

醫藥用 水膨潤性 高分子의 펄스 NMR 및 熱分析 研究

Pulse NMR and Thermal Analysis of Water-Swelling Polymers for Biomedical and Pharmaceutical Applications

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There are considerable interest and research in the biomedical application of synthetic polymers. Biocompatible synthetic polymers are widely used as surgical and dental implants as well as for artificial heart, artificial kidney, blood bags, etc.. Hydrophilic polymer hydrogels have been also considered as materials for medical and pharmaceutical applications. The hydrogels are three dimensional networks of water-swelling polymers, generally covalently or ionically crosslinked, which interact with aqueous solutions. Interest is focused on the utilization of the bulk or the surface properties of the hydrogels for practical applications.

Hydrophilic methacrylate polymers are being considered for biomedical applications¹⁻⁵. Synthetic hydrogels have been extensively discussed in the literature⁶⁻⁸. The transport characteristics of hydrogel membranes have been examined for a broad range of potential applications, including soft contact lenses⁹, reverse osmosis membranes¹⁰⁻¹², kidney dialysis membranes¹³⁻¹⁵, and drug delivery systems for antibiotics¹⁶⁻¹⁸, steroids^{19,20}, and enzymes^{21,22}.

In order to develop useful synthetic biomedical hydrogels, it is of interest to understand the state and properties of water in such hydrogels. Water in hydrogels has been treated in terms of a three-state model²³. To test the validity of the model, dilatometry, specific conductivity, and dielectric studies of water in hydrogels have been carried out

from -15°C to room temperature for poly(2-hydroxyethyl methacrylate) (pHEMA)^{24, 25} and poly(2,3-dihydroxypropyl methacrylate) (pDHPMA) gels²⁶. Some hydrophilic polymers for biomedical and pharmaceutical applications have been developed²⁷⁻³³.

The works presented in this paper are mainly concerned with the study of pulse NMR and thermal analysis of water-swelling methacrylate polymers for biomedical and pharmaceutical applications. The amounts of bound water, intermediate water, and bulk-like(free) water in hydrophilic methacrylate hydrogels have been determined by utilizing differential thermal analysis. The interactions of water with hydrophilic methacrylate polymers have been also studied by using pulse NMR relaxation spectroscopy.

Differential Thermal Analysis

The integral heats of fusion of the water melting transition in hydrogels were measured from the total peak area of the endotherms. Typical melting transition endotherms of water, indium, and water-swollen methacrylate gels are shown in Figure 1. The lower water content (10% H_2O) pHEMA sample does not show any sharp transition near 0°C (Fig. 1, middle). Double peaks in hydrogel systems are found for the higher water content (40% H_2O) pHEMA sample, as shown in Figure 1(top). The

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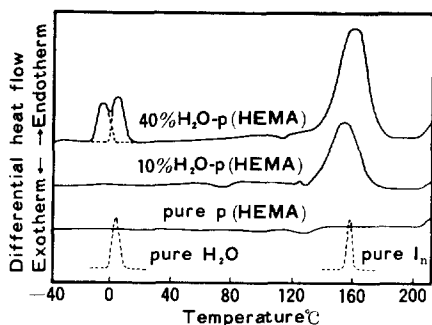


Fig. 1. Endotherms for water, indium, and poly(2-hydroxyethyl methacrylate) hydrogels. The program rate is 5°C/min.; scale is 20°C/in.; flow rate of N₂ gas is 50 ml/min.

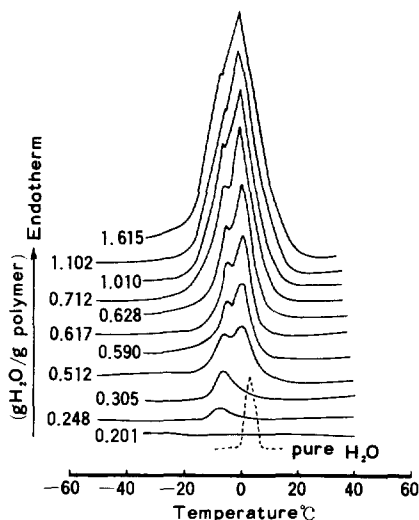


Fig. 2. The endotherms of p(HEMA)-H₂O samples. The program rate is 5°C/min.; scale is 20°C/in.; flow rate of N₂ gas is 50 ml/min.

shape of the endotherm was somewhat dependent upon the freezing conditions, though the total area of the endotherm was approximately constant. We define the total water transition to consist of both peaks in the vicinity of 0°C. Figure 2 presents the detailed endotherms for the pHEMA-H₂O samples and Figure 3 for the TEGDMA crosslinked pHEMA-H₂O samples.

Figures 4 and 5 show the integral heat of fusion of the water melting transition as a function of water content for pHEMA and pHEMA-TEGDMA

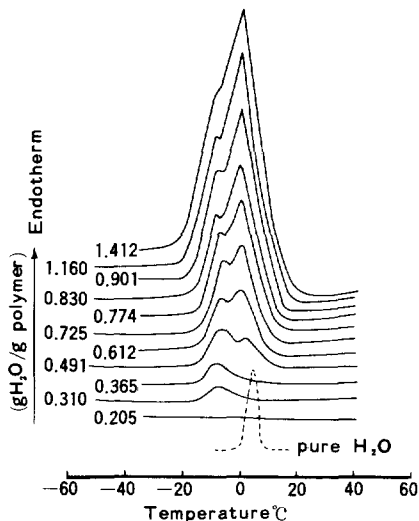


Fig. 3. The endotherms of p(HEMA)-TEGDMA-H₂O sample. The program rate is 5°C/min.; scale is 20°C/min.; flow rate of N₂ gas is 50 ml/min.

hydrogels, respectively. In the figures 4, 5, 6, and 7, W_{nf} represents the nonfreezable water. By similar measurements of the total area under the endothermic curves³⁴⁻³⁶, we have determined the integral heat of fusion of the water melting transition. Extrapolation to $\Delta H = 0$ intercepts the water content axis at a point which is the total bound water content of the sample, given in Table 1.

A plot of the integral heat of fusion versus water content of gels shows approximately a straight line in the measured range³⁶. The slope at high water contents is approximately equal to the heat of fusion of bulk water ($\Delta H_f = 79.7$ cal/g)³⁷. From the slope of the straight line, the specific heats of water transition in the samples were evaluated as listed in Table 1. The values of ΔH_f of polymeric systems, such as pHEMA-H₂O and pHEMA-TEGDMA-H₂O, are less than that of ΔH_f of bulk water. The lower ΔH_f values may be due to volume shrinkage and structuring of water in the gel network, which can be directly observed by dilatometry²⁴. The values of ΔH_f obtained for the hydrogel systems based on pHEMA are reasonable and are similar to related systems^{38,39}. One can also compare with the reported values of 77.6 cal/g for purified elastin⁴⁰ and 77.5 cal/g for native elastin⁴⁰.

Table 1. Total Bound Water Content and Specific Thermal Parameters of Water Transition in Some Methacrylate Systems

Systems	Bound water content (wt %)	Mole ratio of bound H ₂ O/monomer unit	Specific enthalpy of fusion, ΔH_f (cal/g)*	Specific entropy of fusion, ΔS_f (e. u.)*
Ice	100.0	—	79.7	0.292
HEIB-H ₂ O	2.0	0.15	78.8 ± 0.7	0.288 ± 0.003
HEMA-H ₂ O	6.5	0.51	78.5 ± 0.7	0.287 ± 0.003
p(HEMA)-H ₂ O	18.0	1.59	76.3 ± 0.7	0.279 ± 0.003
p(HEMA)-(1 mole% EGDMA)-H ₂ O	20.6	1.89	75.8 ± 0.7	0.278 ± 0.003
p(HEMA)-(1 mole% TEGDMA)-H ₂ O	21.9	2.05	75.2 ± 0.7	0.275 ± 0.003

* For freezing (intermediate and bulk-like) water in the hydrogels.

HEIB: Hydroxyethyl isobutyrate, HEMA: Hydroxyethyl methacrylate.

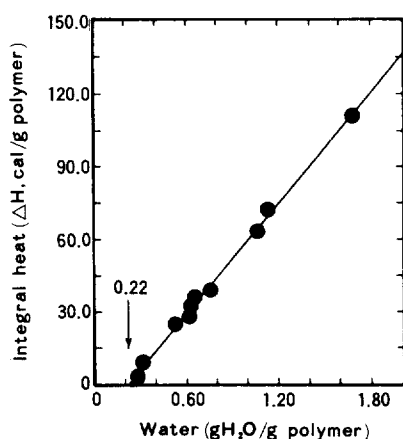


Fig. 4. The integral heat of fusion of the water transition as a function of water content for the p(HEMA)-H₂O system. The content of W_{nf} is 0.22g H₂O/g polymer (18.0 wt% H₂O).

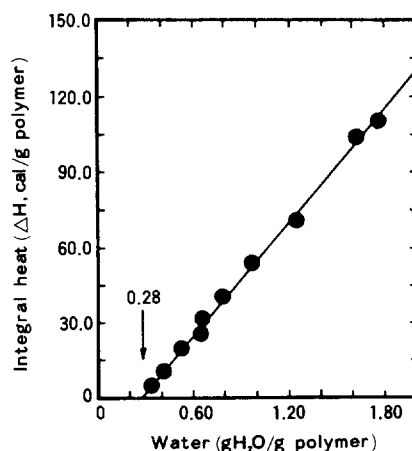


Fig. 5. The integral heat of fusion of the water transition as a function of water content for the p(HEMA)-TEGDMA-H₂O system. The content of W_{nf} is 0.28g H₂O/g polymer (21.9 wt% H₂O).

The specific entropies of fusion of the water transition as the melting point were evaluated from the relationship $\Delta S_f = \Delta H_f/T_m$, using the ΔH_f data listed in Table 1. The observed entropy deficit can be interpreted as the ordering of the bulklike water in the hydrogels and is somewhat greater than the ordering of ordinary water and ice, whose specific entropy of fusion is 0.292 eu²⁷. It is interesting to compare the specific entropy of fusion of the water

transition in pHEMA hydrogels with the values found for various tissues, which range from 0.259 eu to 0.279 eu⁴¹. Water molecules bound to polymer networks are distinguishable from other water molecules by a higher binding energy, an appreciably lower rotational freedom, and an extended lifetime.

Since the endotherms show two different peaks in higher water content gels^{24, 36}, an enthalpic heat

of fusion can be obtained from each peak. Each peak was manually resolved and the individual peak areas were determined³⁶. The water which melts near 0°C is called "bulklike" water; the water which has a lower melting temperature is called "intermediate" water; and the water which does not show any melting transition above -100°C is called "bound" water^{24,36}.

Figures 6 and 7 show the partial enthalpic heats of the freezable water as a function of water content

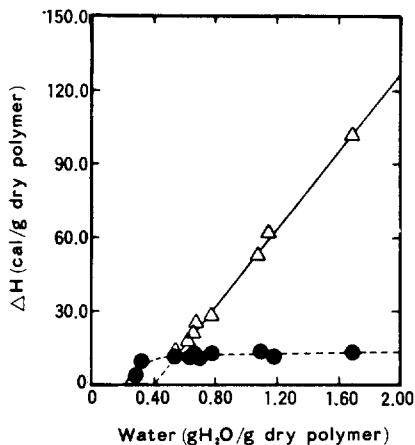


Fig. 6. The heat of fusion of the $W_{f(I)}$ and $W_{f(F)}$ transition as a function of water content for the p(HEMA)-M₂O hydrogels: ●- $W_{f(I)}$; △- $W_{f(F)}$.

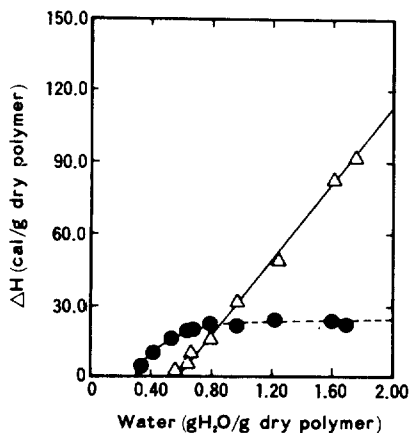


Fig. 7. The heat of fusion of the $W_{f(I)}$ and $W_{f(F)}$ transition as a function of water content for the p(HEMA)-TEGDMA-H₂O hydrogels: ●- $W_{f(I)}$; △- $W_{f(F)}$.

in the system pHEMA-H₂O and pHEMA-TEGDMA-H₂O, respectively. In Figures 6 and 7, $W_{f(I)}$ is the "intermediate" (lower melting) water; $W_{f(F)}$ is the "free" or "bulklike" (0°C melting) water in the hydrogels. The slope of bulklike(free) water in the hydrogels is very close to the heat of fusion of bulk water. The amounts of bound water, intermediate water, and bulklike water in each hydrogel system were determined from the data of Figures 4-7 and are presented in Table 2 for pHEMA hydrogels of different total water contents; Table 3 gives the data for 1 mol % TEGDMA-pHEMA-H₂O systems. As seen in Table 2 and 3, bulklike (free) water in the hydrogels increases only after the bound water and intermediate water are saturated.

Table 2. Determination of Bound Water, Intermediate Water, and Bulk-like Water in p(HEMA) Hydrogels of Different Total Water Content

Wt % of total water in hydrogels	18.0	20.0	25.0	30.0	35.0	40.0	45.0	50.0
Total water/polymer (gm/gm)	0.22	0.25	0.33	0.43	0.54	0.67	0.82	1.00
Bound water/polymer (gm/gm)	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22
Intermediate water/polymer (gm/gm)	0	0.03	0.11	0.16	0.16	0.16	0.16	0.16
Bulk-like water/polymer (gm/gm)	0	0	0	0.05	0.16	0.29	0.44	0.62

Table 3. Determination of Bound Water, Intermediate Water, Bulk-like Water in 1 mole % TEGDMA-p(HEMA) Hydrogels of Different Total Water Content

Wt % of total water in hydrogels	21.9	25.0	30.0	35.0	40.0	45.0	50.0
Total water/polymer (gm/gm)	0.28	0.33	0.43	0.54	0.67	0.82	1.00
Bound water/polymer (gm/gm)	0.28	0.28	0.28	0.28	0.28	0.28	0.28
Intermediate water/polymer (gm/gm)	0	0.05	0.15	0.25	0.29	0.29	0.29
Bulk-like water/polymer (gm/gm)	0	0	0	0.01	0.10	0.25	0.43

Table 4. Proton NMR Spin-Lattice Relaxation Times for Hydrogels Based on p(HEMA) of Different Total Water Content at 100 MHz and 34°C (unit: sec.)

Wt % of total water content in the hydrogel	p(HEMA)-H ₂ O		p(HEMA)-1 mole % EGDMA-H ₂ O		p(HEMA)-1 mole % TEGDMA-H ₂ O	
	T ₁	T ₁₁	T ₁	T ₁₁	T ₁	T ₁₁
25	0.189	0.272	0.186	0.251	0.182	0.217
30	0.214	0.298	0.198	0.274	0.190	0.232
35	0.260	0.311	0.220	0.297	0.207	0.279
40	0.300	0.337	0.259	0.303	0.238	0.304
45	0.340	0.336	0.296	0.303	0.268	0.302

T_{1F} = 4.5 sec. at 34°C

T_{1B} = 0.169 sec. for 18% H₂O-p(HEMA); 0.176 sec. for 20.6% H₂O-p(HEMA)-EGDMA; 0.178 sec. for 21.9% H₂O-p(HEMA)-TEGDMA.

The process of water imbibition in the hydrogels may be interpreted in terms of three steps: (1) An amount of water is first bound to the hydrophilic sites; (2) additional water is preferentially oriented around the bound water and the polymer network structure as a secondary or tertiary hydration shell; and (3) any other water is present as free or bulklike water.

Nuclear Magnetic Relaxation Spectroscopy

Table 4 presents the spin-lattice relaxation times (T₁) as a function of water content for the pHEMA and pHEMA-TEGDMA systems at 100 MHz and 34°C. Comparing with the T₁ of pure water (4.50s at 34°C), the average T₁ values for the hydrogel systems are reduced, suggesting that there are considerable interactions between the water molecules and the polymer networks. The short T₁ of water protons in the hydrogel suggests that the water is less mobile than in pure water. This can be interpreted in terms of the structure ordering of water molecules in gel networks. The most probable binding positions of water molecules are the polar sites, such as the hydroxyl and ester groups. The effect of a crosslinking agent, such as TEGDMA, produces rather slight changes in T₁, though the hydrophilic tendency can be seen. The results are in good agreement with the bound water quantities obtain-

ed from the differential thermal analysis data.

The measured values of the proton spin-lattice relaxation times (T₁) can be considered as an average of three states of water in the hydrogels: bound water, intermediate water, and bulklike (free) water²⁵.

$$\frac{1}{T_1} = \frac{f_B}{T_{1B}} + \frac{f_I}{T_{1I}} + \frac{f_F}{T_{1F}}$$

where f_B, f_I, and f_F are the fraction of bound, intermediate, and bulklike water in the hydrogels, and T_{1B}, T_{1I}, and T_{1F} are the spin-lattice relaxation times for bound, intermediate, and bulklike water in the hydrogels, respectively. T_{1F} is taken to be that of pure water; f_B, f_I, and f_F are obtained from the differential thermal analysis data. T_{1B} corresponds to the measured T₁ for the known content of W_{nf} in Figures 4 and 5. Hence, one can estimate T_{1I} for intermediate water in the hydrogels. Table 4 gives T_{1I} determined for pHEMA-H₂O and 1 mol % crosslinked (TEGDMA)-pHEMA-H₂O systems.

The T₁ values are inversely proportional to the magnitude of the interactions between water protons and lattice environments, i.e., the lower value of T_{1I} means a stronger interaction between water molecule and polymer network.

According to the data in Table 4, the spin-lattice relaxation times (T_{1B}) of bound water in the hydrogels are about 30 times less than that of water

protons in pure liquid water. The values of T_{1f} of intermediate water in the hydrogels are approximately twice that of T_{1b} of bound water. The proton spin-lattice relaxation times directly give the mobility of water molecules in the hydrogels. Comparing the data with the T_{1f} of bulklike (free) water, the mobility of water protons of bound water or intermediate water is less than that of water protons in pure liquid water. This indicates that some water molecules around the polar sites in the gels may be structured and preferentially ordered, probably due to hydrogen bonding or strong polar interactions. That is in line with the specific entropy data obtained from the thermal analysis listed in Table 1.

Figure 8 shows the spin-spin relaxation times (T_2) of water protons as a function of water content in pHEMA, pHEMA-EGDMA, and pHEMA-TEGDMA hydrogel systems. The values of T_2 are approximately 10 times less than those of T_1 , in general agreement with the principles of spin relaxations. In the region of less than 25% water content, the values of T_2 are almost constant, however, beyond this region the T_2 values rapidly increase as the water content gradually increases, indicating the presence of increasing amounts of free and intermediate water. These results are in good agreement with the spinlattice relaxation results.

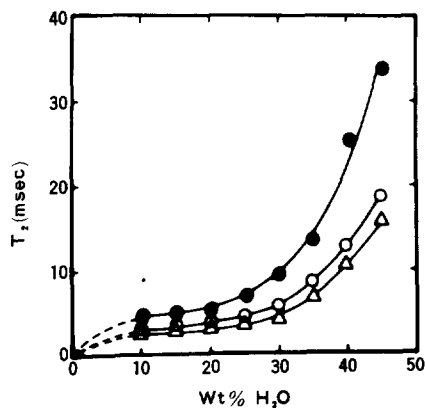


Fig. 8. The spin-spin relaxation times (T_2) of water protons as a function of water content in hydrophilic methacrylate polymers at 34°C and 100 MHz. ●-p(HEMA)-H₂O; ○-p(HEMA)-EGDMA-H₂O; △-p(HEMA)-TEGDMA-H₂O.

The spin-lattice relaxation times of low water content gels clearly demonstrate the existence of two distinct phases (Figures 9 and 10); i.e., two independent relaxation times T_{1a} and T_{1b} are obtained. We define T_{1a} as the spin-lattice relaxation time for strongly bound water; T_{1b} as the spin-lattice relaxation time for weakly bound water.

The longitudinal moment decay expression in this case can be obtained directly from the following equation⁴²:

$$M(\tau) = M_0(\tau) [P_a \exp(-\tau/T_{1a}) + P_b \exp(-\tau/T_{1b})]$$

where $M_0(\tau)$ is the equilibrium nuclear magnetization; P_a and P_b are the apparent fractional state populations; T_{1a} and T_{1b} are the apparent relaxation times of states a and b.

The corresponding signal amplitudes observed are given by

$$A(\tau) = \sum_{i=1}^2 A_{oi} \exp(-\tau/T_{1i})$$

where $i=a, b$, and A_i is an exponential amplitude

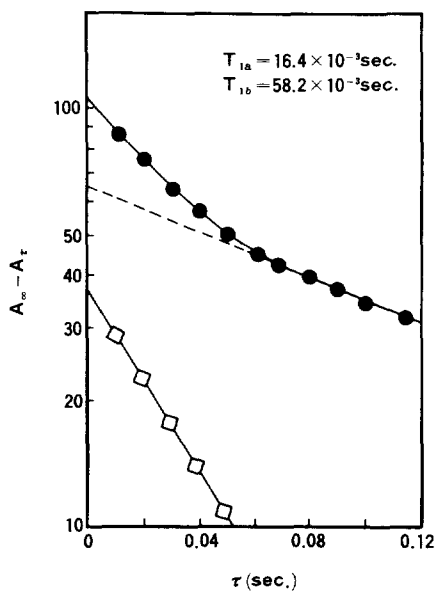


Fig. 9. Spin lattice relaxation times for water protons in low water content (10% H₂O) p(HEMA) hydrogel at 34°C and 100 MHz illustrating two-phase behavior.

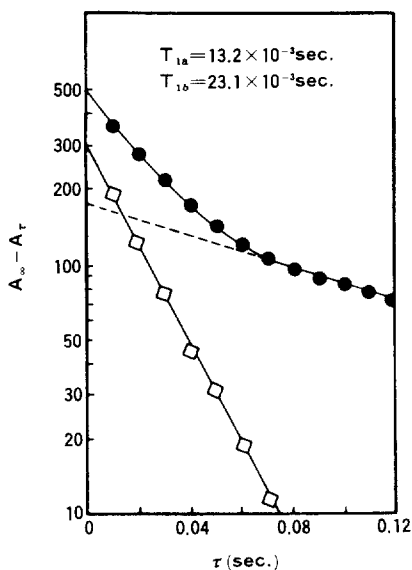


Fig. 10. Spin-lattice relaxation times for water protons in low water content (10% H₂O) p(HEMA)-1 mole % EGDMA hydrogel at 34°C and 100 MHz illustrating two-phase behavior.

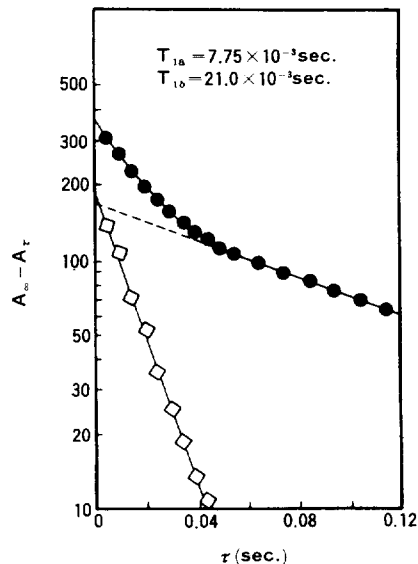


Fig. 11. Spin-lattice relaxation times for water protons in low water content (10% H₂O) p(HEMA)-1 mole % TEGDMA hydrogel at 34°C and 100 MHz illustrating two-phase behavior.

which is directly proportional to the quantity $M_0(\tau)$ P_i . The plots of $\ln(A_\infty - A_\tau)$ vs τ are shown in Figure 9 for a 10% H₂O-p(HEMA) system; Figure 10 for 10% H₂O-p(HEMA)-EGDMA system; Figure 11 for 10% H₂O-p(HEMA)-TEGDMA system.

T_{1b} is obtained from the slope of the plot of the experimental signal intensities; T_{1a} is obtained from the slope of the second plot of the difference between the extrapolated values and the experimental values. The spin-lattice relaxation time data for low water content (all bound water region) hydrogel systems are of particular importance to the overall study.

The data suggest that there are two different kinds of bound water, i.e., strongly bound water and weakly bound water. Strongly bound water may be the primary hydrogen bonding water on the polar sites; weakly bound water may be secondary or tertiary interfacial water.

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