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Water-Soluble Polymers. 73. Electrolyte- and pH-Responsive Zwitterionic Copolymers of 4-[(2-Acrylamido-2-methylpropyl)dimethylammonio]butanoate with 3-[(2-Acrylamido-2-methylpropyl)dimethylammonio]propanesulfonate

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ABSTRACT: Amphoteric copolymers of the carboxybetaine monomer 4-[(2-acrylamido-2-methylpropyl)dimethylammonio]butanoate (AMPDAB), **1**, with the sulfobetaine monomer 3-[(2-acrylamido-2-methylpropyl)dimethylammonio]propanesulfonate (AMPDAPS), **2**, have been synthesized by free radical polymerization in 0.5 M NaBr. The feed ratios of **1**:**2** were varied from 100:0 to 0:100 mol %. Molecular weights were determined by low angle laser light scattering and range from 1.65×10^6 to 3.95×10^6. The homopolymer of **2** was insoluble in deionized water but soluble in aqueous solutions containing a critical concentration of added electrolytes. In contrast, the homopolymer of **1** was soluble in deionized water. The solubility behavior of copolymers of **1** and **2** is complex and varies with copolymer composition, pH, as well as the concentration and nature of the added electrolytes. Coulombic interactions and hydration effects are suggested to be the main factors affecting the solubility behavior of these amphiphilic copolymers. Low shear viscosity studies were conducted at varying electrolyte concentrations and pH values. The copolymers with a higher incorporation of AMPDAPS, **2**, mer units showed greater enhancement in viscosity with increased electrolyte concentration. Copolymers containing AMPDAB, **1**, mer units exhibit polyelectrolyte behavior at low pH in deionized water as the carboxylate groups are protonated, resulting in an overall cationic charge along the polymer chain. The solution behavior of these responsive systems is rationalized on the basis of competitive hydration of the zwitterionic moieties under testing conditions.

Introduction

Polyampholytes, unlike conventional polyelectrolytes, incorporate both anionically and cationically charged moieties into a single polymer chain. These systems exhibit unusual rheological behavior as a result of the attractive Coulombic interactions between oppositely charged species. In addition, the solution behavior of polyampholytes is also related to the ratio of the ionic species incorporated into the polymer.[1−18] This ratio can be varied through synthetic methods as well as through extrinsic changes in the aqueous environment, particularly changes in pH. When an excess of either anionic or cationic groups is present, the systems behave as polyelectrolytes, as typically evidenced by a viscosity decrease in the presence of small molecule electrolytes. However, as the ratio of anionic to cationic species approaches unity, the solution behavior is dominated by Coulombic attractions. These attractions may, in many cases, render the polymer insoluble in deionized water, but soluble in the presence of a critical concentration of added electrolytes as the attractive charge/charge interactions are shielded. Higgs and Joanny have developed a theoretical treatment of the solution behavior of polyampholytes with varying charge ratios.[19] It was concluded that Coulombic interactions, both attractive (polyampholyte contribution) and repulsive (polyelectrolyte contribution), dictate the solution behavior of these systems. Whether the polyampholyte or polyelectrolyte effect dominates the solubility of copolymers is dependent on both the charge ratio and concentration of small molecule electrolytes.

Zwitterionic monomers have been employed in the synthesis of polyampholytes.[20−42] These monomers are unique in that both the cationic and anionic charge are incorporated into the same mer unit and thus, at appropriate pH values, the resulting polyzwitterions will have a charge ratio of exactly one. The most thoroughly investigated polyzwitterions are based on sulfobetaine mer units in which the cationic moiety is a quaternary ammonium group and the anionic moiety a sulfonate group.[20−34] These polyzwitterions are typically insoluble in deionized water and require the addition of small molecule electrolytes to achieve solubility in aqueous media. Furthermore, the sulfonate group is a weak base and thus remains predominantly dissociated in aqueous media. Polyzwitterions based on carboxybetaine mer units in which the anionic species is a carboxylate group have also been investigated, although to a lesser degree.[37−42] These systems are usually more soluble in deionized water than the sulfobetaine analogs. In addition, these mer units can be converted from zwitterionic to cationic by lowering the pH, since the carboxylate groups (in contrast to sulfonate groups) can be protonated in aqueous media. Thus, for these systems, the charge ratio between anionic and cationic species can be varied by adjusting the pH.

The solution properties of polyampholytes based on the sulfobetaine monomer 3-[(2-acrylamido-2-methylpropyl)dimethylammonio]propane sulfonate (AMPDAPS),[33] **2**, and on the carboxybetaine analog 4-[(2-acrylamido-2-methylpropyl)dimethylammonio]butanoate (AMPDAB),[42] **1**, have been elucidated previously in separate studies in our laboratories. It was found that the homopolymer of AMPDAPS, **C(0:100)**, was insoluble in deionized water at all pH values while the homopolymer of AMPDAB, **C(100:0)**, was soluble. Since the only structural variance between these two systems is the anionic group, the contrasting behavior must be

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attributed to solvation differences of the sulfonate and the carboxylate moieties of the zwitterionic group. To further investigate this behavior, we report in this paper the synthesis and characterization of a new series of copolymers of AMPDAB and AMPDAPS, **C(*X*:*Y*)**. The objective of this work is to compare the solution behavior of the two homopolymers of AMPDAB, **C(100:0)**, and AMPDAPS, **C(0:100)**, with copolymers, **C(*X*:*Y*)**, incorporating both zwitterionic monomers, **1** and **2**. It will be subsequently shown that conditions of pH, electrolyte concentration, and the nature of the anionic moiety incorporated into the zwitterionic mer unit dramatically affect the solubility and rheological behavior.

Experimental Section

Monomer Synthesis. (3-Carboxypropyl)(2-acrylamido-2-methylpropyl)dimethylammonium Bromide, 1. The synthesis of (3-carboxypropyl)(2-acrylamido-2-methylpropyl)dimethylammonium bromide (AMPDAB), **1**, involved a multistep procedure and has been reported in detail previously.[42] Briefly, (2-acrylamido-2-methylpropyl)dimethylamine (AMPDA)[43,44] was dissolved in ethyl 4-bromobutyrate and the reaction allowed to proceed for 72 h at 60 °C. The product was purified, dissolved in deionized water, and passed over Amberlite IRA-400(OH) ion-exchange resin. The water and the byproduct ethanol were removed under reduced pressure to yield the zwitterionic product as an oil. After the addition of 1 equiv of HBr and removal of residual water under reduced pressure, the product was obtained as a solid that was recrystallized from ethanol, yielding a white material with a decomposition temperature of 185−187 °C. NMR and FTIR spectral assignments are given in ref 42.

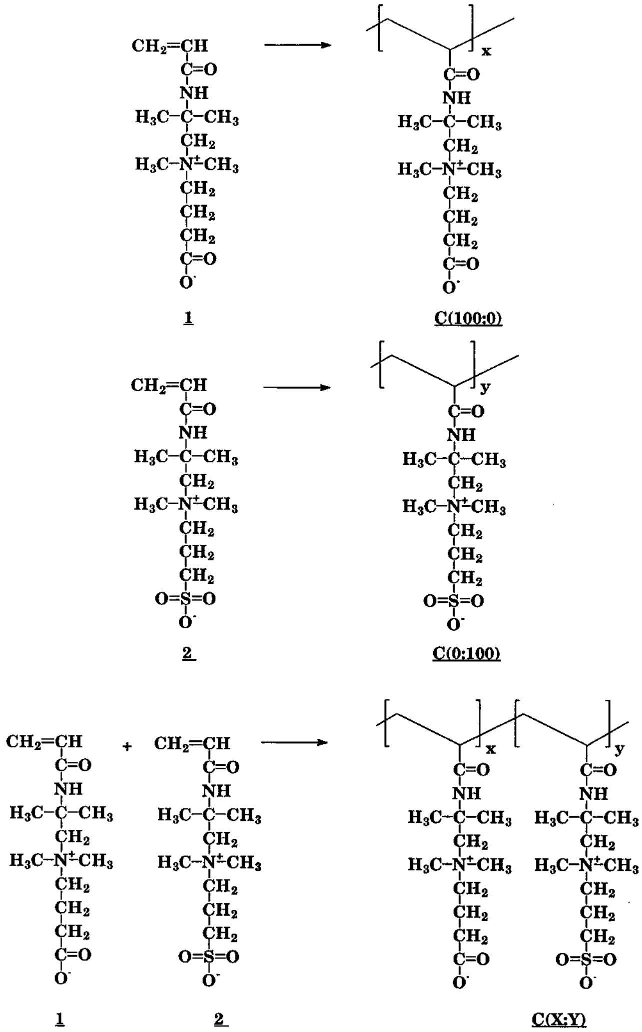
3-[(2-Acrylamido-2-methylpropyl)dimethylammonio]propanesulfonate, 2. The synthesis of 3-[(2-acrylamido-2-methylpropyl)dimethylammonio]propanesulfonate (AMPDAPS), **2**, has been reported previously.[33] Briefly, AMPDAPS was synthesized by the ring-opening reaction of 1,3-cyclopropanesultone with AMPDA in the presence of acetone at 45 °C. The product precipitated from the reaction medium and was subsequently washed with acetone and ether to yield pure **2**. The product was recrystallized from ethanol, yielding a white powder.

Synthesis of Copolymers of 4-[(2-Acrylamido-2-methylpropyl)dimethylammonio]butanoate, 1, with 3-[(2-Acrylamido-2-methylpropyl)dimethylammonio]propanesulfonate, 2. The homopolymers of AMPDAB, **C(100:0)**, and AMPDAPS, **C(0:100)**, as well as the copolymers of AMPDAB with AMPDAPS, **C(*X*:*Y*)**, were synthesized by free radical polymerization in a 0.5 M aqueous NaBr solution under nitrogen at 30 °C using 0.1 mol % potassium persulfate as the initiator (Scheme 1). The feed ratio of AMPDAB:AMPDAPS was varied from 100:0 to 0:100 mol %, with the total monomer concentration held constant at 0.45 M. NaBr was added to ensure that the polymerization medium remained homogeneous.

In a typical synthesis, specified quantities of each monomer were dissolved in small volumes of deionized water. The separate solutions were then combined and 1 equiv of sodium hydroxide/equiv of AMPDAB was added and the pH adjusted to 8. The necessary quantity of NaBr was then added to achieve a 0.5 M NaBr solution. The reaction mixture was sparged with nitrogen and initiated with 0.1 mol % potassium persulfate. The reaction was terminated around 40−60% conversion due to the high viscosity of the reaction medium. The polymers were precipitated in acetone, dissolved in deionized water, and then dialyzed against deionized water adjusted to pH = 8.5 using Spectra/Por 4 dialysis bags with molecular weight cutoffs of 12 000 to 14 000. **C(0:100)** precipitated from solution during dialysis. The polymers were isolated by lyophilization, and conversions were determined gravimetrically from the purified polymers.

Copolymer Characterization. ^{13}C NMR spectra of the copolymers were obtained at 50.3 MHz with a Bruker AC200 spectrometer using 15−20 wt % 0.5 M NaCl (D_2O) polymer solutions with DSS (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt) as a reference. A recycle delay of 8 s, 90° pulse length, and gated decoupling to remove NOE were used for quantitative spectral analysis. Compositions were determined by integration of the resonances of the dimethyl groups of the quaternary carbon of the respective monomers. The peak maxima were 27.6 and 29.6 ppm for **1** and **2**, respectively. These data are accurate within ±5 mol %. Molecular weight studies were performed with a Chromatix KMX-6 low-angle laser light scattering instrument at 25 °C in 1.0 M NaCl. Refractive index increments were obtained using a Chromatix KMX-16 laser differential refractometer at 25 °C in 1.0 M NaCl.

Scheme 1. Structural Composition of Copolymers of 4-[(2-Acrylamido-2-methylpropyl)dimethylammonio]butanoate with 3-[(2-Acrylamido-2-methyl propyl)dimethylammonio]propanesulfonate



Viscosity Measurements. Polymer solutions were made by dissolving designated amounts of polymer in the stock electrolyte solutions. The solutions were then isoionically diluted to appropriate concentrations and allowed to age for 7−10 days before being analyzed with a Contraves LS-30 rheometer. The Contraves LS-30 rheometer is a Couette concentric-cylinder viscometer operated at a constant shear rate and equipped with a thermostated sample bath. Adjustments to pH were performed by adding small aliquots of a concentrated HCl or NaOH solution via a microsyringe.

Turbidimetry. Phase separation was monitored using a Brinkman PC 800 colorimeter using a 620 nm light filter. The sample of polymer solution (15 mL) was stirred by a magnetic stirrer, and small aliquots of a concentrated HCl or NaOH solution were added by a microsyringe. An electrode immersed in the solution was used to determine the pH value at which the phase transition occurred. Values were recorded when the

Scheme 2. Expected Charge Distribution in C(*X*:*Y*) Copolymers at Values of (a) Low, (b) Intermediate, and (c) High pH

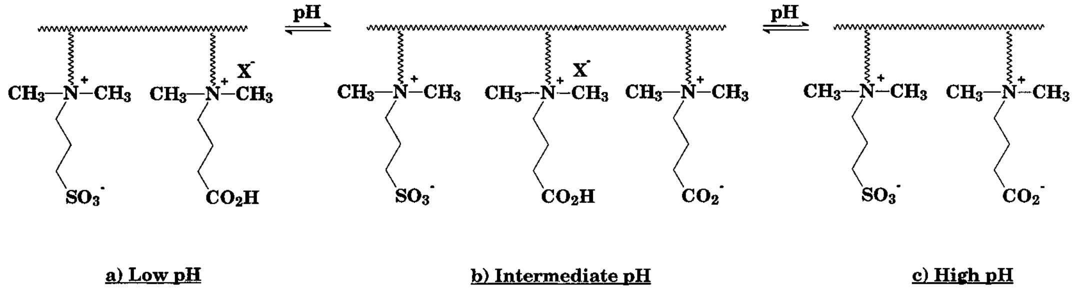


Table 1. Reaction Parameters for the Copolymerization of 4-[(2-Acrylamido-2-methylpropyl)dimethylammonio]-butanoate (1) with 3-[(2-Acrylamido-2-methylpropyl)-dimethylammonio]propanesulfonate (2)

sample	feed ratio (mol %) (**1**:**2**)	rxn time (h)	% conv	**1** found[a] (mol %)
C(0:100)	0.0:100.0	3.0	60	0.0[b]
C(25:75)	25.0:75.0	4.0	45	25 ± 5
C(50:50)	50.0:50.0	4.0	43	50 ± 5
C(75:25)	75.0:25.0	4.0	41	75 ± 5
C(100:0)	100.0:0.0	4.0	52	100.0[b]

[a] Determined from ^{13}C NMR. [b] Theoretical value.

Table 2. Classical Light Scattering Data for the Copolymers of 4-[(2-Acrylamido-2-methylpropyl)-dimethylammonio)butanoate (1) with 3-[(2-Acrylamido-2-methylpropyl)dimethylammonio)propanesulfonate (2)

sample	(**1**) found[a] (mol %)	$M_w \times 10^{-6}$	$A_2 \times 10^4$ (ml·mol/g^2)	DP × 10^{-4}
C(0:100)[b]	0.0	3.1	1.2	1.1
C(25:75)	25.0	2.95	1.2	1.0
C(50:50)	50.0	2.36	2.7	0.9
C(75:25)	75.0	1.65	3.9	0.6
C(100:0)[c]	100	3.9	0.8	1.5

[a] Determined from ^{13}C NMR. [b] d*n*/d*c* = 0.132. [c] d*n*/d*c* = 0.151.

transmittance was approximately 50%. The measurements were performed at least twice and were reproducible to within ±0.2 of the listed pH values at 25 °C. The transitions were found to be sensitive to changes in the temperature.

Results and Discussion

Copolymer Synthesis and Characterization. Scheme 1 shows the structures of the homopolymers of AMPDAB, **C(100:0)**, and AMPDAPS, **C(0:100)**, and copolymers of the two monomers, **C(*X*:Y)**, prepared by free radical polymerization in aqueous media. Syntheses of both monomers are reported in the Experimental Section. These monomers have the attributes of (a) salt- and pH-responsive pendent zwitterionic functionalities, (b) resistance to hydrolysis imparted by the amide and geminal dimethyl groups, and (c) high apparent rates of propagation in aqueous media.

Copolymers were synthesized by varying the feed ratios of **1** and **2** over the entire compositional range. Reaction parameters of feed ratios, reaction time, conversion, and composition are given in Table 1, and conditions of the polymerization are given in the Experimental Section. Copolymer compositions were determined from ^{13}C NMR analysis by integration of the geminal dimethyl carbon resonances bonded to the quaternary carbon of the respective comonomers. Random copolymerization under the experimental conditions is expected due to structural similarity of the monomers. Compositions of the copolymers are designated **C(*X*:*Y*)** where *X* and *Y* represent the relative mole percent of AMPDAB, **1**, and AMPDAPS, **2**, respectively, in the copolymer.

Apparent weight average molecular weights as determined by low-angle laser light scattering at 25 °C in 1.0 M NaCl (Table 2) vary from 1.65×10^6 to 3.95×10^6. The homopolymer of **2**, **C(0:100)**, and the copolymers **C(25:75)** and **C(50:50)** have similar degrees of polymerization while **C(75:25)** has the lowest. The second virial coefficients (A_2) were also determined and range from 0.8×10^{-4} to 3.9×10^{-4} ml mol/g^2. Variations in both molecular weight and copolymer composition affect A_2 values in aqueous NaCl solution. For this limited series, the copolymers **C(50:50)** and **C(75:25)** are more solvated than either of the homopolymers of **1** and **2**. **C(25:75)** and **C(0:100)** have the same A_2 values and similar molecular weights.

Behavior in Aqueous Solution. The behavior of the copolymer series in aqueous media is best analyzed by considering the expected charge distribution at various pH values (Scheme 2) for the copolymers and the homopolymers of AMPDAB, **1**, and AMPDAPS, **2**. The sulfonate moiety, a weak conjugate base, will remain in the dissociated, anionic form at all attainable pH values. In contrast, the carboxylate anion, a stronger conjugate base, will be protonated as the pH is lowered. Therefore, depending on pH and ionic strength, we expect to encounter complex solution behavior based on not only electrostatic interactions (dipolar and ionic) of the mer units but also counterion condensation and hydrophobic effects.

The discussion to follow has been divided into two major sections. The first considers solubility (phase behavior) at 25 °C for the homopolymers and selected copolymers under selected conditions of pH, ionic strength, and added electrolyte type. Two polymer concentrations were chosen (0.2 and 0.5 g/dL) for these studies. The second section deals specifically with the effects of pH and added electrolyte on viscosity behavior at polymer concentrations of 0.5 g/dL for sufficiently solvated copolymers. Since our work deals with aqueous formulation of polymers in dilute solution, we have thus far only examined viscometric behavior at low concentrations, seeking pH and salt-triggered response at significant levels.

Solubility Behavior. ***C(0:100).*** **C(0:100)**, the homopolymer of **2**, is insoluble in deionized water at all pH values investigated in this study (pH = 1−13). This behavior, with a few exceptions,[29] is typical of most polyzwitterions composed of sulfobetaines with three methylene units between the cationic and anionic groups; the lack of solubility is attributed to the attractive dipole Coulombic interactions. These interactions, however, can be shielded by the addition of electrolytes, resulting in solubilization of the polymer. The concentration of electrolyte required for dissolution is depend-

Table 3. Critical Electrolyte Concentration Required for Solubilization of C(0:100)

salt	CEC (M)
NaCl	0.17
CsCl	0.2
NaBr	0.06
NaSCN	0.02

ent on the nature of the electrolyte. Table 3 lists the critical electrolyte concentration (CEC) required for solubilization of **C(0:100)** by various electrolytes. The "salting in" ability of the various electrolytes is in accord with the Hoffmiester series for the anions,[45] $SCN^- > Br^- > Cl^-$; similar rankings have been previously observed for poly(sulfobetaines).[21,24,26,29] This behavior has been rationalized in terms of "hard−soft" acid−base interactions. "Soft" (larger, more highly polarizable) anions are better adapted to interact with the "soft" quaternary ammonium group. This enhanced interaction results in a lower concentration of added electrolytes required to disrupt the attractive Coulombic interactions of the poly(sulfobetaine) and, therefore, more efficiently facilitates solubilization of the polymer. "Salting in" or water structuring effects may also be operative.

Interestingly, **C(100:0)**, the homopolymer of the carboxybetaine mer unit, is soluble in deionized water at all pH values up to 13, the highest value investigated in this study. The solubility of **C(100:0)** and the insolubility of **C(0:100)** in deionized water cannot be explained solely by charge balance since both mer units are zwitterionic at high pH values. It follows that differences in zwitterion solvation must be due to the anionic moieties. The differences in the solubility support the findings of Laughlin, who reported that surfactants possessing a carboxybetaine head group are more hydrophilic than those possessing a sulfobetaine head group based on phase behavior, basicity, and chromatographic data.[46] The enhanced hydration of the carboxylate group compared to that of the sulfonate group weakens the **dipolar** interactions and, therefore, imparts solubility to **C(100:0)** in deionized water.

C(25:75). In deionized water, **C(25:75)** (possessing 25 mol % carboxybetaine and 75 mol % sulfobetaine) is soluble at pH values less than 8. At pH ≤ 8, sufficient numbers of the carboxylate groups of AMPDAB are protonated such that the polymer coil acquires a net positive charge. Solubilization of the polymer results when charge−charge repulsions between the cationic groups reach a critical limit. Conversely, above pH 8, charge repulsions are diminished as **1** is rendered zwitterionic and the charge ratio approaches unity. The attractive dipolar Coulombic interactions between the anionic and cationic charge centers result in phase separation. Copolymers **C(50:50)** and **C(75:25)** and homopolymer **C(100:0)** do not display this behavior and are soluble in deionized water throughout the pH range investigated (pH 1−13). The insolubility of **C(25:75)** at pH ≥ 8 is, therefore, likely a result of the higher incorporation of the sulfobetaine mer unit in the copolymer, a conclusion supported by the insolubility of **C(0:100)** in deionized water. Accordingly, the solubility of **C(50:50)** and **C(75:25)** can be attributed to the higher incorporation of the carboxybetaine mer units into these copolymers.

The solubility behavior of **C(25:75)** as a function of pH and polymer concentration in the presence of added electrolytes is presented in Table 4. As will be discussed below, complex behavior is observed and explained in terms of competitive interactions affecting solubility. A consideration of the ionization state (ionic or zwitterionic), Scheme 2, and the effect of electrolyte on the degree of chain solvation (contraction or expansion) is essential. For example, in the presence of 0.008 M NaCl (C_p = 0.2 g/dL), lower pH values (7.6 vs 8) are necessary for solubilization of **C(25:75)** as compared to deionized water. The presence of NaCl slightly shields the initial charge repulsions, thus requiring that more of the carboxybetaine units be rendered cationic for subsequent solubilization. At pH ≥ 7.6, dipolar interactions between the zwitterionic groups result in phase separation. Apparently, 0.008 M NaCl is not a sufficient concentration of electrolyte to shield the shorter range attractive interactions.

Table 4. Phase Behavior of C(25:75) as a Function of pH[a]

	0.2 g/dL				0.5 g/dL			
[M]	NaCl	CsCl	NaBr	NaSCN	NaCl	CsCl	NaBr	NaSCN
0.008	7.6^{ia}	−	−	−	−	−	−	−
0.017	9.6^{ib} 4.6^{ia}	−	−	−	9.4^{ib} 4.4^{ia}	−	−	−
0.05	8.6^{ib}	8.2^{ib}	6.0^{ib}	4.6^{ib}	8.9^{ib}	8.7^{ib}	8.3^{ib}	7.0^{ib}
0.1	6.0^{ib}	5.8^{ib}	4.2^{ib}	3.7^{ib}	8.2^{ib}	8.0^{ib}	7.3^{ib}	4.0^{ib}
0.3	3.9^{ib}	3.8^{ib}	−	−	4.4^{ib}	4.1^{ib}	−	−
0.5	−	−	−	−	−	−	−	−

[a] ib = insoluble below listed pH. ia = insoluble above listed pH. − = no phase separation observed between pH 1 and 13.

As the concentration of NaCl is increased (0.017 M NaCl), a region of insolubility between pH 9.6 and 4.6 occurs. In this intermediate pH region, **C(25:75)** can be considered to be a terpolymer of sulfobetaine mer units, carboxybetaine mer units, and quaternary ammonium mer units (Scheme 2b). The resulting insolubility is likely due to three factors. First, as the carboxybetaine mer units become protonated, the hydrophobicity of the copolymer increases due to the loss of the anionic charge center that was previously hydrated. Second, inter- and intrapolymer hydrogen-bonding interactions between the partially protonated carboxyl moieties may also decrease solubility. Third, **C(25:75)** is composed of 75 mol % sulfobetaine moieties, functional groups which, when incorporated into polymers, typically require the addition of a critical concentration of electrolyte to facilitate solubilization. Above pH 9.6, **C(25:75)** is essentially polyzwitterionic and the presence of NaCl aids the solubilization by shielding the attractive Coulombic interactions (Scheme 2c). As the pH is lowered below this value, the carboxybetaine groups become progressively more protonated; however, the higher concentration of NaCl (0.017 M vs 0.008 M) efficiently shields the initial cationic sites and thus prevents solubilization. As the pH approaches 4.6, however, a sufficient number of the carboxybetaine groups are rendered cationic such that the repulsions are no longer shielded; i.e., spatial distance is likely approaching the Debye−Huckel reciprocal screening length (which is approximately equal to 23 Å in 0.017 M NaCl).[49] As this occurs, solubility is achieved due to Coulombic repulsions (Scheme 2a).

When the NaCl concentration is further increased to values between 0.05 and 0.3 M, solubility is no longer observed at low pH. Furthermore, as the concentration of NaCl increases, the pH at which the polymer phase separates decreases. Again, NaCl is acting to shield Coulombic interactions (both attractive and repulsive) and to possibly augment hydrophobic interactions. Recall that the homopolymer of **C(0:100)** has a CEC of 0.17 M NaCl; however, **C(25:75)** phase separates even in 0.3 M NaCl at pH 3.9. If the attractive Coulombic

Table 5. Phase Behavior of C(50:50) as a Function of pH[a]

	0.2 g/dL				0.5 g/dL			
[M]	NaCl	CsCl	NaBr	NaSCN	NaCl	CsCl	NaBr	NaSCN
0.05	–	–	–	8.0^{ib}	–	–	–	7.8^{ib}
0.1	–	–	7.0^{ib} 4.0^{ia}	7.7^{ib}	–	–	6.4^{ib}	5.7^{ib}
0.3	–	–	3.0^{ib}	3.8^{ib}	–	–	2.9^{ib}	3.4^{ib}
0.5	–	–	–	–	–	–	–	–

[a] ib = insoluble below listed pH. ia = insoluble above listed pH. – = no phase separation observed between pH 1 and 13.

interactions of **C(25:75)** were the *sole* cause of phase separation at low pH values, then one might expect the polymer solution to remain homogeneous at concentrations of NaCl above 0.17 M. Other factors, such as an increase in the hydrophobicity of the copolymer, are also operating, thus leading to phase separation. However, that attractive Coulombic interactions are still influential in 0.3 M NaCl is supported by the observation that in 0.5 M NaCl, no phase separation is observed for **C(25:75)** over the entire pH range investigated. As the concentration of NaCl is increased to 0.5 M NaCl, the attractive interactions of the zwitterions are finally sufficiently disrupted and the enhanced hydration of the charged groups leads to complete solubility. There is also a polymer concentration dependency on the phase behavior of DABDAPS-25 (Table 4), as different pH values are required for phase separation. This suggests that there may be specific interactions between DABDAPS-25 and sodium chloride.

CsCl, NaBr, and NaSCN Solutions. Shown in Table 4 are the effects of selected electrolytes on the critical pH required for phase separation. The critical pH values reported for sodium chloride and cesium chloride are very similar. However, the cesium cation must be more influential than the sodium cation, as no phase separation is observed at low concentrations of added electrolyte. This behavior is not fully understood but may be due to preferential association with the anionic moieties of the polyzwitterion or a "salting in" effect. Greater effects on the critical pH value are observed for sodium bromide and sodium thiocyanate. This behavior is likely a result of two competing interactions. As noted for the CEC studies of **C(0:100)**, electrolytes composed of the larger polarizable anions require lower concentrations to solubilize the sulfobetaine homopolymer. However, these same "soft" counterions are also anticipated to bind more strongly with the "soft" quaternary ammonium group of **1** as it is converted from a zwitterionic moiety to a cationic moiety. In fact, Stejskal et al. have reported phase separation of polycations in the presence of KSCN.[47] The tighter counterion association leads to a decrease in hydration of these mer units, resulting in enhanced hydrophobicity and, therefore, a decrease in the solubility of the polymer. For **C(25:75)**, however, the "salting in" effect of the added electrolytes appears to be the more dominant factor influencing solubility. Conversely, as discussed in the following section, when the mol % of the carboxybetaine mer unit in the copolymers is increased, counterion binding becomes more influential and actually leads to a decrease in solubility at low pH.

Table 6. Phase Behavior of C(*X*:*Y*) Copolymers in Varied Concentrations of NaSCN as a Function of pH[a]

[M]	C(25:75)	C(50:50)	C(75:25)	C(100:0)
0.05	7.0^{ib}	7.8^{ib}	–	4.3^{ib}
0.1	4.0^{ib}	5.7^{ib}	7.3^{ib}	4.4^{ib}
0.3	–	3.4^{ib}	7.4^{ib}	4.4^{ib}
0.5	–	–	4.7^{ib}	4.4^{ib}
0.8	–	–	–	4.4^{ib}
3.0	–	–	–	4.4^{ib}

[a] ib = insoluble below listed pH. – = no phase separation observed between pH 1 and 13.

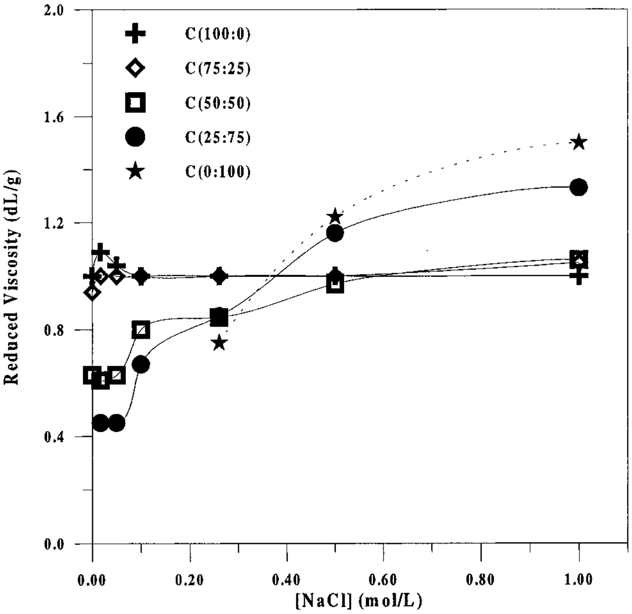


Figure 1. Reduced viscosity of C(*X*:*Y*) copolymers as a function of increasing NaCl concentration at pH = 9.5 (C_p = 0.5 g/dL). (Full line drawn as a guide.)

Copolymers C(50:50), C(75:25), and C(100:0). Table 5 indicates the phase behavior of **C(50:50)** as a function of pH in the presence of different electrolytes. In contrast to **C(25:75)**, no phase separation is observed in sodium chloride and cesium chloride solutions throughout the entire pH range. **C(75:25)** and **C(100:0)** were also soluble throughout the pH range in the presence of sodium chloride and cesium chloride. This behavior is supported by the findings of Laughlin that the carboxybetaine mer unit is more hydrophilic or more strongly hydrated than the sulfobetaine mer unit.[46] Thus for carboxybetaine mer units, attractive dipole–dipole interactions are weakened by the stronger interaction of the carboxylate group with water as compared to the sulfonate group. In the presence of larger anions, i.e., bromide and thiocyanate, phase separation is observed. As discussed above, specific counterion association of the small anion with the quaternary ammonium group of **1** as the pH is lowered would lead to a dehydration of the polymer chain and, as is observed, phase separation.

The counterion association effects of the large anions at low pH is further evidenced by examining the phase behavior of all the copolymers in the presence of sodium thiocyanate (see Table 6). The competing effects of the enhanced solubility of the sulfobetaine mer units (recall that the CEC = 0.02 M NaSCN for **C(0:100)**) versus the reduced solubility of the carboxybetaine mer units in the cationic form are apparent. The higher the mol % of sulfobetaine mer units incorporated into the copolymer, the lower the concentration of sodium thiocyanate required to solubilize the copolymer. Furthermore, **C(100:0)**, the homopolymer of **1**, phase separates as the pH is lowered to ca. 4.4 regardless of the concentration of sodium thiocyanate.

Viscometric Studies. Effects of Electrolytes. The effect of sodium chloride on the reduced viscosity

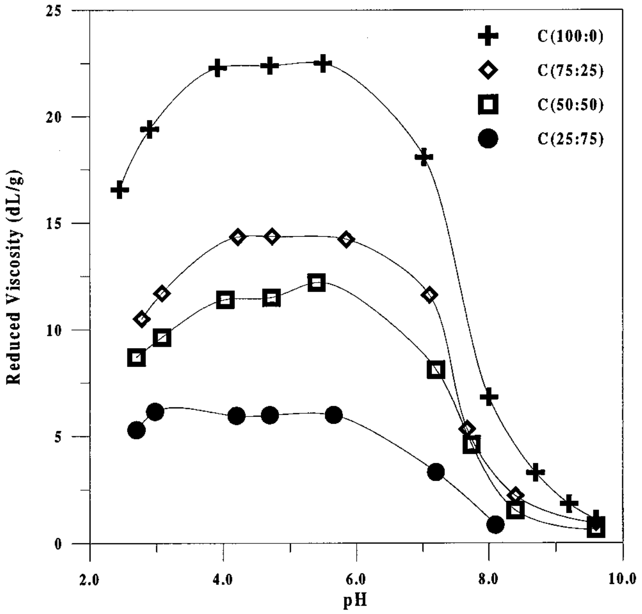


Figure 2. Reduced viscosity of C(*X*:*Y*) copolymers as a function of pH in deionized water (C_p = 0.5 g/dL). (Full line drawn as a guide.)

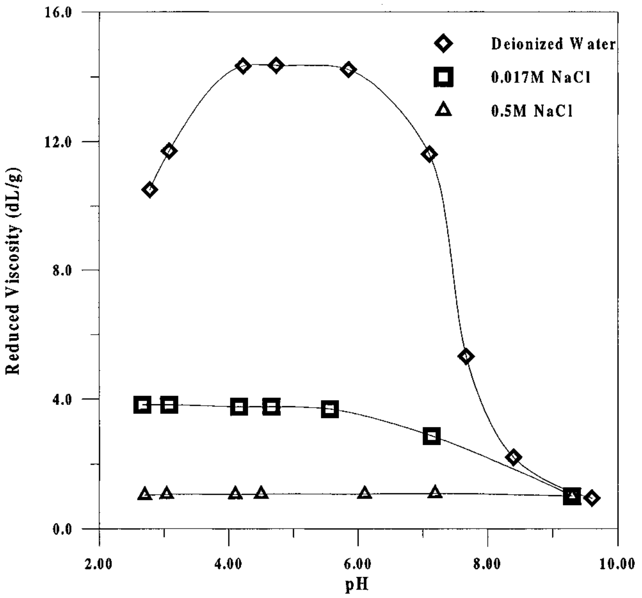


Figure 3. Reduced viscosity of C(75:25) as a function of pH in deionized water and NaCl solutions (C_p = 0.5 g/dL). (Full line drawn as a guide.)

was studied at pH = 9.5 at a polymer concentration of 0.5 g/dL. The results are shown in Figure 1. The reduced viscosities of **C(75:25)** and **C(100:0)** are relatively unaffected by the presence of added electrolytes. **C(0:100), C(25:75), and C(50:50)**, however, do exhibit significant enhancements in viscosity as the concentration of sodium chloride is increased. As noted for the solubility studies, the copolymers with a higher incorporation of the sulfobetaine mer units are more influenced by the concentration of sodium chloride. Accordingly, these copolymers also display the largest increases in hydrodynamic volume as the concentration of electrolytes increases.

Effects of pH. The reduced viscosity of the copolymers was also studied as a function of pH (Figure 2). The presence of the carboxylate group allows the polymers to acquire an overall cationic charge as the pH is lowered. As this occurs, the polymer coil exhibits an increase in hydrodynamic volume as a result of Coulombic repulsions. Potentiometric titration of monomer **1** and **C(100:0)** in deionized water yielded pK_a values of 4.05 and 3.35, respectively. These values are in agreement with previous studies on surfactants and polymers possessing a carboxybetaine group with three methylene units between charged centers.[48,40] For the copolymers in this study, **C(100:0)** experiences an increase in viscosity around pH 8.5−9.0. **C(50:50)** and **C(75:25)** require lower pH values for an increase in viscosity to be observed. The magnitude of the increase in viscosity is also dependent on the mol % of **1** incorporated into the copolymer. The higher the percentage of **1** incorporated, the greater the increase in viscosity as a result of enhanced charge−charge repulsions between the cationic centers. The eventual reduction in viscosity at very low pH values is due to an increase in the ionic strength of the medium.

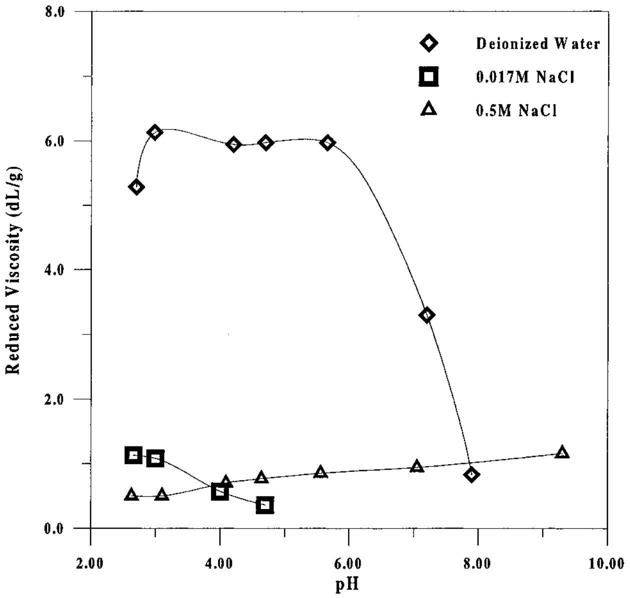


Figure 4. Reduced viscosity of C(25:75) as a function of pH in deionized water and NaCl solutions (C_p = 0.5 g/dL). (Full line drawn as a guide.)

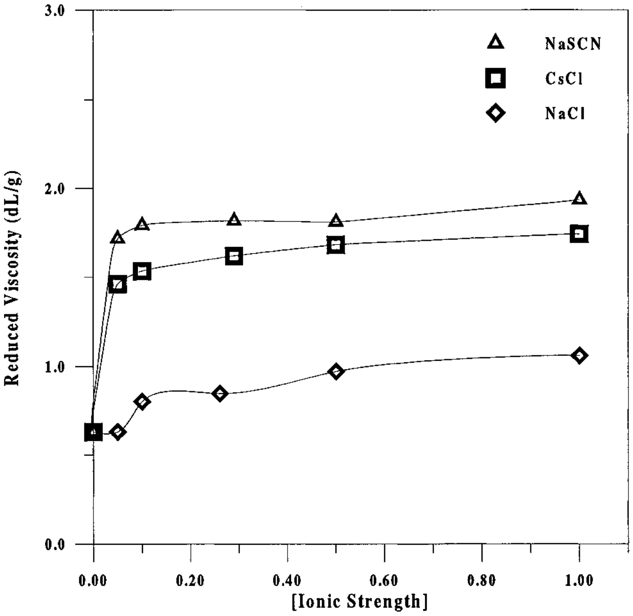


Figure 5. Reduced viscosity of C(50:50) as a function of increasing electrolyte concentration. (Full line drawn as a guide.)

The effects of pH on the reduced viscosity were also studied in the presence of added sodium chloride for **C(75:25)** and **C(25:75)**, and the results are given in Figures 3 and 4, respectively. For **C(75:25)**, at all but the highest pH values, the reduced viscosity decreases as the concentration of sodium chloride is increased. In 0.5 M NaCl, no change in viscosity is observed throughout the pH range. These results are due to shielding of Coulombic repulsions, behavior typical of polyelectrolytes. Similar behavior is observed for **C(25:75)**.

Effects of Counterions. The effects of various electrolytes on the viscosity of **C(50:50)** were studied (Figure 5). As observed for the solubility studies reported earlier, the nature of the added electrolytes influences the viscosity behavior of the copolymer solutions. The results follow the Hoffmiester series and the larger, more polarizable ions lead to higher solution viscosities. This is likely a result of stronger interactions with the ionic moieties along the polymer chain; however, enhanced polymer/solvent interactions due to "salting in" effects may also be operative.

Conclusions

The series of copolyzwitterions, **C(25:75)**, **C(50:50)**, and **C(75:25),** incorporating both carboxybetaine and sulfobetaine mer units, as well as the two homopolyzwitterions **C(0:100)** and **C(100:0),** have been synthesized by free radical polymerization in a 0.5 M NaBr solution. Copolymer compositions determined by ^{13}C NMR indicate random incorporation of both comonomers into the copolymers. Weight average molecular weights in the range 1.65×10^6 to 3.95×10^6 were determined by low angle laser light scattering.

The solubility behavior of the series was investigated as functions of copolymer composition, pH, and added electrolytes. **C(0:100)**, the homopolyzwitterion of the sulfobetaine monomer, was insoluble in deionized water and required the addition of a critical concentration of electrolyte for solubilization. Larger, more highly polarizable anions were more effective in solubilizing **C(0:100)**, in accord with the Hoffmiester series for anions. **C(100:0)**, the homopolyzwitterion of the carboxybetaine monomer, is soluble in deionized water because of the more hydrophilic nature of the carboxybetaine group. **C(25:75)** exhibited the most complex solubility behavior as a function of pH and added electrolytes. This behavior was interpreted as a competition of the attractive and repulsive Coulombic interactions and hydrophobic effects caused by counterion association of small anions with the quaternary ammonium groups as the pH was lowered. **C(50:50)**, **C(75:25)**, and **C(100:0)** remain soluble in the presence of chloride anions at all pH values investigated. In the presence of thiocyanate anions, however, these polymers phase separate at a critical pH and electrolyte concentration. **C(100:0)** precipitated at a pH ca. 4.4 regardless of the concentration of NaSCN. This behavior has been attributed to tighter counterion binding of the thiocyanate anions along the polycation chain, resulting in dehydration and ultimately phase separation.

Viscosity behavior was examined as a function of pH and added electrolytes. **C(25:75)**, **C(50:50)**, and **C(0:100)** exhibited the greatest increase in viscosity as the concentration of electrolytes was increased due to the higher incorporation of the sulfobetaine mer units into these polymers. Copolymers containing the highest mol % of the carboxybetaine mer unit displayed the greatest enhancement in viscosity as the pH of the aqueous medium was lowered. This behavior is a result of the polyzwitterion-to-polycation transition as the carboxybetaine mer units become protonated and is evidenced by the decrease in viscosity in the presence of electrolytes.

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