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Review

Switchable Materials Containing Polyzwitterion Moieties

Markéta Ilčíková [1], Ján Tkáč [2] and Peter Kasák [1,*]

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Academic Editor: Carsten Werner

[1] Center for Advanced Materials, Qatar University, 2713 Doha, Qatar; marketa.ilcikova@savba.sk
[2] Chemistry Institute, Slovak Academy of Sciences, Dúbravská cesta 9, 845 38 Bratislava, Slovakia; jan.tkac@savba.sk
* Correspondence: peter.kasak@qu.edu.qa; Tel.: +974-4403-5674

Abstract: In recent decades, the design and construction of smart materials capable of switching into a polyzwitterionic state by an external trigger have been intensively pursued. Polyzwitterionic states have unique antifouling and surface properties and external triggers, such as pH, light, ions, electric field and CO_2, cause significant changes in materials with regard to overall charge, ionic strength and wettability. This survey highlights current progress in the irreversible as well as the reversible switching process involving polyzwitterionic moieties, which can, in turn, be applied to studying the interaction of various interfaces with biological species as protein, DNA, bacteria or platelets and also for advanced use.

Keywords: responsive materials; polycarboxybetaines; carboxybetaine ester; smart polymers; polyzwitterion

1. Introduction

Smart materials are attracting increased attention due to the possibility of effectively switching their properties in response to external stimuli such as temperature, light, electrical potential, pH and ionic strength. Materials with the capacity to switch their properties can find a variety of applications, *i.e.*, in biosensing, nanomedicine, tissue engineering and intelligent nanoelectronics and optics [1–5].

The switching capacity of a material upon external stimulus plays an important role in biological systems. As an example, the surface properties and characteristics of polypeptides may vary markedly due to changes in the secondary/tertiary structures as a response to an external trigger [6] or an adhesion–repellent switch in a muscle is triggered by changes in pH or by the presence of cooperative ions [7].

Stimuli-responsive polymer surfaces have been described in many review articles [8–10]. Control of the surface properties has been achieved by various stimuli including temperature [11,12], light potential [13], pH and ionic strength [14,15]. Surface properties such as wettability, biocompatibility, roughness, and adhesiveness can be controlled. Such materials can be further used as self-cleaning materials [16], in drug delivery systems [17–21], for designing controlled permeation membranes [22], in separation [23], *etc*.

Currently, progress in the use of smart materials, where one of the states during the switching process involves polyzwitterions, is attracting considerable interest due to their unique properties. Structurally, zwitterions contain both a positive and a negative charge at different non-neighboring atoms and, simultaneously, the overall charge of the substance is neutral with highly ionic properties [24]. Moreover, they are considered to be biomimetic, since the basic zwitterionic structures appear in nature. For example, a phosphoryl choline head-group can be found in the outer layer of

cell membranes creating a hydrophilic polar part of the membrane, in free amino acid as a building block for proteins or as taurine in choline conjugate. A special group of zwitterions is represented by betaines with a cationic group such as quaternary ammonium bearing no hydrogen atoms; these are denoted according to the anionic groups as phosphobetaines, sulfobetaines or carboxybetaines.

The surfaces containing polyzwitterions are mainly formed from zwitterionic monomers based on (meth)acrylates with a quaternary ammonium group due to a simple synthetic protocol [25]. Polyzwitterionic materials consist of highly ionic monomers and form a strong hydration layer based on electrostatic interaction with water molecules [26]. This effect is most remarkable in the formation of polyzwitterionic brushes, which were applied to the formation of surfaces highly resistant to protein adsorption [27], non-specific protein adsorption from serum and plasma [28,29] and bacterial adhesion [30–32].

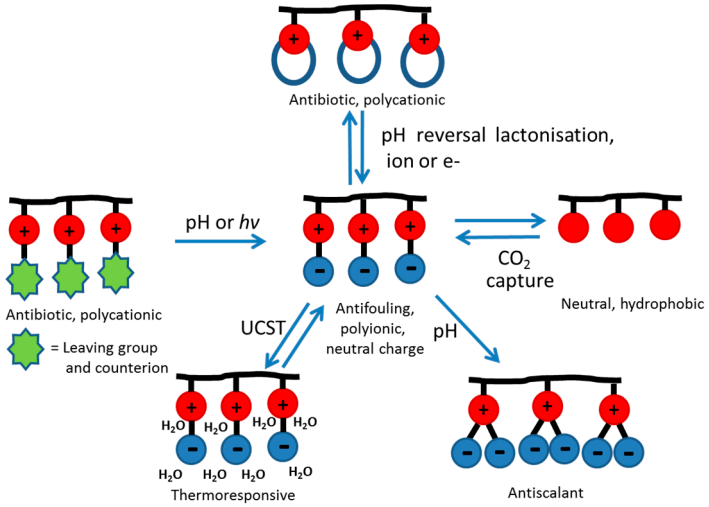
Intensive research has revealed that the best surfaces inhibiting protein adsorption exhibited several common features such as the presence of hydrophilic groups, electrical neutrality and hydrogen-bond donors [33,34]. These features are also common for zwitterionic polymers [35], which nowadays are replacing the widely used polyethyleneglycol (PEG)-based polymers, which can lose their function in biological media due to degradation [36–38].

This review provides a survey of recent progress in attempts to develop smart polymeric materials involving the polyzwitterionic state with the main attention paid to describing a switchable process and the interaction of such switchable polymers with biological species and their use in further applications [27]. As an example, protein adsorption represents one of the major challenges in biomaterials research since the process may lead to the dysfunction of long-term (e.g., implants and biosensors) or short-term devices (e.g., catheters). The process of protein adsorption is highly complex and the main contribution results from a change in forces between the surface of materials and protein [39]. The forces involved are van der Waals, hydrophobic and electrostatic forces, all of which initiate protein conformation change and allow the hydrophobic amino acid side-chains to be oriented to the environment [40]. A common approach to reducing protein adsorption is to attach highly hydrophilic synthetic polymers such as polyzwitterionic or PEG onto the surfaces [41]. The highly hydrophilic character and electrical neutrality of polyzwitterions lead to a decrease in the hydrophobic and electrostatic interactions with the protein [42,43] and, conversely, the polycationic character promotes the adsorption of the protein linked directly to the followed cell adhesion, causing a biofouling film formation in the organism.

The methodology for the synthesis and preparation of polymeric systems based on polyzwitterions has recently been summarized in excellent reviews [44–46] and is outside the scope of this review. In the first and second parts of this review, the irreversible and reversible switching processes of such polymeric materials are described. Reversible switches can be divided into two categories based on physical and chemical principles. The physical principle employs a switch between distinguished states with different properties. A schematic presentation of particular switches is depicted in Scheme 1. In this review, interactions with water and biological species such as proteins, bacteria, DNA, gene drugs, blood samples and miscellaneous applications are also summarized. This survey also includes some experimental details of the switching process to indicate the capacity to perform transformations in certain sensitive applications such as bioengineering, biomedicine, biotechnology, *etc*.

2. Irreversible Switch to Form Polyzwitterionic Moiety

An irreversible switch is effected predominantly by the transformation of polymers containing an ester group into a betaine moiety in the polymeric backbone. This was observed as an irreversible switch from a polycationic into a polyzwitterionic state as well as from a polyzwitterionic into a polyanionic state. This process is related to hydrolysis and its rate varies with the structural composition.



Scheme 1. Schematic presentation of irreversible and reversible switches.

2.1. Switch from Polycationic to Polyzwitterionic State

Conversion from the polycationic to the polyzwitterionic state exhibits dramatic changes in the interaction with water, proteins, drugs, DNA, and bacteria. This conversion is represented solely by transformation of the ester or amide groups into the carboxylate group in the monomer unit. The transformation occurs as a response to an external stimulus (pH, buffering capacity or light) and the polyzwitterionic state is preserved. The progress of the transformation is influenced by several factors such as length of the spacer between the quaternary amine and the carboxyl group, the nature of the hydrolysable group, pH and temperature; these will also be discussed below.

2.1.1. (Meth)acrylic Type Polymers

The most common polymer backbone motifs used in these switches are (meth)acrylic-based polymers due to their simple synthetic modification, ready availability and the possibility to prepare polymer brushes using surface-initiated (SI) atom-transfer radical polymerization (ATRP) or SI photointerpherter mediated polymerization (PMP), mainly through a thiolated initiator immobilized onto the gold surface, or polymers with controlled lengths. The simple synthetic protocol permits the application of a modern method such as surface plasmon resonance (SPR) to evaluate modifications or adsorption change even down to 0.1 ng· cm^{-2}. Typical (meth)acrylic-based pH-triggered irreversible switches, their triggers and applied forms are summarized in Table 1.

Table 1. Irreversible pH-triggered (meth)acrylic-based switches containing polyzwitterionic state.

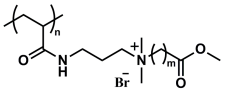
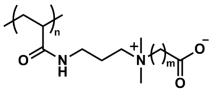
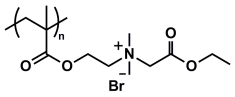
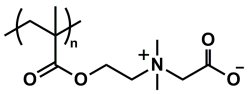
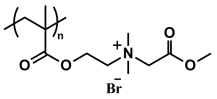
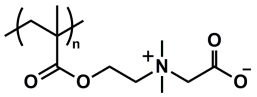
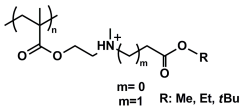
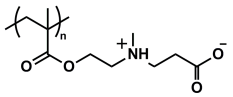
Initial state	Trigger (applied form) reference	Polyzwitterionic state
	NaOH (polymer brush) →	
Poly(1): m = 1 Poly(3): m = 3 Poly(5): m = 5	[47]	Poly(2) m = 1 Poly(4) m = 3 Poly(6) m = 5

Table 1. *Cont.*

Initial state	Trigger (applied form) reference	Polyzwitterionic state
 Poly(7)	pH 10, 37 °C 8 days (polymer brush) → [48]	 Poly(8)
 Poly(9)	pH 10.2, 37 °C, CAPS buffer, 8 h (polymer on PP non-woven fabric) → [49]	 Poly(8)
 Poly(10)	pH 13, 1 h (copolymer with poly(EGMA)) → [50,51]	 Poly(11)

2.1.1.1. pH Trigger

Structural Effect on Hydrolysis

One parameter investigated is the effect of the spacer length between quaternary ammonium and ester groups. This was studied on polyacrylamides having three different spacers: methylene (poly(1)), propylene (poly(3)) and pentene group (poly(5)), respectively (Table 1) [47]. The hydrolysis was studied on polymers in solution as well as on polymer brushes prepared by SI ATRP on gold-coated silicone SPR chips. The completed hydrolyses for poly(1) in the solution and at the surface occurred under rather harsh conditions after treatment with 1 M NaOH solution for 1 h in solution and with 0.1 M NaOH applied for up to 2 h to the surface-confined polymer, respectively. An even slower hydrolysis is expected for poly(3) and poly(5) due to the higher pK_a of carboxylate compared with poly(1). With regard to the approach, an increase in the protein adsorption was observed with the increasing polymer hydrophobicity in zwitterionic polymers. In poly(1), poly(3) and poly(5), the hydrophobicity increased with spacer lengths of one, three and five carbons, respectively [47], as was confirmed by fibrinogen adsorption on the polymer brushes investigated on the SPR sensors. Similarly, after hydrolysis to poly(2) and poly(4), the fibrinogen adsorption was below the SPR limit of detection of 0.3 ng/cm^2 after hydrolysis, while, in the case of poly(6), the fibrinogen was adsorbed at a density of 1.5 ng/cm^2. The polycationic character of poly(1), poly(3) and poly(5) made it possible to condense DNA and the particles thus formed (106 nm, 136 nm and 150 nm, respectively) were smaller than 150 nm [47], hence able to internalize the cells [52].

Moreover, the antibacterial properties of polycarboxybetaine esters poly(1), poly(3) and poly(5) were investigated using *Escherichia coli* (*E. coli*) cells in solution. The most hydrophilic poly(1) exhibited 95% of the bacteria to be alive after 30 min while, in the case of poly(3) and poly(5), 87% and 46%, respectively, were found alive. The most hydrophobic poly(5) exhibited the highest antimicrobial activity, which indicated sufficient binding to the acidic polymers at the outer membrane of the bacteria and the ability to readily permeate the bacterial membranes causing death [53].

Jiang *et al.* reported that polymer brushes of poly(7) with an ethyl ester pendant prepared by SI ATRP were transformed to poly(8) in a *N*-cyclohexyl-3-aminopropanesulphonic acid (CAPS) buffer at 37 °C within 24 h. The transformation also proceeded by the dead bacterial cells or proteins adhered, however, the time could be prolonged [48]. Application of this switch is shown in Figure 1. Poly(7) in the polycationic state destroyed almost 99.9% of *E. coli* and dead bacteria remained on the surface (Figure 1a), and, after hydrolysis to poly(8) (Figure 1b), almost 98% of the dead bacteria were released (Figure 1c). Additionally, poly(8) showed non fouling properties for proteins and bacteria

(Figure 1d). This switchable polymer coating, enabling transformation from initial antibacterial character through self-cleaning process to non-fouling properties, opens opportunity for capable coating for implantable devices.

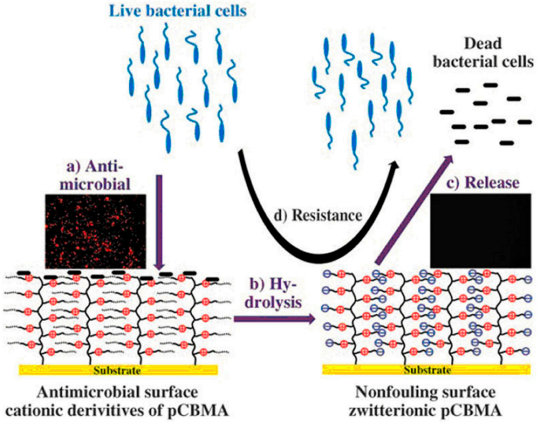


Figure 1. A schematic application of poly(7) as a switch where (**a**) a surface with polycationic state poly(7) possessing antibacterial properties that, (**b**) through alkaline hydrolysis, (**c**) the surface switches to polyzwitterionic state poly(8) and dead bacteria cells are released from surface and, finally, (**d**) the poly(8) surface becomes resistant to bacterial adhesion. Reprinted with permission from Reference [48], Copyright 2008, Wiley-VCH.

Structurally similar, a methacrylate analogue to poly(1), carboxybetaine methylester poly(9), was used for modification of the non-woven polypropylene (PP) membranes [49]. The polymerization was performed via UV-induced radical polymerization from the plasma pre-treated PP membrane surface. The switch from poly(7) to poly(9) was scrutinized to find milder hydrolysis conditions. Complete hydrolysis was observed in the *N*-cyclohexyl-3-aminopropanesulphonic acid (CAPS) buffer (pH 10) within 8 h and the methacrylate backbone ester group remained intact. The PP membrane with poly(7) exhibited antibacterial activities with no bacterial colonies detected. After the transformation of poly(7) to poly(8), strong resistance to platelets adhesion was exhibited and the thromboresistance properties were enhanced. The hemocompatibility and platelet adhesion is a crucial parameter for the preparation of polymers designed for biomedical applications such as catheters, implants, blood bags, *etc*. When blood comes into contact with a surface, first the adsorption of plasma proteins occurs, followed by platelet adhesion, coagulation and finally thrombus formation [54,55]. Accordingly, a material possessing antibacterial properties capable of switching upon mild transformation to antifouling and hemocompatible properties is of extreme interest to abovementioned biomedical applications.

The rate of hydrolysis of the carboxybetaine ester to the zwitterionic state was systematically studied with regard to the different ester leaving groups such as ethyl (Et) or *tert*-butyl (*t*Bu), and a spacer between the ester and the tertiary amine group. Polymers poly(10) were prepared via reversible addition fragmentation (RAFT) polymerization. The effect of the spacer between charged groups in poly(11) was found to affect the buffering capacity of the tertiary amine, which has an important impact on the clinical applications of such polymers as potential DNA vectors that are prone to acidic degradation to form poly(11). It was revealed that poly(10) with a methylene spacer exhibited a buffering range of the amino group in the endosomal environment, the highest buffering capacity and was the most stable in physiological and endosomal pH for ethyl ester group [51]. As the materials enter into endosomes, the pH is decreased from the physiological pH 7.4 to 5 by protons pumped through the endosomal membrane. The tertiary amines with a pK_a value close to the pH values inside the endosomes can adsorb the protons and create an osmotic pressure that results in membrane rupture and the endosomal escape of polymers via a "proton sponge" mechanism [56,57].

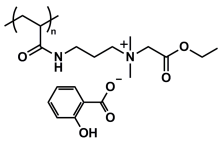
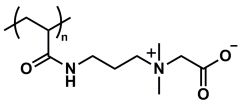
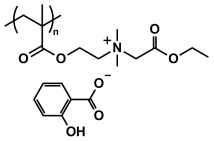
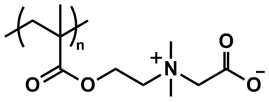
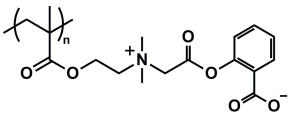
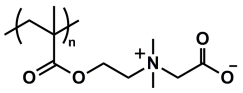
Moreover, the same nontoxic poly(10) mediated transfection of DNA is an order of magnitude better than branched polyethylene imide due to slow hydrolysis rate to poly(11).

Additionally, the poly(10) structure with methyl ester group and ethylene spacer was used for the modification of medical gauze in the form of a copolymer with poly(ethylene glycol) (PEG) methacrylate and cross-linked with hexamethylene diisocyanate [50]. A small amount of PEG methacrylate was used for improvement of the mechanical properties such as flexibility and strength. Further, to inhibit bacterial growth after the switch, a small hydrophobic drug—aspirin—was introduced into the copolymer. The released aspirin inhibited *E. coli* growth within 12 h. After hydrolysis (pH 13, 1 h), the material exhibited resistance to non-specific protein adsorption and HUVEC cell attachment. The normal cell growth around the modified gauze indicated the low cytotoxicity of the material.

Structural Effect on Hydrolysis with Released Active Molecules

In addition to the intrinsic antibacterial character of polycationic state, mild antibacterial agent such as salicylate ion (SA^-) as counter ions or as an esteric part were reported and these switches are summarized in Table 2.

Table 2. Irreversible pH-triggered (meth)acrylic-based switches containing polyzwitterionic state and released active molecule.

Initial state	Trigger (applied form) reference	Polyzwitterion state and released active molecule
 Poly(12)	pH 10, 37 °C 8 days (hydrogel) → [58]	 Poly(2) and SA^-
 Poly(13)	pH 10 (hydrogel) → [59]	 Poly(8) and SA^-
 Poly(14)	pH 7.4, 20 °C (hydrogel) → [60]	 Poly(8) and SA^-

An interesting application of a block copolymer containing poly(12) prepared by reversible addition fragmentation chain-transfer (RAFT) polymerization was shown. Polycationic poly(12), with the ethyl ester terminal group and salicylate (SA^-) as a counter-ion, was used as an inner B block in an ABA triblock copolymer in combination with an A block consisting of poly *N*-isopropyl acrylamide poly(NIPAM). The hydrolysis of poly(12) and transformation from the polycationic to the polyzwitterionic state was investigated indirectly through the release of an anionic counter ion salicylate (SA^-) from a hydrogel disc in a phosphate saline buffer (PBS, pH 7.4) at 37 °C. After 1 h, 50% of SA^- was released and the complete hydrolysis was detected after 10 h [58].

The initial polycation state of poly(12) ensures attachment of the material to mammalian cells and antibacterial properties. Moreover, during mild hydrolysis condition the slow release of SA^- as a mild antibacterial agent occurred and after transformation to polyzwitterionic poly(2) material is biocompatible and prevents further adhesion. Additionally, the outer blocks consisting of thermo-responsive poly(NIPAM) have LCST enabling the transition from liquid to solid above

37 °C, permitting application in a spray solution and gelation occurs at body temperature, as is schematically presented in Figure 2. The combination of the above properties makes this interesting materials highly promising for use as an antimicrobial wound dressing [58].

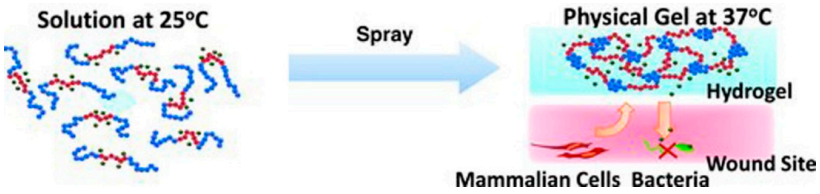


Figure 2. Schematic presentation of spray application of poly(12) as an antibacterial wound dressing hydrogel. Reprinted with permission from Reference [58], Copyright 2011, Wiley-VCH.

Similarly, the methacrylic poly(13) analogue to acrylic poly(12), was investigated in hydrogel form prepared by redox polymerization [59]. The hydrogel based on poly(13) inhibited the growth of planktonic bacteria, both Gram-negative *E. coli* K12 and Gram-positive *Staphylococcus epidermidis* (*S. epidermidis*), by 99.9% due to the polycationic character as well as by the controlled releasing of SA^- as a mild antibacterial agent. After hydrolysis, the hydrogel prevented protein adsorption or bacterial accumulation.

Alternatively, covalent attachment of the salicylate molecule as an ester via the phenolic group in a monomer unit poly(14) was developed for enhancing the controlled SA^- release over the system with an ionic-forces stabilized SA^- in poly(13) [60]. Fabricated hydrogel from poly(14) was prepared redox polymerization. Hydrolysis of the salicylate ester poly(14) was completed in 16 h, while the complete release of the drug SA^- from poly(13) was completed in 3 h under the same condition. The hydrogel after the transformation to poly(5) still retained the non-fouling properties for protein and bacteria.

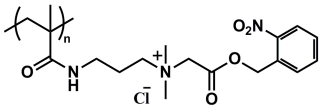
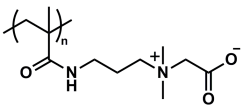
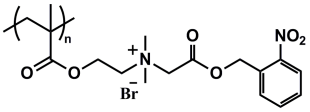
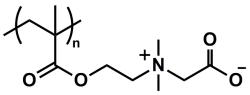
2.1.1.2. Light Trigger

Since photolysis is a non-invasive trigger and initiation is timely and spatially localizable, this approach has attracted the greatest interest in bio-related applications. Recently, a photolysis of a photolabile unit for the preparation of switchable polymers poly(15) and poly(16) [51,61] was reported. Their structures are shown in Table 3.

In the poly(15) [61] switch to the polyzwitterionic state, poly(16) was enabled via the abstraction of a photolabile *o*-nitrobenzyl-carboxymethyl pendant during irradiation at 365 nm in PBS solution. In the polycationic state, poly(15) was able to bind double-strand DNA (dsDNS), showing the size of the DNA complex of 170 nm in solution and on a dextrane-modified surface. Upon irradiation at 365 nm, the polyzwitterionic state poly(16) was formed and the dsDNA was released in solution as well as from the surface [61]. In addition, dramatic differences in polycationic poly(15) and the polyzwitterionic form was observed where the antibacterial activity of poly(15) was tested against *E. coli* cells in solution and on the surface, where 91% was killed compared with the inactive poly(16) [61].

Similarly, poly(17) formed a polycomplex with DNA and, after photolysis at 365 nm, 72.5% of free DNA was released from the polyplex, as confirmed by a quantitative PicoGreen DNA binding assay [51].

Table 3. Irreversible light-triggered (meth)acrylic-based switches containing polyzwitterionic state.

Initial state	Trigger (applied form) reference	Polyzwitterion state
 Poly(15)	UV light 365 nm (polymer) → [61]	 Poly(16)
 Poly(17)	UV light 365 nm (polymer) → [51]	 Poly(8)

The same monomer unit as in poly(15) was copolymerized under ATRP condition with carboxybetaine methacrylate to form a block copolymer poly(18) with switch to poly19 (Figure 3a). Poly(18) formed by self-assembly polyionic complex micelles with a negatively charged protein-bovine serum albumin (BSA)—and was used as a vehicle to internalize the model protein drug to tumor cells. The formation of micelles, as shown in Figure 3b, improves the protection of the protein against denaturation, shields the negative charge of the protein with polyzwitterionic hairy structure and provides an overall positive surface charge to effect an efficient cellular uptake to tumor cell enhancement; penetration to the tumor cell is also due to the EPR effect. Transformation to the fully zwitterionic state poly(19) by UV irradiation at 365 nm significantly accelerated the release of BSA Figure 3b [62].

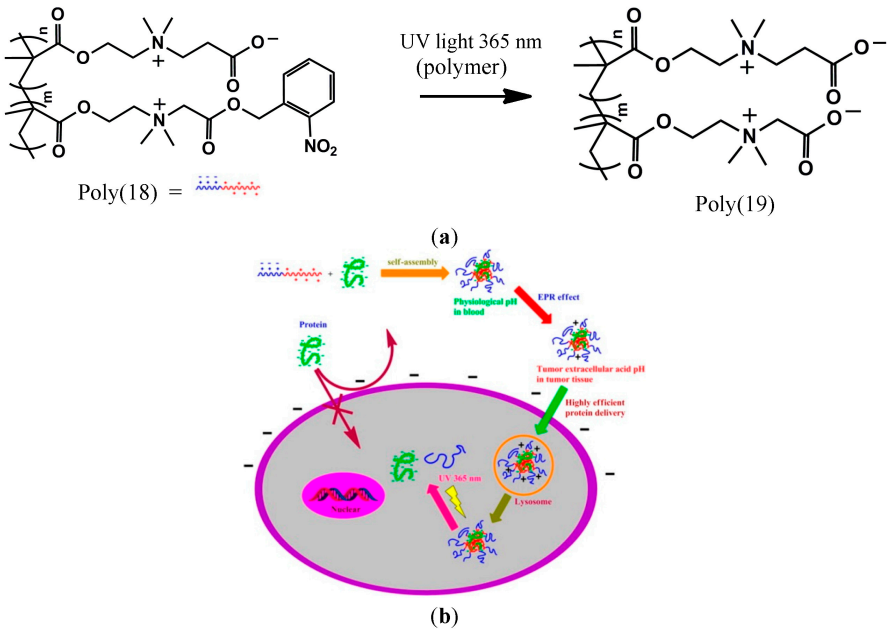


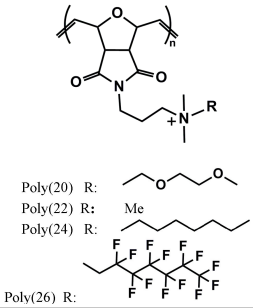
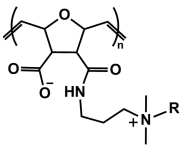
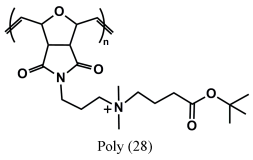
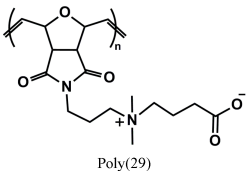
Figure 3. (**a**) Structure of copolymer poly(18) and irreversible switch to poly(19) (**b**) schematic application of poly(18) in the complexation with negatively charged BSA to form self-assembly polyionic complex that improve the protection of the protein against denaturation, shields the negative charge of the protein and penetration to the tumor cell due to the enhanced and permeability and retention (EPR) effect and by UV light irradiation accelerated the release of bovine serum albumin (BSA). Reprinted with permission from Reference [62]. Copyright (2014) American Chemical Society.

Despite the advantages of using photolytic transformation, further studies should be directed towards the employment of a photolabile group (*i.e.*, coumarine type ester) with a non-toxic site product of photolysis [63] and satisfy the two photon absorption properties for improved biomedical applications [64].

2.1.2. Norbornene Type Polymers

Structurally unusual polyzwitterionic polymers that contain anion and cation in the same repeated unit but on a separate side-chain, poly(21), poly(23), poly(25), poly(27) and poly(29) [65,66], were reported and the structures are shown in Table 4. The application of such polymers made it possible to tune the hydrophilicity of the system at a repeating unit level. A direct comparison of various structures based on norbornene carboxy and sulfobetaines, and methacrylate sulfobetaines confirmed that the non-fouling performance was affected by the overall structure, hydrophilicity, charge, and backbone type present within the polymer.

Table 4. Irreversible switches of norbornene polymers containing polyzwitterionic state.

Initial state	Trigger (applied form) references	Polyzwitterion state and released active molecule
	0.1 NaOH pH 7.4 buffer, 20 min (attached to surface) [65]	
	HCl, dioxane 4 h, RT (attached to surface) [65]	

The hydrolysis was investigated on a silicone substrate coated with copolymers with 5-bicycloheptenyl triethoxysilane that provided a stable linkage through Si–O–Si bonds. The zwitterionic forms poly(21), poly(23), poly(25) and poly(27) were prepared by treatment of the modified surface with 0.1 NaOH for 20 min, while the hydrolysis of polycarboxybetaine esters poly(28) to zwitterionic polymer poly(29) was carried out in an acidic medium and proceeded within 4 h at ambient temperature. Norbornene-based zwitterionic polymers of various architecture were investigated and compared in order to follow the effect of a backbone structure on the protein adsorption properties [65]. In comparison with the methacrylate based sulfobetaine, the analogue norbornene sulfobetaine and carboxybetaine poly(29) exhibited lower protein fibrinogen adsorption, being 3.39, 1.03 and 0.84 ng/mm^2, respectively. With the increasing hydrophilicity of the pendant on the ammonium group, the fibrinogen adsorption decreased. Poly(21) exhibited a protein adsorption lower than 0.1 ng/nm^2, *i.e.*, below the limit of a biofilm formation. Since the unique design allows a simple protocol for polycarboxybetaines pendant modification, influence the lipophilicity, respectively, the lipophobicity of pendant attached to a quaternary ammonium group to protein adsorption was studied. Surprisingly, the lowest values of BSA and lysozyme adsorption were detected in the case of the hydrophobic and lipophobic perfluorated poly(27), which was even lower than the hydrophilic PEG-modified poly(21) [66]. This indicates that combination of lipophobic character, which prevents interaction lipophilic fouling species, and

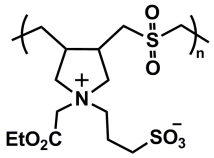
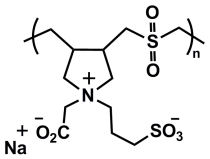
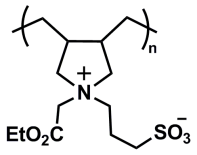
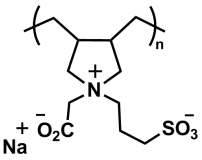
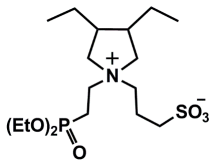
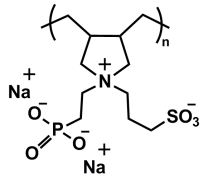
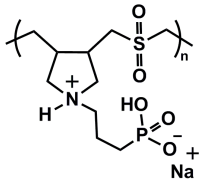
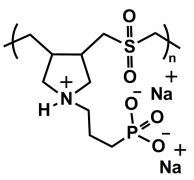
polyzwitterionic character can enhance non biofouling properties. Moreover, the results show that the norbornene-based dual-functional polymer in the polyzwitterion state is comparable with the methacrylate-based polymers with regard to protein antifouling properties. The advantage of these dual-functional polymers is that no hydrolysable ester group is also present, which improves stability under physiological conditions. In addition, even the perfluorated lipophobic and hydrophobic motif can decrease protein adsorption.

2.2. Switch from Polyzwitterionic to Polyanionic State

Recently, transformations from the polyzwitterionic to polyanionic state on polymers were investigated and a summary of this type of switches is given in Table 5. Polysulfobetaines poly(30), poly(32), poly(34) and poly(36) were transformed via hydrolysis to polymers also bearing secondary negatively charged functionalities. In the case of poly(30) and poly(32), acidic hydrolyses of the carboxybetaine ester with 6 M HCl were performed at 53 °C for 48 h and neutralization with two equivalents of NaOH resulted in the formation of polymers poly(31) and poly(33) [67,68]. Similarly, the acidic hydrolysis of phosphate diester in poly(34) and poly(36) was performed at 95 °C in 24 h [69,70].

It should be noted that the introduction of a second negatively charged group increased solubility in water and good anti-scaling properties were observed in a saturated solution of $CaSO_4$ [68,69].

Table 5. Irreversible switches from polyzwitterionic to polyanionic state.

Polyzwitterion state	Trigger (form) reference	Polyanionic state
	(1) 6 M HCl (2) NaOH	
Poly(30)	(polymer) [67]	Poly(31)
	(1) 6 M HCl (2) NaOH	
Poly(32)	(polymer) [69]	Poly(33)
	(1) HCl (2) NaOH (3) NaOH	
Poly(34)	(polymer) [69]	Poly(35)
	(1) HCl (2) NaOH (3) NaOH	
Poly(36)	(polymer) [70]	Poly(37)

3. Reversible Switch

Two principles of the reversible switch of zwitterionic polymers were reported based on either physical or chemical changes in a polymer structure.

3.1. Physically Induced Reversible Switch in Solutions

The physical principle is based on the temperature-dependent self-assembly of polymer chains. The thermally-dependent self-assembly of polyzwitterionic groups is made possible by extremely high dipole moments between zwitterionic groups [71]. The polyzwitterionic feature offers such unique properties as an antipolyelectrolyte effect and upper critical solution temperature (UCST). The cationic and anionic polymers exhibit the polyelectrolyte effect, *i.e.*, the solubility and viscosity decrease upon addition of the electrolyte. On the other hand, in the case of the antipolyelectrolyte effect, the viscosity and solubility increase [24,72]. The addition of electrolyte to the polyzwitterion solution results in an expansion of the polymer chain, hence disintegration of the physical net formed by ions. The electrolyte ions shield the charged polymer parts that prevent the intra-group, intra-chain and inter-chain interactions, which results in an extension of the polymer chains and a subsequent increase in polymer solubility, as shown in Figure 4 [72,73].

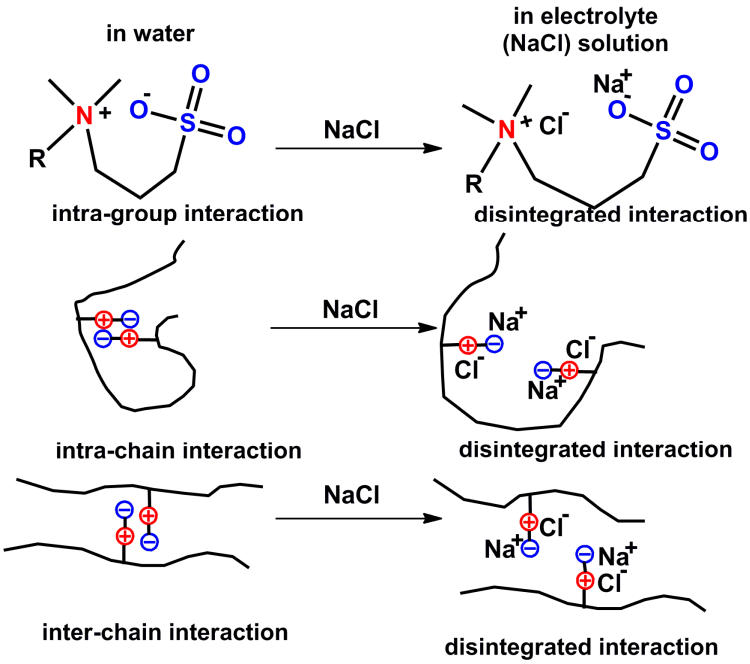


Figure 4. Proposed mechanism for antipolyelectrolyte effect on polyzwitterion structure by simple electrolyte.

Some zwitterionic polymers (mainly polysulfobetaines) exhibit UCST (Figure 5b) as a result of strong inter- and intramolecular interactions leading to a reversible self-association of polymer chains [74] and might signify as a reversible switch in physical properties in a solution or on a surface. Above UCST, the dipolar interactions are broken and the isolated polymer chains are completely solvated. In other words, the high-viscosity gel is transformed into a transparent low-viscosity sol above UCST [75].

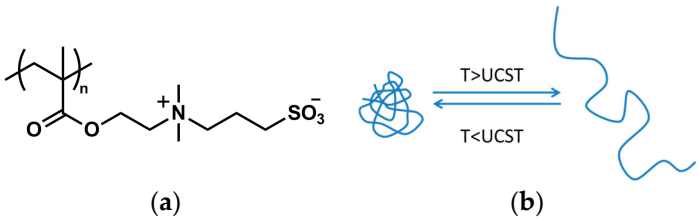


Figure 5. (**a**) Structure of poly(38) and (**b**) schematic illustration of upper critical solution temperature (UCST) of a polymer in solution.

The most studied and applied polymer possessing UCST in an aqueous solution is polysulfobetaine poly(38) depicted in Figure 5a and its UCST is highly dependent on pressure, type of polymer and its molecular mass characteristics as well as on the single electrolyte presence. Schulz *et al.* [76] studied the phase behavior of polysulfobetaine poly(38) in terms of dependence on concentration and salt type. The 0.1% aqueous solution of poly(38) with M_n 4.35 × 10^5 g/mol exhibited the UCST of 32 °C while, in 0.3% NaCl solution, the UCST declined to 15 °C. At low concentrations of aqueous polymer solutions (0.01%–0.1%), an increase in UCST was observed, with the maximal USCT achieved at 0.1%. With increasing the concentration of polymer poly(38) in the aqueous solution, the UCST declined from 32 °C at 0.1% to 18 °C for the 5% solution [76]. The type of salt added significantly affects the UCST of the polymer solution. The anionic dissolving strength accords with the Hofmeister lyotropic series (HLS) [77] and with the Pearson theory of acids and bases [78]. The relatively soft ammonium cation in the polymer prefers soft anions such as SCN^-; in their presence the USCT decreases to 0 °C in a poly(38) solution in concentrations ranging from 0.01% to 10%, even at a low concentration of 0.05 mol/L NaSCN. The sulfate group of poly(38) is soft and prefers interactions with soft cations such as Ag^+ in the presence of which the USCT declines even below 0 °C in a concentration range of poly(38) from 0.01% to 10% [79]. Chen *et al.* [80] studied the dependence of UCST on poly(38) in the presence of polymers complexing poly(38). The polyanion poly(2-acrylamido-2-metylpropan sulfonic acid) and polycation poly(3-acryloylaminopropyl trimethylamonium chloride) were used as complexing agents. It was found that complexation with poly(2-acrylamido-2-methylpropane sulfonic acid) resulted in a decrease in UCST due to the presence of free sulfonic groups at the end of the polymer chains. On the other hand, the complexation with a low amount of poly(3-acryloylaminopropyl trimethylamonium chloride) results in an increase in UCST, while with an increasing ratio of polycation/poly(38) the UCST decreased.

UCST can be further modulated by the copolymerisation of monomer(38) with other monomers containing hydrophobic pentyl-(PAA), benzyl-(BAA) and dodecylacrylamide (DAA) functionalities [81], *N*-vinyl caprolactame (VCL) [82] or blocks of 2-(2-methoxyethoxy)ethyl methacrylate (PEG MA) [83], *N*-isopropyl acrylamide (NIPAM) [84,85] (Figure 6). Hydrophobic monomers in copolymers typically provide an increase in UCST and the presence of a simple electrolyte decreases UCST, which can easily modulate the solubility properties of polymers [81].

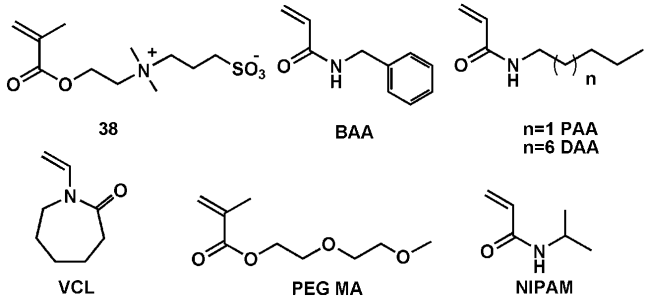


Figure 6. Structures of monomer (38) and monomers used in copolymers to vary UCST.

Additionally, UCST response for different sulfobetaine polymers was investigated and representants are summarized in Figure 7.

Vasanta *et al.* [86] prepared a dual hydrophilic block copolymer containing polyethyleneglycole segment PEG and poly(40). The block copolymer was able to form micelles and undergo core-shell transition depending on the nature of the dispersing medium. In the distilled water (DW), the poly(40) formed the core part, while in an electrolyte solution the PEG was present in the micelle core. The antifouling properties were investigated in seawater. The block copolymers exhibited improved antifouling properties over neat homopolymers.

The lower critical solution temperature (LCST) is a solution characteristic of some polymers where a reversible transition such as UCST occurs. Typical polymers possessing LCST in water contain NIPAM or VCL as monomer units [87].

Thermoresponsive copolymers containing a combination of the sulfobetaine monomer and monomers such as NIPAM [88,89] or VCL [82] can vary their UCST as well as LCST.

The effect of a specific ion on LCST was investigated on a copolymer of poly(NIPAM) and poly(41) by using rheology [90]. The LCST was varied from 28 °C to 33 °C. The change in viscosity reflected the effectiveness of the ions in weakening the interactions of the sulfobetaine groups that provided the electrostatic cross-linking. The anions were observed to follow the HLS, while the cations followed the reverse HLS. In the case of the cations, the viscosity decreased in the order: $Fe^{3+} > Al^{3+} > Ca^{2+} > K^{+} > Ni^{2+}$, while, in the case of the anions, the decrease was in the order: $Cl^{-} < Br^{-} < I^{-}$.

Arotcarena *et al.* [91] prepared block copolymers containing poly(NIPAM) and polysulfobetaine methacrylamide poly(42) which exhibited both the LCST of the poly(NIPAM) blocks and the UCST of the poly(42). The LCST of the neat poly(42) was 12.5 °C and the UCST of the neat poly(NIPAM) was 29.8 °C. The copolymers were soluble in this temperature range; beyond this range they formed micelles with different polarities, polar at low temperatures and unipolar at high temperatures. The authors showed that the transition temperatures could be adjusted by the length of the polymer chains. The copolymer containing 74 mol % poly(NIPAM) (10,800 g/mol) and 26 mol % of poly(22) (9700 g/mol) exhibited LSCT of 8.6 °C and USCT of 31.5 °C. The copolymer composed of 35 mol % poly(NIPAM) (10,800 g/mol) and 65% poly (42) (52,800 g/mol) exhibited LCST of 18.4 °C and USCT of 31.4 °C.

Maeda *et al.* [92] prepared a double-responsive diblock copolymer consisting of poly(38) as a USCT block and poly(*N*,*N*-diethylacrylamide) as an LCST block. By using FTIR and DSC techniques, the mechanism of micelles formation below USCT and above LCST based on selective hydration of the blocks at different temperatures was explained.

The LCST and UCST were controlled by different ratios of the sulfobetaine monomer(38) and *N*-vinylcaprolactam (PVCL) in a random copolymer [82]. While the neat PVCL exhibited the LCST of 34 °C, in the copolymers the LCST increased to 36 °C, 38 °C and 43 °C when 23.6%, 44.1% and 56.8%, respectively, of monomer(39) was incorporated. The USCT appeared for a copolymer with a higher ratio of poly(38) segments and shifted from 9 °C to 27 °C when the ratio of poly(38) increased from 44.1% to 56.8%. The neat poly(38) exhibited the UCST of 46 °C. The copolymers were soluble between LCST and UCST, and were insoluble beyond these temperatures.

The copolymers were used for the preparation of hydrogels with *N*,*N*′-methylenebisacrylamide as a cross-linker. The water contact angle decreased from 59.88° to 45.44° with the monomer(38) content in the feed increasing from 0% to 100%. The adjustment of the ratio between poly(38) and PVCL made it possible to tune protein resistance and cell adhesion. The fouling and proliferation of cells on the hydrogel surface was suppressed by increasing the poly(38) content. The hydrogels containing a higher ratio of PVCL readily detached the cells from the surface at decreased temperatures.

Moreover, changing the monomer character by the introduction of a backbone moiety such as styrene poly(40) [93], or imidazole-based poly(44) [75,94] or changing the distance of the charged

moieties within the polymer backbone can result in polymeric materials with a variability of UCST. It should be noted that the polymers with styrene moieties in the backbone prevent any hydrolytic cleavage of the ester or amide groups in the backbone, which can occur in methacrylic-type polymers [95].

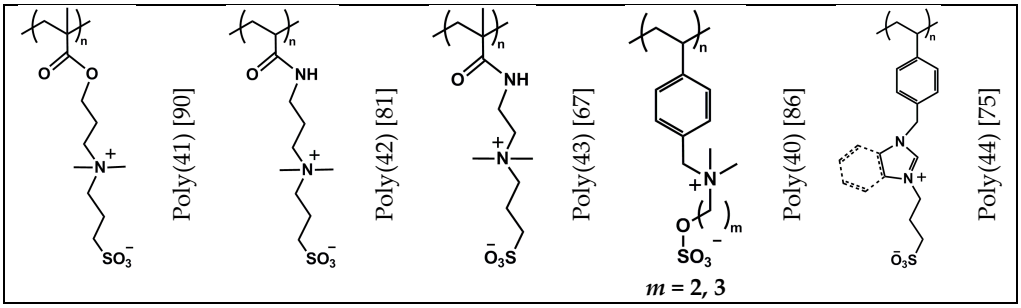


Figure 7. Structures of sulfobetaine zwitterionic polymers with UCST response.

3.2. Physical Switch on Surface

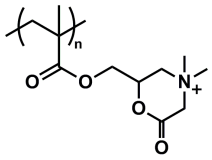
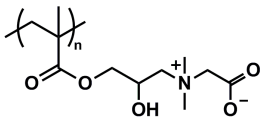
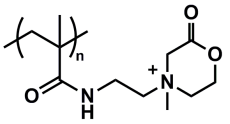
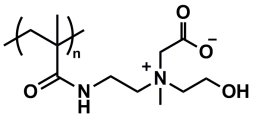
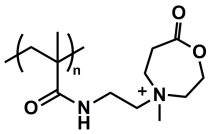
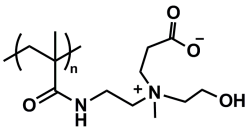
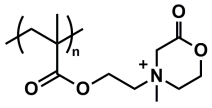
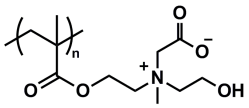
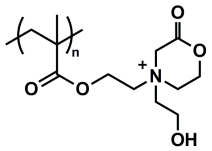
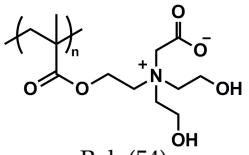
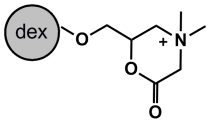
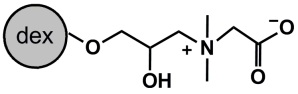
It was observed that the polymeric brushes of poly(38) prepared by SI ATRP on a gold surface varied the wetting characteristics depending on the layer thickness and the temperature applied [96]. A non-associated structure was formed and the water contact angle attained 12° when the polymer brushes were formed from poly(38) with a thickness up to 50 nm. While the increased hydrophobicity with a contact angle up to 75°, due to the formation of self-associated structures, was observed with polymers 110 nm in thickness. Moreover, the UCST of polymeric brushes with an approximate thickness of 180 nm was observed and the contact angle changed from 78° at 22 °C to 53° at 52 °C. A detailed investigation of the surface wetting properties on the polymer layer thickness up to >500 nm showed that the critical thickness, where the transition from hydrophobic to hydrophilic occurred, varied depending on the grafting density and polymerization rate [97].

Another smart switchable surface with a salt-responsive character were developed by polymer brushes of poly(44) prepared by SI ATRP on a glass substrate [14]. Poly(44) in the presence of a simple electrolyte such as NaCl exhibited super low protein adsorption <0.3 ng/cm^2, lower contact angle and higher surface hydration compared to a surface in the presence of water with adsorption up to 145 ng/cm^2. This behavior is related to the anti-polyelectrolyte effect and is reversible. In addition, the surface friction can be tuned by metal ions and counter ions from ultrahigh friction (μ in range 10^0) for water or SO_4^{2-} to superior lubrication (μ in range 10^{-3}) in the presence of Br^- ions, which is comparable to that of natural synovial joints.

3.3. Reversible Switch from Polycationic to Polyzwitterionic State

The reversible switches based on chemical change observed in zwitterions that transform into ring-forming cationic structures are summarized in Table 6. The structure of the cationic ring was observed to be formed at the quaternary amine carboxybetaines having hydroxyl and carboxylate groups at different distances. Under acidic conditions, the lactone rings were formed, while the rings opened under neutral or basic conditions. An increasing number of bonds in the lactone made the ring formation difficult, hence stronger conditions were necessary to form the ring. The switching performance of the polymer was also dependent on the type of backbone. The methacrylamide backbone imparted a marked hydrophilic performance to the carboxybetaine polymer compared with the methacrylate-based carboxybetaine polymer, which resulted in an improvement in the elasticity and tensile strength of the polymers due to the formation of hydrogen-bonding. However, the mechanical properties of carboxybetaine structures with a methacrylate backbone were improved with the introduction of hydroxyl groups to lactone rings that resulted in the formation of intermolecular hydrogen-bonding.

Table 6. Reversible switches containing polyzwitterionic state.

Polycationic state	Trigger (form) (reference)	Polyzwitterionic state
 Poly(45)	OH^- (pH 7 or pH 10) ⇌ H^+ (TFA, HAc) (polymer brushes) [98]	 Poly(46)
 Poly(47)	OH^- ⇌ H^+ (polymer brushes, hydrogel) [99]	 Poly(48)
 Poly(49)	OH^- ⇌ H^+ (polymer brushes, hydrogel) [99]	 Poly(50)
 Poly(51)	OH^- ⇌ H^+ (polymer brushes, hydrogel) [100]	 Poly(52)
 Poly(53)	OH^- ⇌ H^+ (polymer brushes, hydrogel) [100]	 Poly(54)
 poly(55)	OH^- ⇌ H^+ (modified dextran) [101]	 poly(56)

The reversible switch was reported on the surface of poly(45) with a structure based on 2-morpholinone [98,102] prepared by SI ATRP. The structure contained a quaternary amine lactone ring that reversible transforms into a zwitterionic carboxybetaine structure as is schematically depicted in Figure 8. The switch was investigated in both acetic acid (HAc) [98] or trifluoroacetic acid (TFA) [102]. The rate of the reverse switch accelerated with increasing pH [102]. The transformation of the polymer in TFA was faster and more effective; however, the use of acetic acid is advantageous since it does not corrode the gold substrate and does not damage the polymer coating. The slow transformation in acetic acid was assigned to the catalytic process caused by the protonation of the carboxylate group that led to an intramolecular Fisher esterification involving the neighboring hydroxyl group. Application of switchable character of this material is in Figure 8. Polycationic state poly(46) can be formed in acidic condition and such dried surface is able to kill 99.9% of bacterial cells from directly spraying bacterial aerosols onto the material. Exposure of surface to water permit fast hydrolysis to polyzwitterionic form poly(45) release 90% of the killed bacteria and moreover prevent fouling for fibrinogen and lysozyme below the limit of detection of 0.3 ng/cm^2 and, in the case of undiluted plasma, the adsorption attained 3 ng/cm^2. Reversibility of this switchable process was capable to restore initial state through dehydration of surface under acidic conditions (Figure 8) [98].

Reversible switch allowing switch between polycationic coating with antibacterial character and subsequently after switch release of dead bacteria and forming nonfouling surface have particular interest in coating for surgical or medical tools and application.

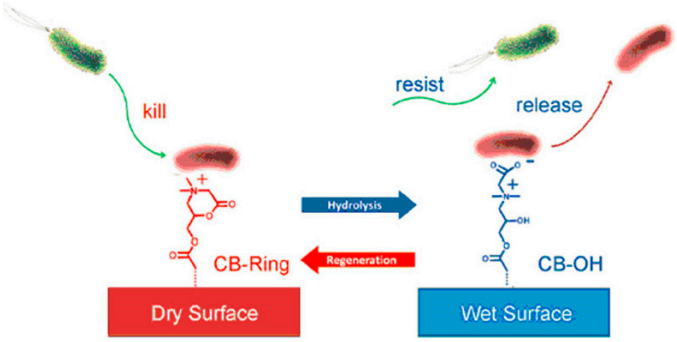


Figure 8. A reversible switch between antibacterial surface of poly(45) enable to kill bacteria in the polycationic state and hydrolysed polyzwitterionic state poly(46) permitting to release dead bacterial cells along with resistance against bacteria cells adhesion. Regeneration to poly(45) is through an acidic dehydration process. Reprinted with permission from Reference [98], Copyright 2012, Wiley-VCH.

Moreover, poly(45) in a pH 10 buffer transferred onto an amine-reactive surface made it possible to immobilize two antibodies (anti-hGC and anti-Salm) through reactive carboxylate. This treatment and reversible transformation of remaining group to poly(45) resulted in the significant specific detection of hCG or Salm proteins [102].

Investigation of the structure–property relationship of reversibly carboxybetaine zwitterionic polymers revealed that even one carbon in spacer can significantly influence the switchability, meachanical properties and stability of the carboxybetaine polymers [99]. Four different switchable polymers poly(47), poly(49) poly(51) and poly(53) were synthetized and studied in this regard. Poly(47) and poly(49) contain a methacrylamine backbone in the monomer unit and form six-membered and seven-membered lactone rings, respectively. Poly(51) and poly(53) contain methacrylate backbone forming six-membered lactone rings and bear methyl and hydroxyethyl group on ammonium group, respectively. The protein adsorption of polymer brushes prepared by surface-initiated photoiniferter-mediated polymerization (sensors on gold-coated chips of poly(48), poly(50) and poly(52) were tested by SPR [99]). All three materials in polyzwitterionic state exhibited ultra-low fouling properties against human fibrinogen, 100% human plasma and 100% human blood serum. The ring formation and transformation from polyzwitterionic state to polycationic states were investigated in both HAc and TFA. Poly(49) with seven membered ring was switched with the lowest rate was due to the high strain upon the ring closure. In acetic acid the ring was not formed; instead, elimination of acrylic acid was observed. Interestingly, the incorporation of hydroxyl groups in the monomer of poly(53) accelerated the ring formation. In TFA, the monomer of poly(53) switched up to 99% in 15 minutes and in 0.2 M HAc, the monomer of poly(53) was able to reach an 84% conversion within 20 h [100]. These results indicate that the monomer of poly(53) is more favorable for ring formation than the monomer of poly(51) due to the symmetrical substitution giving rise to opportunities to cyclize on both sides, resulting in faster ring formation. The ring-opening kinetics was investigated in alkaline condition [100]. Only the poly(47) hydrogel exhibited good switchability and ring stability and thus was able to kill and subsequently release almost 99.5% of the dead *E. coli* cells from the surface [99].

From the perspective of the hydrogels mechanical properties, the methacrylamide backbone imparted more hydrophilic properties affording more pronounced hydrogen bonding, which resulted in improved tensile strength and elasticity. The best results were obtained with poly(47) followed by

poly(49). Since the carboxybetaine zwitterionic hydrogel with 6-membered lactone rings, poly(51), suffers from insufficient mechanical properties, the hydroxyl groups were incorporated into the monomer unit of poly(53) [100]. The introduction of hydroxyl groups resulted in the formation of hydrogen bonds between the polymer chains. When compared with the hydrogel base on poly(carboxybetaine methacrylate), both poly(51) and poly(53) exhibited enhanced break strain. Poly(51) exhibited two times higher break stress and 30% higher break strain, and 73% higher modulus compared with the poly(8) hydrogel. The higher number of hydroxyl groups present in poly(53) resulted in hydrogel softening, hence no enhancement of the modulus was observed. It should be noted that the hydroxyl groups improved the solubility of polymers in DMSO, DMF, $CHCl_3$ and acetonitrile. Antifouling properties of poly(51) and poly(53) were evaluated on polymer brushes prepared on gold-coated SPR chips with a bovine fibrinogen solution (1 mg/mL) and 100% human blood plasma. Both polymers exhibited ultra-low fouling properties in the bovine fibrinogen solution. Poly(53) adsorbed proteins at a density of 0.8 ng/cm^2 and poly(51) at a density lower than the limit of detection of 0.3 ng/cm^2; in the 100% human blood plasma poly(51) modified the surface-adsorbed proteins at a density of 0.2 ng/cm^2 and poly(30) at a density of 2.4 ng/cm^2. Since all the values of fibrinogen adsorption were below 5 ng/cm^2, the material can be expected to delay the blood coagulation caused by platelets activation [100].

The cell viability test confirmed that both poly(51) and poly(53) in a cationic ring form can cause cell damage to more than 99% of the attached bacteria. After overnight hydrolysis, 99.6% and 99.4% of dead cells were released from the surface of poly(51) and poly(53), respectively [100].

It can be stated that careful and rational engineering of the monomer unit can result in improved mechanical properties without sacrificing the switchable character and retaining the combined antibacterial and antifouling properties.

Similarly, the methacrylate-type six-membered lactone ring structure was also used for modification of the dextran surface to poly(55). The use of structure poly(55) enhance optical properties, imparted anti-biofouling properties to the otherwise natural polysaccharide material [101].

Another type of reversible switch was induced by the addition of bisulfite ions HSO_3^- to polymers with a quaternary ammonium group on the pendant aldehyde functionality in poly(57) as shown in Figure 9 [103,104]. The addition of HSO_3^- ions to aldehyde created a sulfate group, and a polyzwitterionic state was formed. This transition was used to deactivate for thin layer-by-layer structures on the surface. Reversibility of this process in this system has not yet been studied in detail.

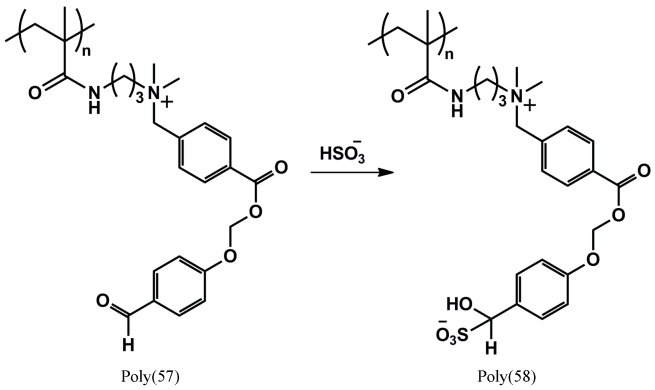


Figure 9. Reversible switch of poly(57) by addition of HSO_3^- ions [103].

The redox switch on polymers bearing viologen with a sulfate moiety should also be considered as a switch involving the polyzwitterionic state as shown in Figure 10. The reduction and oxidation currents in the cyclic voltammetry measurements of the viologen to form the cation radical and dication were observed to be of the same intensity, which indicated the reversibility of this switch.

Moreover, the hydrophilicity was controlled with this process and the hydrophilicity of polymer decreased after reduction was carried out [105].

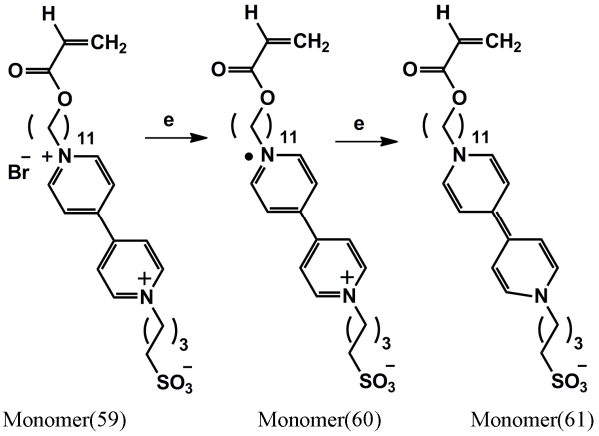


Figure 10. Redox switch on monomer(59) bearing viologen [105].

3.4. Switch in Polymer from Polyneutral to Polyzwitterionic State

The fixation of CO_2 by the addition of CO_2 to a polymer having carbine in the imidazole ring can be assumed to form the polyzwitterion state, and the related polymers are summarized in Figure 11 [106]. Fixation via carbine on the polymer in the structure of poly(70) was performed within 60 min at 40 °C in a CO_2 environment and the release was performed at an elevated temperature of 140 °C in a nitrogen atmosphere [107]. It should be noted that this type of switch is probably only possible in a non-aqueous environment. Amidine is a promising functionality for the addition of CO_2 to form a polyzwitterionic structure of poly(72). Several types based on a polystyrene backbone were synthesized [108,109]. Nowadays, the fixation or capture of CO_2 is of particular interest due to its environmental and economic aspects. CO_2 is not only a cheap and valuable source of "green" C1 synthon in technology and research but, more importantly, the increased CO_2 concentration in the atmosphere promoting global changes and serious environmental problems drives the investigation of the use of such carbon sources in numerous applications.

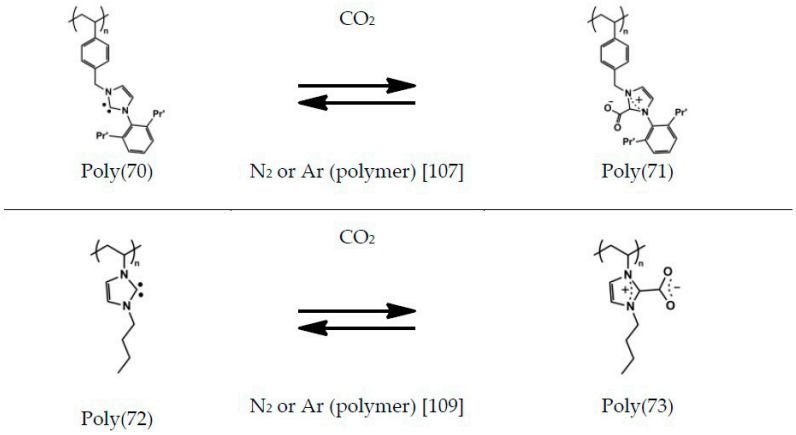


Figure 11. Switch in polymer from polyneutral to polyzwitterionic state triggered by CO_2.

The literature contains frequent references to the switch in polymers from the polyneutral to polyzwitterionic state in polymers containing spiropyrane monomers [110]. These derivatives might switch between two states: open merocyanine-ring and closed spiropyrane-ring isomers as shown in Figure 12 [111]. This switch between states can mainly be triggered by a certain light wavelength

as a light-responsive switch, but the process can also be triggered by different solvents, metal ions, acids/bases, redox potential and mechanical forces. Merocyanines are not correctly postulated as an ionic-zwitterionic state; however, the merocyanine isomer occurs naturally in a quinoidic mesomeric form with a large conjugated system possessing a strong dipole only as shown in Figure 8. Due to this fact, the term polyzwitterion state in such systems is not appropriate.

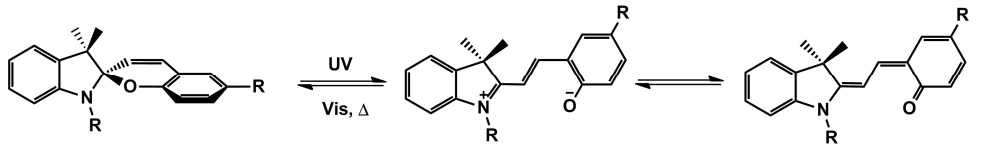


Figure 12. Spiropyran–merocyanine transformation with mesomeric structure.

3.5. Switch in Polymer from Polyanionic to Polyzwitterionic State

This case is limited solely to the redox-responsive switch of the organometallic polymer with a ferrocenylsilane backbone bearing the sulfonate pendant group poly(74), which can transform the ferrocene fragment to ferrocenium at a certain potential, as depicted in Figure 13 [112]. This process was investigated using a 5-layered layer-by-layer (LBL) system of polyanionic ferrocene poly(74) with the poly(ferrocenylsilanes) poly(75) having a quaternary ammonium counterpart, and disassembly based on the repulsive forces due to formation of the polyzwitterionic structure was observed. At a potential of 0.4 V, the oxidation of ferrocene in poly(74) to ferrocenium succeeded and the LBL disassembled within 5 has observed by UV and CV measurements [113].

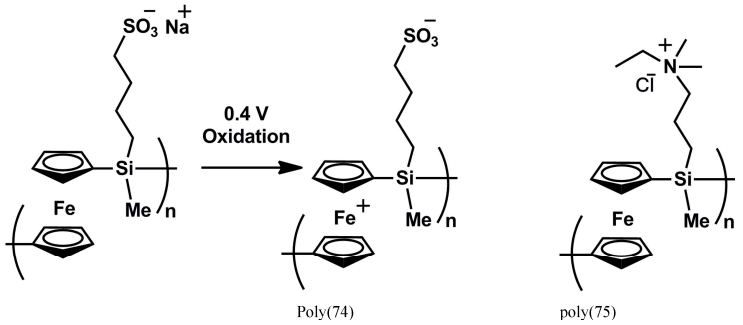


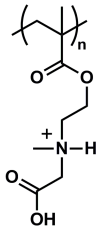
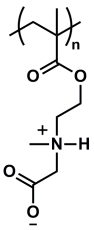
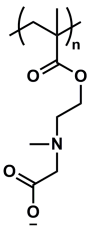
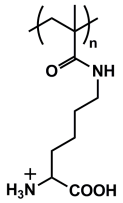
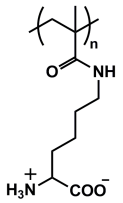
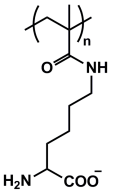
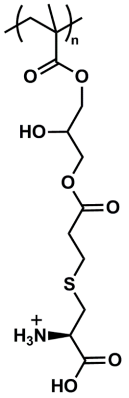
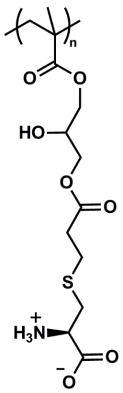
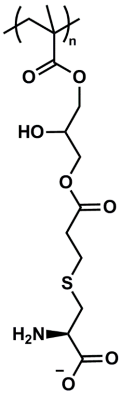
Figure 13. Switch from polyanionic ferrocene to polyzwitterionic ferrocenium state in poly(74) and chemical structure of positively charged polyferrocenylsilane poly(75).

4. Reversible Double Switch

Recently, a structure performing a reversible double switch between the cationic, zwitterionic and anionic states was reported; examples are summarized in Table 7.

In one report, the structure poly(76) with tertiary amine and carboxylic acid separated by one methylene spacer were developed and polymer brushes were prepared by SI PMP [114]. Since the tertiary amine can exist in positive and neutral states, and carboxylic acid can exist in the neutral and negative states, the two fully reversible charged states could be achieved. When the distance between the tertiary amine and the carboxylic group is sufficiently small (one carbon bond), the opposite charged states stimulate one another and thus synergistically affect and stabilize the polyzwitterionic state. In this case, from pH 1 and 2 the tertiary amine was protonated which resulted in the polycationic state. The polyzwitterionic state poly(77) was obtained at pH between 2 and 9 so, in the pH range of 6–8, which is regarded as the physiological condition and suitable for bioapplications, this transition can be performed. Beyond pH 9, the structure was deprotonated resulting in the formation of an anionic charged form poly(78).

Table 7. Reversible double switch.

Initial form	Polyzwitterion	References	Second form
		[114]	
pH 1–2 Poly(76)	pH 2–9 Poly(77)		pH > 9 Poly(78)
		[115,116]	
pH 2–4 Poly(79)	pH ≈ 5 Poly(80)		pH > 5 Poly(81)
		[117]	
pH < 2 Poly(82)	pH 2–9.5 Poly(83)		pH > 9.5 Poly(84)

The protein-fouling properties of double-switch-performing polymers were investigated at various pH values. The resistance of poly(76) was tested with a set of oppositely charged proteins at any given pH, *i.e.*, lysozyme (positively charged, pI ≈ 11) and pepsin (negatively charged, pI ≈ 1). At pH 3 the negatively charged pepsin was strongly adsorbed (24 ng/cm^2) while the positively charged lysozyme was negligibly bound, thereby confirming the surface to be positively charged. On the other hand, at pH 9, the lysozyme was strongly adsorbed (26 ng/cm^2) revealing the negative charge on the surface [114]. The ultra-low fouling properties were confirmed with undiluted human plasma and serum under physiological conditions at pH = 7.4. In the case of serum, an adsorbed protein surface density of 5 ng/cm^2 was detected while, in the case of plasma, an undetectable adsorption was observed [114].

Poly(methacryoyl-L-lysine), structure (79), was reported to perform a double switch from the polycationic state at pH below 4.5 through the polyzwitterionic state at pH = 4.7 to the anionic state at pH > 5 [115,116]. Polymeric brushes poly(79) prepared by SI free radical polymerization in conical nanopores in polyimide membrane were able pH tunable and controllable ionic transport.

Poly(cysteine methacrylate), poly(82) containing a primary amine and carboxylic acid was formed by SI ATPR. The polymer brushes were observed to be highly extended at pH = 2 and above pH= 9, when the structure became positively and negatively charged, respectively [117]. In the pH range of 2–9.5, the polymer brushes were in a polyzwitterionic state as poly(83). Polymer brushes Poly(83) showed antifouling properties and low cytotoxicity to human dermal fibroblast

cells for brushes having a thickness of 24–28 nm. Poly(83) exhibited good long-term stability under physiological condition, while the hydrolysis at pH < 8 was observed [117].

Double switch materials with pH tunability and controllability open the path to novel smart application in nanodevices, biomedical coating and passage and separation processes.

5. Conclusions and Outcome

In this review, the characteristics of switches in materials involving polyzwitterionic moieties were presented by way of irreversible and reversible examples. Exceptional triggers for switches, which included pH, temperature, electrical field, ions and CO_2 molecules, make this type of material particularly attractive mainly due to the significant changes in the overall charges and ionic states. The materials possessing functional switches were summarized as an excellent platform for controlling the release of antimicrobial drugs and solution properties, markedly varying the interaction with biological species such as DNA, bacteria and human plasma/blood samples and smart vehicles for drug and gene deliveries. Switches to polyzwitterionic state materials triggered with CO_2 have also been proposed and, due to environmental and economic concerns, research in this direction is highly motivated. Other unique characteristics for future research into switchable polyzwitterionic materials are worthy of remark. The unique combination of functional antibacterial and biofouling features addresses the huge demand for the coating of biomedical devices and leads to commercialization. Despite the promising results, the bio-distribution and clearance routes for materials are not yet available and can vary with size, form and the coated materials.

Progress in the synthetic chemistry of phosphobetaine derivatives makes it particularly attractive to employ switchable processes in various biological and biomedical applications [118]. In biomedical-related research, interaction with viruses should be considered and a switchable process introducing a trigger with a specific enzyme [119] or metal complexes as mimics [120] would be beneficial as a sophisticated nanosystem for delivery.

Similarly, a carboxybetaine derivative with phosphonium could be used in the preparation of valuable new synthetic products [121]. Thermo-responsive poly(38) polymers have recently been successfully used as ion-permeable membranes in energy storage devices; differences in the specific storage capacity of the electrode for Li ion when heated from 20 to 80 °C showed a reversibly decrease by >50%, compared to a 30% increase without polymer modification [122]. The orthogonal solubility of some polyzwitterions to solvents could typically be used in the processing of organic semiconductors [123,124] and possibly of UCST, representing an open avenue for thermo-responsive and tunable platforms in organic electronic devices [122]. The external trigger as a mechanical force via ultrasonic stimuli as a component of a spatial and time-controlled switchable process represents a highly feasible approach, which was not previously reported [125,126].

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