Traveling Chemical Waves for Measuring Solute Diffusivity in Thermosensitive Poly(*N*-isopropylacrylamide) Gel

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We have evaluated solute diffusivity in a gel by utilizing the Belousov−Zhabotinsky (BZ) reaction which is known as an oscillating reaction generating periodical redox changes of catalyst. The BZ reaction was induced in thermosensitive poly(*N*-isopropylacrylamide) (PNIPAAm) gel. By measurement of the velocity of an excited pulse of the oxidized catalyst (i.e., chemical wave) which propagates in the gel, the diffusivity of $HBrO_2$ as an intermediate in the gel was determined. The temperature dependence of the diffusivity was investigated for the PNIPAAm gel and bulk solution systems. Contrary to the bulk solution system, the diffusivity in the PNIPAAm gel decreased when increasing temperature. It was found that transport of solute through the gel was controlled by regulating the swelling properties of the gel. From a comparison with the diffusivity obtained from a conventional permeability measurement using a gel membrane, the new measuring method was found to be capable of almost same precision as the conventional method. The monitoring of the chemical wave would provide a novel experimental way for study of polymer gels.

Introduction

The Belousov−Zhabotinsky (BZ) reaction[1−3] is known as an oscillating reaction generating periodical redox changes of catalyst. In spatially distributed reacting media, an excited pulse of the oxidized catalyst, i.e., "chemical wave", evolves and propagates due to the diffusion of $HBrO_2$ as an intermediate. Therefore, the velocity of the chemical wave should depend on the diffusivity of $HBrO_2$ in the medium. So far, use of gels as a supporting matrix has provided several advantages in the understanding of the BZ mechanism.[4,5] However, there are few studies to apply the chemical wave for estimation of structure of the medium. Amemiya et al.[6] measured the velocity of the chemical waves in Vycor glass. The reduced velocity was explained in connection with physical structure of Vycor glass by using a model where a fractal-like structure of the channel network is represented by the tortuosity. These results suggest that the monitoring of the chemical wave would provide a novel experimental way to analyze structure and physical property of the medium.

Over the last two decades, many kinds of polymeric gels undergoing abrupt volume change (i.e., volume phase transition) in response to external stimuli such as a change in solvent composition or temperature,[7,8] pH,[9] electric field,[10] etc., have been developed.[11] In particular, gels consisting of *N*-isopropylacrylamide (NIPAAm) which swell by cooling and deswell by heating have been widely studied.[12,13] Recently, a novel "self-oscillating" gel which autonomously swells and deswells periodically without any external stimuli has been prepared by utilizing NIPAAm, and the dynamic oscillating behaviors were investigated.[14−18] Such gels attracted much attention for use in smart materials. Many applications for these gels have been explored for industrial and biomedical fields such as actuator (chemomechanical system),[19,20] purification of chemical or bioactive agents,[21] cell culture,[22] regulation of enzymatic reactions,[23] chemical or biosensor,[24] and drug delivery systems,[25,26] etc.

Solute diffusivity in gels is an important factor when designing polymer gel-based on−off control systems for solute release or permeation. Conventionally, solute diffusivity in gels has been mainly determined by measuring the permeability through a gel membrane using a two-chamber permeation cell.[27] By the coupling of the BZ reaction with gels, however, analyses of structure and physical properties of gels are expected. In this study, we tried to apply the new analytical procedure utilizing the BZ reaction to thermosensitive poly(NIPAAm) (PNIPAAm) gels, which are widely studied. We have performed the measurements of the velocity of the chemical wave, using the PNIPAAm gel in which the $Ru(bpy)_3$ catalyst was physically adsorbed. Through a theoretical analysis of the chemical wave as employed by Amemiya et al.,[6] we have estimated the diffusivity of $HBrO_2$ within the gel phase. The temperature dependence of diffusivity was studied and compared with that for a bulk solution system. The results obtained were discussed in connection with a structural change of the gel network by temperature. To verify the diffusivity obtained from the new measuring method, we also determined the diffusivity by the conventional method of measuring permeability through the gel membrane. These diffusivities obtained from two methods were compared.

Experimental Section

Preparation of PNIPAAm Gels. *N*-Isopropylacrylamide (NIPAAm; Eastman Kodak Co., Rochester, NY) was purified by recrystallization from its toluene solution with *n*-hexane. 2,2′-Azobisisobutyronitrile (AIBN; Wako Pure Chemical Industries, Co., Ltd., Osaka, Japan) was recrystallized from methanol. *N*,*N*′-Methylenebisacrylamide (MBAAm; Kanto Chemical Co., To-

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kyo, Japan) was used as received. NIPAAm (0.156 g) and MBAAm (2.6 mg) were dissolved in 1 mL of O_2-free methanol, and then the solution was mixed with 6.2 mg of AIBN. This monomer solution was quickly injected into a space (0.5 mm) between two Mylar sheets which had been backed by a glass plate and separated by a Teflon spacer. The gelation was carried out at 60 °C for 18 h. To remove unreacted monomers, the gel membrane obtained was immersed in pure methanol for 1 day without stirring; this procedure was allowed to continue for 1 week with fresh methanol. Finally, the purified membrane was carefully hydrated through dipping it in a graded series of water−methanol mixtures, for 1 day each in 25, 50, 75, and 100% (v/v) water.

Measurements of Swelling Behavior. The gelation was also carried out in a glass capillary with inner diameter of 0.273 mm. After gelation was completed, the gels were taken out of the capillary and washed in the same manner for employed in gel membrane. The gel samples obtained were cut into cylinders of approximately 5 mm in length and inserted into a water-jacketed microcell together with either pure water or the BZ solution containing malonic acid (MA) (0.0625 M), sodium bromate (0.084 M), nitric acid (0.3 M), and $Ru(bpy)_3Cl_2$ (25 mM). The gel diameter was then determined as a function of temperature by using a microscope with a calibrated scale. During the measurements, the temperature was controlled by circulating thermostated water through the water-jacket around the cell.

Measurements of Velocity of Chemical Waves in Gels. The obtained PNIPAAm gel membrane was soaked into an aqueous solution containing 33 mM $Ru(bpy)_3Cl_2$ for several hours. The $Ru(bpy)_3^{2+}$-immobilized gel membrane was cut into rectangles (side length, about 1×10 mm). The section was then immersed into 8 mL of an aqueous solution containing MA, sodium bromate, and nitric acid maintained at several constant temperatures. Chemical waves were observed under a microscope (Leica, model M420) equipped with a black−white CCD camera (SONY, model SSC-M370) and a video recorder (Panasonic, model AG-6760). We used monochromatic light passed through a blue filter (Kenko B-390) on the halogen light source. Color changes due to the periodical oxidation and reduction of the $Ru(bpy)_3$ moieties within the gel were measured by means of transmitted light. The time-dependent change in transmittance was then converted to gray scale changes. The video images were transferred through a digital time base corrector (FOR.A, model FA-310) to a computer (NEC, model PC-9801RA) equipped with an image acquisition board (Micro-Technica, MT98-MN). The redox reaction was thus recorded as 8-bit gray scale changes.

A 1-pixel line along the length of recorded gel image was stored at regular time intervals (5 s). The stored pixel line images were sequentially lined up as a function of time by the computer. This image processing procedure constructs a spatio-temporal diagram. From the slope of the diagram, the velocity of the chemical waves was calculated.

Permeation Experiments. Creatinine was purchased from Tokyo Kasei Kogyo Co., Ltd., Tokyo. The creatinine permeation experiments were performed in a thermostated water bath using a two-chamber cell separated by the PNIPAAm membrane (thickness = 0.5 mm). Each cell had a volume of 35 mL and effective surface area of 0.38 cm^2 for permeation. Creatinine solution (0.15 g/L) and pure water were injected into the donor and receiver cells, respectively. Both solutions were stirred with a small Teflon propeller at a speed high enough to neglect the boundary layer effect. Solution in the receiver cell (3 mL) was withdrawn and replaced with the same volume of water at specific time points. The concentration of creatinine was measured from the absorbance at 234 nm with a UV spectrophotometer (Shimazu, model UV-2500PC) to determine the diffused amount through membrane.

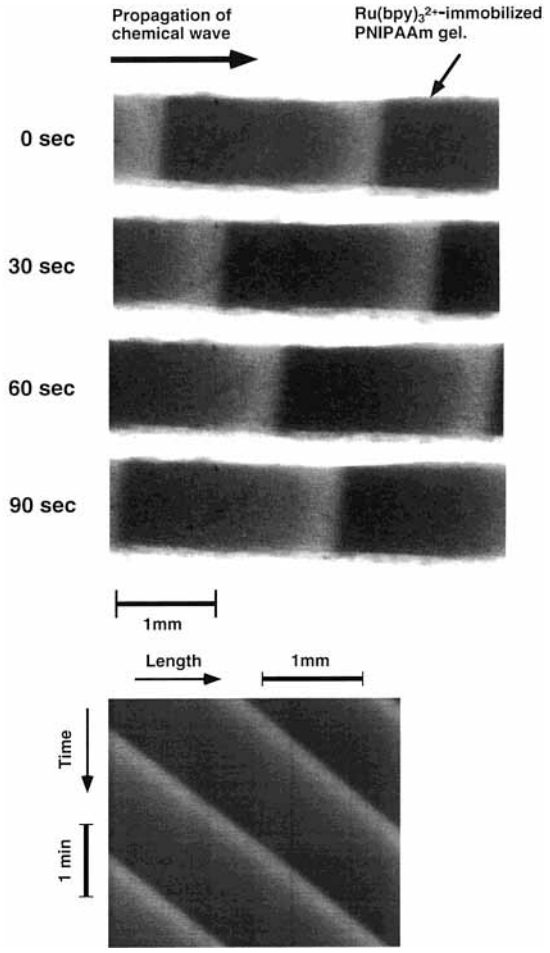

Figure 1. (a) Images of propagating chemical waves in the rectangular $Ru(bpy)_3$-immobilized PNIPAAm gel. Outer solution: [MA] = 0.0625 M; [$NaBrO_3$] = 0.15 M; [HNO_3] = 0.3 M; 22.5 °C. (b) Spatio-temporal pattern constructed from image-processing.

Absorption Experiments. Swollen PNIPAAm gel membranes in pure water were cut into disks (18 mm diameter) using a cork borer and dried ambiently for 1 day and under vacuum for 3 days at room temperature. Dried PNIPAAm gels were soaked into creatinine solutions ranging in concentration from 0.01 to 0.0175 g/L and incubated for 24 h at several constant temperatures. The concentration of outer solution and the gel volume were then measured. The partition coefficient, K, was calculated as the ratio of the concentration in the gel phase (C_{gel}) and that in outer solution (C_{sol}) after equilibrium by the following equation: $K = C_{gel}/C_{sol} = V_s(C_{pre} - C_{post})/(V_pC_{post})$, where V_p is volume of polymer gel, V_s is volume of solution, and C_{pre} and C_{post} are solute concentrations at time = 0 and at equilibrium, respectively.

Results and Discussion

Chemical Waves in PNIPAAm Gels. A rectangular piece of $Ru(bpy)_3$-immobilized PNIPAAm gel was immersed in an aqueous solution containing the three reactants (MA, $NaBrO_3$, HNO_3) of the BZ reaction. Figure 1a shows chemical patterns in PNIPAAm gels at steady state. By the coupling of chemical oscillation with the diffusion of a reaction intermediate ($HBrO_2$)

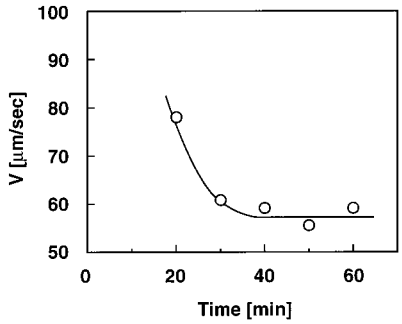

Figure 2. Time course of the velocity of chemical wave in the $Ru(bpy)_3$-immobilized PNIPAAm gel. Outer solution: [MA] = 0.0625 M; [$NaBrO_3$] = 0.13 M; [HNO_3] = 0.42 M; 27.5 °C.

through the gel phase, a periodical redox pattern (light, oxidized state; dark, reduced state) develops along the length of a rectangular gel. This pattern moves through the gel at a constant rate; thus, we observed the moving pattern as the train of chemical wave (i.e., wavetrain). It is indicated that the present gel system with aspect ratio of 10:1 can be regarded as quasi-1-dimensional with respect to the wave propagation.

Spontaneous initiation of the waves tends to appear from the corner at the end of the rectangular gel because the oscillation take places earliest there after the gel is soaked into the solution. Then the corner acts as a source of oscillation (i.e., pacemaker). A chemical wave has nonlinear characteristics to annihilate when two waves collide.[3] As the subsequent wave for the higher frequency pattern comes closer on the heels of the annihilated wave than that for the low-frequency source, the next collision occurs closer to the latter. Therefore, even if the waves initially evolve from two corners of both ends and propagate in the opposite direction each other, the wavetrain from the higher frequency source finally entrains the whole gel. As a result, the wave propagates in one direction along the major axis as shown in Figure 1a. From the video image, a space−time pattern was constructed by image-processing to obtain the velocity of the chemical waves (Figure 1b). The wave velocity was calculated from the slope of the space−time pattern.

Velocity of Chemical Waves. Figure 2 shows a time course of the velocity of chemical waves in PNIPAAm gel. The chemical waves appeared in about 20 min after soaking the gel into the BZ solution. The wave propagation continued over 1 h. The velocity initially decreased but became nearly constant after 30 min. In the following analysis, therefore, we employed the value of average velocity at around 40 min after soaking.

The chemical wave is driven by the diffusion of $HBrO_2$ into the reduced state ahead of the front. There, the $HBrO_2$ reduces the local Br^- concentration via the Br^- consumption process (called "process A" in the Field−Körös−Noyes (FKN) mechanism[2,3]). Once [Br^-] decreases below the critical value, the following autocatalytic process (called "process B") leads to the local oxidation and production of $HBrO_2$:

$$BrO_3^- + HBrO_2 + 2M_{red} + 3H^+ \rightarrow 2HBrO_2 + 2M_{ox} + H_2O$$

The wave velocity of the BZ reaction is theoretically given by[23]

$$v \propto (4k_5 D[H^+][BrO_3^-])^{1/2} \quad (1)$$

where k_5 is the rate constant of the autocatalytic reaction of $HBrO_2$ and D is the diffusion coefficient of activator ($HBrO_2$).

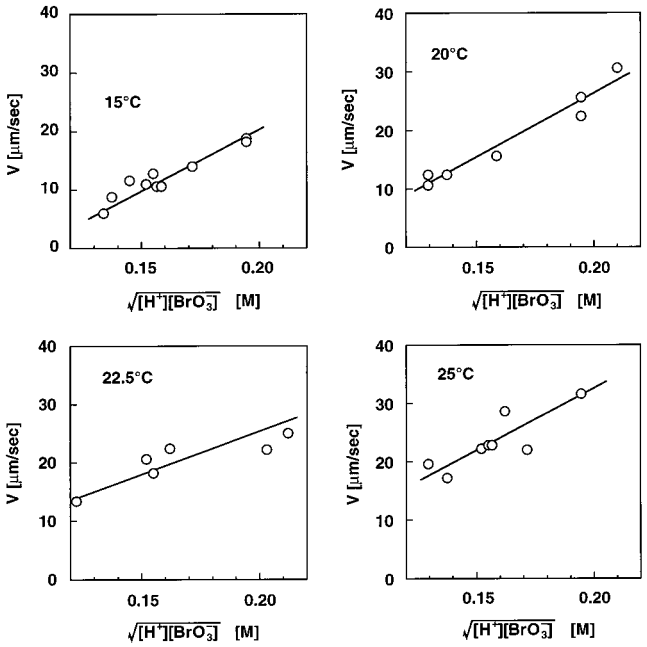

Figure 3. Velocity of chemical waves in the PNIPAAm gel vs the square root of the product of proton and bromate concentrations at various temperatures.

Figure 3 shows the dependence of the wave velocity on the square root of the initial concentration product $([H^+][HBrO_3^-])^{1/2}$ at various temperatures. As predicted from eq 1, the wave velocity increases in proportion to the square root of the product of proton and bromate concentrations.

Calculation of Diffusion Coefficient. According to eq 1, the slope of v vs $([H^+][BrO_3^-])^{1/2}$ plots represents $(4k_5D)^{1/2}$. From the slope, therefore, we can calculate the diffusivity (D) in the PNIPAAm gel at each temperature. Prior to the calculation, we must know the rate constant (k_5) of the autocatalytic reaction at each temperature. The activation energy (E_k) of the autocatalytic reaction in the acidic bromate−MA−$Ru(bpy)_3^{2+}$ system was estimated to be 58 kJ/mol by Kuhnert and Krug.[28] Further, the k_5 at 20 °C was reported to be 42 M^{-2} s^{-1}.[29] Using both of the known E_k and k_5 values, therefore, k_5 at any temperature can be determined by employing the Arrhenius equation. From the estimated k_5 values and the slope of straight lines in Figure 3, the diffusivities at several temperatures were calculated.

Figure 4 b shows the calculated D values in PNIPAAm gel as a function of temperature as well as the normalized swelling ratio of the gel (d/d_0) in the BZ solution under steadily oscillating condition. The normalization of each observed equilibrium diameter (d) was performed using the inner diameter (d_0) of the capillary utilized in the gel preparation. PNIPAAm gel is known as a temperature-responsive gel which undergoes abrupt volume phase transition around 32 °C in pure water.[12] In the BZ solution, the phase transition temperature shifted to lower temperature around 27 °C. The lowering phase transition temperature may be due to increasing ionic strength and acidity. Over the phase transition temperature, we could not observe the chemical wave because the gel collapsed. Below the phase transition temperature, the diffusivity decreased with an increase in temperature, corresponding to the change in swelling of the gel. As a control experiment, we also measured the velocity of chemical waves which was induced in stagnant and thin bulk solution (i.e., an aqueous solution containing MA, $NaBrO_3$, HNO_3, and $Ru(bpy)_3Cl_2$) with one-dimensional narrow path (ca. 1 mm width). The D values for the bulk solution system were

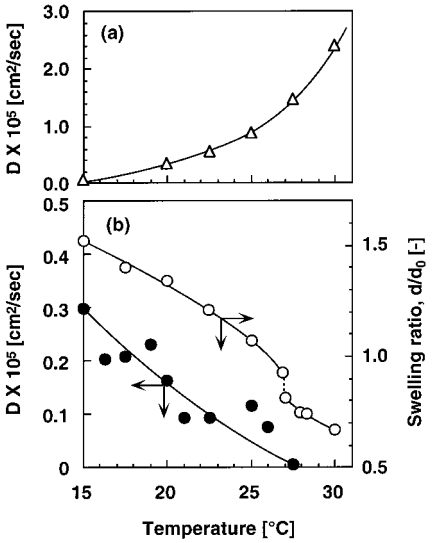

Figure 4. Diffusion coefficients of $HBrO_2$ in the bulk solution and the thermosensitive PNIPAAm gel obtained from the measurement of the traveling wave velocity as a function of temperature: (a) diffusivities in the stagnant bulk solution system; (b) diffusivities in the PNIPAAm gel (solid circles) and the normalized equilibrium diameters (d/d_0) for the gel in the BZ solution containing [MA] = 0.0625 M, [$NaBrO_3$] = 0.084 M, [HNO_3] = 0.3 M, and [$Ru(bpy)_3$] = 25 mM (open circles). Lines added are to guide the eye.

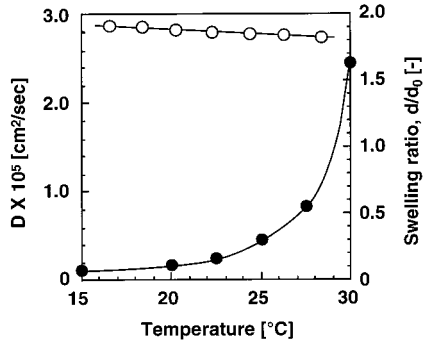

Figure 5. Diffusion coefficients of $HBrO_2$ in the PDMAAm gel obtained from the measurement of the traveling wave velocity (solid circles) and the normalized equilibrium diameters (d/d_0) for the gel (open circles) as a function of temperature. Lines added are to guide the eye.

calculated in the same manner as for the gel system (Figure 4a). The diffusivity in the bulk solution increased with increasing temperature. This is due to enhanced thermal motion of solute molecule by heat as expressed by the Stokes−Einstein equation. In the case of gel system, although the thermal motion of solute itself increases, the apparent D decreases with increasing temperature. Structural changes of the PNIPAAm gel network by temperature greatly affect the solute diffusivity in the gel. To compare the results with those for the gel which exhibits no structural changes by temperature, we used the poly(dimethylacrylamide) (PDMAAm) gel for the experiments. Figure 5 shows the equilibrium swelling ratio of PDMAAm gel (d/d_0) and the determined D values in the gel. Swelling curve exhibits that the PDMAAm gel has little thermosensitivity. In this gel, temperature dependence of D showed the same tendency as observed in the bulk solution system.

The dependence of diffusion coefficient on hydration of gel has been discussed on the basis on the free volume theory.[30] Free volume may be visualized as the membrane matrix volume which is not occupied by the polymer and solvent molecules but constitutes an integral part of the bulk volume of the polymer

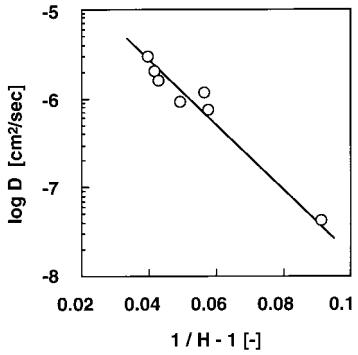

Figure 6. Plots of diffusion coefficients in the PNIPAAm gel determined by the chemical wave velocity as a function of inverse gel hydration.

membrane. In this theory, the diffusion coefficient can be expressed by the following equation:

$$\log D = \log D_0 - \kappa(1/H - 1) \tag{2}$$

where $H = (V_s - V_0)/V_s$, V_s and V_0 are the swollen volume and original volumes of the membrane, and D is the diffusion coefficient in the swollen gel. D_0 is the diffusion coefficient in solution, and κ is a proportionality constant. Figure 6 shows the relationship between $1/H - 1$ and log D. Here H was calculated as the weight of absorbed water per weight of swollen gel as a first approximation assuming volume additivity of water and polymer in the swollen hydrogel. An almost linear relationship was observed between D and $1/H - 1$, which suggests that solute diffusion occurs primarily through water filled pores of channels within the gels. Therefore, D directly reflects the structural changes of the gel due to swelling and deswelling.

Verification of Evaluated *D Value*. To verify the diffusivity obtained from the new method of measuring the velocity of chemical waves, we also determined the D values by another conventional method of measuring permeability through gel membrane. The D values obtained from two methods were compared. As $HBrO_2$ is an unstable intermediate, we cannot use it for the permeation experiment. As an alternative agent, creatinine which has the same molecular weight (M_w = 113) as $HBrO_2$ and no charge was used for permeation experiment. According to the Stokes−Einstein equation, we assumed that a substance with the same molecular weight has the same Stokes radius and hence the same diffusion coefficient. Figure 7 shows the results from the permeation experiments using a two-chamber cell at various temperatures. Permeation rates of creatinine became almost constant within 40 min. At the early stage of steady state, the cumulative amount of permeated solute, Q, is expressed by

$$Q = PA(\Delta C)t \tag{3}$$

where P is the permeation coefficient, A is the surface area of the gel membrane, and ΔC is the concentration difference between donor and receiver cells. From the slope of the linear part in the permeation curve in Figure 8, P values for the PNIPAAm membrane were calculated. P is defined as follows using the partition coefficient (K), diffusivity (D), and membrane thickness (l):

$$P = KD/l \tag{4}$$

The partition coefficient, K, is an equilibrium property which is only a function of temperature and pressure and defined as the ratio of solute concentration in the material to the concentra-

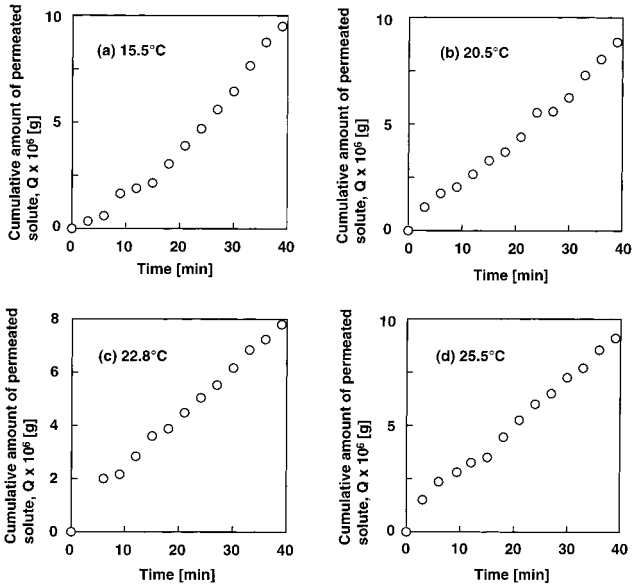

Figure 7. Permeated amount of creatinine through the PNIPAAm membrane at various temperatures.

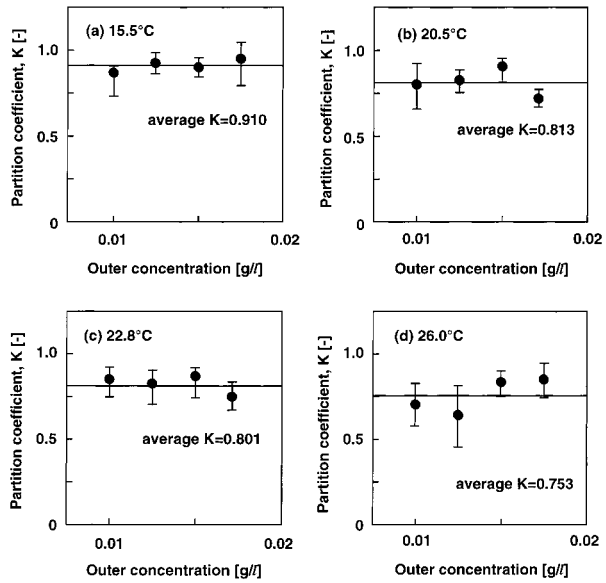

Figure 8. Dependence of the partition coefficient of creatinine on the outer concentration at various temperatures.

tion in the solution. It is a measure of the interaction between the gel and the solute. Generally, these interactions include size exclusion, hydrophobic interactions, and electrostatic interactions. As the PNIPAAm gel has no electrostatic interactions with respect to creatinine, size exclusion and hydrophobic interactions will be the significant interactions between the gel and the solute. Figure 8 shows the *K* values obtained from absorption experiment at various temperatures when the initial concentration of solute in the outer solution was changed. As expected, *K* was nearly constant for various outer concentrations. *K* was determined to be constant value independent of outer concentration. *K* declines as the gel shrinks with increasing temperature. As the temperature increases, the gel shrinks and the average pore size declines. As a result, size exclusion becomes significant and *K* decreases. And also, as the temperature increases, the PNIPAAm gel becomes more hydrophobic. Then hydrophilic creatinine prefers to distribute to the solution rather than the gel phase, leading to a decrease in *K*. Using the

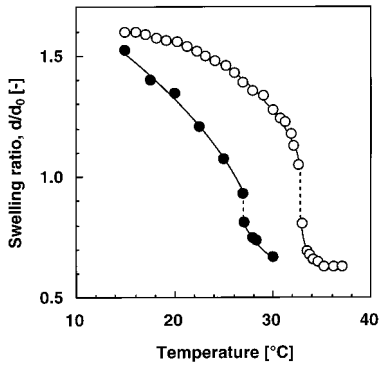

Figure 9. Equiilibrium swelling ratio (d/d_0) of the PNIPAAm gel as a function of temperature in water (open circles) and the BZ solution (solid circles) containing [MA] = 0.0625 M, [$NaBrO_3$] = 0.084 M, [HNO_3] = 0.3 M, and [$Ru(bpy)_3$] = 25 mM. Lines added are to guide the eye.

obtained *P* and *K* values independently, *D* values at several temperatures can be calculated from eq 4.

In the permeation experiment, pure water was used as a solvent. The swelling ratio of PNIPAAm gel in pure water is different from that in the BZ solution. Therefore we cannot directly compare the *D* values obtained from the membrane permeability with those obtained from the BZ wave velocity, even if both experiments were performed under the same temperature. Figure 9 shows the equilibrium swelling ratio of PNIPAAm gel as a function of temperature in pure water and the BZ solution. In pure water, the PNIPAAm gel undergoes critical phase transition in the vicinity of 32 °C. On the other hand, in the BZ solution, the phase transition temperature shifts to lower temperature as well as the swelling ratio decreases. We must compare the *D* values under the condition that the gel has the same swelling ratio in two solutions because hydration of gel mainly affects the diffusivity within the gel. When the swelling ratios are the same in two solutions, temperatures become different. Therefore, we must compensate temperature effect on self-diffusivity of a solute. Temperature compensation for the diffusivity obtained from the BZ chemical wave was carried out by using the Arrhenius equation for diffusion coefficient. The activation energy of diffusion (E_D) has the following relationship with the activation energies of wave propagation (E_v) and autocatalytic reaction (E_k):[28]

$$E_v = (E_k + E_D)/2 \tag{5}$$

We measured the velocity of traveling waves in the temperature range from 15 to 30 °C in stagnant bulk solution. From an Arrhenius plot of the velocity, the activation energy for wave propagation (E_v) was determined to be 78 kJ/mol (data not shown here). Since the E_k value is 58 kJ/mol, E_D is calculated to be 98 kJ/mol from eq 5. By using the Arrhenius equation for diffusivity with the evaluated E_D value, the *D* values shown in Figure 4b were corrected to the values at the temperatures under which the swelling ratio of the gel in the BZ solution agrees with that in pure water.

Figure 10 shows the corrected *D* values obtained from the measurement of wave velocity and the values from permeation experiment as a function of temperature. Although there are small deviations, the two values are in good agreement. This indicates that the new measuring method is capable of almost same precision as conventional permeability measurements. The new method would be a convenient way to estimate the diffusivity of solute in the gel. Empirically, dependence of

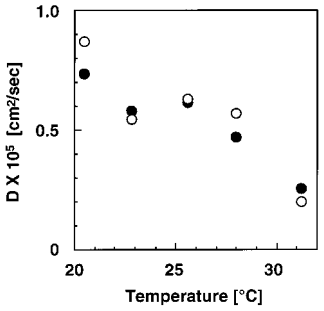

Figure 10. Comparison of the diffusion coefficients in the PNIPAAm gel determined by two different measuring methods. Solid circles are the diffusivities corrected by temperature compensation for the *D* values obtained from the measurement of the traveling wave velocity. Open circles are the diffusivities obtained from the conventional measurement of permeability through the gel membrane.

diffusion coefficient on molecular weight can be expressed as follows:[31]

$$D = k(M_w)^{-n} \tag{6}$$

Here k is the diffusion coefficient of a solute of unit molecular weight; this is estimated to be approximately 1×10^{-4} cm^2/s. The exponent n in eq 6 is approximately 0.5 for water but varies depending on material as a diffusion medium (e.g., almost 5 for polystyrene).[31] Using the obtained D value for $HBrO_2$ ($M_w = 113$) from the measurement of wave velocity, we can determine the n value in the eq 6 for the prepared gel. From the correlation equation, we could estimate the diffusivity of any solute with known molecular weight. The new measuring method would be applicable for many kinds of gels other than PNIPAAm gel because the $Ru(bpy)_3$ catalyst is easily entrapped or adsorbed in gels by soaking the gel into the catalyst solution.

Conclusions

A new method for measuring solute diffusivity in gels by utilizing the BZ reaction was employed for thermosensitive PNIPAAm gel. From the velocity of chemical wave which propagates in PNIPAAm gel, the diffusivity of $HBrO_2$ was determined as a function of temperature. Contrary to the bulk solution system, the diffusivity of $HBrO_2$ within the gel decreases when increasing temperature. It was found that the change in network structure of the gel greatly affected the solute diffusivity in the gel. The correlation between the hydration gel and the diffusivity obeyed the free volume theory. The precision of the obtained diffusivites was evaluated by comparison with the values which were determined by the conventional permeation method using a gel membrane. The diffusivities obtained from the two measuring methods gave a good agreement at various temperatures. The new method utilizing the BZ wave reported here would be useful for the estimation of solute diffusivity for many kinds of gels and the analysis of their structures.

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