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Synthesis and Solution Properties of Zwitterionic Polymers[†]

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Contents

I. Introduction

Polymers containing ionic groups are among the most important classes of macromolecules. These types of polymers range from naturally occurring biopolymers such as proteins and nucleotides to synthetic viscosifiers and soaps. Ionic polymers may be divided into two groups, polyelectrolytes[1−4] and polyzwitterions. Polyelectrolytes contain anionic *or* cationic groups, while polyzwitterions contain *both* anionic and cationic groups. Polyzwitterions have a wide variety of applications that include ion exchange, chelation to bind trace metals (Hg, Cd, Cu, and Ni) from drinking water, sewage treatment, soil conditioning, paper reinforcement, pigment retention, and formulation in shampoos and hair conditioners.[5]

A characteristic of polyelectrolytes is chain extension, and thus large hydrodynamic volume, in deionized water at low concentrations. This is due to Coulombic repulsions between charged groups along the polymer chain, forcing the polymer into an extended rodlike conformation. The addition of low molecular weight electrolyte or changes in solution pH screens the repulsive electrostatic forces, and the polymer coil shrinks, adopting a more entropically favored conformation. This is known as the *polyelectrolyte effect*.[6]

For polyzwitterions, the charges may be located either on the pendent side chains of different monomer units or the same monomer unit, or in the case of some polyesters,[7] polyphosphazenes,[8] and polyphosphobetaines,[9] one or both of the charges may be located along the polymer backbone. It is perhaps prudent at this time to clarify the nomenclature regarding these different polymeric species. The distinction between zwitterionic polyampholytes and polybetaines is not always clear from the literature. For this review, the term polyzwitterion includes *all* polymers that possess both cationic and anionic groups. Polyampholyte refers to those polymers that specifically possess the charged groups on *different* monomer units, while polybetaine refers to those polymers with the anionic and cationic groups on the *same* monomer unit.

The solution behavior of polyzwitterions is often opposite that of polyelectrolytes, exhibiting the so-called *antipolyelectrolyte effect*. Chain expansion occurs upon the addition of low molecular weight electrolyte, although this is very much dependent upon chemical structure, composition, and solution conditions (see later text).

II. Synthesis of Polyampholytes

Polyampholytes are interesting for numerous reasons, not the least of which is the fact that they are synthetic analogues of naturally occurring biological molecules such as proteins and find applications in areas such as lithographic film,[10] emulsion formulations,[11] and drag reduction.[12] The structure−property relationships of polyampholytes are dictated by Coulombic attractions between anionic and cationic species on different monomer units. The response in aqueous solution exhibited by polyampholytes is very much dependent upon both the chemical structure and composition of the polymer. There exist four subclasses of polyampholytes based on their responses to changes in pH as described previously.[13] First, the polyampholyte may contain both anionic and cationic species that may be neutralized (Figure 1a). Second, the anionic group may be neutralized while the cationic species is insensitive to changes in pH (Figure 1b). Third, the cationic species may be neutralized while the anionic species is insensitive to changes in pH (Figure 1c). Finally, both the anionic and cationic species may be insensitive to changes in solution pH over the useful range.

Synthetic polyampholytes were first reported in the 1950s.[14−21] All of these examples were synthesized via conventional free radical polymerization techniques. Examples include the methacrylic acid-*stat*-2-(dimethylamino)ethyl methacrylate copolymers reported by Ehrlich and Doty,[18] the acrylic acid-*stat*-2-vinylpyridine copolymers reported by Alfrey and Morawetz,[15] and the acrylic acid-*stat*-2-(diethylamino)ethyl methacrylate copolymers reported by Alfrey and Pinner.[17] Since these early publications, numerous workers have reported on the synthesis and

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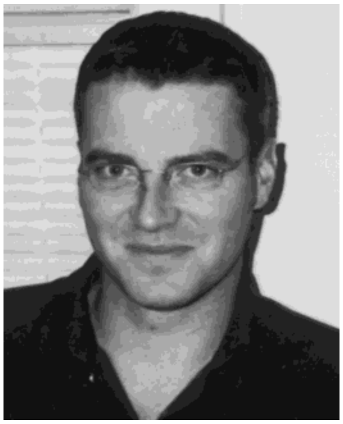

Andrew B. Lowe received his B.Sc. (Hons) degree in chemistry (1993) and his D.Phil. degree (1997) at the University of Sussex, where he worked on the controlled synthesis of water-soluble polymers via group-transfer polymerization under the direction of Profs. Steven Armes and Norman Billingham. After a one year postdoctoral position, also at The University of Sussex, he moved to the Department of Polymer Science at the University of Southern Mississippi, where he worked as a senior postdoctoral research associate under Prof. Charles McCormick. As of June 2002, he has assumed the position of Assistant Professor in the Department of Chemistry and Biochemistry also at the University of Southern Mississippi. His research interests cover water-soluble polymers, controlled radical polymerizations, supramolecular self-assembly, biocompatible polymers, and biomimetic polymers.

Charles L. McCormick is a professor of polymer science and of chemistry and biochemistry at the University of Southern Mississippi, where he has mentored 34 Ph.D. students and published over 150 manuscripts in the areas of water-soluble polymers and biopolymers. He received his B.S. degree in chemistry in 1968 from Millsaps College and his Ph.D. degree in 1973 from the University of Florida under the direction of Professor George Butler. Professor McCormick is a recipient of the Bennett Distinguished Research Professorship and has been a visiting professor at Cambridge University and at the Royal Institute of Technology. His current research interests include water-soluble polymers, the chemistry of naturally occurring polysaccharides, phase-transfer polymeric micelles, and recombinant DNA technologies to tailor water-soluble proteins.

properties of a wide range of statistical polyampholytes; see Figure 2.[22−36]

For example, McCormick and Johnson have reported extensively on ampholytic copolymers comprised of acrylamido-based monomers.[22,23,37−40] Low charge density statistical terpolymers of 2-acrylamido-2-methylpropanedimethylammonium chloride, 2-acrylamido-2-methylpropanesulfonate, and acrylamide were synthesized in aqueous solution, using potassium persulfate as the free radical initiator.[38] The total ionic content of the terpolymers was at, or below, 30 mol %. Weight-average molecular weights, as determined by static light scattering, were in the range ∼(1.0−12.0) × 10^6.

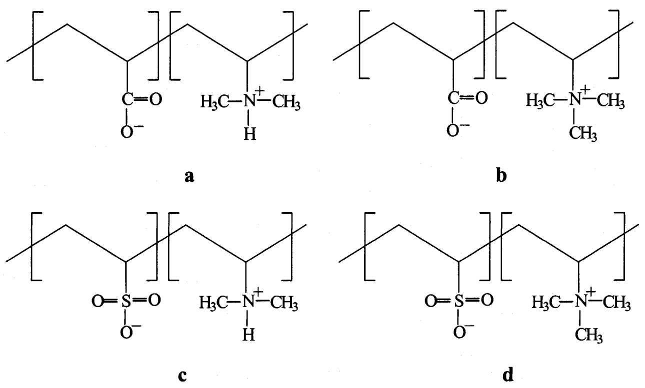

Figure 1. Representative structures of the four subclasses of polyampholytes. Reprinted with permission from ref 13. Copyright 1996 CRC Press Inc.

Stille's group, in the early 1970s, was the first to report the synthesis of block polyampholytes, via anionic polymerization.[41,42] These were block copolymers of 2-vinylpyridine (2VP) with trimethylsilyl methacrylate (TMSMA). The poly(TMSMA) (PTMSMA) residues were readily hydrolyzed to poly(methacrylic acid) (PMAA) with a water/methanol mixture. These block copolymers were evaluated as desalination membranes. Subsequently, Varoqui, Tran, and Pefferkorn[43] synthesized AB diblock polyampholytes of poly(styrenesulfonate−2VP). The styrenesulfonate residues were introduced by sulfonation of a precursor styrene-*block*-2VP copolymer, to a degree of 96%. Subsequently, Morishima et al.[44] reported the synthesis of block copolymers of TMSMA with *p*-*N*,*N*′-dimethylaminostyrene, and Bekturov et al.[45,46] described the synthesis and aqueous solution behavior of poly(1-methyl-4-vinylpyridinium chloride-*block*-methacrylic acid). Creutz et al.[47,48] have described the synthesis of block copolymers of methacrylic acid with (dimethylamino)alkyl methacrylate comonomers. These were synthesized by anionic polymerization using *tert*-butyl methacrylate (TBMA) as a protected precursor to the poly(methacrylic acid) residues.

Until recently, classical anionic polymerization apparently offered the most attractive route to block polyampholytes. In 1994 Patrickios et al.[49,50] reported the synthesis of diblock, triblock, and statistical methacrylic polyampholytes utilizing group transfer polymerization (GTP).[51] As with anionic polymerization, monomers with labile protons, i.e., MAA, could not be directly polymerized, and protected acid monomers were required. Of four generally suitable protected acid monomers (TMSMA,[52,53] 2-tetrahydropyranyl methacrylate[54,55] (THPMA), benzyl methacrylate[56,57] (BZMA), and TBMA[58]), Patrickios et al. selected TMSMA and THPMA. TMSMA was chosen in view of its commercial availability and ease of conversion, via methanolysis, to MAA, and THPMA due to its facile conversion to MAA either in the solid state (thermolysis) or in solution (very mild acid hydrolysis). However, the acid hydrolysis route was not explored. The protected MAA monomers were copolymerized with 2-(dimethylamino)ethyl methacrylate (DMAEMA), and in the case of the triblocks,

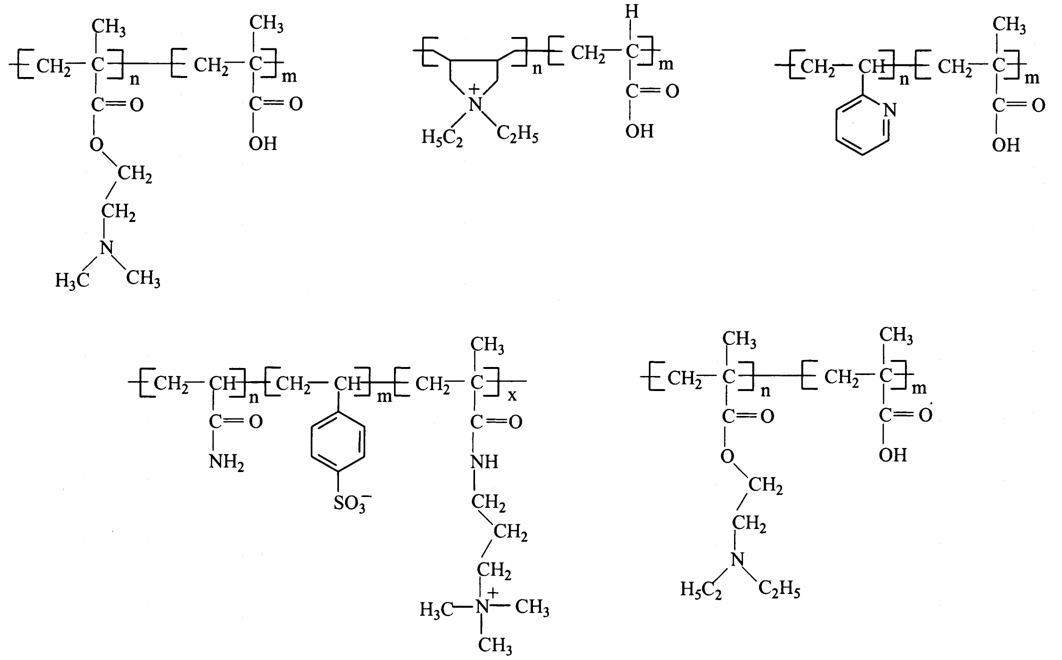

Figure 2. Some representative chemical structures of statistical polyampholytes that have been synthesized.

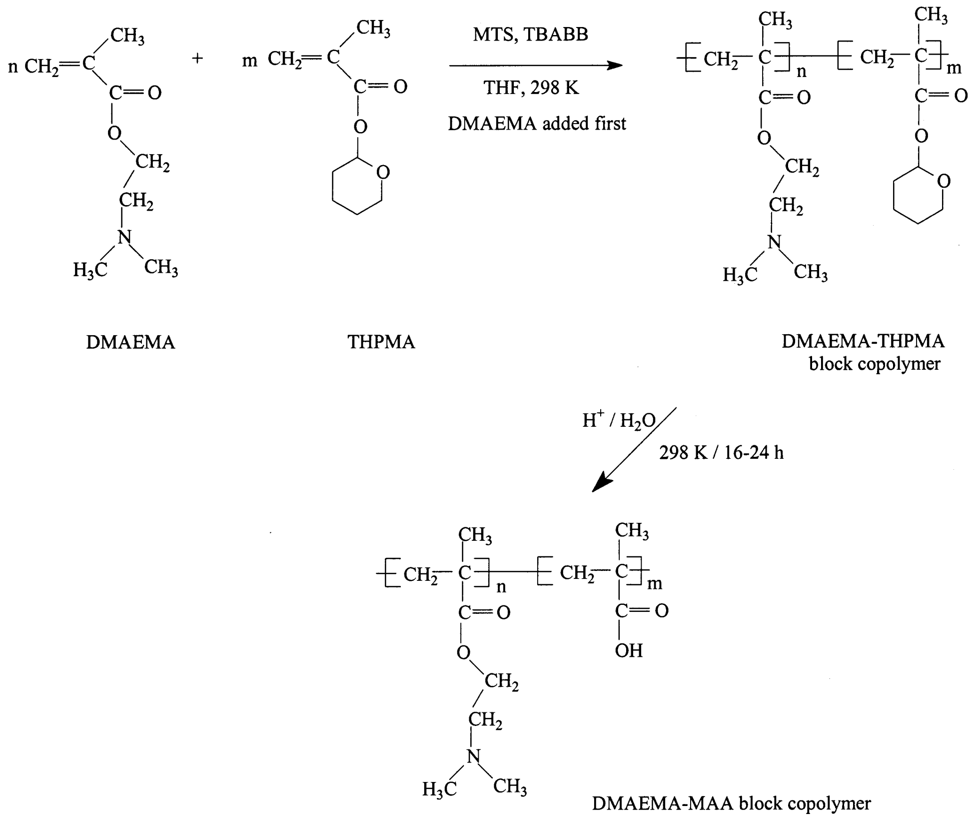

Figure 3. Reaction scheme for the synthesis of DMAEMA−MAA polyampholytic block copolymers via GTP. Reprinted with permission from ref 60. Copyright 1997 The Royal Society of Chemistry.

methyl methacrylate (MMA) was introduced as the third hydrophobic comonomer. Subsequently, Lowe, Billingham, and Armes[59−61] synthesized AB diblock copolymers of DMAEMA with MAA using THPMA as a protected precursor, Figure 3.

Conversion to the PMAA residues was achieved via acid hydrolysis at room temperature. In contrast, the deprotection route favored by Patrickios et al.[49] (thermolysis of the THPMA residues—145 °C, 48 h, in vacuo) was shown to be unsatisfactory. It was demonstrated that prolonged thermolysis of a PTHPMA homopolymer led to significant dehydration of the PMAA residues, resulting in inter- and intramolecular methacrylic anhydride formation,[57] a phenomenon that had been observed and reported previously.[62,63]

Goloub, de Keizer, and Cohen-Stuart[64] recently reported similar DMAEMA−MAA diblock copolymers. Precursor diblock copolymers of DMAEMA–TBMA were synthesized by anionic polymerization, with subsequent acid hydrolysis of the TBMA residues. Patrickios and Lowe[65] have also synthesized the ABC, ACB, and BAC topological triblock isomers of DMAEMA, THPMA, and MMA via GTP. The THPMA residues were converted to MAA residues by mild acid hydrolysis, yielding the triblock polyampholytes. Other examples of terpolyampholytes include those reported by Giebeler and Stadler[66] and Ge et al.[67]

The recent developments in controlled free radical polymerization techniques, such as stable free radical polymerization (SFRP), best exemplified by nitroxide-mediated polymerization (NMP),[68,69] atom-transfer radical polymerization (ATRP),[70–74] and reversible addition–fragmentation chain-transfer (RAFT) polymerization,[75–79] allow for direct synthesis of many polyampholytic block copolymers without the need for protecting group chemistry. All of the above techniques allow for the synthesis of block copolymers, either by sequential monomer addition, or by isolation of the first block, which is subsequently used as a "macroinitiator" for the second block. Each technique has advantages and disadvantages depending on monomer types and specific functional groups. For example, Ashford et al.[80] reported the direct aqueous polymerization, by ATRP, of sodium methacrylate. Similarly, McCormick and co-workers have polymerized sodium acrylate[81] directly in aqueous solution via RAFT as well as the anionic acrylamido monomers 2-acrylamido-2-methylpropanesulfonic acid (AMPS) and 3-acrylamido-3-methylbutanoic acid (AMBA).[82] Sodium 4-styrenesulfonate has been polymerized by RAFT[76,83] and SFRP.[84–87] DMAEMA has been polymerized by RAFT,[75] SFRP,[88] and ATRP,[89,90,91] and the polymerization of 4-vinylpyridine has been reported by ATRP.[92] However, very little is in the literature at present regarding the synthesis of polyampholyte block copolymers utilizing pseudo living free radical techniques. Gabaston et al.[86] have described the TEMPO-mediated polymerization of block copolymers comprising sodium 4-styrenesulfonate (first block) and 4-(dimethylamino)methylstyrene (second block), and Donovan, Lowe, and McCormick[93,94] have prepared AB diblock copolymers of DMAEMA with acrylic acid (AA) via RAFT. DMAEMA was polymerized in THF in the presence of benzyl dithiobenzoate. The DMAEMA homopolymer was subsequently used as a macro-chain-transfer agent for the aqueous polymerization of AA.

III. Aqueous Solution Properties of Polyampholytes

In this section we will review certain experimental results regarding the solution properties of polyampholytes. Theoretical models will not be presented since several recent papers have dealt with the theoretical treatment of synthetic polyampholytes in aqueous solution.[95–101]

The aqueous solution behavior of polyampholytes is dictated by Coulombic interactions between anionic and cationic species located on different monomer units. Polyampholytes have the ability to demonstrate both polyelectrolyte and antipolyelectrolyte behavior depending on factors such as solution pH, copolymer composition, the absence/addition of low molecular weight electrolyte, and the relative strengths of the acidic and basic residues.

A characteristic feature of polyampholytes (in particular those that are composed of weak acid and base species) is that they possess an *isoelectric point* (IEP, p*I*). The IEP is defined as the pH at which the polyampholyte is electrically neutral.[14] The solubility of a polyampholyte at the IEP is very much dependent upon the copolymer architecture and composition. For example, statistical polyampholytes tend to be soluble at the IEP, whereas block polyampholytes tend to be soluble above and below the IEP, but precipitate at/around this critical pH.[102] IEPs may be determined experimentally—typically by titration, or by measuring the reduced viscosity. For example, Ascoli and Botré[27] measured the reduced viscosity, as a function of pH, for a statistical polyampholyte composed of *N*,*N*-diethylallylamine and acrylic acid, Figure 4.

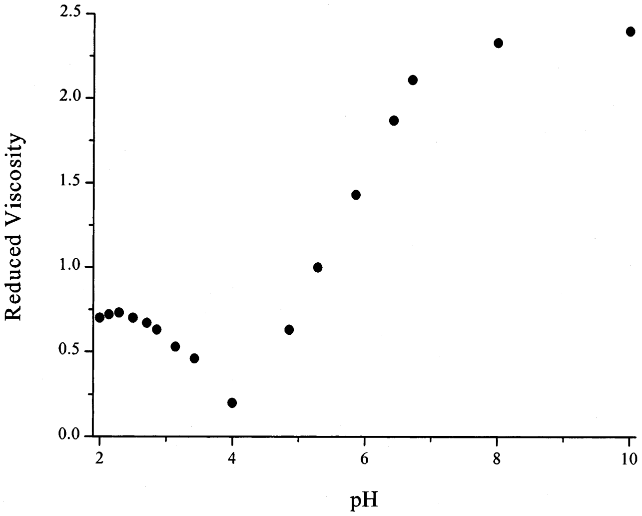

Figure 4. Reduced viscosity versus pH of a solution of 0.4 g/100 mL of the *N*,*N*-diethylallylamine–acrylic acid polyampholyte. Reprinted with permission from ref 27. Copyright 1962 John Wiley & Sons, Inc.

The IEP represents the pH at which the polyampholyte is electrically neutral; also at this point the copolymer is in its most compact conformation as reflected by the minimum in reduced viscosity (η_{sp}/c). The low value of p*I* indicates that the copolymer is acrylic acid rich. As the pH is adjusted from the p*I* (either above or below) the reduced viscosity increases. The polyampholyte becomes either predominantly positively (lower pH) or negatively (higher pH) charged. Electrostatic repulsive forces progressively dominate the attractive interactions, and the copolymer coil expands as the copolymer behaves as a polyelectrolyte.

It is also possible to predict the IEP theoretically.[103] It can be shown that

$$\mathrm{p}I = \mathrm{p}K_b + \log\{(1/2)[(1 - R)/R + [((1 - R)R)^2 + (4/R) \times 10^{\mathrm{p}K\mathrm{a}-\mathrm{p}K\mathrm{b}}]^{1/2}]\} \quad (1)$$

where $\mathrm{p}K_b = -\log K_b$, where $K_b =$ the equilibrium dissociation constant for basic residues, $pK_a = -(\log K_a)$, where K_a = the equilibrium dissociation constant for acidic residues, and R = the ratio of acidic to basic residues. Equation 1 is useful in instances where $R < 1$, i.e., for base-rich polyampholytes. An equivalent form for acid-rich copolymers ($R > 1$) is given by eq 2,

$$pI = pK_a + \log\{(1/2)[(1 - R)/R + [((1 - R)R)^2 + (4/R) \times 10^{pKa - pKb}]^{1/2}]\} \quad (2)$$

as was first proposed by Ehrlich and Doty in 1954,[18] but was only solved recently by Patrickios.[103] At certain compositional ratios, specifically $R = 1$, 1/2, and 2, calculation of the theoretical IEP is significantly easier. When $R = 1$ (equal number of acidic and basic residues)

$$pI = (pK_a + pK_b)/2 \quad (3)$$

i.e., the isoelectric point is simply the arithmetic average of the respective pK_a and pK_b values of the acidic and basic residues. At $R = 2$ (twice as many acidic residues as basic)

$$pI = pK_a \quad (4)$$

and at $R = 1/2$ (twice as many basic residues as acidic)

$$pI = pK_b \quad (5)$$

Table 1 lists the calculated and theoretical IEPs for a series of DMAEMA−MAA block copolymers of varying composition.[61]

Table 1. Calculated and Observed Isoelectric Points for a Series of Zwitterionic DMAEMA−MAA Block Copolymers

block copolymer composition,[a] DMAEMA:MAA	calcd IEP[b]	obsd IEP[c]	block copolymer composition,[a] DMAEMA:MAA	calcd IEP[b]	obsd IEP[c]
77:23	8.52		51:49	6.86	6.74
82:18	8.65	8.56	43:57	5.83	5.62
64:36	7.89	7.40			

[a] As determined by ^{1}H NMR spectroscopy. [b] As determined using eqs 1 and 2. [c] As determined by hydrogen ion titration. The IEP was taken as the midpoint of precipitation.

In this particular example, the pK_a of MAA was taken as 5.35 and the pK_b of DMAEMA was 8.00, as reported by Merle.[104] Given the compositional heterogeneity in the block copolymers, and the associated experimental error in determining the onset of precipitation/redissolution, the agreement between the calculated and observed IEPs is excellent.

Di- and triblock polyampholytes are able to self-assemble in aqueous solution (above a critical concentration), forming a variety of spherical and non-spherical structures. Lowe, Billingham, and Armes described the aggregation behavior of DMAEMA−MAA block copolymers.[60,61] It was demonstrated, using dynamic light scattering and variable-temperature ^{1}H NMR spectroscopy, that the AB diblock copolymers undergo reversible aggregation, forming micelles with DMAEMA cores and MAA coronas, when the temperature of a 1% w/w aqueous solution is raised above the cloud point of the DMAEMA block (the pH was ~9.5 to ensure ionization of the methacrylic acid residues and deprotonate any quaternary amine residues). Gohy et al. have also described the aggregation behavior of MAA−DMAEMA block copolymers in aqueous media, as a function of pH and salt concentration.[105] The authors demonstrated the ability of the block copolymers to form aggregates with different morphologies depending on the pH and block copolymer composition using techniques such as dynamic light scattering and transmission electron microscopy.

Recently, the DMAEMA−MAA and precursor DMAEMA−THPMA diblock copolymers reported by Lowe, Billingham, and Armes[60,61] were used to prepare the first examples of zwitterionic shell cross-linked “Knedel” (SCK) micelles/nanoparticles in aqueous media.[106,107] So-called *type 1* and *type II* SCK micelles can be prepared. Type I micelles have anionic cores and cationic coronas, and type II micelles have cationic cores and anionic coronas. In both instances, the micelle coronas were cross-linked using 1,2-bis(2-iodoethoxy)ethane (BIEE). In the case of type I zwitterionic SCK micelles, reaction with BIEE involved quaternization of the DMAEMA residues in the corona, while for type II micelles, reaction with BIEE led to esterification of the MAA residues. These SCK micelles also exhibited IEPs very close to those of the precursor AB diblock copolymers (variations are due to the introduction of permanent cationic residues and the lowering of methacrylic acid content due to the reaction of the tertiary amine and methacrylic acid residues with BIEE, respectively).

Patrickios et al. described the micellization behavior of the three topological isomers of DMAEMA−MMA−MAA triblock polyampholytes.[65] It was demonstrated, by aqueous size exclusion chromatography, that the triblocks do form micelles in aqueous solution and that the size is dependent upon the block copolymer sequence.

An example of a potential application for synthetic polyampholytes is the purification/complexation of different proteins as described by Patrickios and coworkers.[108−110] Low molecular weight methacrylic triblocks of DMAEMA, MMA, and MAA, synthesized by GTP, were used in all the studies. For example, the interaction of soybean trypsin inhibitor (acidic protein), ribonulease A, and lysozyme (basic proteins) with the triblock polyampholytes was investigated.[110] The authors demonstrated that the triblock polyampholytes interact strongly with themselves and with the proteins. Precipitation of the polyampholyte−protein complexes occurs within a pH range dictated by the polyampholyte and protein net charges. This may offer an attractive route to protein separation. An added advantage is that the triblock polyampholyte is readily recovered by precipitation at its IEP.

In summary, there are certain characteristics that are typical of synthetic polyampholytes when examined in dilute aqueous solutions:

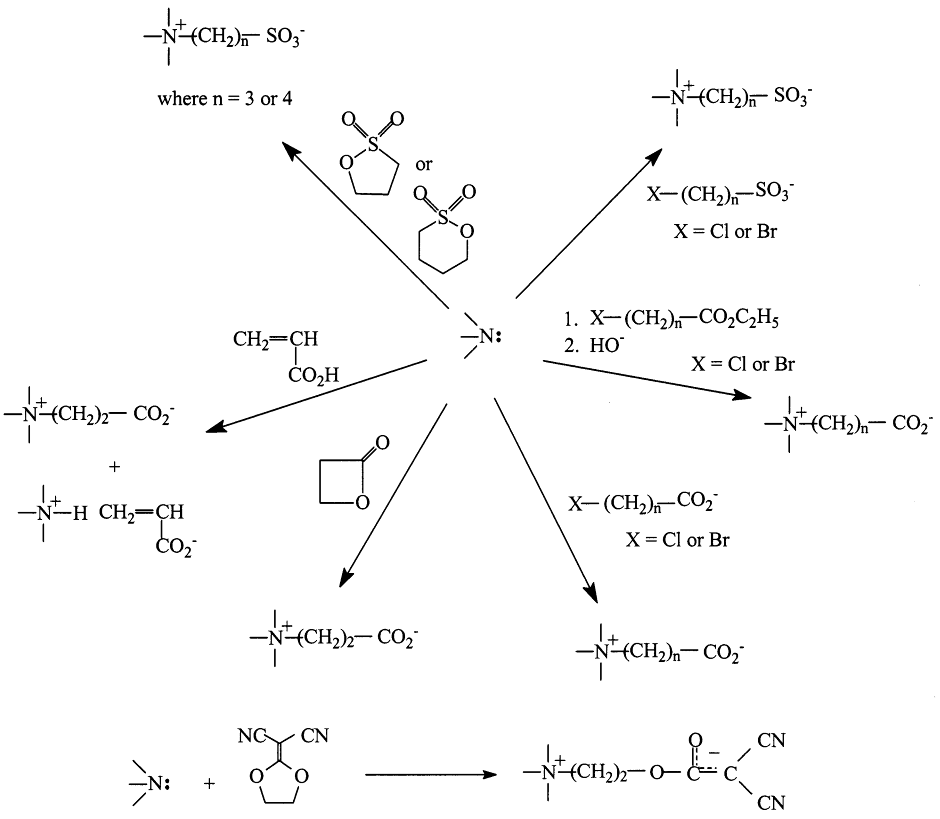

Figure 5. Synthetic routes to polysulfobetaines, polycarboxybetaines, and poly(ammonium alkoxydicyanoethenolates).

(1) Those that are highly hydrophobic, or as a rule possess block rather than statistical architectures, tend to precipitate at, or around, the isoelectric point.

(2) For polyampholytes with near charge balance, the addition of salt to an aqueous solution results in a viscosity enhancement and thus coil size increase. This is referred to as the antipolyelectrolyte effect.

(3) For polyampholytes with a large net charge (either positive or negative), the addition of salt results in a drop in solution viscosity and coil size. With large net charge, the polyampholytes behave like polyelectrolytes and thus exhibit the polyelectrolyte effect.

(4) The solution viscosity and coil size exhibit minima at/around the isoelectric point—the isoelectric point itself being dependent upon copolymer composition.

(5) Block polyampholytes may self-assemble to form more complex structures, such as polymeric micelles. The self-assembly process often requires judicious choice of block copolymer composition/molecular weight and solution conditions.

IV. Synthesis of Polybetaines

Polymeric betaines differ from polyampholytes in that both the cationic and anionic species are on the same monomer residue. Typically the cationic moiety is a quaternary ammonium, whereas the anionic species may be a sulfonate (sulfobetaines),[111] a carboxylate (carbo- or carboxybetaines),[112,113] a phosphate/phosphonate/phosphinate (phosphobetaines),[114] or some more exotic species such as the dicyanoethenolates reported by Pujol-Fortin, Galin, and Galin.[115] Betaines find wide-ranging applications as fungicides, fire-resistant polymers, lubricating oil additives, emulsifying agents, wetting agents in the cleaning industry, and cryoprotectants,[116−124] to mention a few.

Polymeric betaines may be synthesized in a number of ways. Sulfobetaines are typically prepared from the reaction of a tertiary amine (monomer or polymer) with a sultone, usually 1,3-propanesultone or 1,4-butanesultone.[125] Here the sultone is acting as an alkylsulfonating agent. Alternatively, they may be synthesized from the reaction of a tertiary amine with a haloalkylsulfonate.[126] Carboxybetaines may also be synthesized via a number of routes. The reaction of tertiary amine monomers/polymers with α,β-unsaturated acids (such as acrylic acid) can yield carboxybetaines, but often gives a mixture of betaine and salt products.[127] Alternatively, the tertiary amine species may be reacted with either haloalkylcarboxylates[128] or haloalkylcarboxylic esters.[129,130] Lactones (the carbon analogues of sultones) have also been utilized in the synthesis of polymeric carboxybetaines, Figure 5.[131] The polydicyanoethenolate betaines are synthesized by the reaction of a tertiary amine monomer/polymer with cyclic dicyanoethylene or propylene acetals, such as 2,2-dicyanoketene ethylene acetal, Figure 5.[132−134] Phosphobetaines may also be synthesized via a number of different routes, as discussed later.

Ladenheim and Morawetz reported the first example of a synthetic polybetaine in 1957.[135] This was a polycarboxybetaine based on poly(4-vinylpyridine) (P4VP). The first synthetic polysulfobetaines were reported shortly afterward by Hart and Timmerman.[136] 2VP and 4VP monomers were initially re-

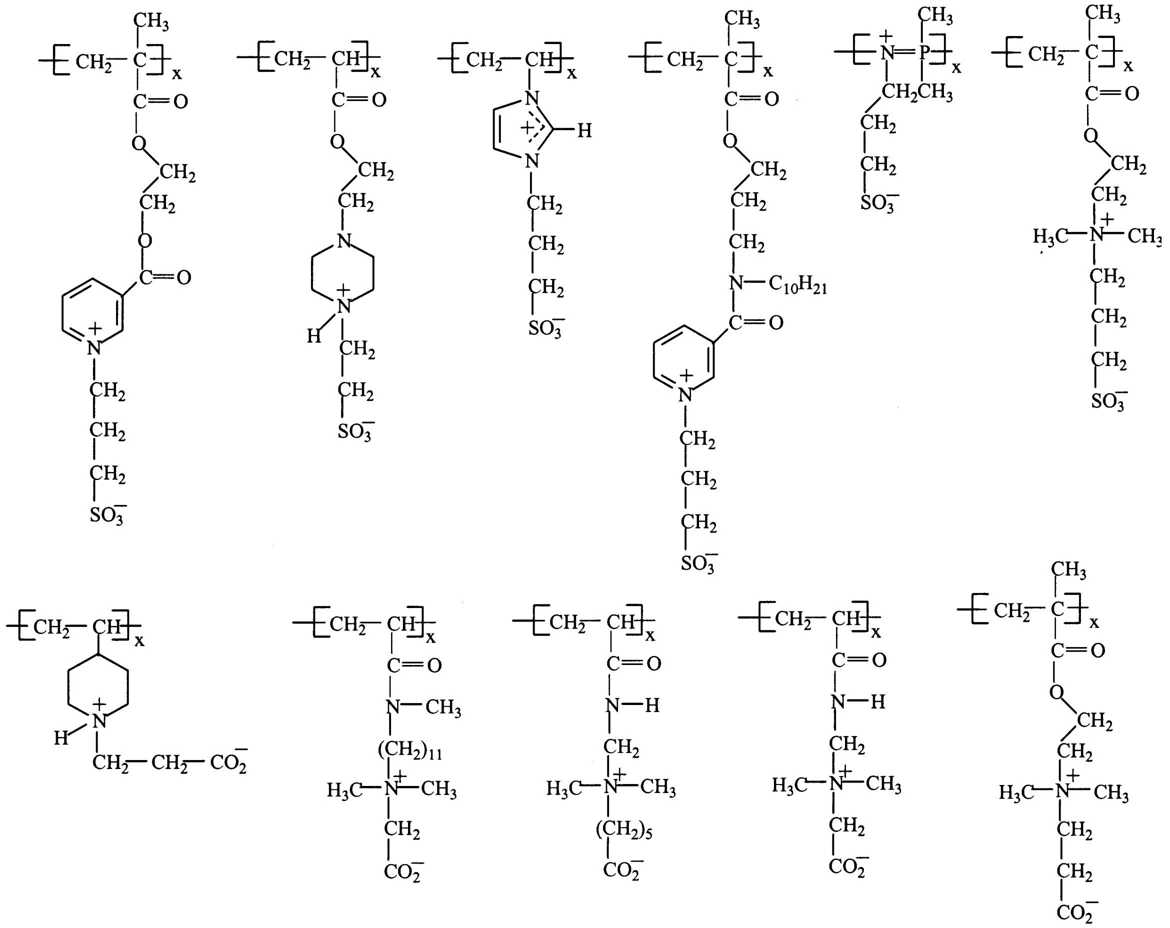

Figure 6. Representative examples of polymeric sulfo- and carboxybetaines that have been reported in the literature.

acted with 1,4-butanesultone to yield the sulfobetaine monomers. Subsequent polymerization in aqueous solution, using a free radical initiator, yielded the corresponding sulfobetaine polymers. Since these early publications, numerous workers have described the synthesis of many different polymeric betaines. For example, Galin and co-workers have described the synthesis and solution properties of a series of polysulfobetaines based on vinylpyridines,[137,138] methacrylamides,[139] methacrylates,[140−143] and the poly(ammonium alkoxydicyanoethenolates).[132,133,144] Laschewsky and co-workers have reported both sulfobetaine[145−147] and carboxybetaine[148,149] based polymers. Salamone et al. have described the synthesis and aqueous solution properties of a poly(vinylimidazolium sulfobetaine).[150,151] Novel sulfobetaines based on polyphosphazenes and poly(styrene−maleic anhydride) copolymers have been reported by Allcock, Klingenberg, and Welker[8] and Lee and Lee,[152] respectively. Likewise, Schulz et al. have synthesized and studied the solution properties of methacrylic-based sulfobetaine homopolymers.[153] (Meth)acrylamido-based sulfobetaine copolymers have been described by Koňák et al.[154,155] Rego and Huglin have reported hydrogels of 2-hydroxyethyl methacrylate with a sulfobetaine comonomer.[156] Itoh, Abe, and Senoh have prepared a novel sulfobetaine, poly(3-methacryloylethoxycarbonylpyridinium sulfopropylbetaine),[157] and Ali and Rasheed have described the synthesis of cyclocarboxybetaine−sulfur dioxide copolymers.[158] Apen and Rasmussen have also reported a novel polymeric betaine, Figure 6.[159] Here the authors modified preformed poly(4-vinylpyridine) with 1-methyl-2-bromo-4,5-dicyanoimidazole.

McCormick and co-workers have conducted extensive studies of both sulfo- and carboxybetaine polymers. The majority of the work has focused on acrylamido-based copolymers,[130,160−164] as well as cyclopolymers derived from quaternary diallyl monomers.[165,166] For example, Armentrout and McCormick recently described the synthesis and aqueous solution behavior of statistical copolymers comprising *N*,*N*-diallyl-*N*,*N*-dimethylammonium chloride (DADMAC) with the sulfobetaine comonomer 3-(*N*,*N*-diallyl-*N*-methylammonio)propanesulfonate (DAMAPS).[165] The copolymers were prepared in 0.5 M aqueous NaCl solution using 2-hydroxy-1-[4-(hydroxyethoxy)phenyl]-2-methyl-1-propanone as the free radical photoinitiator. The feed ratio of DADMAC to DAMAPS was varied from 100:0 to 0:100. ^{13}C NMR spectroscopy confirmed that the resulting statistical copolymers had a five-membered ring structure in the cis conformation, common to diallylammonium salts, Figure 7.

Phospholipids have received considerable attention recently because they are known to be very important constituents in biological membranes.[167] Given this, there has been a concerted effort toward the synthesis and characterization of synthetic polymeric phospholipid analogues (phosphobetaines). A recent paper

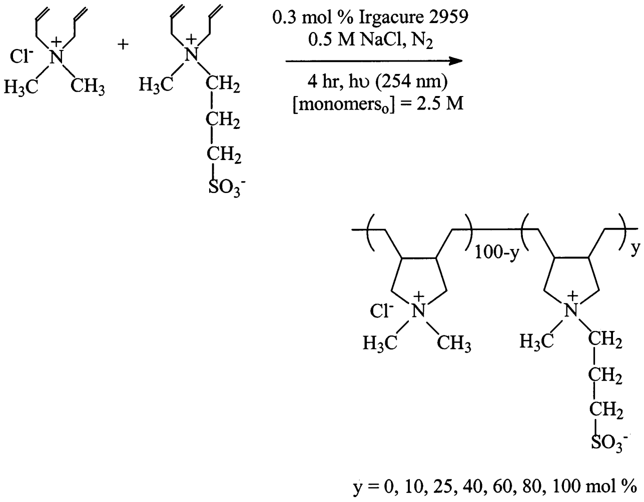

Figure 7. Synthetic scheme for the synthesis of poly(DADMAC-*co*-DAMAPS) copolymers.

by Nakaya and Li provides a comprehensive review of phospholipid polymers (phosphobetaines).[168] Typically, the phosphobetaine monomer is synthesized from the reaction of an alcohol-containing monomer with 2-chloro-2-oxo-1,3,2-dioxaphospholane, with subsequent ring opening using trimethylamine, Figure 8.

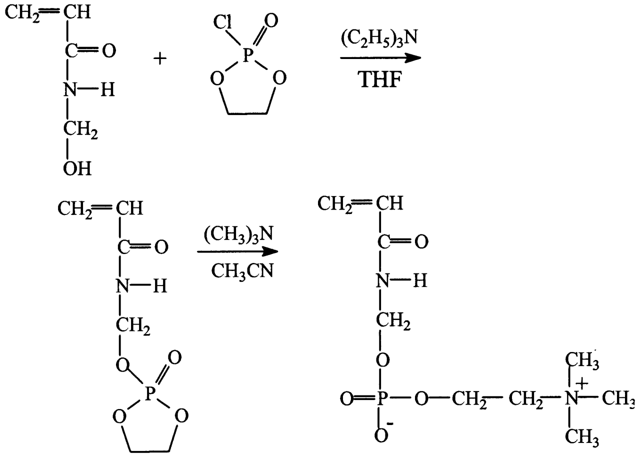

Figure 8. Synthetic scheme for the synthesis of an acrylamido-based phosphatidylcholine monomer.

These monomers are typically (meth)acrylate[169−177] or (meth)acrylamido based.[178,179] However, there are alternative methods of synthesizing phosphobetaine monomers/polymers. For example, Hamaide, Germanaud, and Le Perchec reported the synthesis of phosphonate- and phosphinato-based betaine polymers using phosphonate/phosphinato-based quaternizing agents, Figure 9.[180]

Nakaya, Toyoda, and Imoto described the synthesis of 2-(methacryloyloxy)ethyl 2-(trimethylammonio)ethyl phosphate using 2-hydroxyethyl methacrylate and 2-bromoethyl dichlorophosphate as starting materials; see Figure 10.[181]

Most recently, Miyazawa and Winnik[182] reported the synthesis of phosphorylcholine-based statistical terpolymers. The route described by these authors involved the attachment of phosphorylcholine groups to a preformed hydrophobically modified copolymer to yield copolymers, with varying compositions, of *N*-isopropylacrylamide and *N*-(phosphorylcholine)-*N*-(ethylenedioxybis(ethyl))acrylamide with the hydrophobic comonomers *N*-(*n*-octyldecyl)acrylamide, *N*-(1*H*,1*H*-perfluoro-*n*-octyldecyl)acrylamide, and *N*-[(1-pyrenyl)-4-butyl]-*N*-(*n*-octyldecyl)acrylamide.

It is also possible to synthesize polyphosphobetaines so that the charges are located on the backbone, or attached directly to the backbone.[183−185] These are synthesized by a step-growth mechanism. For example, Nakaya, Yasuzawa, and Imoto[186] described the synthesis of linear polyphosphatidylcholine analogues. 2-(Dimethylamino)ethanol, 11-(dimethylamino)decanol, and *p*-[(dimethylamino)ethanamido]phenol were reacted with 2-chloro-2-oxo-1,3,2-dioxaphospholane to yield the desired monomers. These monomers were subsequently heated in DMF at 60 °C for 20 h, yielding the linear polyphosphobetaines.

Matsushita et al. have reported the synthesis of polymers derived from styrene functional 1-[9-(*p*-vinylbenzoyl)nonanoyl]-2-*O*-octadecyl-*rac*-glycero-3-phosphocholine.[187] Similarly, Letourneru, Douzon, and Jozefowicz described the synthesis of a wide range of phosphorylated cross-linked polystyrene derivatives.[188] Other polymers/surfaces that have been modified to yield phosphobetaine structures include siloxanes[189,190] and urethanes.[191,192] O'Brien and co-workers have described the synthesis and bilayer polymerization of phospholipid bilayers[193] as well as primary termination and cross-linking polymerization within the bilayer membranes. Regen and co-workers have described polymerized phosphatidylcholine vesicles[194] as well as reversibly polymerizable thiol−disulfide phosphatidylcholine membranes.[195,196] These structures are particularly interesting due to their potential biodegradability and application as drug carriers.

Until recently there were no examples of directly synthesized *nearly monodisperse* polymeric betaines. In 1996 Lowe, Billingham, and Armes[197] reported the direct synthesis of such polysulfobetaines. Homopolymers of DMAEMA, synthesized by GTP with polydispersity indices in the range 1.05−1.16, were nearly quantitatively betainized under mild conditions using 1,3-propanesultone. Subsequently, Lowe and co-workers reported the first synthesis of sulfobetaine-based hydrophilic−hydrophobic nearly monodisperse block copolymers.[198,199] Precursor diblock copolymers of DMAEMA with a hydrophobic comonomer, such as methyl or lauryl methacrylate, were synthesized by GTP via sequential monomer addition. Subsequent reaction of the tertiary amine residues on DMAEMA with 1,3-propanesultone yielded the corresponding sulfobetaine block copolymers. Similarly, it is possible to selectively betainize hydrophilic−hydrophilic tertiary amine methacrylate block copolymers.[200] Precursor diblocks of DMAEMA with DEAEMA, 2-(diisopropylamino)ethyl methacrylate (DPAEMA), or 2-(*N*-morpholino)ethyl methacrylate (MEMA) were synthesized by GTP. DMAEMA is readily betainized under mild conditions (THF, room temperature, 12−16 h), while the more sterically

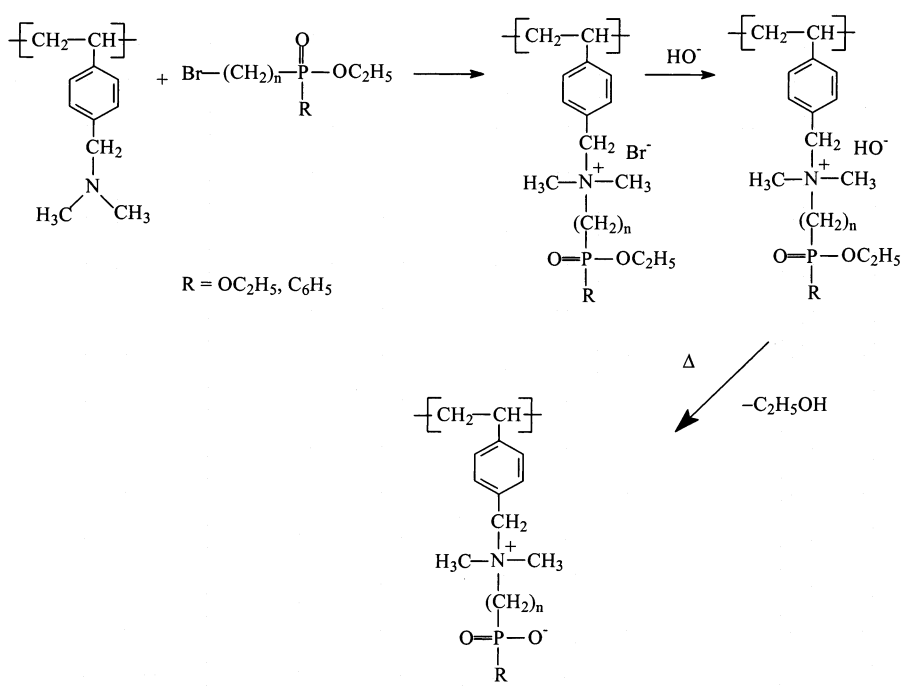

Figure 9. Synthesis of a phosphobetaine monomer via reaction with ω-bromoalkylphosphonate or ω-bromoalkylphosphinate. Reprinted with permission from ref 114. Copyright 1986 Wiley-VCH, STM.

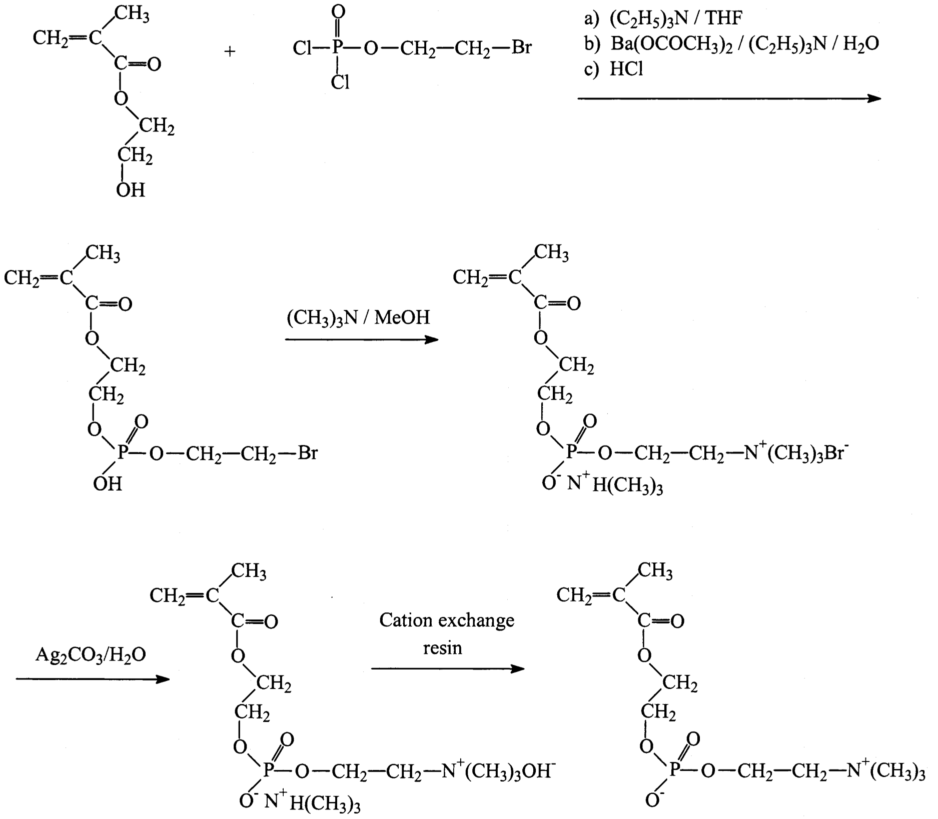

Figure 10. Synthesis of a phosphobetaine monomer via 2-bromoethyl dichlorophosphate. Reprinted with permission from ref 183. Copyright 1986 The Society of Polymer Science, Japan.

hindered DEAEMA and MEMA are only partially betainized under prolonged reflux conditions and DPAEMA is not converted to the sulfobetaine, even under reflux conditions. Jaeger et al. also reported the synthesis of relatively nearly monodisperse betaine block copolymers via the modification of precursor blocks of, for example, 4-vinylbenzyl chloride and styrene (synthesized by nitroxide-mediated polymerization) with ethyl *N*,*N*-dimethylglycinate followed by alkaline hydrolysis.[201] The authors subsequently reported certain bulk and solution properties of these nearly monodisperse polycarboxybetaines.[202]

At present there are very few examples concerning the *direct* controlled free radical polymerization of betaine monomers. Lobb et al.[203] described the synthesis of 2-(methacryloyloxy)ethyl phosphorylcholine homopolymers and block copolymers via ATRP in aqueous media under mild conditions. Resulting polydispersities of the polymers were in the range 1.12−1.45 with good control over molecular weight. Laschewsky et al.[204] reported the synthesis and aqueous solution characterization of AB diblock copolymers of *N*-isopropylacrylamide with the sulfobetaine comonomer 3-[*N*-(3-methylacrylamidopropyl)-*N*,*N*-dimethyl]ammoniopropanesulfonate. More recently, McCormick et al. reported the synthesis of methacrylate-, acrylamide-, and styrene-based sulfobetaine homopolymers and statistical and block copolymers directly in aqueous media via RAFT.[205,206]

V. Aqueous Solution Properties of Polybetaines

Numerous workers have described in detail the aqueous solution properties of polymeric betaines. Perhaps the most interesting feature of the aqueous solution properties is general lack of solubility in pure water. This insolubility is due to the formation of intra- and interchain ionic contacts resulting in an ionically cross-linked network structure. Those polybetaines that are not soluble in pure water become soluble upon the addition of low molecular weight electrolytes, e.g., NaCl. This dissolution process can best be understood in terms of the electrolyte penetrating the ionic network, screening the net attractive electrostatic interactions between the polymer chains, and hence promoting solubility.[207] The addition of salt also results in *antipolyelectrolyte* behavior, i.e., chain expansion.[208] It is well-known that different salts, as well as their concentration, have different solubility-promoting abilities. Salamone et al.,[150] Schulz et al.,[153] and Monroy Soto and Galin[137] have all studied the solubility behavior of sulfobetaine polymers in aqueous salt solutions and have demonstrated the effect of different anion/cation pairs and their respective ability at solubilizing the polymers. Generally, the trend closely follows the Hoffmeister lyotropic series.[209] As an example, the critical salt concentration (CSC, the concentration of salt required to promote solubility) for poly[*N*-(3-sulfopropyl)-*N*-[(methacryloyloxy)ethyl]-*N*,*N*-dimethylammonium betaine] falls within the range $\sim 0.0005 < \text{CSC} < 0.088$ mol/L depending on the anion/cation pair.[137] In sharp contrast to the relatively low salt concentrations required for the solubilization of the above polysulfobetaine are those required for the solubilization of the poly(ammonio alkoxydicyanoethenolates) reported by Pujol Fortin and Galin.[132] These polybetaines are not water soluble between 0 and 100 °C, but become soluble upon addition of either very strong acids, e.g., 40−60 wt % H_2SO_4, or salt. In this case the acid partially protonates the anionic segment of the polymer chain, converting the polybetaine into a cationic polyelectrolyte. A unique feature of this class of polybetaines, as compared to polysulfobetaines, is the very high electrolyte concentration required to promote solubility. For example, the former polymer remains insoluble in 6.0 M NaCl and 7.0 M NaBr. Even for the more efficient anions, such as I^-, concentrations must be increased by a factor of 10^3 compared to those required for the solubilization of polysulfobetaines.

The solubility of polybetaines is also limited in organic solvents, although the range of solubility in different solvents is greater for phospho- and carboxybetaines than it is for sulfobetaines. Solubility is typically limited to solvents with a high hydrogen-bond-donating ability, i.e., solvents with the ability to disrupt the attractive ionic interactions, such as fluorinated acids and alcohols. For example, Huglin and Radwan studied the solubility properties of poly[*N*-(3-sulfopropyl)-*N*-[(methacryloyloxy)ethyl]-*N*,*N*-dimethylammonium betaine] in both 1.0 M NaCl and 2,2,2-trifluoroethanol (TFE).[210,211] From the experimentally determined intrinsic viscosities, second virial coefficients (A_2 values), and Mark−Houwink exponents, the authors demonstrated that TFE is a thermodynamically better solvent than 1.0 M NaCl.

To date, there are only two reports concerning polybetaine block copolymers and their micellization behavior in aqueous salt solution.[198,199] Precursor block copolymers of DMAEMA and a hydrophobic comonomer, such as MMA, were prepared by GTP and subsequently reacted with 1,3-propanesultone to yield the sulfobetaine block copolymers. It is well-known that block copolymers in selective solvents associate to form spherical micelles that are typically in dynamic equilibrium with unimers in solution.[212−214] Lowe, Billingham, and Armes demonstrated that the sulfobetaine block copolymers generally form polydisperse micelles upon direct dissolution in water. However, if the block copolymers are first molecularly dissolved in TFE (a nonselective solvent) and subsequently diluted with water, then nearly monodisperse micelles are obtained. The micelle aggregation numbers are controlled by the length of the hydrophobic block and are essentially independent of the sulfobetaine block. The authors also demonstrated the ability of the micelles to exhibit antipolyelectrolyte behavior. The addition of salt (NaCl) led to an increase in the observed hydrodynamic diameter of the micelles, with the maximum being observed at ca. 0.1 M NaCl. Tuzar et al. also demonstrated the ability of these block copolymer sulfobetaine micelles to sequester chloroform, using SANS, from an aqueous solution into the hydrophobic micelle core (a block copolymer in which the hydrophobic block was d_8-MMA was employed in the study).[198]

Polycarboxybetaines exhibit more varied aqueous solution behavior because of the weak acid nature of the carboxylic acid group. Kathmann and McCormick have published a series of papers detailing the synthesis and aqueous solution behavior of two carboxybetaine polymers, 4-(2-acrylamido-2-methylpropanedimethylammonio) butanoate (AMPDAB) and 6-(2-acrylamido-2-methylpropanedimethylammonio) hexanoate (AMPDAH), Figure 11.[162−164]

The monomers were copolymerized with acrylamide, sodium acrylate/acrylamide or the sulfobetaine monomer 3-[(2-acrylamido-2-methylpropyl)dimethylammonio) propanesulfonate. As an example,[165] statistical copolymers of AMPDAH with acrylamide exhibit solubility behavior that is very much dependent on the mole percent of incorporated AMPDAH.

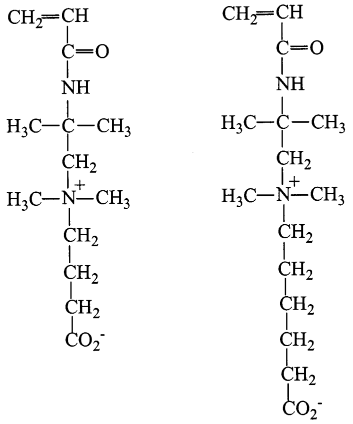

Figure 11. Chemical structures of AMPDAB and AMPDAH.

At 25 mol %, or more, the copolymers are only swellable in aqueous media. At 10 mol %, or less, the copolymers are soluble in aqueous media under a range of conditions. At high pH, in deionized water, the polycarboxybetaines show both intra- and intermolecular associations, which are disrupted by the addition of NaCl. As the pH is lowered, the copolymers exhibit a dramatic increase in the viscosity as the carboxylate groups become protonated and charge−charge repulsions of the quaternary ammonium groups induce polyelectrolyte behavior.

One very interesting property of polymeric betaines is bio- and haemocompatibility, which is a direct result of their highly hygroscopic nature. To date, much of the research has focused on phosphobetaine polymers. The development of the phosphobetaine technology has been based on the concept of biomimicry, in which phosphobetaine copolymers are used to create a surface that mimics a biomembrane (these are composed, among others, of phosphatidylcholine betaine species), thus reducing biological interactions. Various groups have demonstrated that phosphobetaine-based copolymer coatings, which mimic the phosphatidylcholine headgroups, are nonthrombogenic.[215−220] Also these coatings, and bulk copolymers containing phosphatidylcholine-based monomers, can be employed to improve the biocompatibility of ocular devices by reducing the adhesion of microorganisms and eukaryotic cells.[221−223] Recently, Lowe et al.[224] reported well-defined, nearly monodisperse sulfobetaine-based statistical copolymers as potential bioadherent coatings. Precursor statistical copolymers of DMAEMA with *n*-butyl methacrylate (BuMA) were synthesized by GTP. The DMAEMA residues were subsequently converted to sulfobetaine species by reaction with 1,3-propanesultone. Poly(methyl methacrylate) (PMMA) disks were coated with the sulfobetaine copolymers and then exposed to *Pseudomonas aeruginosa* as a model microorganism, human macrophages, and 3T3 mouse embryonic fibroblasts. Statistically fewer bacteria, macrophages, and fibroblasts adhered to the coated PMMA disks than uncoated disks. This demonstrates that the biomimetic property of phosphobetaine polymers is not unique and is more likely a universal property of all polybetaines.

VI. Conclusions

In this review we have highlighted the methods of synthesis of both polyampholyte and polybetaine polymers. Although many examples exist concerning statistical polyzwitterions, there is still at present little in the literature regarding block copolymers (especially for polybetaines). The challenge for the future will no doubt involve the direct synthesis, i.e., without the need for protecting group chemistries, of both polyampholyte and polybetaine block copolymers. Controlled free radical polymerization appears to offer the greatest potential. As well as general synthetic methods for their preparation, we have examined the solution behavior and some potential applications that these polymers may possess. We have demonstrated that both polyampholytes and polybetaines can exhibit polyelectrolyte or antipolyelectrolyte behavior, depending on the composition, solution pH, and added low molecular weight electrolyte.

VII. References

(1) Dubin, P.; Bock, J.; Davies, R. M.; Schulz, D. N.; Thies, C. *Macromolecular Complexes in Chemistry and Biology*; Springer-Verlag: Berlin, 1994.
(2) Mortimer, D. A. *Polym. Int.* **1991**, *25*, 29.
(3) Bromberg, L. In *Handbook of Surfaces and Interfaces of Materials*, Nalwa, H. S., Ed.; Academic Press: New York, 2001; Vol 4., Chapter 7.
(4) Oosawa, F. *Polyelectrolytes*; Marcel-Dekker: New York, 1971.
(5) Salamone, J. C.; Rice, W. C. *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Wiley-Interscience: New York, 1988; Vol. 11, p 514.
(6) Munk, P. *Introduction to Macromolecular Science*; Wiley-Interscience: New York, 1989; p 59.
(7) Wang, C.; Nakamura, S. *J. Polym. Sci., Polym. Chem.* **1994**, *32*, 413
(8) Allcock, H. R.; Klingenberg, E. H.; Welker, M. F. *Macromolecules* **1993**, *26*, 5512.
(9) Nakaya, T.; Yasuzawa, M.; Imoto, M. *Macromolecules* **1989**, *22*, 3180
(10) Fuoss, R. P. U.S. Patent 4,749,762, 1988.
(11) Farwaha, R.; Currie, W. U.S. Patent 5,240,982, 1993.
(12) Mumick, P. S.; Welch, P. M.; Salazar, L. C.; McCormick, C. L. *Macromolecules* **1994**, *27*, 323.
(13) McCormick, C. L.; Kathmann, E. E. *Polymeric Materials Encyclopedia*; CRC Press: Boca Raton, FL, 1996; Vol. 7, p 5462.
(14) Alfrey, T.; Morawetz, H.; Fitzgerald. E. B.; Fuoss, R. M. *J. Am. Chem. Soc.* **1950**, *72*, 1864.
(15) Alfrey, T.; Morawetz, H. *J. Am. Chem. Soc.* **1952**, *74*, 436.
(16) Alfrey, T.; Fuoss, R.; Morawetz, H.; Pinner, S. H. *J. Am. Chem. Soc.* **1952**, *74*, 438.
(17) Alfrey, T.; Pinner, S. H. *J. Polym. Sci.* **1957**, *23*, 533.
(18) Ehrlich, G.; Doty, P. *J. Am. Chem. Soc.* **1954**, *76*, 3764.
(19) Katchalsky, A.; Miller, I. R. *J. Polym. Sci.* **1954**, *14*, 57.
(20) Mazur, J.; Silberberg, A.; Katchalsky, A. *J. Polym. Sci.* **1959**, *35*, 43.
(21) Jordan, D. O.; Kurucsev, T. *J. Polym. Sci.* **1956**, *21*, 495.
(22) McCormick, C. L.; Johnson, C. B. *Macromolecules* **1988**, *21*, 686.
(23) McCormick, C. L.; Johnson, C. B. *Macromolecules* **1988**, *21*, 694.
(24) Park, J. S.; Lim, Y. B.; Kwon, Y. M.; Jeong, B.; Choi, Y. H.; Kim, S. W. *J. Polym. Sci., Polym. Chem.* **1999**, *37*, 2305.
(25) Bekturov, E. A.; Kudaibergenov, S. E.; Rafikov, S. R. *Macromol. Sci. Rev., Macromol. Chem. Phys.* **1990**, *C30* (2), 233.
(26) Kudaibergenov, S. E.; Sigitov, V. B. *Langmuir* **1999**, *15*, 4230.
(27) Ascoli, F.; Botré, C. *J. Polym. Sci.* **1962**, *62*, S56.
(28) Salamone, J. C.; Watterson, A. C.; Hsu, T. D.; Tsai, C. C.; Mahmud, M. U. *J. Polym. Sci., Polym. Lett. Ed.* **1977**, *15*, 487.
(29) Salamone, J. C.; Watterson, A. C.; Hsu, T. D.; Tsai, C. C.; Mahmud, M. U.; Wisniewski, A. W.; Israel, S. C. *J. Polym. Sci., Polym. Symp.* **1978**, *64*, 229.
(30) Salamone, J. C.; Tsai, C. C.; Watterson, A. C. *J. Macromol. Sci., Chem.* **1979**, *A13* (5), 665.
(31) Salamone, J. C.; Quach, L.; Watterson, A. C.; Krauser, S.; Mahmud, M. U. *J. Macromol. Sci., Chem.* **1985**, *A22* (5−7), 653.
(32) Peiffer, D. G.; Lundberg, R. D. *Polymer* **1985**, *26*, 1058.
(33) Peiffer, D. G.; Lundberg, R. D.; Duvdevani, I. *Polymer* **1986**, *27*, 1453.

(34) Corpart, J. M.; Selb, J.; Candau, F. *Polymer* **1993**, *34*, 3873.
(35) Corpart, J. M.; Candau, F. *Macromolecules* **1993**, *26*, 1333.
(36) Skouri, M.; Munch, J. P.; Candau, S. J.; Neyret, S.; Candau, F. *Macromolecules* **1994**, *27*, 69.
(37) McCormick, C. L.; Johnson, C. B. *J. Macromol. Sci., Chem.* **1990**, *A27* (5), 539.
(38) McCormick, C. L.; Johnson, C. B. *Polymer* **1990**, *31*, 1100.
(39) McCormick, C. L.; Johnson, C. B. In *Water Soluble Polymers for Petroleum Recovery*; Stahl, G. A., Schulz, D. N., Eds.; Plenum Publishing Co.: New York, 1988; p 161.
(40) McCormick, C. L.; Johnson, C. B. In *Polymers in Aqueous Media*; Glass, J. E., Ed.; Advances in Chemistry Series No. 223; American Chemical Society: Washington, DC, 1989; p 437.
(41) Kamachi, M.; Kurihara, M.; Stille, J. K. *Macromolecules* **1972**, *5*, 161.
(42) Kurihara, M.; Kamachi, M.; Stille, J. K. *J. Polym. Sci., Chem. Ed.* **1973**, *11*, 587.
(43) Varoqui, R.; Tran, Q.; Pefferkorn, E. *Macromolecules* **1979**, *12*, 831.
(44) Morishima, Y.; Hashimoto, T.; Itoh, Y.; Kamachi, M.; Nozakura, S. *J. Polym. Sci., Polym. Chem.* **1982**, *20*, 299.
(45) Bekturov, E. A.; Frolova, V. A.; Kudaibergenov, S. E.; Schulz, R. C.; Zoller, J. *Makromol. Chem.* **1990**, *191*, 457.
(46) Bekturov, E. A.; Kudaibergenov, S. E.; Khamzamulina, R. E.; Frolova, V. A.; Nurgalieva, D. E.; Schulz, R. C.; Zoller, J. *Makromol. Chem., Rapid Commum.* **1992**, *13*, 225.
(47) Creutz, S.; Teyssié, P.; Jérôme, R. *Macromolecules* **1997**, *30*, 6.
(48) Creutz, S.; van Stam, J.; De Schryver, F. C.; Jérôme, R. *Macromolecules* **1998**, *31*, 681.
(49) Patrickios, C. S.; Hertler, W. R.; Abbott, N. L.; Hatton, T. A. *Macromolecules* **1994**, *27*, 930.
(50) Chen, W. I.; Alexandridis, P.; Su, C. K.; Patrickios, C. S.; Hertler, W. R.; Hatton, T. A. *Macromolecules* **1995**, *28*, 8604.
(51) Webster, O. W.; Hertler, W. R.; Sogah, D. Y.; Farnham, W. B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1983**, *105*, 5706.
(52) Dicker, I. B.; Hertler, W. R.; Ma, S. H. U.S. Patent 5,219,945, 1993.
(53) Ma, S. H.; Matrick, H.; Shor, A. C.; Spinelli, H. J. U.S. Patent 5,085,698, 1992.
(54) Kearns, J. E.; McLean, C. D.; Soloman, D. H. *J. Macromol. Sci., Chem.* **1974**, *A8* (4), 673.
(55) Taylor, G. N.; Stillwagon, L. E.; Houlihan, F. M.; Wolf, T. M.; Sogah, D. Y.; Hertler, W. R. *Chem. Mater.* **1991**, *3*, 1031.
(56) Mykytiuk, J.; Armes, S. P.; Billingham, N. C. *Polym. Bull.* **1992**, *29*, 139.
(57) Rannard, S. P.; Billingham, N. C.; Armes, S. P.; Mykytiuk, J. *Eur. Polym. J.* **1993**, *29*, 407.
(58) Doherty, M. A.; Muller, A. H. E. *Makromol. Chem.* **1989**, *190*, 527.
(59) Lowe, A. B. D.Phil. Thesis, University of Sussex, U.K., 1997.
(60) Lowe, A. B.; Billingham, N. C.; Armes, S. P. *Chem. Commun.* **1997**, 1035.
(61) Lowe, A. B.; Billingham, N. C.; Armes, S. P. *Macromolecules* **1998**, *31*, 5991.
(62) Grand, D. H.; Grassie, N. *Polymer* **1960**, *1*, 125.
(63) Ito, H.; Ueda, M. *Macromolecules* **1988**, *21*, 1475.
(64) Goloub, T.; de Keizer, A.; Cohen Stuart, M. A. *Macromolecules* **1999**, *32*, 8441.
(65) Patrickios, C. S.; Lowe, A. B.; Armes, S. P.; Billingham, N. C. *J. Polym. Sci., Polym. Chem.* **1998**, *36*, 617.
(66) Giebeler, E.; Stadler, R. *Macromol. Chem. Phys.* **1997**, *198*, 3815.
(67) Ge, X.; Sheng, M.; Ye, Q.; Xu, X.; Zhang, Z. *Polym. J.* **1999**, *31*, 1243.
(68) Solomon, D. H.; Rizzardo, E.; Cacioli, P. U.S. Patent 4,581,429.
(69) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. *Trends Polym. Sci.* **1994**, *2*, 66.
(70) Wang, J. S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614.
(71) Wang, J. S.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 7901.
(72) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Polym. Prep. Jpn.* **1994**, *43*, 1792.
(73) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721.
(74) Ando, T.; Kato, M.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **1996**, *29*, 1070.
(75) Le, T. P.; Moad, G.; Rizzardo, E.; Thang, S. H. PCT Int. Appl. WO 9801478 A1 980115.
(76) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559.
(77) Chong, Y. K.; Le, T. P. T.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1999**, *32*, 2071.
(78) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Krstina, J.; Moad, G.; Postma, A.; Thang, S. H. *Macromolecules* **2000**, *33*, 243.
(79) Rizzardo, E.; Chiefari, J.; Mayadunne, R. T. A.; Moad, G.; Thang, S. H. In *Controlled/Living Radical Polymerization*; Matyjaszewski, K., Ed.; Advances in Chemistry Series No. 768; American Chemical Society: Washington, DC, 2000; p 278.
(80) Ashford, E. J.; Naldi, V.; O'Dell, R.; Billingham, N. C.; Armes, S. P. *Chem. Commun.* **1999**, 1285.
(81) Lowe, A. B.; McCormick, C. L. Unpublished results.
(82) Summerlin, B.; Donovan, M. S.; Mitsukami, Y, Lowe, A. B.; McCormick, C. L. *Macromolecules* **2001**, *34*, 6561.
(83) Mitsukami, Y.; Donovan, M. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2001**, *34*, 2248.
(84) Keoshkerian, B.; Georges, M. K.; Boils-Bossier, D. *Macromolecules* **1995**, *28*, 6381.
(85) Bouix, M.; Gouzi, J.; Charleux, B.; Vairon, J.-P.; Guinot, P. *Macromol. Rapid Commun.* **1998**, *19*, 209.
(86) Gabaston, L. I.; Furlong, S. A.; Jackson, R. A.; Armes, S. P. *Polymer* **1999**, *40*, 4505.
(87) Nowakowska, M.; Zapotoczny, S.; Karewicz, A. *Macromolecules* **2000**, *33*, 7345.
(88) Lokaj, J.; Vlček, P.; Křiz, J. *Macromolecules* **1997**, *30*, 7644.
(89) Zhang, X.; Xia, J.; Matyjaszewski, K. *Macromolecules* **1998**, *31*, 5167.
(90) Zhang, X.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 1763.
(91) Zeng, F.; Shen, Y.; Zhu, S.; Pelton, R. *J. Polym. Sci., Polym. Chem.* **2000**, *38*, 3821.
(92) Xia, J.; Zhang, X.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 3531.
(93) Donovan, M. S.; Lowe, A. B.; McCormick, C. L. Unpublished results.
(94) Donovan, M. S.; Lowe, A. B.; McCormick, C. L. *Polym. Prep.* **1999**, *40* (2), 281.
(95) Wittmer, J.; Johner, A.; Joanny, J. F. *Europhys. Lett.* **1993**, *24*, 263.
(96) Borkovec, M.; Koper, G. J. M. *Langmuir* **1994**, *10*, 2863.
(97) Kantor, Y.; Li, H.; Kardar, M. *Phys. Rev. Lett.* **1992**, *69*, 61.
(98) Kantor, Y.; Kardar, M. *Europhys. Lett.* **1994**, *27*, 643.
(99) Higgs, P. J.; Joanny, J. F. *J. Chem. Phys.* **1991**, *94*, 1543.
(100) Dobrynin, A. V.; Zhulina, E. B.; Rubinstein, M. *Macromolecules* **2001**, *34*, 627.
(101) Zhulina, E. B.; Dobrynin, A. V.; Rubinstein, M. *J. Phys. Chem. B* **2001**, *105*, 8917.
(102) Kudaibergenov, S. E. In *Polyampholytes: Synthesis, Characterization, and Application*; Kluwer Academic/Plenum Publishers: New York, 2002; p 55.
(103) Patrickios, C. S. *J. Colloid Interface Sci.* **1995**, *175*, 256.
(104) Merle, Y. *J. Phys. Chem.* **1987**, *91*, 3092.
(105) Gohy, J. F.; Creutz, S.; Garcia, M.; Mahltig, B.; Stamm, M.; Jérôme, R. *Macromolecules* **2000**, *33*, 6378.
(106) Bütün, V.; Lowe, A. B.; Billingham, N. C.; Armes, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 4288.
(107) Bütün, V.; Armes, S. P. In *Stimuli-Responsive Water-Soluble and Amphiphilic Polymers*; McCormick, C. L., Ed.; Advances in Chemistry Series No. 780; American Chemical Society: Washington, DC, 2001; p 115.
(108) Patrickios, C. S.; Gadam, S. D.; Cramer, S. M.; Hertler, W. R.; Hatton, T. A. *Biotechnol. Prog.* **1995**, *11*, 33.
(109) Patrickios, C. S.; Hertler, W. R.; Hatton, T. A. *Biotechnol. Bioeng.* **1994**, *44*, 1031.
(110) Patrickios, C. S.; Sharma, L. R.; Armes, S. P.; Billingham, N. C. *Langmuir* **1999**, *15*, 1613.
(111) Liaw, D. J.; Lee, W. F.; Whung, Y. C.; Lin, M. C. *J. Appl. Polym. Sci.* **1987**, *34*, 999.
(112) Rosenheck, K.; Katchalsky, A. *J. Polym. Sci.* **1958**, *32*, 511.
(113) Nagaya, J.; Uzawa, H.; Minoura, N. *Macromol. Rapid Commun.* **1999**, *20*, 573.
(114) Hamaide, T.; Germanaud, L.; Perchec, P. L. *Makromol. Chem.* **1986**, *187*, 1097.
(115) Pujol-Fortin, M. L.; Galin, M.; Galin, J. C. *Macromolecules* **1991**, *24*, 4523.
(116) Cleary, J. W. *Chem. Abstr.* **1975**, *82*, 32364f.
(117) Hayama, K.; Ito, I. *Chem. Abstr.* **1976**, *85*, 117990u.
(118) Pusey, M. S. *Chem. Abstr.* **1974**, *81*, 106899n.
(119) De Vries, L. *Chem. Abstr.* **1973**, *79*, 106633e.
(120) Ohashi, T.; Fujii, S.; Kozuka, K. *Chem. Abstr.* **1976**, *85*, 5201f.
(121) Ernst, R.; Miller. E. L. Surface Active Betaines. In *Amphoteric Surfactants*; Bluestein, B. L., Wilton, C. L., Eds.; Marcel Dekker: New York, 1982; p 71.
(122) Lloyd, A. W.; Baker, J. A.; Smith, G.; Olliff, C. J.; Rutt, K. L. *J. Pharm. Pharmacol.* **1992**, *44*, 507.
(123) Lloyd, A. W.; Baker, J. A.; Olliff, C. J.; Rutt, K. L. *Cryoletters* **1992**, *13*, 337.
(124) Lloyd, A. W.; Olliff, C. J.; Rutt, K. L. *Int. J. Pharm.* **1996**, *131*, 257.
(125) Roberts, D. W.; Williams, D. L. *Tetrahedron* **1987**, *43* (6), 1027.
(126) Samour, C. M.; Falxa, M. L. U.S. Patent 3,671,502, 1972.
(127) Barboiu, V.; Streba, E.; Luca, C.; Simionescu, C. I. *J. Polym. Sci., Polym. Chem.* **1995**, *33*, 389.
(128) Lush, R. B.Sc. Thesis, University of Sussex, U.K., 1998.
(129) Bonte, N.; Laschewsky, A. *Polymer* **1996**, *37*, 2011.
(130) Kathmann, E. E.; White, L. A.; McCormick, C. L. *Polymer* **1997**, *38*, 879.
(131) Hahn, M.; Görnitz, E.; Dautzenberg, H. *Macromolecules* **1998**, *31*, 5616.

(132) Pujol-Fortin, M.-L.; Galin, J.-C. *Polymer* **1994**, *35*, 1462.
(133) Galin, J.-C.; Galin, M. *J. Polym. Sci., Polym. Phys.* **1995**, *33*, 2033.
(134) Bieglé, A.; Mathis, A.; Galin, J.-C. *Macromol. Chem. Phys.* **2000**, *201*, 113.
(135) Ladenheim, H.; Morawetz, H. *J. Polym. Sci.* **1957**, *26*, 251.
(136) Hart, R.; Timmerman, D. *J. Polym. Sci.* **1958**, *28*, 638.
(137) Monroy Soto, V. M.; Galin, J. C. *Polymer* **1984**, *25*, 121.
(138) Monroy Soto, V. M.; Galin, J. C. *Polymer* **1984**, *25*, 254.
(139) Ehrmann, M.; Mathis, A.; Meurer, B.; Scheer, M.; Galin, J. C. *Macromolecules* **1992**, *25*, 2253.
(140) Mathis, A.; Zheng, Y. L.; Galin, J. C. *Makromol. Chem., Rapid Commun.* **1986**, *7*, 333.
(141) Zheng, Y. L.; Galin, M.; Galin, J. C. *Polymer* **1988**, *29*, 724.
(142) Bazuin, C. G.; Zheng, Y. L.; Muller, R.; Galin, J. C. *Polymer* **1989**, *30*, 654.
(143) Zheng, Z. L.; Knoesel, R.; Galin, J. C. *Polymer* **1987**, *28*, 2297.
(144) Pujol-Fortin, M. L.; Galin, J. C. *Macromolecules* **1991**, *24*, 4523.
(145) Bonte, N.; Laschewsky, A. *Polymer* **1996**, *10*, 2011.
(146) Laschewsky, A.; Zerbe, I. *Polymer* **1991**, *32*, 2081.
(147) Köberle, P.; Laschewsky, A.; Lomax, T. D. *Makromol. Chem., Rapid Commun.* **1991**, *12*, 427.
(148) Laschewsky, A.; Zerbe, I. *Polymer* **1991**, *32*, 2070.
(149) Favresse, P.; Laschewsky, A. *Polymer* **2001**, *42*, 2755.
(150) Salamone, J. C.; Volksen, W.; Olson, A. P.; Israel, S. C. *Polymer* **1978**, *19*, 1157.
(151) Salamone, J. C.; Volksen, W.; Israel, S. C.; Olson, A. P.; Raia, D. C. *Polymer* **1977**, *18*, 1058.
(152) Lee, W. F.; Lee, C. H. *Polymer* **1997**, *38*, 971.
(153) Schulz, D. N.; Peiffer, D. G.; Agarwal, P. K.; Larabee, J.; Kaladas, J. J.; Soni, L.; Handwerker, B.; Garner, R. T. *Polymer* **1986**, *27*, 1734.
(154) Koňák; Rathi, R. C.; Kopčková, P.; Kopeček, J. *Macromolecules* **1994**, *27*, 1992.
(155) Koňák; Rathi, R. C.; Kopčková, P.; Kopeček, J. *Polymer* **1993**, *34*, 4767.
(156) Rego, J. M.; Huglin, M. B. *Polym. J.* **1991**, *23*, 1425.
(157) Itoh, Y.; Abe, K.; Senoh, S. *Makromol. Chem.* **1986**, *187*, 1691.
(158) Ali, S. A.; Rasheed, A. *Polymer* **2000**, *40*, 6849.
(159) Apen, P. G.; Rasmussen, P. G. *J. Polym. Sci., Polym. Chem.* **1992**, *30*, 203.
(160) McCormick, C. L.; Salazar, L. C. *Polymer* **1992**, *33*, 4617.
(161) Kathmann, E. E.; Davis, D. D.; McCormick, C. L. *Macromolecules* **1994**, *27*, 3156.
(162) Kathmann, E. E.; McCormick, C. L. *J. Polym. Sci., Polym. Chem.* **1997**, *27*, 231.
(163) Kathmann, E. E.; McCormick, C. L. *J. Polym. Sci., Polym. Chem.* **1997**, *27*, 243.
(164) Kathmann, E. E.; White, L. A.; McCormick, C. L. *Macromolecules* **1997**, *30*, 5297.
(165) Armentrout, R. S.; McCormick, C. L. *Macromolecules* **2000**, *33*, 419.
(166) Armentrout, R. S.; McCormick, C. L. *Macromolecules* **2000**, *33*, 2944.
(167) Gennis, R. B. *Biomembranes—Molecular Structure and Functions*; Springer-Verlag: New York, 1989; p 23.
(168) Nakaya, T.; Li, Y.-J. *Prog. Poly. Sci.* **1999**, *24*, 143.
(169) Ishihara, K.; Ueda, T.; Nakabayashi, N. *Polym. J.* **1990**, *22*, 355.
(170) Muroga, Y.; Amano, M.; Katagiri, A.; Noda, I.; Nakaya, T. *Polym. J.* **1995**, *27*, 65.
(171) Umeda, T.; Nakaya, T.; Imoto, M. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 457.
(172) Furukawa, A.; Shoji, H.; Nakaya, T.; Imoto, M. *Makromol. Chem.* **1987**, *188*, 265.
(173) Wang, Y. F.; Chen, T. M.; Li, Y. J.; Nakaya, T. *J. Macromol. Sci., Pure Appl. Chem.* **1996**, *A33* (6), 771.
(174) Liu, S.; O'Brien, D. F. *Macromolecules* **1999**, *32*, 5519.
(175) Lei, J.; Sisson, T. M.; Lamparski, H. G.; O'Brien, D. F. *Macromolecules* **1999**, *32*, 73.
(176) Lamparski, H. G.; Oblinger, E.; O'Brien, D. F. *Macromolecules* **1999**, *32*, 5450.
(177) Sells, T. D.; O'Brien, D. F. *Macromolecules* **1994**, *27*, 226.
(178) Wang, Y. F.; Chen, T. M.; Li, Y. J.; Kitamura, M.; Nakaya, T.; Sakurai, I. *Macromolecules* **1996**, *29*, 5810.
(179) Wang, Y.; Chen, T.; Kitamura, M.; Nakaya, T. *J. Polym. Sci., Polym. Chem.* **1996**, *34*, 449.
(180) Hamaide, D.; Germanaud, L.; Le Perchec, P. *Makromol. Chem.* **1986**, *187*, 1097.
(181) Nakaya, T.; Toyoda, H.; Imoto, M. *Polym. J.* **1986**, *18*, 881.
(182) Miyazawa, K.; Winnik, F. M. *Macromolecules* **2002**, *35*, 2449.
(183) Umeda, T.; Nakaya, T.; Imoto, M. *Makromol. Chem., Rapid Commun.* **1985**, *6*, 285.
(184) Sugiyama, K.; Nakaya, T. *Makromol. Chem., Rapid Commun.* **1986**, *7*, 679.
(185) Yamada, M.; Li, Y.-J.; Nakaya, T. *J. Macromol. Sci., Pure Appl. Chem.* **1995**, *A32*, 1723.
(186) Nakaya, T.; Yasuzawa, M.; Imoto, M. *Macromolecules* **1989**, *22*, 3180.
(187) Matsushita, Y.; Hasegawa, E.; Eshima, K.; Ohno, H.; Tsuchida, E. *Makromol. Chem., Rapid Commun.* **1987**, *8*, 1.
(188) Letourneur, D.; Douzon, C.; Jozefowicz, M. *J. Polym. Sci., Polym. Chem.* **1991**, *29*, 1367.
(189) Yamada, M.; Li, Y.-J.; Nakaya, T. *Macromolecules* **1995**, *28*, 2590.
(190) Durrani, A. A.; Hayward, J. A.; Chapman, D. *Biomaterials* **1986**, *7*, 121.
(191) Li, Y.-J.; Shibata, Y.; Nakaya, T. *Macromol. Rapid Commun.* **1995**, *16*, 253.
(192) Li, Y.-J.; Nakamura, N.; Chen, T. M.; Wang, Y. F.; Kitamura, M.; Nakaya, T. *Macromol. Rapid Commun.* **1996**, *17*, 737.
(193) Lee, Y.-S.; O'Brien, D. F. *J. Polym. Sci., Polym. Chem.* **1994**, *32*, 1437.
(194) Regen, S. L.; Singh, A.; Oehme, G.; Singh, M. *J. Am. Chem. Soc.* **1982**, *104*, 791.
(195) Regen, S. L.; Yamaguchi, K.; Samuel, N. K. P.; Singh, M. *J. Am. Chem. Soc.* **1983**, *105*, 6354.
(196) Samuel, N. K. P.; Singh, M.; Yamaguchi, K.; Regen, S. L. *J. Am. Chem. Soc.* **1985**, *107*, 42.
(197) Lowe, A. B.; Billingham, N. C.; Armes, S. P. *Chem. Commun.* **1996**, 1555.
(198) Tuzar, Z.; Pospisil, H.; Plestil, J.; Lowe, A. B.; Baines, F. L.; Billingham, N. C.; Armes, S. P. *Macromolecules* **1997**, *30*, 2509.
(199) Lowe, A. B.; Billingham, N. C.; Armes, S. P. *Macromolecules* **1999**, *32*, 2141.
(200) Bütün, V.; Bennett, C. E.; Vamvakaki, M.; Lowe, A. B.; Billingham, N. C.; Armes, S. P. *J. Mater. Chem.* **1997**, *7*, 1693.
(201) Jaeger, W.; Wendler, U.; Lieske, A.; Bohrisch, J.; Wandrey, C. *Macromol. Symp.* **2000**, *161*, 87.
(202) Bohrisch, J.; Schimmel, T.; Engelhardt, H.; Jaeger, W. *Macromolecules* **2002**, *35*, 4143.
(203) Lobb, E. J.; Ma, I.; Billingham, N. C.; Armes, S. P.; Lewis, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 7913.
(204) Arotçaréna, M.; Heise, B.; Ishaya, S.; Laschewsky, A. *J. Am. Chem. Soc.* **2002**, *124*, 3787.
(205) Lowe, A. B.; McCormick, C. L. *Aust. J. Chem.* **2002**, *55*, 367.
(206) Donovan, M. S.; Sumerlin, B. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules*, in press.
(207) Salamone, J. C.; Tsai, C. C.; Watterson, A. C.; Olsen, A. P. *Polymer* **1978**, *19*, 1157.
(208) Lowe, A. B.; McCormick, C. L. In *Stimuli-Responsive Water-Soluble and Amphiphilic Polymers*; McCormick, C. L., Ed.; Advances in Chemistry Series No. 780; American Chemical Society: Washington, DC, 2001; p 1.
(209) Collins, K. D.; Washabaugh, M. W. *Q. Rev. Biophys.* **1985**, *18* (4), 323.
(210) Huglin, M. B.; Radwan, M. A. *Polym. Int.* **1991**, *26*, 97.
(211) Huglin, M. B.; Radwan, R. A. *Makromol. Chem.* **1991**, *192*, 2433.
(212) Nagarajan, R.; Ganesh, K. *J. Chem. Phys.* **1989**, *90*, 5843.
(213) Tuzar, Z.; Kratochvil, P. *Surf. Colloid Sci.* **1993**, *15*, 1.
(214) Baines, F. L.; Armes, S. P.; Billingham, N. C.; Tuzar, Z. *Macromolecules* **1996**, *29*, 815.
(215) Ishihara, K. *Trends Polym. Sci.* **1997**, *10*, 275.
(216) Ueda, T.; Oshida, H.; Kurita, K.; Ishihara, K.; Nakabayashi, N. *Polym. J.* **1992**, *24*, 1259.
(217) Sugiyama, K.; Shiraishi, K.; Okada, K.; Matsuo, O. *Polym. J.* **1999**, *31*, 883.
(218) Ishihara, K.; Aragaki, R.; Ueda, T.; Watenabe, A.; Nakabayashi, N. *J. Biomed. Mater. Res.* **1990**, *24*, 1069.
(219) Ishihara, K.; Ziats, N. P.; Tierney, B. P.; Nakabayashi, N.; Anderson, J. M. *J. Biomed. Mater. Res.* **1991**, *25*, 1397.
(220) Kojima, M.; Ishihara, K.; Watanabe, A.; Nakabayashi, N. *Biomaterials* **1991**, *12*, 121.
(221) Andrews, C. S.; Lloyd, A. W.; Sharma, D. P.; Hall, B.; Hanlon, G. W.; Denyer, S. P. *Vision Res.* **1996**, *36*, 325.
(222) Lloyd, A. W.; Dropcova, S.; Mikhalovsky, S. V.; Denyer, S. P.; Gard, P. R.; Hanlon, G. W.; Olliff, C.; Faragher, R. G. A.; Bowers, R. W. J.; Hall, B.; Muir, A.; Jones, S.; Rosen, P.; Riding, M. *Vision Res.* **1996**, *36*, 73.
(223) Andrews, C. S.; Denyer, S. P.; Hanlon, G. W.; Lloyd, A. W.; Hall, B.; Bowers, R. W. J. *Invest. Opthalmol. Visual Sci.* **1997**, *38*, 2401.
(224) Lowe, A. B.; Vamvakaki, M.; Wassall, M. A.; Wong, L.; Billingham, N. C.; Armes, S. P.; Lloyd, A. W. *J. Biomed. Mater. Res.* **2000**, *52*, 88.

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