

Effects of Salts in the Hofmeister Series and Solvent Isotopes on the Gelation Mechanisms for Hydroxypropylmethylcellulose Hydrogels

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ABSTRACT: The effects of various inorganic salts and isotopic solvents on the thermal gelation behavior of hydroxypropylmethylcellulose (HPMC) in aqueous solutions were examined by micro-differential scanning calorimetry and rheological measurements. It was found that salting-out salts, such as NaCl, promoted the sol–gel transition of HPMC at a lower temperature. An analysis of solvent isotope effects on the changes in the temperature at maximum heat capacity (T_m) with salt concentration showed that interchain hydrogen bonding (hydrogen bonding between the hydroxyl groups of different HPMC chains) was involved in the sol–gel transition, and its strength depended on the temperature and salt concentration. It was demonstrated that the effectiveness of anionic species in changing the T_m of the HPMC solutions was in the sequence

of the Hofmeister series. Anionic species play a role in reducing T_m by their influence on the structure of the water, which in turn affects interactions between hydroxyl groups and water molecules, interchain hydrogen bonding, and the strength of the water cages prohibiting hydrophobic association. Rheological and microcalorimetric results indicated that the change in the thermodynamics of gelation of the HPMC aqueous solution was determined by the salt types and concentration, and the effect of monovalent salts was found to be more cooperative than that of multivalent salts on the sol–gel transition. © 2008 Wiley Periodicals, Inc. *J Appl Polym Sci* 109: 363–372, 2008

Key words: differential scanning calorimetry (DSC); hydrogels; thermodynamics

INTRODUCTION

The thermoreversible gelation of aqueous solutions of nonionic cellulose ethers has attracted great interest in recent years because of their applications as thickeners, binders, and matrices in the food and pharmaceutical industries.^{1–3} Methylcellulose (MC) and hydroxypropylmethylcellulose (HPMC) are typical cellulose derivatives that undergo thermoreversible sol–gel transitions in their aqueous solutions on heating. The thermal gelation behaviors of MC and HPMC have been studied extensively, and various mechanisms have been proposed.^{4–10} However, it is widely accepted that the gelation of MC and HPMC is mainly caused by hydrophobic associations among the molecules with hydrophobic substitutions, such as methyl groups, and less hydrophobic substitutions, such as hydroxypropyl groups,^{5–7,10,11} which leads to the formation of a three-dimensional network accompanied by an endothermic heat effect and an abrupt increase in the dynamic storage mod-

ulus (G').⁵ HPMC is a much weaker gel compared to MC because of the incorporation of hydroxypropyl groups.⁶ Moreover, the gel strength decreases further with increasing degree of hydroxypropyl substitution.¹¹ Because there are no covalent bonds forming or breaking during the gelation–degelation (gel–sol transition) process, the formed gels from aqueous solutions of HPMC are physically crosslinked and completely reversible.¹¹

Salts are known to influence the temperature-induced phase transitions of aqueous solutions of thermosensitive polymers, such as MC, poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) triblock copolymers, triblock copolymers of poly(ethylene glycol) (PEG) and poly(D,L-lactide-co-glycolide) (PLGA), and copolymers of *N*-isopropylacrylamide.^{12–15} Kim et al.¹³ investigated the effects of salt on the thermogelation behavior of PEG–PLGA–PEG. They found that salting-out salts, such as NaCl, decreased the gelation temperature through their water-structure formation properties. On the other hand, salting-in salts, such as NaSCN, increased the gelation temperature through their water-structure breaking properties. It is well known that the influence of ions follow the Hofmeister series, which originates from the abilities of ions to precipitate proteins,¹⁶ and anions decrease in the order $\text{SCN}^- < \text{ClO}_4^- < \text{I}^-$

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$\langle \text{NO}_3^- \approx \text{Br}^- < \text{Cl}^- < \text{F}^- < \text{H}_2\text{PO}_4^- < \text{S}_2\text{O}_3^{2-} < \text{SO}_4^{2-}$, and the cations increase in the order $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Mg}^{2+} > \text{Ca}^{2+} > \text{Ba}^{2+}$. However, the effect of cations is less significant than that of anions.¹⁷ The anions on the right are destabilizing ones or kosmotropes, whereas those on the left are referred to as stabilizing ions or chaotropes.¹⁵ Various mechanisms have been proposed to explain effects of the Hofmeister series,^{17–23} and most theories are based on the capability of an ion to make or break water structure.¹⁹ Collin²⁰ suggested that an ion's effect on water structure was attributed to a competition between water–ion interactions, whereas Omta et al.²¹ reported that the presence of ions does not change the structure of the bulk water. This difference in explanation may be due to ionic concentration and the sensitivity of the methods to bulk structural changes.²² An alternative explanation is that the ions disrupt the hydration structure at the water–solute interface.²³ New theories, such as specific ion binding, have also been proposed to explain the Hofmeister series.^{14,15} Although the effects of salt on some gelation systems, including MC, have been investigated in our earlier studies,^{12,24,25} few reports have been made on the effects of salt on the gelation of HPMC, even though HPMC has more applications in pharmaceuticals.² Mitchell et al.²⁶ showed that various salts that lower the cloud point of HPMC gels follow the order of the Hofmeister series. However, turbidity measurement has many limitations. As a more powerful technique, microcalorimetry has been widely applied to study structure transitions in proteins and thermoresponsive polymers, such as poly(*N*-isopropylacrylamide) (PNIPAm) and cellulose derivatives.^{5,10,27,28} This technique allows the structure transitions related to thermal changes to be determined precisely¹⁰ and also determines the transition thermodynamics.

In this study, first, the ability of a typical salting-out salt, NaCl, to affect the thermogelation of HPMC was systematically studied. Solution isotope effects on the temperature at maximum heat capacity (T_m) were analyzed. Second, the effects of various anionic species on thermodynamic parameters, such as T_m , the temperature range between two points at which the relative heat capacity (C_p) reaches half of the maximum value ($T_{1/2}$), enthalpy change (ΔH), and entropy change (ΔS), were determined from thermal curves and checked with the Hofmeister series. On the basis of these thermodynamic data, the effectiveness of anions on the thermogelation of HPMC was elucidated in terms of their influence on water structure. Finally, the effects of salt on the viscoelastic properties were examined. We expected that this study would provide a better understanding of the gelation mechanism of HPMC in different salt environments.

EXPERIMENTAL

Materials and sample preparation

HPMC was purchased from Sigma-Aldrich, Inc. It was dried *in vacuo* at 60°C and stored in a desiccator before use. The HPMC had a molecular weight of 86,000 g/mol and a viscosity of 4000 cps for a 2 wt % aqueous solution at 20°C. The average degrees of substitution of the methyl and hydroxypropyl groups were 1.8–2.0 and 0.2, respectively. Analytical grade salts purchased from Sino Chemical Co., Ltd. (Singapore), were used as received and included monovalent salts (NaCl, KCl, NaBr, and NaI), divalent salts (Na_2HPO_4 , K_2HPO_4 , and Na_2SO_4), and trivalent salt (Na_3PO_4). Deuterated water (D_2O , 99.9%, Aldrich) was used without further purification. The deionized water was from an Alpha-Q Millipore water purification system. A 1.0 wt % HPMC solution was prepared by dissolution of the polymer in deionized water under stirring; it was stored in a refrigerator (4°C) for 24 h to get a homogeneous and transparent solution. The salt weighed in correct proportions was added to the HPMC solution, and the mixture was stirred overnight. The maximum salt concentrations for monovalent, divalent, and trivalent salts were 0.8, 0.2, and 0.15M, respectively. Higher concentration of salts yielded highly viscous solutions that could not be injected into the sample cells of the microcalorimeter. All of the samples were allowed to equilibrate at 4°C for at least 24 h before the measurements.

Micro-differential scanning calorimetry

A differential scanning calorimeter (VP-DSC MC-2 microcalorimeter, MicroCal, Inc.) was used to study the thermodynamic properties of HPMC in various salt solutions. A 0.5158-mL sample of solution and an equal amount of reference fluid (deionized water or salt solution as required) were hermetically sealed in the sample cell and the reference cell, respectively. Aqueous salt solution as a reference resulted in no difference in the onset and peak temperature and less than a 1.0% difference in the enthalpy values, which was in agreement with previous reports.¹⁷ The cooling and heating (at a rate of 1.0°C/min) differential scanning calorimetry (DSC) curves were recorded in the temperature range 20–90°C.

Rheological measurements

A control-strain rheometer (ARES 100FRTN1, Rheometric Scientific) was used to measure the flow properties and dynamic viscoelasticity of the HPMC solutions. The rheometer was equipped with two sensitive force transducers for torque ranging from 0.004 to 100 g-cm. The sample solution was poured

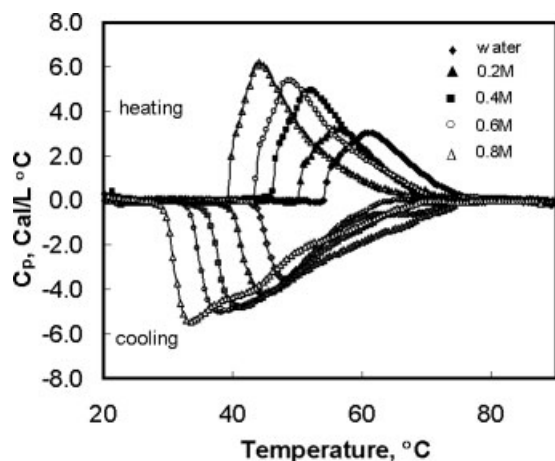


Figure 1 C_p as a function of temperature for 1% (w/w) HPMC solutions with various NaCl concentrations.

onto parallel-plate geometry (50 mm in diameter), and a small amount of silicone oil was applied at the periphery of the solution to prevent evaporation. G' and loss modulus (G'') were examined as a function of temperature from 20 to 75°C at a heating rate of 1°C/min. The measurements were carried out at a frequency of 1 rad/s and with a strain amplitude of 5% to ensure the linearity of viscoelasticity.

RESULTS AND DISCUSSION

The properties of HPMC in aqueous solution are affected by the presence of salt because they alter the HPMC–water interaction. In this section, the effects of various salts in different concentrations on the thermal gelation of HPMC are discussed with the experimental results obtained by the VP-DSC and the rheometer.

Thermal behavior

Effects of the salt concentration in H₂O

A typical salting-out salt, NaCl, was used to examine the effect of salt concentration on the thermal behavior of HPMC aqueous solutions in H₂O, and the results are illustrated in Figure 1. First, each thermogram of the sample solutions showed a relatively narrow endothermic peak in the heating process. A broad exothermic peak was observed during the subsequent cooling process. Second, although all of the thermograms showed similar curve patterns, the peaks shifted to lower temperatures, and the area under the endothermic and exothermic peaks increased with increasing NaCl concentration.

The thermogelation of HPMC proceeded in two stages [Fig. 2(a1,a2)].⁶ At low temperatures, water molecules formed (1) hydrogen bonding with the hydroxyl group of the HPMC chains (intermolecular

hydrogen bonding) and (2) structured water cages surrounding hydrophobic clusters of the HPMC chains (methyl-substituted regions) and less hydrophobic substitutions [hydroxypropyl moieties; Fig. 2(a1)]. On heating, intermolecular hydrogen bonding was gradually weakened. On further heating to the gelation onset temperature, external heat was absorbed and consumed to deform and break surrounding the water structures (cages) to expose the

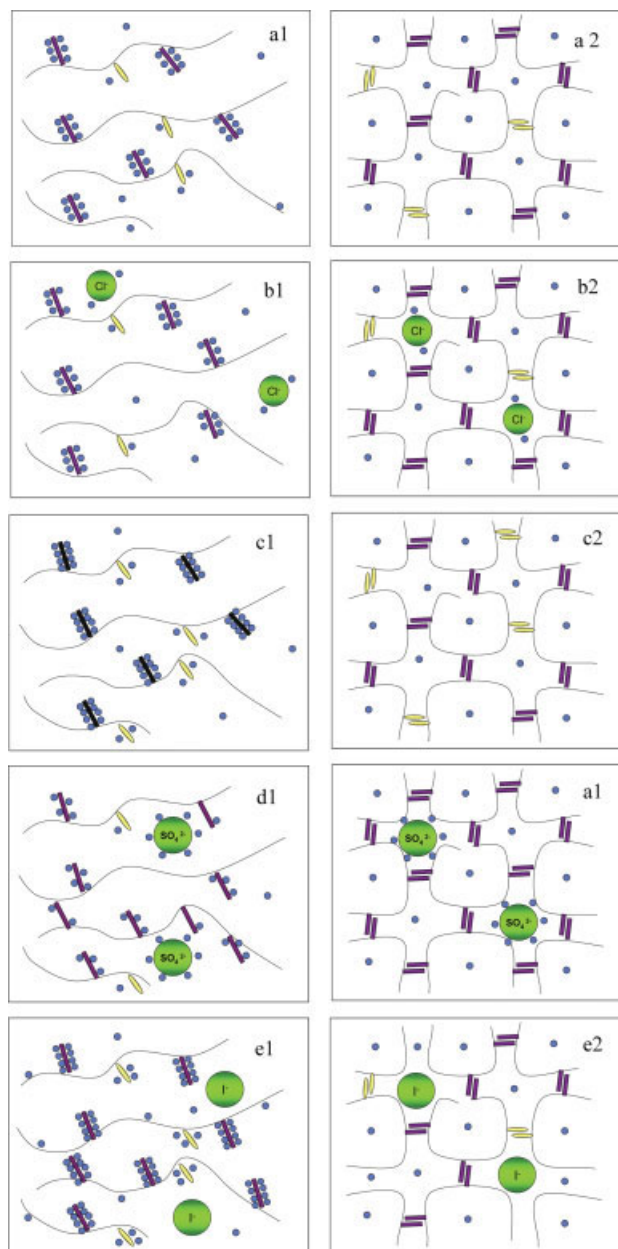


Figure 2 Physical structures of the aqueous HPMC hydrogels in various solutions at lower temperatures (solutions, a1–e1) and at higher temperatures (gels, a2–e2): (a) H₂O, (b) 0.2M NaCl in H₂O, (c) D₂O, (d) 0.2M Na₂SO₄ in H₂O, and (e) 0.2M NaI in H₂O. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

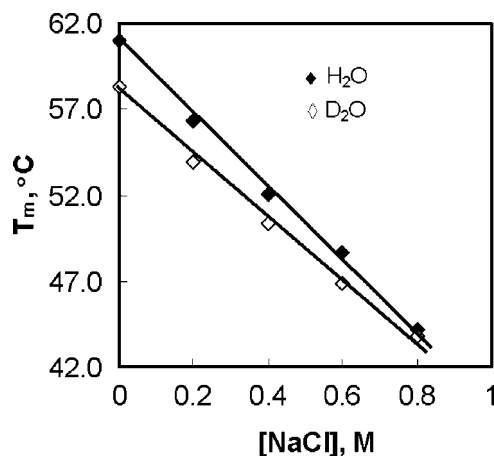


Figure 3 Endothermic peak temperature of the HPMC solution (1 wt %) in H₂O and D₂O during gelation as a function of NaCl concentration.

methyl groups to the aqueous environment. The exposed methyl groups simultaneously induced hydrophobic association between the HPMC chains, which resulted in the formation of a gel network [Fig. 2(a2)]. The association between different HPMC chains through hydroxyl groups (interchain hydrogen bonding) also contributed to gel formation. The addition of NaCl resulted in a shift of the endothermic peak to the lower temperature, which indicated that NaCl promoted this thermogelation. T_m , corresponding to the sol–gel transition, was considered to be the sol–gel transition temperature¹⁰ and was plotted against the NaCl concentration (Fig. 3). A shift in T_m was linearly in proportion to the NaCl concentration with the line fitted with a slope of $-20.6^\circ\text{C}/\text{M}$. As mentioned earlier, NaCl is a typical water structure maker and exhibits a salting-out effect, which tends to attract and interact with water molecules strongly because of its strong hydration abilities;²⁰ thus, the intermolecular hydrogen bonding of HPMC was weakened and easily disrupted. At the same time, water cages were more easily broken, and hydrophobic methyl groups were more easily exposed. This promoted temperature-related hydrophobic association, which led to the shift in the endothermic peak to lower temperatures [Fig. 2(b1,b2)]. With increasing NaCl concentration, the salt ions attracted more hydration water molecules around them and, thus, disrupted the structured water around the hydrophobic side groups on the HPMC chains to form water cages. This also affected intermolecular hydrogen bonding.

As shown in Figure 1, the typical degelation process also proceeded in two stages. On cooling, the hydrophobic associations were gradually weakened, and the gel network dissociated gradually. On further cooling, intermolecular hydrogen bonding and water cages re-formed around the hydrophobic

groups on the HPMC chains. The competition between ions and HPMC chains for water molecules made it more difficult to re-form intermolecular hydrogen bonding and water cages; thus, the exothermic peak shifted to a lower temperature in the presence of NaCl. The re-formation of intermolecular hydrogen bonding and water cages at lower temperatures in the presence of NaCl was attributed to the fact that intermolecular hydrogen bonding became stronger with decreasing temperature. Although the gelation process was thermoreversible, the endothermic curve and exothermic curve (Fig. 1) were not symmetrical. A thermal hysteresis between the exothermic and endothermic peaks was observed, which might have been due to the facts that the kinetic rate of the degelation process was slower than that of the gelation process and the dissociation from a structured gel network was much more difficult than the association of HPMC chains from aqueous solution. Similar results were reported by Morris, Li, and coworkers.^{5,6,10} Scan rate might have influenced the shift in the peak, so a low temperature ramp rate ($1^\circ\text{C}/\text{min}$) was adopted to ensure the approach to equilibrium and to reduce the impact of the heating rate to a minimum.^{29,30} Because the trends in DSC show that the effects of salt on gelation and degelation are similar, we focus only on the heating process in the following discussion.

Thermodynamic properties such as enthalpy and entropy can be obtained from endothermic thermograms in addition to the onset, offset, and peak temperatures. ΔH can be calculated by integration of the thermograms over temperature. ΔS can be calculated by the following equation:

$$\Delta S = \int_{T_1}^{T_2} (C_P/T) dT$$

where T is the temperature, and T_1 and T_2 are the onset and offset temperatures, respectively. The results are summarized in Table I and are plotted in Figure 4. Both ΔH and ΔS were dependent on NaCl concentration. Both of them increased with increasing salt concentration and exhibited three regions, as shown in Figure 4. The three regions of each curve suggested that there were two critical concentrations. The first region ($<0.2\text{M}$) was characterized by a relatively slow increase in ΔH . At concentrations higher than 0.2M , ΔH started to increase rapidly until the NaCl concentration reached 0.6M . Subsequently, it reached a plateau at higher NaCl concentrations. Similar trends were observed for ΔS . According to Li et al.,¹⁰ compared to the energy needed in the destruction of water cages, the energy needed to break down the intermolecular hydrogen bonding and that between ions and water molecules as well

TABLE I
Thermodynamic Characteristics of the HPMC Solution with Various Solvents and NaCl Concentration

	0M NaCl		0.2M NaCl		0.4M NaCl		0.6M NaCl		0.8M NaCl	
	H ₂ O	D ₂ O	H ₂ O	D ₂ O	H ₂ O	D ₂ O	H ₂ O	D ₂ O	H ₂ O	D ₂ O
T_m on heating (°C)	61.0	58.3	56.3	53.9	52.1	50.1	48.7	46.9	44.2	43.7
T_m on cooling (°C)	48.0	45.8	44.9	41.8	41.3	38.0	37.8	35.4	33.5	32.2
ΔH (cal/L) on heating	36.78	39.65	38.92	46.13	61.50	59.30	71.59	66.28	73.06	69.47
ΔS (cal L ⁻¹ K ⁻¹) on heating	0.11	0.12	0.12	0.14	0.19	0.18	0.22	0.20	0.23	0.22

as hydrophobic associations is much lower. Meanwhile, the release of water molecules from the water cages mainly contributes to an increase in the entropy of the system.^{5,10} In the presence of NaCl, most water cages are weakened, and therefore, less energy is required to break an individual water cage as compared to a water cage in the case of solutions without salt. Thus, with the given energy input at a low temperature, most of the water cages broke, which facilitated a higher number of hydrophobic associations. However, total energy input was higher in the case of salt addition. This was because the total number of hydrophobic substitutions increased with the addition of NaCl. Moreover, because the absorbed heat was mainly used to break the water cages compared to other processes, such a NaCl concentration effect on ΔH could be attributed to the changes in the total number of breakable water cages. When the NaCl concentration was below 0.2M, most ions got into the bulk water and attracted water molecules in the bulk water instead of around water-polymer interfaces. Thus, the water cages that surrounded hydrophobic substitutes may not have been affected greatly. However, with increasing NaCl concentration to 0.2–0.6M, enough ions may have surrounded the water cages and competed for water molecules, which resulted in a large increase in the number of weakened and breakable water cages. With the further increase in NaCl concentra-

tion, the remaining few water cages also became available to be broken, which led to a slow increase in ΔH and ΔS .

Effects of the salt concentration in D₂O

It has been known that the balance among intermolecular hydrogen bonding, interchain hydrogen bonding, and hydrophobic effect is a determining factor in the sol-gel transition of aqueous HPMC solutions.⁹ The first of these effects should lead to the salting-in of the polymer, whereas the second and the third lead to the salting-out of the polymer. D₂O, a liquid more structured than light water, was used to increase the contrast because these two solvents are chemically identical, whereas their physical properties are different.²⁸ As shown in Figure 5, the patterns of the thermograms of the HPMC solutions in H₂O and D₂O solvents were similar, yet the T_m of the solution in D₂O (58.3°C) was lower than that in H₂O (61.0°C). The deuterium isotope effect on the heat-induced thermal transition temperature of PNIPAm and cellulose has been investigated by other researchers,^{28,31} and the results were found to be different. The T_m value for the PNIPAm solution in D₂O was higher by 2°C as compared that for H₂O.²⁵ This was because the hydrogen bond in D₂O is about 5% stronger than that in H₂O.²⁸ The increase

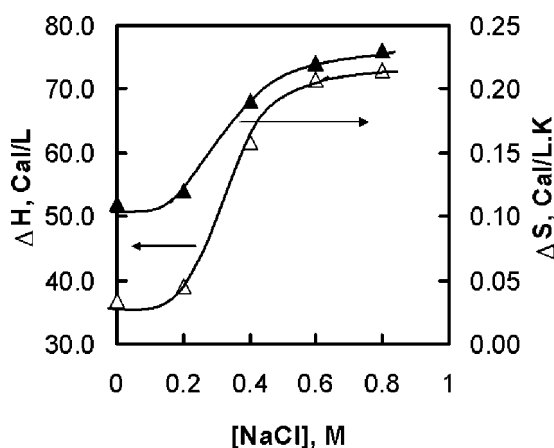


Figure 4 Endothermic ΔH and ΔS of the HPMC solution (1 wt %) in H₂O as a function of NaCl concentration.

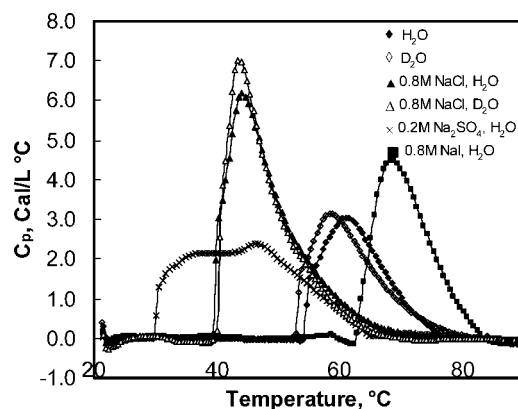


Figure 5 C_p of the HPMC aqueous solutions in H₂O and D₂O with various salts during heating.

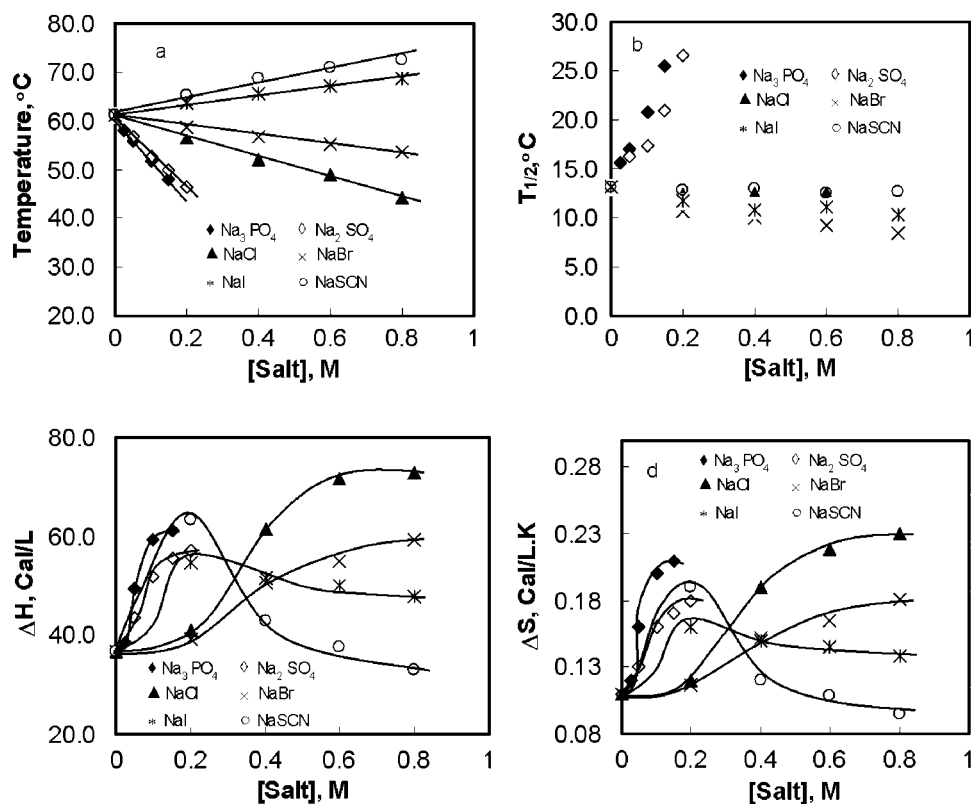


Figure 6 Thermodynamic properties of the 1% (w/w) aqueous HPMC solutions as a function of the concentration of added salt during the heating process: (a) peak temperature (T_m), (b) $T_{1/2}$, (c) ΔH , and (d) ΔS .

in the heat-induced thermal transition temperature of PNIPAm in D₂O has also been found in other reports.^{15,32} In contrast to PNIPAm, in this study, the transition temperature of HPMC in D₂O was significantly lower (by 2.7°C) compared to that of H₂O. Because the hydrophobic interactions were slightly weaker in D₂O than in H₂O,³³ this difference between PNIPAm and HPMC should have stemmed from different polymer–solvent interactions caused by the isotopic substitution of the hydrogen-bonding network. In the case of HPMC, both the strength of intermolecular and interchain hydrogen bonding increased in D₂O. It is possible to argue that the first effect was dominant, whereas the second was weak, together with the formation of water cages, which made HPMC soluble at low temperatures [Fig. 2(c1)]. However, it is important to consider that the second effect was strengthened, whereas the first was weakened at elevated temperatures [Fig. 2(c2)]. A similar result on the influence of D₂O was reported by Winnik,³¹ who showed that the phase transition point of (hydroxypropyl) cellulose in D₂O was slightly lower than that in water (i.e., 40.0°C in D₂O and 40.5°C in H₂O). The solvent isotope effect on HPMC in the presence of NaCl was concentration dependent (Fig. 3). The magnitudes of the difference in T_m became smaller with increasing amount of NaCl. For example, T_m of HPMC in D₂O was 2.7°C

lower than that in H₂O, whereas it was 2.4°C lower with 0.2M NaCl. T_m in H₂O approached closely that in D₂O at high NaCl concentrations. In aqueous solution or solutions with lower salt concentrations, the thermal gelation of HPMC was mainly driven by hydrophobic associations and partly by interchain hydrogen bonding [as schematically shown in Fig. 2(a1–b2)]. However, the interchain hydrogen bonding became less effective, and thermal gelation was dominated by the hydrophobic interactions at high NaCl concentrations.

Hofmeister series

As shown in Figure 6(a), all ions showed a linear dependence on salt concentration, which indicated a linear decrease in T_m with the salt concentration in the solutions. T_m was lowered with the addition of kosmotropic anions and elevated in the case of chaotropes. Moreover, the ability of ions to change the T_m depended strongly on the anions and was characterized with the slope (K) of the fitted straight line (Table II). The more negative the K value was, the stronger the salting-out effect was. PO₄³⁻ had the strongest salting-out effect among all of investigated anions, and T_m decreased sharply with a negative K of $-86.0^\circ\text{C}/\text{M}$. The slopes for the other three kosmo-

TABLE II
Linear Correlation Between K of the Fitted Curves and the Entropy of Hydration (ΔS_{hydr}), Viscosity B Coefficient of the Anions, and Anion Radius

Ion	K (°C/mol)	ΔS_{hydr} (J K ⁻¹ mol ⁻¹)	Viscosity B coefficient (L/mol)	Radius (Å)
PO ₄ ³⁻	-86.0	-421	0.495	2.38
SO ₄ ²⁻	-72.6	-200	0.206	2.30
Cl ⁻	-20.6	-75	-0.005	1.81
Br ⁻	-9.2	-59	-0.033	1.96
I ⁻	9.4	-36	-0.073	2.20
SCN ⁻	14.3	—	-0.103 ²⁰	2.13
R ²		0.84	0.90	

ΔS_{hydr} , viscosity B coefficient, and anion radius are from ref. 35.

tropic anions (SO₄²⁻, Cl⁻, and Br⁻) were -72.6, -20.6, and -9.2°C/M, respectively. The negative slope for the kosmotropic anions indicated that they promoted the sol-gel transition of the HPMC solutions. In contrast to kosmotropic anions, the slopes of chaotropic anions such as I⁻ and SCN⁻ were positive, and they were 9.4 and 14.3°C/M, respectively, which indicated that they retarded the thermal gelation of the HPMC solutions. The results showed that the effects of anions on T_m of the HPMC solutions followed the sequence of the Hofmeister series.

As most studies have agreed and demonstrated that the ions exert their salting-out/salting-in effects via their water structuring capability and not via direct interactions between ions and polymer chains,³⁴⁻³⁶ a similar mechanism is used to explain the Hofmeister series in this study. The ions' effects on water structure were attributed to the competitions between ion-water interactions and water-water interactions.²⁰ The former interactions were dominated by charge density, and the latter interactions were dominated by hydrogen bonding. The ability of halide to lower T_m decreased with its size (Table II; regression coefficient = 1.0).³⁷ This was consistent with halide anion surface charge densities, which are -4.42×10^{-21} , -3.64×10^{-21} , and -2.84×10^{-21} C/Å², respectively (regression coefficient = 0.99).²² Because the chloride ion had the smallest radius and largest charge density among the halides investigated in this study, it had the strongest ability to compete for water molecules and form hydrogen bonds with water molecules, which minimized or weakened water-polymer hydrogen bonding. On the other hand, the low charge density of ions such as I⁻ provided the weakest competition for water molecules, which thus led to salting-in effects and increased the solubility of the polymer. An alternative explanation proposed by Hribar¹⁹ is that water structure is determined by the balance between electrostatics and hydrogen bonding. Multivalent anions and the smallest anions such as F⁻ and Cl⁻ cause a

strong electrostatic orientation of water molecules with respect to the anion, which makes water structure more ordered. Therefore, there are less free water molecules available to solvate the polymer chains. This facilitates and accelerates the hydrophobic association of methyl substitutions, which leads to a decrease in T_m of the HPMC solutions [Fig. 2(d1,d2)]. On the contrary, large monovalent anions such as I⁻ and SCN⁻ have a low charge density, and water structures around them are less organized than in the bulk solutions. They tend to increase the hydrogen bonding between water molecules and the polymer, which results in an increase in T_m of the HPMC solutions [Fig. 2(e1,e2)]. On the basis of these analyses, it is clear that both mechanisms could be applied to interpret the results in this study. The trivalent anion (PO₄³⁻) was more effective in the salting-out effects than the divalent anion (SO₄²⁻), followed by monovalent anions such as Cl⁻. However, the trend of radius of these ions was reversing, as shown in Table II. This indicated that valence was a dominating factor in comparison to anionic radius.

Although the initial argument on the Hofmeister series was conclusive, further quantification is necessary for a better understanding of it. Hribar¹⁹ argued that the effect of salt on the degree of water structuring is determined mainly by the entropies of ion solvation and viscosity changes.¹⁹ Anions with a more negative entropy value are considered more effective in ordering water molecules. A plot of the slopes for the T_m values of various salts against the corresponding hydration entropy of the anions yielded a straight line with a regression coefficient of 0.84, which indicated that they were not well correlated linearly. On the other hand, the viscosity B coefficient was used to quantify the degree of water structuring because it was related to the viscosity of an aqueous salt solution. Anions with a large viscosity B coefficient value exhibited strong water structure making capabilities. The regression coefficient between K of the HPMC salt solutions and the corre-

sponding viscosity B coefficient of the anions was found to be 0.91. We concluded that the linear correlation between slopes for T_m and these quantities were not well-defined, although most anions followed the sequence of these quantities. This seemed to further demonstrate that different mechanisms were involved in the thermogelation in the presence of salt, as discussed in previous section.³⁸

Multivalent anions such as PO_4^{3-} and SO_4^{2-} had a strong salting-out effect compared to monovalent anions. It was interesting that the pattern of thermograms of HPMC in the presence of SO_4^{2-} was much broader than that of monovalent anions (Fig. 5). The corresponding $T_{1/2}$ is illustrated in Figure 6(b). $T_{1/2}$ for all monovalent anions was almost constant, whereas it increased sharply for multivalent anions with increasing salt concentration. The results suggest that the effect of monovalent anions was more cooperative, whereas that of multivalent anions was less cooperative. Because multivalent anions have a strong ability to compete for water molecules in bulk solution and interface, it is unlikely that all of them could have competed for water molecules at the interface because of their big size and tetrahedral coordination. Additionally, the ring structure of HPMC would have made it difficult for all big hydration multivalent anions to approach the water cages. Therefore, water cages were weakened to a different extent by multivalent anions than they were by monovalent anions. That is, the strength of the water cages had a larger polydispersity in the presence of multivalent anions.

Figure 6(c,d) shows the endothermic ΔH and ΔS for HPMC aqueous solutions with various salts and salt concentrations. The endothermic ΔH and ΔS increased with increasing salting-out salt concentration. All salting-out salts showed similar trends as NaCl, as discussed earlier. The interpretation for such ΔH and ΔS values for HPMC in salting-out salt

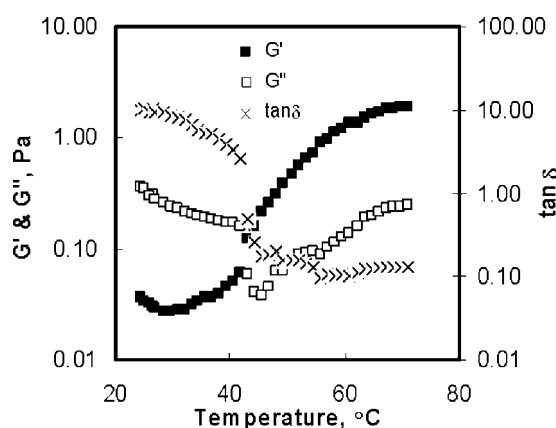


Figure 7 Sol-gel transition of 1 wt % HPMC with 0.8M NaCl as examined by dynamic viscoelasticity measurement (frequency = 1 rad/s, heating rate = 1°C/min).

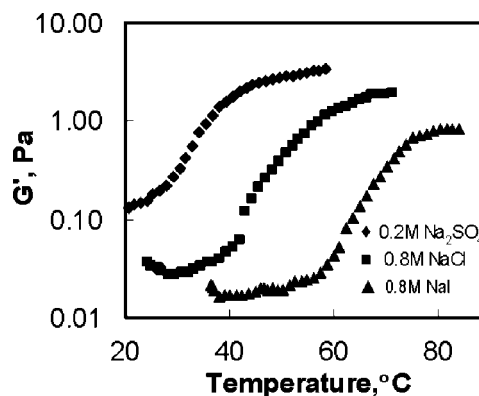


Figure 8 G' as a function of temperature for the aqueous solution of 1 wt % HPMC with various salts in the heating process (frequency = 1 rad/s, heating rate = 1°C/min).

solutions could be explained by the same mechanism as used for NaCl. On the other hand, the endothermic ΔH and ΔS for salting-in salts such as NaI and NaSCN showed a different pattern than salting-out salts. Both ΔH and ΔS increased initially with increasing salt concentration until the salt concentration reached 0.2M. Subsequently, they decreased with a further increase in salt concentration.

As stated earlier, salting-in salts are water structure breakers, which strengthen the intermolecular hydrogen bonding and water cages [Fig. 2(e1,e2)]. A higher amount of energy was required to break water cages to explore the hydrophobic association that led to the gel formation. With a further increase in concentration, the water cages were further strengthened. As a result, some water cages were too strong to be broken even at high temperatures. This caused a decrease in ΔH and ΔS .

Rheological characterization on heating

Figure 7 shows the temperature dependence of G' and G'' for a 1 wt % HPMC solution with 0.8M NaCl. There were two different regions. In the first region, at a temperature below 40°C, the solution behaved as a liquid, in which G'' was much greater than G' ($G'' \gg G'$). G' decreased initially and then increased gradually with increasing temperature up to 42°C. This finding was consistent with previous reports, which showed a similar trend for both MC and HPMC.^{5,6,11} The initial decrease in G' may have been due to the loss of viscous and elastic consistency as the temperature increased. The initial entanglement between cellulose chains at low temperature (<30°C) were disrupted and reduced when the temperature started to increase.^{39,40} The subsequent increase in G' was due to the weak entanglement of polymer chains induced by the interchain hydrogen bonding, as evidenced through isotope analysis. This

TABLE III
 G' and G'' of the HPMC Aqueous Solutions with Various Salts and Salt Concentrations at 70°C, 1 rad/s, and 5% Strain

	HPMC sample						
	Aqueous solution	0.8M NaI	0.2M NaCl	0.4M NaCl	0.6M NaCl	0.8M NaCl	0.2M Na ₂ SO ₄
G' (Pa)	16.33	11.25	19.24	31.48	40.88	44.60	65.38
G'' (Pa)	2.91	2.82	4.80	3.08	3.57	11.60	18.74

observation was in line with previous reports.⁹ In the second region, G' increased rapidly with temperature before it achieved a plateau above 60°C ($G' \gg G''$), whereas G'' fell sharply at 42°C and rose at 55°C. This was coincident with an abrupt decrease in the phase angle. The onset of a rapid increase in G' served as an indication of gelation, which was in the vicinity of the T_m observed from the VP-DSC. Also, the rapid increase in G' over a temperature region corresponded to the endothermic peak observed with the VP-DSC (Fig. 1).

The effects of different salts on G' on heating are illustrated in Figure 8. Typical samples of 0.2M Na₂SO₄, 0.8M NaCl, and 0.8M NaI were chosen for comparison. The general pattern for the samples in the presence of Na₂SO₄ and NaI were found to be similar to that of NaCl, as stated previously. The curves shifted toward lower temperature in the presence of the salting-out salt NaCl, and this tendency became more pronounced in the presence of the multivalent salting-out salt Na₂SO₄. In contrast to salting-out salts, the curve for NaI shifted toward higher temperature, which indicated a salting-in effect. Interestingly, the final values of G' were salt dependent. As shown in Table III, G' increased with the addition of salting-out salts, whereas it decreased in the presence of salting-in salts. This means that the gel was strengthened in the presence of salting-out salts and weakened when salting-in salts were added in. A similar trend was reported by Cho, An, and Song⁴¹ in their study of the effects of salts on the viscosity of polyorganophosphazenes.⁴¹ As discussed earlier, the thermally induced gelation of HPMC solutions mainly involves hydrophobic association, which leads to a three-dimensional network. Therefore, gel strength is governed by the hydrophobic associations. In the presence of salting-out salts, the number of physical junctions formed by the hydrophobic association and association strength increased, which resulted in increased gel strength.⁴¹ On the contrary, NaI showed a salting-in effect and enhanced the solubility of the HPMC chains, which resulted in decreased gel strength. G' increased with increasing NaCl concentration. Moreover, the trend correlated well with that of ΔH . This further demonstrated that gel strength was affected by hydrophobic associations.

CONCLUSIONS

The thermal gelation behavior of HPMC aqueous solutions with various salts was investigated. Most salts (except NaI and NaSCN) exhibited salting-out effects and, therefore, promoted the thermogelation of HPMC, whereas NaI and NaSCN showed salting-in effects and suppressed the thermogelation of HPMC. The effect of interchain hydrogen bonding between the hydroxyl groups of the HPMC chains in the heating process was identified through solvent isotope. The effectiveness of anionic species for reducing T_m was in the sequence of the Hofmeister series and was attributed to their ability to influence water structure. Microcalorimetry results revealed that the thermodynamic properties of the HPMC solutions correlated with salt type and salt concentration. Moreover, the effect of monovalent salts on the sol-gel transition was more cooperative than that of multivalent salts. The effects of anions on the rheological properties of the HPMC solutions were in good agreement with the thermal properties. The gel strength was enhanced in the presence of salting-out salts, whereas it decreased slightly in the presence of salting-in salts. This may have been due to changes in the density of physical junctions caused by the salts.

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