

¹H-NMR Studies on Water in Methacrylate Hydrogels. I

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Synopsis

The behavior of water contained in a hydrophilic hydrogel poly(hydroxyethyl methacrylate) membrane and a hydrophobic hydrogel poly(methyl methacrylate) membrane was studied by proton nuclear magnetic resonance (NMR) spectroscopy. Significant differences between the two hydrogels were observed in their relaxation times, the temperature dependence, and frequency dependence of these relaxation times, and changes of signal intensity of water protons on freezing and thawing. The water in these hydrogels was classified into three states: free, intermediate, and bound states. Poly(hydroxyethyl methacrylate) contains relatively more water in bound and intermediate states than poly(methyl methacrylate). The mobility of water decreases in the order, free water, intermediate water, bound water. The correlation times of the three states were roughly estimated to be 10^{-11} , 10^{-9} , and 10^{-6} s, respectively. The mobility of water in poly(methyl methacrylate) is several orders of magnitude higher than that in poly(hydroxyethyl methacrylate). In poly(hydroxyethyl methacrylate), the exchange between intermediate and free water is slow in the NMR time scale: the apparent exchange rate and the activation energy were estimated to be $3.6 \times 10^2 \text{ s}^{-1}$ (28°C) and 2.0 kcal/mol, respectively.

INTRODUCTION

Hydrogels made from various polymer materials are now widely used for medical purposes. However, the correlation between their permeabilities and polymer characteristics are not yet well understood. Sakai et al. compared the permeabilities to water and urea of homogeneous membranes made from hydrophobic poly(methyl methacrylate) and hydrophilic poly(*N*-vinylpyrrolidone-co-methyl methacrylate).¹ They reported that the permeability to water of the hydrophobic poly(methyl methacrylate) membrane was much higher than that of the hydrophilic membrane with the same water content, whereas the permeability to urea was scarcely affected by the chemical structure of the membrane but was affected by its water content. These phenomena have been explained in relation to the bound water or structural water constrained by polar groups of the polymer materials: Free water is considered to be unable to permeate into the region of bound water, whereas urea can break the hydrogen bonds of bound water and permeate into this region. If this is so, the properties of water contained in various membrane materials should be correlated with the permeabilities of these materials to

various molecules. Therefore, detailed studies on the properties of water in various hydrogels should be helpful in selection or design of polymer materials for given purposes. In this work, as a first step in such studies, we examined the properties of hydrophobic poly(methyl methacrylate) and hydrophilic poly(hydroxyethyl methacrylate) by proton nuclear magnetic resonance (NMR) spectroscopy. The properties of water contained in these hydrophilic and hydrophobic membranes are discussed on the basis of results on changes of signals in intensity on freezing and thawing the samples, saturation transfer, and the temperature and frequency dependence of relaxation times.

EXPERIMENTAL

Materials

Isotactic poly(methyl methacrylate) was prepared by anion polymerization (isotacticity > 95%). Syndiotactic poly(methyl methacrylate) prepared by radical polymerization was purchased (syndiotacticity 55%, heterotacticity 32%, and isotacticity 13%). The molecular weights of both polymers were 1.3×10^5 – 1.45×10^6 . Isotactic and syndiotactic poly(methyl methacrylate) were dissolved in hot dimethylsulfoxide solution at a ratio of 1 to 5, and the solution was introduced between two glass plates and cooled. The resulting membrane was soaked in water to substitute dimethylsulfoxide in the gel by water.

Poly(hydroxyethyl methacrylate) was prepared by adding ADVN (azobisdimethylvarelonitrile) as an initiator of polymerization to 2-hydroxyethyl methacrylate. The mixture was heated at about 45–50°C and polymerized between glass plates. The resulting sheet of polymer was swelled first in deionized water, then in methanol and then again in distilled water.

The water content was estimated as follows:

$$\text{Water content} = \frac{(W_1 - W_2)}{W_1} \times 100 \quad (1)$$

where W_1 and W_2 are the weight of the hydrogel containing water and that of the dried hydrogel, respectively. The water content of poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) were determined to be $40.3 \pm 1.0\%$ and $39.2 \pm 1.0\%$, respectively. To eliminate traces of paramagnetic metal ions which might affect the relaxation times, the sample was soaked in 0.1 mM EDTA solution for 30 minutes and then washed with several changes of distilled water before NMR measurement. Relaxation times did not increase at higher concentration of EDTA or longer soaking time. Since it is quite difficult to degas the membrane sample without changing the water content and set it in a NMR sample tube under inert atmosphere, we did not remove dissolved oxygen which might also affect the relaxation times.

Methods

The NMR measurements were performed at 90 MHz and 400 MHz with JEOL FX90Q and GX400 instruments, respectively. The sample was set in

the NMR sample tube of 10 mm OD with the plane of the polymer sheet parallel to the external magnetic field. The sample was maintained at the probe temperature for 30 min before NMR measurement. A solution of 1% tetramethylsilane (TMS) in chloroform was used as an external standard of signal intensity. Intensities were determined from spectral areas with a planimeter. Spin-lattice and spin-spin relaxation times were measured by the inversion recovery and Carr–Purcell–Meiboom–Gill methods, respectively.⁷ Li external lock mode was used for FX90Q, whereas the measurements were performed without a lock for GX400.

RESULTS AND DISCUSSION

When sheets of poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) were put into the NMR sample tubes rolled into cylinders, both polymers showed splitting of proton NMR signals of water in the 5–10 ppm region [Fig. 1(a) and (c)]. On the other hand, when placed in the sample tubes as single sheets parallel to the external magnetic field, each polymer showed

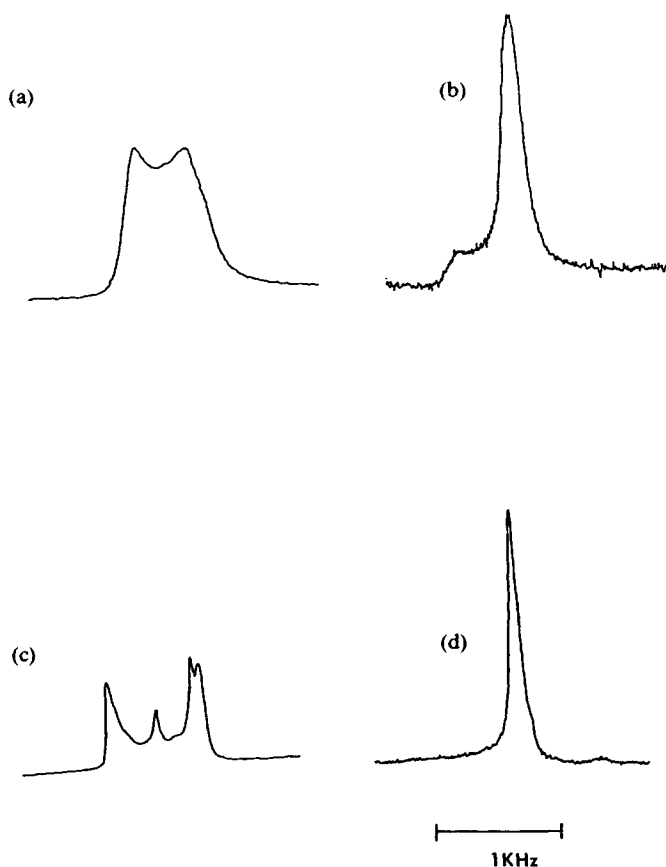


Fig. 1. Proton NMR spectra of poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) measured at 90 MHz and 28.5°C: (a) and (b), poly(hydroxyethyl methacrylate); (c) and (d), poly(methyl methacrylate). (a) and (c), sheets rolled into cylinders; (b) and (d), single sheets set parallel to the external magnetic field.

one sharp signal [Fig. 1(b) and (d)]. These results are consistent with those reported for cellulose films.^{2,3} From measurements of the angular dependence of the dipolar splitting of water in cellulose acetate films, Matsumura et al.³ reported that splitting was maximal when the surface of the film was perpendicular to the magnetic field. They concluded that the proton-proton dipolar axis of water molecules tends to be oriented perpendicular to the surface of the film. Therefore, to minimize dipolar splitting, in all subsequent experiments we used single sheets and set their surface parallel to the magnetic field.

Freezing and Thawing

Figure 2 shows the change in intensity of the proton signal of water on decrease of the temperature from 28°C to -40°C and increase of the temperature from -60°C to 28°C. The signal intensity of water in poly(methyl methacrylate) began to decrease at about -15°C and on further decrease in temperature it decreased to 5% of that observed at 28°C [Fig. 2(a)]. As the mobility of water decreases with decrease in temperature, the proton signal of water in the frozen state was too broad to be observed. Therefore, a decrease in the signal intensity corresponds to an increase in the amount of the frozen water. In poly(methyl methacrylate) less than 5% of the water remained unfrozen below -25°C, whereas in poly(hydroxyethyl methacrylate) about 40% of the water remained unfrozen even at -60°C, as shown in Figure 2(b). The state of existence of this kind of unfrozen water in polymers has been interpreted by considering the specific structure of water molecules, their interaction with polymer molecules and the effect of pressure on polymer pores.⁴⁻⁷

Using a solid echo method, Inoue and Hoshino⁸ calculated the spin-spin relaxation time, T_2 , of water adsorbed by polyamide to be about 8 μ s. Assuming that the T_2 of water molecule directly bound to the hydrogels used here was close to this value, the line width of the bound water signal would be about 40 kHz, which is too broad to be observable with high-resolution NMR. Therefore, the unfrozen water observed here might not be the bound water. If such a broad signal of the bound water exists in this system, on irradiation of a part of the bound water, saturation of the bound water is transferred to the observable water, and intensity of the observable water is expected to decrease when chemical exchange between the bound water and the observable water is fast compared with the relaxation time. Actually for both these hydrogels on irradiating the position at 20 ppm higher than water signal, where no signal was observed, intensities of the water signal decreased. Thus, this phenomenon could be ascribed to saturation transfer between unobservable bound water with a considerably rigid structure and the observable water.⁹⁻¹⁴ However, another possibility is the cross-relaxation between the polymer molecule and the observable water.^{13,14} In this case saturation would be transferred through spin diffusion.^{13,14} However, for a random copolymer of methylmethacrylate and methoxypolyethyleneglycol-monomethacrylate, saturation transfer was not observed, indicating that in this polymer bound water with such a rigid structure does not exist and the cross-relaxation between polymer molecule and the observable water can be neglected. Therefore, we also may be able to neglect the contribution of the cross-relaxation between polymer

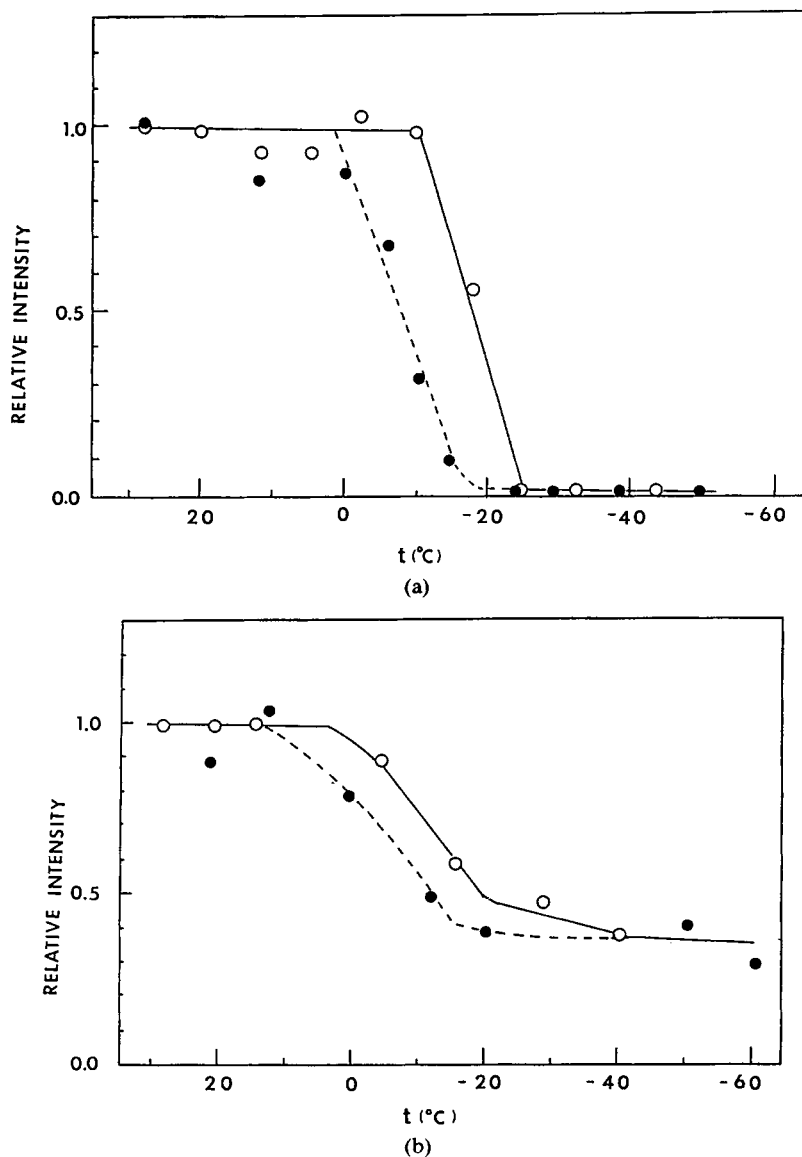


Fig. 2. Change in intensity of the water proton signal on freezing and thawing measured at 90 MHz. TMS was used as an external reference. Values for (a) poly(methyl methacrylate) (b) poly(hydroxyethyl methacrylate) on cooling (○) and on heating (●) are shown.

molecule and observable water here. Thus, this saturation transfer phenomenon suggests the existence of very rigid bound water in this system as in polyamide. Therefore, it is reasonable to assume that the water that remains unfrozen at lower temperature is not actual bound water but water with relative flexibility.

Thus, we could roughly classify the water in the gels into three states: frozen water, unfrozen water observable at room temperature by high-resolution NMR spectroscopy, and water unobservable at room temperature. We

refer to these three states of water as free, intermediate, and bound water. The intermediate water, which exchanges with the bound and the free water, may play an important role in permeability.

Figure 2 also shows that the changes during freezing and thawing procedures were not superimposable above -25°C for poly(methyl methacrylate) and above -60°C for poly(hydroxyethyl methacrylate). This hysteresis may be explained as follows. During freezing, water molecules in the gel network are pushed out but on thawing the gel network would not be readily hydrated to the same state.

Frequency Dependence of Relaxation Times

Table I shows the T_1 and T_2 values measured at 90 and 400 MHz. T_1 showed frequency dependence while T_2 showed very little. Oxygen dissolved in the samples was not removed. However, since the paramagnetic effect of dissolved oxygen on the relaxation rates of this order is not considered to be serious,¹⁵ we assumed that the contribution to the observed relaxation rates could be neglected.

As the exchange among the three states of water is faster than T_1 , the observed T_1 can be expressed as a weighted average of the T_1 s of bound, intermediate, and free water:

$$1/T_1 = B/T_{1B} + I/T_{1I} + F/T_{1F} \quad (2)$$

where T_{1B} , T_{1I} , and T_{1F} are the spin-lattice relaxation times and B , I , and F are the relative proportions of bound, intermediate, and free water.

As stated above, saturation transfer phenomena were observed on irradiation at a position 20 ppm higher than the observed water signal. Therefore, the line width of the bound water of the hydrogel was estimated to be in the order of 16 kHz (when measured at 400 MHz). This means that T_2 is about 20 μs . Provided that the relaxation of the water proton is determined only by the dipole-dipole interaction within the same water molecule, taking the interproton distance of water as 1.54 \AA , the correlation time τ_c can be estimated to be 2.6×10^{-6} s.¹⁶ With these values, the T_{1B}^{-1} s are estimated to be 3.1×10^{-2} s $^{-1}$ and 1.6×10^{-3} s $^{-1}$ for 90 MHz and 400 MHz, respectively. Therefore, the contribution of T_{1B}^{-1} to the observed T_1^{-1} (0.7 – 5.2 s $^{-1}$) can be neglected, and so the first term of eq. (2) can also be neglected.

TABLE I
Frequency Dependence of Relaxation Times of Water in Poly(methyl Methacrylate)
and Poly(hydroxyethyl Methacrylate)

Frequency	$T_{1\text{obs}}$ (s) ^a		$T_{2\text{obs}}$ (s) ^b	
	90 MHz	400 MHz	90 MHz	400 MHz
Poly(methyl methacrylate)	0.64	1.40	0.048	0.049
Poly(hydroxyethyl methacrylate)	0.19	0.60	0.0028	0.0030

Values were measured at 28°C .

^aThe inversion recovery method was used.

^bThe Carr-Purcell-Meiboom-Gill method was used.

TABLE II
 T_1 s, τ_c s, and Relative Proportions of Bound, Intermediate, and Free Water for
 Poly(methyl Methacrylate) and Poly(hydroxyethyl Methacrylate)

	Poly(methyl methacrylate)			Poly(hydroxyethyl methacrylate)		
Water	T_1 (s) ^a	τ_c (s) ^a	R^b	T_1 (s) ^a	τ_c (s) ^a	R^b
Free	1.4	10^{-11}	0.77	0.40	4×10^{-11}	0.48
Intermediate	0.045	4×10^{-9}	0.03	0.11	9×10^{-9}	0.32
Bound	67	10^{-6}	0.20	67	10^{-6}	0.20

^a Values estimated by Eq. (2) from results at 90 MHz and 28°C.

^b Values estimated from results by DSC^{17,18} (bound and intermediate water) and Fig. 2 (intermediate water).

Here, we assume that the amount of water that did not freeze below -40°C corresponds to that of intermediate water. From Figure 2, I and F were estimated to be 0.04 and 0.96 for poly(methyl methacrylate), and 0.4 and 0.6 for poly(hydroxyethyl methacrylate).

Actually quantitative treatment of relaxation times is quite complicated for this system because τ_c of free water may be treated as isotropic and that of intermediate water as anisotropic and the distribution of τ_c should be taken into account. It may be meaningful, however, to make a qualitative comparison of the overall correlation times of free and intermediate water deduced for poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) under the first approximation that for both intermediate and free water the relaxation is determined only by the dipole-dipole interaction of protons on the same water molecule and that the correlation time τ_c is isotropic without taking the distribution of τ_c values into account. From the ratio of T_1 values measured at 90 MHz to those measured at 400 MHz, the values for τ_c were calculated to be as shown in Table II, those of bound water being estimated from saturation transfer experiment.

Table II shows that τ_c values for both free and intermediate water of poly(hydroxyethyl methacrylate) are several times longer than those of poly(methyl methacrylate), indicating that the mobility of water in the poly(hydroxyethyl methacrylate) membrane is more restricted. The τ_c of free water is close to the value of pure water (10^{-11} – 10^{-12} s). τ_c increases in the order, free, intermediate, bound, in steps of powers of three, indicating decrease in mobility in this order.

The amounts of unfrozen water in poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) have been determined by differential scanning calorimetry (DSC) to be 23% and 52%, respectively.^{17,18} These values are considered to correspond to the sums of the amounts of bound and intermediate water. Using the values for the amounts of unfrozen water obtained by DSC and those for the amounts of intermediate water and free water obtained by NMR, the relative proportions of bound, intermediate, and free water in the hydrogels, R , were estimated to be as shown in Table II. As expected, these values indicate that the amount of bound water is higher in poly(hydroxyethyl methacrylate), which has hydrophilic groups, than in poly(methyl methacrylate). They also show that poly(hydroxyethyl methacrylate) also has a higher content of intermediate water.

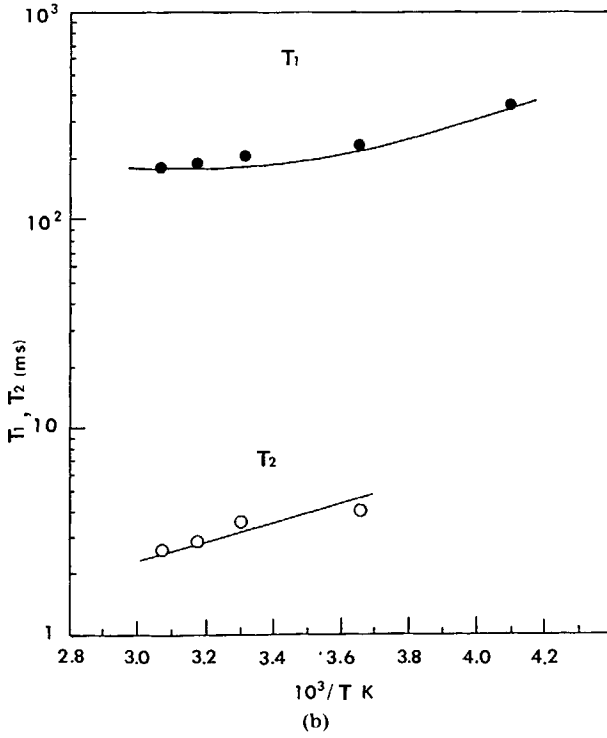
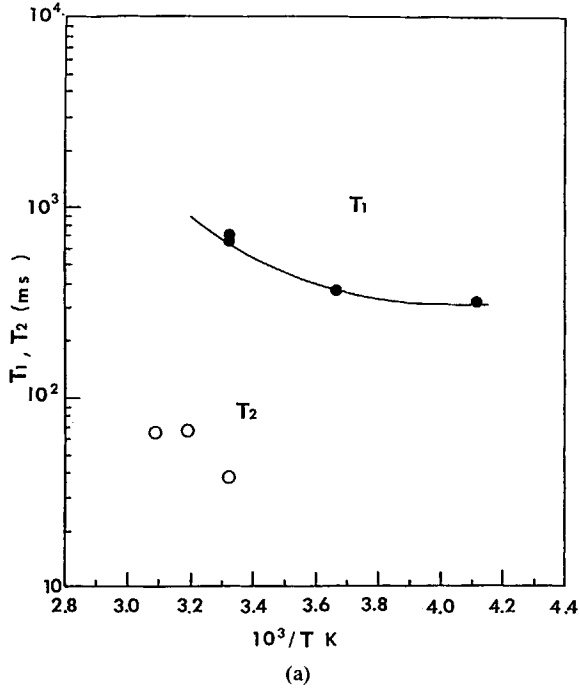


Fig. 3. Semilogarithmic plots of T_1 and T_2 against the reciprocal of temperature (measured at 90 MHz at 28°C) for (a) poly(methyl methacrylate) and (b) poly(hydroxyethyl methacrylate)

Temperature Dependence of the Relaxation Time

Figure 3 shows the temperature dependences of the relaxation times T_1 and T_2 measured at 90 MHz for poly(methyl methacrylate) and poly(hydroxyethyl methacrylate). The minimum T_1 indicates the temperature at which $\omega\tau_c \approx 1$ (where ω is the Larmor frequency).¹⁶ Within the temperature region studied (28°C to -30°C), the values of T_1 of water in poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) show opposite dependences on temperature: T_1 was in the region of $\omega\tau_c \ll 1$ for poly(methyl methacrylate), while it was in the region of $\omega\tau_c \gg 1$ for poly(hydroxyethyl methacrylate). This means that the temperature dependence of T_1 also indicated that the mobility of the water was much more restricted in poly(hydroxyethyl methacrylate) than in poly(methyl methacrylate).

The T_2 values for poly(hydroxyethyl methacrylate) were more than one order of magnitude greater than that for poly(methyl methacrylate) and showed the opposite temperature dependence. When T_2 is described by dipole-dipole interaction, it decreases with decreasing temperature. In cases of slow chemical exchange, the exchange rate contributes to the relaxation rate. When the contribution of the exchange rate to T_2^{-1} is dominant, the temperature dependence is the opposite of that when the dipolar term is dominant.¹⁶ Therefore, the T_2 of poly(hydroxyethyl methacrylate) would be determined by the exchange rate. This rate is considered to reflect the exchange between free and intermediate water. Using the T_2 value of Figure 3(b), we estimated the apparent exchange rate at 28°C to be $3.6 \times 10^2 \text{ s}^{-1}$ and from the slope of T_2 in Figure 3(b), we estimated the apparent activation energy ΔE^\ddagger to be 2.0 kcal/mol. This value is close to that of a hydrogen bond.

The above results indicate that: (1) the proportions of bound and intermediate water relative to that of free water in the hydrophilic poly(hydroxyethyl methacrylate) membrane are twice as high as those in the hydrophobic poly(methyl methacrylate) membrane because of the introduced hydrophilic groups, (2) τ_c values for both free and intermediate water of poly(hydroxyethyl methacrylate) are several times longer than those of poly(methyl methacrylate) membrane, indicating that the mobility of water in the poly(hydroxyethyl methacrylate) membrane is more restricted, and (3) the exchange between intermediate and free water is slower in the NMR time scale in the hydrophilic poly(hydroxyethyl methacrylate) membrane than in the hydrophobic poly(methyl methacrylate) membrane. These differences explain the findings of Sakai et al.¹ that the permeability of hydrophilic membranes to water is much lower than that of hydrophobic membranes of poly(methyl methacrylate) of the same water content, and suggest that the characteristics of bound and intermediate water play significant roles in permeability.

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