Structures and Synthesis of Zwitterionic Polymers

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Abstract: The structures and synthesis of polyzwitterions (“polybetaines”) are reviewed, emphasizing the literature of the past decade. Particular attention is given to the general challenges faced, and to successful strategies to obtain polymers with a true balance of permanent cationic and anionic groups, thus resulting in an overall zero charge. Also, the progress due to applying new methodologies from general polymer synthesis, such as controlled polymerization methods or the use of “click” chemical reactions is presented. Furthermore, the emerging topic of responsive (“smart”) polyzwitterions is addressed. The considerations and critical discussions are illustrated by typical examples.

Keywords: review; polyzwitterion; polyampholyte; zwitterionic group; betaine; synthesis; monomer; polymerization; post-polymerization modification

1. Introduction

This review is focused on the structure and synthesis of zwitterionic polymers. Polyzwitterions or synonymous polybetaines bear, within their constitutional repeat unit, the same number of anionic and cationic groups [1]. Essentially, the ionic groups are functional over a large pH-window. Accordingly, the overall charge of polyzwitterions is zero under normal conditions, notwithstanding that they are characterized by a high density of polymer-bound ion pairs attached to the polymer chain. Thus, polyzwitterions represent a special subclass of polyamphotelites featuring a very particular property profile [2–5]. The latter polymer class carries simultaneously anionic and cationic groups, too, yet there is a priori no particular mutual correlation between them (Scheme 1) [2,5,6]. Thus in polyamphotelites, anionic and cationic sites may be scattered at random along the polymer chains, one charged species
may outnumber the other one (often by far), and one (or even both) of the charged species may be present only in a narrow pH-range. Hence, polyampholytes typically bear an overall net charge (except for a specific narrow pH range, where the number of cationic and anionic sites may be equal, thus behaving like polyzwitterions). The net charge can be positive or negative, and may sensitively vary with the pH and ionic strength of the system studied, with respect to the absolute amount as well as the change of the sign. Therefore, polyampholytes behave mostly either as polyanionic or as polycationic species, whereas polyzwitterions due to their overall charge neutrality exhibit a different, hybrid-like property profile. On the one hand, strong Coulomb interactions prevail in polyzwitterions, which thus generally exhibit high hydrophilicity [3,7]. On the other hand, polyzwitterions do not show the typical polyelectrolyte effects, but their behavior shares many similarities with polar non-ionic polymers [5].

**Scheme 1.** Simplistic model of polyampholytes (left) and polyzwitterions (right).

Polyzwitterions should be also clearly distinguished from other polymer classes such as mesoionic polymers and polymeric ylides (Scheme 2). Mesoionic compounds can be only presented by canonical formulas via a set of mesomeric structures that contain formally cationic and anionic sites; yet, they do not carry separate charges but dispose only of a high dipole moment. Generally, they are not even effective hydrophilic groups [7,8]. Ylides are 1,2-dipolar compounds with a semi-polar bond, which may be represented by canonical formulas with formally separate positive and negative charges on neighbouring atom. Yet, ylide moieties typically exhibit a high double bond character and low hydrophilicity, too.

**Scheme 2.** Models for mesoionic (left, here: a sydnone) and ylide structures (right).

Polyzwitterions are speciality polymers with low production volume so far. Although known at least since the late 1950s [9–11], they have been considered to be rather exotic compounds for long. They found a certain interest as ionomers [12–15], for fibres due to strong interactions with charged dye stuffs [16–18], and as rheology modifiers in aqueous solutions [19], due to their great tolerance to highly saline environments [5]. Continuously increasing interest in polyzwitterions has risen only since the 1980s, when they were recognized as analogs of important biological structures, such as phospholipids that are the major constituents of cell membranes [20–25]. Apart from certain alkaloids and hormones such as trigonelline or homarine, other important zwitterionic biological structures are compatible solutes, which are crucial for the osmotic regulation of organisms, such as ectoine or betaine (Scheme 3). As a “*pars pro toto*”, the name of the latter compound is even frequently used
synonymously for zwitterions. DMSP and arsenobetaine are found in plankton and fish. Also, the RGD (arginine-glycine-aspartic acid) tripeptide motif that plays a key role in cell adhesion [26] represents a zwitterionic unit under physiological conditions. Thus not surprisingly, many polyzwitter-ions have been shown to be highly biocompatible [21,27,28], combining strong hydrophilicity with zero net charge and high salt tolerance.

Scheme 3. Examples for natural zwitterionic compounds. From left to right: phospholipid 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine (DMPC), trigonelline, ectoine, betaine, 3-dimethylsulfoniopropanoate (DMSP), arsenobetaine.

In an extension of this reasoning, much interest has focused on polyzwitterions for mimicking cell membranes [29–32] and for preparing tailored surfaces, as they can confer excellent lubrication [33–35] and excellent resistance to (bio)fouling to various materials [27,28,36–41]. The strong interest comprises equally materials for biomedical as well as technical uses. Furthermore, the combination of hydrophilicity and tolerance to high ionic strength makes polyzwitterions attractive candidates for hydrogels or viscosity modifiers in aqueous media under extreme conditions, such as oil field applications. Interestingly, many polyzwitterions show an upper critical solution temperature (UCST) in aqueous media [19,42–48]. This has been exploited in recent years for designing stimuli-responsive polymer systems [49–51] from polyzwitterions, being reversibly sensitive to changes in temperature, ionic strength, specific ion pairing, and chemical reactions, or, more rarely, to changes in pH (see Section 4.2).

The field of polyzwitterions has been occasionally reviewed, often mixed up with polyampholytes. The intention and quality of these reviews vary strongly. Comprehensive critical treatments are the exception [2–5]. A number of the large reviews have mostly descriptive character, confining themselves to an enumeration of the literature published [52,53]. The majority of reviews dealing with polyzwitterions have focused on one specific aspect, such as synthetic phospholipid polymers [21,29–32,54], membranes [55], or on ultralow-fouling behaviour [27,38]. In particularly, the synthesis of polyzwitterions has been hardly treated systematically, as shall be done here. The literature of the past decade will be emphasized in more detail, while earlier reports will be only highlighted. This review cannot be exhaustive; choices had to be made to keep the contents manageable, which inevitably may be subjective and arbitrary to a certain extent. In any case for detailed surveys of the literature up to 2005, the reader is referred to previous reviews covering this period.

2. General Structures of Zwitterionic Polymers

2.1. Possible Polymer Architectures

Before looking in more detail at specific synthesis strategies to prepare polyzwitterions, it is helpful to consider first the basic zwitterionic structures that are possible, as well as the general pathways to
them. Scheme 4 illustrates the various possibilities to implement ion pairs within polymers in order to produce polyzwitterions.

**Scheme 4.** Possible distribution of ionic groups within polyzwitterions.

With the apparent exception of architecture K, all of the various options have been realized [5,21]. Nevertheless, the by far most widespread architecture of polyzwitterions is type C. Considering the various chemist's options for their synthesis, a zwitterionic moiety is easier to implement into the polymer side chains (architectures A–E) than into the main chain (architectures F–K). Moreover, the necessary chemical functionalization for polymer attachment is more versatile and is more easily achieved for organic cationic groups, in particular for ammonium groups, than for organic anionic groups (see below). All these aspects have favored so far architecture C over A, B and D for the design of polyzwitterions, with the exception of polymeric phosphatidylcholine mimics (“synthetic cell membranes”) [21,29], which represent type B architectures. Moreover, a few zwitterionic monomers leading to architecture C are readily commercially available, thus adding to the dominance of the derived homo- and copolymers (cf. Section 3.1).

The possible synthetic pathways to polyzwitterions are outlined in Scheme 5, for the sake of simplicity exemplified only for architecture A. Clearly, the most straightforward strategy is the polymerization of prefabricated zwitterionic monomers (path 1, starting from A), as discussed in Section 3.1. However, a number of practical problems have led to a wealth of strategies applied alternatively to synthesize polyzwitterions. Apart from the possible difficulty to prepare a certain zwitterionic monomer, or from its possible inherent instability, the zwitterionic moiety may be not chemically inert during the polymerization reaction. If the zwitterion is consumed by the reaction, or inhibits the polymerization, this precludes from the use of path 1. Thus, it can be necessary to establish the cationic (path 2) or the anionic group (path 3), respectively, of the zwitterion moieties only after the polymerization step. This can be done either by coupling to, activation of, or liberation of protected reactive precursor groups “X” on polyanion or polycation precursors (see Section 3.2). It may be even opportune to introduce both the cationic and the anionic sites only after polymerization into a precursor polymer P-Ax (path 4, starting from Ax), either in one step (path 4b), or successively in two steps (paths 5 and 6).
Frequently, the choice of the synthesis strategy is not dictated by possible chemical incompatibilities, but rather by practical aspects, such as the notorious problematic solubility of many polyzwitterions [56,57]. Due to the a priori self-sufficient, strong intra- and intermolecular electrostatic interactions of polyzwitterions, few solvents can successfully compete to achieve dissolution. Polar protic solvents as well as aqueous salt solutions are particularly useful. They tend to screen the electrostatic attractive forces between the zwitterionic moieties efficiently, thus favoring dissolution in the reaction medium [42]. Fluorinated alcohols such as trifluoroethanol and hexafluoroisopropanol are often excellent choices [58]. Such solvents, however, are not compatible with many polymerization methods, such as carbocationic or carboanionic polymerization, just to cite a few. Also, they may interfere with metal based polymerization catalysts. Ionic liquids may be advantageous alternative solvents [59–61], in particular if zwitterionic and hydrophobic components are simultaneously present in the reaction mixture (as, e.g., it is frequently the case in copolymerizations) [59,60]. Yet, a practical limitation of ionic liquid solvents is the difficulty of their complete removal after the successful polymerization [60], let alone their high costs. In any case, appropriate solvents for the polymerization process are not always at hand, so that frequently, path 1 in Scheme 5 cannot be realized.

2.2. Zwitterionic Moieties

2.2.1. General Requirements for Useful Zwitterionic Moieties

If we come to fill the abstract symbols of the ionic moieties in Schemes 4 and 5 with chemical reality, one may a priori imagine a plethora of combinations of organic cationic and anionic groups to construct zwitterionic moieties. However, only few have been realized up to now (see Figure 1). The strongly selective occurrence of possible building blocks has several reasons. First of all, it is due to the manifold boundary conditions, which generally ought to be respected: The zwitterionic moiety
must be inherently stable under ambient conditions, and preferentially also at temperatures of 100 °C at least. The zwitterionic moiety must allow fixing an additional functional group, which enables the binding to the polymer chain. Both the cationic and the anionic groups should preferentially not be subject to protonation/deprotonation equilibria, i.e., they should be present over a maximum pH range. This means that cations and anions that are stable in the pH range of 2–12 are preferred. This implies the use of inherently quenched ionic species, such as quaternized nitrogen containing compounds, or of strongly acidic or basic moieties, such as sulfonic acid or guanidine groups (see Section 2.2.2). The ionic groups should be sufficiently inert during storage and use, which is mostly envisaged in humid or even aqueous environments. This asks implicitly for a minimum long-term stability of the zwitterionic moiety against hydrolysis, nucleophilic and electrophilic attacks.

2.2.2. Zwitterionic Moieties Realized in Polyzwitterions and Their Characteristic Features

The boundary conditions considered in the previous section are reflected in the structures in Figure 1, which presents zwitterionic moieties that have been used to prepare polyzwitterions so far. Within the zwitterionic moieties presented, we find as anionic groups first of all phosphates (I, XIV), sulfonates (V, XVI, XX), and carboxylates (VII, X, XI, XVIII, XIX, XXI). These groups dominate the field [2,4,52,53]. Occasionally, phosphonates (II, IV, XV) [62–64], phosphinates (III) [63], sulphates [65] (VI, XVII), alkoxydicyanoethenolates (XII) [66–69], boronates (XIII) [70], phenolates (XXIII, XXIV) [71], sulfonamides (VIII) [72] and sulfonimides (IX) [72] have been employed.

Sulphuric acids have typically pKa values of \(\leq 1\), phosphinic acids of 1–2, phosphates and phosphonates of about 2. Hence, these groups in zwitterions I–VI stay fully deprotonated over a very broad pH range. Also, alkoxydicyanoethenols (XII) and enols derived from squaric acid (XXII) are strongly acidic (pKa \(\leq 0\), and \(= 1.5\), respectively), thus satisfying the above defined boundary conditions very well. A particularity of the anionic phosphonate group is that the link to the cationic group of the zwitterion can be made via a P–C bond (II, XV) [63], or via a P–O bond (IV) [62], adding to the diversity of possible structures.

In the case of the carboxylates, however, the situation is less obvious, as their acidity is modulated by the distance between the carboxyl group and the cationic site. In the case of the ammoniocarboxylates (basic form VII in Figure 1), pK\(_a\) values of 1.8, 3.3, 4.0 and 4.2 were reported for \(x\), the number of methylene groups between the ionic sites, increasing from 1 to 4 [73]. This is due to the strong electron withdrawing effect of the ammonium group, which levels off for \(x \geq 4\), resulting in pK\(_a\) values of about 4.5. The acidity of carboxyl groups is also increased by attachment to aromatic cations, with comparable distance effects, as reported for imidazolio-carboxylates [74]. The same effect also decreases the pK\(_a\) value of pyridinio-carboxylates XI to 1.8 [75]. One study supports the view that the charge distance effect in polymeric pyridiniobetaines is considerably less pronounced than in low molar mass carboxybetaines. The pK\(_a\) values the carboxyl groups was found to stay below 2.5 even for large spacer groups (\(x \leq 8\)) separating the ammonium and carboxylate sites [76]. In contrast, another study observes the preservation of a clear spacer effect on the acidity of the carboxyl group in such polybetaines [77].

Analogous effects of the distance between the cationic and the anionic site apply to other oxyanions. In the case of the normally only weakly acidic boronic acid, a pK\(_a\) value of about 4 was
found for pyridinioboronates XIII [70]. Under physiological conditions pH is about 7–8, thus for related uses, the only moderate acidity of the –COOH group will not endanger the zwitterionic state. However in other, more acidic or less defined environments, deprotonation of the anionic site may be partially or even fully suppressed, turning thus the supposed polyzwitterion into a polycation [77,78].

Similar problems are faced for sulfonimides, and even more for sulfonamides and phenols. While the acidity of sulfonimides corresponds roughly to the one of the carboxyl group, sulfonamides and phenols are generally much less acidic (unsubstituted forms have pK_a values around 10). However, strong electron withdrawing inductive effects may increase acidity notably (XXIII, XXIV in Figure 1). Conjugated electron withdrawing groups may increase acidity even more drastically. For instance, the pK_a values of phenols decrease from 10 via 7 and 4 to 0.4 after single, double and triple nitration in the 2-, 4-, and 6- positions. Yet, the increasing smearing of the negative charge over many atoms renders such anions less and less hydrophilic.

Concerning the more compact and generally more acidic groups, their hydrophilicity decreases with increasing acidity as a general trend. Thus, hydrophilicity (and also hygroscopy) of the anionic groups decreases in the order –COO^- > (RO)_2-P(=O)O^- > –SO_3^- > –O–SO_3^- [3,7,8,79]. Alkoxydicyno-ethenolates (XII) are the most acidic and the least hydrophilic anionic groups, so that the derived polyzwitterions are typically not water soluble [66,69]. In return, not only the basicity, but also nucleophilicity of these anionic groups decreases in the same order. This must be taken into account for their respective synthesis and handling, and possible precautions have to be taken. For instance, while due to the low nucleophilicity, sulfonate groups are inert during most alkylating reactions, carboxylate groups may be not. This may call for the use of protecting groups during the synthesis of carboxylate bearing polyzwitterions (cf. below, Scheme 6).

The most generally employed cationic groups in polyzwitterions contain nitrogen, in form of quaternized ammonium groups, or of protonated amines. The latter, however, have only a limited basicity. In the advantageous case of aliphatic amines, pK_a values of the protonated forms are rather high, i.e., typically in the range of 8–10. Unfortunately, the lower values around 8 and even less are characteristic for many functional amines, as, e.g., for derivatives of aminoethanol or amino acids. Accordingly, the zwitterionic status of motifs XIV–XVIII may be even more easily compromised by the solution pH than motifs containing the carboxyl group, but now not in acidic but in basic milieus. Hence, the pH window for obtaining polyzwitterions of poly(αmino acids) bearing motif XVIII gets very narrow. Therefore, such compounds are for good reason generally not considered as polyzwitterions, but treated as typical polyampholytes instead.

Nitrogen based azomethines, amidines, and guanidines are more basic than simple amines, in particular the guanidines. With a pK_a < 1, the latter are operative as cationic group throughout the whole pH window of water (Figure 1, motif X). Still, azomethines are highly sensitive to hydrolysis, in particular when protonated or quaternized, and such fragile structures have been reported only exceptionally as cationic groups for polyzwitterions [80].
Figure 1. Zwitterionic groups, which have been incorporated in polymers: ammoniophosphates (phosphobetaines or lecithin analogues) I and XIV, ammoniophosphonates (phosphonobetaines) II, IV and XV, ammoniophosphinates (phosphinobetaines) III, ammoniosulfonates (sulfobetaines) V and XVI, ammoniosulfates VI and XVII, ammoniocarboxylates (carbo- or carboxybetaines) VII, X, XI, XVIII and XXI, ammoniosulfonamides VIII, ammoni-sulfon-imides IX, guanidiniocarboxylates (asparagine analogs) X, pyridiniocarboxylates XI, ammonio(alkoxy)dicyanoethenolates XII, ammonioboronates XIII, sulfoniocarboxylates XIX, phosphoniosulfonates XX, phosphoniocarboxylates XXI, squaraine dyes XXII, oxypyridine betaines XXIII and XXIV.

Alternative cationic groups that are free of nitrogen have been exceptional in polyzwitterions. There are some rare reports of sulfonium groups (XIX) in combination with carboxylates [11, 81]. Presumably, the high chemical sensitivity of sulfonium groups against nucleophilic attack, even by weak nucleophiles such as water or alcohols, as well as their instability under thermal stress has precluded a wider use. This is not the case for the phosphonium group (XX, XXI), which in fact has...
been occasionally incorporated in zwitterionic surfactants which seem perfectly stable in aqueous media [79,82]. Yet, to our knowledge, phosphonium groups have not been employed for constructing zwitterionic polymers so far. In fact, the most probable intermediates in their synthesis would be functional trialkylphosphines, which are difficult to handle and are hardly commercially available.

2.3. Synthetic Strategies towards Zwitterionic Moieties: Scope and Limitations

Zwitterionic compounds are often assembled via a complex multi-step synthesis (Scheme 6, cf. also Figure 13). The key step is typically the coupling of the anionic and the cationic groups, for which manifold pathways have been employed, including enzymatic reactions in the case of the ammoniophosphates (I in Figure 1). Still, the most often performed coupling reaction is the alkylation of amines (Scheme 6) [5]. For reasons of better solubility and miscibility, but also to avoid possible side reactions, the anionic group is often not directly introduced during the coupling procedure (i.e., converting Im-1 to Im-3), but in a protected form, for instance in form of an ester, as exemplified as Im-2 in Scheme 6. Beside of ammoniocarboxylates (Figure 1, VII), this “detour” (instead of converting the amine directly to the betaine-salt complex Im-3) has been in particular chosen for preparing ammoniophosphonates and -phosphinates (Figure 1, II, IV) [63,83]. In contrast for ammoniosulfonates, the direct alkylation by halogenated sulfonates, which are inherently the less nucleophilic, is preferred [84,85]. Frequently, such multi-step syntheses imply painstaking purification operations of the final zwitterion in practice. In particular, salts tend to stick tenaciously to the zwitterions and may require cumbersome work-up procedures. This problem has been remedied at least in parts by the use of ion exchange resins. Their use is particularly effective when inverting the second and third steps of the sequence shown in Scheme 6 [63,86–89], so that the counterion X⁻ in Im-2 becomes OH⁻ and the final zwitterion is liberated without producing salts. However, this strategy cannot be applied universally due to the strongly alkaline conditions [86].

Scheme 6. Synthesis of zwitterions by a classical multi-step procedure starting from a functionalized tertiary amine, as exemplified for ammoniocarboxylates (“carboxybetaines”).

Therefore, addition reactions are preferred over substitutions when alkylation the nitrogen. This can be either achieved by ring opening alkylation with heterocycles (cf. Scheme 7), or by hetero-Michael additions (cf. Scheme 8) [90,91]. Yet, ring opening alkylation work only if the heterocycle is sufficiently strained. Hence, typically employed reagents are 2-oxo-1,3,2-dioxaphospholane (for ammoniophosphates I, p = 2) [21], propane- and butanesultone (for ammoniosulfonates V, n = 3 or 4), or propiolactone (for ammoniocarboxylates VII, m = 2), as illustrated in Scheme 7. However, while the former reagents give stable adducts the addition of propiolactone produces 3-ammoniopropionates
that representing Mannich bases are prone to facile Hoffmann elimination. This is particularly problematic at elevated temperatures or pH values. In fact, 3-ammoniopropionates have been described to be instable and to be in equilibrium with the ammonium acrylate salt that is formed after elimination [89,90,92]. This limits the usefulness of polyzwitterions bearing this motif severely, which has become rather popular these days due to their straightforward access. Elimination can be only safely excluded if all abstractable hydrogen atoms next to the carboxyl group are eliminated [93,94], by using, e.g., the dimethylated derivative pivalolactone.

**Scheme 7.** Synthesis of zwitterions via ring-opening alkylation (clockwise from upper left): by lactones, by sultones, by dicyanoketene alkylene acetalts, and by 2-alkoxy-2-oxo-1,3,2-dioxaphospholanes.

Note that occasional claims about ring opening alkylation by \(\gamma\)-butyrolactone (Scheme 7, \(m = 3\)) [55,80] must be taken with great care, as they are most probably erroneous. In particular in the case of primary and secondary amines, the reaction of \(\gamma\)-butyrolactone will anyhow result in ring opening acylation to create amides instead of amines. Similarly, claims of successful alkylation of tertiary amides by sultones and lactones to produce zwitterionic sites [55], must be questioned, because of the negligible nucleophilicity of amides as well as the instability of the postulated adducts.

**Scheme 8.** Synthesis of zwitterions via hetero-Michael addition. EWG = electron withdrawing group.

The limitations of zwitterion synthesis via hetero-Michael addition are similar. In practice the systems seem to have been confined to ethylene spacers (see Figure 1, \(x = 2\)), although the use of conjugated polyenes should be a priori feasible, too. To our knowledge in the synthesis of zwitterionic monomers or polymers, the Michael addition route has been restricted up to now to
ammoniosulfonates [91] and, in particular, to ammoniocarboxylates. For the latter, not only alkenes, but also alkynes have been employed successfully, such as propiolic acid [95]. Yet, the addition products are the same Mannich bases as the ones discussed above when reacting tertiary amines with propiolactone. Thus, these adducts suffer from low stability, in particular at elevated temperatures or under basic conditions. Surprisingly, this problem has received little attention when discussing potential applications of polymeric ammoniopropionates, as e.g., the leaching of acrylic acid [90] etc., may pose severe problems, especially in the biomedical field.

3. Synthesis of Polyzwitterions

Compared to the status reviewed about ten years ago [5], the progress in the synthesis of polyzwitterions made in the past years is notable. On the one hand, much incremental innovation derived from the established macromolecular design strategies has led to a gradual, but steady growth of the structural versatility. On the other hand, a large number of novel building blocks as well as polymer structures have evolved recently, too. This concerns to a lesser degree the nature of the zwitterionic moieties incorporated into the polymer, but mostly the nature of the polymer skeleton, including electronically conjugated ones [96–105], as well as the overall polymer architecture.

The latter aspect is probably the most striking one, and is closely connected to new synthetic methods for making polymers bearing charged groups [106]. The increasingly versatile and mature methods of the so-called controlled polymerizations [107], in particular of the “reversible-deactivation radical polymerization” (RDRP) methods [108] (which alternatively often are referred to as “controlled free radical polymerization” (CFRP), or even “living radical polymerization” (LRP)) have enormously fertilized the field [107,109,110]. The progress in metathesis polymerization [111–113], in particular the emergence of powerful and tolerant catalysts, as the so-called Grubbs catalysts of the 1st to 3rd generation, has given an additional impetus. All these aspects have contributed to a plethora of new zwitterionic polymers.

Many difficulties in the synthesis of polyzwitterions result from the sensitivity, or even incompatibility, of most chemical reactions toward the simultaneous presence of electrophiles and nucleophiles. Unfortunately, this is in analogy to all polyelectrolytes and polyampholytes the typical situation found for most monomers bearing zwitterionic moieties (cf. Figure 1). This problem occurring in the direct synthesis of polyzwitterions (Scheme 5, path 1) is not only encountered for the monomers themselves. It also applies to most solvents, which are suited for zwitterionic compounds, such as water, alcohols, other polar protic solvents, and ionic liquids. Furthermore, many zwitterionic compounds are hygroscopic, adding to the difficulties.

In order to minimize the resulting problems, one can implement the zwitterionic moieties into precursor polymers (Scheme 5, paths 2–6) by post-polymerization modification after the successful polymerization process. Clearly, this strategy has its merits. However, post-polymerization modifications are seldom complete and/or completely devoid of side reactions. In particular, this may put the exact 1:1 stoichiometric balance between the anionic and the cationic groups at risk, especially when following paths 2b and 3b in Scheme 5. Depending on the intended use, the loss of overall charge neutrality of the individual macromolecules, implying the presence of mobile counterions, may pose major problems. For in vivo applications, for instance, an excess of cationic charges seems to be
particularly critical [114]. Therefore, direct pathways to polyzwitterions, by path 1 or at least the
indirect path 4b, seem a priori more attractive. Hence, apart from the design of new polyzwitterion
structures, there is a continuous interest in improving polymerization methods in order to prepare
polyzwitterions directly in the betaine form, even though the targeted structures have been already
known, but made via a post-polymerization strategy.

3.1. Synthesis from Zwitterionic Monomers

3.1.1. Synthesis by Chain Growth Polymerizations

The direct synthesis of polyzwitterions by chain growth polymerization from zwitterionic
monomers is generally done by free radical polymerization [4,5]. By virtue of the high tolerance of
radicals toward electrophiles as well as nucleophiles including water, free radical polymerization is the
natural choice for preparing zwitterionic polymers directly from the corresponding monomers, even in
aqueous solution. Moreover, free radical polymerization is particularly suited for statistical
copolymerizations. This enables the facile and versatile combination of mixed monomeric building
blocks. Consequently, free radical polymerization has been the dominating method for synthesizing
polyzwitterions, and doubtless will be also in the future.

Still, the synthesis of polyzwitterions is often handicapped by their notorious poor solubility in most
solvents (cf. Section 2.1), by their demanding molecular characterization, and by the limited
availability of convenient building blocks. Only few zwitterionic monomers that can be directly
polymerized into polyzwitterions are easily commercially available. The most prominent ones are the
methacrylic sulfobetaine monomers 1 (“SPE”) and 2 (“SPP”) and phosphatidylcholine monomer 3
(“MPC”) shown in Figure 2. They dominate the literature so far, either as homopolymers or even more
as components of copolymers. Another commercially available sulfobetaine monomer 4 (“SPV”) is
derived from 2-vinylpyridine, although reports using this monomer are much less frequent [115–120].

Figure 2. Chemical formula of the most widely employed and commercially available
zwitterionic monomers (from left to right): N-(2-methacryloyloxy)ethyl-\(N,N\)-dimethyl-
ammonio propanesulfonate (1, “SPE”), \(N\)-(3-methacryloylimino)propyl-\(N,N\)-dimethyl-
ammonio propanesulfonate (2, “SPP”), \(2\)-(methacryloyloxy)ethylphosphatidylcholine (3, “MPC”), and \(3\)-(2’-vinyl-pyridinio)propanesulfonate (4, “SPV”).

Inspired by the structure of monomers 1 and 2, four major families 5–8 of aliphatic zwitterionic
monomers bearing a sulfobetaine or a carboxybetain moiety have been concentrated on in the
literature [4,5,52,53] (Figure 3). While the alkylene spacer between the cationic and the anionic sites
and the one between the ammonium group and the polymerizable group can be varied at will, most
variations have been confined to a few spacer lengths only, as defined by the number of carbons \(s, n\)
and $m$. Mostly for the (meth)acrylic ester series 5 and 7, we find $s = 2$, whereas for the (meth)acrylamide series 6 and 8, we find $s = 3$ and to a lesser extent, $s = 2$.

This practical restriction is not a consequence of an unfavorable hydrophilic-hydrophobic balance encountered for higher values of $s$, as polymers of the series 5–8 were shown to be soluble at least to spacer lengths of $s = 11$ [86,121–125]. It is explained by the availability (or not) of the underlying tertiary amine monomers, which can be converted with moderate effort into the zwitterions analogously to Schemes 4 and 5. Still, other spacer lengths have been implemented occasionally [57,86,126–128].

Concerning the alkylene spacers separating the cationic and the anionic moiety, variations have been even more limited. For the sulfobetaine series 5 and 6, $n$ is typically 2–4, most often 3, while for the carboxybetaine series 7 and 8, $m$ is mostly 1–3, though longer spacers have been explored occasionally [129,130]. Again, this is rather explained by the ready availability of the needed reagents, typically the cyclic esters (Scheme 7), and the vinyl derivatives (Scheme 8) or ω-halogene substituted organic acids (Scheme 6). The reason has so far not been a deeper concern about possible optimum physico-chemical properties or stability (keeping in mind that the betaine group in monomers 7 and 8 is labile for $n = 2$), apart from the pKa issue already discussed for the ammonio-carboxylates in Section 2.2.2.

Figure 3. Frequently reported aliphatic zwitterionic (meth)acrylic monomers, with $s \geq 2$, $n = 2–11$, $m = 1–10$.

As convenient building blocks are even scarcer for the phosphorous containing anionic groups, their occurrence and variation with respect to the spacer length $p$ (see Scheme 7) is very limited [61] beyond the natural phosphatidylcholine motif typically incorporated (see 1 with $x = 2$ in Figure 1, and monomer 3).

Nevertheless by virtue of the tolerance of zwitterions toward radicals, there is no intrinsic reason not to implement different spacer groups in zwitterionic monomers than the “usual” ones, or to use other polymerizable groups suited for radical polymerization than (meth)acrylic ones (Figure 4). In fact, it seems that nearly the full spectrum of polymerizable groups suited for radical polymerization has been used to make polyzwitterions in the past, including not only styrenes, vinylpyridines, vinylimidazoles or vinylesters [124], but also rather uncommon polymerizable groups such as dienoic acids [123,124,131–139], vinylcyclopropanes [124,134] or isocyanides [69], and cyclopolymerizing species such as diallylammonium [64,87,88,124,134,140–153] and closely related divinyl monomers [93,94]. Moreover, a number of monomers confined exclusively to (often alternating) radical copolymerization, such as vinyl ethers [124,134], fumarates and maleates [124,134,154–156], isobutylenes [157] and even simple olefins in combination with sulfur dioxide [134,158] have been...
used with good success over the years. Also, there is no need to limit the structural variety to purely aliphatic systems, no matter whether the ionic groups, the spacer between the ionic groups, or the spacer between zwitterionic moiety and the polymerizable group is concerned (cf. Figures 4,5). For instance, a systematic study recently focused on the effects of increasing spacer lengths separating the cationic and anionic sites in polysulfobetaines related to monomer 11, with respect to their use in chromatographic separations [85,159].

Figure 4. Zwitterionic monomers suited for free radical polymerization, Top row: sulfobetaines based on vinylimidazole [160,161], vinylpyridine [162], styrene [85,159,163–169], methacrylate [124,170,171], and isocyanide [69]; Central row: carboxybetaines based on vinylimidazole [90], acrylamide [86], methacrylamide [172,173], isobutylene [157], and diallylamine [87,88,143,174]; Bottom row: various polymerizable zwitterions derived from phosphatidylcholine [175], condensed hydroxypyridines [71], ammoniosulfonamide [72], ammoniosulfonimide [72], alkoxydicyanoethenolates [66], and sulfoniocarboxylate [81].

The presence of only one polymerizable phosphobetaine within the examples of zwitterionic monomer shown in Figure 4 is not accidental. In fact, the past decade has very much focused either on established polymerizable phospholipids [30–32], or on polymers containing the commercial monomer
3 (MPC), so that new related monomeric structures are nearly missing compared to previous reviews [5,21]. To mention is in this context the use of crosslinkers containing the phosphatidyl moiety (Figure 5).

**Figure 5.** Examples for zwitterionic crosslinkers incorporating phosphobetaine [176–178], sulfobetaine [179] or carboxybetaine [180,181] moieties.

![Examples for zwitterionic crosslinkers](image.png)

Much creative and innovative work has been incited in the past 15 years by establishing the continuously evolving and now maturing methods of “reversible-deactivation radical polymerization” (RDRP). Similar to the revolutionary changes brought to polyelectrolyte synthesis [106], polyzwitterions have equally profited from this development. RDRP techniques offer direct access to polymers bearing zwitterionic groups with previously unthinkable features, such as predefined molar masses and narrow molar mass distributions [163,182–189] as well as well-defined functional end groups [61,166,182,190–208]. Moreover, complex architectures, such as block copolymers [14,46–48,166,167,169,173,187,209–240], graft copolymers [164,213,237,241–246], hyperbranched [247] or star polymers [248,249] can be prepared conveniently and in good yields by RDRP. Thus, the past decade of polyzwitterion synthesis is marked by the extensive use of RDRP methods to create polyzwitterions with unusual or novel polymer architectures, let it be by nitroxide mediated polymerization (NMP), atom transfer radical polymerization (ATRP), reversible addition fragmentation chain transfer polymerization (RAFT), or other variants.

A particularly fertile aspect of the evolving RDRP methods for polyzwitterions has been the possibility to control “grafting-from” processes on surfaces [33,35,129,165,186,187,195,199,202,250–303]. This development has given rise to a wealth of activities aimed at producing thin, but dense tethered zwitterionic hydrogel films that control friction and adhesion, and may be above all, the fouling behavior of surfaces. Here ultra-low fouling thanks to polyzwitterion films has been demonstrated for multiple examples, e.g., for separation membranes, medical materials or biomaterials. For all of these, fouling, i.e., the undesired and uncontrolled adsorption/deposition of compounds and objects, such as dirt, pyrogens, proteins, spores, bacteria or cells, is a primary concern. Amidst the various RDRP techniques, ATRP has been used in the vast majority of studies, presumably by virtue of its facile implementation in such heterogeneous systems. Nevertheless, the iniferter [304–306], RAFT [307–311] and NMP [130,312] methods have been demonstrated to work well, too. Importantly, the RDRP methods do not only allow to tailor anti-fouling zwitterionic polymer films, they also allow to functionalize them conveniently with reactive groups [268,270]. This is most valuable for anchoring additional functionalities to the tethered polymers, for instance, for incorporating specific recognition units for biomolecules. This is crucial for designing biomaterials or sensor surfaces.

RDRP methods enable also the anchoring of polyzwitterions to surfaces by “grafting-through” [105] and “grafting-to” processes [193,203,313–317]. In particular, the latter profits from the facile
incorporation of reactive groups in special positions, e.g., in the center or at the ends of the polymers, that enable efficient attachment of the macromolecules onto the substrates. Still, classical grafting-from [318–335], grafting-to [336–346], and grafting-through [316,347] procedures are of course continuously in use, especially in industrial applications, where the activation of the surfaces for the grafting process by physical means or by simple, “unpretentious” chemistry is preferred for reasons of experience, cost and high-throughput.

Albeit the synthesis of zwitterionic polymers via chain growth polymerizations is dominated by free radical polymerization, the big progress made in the design of metathesis catalysts, and their use in polymerization reactions, including living processes, has fertilized the synthesis of polyzwitterions, too. This concerns in particular ring opening metathesis polymerization (ROMP), whereas metathesis (cyclo)polymerization of zwitterionic alkynes was reported already some time ago [348]. The new zwitterionic polymers reported have all been based on cycloolefins, mainly on strained tricyclic imides derived from \textit{exo}-7-\textit{oxa}-norbornenedicarboxylic acid (Figure 6) [349–356]. This has enabled the facile preparation of polyzwitterions with double bonds in their backbone.

**Figure 6.** Zwitterionic monomers employed in ring opening metathesis polymerization (ROMP), including phosphobetaine 34 [352], sulfobetaines 35 and 36 [349,350,354,357], and carboxybetaines 37 and 38 [350,357].

Still, different from the phosphobetaine and sulfobetaine monomers, the carboxylate group is nucleophilic enough in the less acidic carboxybetaines ($x > 1$ in VII, Figure 1) to compete with other ligands for complexing the metal center of the ROMP catalysts. Therefore, the carboxylate group must be converted prior to polymerization into the carboxyl group by protonation by strong inorganic acids, or must be protected in form of an ester (as in monomer 38), so that the free zwitterionic groups had to be liberated in an additional step after polymerization.

Photopolymerizations should be accounted for here, too, as alternative way for the synthesis of polyzwitterions by chain growth polymerizations. They have been an important pathway to polymeric lipids, \textit{i.e.}, for phosphobetaines [29,54,358]. Photopolymerizations of (meth)acryl and dienoyl bearing zwitterions must be subsumed under photo-initiated radical polymerization. Yet, the topochemical polymerization of conjugated diynes (“diacetylenes”) producing strongly colored polymers is unique (Scheme 9), and has been continuously used for stabilizing lipid model membranes [30–32,359–369].
Scheme 9. Polymeric zwitterions prepared via topochemical photo-polymerization of conjugated diynes (left) [20,22,131,370], and via alkylation induced polymerization of pyridylacetylenes (right) [371].

This strategy toward polyzwitterions has been mostly applied to phosphobetaines so far, though no restrictions concerning the chemical nature of the hydrophilic groups are known. In fact, sulfobetaines and carboxybetaines bearing diynes have been polymerized, too [22,372–374]. Importantly, successful polymerization is confined to an appropriate arrangement of the diyne moieties in the solid-state. Hence, solutions or fluid-like micellar or bilayer aggregates of diyne monomers cannot be converted into polymers. Another unusual method to mention is the spontaneous polymerization of alkyne-pyridines in the presence of strong alkylating agents such as strained lactones or sultones (cf. Scheme 7) [371,375]. After alkylation, the alkyne group is highly activated against the attack by nucleophiles, such as residual amine groups, thus initiating presumably an anionic polymerization process (Scheme 9). However, little is known about the specific polymerization process and its kinetics so far.

3.1.2. Synthesis by Step Growth Polymerizations

The synthesis of polyzwitterions by step growth methods is applied rarely, though various strategies have been reported as exemplified in Figures 7–9. For obvious reasons, the “text book classics” such as polycondensation of alcohols with acid chlorides, or with carboxylic acids with via melt processes are virtually missing.

Hygroscopy, preferential solubility in nucleophilic and protic solvents, and high melting points due to the ionic nature, pose severe obstacles for the use of zwitterionic monomers in such polymerizations. Nevertheless, the reaction of diisocyanates with zwitterionic diols has been applied occasionally [5,21], mostly for polymeric phosphobetaines (Figure 7a) [376–379]. Still generally, post-polymerization reactions have been preferred for preparing zwitterionic polyurethanes (see Section 3.2). Analogously, the synthesis of polycarbonates under phase transfer catalysis has been adapted from classical step growth protocols (Figure 7b) [380]. Yet, occasional remarks that such polyurethanes, etc., may show physico-chemical behavior similar to the one of polyelectrolytes [21], may hint to side reactions occurring (if so, probably on the phosphate moieties), which unbalance the numbers of the anionic and the cationic groups. Another classical step growth polymerization method applied to polyzwitterions is the condensation of silanols, yielding, e.g., mesoporous organosilica [381]. Recently, transition metal catalyzed couplings, such as Suzuki couplings, were
shown to afford polyzwitterions, too (Figure 7c) [101,104,105]. Such conjugated zwitterionic polymers are particularly sought for electrical, optical, and optoelectronic devices.

**Figure 7.** Examples for polyzwitterions produced via step growth polymerization: (a) polyurethanes [376]; (b) polycarbonates [380]; (c) polysiloxanes[381]; (d) conjugated backbones [105].

Other reported examples of step growth polymerizations toward polyzwitterions (Figure 8) seem rather exotic at the first view, such as radical polyadditions of isolated dienes with bisthiols via thiol-ene reaction [382], or the oxidative coupling of bisthiols [383–387]. Yet, for the reasons discussed in Section 3.1.1, such methods seem particularly attractive from the chemical point of view, as they are not affected by ionic compounds. Within the same logic, step growth polymerization of zwitterionic monomers via 2 + 2 photo-cycloaddition [388] is definitely not a standard method, but seems well adapted to the general problems encountered for zwitterions.

All the methods discussed above deal with reactions, in which the monomers employed bear already the preformed zwitterionic moiety. This strategy is universal with respect to the various polyzwitterion architectures than can be produced, covering *a priori* the full spectrum of options illustrated in Scheme 4. Additionally, step growth polymerizations enable the production of polyzwitterions of architectures F–K in Scheme 4, whilst the zwitterionic moieties are created *in situ* by the polyreaction itself (Figure 9).
**Figure 8.** Examples for polyzwitterions produced via step growth polymerization: (a) Polythioether via thiol-ene addition [382]; (b) Polydisulfide via oxidative coupling [383]; (c) Polyester via 2 + 2 photo-cycloaddition [388].

![Polythioether via thiol-ene addition](image1)

![Polydisulfide via oxidative coupling](image2)

![Polyester via 2 + 2 photo-cycloaddition](image3)

**Figure 9.** Examples for polyzwitterions produced via step growth polymerization, in which the zwitterionic moieties are created *in situ*: (a) Ionene type poly(phosphatidylcholine) [389]; (b) Polysquaraine [390].

![Ionene type poly(phosphatidylcholine)](image4)

![Polysquaraine](image5)

Most noteworthy for this strategy seems so far the polyaddition of tertiary diamines with bis-2-alkoxy-2-oxo-1,3,2-dioxaphospholanes, *etc.*, via ring opening alkylation of the latter (*cf.* Scheme 7), in analogy to the synthesis of ionenes by the Menshutkin reaction. This produces polyzwitterions that bear both the anionic and cationic groups within the polymer backbone (see Scheme 4, architectures F and G). Different from the example given in Figure 9, this strategy has been mostly based on the polyaddition of bis(tertiary)amines and bis(2-alkoxy-2-oxo-1,3,2-dioxaphospholanes [21]. Another, somewhat related pathway is the substitution of activated aromatic groups by strong electrophiles, as exploited for the synthesis of polysquaraines (*cf.* XXII in Figure 1 and Figure 9).
3.2. Synthesis of Polyzwitterions by Post-Polymerization Modification

Post-polymerization modifications allow for introducing the zwitterionic moieties on the finished polymer chain (cf. Scheme 5). This strategy circumvents the mostly painstaking synthesis of the underlying zwitterionic monomers and their often cumbersome handling in polymerizations on the one hand. On the other hand, post-polymerization modifications broaden the scope of useful reactions for constructing a desired polymer structure, not only with respect to the nature of the repeat units, but also to their distribution within the individual macromolecule in the case of copolymers, to their molar mass, as well as to the overall polymer architecture and geometry, as already pointed out in Section 2.1. Also, they allow for implementing complex multi-step procedures.

A priori, the synthesis of zwitterionic polymers via post-polymerization modification shares the same advantages and inconveniences as the synthesis of other functional polymers by this approach [391]. An additional difficulty, which is particular to polyzwitterions, arises from the need to ensure the absence of excess ionic or ionizable groups after the chemical reaction(s), due to side reactions or due to incomplete conversion of reactive sites, in order to guarantee the overall zero charge condition. This criterion is difficult to meet precisely in practice, with the corresponding consequences for any intended use of polyzwitterions prepared by this route. In many cases, a small number of defects and thus a small deviation from charge neutrality may not be noted. If however rigid conditions apply, if for example the presence of mobile low molar mass ions must be strictly minimized or even fully excluded, the synthesis of polyzwitterions by post-polymerization modification is not advisable. If nevertheless such an approach is chosen, reactions must be very carefully designed and carried out. Additionally, the products must be thoroughly analyzed (which poses a severe problem of its own), to ensure the quality of the polyzwitterion produced.

The most frequently applied post-polymerization modification in the synthesis of polyzwitterions is the introduction of the anionic groups by alkylation of polymer-bound, preferentially tertiary amines (cf. Scheme 5, path 3b). Noteworthy, in the case of polycarboxybetaines derived from vinylpyridines, post-polymerization modification following this strategy seems to be virtually the only path realized up to now [9,77,78,392–397]. The polymeric amine itself may result from a previous modification step (cf. Scheme 5, path 6). Still mostly, it is made by polymerizing the corresponding weak polycation (cf. Scheme 5, path 3a), as numerous polymerizable amines are commercially available, for both chain growth and step growth polymerizations. The chemistry indicated in Schemes 6–8 for synthesizing zwitterionic monomers is equally fit for reacting polymers, and has been widely applied with various permutations since the first mentioning of polyzwitterions. The anion may be added directly using an alkylating function, e.g., by using carboxylic acids that bear halogens as leaving groups (cf. Scheme 6, direct passage from \(\text{Im-1}\) to \(\text{Im-3}\)). However often, it is more convenient to protect the anionic site during the alkylation step (e.g., in form of an ester) and then liberate it in a second step (cf. Scheme 6, passage from \(\text{Im-1}\) via \(\text{Im-2}\) to \(\text{Im-3}\)).

This stepwise conversion via an intermediate polycation form often helps to maintain homogeneous reaction conditions, typically favoring high conversions. As the cleavage of such an ester function often has the character of the deprotection step in protecting group chemistry, especially if tert-butyl esters are employed [93,94,349,357,398–402], it generally provides excellent yields. Thus, chances are very high to obtain rather clean polyzwitterions if not the amine, but the quaternized ammonium...
derivative is already engaged as monomer in the polymerization. This variant has been refined recently to selectively labile ester groups such as photo-cleavable ones (Figure 10) [398,403].

**Figure 10.** Examples for polycations that can be converted to polyzwitterions by photo-deprotection of the carboxylate group [398,403].

Intermediate protection of the anionic group as ester and its post-polymerization cleavage to liberate the anionic site has also proven to be the most convenient strategy for preparing polymeric ammoniophosphates, ammoniophosphonates and ammoniophosphinates [63,64,153,404–407].

Note that frequently, the removal of the low molar mass salt by-products formed in all these variants discussed above is taken for granted, though this is not necessarily true yet often not verified. As mentioned in Section 2.3, most salts tend to stick tenaciously to polyzwitterions, giving rise to painstaking work-up procedures. This problem is circumvented by alkylation the polymeric amines by ring-opening alkylation or by hetero-Michael additions according to Schemes 4 and 5, with the limitations discussed above. In any case, whatever strategy is used to convert polyamines into polyzwitterions, reaction yields will seldom be 100%. When protonated, the residual amine groups may implement a slightly cationic character, typically at pH values below 8–10 (*i.e.*, this includes physiological conditions).

The orientation of the zwitterionic moiety in the side chain is inverted, if the ring opening alkylating group, typically a cyclic ester, is attached on the precursor polymer and a low molar mass amine is added [408–410]. This strategy has been rarely chosen so far and mostly confined to poly(phosphobetaine)s, as the corresponding precursor polymers generally are more difficult to prepare. In any case, the problem of the fate of residual unreacted groups is shifted to another direction, but hardly improved. The cyclic ester tends to hydrolyze spontaneously to yield the acid, so that excess anionic groups risk to be created and to confer a weak polyanion character to the products. With increasing reactivity of the cyclic ester, conversions may become higher, but the tendency of the residual units to hydrolyze is enhanced, too.

The problem of incomplete conversion unbalancing the charge neutrality of polyzwitterions in post-polymerization modifications can in principle be avoided when reacting the precursor polymer with prefabricated zwitterionic reagents (Figure 11) [193,411–418]. Still, this implies the judicious choice of the reactive groups used for the modification. As again, the conversion of such reactions will be rarely 100%, the remaining reactive sites should not be ionizable, as otherwise, the use of zwitterionic reagents to conserve the overall charge neutrality of the polymers will fail. Thus, amines, carboxylic acids, or activated esters may be problematic for attaching zwitterionic reagents to the precursor polymer by well-established coupling reactions, if the remaining groups cannot be fully blocked by subsequent scavenging reactions.
**Figure 11.** Polyzwitterions made by post-polymerization coupling of zwitterionic reagents onto a precursor polymer, exemplified for the fixation of phosphobetaine reagents onto poly(glutamic acid) and poly(lysine) [411].

![Chemical structures](image-url)

Within the same line, hetero-Michael addition of the commercial zwitterionic monomers 1–4, or 5a–8a onto amines, as reported e.g., for hyperbranched polymers and dendrimers [326,419,420], may render certain polyamines less toxic, but the products remain polyanpholytes. They can overcome the polycation character only for rather high (mostly non-physiological) pH values.

Most helpful for the post-polymerization approach to polyzwitterions has been the advent of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes. If one of these functional groups is fixed on the precursor polymer and the other one to the zwitterionic reagent, this coupling strategy holds both the potential for high coupling efficiencies and selectivities as well as (for charge neutrality) harmless residual reactive sites if remaining. So far, the use of zwitterionic alkynes has been preferred, which are coupled to polymeric azides (Figure 12) [193,414–418]. Still, the inverse strategy should be equally feasible. As illustrated in Figure 12, the Huisgen reaction has been employed to prepare various poly(phosphatidylcholine)s, which are bound to the polymer backbone via the phosphate group (i.e., the natural geometry as typically realized in poly(phosphobetaines)), as well as via the ammonium group, resulting in an inverted geometry of the side chains (cf. architectures B and C in Scheme 4).

**Figure 12.** Polyzwitterions made by post-polymerization Huisgen 1,3-dipolar cycloaddition, modifying polymeric azides [414–416,418].

![Chemical structures](image-url)

Of course, the Huisgen 1,3-dipolar cycloaddition can be also employed in less direct approaches. For instance, zwitterionic dendrimers were made by clicking α-azido-tert-butylacetate to polymer
bound alkyne groups, followed by methylation of the triazole formed and subsequent hydrolysis of the tert-butylester to yield triazoliocarboxylate moieties [400].

All these considerations provide useful guidelines for preparing rather clean polyzwitterions by post-polymerization reactions, but require specialized reagents. Therefore, the wealth of organic chemistry may offer interesting solutions with more accessible building blocks for specific problems, even though the resulting polyzwitterions may be less clean and require careful optimization of the reactions. Some examples for such cases, which often are conducted as multi-step sequences, are presented in Figures 13–15.

The sulfatation of hydroxylated polymeric ammonium compounds, as illustrated in Figure 13a, appears to be strikingly simple. However, it seems that clean reactions are difficult. The exceptional report noted conversions $\leq 80\%$ only [65]. The multi-step sequence based on copolymers of maleic anhydride shown in Figure 13b, in contrast, seems to allow for considerably higher yields. Exploiting once more the alkylation of an intermediate polyamine (cf. Scheme 7) as key step with all implications discussed above, this approach allows for the synthesis of both sulfobetaines as P-59 and carboxybetaines as P-60.

**Figure 13.** Polyzwitterions made by unusual post-polymerization modifications: (a) Poly(ammoniosulfate)s by sulfatation[65]; (b) Poly(ammoniosulfonate)s [421,422] and poly(ammoniocarboxylate)s [422,423] and (c) Poly(ammoniophosphonate)s [61] by multi-step sequences using alkylations.
**Figure 14.** Zwitterionic polysaccharide made by coupling polycations to sulfonated reagents: (a) via hydrazone bonds [424]; (b) via aldol condensation [424,425]; (c) via azo coupling [424,425].

Note: While the image contains a chemical structure, the natural text description is as follows:

Noteworthy, closely related products may be obtained by the nearly alternating copolymerization of N,N-diallyl-N,N-dimethyl ammonium chloride with maleamic acids [426–428], as intriguingly convenient and versatile access to poly(ammoniocarboxylate)s.

Figure 13c exemplifies a related reaction scheme for obtaining poly(ammoniophosphonates). This polyzwitterion class has been hardly studied up to now, although it offers a great potential as permanent polyzwitterions. The reactions shown in Figure 14 demonstrated that basically every efficient coupling reaction may be applied to convert strong polycations into the corresponding zwitterions. Of course, similar considerations may be applied to strong polyanions, but analogous examples seem to be absent yet. All the polyzwitterion examples displayed in Figure 14 have the advantage that they are intensely colored, i.e., that the progress of modification can be easily monitored and assessed.

**Figure 15.** Zwitterionic chitosane derivative made via Atherton-Todd reaction [404,405].
Figure 15 exemplifies the options to convert natural polymers, such as polysaccharides, into zwitterionic species. Again, the limiting factor for using such reaction sequences is their yield, and the possibilities to block remaining primary amine groups against protonation at pH values < 8.

In any case, the examples presented illustrate that the potential of the modification of precursor polymers for polyzwitterion synthesis is enormous. Keeping the various drawbacks discussed in mind, it must be decided according to the specific situation and requirements, whether this strategy is appropriate or advantageous.

4. Special Aspects in the Chemistry of Polyzwitterions

4.1. Stability of Zwitterionic Moieties in Aqueous Media

Section 2.3 addressed already certain aspects of the inherent stability of zwitterionic moieties. A particular problem is of course the stability of zwitterionic polymers against nucleophilic and protic (co)solvents, as they are typically encountered. This concerns especially the stability in aqueous or alcoholic media, a problem that is not limited to the zwitterionic group as such, but this concerns also their linkage to the polymer skeleton. In particular, hydrolysis may be a concern, and attack by hydroxide ions in dependence on the pH value. Here one may distinguish three scenarios: (i) the stability of the ionic groups; (ii) the stability of the linkage between the cationic and the anionic groups; and (iii) the stability of the linkage between zwitterionic moiety and the polymer chain.

Concerning scenarios (i) and (ii), a number of aspects are already discussed above in Section 2.2.2 (protonation/deprotonation, thermal stability of Mannich-base structures, etc.), which need no repetition. Other potential fragile sites against hydrolysis are found in zwitterions containing bivalent and trivalent acid groups (cf. Figure 1), such as phosphates (I, XIV), phosphonates (II, XV), sulfates (VI, XVII), or boronates (XIII). If the second or third acidic sites are not safely blocked, e.g., in form of a robust ester, the stoichiometry of the anionic and cationic groups and thus the zwitterionic character is lost [64,151,153].

This is for sure a real concern for sulfates and boronates, but also to a certain degree for phosphates and phosphonates. Moreover, hydrolysis of the ester bond linking the cationic and anionic site inherently in ammoniophosphates (I), certain ammoniophosphonates (IV), or ammonio(alkoxy)dicyano-ethenolates (XII) will cleave either the anionic or the cationic group from the polymer, with negative consequences for the overall charge neutrality. This problem is completely avoided, when polyzwitterions carrying ammoniophosphinates (III) as in P-70, ammoniosulfonates (V, XVI) as in P-67, P-68 or P71, or ammoniocarboxylates (VII, X, XI, etc.) as in P-69 are employed (Figure 16).
Figure 16. Examples of permanent polyzwitterions with improved resistance to hydrolysis compared to (meth)acrylic polymers: sterically hindered polyacrylamides P-66 and P-67 [429,430], diallylammonium polymers P-68 and P-69 [87,88,431], and polystyrenes P-70 and P-71 [63,168].

Scenario (iii), the possible instability of the linkage between the zwitterionic moiety and the polymer chain, has found some thought in the literature for polyzwitterions carrying the ionic groups in the side chains, i.e., of architecture types A–E (cf. Scheme 4). Such considerations are found in particular in the context of oil field chemicals and separation membranes, but also of biomaterials. For architectures A–E, however, the most popular and most versatile polymer backbones are poly(acrylate)s, poly(acrylamide)s, poly(methacrylate)s and poly(methacrylamide)s. Unfortunately these are also amidst the rather vulnerable ones against hydrolysis, the former being the most sensitive and the latter being the least sensitive. The exceptionally reported (co)polymers of zwitterionic fumarates and poly(vinylester)s may be even more problematic than the (meth)acrylic polymers. The spacer between polymer backbone and zwitterionic moiety in the side chain becomes particularly sensitive and thus critical, if quaternized glycine esters are incorporated [432].

The risk for hydrolysis may be reduced by certain substitution patterns, profiting, e.g., from steric crowding of the carboxyl group in the spacer (Figure 16, P-66 and P-67) [429,430]. Still, if the hydrolytical stability of polyzwitterions shall be maximized, backbones with more resistant linkers than carboxyl derivatives between the backbone and the side chains should be considered. Zwitterionic monomers based on vinylethers [134] provide already much improvement against basic conditions. Yet, the most obvious solution is the use of vinyl polymers that have linker groups consisting exclusively of all carbon bonds. This has resulted in a continuous interest in zwitterionic diallylammonium carboxy-, phosphono- and sulfobetaines (cf. Figure 16, P-68 and P-69) [64,87,88,124,134,140–153,431,433].

As the polymerizability of allyl monomers is often low, it has been often improved by alternating copolymerization with sulfur dioxide, SO₂ [134,141,144–147,150,153,174,434–436]. Though this approach provides a non-hydrolyzable all-carbon linker between the zwitterionic site and the polymer chain, it is somewhat ambiguous, as the aliphatic polysulfone backbone produced is sensitive to thermal stress and strongly basic conditions by itself. Alternatively, certain polyzwitterions derived from polystyrene (Figure 16, P-71) have been postulated to be particularly stable against hydrolysis [168]. Yet, the proposed examples are somewhat deceiving, as the underlying benzyl-ammonium motif is known to be sensitive to attack by strong nucleophiles such as hydroxide ions, resulting in dealkylation. Thus, such structures cannot a priori be considered truly inert in water at high pH values.
and/or high concentrations of various anions. This may be crucial, for instance, when uses in alkaline fuel membranes are envisaged.

Also, zwitterionic poly(vinylpyridinium) derivatives (cf. Figure 4, monomers 10, 17, or 20) are less stable in aqueous media than might be supposed due to the lack of any potentially fragile ester bond, etc., as strong nucleophiles tend to add on the activated aromatic ring in the 2- or 4-position. This is often accompanied by the discoloration of such compounds under strongly basic conditions and by molar mass degradation [116,117]. Presumably, the C–H acidic methine groups in the backbone, resulting from the inherent N-alkylpicolinium motif, are attacked, inciting degrading follow-up reactions. It should be realized that polyzwitterions with other heterocycles may also be prone to attack under strongly basic conditions, such as imidazolium rings (cf. Figure 4, monomers 9, 16, or 28) at the C-2 position (cf. below, Figure 17c–d).

4.2. Responsive Polyzwitterions

Responsive (often popularly called “smart” or “intelligent”) polymers, i.e., polymers which change their property profile drastically and reversibly upon a small stimulus applied (“switching”), are gaining increasing interest for various purposes [49,51]. Polyzwitterions in aqueous solution, for instance, are known to show frequently a thermal coil-collapse transition of the upper critical solution (UCST) type. Characteristically, the UCST-transition can be modulated by adding specific salts [19,42–48]. As these are physico-chemical effects, they are outside the scope of this review. However additionally, the solution behavior of polyzwitterions may be influenced by several chemical stimuli. First of all, pH-responsivity, which is equivalent to acid-base reactions, is occasionally discussed in the literature [437]. This concept tries to exploit the limited acidity of certain anionic or the limited basicity of certain cationic forming groups or even both (see Section 2.2.2), to induce protonation-deprotonation changes. This point of view is somewhat confusing, as by definition, polyzwitterions should be not subject to such transitions in the normal pH-window, whereas this behavior is characteristic for polyampholytes. Hence, the concept of pH-sensitivity of polyzwitterions will not be pursued here.

Equally, “smart” behavior has been attributed to polyzwitterions, if they are created by chemical reactions from a polyelectrolyte (e.g., from a polycation precursor), or, inversely, if they are converted into a polyelectrolyte. This is indeed a valid option, as polyelectrolytes, by virtue of their low molar mass mobile counterions, are generally more hydrophilic than their polyzwitterion analogues. Still, it must be kept in mind that responsiveness implies reversibility of the changes induced after applying a counter-stimulus. Many chemical “switching” processes, as e.g., the hydrolysis or photo-deprotection of ester groups that convert polycations into polycarboxybetaines (see Figure 10) [398,403,438,439], or polyzwitterions into polyanions [151–153,440], are not reversible, at least not under aqueous conditions.

In contrast, the acid or base catalyzed aldol condensations of aldehydes with hydrazones (Figure 14a) or picolinium salts (Figure 14b) are reversible. Still, the reversibility of these systems has not been studied in detail. At least the kinetics of the latter reaction is probably rather slow for typical switching purposes. However, the reversible lactonization of the hydroxylated polycarboxybetaine P-72 (in analogy to indicator dyes such as phenolphthaleine), or the reversible addition of bisulfite to aldehydes are fast, thus being more suited for polyzwitterion-polyelectrolyte switches (Figure 17a,b).
Similar considerations apply to the addition of CO$_2$ to polymeric amidines, or to polymeric carbenes obtained from imidazolium salts (Figure 17c,d) [441–444]. Although the last reaction seems to be limited to non-aqueous systems, in any case, such chemically induced “switching” systems have been hardly studied up to now, so that they cannot be adequately judged yet. Still, they present interesting options.

Alternative chemical switches for converting polyzwitterions into polyelectrolytes, or *vice versa*, may be photoreactions (cf. Figure 10)) or redox-reactions (Figure 18). For the former switch, the reversible ring-opening of spiropyranes into merocyanines is cited frequently (Scheme 10). Yet, the electronic ground state of merocyanines is typically the non-ionic quinoid form, but not the charge-separated one (which is however most often shown in drawings). Hence, addressing the open merocyanine form as “zwitterionic” is misleading, as it typically shows a strong dipole moment only but does not dispose of ionic sites.

**Figure 17.** Chemically switchable polyzwitterions: (a) By pH-induced lactonization [128,445]; (b) Via bisulfite-aldehyde addition [425,446]; (c) and (d) Via addition of CO$_2$ to amidines [441] or carbenes [442,443], respectively.

**Scheme 10.** Photo-induced ring opening/closure of spiropyran-merocyanine systems [447].

Redox reactions offer better chances for implementing a switching process, though reversible organic redox systems, for which the oxidized as well as the reduced states are stable under aqueous conditions, are rare. Figure 18 presents two systems, which seem to behave well. One is based on viologene as redox-active moiety, where the reduced state is zwitterionic [448–450]. The other one is based on ferrocene, where the oxidized state is zwitterionic [451,452].
Figure 18. Reversible conversion of polyzwitterions into polyelectrolytes by redox-reactions: (left): viologene based [448–450]; (right): ferrocene-based examples [451,452].

Still, also for these systems, the “switching” between the ionic and zwitterionic states has been little studied. Although for P-76, stimulated uptake and release of hydrophobic cargos was shown [450], it is neither clear yet for any of these systems, how far the redox process can drive the polyelectrolyte towards the fully zwitterionic state, nor which stabilities and lifetimes one can expect of the involved redox-pairs under aqueous conditions.

5. Conclusions

The synthesis of polyzwitterions has much developed during the past decade, with respect to new building blocks and novel polymer structures. While the nature of the zwitterionic moieties incorporated into the polymer has evolved only little during this period, new effective reactions for the preparation of zwitterionic polymers have been introduced and established, such as “reversible-deactivation radical polymerization” (RDRP) techniques, ring opening metathesis polymerization (ROMP) and the methods of “click chemistry”. Thus, new polymer skeletons as well as polymer architectures have been implemented. The majority of work seems motivated by the occurrence of zwitterionic structures in biology. This has incited the preparation of polyzwitterions for biomimicking structures, such as lipid membrane models, or for biocompatible materials and surfaces. Originating from that, an important thrust has evolved toward zwitterionic coatings to achieve surfaces with ultra-low fouling behavior, which is not limited to biomedical purposes. Also, the use as ionomers or viscosity modifiers or for electrooptical devices has added to the developments. The latter has led, e.g., to the advent of conjugated zwitterionic polymers. An additional impetus stems from the search for responsive polymer systems. All these aspects have contributed to a plethora of new polyzwitterions, and will continue to do so in the coming years.

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Conflicts of Interest

The author declares no conflict of interest.
References


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