Molecular Specific Swelling Change of Hydrogels in Accordance with the Concentration of Guest Molecules

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This study shows the first example of synthetic polymer gels which can undergo a large swelling change (conformational change) but still retain the molecular recognition ability in the shrunken states, as indicated by the specific volume change in response to the concentration of guest molecules. Stimuli-responsive gels,[1−9] i.e., solvent-swollen polymer networks, that abruptly change their volume many times in response to a small change in solvent composition,[1,2] pH,[2] temperature,[1,3−5] light,[6] and electric field,[7] have been recognized as intelligent materials. These gels can interconvert between a solvent-absorbed swollen phase and solvent-expelled shrunken phase in response to the external stimuli. Much interest has been focused on these changes not only from the fundamental point of view but also from the applied aspects of gels.[10−15] However, the stimuli response of the polymer gels usually indicates the interconversion between the swollen and shrunken phases, and the potential applications of polymer gels[10−15] have been concerned with the utilization of the change in the properties between these two phases.

It has been considered to be essential that for molecules (macromolecules) to have molecular recognition ability they have molecular cavities, which have a minimum freedom of conformation change and fit guest molecules, as seen in host−guest chemistry[16] and in molecular imprinting chemistry.[17−19] Pre-reduced entropy of the host molecules has been considered to favor the formation of host−guest complexes. It is quite interesting that hydrogels, which undergo large conformation changes during swelling change, have molecular specific swelling change and further molecular recognition ability. Recently, multiple phases of polymer gels have been discovered in certain copolymer gels.[20] The existence of stable phases other than swollen and shrunken phases has been discussed in relation to stable structures and their functions of biopolymers such as proteins and DNA both by implication[20] and by theoretical studies.[21] These studies have also stimulated us to prepare synthetic polymer gels which undergo swelling changes and at the same time have their molecular specificity.

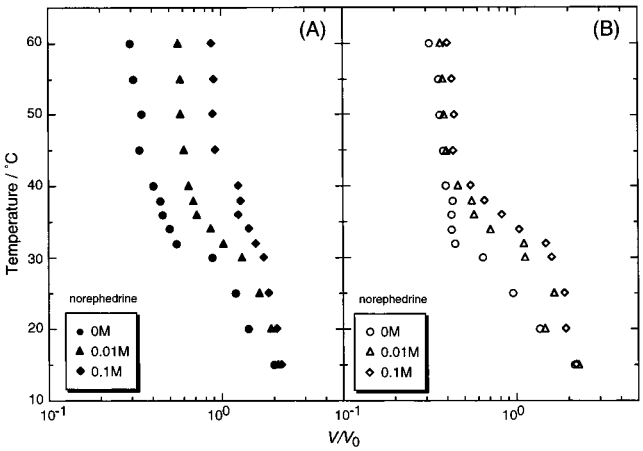

Figure 1. Equilibrium swelling ratios (relative volume of gels, V/V_0) as a function of temperature for the MR gel prepared in the presence of norephedrine (A) and for the RF gel prepared in the absence of norephedrine (B), measured in aqueous solution of a given norephedrine concentration as indicated in the insets. The equilibrium swelling ratios were measured with increasing temperature.

Thermosensitive copolymer gels consisting of *N*-isopropylacrylamide (NIPAAm) and acrylic acid (AAc) have been prepared in the presence of guest molecules (molecular recognition, MR, gels) and in the absence of them (reference, RF, gels). NIPAAm (1.81 g, 16 mmol), AAc (0.288 g, 4 mmol), *N*,*N*′-methylenebis-(acrylamide) (0.154 g, 1 mmol), and benzoyl peroxide (0.018 g, 0.08 mmol) were dissolved in a 13 g portion of 1,4-dioxane. Into the solution either *dl*-norephedrine hydrochloride (0.375 g, 2 mmol) or *dl*-adrenaline hydrochloride (0.439 g, 2 mmol), as a guest molecule, was added (a part of the guest molecule remained undissolved due to the solubility limit), and the contents were degassed. *N*,*N*-Dimethylaniline (10 μL, 0.08 mmol) was added to initiate redox polymerization, and the polymerization was carried out for 12 h at 25 °C in a glass vial in which glass capillaries with inner diameter of 145 μm were immersed. During the polymerization a lump of turbid gel was phase separated from the solution. Fibrous gels were taken out from the capillaries and washed with an water/acetic acid mixture (9/1 in volume) and then with water several times. The RF gels were also prepared in the same way except that the polymerization was carried out in the absence of the guest molecules.[22] The volume change of the purified gels was determined by using an optical microscope and was expressed by the swelling ratios of the gels (V/V_0), where V is the volume of the gels under a certain condition, and V_0 is the volume of the gels at preparation.

Figure 1 shows the correlation between V/V_0 and temperature for the MR gel prepared in the presence of norephedrine (A) and for the RF gel prepared in the absence of norephedrine (B) in

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(22) The results of elemental analyses and infrared spectra for both of the MR and RF gels were identical, and the discrimination could not be made by these analyses.

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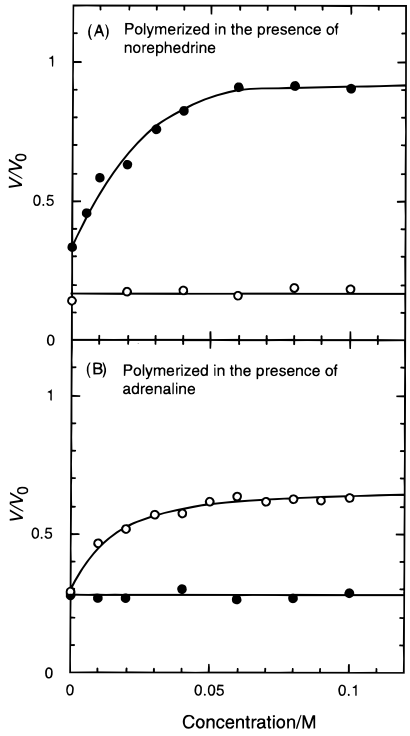

Figure 2. Equilibrium swelling ratios at 50 °C as a function of concentration of either norephedrine (●) or adrenaline (○) for molecular recognition gels prepared in the presence of norephedrine (A) and adrenaline (B). Each swelling ratio at 50 °C was plotted in this figure from the temperature dependence experiments (from 15 to 60 °C) of the swelling ratios, like Figure 1.

aqueous solutions of a given norephedrine concentration. Both of the MR and RF gels are temperature sensitive, and are swollen at low temperatures and collapsed at high temperatures. For the RF gels (B), the swelling ratios at a completely swollen state, e.g., at 15 °C, and at a completely collapsed state, e.g., at 50 °C, are almost the same. In contrast, for the MR gels (A), the swelling ratios at 15 °C are identical irrespective of norephedrine concentrations as well as the same as those for the RF gels, whereas the swelling ratios at collapsed states increase with increasing norephedrine concentrations. It is interesting to note that the change in swelling ratios of the MR gel in accordance with norephedrine concentration appears only in the shrunken phase and that the gels, similarly prepared in water instead of 1,4-dioxane in the presence of the guest molecule, do not exhibit the specific volume change (results not shown). We have also revealed that the composition of AAc is quite sensitive to the specific swelling change. When AAc is not used, that is NIPAAm gels are similarly prepared, no specific swelling change in the shrunken state, as seen in Figure 1, is observed. With increasing AAc composition (up to 20 mol %) in the gels, the swelling change of MR gels in accordance with the concentration of guest molecules becomes larger. The polymerization temperature (25 °C) is lower than the range where the present gels undergo large volume changes. This means that the polymerization is conducted in the swollen states. However, the gels obtained are not transparent but turbid, because of the phase separation during the polymerization. We also have experimental results that the gels polymerized at different temperatures (15−40 °C) exhibit specific swelling change, seen in Figure 1, in the shrunken states. We now consider that the phase separation takes an important role for the unique swelling change.

To demonstrate the feasibility of this phenomenon for the other guest molecules and also to examine the molecular specificity of the volume change, adrenaline was selected as another guest molecule, and similar experiments to Figure 1 were conducted for adrenaline. The results are similar to those in Figure 1. The molecular specificity of this phenomenon is demonstrated in Figure 2, where the swelling ratios at 50 °C as a function of concentration of either norephedrine or adrenaline are shown for the MR gels prepared in the presence of norephedrine (A) and adrenaline (B), respectively. The former gel is sensitive to norephedrine and insensitive to adrenaline in terms of the change in its volume, and *vice versa* for the latter gel.

Adsorption isotherms of norephedrine in water to the MR gel prepared in the presence of norephedrine and to the RF gel have been compared. In the swollen state, the adsorbed amounts of norephedrine are identical for both of the MR and RF gels. This may be a reason for identical swelling ratios for both of the MR and RF gels in swollen states. In contrast, in the shrunken state, the adsorbed amounts are larger for the MR gel than for the RF gel, though the adsorbed amounts for the RF gel are similar for both states. The enhanced adsorption for the MR gel is implicated to be due to the formation of molecular specific binding sites during the shrinking process. The MR gels in the shrunken states seem to remember the guest molecule when prepared and exhibit the specific increase in its adsorption, resulting in their specific volume change in response to the guest molecule.

The preparation procedure of the MR gels is akin to the molecular imprinting technique[17−19] for cross-linked synthetic polymers. However, cross-linking density of the polymers in the conventional imprinting technique is extremely high, and the resulting imprint polymer networks are hard resins and do not undergo a large swelling change in response to guest molecules, as is seen in the present study. In other words, conformation of polymer chain in the imprint networks hardly changes and is fixed as imprints of guest molecules. Molecular recognition of the imprint polymers is usually effective in nonpolar solvents, whereas the specific volume change of the present molecular recognition gels is observed in aqueous media. The present MR gels are thermosensitive and show the swollen and shrunken phases in pure water, like conventional NIPAAm-based gels.[3−5] The swelling change indicates the capability of conformation change in the MR gels, depending on temperature. However, when the guest molecule is present in the soaked solutions, they exhibit another phase ("molecular recognition phase"), whose volume is responsive to concentration of the guest molecules.

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Supporting Information Available: Figure showing the adsorption isotherms of norephedrine in water to the MR gel and RF gel (2 pages, print/PDF). See any current masthead page for ordering and Internet access instructions.

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