Polyelectrolyte Complex Gel with High pH-Sensitivity Prepared from Dextran Sulfate and Chitosan

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ABSTRACT: Swelling equilibria of polyelectrolyte complex gels composed of dextran sulfate and chitosan were studied in dilute NaOH or HCl solutions of various pH values with or without NaCl. The complex gel with approximately equal concentrations of sulfate and amino groups was found to be highly sensitive to the change in external pH in a narrow alkaline range. The maximum equilibrium volume of the complex gel was observed at pH 10.5 and was about 300 times as large as the initial one. Compared with the swelling equilibria of a complex gel prepared from κ-carrageenan and chitosan with approximately equal concentrations of sulfate and amino groups, it is suggested that the initial high density of the ionizable functional groups as well as the flexibility of acidic polymer chain contributes to the high pH sensitivity. The increase in ionic strength of the external solution caused the decrease in gel volume and the shift of the pH value at which the maximum swelling occurred. The shift of the pH value was shown to be understood in terms of the change in the internal pH. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 2227–2233, 1999

Key words: polyelectrolyte complex gel; pH-sensitive swelling; chitosan; dextran sulfate; Donnan equilibrium

INTRODUCTION

Several hydrogels can change their volume in response to change in such environmental factors as temperature,[1–4] pH,[5–8] electric field,[9] and light.[10] Those stimuli-sensitive hydrogels have attracted considerable attention not only from the scientific point of view but also due to their technological importance. Volume change of stimuli-sensitive hydrogels may be utilized in various application areas including drug delivery systems to control the drug release, mechano-chemical devices, and separation agents.

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Previously, one of the authors showed that hydrogels sensitive to external pH change can be prepared by polyelectrolyte complex formation between an acidic polymer, κ-carrageenan having sulfate groups or xanthan gum having carboxyl groups, and a basic polymer, chitosan.[11,12] Chitosan, having amino groups, acts as a polycation at low pH values and hence forms a polyelectrolyte complex with a polyanion. In a range of alkaline pH, the net charge fixed on the complex gel, which is an essential factor determining the volume of polyelectrolyte complex gels,[13] is affected by pH due to the variation in the degree of ionization of amino groups of chitosan. Thus, the complex gels prepared from an acidic polymer and chitosan exhibit pH-sensitive swelling in a range of alkaline pH. However, the degrees of volume change induced by the change in external pH were not so large for the polyelectrolyte complex gels prepared using chitosan as a basic polymer in previous works.[11,12]

In this article, we report the swelling equilibria of a polyelectrolyte complex gel prepared from dextran sulfate and chitosan. The dextran sulfate/chitosan complex gel was found to have considerably high sensitivity to external pH change. The swelling equilibria of a complex gel prepared from κ-carrageenan and chitosan are also reported here for comparison. The swelling behavior of a κ-carrageenan/chitosan complex gel was studied in a previous work,[11] where no attention was given to the composition of cations originally contained in κ-carrageenan. In this study, sodium salt of κ-carrageenan was prepared and used for gel preparation. The effect of ionic strength on the swelling equilibria of the dextran sulfate/chitosan complex gel is also discussed in terms of internal pH of the complex gel.

EXPERIMENTAL

Polyelectrolytes

Chitosan (Chitosan 8B) was a product of Katokichi (Kagawa, Japan). Degree of *N*-acetylation of the chitosan was 18.1%. Viscosity of 0.5% solution of the chitosan in 0.2 M acetic acid was 0.257 Pa · s at 20°C. Dextran sulfate sodium salt, an average molecular weight of which was 5×10^5, was purchased from Pharmacia (Uppsala, Sweden). These materials were used without further purification. Kappa-Carrageenan (type III) was purchased from Sigma (St. Louis, MO). It contained calcium (2.7%) and potassium (3.7%) in addition to sodium (0.7%) as counterions. To prepare sodium salt of κ-carrageenan, 10 g of cation exchange resin (Dowex MSC-1, Na^+ form) was suspended in 100 ml of aqueous solution of 1% κ-carrageenan and incubated at room temperature for 1 day with gentle shaking. The supernatant obtained by decantation was incubated again with 10 g of the cation exchange resin for 1 day. Negligible amounts of potassium and calcium were found in the final supernatant by the measurement with an atomic adsorption spectrophotometer (Hitachi 150-50A, Tokyo, Japan). The solution of κ-carrageenan sodium salt thus obtained was appropriately concentrated with a rotary evaporator at about 50°C.

Preparation of Cylindrical Polyelectrolyte Complex Gel

Chitosan and dextran sulfate were dissolved in 2% acetic acid and deionized water, respectively. After one tenth part of NaCl was added to each solution, the solutions were heated in boiling water to decrease their viscosity, and then mixed with each other. The addition of NaCl is essential to prepare a polyelectrolyte complex gel as shown in the previous article.[11] In most cases, final concentrations of chitosan and dextran sulfate in the mixture were both 3%. The molar ratio of sulfate groups to amino groups contained in the mixture (referred to as S/N ratio hereafter) was 1.04 for this composition. In some preparations, S/N ratio of the mixture was varied by changing the final concentration of dextran sulfate. Cylindrical frames (1 mm in inner diameter and 8 mm in length) were put into the mixture. The mixture was centrifuged at 3000 rpm for 10 min to remove air bubbles, and left at 5°C for 1 day. The cylindrical frames filled with the mixture were taken out and rinsed in distilled water to remove salts contained in the gel at least for 2 days. The cylindrical complex gel thus formed was withdrawn from the frame and stored in deionized water until use for swelling experiments.

For comparison, a complex gel in a cylindrical form was prepared from κ-carrageenan and chitosan by the same procedure as described in the previous article,[11] using sodium salt of κ-carrageenan. The final concentrations of chitosan and κ-carrageenan in the mixture before gel formation were 1.5 and 3%, respectively, corresponding to the S/N ratio of 0.96.

Swelling Experiments

In a 50-ml tissue culture flask, a piece of the cylindrical complex gel was immersed in 30 ml of a dilute HCl or NaOH solution at 30°C. In some experiments, NaCl was added to the solution to study the effect of ionic strength on the swelling equilibrium. The flask was purged with N_2 gas and sealed to avoid the dissolution of CO_2. The diameter of the gel was measured microscopically at appropriate intervals until the size of the gel ceased to change. The degree of swelling at the equilibrium was evaluated by means of the equilibrium swelling ratio defined as $(d_e/d_i)^3$, where d_e and d_i are the equilibrium and initial diameters of the cylindrical gel, respectively.

Estimation of pH Value Inside the Complex Gel

Information on pH inside the complex gel is important to understand the swelling behavior. The value of pH inside the complex gel in a swelling equilibrium was estimated by using a model based on the Donnan equilibrium[13] as follows.

According to the Donnan potential created by fixed charge of a polyelectrolyte gel, mobile ions are distributed between the gel and the external solution as described in the following equation, where activity coefficients of all the ions are assumed to be unity for simplicity and the effect of swelling pressure is negligible.

$$C_i^G/C_i^S = K^{Z_i} \quad (1)$$

where C_i^G and C_i^S are the concentrations of the mobile ion i in the gel and in the solution, respectively, and Z_i, the valency of the ion i. The Donnan ratio, K, which depends on such external conditions as pH and ionic strength, is identical for all ion species.

For a polyelectrolyte complex gel with a species of univalent acidic group and a species of univalent basic group, the charge balance equation in the gel is

$$\sum_i Z_i C_i^G - \alpha_a C_a^G/X + \alpha_b C_b^G/X = 0 \quad (2)$$

where C_a^G and C_b^G are the initial concentrations of acidic and basic groups fixed in the complex gel, respectively, α_a and α_b, degrees of ionization of the acidic and basic groups, respectively, and X, the equilibrium swelling ratio.

Both kinds of the complex gels used in this study have sulfate group as the acidic group and amino group as the basic group. The degree of ionization of the sulfate groups, α_a, can be assumed as unity unless pH is extremely low. The degree of ionization of the amino groups, α_b, is related to the dissociation constant of protonated amino groups, K_b, as follows:

$$K_b = C_H^G(1 - \alpha_b)/\alpha_b \quad (3)$$

where C_H^G is the concentration of proton in the gel.

Using Eqs. (1) and (3), Eq. (2) can be expressed in terms of the external concentrations of mobile ion species including proton:

$$\sum_i Z_i K^{Z_i} C_i^S - C_a^G/X + K C_H^G C_b^G/\{(K C_H^G + K_b)X\} = 0 \quad (4)$$

We obtained the value of Donnan ratio, K, from Eq. (4) with experimental values for C_i^S, C_a^G, C_b^G, and X. In the calculation, we assumed that the dissociation constant of protonated amino groups in the complex gel was equal to that of protonated amino groups in chitosan, and hence $pK_b = -\log K_b = 6.3$.[14] With the value of K obtained, the value of pH inside the gel was calculated as $-\log C_H^G = -\log (K C_H^S)$.

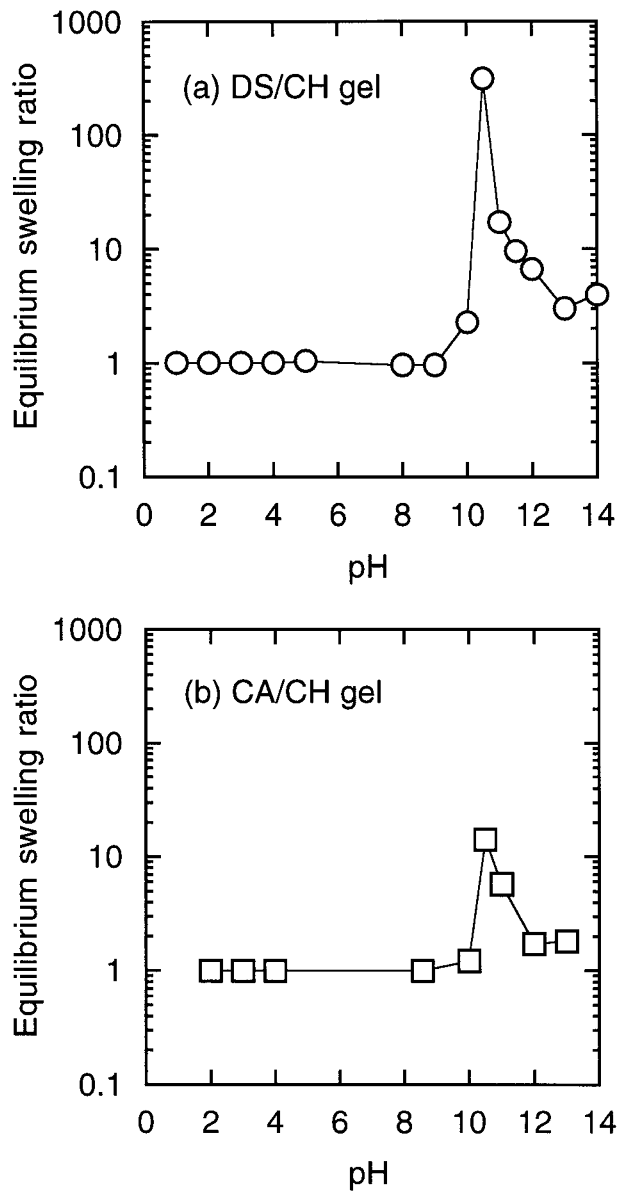

Figure 1 Equilibrium swelling ratios of (a) DS/CH gel and (b) CA/CH gel in dilute NaOH or HCl solutions.

RESULTS AND DISCUSSION

Figure 1 compares the equilibrium swelling ratios of a dextran sulfate/chitosan complex gel (DS/CH gel) and a κ-carrageenan/chitosan complex gel (CA/CH gel) in dilute NaOH or HCl solutions. The values of S/N ratio were approximate unity for both gels: 1.04 for DS/CH gel and 0.96 for CA/CH gel. Estimated from the initial diameters of the cylindrical gels, the concentrations of amino group in DS/CH gel and in CA/CH gel were 455 mM and 94 mM, respectively. Each gel swelled only in the range of pH between 10 and 12, and took the maximum volume at pH 10.5. The maximum equilibrium swelling ratio of DS/CH gel was about 300, which was much greater than that of CA/CH gel. Similar swelling profiles in the region of alkaline pH have been reported for a complex gel prepared from xanthan gum and chitosan[12] and for a membrane prepared from poly(acrylic acid) and chitosan.[15] The xanthan/chitosan complex gel was reported to take the maximum swelling ratio of about 50 at pH 10. The poly(acrylic acid)/chitosan membrane was reported to swell at pH values above 8 and to take the maximum weight, which was about 6 times its dry weight, at pH 11. Thus, DS/CH gel prepared in this study was highly sensitive to the pH change in a narrow alkaline region.

Swelling of each gel at an alkaline pH can be ascribed to the dissociation of protonated amino groups of chitosan into the uncharged form. In the initial state, sulfate groups and amino groups in the complex gel are considered to be oppositely charged and electrostatically bound to each other. When the complex gel is immersed in an alkaline solution, the amino groups become neutralized, while the sulfate groups remain negatively charged. Thus, electrostatic interaction between the two functional groups disappears, and the complex gel becomes negatively charged. Due to the increase in the net negative charge, mobile cations are taken up by the gel from the external solution. Thus, swelling occurs due to the increase in the osmotic pressure of the complex gel. At pH values above 10.5, the equilibrium swelling ratio decreased with the increase in pH, which may be ascribed to the increase in ionic strength of the external solution with its pH.

Based on the above discussion, pH sensitivity of a complex gel can be affected by the concentration of amino group in the complex gel. As mentioned above, the initial concentration of amino group in DS/CH gel was about 5 times as large as that in CA/CH gel. However, the degree of maximum volume change of DS/CH gel was about 20 times as large as that of CA/CH gel. This suggests that the high pH sensitivity of DS/CH gel cannot be explained by the difference in the amino group concentration alone. Generally, the volume of an ionic gel is assumed to be determined by a balance of two pressures.[6] One is the ion swelling pressure or osmotic pressure, which is due to the difference in mobile ion concentrations between the gel and the external solution. The other is the network swelling pressure that tends to keep the gel volume constant. In swelling equilibrium, the osmotic pressure should be balanced with the network swelling pressure or contractile force. In swelling equilibria at pH 10.5, the amino group concentrations in DS/CH gel and in CA/CH gel were 1.4 mM and 6.6 mM, respectively. Thus, at maximum swelling, the amount of net negative charge in CA/CH gel was larger than that in DS/CH gel, and hence the osmotic pressure of CA/CH gel was higher than that of DS/CH gel. Therefore, compared with DS/CH gel, CA/CH gel reached swelling equilibrium with a lower degree of swelling and stronger contractile force. Since κ-carrageenan itself is a gel-forming polymer,[16] it may form a rigid matrix in CA/CH gel. In contrast, dextran sulfate never forms gel by itself. Flexibility of the acidic polymer chain probably contributed to the higher sensitivity of DS/CH gel.

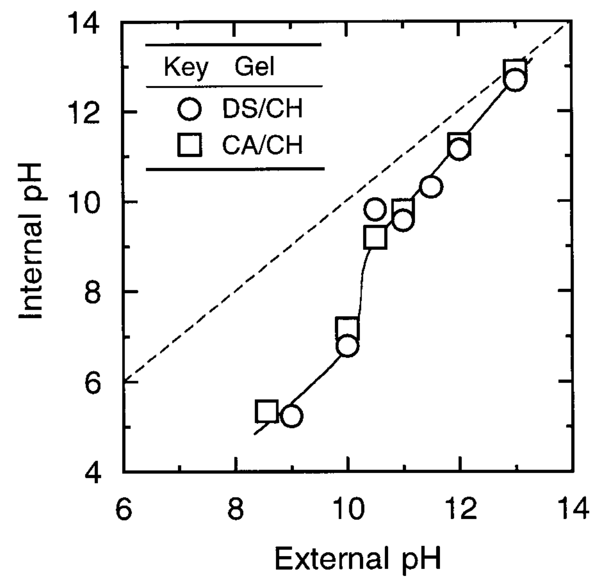

Figure 2 Values of pH inside the complex gels estimated from the data shown in Figure 1. Key: (○), DS/CH gel; (□), CA/CH gel. The broken line represents the points at which the internal pH equals the external pH.

Each complex gel did not swell even at pH 9, though the value of pK_b (K_b refers to the dissoci-

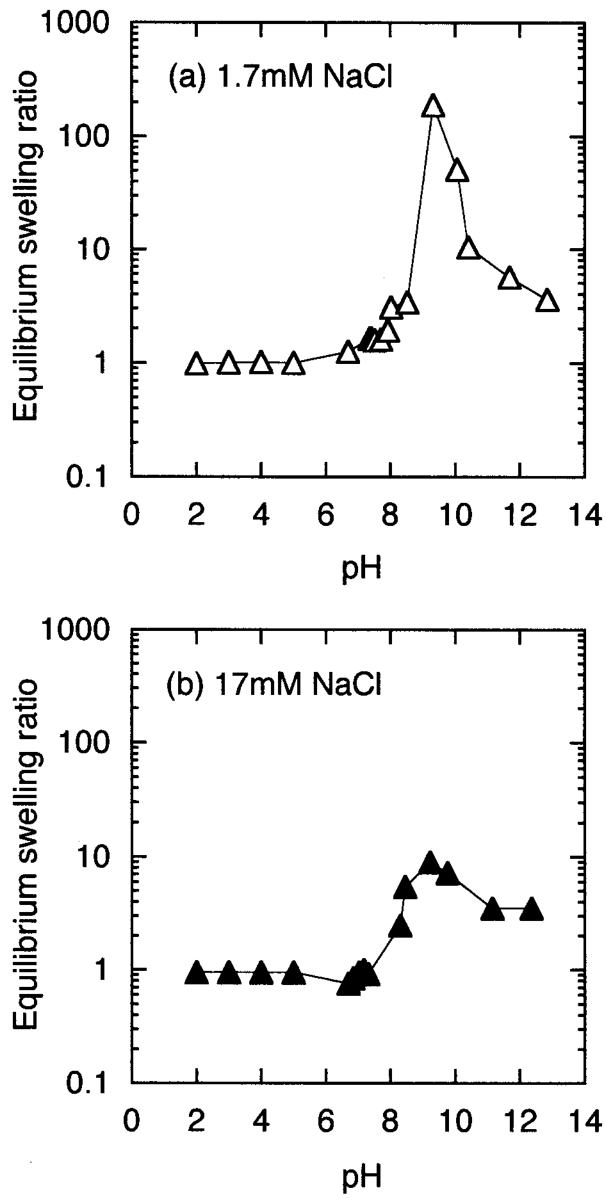

Figure 3 Equilibrium swelling ratios of DS/CH gel in the presence of NaCl. NaCl concentration: (a) 1.7 mM; (b) 17 mM.

ation constant of protonated amino groups) of chitosan is 6.3.[14] This discrepancy may be due to the difference between the internal and external pH values. If the complex gel has net negative charge, anions including OH^- will be excluded from the complex gel, and hence the internal pH becomes lower than the external pH. To confirm this, the internal pH value was estimated assuming Donnan equilibrium for each swelling experiment done at the external pH above 8. The results are shown in Figure 2 as a function of external pH. It is noteworthy that the profiles of the internal pH for DS/CH gel and CA/CH gel were almost the same despite the difference in the degree of swelling. The internal pH was always lower than the external pH. Moreover, the lower the external pH, the larger the difference between the external and internal pH values. The ionic strength of the external solution, which varied with pH in this case, is probably one of the factors affecting the difference between the external and internal pH values, especially at the external pH values above 10.5. High ionic strength can reduce the difference in the external and internal pH values by shielding the electrostatic interaction. As shown in Figure 2, the internal pH steeply increased and got closer to the external pH when the external pH was raised from 10 to 10.5. This is probably due to the change in net charge density of the complex gel. In the range of the external pH from 10 to 10.5, the net charge density of the complex gel is affected by the dissociation of protonated amino groups that occurred at the internal pH near the pK_b value and the considerable increase in gel volume. The effects of the two factors are opposite to each other. The steep increase in the internal pH shown in Figure 2 indicates that the effect of volume change on the charge density is much greater than the effect of the dissociation of protonated amino groups.

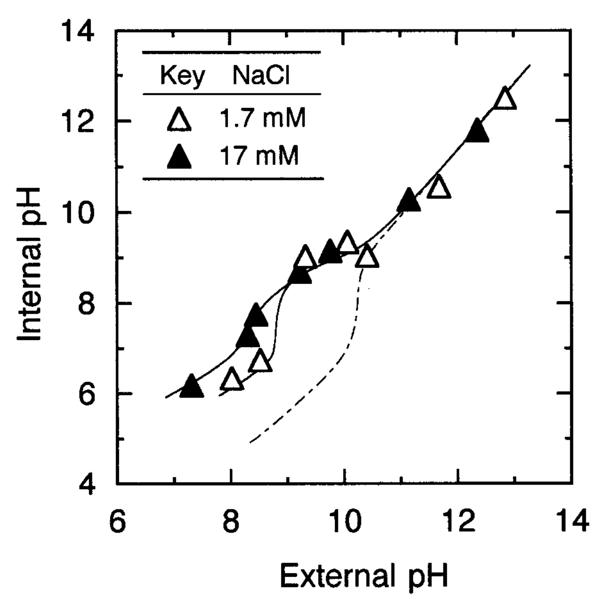

Figure 4 Values of pH inside DS/CH gel estimated from the data shown in Figure 3. NaCl concentration: (△), 1.7 mM; (▲), 17 mM. The dash-dotted curve represents the result estimated for 0 mM NaCl shown in Figure 2.

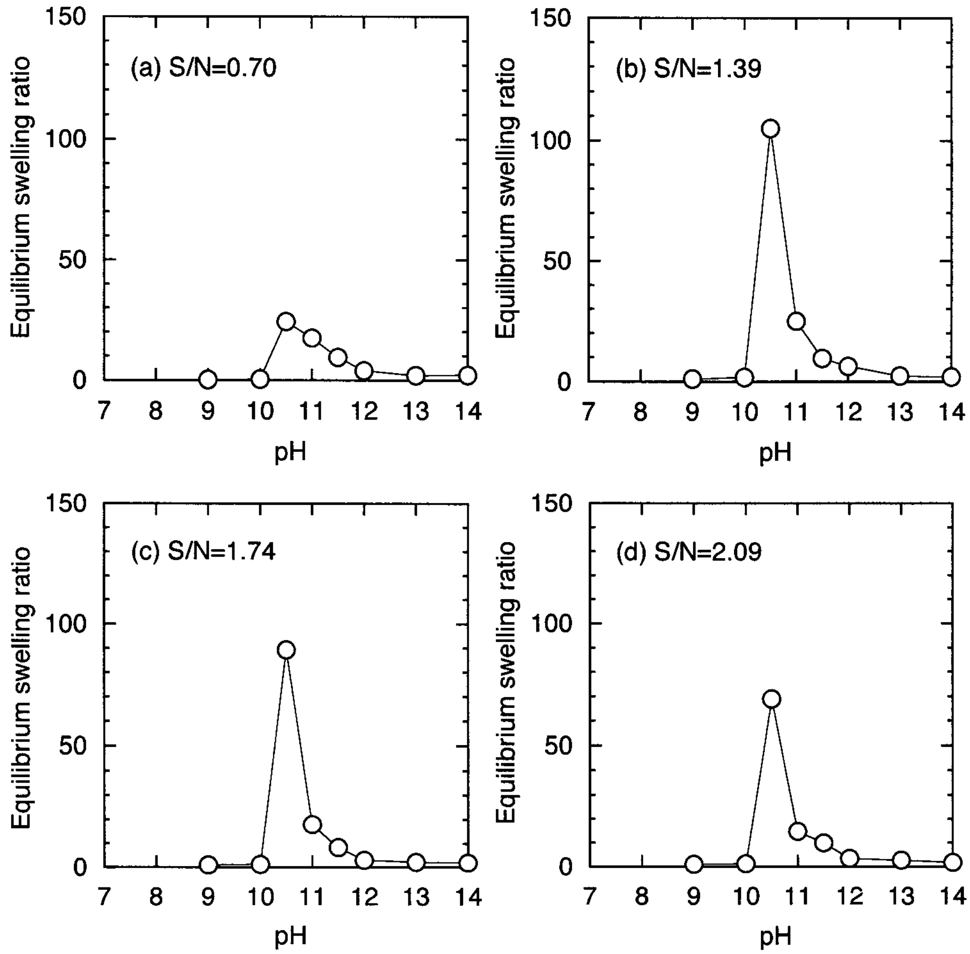

Figure 5 Equilibrium swelling ratios of DS/CH gels with different compositions in dilute NaOH solutions. S/N ratio refers to the molar ratio of sulfate groups to amino groups in the complex gel.

Figure 3 shows the equilibrium swelling ratio of DS/CH gel in aqueous NaOH or HCl solutions containing 1.7 mM or 17 mM NaCl. As the concentration of NaCl in the external solution increased, the equilibrium swelling ratio decreased. This can be ascribed to the increase in osmotic pressure of the external solution. In addition to that, the increase in NaCl concentration shifted the value of pH at which the maximum swelling occurred to the neutral side. This can be understood by taking into consideration the pH variation inside the complex gel. Figure 4 shows the internal pH values estimated for swelling equilibria in the presence of 1.7 mM or 17 mM NaCl. For comparison, the internal pH values estimated for the swelling experiments without NaCl addition (results shown in Fig. 2) are shown again in Figure 4 as a dash-dotted curve. When NaCl concentration increased, the internal pH got closer to the external pH, especially in the range of external pH between 8 and 10. Thus, the high ionic strength of the external solution caused the shift of pH value at which the maximum swelling occurred by reducing the difference in the external and internal pH values.

Figure 5 shows a comparison of the equilibrium swelling ratios of DS/CH gels with different S/N ratios in dilute solutions of NaOH without addition of NaCl. Irrespective of S/N ratio, DS/CH gels swelled in a narrow range of alkaline pH and took the maximum volume at pH 10.5. However, the maximum value of swelling ratio decreased as S/N ratio was moved apart from unity. Especially for the gel with insufficient sulfate groups (S/N = 0.70), the maximum value of equilibrium swelling ratio was quite low. For further discussion, the initial volume (the volume in deionized water just before the swelling experiment) and the equi-

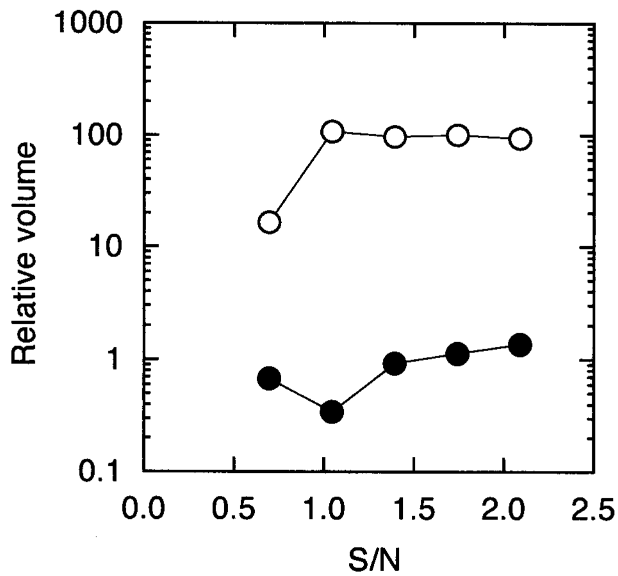

Figure 6 Comparison of initial and equilibrium volumes of DS/CH gels with different composition. The gel volume was normalized with the inner volume of the cylindrical frame used for gel preparation. Key: (●), initial volume; (○) equilibrium volume in a dilute NaOH solution of pH 10.5.

librium volumes at pH 10.5 are compared in Figure 6. The initial volume of DS/CH gel became minimum when S/N ratio was approximately at unity because of the minimum net charge fixed on the gel. When S/N ratio was lower than unity, the equilibrium volume at pH 10.5 was low. The reason for this can be considered as follows. DS/CH gels are negatively charged at pH 10.5. The negative charge density, which affects the equilibrium volume, is determined by the concentration of sulfate group in DS/CH gel. Thus, DS/CH gel with a low S/N ratio should have small equilibrium volume because of a low content of sulfate group. For DS/CH gels with S/N ratio higher than unity, however, the equilibrium volumes at pH 10.5 were almost the same. This might be due to the increase in contractile force caused by more entanglements induced by the increased concentration of dextran sulfate.

CONCLUSIONS

A hydrogel with high sensitivity to the change in external pH was prepared by polyelectrolyte complex formation between dextran sulfate and chitosan. The volume change of the complex gel occurred in a rather narrow range of alkaline pH. The maximum volume of the complex gel was observed in a dilute NaOH solution at pH 10.5, and was about 300 times as large as the volume at pH values below 9. Factors contributing to the high sensitivity of the complex gel can be summarized as follows: 1. equal and high densities of amino and sulfate groups in the initial state; and 2. flexibility of the acidic polymer chain. The increase in ionic strength of the external solution caused the decrease in gel volume and the shift of the pH value at which the maximum swelling occurred. This shift of the pH value was shown to be understood in terms of the change in the internal pH.

The sensitivity of the complex gel reported herein was substantially great. The complex gel prepared from dextran sulfate and chitosan might be useful in various application areas because a large volume change can be induced by a small change in pH around 10.

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