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Synthesis of Novel Sulfobetaine Polymers with Differing Dipole Orientations in Their Side Chains, and Their Effects on the Antifouling Properties

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The impact of the orientation of zwitterionic groups, with respect to the polymer backbone, on the antifouling performance of thin hydrogel films made of polyzwitterions is explored. In an extension of the recent discussion about differences in the behavior of polymeric phosphatidylcholines and choline phosphates, a quasi-isomeric set of three poly(sulfobetaine methacrylate)s is designed for this purpose. The design is based on the established monomer 3-[N-2-(methacryloyloxy)ethyl-N,N-dimethyl]ammonio-propane-1-sulfonate and two novel sulfobetaine methacrylates, in which the positions of the cationic and the ionic groups relative to the polymerizable group, and thus also to the polymer backbone, are altered. The effect of the varied segmental dipole orientation on their water solubility, wetting behavior by water, and fouling resistance is compared. As model systems, the adsorption of the model proteins bovine serum albumin (BSA), fibrinogen, and lysozyme onto films of the various polyzwitterion surfaces is studied, as well as the settlement of a diatom (*Navicula perminuta*) and barnacle cyprids (*Balanus improvisus*) as representatives of typical marine fouling communities. The results demonstrate the important role of the zwitterionic group's orientation on the polymer behavior and fouling resistance.

Zwitterionic polymers, or synonymously polybetaines or polymeric inner salts, represent a subclass of ampholytic polymers that contain pairs of ionic groups of opposite sign on the same pendant groups (Figure 1).^[1,2] By virtue of their high content of ionic groups but overall charge neutrality, zwitterionic polymers exhibit a unique property profile that combines many features of both ionic and nonionic polymers, which results, for example, in high hydrophilicity and high biocompatibility for many of the known

polyzwitterions.^[3,4] This has raised interest in this polymer class for biomimetic materials, such as artificial lipid membranes, medical nano carriers, or non-immunogenic and hemocompatible surfaces.^[5–14] Further, the growing concern about the toxic side effects of established antifouling coatings that contain biocides, has recently stimulated the study of zwitterionic polymers for uses in alternative, nontoxic low-fouling systems.^[9,15–21] Three families of zwitterionic moieties are prominent up to now in polymers, namely the combinations of the quaternary ammonium group with the sulfonate group (ammoniosulfonates, sulfobetaines), with the carboxylate group (ammoniocarboxylates, carboxybetaines), and with the phosphate group (ammonio-phosphates).^[2–4] While sulfobetaines are the most stable groups among these zwitterions,^[22,23] ammoniophosphates represent the most widespread zwitterion family in nature. They subsume the phospholipids, in particular, the phosphatidylcholines that are major constituents of the cell membrane, and which inherently must exhibit low-fouling behavior.^[5,24]

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In the phospholipids, and in their by far most used polymeric analogue poly(2-methacryloyloxyethyl phosphorylcholine) (frequently referred to as “poly(phosphatidylcholine methacrylate)”, PMPC),^[11,12,25–27] the zwitterionic group is anchored to the membrane surface, or to the polymer backbone, respectively, in an oriented way via the phosphate group. Hence, the anionic group

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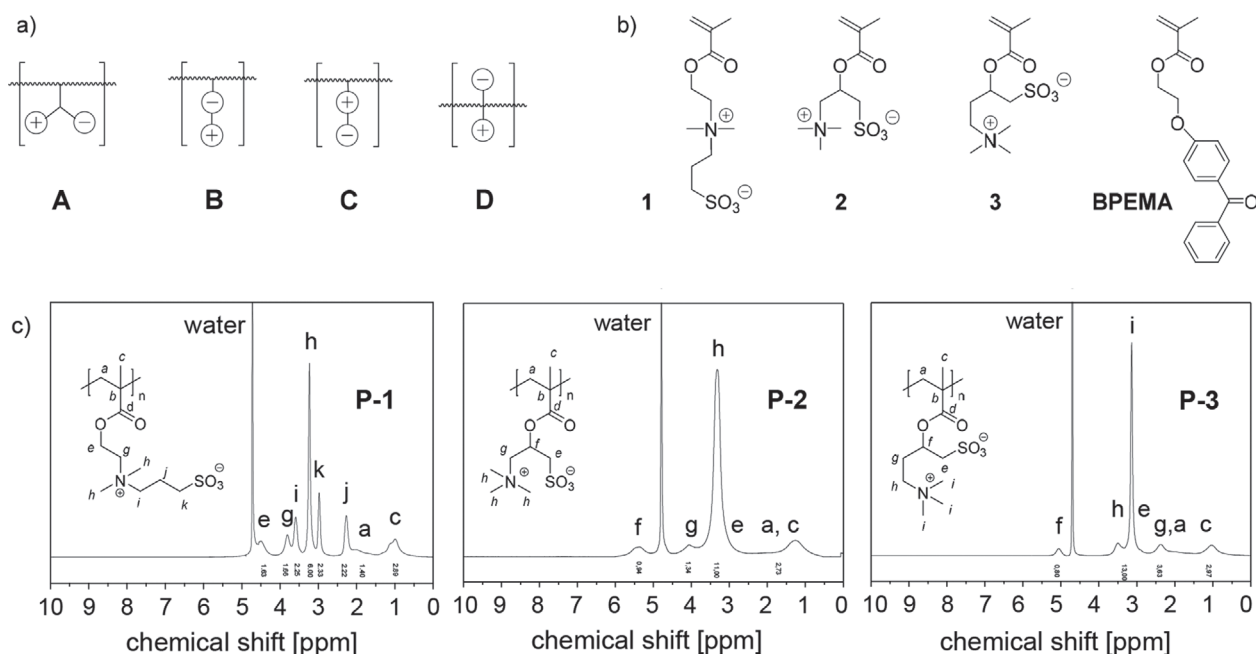


Figure 1. a) Examples of different polyzwitterion architectures; b) chemical structure of the sulfobetaine monomers and the photo-reactive comonomer used; c) ^1H NMR spectra of homopolymers P-1 to P-3 in water.

is placed closer to the polymer backbone than the cationic one (Figure 1a, architecture B). Possible interfacial and biological effects of the zwitterions' segmental dipole orientation imposed by the chemical binding have been subject of recent discussions.^[28–32] In these reports, PMPC analogues with a reverse segmental orientation of the zwitterion dipoles have been investigated. In such polymers, the polymerizable group is attached via the cationic group of the zwitterion moiety, and consequently, the cationic group is placed closer to the membrane surface (or the polymer backbone) than the anionic one (Figure 1a, architecture C). Prominent differences of these so-called choline phosphates compared to the behavior of the analogous polyphosphatidylcholines (as PMPC) were reported, for example, strong attractive interactions with red blood cells, or improved separation capabilities when used in chromatographic stationary phases.^[28,32–36] Still, the few reports differ considerably concerning the extent of the observed effects.^[37,38] Conversely, as interactions with dissolved material and surfaces are seemingly weaker, these reports suggest that the particular segmental dipole orientation of the ammoniophosphate moieties in PMPC^[24] of type B is advantageous for low-fouling behavior.

Not only coatings made of polyphosphatidylcholines, but also those made of polycarboxybetaines and polysulfobetaines, which are particularly resistant to hydrolysis, have been used with good success in low-fouling coatings.^[12,19,39–41] However, virtually all of these studies have employed polyzwitterion architectures in which the segmental dipole orientation of the zwitterionic moieties correspond to the architecture type C in Figure 1a.^[12] Major representatives of such polymers are derived from the commercially available monomer **1** (*N*-(2-methacryloyloxyethyl)-*N,N*-dimethylammoniumpropanesulfonate), often referred to as SPE or as “sulfobetaine methacrylate” (SBMA) (see Figure 1b).^[40–44] Following the reasoning above, we hypothesized that polysul-

fobetaines and polycarboxybetaines with an altered segmental dipole orientation might be even more effective in reducing fouling than the currently used representatives of these polymer classes of architecture C. As the acidity of the carboxyl group is sensitive to the precise chemical structure of the spacer separating the ammonium and the carboxyl groups (possibly interfering with the charge neutrality of the carboxybetaine moiety in the ambient pH window, and thus rendering interpretation of experimental findings ambiguous),^[2] we selected sulfobetaine polymers for model studies to test the hypothesis. Hence, we synthesized the novel sulfobetaine methacrylates **2** and **3** (Figure 1b) and their polymers P-2 and P-3. They are designed as structural (quasi) isomers of the established polymer P-1 (“P-SPE”) of architecture C, representing polyzwitterion architectures A and B, respectively (Figure 1a).^[2] Moreover, the very short spacer groups separating the bulky zwitterionic moieties from the sterically already crowded polymethacrylate backbone limit conformational adaptations that might try to reorient the zwitterions relative to the backbone. We employed them for the preparation of thin photo-crosslinkable hydrogel films, and explored their fouling resistance against model proteins and model marine organisms in comparison to the behavior of identically prepared films of P-1 that served as reference.

The focus on polycarboxybetaines and polysulfobetaines of architecture type C in the past can be attributed to constraints in the synthesis of these polyzwitterion families. Most conveniently, such compounds are prepared by ring-opening alkylation of polymerizable tertiary amines by cyclic esters of the underlying acids as precursors for the anionic sites.^[2,3] As zwitterions are notoriously fastidious with respect to useful solvents, this strategy simplifies not only the search for suitable reaction media, but also offers a facile separation of the zwitterionic products from the uncharged intermediates and reagents. Fur-

thermore, the formation of inorganic salts as byproducts that are often difficult to remove quantitatively is avoided.^[45] Yet, carboxylate and sulfonate groups can bear only one functional substituent, while the phosphate group can bear two. Accordingly, alkylation by lactones and sultones can only produce architecture C, whereas cyclic phosphates allow a priori for the synthesis of architectures B and C.^[2] Therefore, we developed an alternative, versatile synthetic strategy toward methacrylic monomers of diverse architectures such as **2** and **3**, which converts halogenated sulfonates into zwitterionic alcohols, which are esterified with methacrylic acid in trifluoroacetic acid as reaction medium to yield the monomers (see Supporting Information for details). A related strategy had been described by Kratzer et al., though addressing exclusively type C polyzwitterion architectures.^[46] The analytical data (including elemental analysis, mass spectrometry, infrared spectroscopy, ¹H NMR and ¹³C NMR spectroscopy, see Supporting Information) confirmed the successful synthesis and the purity of monomers **2** and **3**.

Homogeneous solution (co)polymerization of **1** to **3**, optionally with comonomer **BP**EMA (Figure 1b) in trifluoroethanol produced homopolymers **P-1** to **P-3** and the photoreactive copolymers **Px1** to **Px3**, typically in high yields (about 80% after purification). Table 1 summarizes key data of these polyzwitterions. The comonomer contents in the copolymers of about 1 mol% correspond to the compositions of the comonomer feed within the precision of analysis. All three monomers polymerized smoothly irrespective of their architecture type, yielding relatively high number average molar masses M_n in the range of 100–200 kg mol⁻¹. Dispersities \mathcal{D} are between 2.2 and 5.4, as could be expected for standard free radical polymerization conducted to high conversions. Thermogravimetric analysis (TGA) indicates decomposition above 250 °C, while differential scanning calorimetry (DSC) did not show a glass transition of the dry polymers before thermal degradation starts, in agreement with most reports on polysulfobetaines.^[45,47,48] All polymers dissolve readily in trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP). Noteworthy, both **P-2** to **P-3** are soluble in pure water at all temperatures, whereas the phase diagram of **P-1** features a miscibility gap with an elevated upper critical solution temperature, the cloud point (Table 1) depending

sensitively on the molar mass.^[49–52] As all three polymers are subject to an effective salting-in behavior that is characteristic for polysulfobetaines,^[49,51,53–56] all were soluble in aqueous salt solutions, for example, in physiological saline (0.14 M aq NaCl), phosphate buffered saline (PBS), or artificial sea water, as employed in our model fouling studies.

Hydrogel films of about 100 nm thickness were obtained by spin-casting of the respective polymers from trifluoroethanol solutions on glass, quartz, or gold supports pretreated with an organic monolayer, and subsequent UV-irradiation (Figure 2), as described recently.^[44,52] Previous studies on other zwitterionic polymethacrylates showed that for the high molar masses used, incorporation of 1 mol% of **BP**EMA is sufficient to enable effective photo-crosslinking, yielding stable thin hydrogel films (Figure 2b).^[44,52] These are internally crosslinked and simultaneously covalently anchored to the solid substrate exploiting the characteristic photochemistry of benzophenone (C,H-insertion crosslinking “CHiC”),^[57–59] thus avoiding the incorporation of two different reactive groups into the polymers for crosslinking and fixing the coatings, respectively.^[60,61] Photo-crosslinked films of poly(butylmethacrylate) **PxBMA** of comparable thickness were prepared following an analogous protocol.^[52] They served as the second reference, representing a model surface with low resistance against fouling,^[62] due to their hydrophobic character as indicated by a static water–air contact angle higher than the so-called “Berg limit” (Figure 2c).^[63,64] In contrast, all polysulfobetaine films were strongly hydrophilic, exhibiting low contact angles in the range of 15–25°, in good agreement with previous studies on related polyzwitterions.^[44,52] Atomic force microscopy (AFM) studies also revealed that the spin-cast polyzwitterion films were very smooth (root mean squared (RMS) roughness of about 0.25 nm). Spin-cast **PxBMA** films were much rougher with an RMS value of ≈7 nm when TFE was used as common solvent, due to the rather low solvent quality for **PBMA**.^[44] However, when spin-cast from the good solvent ethyl acetate, **PxBMA** films were also very smooth (RMS ≈0.33 nm)^[52]; such films were used for protein adsorption experiments using fluorescence detection.

Previous studies have shown that the fouling behavior of a given system depends not only on the nature of the surface attacked, but also on the attacking fouling species.^[12,44] Therefore, we used in our exploratory study several different foulants, such as positively charged (lysozyme), negatively charged (BSA), and approximately neutral (fibrinogen) model proteins, as well as passively (diatoms) and actively (barnacle cyprids) settling marine fouling organisms. Figure 3 summarizes the results of the various fouling experiments.

Protein adsorption was studied by two analytical methods, surface plasmon resonance (SPR) for virgin model proteins (Figure 3a), and quantitative fluorescence microscopy for fluorophore-labeled proteins (Figure 3b). While SPR enables the direct comparison of the irreversibly adsorbed amounts of the various proteins, the use of the absolute fluorescence intensities for comparing the adsorbed amounts of the various proteins is not straightforward as intensities may depend on the protein samples studied (e.g., due to different degrees of labeling). Also, for both methods, the response is not necessarily linear (e.g., if more than a monolayer is adsorbed in SPR experiments, or if quenching, self-quenching or photobleaching of the fluorescence signal occurs). Therefore, depending on the

Table 1. Key parameters of the homo- and copolymers investigated.

Polymer	Content of BP EMA [mol %] ^{a)}	M_n^{app} [kg mol ⁻¹] ^{b)}	Dispersity \mathcal{D} ^{b)}	T_{decomp} [°C] ^{c)}	CP [°C] ^{d)}
P-1	–	210	2.2	260	>50
Px1	1.1 ± 0.5	90	5.4		n.d. ^{e)}
P-2	–	140	2.5	250	<0
Px2	0.9 ± 0.5	110	3.9		<0
P-3	–	140	4.4	250	<0
Px3	1.5 ± 0.5	140	3.4		<0
PxBMA	1.3 ± 0.5	50	2.8		–

^{a)}By integration of ¹H NMR signals; ^{b)}Apparent number average molar mass M_n^{app} and dispersity \mathcal{D} ($M_w^{\text{app}} / M_n^{\text{app}}$) by SEC, eluent HFIP containing 50 mM of CF₃COONa, calibration with linear poly(methyl methacrylate) PMMA standards; ^{c)}Onset by TGA in nitrogen atmosphere, heating rate 10 K min⁻¹; ^{d)}Cloud point (upper critical solution temperature type) in water, cooling run, concentration 3 g L⁻¹; ^{e)}Not determined, sample is insoluble in pure water at ambient temperature.

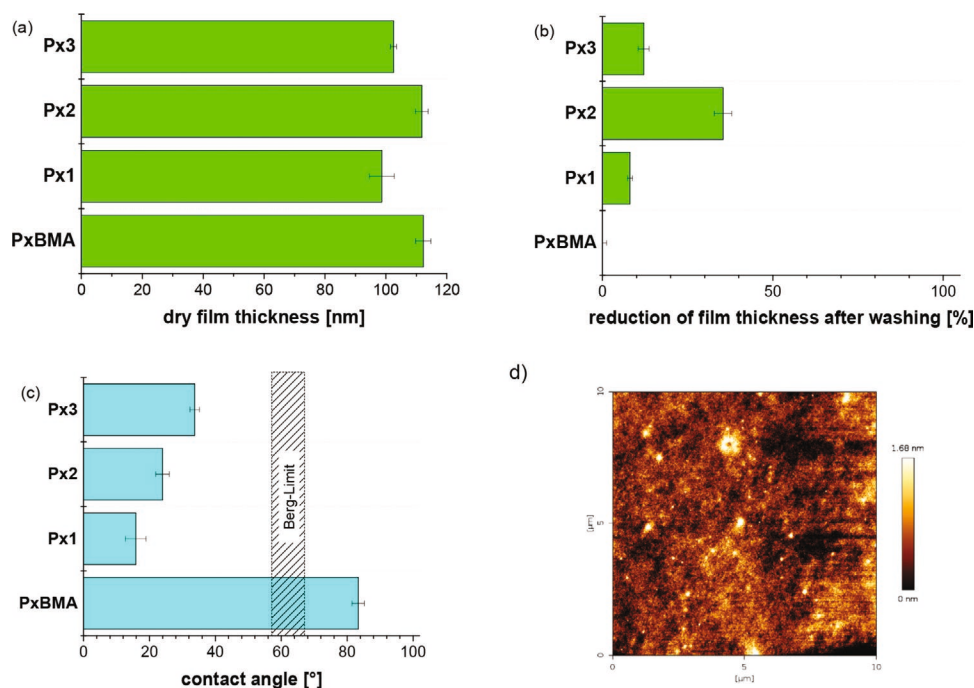


Figure 2. a) Ellipsometric thickness of typical coatings obtained from copolymers **Px1** to **Px3** and reference **PxBMA** after photo-crosslinking; b) typical relative losses of coating thicknesses after the washing procedure, as studied by ellipsometry; c) static water–air contact angles of typical coatings, the cross-hatched bar indicating the zone of the Berg-limit; d) representative AFM image of a polyelectrolyte hydrogel coating (**Px3**), of about 100 nm thickness with RMS roughness of 0.25 nm.

specific case, the quantitative comparison of SPR and fluorescence data may be complicated, but importantly, the data from the two measurements can be qualitatively correlated in any case. As a general picture, it emerges that all polyelectrolyte films reduce protein fouling effectively compared to the reference **PxBMA**. In fact, the strong adsorption on the reference likely results in self-quenching of the labels, and thus in an underestimation of the relative antifouling effects of the polyelectrolyte films by fluorescence microscopy. The protein-repellent capability increases in the order lysozyme < BSA < fibrinogen. The comparatively lower fouling resistance of polysulfobetaine coatings against the polycation lysozyme confirms previous reports.^[44,65] Comparing the polyelectrolyte films with each other, we find improved fouling resistance in the order **Px3** < **Px2** ≤ **Px1**. The stronger antifouling performance of **Px1** is particularly notable for BSA and fibrinogen.

Fouling experiments involving laboratory assays with typical marine organisms, the diatom *Navicula perminuta* (Figure 3c) and cyprids of the barnacle *Balanus improvisus* (Figure 3d), provide a somewhat modified picture. As in the case of the proteins, all polyelectrolyte films reduced the attachment of diatoms and the settlement of barnacle cyprids statistically significantly ($p < 0.05$) compared to the reference **PxBMA**. When comparing the polyelectrolyte films with each other, we note the very similar, excellent performance of the three polysulfobetaines in resisting diatom attachment. In the case of the barnacle cyprids (six settlement runs, each with ten cyprids), only an average of 7% cyprids settled on films of **Px2**, while films of **Px1** and **Px3** completely inhibited the settlement. An independent repeat of the assay confirmed the observed trends.

Still, the small differences observed in the—compared to **PxBMA**—markedly impaired cyprid settlement on the different polyelectrolyte coatings are not statistically significant ($p < 0.05$). In fact, the analysis of settlement data for highly fouling-resistant surfaces in order to reveal rather subtle differences is challenging and currently under investigation.^[21,66]

The diversified picture concerning the antifouling performance corroborates previous investigations on this set of model foulants in many aspects: polysulfobetaines in general seem to provide good fouling protection, cationic proteins as foulant species seem to be more problematic than neutral or anionic ones, and no universal champion can be identified that outperforms all other polymers. Clearly, the relative antifouling performance is sensitive to the precise combination of the foulant species and the polyelectrolyte used. In particular, our study suggests that in addition to the previously shown structural variables, such as the nature of the zwitterionic group (e.g., sulfobetaine, carboxybetaine, or phosphatidylcholine), the spacer group separating the cationic and the anionic sites within the zwitterionic moiety, the substitution pattern of the ammonium group, and the polymer backbone,^[12] the segmental orientation of the zwitterionic moiety relative to the polymer backbone (see Figure 1a,b) is also an important parameter affecting fouling.

Possibly, the particularly high resistance of **Px1** against the overall negatively charged proteins BSA and fibrinogen profits from such a segmental orientation effect, as statistically, the anionic sulfonate groups could be overrepresented at the interface for the architecture type C. Such an orientation effect could provoke a charge selective repulsion as found in SAMs made of non-stoichiometric mixtures of cationic and anionic thiols^[67,68]; while

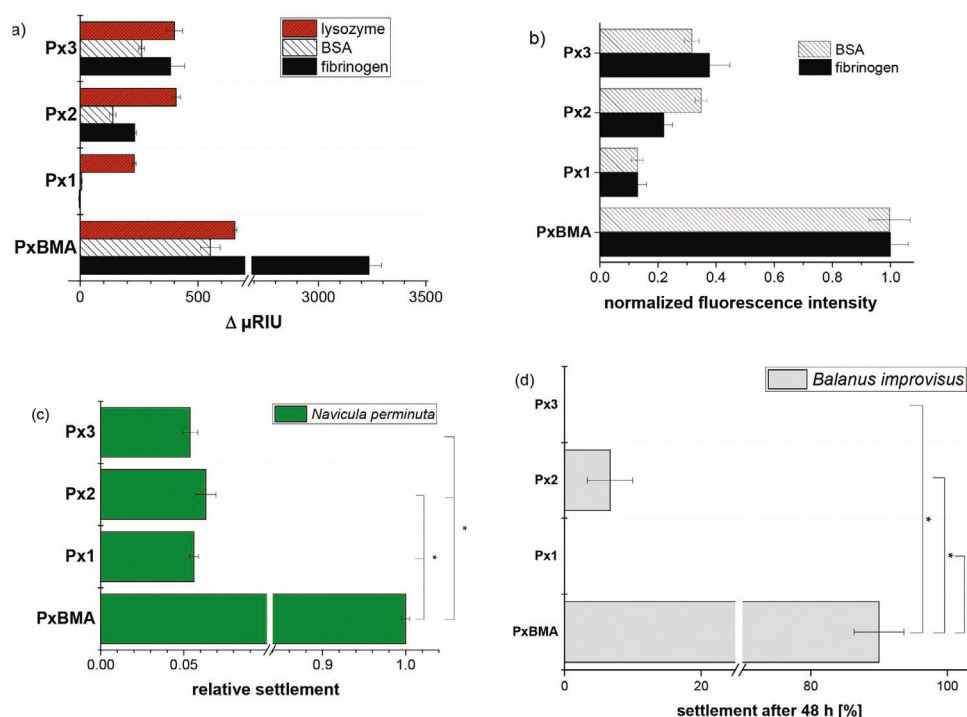


Figure 3. Fouling resistance of the polymer coatings against the adsorption of model proteins and model marine organisms: a) non-specific adsorption of proteins lysozyme (red bars), bovine serum albumin (BSA) (hatched bars), and fibrinogen (black bars) as followed by surface plasmon resonance (SPR), the error bars are the standard error ($n = 3$); b) fluorophore-labeled proteins bovine serum albumin (BSA) (hatched bars) and fibrinogen (black bars) as followed by the integrated fluorescence intensity, the error bars are the standard error ($n = 18$); c) relative attachment of the diatom *Navicula perminuta* after 90 min dynamic attachment assay. The reported values are the average of three replicates. The error bars are the standard error (data represent the average of 30 fields of view on $n = 3$ replicates per chemistry). Brackets indicate statistically significant differences ($p < 0.05$, *); d) settlement of cyprids of the barnacle *Balanus improvisus* after 48 h of exposure. The reported values are the average of six replicate slides, error bars are the standard error ($n = 6$). Brackets indicate statistically significant differences ($p < 0.05$, *).

electrostatic repulsion helps to minimize the unspecific adsorption of the negatively charged proteins BSA and fibrinogen, the positively charged protein lysozyme faces some electrostatic attractive force by the surface, thus reducing the antifouling effect of Px1 films. Yet, this simplistic picture might correctly catch only one molecular aspect contributing to effective protein repulsion, as it cannot describe the complete situation. Namely, this explanation would imply that conversely, lysozyme adsorption on Px3 and Px2 should be reduced compared to Px1, which is obviously not true (see Figure 3a,b). Conformational adaptations of the zwitterionic side chains that alter the relative positions of the cationic and anionic groups, for instance, and which are for Px1 the least restricted by steric requirements, might contribute to the effect. In any case, it becomes clear that the “natural” polyzwitterion architecture of type B, as present in phospholipids, is not necessarily superior to others,^[31] such as of types A or C. In fact, among the triple of poly(sulfobetaine methacrylate)s studied, coatings of the established representative Px1 (“PSPE”), which represents architecture type C, are overall the most efficacious against the five proteins and model fouling organisms tested.

Summarizing, we synthesized two novel poly(sulfobetaine methacrylate)s with a different segmental orientation of the zwitterionic moiety toward the polymer backbone than the polysulfobetaines reported so far. Together with the established polysulfobetaine methacrylate PSPE (“PSBMA”), they form a quasi-isomeric set of polymers of differing polyzwitterion archi-

tectures. Functionalization by small amounts of benzophenone as photo-crosslinker groups enables the preparation of thin, homogeneous, and smooth stable hydrogel coatings via C,H-insertion crosslinking. Orienting studies reveal that these polyzwitterion films feature highly effective low-fouling characteristics in laboratory assays against a wide range of foulants, including differently charged proteins as well as marine organisms representing passive and active foulers. Importantly, our study demonstrates that the antifouling effects of the particular polyzwitterion architecture that is characteristic for polyphosphatidylcholine methacrylate (PMPC), and which is often assumed to be the most biomimicking representative of polybetaines, is a priori not superior to the other polyzwitterion architectures. Moreover, no universal champion, outperforming all other polyzwitterions, can be identified, as the relative antifouling performance depends on the precise combination of the foulant species involved and the polyzwitterion employed.

Experimental Section

The material and equipment used are specified in the Supporting Information, as are synthetic and analytical details of the new sulfobetaine monomers 2 and 3. Homo- and copolymerizations followed established procedures; details are summarized in Table S1, Supporting Information. The synthesis of comonomer 2-(4-benzoylphenoxy)ethyl methacrylate (BPMEA) was reported before,^[69] as were the syntheses

of the reference polymers P-1, Px1, and PxBMA.^[44,52] The equipment and procedures employed for fabricating the polymer coatings and their photo-crosslinking were described in detail previously,^[52,70,71] as well as the setups and conditions for the protein adsorption^[44,52] and the fouling experiments with the marine organisms.^[44,72]

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

antifouling, coatings, crosslinking, hydrophilic polymers, polyzwitterions

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