Synthesis and aqueous solution behaviour of copolymers containing sulfobetaine moieties in side chains

I.V. Berlinova[*], I.V. Dimitrov, R.G. Kalinova, N.G. Vladimirov

Institute of Polymers, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

Abstract

A two-step method was developed to synthesize sulfobetaine copolymers with different comonomer units in the main chain. The alternating copolymers, poly(N-vinyl-2-pyrrolidone-co-phthalimidoacrylate) and poly(styrene-co-phthalimidoacrylate) were modified with 3-dimethylaminopropylamine to yield copolymers containing tertiary amine groups in the side chains. They were then quaternized with 1,3-propanesultone. The aqueous solution behaviour of the zwitterionic copolymers depended on the structure of the backbone. Thus, the copolymer derived from the N-vinyl-2-pyrrolidone-based precursor dissolved only in aqueous salt solutions. The reduced viscosities of these solutions were insensitive to the polymer concentration. Increasing the salt concentration and "softness" of the salt ions slightly increased the intrinsic viscosity. The results suggest the important role of the intramolecular interactions in the solution behaviour of this sulfobetaine copolymer. In contrast, the sulfobetaine copolymer containing styrene units in the main chain formed micellar solutions whose intrinsic viscosity decreased on salt addition. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Sulfobetaine copolymers; Solution behaviour; Micellar copolymers

1. Introduction

Zwitterionic polymers are a class of ionic polymers developed to overcome the disadvantages of polyelectrolytes. Their water solubility is promoted by salts and they display "antipolyelectrolyte" behaviour which is characterized by enhanced viscosity in aqueous salt solutions.

An intrinsic characteristic of zwitterionic polymers is that the cation and anion are covalently bonded in the same side chain, thus creating a permanent dipole. This is the major difference between polyzwitterions and polyelectrolytes, whose behaviour in aqueous solutions is determined by the coulombic interactions arising from the dissociation of the macroion–counterion ion pairs.

The synthetic approach to zwitterions of sulfobetaine type

$$\geqslant \overset{+}{N}-(CH_2)_n SO_3^-$$
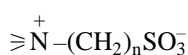
is based on the reaction of tertiary amine groups with 1,3-propane- or 1,4-butanesultone [1–5] or on their addition to alkenylsulfonylchlorides [6]. Polysulfobetaines were derived from radical homopolymerization of monomeric sulfobetaines [3–8] or from their copolymerization with polar monomers such as N-vinyl-2-pyrrolidone [9], acrylamide [5], acrylic acid [10], a carboxybetaine monomer [11] or with the non-polar ethylacrylate [12].

Another approach to polyzwitterions with defined structure and molar mass of the backbone is to functionalize precursor polymers obtained via different mechanisms [4,13–16]. Group transfer polymerization of methacrylic monomers was used to prepare near-monodisperse homopolymers, statistical and block copolymers of different composition which were subsequently quaternized with 1,3-propanesultone [13–15]. Sulfobetaine copolymers with alternating structures were derived from poly-(styrene-co-maleic anhydride) applying a multistep process [16]. The presence of hydrophobic units in the main chain or a hydrophobic block determines the amphiphilic behaviour of these copolymers [14,16].

The aqueous solution properties of polysulfobetaines are dominated by the presence of zwitterionic groups along the main chain. Due to the equal number of cationic and anionic groups the polymers are electroneutral but sensitive to the addition of salts. They preserve their zwitterionic character in a wide range of pH [17] and the transition to polyelectrolyte behaviour can be achieved only at low or high

---

* Corresponding author.

$$x \ CH_2=CH \ + \ x \ CH_2=CH \xrightarrow[\text{60°C}]{\text{AIBN}}$$

I

$$\text{I} \ + \ \ldots$$

II

$$\text{II} \ + \ H_2C-CH_2 \longrightarrow$$

III

R	III
$-C_6H_5$	III_S
(pyrrolidone ring structure)	III_P

Scheme 1.

pH [18]. Since the anion and cation of each pair are covalently bonded to each other they give rise to intragroup or associative intra- or inter-chain dipole–dipole interactions. These interactions lead to both collapse and aggregation of the polymer chains [3,7,9,16,17]. Therefore, they act as ionic crosslinks and cause insolubility of most polysulfobetaines.

Dipole–dipole interactions can be effectively screened by ions of low molar mass electrolytes. They render polysulfobetaines soluble in aqueous solutions and enable studies on phase behaviour and hydrodynamic properties [7,8,17,19]. The binding ability of sulfobetaine ions follows the Pearson principle [20] of "soft" and "hard" ion interactions. The "soft" quaternary ammonium and sulfonate ions bind more effectively to large and highly polarizable counterions [17,19]. The chain extension of polysulfobetaines in the

presence of different electrolytes reflects the degree of the site binding interaction of salt ions and zwitterions. Intrinsic viscosities of polysulfobetaines are increasing functions of the salt concentration indicating that the charge screening upon addition of salt yields better solvated chains [5,16,17,19]. From light scattering and viscosity measurements Galin et al. [17] inferred that aqueous salt solutions are very poor solvents for polyzwitterions.

The present article deals with the synthesis and aqueous solution behaviour of sulfobetaine copolymers with different backbone structures. The aim was to introduce dimethylamine groups in the side chains of alternating copolymer precursors of phthalimidoacrylate (IA) with styrene (S) or *N*-vinyl-2-pyrrolidone (VP) and subsequently to quaternize these groups with 1,3-propanesultone. The influence of the backbone structure on the aqueous solution properties of the

synthesized sulfobetaine copolymers is the main interest in this article.

2. Experimental

2.1. Materials

All reagents were obtained from Aldrich. S and VP were distilled and stored over CaH$_2$. 3-Dimethylaminopropylamine was distilled prior to use. N,N-Dimethylformamide (DMF) was dried over P$_2$O$_5$ and distilled under vacuum. 1,3-propanesultone was used as received. Phthalimidoacrylate was synthesized as previously described [21].

2.2. Polysulfobetaine synthesis

Scheme 1 illustrates the synthesis of precursor copolymers (**I**), copolymers bearing tertiary amine groups in the side chains (**II**) and polysulfobetaines (**III**).

2.2.1. Precursor copolymers (**I**)

IA and S or VP were copolymerized at equimolar ratio in DMF solution at 60°C in the presence of AIBN. The composition of poly(IA-co-S) was determined by ^{1}H-NMR from the relative intensities of IA and S aromatic protons. The composition of poly(IA-co-VP) was determined by spectrophotometry in DMF solution from the absorption of the phthalimido units at 295 nm [22]. The mole fraction of each monomer in the synthesized copolymers was equal to 0.5. Copolymers with the following characteristics were synthesized:

Poly(IA-co-S): $M_n = 72\ 000$ g mol^{-1}, $M_w = 100\ 000$ g mol^{-1} (from GPC analysis in THF using polystyrene standards);

Poly(IA-co-VP): $M_n = 16\ 000$ g mol^{-1}, $M_w = 23\ 000$ g mol^{-1} (from GPC analysis in DMF using polystyrene standards).

2.2.2. Copolymers bearing tertiary amine groups in the side chains (**II**)

In a typical reaction, a solution of 3-dimethylaminopropylamine (0.11 mol) in 120 ml of DMF was added dropwise with stirring under N$_2$ to poly(IA-co-S) (12 g, 0.037 mol of ester groups) dissolved in 60 ml of DMF. The mixture was then heated at 95°C for 4 h. DMF was evaporated under vacuum. The residue was extracted with CHCl$_3$, then dissolved in methanol and treated with 0.1 M KOH in methanol. The product was precipitated in acetone and purified by dissolving in methanol and reprecipitating in acetone. Yield 10.7 g (89%).

The VP-based copolymer **II** was obtained as above but the product was precipitated in diethyl ether.

2.2.3. Sulfobetaine copolymers (**III**)

In a typical reaction, **II** (0.019 mol of tertiary amine groups) and 50 ml of DMF were stirred at 65°C under N$_2$ until complete dissolution. The solution was then cooled to room temperature and 1,3-propanesultone (0.021 mol) dissolved in 25 ml of DMF was added dropwise with stirring. The reaction was conducted at room temperature for 2 h and then at 60°C for 3 days. The solvent was evaporated under vacuum, the residue extracted with acetone and dried at 60°C under 10^{-2} torr. The copolymers were stored in a desicator and were further dried before analysis.

Anal. calcd for C$_{19}$H$_{30}$N$_2$O$_4$S (**III$_S$**): C, 59.79%; H, 7.85%; N, 7.33%; S 8.38%; found: C, 54.61%; H, 7.76%; N, 6.84%; S, 7.5%. Degree of sulfobetaine formation 89%.

Anal. calcd for C$_{17}$H$_{31}$N$_3$O$_5$S (**III$_P$**): C, 52.44%; H, 7.97%; N, 10.80%; S, 8.22%; found: C, 53.60%; H, 8.02%; N, 11.35%; S, 7.41%. Degree of sulfobetaine formation 90%.

3. Characterization

The IR spectra were recorded on a Bruker Vector 22 spectrometer. The UV spectra were measured using a Carl Zeiss Specord UV VIS spectrophotometer. The ^{1}H-NMR spectra were taken on a Bruker 250 MHz instrument. GPC measurements in THF and DMF were performed on Ultrastyragel columns. The aqueous GPC analyses were performed on Suprema 1000 and Suprema 30 columns at a flow rate of 0.8 ml min^{-1} at 30 and 50°C.

3.1. Viscosity measurements

Solution viscosities were determined with an Ubbelohde viscometer at 30°C. Solvent flow time always exceeded 250 s. Stock solutions of the salt were prepared by dissolving the appropriate amount of the salt in deionized water. Sulfobetaine copolymers were dissolved in water or in the salt solutions to yield 0.25% stock solutions. These solutions were subsequently diluted with water or the appropriate salt solution.

Viscosity data for **III$_S$** were analyzed using the Huggins equation [23]

$$\eta_{sp}/c = [\eta] + k_H[\eta]^2 c. \tag{1}$$

Intrinsic viscosities for **III$_P$** were determined using the modified Einstein–Simha equation:

$$\eta_{rel} = 1 + [\eta]c \tag{2}$$

proposed by Salamone et al. [24] for polymers which behave as suspensions.

3.2. Determination of critical micelle concentration (CMC) of **III$_S$**

The dye solubilization method of Alexandridis et al. [25] was employed to determine the CMC of **III$_S$** in water at
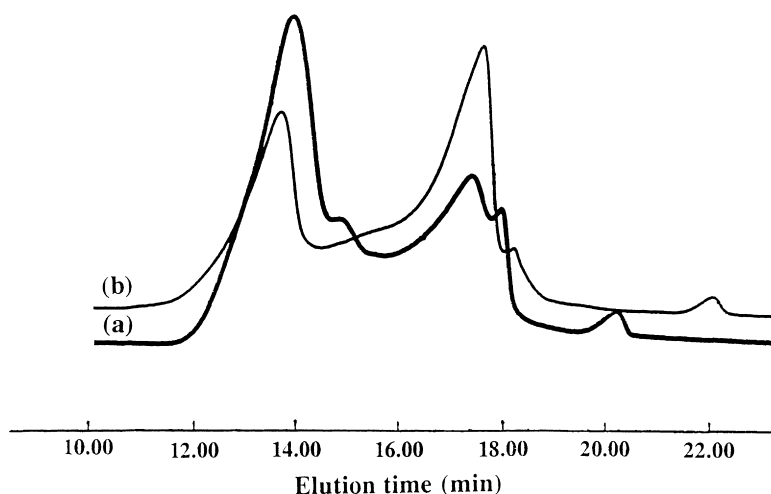
Fig. 1. GPC traces of **III**$_P$ aqueous solutions: (a) filtered solution and (b) solution diluted after filtration.

30°C. It is based on UV measurements of solutions of 1,6-diphenyl-1,3,5-hexatriene (DPH) in the presence of an increasing amount of the micelle-forming copolymer. Aqueous solutions of **III**$_S$ were prepared which contained 0.01–2 g copolymer in 100 ml. 25 μl of 0.4 mM DPH in methanol were added to 2.5 ml of the copolymer solution. The solutions were left in the dark before measurements. While DPH does not dissolve in water it solubilizes in micellar solution, giving a characteristic spectrum with absorption maximum at 356 nm. By plotting the intensity of this maximum vs. log concentration the CMC was evaluated from the first inflection of the respective curve. The uncertainty in the CMC value is less then 10%.

4. Results and discussion

4.1. Synthesis of sulfobetaine copolymers

Two sulfobetaine copolymers with either S or VP units in the backbone were synthesized according to the reaction sequence of Scheme 1. Copolymerization reactivity ratios of IA and S [21] or VP [22] were reported and it was found that by using an equimolar mixtures of the monomers a predominantly alternating copolymers are formed. The good leaving phthalimido groups on the copolymer precursors (**I**) were displaced by 3-dimethylaminopropylamine, thus preparing copolymers bearing tertiary amine groups in the side chains (**II**). The complete transformation from I to II was verified by IR and ^{1}H-NMR spectroscopy. The carbonyl absorptions for the phthalimido ester groups in the range of 1740–1815 cm^{-1} completely disappeared and the expected amide bands appear at 1660 cm^{-1} (C=O, amide **I**) and at 1548 cm^{-1} (N–H, amide **II**). The ^{1}H-NMR spectrum of **II** in D$_2$O did not show phthalimido resonances at 7.8 ppm even at 80°C, where the actual composition of a micelle-forming copolymer can be seen. Since the leaving

hydroxyphthalimide can quaternize the tertiary amine groups, a large excess of 3-dimethylaminopropylamine was used and the crude product was treated with methanolic KOH.

Copolymers **II** were quaternized with 1,3-propanesultone. The degrees of betainization were high (about 90%) as determined by elemental analyses. In the IR spectra of **III** characteristic absorptions for sulfonate groups appear at 1187 and 1038 cm^{-1} (S=O, stretch).

4.2. Aqueous solution properties of sulfobetaine copolymers III

4.2.1. Solution behaviour of III$_P$

The behaviour of **III**$_P$ in aqueous solutions was studied by GPC and viscometry. Although **III**$_P$ was insoluble in water at concentrations suitable for viscosity measurements we succeeded in GPC analysis of highly diluted solutions in deionized water and in salt solutions as well.

Fig. 1 shows the GPC traces of **III**$_P$ in deionized water at 30°C. Peaks at low and high elution times are observed which correspond to apparent molar masses of the order of 10^6 and 10^4, respectively. The relative intensities of the peaks are changed on dilution so that an increasing amount of the copolymer contributes to the lower mass peak (Fig. 1(b)). Apparently, an equilibrium between aggregates and molecularly dissolved chains was established. It was not affected by increasing the temperature up to 50°C, while addition of salts had a dramatic effect. Low molar mass electrolytes caused rupture of the aggregates, which disappeared in 0.08 M KCl solution.

The presence of zwitterionic groups in the side chains of polysulfobetaines governs their behaviour. It is dominated by attractive dipole–dipole interactions which may be of inter- or intramolecular type. While the intramolecular interactions lead to collapse of the polymer chains, the intermolecular associations result in aggregate formation. GPC
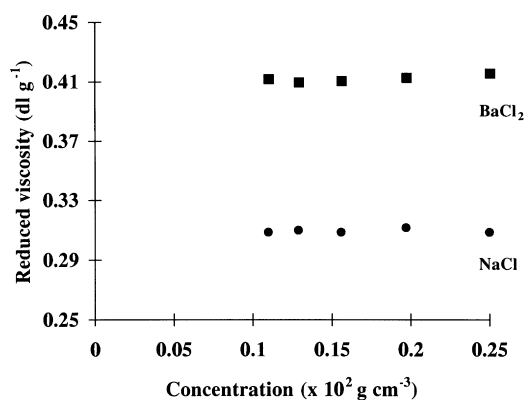
Fig. 2. Reduced viscosity as a function of $\mathbf{III}_P$ concentration in 0.5 M NaCl and 0.5 M BaCl$_2$ at 30°C.

provided evidence that the intermolecular dipole–dipole interactions can be effectively screened by the ions of the added salt. One can assume that the insolubility of $\mathbf{III}_P$ in deionized water is most likely a result of dipolar intermolecular interactions whose elimination at higher ionic strength promotes water solubility of $\mathbf{III}_P$. This phenomenon, which is known as the "antipolyelectrolyte" effect, is characteristic of most polysulfobetaines [3,5–11,17].

GPC data showed that $\mathbf{III}_P$ does not aggregate in aqueous solution on addition of a given amount of salt (>0.08 M). Since the viscometric measurements were carried out at higher salt concentrations all data reflect the changes in polymer dimentions arising from the screening of the intra-chain attractive forces by site-binding of salt ions with the zwitterions.

The reduced viscosity data described by Eq. (1) are plotted in Fig. 2. It can be seen that the data do not fit the linear relation defined by the Huggins Eq. (1). The reduced viscosities are insensitive to the polymer concentration. The behaviour is typical for hard-sphere suspensions and for such systems the viscosity data may be analyzed through a modified form of the Einstein–Simha equation (Eq. (2)) [24,26]. The corresponding plots are given in Fig. 3. The linearity of the data and an intercept value of 1 suggest that
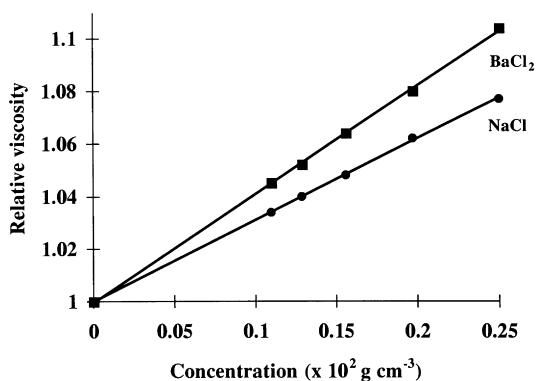

Fig. 3. Relative viscosity as a function of $\mathbf{III}_P$ concentration in 0.5 M NaCl and 0.5 M BaCl$_2$ at 30°C.

$\mathbf{III}_P$ behaves as a suspension in aqueous salt solutions. Since salt solutions are poor solvents for polysulfobetaines [17] the polymer chains would be in a collapsed conformation which results in the low values of the intrinsic viscosities (Tables 1 and 2). Increasing the salt concentration or using different salt solutions does not change the polymer behaviour.

$\mathbf{III}_P$ shows an enhancement of the intrinsic viscosity as the concentration of the salt is increased (Table 1). As anticipated, this behaviour results from a shielding of the intra-chain dipolar interactions and extension of the polymer chain. The dependence of the intrinsic viscosity on the nature of the added ions reflects the site-binding of the salt ions to the zwitterions (Table 2). For a given concentration of added salt the trend of increasing viscosity follows the order of increasing "softness" of the salt ions. According to the Pearson principle [20] "hard" acids and bases are small radii slightly polarizable species while "soft" acids and bases are larger highly polarizable species. "Hard" ("soft") acids prefer to bind to "hard" ("soft") bases. Since the quaternary ammonium cation and the sulfonate anion are "soft" ions they are more easily attracted by larger and polarizable counterions.

The data collected in Table 2 show that the intrinsic viscosity of $\mathbf{III}_P$ in 0.5 M salt solutions containing common cations increases in the order:

$$Cl^- < Br^- < I^- = SCN^- (K^+)$$

$$Cl^- < ClO_4^- (Na^+).$$

This is the sequence of increasing the "softness" of the anions and their attraction by the quaternary ammonium group.

For a common anion the increase of the cationic radius leads to increasing intrinsic viscosity (Table 2). Substituting the divalent Ba^{2+} cation for Na^+ or K^+ had a larger effect on the viscosity enhancement compared to that of increasing the "softness" of the anion.

The behaviour of $\mathbf{III}_P$ in aqueous salt solution shows that the copolymer chains are weakly solvated. The insignificant chain expansion in the presence of "soft" ions reflects the strength of the intramolecular dipolar interactions which cannot be effectively screened by the added ions.

4.2.2. Solution behaviour of $\mathbf{III}_S$

In contrast to the VP-based sulfobetaine copolymer, $\mathbf{III}_S$ contains S units in the main chain which give rise to hydrophobic interactions in aqueous solution. The attractive interactions among the hydrophobic groups yield micellar structures which protect them from the unfavourable environment. The micelles are stabilized by the zwitterionic groups exposed to the aqueous phase. Their stability depends on the solvent quality and temperature.

The parameter of greatest importance for micellar solutions is the CMC, the copolymer concentration at which

Table 1
Effect of NaCl concentration on the intrinsic viscosity of III_P solutions at 30°C

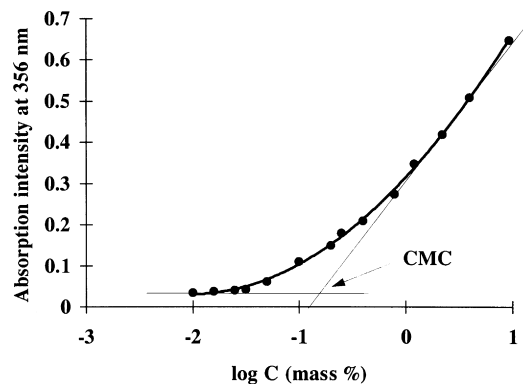| [NaCl] (mol l^{-1})	[η] (dl g^{-1})
0.10	0.230
0.25	0.290
0.50	0.310
1.00	0.309
2.00	0.285

Fig. 4. Effect of III_S concentration on the absorption intensity of DPH at 356 nm in aqueous solution at 30°C.

micelles start forming. One of the remarkable properties of the micellar solutions is the ability of the hydrophobic microdomains to dissolve water-insoluble chromophores. The partitioning of aromatic probes into hydrophobic microdomains is widely used to determine the onset of micellization by spectral methods. We followed the procedure proposed by Alexandridis et al. [25] to determine the CMC of III_S in water at 30°C. The UV absorption of DPH in water was measured in the presence of increasing amount of the micelle-forming zwitterionic copolymer. The absorption intensity at 356 nm was plotted against the log of the copolymer concentration (Fig. 4). The estimated value for CMC was 0.17 g dl^{-1}. The viscosity measurements were performed on solutions ranging from 0.25 to 0.1 g dl^{-1}. It may be inferred therefore that the negative slope of the concentration dependence of the reduced viscosity (Fig. 5) is due to dissociation of the micelles to unimers [27]. Addition of salt leads to decreases in [η] for the III_S solutions (Table 3).

In the hydrophobically modified zwitterionic copolymers the intramolecular hydrophobic and dipole–dipole interactions contribute to the collapse of the polymer chain. The zwitterionic groups form inner salts [7,9,16] and provide insufficient stabilization of the monomolecular micelles. Therefore, the polymolecular micelles appear more stable in deionized water. Upon salt addition the zwitterionic group becomes better solvated and a transition from intermolecularly associating system to monomolecular micelles occurs. The low [η] values of III_S in aqueous salt solutions reflect the compact structure of the monomolecular micelles. This interpretation is supported by the aqueous GPC analyses of III_S. While in deionized water aggregated species appear at low elution time, only compact non-aggregated species appear in aqueous salt solutions (Fig. 6).
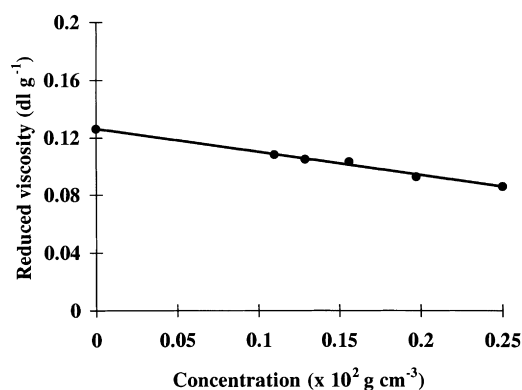

Fig. 5. Reduced viscosity as a function of III_S concentration in deionized water at 30°C.

5. Conclusions

Sulfobetaine copolymers with different backbone structures can be synthesized by a two-step modification of precursor copolymers containing phthalimidoacrylate units. Ester substitution with 3-dimethylaminopropylamine, followed by quaternization with 1,3-propanesultone, yields sulfobetaine copolymers with a high degree of betainization. The sulfobetaine copolymer containing N-vinyl-2-pyrrolidone in the main chain dissolves only in aqueous salt solutions and exists as aggregates. Increasing the salt concentration and the "softness" of the salt ions results in a slight increase of the intrinsic viscosity. The behaviour of this sulfobetaine copolymer is governed by strong

Table 2
Intrinsic viscosity of III_P in 0.5 M aqueous salt solutions at 30°C

Potassium salts		Sodium salts		Chlorides	
Anion	[η] (dl g^{-1})	Anion	[η] (dl g^{-1})	Cation	[η] (dl g^{-1})
Cl$^-$	0.360	Cl$^-$	0.310	Na$^+$	0.310
Br$^-$	0.385	ClO$_4^-$	0.396	K$^+$	0.360
I$^-$	0.394			Ba^{++}	0.423
SCN$^-$	0.400				

Table 3
Variation of the intrinsic viscosity of III_S as a function of added salt (0.25 mol l^{-1}) at 30°C

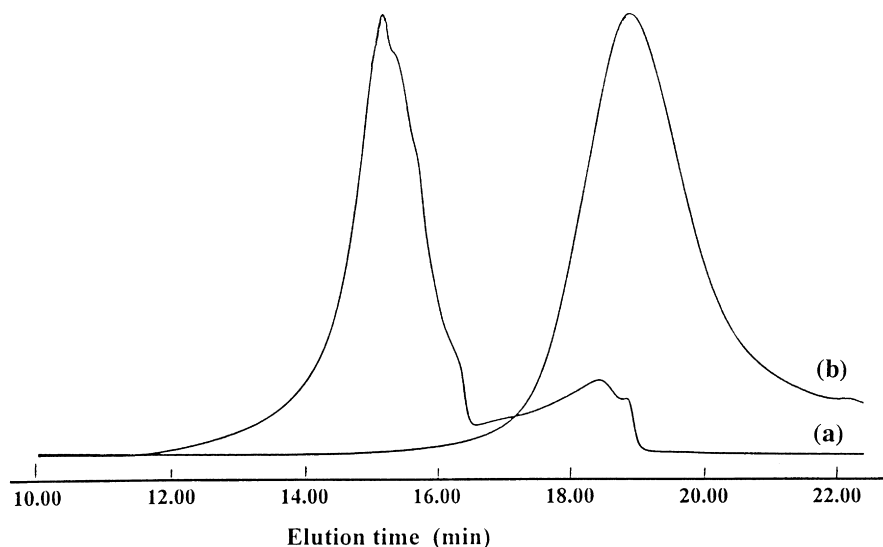| Salt	[η] (dl g^{-1})
–	0.126
KCl	0.032
KBr	0.054
KI	0.057

Fig. 6. GPC traces of **III**$_S$ in: (a) deionized water and (b) 0.04 M KCl.

intramolecular interactions which prevail over the site binding of the salt ions to the zwitterions. In contrast, in water the styrene-based sulfobetaine copolymer gives a micellar solution whose intrinsic viscosity decreases in the presence of a salt.

Acknowledgements

References

[1] Hart R, Timmerman D. J Polym Sci 1958;28:638.
[2] Hoover MF. J Macromol Sci A 1970;4:1327.
[3] Salamone JC, Volksen W, Israel SC, Olson AP, Raia DC. Polymer 1977;18:1058.
[4] Monroy Soto VM, Galin JC. Polymer 1984;25:121.
[5] McCormick CL, Salazar LC. Polymer 1992;33:4617.
[6] Wielema TA, Engberts JBFN. Eur Polymer J 1987;23:947.
[7] Schulz DN, Peiffer DG, Agarwal PK, Larabee J, Kaladas JJ, Soni J, Handwerker B, Garner RT. Polymer 1986;27:1734.
[8] Lee WF, Tsai CC. Polymer 1994;35:2210.
[9] Schulz DN, Kitano K, Danik JA, Kaladas JJ. Polymers in aqueous media, Ch. 9. In: Glass JE, editor. Advances in Chemistry Series No. 223, Washington, DC: American Chemical Society, 1989.
[10] Kathmann EEL, Davis DD, McCormick CL. Macromolecules 1994;27:3156.
[11] Kathmann EEL, White LA, McCormick CL. Macromolecules 1997;30:5297.
[12] Zheng YL, Galin M, Galin JC. Polymer 1988;29:724.
[13] Lowe AB, Billingham NC, Armes SP. Chem Commun 1996;1555.
[14] Tuzar Z, Pospisil H, Plestil J, Lowe AB, Baines FL, Billingham NC, Armes SP. Macromolecules 1997;30:2509.
[15] Vamvakaki M, Billingham NC, Armes SP. Polymer 1998;39:2331.
[16] Lee WF, Lee CH. Polymer 1997;38:971.
[17] Monroy Soto VM, Galin JC. Polymer 1984;25:254.
[18] Koňak Č, Rathi RC, Kopečková P, Kopeček J. Macromolecules 1994;27:1992.
[19] Lee WF, Tsai CC. Polymer 1995;36:357.
[20] Pearson RG. J Chem Edu 1968;45:581.
[21] Berlinova IV, Amzil A, Vladimirov NG. J Polym Sci, Part A: Polym Chem Ed 1995;33:1751.
[22] Nazarova OV, Solovskij MV, Panarin EF, Denisov VM, Khachaturov AS, Koltsov AI, Purkina AV. Eur Polym J 1992;28:97.
[23] Huggins ML. J Am Chem Soc 1942;64:2716.
[24] Salamone JC, Tsai CC, Olson AP, Watterson AC. Ions in polymers, Ch. 22. Advances in Chemistry Series No. 187. Washington DC: American Chemical Society, 1980.
[25] Alexandridis P, Holzwarth JF, Hatton TA. Macromolecules 1994;27:2414.
[26] Ezzell SA, McCormick CL. Macromolecules 1992;25:1881.
[27] Watterson JG, Lasser HR, Elias H-G. Kolloid Z.U. Z-Polymere 1972;250:64.