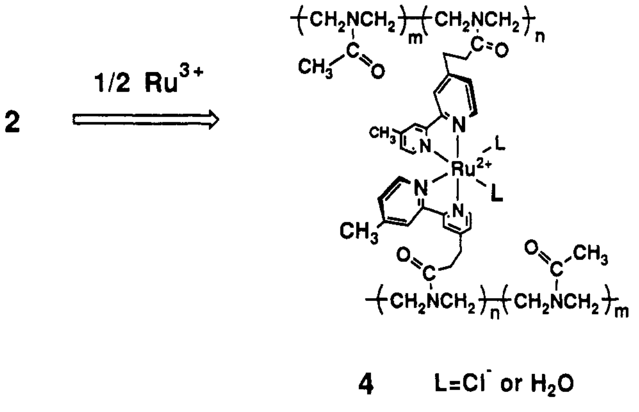
Bipyridyl-branched PAEIs 2 were subjected to gelation via the metal coordination by treatment with aqueous metal salts according to the previously reported method (Scheme I).[15] The results of the gelation are shown in Table I, together with the results of their degrees of swelling

Table I. Gelation of Bpy–PAEI by Metal Coordination[a]

	2			metal complex gel	
run	$\bar{M}_n$[b]	$n/(m+n)$[c]	M^{n+}	yield (%)	degree of swelling[d]
1	28 200	0.010	Fe^{II}	0[e]	
2	28 200	0.033	Fe^{II}	90	55.5
3	28 200	0.084	Fe^{II}	78	10.9
4	28 200	0.144	Fe^{II}	72	4.7
5	24 500	0.072	Fe^{II}	93	19.5
6[f]	24 500	0.072	Ru^{II}	99	12.2
7[g]	24 500	0.072	Ru^{II}	88	66.2
8	24 500	0.072	Ni^{II}	99	*h*

[a] Feed ratio: $[M^{n+}]/[Bpy] = 2/3$; formed complex $[M^{n+}]/[Bpy] = 1/3$. [b] Determined by GPC (PS standard). [c] Determined by UV and ^1H NMR. [d] g of H_2O/g of dry gel (in water for 24 h). [e] No gelation was observed. [f] Feed ratio: $[Ru^{III}]/[Bpy] = 1/3$. [g] Feed ratio: $[Ru^{III}]/[Bpy] = 1/2$. [h] Dissolved within a few hours.

Scheme II.



after incubation in water at room temperature for 24 h.

The gelation was observed within a few minutes after addition of the metal salts such as Fe(II) and Ni(II). In the case of Ru(III), it was necessary to reflux in water for 3 days to form a stable gel (runs 6 and 7). In all cases, the complex gels were obtained in good yields. The gels obtained showed large degrees of swelling in water and enough stability and strength to be handled as a hydrogel at room temperature, except the Ni(II) complex gel (run 8). The complexation of bipyridyl moieties with these metal ions to form the tris chelate complex was confirmed by their UV spectra. The absorption maxima of red Fe(II) gel were located at 278 and 517 nm. The colorless Ni(II) gel showed its absorption maxima at 296 and 302 nm. The orange-red Ru(II) tris chelate gel prepared by ruthenium/bipyridyl = 1/3 (run 6) showed MLCT bands at 465 and 448 (sh) nm and π–π^* transitions at 286 and 325 nm. The absorption spectra of these complex gels were similar to those of their model tris(2,2′-bipyridyl) complexes. When the ratio between Ru(III) and the bipyridyl moiety was reduced to 1/2 (run 7), the purple-black gel was obtained. From its UV spectrum (λ_{max} = 289, 350, 474 nm), the complex gel was found to consist mainly of Ru(II) bis(bipyridyl) complex 4 (Scheme II).[19]

Swelling Properties and Stability in Water. The degrees of swelling of the tris complex gels using Fe(II) and Ru(II) (about 12–19.5) were close to each other. This means that these values may depend on the degree of functionalization in 2, although the effect of the nature of the metal ions on the degree of swelling is not clear at present. In the case of the bis chelate complex gel, the degree of swelling (66) was much larger than those of tris chelate complex gels even with the same degree of functionalization and the same metal ion (Ru(II)) (runs 5–7).

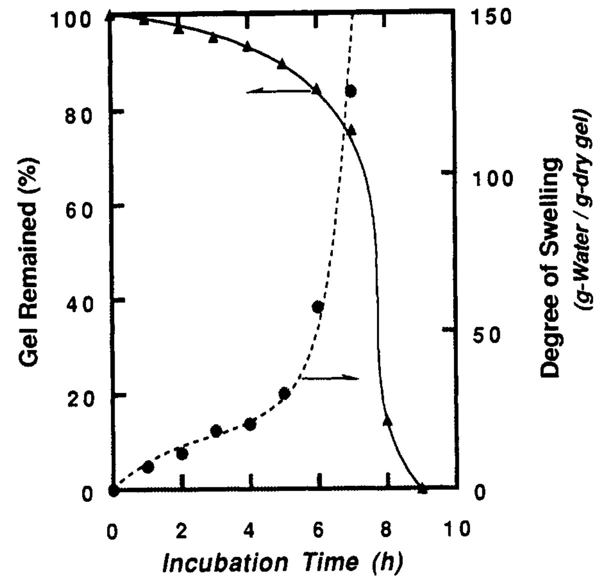


Figure 1. Thermal cleavage of iron(II) 2,2′-bipyridyl-modified PAEI complex gel 3.

As reported before, the degree of swelling could be easily controlled by the degree of substitution of the bipyridyl group.[15] This result shows that the cross-linking density, i.e., the degree of swelling, can be controlled both by the feed ratio of the metal ions to the bipyridyl group and by the degree of functionalization of the prepolymer.

These ruthenium gels having either tris or bis chelates showed extreme stability. That is, they were stable in water more than 1 month, and no solubilization was observed. On the other hand, Fe(II) and Ni(II) gels were not so stable in comparison with Ru(II) gels. They swelled in water and turned soluble within a few days. Especially, the Ni(II) gel was dissolved within a few hours. This cleavage of the cross-linking might be caused by the change of the metal coordination from an intermolecular manner to an intramolecular one by swelling or diluting in water. Thus, the stability of the hydrogel depends on the kinetic inertness, that is, the rate of the ligand exchange reaction, according to the order Ru(II) > Fe(II) > Ni(II).[20,21]

Kinetic Approach to the Cleavage of Cross-Linkings. Figure 1 shows the results of the kinetics of the thermal cleavage of 7.2% functionalized PAEI gels at 40 °C in 10 mL of distilled water with constant shaking (160 strokes/min) together with the results of the change of degrees of swelling. The degree of swelling of the gel was at first increased by increasing the incubation time until 2 h and was saturated at the value of 20. This value of the degree of swelling was in good agreement with that of the gel incubated in water at room temperature for 24 h without stirring. During this time, the yield of the remaining gel was still up to 90%. No apparent cleavage of the gel was observed. This initial process might be caused mainly by the swelling equilibrium. The dry shrunk gel swelled more and more. It took about 2–3 h to be swollen to its full extent in the covalently cross-linking systems based on the same polymer.[15] After the swelling equilibrium was maximized (~20), i.e., the degree of swelling was saturated at the constant value, the cleavage of the cross-linking of the Fe(II) gel took place slowly by changing the cross-linking points from the initial intermolecular manner to the entropically favorable intramolecular one due to the slow ligand exchange reaction between iron(II) tris(bipyridyl) complexes in the polymer pendant. Therefore, the network was broken slowly from its surface to be solubilized into water, and simultaneously, the inside of the gel was subjected to the same reaction, and the degree of swelling increased largely from 20 to more than 100. After the degree of swelling reached the limit for holding the stable structure, the cleavage of the cross-linking occurred not only at the surface but also from the inside of the gel, and the yield of remaining gel fell down suddenly to about 15% (8 h). Finally, after the incubation for 9 h, the gel was completely dissolved in water to give a soluble iron(II) bipyridyl-branched PAEI complex. In this complex gel, whose degree of swelling was relatively large, the rate of the swelling equilibrium was slower than that of the cleavage reaction. Thus, the change of the degree of swelling should include two steps. In the first step, the normal swelling behavior was observed. As the second step, the increase of the swelling property was caused by the cleavage of the cross-linking.

The UV spectrum of the soluble polymer indicated no apparent change from its original gel. The gel permeation chromatographic analysis also indicated that the molecular weight of the red soluble polymer was found to be similar to that of the original bipyridyl polymer (2), and no cross-linked microgel or degraded product was observed.

These results show that the network via the intermolecular complexation was completely broken to give the intramolecular metal–bipyridyl complex. In other words, the interconversion from the hydrogel to the soluble polymer was caused only by this ligand substitution reaction rather than by any other side reactions.

Effect of Degree of Substitution on the Rate of Thermal Cleavage Reaction. The thermal stabilities of Fe(II) gels with various degrees of functionalization are summarized in Table II. The cross-linking density, the number of the cross-linking points in the hydrogel network, plays an important role both for the degree of swelling and for the stability of the network. With increasing degree of functionalization, i.e., increasing cross-linking density, the lifetime of the complex gel increased from 2 h to 6 days and the degree of swelling decreased from 56 to 5.

The rate of ligand exchange reaction from intermolecular to intramolecular was assumed to be affected by the degree of swelling of the gel. From the kinetic aspect, at first, during the transformation of the gel from a shrunken state to a swollen state, the cleavage of the cross-linking was followed by swelling equilibrium. After the gel was swollen to some extent, the cleavage reaction took place together with the swelling. This gain in the degree of swelling caused the acceleration of the cleavage reaction. In the case of a lower degree of functionalization (3.3%), the cleavage of the gel and the swelling equilibrium occurred simultaneously, because this hydrogel had a potential of a large swelling property, which caused the cleavage reaction. The gel was solubilized in water only within 2 h. On the other hand, the Fe(II) complex gel, having a much higher cross-linking density, showed a longer lifetime. In this case, the degree of swelling of the gel was lower, which was not enough to accelerate the ligand exchange reaction to break the network. Although the swelling equilibrium was attained within a few hours, the complex gel was solubilized in water completely after the incubation for 6 days.

Temperature Dependence of the Lifetime of the Complex Gel. The ligand exchange or substitution reaction between the model metal tris(bipyridyl) complexes is known to be accelerated at higher temperatures. Table III illustrates the results of the thermal cleavage reaction of the metal complex gels.

In the case of the Ni(II) complex, the gel was easily converted to the soluble polymer even at low temperatures (40 °C, 38 min). The short lifetime of the Ni(II) complex gel was caused by the rapid ligand exchange reaction. The model Fe(II) tris(bipyridyl) complex is known to be more inert than that of Ni(II).[20,21] Therefore, the Fe(II) gel was much more stable under the same conditions (40 °C, 540 min). The Ru(II) tris(bipyridyl) model complex is known to be one of the most inert complexes. In fact, the gel from Ru(II) was extremely stable. Even after this gel was refluxed for 1 day in water, no cleavage product was detected by UV in a solution, and no change of the degree of swelling was observed. This incredible stability like the covalently cross-linked gel might be caused by the inertness of the Ru(II) tris(bipyridyl) complex toward the ligand substitution and exchange reaction. It should be noted again that the stability of the complex gel could be controlled by the nature of the central metal of the bipyridyl-modified PAEI complex and could be predicted from the kinetic inertness of the model complexes.[15]

Table II. Thermal Stabilities of Fe(II) Gels[a]

run	3		time (h)	degree of swelling[d]
	$\bar{M}_n$[b]	$n/(m+n)$[c]		
1	28 200	0.033	2	55.5
2	28 200	0.084	13	10.9
3	28 200	0.144	128	4.7
4	24 500	0.072	9	19.5

[a] Incubated at 40 °C, in 10 mL of H_2O, 160 stroke/min. [b] Determined by GPC (PS standard). [c] Determined by UV and ^1H NMR. [d] g of H_2O/g of dry gel (24 h in water).

Table III. Thermal Cleavage of Metal Complex Gels[a]

run	metal ion	temp (°C)	time (min)
1	Fe^{II}	40	540
2	Fe^{II}	60	35
3	Fe^{II}	72	14
4[b]	Fe^{II}	100[c]	<5
5[b]	Ru^{II}	100[c]	>1 day[d]
6	Ni^{II}	40	38

[a] Prepolymer: 7.2 mol % 2,2′-bipyridyl-modified, M_n = 24 500, incubated in 10 mL of H_2O, shaking with 160 stroke/min. [b] No stirring. [c] In boiling H_2O. [d] No apparent cleavage was observed.

The thermal behavior of the Fe(II) complex gel is especially noted here. At 40 °C, the Fe(II) gel was relatively stable and the lifetime was up to 6 h. However, at 100 °C, the same gel was dissolved within 5 min. This large difference in lifetime of the iron gel can be explained by the thermal activation of the ligand exchange reaction of the Fe(II) tris(bipyridyl) complex. Thus, the thermally-responsive gel system has been accomplished here.

A wide variety of the gels having various swelling properties and stabilities in water could be prepared by changing the metal salts. Ni(II) or more labile bivalent metal ions such as Co(II), Cu(II), and Zn(II) gave unstable gels or no gel. The gels as stable as the covalently cross-linked one could be prepared by using Ru(II) or more inert metal ions. The Fe(II) ion, the medium inert metal ion to bipyridyl, offered a thermally-responsive gel system.

Thermally Reversible Cycle. The Fe(II) complex gel turned soluble in water by heating or by swelling in water for a long time. The resulting soluble polymer was characterized as an intramolecular cross-linked Fe(II) tris(bipyridyl-branched PAEI) complex by UV and GPC analyses. This red polymer was dissolved in a small amount of water and concentrated to dryness slowly under normal pressure at a high temperature to form an insoluble red gel again. This red gel was also stable enough to be handled and swelled in water as large as its original gel. At the boiling point of water, the ligand exchange reaction should take place very rapidly. In other words, under this condition, the cross-linkings were gradually changed from the intramolecular manner to the intermolecular one to form a stable network. Thus, the Fe(II) tris(bipyridyl) complex gel can be recognized as an example of the thermally reversible hydrogels. This thermally reversible system was caused by the kinetic control of the ligand exchange reaction of the Fe(II) bipyridyl complex.

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