Synthesis of Multifunctional, Nonionic Vinyl Polymers and Their ^{13}C Spin-Lattice Relaxation Times in Deuterium Oxide Solutions

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ABSTRACT: A study was conducted to molecularly design very hydrophilic vinyl polymers. Various nonionic, water-soluble polymers with hydroxyl or primary amide groups in their side chains were prepared by radical polymerization of corresponding monomers or by polymer reactions to modify side chains derivatized in poly(vinyl ether)s. The functional groups interconnecting a hydrophobic main chain and a side chain included ether, secondary and tertiary amide, and ester groups. The number of hydroxyl groups incorporated in the side chains per monomer unit ranged from one to nine, and that of primary amide groups ranged from one to three. The spin-lattice relaxation times (T_1) of individual carbon atoms were measured in deuterium oxide (D_2O) by an inversion−recovery Fourier transform method as an indicator of chain or group mobility. As for the effect of interconnecting groups on the mobilities of main and side chains, these increased in the following order: ether > ester and tertiary amide > secondary amide. Considerably reduced T_1 values were found with increasing number of hydroxyl groups in the side chains. The addition of lithium bromide to D_2O solutions substantially increased T_1 values for hydroxyl group-derivatized polymers, indicating that intramolecular hydrogen bonds responsible for reduced T_1 values are broken to enhance chain or group mobility. On the other hand, minimal effect of lithium bromide addition was found for ether- or primary amide-derivatized polymers. These results suggest that, when an ether group is incorporated as an interconnecting group into a vinyl polymer and primary amide groups are well distributed at the terminal ends of the side chains, such a polymer could have high chain and group mobility, which may impart high hydrophilicity. The molecular structure−mobility relationship was discussed in terms of T_1 values. It is suggested that a combination of factors, such as the structure of interconnecting group, the structure of hydrophilic group, intra- and inter-pendant-group interactions, hydrogen bonding, and steric factors, all contribute to T_1 values.

Introduction

Nonionic, water-soluble polymers have been used in various industrial applications, such as surface coatings of biomedical devices and ships, to prevent biocolloidal adsorption and adhesion in an aqueous environment. This is due to the minimal interaction of water-soluble polymers with proteins, peptides, and polysaccharides in water.[1−10] Synthetic polymers most often used for these purposes include poly(ethylene glycol) (PEG),[7,8] poly(vinyl alcohol) (PVA),[3] poly(methyl vinyl ether), and poly(acrylamide) (PAAm).[2,10] Although these polymers contain one hydratable functional group per monomer unit, the very hydrophobic nature of the main chains of these polymers, which consist only of hydrocarbons, may considerably reduce hydrophilicity due to potential access of water molecules to main chains. If a main chain of a vinyl polymer is completely shielded from water molecules, such a polymer is expected to be very hydrophilic, resulting in protein nonadsorptive properties in nature.

To design a water-soluble polymer showing minimal hydrophobic interaction with biocolloids, we have attempted to design "superhydrophilic" polymers. The design concept was based on the following: Nonionic, polar groups such as hydroxyl, ether, and primary amide groups are multifunctionally incorporated into a repeating unit of vinyl polymer. If such functional groups are spatially well distributed, water molecules cannot access the hydrocarbon main chain due to the presence of densely packed by hydratable groups in the side chains.

In our previous study,[11] we prepared three vinyl polymers in which one, three, and six hydroxyl groups in their side chains were incorporated into their repeating units, and we evaluated the physicochemical characteristics of these polymers, including interfacial free energy in water by the Wilhelmy plate technique, nonfrozen water content by differential scanning calorimetry, and proton−deuterium exchange rate by ^1H NMR spectroscopy and ^1H relaxation time measurements.

As a continuation of our studies, this research was undertaken to prepare a wide spectrum of water-soluble vinyl polymers in terms of structure and functionality: various types of nonionic hydratable groups of the side chain, including hydroxyl and primary amide groups, multifunctionality with one to nine groups per monomer unit, and various types of interconnecting groups between the main chain and side chain. The interconnecting groups used here were ether, ester, and secondary and tertiary amide groups. Spin-lattice relaxation times of these polymers in D_2O solution, which may reflect the mobility of the targeted carbon, were measured by ^{13}C NMR spectroscopy. The molecular structure−T_1 relationship is discussed.

Experimental Section

Reagents. All solvents and reagents were commercial products of special reagent grade, obtained from Wako Pure Chemicals Inc. (Osaka, Japan), except for the following reagents and polymers. 2-Hydroxyethyl vinyl ether was donated by Nisso Maruzen Chemical Co., Ltd. (Tokyo, Japan). Poly(acrylamide) (PAAm) was purchased from Sanyo Chemical Industries, Ltd. (Kyoto, Japan). Poly(*N*,*N*-dimethylacrylamide) was obtained from Polysciences, Inc. (Warrington, PA). The seamless cellulose tube for dialysis (cutoff MW, ~12 000) was purchased from Viskase Sales Corp. (Chicago, IL).

Polymerization Procedures. The preparation methods for poly(methyl vinyl ether) (**3**), poly(*N*-(2-hydroxyethyl)-acrylamide) (**6**), and poly(*N*,*N*-bis[*N*-[tris(hydroxymethyl)-

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methyl]amido]methylacrylamide) (**10**) were reported in our previous paper.[11] Polymers except for these and commercially available ones were obtained either by radical polymerization initiated with potassium peroxosulfate (KPS) treatment at 80 °C for 0.5−1 h in aqueous solution in a Pyrex glass tube, which was sealed under reduced pressure after three freeze−thaw cycles, or by cationic polymerization, initiated with boron trifluoride etherate (BF_3·$(C_2H_5)_2O$) as an initiator in tetrahydrofuran (THF) or toluene at −78 °C or −40 °C for 3−5 h. The polymers were purified by extensive dialysis with the cellulose tube against running water for 1 week. Freeze-drying yielded white powdery solids.

Polymerization of 2-Hydroxyethyl Acrylate. Poly(2-hydroxyethyl acrylate) (1.0 g, 8.6 mmol) was obtained by radical polymerization, initiated with KPS (59 mg, 2.2×10^{-4} mol) in H_2O (20 mL), at 80 °C for 0.5 h. After dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.27 g (27%).

Polymerization of 2-Hydroxyethyl Vinyl Ether. To a THF solution (20 mL) of 2-hydroxyethyl vinyl ether (10.0 g, 0.11 mol) was added BF_3·$(C_2H_5)_2O$ (43 mg, 3.1×10^{-4} mol) at −40 °C with stirring and cooling in a dry ice/methanol bath. The reaction mixture was kept at −40 °C for 3 h with stirring and was warmed to −15 °C with stirring for 1 h. Ten milliliters of cold methanol was added to terminate the polymerization. The solution was subjected to dialysis and subsequent freeze-drying to give a white solid at a yield of 6.2 g (62%).

Preparation and Polymerization of 2-Acrylamido-2-(hydroxymethyl)-1,3-propanediol. To a suspension of Tris (10.1 g, 83 mmol) in acetonitrile (200 mL) was added acryloyl chloride (15.2 g, 0.17 mol) with vigorous stirring in an ice bath. After 3 h, the suspension was warmed to room temperature and allowed to stand for 1 day with stirring. A white solid was filtered off, and the solvent was removed under reduced pressure. The residue was recrystallized from hot acetonitrile. A white crystal (needle) was obtained at a yield of 7.4 g (51%): 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 7.8 (1H, b, amide), 6.4 (1H, m, COCH═), 6.3 (1H, m, C*H*═CHCO, anti), 5.7 (1H, m, C*H*═CHCO, syn), 3.9 (3H, b, OH), and 3.6 (6H, s, CH_2).

The radical polymerization of 2-acrylamido-2-(hydroxymethyl)-1,3-propanediol (1.4 g, 8.0 mmol), initiated with KPS (13.5 mg, 5.0×10^{-5} mol) in H_2O (12 mL), was carried out at 80 °C for 1 h. The solution was subjected to dialysis and subsequent freeze-drying to give a white solid at a yield of 0.54 g (38%).

Preparation and Polymerization of *N*-Acryloyl-D-Glucamine. D-Gucamine (12.0 g, 70 mmol) and $NaNO_2$ (0.23 g, 3.3 mmol) were dissolved in a 2 M aqueous solution of K_2CO_3 (33 mL) under stirring. Acryloyl chloride (6.6 g, 73 mmol) was added to the solution under vigorous stirring in an ice bath. After 2.5 h, the reaction mixture was slowly warmed to room temperature with stirring overnight and then poured into large amount of 99% ethanol (330 mL), and the resultant white solid was filtered off. The solvent was removed *in vacuo*. The product was recrystallized from a mixed solution of methanol/2-propanol/diethyl ether. A white crystal (needle) was obtained at a yield of 7.3 g (50%): 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 7.1 (1H, m, amide), 6.3 (1H, m, COCH═), 6.1 (1H, m, C*H*═CHCO, anti), 5.4 (1H, m, C*H*═CHCO, syn), 4.4−4.2 (5H, b, OH), 3.6−3.2 (6H, m, C*H*OH), and 2.8 (2H, m, N-CH_2).

N-Acryloyl-D-glucamine (2.2 g, 12 mmol) was polymerized with KPS (20 mg, 7.4×10^{-5} mol) in H_2O (16 mL) at 80 °C for 40 min. Upon extensive dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.96 g (47%).

Preparation and Polymerization of *N*-Acryloyl-D-glucosamine. D-Glucosamine hydrochloride (8.6 g, 40 mmol) and $NaNO_2$ (0.14 g, 2.5 mmol) were dissolved in a 2 M aqueous solution of K_2CO_3 (20 mL) under stirring. Acryloyl chloride (4.0 g, 73 mmol) was added to the solution with vigorous stirring in an ice bath. After 2.5 h, the reaction was slowly warmed to room temperature with stirring for 1 day and then poured into 200 mL of 99% ethanol. The white solid obtained was filtered off. The solution was concentrated under reduced pressure. The product was recrystallized with methanol/ethyl acetate/diethyl ether. A white crystal (needle) was obtained at a yield of 3.8 g (38%): 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 7.3 (1H, s, amide), 6.4 (1H, m, COCH═), 6.3 (1H, m, C*H*═CHCO, anti), 5.2 (1H, m, C*H*═CHCO, syn), 4.8−2.6 (5H, m, CH), and 4.4−4.2 (5H, b, overlapping with signals of CH, OH).

N-Acryloyl-D-glucosamine (0.44 g, 2.4 mmol) was polymerized with KPS (2.2 mg, 8.1×10^{-6} mol) in H_2O (1.6 mL) at 80 °C for 1.5 h. Upon extensive dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.28 g (64%).

Preparation and Polymerization of *N*-(Carbamoylmethyl)Acrylamide. Glycine hydrochloride (7.0 g, 64 mmol) and K_2CO_3 (9.4 g, 68 mmol) were dissolved in H_2O (200 mL) with stirring. Ethyl ether (100 mL) and acryloyl chloride (4.0 g, 73 mmol) were added to the solution with vigorous stirring in an ice bath. Stirring was continued for 2.5 h at 0 °C and for 1 day at room temperature. The reaction mixture was concentrated under reduced pressure, and a large amount of ether was added to precipitate the product. The product was recrystallized with dimethyl sulfoxide (DMSO)/THF/diethyl ether. A white crystal (needle) was obtained at a yield of 2.1 g (22%): 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 7−8 (5H, m, amide), 6.2 (1H, m, COCH═), 6.1 (1H, m, C*H*═CHCO, anti), 5.2 (1H, m, C*H*═CHCO, syn), and 3.8 (2H, d, CH_2).

N-(Carbamoylmethyl)acrylamide (1.5 g, 12 mmol) was polymerized with KPS (19 mg, 7.0×10^{-5} mol) in H_2O (20 mL) at 80 °C for 0.5 h. After dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.14 g (10%).

Preparation and Polymerization of *N*,*N*-Bis(carbamoylmethyl)acrylamide. A 28 wt % aqueous solution of NH_3 (12 mL, 180 mmol) and NH_4Cl (1.2 g, 22 mmol) were added to diethyl iminoacetate (11.6 g, 60 mmol). The solution was stirred for 4 days and concentrated under reduced pressure. The residue was precipitated with H_2O/methanol/chloroform/THF. A light yellowish solid was obtained at a yield of 2.85 g (33%): 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 7.8 and 7.4 (4H, d, amide), 3.6 (4H, d, CH_2), and 3.2 (1H, d, NH). Bis(carbamoylmethyl)amine (1.1 g, 9 mmol) and K_2CO_3 (1.2 g, 9 mmol) were dissolved in H_2O (80 mL). A diethyl ether solution (50 mL) of acryloyl chloride (1.0 g, 11 mmol) was added to the solution under stirring in an ice bath. After 12 h, the solution was concentrated under reduced pressure, and the residue was recrystallized with H_2O/methanol/THF. A white crystal (needle) was obtained at a yield of 1.5 g (90%): 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 7.8 and 7.4 (4H, d, amide), 6.4 (1H, m, COCH═), 6.2 (1H, m, C*H*═CHCO, anti), 5.5 (1H, m, C*H*═CHCO, syn), and 3.6−3.2 (4H, m, N-CH_2).

To an aqueous solution (2 mL) of *N*,*N*-bis(carbamoylmethyl)-acrylamide (0.50 g, 2.3 mmol) was added KPS (6.2 mg, 2.3×10^{-5} mol). The polymerization was conducted at 60 °C for 3 h. A large amount of methanol was added to precipitate the product. The polymer was dried *in vacuo*. A white solid was obtained at a yield of 0.38 g (76%).

Preparation and Polymerization of 2-(Vinyloxy)ethyl Malonate. Synthesis of 2-(vinyloxy)ethyl malonate was carried out according to the method reported by Sawamoto et al.[12] Na (0.63 g, 27 mmol) was added to absolute ethanol (50 mL) at room temperature. Ethyl malonate (3.8 mL, 25 mmol) and 2-chloroethyl vinyl ether (5.0 mL, 50 mmol) were added to the solution in that order with stirring at room temperature. The solution was refluxed for 5 h and cooled to room temperature. The reaction mixture was concentrated by evaporation, and diethyl ether (100 mL) was added to extract the product. The precipitated NaCl was removed by filtration, and the ether layer was washed with 100 mL aliquots of saturated NaCl aqueous solution three times. The solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was distilled *in vacuo* over $CaCl_2$ to yield a colorless oil: bp 106−109 °C (5 Torr); lit.[12] bp 106 °C (5 Torr); yield 11.4 g (29%); 270 MHz ^{1}H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 6.4 (1H, m, OCH═), 4.2 (1H, m, C*H*═CHO, anti), 4.0 (1H, m, C*H*═CHO, syn), 4.2 (4H, overlapping with a signal

of vinyl, $COOCH_2$), 3.7 (2H, t, CH_2OCH═), 3.5 (1H, t, $CH(COOC_2H_5)_2$), 2.1 (2H, m, OCH_2CH_2CH), and 1.2 (6H, t, CH_3).

To a dried toluene solution (6 mL) of the monomer obtained (3.0 g, 13 mmol) was added $BF_3{\cdot}(C_2H_5)_2O$ (8.7 mg, 6.1×10^{-5} mol) at −78 °C with stirring in a dry ice/methanol bath. After 5 h, the solution was warmed to −40 °C, and stirring was continued for 1 h. Twenty milliliters of cold methanol was added to terminate the polymerization. Subsequently, diethyl ether (100 mL) was added. The ether layer was washed with a 30 mL aliquot of H_2O and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue reprecipitated with THF/acetonitrile/diethyl ether/*n*-hexane. The supernatant was decanted. The residue was concentrated under reduced pressure. A colorless oil was obtained at a yield of 2.55 g (83%).

Amidation of Poly(2-(vinyloxy)ethyl malonate). A DMSO/ethylene glycol (2/1 v/v, 100 mL) mixed solution of poly(2-(vinyloxy)ethyl malonate) (0.25 g) was treated with Tris (3.2 g, 26 mmol, 24 equiv relative to the ethyl ester units in the polymer) in the presence of anhydrous K_2CO_3 (0.29 g, 2.2 mmol). Stirring was continued for 6 days at room temperature and for 20 h at 70 °C. After dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.18 g (43%). Completion of aminolysis was confirmed by disappearance of the ester peak at 1733 cm^{-1} from the IR spectrum and of the signal of the methyl proton of the ethyl ester group at 1.3 ppm from the ^1H NMR spectrum.

Ammonolysis of Poly(2-(vinyloxy)ethyl malonate). Poly(2-(vinyloxy)ethyl malonate) (2.0 g) and NH_4Cl (55 mg, 1.0 mmol) were dissolved in a mixed solvent of 28 wt % aqueous solution of NH_3 (70 mL) and *N*,*N*-dimethylformamide (DMF) (30 mL). The solution was stirred for 2 weeks at room temperature and concentrated under reduced pressure. After dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.82 g (37%). Complete ammonolysis was confirmed by disappearance of the ester peak at 1733 cm^{-1} from the IR spectrum and of the methyl proton signal at 1.3 ppm from the ^1H NMR spectrum.

Preparation and Polymerization of 3,3,3-Tris(ethoxycarbonyl)propyl Vinyl Ether. To a dried DMF/benzene (1/1 v/v, 75 mL) mixed solution were added NaOH (4.3 g, 0.18 mol), triethyl methanetricarboxylate (25 g, 0.16 mol), and 2-chloroethyl vinyl ether (35 g, 0.32 mol) with stirring in an ice bath. The suspension was heated at 100 °C in an oil bath and stirred for 22 h. The precipitated white solid (NaCl) was removed by filtration, and the solution was concentrated by evaporation. The product was purified with a silica gel column (eluent, chloroform). A colorless oil was obtained at a yield of 2.4 g (6%): 270 MHz ^1H NMR [$(CD_3)_2SO$; ppm from $(CH_3)_4Si$] δ 6.2 (1H, m, OCH═), 4.2 (1H, m, CH═CHO, anti), 3.9 (1H, m, CH═CHO, syn), 4.2 (6H, overlapping with the signal of vinyl, $COOCH_2$), 3.7 (2H, t, CH_2OCH═), 2.3 (2H, m, OCH_2CH_2C), and 1.2 (9H, t, CH_3).

To a toluene solution (6 mL) of 3,3,3-tris(ethoxycarbonyl)propyl vinyl ether (1.0 g, 3.3 mmol) was added $BF_3{\cdot}(C_2H_5)_2O$ (8.7 mg, 6.1×10^{-5} mol) at −78 °C with stirring in a dry ice/methanol bath. After 5 h, the solution was continued with stirring for 3 h at −40 °C. Twenty milliliters of cold methanol was added to terminate the polymerization, followed by addition of diethyl ether (100 mL). The organic layer was washed with a 30 mL of aliquot of H_2O and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. A colorless oil was obtained at a yield of 0.68 g (68%).

Amidation of Poly(3,3,3-tris(ethoxycarbonyl)propyl vinyl ether). A DMSO/ethylene glycol (4/3 v/v, 140 mL) mixed solution of poly(3,3,3-tris(ethoxycarbonyl)propyl vinyl ether) (0.25 g) was treated with Tris (3.61 g, 30 mmol, 36 equiv relative to the ethyl ester units in the polymer) in the presence of anhydrous K_2CO_3 (0.22 g, 1.6 mmol). Stirring was continued for 3 weeks at room temperature. Upon dialysis and subsequent freeze-drying, a white solid was obtained at a yield of 0.18 g (43%). Complete aminolysis was confirmed by disappearance of the ester peak at 1733 cm^{-1} from the IR spectrum and of the methyl proton signal at 1.3 ppm from the ^1H NMR spectrum.

Ammonolysis of Poly(3,3,3-tris(ethoxycarbonyl)propyl vinyl ether). Poly(3,3,3-tris(ethoxycarbonyl)propyl vinyl ether) (0.25 g) and NH_4Cl (250 mg, 4.5 mmol) were dissolved in a mixed solution of 28 wt % aqueous solution of NH_3 (6 mL), methanol (10 mL), and THF (30 mL). The solution was stirred for 3 weeks at room temperature and concentrated under reduced pressure. The solution was subjected to dialysis and subsequent freeze-drying to give a white solid at a yield of 52 mg (23%). Complete ammonolysis was confirmed by disappearance of the ester peak at 1733 cm^{-1} from IR spectrum and of the methyl proton signal at 1.3 ppm from the ^1H NMR spectrum.

Physical Measurements. FT-IR spectra were recorded using KBr pellets on a Nicolet 5DX (Madison, WI). FT-^1H NMR spectra at 270 MHz for characterizing the compound and FT-^{13}C NMR spectra at 67.8 MHz for T_1 measurement were obtained on a JEOL GX-270 (Tokyo, Japan). The apparatus was equipped with an internal ^2D lock and a noise-modulated proton decoupler. The inversion−recovery Fourier transform method was employed for the determination of T_1. The relationship between the T_1 and the change in intensity of the magnetization vector is given as[13]

$$\ln(M_z^0 - M_z) = \ln(2M_z^0) - \tau/T_1 \qquad (1)$$

where M_z is the magnetization vector along the *z*-axis τ milliseconds after the application of 180° pulse, M_z^0 is the equilibrium value of the vector, and τ is the interval between 180° and 90° pulses. Hence, a plot of $\ln(M_z^0 - M_z)$ against τ will afford a straight line, with a slope of $-1/T_1$, from which T_1 can be determined. The values of T_1 were calculated from the peak heights of individual carbon atoms by the least-squares method. The pulse sequence (180° pulse − delay τ − 90° pulse − $T)_n$ was repeated at least 2000 times. The 180° pulse recycle times were chosen to be at least 5 times the longest spin-lattice relaxation time of the polymers. The value of M_z^0 can be determined from the equilibrium value of peak height at the long delay times.

Samples were dissolved in D_2O and were not degassed since the relaxation times of the polymer are not substantially affected by the presence of dissolved oxygen at atmospheric pressure.[14,15] The polymer concentration was fixed at 5.0 wt %, except for that of PAAm and poly(*N*-(2-hydroxyethyl)-acrylamide), which was fixed at 2.5 wt % due to the extremely high viscosity. The measurements of polymers were carried out at 30 °C, except in the case of poly(*N*,*N*-bis(carbamoylmethyl)acrylamide), which was measured at 40 °C due to its low solubility at 30 °C.

The viscosities of two different molecular weight poly(vinyl alcohol)s (PVAs; $M_n = 2.2 \times 10^4$ and 8.8×10^4) were measured in aqueous solutions at 30 °C with an Ostwald viscometer. The intrinsic viscosity (η) of the polymers was determined from a Schulz−Blaske plot, $(\eta_{rel} - 1)/C$ vs C, where C is the polymer concentration and η_{rel} is the ratio of the viscosity of a solution to that of water.

Results and Discussion

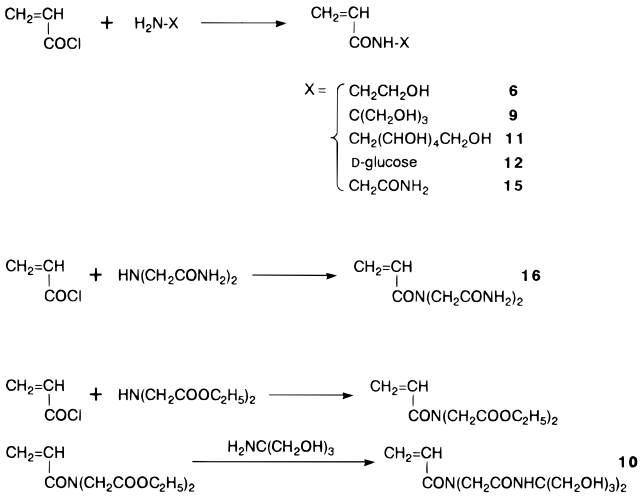
Preparation and Characterization of Monomers and Polymers. Table 1 lists the polymers used in this study. Polymers **1**−**5** were commercially obtained. Poly(2-hydroxyethyl acrylate) (**7**) and poly(acrylamide) derivatives (**6**, **9**−**12**, **15**, and **16**) were obtained by radical polymerization, initiated with KPS in aqueous solutions. Monomers for polymers **6**, **9**, **11**, **12**, **15**, and **16** were prepared by Schotten−Baumann reaction of acryloyl chloride with corresponding amino compounds, as shown in Scheme 1. Polymer **10** was obtained by radical polymerization of the monomer, *N*,*N*-bis(ethoxycarbonyl)methylacrylamide, which was prepared by Schotten−Baumann reaction, and by subsequent aminolysis of the polymer with tris(hydroxymethyl)-

Table 1. Polymerization Conditions and Molecular Weights of Polymers

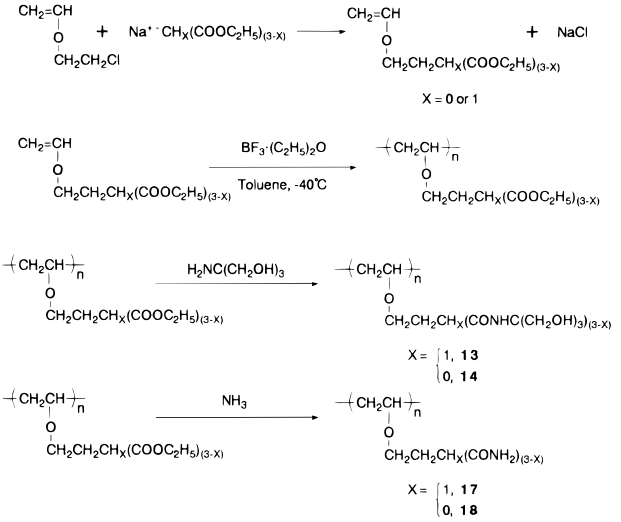
polymer no.	polymer/side chain structure	solvent	temp (°C)	initiator	$M_n \times 10^{-3}$
	Commercially Obtained Polymers				
1	poly(ethylene glycol)				20
2	poly(vinyl alcohol)				88
3	poly(methyl vinyl ether)				11
4	poly(acrylamide)				44
5	poly(*N*,*N*-dimethylacrylamide)				28
	Prepared Polymers (side chain is shown)				
6	$CONHCH_2CH_2OH$	H_2O	80	$K_2S_2O_8$	8.9
7	$COOCH_2CH_2OH$	H_2O	80	$K_2S_2O_8$	25
8	OCH_2CH_2OH	THF	−40	$BF_3{\cdot}(C_2H_5)_2O$	19
9	$CONHC(CH_2OH)_3$	H_2O	80	$K_2S_2O_8$	8.5
10	$CON(CH_2CONHC(CH_2OH)_3)_2$	H_2O	80	$K_2S_2O_8$	nd[b]
11	$CONHCH_2(CHOH)_4CH_2OH$	H_2O	80	$K_2S_2O_8$	13
12	CONH-D-glucose	H_2O	80	$K_2S_2O_8$	7.7
13	$OCH_2CH_2CH(CONHC(CH_2OH)_3)_2$	toluene	−40	$BF_3{\cdot}(C_2H_5)_2O$	38[a]
14	$OCH_2CH_2C(CONHC(CH_2OH)_3)_3$	toluene	−40	$BF_3{\cdot}(C_2H_5)_2O$	21[a]
15	$CONHCH_2CONH_2$	H_2O	80	$K_2S_2O_8$	9.4
16	$CON(CH_2CONH_2)_2$	H_2O	80	$K_2S_2O_8$	nd[b]
17	$OCH_2CH_2CH(CONH_2)_2$	toluene	−40	$BF_3{\cdot}(C_2H_5)_2O$	38[a]
18	$OCH_2CH_2C(CONH_2)_3$	toluene	−40	$BF_3{\cdot}(C_2H_5)_2O$	21[a]

[a] M_n of the precursor polymer. [b] Not determined.

Scheme 1. Preparation of Poly(acrylamide) Derivatives with Hydroxyl or Primary Amide Groups



Scheme 2. Preparation of Poly(vinyl ether) Derivatives with Primary Amide Groups



aminomethane (Tris). Details of the preparation of polymers **6** and **10** were reported elsewhere.[11]

Poly(vinyl ether) derivatives (**8**, **13**, **14**, **17**, and **18**) were obtained by cationic polymerization initiated with $BF_3{\cdot}(C_2H_5)_2O$ in THF or toluene solutions and by subsequent polymer reactions (Scheme 2). Polymers **13** and **14** were prepared essentially according to the method previously reported.[11] Precursors of polymers **13**, **14**, **17**, and **18** were obtained by cationic polymerization of 2-(vinyloxy)ethyl malonate or 3,3,3-tris(ethoxycarbonyl)propyl vinyl ether, which were prepared by reaction of 2-chloroethyl vinyl ether with ethyl malonate or triethyl methanetricarboxylate in the presence of Na or NaOH, respectively. Multihydroxylated vinyl ether polymers **13** and **14** were obtained by aminolysis of side chains of corresponding precursor polymers with Tris. Multiamidated vinyl ether polymers **17** and **18** were obtained by ammonolysis of corresponding precursor polymers, as shown in Scheme 2.

The complete aminolysis of polymers **13** and **14** and complete ammonolysis of polymers **17** and **18** were confirmed as follows. IR spectral measurements of samples subjected to aminolysis or ammonolysis showed complete disappearance of ester bonds and appearance of amide groups, and ^{1}H NMR spectroscopic analysis showed that methyl groups completely disappeared. An example of IR spectral changes upon aminolysis of ester groups in the side chain of precursor polymer **14** with Tris is shown in Figure 1. Prior to aminolysis, a very strong absorption peak, characteristic of an ester bond, was evident at 1733 cm^{-1}, whereas after aminolysis, complete disappearance of the ester band and appearance of strong absorption peaks assigned to amide I at 1674 cm^{-1} and amide II at 1531 cm^{-1} were noted. ^{1}H NMR spectra before and after aminolysis are shown in Figure 2a, in which the signal of the terminal methyl proton of the ethyl ester group, which appeared at 1.3 ppm in DMSO-d_6 solution of the precursor polymer, disappeared in D_2O solution upon aminolysis (Figure 2b). Significant spectral change was observed upon ammonolysis of polymers with multifunctional terminal ends of ethyl ester groups in their side chains. Upon ammonolysis of the precursor polymer, disappearance of the methyl proton signal at 1.3 ppm was noted, as shown in Figure 2c.

Measurement of ^{13}C Spin-Lattice Relaxation Time (T_1). The T_1 values of the individual carbon atoms of hydrophilic polymers were determined to investigate the relationship between the chemical structure and the molecular motion of polymers in D_2O

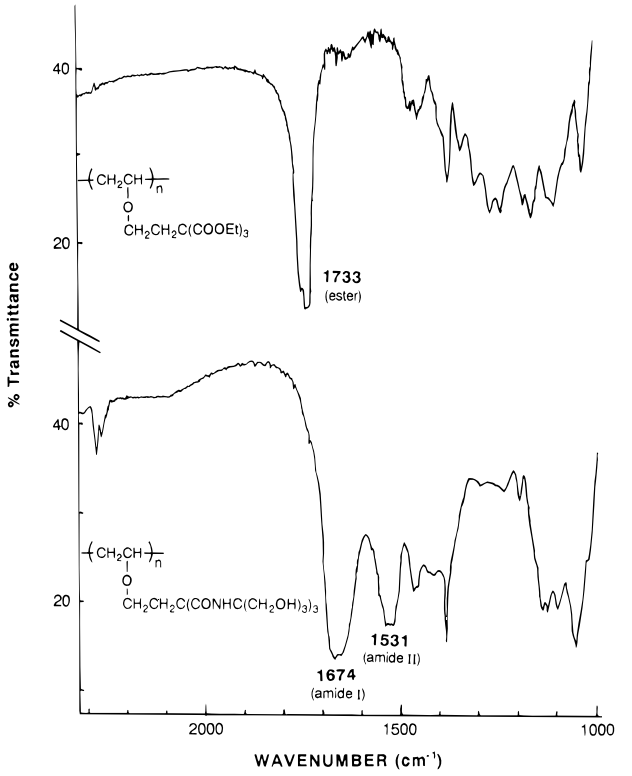


Figure 1. IR spectra of poly(3,3,3-tris(ethoxycarbonyl)propyl vinyl ether) (top) and its aminolysis product (polymer **14**, bottom).

solution. The spin-lattice relaxation time (T_1) generally comprises at least three possible relaxation mechanisms, i.e., $^{13}C-^{1}H$ dipole−dipole interactions, spin rotation, and chemical shift anisotropy.[16,17] The first mechanism mainly determines T_1 values of protonated carbon atoms in polymers. Therefore, the molecular motions of polymers, estimated from T_1 values, should be discussed in the comparison of the T_1 values of individual carbon atoms with the same number of hydrogen atoms. If a segmental mobility of the main chain or the side chain of a water-soluble polymer is very rapid, T_1 values in ^{13}C relaxation measurements should be quite large. Intramolecular hydrogen bonding between hydratable groups and extensive hydration may restrict the segmental or group free rotation, resulting in a low T_1 value. The chemical shifts of carbon atoms were estimated from those of compounds appearing in a data book of ^{13}C NMR spectra.[18] All T_1 values were measured in D_2O by the inversion−recovery Fourier transform method.[13] Typical examples of proton-decoupled FT-^{13}C NMR spectra of poly(*N*-(2-hydroxyethyl)acrylamide) (**6**) and poly(*N*,*N*-bis[*N*-[tris(hydroxymethyl)methyl]acetamido]acrylamido) (**10**), both of which were plotted as a function of τ (the interval between 180° pulse and 90° pulse), are shown in Figures 3 and 4, respectively. The T_1 value of each carbon atom was determined by a linear regression method from the plot obtained using eq 1.

At first, viscosity or molecular weight effects on T_1 values were studied for PVA with different molecular weights ($M_n = 2.2 \times 10^4$ and 8.8×10^4). The intrinsic viscosities of these polymers were 0.28 and 0.82, respectively. Regardless of the large difference in the molecular weight or viscosity, T_1 values of methylene and methine carbons, measured at 5.0 wt % at 30 °C, were 154 and 70 ms for the lower molecular weight PVA, and 166 and 75 ms for the higher molecular

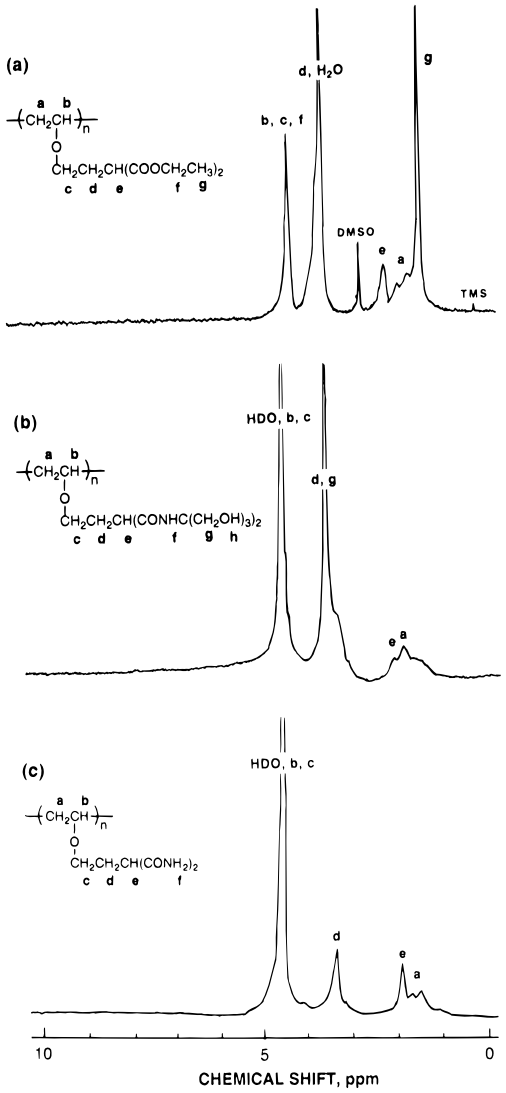


Figure 2. ^{1}H NMR spectra of poly(2-(vinyloxy)ethyl malonate) (a) and its aminolysis product (polymer **13**, b) and ammonolysis product (polymer **17**, c).

weight one, respectively, indicating that viscosity or molecular weight effects were minimal under these experimental conditions.

Water-Soluble Polymers with Simple Structure. The T_1 values of the simple-structure, water-soluble polymers PEG (**1**), PVA (**2**), poly(methyl vinyl ether) (**3**), PAAm (**4**), and poly(*N*,*N*-dimethylacrylamide) (PDAAm, **5**) are shown in Figure 5. T_1 values of the methylene group in the main chains ranged from around 130 to around 700 ms; an extremely large value (690 ms) was found for polymer **1**, followed by those of polymers **2**, **3**, and **5** (around 160 ms). The smallest one was that of polymer **4** (127 ms). There was little difference in T_1 values of the methine groups between these polymers, which were around 60−80 ms. These results indicate that the segmental mobility of PEG is very high as compared with those of other vinyl polymers. The T_1 value of methyl carbons (537 ms) in polymer **3** was much higher than that in polymer **5** (360 ms), suggesting that the degree of free rotation of the methoxy group attached to the polymer backbone is higher than that of the *N*-methyl group in the side chain.

Figure 5 also shows T_1 values of three vinyl polymers that contain one hydroxyethyl group in their side chains but have different interconnecting groups between the main chain and the side chain, such as secondary amide,

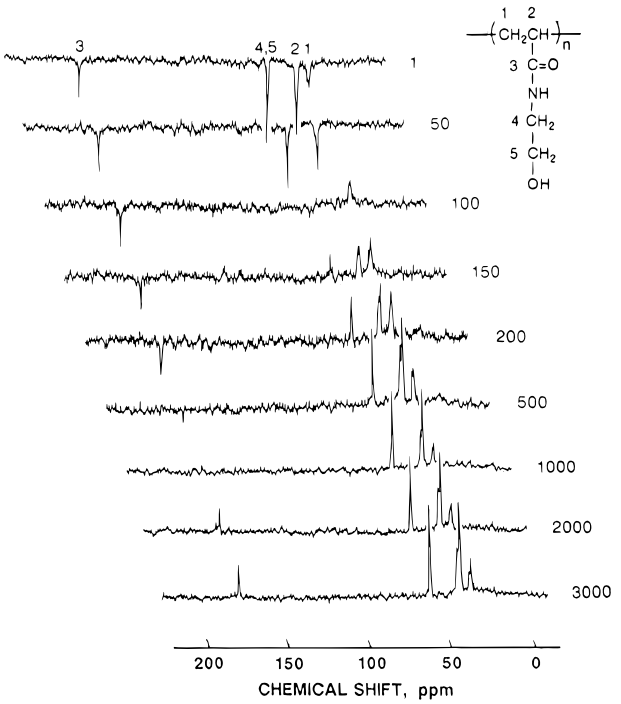


Figure 3. Proton-decoupled natural abundance Fourier transform ^{13}C NMR spectra of poly(*N*-(2-hydroxyethyl)acrylamide) (**6**) (MW = 8.9×10^3) in 2.5% (w/v) D_2O solution at 30 °C and 67.8 MHz. The outer diameter of the sample tube was 5.0 mm. The number to the right of each spectrum is τ, the interval between the 180° pulse and the 90° pulse in milliseconds. Each spectrum is the result of 2000 accumulations of time domain signals with a recycle time of 10 s.

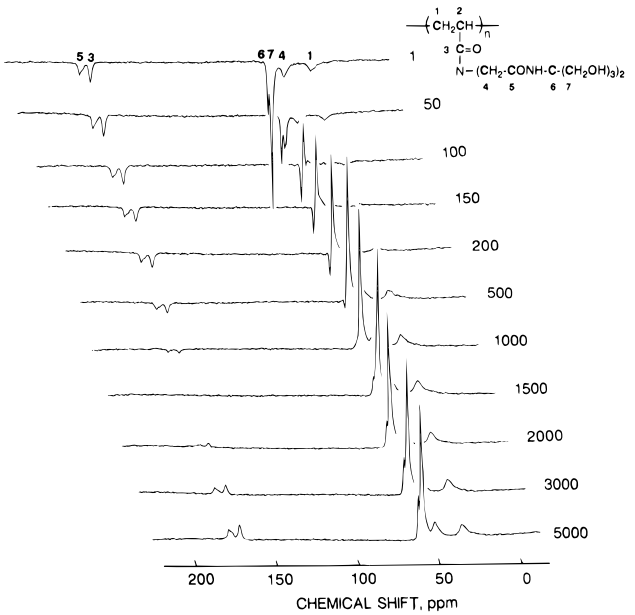


Figure 4. Proton-decoupled natural abundance Fourier transform ^{13}C NMR spectra of poly(*N*,*N*-bis[*N*-[tris(hydroxymethyl)-methyl]acetamido]acrylamide) (**10**) in 5.0% (w/v) D_2O solution at 30 °C and 67.8 MHz. The outer diameter of the sample tube was 10.0 mm. Other conditions were the same with those in Figure 3.

ether, and ester groups: poly(*N*-(2-hydroxyethyl)acrylamide) (**6**), poly(2-hydroxyethyl acrylate) (**7**), and poly(2-hydroxyethyl vinyl ether) (**8**). The T_1 value of the methylene group of the main chain of polymer **8** (254 ms) was almost 3 times larger than those of the methylene groups of polymer **6** (72 ms) and polymer **7** (79 ms). In addition, the T_1 value of the hydroxymethylene carbon of polymer **8** (165 ms) was the largest among those of the three polymers and was 1.7 times that of polymer **6** (95 ms). The T_1 values of the hydroxymethylene and carbonyl carbon of polymer **7** (151 and 1188 ms, respectively) were much larger than those of polymer **6** (95 and 798 ms, respectively). These results suggest that the degree of free rotation of the main chain as well as the side chain increases in the following order of the interconnecting linkage group: ether > ester > secondary amide.

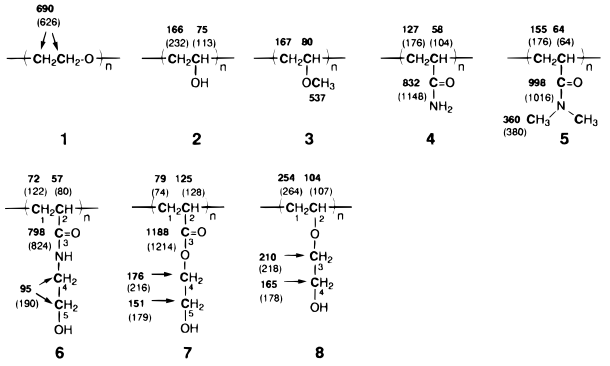


Figure 5. ^{13}C spin-lattice relaxation times of simple-structure polymers and polymers having one hydroxyethyl group in their side chains in D_2O solution (5.0 wt %, except for **4** and **6**; **4**, 2.5%, and **6**, 2.5%) at 30 °C.

Water-Soluble Polymers Having Hydroxyl Groups. T_1 values for each of the carbon atoms of water-soluble polymers with multifunctional hydroxyl groups are shown in Figure 6. The side chains of four polymers, **9**−**12**, are attached to their main chains via a secondary amide group, and those of two polymers, **13** and **14**, are bonded via an ether group. Of these polymers, Tris groups were incorporated into the side chains of polymers **9**, **10**, **13**, and **14**. Polymer **11** contains a glucamine unit, and polymer **12** contains a D-glucose unit. These multifunctional polymers, **9**−**14**, have 3, 6, 5, 4, 6, and 9 hydroxyl groups in their monomer units, respectively. The T_1 values of the methylene carbon of the main chains of the poly(acrylamide) derivatives (**9**−**12**) ranged from around 70 to around 160 ms, but those of the poly(vinyl ether) derivatives (**13** and **14**) ranged from around 200 to around 260 ms. These results indicate that the type of interconnecting linkage group between the side chain and the main chain may be a determinant of the mobilities of the main chain and the side chain, as will be described below.

The T_1 values of the hydroxymethyl group in Tris-incorporated polymers (**10**, **13**, and **14**) were almost identical (93−116 ms) except for polymer **9**, which had a considerably lower T_1 value (32 ms). However, a difference in T_1 values between these polymers was noted for the quaternary carbon of the Tris groups in their side chains. Polymer **9**, which has a single Tris group in its side chain, showed the highest T_1 value (903 ms) among Tris-containing polymers; polymers containing two or three Tris groups showed considerably lower T_1 values: 650 ms for polymer **10**, 320 ms for polymer **13**, and 427 ms for polymer **14**. On the other hand, the T_1 values of the secondary amide carbon attached to the Tris group ranged from 873 to 1270 ms. The lowest T_1 value was observed for polymer **9**, in which the secondary amide group was attached to the main chain, suggesting that the mobility of the secondary amide group is enhanced with increasing distance of the Tris group from the main chain.

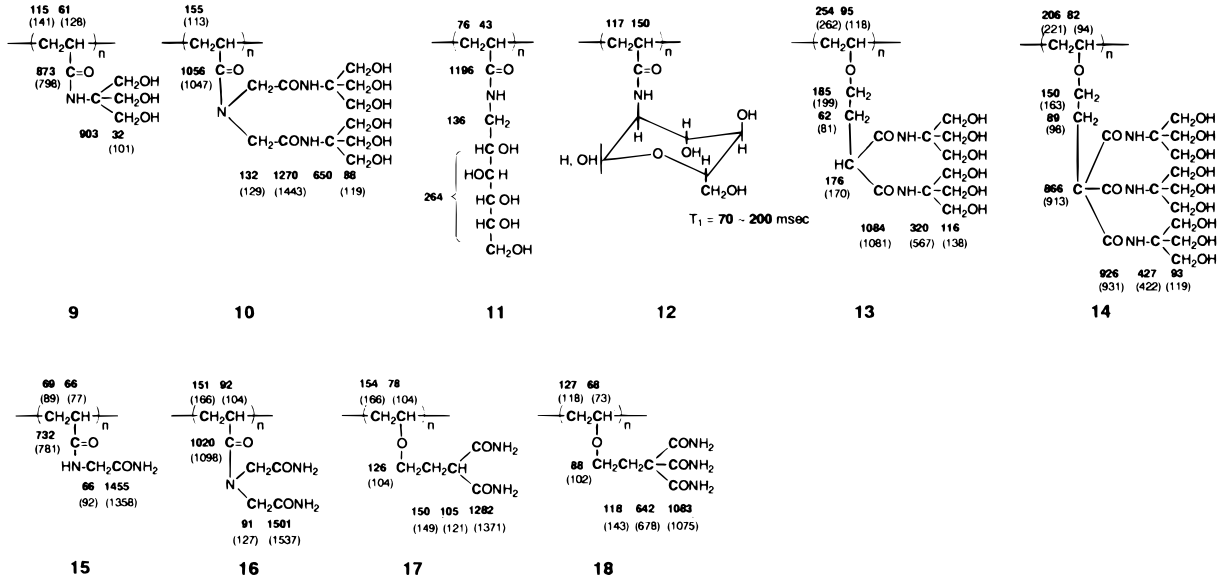


Figure 6. ^{13}C spin lattice relaxation times of polymers having multifunctional hydroxyl groups and primary amide groups in their side chains in D_2O solution (5.0 wt %) at 30 °C.

The hydroxymethine group of the glucamine-derivatized polymer **11** gave a single peak in ^{13}C NMR spectra. The T_1 value (264 ms) of the hydroxymethine group was almost 3 times larger than that of the hydroxymethine group of PVA. The hydroxylmethine group of polymer **12**, which has a D-glucose unit in its side chain, also showed complex peaks, with T_1 values ranging from 70 to 200 ms. These results indicate that the mobility of hydroxylmethine groups increases with distance from the main chain.

Water-Soluble Polymers Having Primary Amide Groups. The T_1 values of water-soluble polymers with primary amide groups in their side chains are shown in Figure 6. Polymers **15** and **16** are poly(acrylamide) derivatives, and polymers **17** and **18** are poly(vinyl ether) derivatives. These polymers, **15**−**18**, have 1, 2, 2, and 3 primary amide groups in their monomer units, respectively. The T_1 values of methylene (69 ms) and methine (66 ms) carbons of the main chain of polymer **15** were almost same as those of polymer **6** (72 and 57 ms, respectively). As compared with those of polymer **15**, increased T_1 values were noted for polymer **16** (151 and 92 ms, respectively), in which the secondary amide group as an interconnection group was replaced with a tertiary amide group. Furthermore, the T_1 value of the carbonyl carbon of the interconnecting group of polymer **16** (1020 ms), which was almost the same as that of the corresponding carbonyl carbon of the tertiary amide of polymer **5** (998 ms), was larger than that of polymer **15** (732 ms).

The T_1 values of the main chains of amidated poly(vinyl ether) derivatives, **17** and **18**, were much smaller than those of hydroxylated poly(vinyl ether) derivatives, **8**, **13**, and **14**, but larger than those of polymer **15**. The T_1 values of the primary amide carbon in the terminal end group of the side chain were about 1450−1500 ms for polymers **15** and **16**. Reduced T_1 values upon attachment of primary amide groups to the same carbon were noted for polymers **17** (1282 ms) and **18** (1083 ms). The higher the degree of derivatization, the smaller the T_1 value that was recorded. Among polymers with a primary amide group as a terminal end group of the side chain, the minimum T_1 value (832 ms) was observed for polymer **4**, in which the primary amide group is directly attached to the main chain, which was almost one-half the value of polymers **15** (1455 ms) and **16** (1501 ms), which are the largest ones among the primary amide-derivatized polymers studied here.

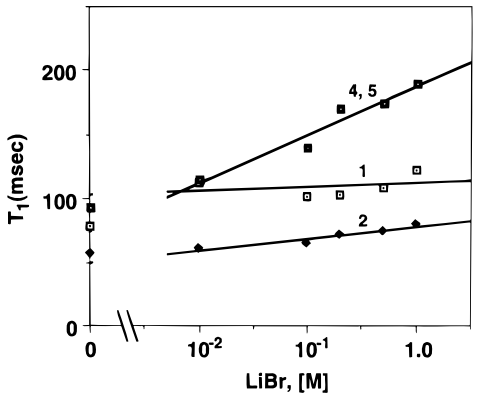


Figure 7. Changes of ^{13}C spin-lattice relaxation times of poly(*N*-(2-hydroxyethyl)acrylamide) in D_2O solution (2.5 wt %) containing various concentrations of LiBr at 30 °C. The numbers denote the position of the carbon atom in the polymer, as shown in Figure 3.

***T_1* Measurements in Lithium Bromide (LiBr)-Containing D_2O Solutions.** Since LiBr is known as a strong hydrogen bond breaker in water, the addition of LiBr may alter intra- and intermolecular hydrogen bonding and hydration states. T_1 measurements of polymer **6** were carried out in D_2O solutions with various concentrations of LiBr (Figure 7). All T_1 values increased with increasing concentration of LiBr. The largest effect was observed for the hydroxyethyl group, followed by the methine group in the main chain. The smallest effect was observed for the methylene group in the main chain.

The T_1 values determined in 1.0 M LiBr D_2O solutions of all polymers except for polymers **3**, **11**, and **12** are given in parentheses in Figures 5 and 6. Little appreciable change of T_1 values of methylene and methine carbons of main chains upon addition of LiBr was noted for polymers **1**, **5**, **7**, **8**, **13**, **14**, and **16**−**18**, where polymer **1** is PEG, polymers **5** and **16** have interconnecting tertiary amide groups, polymer **7** is poly(2-hydroxyethyl acrylate), and polymers **8**, **13**, **14**, **17**, and **18** are poly(vinyl ether) derivatives. On the other hand,

increased T_1 values of carbon atoms of the main chains were noted for polymers with hydroxyl groups, such as PVA (**2**), **6**, **9**, and PAAm (**4**).

As for side chains of 2-hydroxylethyl-derivatized vinyl polymers **6**−**8**, a markedly increased T_1 value of the hydroxymethylene carbon upon LiBr addition was noted for polymer **6**, followed by that of polymer **7**. Little appreciable change was noted for polymer **8**. The T_1 values of the hydroxylethyl group of polymer **6** in the presence of 1.0 M LiBr were almost the same as those of polymer **8** in the absence of LiBr. These results strongly suggest that the highly restricted side chain and main chain mobilities for polymer **6**, both of which are probably due to intra- or intermolecular hydrogen bonding and hydration, are considerably diminished at a high LiBr concentration. The T_1 values of the hydroxymethyl group of Tris-containing polymers, except for polymer **9**, in which a marked increase in T_1 value was noted, were slightly increased upon the addition of LiBr. Interestingly, T_1 values of the amide carbon of primary amide-derivatized polymers (polymers **15**−**18**), except for polymer **4**, did not change upon addition of LiBr.

Molecular Structure−T_1 Value Relationship. Inoue et al. showed that the activation energy of conformational change of poly(vinyl alcohol), determined from temperature-dependent T_1 values for both methine and methylene carbons, was 3.3 kcal/mol in D_2O, which is much larger than that of thermal motion (0.6 kcal/mol).[14] Experimental results obtained using systematically designed water-soluble polymers may indicate the following relationships between the structure of nonionic, water-soluble polymers and T_1 values of carbon atoms.

(1) The presence of an ether group, irrespective of whether it is incorporated into the main chain or a side chain, results in a large T_1 value for the carbon atom adjacent to the ether oxygen with minimum effect of changes in LiBr concentration. When an ether linkage was used as an interconnecting group, a very high T_1 value of the carbon atom adjacent to the ether oxygen, irrespective to whether the latter was present in the main chain or side chain, was obtained, as exemplified with polymers **8**, **13**, and **14**. These results suggest that the incorporation of an ether linkage as a water-soluble group may result in high segmental or group mobility in water.

(2) The presence of a secondary amide group as an interconnecting group tended to considerably reduce T_1 values of the main chains as compared with those of the tertiary amide group (polymers **6**, **9**, and **15** vs polymers **10** and **16**). The addition of LiBr greatly increased T_1 values of polymers with a secondary amide group as an interconnecting group, suggesting that intramolecular hydrogen bonding or hydration is broken by the presence of LiBr molecules, resulting in enhanced side chain mobility, as exemplified by polymer **6**. On the other hand, such an effect was not found for those polymers with a tertiary amide group (polymers **5**, **10**, and **16**).

(3) From these results, it can be said that the effect of the interconnecting group on T_1 values of main chains decreases in the following order: secondary amide > tertiary amide and ester > ether. This may suggest that the partial double bond character of amide and ester linkages reduces the segmental mobility of the main chain.

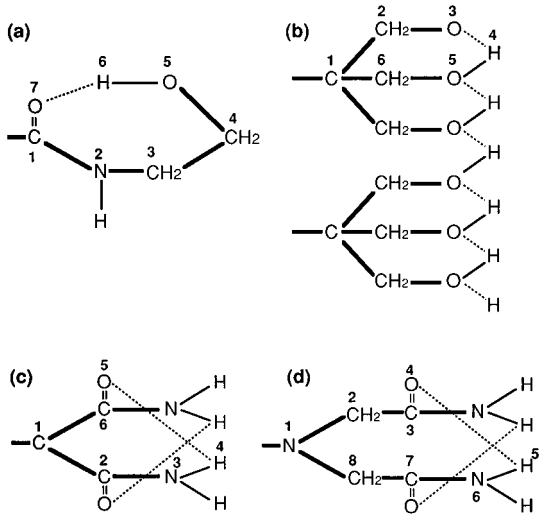


Figure 8. Possible intramolecular hydrogen bonding in side chains (a, hydroxyethyl amide in polymer **6**; b, Tris groups in polymer **10** or **13**; c, primary amide groups in polymer **17**; and d, primary amide groups in polymer **16**). Note that a thermodynamically stable six-membered ring is formed in a−c, whereas an unstable eight-membered ring is formed in d.

(4) The incorporation of a hydroxyl group into a side chain considerably reduced T_1 values of the carbon atom adjacent to the oxygen of the hydroxyl group. However, the addition of LiBr increased T_1 values, indicating that intramolecular hydrogen bonding, which may be broken by the presence of LiBr, significantly restricts mobilities of the main chain and side chains, as exemplified by polymer **6**, in which a seven-membered ring connected by intramolecular hydrogen bonds was formed between a secondary amide group and a hydroxyl group (Figure 8a).

(5) The incorporation of a Tris group considerably reduced T_1 values. The highest T_1 value of the quaternary carbon of the Tris group was found for monofunctional polymer **9** and was much larger than those of bi- and trifunctional polymers **10**, **13**, and **14**. This correlates well with results of our previous study.[11] That is, the degree of hydrogen bonding between hydroxyl groups in each Tris group or between Tris groups was reduced as the number of Tris groups in a side chain increased, which was experimentally verified by results of ^1H relaxation time measurement, deuterium−proton exchange rate measurement, and frozen water content measurement by DSC. This may be due to the intraside chain formation of hydrogen bonding stabilized with six-membered ring, as shown in Figure 8b.

(6) Increasing T_1 value of the carbonyl carbon of the primary amide group was observed with increasing distance from the main chain. An almost 2-fold higher T_1 value was observed for polymer **16** as compared with that of PAAm (**4**). On the other hand, T_1 values of primary amide groups were not changed upon addition of LiBr, except for the simplest primary amide-derivatized polymer, PAAm (**4**). Judging from T_1 values, the highest chain mobilities of the primary amide group among polymers studied here may be those of polymers **15** and **16**. Considerably retarded side chain mobilities of polymers **17** and **18** would be expected in comparison with those of polymers **15** and **16**. This may be due to intramolecular hydrogen bonding in a side chain, which is stabilized with a six-membered ring, as schematically shown in Figure 8c. However, for the polymer **16**, intramolecular hydrogen bonding, if it occurred, may form an eight-membered ring, which is quite thermo-

dynamically unstable.

(7) Thus, it can be said that T_1 values are affected by various factors, including the structure of the group between the main chain and the pendant group, the distance of the main chain, the structure of the hydrophilic group, steric interactions, and intra- and interpendant-group hydrogen bonding. Thus, the present study indicates the absence of a single factor that determines side chain mobility.

It may be concluded that the mobilities of main and side chains of nonionic vinyl polymers depend on the type of hydratable group present and its distribution and density. If hydratable groups are well distributed along a main chain and intramolecular hydrogen bonding does not occur between hydratable groups in a side chain or between those of neighboring monomer units in water, then a hydrophobic main chain should be shielded with a well-hydrated "envelope" from access of water. To molecularly design a "superhydrophilic" vinyl polymer based on our previous and present studies, we hypothesize that an ether group should be used as an interconnecting group, and that primary amide groups should be incorporated in terminal ends of side chains at appropriate distances from the main chain such that they do not undergo intramolecular hydrogen bonding with formation of thermodynamically stable six- or seven-membered rings.

The present paper deals with synthesis of multifunctional, nonionic vinyl polymers and spin-lattice relaxation time (T_1) of carbon atoms, mainly discussing chain mobilities in terms of T_1 values. Further study is necessary to elucidate the degrees of hydrophilicity of these polymers at various physicochemical scales, including hydration states. Such a study is underway, and results will be reported in the near future.

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