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Protected Poly(3-sulfopropyl methacrylate) Copolymers: Synthesis, Stability, and Orthogonal Deprotection

Anton H. Hofman,* Matteo Pedone, and Marleen Kamperman

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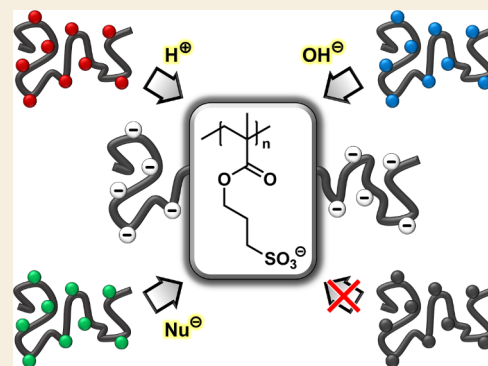
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Supporting Information

ABSTRACT: Because of their permanent charge, strong polyelectrolytes remain challenging to characterize, in particular, when they are combined with hydrophobic features. For this reason, they are typically prepared through a postmodification of a fully hydrophobic precursor. Unfortunately, these routes often result in an incomplete functionalization or otherwise require harsh reaction conditions, thus limiting their applicability. To overcome these problems, in this work a strategy is presented that facilitates the preparation of well-defined strong polyanions by starting from protected 3-sulfopropyl methacrylate monomers. Depending on the chemistry of the protecting group, the hydrophobic precursor could be quantitatively converted into a strong polyanion under nucleophilic, acidic, or basic conditions. As a proof of concept, orthogonally protected diblock copolymers were synthesized, selectively deprotected, and allowed to self-assemble in aqueous solution. Further conversion into a fully water-soluble polyanion was achieved by deprotecting the second block as well.

KEYWORDS: polyelectrolytes, strong polyanions, protection chemistry, RAFT polymerization, block copolymers, solution self-assembly



1. INTRODUCTION

Polyelectrolytes are macromolecules that carry ionic groups in their repeating unit, which renders them soluble in water and a limited number of polar organic solvents.¹ Typical applications of these charged polymeric materials include their use in ultrafiltration membranes,^{2,3} stabilizing agents,^{4–6} underwater adhesives,^{7–9} hydrogels,¹⁰ antifouling coatings,^{11–13} and food packaging.¹⁴ Enhanced properties can often be achieved when the polymer of interest is combined with an oppositely charged species or a hydrophobic component, thereby resulting in a polyelectrolyte complex^{15,16} or an amphiphilic copolymer,¹⁷ respectively.

Regardless of being positively or negatively charged, two types of polyelectrolytes should be distinguished: weak and strong polyelectrolytes.¹⁸ In the case of a weak polyelectrolyte, the charge density is pH-dependent, as protonation/deprotonation is directed by the pK_a of the chargeable group. Most weak polyelectrolytes are based on carboxyl (anionic)¹⁹ or amine (cationic)²⁰ functional groups. While the weak ionic nature is a significant advantage for both the synthesis, analysis, and processing, as a neutral organo-soluble polymer can be obtained under the right conditions, the applicable pH range of weak polyelectrolytes is limited if a high charge density is desired. Since they are permanently charged, strong polyelectrolytes do not suffer this pH-related problem. However, the characterization of them remains challenging for exactly the same reason, in particular, when they are combined with a

hydrophobic building block due to the nonexistence of a common solvent.^{21–24}

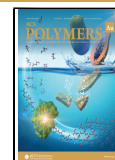
To overcome this solubility issue, the strong ionic functionality is usually introduced via postmodification of a neutral precursor, for instance, by quaternization of an amine²⁵ or vinyl pyridine,²⁶ or sulfonation of a styrene-based copolymer,²⁷ resulting in a strong polycation or polyanion, respectively. Disadvantages of these methods are that they often give incomplete functionalization^{28,29} or otherwise require harsh reaction conditions,^{30,31} thus potentially harming the hydrophobic component or the end groups of the polymer. This remains a particular challenge for sulfonate-based strong polyanions. For such sulfonates, work-arounds have been reported where the inorganic counterion was replaced by a bulky quaternary ammonium salt, which renders the polyelectrolyte more soluble in polar organic solvents.^{32,33} Disadvantages of this approach, however, remain similar to the directly synthesized strong anionic/hydrophobic copolymers, as the choice of the hydrophobic component is still limited, and the molecular weight characterization of charged species remains challenging.

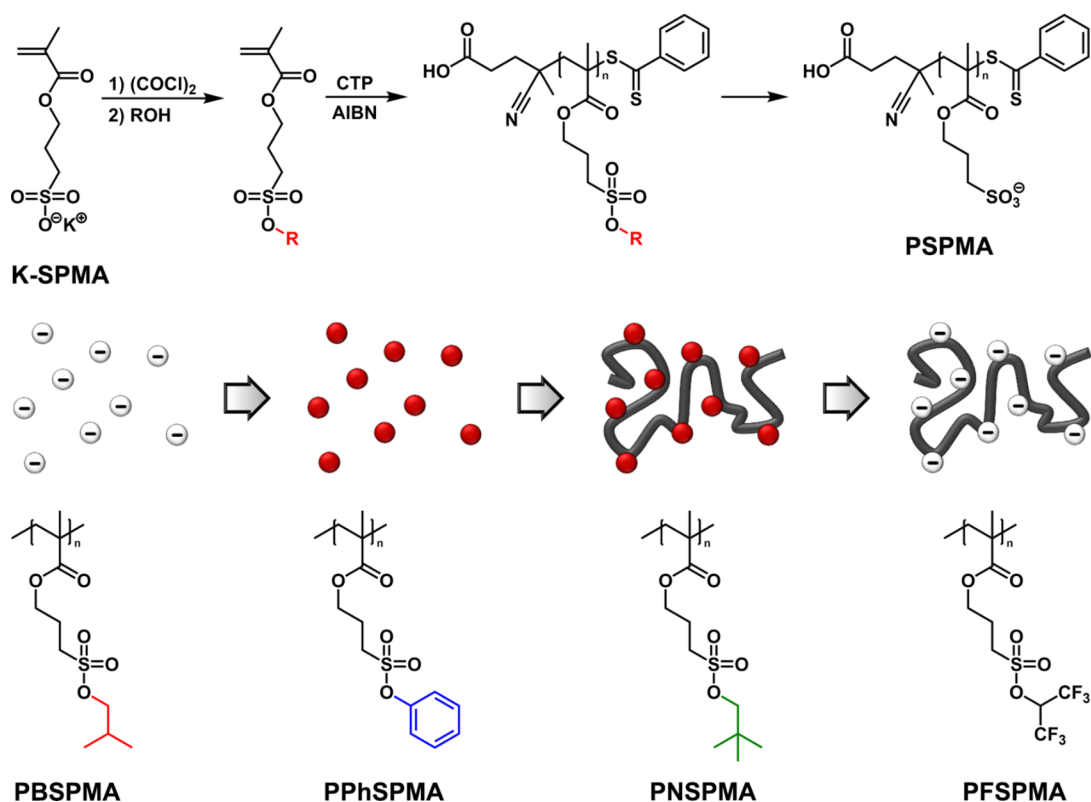
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Scheme 1. General Reaction Scheme and Schematic Illustration Describing the Strategy for the Synthesis and Deprotection of the Hydrophobic Polymeric Precursors^a

^aDepending on the deprotecting conditions, the strong polyanion (PSPMA) is obtained as either the sulfonate salt or sulfonic acid. This work describes four different protecting groups (R = isobutyl, phenyl, neopentyl, and HFIP), resulting in PBSPMA, PPhSPMA, PNSPMA, and PFSPMA after polymerization, respectively.

Table 1. Polymerization Conditions for the Synthesis of Protected Homopolymers by RAFT^a

polymer	[CTA]	[AIBN]	[AIBN]/[CTA]	[M]	<i>t_r</i> (h)	conv (%)	<i>M_{n,calc}</i>	<i>M_{n,GPC}</i>	Đ
PBSPMA-1	42.1	1.30	1/32.2	1.77	21	77	8.82	14.7	1.15
PBSPMA-2	13.5	1.26	1/10.7	1.52	20	92	27.7	40.4	1.11
PBSPMA-3	7.0	0.84	1/8.3	1.82	21	92	63.7	85.6	1.27
PBSPMA-4	3.8	0.71	1/5.3	1.89	22	83	110.3	142.7	1.38
PPhSPMA-1	14.3	1.45	1/9.9	1.48	22	93	27.7	21.6	1.13
PPhSPMA-2	7.9	0.90	1/8.8	1.88	22	82	55.7	53.2	1.19
PFSPMA-1	18.1	1.82	1/10.0	1.46	22	93	27.2	28.0	1.10
PNSPMA-1	15.8	1.51	1/10.4	1.52	20	80	21.6	19.7	1.12

^aConcentrations of CTA and AIBN are in units of mM, and monomer [M] is in units of M. Molecular weights are reported in units of kg mol⁻¹, and the calculated molecular weight (*M_{n,calc}*) is based on the initial concentrations and monomer conversion. GPC-measured molecular weights (*M_{n,GPC}*) are reported as PMMA equivalents.

A more elegant route toward well-defined polyelectrolytes is the use of protection chemistry. While being the method of choice for weak poly(acrylic acid)-based systems through the hydrolysis of poly(*tert*-butyl acrylate) using trifluoroacetic acid³⁴ or hydrochloric acid,^{35,36} such an approach remains very uncommon for strong sulfonate-based polyanions. Only a few examples have been reported in the literature, all of which involve a neopentyl-protected styrene sulfonate.^{37,38} Because of the low reactivity of this monomer, however, the applicability of this precursor is unfortunately limited to low molecular weight materials,^{39,40} while its deprotection is often achieved via an uncontrolled thermolysis.^{41,42} Since this thermal treatment generates the sulfonic acid analogue, which is

accompanied by a local pH decrease, it may potentially damage the hydrophobic segment and/or end groups.

As an alternative, in earlier work we designed an improved system that is based on isobutyl-protected 3-sulfopropyl methacrylate (SPMA). Using Reversible Addition–Fragmentation chain Transfer (RAFT) polymerization, we managed to obtain high molecular weight precursors that could be deprotected quantitatively under very mild conditions.⁴³ Amphiphilic strong anionic/hydrophobic diblock copolymers that readily self-assembled in aqueous solution could be prepared with great precision. It may, however, be desired that the protected poly(3-sulfopropyl methacrylate) (PSPMA) hydrophobic precursor remains intact under these conditions or that the protecting group can be cleaved under other

conditions, for instance, in an acidic or alkaline environment. Inspired by the work of Miller and co-workers on small molecules,^{44,45} we here report three more variants of the protected PSPMAs. The stability of all protecting groups was assessed under weak nucleophilic, strong nucleophilic, acidic, and basic conditions. By choosing the right combination, orthogonal deprotection (i.e., selective deprotection) can be achieved when two different monomers are combined in a single macromolecule. As a proof of concept, three diblock copolymers were synthesized, selectively deprotected, and allowed to self-assemble in aqueous solution. Finally, a strong polyanion with a doubled molecular weight could be obtained by cleaving the protecting group of the second block as well.

2. RESULTS AND DISCUSSION

2.1. Monomer Synthesis

Protected 3-sulfopropyl methacrylate monomers were synthesized via the same two-step, one-pot procedure as reported previously (Scheme 1).⁴³ First the potassium salt of 3-sulfopropyl methacrylate (K-SPMA) was dispersed in *N,N*-dimethylformamide (DMF) and activated using oxalyl chloride. Anhydrous DMF is required in this first step, as residual water will interfere with the formation of the catalytic Vilsmeier reagent. Furthermore, we note that the sulfonyl chloride intermediate is prone to hydrolysis and cannot be isolated. Next, an esterification of the sulfonate can be achieved by a slow addition of the sulfonyl chloride to an alcohol/triethylamine solution. An extraction was performed with diethyl ether (instead of, e.g., dichloromethane) to reduce the uptake of DMF, while compared to our earlier work, a final water wash was introduced to remove the unavoidable traces of DMF. Experimental details are provided in the Supporting Information.

Besides isobutanol (giving 3-(isobutoxysulfonyl)propyl methacrylate; BSPMA), three other protecting groups were introduced from their corresponding alcohols: phenyl (3-(phenoxysulfonyl)propyl methacrylate; PhSPMA), neopentyl (3-((neopentyl)oxy)sulfonyl)propyl methacrylate; NSPMA), and hexafluoro-2-propanol (3-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)sulfonyl)propyl methacrylate; FSPMA). All four monomers were obtained in a high yield and high purity after silica gel column chromatography. ¹H NMR and ¹³C NMR spectra can be found in the Supporting Information (Figures S1–S4). This procedure is not limited to the four alcohols described here, as long as it is stable during workup and polymerization. An ethyl protecting group, for instance, could be introduced without any problems, but turned out to be partially cleaved during polymerization.

2.2. RAFT Polymerization

The purified monomers were polymerized by RAFT polymerization. 4-Cyano-4-(thiobenzoylthio)pentanoic acid (CTP) was employed as the chain transfer agent (CTA), as dithiobenzoates are known to provide better control over the polymerization of methacrylates as compared to trithiocarbonates (Scheme 1).⁴⁶ Irrespective of the monomer, conversions typically reached values of over 80% based on an NMR analysis of aliquots withdrawn from the reaction mixture. Precipitation was always performed in pentane/ethanol mixtures in order to remove DMF and unreacted monomer (both DMF and monomers are not miscible with pentane).

¹H NMR spectra of the purified protected homopolymers are given in the Supporting Information (Figures S5 and S6). The successful polymerization is evidenced by the disappearance of the vinyl protons, and in addition, some broadening of the other signals was observed as well. Interestingly, the protecting groups always gave sharp peaks, and their splitting patterns are well-separated, which is likely caused by the higher flexibility of the side chains.

PBSPMA homopolymers of varying molecular weight were synthesized by adjusting the BSPMA/CTA ratio and ranged from 15 kg mol⁻¹ up to as high as 143 kg mol⁻¹ (Table 1). Here the molecular weights as estimated by gel permeation chromatography (GPC) are reported as poly(methyl methacrylate) (PMMA) equivalents (i.e., via conventional calibration), which explains the deviation compared to the theoretical molecular weights and is most prominent for the isobutyl-protected homopolymers. *M_n* values were calculated by other methods as well (universal calibration and light scattering) but typically resulted in a significant overestimation (Table S1).^{47,48} A more detailed discussion of the GPC data is provided in the Supporting Information.

On the one hand, as expected, better control was maintained compared to the trithiocarbonate CTA that we employed in our previous work, as for most experiments the molecular weight distribution (*Đ*) was demonstrated to adopt a value below 1.2. Conversions, on the other hand, were often slightly lower, in particular, for the lower molecular weight homopolymers (e.g., PBSPMA-1), possibly due to the retardation effect,⁴⁹ even though this was initially compensated for by starting from a higher monomer and AIBN concentration. Similar results were obtained for the other monomers (PhSPMA, NSPMA, and FSPMA), although a library of different molecular weight materials was not created. However, on the basis of their successful polymerization, there is no reason to assume that both higher and lower molecular weight homopolymers could not be prepared. Only the polymerization of NSPMA resulted in a slightly lower conversion (80% vs 90+%), which may be caused by the monomer itself (it simultaneously acts as solvent) or a minor impurity.

3. THERMAL PROPERTIES

A thermogravimetric analysis (TGA) was performed to assess the stability of the polymers and their protecting groups (Figure S7a). PBSPMA and PNSPMA displayed a different thermal behavior compared to that of PPhSPMA and PFSPMA. On closer inspection of the degradation profiles (Figure S7b), it can be seen that ~20% of the mass of both the isobutyl- and neopentyl-protected polymers was lost near 200 °C and continued to degrade until a stable remaining weight of 30% was reached at ~300 °C before being fully degraded when heated further. Such a stepwise process indicates cleavage of the protecting groups and a sequential acid-catalyzed hydrolysis of the methacrylic ester group by the released sulfonic acid functionality. The remaining weight of ~30% matches the structure of poly(methacrylic acid) remarkably well. PPhSPMA and PFSPMA do not show such behavior: only a minor weight loss (<10%) was observed above 200 °C, before being fully degraded on reaching a temperature of 350 °C. Thus, for these polymers the bonds between the monomer units are presumably less stable than the bonds within the side groups, including the protecting groups. To see whether the rate of the TGA experiment had any effect, the measurement

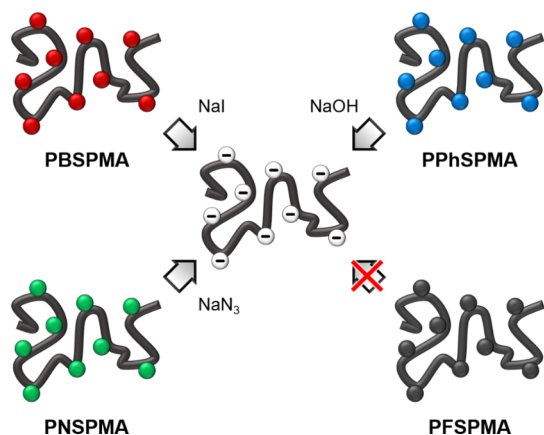
was also performed at a lower heating rate (2 vs 10 °C min⁻¹). The shapes of the profiles were identical; degradation of the polymers was only delayed when the heating was done faster (Figure S8). We therefore expect that it will only be possible to cleave the protecting groups of PBSPMA and PNSPMA thermally (e.g., at ~150 °C),^{41,43} although this method is not recommended, as it may result in an uncontrolled and incomplete conversion into PSPMA.

The glass transition temperature (T_g) was determined by differential scanning calorimetry (DSC) in the modulated mode (Figure S7c) and varied between 19 and 40 °C: PBSPMA ($T_g = 19$ °C), PPhSPMA ($T_g = 27$ °C), PFSPMA ($T_g = 38$ °C), and PNSPMA ($T_g = 40$ °C). The small differences are difficult to address, as it is a combination of inter- and intramolecular interactions, polarity of the protecting group, polymer rigidity, and the free volume. Since the glass transitions of PPhSPMA, PFSPMA, and PNSPMA are just above room temperature (hard solids), these polymers are easier to work with than PBPMMA (soft solid).

4. DEPROTECTION

In this section the stability of all four protected poly(3-sulfopropyl methacrylates), under either weak nucleophilic,

Scheme 2. Schematic Description of the Deprotection of Isobutyl-Protected (PBSPMA), Neopentyl-Protected (PNSPMA), Phenyl-Protected (PPhSPMA), and Hexafluoroisopropyl-Protected (PFSPMA) Poly(3-sulfopropyl methacrylates)



strong nucleophilic, basic, or acidic conditions, will be discussed (Scheme 2). Although the general procedures are inspired by the work of Miller and co-workers,⁴⁴ who studied the stability of protected dansylates, some optimization was required, because (1) ideally the polymer should remain in solution throughout the reaction, (2) quantitative deprotection should be achieved, and (3) side reactions should be suppressed. Sodium iodide (NaI) was employed as a weak nucleophile (in dimethyl sulfoxide (DMSO) at 70 °C), sodium azide (NaN₃) as a strong nucleophile (in DMSO at 100 °C), sodium hydroxide as a base (in methanol/DMSO at room temperature), and aqueous hydrobromic acid (HBr) as an acid (in dioxane at 100 °C). In case no side reactions occurred, the polymer remained soluble (NaI, NaN₃, and NaOH treatment) or became soluble upon deprotection (HBr treatment). The combination of having a homogeneous reaction medium and

the employed purification method ensures that deprotection occurs randomly and that none of the polymers are lost during workup.

4.1. PBSPMA (Isobutyl Group)

Previously we reported the quantitative deprotection of isobutyl-protected poly(3-sulfopropyl methacrylate) using the weak nucleophile NaI.⁴³ For the sake of completeness, a brief discussion on the NaI-mediated deprotection of PBSPMA is included here as well. Even though the sodium salt of the strong polyanion PSPMA is more soluble in water, NMR analysis was performed in DMSO, as it allows one to directly compare it with the protected polymer. Moreover, since both protected and deprotected polymers are soluble in DMSO, incomplete deprotection can be readily identified by ¹H NMR. From Figure 1a, it can be seen that the NaI treatment led to the complete disappearance of the signals corresponding to the isobutyl protons [F], [G], and [H]. Furthermore, a clear shift of protons [E] was observed due to their changed chemical environment (sulfonate vs sulfonic ester). These data confirm the complete removal of the isobutyl group.

Although the exact mechanism is not known, it presumably involves an S_N2 substitution reaction because of the nucleophilic character of the iodide anion, thus resulting in release of the corresponding alkyl iodide. The decomposition of this side product (e.g., via an elimination) explains the discoloration of the reaction mixture through the formation of molecular iodine. As this deprotection reaction is governed by the iodide anion, PSPMA's counterion could be easily exchanged by starting from a different iodide.⁵⁰ Besides having a significant effect on the solubility of the resulting polyelectrolyte, workup sometimes also became more challenging. For example, on the one hand, when performed with KI, PSPMA seemed to become more hygroscopic and less soluble in DMSO compared to the sodium salt (Figure S9a). Tetraethylammonium iodide (Et₄NI), on the other hand, resulted in a polyanion with properties that are very similar to the sodium salt form, but removal of the excess salt was found to be more difficult. Compared to inorganic iodides, an advantage of quaternary ammonium salts is their visibility in ¹H NMR (Figure S9b). Larger alkyl groups, such as tetrabutylammonium iodide (Bu₄NI), resulted in PSPMA becoming insoluble in water but did render the polyelectrolyte soluble in polar organic solvents, such as acetone, acetonitrile, and alcohols (Figure S10a). PBSPMA could also be deprotected using 1-ethyl-3-methylimidazolium iodide (EMIMI), resulting in a soft polymeric material ("polymer ionic liquid") (Figure S10b).^{51,52}

Since quantitative deprotection was achieved through the weak nucleophile NaI, it is no surprise that a treatment with a strong nucleophile (NaN₃) afforded the sodium salt of PSPMA as well (Figure S11a).

A treatment with base led to an almost complete removal of the isobutyl group (>90%; Figure S11b). A longer reaction time or a slight increase of the NaOH concentration (e.g., 3 equiv instead of 2.5 equiv) is expected to result in a quantitative deprotection. Note that base-mediated deprotection of PBSPMA may be occurring through either a substitution or deprotonation mechanism, because the in situ formed base sodium methoxide can act as a nucleophile as well.

Finally, an acid treatment of PBSPMA by using HBr cleaved all isobutyl groups (Figure S12). Obtaining the sulfonic acid

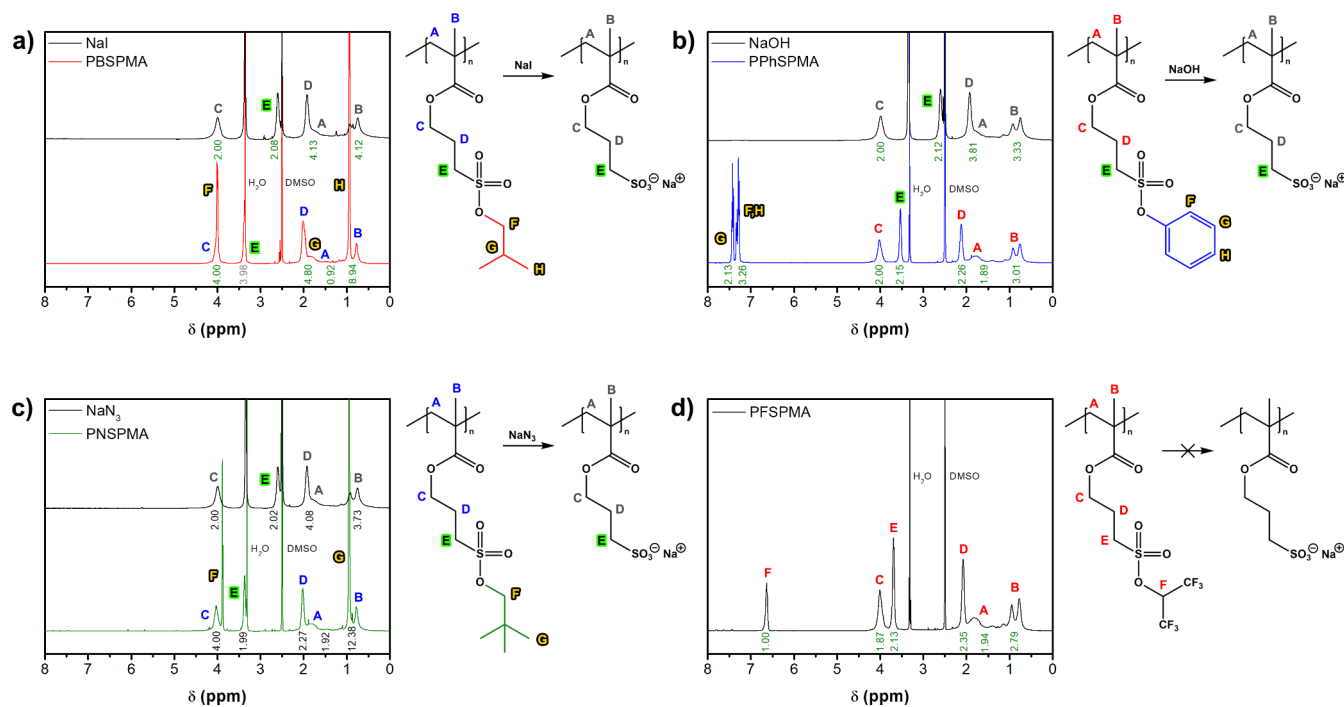


Figure 1. ^1H NMR spectra of RAFT-synthesized homopolymers before and after deprotection. (a) PBSPMA treated with NaI (weak nucleophile), (b) PPhSPMA with NaOH (base), and (c) PNSPMA with NaN_3 (strong nucleophile). (d) PFSPMA's protecting group could not be removed under the tested conditions. All spectra were recorded in $\text{DMSO}-d_6$.

Table 2. Stability of the Protected Poly(3-sulfopropyl methacrylates)^a

polymer	NaI	NaOH	HBr	NaN_3
PBSPMA	–	–	–	–
PNSPMA	+	+	+	–
PPhSPMA	+	–	+	R
PFSPMA	+	R	+	R

^a(–) Indicates that the protecting group is cleaved under the indicated conditions, (+) stable, and (R) means that deprotection is accompanied by side reactions. Deprotection was performed under weak nucleophilic (NaI), strong nucleophilic (NaN_3), basic (NaOH), or acidic conditions (HBr).

form of PSPMA via a precipitation turned out to be challenging, so the reaction mixture was precipitated into ethanol that contained an excess of NaI. This procedure ensured the conversion of PSPMA into its sodium salt form, which facilitated the isolation of the polyelectrolyte. We remark that stronger acids, such as HBr in acetic acid (33 wt %), even resulted in a hydrolysis of the methacrylic ester when the deprotection was performed at 100 °C. Despite being initially heterogeneous, for acid-catalyzed deprotection, $\text{HBr}_{(\text{aq})}$ in dioxane would therefore be the method of choice.

4.2. PPhSPMA (Phenyl Group)

The phenyl protecting group was selected because, for small molecules, it was reported to be only cleavable under alkaline conditions.⁴⁴ Indeed, the original PPhSPMA could be recovered in an unharmed form after a treatment with both NaI and HBr (Figure S13a,b).

Reacting the polymer with NaOH in methanol/DMSO at room temperature, however, resulted in the quantitative deprotection of PPhSPMA as evidenced by ^1H NMR (Figure 1b): aromatic protons [F], [G], and [H] disappeared

completely, and the same shift of protons [E] could be observed as for PBSPMA/NaI.

When treated with NaN_3 at 100 °C, the phenyl protecting group initially seemed to be stable, but on closer inspection of the product by ^1H NMR (Figure S14), a few inconsistencies were found compared to the neat polymer: (1) significant broadening of the aromatic region was observed and (2) the integral of the aliphatic region was incorrect (8.1 vs the theoretical value of 7). Combined with the reduced solubility of the product in chloroform, this may indicate a partial deprotection of PPhSPMA; the typical shift of protons [E] was, however, absent. A comparison of the neat and NaN_3 -treated polymer by Fourier transform infrared (FTIR) spectroscopy revealed the presence of an additional band at 2127 cm^{-1} after the reaction, which corresponds to a sulfonyl azide functional group (Figure S15).⁵³ Thus, some phenyl groups are replaced by an azide, and their contribution is estimated to be $\sim 10\%$ based on NMR.

Interestingly, while most phenyl groups remained intact in the presence of NaN_3 , a quantitative deprotection was achieved by using NaOH in methanol/DMSO. Since the in situ-formed sodium methoxide is a weaker nucleophile than NaN_3 , the deprotection of PPhSPMA presumably proceeds via an acid/base mechanism.

4.3. PNSPMA (Neopentyl Group)

PNSPMA's protecting groups remained intact under both weak nucleophilic (NaI) and acidic conditions (HBr), which enabled a full recovery of the original polymer (Figure S16a,b). Also, no deprotection was observed in the case of a base treatment (absence of the shift of protons [E]), although some methylation ($\sim 10\%$) may have occurred via a transesterification reaction (Figure S17a). Still, we are convinced that it is safe to use PNSPMA under basic conditions, as the polymer remains fully hydrophobic. Another possibility would be to

switch to a less nucleophilic base, in case such a side reaction could be completely avoided.

Neopentyl groups could be removed by using the strong nucleophile NaN_3 , but an optimization of the reaction conditions was required. Stirring at 100 °C overnight in the presence of 3 equiv of NaN_3 only led to 50% deprotection, but it could be increased to almost 90% through an extended reaction time of 3 d (Figure S17b). The best results were obtained by increasing the temperature to 130 °C: quantitative deprotection was achieved within 20 h as evidenced by the complete disappearance of protons [F] and [G] and the clear observation of the shift of protons [E] (Figure 1c).

4.4. PFSPMA (Hexafluoroisopropyl Group)

In contrast to Miller's previous work on protected dansylates,⁴⁴ where the hexafluoroisopropanol (HFIP) group could be cleaved in a basic environment, no suitable deprotection conditions were found for PFSPMA (Figure 1d). PFSPMA survived both HBr and NaI treatments (Figure S18), while basic and strong nucleophilic conditions resulted in ill-defined polymers; complex, noninformative NMR spectra were recorded for these products (Figure S19). Even though the disappearance of the typical HFIP signal (peak [F]) would indicate PFSPMA's deprotection, the shift of protons [E] remained absent. Besides a minor amount of deprotection, side reactions may include methylation (NaOH in methanol/DMSO), sulfonyl azide formation (NaN_3 in DMSO), or even hydrolysis of the methacrylic ester. Despite being not useful for this protection/deprotection study, FSPMA may still be interesting for other applications due to its high polarity, for instance, for the preparation of high- χ /low- N block copolymers to produce sub-10 nm structures.⁵⁴

4.5. Summary

The stability of all four protected PSPMAs is summarized in Table 2: protecting groups are either stable (+) or can be cleaved quantitatively (−), or side reactions (R) were observed. In general, the polymers followed the same trend as reported for small molecules,⁴⁴ although a few deviations were encountered. This can be explained as follows: if a minor amount of deprotection or side reaction occurs for a small molecule (<10%), this would have a negligible impact on the experiment, since the deprotected sulfonate or side product can be easily removed afterward. For polymers this is not the case, as the affected monomer unit remains part of the (mostly) protected polymer chain. Removal of these "impurities" is practically impossible, which is the case in, for instance, NaN_3 -treated PPhSPMA.

Another factor that should be considered is the character of the sulfonic ester: the polymers discussed in this work are aliphatic, while the reports on sulfonate-protected small molecules are mostly based on aromatic esters (e.g., dansylates or tosylates). Since aliphatic esters are more electrophilic, which becomes evident through 3-(chlorosulfonyl)propyl methacrylate being much more sensitive to moisture compared to *p*-styrene sulfonyl chloride (which can be isolated through extraction), this likely plays a role for the increased stability of PNSPMA in the presence of acid and the higher reactivity of PFSPMA in the presence of base.

5. END GROUP STABILITY

Because the protected poly(3-sulfopropyl methacrylates) were synthesized by RAFT using a dithiobenzoate-based RAFT agent, all polymers were typically obtained as pink solids. Once

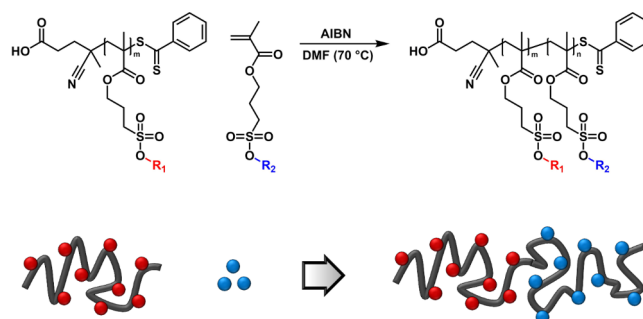
deprotected, PSPMA was only recovered as a pink powder after NaI treatment; all other conditions (HBr, NaOH, and NaN_3) resulted in white products. This color change indicates a loss of the CTA functionality. While it is not relevant in the previous sections, its survival is of the utmost importance if the deprotected polymer will be employed as a macro-CTA, for example, for polymerization-induced self-assembly (PISA)-related studies.^{24,55} Furthermore, as CTA removal often results in thiol end groups, a potential disulfide bridge formation can cause a doubling of the molecular weight, which should be avoided when studying the solution self-assembly of amphiphilic diblock copolymers.

Because comparison of protected and deprotected homopolymers is challenging due their difference in solubility and molecular weight, control experiments were performed on a low-molecular weight PMMA macro-CTA that was synthesized from the same CTA (CTP). ¹H NMR analysis confirmed the visual changes: the complete removal of the CTA was observed for HBr and NaOH treatments, while it remained intact for NaI (Figures S20 and S21). The result of NaN_3 is not included, as this reagent affected PMMA itself under the employed conditions (35 mg mL^{−1} NaN_3 , 100 °C, 20 h). However, in an earlier publication by Wu and co-workers, dithiobenzoate CTAs were already demonstrated to be quantitatively removed by NaN_3 at room temperature.⁵⁶ Even though no shoulders due to thiol–thiol coupling could be identified in the GPC traces of the treated PMMA homopolymers (Figure S22), the use of the PBSPMA/NaI system is recommended if either a high end group fidelity or well-defined molecular weight is desired. Another option would be to first remove the CTA in a controlled manner before performing the deprotection, although an extension of PSPMA would no longer be a possibility.

6. ORTHOGONALLY PROTECTED DIBLOCK COPOLYMERS

To demonstrate the versatility of our method, three diblock copolymers were prepared from two differently protected

Scheme 3. General Reaction Scheme and Schematic Illustration Describing the Route towards Orthogonally Protected Diblock Copolymers through RAFT Polymerization



SPMA monomers: PNSPMA-*b*-PPhSPMA (PNeo-*b*-PPh in short), PBSPMA-*b*-PPhSPMA (PiBu-*b*-PPh), and PBSPMA-*b*-PNSPMA (PiBu-*b*-PNeo) by starting from either a PNSPMA macro-CTA (PNSPMA-1) or PBSPMA macro-CTA (PBSPMA-2) (Scheme 3). All reaction conditions are summarized in Table S2. Since the GPC analysis of isobutyl-protected PSPMAs through conventional calibration always

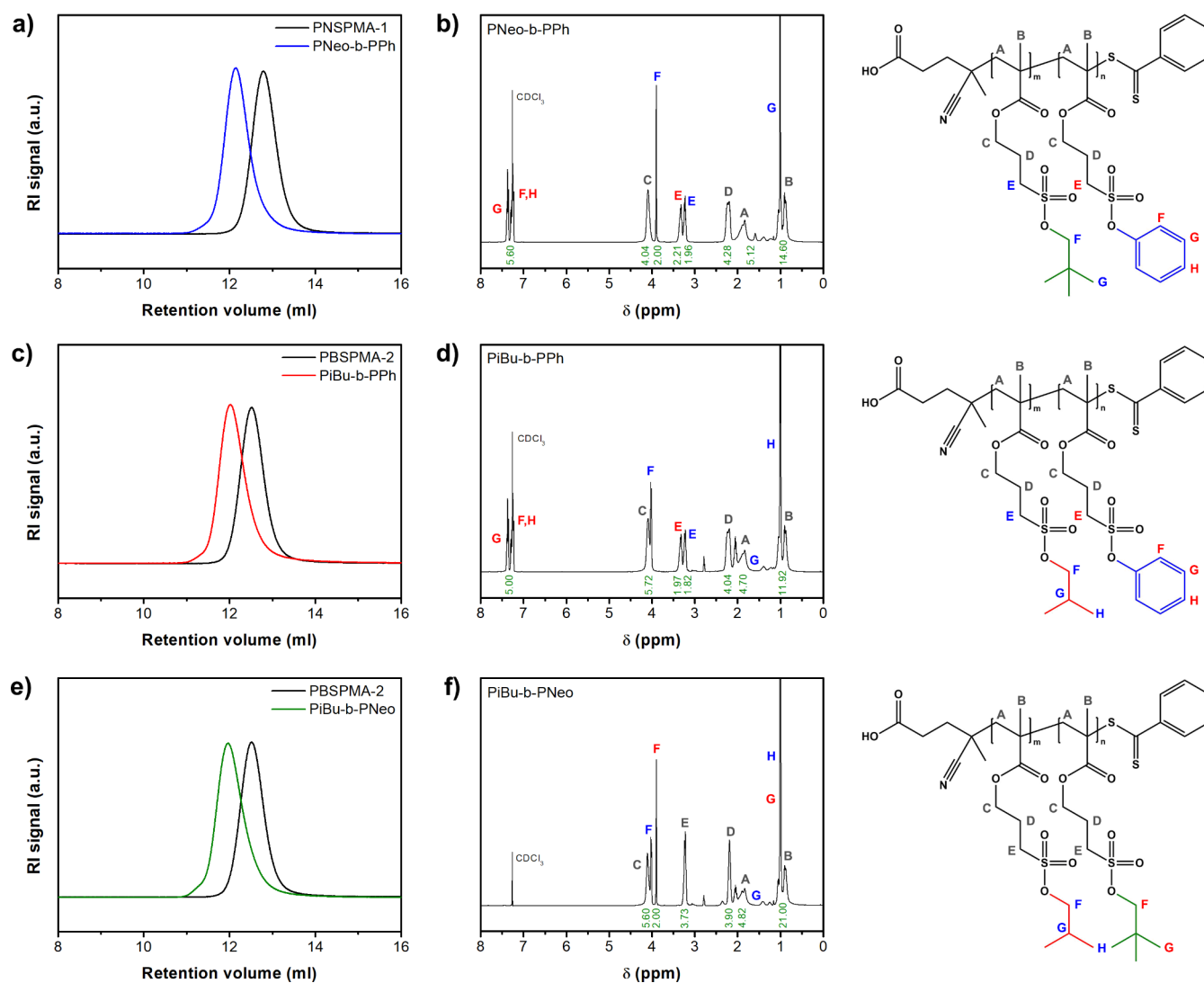


Figure 2. GPC elugrams and ^1H NMR spectra (CDCl_3) of the orthogonally protected diblock copolymers. (a, b) PNeo-*b*-PPh, (c, d) PiBu-*b*-PPh, and (e, f) PiBu-*b*-PNeo. Copolymer compositions were calculated by comparing the signals of the protecting groups.

Table 3. Overview of the RAFT-Synthesized Orthogonally Protected Diblock Copolymers^a

polymer	M_n	$M_{n,\text{GPC}}$	\bar{D}	f_1	R_h (nm)	PDI	ζ (mV)
PNeo- <i>b</i> -PPh	39.9	38.0	1.17	0.49	55.0	0.184	-35.8
PiBu- <i>b</i> -PPh	59.7	62.1	1.19	0.46	25.1	0.041	-36.2
PiBu- <i>b</i> -PNeo	60.1	65.9	1.20	0.46	46.1	0.094	-36.9

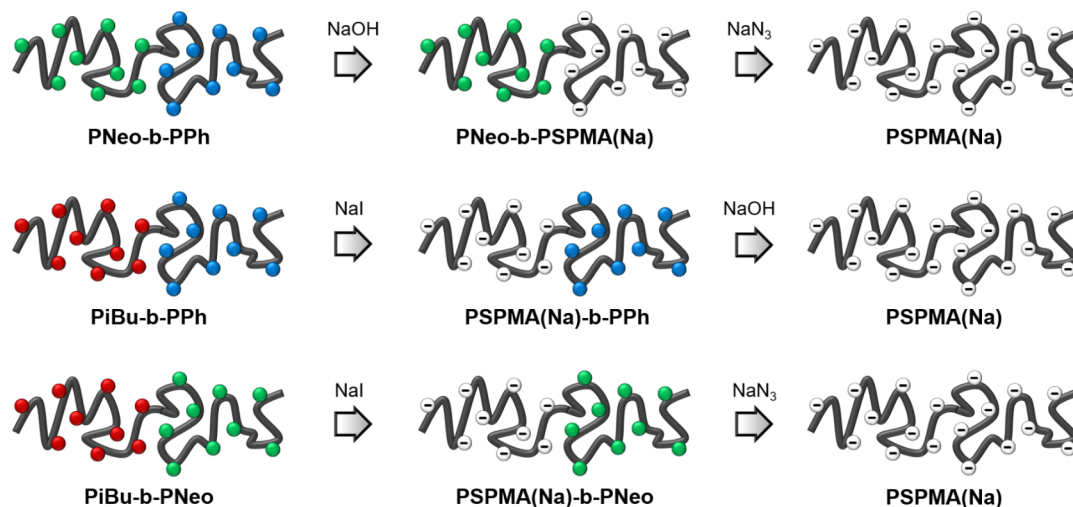
^a M_n (kg mol^{-1}) corresponds to the molecular weight calculated from the M_n of the macro-CTA and composition (^1H NMR), $M_{n,\text{GPC}}$ and \bar{D} are the molecular weight and distribution that were directly obtained from GPC (conventional calibration), and f_1 is the weight fraction of the first block. Hydrodynamic radii (R_h), polydispersities (PDI), and zeta potentials (ζ) represent the characteristics of the micellar aggregates prepared from the selectively deprotected diblocks. The deprotected block is underlined.

resulted in an overestimation of the molecular weight, both the concentrations and final molecular weights were calculated by assuming the theoretical molecular weight of the PBSPMA macro-CTA (Table 1). As this problem was not encountered for PNSPMA, the measured molecular weight was used. After

polymerization of the second monomer, an increase of molecular weight was observed by GPC (i.e., a lower retention volume), tailing or shouldering remained absent (Figures 2a,c,e), and molecular weight distributions reached values of 1.2 at most. Block copolymer compositions of the fully hydrophobic precursors were calculated through ^1H NMR analysis by using the signals of the protecting groups (Figures 2b,d,f) and resulted in the intended symmetric composition ($f_1 \approx 0.5$). An overview is provided in Table 3.

Since each protecting group has a different reactivity profile (Table 2), an orthogonal protecting strategy can be employed that allows one to selectively deprotect a specific block (Scheme 4). Block copolymers were treated with the required reagents under the same conditions as previously used for the protected homopolymers, where the concentrations were adapted to the copolymer composition. The phenyl group of PNeo-*b*-PPh was cleaved by using a base (NaOH): the characteristic aromatic protons [A], [B], and [C] disappeared completely as indicated by ^1H NMR (Figure 3a), and a clear shift of protons [*] could be observed, while the base-resistant neopentyl group of the PNeo block remained intact.

Scheme 4. Schematic Representation of the Sequential Deprotection of Orthogonally Protected PNeo-*b*-PPh, PiBu-*b*-PPh, and PiBu-*b*-PNeo Diblock Copolymers under Weak Nucleophilic (NaI/PiBu), Strong Nucleophilic (NaN₃/PNeo), or Basic (NaOH/PPh) Conditions



Thus, PPhSPMA was successfully converted into the sodium salt of PSPMA. Similarly, the PBSPMA block of both PiBu-*b*-PPh and PiBu-*b*-PNeo was deprotected by using NaI: protons [1], [2], and [3] vanished, and the same shift of protons [*] could be recognized due to the changed chemical environment (Figure 3b,c).

Because these strong anionic/hydrophobic intermediates are amphiphilic, their self-assembly in aqueous solution was briefly investigated before the second block was deprotected.⁵⁷ Surprisingly, compared to our previous study on PMMA-*b*-PSPMA diblock copolymers,⁴³ preparing micellar aggregates through direct dissolution (DD) turned out to be impossible.⁵⁸ Even though PNSPMA and PPhSPMA both have a lower T_g than PMMA, their increased hydrophobicity likely hinders the direct solubility in water.^{59,60} On the contrary, well-defined aggregates with low polydispersity indexes (PDIs) could be formed (PDI < 0.2) when using the solvent addition (SA) method by starting from a DMSO/KNO₃ solution followed by a dropwise addition of water. The final composition of the dispersions consisted of 1.0 mg mL⁻¹ polymer, 11 mM KNO₃, and 13 wt % DMSO in H₂O. Since this mixture is a poor solvent for the hydrophobic block (a few drops of water is already sufficient to precipitate a homopolymer from DMSO), the organic solvent was not removed prior to an analysis by dynamic light scattering (DLS). Instead, the refractive index (n) and viscosity (η) were adjusted according to the composition (Figure 4a–c).⁶¹ As a 10-fold dilution of the samples did not have any effect on the sizes and distributions (Table S3: 0.1 mg mL⁻¹ polymer, 10 mM KNO₃, and 1 wt % DMSO), this indicates that the particles are not swollen by DMSO. For an extensive self-assembly study, which is not the aim of this work, it is still advised to remove the remaining DMSO by dialysis. The acquired DLS data of the undiluted dispersions are summarized in Table 3, with the negative zeta potentials confirming the aggregates' negatively charged corona.

Despite having almost identical molecular weight characteristics, it is interesting to see that the self-assembly of PSPMA-*b*-PPh (from PiBu-*b*-PPh) and PSPMA-*b*-PNeo (from PiBu-*b*-PNeo) resulted in quite different hydrodynamic radii (R_h). We assume this is caused by the different hydrophobicity and chain

conformation of PPhSPMA compared to that of PNSPMA, thereby resulting in a lower aggregation number of the PPhSPMA-containing diblocks and consequently a smaller particle size. Indeed, PNeo-*b*-PSPMA (prepared from PNeo-*b*-PPh), which gives micelles with a PNSPMA core as well, formed aggregates that are more similar to PSPMA-*b*-PNeo (from PiBu-*b*-PNeo). On the basis of the copolymer composition, transmission electron microscopy (TEM) confirmed the expected spherical micelles,⁶² with PSPMA-*b*-PPh indeed clearly forming the smallest aggregates (Figure 4d–f). Additional TEM images can be found in the Supporting Information (Figure S23).

After investigation of the solution self-assembly of these three amphiphilic copolymers, each second block was deprotected as well (Scheme 4). PNeo-*b*-PSPMA (from PNeo-*b*-PPh) and PSPMA-*b*-PNeo (from PiBu-*b*-PNeo) were both treated with the strong nucleophile NaN₃, which led to the complete disappearance of the characteristic neopentyl signals in the NMR spectrum (Figure 3a,c). The phenyl groups of PSPMA-*b*-PPh (from PiBu-*b*-PPh), however, were cleaved by using a base (NaOH) and, thus, resulted in the disappearance of peaks [A], [B], and [C] in the aromatic region (Figure 3b). The obtained materials were identical to the earlier described deprotected homopolymers as indicated by the typical [*] signal of the sulfonate, with the only difference being that, in the case of a diblock copolymer, a PSPMA strong polyanion with a doubled molecular weight (i.e., $m + n$) is retrieved.

7. CONCLUSIONS

In this work we described the synthesis and polymerization of isobutyl-, phenyl-, neopentyl-, and hexafluoroisopropyl-protected 3-sulfopropyl methacrylate monomers. The obtained hydrophobic precursors could be analyzed using conventional techniques in an organic solvent, while the protected polymers could be quantitatively converted into the corresponding strong polyanion under either acidic, basic, or nucleophilic conditions. Depending on the protecting group's chemical nature, the precursor remained intact under various other conditions, for example, in an acidic (PPhSPMA) or basic (PNSPMA) environment. As a proof of principle, amphiphilic

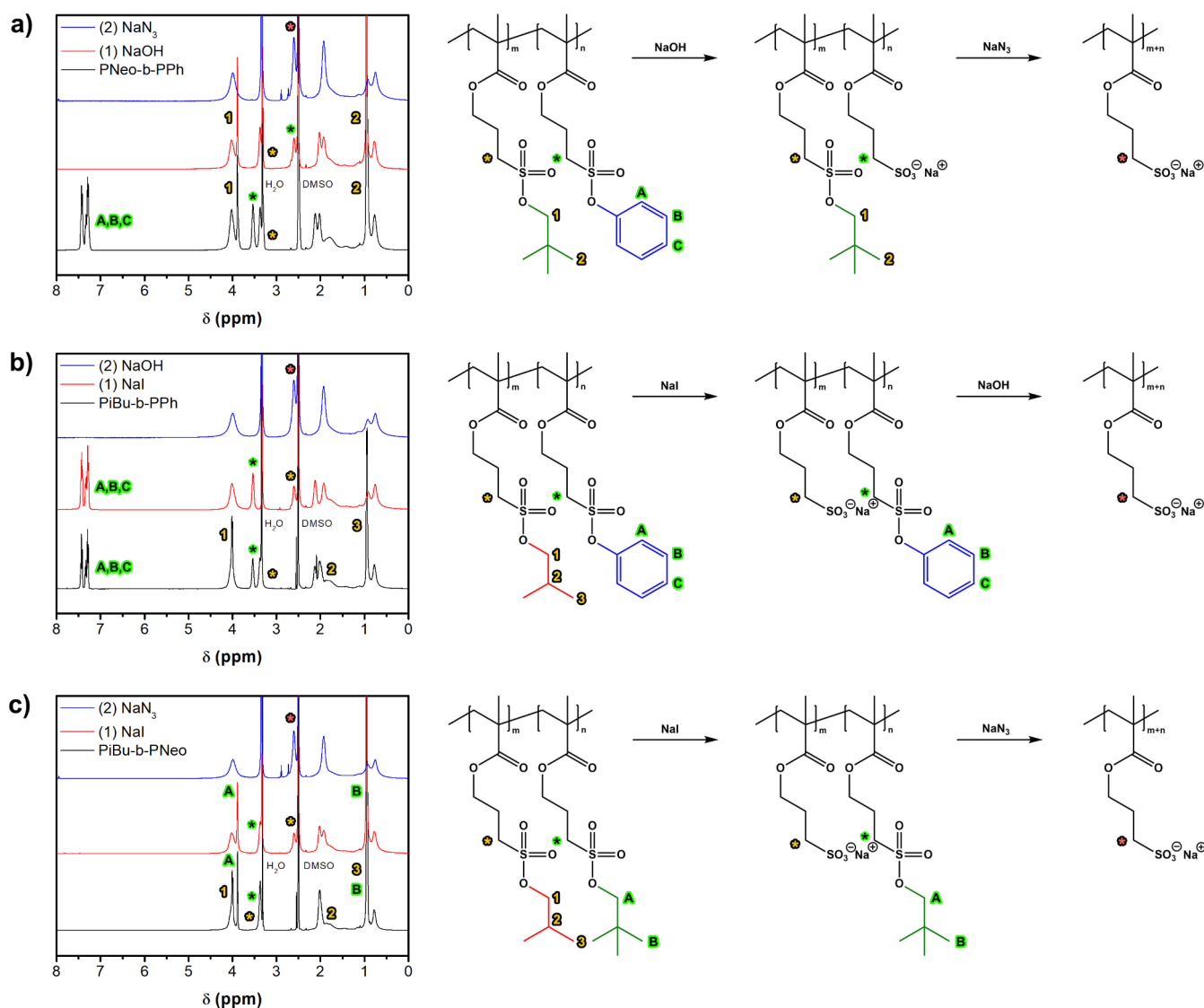


Figure 3. Reaction schemes and ^1H NMR spectra of the stepwise deprotection of the orthogonally protected diblock copolymers: (a) PNeo-*b*-PPh by NaOH/ NaN_3 treatment, (b) PiBu-*b*-PPh via NaI/NaOH treatment, and (c) PiBu-*b*-PNeo via reaction with NaI/ NaN_3 . All spectra were recorded in $\text{DMSO}-d_6$.

materials were prepared from orthogonally protected diblock copolymers by a selective deprotection of one of the blocks.

Since both the monomers and polymers are easy to prepare, they are a great alternative for the more commonly employed poly(*tert*-butyl acrylate) and quaternized polyvinylpyridine routes, especially when a strong polyanion and/or complete functionalization is desired. We remark that the presented strategy is not limited to the four monomers presented in this work; other protecting groups can be introduced by simply changing the alcohol in the monomer design stage, which may facilitate deprotection under even milder conditions and would enable the design of more advanced polymer systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acspolymersau.1c00044>.

Experimental details (monomer synthesis, polymerization, deprotection, sample preparation), ^1H and ^{13}C NMR spectra, thermal analysis (DSC and TGA), FTIR

spectra, GPC chromatograms and discussion, DLS data, and additional TEM images recorded at a lower magnification (PDF)

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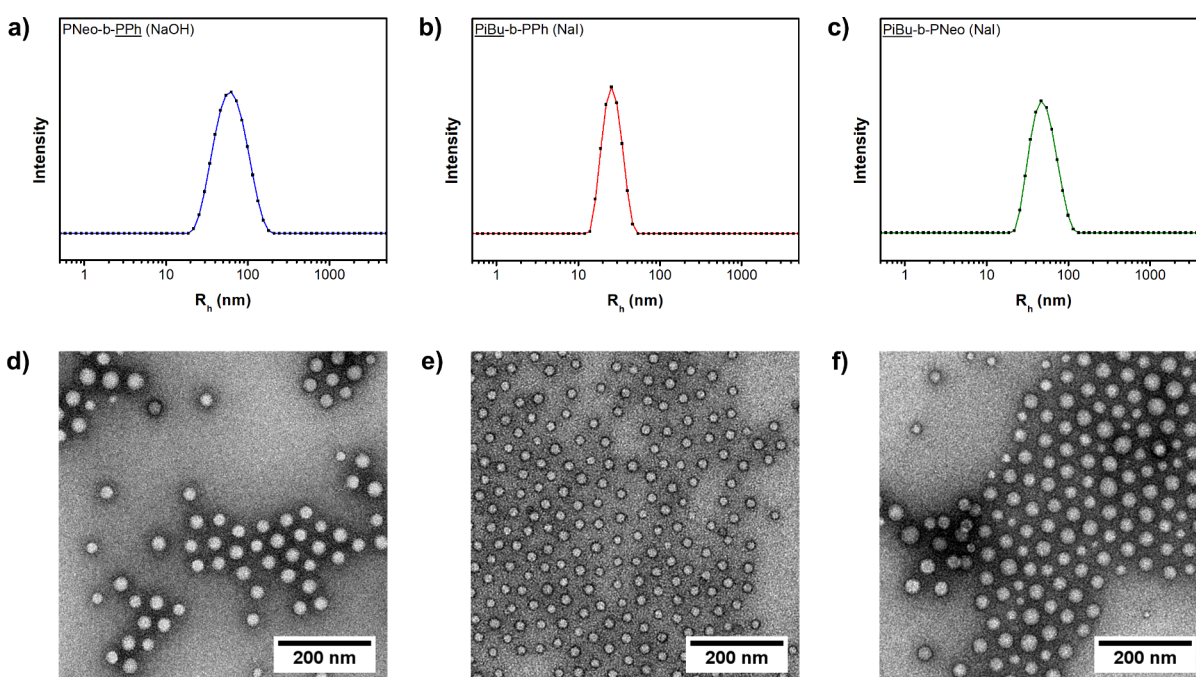


Figure 4. (a–c) DLS size distribution plots of the self-assembled micellar aggregates prepared from the partially deprotected diblock copolymers; the deprotected block is underlined. (d–f) Transmission electron micrographs of negatively stained block copolymer aggregates: (d) PNeo-b-PPh, (e) PiBu-b-PPh, and (f) PiBu-b-PNeo. Particles were formed via the solvent addition method. Final composition: 1.0 mg mL⁻¹, 13 wt % DMSO in H₂O, and 11 mM KNO₃.

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acspolymersau.1c00044>

Notes

The authors declare no competing financial interest.

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