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Polymeric Betaines: Synthesis, Characterization, and Application

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Abstract This review summarizes mostly the literature data accumulated during the last decade on betaine-type polyampholytes. Synthetic pathways to polybetaines consisting of radical polymerization, the Michael addition reaction, and polymer-analogous transformation are discussed together with methods of controlled polymerization, such as group transfer polymerization, atomic transfer radical polymerization, and reversible addition fragmentation transfer. The role of intra- and interchain associates resulting in insolubility in pure water due to the formation of ionically cross-linked network structures, and solubility in saline water because of the disruption of the ionic networks, are outlined. Attention is also paid to the recent advancement of hydrophobically modified polymeric betaines with emphasis on phospholipid-containing vinyl polymers. Polymer complexes of polybetaines, in particular interpolyelectrolyte, polymer–surfactant, and polymer–metal complexes, are considered in the light of the competition between intra- and intermolecular ionic contacts and the cooperative character of interactions. Stimuli-sensitive behavior and morphological changes of polybetaine hydrogels triggered by

changes of the pH, ionic strength, water–organic solvent mixture, metal complexation, and DC electric field are discussed with respect to the ionization state of the macromolecules and the thermodynamic quality of solvents, as well as osmotic, chelating, and polarization effects. Some application aspects of polybetaines in medicine, biotechnology, hydrometallurgy, and the oil industry are also discussed.

Keywords Application · Complexes · Polymeric betaines · Solutions and gels · Zwitterions

Abbreviations

AMBNa	Sodium 3-acrylamido-3-methylbutanoate
AMPDAPS	3-[(2-Acrylamido-2-methylpropyl)dimethylammonio]-1-propanesulfonate
APDAPS	3-[*N*-(3-Acrylamido)propyl-*N*,*N*′-dimethylammonio]-propanesulfonate
APDMAE	2-(3-Acrylamidopropyldimethylammonio)-ethanoate
APE	Anionic polyelectrolyte
ATRP	Atom transfer radical polymerization
BMA	*n*-Butyl methacrylate
BSA	Bovine serum albumin
Chol	Cholesterol
CPE	Cationic polyelectrolyte
CRP	Controlled radical polymerization
CTA	Chain transfer agent
DADMAC	*N*,*N*-Diallyl-*N*,*N*-dimethylammonium chloride
DC	Direct current
DEAEM	2-(Diethylamino)ethyl methacrylate
DIPAEM	2-(Diisopropylamino)ethyl methacrylate
DLS	Dynamic light scattering
DMAAPS	*N*,*N*-Dimethyl(acrylamidopropyl)ammonium propanesulfonate
DMAEM	*N*,*N*-Dimethylaminoethyl methacrylate
DMAPS	*N*,*N*-Dimethyl-*N*-(2-methacryloyloxyethyl)ammonium propanesulfonate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EDMA	Ethylene dimethacrylate
EDTA	*N*,*N*-Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
GPC	Gel-permeation chromatography
GTP	Group transfer polymerization
HPLC	High-performance liquid chromatography
IEP	Isoelectric point
IPC	Interpolyelectrolyte complexes
LB	Langmuir–Blodgett
LCST	Lower critical solution temperature
MAA	Methacrylic acid
MEMA	2-(*N*-Morpholino)ethyl methacrylate
MPC	2-Methacryloyloxyethyl phosphorylcholine
NaPSS	Poly(styrenesulfonate sodium salt)
NIPAM	*N*-Isopropylacrylamide
PAA	Poly(acrylic acid)
PAAm	Polyacrylamide

PAESD	Poly(diallylaminoethanoate-*co*-sulfur dioxide)
PAMPS	Poly(2-acrylamido-2-methylpropanesulfonic acid)
PBA	Poly(butyl methacrylate)
PCB	Polycarbobetaine
PCEAC	Poly(carboxyethyl 3-aminocrotonate)
PCEAC-Ala	Poly(carboxyethyl 3-aminocrotonate) modified by β-alanine
PCEAC-Ea	Poly(carboxyethyl 3-aminocrotonate) modified by ethanolamine
PCEAC-Gly	Poly(carboxyethyl 3-aminocrotonate) modified by glycine
PCEAC-Lys	Poly(carboxyethyl 3-aminocrotonate) modified by lysine
PCECHAC	Poly(carboxyethyl 3-cyclohexylaminocrotonate)
PCEPAC	Poly(carboxyethyl 3-propylaminocrotonate)
PCMEDDAC	Poly3-[(2-carboxy-1-methylethyl)dodecylaminocrotonate]
PDADMAC	Poly(*N*,*N*-diallyl-*N*,*N*-dimethylammonium chloride)
PDI	Polydispersity index
PDMAPAA-Q	Quaternized poly*N*-[3-(dimethylamino)propyl]acrylamide chloride
PDMAPS	Poly[3-dimethyl(methacryloyloxyethyl)ammonium propanesulfonate]
PEG	Poly(ethylene glycol)
PEI	Polyethyleneimine
PEO	Poly(ethylene oxide)
PHMG	Poly(hexamethylene guanidine)
PMAA	Poly(methacrylic acid)
PMMA	Poly(methyl methacrylate)
PNIPAM-PC	Phosphorylcholine-based poly-*N*-isopropylacrylamide
polyAMPS	poly(2-acrylamido-2-methylpropanesulfonic acid)
polyCEACPhos	Poly(carboxyethyl 3-aminocrotonate) modified by phosphatidylethanolamine
polyTRIM	Poly(trimethylpropane trimethacrylate)
PPD	Pour point depressant
PPO	Poly(propylene oxide)
PSB	Polysulfobetaine
PVA	Poly(vinyl alcohol)
PVP	Poly(*N*-vinylpyrrolidone)
RAFT	Reversible addition fragmentation chain transfer
UCST	Upper critical solution temperature
VPPS	2-Vinylpyridiniopropanesulfonate
XPS	X-ray photoelectron spectroscopy
ZPE	Zwitterionic polyelectrolyte
a	Exponent of Mark–Kuhn–Houwink equation
A_2	Second virial coefficient
α	Ionization degree
α_e	Electrostatic expansion factor
$C_{protein}$	Protein concentration
C_s	Low molecular weight salt concentration
d_h	Hydrodynamic diameter
E	Voltage
E_A	Activation energy
$[\eta]$	Intrinsic viscosity
η_{sp}/C	Reduced viscosity
G_{el}	Electrostatic Gibbs energy
I_E	Fluorescence intensity of excimer

I_M	Fluorescence intensity of monomer
k_i	($i = 1, 2, 3, \ldots$) Microscopic ionization constant
K_i	($i = 1, 2, 3, \ldots$) Macroscopic ionization constant
K_t	Tautomeric constant
L	Distance
M_n	Number average molecular weight
M_w	Weight average molecular weight
μ	Ionic strength of the solution
pK_a	Ionization constant of acidic group
pK_b	Ionization constant of basic group
pH_c	Boundary between the primary and nonassociative phases
pH_{iep}	Isoelectric pH
pH_ϕ	Boundary between the primary and aggregate phases
R	Molar ratio of polyelectrolyte/polybetaine
R_g	Radius of gyration
R_h	Hydrodynamic radius
R_p	Propagation rate
t	Time
T_g	Glass transition temperature
Z_{pr}	Protein charge

1 Introduction

Polymeric betaines (also referred to as polyzwitterions) are macromolecules containing identical numbers of anionic and cationic species on the same monomer units. Thus, they present a special case of polyampholytes. In dependence on the nature of the ionic groups, polymeric betaines may be grouped into various subclasses, the most widespread ones being polycarbobetaines, polysulfobetaines, and polyphosphobetaines. The specific properties of polymeric betaines are dominated by the number and type of zwitterionic groups. In combination with hydrophobic and hydrophilic fragments, polymeric betaines can form well-defined nanosized assemblies, such as spheres, capsules, ultrathin films, or structured hydrogels. Also, self-organized systems such as monolayers, Langmuir–Blodgett (LB) multilayers, and vesicles are easily formed from hydrophobized polymeric betaines. Particularly, polyphosphobetaines—phospholipid-analogous polymers—have attracted much attention for the mimicking of biomembranes, good bio- and hemocompatibility, and nontrombogenicity. Moreover, the structural and behavioral similarity of polybetaines to biopolymers and biomembranes gives access to models for protein folding, or to biomimetic functions. Application areas of polybetaines include enhanced drag reduction, oil recovery, catalysts, drug delivery systems, and cosmetic and pharmaceutical formulations.

2
Synthesis and Structure of Polymeric Carbo-, Sulfo-, and Phosphobetaines

As the synthesis of polymeric betaines has already been the subject of several reviews [1–5], this chapter is focused on the developments and progress made during the last decade.

The polybetaines (or "polyzwitterions") are dipolar species, in which the cationic and anionic groups are separately bound to the same monomer unit and can be completely dissociated in a medium of sufficient dielectric permittivity. Typically, the use of the term "polybetaine" implies that the cation is a permanently cationic species, such as fully quaternized ammonium or phosphonium groups, and that the coexistence of the different charges applies to a broad range of physicochemical conditions, e.g., pH and ionic strength. The following overview also contains copolymers made of at least one zwitterionic monomer, as well as alternating copolymers of cationic and anionic monomers, giving rise to a zwitterionic constitutional repeat unit. However, polymers for which the zwitterionic structure is in equilibrium with a nonpolar form (such as polymeric merocyanines), or mesoionic polymers and polymeric ylides, are not discussed in this overview, except for some brief remarks. Also excluded are polyampholytes synthesized by statistical copolymerization of cationic and anionic monomers or corresponding ion pairs, as the oppositely charged groups are not regularly distributed within such copolymers.

As for any other functional polymer, polymeric betaines are accessible by two different synthetic routes: (1) the polymerization of zwitterionic monomers or (2) the zwitterionic functionalization of reactive precursor polymers. Both routes have inherent advantages and disadvantages. The polymerization of the zwitterionic monomers leads to polymers with 100% betaine functionality, but their molecular characterization is difficult for several reasons. For instance, the conformation of the polymers in aqueous solution is very sensitive, not only to the ionic strength but also to the type of added salt, and in the case of polycarbobetaines also to the pH. Furthermore, polymeric zwitterions often exhibit strong interactions with other matter, e.g., chromatographic columns. Hence, reliable GPC or HPLC measurements are very difficult to perform, if at all.

In contrast to the direct polymerization of zwitterionic monomers, the polymerization of precursor monomers is generally easy to conduct and leads to reactive polymers with adjustable molecular parameters whose characterization can usually be carried out without problems. However, neighboring group effects may involve complex reaction kinetics during the chemical functionalization to the betaine form, and the polymer-analogous reaction cannot be carried out to 100% yield in every case. Nevertheless providing a high yield, this strategy leads to well-defined polymeric betaines. Using different reagents, polymers with varied chemical structure but constant degree

of polymerization are available by this strategy. This is most useful for all investigations concerning structure–property–performance relationships.

The most widespread chemical classes of polybetaines are carbo-, sulfo-, and phosphobetaines, i.e., polymers with repeat units bearing simultaneously a quaternized ammonium group and a carboxylate, a sulfonate, or a phosphate group, respectively. These three classes will be focused on in the following discussion. Mostly, these polybetaines are prepared by free radical polymerization by virtue of the tolerance of this method to many functional groups and the presence of water, keeping in mind that most zwitterionic monomers are more or less hygroscopic. The preference for free radical polymerization was for a long time a major obstacle to preparing well-defined (model) polymers or complex polymer architectures, such as block copolymers. Therefore, the newly emerging methods of the so-called controlled radical polymerization (CRP) of both the zwitterionic and the reactive precursor monomers has given a fresh impetus to polybetaine synthesis in recent years [6, 7]. CRP of the precursor monomers in organic solvents or in bulk is now well known, but CRP in aqueous media has been established, too [4, 8, 9]. Atom transfer radical polymerization (ATRP) and particularly the reversible addition fragmentation transfer (RAFT) method are promising routes to overcome certain shortcomings in the polymerization of zwitterionic monomers. CRP in aqueous solution has not only been demonstrated to be a convenient method to polybetaines with defined end groups, but also to block copolymers containing betaine blocks. Moreover, the narrow molecular weight distributions of betaine polymers prepared by CRP improve and facilitate the precision of any physical or physicochemical measurement.

2.1 Polycarbobetaines

The chemical structure of most polycarbobetaines falls into one of three groups:

- Quaternary polypyrrolidinium compounds containing linear and branched alkylcarboxy groups
- Quaternary esters or amides of (meth)acrylic acid, in which the quaternary nitrogen is substituted by an alkoxy group of different chain length
- Polyzwitterions derived from polymeric heterocyclic or aromatic vinyl compounds

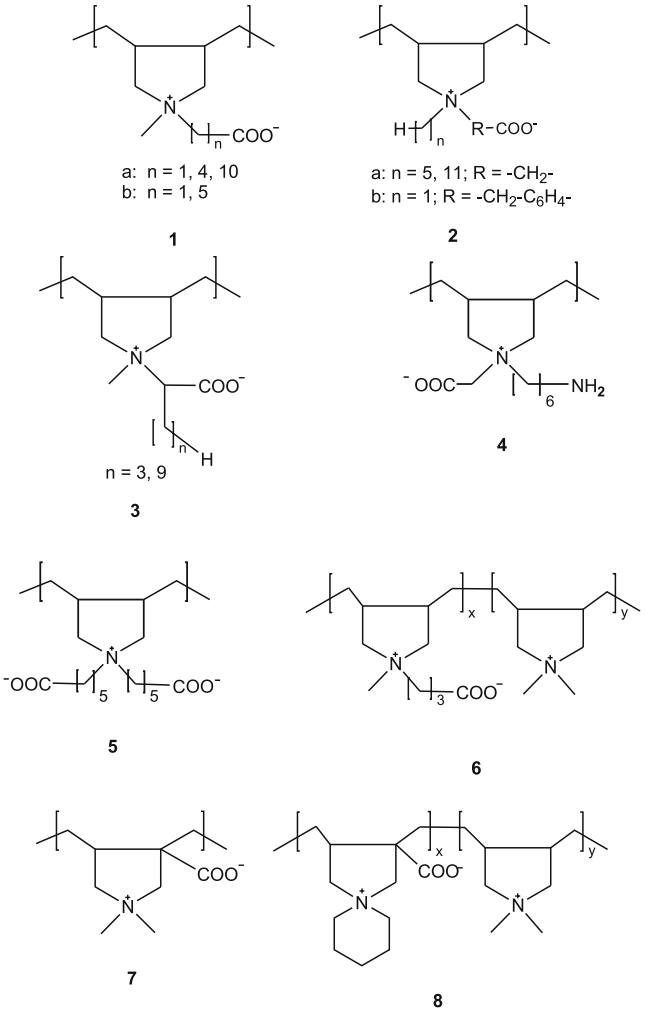
Polycarbobetaines may be synthesized via a number of reaction pathways by functionalization of suitable monomers or polymers, most commonly by reaction of a tertiary amine with a strained lactone, an α,β-unsaturated acid, a haloalkylcarboxylate, or a haloalkylcarboxylic ester followed by hydrolysis of the ester. Alternatively, the quaternization of halogen-containing

monomers and polymers with esters of amino acids were reported. Due to the possible protonation of the carboxylate moiety in aqueous (acidic) solution, the polymerization kinetics of carbobetaine monomers may be strongly pH dependent [10], but this aspect did not receive further attention. In some cases, the ionic strength of the solvent was increased by inorganic salts [11, 13], obviously to increase the solubility of the polymers.

The free radical cyclopolymerization of diallylammonium compounds leads to linear water-soluble polymers containing predominantly pyrrolidinium rings as the structural unit of the polymer chain [14, 15]. This well-established principle of polymer synthesis was used for the synthesis of the polycarbobetaines from their zwitterionic monomers (route (1), see above), which are summarized in Scheme 1.

Such polymers excel in their hydrolytic stability, as potentially labile carbon–heteroatom bonds are a priori absent. Polycarbobetaines of type **1a**, containing linear alkoxy groups with up to ten methylene groups separating N^+ and COO^-, were obtained by the polymerization of their pure monomers to provide polymers completely free of salt impurities [16, 17]. The monomers were synthesized by reacting diallylamine with an ester of ω-bromoalkanoic acids, followed by alkylation of the tertiary amine with CH_3I. The key step in the salt-free synthesis is the conversion of this cationic precursor to the zwitterionic monomer by treatment with an OH^--loaded anion-exchange resin. In a similar way, polymers **2a**, **2b**, and **3** were obtained by varying the length and the position of hydrophobic side chains [17]. However, the polymerization ability of diallylammonium monomers decreases generally with the size of the substituents on the nitrogen. Accordingly, high monomer and initiator concentrations were required to obtain polymers. The synthesis of **2a** and **3** needed peroxide initiators and a comparatively high temperature.

Several similar polycarbobetaines were prepared via polymer-analogous reaction, too (route (2), see above). Diallylammonium monomers bearing a carboxyalkyl group are reacted to form precursor polycations, which by subsequent hydrolysis of the ester group provide the desired polyzwitterions. In this way polymers **1b** were synthesized by complete hydrolysis of the cationic methyl ester precursors [18, 19]. Polymers **4** and **5** were obtained by a similar procedure [20, 21]. They are not classical polyzwitterions, because they may carry an excess charge in every monomer unit in dependence on the pH. Such so-called poly(ampholyte–electrolyte)s exhibit both polyelectrolyte and polyampholyte character simultaneously [3]. Photoinitiated cyclocopolymerization of 4-(*N*,*N*-diallyl-*N*-methylammonio)-butanoate with *N*,*N*-diallyl-*N*,*N*-dimethylammonium chloride (DADMAC) proceeded in NaCl-containing aqueous solution in a nearly ideal fashion, and resulted in copolymers **6** [22]. Copolymers with a large excess charge exhibit typical polyelectrolyte behavior, while those with a balanced charge show antipolyelectrolyte behavior like true polyzwitterions.

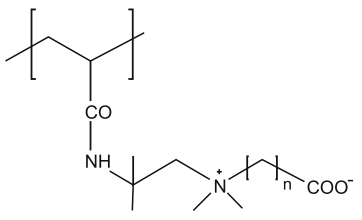


Scheme 1 Polycarbobetaines with quaternary pyrrolidinium units

An interesting extension of the cyclopolymerization strategy is the polymerization of allyl acrylate quaternary ammonium salts, where the resulting ester precursor of **7** is easily hydrolyzed by trifluoroacetic acid to the polybetaine [23]. Polyampholyte **8** was prepared by copolymerization with a high excess of DADMAC [24].

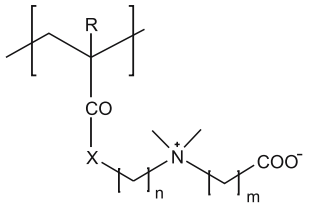
Poly(meth)acrylates and poly(meth)acrylamides offer at present the most versatile, straightforward access to polycarbobetaines (Scheme 2). Mostly, they are derived from quaternary esters or amides of (meth)acrylic acid and are prepared by free radical polymerization of the corresponding monomers. The pure monomers of **9a** [11], **9b** [12], and **9c** [13] are available by quaternization

of 2-acrylamido-2-methylpropanedimethylamine with bromoacetate, ethyl-4-bromobutyrate, or ethyl 6-bromohexanoate followed by saponification with an anion-exchange resin. Polymerization occured in 0.5 M NaBr using persulfate as initiator; the reaction was terminated at low conversion. Polymer **10a** was obtained by quaternization of poly(*N*,*N*-dimethylaminoethyl methacrylate) with 1,4-butyrolactone [25]. Polymers **10b–e** were synthesized for NMR studies and investigations of structure-dependent differences of the properties in solution [26]. Monomers were prepared by quaternization of the dimethylaminoalkyl (meth)acrylates or amides with propiolactone, and polymerized in 0.4 M aqueous solution using azo initiators. High yields were obtained after long reaction times, but such poly(3-ammoniopropanoates) are Mannich bases, and thus are subject to facile fragmentation. Light scattering studies of solutions of **10e** in deionized water indicate that the polymer exists as a mixture of individual chains and interchain associates [27]. Polymers **11** and **12** are prepared by the 2,2′-azobisisobutyronitrile-initiated polymerization of the zwitterionic monomers exhibiting surfactant properties in water. Monomers (and polymers) are tertiary acrylamides and, therefore, exhibit improved re-



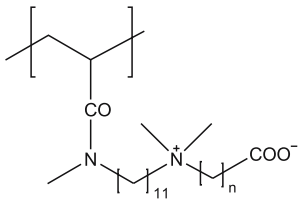
a: n =1; b: n = 3; c: n = 5

9



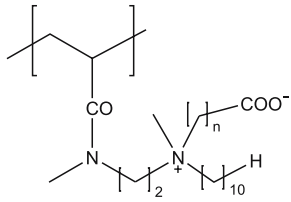
10

10	R	X	n	m
a	-CH_3	O	2	3
b	H	O	2	2
c	-CH_3	O	2	2
d	H	NH	3	2
e	-CH_3	NH	3	2



n = 1, 3

11



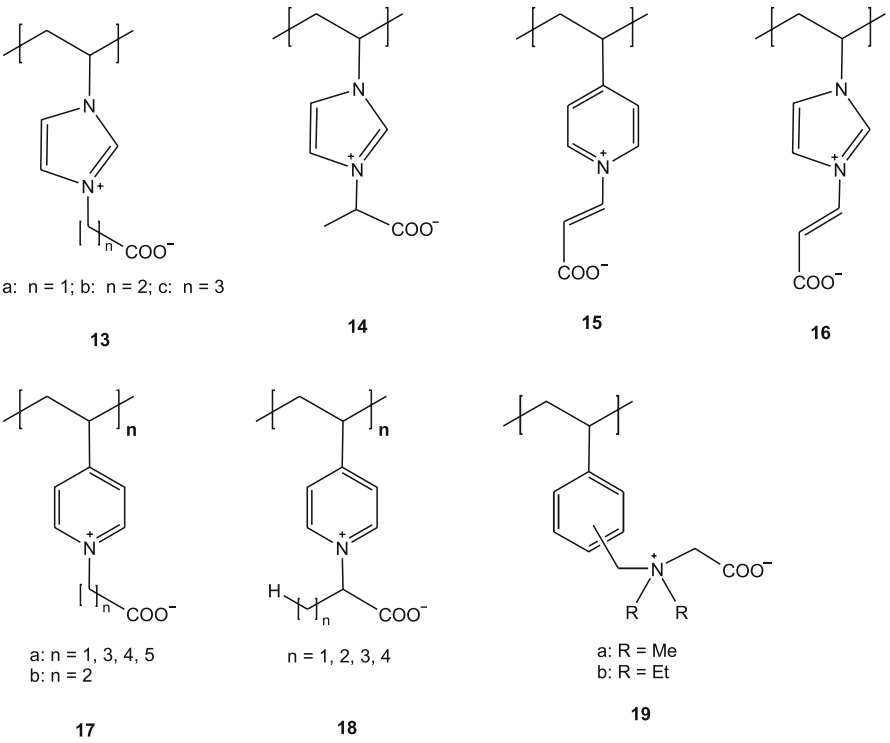
n = 1, 3

12

Scheme 2 Polycarbobetaines derived from quaternary esters or amides of (meth)acrylic acid

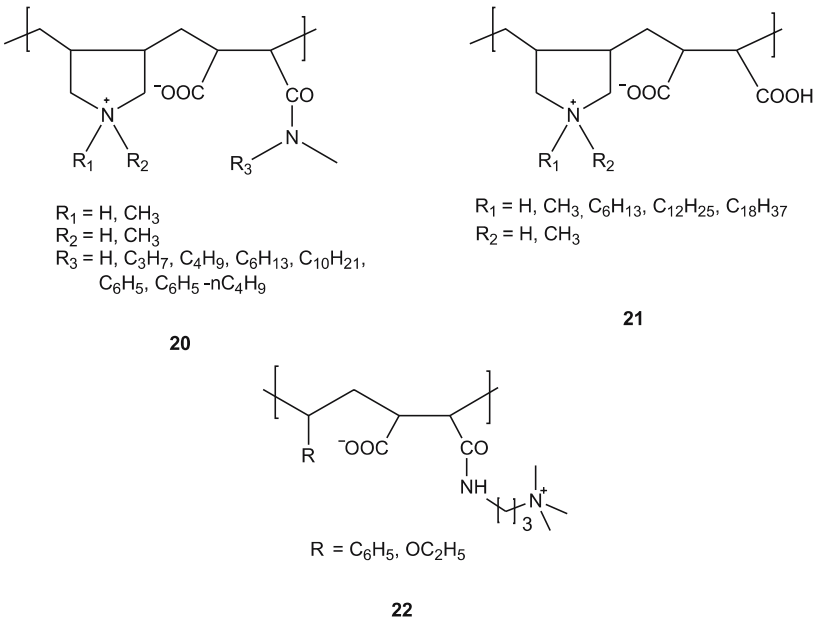
sistance to hydrolysis. This is a necessary presupposition for the success of the multistep monomer synthesis which includes the preparation of a mixed secondary–tertiary diamine, conversion to the tertiary acrylamide, alkylation by an ω-bromoester and, finally, conversion to the carbobetaine monomer by an OH^--loaded anion exchanger [28]. In this way, completely salt-free polybetaines are obtained. Notably, the "tail-end" type polymers **11** dissolve in highly polar solvents such as water. In contrast, the isomeric "head"-type polymers **12** dissolve in only some organic solvents, but are insoluble in water and, therefore, precipitate during the polymerization.

Polycarbobetaines derived from aromatic or heteroaromatic systems are listed in Scheme 3. The vinylimidazolium betaines **13** and **14** were prepared by alkylation of 1-vinylimidazole with the corresponding bromocarboxylic acid, and aqueous solution polymerization using an azo initiator [29]. Polymers **13b**, **15**, **16**, and **17b** were made by the addition of acrylic or propiolic acid to poly(4-vinylpyridine) and poly(*N*-vinylimidazole). Kinetic measurements revealed a mechanism consisting of two reactions: first, addition of two molecules of acid to the polymer; second, the formation of an equilibrium between the adduct and the betaine structure [30, 31].



Scheme 3 Polycarbobetaines derived from aromatic or heteroaromatic systems

The *N*-oxyl-mediated CRP of 4-vinylpyridine [32] and vinylbenzyl chloride [33] results in useful precursors for the synthesis of polycarbobetaines with narrow molecular weight distribution. Alkylation with bromocarboxylic acid esters, or quaternization with amino acid esters, respectively, both followed by hydrolysis of the ester moiety, led to **17a**, **18**, and **19** with very high degrees of functionalization. This approach is extremely versatile and enables the facile variation of the alkyl spacer length between both charges, the length of an additional alkyl chain at the α carbon, and different substitution at as well as hybridization of the quaternary nitrogen [34, 35]. The influence of the chemical structure on the pH-dependent solution properties in aqueous systems and the interaction of the different charges of the polybetaines were demonstrated by capillary electrophoresis and charge titration [34–37]. Acid–base titrations of **17a** and **18** became possible provided the betaines were complexed by strong polyanions [38]. An interesting pathway to linear and cross-linked polycarbobetaines based on acrylic acid and the ethyl ester of 3-amino-2-butenoic acid comprises a Michael addition reaction of these reactants followed by a spontaneous polymerization [39, 40]. Also, cross-linked betaine gels were synthesized similarly in the presence of *N*,*N*-methylenebisacrylamide. The alternating copolymerization of maleamic acids and diallylammonium derivatives results in copolymers **20** with alternating cationic and anionic charges [41–43] (Scheme 4).



Scheme 4 Polycarbobetaines derived from alternating copolymers of maleic or maleamic acid

Increasing the chain length of R_3 results in an increase of the polymerization rate, probably caused by the formation of ordered structures in the monomer solution, as well as an increase of the surface-active properties of the polymers [42]. Polycarbobetaines **20** (R_1, $R_2 = CH_3$; $R_3 = H$, C_6H_5, C_6H_5-n-C_4H_9) form complexes with fatty acids which self-assemble into nanoparticles with sizes in the range of 3–5 nm [43]. Alternating copolymerization is also successful with maleic acid to give **21** [41, 44], the water solubility of which decreases with increasing length of R_1 [44]. Polymers **21** are used to prepare new organic–inorganic blends [45, 46], and multimetallic oxide catalysts therefrom after calcination.

Carbobetaine units are employed in many copolymers with uncharged monomers. Examples are the alternating copolymers of **1a** ($n = 1$) [47], **4** [20] or **5** [21] with SO_2, or alternating copolymers **22** with betaine structures derived from maleamic acid [48, 49].

Statistical copolymers were reported for *N*-vinylimidazole and **13b** [50], for acrylamide with **9a** [11], **9b** [12], and **9c** [13], and for terpolymers of acrylamide, sodium acrylate, and **9b** [51]. Several hydrolytically stable ammonioacetate and pyridiniocarboxylate monomers based on isobutylene with variable length of hydrophobic side chains did not homopolymerize, but these monomers with surfactant properties are suited for copolymerization with electron-poor monomers [52].

2.2 Polysulfobetaines

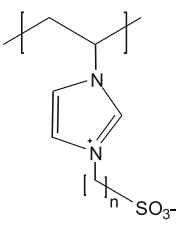
Similar to polycarbobetaines, the chemical structure of polysulfobetaines can be subsumed in several groups, where the different polymers bear an alkylsulfonate group. Most widespread are:

- Quaternary polypyrrolidinium compounds
- Quaternary esters or amides of (meth)acrylic acid
- Polyvinylpyridinium or polyvinylimidazolium compounds
- Ionenes

Also, various unconventional polymerizable sulfobetaines have been prepared occasionally in the context of hydrophobized polybetaines, and will be discussed in Sects. 2.5 and 4.

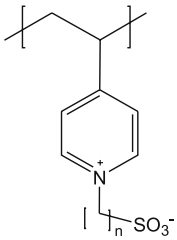
Sulfobetaines are typically prepared by alkylsulfonation of a monomeric or polymeric tertiary amine with strained sultones, usually 1,3-propanesultone or 1,4-butanesultone. An alternative route is the reaction of tertiary amines with a haloalkylsulfonate. Most of the early investigations on polymeric betaines relate to the sulfo derivatives **23a–e**, **24**, **25**, and **26** listed in Scheme 5 [1–4, 178].

In recent years, only a few new polysulfobetaines have been described. Polymers containing pyrrolidinium rings were synthesized by cyclopolymer-



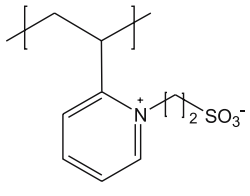
n = 2, 3, 4

24



n = 3, 4

25



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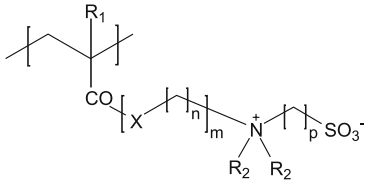


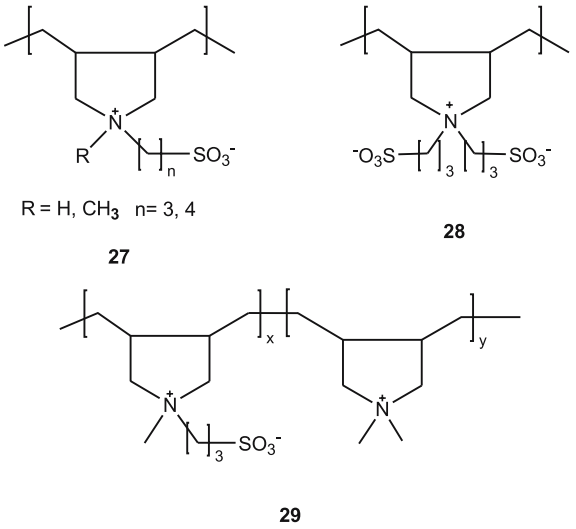
23

23	R_1	X	n	m	R_2	p
a	H	NH	3	1	$-CH_3$	3
b	$-CH_3$	O	2	1	$-CH_3$	3
c	H	O	2	1	$-CH_3$	3
d	$-CH_3$	O	2	2,3,4	$-CH_3$, $-C_2H_5$	4
e	$-CH_3$	NH	3	1	$-CH_3$	3

Scheme 5 Polysulfobetaines compiled in several reviews

ization of the corresponding diallylammonium sulfobetaines (Scheme 6). The monomers of **27** were prepared by the usual sultone procedure [17, 28, 53, 54]. The poly(electrolyte–zwitterion) **28** [55] and the polyampholyte copolymer **29** [56] are analogues to **5** and **6.** The photoinitiated copolymerization process leading to **29** is a random one; the reactivity ratios were determined by NMR spectroscopy. Cyclocopolymers containing less than 40 mol % of sulfobetaine show classical polyelectrolyte behavior.

As for polycarbobetaines, mechanistic studies of the polymerization of these sulfobetaine monomers are scarce. An example is the investigation of the influence of the ionic strength on the propagation rate of some ammoniosulfonates, which increases after adding NaCl [57]. Kinetic investigations of the polymerization of **23a** indicate that high monomer conversion can be achieved at lower temperatures. The conversion is enhanced in the presence of various salts in aqueous solution [58]. FTIR studies of the persulfate-initiated polymerization of **23b** in water showed significant changes of the overall rate equation and a decrease of the overall activation energy after adding inorganic salts [59].

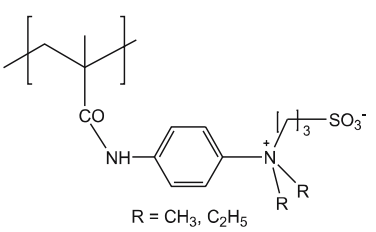


Scheme 6 Polysulfobetaines containing quaternary pyrrolidinium moieties

Several papers compare the properties of sulfobetaine (meth)acrylic polymers. NMR spectra and solution properties of **23a** and **23b** [59, 60] are correlated with data from the corresponding polycarbobetaines [26]. The photophysical and solution properties of pyrene-labeled **23c** were studied in terms of fluorescence emission. Addition of surfactants induces the formation of mixed micelles in aqueous solution [61]. Excluded volume effects of the unlabeled polymer were measured by light scattering [62], its adsorption on silica was studied by adsorbance measurement and ellipsometry [62, 63], and the electrostimulated shift of the precipitation temperature was followed at various electric field intensities [64]. Polysulfobetaines may accelerate interionic reactions, e.g., oxidation of ferrocyanide by persulfate [65]. The thermal and dielectric properties of polysulfobetaines **23d** were investigated. The flexible lateral chain of the polymers decreased T_g, for which a linear relationship with the number of C atoms was shown [66, 67].

A series of sulfobetaine monomers derived from *N*,*N*-dialkylaminophenylmethacrylamide were synthesized using conventional pathways and polymerized to give polymers **30** (Scheme 7). The NMR spectra and solution properties were compared with those of **31** and the corresponding cationic polyelectrolytes [68, 69].

Polysulfobetaines derived from alternating styrene–maleic anhydride copolymers **32** are easily prepared by ring opening of the anhydride moiety with 3-dimethylaminopropylamine, imidizing the resulting poly(amic acid) by heating, and alkylation with propane sultone [70–72]. For investigations of structure–property relationships additionally to **32b**, the polymers **33** and **34** were synthesized [71]. The ionene-like polymer **33** was prepared



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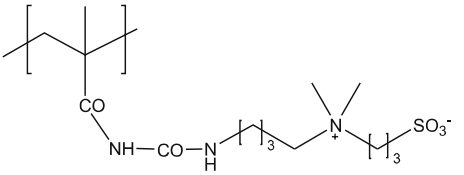

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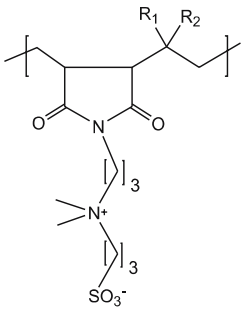
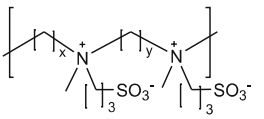


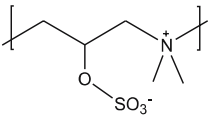
a: R_1 = H, R_2, C_6H_5
b: R_1, R_2 = H, H; H, CH_3; CH_3, CH_3; H, $C_{16}H_{33}$

32



x, y = 3, 6; 6, 6 ; 6, 10

33



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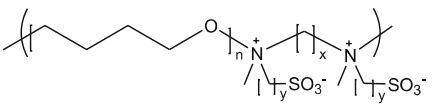
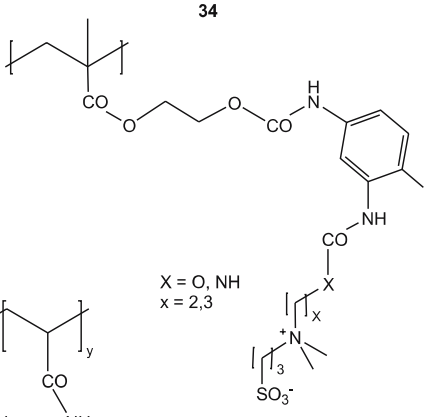


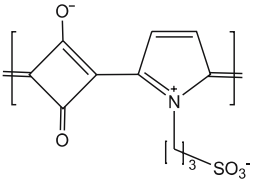
x = 3,6 y = 3,4

35



X = O, NH
x = 2,3

36



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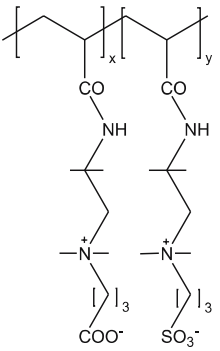


38

Scheme 7 Polysulfobetaines prepared for investigations of structure–property relationships

by dealkylation of a typical quaternary ionene polymer followed by reaction with propane sultone. The zwitterionic ionene **34** is made by reacting stoichiometric amounts of dimethylamine and epichlorhydrin, followed by sulfatation of the OH group. In the series **32b**, **33**, and **34**, the charged groups are increasingly moved from the side chain to the polymer backbone. This reduces markedly the solubility in aqueous solutions, as apparently the intermolecular Coulombic interactions are increased. Hydrophobic substituents and higher charge densities enhance these effects [71]. Several segmented poly(tetramethylene oxide) zwitterionomers **35** were investigated with respect to phase separation [73, 74]. Polysulfobetaines **36** were prepared via functionalization of the urethanes derived from 2,4-toluene diisocyanate, which bear a tertiary amino group [75].

Alternating sulfobetaine copolymers were reported for **27** with SO_2 [76], by analogy with the carbobetaine analogues described above. A very different approach was chosen for the alternating copolymer poly(ampholyte–electrolyte) **37**, by condensing sodium 3-(pyrrol-1-yl) propanesulfonate with squaric acid [77].

Many more papers deal with statistical copolymers containing sulfobetaine units, mostly prepared by free radical polymerization in solution. This includes copolymers of **23e** [78] or **23b** [79, 80] with butyl acrylate, of **23a** with styrene or *N*-vinylpyrrolidone [81], of **23e** with *N*-isopropylacrylamide (NIPAM) [82], and of **30** ($R = CH_3$) with methacrylamide [83]. Copolymers of *N*,*N*-dimethylmaleimidopropylammonium propanesulfonate and acrylamide [84] with a structure similar to **32** were labeled with naphthalene for investigations of the solution behavior on the microscopic level [85]. Statistical copolymers **38** containing both carbobetaine and sulfobetaine groups were obtained from the corresponding monomers in aqueous solution containing NaBr [86]. Their solubility behavior is complex and varies with composition, pH, and ionic strength.

Water-soluble graft copolymers of polysaccharides and polysulfobetaines were synthesized by grafting 3-dimethyl(methacryloyloxyethyl)ammonium propanesulfonate (DMAPS) onto hydroxyethyl cellulose using a ceric ammonium nitrate/EDTA initiating system [87]. Similar terpolymers containing additionally acrylamide were also described [88]. Sulfobetaine copolymers found a particular interest as hydrogels, e.g., for thermoreversible crosslinked hydrogels of NIPAM and 1-(3-sulfopropyl)-2-vinylpyridine [89] or DMAPS together with a cationic monomer [90], 1-vinyl-3-(3-sulfopropyl)imidazolium betaine [91], or *N*,*N*-dimethyl(acrylamidopropyl)ammonium propanesulfonate (DMAAPS) [92]. Other sulfobetaine hydrogels were made by copolymerization of 2-hydroxyethyl methacrylate and DMAPS [93], and superabsorbents were obtained by the copolymerization of sodium acrylate and DMAAPS together with a cross-linker [94, 95].

Polysulfobetaines were also used to modify surfaces. For instance, polysulfobetaines were grafted onto argon plasma-pretreated polytetrafluorethy-

lene films and the chemical composition of the surfaces was studied by X-ray photoelectron spectroscopy [96, 97]. Also, silica gel surfaces were modified by polysulfobetaines for different purposes, by grafting of 2-(dimethylamino)ethyl methacrylate with subsequent reaction with propanesultone [98]. Silicone rubber was also grafted after ozonization directly with betaine monomers [99]. In another example, polysulfobetaine grafts were prepared by first self-assembling a disulfide-functionalized azo initiator on a gold surface, and subsequently initiating the polymerization of the zwitterionic monomer to produce an ultrathin film of **23e** as a stimulus-sensitive hydrogel layer [100].

2.3 Polyphosphobetaines

Most of the known polyphosphobetaines are polymeric phospholipid analogues, as many research groups have been interested in mimicking lipid bilayer biomembranes with such polymers (see Sect. 4). The work up to the mid-1990s is described in the excellent review of the late D. O'Brien [101], who pioneered the field together with the groups of D. Chapman, S.L. Regen, H. Ringsdorf, and E. Tsuchida. Whereas the basic lecithin structure is maintained in most of these approaches, a plethora of polymerizing groups such as diynes [102, 103], (meth)acrylates [104–108], acrylamides [104–106], styrenes [109], dienes [110], and polyunsaturated fatty acids [111] have been incorporated at various positions of the phosphorylcholine moiety or of the fatty acid chains. Polymerization is mostly achieved by redox-initiated, or thermally or photochemically induced free radical polymerization of the zwitterionic monomers. Occasionally, the (different) polymerizable groups were cumulated in such reactive lipids, in order to achieve stepwise polymerization and cross-linking of self-organized structures [112–114]. An interesting extension of the use of such polymeric lipids is the preparation of organic nanotubes, as reviewed recently [115].

A major difficulty in the synthesis used to be the incorporation of the phosphatidylcholine moiety into the polymerizable lecithins. Nowadays, the main pathway to phosphobetaine vinyl monomers is the reaction of an OH group containing (meth)acrylate or (meth)acrylamide with 2-chloro-2-oxo-1,3,2-dioxaphospholane, with subsequent ring opening by trimethylamine leading to phosphorylcholine-containing compounds. This strategy is highly versatile [5]. Many of the known polymers which do not directly copy natural lecithins contain 2-methacryloyloxyethyl phosphorylcholine (MPC) as structural unit. Polymers based on MPC are well known for excellent bio- and blood compatibilities. They have delivered clinically proven benefits in various biomedical applications. A review compiles the literature up to 1997; attention is mainly focused on the development of phosphatidylcholine-analogous polymers, describing the synthesis of vinyl phospholipid poly-

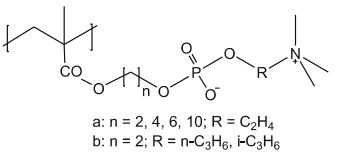
mers, phospholipid-modified polypeptides, phospholipid organosiloxanes, and phospholipid urethanes [5] (Scheme 8). The published data of the last few years continue this development.

The kinetics of free radical polymerization of MPC leading to **39a** ($n = 2$) were studied in ethanol [116] and water [117]. In both cases a higher than normal dependence of the overall rate of polymerization on the monomer concentration was observed due to monomer aggregation. The presence of alkaline halides accelerated the polymerization in aqueous media [118]. Polymers **39a** with an increasing number of CH_2 groups between the ester and the phosphate group ($n = 4$, 6, 10) are available in good yields [118]. Several other polymeric methacrylates **39b** [119, 120] and fumarates **40** [121] bearing a phosphorylcholine moiety were synthesized and characterized. The phospholipid-analogous polymers **41a** and **41b**, prepared by radical polymerization in water, show the properties of polyelectrolytes in polar solvents [103]. Similar results were obtained with **42** [105]. Polymer **41b** containing a vitamin E moiety was easily prepared in high yield by polymerization in chlorobenzene/methanol [106]. A stacked bilayer structure was proposed from X-ray diffraction analysis.

A multistep reaction pathway leads to polymers **43** and **44** with phosphatidylcholine moieties in the main chain and long alkyl groups in the side chain [122]. These polymers exhibit thermotropic liquid-crystalline behavior. Polyamides **45** were obtained by interfacial polycondensation; they are insoluble in any normal solvent [123]. Poly-MPC capped with cholesteryl moieties at one or both polymer ends was prepared by the radical polymerization of MPC initiated with 4,4′-azobis[(3-cholesteryl)-4-cyanopentanoate] in the presence of a chain transfer agent [124]. The self-organization of these polymers was analyzed with fluorescence and NMR measurements.

Polyurethanes were modified with phosphobetaines to improve their hemocompatibility. Polyurethanes **46** containing cholesterol were synthesized by step growth polymerization. Surprisingly, they showed the viscosity behavior of common polyelectrolytes [125]. Excellent blood compatibilities were reached by introducing long-chain alkyl groups instead of cholesterol in polymer **46** [125], or by placing the phosphate group in the side chain [126]. The latter case results again in polymers with properties similar to those of the usual polyelectrolytes. Another variation led to segmented polyurethanes with polybutadiene and phosphobetaines in the main chain and long-chain alkyl groups in the side chain [127, 128]. A further successful attempt was the grafting of MPC and similar monomers onto polyurethane surfaces [129–131].

Microspheres containing a corona of polyphosphobetaines were obtained by emulsifier-free emulsion copolymerization of methyl methacrylate and 1-methyl-2-methacrylamidoethyl phosphorylcholine [132], MPC [133], or the fumarate monomers of **40** [133], as well as by precipitation polymerization of styrene with MPC macromonomers [134]. Poly-L-lactic acid nanoparti-



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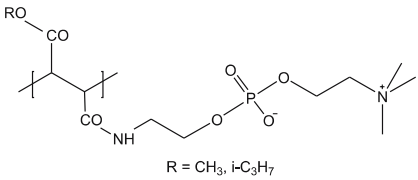

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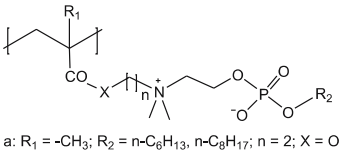

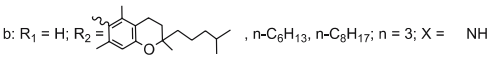

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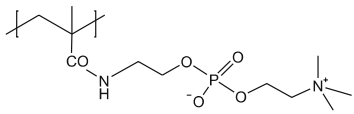

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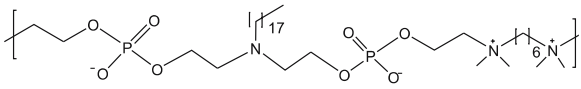

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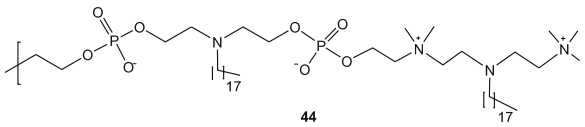

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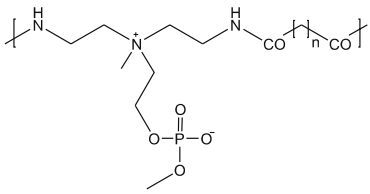

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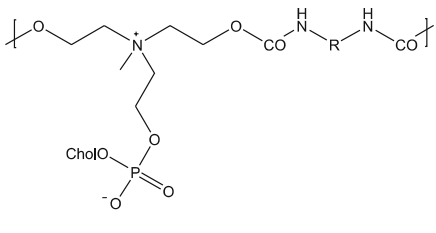
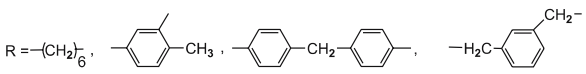




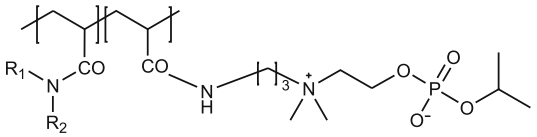
46

Scheme 8 Polymeric phospholipid analogues

cles covered with both bioinert phosphorylcholine groups and *p*-nitrophenyl ester groups are useful for immobilizing enzymes [135]. Surface modification of polypropylene membranes by tethering phosphatidylcholine analogous polymers created biocompatible interfaces [136, 137]. A similar result was obtained by reacting the OH groups of poly(acrylonitrile-*co*-hydroxyethyl methacrylate) membranes with 2-chloro-2-oxo-1,3,2-dioxaphospholane followed by ring opening with trimethylamine [138].

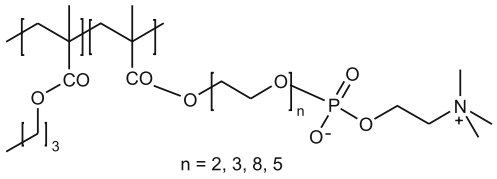
MPC is part of several statistical copolymers prepared by free radical polymerization. Copolymers with poly(ethylene glycol) monomethyl ether methacrylate show polyelectrolyte behavior [139]. The surface of copolymers with 2,2,2-trifluoroethyl methacrylate was analyzed by different methods. The amount of protein adsorbed could be strongly reduced [140]. Copolymers with 2-aminoethyl methacrylate were employed as DNA carrier [141]. The structure and hydrogen bonding of water in the vicinity of copolymers with *n*-butyl methacrylate was studied by vibrational spectroscopy [142], and copolymers with styrene were developed as effective blocking agents for the enzyme-linked immunosorbent assay (ELISA) method [143]. Several new monomers were only used for the synthesis of copolymers. Typical examples are **47**, useful for stable Langmuir–Blodgett films [144], and **48**, useful for coatings which are resistant to protein absorption [145] (Scheme 9).

Phosphobetaines are known as a component of hydrogels, too. MPC copolymers with methacrylic acid prepared by radical polymerization in water show spontaneous gelation [146]. To improve the hydrogel proper-



a: $R_1 = C_{18}H_{37}$, $R_2 = (CH_2)_8CH{=}CH(CH_2)_7CH_3$
b: $R_1 = R_2 = C_{18}H_{37}$
c: $R_1 = C_{22}H_{45}$, $R_2 = (CH_2)_8CH{=}CH(CH_2)_7CH_3$

47



n = 2, 3, 8, 5

48

Scheme 9 Statistical phosphatidyl analogue copolymers

ties a new dimethacrylate cross-linker with a phosphorylcholine-like linkage was used in the copolymerization of MPC and 2-hydroxyethyl methacrylate [147]. Cross-linking of the acrylamide derivative of **39a** ($n = 2$) with *N*,*N*-methylenebisacrylamide leads to hydrogels whose degree of swelling decreases with increasing temperature [148]. Phosphorylcholine-based statistical terpolymers were obtained by adding phosphorylcholine groups to a preformed hydrophobically modified copolymer of NIPAM with several hydrophobic comonomers [149].

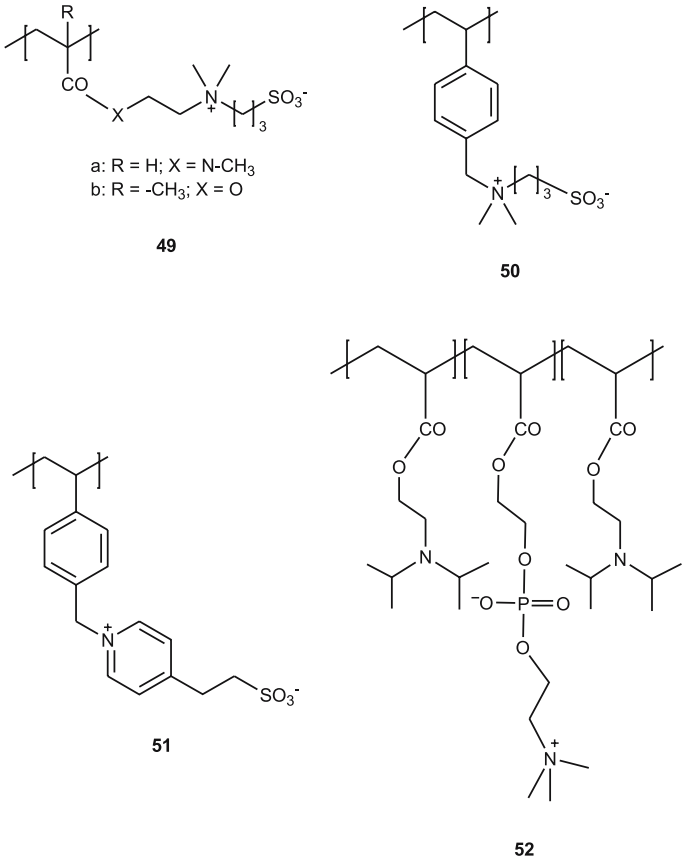
2.4 Narrowly Distributed Homopolymers and Block Copolymers

CRP is a powerful tool for the synthesis of both polymers with narrow molecular weight distribution and of block copolymers. In aqueous systems, besides ATRP, the RAFT method in particular has been used successfully. A number of uncharged, anionic, cationic, and zwitterionic monomers could be polymerized and several amphiphilic block copolymers were prepared from these monomers [150, 153]. The success of a RAFT polymerization depends mainly on the chain transfer agent (CTA) involved. A key question is the hydrolytic stability of the terminal thiocarbonyl functionality of the growing polymers. Here, remarkable progress could be achieved by the synthesis of several new dithiobenzoates [150–152].

The RAFT homopolymerization was mainly applied to vinylic sulfobetaines, for the synthesis of homopolymers as well as of block copolymers. The synthesis of the latter proceeds mainly in two steps: a macromolecular CTA of a monomer A is synthesized, which is subsequently employed in the polymerization of a monomer B. Polymers **49a**, **49b**, and **50** (Scheme 10) were prepared using 4-cyanopentanoic acid dithiobenzoate as CTA. M_w/M_n values between 1.04 and 1.08 at higher conversion were reported [154].

Recent attempts to prepare **26** by RAFT, however, failed [153]. Double hydrophilic block copolymers of NIPAM and **23e** [154], as well as of *N*,*N*-diethylacrylamide and **23b** [155], were prepared with the CTA benzyl dithiobenzoate, and exhibit LCST and UCST behavior in water. The new polymer **51** is also part of amphiphilic di- and triblock copolymers [152]. Diblock copolymers with poly(ethylene glycol) methyl ether acrylate, dimethylacrylamide, or 4-vinylstyrene sulfonate are macrosurfactants with a switchable hydrophobic block. Triblock copolymers containing additionally 4-vinylbenzoic acid differ in the nature of the hydrophilic part [152]. Near-monodisperse block copolymers of *N*,*N*-dimethacrylamide and **49a** were synthesized in different ways via macro-CTAs of both monomers as the first step. Such sulfobetaine block polymers form aggregates in pure water but are molecularly dissolved after addition of salt [152, 156, 157].

Another route to narrowly distributed sulfobetaine homopolymers and block copolymers is the functionalization of precursors prepared by group



Scheme 10 Polysulfobetaines prepared by RAFT polymerization as homopolymers and part of block copolymers

transfer polymerization (GTP). Using 2-(dimethylamino)ethyl methacrylate (DMAEM), nearly monodisperse polymeric amines were made which were betainized in high yields via 1,3-propanesultone, resulting in **23b** [158, 159]. This principle was extended to block copolymers of *n*-butyl methacrylate (BMA) and DMAEM, resulting in hydrophilic–hydrophobic sulfopropylbetaine block copolymers BMA-*b*-**23b** [158, 160].

The synthesis of narrowly distributed polycarbobetaines **17a**, **18**, and **19** has already been mentioned. Block copolymers containing these structures and styrene were prepared likely by functionalization of reactive block copolymer precursors [161]. Well-defined block copolymers with phospholipid sequences were prepared using both RAFT and ATRP techniques.

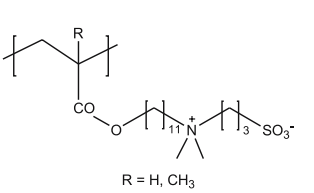
Amphiphilic block copolymers composed of poly(butyl acrylate) and poly(2-acryloyloxyethyl phosphorylcholine) were synthesized via RAFT using a poly(butyl acrylate) macro-CTA with a ratio $M_w/M_n = 1.11–1.18$. The

conversion was followed by FT-NIR spectroscopy. The polymers have a strong tendency to aggregate in different solvent compositions [162]. RAFT polymerization of MCP leads to a dithioether end-capped macro-CTA used for the preparation of block copolymers with BMA with variable block length, whose associative properties [163] and interaction with enzymes [164] were investigated. MPC can also be polymerized in aqueous media via ATRP, showing first-order monomer kinetics to high conversion in protic solvents at ambient temperature. Polymers with relatively narrow polydispersities (M_w/M_n = 1.15–1.35) were thus obtained [165, 166]. Several MPC diblock copolymers were synthesized using the same principle. Macroinitiators were employed to prepare PEO-MPC and PPO-MPC diblocks, and the sequential monomer addition route was used for the block copolymerization of MPC with 12 different methacrylic comonomers. Generally high conversions were achieved with low polydispersities of 1.1–1.3 [167]. MPC-based ABA triblock copolymers with 2-(diisopropylamino)ethyl methacrylate (DIPAEM) **52** or 2-(diethylamino)ethyl methacrylate (DEAEM), prepared by ATRP using a bifunctional ATRP initiator, lead to polymers with adjusted block length. Polydispersities of the initial MPC homopolymers prior to the addition of the comonomer were less than 1.20, and final triblock polydispersities ranged from 1.5 to 1.8. The copolymers dissolve in acids but form freestanding gels at neutral pH [168]. Similarly obtained triblock copolymers with NIPAM building the outer block form gels over a narrow temperature range [169]. Folic acid functionalized MPC-*b*-DIPAEM or MPC-*b*-DEAEM block copolymers were synthesized by ATRP using a protected primary amine-based initiator. After deprotection, folic acid was chemically conjugated via the primary amine terminus of the MPC block with a degree of functionalization in the range 38–100%. The copolymers were designed for gene delivery and encapsulation of hydrophobic drugs [170]. Using a cholesterol-based macroinitiator, the ATRP of MPC results in block copolymers whose association behavior in aqueous solution was studied extensively [171].

2.5 Polymeric Surfactants

Zwitterionic polysoaps have been considered to combine ionic and nonionic polysoap behavior advantageously. The ionic groups with an overall neutral charge render the polymer very hydrophilic, avoid problems of a LCST, and hold the possibility of modifying the properties in solution by adding salt. A series of zwitterionic vinyl surfactants free of salt contamination was prepared by attaching a polymerizable moiety to a tertiary amine followed by sulfopropylation with propanesultone. The structural variation includes the nature and the position of the polymerizable moiety while keeping the length of the hydrophobic tail constant. Thus, polymers **53–56** with "head" or "tail"-end structure were obtained by free radical polymerization in wa-

ter or ethanol [172], and the effects of added salt on the solution properties [173] as well as on the molecular packing [174] were investigated. Furthermore, several alternating SO_2-containing polysoaps like **57** were synthesized by copolymerization of olefinic zwitterionic surfactants and SO_2, and a series of zwitterionic polysoaps containing oligo(ethylene oxide) spacers such as **58** was prepared [175]. Copolymers of sulfobetainic surfactant monomers of different geometry like that corresponding to **55** and polar nonionic comonomers such as acrylamide were synthesized and their



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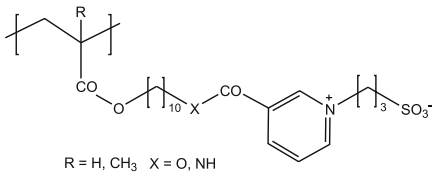

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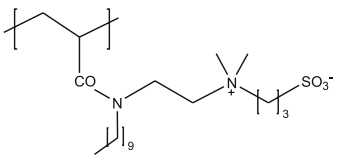

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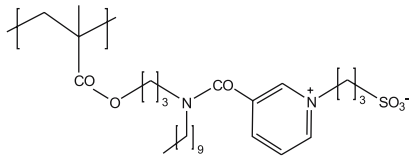

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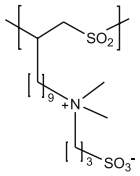

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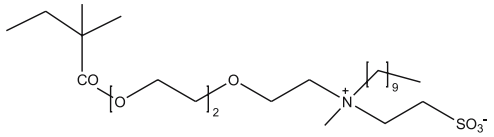

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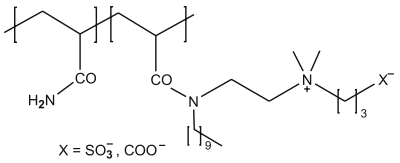

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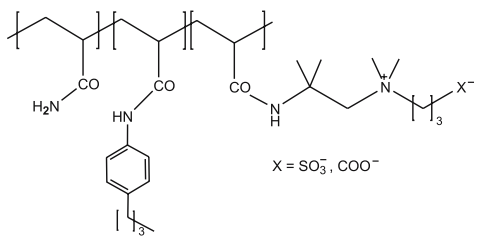

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Scheme 11 Zwitterionic polysoaps

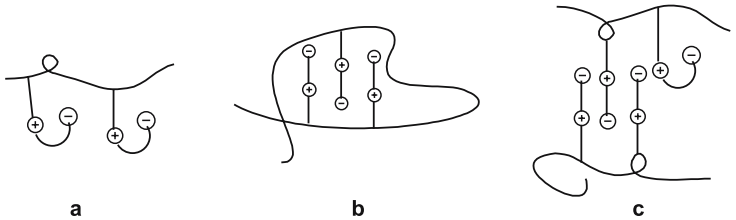
bulk and solution properties were extensively investigated [176]. A great number of polymeric surfactants all bearing the ammoniopropanesulfonate head group were prepared by radical homopolymerization of monomers containing diallyl, diene, or vinylcyclopropane moieties, thereby varying the density of surfactant side groups. The solubility of these polymers is dominated by the polymer geometry [176–178]. This work was continued by the synthesis of a series of polysulfobetaines with the principal structure of **53**, but variation of the spacer lengths and the substituents at the quaternary nitrogen. The influence of the structural variation on the bulk properties was the subject of detailed investigations [178]. A number of sulfobetaine monomers were characterized by one- and two-dimensional NMR spectroscopy [179]. Instead of synthesis by free radical chain growth polymerization, polymeric sulfobetaine surfactants were also synthesized from hydrophobized sulfopropylammonio monomers containing two olefinic groups by free radical step growth polymerization, namely via thiol/ene addition [180] (Scheme 11).

Copolymers **59** [181] and terpolymers **60** [182] were synthesized by micellar copolymerization and characterized with respect to their molecular and solution properties. The subject of further investigations was the interaction with low molecular weight surfactants [181, 183]. Another interesting use was made of hydrophobized sulfopropylammonio monomers as surface-active monomers (or "surfmers") [184]. Their use in emulsifier-free emulsion polymerizations [185] reduced the water uptake and improved the mechanical stability of the resulting filmed latexes.

3
Properties of Polybetaines in Solution, Condensed, and Gel States

The unique properties of polymeric betaines are strongly related to the interaction of the opposite charges in aqueous and aqueous salt solutions [1–4, 186]. One of the features of betaine-type polyampholytes is the tendency of the zwitterionic fragments to form a cyclic conformation of the cationic and anionic groups of neighboring monomer residues (intragroup), or a head-to-tail stacking (intrachain) within single macromolecules and interchain ion contacts between neighboring macromolecules. This results in the appearance of cross-linked networks (Scheme 12).

Therefore, polymeric betaines are usually sparingly soluble in pure water, and present gel-like characteristics, but they are soluble in salt-containing solutions. In contrast to ordinary polyelectrolytes, polymeric carboxy-, sulfo-, and phosphobetaines in dilute solutions have a very small disturbing effect on the structure of the hydrogen-bonding network of water molecules, because of the intra- and intertether proximity between the oppositely charged groups [187].



Scheme 12 Intragroup (**a**), intrachain (**b**), and interchain (**c**)salt bonds in polybetaines

According to molecular modeling calculations and NMR spectra [188], low molecular weight zwitterions are able to fold intramolecularly into a loop conformation in which the positive charge on one end of the molecule interacts with the negative charge on the other end, in dependence on the length and flexibility of the spacer. This folding motif can be useful for the design of supramolecular polymers by varying the linker length and its flexibility. The design of self-assembling molecules that are able to fold into predictable, specific conformations can help us to learn more about the self-organization, in particular protein folding processes.

Capillary electrophoresis proved to be a powerful tool for studying the intra- and interchain associations in various polycarboxybetaines as a function of the structure, the pH, and the molecular weight [35–37]. At low pH, the polymer particles migrate to the cathode side as the dissociation of the carboxylic groups is suppressed. The mobility differences of the charged species depend on their primary structure. For instance, the cationic group of **19b** is more effectively shielded by ethyl substituents than that of **19a**, which is surrounded by methyl groups. This lowers the association of the carboxylic groups with the quaternary ammonium groups. It is therefore easier to protonate the carboxylic functions in compound **19b**. The overall cationic charge of **19b** is higher, and the mobility is greater than that of **19a**. If intramolecular association prevails, the resulting electropherogram of the mixture of two samples of different molecular mass should be the overlap of the two single injections. When the electropherogram of the mixture results in a narrow peak with a mobility in between the peak maxima of the single injections, the dominating process should be intermolecular association. The intramolecular association is pH dependent. With increasing pH of the buffer solution the mobility of polycarboxybetaines drastically decreases due to the increased ionization of the carboxylic groups [36].

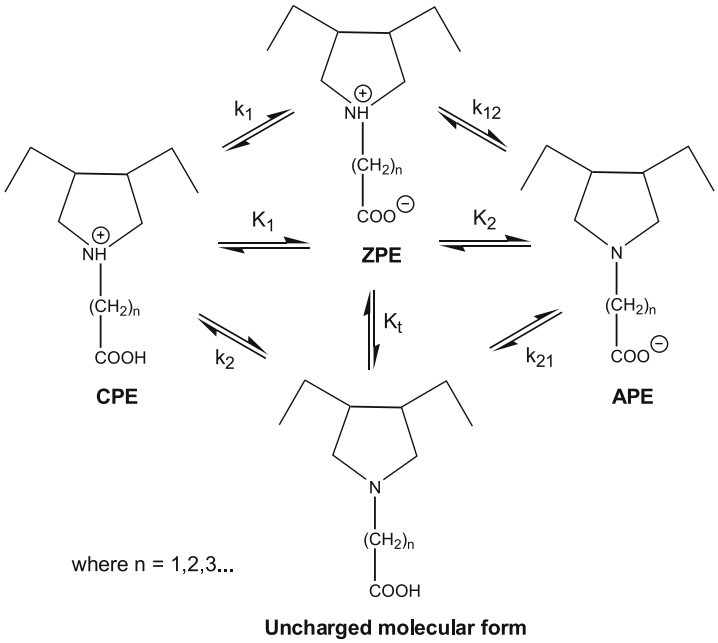
The effects of alkyl spacer length between both charged moieties with different substitution at, and with different hybridization of, the quaternized nitrogen were studied for a series of poly(carboxybetaines) derived from poly(4-vinylpyridine) and poly(vinylbenzyl chloride) by capillary electrophoresis, charge titration, and FTIR spectroscopy. A strong pH- and structure-dependent shift in electrophoretic mobilities is revealed for

the samples bearing different numbers of methylene groups between the charges [35–37]. The protonation of carboxylic units is increased with increasing charge distance and leads to enhanced mobility. The efficiency of the intramolecular electrostatic interaction is decreased by additional alkyl chains at the α carbon atoms. The "ion pair" formation ability of dimethyl- and diethylammonium acetate having sp^3 hybridization was compared with some sp^2-nitrogen-containing pyridiniocarboxylates. As expected, the intensity of interaction drops with an sp^3 hybrid orbital instead of an sp^2 ammonium ion. The findings of the FTIR measurements reveal that the association structures of the polycarboxybetaines are preformed in bulk. Strong interaction of sterically less shielded positive charges with a carboxylate moiety leads to increasing bond strength of the COO^- moiety and therefore to a higher wave number of the IR band (1643.1 cm^{-1}). The opposite happens with highly shielded cationic charges as in **19b** (1627.8 cm^{-1}) or with charges separated by four methylene spacers (1640.3 cm^{-1}). The increase in distance from one carbon up to four and ten carbons in polycarboxybetaines caused the carboxylate band to shift from 1632 to 1570 and 1561 cm^{-1} [16].

The pK_a values of ionizable groups in macromolecules can significantly differ from those of the isolated groups in solution because of interactions between neighboring ionizable groups, solvation effects, and conformational changes [189]. The approach developed in [190] for equimolar annealed polyampholytes can be applied to a comprehensive analysis of the potentiometric titration data of the polycarboxybetaines and -sulfobetaines derived from *N*,*N*-diallyl-*N*-carboethoxymethylammonium chloride and 3-(*N*,*N*-diallylammonio)-propanesulfonate [75, 191]. These zwitterionic polyelectrolytes can also exist in the form of anionic and cationic polyelectrolytes and in an uncharged form in dependence on pH (Scheme 13). The transformation from the uncharged form to the polyzwitterion or vice versa is determined by micro- and macroscopic ionization constants. The relationships between the microscopic (k_1, k_2, k_{12}, k_{21}) and macroscopic (K_1, K_2) ionization constants as well as the tautomeric (K_t) constant can be described as follows:

$$K_1 = k_1 + k_2$$
$$1/K_2 = 1/k_{12} + 1/k_{21}$$
$$K_1K_2 = k_1k_{12} = k_2k_{21}$$
$$K_t = k_1/k_2 = k_{21}/k_{12}\,.$$

As in the case of the simple amino acid glycine, the zwitterionic form of the polycarbobetaine should be more stable than its uncharged form because of $K_t \gg 1$. The polycationic form might be considered as a two-base acid having pK_a^1 and pK_a^2, which correspond to successive titration of COOH and NH^+ groups, while the polyanionic form can be considered as a two-base base with pK_b^1 and pK_b^2, which reflect the protonation of tertiary amine N groups and



Scheme 13 Transformation of zwitterionic polybetaine (ZPE) to anionic (APE) and cationic (CPE) polyelectrolytes and uncharged molecular form [191]

carboxylate ions COO^-. In its turn, the polyzwitterionic form can serve as both an acid that loses protons and is converted to the polyanion (k_{12}), or as a base that binds protons and is transformed to the polycation (k_1).

Table 1 summarizes the values of k_1 and k_{12} determined in salt-free and saline water containing 0.1 M KCl, together with the solubilities of the poly-

Table 1 Ionization constants and solubility behavior of polycarboxybetaines and -sulfobetaines in salt-free water and 0.1 M KCl solutions

Polybetaine	Salt-free water		0.1 M KCl		Solubility	
	k_1	k_{12}	k_1	k_{12}	Salt-free water	0.1 M KCl
PCB ($n = 1$)	2.52	10.70	2.66	9.87	Soluble	Soluble
PCB ($n = 5$)	3.52	—	4.36	—	Soluble	Soluble
PCB-*co*-SO_2 ($n = 1$)	—	8.73	—	7.88	Insoluble	Insoluble
PCB-*co*-SO_2 ($n = 5$)	—	8.88	—	8.04	Insoluble	Soluble
PSB ($n = 1$)	—	10.82	—	9.88	Soluble	Soluble
PSB-*co*-SO_2 ($n = 1$)	—	8.51	—	7.54	Insoluble	Soluble
PSB-*co*-SO_2 ($n = 3$)	—	—	—	—	Insoluble	Insoluble

betaines. It is evident that the presence of the electron-withdrawing SO_2 unit considerably lowers k_{12}. As can be seen from Table 2, the polycarbobetaine with the shorter spacer ($n = 1$) is easier to protonate. The microscopic ionization constant k_1 of the polycarbobetaine with $n = 5$ in 0.1 M KCl is close to those of polycarboxylic acids. The strong acidic character of the polycarbobetaine with $n = 1$ may be attributed to a "nearest-neighbor effect" specific for polyampholytes [192]. Also, the changes in the dissociation constant of a weak acid (carboxyl) in the vicinity of strong basic (ammonium) groups based on Hill's theory should be taken into account [189].

The distribution of the cationic, anionic, and zwitterionic forms of the polyampholyte calculated from the k_1 and k_{12} and the viscosity data show that polybetaine molecules exist in the zwitterionic form and as a compact coil in the vicinity of the isoelectric point (IEP) (Fig. 1). Deviation from the IEP leads to prevalence of the anionic or cationic forms and expanding conformations.

The viscometric curves of the polyzwitterion form are not symmetrical, e.g., the increment in the reduced viscosity is significantly lower on the acidic side in contrast to the basic region. The reason is either the formation of hydrogen bonds between carboxylate ions and H^+ of the type $COO^- \cdots H^+ \cdots {}^-OOC$ that reduce the hydrodynamic volume of the polybetaines, or the specific binding of chloride ions to the protonated amine groups.

The intramolecular dipolar interaction in solution should decrease with increasing size of the substituents in the order: pyridinium $> N^+(CH_3)_2 > N^+(C_2H_5)_2$ [34]. The potentiometric titration curves of polybetaines resemble those of the titration of weak acids and weak bases. Measurements of the

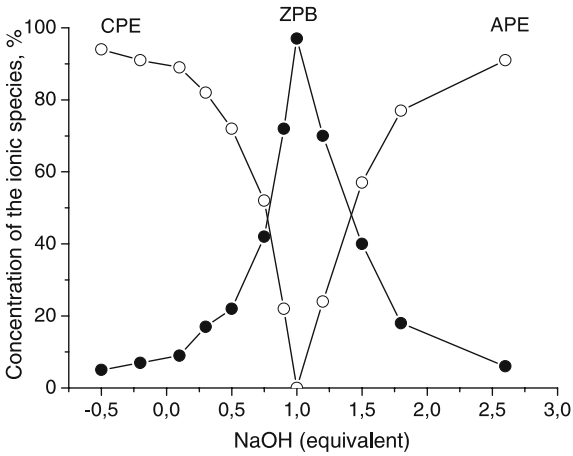


Fig. 1 Distribution curves for the anionic, cationic, and zwitterionic forms of polybetaines [191]

accessibility of the carboxylic group to protons show significant differences as a function of the chemical structure of polycarboxybetaines derived from poly(4-vinylpyridine) (**17**) and from poly(vinylbenzyl chloride) (**19**). Only 6% of the carboxylic groups of **17** were titrated in pure water. The addition of NaCl resulted in an increase of protonated carboxylates up to only 15%. The larger ethyl groups in **19b** are responsible for decreasing intramolecular interactions, so that a much higher proportion of acid groups can be titrated (up to 75% in 0.5 M NaCl). These results are in good agreement with viscosity measurements. Polycarboxybetaine **19b** shows a typical polyelectrolyte effect in water, while polycarboxybetaine **17** ($n = 1$) shows a nearly linear slope. The reason is that the free charges of the polycarboxybetaine **17** ($n = 1$) is close to zero in contrast to polycarboxybetaine **19b**, which has a noticeable number of free charges because of the hindered formation of an internal salt. The reduced viscosity of **19a** and **19b** passes through a minimum as a function of pH (Fig. 2) [193].

The difference in replacement of the IEP for **19a** ($pH_{IEP} = 3.6$) and **19b** ($pH_{IEP} = 2.9$) is probably connected with the different hydrophobicity of polycarboxybetaine chains, e.g., the cationic group of **19b** is more effectively screened by ethyl substituents, as they are bulkier than the methyl groups of **19a**. The effect of organic solvent on the solution behavior of **19b** was studied [193]. In saline water, the conformation of **19b** is compact due to the screening of the electrostatic repulsion by the neutral salt KCl. Addition of ethanol improves the thermodynamic quality of the solvent with respect to the hydrophobic parts of the macromolecules, and the reduced viscosity increases and has the maximal value at 60–80 vol % of ethanol in a water/ethanol mixture.

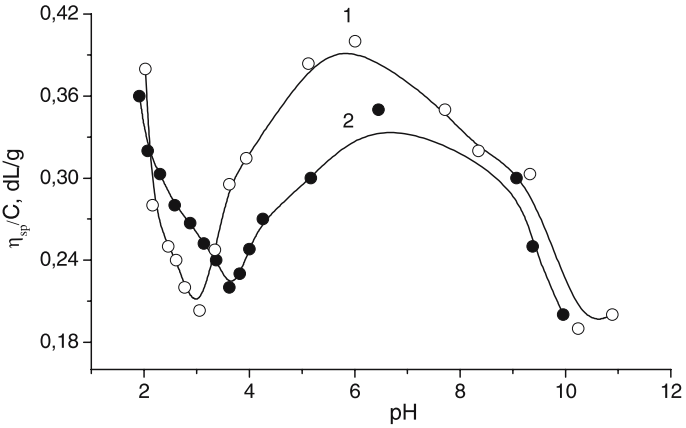


Fig. 2 Dependence of the reduced viscosity of **19b** (curve 1) and **19a** (curve 2) on pH in water. Concentration = 0.3 g/dL [193]

A reasonable explanation of this phenomenon may be the unfolding of the macromolecules due to preferential solvation of the betaine parts of **19b** by water, and of the benzyl ones by the organic solvent. The viscosity of **19b** decreases in pure ethanol because of the low solubility of ionic species and enhanced condensation of counterions to polyions.

The main distinction between polycarboxybetaines and -sulfobetaines is the difference in basicity, the carboxylate group in polycarboxybetaine being a stronger base than the sulfonate group of polysulfobetaine [13, 51]. In aqueous solution, the carboxylate group can be rendered nonionic by lowering the pH, whereas the sulfonate group remains anionic even at low pH due to the low pK_a. As a result, the reduced viscosity of polycarboxybetaine passes through a minimum undergoing a polyanion ↔ polyzwitterion ↔ polycation transition. In contrast, the polysulfobetaine does not exhibit an enhanced viscosity at low pH due to the weak basicity of the sulfonate group. A combination of static and dynamic laser light scattering was used to study the effects of temperature, pH, and ionic strength on inter- and intrachain interactions in poly(*N*,*N*-dimethylmethacrylamidopropylammonium propiolactone) [28]. An increase of the temperature to 50 °C shifts the equilibrium from associates toward individual chains. The addition of NaOH also suppresses interchain aggregates due to the ionization of carboxylic groups. The addition of a small amount of NaCl (at pH 12) at first enhances the dissociation of interchain associates, because both the hydrodynamic radius and molar mass decrease. The further addition of salt results in chain extension as the intrachain association is broken up. Thus intragroup, intrachain, and interchain ion contacts are disrupted at sufficiently high salt concentration. The solubility of polybetaines in aqueous solution depends on the nature of the anions and cations of added salts [194, 195]. For salts with a common anion (Cl^-) and monovalent cations, the solubility decreases as $K^+ > Na^+ > NH_4^+ > Li^+$, while for divalent cations the solubility decreases in the order $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$. In the presence of salts with a common cation (K^+) but different anions, the solubility decreases in the order $ClO_4^- > I^- > Br^- > Cl^- > F^-$. The Hofmeister lyotropic sequence can successfully be applied to describe the solubility behavior of most polybetaines.

The common feature of polyampholytes with betaine structure is that the viscosity of the solution and the second virial coefficient A_2 increase with increasing salt concentration [196] beyond a critical minimum value [173]. The Huggins constant K, which is generally considered to be related to polymer–solvent interaction, decreases as the salt content is increased. In other words, the solvent quality for polybetaines increases with increasing salt concentration. However, the properties of copolymeric polysulfobetaines [197, 198] based on styrene–*N*,*N*-dimethyl(maleimidopropyl)ammonium propanesulfonate, styrene–*N*,*N*-dimethyl(maleamidic acid)propylammonium propanesulfonate, or acrylamide–*N*,*N*-dimethyl(maleimidopropyl)ammonium propanesulfonate in aqueous salt solutions are different from the gen-

eral polysulfobetaines containing just a single sulfobetaine group [70, 199]. This may be attributed to the hydrophobic or hydrophilic character of macromolecules induced either by the presence of styrene segments or carboxylic (acrylamide) moieties in addition to sulfobetaine groups.

Poly(ampholyte–electrolyte)s containing both polybetaine and anionic (or cationic) polyelectrolyte can exhibit simultaneously both "antipolyelectrolyte" (the viscosity increases with growth of the ionic strength) and polyelectrolyte behavior (the viscosity decreases with increasing ionic strength) [22, 57]. The study in [56] provides an interesting opportunity to investigate which structural features—polyelectrolytic or polyzwitterionic—dictate the solution properties of novel poly(electrolyte–zwitterions) synthesized from sodium *N*-(3-sulfopropyl)-3-(*N*,*N*-diallylamino)propanesulfonate. As distinct from classical polybetaines, such poly(electrolyte–zwitterion)s have two negative and one positive charges in each monomer unit. This explains their very good solubility in water and many protic solvents except methanol, triethylene glycol, and acetic acid. In the absence of added salts, poly(electrolyte–zwitterion)s behave as typical polyelectrolytes. The polyelectrolyte effect disappears in salt-containing solutions, and the intrinsic viscosity values decrease with increase in various salt concentrations in favor of polyelectrolyte character. It is interesting to note that the hydrodynamic volume of poly(electrolyte–zwitterion)s increases continuously with increasing temperature in both 0.1 and 0.5 M NaCl. This property could be useful for viscosification of water at high temperatures. The polybetaines obtained by cyclopolymerization from *N*-(4-sulfobutyl)-*N*-methyl diallylammonium betaine show enhanced solubility in salt water, increased stability in the solid state, and enhanced thermal hydrolytic stability in comparison with betaines containing ester or amide linkages [56].

The aqueous solutions of aromatic and aliphatic polyzwitterions exhibit significantly different phase behavior: while **26** has an upper critical solution temperature (UCST) at 286 K, **23b** shows both an UCST at 306 K and an "apparent inverted" lower critical solution temperature (LCST) at 289 K [196, 200]. Compound **25** is insoluble over the whole temperature range between 273 and 373 K. Thus, **23b** is considered to be in a collapsed coil in water below the UCST due to intra- and/or interchain association.

The solution properties of a polybetaine containing the phosphatidylcholine group, poly[(2-methacryloyloxy)ethyl-2-(trimethylammonioethyl phosphate)], which has PO_4^- and $N^+(CH_3)_3$ groups separated by two methylene groups, were reported [201, 202]. A linear relationship between $[\eta]$ and $1/\mu$ was observed for the polyampholyte at low μ near pH_{IEP}. When $\mu > 0.0025$, $[\eta]$ increases as the attractive interactions between the oppositely charged units are diminished. By comparing the μ dependence of the electrostatic expansion factor of the polyampholyte with that of poly(sodium acrylate), it is suggested that there is a pronounced intramolecular attraction between the oppositely charged segments even when the pH deviates from

the IEP. For the sulfobetaine-type polyampholyte [66], the intrinsic viscosity $[\eta]$, second virial coefficient A_2, exponent a in the Mark–Kuhn–Sakurada equation, radius of gyration R_g, and hydrodynamic radius R_h increase with increasing salt concentration C_s. The exponents of the Mark–Kuhn–Sakurada equation are $a = 0.5$, 0.67, 0.70, and 0.70 for $C_s = 0.06$, 0.3, 1.0, and 4.0 M NaCl aqueous solution, respectively. Judging from the experimental results for $a = 0.5$, it was found that the NaCl solution of $C_s = 0.06$ M is a theta-solvent at 30 °C. The electrostatic expansion factors for the polyampholyte effect, α_e, were estimated over a wide range of molecular weights and C_s values. It was concluded that the chain expansion for a neutral polyampholyte is controlled by the nonionic excluded volume effect and the electrostatic excluded volume effect (polyampholyte effect) at moderate concentrations of added salt. The electrostatic expansion factor can reasonably be described by an α_e^3-type equation, although no such equation has so far been proposed for the polyampholyte.

The adsorption of **23** onto a silica surface from aqueous NaCl solutions with various concentrations was studied [203]. Comparison of the thickness of the adsorbed layer with the radius of gyration of **23** in NaCl solutions revealed the existence of collapsed (pancake)-, normal (fence)-, and elongated (pole)-like conformational regimes that were described theoretically by Joanny [204].

The three-dimensional plot [57] of R_h as a function of salt and polymer concentrations for cyclocopolymers consisting of sulfobetaine and cationic monomers shows that the value of R_h passes through a minimum at any polymer concentration as the ionic strength of the medium is increased. The initial decrease of R_h is attributed to the screening of electrostatic repulsions between positive charges by small ions. The minimum R_h corresponds to the collapsed state of the polymer chain. The reexpansion of the macromolecular chain with increasing ionic strength is due to the suppression of intramolecular dipole–dipole interactions between the sulfobetaine mer units.

Figure 3 shows the influence of pH on the viscosity and electrophoretic mobility of poly(carboxyethyl 3-aminocrotonate) (PCEAC) [205–211]. The minimal viscosity and the zero mobility are observed at extremely low pH (2.1–2.2) and correspond to the isoelectric point (IEP). The "asymmetric" character of chain stretching and the "anomalous" low magnitude of the IEP ($pH_{IEP} \approx 2.0$–2.1) may be explained by the different accessibility of the carboxylic and secondary amine groups to ionization. Carboxylic groups placed far from the polymer main chain can be ionized more easily than the secondary amine groups that are close to the main chain and in a hydrophobic environment. These results are in good agreement with the electrophoretic data, e.g., the number of negative charges on the macromolecules is significantly higher at pH > 2 than the number of positive charges at pH < 2. The values of R_g, A_2, and η_{sp}/C at pH = 2.1 (IEP) and 7.0, when the PCEAC chains are correspondingly in the collapsed and expanded state, correlate well with the data of Fig. 3 (Table 2).

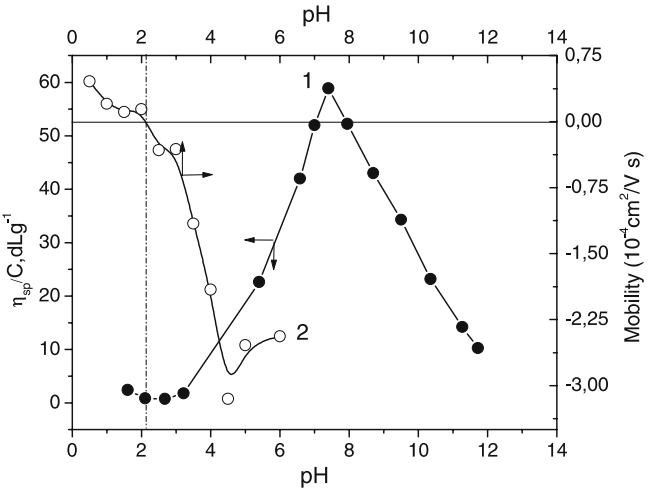


Fig. 3 Reduced viscosity (curve 1) and electrophoretic mobility (curve 2) of PCEAC vs pH of the solution [255]

Table 2 Hydrodynamic parameters of PCEAC in aqueous solution at different pH and μ = 0.1 [212]

Polybetaine	pH	$M_n 10^3$ [a]	PDI [a]	$M_w 10^3$	R_g, nm	η_{sp}/C, dL g^{-1}	$A_2 \times 10^{-4}$, cm^3 mol g^{-2}	Mean [b] d_h, nm	Peak [b] d_h, nm
PCEAC	2.1	—	—	44	—	0.5	– 38.8	40	18
	7.0	31	2.15	96	32	60.0	18.9	191	16

[a] Results are obtained using SEC
[b] DLS results are obtained at fixed polymer concentration and 90° scattering angle

The negative value of the second virial coefficient and the low value of the reduced viscosity at pH = 2.1 confirm a globular conformation of the polymer particles at the IEP [212]. The pH-dependent swelling behavior of the PCEAC gel is consistent with its linear analogue and a minimum at $pH_{IEP} \approx 2.1–2.2$.

The electrostatic self-assembly of thermally responsive copolymers of *N*-isopropylacrylamide with up to 10 mol % of the sulfobetaine monomer 3-[*N*-(3-methacrylamidopropyl)-*N*,*N*-dimethyl]ammonium propanesulfonate) and poly(ethylene oxide) modified with terminal cationic or anionic groups was studied in methanol and aqueous solutions by static light scattering, turbidimetry, viscometry, and rheological measurements [82]. The formation of graftlike complexes at stoichiometric dipole–ion ratio and their self-association was detected in the dilute and semidilute regime at temperatures below and above the LCST. The ability of the graftlike complexes

to associate below the LCST depended on the sulfobetaine content of the copolymers, the functionality of cationic or anionic groups, and the polymer concentration. The effect of the terminal group on the solution behavior of the graftlike complexes was less pronounced. With increasing temperature their semidilute aqueous solutions form gels, which are stable over a wide temperature range.

Polybetaines in the solid state are able to form ionic aggregates or clusters [2]. The microphase separation in various zwitterionomers was analyzed [67, 213, 214]. Copolymers based on five different sulfobetaine monomers and butyl methacrylate (or 2-ethoxyethyl acrylate) exhibited a biphasic morphology with the appearance of ion-rich and ion-poor phases in dependence on spacer length between positive and negative charges and on the bulkiness of the alkyl substituents at the quaternary ammonium functionality [213]. The cluster phase undergoes a glass transition at a higher temperature than the ion-poor matrix. A series of segmented poly(tetramethylene oxide) zwitterionomers of the ammonioalkanesulfonate ($N^+(CH_2)_pSO_3^-$, $p = 3, 4$) or the alkoxydicyanoethenolate ($N^+(CH_2)_pOCOC^-(CN)_2$, $p = 2, 3$) displays thermally stable biphasic structures as a result of the quantitative segregation of the dipolar segments within the highly mobile and weakly polar poly(tetramethylene oxide) matrix [74, 215]. Transition from a lamellar structure for the shorter poly(tetramethylene oxide) segments (high zwitterion density, lamellar spacings between 7 and 8 nm with a thickness of the zwitterionic layer of about 1 nm) to a hexagonal structure (low zwitterion density, radius of the zwitterionic cylinder of about 1.2 nm) for the longer ones is observed. Matrix polarity effects on the microphase separation in zwitterionic A_iB random copolymers (where A_i units are $-CH_2CH(CH_2R_i)O-$ corresponding to epichlorohydrin (PEC, $R_i = Cl$), glycidol (PGOH, $R_i = OH$), glycidyl acetate (PGAC, $R_i = OCOCH_3$), or glycidyl *p*-nitrobenzoate (PGNB, $R_i = OCOC_6H_4NO_2$); B unit is $-CH_2CH[CH_2O(CH_2)_2N^+(C_2H_5)_2(CH_2)_2OCOC^-(CN)_2]O-$, the ammonioethoxydicyanoethenolate type) were further analyzed [214, 216]. DSC and NMR results show that (1) PGOH zwitterionomers are monophasic (one T_g between 3 and 31 °C) as a result of hydrogen bonding; (2) PGNB zwitterionomers are likely monophasic (one T_g around 58 °C) as a result of strong dipolar and dispersion interactions; (3) PEC zwitterionomer is a biphasic material characterized by a quasi-quantitative segregation of the dipolar units in the "hard" phase (high $T_g \sim 22$ °C) and a segregation rate of PEC units in the "soft" phase (low $T_g \sim -18$ °C) of about 84%; and (4) PGAC zwitterionomers are monophasic (one T_g between – 12 and 15 °C), despite fairly close and weak van der Waals interactions and a fairly similar matrix mobility when compared to the previous PEC case. Thus, the development of a two-phase structure in random A_iB zwitterionomers is very sensitive to small variations of the matrix characteristics and of the A–B interactions. Microscopic structural features of three methacrylate polymers with different

numbers of diethylene glycol residues and sulfobetaine pendant groups (**23d**) were determined by WAXS, SAXS, SEM, TEM, scanning probe microscopy, and AFM [67]. The basic morphology of methacrylate-based polysulfobetaines was found to be a core–shell configuration of molecular aggregates embedded in an amorphous polymer matrix. The studied polysulfobetaines are crystalline systems that can be adequately described by a lamellar structure. As the number of pendant groups increases, the crystallinity decreases, and the lamellar aggregates become smaller.

Due to the high density in dipolar units and dipole moment, polybetaines have a strong binding capacity with respect to low molecular weight salts and may be used as solid electrolytes for high-energy batteries. Such behavior was demonstrated for a number of polybetaines blended with $LiClO_4$, $NaClO_4$, $NaNO_3$, NaBr, or NaI [16, 28, 174, 178, 217–219]. Equimolar mixtures of polycarbobetaines with NaI give homogeneous blends, as indicated by the missing signals of residual NaI in X-ray diffractograms demonstrating the full miscibility. Moreover, the small-angle peaks in the diffractogram of polycarbobetaine change or disappear, indicating modification or loss of the superstructure, and giving additional evidence for the miscibility of polymer and salt. Dielectric spectroscopy was used to analyze the molecular dynamics and the charge transport in mixtures of poly3-[*N*-(ω-methacryloyloxyalkyl)]-*N*,*N*-dimethylammonium propanesulfonate with NaI in the frequency range of 10^2–10^7 Hz and in the temperature range of 110–400 K for different salt concentrations (0, 100, and 200 mol %) [220]. One relaxation process is observed whose relaxation rate depends strongly on the length of the aliphatic spacer between the polymethacrylate main chain and the zwitterionic groups. This relaxation process with activation energy $E_A = 47$ kJ/mol is assigned to the fluctuation of the quaternary ammonium groups in the side chains. At higher temperatures, the dielectric properties and the conductivity are primarily dominated by the mobile inorganic ions: conductivity strongly depends on the salt concentration, showing a pronounced electrode polarization effect. The conductivity contribution can be quantitatively described by the hopping of charge carriers in the frame of a random free-energy model. The Barton–Nakajima–Namikawa relationship is fulfilled for the low-frequency regime and for the critical frequency.

Similar to polyelectrolyte gels, polybetaine gels are also sensitive to the variation of external stimuli such as pH, temperature, ionic strength, solvent nature, and DC electric field. The pH-dependent behavior of xerogels based on sodium acrylate and *N*,*N*-dimethyl(acrylamidopropyl)ammonium propanesulfonate is bell-shaped [94, 95]. The contraction of the hydrogels in the strong acidic region is explained by the suppression of the ionization of the sulfonate and carboxylic moieties by mineral acid. The sharp swelling of hydrogels in the region of pH 2–3 is accounted for by the ionization of mostly sulfonate groups (with $pK_a \approx 2.8$), which results in electrostatic repulsion by the negative charges. A roughly constant swelling of the hydrogels between

pH 4 and 10 is the result of the ionization of both the carboxylic and sulfonate groups. The considerable shrinking of gel specimens at pH > 10 is probably explained by the suppression of the polyelectrolyte effect by the excess of NaOH that plays the role of the low molecular weight electrolyte.

Discontinuous and continuous collapse of PCEPAC and poly(carboxyethyl 3-cyclohexylaminocrotonate) (PCECHAC) hydrogels was observed [221] in water/acetone and water/ethanol mixtures (Fig. 4). These results confirm the universal behavior of hydrogels with respect to the thermodynamic quality of solvents.

SEM pictures of PCECHAC taken in water/acetone mixtures are also in good agreement with the swelling–shrinking behavior of such hydrogels (Fig. 5). The average pore size of PCECHAC gel in pure water is 30–40 μm. Increasing the acetone content in the water/organic solvent mixture results in a decrease of the gel pore size down to 15–20 μm. In pure acetone the gel sample is in a collapsed state with pore sizes of 1–2 μm. The swelling of hydrogels in polar solvents changes in the sequence: water ≫ DMSO ≫ DMF > ethanol > acetone.

It is well known that polyelectrolyte gels swell, shrink, or bend when an external electric current is applied [222, 223]. The electric-stimuli property of polybetaine gels depends on the pH of the outer solution, the ionic strength, the applied voltage, and the direction of the electric field with respect to the gel specimen [208, 221]. The bending behavior of PCEPAC gels was studied under an externally imposed DC electric field. A gel rod placed parallel to the electrodes bends to the cathode side. If the electric stimulus is removed, the gel gradually returns to the original position. When the polarity of the electrodes is altered, the gel bends toward the opposite direction. The bending

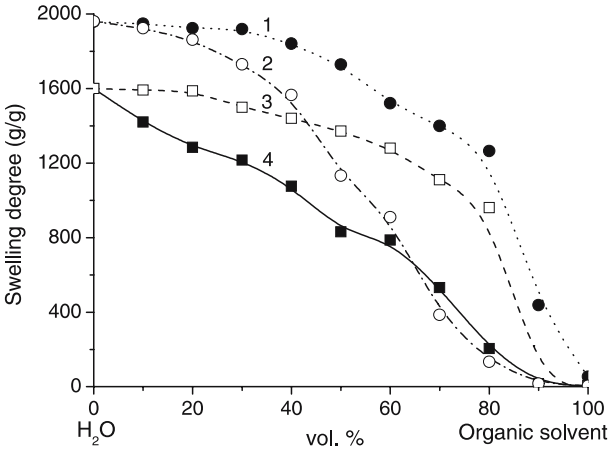


Fig. 4 Swelling–deswelling behavior of PCEPAC (1,2) and PCECHAC (3,4) gels in water/acetone (1,3) and water/ethanol (2,4) mixtures [221]

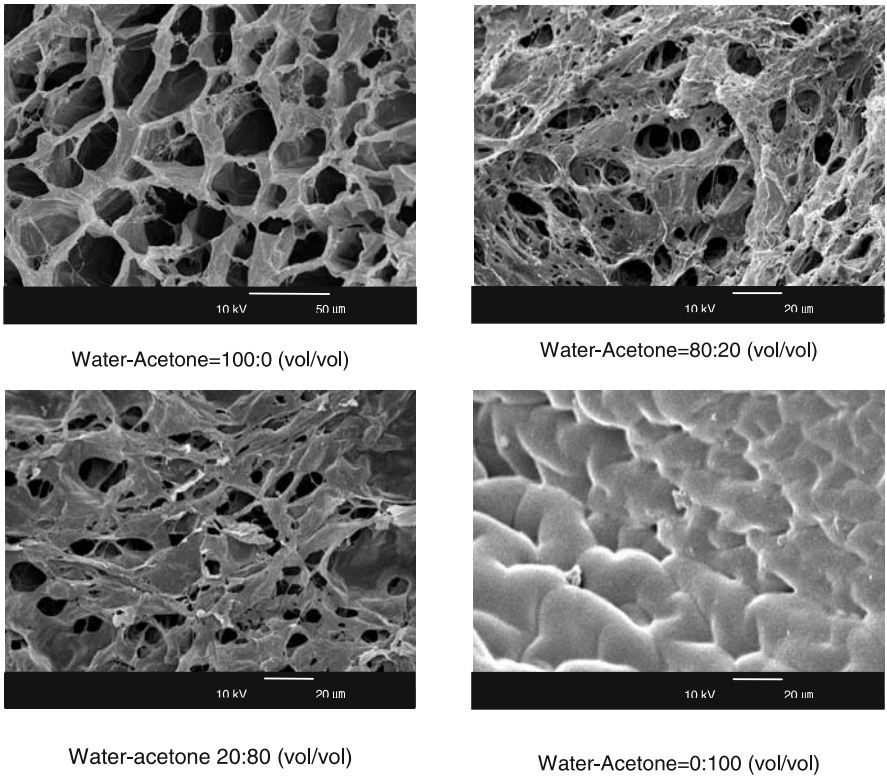


Fig. 5 SEM pictures of PCECHAC gel in water, acetone, and water/acetone mixtures [221]

angle increases with increasing voltage across the gel. The driving force of the bending toward the negative electrode is the swelling of the gel on the anode, and the shrinking on the cathode side induced by the osmotic pressure difference.

If the gel rod is placed perpendicular to the electrodes, the applied DC electric field causes a sharp appearance of pH gradient during 1–2 min [208]. After 5 min, the pH value becomes stable. The magnitude of the pH in the gel volume returns quickly to the initial state if the electricity is switched off. The values of $\Delta pH = pH_0 - pH_{t\to 0}$ (where pH_0 and $pH_{t\to 0}$ are the initial value of pH and pH value extrapolated to $t \to 0$, respectively) are a function of the DC electric field. Figure 6 presents the dependence of the pH on the distance $\pm L$ when the glass electrode is placed on the cathode or anode side of a gel specimen in comparison with its central section where $L = 0$.

Without an applied DC electric field, the pH gradient along the sample is uniform and equal to 5.46. An increase of the electric field shifts the pH gradient to the more acidic region. The dependence of the pH gradient on L is linear, but the slopes of the straight lines differ and depend on the value of

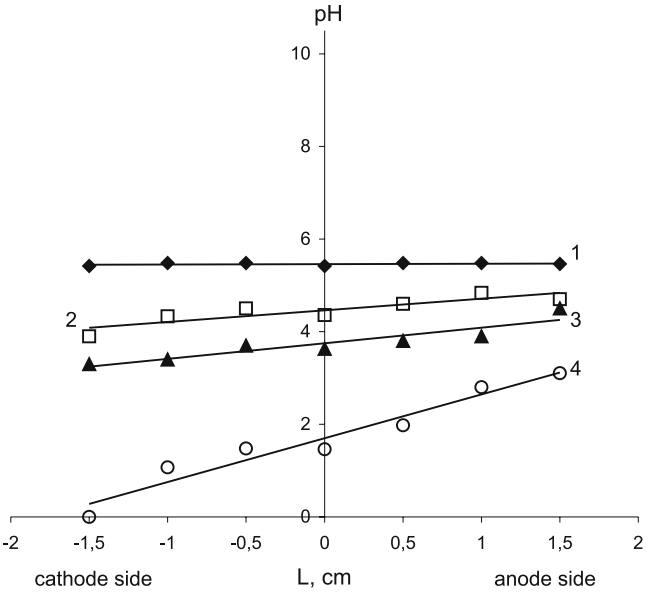
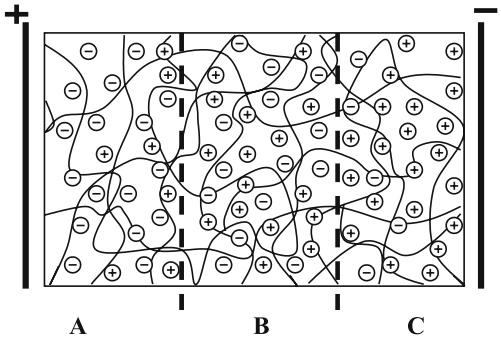


Fig. 6 Dependence of pH gradient on distance L without the imposed DC electric field (1) and at $E = 5$ (2), 10 (3), and 15 V (4) [208]



Scheme 14 Distribution of fixed and mobile charges in polybetaine gels under the imposed external DC electric field [208]

the applied DC electric field. In order to interpret these data, the distribution of fixed network charges and counterions along the gel specimen should be considered (Scheme 14).

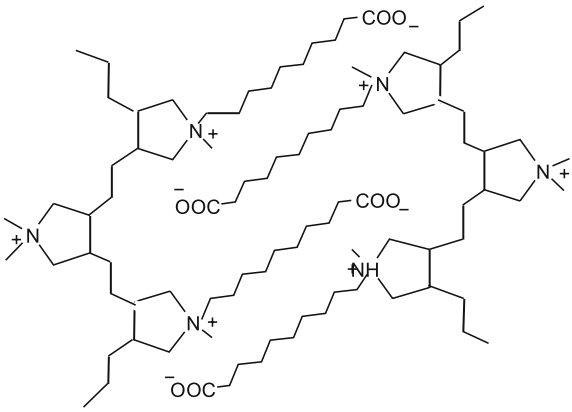
The externally imposed potential across the gel causes the accumulation of negative fixed charges (COO^-) and mobile ions (OH^-) on the anodic side (zone A), while the accumulation of positive fixed charges (NH_2^+) and mobile ions (H^+) takes place on the cathodic side (zone C). Zone B probably contains an equal number of positive and negative charges.

As a result, zones A, B, and C have comparatively a basic, neutral, and acidic character, respectively. Increasing the DC electric current leads to the overall acidification of the gel sample (see Fig. 6, curve 4) due to the easy ionization of the acidic groups. Consequently, this narrows the zones B and C and expands zone A. Polybetaine hydrogel membranes of isopropyl-2-[2′-(trimethylammonium)ethyl phosphoryl] ethyl fumaramate and 2-hydroxyethyl methacrylate effectively enhance the water content in comparison with poly(2-hydroxyethyl methacrylate) [224]. The content of water in hydrogel membranes increases, but the amount of adsorbed BSA decreases with the increase of the betaine content in the feed. The values of the tensile strength and tensile elongation of the hydrogel reach 68.4 g mm^2 and 239%, respectively.

4
Behavior of Hydrophobically Modified Polybetaines

Hydrophobically modified polybetaines combine the behavior of zwitterions and amphiphilic polymers. Due to the superposition of repulsive hydrophobic and attractive ionic interactions, they favor the formation of self-organized and (micro)phase-separated systems in solution, at interfaces as well as in the bulk phase. Thus, glasses with liquid-crystalline order, lyotropic mesophases, vesicles, monolayers, and micelles are formed. Particular efforts have been dedicated to hydrophobically modified polyphosphobetaines, as they can be considered as polymeric lipids [5, 101, 225–228]. One can emphasize that much of the research on polymeric phospholipids was not particularly focused on the betaine behavior, but rather on the understanding of the lipid membrane, and on biomimicking. So, often much was learnt about biology and the life sciences, but little on polybetaines as such.

Although deviating chemically more from the natural prototype than polyphosphobetaines, hydrophobically modified polybetaines with other zwitterionic groups behave similarly. If the density and size of the hydrophobic fragments is reduced, the polymeric betaines become soluble in water (or in brine, see Sect. 3), but are still able to self-organize in aqueous solution and in bulk [17, 18, 28, 53, 172–174, 177, 178]. For instance, the low viscosities of so-called zwitterionic polysoaps are attributed to the intra- and intermolecular aggregation of the zwitterionic and hydrophobic side chains, keeping the hydrodynamic radius small. Simultaneously, X-ray studies of the same zwitterionic polysoaps reveal the formation of superstructures in the bulk. In the example in Scheme 15, both electrostatic attractions between ammonium and carboxylate groups and hydrophobic interactions between long hydrophobic side chains are the driving force of superstructure formation [17, 45, 174], supported by an appropriate spacer length in the polymer backbone.



Scheme 15 Proposed spatial arrangement of the zwitterionic and hydrophobic parts in a hydrophobically modified polycarboxybetaine [17]

Fluorescent hydrophobes (naphthyl and pyrenyl groups) incorporated into the polysulfobetaines are a powerful tool for studying the formation of intra- and interpolymer aggregates in aqueous and aqueous salt solutions [85, 229–231]. Intermacromolecular hydrophobic association is observed as an increase in the excimer emission relative to that of the "monomer" emission, where I_E/I_M is the ratio of intensities of excimer and monomer fluorescence which reflects the extent of inter/intra macromolecular interactions. Intramolecular micellization is easily monitored by the quenching efficiency of the thallium ions. The decrease of I_E/I_M reflects the breaking of the intra- and interchain associations in aqueous salt solutions, leading to chain expansion.

The surface activity and solubilization capacity of amphoteric polysoaps were studied [172, 177, 178]. The surface activity of zwitterionic polysoaps is diminished by added salt due to their "antipolyelectrolyte" character. The sequence to solubilize hydrophobic dyes is often "mid-tail" > "head" > "tail-end" geometry. An extended study on the solubilization ability of hydrophobically modified polybetaines can be found in [232]. The surface activity of the cyclocopolymers containing the pH-responsive hydrophobic monomer *N*,*N*-diallyl-*N*-methylamine and the salt-sensitive sulfobetaine monomer 3-(*N*,*N*-diallyl-*N*-methylammonio) propanesulfonate was utilized to solubilize *p*-cresol within microdomains [233]. Other studies corroborate the general picture [182, 183].

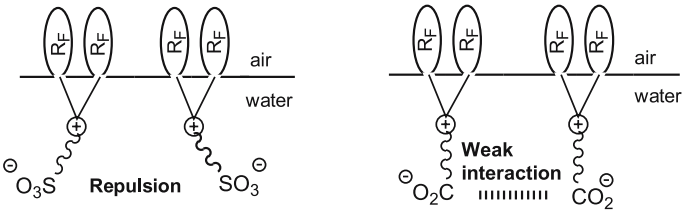
Amphiphilic polybetaines that are end-capped by fluoroalkyl chains and which possess unique properties imparted by the fluorocarbon fragments were developed [234–236]. The polymers of common structure [R_F-**26**-R_F], [R_F-**23a**-R_F], and [R_F-(APDMAE)$_n$-R_F] (where APDMAE is 2-(3-acrylamidopropyldimethylammonio)-ethanoate and R_F is fluorinated hydrocarbons) were shown to exhibit a wide variety of dispersing, aggregate, and emulsion properties. The viscosity of [R_F-(APDMAE)$_n$-R_F] in water consid-

erably increases in comparison with that of [R_F-**23e**-R_F]. The gelation of [R_F-(APDMAE)$_n$-R_F] at a concentration of 10 g L^{-1} is connected with the aggregation of the end-capped fluoroalkyl segments and the strong ionic interactions between the betaine segments. Polymer [R_F-**23e**-R_F] could not form gels in water because of the electrostatic repulsion between the sulfonate units (Scheme 16), but was able to induce gelation in methanol. The reduction in the surface tension of water depends on the length of the fluoroalkyl segments in the polymers. The longer perfluoro-oxyalkylated polymers are more efficient for reducing the surface tension of water than the corresponding polymers with shorter fluoroalkyl chains, or polyAPDMAE without fluorinated end groups.

Whereas the above examples focused on end-capped polybetaines, the other molecular structural extreme is polymers end-capped with betaine groups, which are known, too. The dilute solution and bulk properties of such polymers with zwitterionic end groups were reviewed by Hadjichristidis et al. [237].

Block copolymers of **23b** and alkyl methacrylates [158] and diblock copolymers of **23b** with 2-(diethylamino)ethyl methacrylate (**23b**-DEAEM), 2-(diisopropylamino)ethyl methacrylate (**23b**-DIPAEM), or 2-(*N*-morpholino) ethyl methacrylate (**23b**-MEMA) exhibited reversible pH-, salt-, and temperature-induced micellization in aqueous solution under various conditions. The micelle diameters were 10–46 nm [238]. The micelles of these hydrophobically modified polybetaines consist of coronas from **23b** and cores from polyDEAEM, polyDIPAEM, or polyMEMA. In aqueous solution, the **23b**-MEMA diblock copolymers form micelles with cores of polyMEMA above an upper critical micelle temperature of about 50 °C, and reversibly betainized-DMAEM core micelles below a lower critical micelle temperature of approximately 20 °C [239].

Reversible pH-, salt-, and temperature-induced micellization has been reported for several other block copolymers containing a zwitterionic



[R_F-(APDAPS)$_n$-R_F] [R_F-(APDMAE)$_n$-R_F]

R_F = $C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$

Scheme 16 Surface arrangement of fluoroalkylated betaine-type polysoaps in aqueous solutions [236]

block [152, 154, 240–242]. In certain cases, multiple switching between complex self-organized structures becomes possible [152, 240–242].

Another parameter suitable for modifying the aggregation behavior of hydrophobically modifed polybetaines is the composition of the solvent used. This is exemplified in Fig. 7, which illustrates the changes of the intrinsic viscosity and of the swelling degree of linear and cross-linked poly3-[(2-carboxy-1-methylethyl)dodecylaminocrotonate] (PCMEDDAC) in water/DMSO mixtures [243]. The insoluble betaine parts of PCMEDDAC tend to aggregate in pure DMSO and form intra- or interchain associates surrounded by a hydrophobic corona. Addition of 10 vol % of water to DMSO considerably increases both the swelling degree and the intrinsic viscosity. A reasonable explanation of this phenomenon may be the unfolding of the macromolecules due to the preferential solvation of the betaine fragments of PCMEDDAC by water, and of the dodecyl chains by the organic solvent. However, a further enrichment of the solvent mixture by water causes the shrinking of the macromolecules, due to reversible micelle formation stabilized by hydrophobic interactions of the long alkyl chains. The insolubility of PCMEDDAC at more than 30 vol % of water is probably connected with a strong compactization of the polymer particles. A hypothetical structure of PCMEDDAC in DMSO, water/DMSO, and water environments is presented in Scheme 17.

The behavior of linear PCMEDDAC in water/DMF mixtures differs from the water/DMSO system. Increased temperatures increase the intrinsic viscosity of PCMEDDAC in DMSO, while they decrease it in DMF. This opposite behavior may be the result of the different solvent qualities with respect to the functional groups of PCMEDDAC.

A particular interest in hydrophobically modified phosphorylcholine polymers is due to the remarkable bio- and hemocompatibility of the surfaces

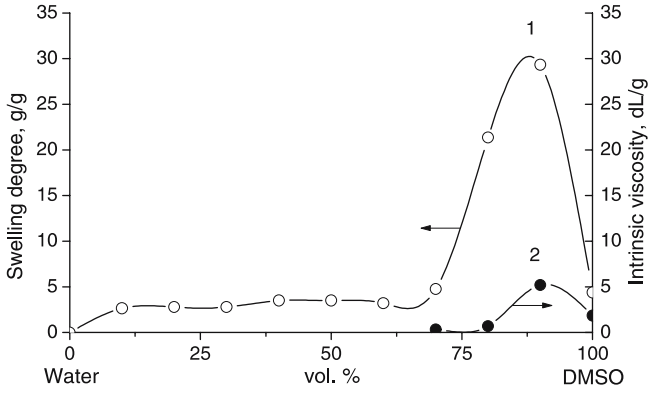
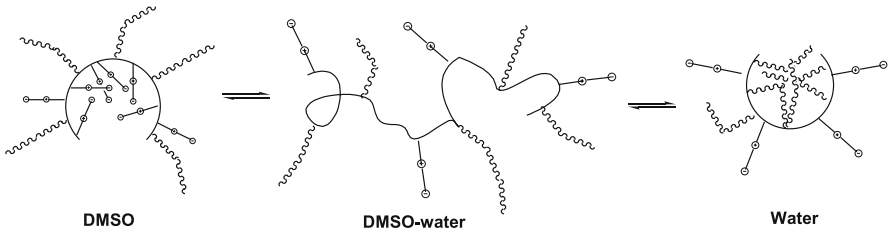


Fig. 7 Dependence of the swelling degree (1) and intrinsic viscosity (2) of PCMEDDAC on water/DMSO mixture [243]

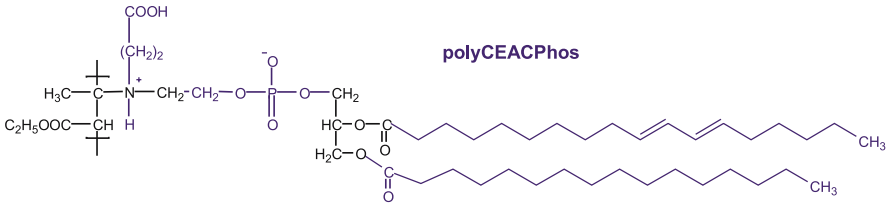


Scheme 17 Hypothetical scheme of the conformation of PCMEDDAC in DMSO, DMSO/water, and water solutions [243]

onto which they are coated. Conformational transitions of phosphorylcholine-based hydrophobically modified polybetaines were studied by ^{1}H NMR spectroscopy in D_2O, CD_3OD, and $CDCl_3$ [149]. The line broadening of the proton signals in D_2O indicates that the motion of the corresponding protons is restricted, providing evidence for the occurrence of hydrophobic microdomains stabilized by the association of the long alkyl chains. The assembly of the polymers in water is triggered by two cumulative effects: (1) hydrophobic interactions between the hydrocarbon chains and (2) ion pair formation between the phosphorylcholine groups. The hydrophobic interactions disappear when the polybetaine is dissolved in CD_3OD, while the solvation of the betaine moieties persists so that no aggregation is observed. In $CDCl_3$, however, inverse micelles are formed in which the core is made of agglomerated phosphorylcholine units and the corona is made of freely moving alkyl chains. In $CD_3OD/CDCl_3$ mixtures, a gradual conformational change from the swollen coil in CD_3OD to the collapsed structure in $CDCl_3$ is observed [244].

The behavior of polymerized phospholipids and analogues is exemplified in the following by the example of the new polyCEACPhos (poly(carboxyethyl 3-aminocrotonate) modified by phosphatidylethanolamine). The FTIR spectra of polyCEACPhos synthesized in bulk, chloroform, and ethanol are similar (Scheme 18) [245, 246].

The potentiometric titration curve of polyCEACPhos shows three bends due to the presence of three ionizing groups, namely OPOH, COOH, and



Scheme 18 Derived structure of phosphatidyl-containing poly(carboxyethyl 3-aminocrotonate) [245]

NH^+. The apparent ionization constants (pK_a) of OPOH, COOH, and NH^+ groups found from the Henderson–Hasselbalch equation are 2.57, 4.75, and 7.08, respectively. These values coincide well with the acidic strengths of phosphatidyl, carboxyl, and amine groups. The dependence of the pK_a on the ionization degree (α) plotted for the entire region of the potentiometric titration exhibits a nonmonotonic change of the pK_a (Fig. 8). The values of pK_a increase with α and show a local maximum at $\alpha \approx 0.4$. This is attributed to a change of polyCEACPhos from a compact conformation to an expanded polyelectrolyte-like state. The electrostatic Gibbs energy (G_{el}) that corresponds to the additional work required to remove the protons from the macromolecule was calculated according to the equation: $\Delta G_{el} = 2.303RTA$ (where R is the Boltzmann constant, T is absolute temperature, and A is area of conformational change). The value of $\Delta G_{el} = 45.72$ kJ mol^{-1} found for polyCEACPhos is much higher than that for poly(methacrylic acid) [247] and hydrophobically modified polyelectrolytes of 8.68 kJ mol^{-1} [248]. This is explained by a more stable compact conformation of polyCEACPhos, due to the stabilization of the globular structure by the hydrophobic interactions of the phospholipid fragments, which needs more electrostatic force to undergo the globule-to-coil transition.

The construction of biomembrane systems from polymers containing phosphatidylethanolamine and -choline analogues in the side chains by spreading at the air/water interface and by the Langmuir–Blodgett technique is of great interest [5, 101, 249, 250]. For instance, multilayers of dipalmitoyl-DL-α-phosphatidylethanol methacrylamide polymerized under γ radiation resemble a natural phospholipid structure and show a fine lamellar structure with a periodicity; the average monolayer was estimated to be 32 Å thick [251].

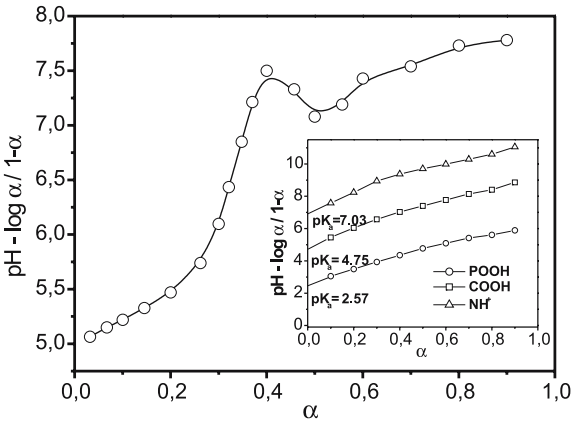


Fig. 8 Conformational transition and pK_a values of functional groups of polyCEACPhos in aqueous solution. [polyCEACPhos] = 1.4×10^{-3} mol L^{-1}, $T = 303$ K [245]

5
Interpolymer, Polymer–Surfactant, and Coordination Complexes of Polybetaines

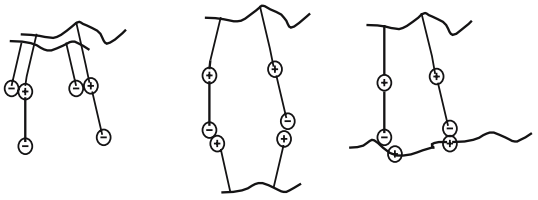
The formation of interpolyelectrolyte complexes (IPC) of polybetaines with anionic or cationic polyelectrolytes differs in important aspects from the complex formation between two oppositely charged polyelectrolytes. In the latter case, the main driving force is the liberation of the low molar mass counterions, which is not possible for complexes with polybetaines. Also, the composition of the complexes with polybetaines may be nonstoichiometric, in contrast to the usual stoichiometric complexation found for two polyelectrolytes. Characteristic features of IPC formation of polybetaines are exemplified in the following for selected polysulfobetaines, polycarboxybetaines, and polyphosphobetaines.

Osada et al. [252] studied the complexation of **23b** with poly(2-acrylamido-2-methylpropanesulfonic acid) (polyAMPS), quaternized poly*N*-[3-(dimethylamino)propyl]acrylamide chloride (PDMAPAA-Q), and *x*, *y*-ionene bromides ($x = 3, 6$; $y = 3, 4$) in aqueous solution. Depending on the concentration and the mixing ratio of the constituent polymers, water-soluble IPCs were formed which exhibit an UCST, like the parent polybetaine. The UCST decreased markedly when a small amount of the polyanion polyAMPS was added to the solution of **23b**, and eventually disappeared at high concentrations of polyAMPS.

This pronounced change in the UCST indicates a strong interaction between the two polymers. The addition of the polycation PDMAPAA-Q until $R = 0.17$ (where R signifies the molar ratio of polyelectrolyte/polyDMAPS) decreases the UCST first from 65 to 15 °C. The mixtures with the cationic ionenes show a similar evolution of the UCST, but also exhibit a minimum at $R = 0.1$–0.17. Thus, when polycations are added to **23b**, the UCST decreases first, then passes through a minimum and increases again. This was attributed to the different geometrical structure of polyelectrolyte complexes (Scheme 19).

Since the ammonium cations are placed in the middle and the sulfonate anions at the end of the side chain of **23b**, the complex can be solubilized due to free anionic groups of **23b** (Scheme 19a). In contrast, PDMAPAA-Q and ionenes bind to **23b** via the sulfonate groups, which are located at the end of side chain (Scheme 19b and c). The ammonium cations of PDMAPS are thus strongly shielded as hydrophilic solubilizing groups because they are surrounded by two hydrophobic polymer main chains in the complex. Table 3 summarizes the yields and UCSTs of the IPCs resulting from the addition of anionic (PAA, PMAA, NaPSS), cationic (polyDADMAC, PDMAPAA-Q), and nonionic (polyacrylamide, PAAm) polymers to **23b**.

A "cascade"-type complexation with self-propagating association of **23b** was reported when small amounts of *x*, *y*-ionene bromides ($x = 3$ or 6; $y = 3$,



Scheme 19 Polyelectrolyte complexes of polybetaines with anionic (**a**) and cationic (**b**, **c**) polyelectrolytes [252]

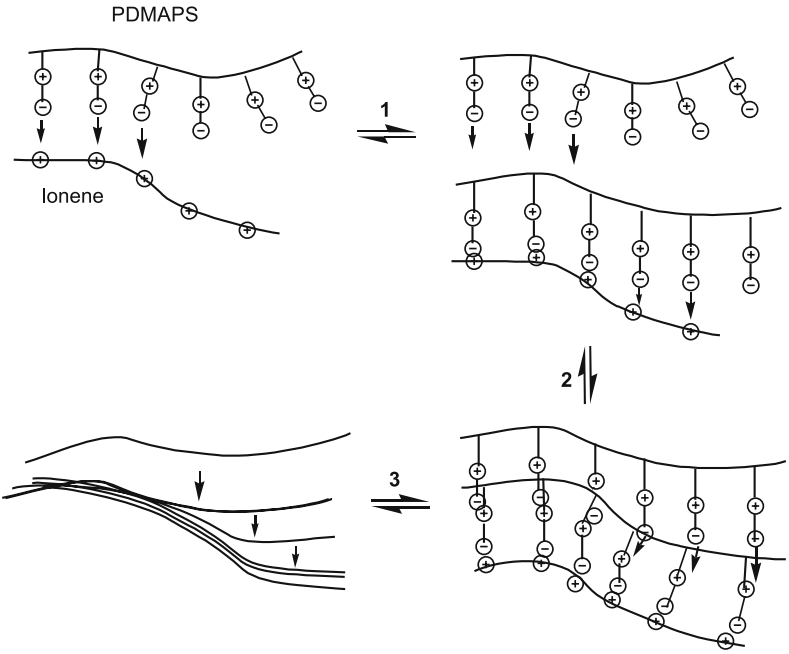
Table 3 The yield and UCST of IPCs formed between polyDMAPS and anionic, cationic, and nonionic polymers at $\mu = 0.1$ M NaCl [252]

Polymer type	Polymer name	UCST (°C)	Yield [a] (mol %)
None	PDMAPS	65	—
Polycation	3,3-ionene bromide	26.1	93.1
	PDMAPAA-Q	— [b]	7.9
	PDADMAC	— [b]	11.9
Polyanion	PAMPS	11.6	— [c]
	PAA	11.5	— [c]
	PMAA	11.0	— [c]
	NaPSS	10.7	— [c]
Nonionic polymer	PAAm	11.4	— [c]

[a] Yield is defined as the weight ratio of precipitates to PDMAPS in feed
[b] No UCST was observed until 98 °C
[c] No precipitate was formed at 15 °C

4, 6, 10, or 12) were added [253]. Large amounts of IPCs are formed and precipitate. This behavior, specifically observed for polycations, is attributed to the particular geometry of the IPCs. The addition of some polycation to **23b** provides an overall cationic complex where the positive charges are located in the middle of two polymers (Scheme 20).

This may favor the subsequent complexation with more macromolecules of **23b** due to the suppressed thermal fluctuation and the solvation of the cations, and initiates a cascade reaction until most of the **23b** is consumed. In the case of added polyanions, however, the IPC is overall anionic, but with the negative charges on the surface of the complex. Therefore, the solvation is favored and an association of excess **23b** is unfavorable. The equilibrium at step 1 corresponds to chain initiation, and steps 2 and 3 to chain propagation. The observed phenomenon is useful for the selective separation of charged polymer systems.



Scheme 20 A "cascade"-type complexation of polyDMAPS and ionene bromide [253]

For IPCs between polycarboxybetaines and negatively charged natural and synthetic polyelectrolytes such as DNA, PMAA, and NaPSS, competition between the intra- and intermacromolecular ion pairing was observed [38]. The weak interaction with DNA and PMAA with polycarboxybetaines was attributed to the formation of stable ion pairs between the carboxylate and quaternary ammonium groups within the repeat units of the polybetaine chains. In contrast, the sulfonate groups of NaPSS bind more strongly to the ammonium groups, thus destroying the internal ion pairs and liberating the carboxylate groups. The titration of 10^{-3} M polycarboxybetaine solution with 10^{-3} M NaPSS may result in soluble as well as insoluble IPCs [36]. The amount of positive charge involved in the IPC formation is pH dependent in the range of pH 1.4–4.0. It is extremely high (53–81%) at pH 1.5 and drastically low (0.7–13%) at pH 4.0. These findings can be interpreted by a competition of intra- and interpolymeric ion-pair associations. At low pH, when the dissociation of the carboxylic groups is suppressed, the polycarbobetaines are positively charged and efficently complexed by the sulfonate groups of NaPSS. But higher pH values provoke the cooperative formation of internal ion pairs between the ammonium and carboxylate groups.

Due to the simultaneous presence of ammonium and carboxylate groups, polycarboxybetaines are able to form interpolymer complexes stabilized by cooperative hydrogen or ionic bonds. Linear and cross-linked poly(carboxy-

ethyl 3-aminocrotonate)s (PCEAC) were involved in the complexation with anionic (PAA, NaPSS) and cationic (polyethyleneimine, poly(hexamethylene guanidine)) polyelectrolytes, as well as the nonionic polymers poly(*N*-vinylpyrrolidone), PEO, and poly(vinyl alcohol) [254]. The composition of the IPCs and some of their characteristics are summarized in Table 4.

IPC formation diminished the high viscosity and swelling degree of linear and cross-linked PCEAC by one to two orders of magnitude. The influence of external factors, such as temperature, pH, ionic strength, and thermodynamic quality of solvent, on the conformation (coil–globule) and volume (swelling–collapsing) transitions of the IPCs was studied [254].

The turbidimetric titration curves of BSA by PCEAC indicate three regions of complex formation [255]. The first region of constant turbidity is due to electrostatic repulsive forces between the oppositely charged protein and PCEAC that retard complex formation. The weak plateau on the curve can be considered as the region of primary or soluble complex formation. In the third region, the sharp increase in turbidity indicates phase separation. Here, pH_c represents the boundary between the nonassociative and primary phases, and pH_ϕ represents the boundary between the primary and aggregate phases. The phase boundaries of the PCEAC–BSA system as a function of pH and ionic strength are presented in Fig. 9. Complex formation takes place in the region between their isoelectric points. An increase of ionic strength leads to a shielding effect of charged groups of both the BSA and PCEAC, and increases both pH_c and pH_ϕ.

Table 4 Some characteristics of IPCs made of linear and cross-linked PCEAC and anionic, cationic, and nonionic polymers in water [254]

PCEAC	Polymer	Composition of IPC (mol/mol)	Intrinsic viscosity (dL/g)	Swelling degree (g/g)
Linear	—	—	14.2	—
	PVP	2 : 1	0.14	—
	PEG	2 : 1	0.13	—
	PVA	2 : 1	—	—
	PAA	1 : 1	—	—
	NaPSS	1 : 1	—	—
	PEI	1 : 1	0.08	—
	PHMG	2 : 1	0.11	—
Cross-linked	—	—	—	115
	PEI	1 : 1	—	8
	PHMG [a]	3 : 1	—	5

[a] PHMG is poly(hexamethylene guanidine)

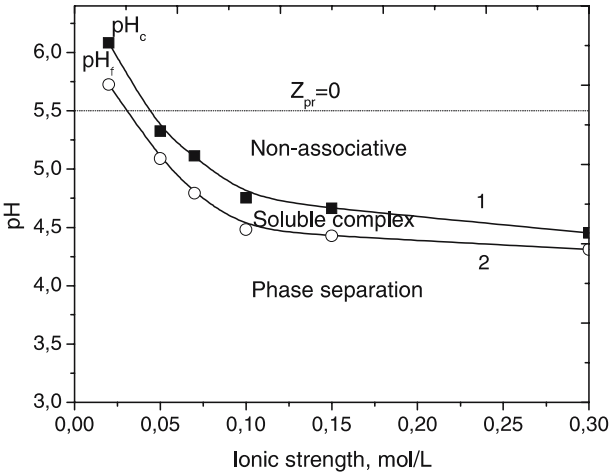


Fig. 9 Phase boundary for BSA/PCEAC. $C_{protein} = 1\ g\ L^{-1}$ [255]

The phase behavior of aqueous two-phase systems containing poly(diallylaminoethanoate-*co*-sulfur dioxide) (PAESD) and PEO is very sensitive to pH and salt concentration [256]. The reason is the dualistic character of PAESD, which can transform to a polyanion with expanded conformation at pH 7.89 and to a polybetaine with a collapsed structure at pH 7.37. At high pH, the mixture of PAESD and PEO is compatible because the hydrodynamic sizes of the two polymers are close. At low pH, however, PAESD and PEO are incompatible due to a large size asymmetry between the two polymers. The addition of salt was found to screen charges and to minimize the influence of pH on their compatibility. The coexistence curve of the PAESD–PEO aqueous two-phase system is described by a semiempirical two-parameter model. The model describes the experimental data accurately, especially when the size asymmetry of the two polymers increases. Further partitioning of two model proteins (BSA and cytochrome c) was studied in an aqueous two-phase system of PAESD and PEO as a function of polymer concentration, salt concentration, and pH [257]. Under all the pH values and salt concentrations investigated, cytochrome c prefers the PAESD-rich (bottom) phase due to its complexation with the protein. For BSA, the best uneven partitioning and separation were obtained at pH 7.89 and in 0.1 M KCl.

Cross-linking of **23b** by ethylene dimethacrylate (EDMA) leads to formation of porous monolithic sulfobetaine polymers [258]. Alternatively, grafting of the internal surfaces of porous poly(trimethylpropane trimethacrylate) (polyTRIM) by DMAPS provides grafted monoliths. Both synthesis routes yielded polymers capable of interacting reversibly with proteins in aqueous solutions. The SEM pictures show the copolymerized monolith poly(DMAPS-*co*-EDMA) comprised of spherical units with average diameter approximately

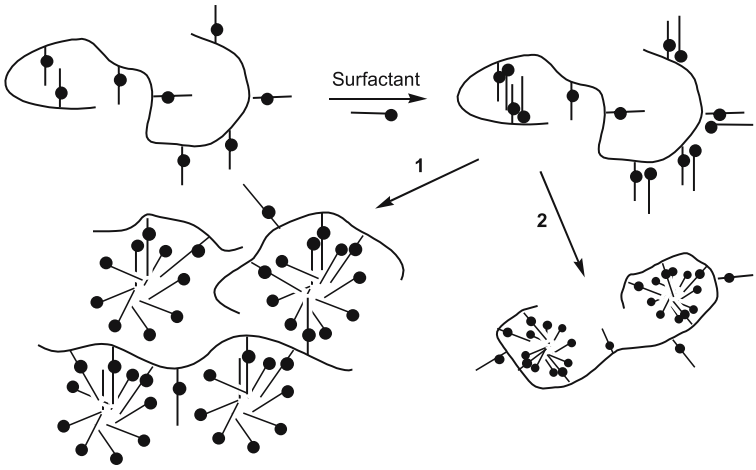
1.5–2 μm agglomerated into larger clusters transected by a large pore size. Such a structure allows liquids to be forced through the monolith sorbent without compression of the particles using flow rates suitable for chromatographic purposes. Indeed, poly(DMAPS-*co*-EDMA) monoliths adsorbed the basic proteins lysozyme, chymotrypsinogen A, and cytochrome c when loaded from pure water, whereas acidic and neutral proteins eluted in the void volume. It is reasonable to assume that the terminal sulfobetaine moieties interact electrostatically with the net cationic charges of basic proteins, because their elution is achieved by increasing the ionic strength according to the Hofmeister lyotropic series ($SCN^- > I^- > Br^- > Cl^-$). Perchlorate ions strengthened substantially the interactive forces between the proteins and the poly(DMAPS-*co*-EDMA) monoliths. The role of hydrophobic interactions in stabilizing polybetaine–protein complexes was tested using a strong promotor for hydrophobic interaction (2 M ammonium sulfate buffer, pH 7) as eluent. None of the model proteins was adsorbed on the monoliths. Thus, hydrophobic interactions were only minor for the interaction behavior of the sulfobetaine-based monoliths.

Interestingly, the interaction of polybetaines with many polyelectrolytes is strong enough and/or sufficiently kinetically favored to give nonstoichiometric complexes at interfaces, and thus to enable the formation of polyelectrolyte multilayers via the layer-by-layer technique [259, 260]. Such unusual variations of the layer-by-layer growth of ultrathin coatings are potentially useful for analyzing proteins, or for producing nonlinear optical coatings [261, 262]. The membranes of terpolymers having 2-methacryloyloxyethyl phosphorylcholine (MPC), methacryloyl or acryloyl poly(oxyethylene) macromonomers, and *n*-butyl methacrylate (BMA) were found to complex with BSA [263].

Low charge density, hydrophobically modified polybetaines were shown to interact and comicellize with nonionic, anionic, cationic, and amphoteric surfactants [181–183] and many ionic organic dyes [264, 265]. The association mechanism of hydrophobically modified polymers and surfactants in dependence on the concentration of interacting components can be modeled by two pathways (Scheme 21) [183].

The first pathway is the formation of mixed micelles or hemimicelles, composed of polymer-bound hydrophobes comicellized with surfactant molecules. Intermolecular physical cross-links often enhance the viscosity of the micellar solutions. The second pathway is intramolecular comicellization so that the hydrodynamic size of the associates contracts.

The addition of surfactants increases the viscosity much more for low charge density polybetaines than for high charge density polybetaines [183]. The addition of the anionic surfactant sodium dodecyl sulfate (SDS) produced the largest increase in solution viscosity for low charge density polybetaines, while the cationic *N*-dodecyl-*N*,*N*,*N*-trimethylammonium bromide, the zwitterionic *N*-dodecyl-*N*,*N*-dimethylammonio-1-propanesulfonate, and



Scheme 21 Formation of hydrophobically modified polybetaine–surfactant complexes [182]

the nonionic Triton X-100 surfactants were less efficient. In most cases, high charge density polycarbobetaines exhibited diminished solution viscosity upon addition of surfactants.

The interaction between a phosphorylcholine-based polybetaine (equimolar copolymer PNIPA-PC of *N*-isopropylacrylamide and *N*-phosphorylcholine-*N*′-ethylenedioxybis(ethyl)acrylamide) and anionic, cationic, amphoteric, and neutral surfactants was studied by a fluorescence probe, isothermal titration calorimetry, and ^{1}H NMR spectroscopy [266]. The main results obtained in this study can be summarized as follows. The charge of the surfactant headgroup is the major determinant that controls the interactions. Only anionic surfactants associate with PNIPA-PC. For such associating systems, the surfactant concentrations at which binding first takes place are much lower than the respective critical micelle concentrations of the surfactants. The association between PNIPA-PC and the anionic surfactants occurs first via the electrostatic attraction between the surfactant headgroups and the polymer-bound ammonium groups. None of the mixed systems investigated underwent macroscopic phase separation, as the neutral comonomer (NIPAM) may act as solubilizing agent.

It is interesting to compare the behavior of polyelectrolyte–surfactant, polyampholyte–surfactant, and polybetaine–surfactant complexes. Addition of ionic surfactants to solutions of oppositely charged polyelectrolytes results in the precipitation of polyelectrolyte–surfactant complexes even at low polymer concentration. While partially charged polyampholytes are often insoluble in water, the association with either anionic or cationic surfactants results in solubilization due to the neutralization of one type of charge. The remaining nonneutralized charges confer polyelectrolyte character to the polyampholyte, ensuring its solubility. The addition of anionic or cationic surfactants

to polybetaines results in soluble polybetaine–surfactant complexes, converting the whole macromolecule either to a polycation or to a polyanion.

The interaction of low molar mass salts with polybetaines differs from the behavior of polyelectrolytes in that both low molar mass ions of the added salt may bind to the polymer [46, 47, 178, 267]. Typically, the intensity of interaction follows the well-known Hofmeister lyotropic series. This can be exploited for separation purposes. In particular, polycarboxybetaines containing acidic and basic groups are able to bind metal ions efficiently via their multidentate character. For example, poly(*N*-propylene glycine) (PPG), poly(1-isopropylcarboxylethyleneimine) (PIPCEI), and poly(ethylene alanine) (PEA) form five-membered chelate cycles [268]. The stability of polyampholyte–metal complexes with respect to bivalent ions decreases as $Zn^{2+} > Ni^{2+} > Cd^{2+} > Co^{2+} > Pb^{2+} > Fe^{2+} > Ca^{2+} > Mg^{2+}$ and coincides well with the stability constants of their complexes with EDTA. In another example, the binding ability of poly(carboxyethyl 3-aminocrotonate) modified by ethanolamine (PCEAC-Ea), glycine (PCEAC-Gly), β-alanine (PCEAC-Ala), and lysine (PCEAC-Lys) was studied with respect to various metal ions [269–275] (Table 5).

The polymer–metal complexes stabilized by the formation of intra- or intermacromolecular ionic and coordination bonds were precipitated. The adsorption capacity of linear polybetaines decreases with PCEAC-Gly > PCEAC-Ala > PCEAC-Lys, and depends on the metal cation to be bound with the following orders:

PCEAC-Gly:

$$Cd(II) > Cr(III) > Ga(III) > Cu(II) > Fe(III) \approx Ni(II) > Co(II) > Al(III)$$

PCEAC-Ala:

$$Cd(II) > Cr(III) > Ga(III) > Cu(II) > Co(II) > Fe(III) > Ni(II) > Al(III)$$

PCEAC-Lys:

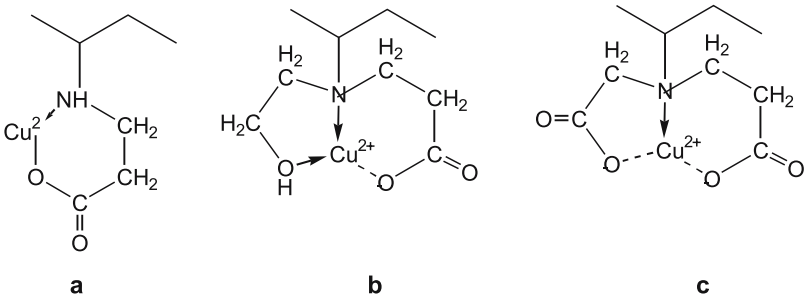
$$Ga(III) > Cd(II) > Cu(II) > Cr(III) > Fe(III) > Co(II) > Ni(II) > Al(III)$$

Accordingly, the detailed polymer and betaine structures are important for the strength of the complexation. The high adsorption capacity of PCEAC-Gly and PCEAC-Ea in comparison with that of the parent PCEAC is probably due to the additional chelating groups such as OH and COOH that can form very stable mixed five- and six-membered cyclic structures with metal ions (Scheme 22).

The sorption of metal ions by betaine hydrogels is accompanied by gel contraction. At first, a thin colored layer is formed on the gel surface. Then the colored zone gradually moves into the gel interior. The driving force of this process is “ion-hopping transportation” of metal ions through intra- and intermolecular chelate formation, e.g., constant migration of metal ions deep into the gel volume by exchange of free ligand vacancies. In min-

Table 5 Metal ion binding capacity of linear PCEAC-Gly, PCEAC-Ala, and PCEAC-Lys [275]

Linear polybetaine	Amount of metal ion (mg) adsorbed by 1 g of linear polymer							
	Al(III)	Cd(II)	Co(II)	Cr(III)	Cu(II)	Fe(III)	Ga(III)	Ni(II)
PCEAC-Gly	153	984	345	791	600	373	726	366
PCEAC-Ala	164	1007	408	732	560	400	711	391
PCEAC-Lys	126	609	345	465	475	385	633	293



a b c

Scheme 22 Chelate complexes of Cu(II) with PCEAC (**a**), PCEAC-Ea (**b**), and PCEAC-Gly (**c**) [275]

eral acids, metal ions are replaced by protons and desorption of the metal ions takes place. Regeneration of the gel samples occurs in fresh water, e.g., the gel samples gradually return to the initial state. These experiments clearly demonstrate the ability of gel samples to adsorb and desorb metal ions several times. They imply the potential application of water-soluble and water-swelling polybetaines for purification of wastewater from metal ion contaminants.

6 Application of Polybetaines

Polybetaines are specialty polymers. Accordingly, they are typically discussed for high added value applications, or in cases where no satisfactory alternative materials exist. The application fields of polybetaines comprise, for instance, the oil industry, hydrometallurgy, biotechnology, medicine, and catalysis.

The drag reduction behavior was examined for poly3-[(2-acrylamido-2-methylpropyl)dimethylammonio]-1-propanesulfonate (AMPDAPS) [276]. In this study, the polybetaine excelled by having good long-term stability. The drag reduction properties of polyAMPDAPS and PEO in 0.5 M NaCl are compared in Fig. 10. PolyAMPDAPS retains approximately 60% of its initial level

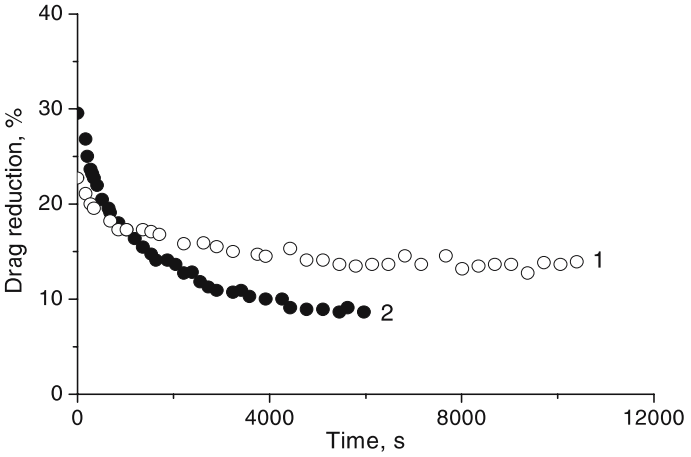


Fig. 10 Drag reduction profile for 3-ppm solutions of polymer of AMPDAPS (1) and PEO (2) in 0.5 M NaCl at $T_w = 1122$ dyne cm^{-2} in the rotating-disk rheometer [276]

of drag reduction after 100 min at 1000 rpm in the rotating disk. PEO retains only 28.5% of its initial drag reduction under similar conditions.

The most widely used synthetic and natural enhanced oil recovery polymers, such as partially hydrolyzed polyacrylamide, carboxymethyl(ethyl) cellulose, polysaccharides, or xanthan gums, are not suitable for high-temperature reservoirs (> 90 °C) with high-density brine fluid due to excessive hydrolysis and precipitation [277]. The main advantages of polymeric betaines over the mentioned standard polymers are: (1) thermostability (up to 120 °C); (2) brine compatibility; and (3) viscosification in brine solution [278]. Carbobetaines grafted onto hydroxyethyl cellulose were tested as a drilling-mud additive for clay hydration inhibition and mud rheological control [279]. An increase in the content of carbobetaine moieties resulted in an enhanced inhibitive ability, especially for saline mud.

Polybetaine gels were used for the separation of water and oil from water-in-oil emulsions [280]. These gels destructed water-in-oil emulsions by absorbing water, which was subsequently released under an externally imposed DC electric field that made the swollen gel shrink. The invention [281] concerns an improved process for stabilizing asphalt in a water emulsion using certain polybetaine surfactants as an asphalt emulsifier.

A hydrophobically modified polybetaine proved to be an efficient pour point depressant (PPD), to inhibit the deposition of wax, and to improve the viscosity of waxy crude oil from the Kumkol–Akshabulak oil field (western Kazakhstan) [282]. The inhibition of wax deposits in the presence of the hydrophobic polybetaine was interpreted in terms of its interference with the wax crystallization process, due to the formation of inverse micellar structures. While the zwitterionic parts on the polymer backbone stabilize the

Table 6 The pour point and kinematic viscosity of a Kumkol–Akshabulak oil mixture [282]

PCMEDDAC, 100 ppm	Kinematic viscosity (cSt)					Pour point (°C)
	20 °C	30 °C	40 °C	50 °C	60 °C	
Crude oil without depressant	9.87	5.43	4.07	3.22	2.76	15
Preheated oil without added depressant	9.40	5.68	4.21	3.33	2.76	6
Depressant prepared in DMF	7.44	5.81	4.42	3.46	2.91	0
Depressant prepared in *o*-xylene	7.21	5.56	4.33	3.10	2.80	3
Depressant prepared in *n*-hexane	7.37	5.60	4.36	3.13	2.89	– 3

small size of the aggregates, the hydrophobic side chains of the polymer provide nucleation sites and cocrystallize with the paraffins, thus modifying the paraffin crystal structure. The PPD effectiveness of poly3-[(2-carboxy-1-methylethyl)dodecylaminocrotonate] (PCMEDDAC) is shown in Table 6 for a Kumkol–Akshabulak oil mixture (89 : 11 wt %).

The best activity was observed for PCMEDDAC dissolved in *n*-hexane. Initial waxy crude oil behaves like a viscoplastic fluid. Doped by PCMEDDAC, waxy oil approaches a Newtonian liquid, and the shear stress decreases considerably due to the modification of the paraffin crystals by the hydrophobized macromolecules. In oily environments, PCMEDDAC forms micelles consisting of a hydrophilic core (made of the betaine groups) and a hydrophobic corona (made of the dodecyl groups). The PPD mechanism of PCMEDDAC with respect to waxy crude oil suggests the adsorption of definite fractions of paraffin molecules on the surface of micelles and further retardation of agglomeration.

The antipolyelectrolyte effect of polymeric betaines in saline media is used to thicken, retain saline water, or stabilize electrolyte-containing aqueous media. Polybetaines were applied to absorbing aqueous electrolyte solution [283], as viscosifying agents [284] for aqueous solutions within a wide salinity and temperature range, and as modifying agents for the surfaces of particles in aqueous suspensions.

The recovery of transition metal ions and organic impurities by both water-soluble and water-swelling polybetaines is especially important for hydrometallurgy processes and environmental protection [285]. The formation of five- or six-membered chelate "bridges", where transition metal ions bind to at least two monomeric units, is specific for polycarboxybetaines [286, 287]. Figure 11 shows the ability of PCEPAC hydrogels to absorb and desorb copper(II) ions [40, 269–275]. Adsorption of copper(II) ions starts from the gel surface, then the shell layer gradually moves into the gel interior. Desorption of copper(II) ions from the gel interior takes place in the medium of mineral acid due to destruction of ligand–metal complexes and replacement

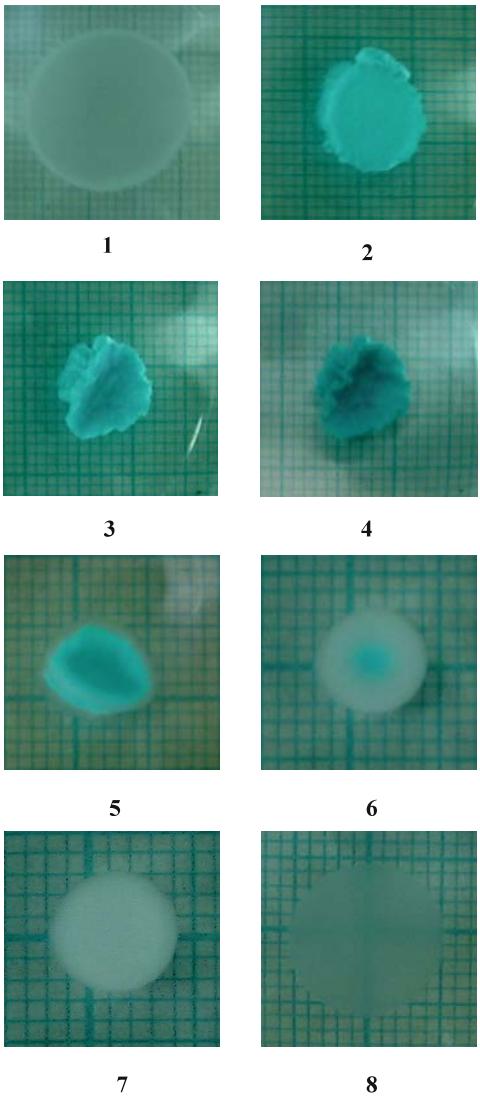


Fig. 11 Adsorption (1–4) and desorption (5–7) of copper(II) ions by a PCEPAC gel, and washing of the gel by water (8) as a function of time. Initial state (1), after 30 min (2), 1 h (3), 7 h (4), 3 min (5), 15 min (6), 1 h (7), 2 days (8) [273]

of metal ions by protons. According to UV/Vis measurements, up to 90% of copper(II) ions are released from the gel volume over 2 h. Regeneration of the gel sample can be realized in fresh water. As seen from Fig. 11, the gel sample gradually returns to its initial state after 2 days. Adsorption and desorption of copper(II) ions followed by gel regeneration were repeated ten times without the loss of gel capacity, durability, and reusability. Thus, the ad-

vantages of polycarbobetaine-type gels over others are: (1) high adsorption capacity (1 g of dry gel adsorbs up to 500 mg of copper(II) ions); (2) easy and fast desorption of metal ions by mineral acid (for instance, by 0.1 M HCl); (3) durability of the hydrogel materials (ten times repeatable use of the adsorbent); and (4) good mechanical stability (preservation of gel shape without cracks). Therefore, one can conclude that betaine-type hydrogels are attractive materials for the removal and recovery of metal ions from wastewater.

Among the various protein analysis and purification techniques, isoelectric focusing and chromatofocusing are the main tools for separating and purifying proteins for analytical and preparative purposes. However, the main disadvantage of these methods is that they use expensive polyampholyte buffers (a mixture of hundreds or thousands of low molecular weight amphoteric molecules) to generate linear or quasi-linear pH gradients and high applied voltage (up to 200 V/cm). Moreover, amphoteric buffers tend to associate with proteins and often yield irreproducible gradient shapes. A new approach [288–290] was developed for the electrophoretic resolution of proteins, which combines both the gel matrix and carrier ampholytes in one and the same sample, as in polycarbobetaine gels (Fig. 12).

In practice, the aqueous solution of proteins to be separated is injected by a syringe into the central section of the polyampholyte gel specimen. Then, the DC electric field is switched on, which induces the formation of a linear pH gradient along the gel sample. In its turn, the generated pH gradient promotes the migration of protein molecules until they are gradually localized at their isoelectric pH. Protein molecules will be separated and concentrated if the isoelectric pH of the proteins coincides with appropriate pH zones of the amphoteric gel.

Polybetaine-based materials [291] and polybetaines grafted (or adsorbed) onto an inorganic particle surface are applicable as a stationary phase for ion chromatography [292]. The separation capability of poly[3-diethyl(methylmethacryloylethyl)ammonium propanesulfonate] (polyDMAPS) grafted to silica gel and physically adsorbed onto silica gel was compared with respect

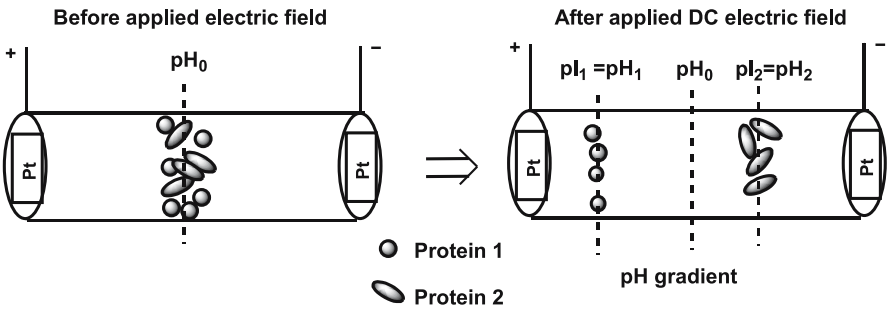


Fig. 12 Resolution of protein mixtures with the help of carbobetaine gels [288]

to various anions. The columns packed with polyDMAPS-grafted silica gel were able to separate Ce^{4+}, Li^{+}, Ca^{2+}, and Mg^{2+}. Moreover, the polyDMAPS-grafted silica gel has better durability than that of the physically immobilized polybetaine.

Polyetherurethanes end-capped with zwitterions of sulfobetaine via a hexamethylene diisocyanate spacer were found to show good blood compatibility [293]. Phospholipid-based polymers can serve as coatings for blood contact devices, drug carriers [294], and bioconjugates [295] due to their excellent biocompatibility, or as templates for the structure-directed synthesis of organic polymers [296]. The controlled permeation and release of drugs from polybetaine-coated implants provides a new approach to treating device-based infection, tumors, and stent restenosis [294].

The enzymatic activity profiles of the native papain and polybetaine-conjugated papain at 40 °C were compared [295]. The enzymatic activity of the native enzyme decreases continuously with the storage period, while papain maintains 50% of the initial enzymatic activity when conjugated with polybetaine. Enrichment of the polybetaine chain by hydrophobic monomers such as butyl methacrylate maintains the enzymatic activity of papain for 28 days. DMAEM-MPC diblock copolymers exhibit a stabilization effect with respect to DNA and can serve as a synthetic vector for gene delivery [297]. Highly condensed, sterically stabilized DMAEM-MPC/DNA complexes of 120–140-nm diameter or partly condensed with "spaghetti" structures are formed which prevent promiscuous interactions with tissues in the body. They potentially allow for the cell-specific delivery of the condensates following the attachment of a targeting ligand.

Fluoroalkylated end-capped 2-(3-acrylamidopropyldimethylammonio)-ethanoate (APDMAE) polymers (R_F-(APDMAE)$_n$-R_F) were found [235] to exhibit high antibacterial activity against *Staphylococcus aureus* or *Penicillium aeruginosa*. It is suggested that the cationic moieties in the betaine segments of the fluorinated APDMAE polymers are able to interact tightly with the negatively charged bacterial cell. In particular, the longer perfluorooxyalkylated APDMAE polymer was more active against both *S. aureus* and *P. aeruginosa* (below 10^3 colony-forming unit levels).

Several authors [298–300] reported on the preparation of platinum and palladium nanoparticles having a preferential diameter from about 1 to 2 nm stabilized by polymeric carbo-, phospho-, and sulfobetaines for fuel-cell catalysts and vinyl acetate production.

7 Concluding Remarks

The synthetic strategy, solution properties, complexation ability, and application aspects of polymeric carbo-, sulfo-, and phosphobetaines are outlined in

this review. The advantages and disadvantages of direct polymerization of the zwitterionic monomers and betainization of polymeric precursors are discussed. The newly developed controlled radical polymerization (CRP) of both the zwitterionic and the reactive precursor monomers in organic solvents, bulk, and aqueous media has become a powerful tool to obtain polybetaines with narrow polydispersities and defined end groups, as well as copolymers containing betaine blocks. The narrow molecular weight distribution of betaine polymers prepared by CRP supports the precision of any physical or physicochemical characteristics in solution and in the condensed and gel states. Atom transfer radical polymerization (ATRP), and particularly the reversible addition fragmentation transfer (RAFT) method, are promising routes to overcome certain shortcomings in the polymerization of zwitterionic monomers. A novel approach to designing zwitterionic polysoaps has been developed most recently.

The existence of intragroup, intrachain, and interchain interactions of the positive and negative charges in dependence on the length and flexibility of spacer between opposite charges determines the solubility, ionization ability, phase, volume, and conformational state of polymeric betaines in aqueous and saline media. The solubility of polybetaines in salt-containing solutions can satisfactorily be described by the charge/radius ratio, Hofmeister series, and Pearson theory. Transformation of zwitterionic species to anionic, cationic, and molecular forms can be determined by micro- and macroscopic ionization constants. The antipolyelectrolyte character comprising chain expansion upon addition of neutral salts is specific for polybetaines. Hydrophobically modified polybetaines exhibit reversible pH-, salt-, solvent-, and temperature-induced micellization and conformational transition from the coil (collapsed) to expanded (swollen) structure. The conformational and phase (or volume) transitions of linear and cross-linked polybetaines in response to pH, ionic strength, temperature, solvent nature, etc. expands our knowledge on the universality of synthetic and natural systems.

Interpolymer, polymer–surfactant, and coordination complexes of polybetaines are less developed. The "cascade"-type complexation observed for the polybetaine–polyelectrolyte system is similar to the "layer-by-layer" deposition found for oppositely charged polyelectrolytes. The behavior of the polybetaine–surfactant system differs from that of polyelectrolyte–surfactant and polyampholyte–surfactant complexes, leading to inter- or intramolecular comicellization or converting the whole macromolecule to either a polycation or polyanion.

The accumulated knowledge on synthesis–structure–property relationships can be exploited for technological purposes. Polymeric betaines are finding increased use in separation and enrichment technologies through combined adsorption, chelating, and ion-exchange processes. The antipolyelectrolyte effect can be applied to drag reduction, enhanced oil recovery, and desalination. Formation of a pH gradient within a monolithic betaine

gel, stimulated by an externally imposed DC electric field, may provide an alternative protein separation and purification principle.

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