Cobalt(III) Bipyridyl-Branched Polyoxazoline Complex as a Thermally and Redox Reversible Hydrogel

Yoshiki Chujo,* Kazuki Sada,[1] and Takeo Saegusa[2]

Division of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-01, Japan

Received April 26, 1993; Revised Manuscript Received September 9, 1993[⊗]

ABSTRACT: Redox behavior and thermally reversible nature were observed in an intermolecular cross-linked metal complex between bipyridyl-branched polyoxazoline and the cobalt(III) ion. The 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 brown orange solution was concentrated slowly to dryness under atmospheric pressure to regenerate the cross-linked product in a 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 acceleration of the ligand exchange reaction changed these complex gels to the thermally reversible hydrogel. The results of the swelling behavior and the kinetics of the thermal cleavage reaction of the complex gel at 30 °C revealed 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. This gel was also completely dissolved in water by the rapid reduction of the central cobalt ion from the trivalent state to the divalent one. This interconversion from a hydrogel to a soluble polymer by reduction can be regarded as a novel redox reversible hydrogel system by means of kinetic control of the ligand exchange reaction coupled with the redox of the metal ions. Thus, this system can be recognized as the first example of a multisensitive hydrogel, i.e., the redox and thermally reversible hydrogel system.

Introduction

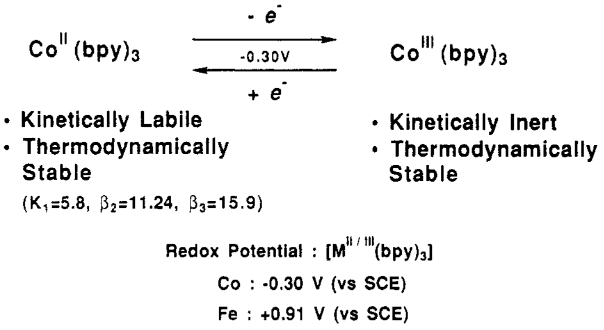
During the course of our study on the intermolecular complex of the bipyridyl-modified polyoxazoline and metal ions, the stability of the gel was found to be dependent not only on the thermodynamic stability but also on the kinetic inertness of the formed 2,2′-bipyridyl complexes.[3] For example, as reported in the preceding paper of this issue, the iron(II) ion afforded the thermally reversible hydrogel, but the ruthenium(II) complex gel was stable without solubilizing in water.

The thermally reversible hydrogel system is one of the topics of study on the hydrogel for use as a drug delivery system.[4–8] 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 water soluble polymers such as poly(*N*-alkylacrylamide)[9,10] or poly(vinyl alcohol).[11] Previously, we have reported the thermally reversible hydrogel system, which was caused by means of a Diels–Alder reaction between maleimide- and furan-modified polyoxazoline through the covalent bonds.[12]

The redox-active hydrogel system was also reported.[13] The reduction of the disulfide-bridged gel caused the cleavage of the cross-linkings to form the linear polymer containing the thiol groups. This thiol-modified polymer was oxidized under air in bulk film to regenerate the gel. This interconversion between the gel and the soluble polymer was based on the redox reaction of disulfide and thiol.

In this paper, the preparation of cobalt 2,2′-bipyridyl-modified polyoxazoline complex gels is described together with their thermal and redox properties. Cobalt bipyridyl complexes were studied extensively from the viewpoints of coordination chemistry of 2,2′-bipyridyl. The redox potential of Co(II)/(III) is reported to be −0.30 eV (vs SCE), as summarized in Scheme I. Compared with iron or ruthenium complexes, this redox potential is relatively low, so the redox of the central metal ion can be controlled more easily. Generally, the kinetic stability of the cobalt complex was changed by its oxidation state. In the case of divalent cobalt, the complexes with nitrogen-donor ligands are kinetically labile. On the contrary, the trivalent cobalt complexes are kinetically inert. Thus, the redox couple of cobalt(II) and cobalt(III) could offer the redox-sensitive hydrogel system.

Scheme I. Cobalt Tris(2,2′-bipyridyl) Complex



Experimental Section

Instruments and Materials. 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.

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.

2-Methyl-2-oxazoline was polymerized in the presence of methyl *p*-toluenesulfonate as an initiator to form poly(*N*-acetylethylenimine) (PAEI) and then was partially hydrolyzed by treatment with aqueous sodium hydroxide.[12] The degree of

---

[⊗] Abstract published in *Advance ACS Abstracts*, October 15, 1993.

0024-9297/93/2226-6320$04.00/0

hydrolysis, i.e., the amount of the 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.[3] 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 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.[3] The degree of swelling of the hydrogel was measured by the conventional filtration method.

Oxidative Gelation of Co(II) Bipyridyl Complex 2. A typical gelation reaction of bipyridyl-branched PAEI 1 is described as follows. Bipyridyl-modified PAEI (1) (3.8% modified, 101.7 mg, 0.074 mmol equiv) was dissolved in 0.175 mL of distilled water. Under vigorous stirring, 50 mL (0.03 mmol) of the stock solution (0.902 g/10 mL) of aqueous cobalt(II) nitrate hexahydrate was added to this polymer solution. The orange-yellow gel 2 was obtained, was oxidized to cobalt(III) by the addition of 0.1 mL of 30% aqueous hydrogen peroxide, and then kept stirring for 30 min more. To remove the unreacted polymer, the gel was immersed in 10 mL of methanol for 30 min. The brown gel was collected by filtration (glass frit, 1G4) and washed well with methanol. After drying in vacuo, 90.5 mg (70%) of the cobalt(III) PAEI gel 3 was obtained. The blank experiments were carried out under the same conditions described above.

Thermal Cleavage of Co(III) Complex Gel 3. The cobalt(III) complex gel (3, 38.7 mg) was swollen in 5 mL of distilled water. After the suspension was heated for 20 min, the solution was transferred to a dialysis tube, and dialyzed for several hours with distilled water. The polymer (30.8 mg, 79.5%) was obtained after the removal of the solvent and drying in vacuo.

Reductive Cleavage of the Co(III) Complex Gel (3). The cobalt(III) complex gel (3, 49.2 mg) was swollen in 3 mL of distilled water. To this solution was added 180 mg of sodium hydrosulfite. Within 5 min, the complex gel (3) dissolved. The orange solution was transferred into a dialysis tube. After the purification by dialysis in distilled water for several hours, the solution was concentrated to dryness under reduced pressure at room temperature. The orange-yellow polymer was recovered quantitatively.

Thermal Reversibility. The regelation of the intermolecular complexes of cobalt(III) bipyridyl PAEI by the concentration at high temperature was carried out by the similar method described previously.[14]

Kinetic Measurements. The kinetics of the cleavage reaction and the change of the swelling property of the cobalt(III) complex gel (3) were measured by the previously reported method except that the incubation temperature was adjusted at 30.0 °C.[14]

Synthesis of Intermolecular Complexes of Cobalt(II) or Cobalt(III) Bipyridyl-Branched PAEI. The intermolecular complexes of cobalt(II) or cobalt(III) bipyridyl-branched PAEIs were prepared by the same method as the complex gel described above except for the concentration of the polymer solution. In the cases of the intramolecular complexes, the coordination reaction was carried out in the diluted state (100 mg/3 mL).

Results and Discussion

Synthesis and Characterization of the Cobalt(III) Tris(Bipyridyl-Branched PAEI) Complex Gel (3). Bipyridyl-branched PAEIs (1) prepared by the reaction of partially hydrolyzed polymers with 3-{4-(4′-methyl-2,2′-bipyridyl)}propanoic acid in the presence of dicyclohexylcarbodiimide (DCC) were subjected to gelation via the metal coordination by treatment with aqueous cobalt(II) chloride followed by oxidation with hydrogen peroxide (Scheme II). The results of the gelation are shown in Table I, together with their degrees of swelling after incubation in water at room temperature for 24 h.

The gelation and the complex formation occurred within a few minutes after addition of aqueous cobalt(II) salt to the concentrated solution of bipyridyl-branched PAEI (1). However, the stability of the gel 2 was not enough to be handled in water or in methanol. The cobalt(II) complex gel (2) was dissolved within 30 min during washing with several portions of methanol (run 1 in Table I). This solubilization was caused by the ligand exchange reaction between the ligands bearing in the polymers from the intermolecular cross-linkings to the intramolecular ones. Under the same conditions, the cobalt(II) complex gel (2) was directly oxidized to the cobalt(III) tris(bipyridyl) complex by hydrogen peroxide. After the oxidation to the cobalt(III) complex, the complex gel 3 became stable even in water. After purification of the gel by washing with sufficient amounts of methanol and drying in vacuo, the complex gel was obtained in a relatively good yield. The formation of these cobalt complexes (2, 3) was confirmed by their UV spectra (λ_{max} = 303, 295 nm for the cobalt(II) complex (2), and λ_{max} = 312, 302 nm for the cobalt(III) complex gel (3), respectively). The cobalt(III) complex gels (3) were much more stable than the cobalt(II) complexes (2), and they had enough stability to be handled even in water, similarly to ferrous or ruthenium complex gels.[3]

Scheme II

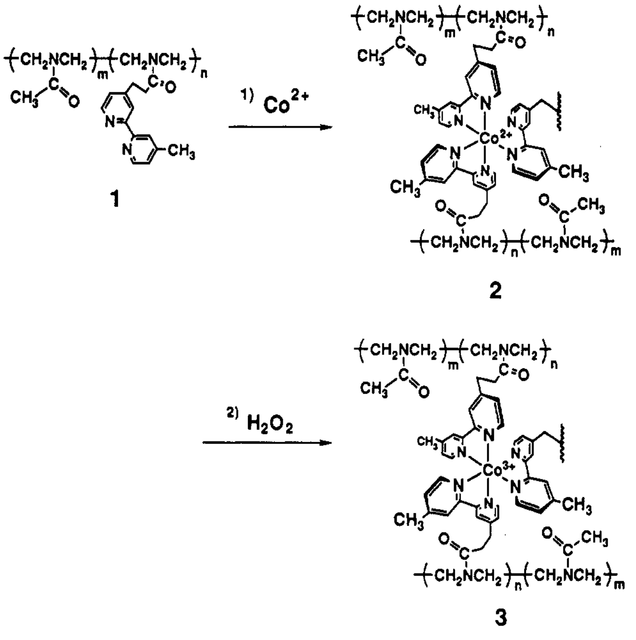


Table I. Gelation of Bpy–PAEI by the Cobalt Ion[a]

	2			metal complex gel	
run	$\bar{M}_n$[b]	$n/(m + n)$[c]	M^{n+}	yield (%)	degree of swelling[d]
1	15 800	0.038	Co^{II}	0[e]	
2[f]	15 800	0.038	Co^{III}	62	46.2
3[f]	24 500	0.072	Co^{III}	85	37.8
4[g]	24 500	0	Co^{II}	0[h]	
5[f,g]	24 500	0	Co^{III}	0[h]	

[a] [M^{n+}]/[Bpy] = 1/3, polymer/water = 1/2 (w/v). [b] Determined by GPC (PS standard). [c] Determined by UV and ^{1}H NMR. [d] g of H$_2$O/g of dry gel (in water for 24 h). [e] Dissolved in methanol within 30 min. [f] Oxidation by H$_2$O$_2$. [g] Hydrolyzed or nonhydrolyzed PAEI, with CoCl$_2$. [h] No gelation was observed.

In the absence of the bipyridyl moiety as a pendant group, the hydrolyzed or nonhydrolyzed PAEIs formed no cross-linked product by treatment with aqueous cobalt(II) salt, and/or the further oxidation of the cobalt(II) by aqueous hydrogen peroxide (runs 4 and 5 in Table I).

Thus, the stable hydrogel was obtained by oxidation of cobalt(II) tris(bipyridyl-branched PAEI) complex (2). Because of the kinetic inertness of the cobalt(III) complex, the gel was stable in water against the ligand exchange reaction and swollen as a hydrogel.

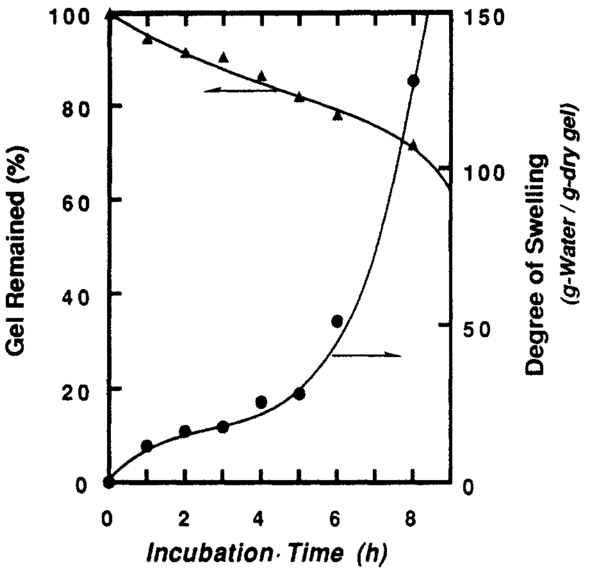


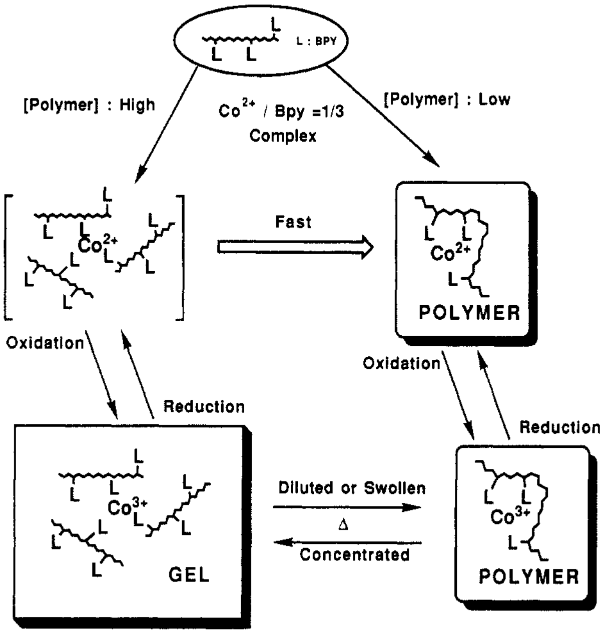
Figure 1. Thermal cleavage of cobalt(III) 2,2′-bipyridyl-modified PAEI complex gel 3.

Swelling Properties in Water. The degrees of swelling of the tris complex Co(III) gel are summarized in Table I. In this case, as reported before, the degree of swelling could be easily controlled by the degree of substitution of the bipyridyl groups.[3] This result shows that the cross-linking density, i.e., the degree of swelling, can be controlled by the degree of functionalization of the prepolymer.

Thermal Stability of the Cobalt(III) Complex PAEI Gel (3). Compared with other metal bipyridyl PAEI complex gels, the cobalt(III) complex gel (3) was moderately stable and swollen in water. On the other hand, the cobalt(II) complex gel (2) was too labile to be handled as a hydrogel in water. The cobalt(II) tris(2,2′-bipyridyl) complex is known as a labile complex, while the cobalt(III) complex is inert. The difference of the stability in water between the trivalent and divalent cobalt bipyridyl-PAEI gels was caused by the kinetic inertness of the formed complexes. The stability of the cobalt(III) complex gel was located just between the iron(II) complex and nickel(II). This order of stability as a PAEI gel is consistent with the kinetic inertness of the complexes.

Figure 1 shows the results of kinetics of the thermal cleavage of 7.2% functionalized PAEI gels at 30.0 °C in 10 mL of distilled water at 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 3 h and was saturated at the value of 20. The yield of the remaining gel was still up to 80%. This initial process might be caused mainly by the swelling equilibrium. During this time, the dry shrunk gel swelled more and more. It was reported that the time of 2–3 h was required for swelling to full extent in the covalently cross-linking systems based on the same polymer.[15,16] 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 Co(III) 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 the cobalt(III) tris(bipyridyl) complexes in the polymer pendant. As a result, the network was broken slowly from its surface to be solubilized in 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. Thus, in the first step, the normal swelling behavior was observed. As the second step, the swelling property was increased by the cleavage of the cross-linking points.

Scheme III



The UV spectrum of the resulting soluble polymer indicated no apparent change from its original gel, which was recognized mainly as a cobalt(III) tris(bipyridyl) complex. The gel permeation chromatographic analysis also indicated that the retention time of the soluble polymer was found to be longer than that of the original bipyridyl polymer (1). From the calculation based on polystyrene standard samples, the molecular weight of the regenerated polymer was found to be half that of its original bipyridyl-branched PAEI (1). This finding is different from that in the case of the Fe(II) complex.[14] To clarify this, the intermolecular complex of cobalt(II) or cobalt(III) bipyridyl PAEI was prepared under the diluted condition. These complexes had retention times similar to that of the regenerated polymer from the gel in the GPC analysis. Thus, the unexpected lower molecular weight in the case of the cobalt complexes might be due to the compact shape of the polymer by intramolecular cross-linkings or due to the interaction with the GPC column, which should be dependent on the nature of metal ions.[17]

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.

Thermally Reversible Cycle. The cobalt(III) complex gel (3) turned soluble in water by heating as described above. The resulting soluble polymer was characterized as an intramolecular cross-linked cobalt(III) tris(bipyridyl-modified PAEI) complex by UV and GPC analyses. This brown polymer was dissolved in a small amount of water, and the solution was concentrated to dryness slowly under the normal pressure at a high temperature to form an insoluble gel. At the boiling point of water, the ligand exchange reaction should be performed very fast. In other words, under this condition, the cross-linkings were gradually changed from an intramolecular manner to an intermolecular manner to form a stable network. Thus, the cobalt(III) tris(bipyridyl) complex gel can be recognized as an example of the thermally reversible hydrogels as well as the iron(II) complex gel.[14] This thermally reversible system was caused by the kinetic control of the ligand exchange reaction.

Reductive Cleavage of the Co(III) Complex Gel (3). The cobalt(III) complex gel (**3**) was reduced by sodium hydrosulfite to form a cobalt(II) complex. After addition of the reducing agent, the cobalt(III) complex gel (**3**) was dissolved within 20 min even at room temperature. The change of the color of the cobalt(III) gel to the bright cobalt(II) complex occurred gradually at the surface of the gel. The interface between the gel and the solvent became unclear. The reduction of the central metal ion of the intermolecular complexes to cobalt(II) caused the change of the kinetic and the thermodynamic stability of the complex. In this case, the resulting cobalt(II) complex was labile, so the intermolecular cross-linking by the metal coordination was broken by the rapid ligand exchange reaction between the ligands as a pendant group of the polymer. From UV absorption of the regenerated polymer, the cobalt(II) tris(bipyridyl) PAEI complex was formed. The regenerated polymer could be oxidized with hydrogen peroxide to yield the trivalent metal complex again. The cobalt(III) complex gel was reduced to the cobalt(II) complex gel, which was unstable in water because of its kinetic lability, and turned soluble to form the intermolecular cross-linked cobalt(II) complex. Thus, this cobalt(III) bipyridyl-modified PAEI complex gel can be recognized as an example of a redox reversible hydrogel.

In conclusion, it should be noted that the present system can be regarded as the first example of a multiresponsed reversible hydrogel system (redox and thermally reversible system) based on the kinetic control of the cobalt tris(pyridyl) complex (Scheme III). The control of the kinetic and the thermodynamic stability of the intermolecular metal complex by the redox reaction (the oxidation state) of the central metal or the thermal activation of the ligand exchange reaction afforded us a multiresponsed gel. From the viewpoint of macromolecular coordination chemistry, the present system may offer interesting hydrogel materials.

References and Notes

(1) Present address: Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 505-11, Japan.
(2) Present address: KRI International Inc., Chudoji, Shimogyo-ku, Kyoto 600, Japan.
(3) Chujo, Y.; Sada, K.; Saegusa, T. *Polym. J.* **1993**, *25*, 599.
(4) Hoffman, A. S.; Afrassiabi, A.; Dong, L. C. *J. Controlled Release* **1986**, *4*, 213.
(5) Dong, L. C.; Hoffman, A. S. *J. Controlled Release* **1986**, *4*, 223.
(6) Afrassiabi, A.; Hoffman, A. S.; Cadwell, L. A. *J. Membr. Sci.* **1987**, *33*, 191.
(7) Bae, Y. H.; Okano, T.; Hsu, R.; Kim, S. W. *Makromol. Chem., Rapid Commun.* **1987**, *8*, 481.
(8) Bae, Y. H.; Okano, T.; Kim, S. W. *Makromol. Chem., Rapid Commun.* **1988**, *9*, 185.
(9) Yoshida, M.; Asano, M.; Kumakura, M. *Eur. Polym. J.* **1989**, *25*, 1197.
(10) Hirotsu, S.; Hirokawa, Y.; Tanaka, T. *J. Chem. Phys.* **1987**, *87*, 1392.
(11) Hyon, S. H.; Cha, W. I.; Ikada, Y. *Polym. Bull.* **1989**, *22*, 119.
(12) Chujo, Y.; Sada, K.; Saegusa, T. *Macromolecules* **1990**, *23*, 2638.
(13) Chujo, Y.; Sada, K.; Saegusa, T. *Macromolecules* **1993**, *26*, 883.
(14) Chujo, Y.; Sada, K.; Saegusa, T. Preceding paper in this issue.
(15) Chujo, Y.; Yoshifuji, Y.; Sada, K.; Saegusa, T. *Macromolecules* **1989**, *22*, 1074.
(16) Chujo, Y.; Sada, K.; Matsumoto, K.; Saegusa, T. *Macromolecules* **1990**, *23*, 1234.
(17) It is at present not clarified that the Fe(II) and Co(II) polymer complexes showed different natures in the GPC measurement.