# Hydrogen-Bonded Network Structure of Water in Aqueous Solution of Sulfobetaine Polymers $^{\dagger}$

# Hiromi Kitano,\* Makoto Imai, Kurao Sudo, and Makoto Ide

Department of Chemical and Biochemical Engineering, Toyama University, Toyama 930-8555, Japan Received: January 18, 2002; In Final Form: July 8, 2002

Poly(N,N-dimethylaminopropyl methacrylamide) (poly(DMAPMA)) was incubated with 1,3-propanesultone and 1,4-butanesultone to afford polymers with various contents of N,N-dimethyl-N-(3-sulfopropyl)-3'methacrylamidopropanaminium inner salt residues and N,N-dimethyl-N-(4-sulfobutyl)-3'-methacrylamidopropanaminium inner salt residues, respectively. The structure and hydrogen bonding of water in an aqueous solution of the sulfobetaine polymers were analyzed using the contours of the O-H stretching in the polarized Raman spectra. With an increase in the content of the sulfobetaine residue, the relative intensity of the collective band (C value) corresponding to a long-range coupling of the O–H stretching in the aqueous polymer solutions became larger and approached the C value of pure water. The number of hydrogen bonds disrupted because of the presence of one monomer residue (N value) for the polymers with a large sulfobetaine content was a small positive value and comparable to those for neutral polymers such as poly(ethylene glycol) and poly-(N-vinylpyrrolidone). This is in significant contrast with the largely positive N values for the precursor polymer (poly(DMAPMA)), and ordinary polyelectrolytes such as sodium polyethylenesulfonate, poly-L-lysine hydrobromide, sodium polyacrylate, and poly(acrylic acid). The N value for a small molecular weight zwitterionic compound, 3-aminopropanesulfonic acid, was also slightly positive, which is consistent with the tendency observed for the sulfobetaine polymers. The present results clearly indicate that the zwitterionic polymers do not significantly disturb the hydrogen-bonded network structure of water, probably because of the counteraction of the electrostriction effect by the proximity between the anionic and cationic groups.

# Introduction

The anomalous physical properties of liquid water (for example, the heat capacity, the heat of solidification, and the heat of vaporization are the largest among ordinary liquids) can be ascribed to hydrogen bonding between the oxygen atom of the water molecule and hydrogen atom of a neighboring water molecule.<sup>1</sup> A nonlinear bent structure of water molecules, furthermore, makes a fluctuated hydrogen-bond network in the liquid state. Vibrational spectroscopic methods (VSs) including Raman spectroscopy have been very often used to analyze the so-called V structure (vibration-averaged structure) of water reflecting orientation of water molecules,<sup>2</sup> because these methods utilize smaller observation times ( $\tau = 10^{-13} - 10^{-14}$  s) than the relaxation times of the rotational rearrangement ( $\tau_{\rm R}$ ) of water molecules in the liquid phase ( $\tau = 10^{-11} - 10^{-12}$  s). Furthermore, the average lifetime of the hydrogen bond between water molecules (on the order of  $10^{-12}$  s) is larger than the vibrational relaxation time of chemical bonds used as a probe in the VSs. Therefore, the VSs can detect not only the rotational rearrangement of water molecules but also the changes in the hydrogenbonded networks between water molecules. On the other hand, other techniques (differential scanning calorimetry (DSC), X-ray diffraction, dielectric dispersion, and NMR), which utilize larger observation times ( $\tau \simeq 10^1$ ,  $10^1$ ,  $10^0 - 10^{-11}$ , and  $10^{-6} - 10^{-11}$ s, respectively) compared with the  $\tau_{\rm R}$  or the lifetime of hydrogen bond between water molecules, can detect the state of water based on the diffusion property of the water molecule. Therefore, these techniques cannot directly detect the changes in the water structure.

The physical properties of polymer systems in all concentration regions from dilute aqueous solutions to hydrated solids are very often determined by the interaction between water and the polymer chain. The thermodynamic properties of water in polymer solutions have been analyzed by NMR,<sup>3</sup> DSC,<sup>4</sup> and other techniques.<sup>5</sup> However, as mentioned above, it is difficult to reveal the hydrogen-bonded network structure of water using these methods. We have been interested in the analyses of the structure of water in aqueous polymer solutions from a Raman scattering of water attributable to the O-H stretching vibration band (2800-3800 cm<sup>-1</sup>).<sup>6,7</sup> It was pointed out that the number of hydrogen bonds disrupted because of the presence of one monomer residue (N value) of a polyelectrolyte with an ionic group in the side chain (sodium poly-L-glutamate, poly-L-lysine hydrobromide, and sodium polyacrylate with a small  $M_{\rm w}$  value, etc.) was much larger than those for neutral polymers (poly-(ethylene glycol) and poly(N-vinylpyrrolidone)).<sup>6b,e,f</sup> Moreover, the N value for the polymer with an *ionizable* group in the side chain (poly(acrylic acid) (HPAA), for example) was smaller than those for the polyelectrolytes with a fully ionized group and larger than those for neutral polymers.<sup>6b</sup>

Quite recently, it was found that a zwitterionic polyelectrolyte, poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC), did not disturb the hydrogen-bond network structure of water.<sup>6f</sup> To examine the possibility that zwitterionic polymers *in general* do not significantly affect the structure of water, we examined the polarized Raman scattering of the O–H stretching vibration band of water in an aqueous solution of another kind of zwitterionic polymer, a sulfobetaine polymer with various degrees of quaternization.

About fifty years ago, the properties of an aqueous solution of zwitterionic polymers prepared by the free radical copolymerization of cationic and anionic comonomers were studied.<sup>8a,b</sup>

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<sup>\*</sup> To whom correspondence should be addressed. Tel: +81-76-445-6868. Fax: +81-76-445-6703. E-mail: kitano@eng.toyama-u.ac.jp.

Afterward, zwitterionic polymers based on carboxybetaine monomer units were also investigated.<sup>8c,d</sup> In the past 10 years, preparation and characterization of sulfobetaine polymers have been extensively studied.<sup>9,10</sup> It was found that zwitterions in the sulfobetaine polymers remain in their diionic form over a broader pH range than the carboxybetaine polymers.<sup>9h</sup>

Furthermore, the anomalous properties of aqueous solution of sulfobetaine polymers (so-called "anti-polyelectrolyte" behavior as described below) have been fascinating many researchers: By taking into account the large solubility of sulfobetaine derivatives in salt solutions, for example, researchers prepared super-adsorbent gels, which can swell at high electrolyte concentrations, by the copolymerization of the sulfobetaine monomer with other hydrophilic comonomers.<sup>9d,e,f</sup> Polystyrene latex particles were also prepared at high electrolyte concentration (1.0 M NaCl) by using sulfobetaine macromonomers.<sup>10c</sup>

Meanwhile, zwitterionic compounds are characterized by having excellent dermatological properties. They also exhibit low eye irritation and are frequently used in shampoos and other cosmetic products.<sup>11</sup> Carboxybetaine derivatives, for example, are widely used in cleansing compositions, fabric conditioner, hair and skin cosmetic compositions,<sup>12</sup> etc. Similarly, sulfobetaine surfactants reduce the skin irritation of other surfactants,<sup>13</sup> and therefore, they are widely used as skin-compatible dishwashing detergents with good foaming properties.<sup>14</sup> Furthermore, sulfobetaine derivatives are used as a component in various cosmetics (reducing agent for permanent wave, conditioning and hair washing composition, etc.). As previously pointed out,<sup>6f</sup> the phosphobetaine polymer, PMPC, also has a large biocompatibility (no thrombus formation).<sup>15</sup> Quite recently, it was reported that zwitterionic self-assembled monolayers (SAMs) resist the nonspecific adsorption of various proteins from an aqueous buffer.<sup>16</sup> There is a possibility that the structure of water at the interface of the zwitterionic SAMs plays an essential role in the adsorption behavior of proteins.

As mentioned above, the unique properties of sulfobetaine polymers might be strongly related to the interaction of the zwitterionic polymers with water. Therefore, Raman spectroscopy would be an excellent technique to explore the structure of water in aqueous solution of sulfobetaine polymers.

#### **Experimental Section**

**Materials.** *N*,*N*-Dimethylaminopropyl methacrylamide (DMAPMA) was obtained from Aldrich, Milwaukee, WI. 1,3-Propanesultone and 1,4-butanesultone were obtained from Wako Pure Chemicals, Osaka, Japan. The other reagents were commercially available. Milli-Q grade water was used for the preparation of the sample solutions.

Sulfobetaine Vinyl Monomer (Scheme 1). *N*,*N*-Dimethylaminopropyl methacrylamide (DMAPMA, 3.2 mL) was dissolved in diethyl ether (20 mL), and 1,3-propanesultone (2.15 g) was added. The solution mixture was incubated at room temperature for 1 day. The obtained white precipitates were collected by filtration and, after being washed with acetone, dried in vacuo (*N*,*N*-dimethyl-*N*-(3-sulfopropyl)-3'-methacrylamidopropanaminium inner salt, SPB) (4.45 g, yield 86%). <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.93 (s, 3H), 2.05 (m, 2H), 2.20 (m, 2H), 2.97 (t, 2H), 3.11 (s, 6H), 3.36 (m, 4H), 3.47 (m, 2H), 5.47 (s, 1H), and 5.71 (s, 1H).

**Preparation of Polymeric Sulfobetaine (Scheme 2).** Sulfobetaine polymers were prepared by the method of Lee and Tsai.<sup>9a</sup> *N*,*N*-Dimethylaminopropyl methacrylamide (DMAPMA, 12.0 g) was polymerized in tetrahydrofuran (THF, 100 mL) at 70 °C for 8 h using 2,2'-azobisisobutyronitrile (AIBN, 120 mg)









and 3-mercaptopropionic acid (MPA, 900 mg) as the initiator and chain transfer reagent, respectively. After evaporation of the solvent, the obtained polymer was dissolved in water and purified by ultrafiltration using Amicon membranes (YM-10 (exclusion limit, 10<sup>4</sup>) and YM-50 (5 × 10<sup>4</sup>)) to obtain a fraction between 10<sup>4</sup> and 5 × 10<sup>4</sup> daltons. The purified polymer was finally lyophilized (poly(DMAPMA), 353 mg). The weightaverage and number-average molecular weights ( $M_w$  and  $M_n$ ) of poly(DMAPMA) were determined to be 1.54 × 10<sup>4</sup> and 1.22 × 10<sup>4</sup> ( $M_w/M_n = 1.26$ ) by gel permeation chromatography (GPC) (Waters HPLC system; column, Wako Gel G-40, Wako Pure Chemicals; mobile phase, acetate buffer (0.5 M, pH 4.06)) using pullulan standards (Showa Denko, Tokyo, Japan).

Poly(DMAPMA) (100 mg) dissolved in THF (20 mL) was incubated with 1 or 2 equiv of 1,3-propanesultone in a tightly sealed round-bottomed small flask at 30 °C for 24 h.9,10 After evaporation, the oily mixture was dissolved in water and repeatedly passed through an ion-exchange column (Amberlite IRA96SB,  $2 \times 20$  cm) to remove the ionic impurities. The polymer solution was further dialyzed against pure water for 3 days in a seamless cellulose dialysis tube (molecular cutoff, 13 000; Wako Pure Chemicals) and finally lyophilized (poly-(N,N-dimethyl-N-(3-sulfopropyl)-3'-methacrylamidopropanaminium inner salt), PSPB) (Table 1). Similarly, poly(DMAPMA) was incubated with 1,4-butanesultone in THF to give poly(N,Ndimethyl-N-(4-sulfobutyl)-3'-methacrylamidopropanaminium inner salt) (PSBB) with various degrees of quaternization (DQ) (Table 1). The degree of quaternization (DQ) of the polymeric sulfobetaine was estimated by <sup>1</sup>H NMR measurements.

**Raman Spectroscopy.** The O–H stretching Raman spectra of water between 2500 and 4000 cm<sup>-1</sup> in various aqueous poly-

**TABLE 1: Preparation of Polymeric Sulfobetaines** 

polymer	poly(DMAPMA) (mg)	sultone (mg)	solvent (mL)	time (h)	temp (°C)	yield (mg)	$\mathrm{D}\mathrm{Q}^{e}\left(\% ight)$	$1/[\eta]^f (g/dL)$
PSPB-1	100	140 <sup>a</sup> (2 equiv)	$20^{c}$	24	30	86	66	15.3
PSPB-2	100	290 <sup>a</sup> (4 equiv)	$20^{c}$	24	40	114	89	27.5
PSPB-3	100	290 <sup>a</sup> (4 equiv)	$20^d$	24	40	83	95	40.8
PSBB-1	100	160 <sup>b</sup> (2 equiv)	$20^{c}$	24	30	98	63	11.1
PSBB-2	200	640 <sup>b</sup> (4 equiv)	$20^{c}$	24	40	183	68	19.6
PSBB-3	200	640 <sup>b</sup> (4 equiv)	$20^{d}$	24	40	189	83	30.3
PSBB-4	220	700 <sup>b</sup> (4 equiv)	$20^d$	24	40	175	91	40.9

<sup>*a*</sup> 1,3-Propanesultone. <sup>*b*</sup> 1,4-Butanesultone. <sup>*c*</sup> THF. <sup>*d*</sup> CH<sub>3</sub>CN. <sup>*e*</sup> The degree of quaternization (DQ =  $(m/n) \times 100$ . See Scheme 2). <sup>*f*</sup> In water at 25 °C.



**Figure 1.** Raman spectra of O–H stretching region: (a)  $I_{\parallel}$  (solid) and  $I_{\perp}$  (broken) spectra of pure water at 25 °C ( $I_{\perp}/\rho_{O-H}$  spectrum is also shown by the dotted line); (b) the collective band of pure water.

meric sulfobetaine solutions were recorded on a NR-1100 spectrophotometer (Japan Spectroscopic, Co., Tokyo, Japan; light source, argon laser 488.0 nm) with a spectral resolution of 5 cm<sup>-1</sup>. The details of the measurements were described elsewhere.<sup>6,7</sup>

As exemplified in Figure 1, the component of the O–H stretching band of water centered at 3250 cm<sup>-1</sup> was highly polarized and diminished in the spectra at a perpendicular position.<sup>17</sup> The polarized O–H stretching band of water, which is called the "collective band", is ascribed to the H<sub>2</sub>O molecule executing  $\nu_1$  vibrations all *in phase* with each other but the vibrational amplitude varying from molecule to molecule in water clusters, which are strongly hydrogen-bonded.<sup>18</sup> Theoretical calculations of a random network model,<sup>19</sup> which is characterized by the fluctuated defects in water–water hydrogen bonds in a distorted tetrahedral network, support the interpretation. The intensity of the collective band (*I*<sub>c</sub>) observed around 3250 cm<sup>-1</sup> was separated from the spectra using eq 1 (Figure 1).

$$I_{\rm c} = I_{\rm \parallel} - I_{\perp} / \rho_{\rm O-H} \tag{1}$$

where the depolarization ratio,  $\rho$ , is an indicator of symmetry of the vibration mode and is expressed by  $\rho = I_{\perp}/I_{\parallel}$ , where  $I_{\perp}$ and  $I_{\parallel}$  are the intensities of the spectra observed with the polarizer oriented perpendicular and parallel to the incident laser beam, respectively.

Because the intensities of the Raman spectra are not absolute, the area of  $I_c$  was normalized by eq 2

$$C = \int I_{\rm c}(w) \, \mathrm{d}w / \int I_{\rm I}(w) \, \mathrm{d}w \tag{2}$$

where *w* is the Raman shift in  $cm^{-1}$ .

**Viscometric Measurements.** The reduced viscosity  $(\eta_{sp}/\phi, \eta_{sp} = (\eta - \eta_0)/\eta_0, \phi = \text{concentration of polymer in g/dL})$  for



**Figure 2.** Reduced viscosity vs concentration of sulfobetaine polymers at 25 °C in water: ( $\bullet$ ) poly(DMAPMA) (precursor); ( $\triangle$ ) PSPB-1; ( $\blacksquare$ ) PSPB-2; ( $\bigtriangledown$ ) PSPB-3.

various kinds of aqueous polymeric sulfobetaine solutions at 25 °C was determined using an Ubbelohde dilution type viscometer (type 0B; Kusano, Tokyo, Japan).

## **Results and Discussion**

**A. Viscosity Behavior of Polymeric Sulfobetaine Solution.** It has been widely accepted that, in aqueous polyelectrolyte solutions, a decrease in the polymer concentration results in an increased Debye length and, consequently, the increase in the electrostatic repulsion between the charged groups within the polymer chain induces expansion of the polymer chain.<sup>20</sup> However, highly precise viscometric measurements showed that, even for an infinitely diluted solution, polyelectrolyte molecules such as sodium poly(styrenesulfonate) do not completely stretch out.<sup>21</sup>

The viscosity behavior of sulfobetaine-type polymers prepared with 1,3-butanesultone (PSPBs) are shown in Figure 2. The reduced viscosity ( $\eta_{sp}/\phi$ ) for an aqueous solution of polymeric sulfobetaine with a large DQ value (PSPB-2 and PSPB-3) decreased with the decrease in the polymer concentration. This is in good contrast with the increase of  $\eta_{sp}/\phi$  with the decrease in the concentration of the precursor polymer, poly(DMAPMA), which is the typical viscosity behavior of the aqueous solution of ordinary polyelectrolytes.

When the DQ value was small (PSPB-1), a slight increase in  $\eta_{sp}/\phi$  upon dilution was observed. A similar tendency was also observed for another type of sulfobetaine polymers prepared with 1,4-butanesultone (PSBBs) (data not shown). These results were consistent with the previous reports: despite the sufficient solubility of the monomer in water, it has been often pointed out that polymeric sulfobetaines show "*anti-polyelectrolyte* behaviors", that is, a greatly enhanced solubility and an extensive chain expansion upon increasing salt concentration.<sup>9,10</sup>

When the sulfobetaine monomer, *N*,*N*-dimethyl-*N*-(3-sulfopropyl)-3'-methacrylamidopropanaminium inner salt, was polymerized, the product polymer (PSPB, DQ = 100%) could not be dissolved in pure water at all, which is in agreement with the result by Lee and Tsai.<sup>9a,b</sup> This might be partly due to the cyclization of the side chain to form an ion pair<sup>9a</sup> and partly



**Figure 3.** The relationship between the  $C_x/C_w$  value of water and the concentration ( $p_X$ , molar fraction of monomer unit) of sulfobetaine polymers at 25 °C: ( $\blacksquare$ ) poly(DMAPMA) (precursor); ( $\bigcirc$ ) PSBB-2 (DQ = 68%); ( $\triangle$ ) PSBB-3 (DQ = 83%); ( $\triangle$ ) PSBB-4 (DQ = 91%); ( $\square$ ) HPAA.

due to the stacking between the cationic and anionic groups of neighboring monomer residues. Both phenomena would decrease the characteristics of the electrolytes, resulting in a reduced solubility in water.

The cyclization of various kinds of sulfobetaine monomers including SPB has not been reconfirmed by the NMR method at present.<sup>22</sup> Weers et al. examined the effect of the intramolecular charge separation distance on the solution properties of betaines and sulfobetaines using FT-IR and NMR.<sup>23</sup> They reported that no evidence could be seen for the intramolecular ion-pair formation, indicating that in a polar medium such as water, the distance between the charge sites monotonically increases with the increasing number of methylene units in the tether. Using a molecular orbital calculation (WinMOPAC 3.0, Fujitsu Computer Chemistry Systems, Tokyo, Japan), however, we found the sulfobetaine monomer residues examined in this study to be able to be cyclized in water (unpublished results).

**B.** Structure of Water in Aqueous Polymer Solutions. The O–H stretching Raman band of liquid water gave a broad band (Figure 1a) composed of several overlapping components, which were attributed to the unperturbed O–H stretching band by the intra- and intermolecular vibrational coupling of the O–H oscillators.<sup>2b,24</sup> The relative intensities of the collective bands (*C*) are reduced by the decoupling of the O–H oscillator is quite different from that of the O–H oscillator that is combined by a hydrogen bond with the former one and (2) when the hydrogen bond between the coupled O–H oscillators is broken by translational or rotational rearrangement of the water molecules.<sup>17a</sup> In pure water, the values of *C* at a certain temperature *T* ( $C_w$ -(T)) are reduced with an increase in the temperature by intrinsic hydrogen-bond defects caused by thermal motion.<sup>25</sup>

Next, the effect of various polymeric sulfobetaines on the Cvalue at the constant molar fraction of monomer units ( $p_{\rm X} =$ 0.01) was examined. Figure 3 shows the effect of concentrations of various sulfobetaine polymers on the  $C_x/C_w$  value, where  $C_x$ and  $C_{\rm w}$  are the C values for an aqueous polymer solution and pure water, respectively. The  $C_x/C_w$  values for the polymer solutions were slightly smaller than unity, and with an increase in the degree of quaternization, the  $C_x/C_w$  value increased. In precursor polymer solution, poly(DMAPMA), the  $C_x/C_w$  value significantly decreased with an increase in the concentration, whereas in the solution of PSBB-2, the  $C_x/C_w$  value more gradually decreased. In the solution of PSBB-3, the  $C_x/C_w$  value was always larger than those for the precursor polymer and the PSBB-2. The  $C_x/C_w$  value of poly(acrylic acid) (HPAA) decreased with an increase in the concentration much more significantly than the precursor polymer. These results are due to the difference in the disturbing effect of the polymers on the structure of water.

In a dilute solution, polymer coils are separated from each other and the intermolecular interaction between the coils is sufficiently weak that the solution can be described as a nonideal gas. When the polymer concentration ( $\phi$ ) approaches a critical value ( $\phi^*$ ), the polymer coils begin to overlap and make a pseudonetwork. In the concentration region ( $\phi > \phi^*$ ), the polymer solutions are called "semidilute" solutions.<sup>26</sup> Graessley suggested a concentration criterion between the low- and high-concentration regimes for random coils in a good solvent as 1 <  $\phi[\eta] < 10.^{27}$  Therefore, the value of  $\phi^*$  can be roughly related to the intrinsic viscosity [ $\eta$ ] as stated in eq 3.

$$\phi^* \simeq 1/[\eta] \tag{3}$$

From the value of  $[\eta]$  for aqueous solutions of sulfobetaine polymers at 25 °C, it was concluded that almost all the sulfobetaine polymers examined here make dilute solutions at  $p_X = 0.01$  (for example, the  $\phi^*$  values of PSBB-2 and PSBB-3 were 19.6 g/dL ( $p_X = 0.013$ ) and 30.3 g/dL ( $p_X = 0.021$ ), respectively). Only in the case of PSBB-1, the  $p_X$  value of 0.01 was slightly larger than the  $\phi^*$  value ( $p_X = 0.008$ ).

In aqueous solutions, water molecules interact with hydrophilic or hydrophobic solutes and change their positions and orientations in the hydration shell around the solutes. Consequently, the intensities of the collective band of aqueous solutions at a certain temperature  $T(C_x(T))$  are reduced or increased by breaking or enhancing the water—water hydrogen bonding in comparison with those of pure water ( $C_w(T)$ ) at the same temperature. The probability,  $P_d$ , that an O–H oscillator is excluded from the hydrogen-bonding network of water molecules because of an unfavorable position or orientation is defined as eq 4.

$$P_{\rm d} = \frac{C_{\rm w}(T) - C_{\rm x}(T)}{C_{\rm w}(T)}$$
(4)

The C values of aqueous solutions of simple electrolytes<sup>17d</sup> and polar substances were smaller than that of pure water at the same temperature. This is caused, as mentioned above, by the exclusion of the O-H oscillator of hydrating water (HOH··· solute or H2O...solute or both) from the collective O-H oscillators of the water cluster. On the contrary, those of hydrophobic substances such as tetra-*n*-butylammonium hydroxide<sup>17f</sup> ( $p_X =$ 0.013) and *tert*-butyl alcohol<sup>17e</sup> ( $p_X = 0.04$ ) were higher than that of pure water because of an enhancement of the hydrogen bond between water molecules in hydrophobic hydration shells around the hydrocarbon moiety.<sup>28</sup> These results show that the vibrational band attributed to the O-H oscillators of water cluster can be distinguished from that of the water hydrated to solutes by using the polarized Raman spectroscopy and that this method has an ability to detect the changes in the hydrogenbonded network structure of water even in dilute-semidilute aqueous solutions ( $p_X = 0.01 - 0.05 (0.55 - 2.8 \text{ mol/L})$ ).

**C. Elucidation of** *N* **Values for Polymers.** To elucidate the effects of the properties of the monomeric unit of various polymers, the number of hydrogen-bond defects introduced into the hydrogen-bonded network structure of water per one monomer unit of a polymer, N, was calculated from the defect probability ( $P_d$ ) using eq 5.

$$N = P_{\rm d} / f_{\rm X} \tag{5}$$

where  $f_X$  is the number of monomer units per one O–H oscillator in a water molecule.<sup>6b,d–f, 29</sup>

Similar to small molecular solutes, ionized and polar groups in water-soluble polymer chains and counterions may disturb the hydrogen bond between the water molecules and raise the

TABLE 2: The N Values for Various Polymers<sup>a</sup>

polymer	N value
NaPES	$7.5^{b}$
PLL•HBr	$8.1^{b}$
NaPAA <sup>c</sup>	$8.7^{d}$
$HPAA^{e}$	$3.4^{d}$
PMPC	$-1.1^{b}$
PEG	$1.0^{b}$
PVPy	$0.9^{b}$
poly(DMAPMA)	5.4
PSPB-1	3.8
PSPB-2	3.2
PSPB-3	1.8
PSBB-1	3.8
PSBB-2	3.2
PSBB-3	1.0

<sup>*a*</sup> In H<sub>2</sub>O at 25 °C and  $p_X = 0.01$ . The uncertainties of *N* values are ±1 at the most. <sup>*b*</sup> Reference 6f. <sup>*c*</sup> Sodium polyacrylate ( $M_w = 5000$ ) at  $p_X = 0.05$ . <sup>*d*</sup> Reference 6b. <sup>*e*</sup> Poly(acrylic acid) ( $M_w = 5000$ ) at  $p_X = 0.05$ .

N value, whereas hydrophobic moieties such as hydrocarbon chains may enhance the hydrogen bond and reduce the N value. The exposure area of the chemical groups to water is also important to the structure of water around them. The values of N obtained for the dilute solutions of various polymers, in which the hydrogen-bond defects are expected to be localized in the hydration shell of polymer chains and their counterions, were determined and are listed in Table 2.

The *N* values of ordinary polyelectrolytes with one kind of ionic group (sodium polyacrylate,<sup>6b,f</sup> sodium poly(ethylenesulfonate), and poly-L-lysine HBr salt)<sup>6f</sup> are larger than those of water-soluble electrically neutral polymers (PEG and PVPy),<sup>6b,f</sup> indicating that ionic groups and the counterions of polyelectrolytes strongly disturb the structure of water in their hydration shells (electrostriction). Previously, Tao et al. evaluated the *N* value of an aqueous DNA solution to be around 30 using eq 5.<sup>29</sup> Such a large *N* value could be attributed to both the bulkiness and polar and ionic moieties of the nucleotide unit.

As shown in Table 2, the *N* values for electrically neutral water-soluble polymers (PEG and PVPy) were very small. From the use of time domain reflectometry, it was reported that oligo-(ethyleneglycol)s (degree of polymerization, 4-7) dissolve in water without much perturbation to the water structure,<sup>30</sup> which coincides with the present data.

D. The N Values for Sulfobetaine Polymers. Table 2 shows that the N value for zwitterionic-type polyelectrolytes, PSPBs and PSBBs, was a relatively small positive value and, with the increase in the degree of quaternization, the N value decreased. It is worth noting that the N values of PSPB-3 and PSBB-3 with a large DQ value (95% and 83%, respectively) were smaller than that of poly(acrylic acid) (HPAA). HPAA has an ionizable group (-COOH) in the side chain and is scarcely ionized under neutral conditions. Therefore, the water structure in poly-(DMAPMA), PSPBs, and PSBBs solutions should be more significantly disturbed in comparison with that in HPAA solution because the amount of ionic species in these polymers is much larger than that in HPAA. Actually, the obtained results that the N values of poly(DMAPMA), PSPBs and PSBBs with a lower DQ value were larger than that of HPAA are not in conflict with the general knowledge and our previous reports. However, as mentioned above, the disturbing effects of PSPB-3 and PSBB-3 on the water structure were smaller than that of the ordinary polyelectrolytes. This is in accordance with the previous result that the zwitterionic polymer, poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC), did not disturb the structure of water (N = -1.1 and -0.1 for PMPC 4.3 K ( $M_w$ = 4300) and 8.3 K ( $M_{\rm w}$  = 8300), respectively).<sup>6f</sup> These slightly negative *N* values for PMPC are probably due to the small error associated with separation of the collective band from the OH stretching band, and therefore, they can be regarded as zero approximately. Furthermore, the *N* value for PSBB seemed to have the quite similar tendency as that for PSPB, despite a difference in the distance between the quaternary ammonium and sulfonate groups. A recent <sup>1</sup>H NMR study by El Seoud et al. showed that a sulfobetaine surfactant, *N*,*N*-dimethyl-*N*-(3-sulfopropyl)dodecylaminium inner salt, does not affect the state of interfacial water because of the strong intermolecular interactions between the head ions of neighboring molecules in the micelles,<sup>31</sup> which is consistent with the present results.

It should be mentioned here that PMPC could be very easily dissolved in water, whereas PSPB (DQ = 100%) could not. This might be due to the bulkiness around the phosphate and quaternary ammonium groups in the MPC residue, which inhibits the tight ionic association between the oppositely charged groups. As for the sulfobetaine polymers, on the contrary, the anionic sulfonate group might easily electrostatically associate with the quaternary ammonium group, resulting in a cross-linked network that can be regarded as a ring (in the case of ion stacking within the residue) or a head-to-tail stacking (in the case of ionic associations might diminish the electrostatic hydration (electrostriction) and induce the precipitation of the completely quaternized sulfobetaine polymer.

Such a disadvantageous ionic association can be weakened by the introduction of hydrophilic comonomer residues between the sulfobetaine monomer residues.<sup>9g,i,j</sup> McCormick et al., for example, prepared amphoteric copolymers composed of sulfobetaine and carboxybetaine monomer residues and showed that the electrolyte and pH responsiveness of the copolymers largely depended on the monomer ratio.<sup>9h</sup>

In the case of 3-aminopropanesulfonic acid, which is also zwitterionic at neutral pH, the *N* value was evaluated to be 0.7 at  $p_X = 0.01$  and 25 °C. This value is consistent with the *N* values for PSPB-3 and PSBB-3. Previously, it was reported that the *C* values of aqueous amino acid solutions under neutral conditions were slightly smaller than that of pure water and almost constant despite the difference in hydrophobicity of the side chain.<sup>32</sup> In other words, when both  $\alpha$ -amino and  $\alpha$ -carboxyl groups of amino acids are ionized (zwitterionic), the *N* value for amino acids is slightly positive and independent of the hydrophobicity of the side chain.

Because zwitterionic compounds with a small molecular weight did not disturb the structure of water, there might be the same reason for the small N values evaluated for the sulfobetaine polymer systems. The anionic sulfonate group and cationic quaternary ammonium group, which are in close proximity to each other in the SPB and SBB residues, might counteract the electrostatic hydration. The partially negative oxygen atom of the water molecule is toward the positively charged ions in solution, whereas the negatively charged ions attract the partially positive hydrogen atoms of water, creating their hydration shells.<sup>33</sup> When the cation and anion are in close proximity, the orientation of the hydrating water might be largely disturbed resulting in the collapse of electrostriction. The hydrocarbon main chain in the sulfobetaine polymers might be hidden behind the bulky zwitterionic groups from water. Previously, Høiland reported that when hydration sheaths for ionizable groups of a dicarboxylic acid are in close proximity and overlapped, an additivity rule for the hydration of each component is not applicable.<sup>34</sup> His result supports the tendency observed in this work.

As described in the Introduction, various kinds of sulfobetaine, carboxybetaine, and phosphobetaine derivatives have been found to be dermatologically inert and blood-compatible. Though many other factors affect the biocompatibility of polymeric materials in a complicated manner,<sup>35</sup> the experimental results obtained here seem to indicate that zwitterionic polymers without disturbing the structure of the surrounding water have a significant potential to show a good biocompatibility. One should note here that the *N* value for gelatin ( $M_w = 10\ 000$ ) was estimated to be 0 at 20 °C and 10 wt %.<sup>6d</sup> Because gelatin is a highly biocompatible denatured protein with many cationic and anionic charges (at least 11.4% of the amino acid residues had an ionizable side chain), the *N* value obtained for gelatin strongly supports the hypothesis proposed above.

## Conclusion

The structure of water in various aqueous sulfobetaine polymer systems could be analyzed using Raman spectroscopy to obtain important information concerning the interaction between water and the polymer chains. In contrast to ordinary polyelectrolytes with one kind of ionized group, polymeric sulfobetaines had a very small disturbing effect on the structure of the hydrogen-bonding network of water molecules in dilute solutions because of the intra- and intertether proximity between the oppositely charged groups. Namely, the weak disturbing effect of sulfobetaine polymers on the water structure was due to the intrinsic property of the zwitterionic sulfobetaine polymers themselves and not due to the polymer–polymer coordination. The usability of sulfobetaine polymers in biomedical fields was strongly suggested.

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