RESEARCH ARTICLE

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Degradable Poly(styrene sulfonate) Polyanions for Biomedical and Electrochemical Applications

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The synthesis of poly(styrene sulfonate) with hydrolysable ester groups in the main chain is reported. The material is obtained by free radical copolymerization of either styrene sulfonate sodium salt (SSNa) or styrene sulfonate alkyl esters (SSA) with the cyclic ketene acetal 2-methylen-1,3,6-trioxocane (MTC). As for other systems made from cyclic ketene acetals, the reactions are difficult to control and give copolymers with high polydispersity index. MTC homopolymer is obtained as a side product in both cases. Thermal cleavage of the alkyl protective groups of the poly(styrene sulfonate alkyl esters) to obtain the target polystyrene sulfonate anions remains incomplete. Thus, direct synthesis of the polyanion from SSNa and MTC is the more efficient process, especially since the poly(SSNa-co-MTC) copolymer can be easily separated from MTC homopolymer. ^{1}H-NMR analytics indicates MTC repeat unit contents of 2–11%, depending on the initial SSNa to MTC ratio. The MTC ester groups of the copolymers are hydrolyzed in aqueous conditions, with and without enzyme, and a marked decrease in the molar mass is observed after hydrolysis. This confirms that these copolymers have the designed intended break points in the main chain, and could become a part of fully degradable electroactive polymer systems.

1. Introduction

Poly(styrene sulfonate) (PSS) is an important polyelectrolyte material found in many application contexts. For example, it is used in ion exchange materials for water purification, in membranes of fuel cells, and as the counterion of the electroactive poly-3,4-ethylendioxythiophen (PEDOT) in the important conductive polymer PEDOT:PSS.[1] In this material, the negatively charged PSS stabilizes the otherwise insoluble, cationic PEDOT, so that stable aqueous dispersions are obtained. These colloidal aggregates form thin, conducting films when cast onto various substrates. They are used in metal-polymer electrolyte capacitors, sensors, solar cells and light emitting diodes. Implanted electrodes and sensors containing PEDOT:PSS have also been reported.[2–5] Particularly for these biomedical applications, it would be desirable to obtain a degradable variant of PSS. Fully degradable in-dwelling medical devices could disintegrate after end-of-lifetime, which would eliminate the need for additional surgery. In other cases of PSS use, a molar mass reduction by degradation would make polymer fragments that are accidentally released into the ecosystem more accessible to environmental degradation of polymers, e.g., by oxidation and UV-driven erosion.

Many other electroactive polymers besides PEDOT:PSS also contain a non-degradable PSS counterion, e.g., poly(pyrroles), other poly(thiophene) derivatives, or poly(anilines). Quite a substantial amount of research has been dedicated to obtaining fully degradable versions of these conducting materials for in vivo applications. For example, instead of using PSS, it was attempted to blend the conductive polycations with degradable polymers like poly(lactide), poly(ϵ-caprolactone), collagen, or heparin.[4,6] In other approaches, conductive oligomers of pyrrole, thiophene, or aniline were connected via hydrolysable linkers to make the resulting polymers degradable.[3,6–8] An alternative approach toward such materials (which, to our knowledge, was not yet attempted) is to combine such conducting oligomers with degradable PSS-like polyanions.

The synthesis of such a polyanion was the aim of the work presented here, as shown in **Figure 1**. We introduced ester groups as intended break points into a PSS backbone by free radical copolymerization of PSS with the hydrophilic cyclic ketene acetal (CKA) 2-methylen-1,3,6-trioxocane (MTC). The homopolymerization of MTC proceeds via ring-opening radical polymerization, as described by Undin et al.[9] Its free radical

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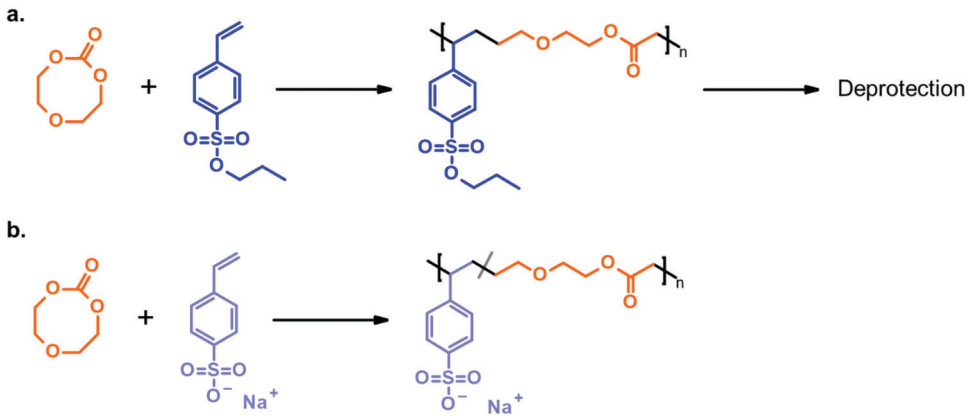


Figure 1. Synthesis of degradable polyanions: a) Copolymerization of 2-methylene-1,3,6-trioxocane (MTC) with styrene sulfonate propyl ester (SSP), followed by deprotection; b) Copolymerization of MTC with styrene sulfonate sodium salt (SSNa). Both approaches yielded polymers with degradable ester groups in the backbone.

copolymerization with vinyl monomers yields copolymers with ester groups in the polymer main chain. MTC is one of the few CKAs that yield hydrophilic (co)polymers. Previous research has focused on the structurally similar, but more hydrophobic 2-methylene-1,3-dioxepane (MDO). For example, 12% of degradable ester groups could be incorporated into a polymer backbone by copolymerization of MDO with styrene.[10] At the beginning of this study, the state-of-the-art was that in batch reactions (where all of the cyclic ketene acetal and the vinyl comonomer are present at the start of the reaction) only limited amounts of degradable groups are incorporated into the backbone, while the rest is converted into homopolymer.[10] More recent work has shown that this can be considerably improved with a semi-batch approach.[11] For example, in a very detailed mechanistic study, Van Herk and coworkers compared batch and semi-batch reactions of a cyclic ketene acetal comonomer with and acrylic monomer, and also analyzed the side reactions of these polymerizations.[11] For the semi-batch reaction, they used a specialized software package to calculate the optimized feeding ratio of the cyclic ketene acetal. This resulted in increased cyclic ketene acetal incorporation into the copolymer, and a more even distribution of the degradable ester units along the copolymer chain.[11]

To obtain a degradable PSS analogue using MTC as comonomer, we here present two approaches: first, the copolymerization of styrene sulfonate alkyl esters with MTC, followed by removal of the ester groups; and second, the direct copolymerization of styrene sulfonate sodium salt with MTC (Figure 1).

2. Experimental Section

General information about chemicals, instrumentation and monomer synthesis can be found in Section S1 and Schemes S1–S5 (Supporting Information). The synthesis of the reference polymers poly(styrene sulfonate propyl ester) (PSSP), poly(styrene sulfonate isobutyl ester) (PSSiB), and the homopolymer obtained from 2-methylen-1,3,6-trioxocane (polyMTC)) is found in Section S1.3.2 and Schemes S6–S8 (Supporting Information).

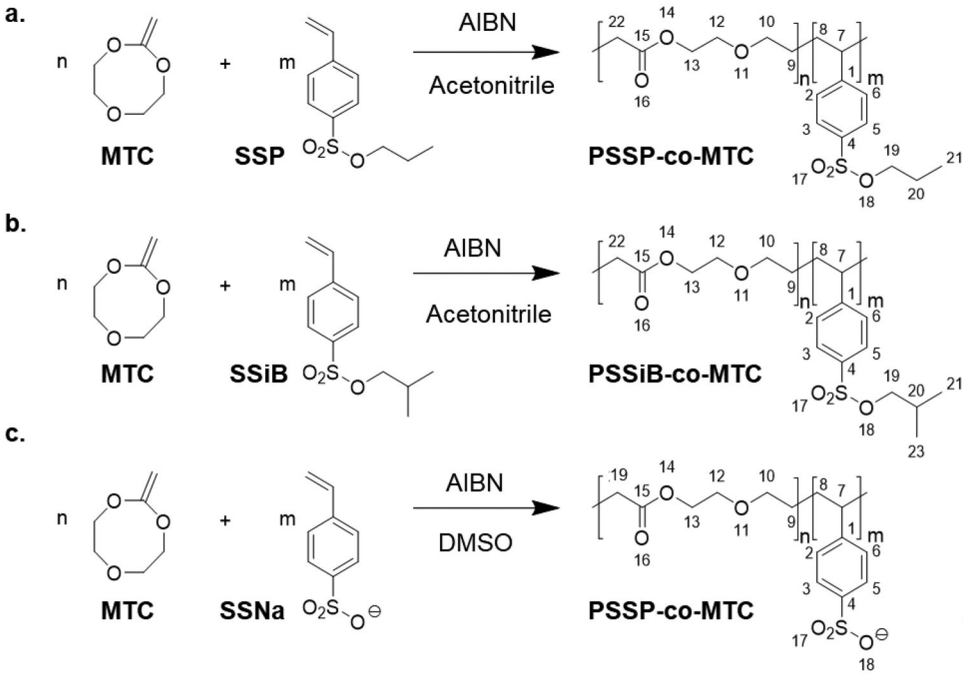
2.1. Copolymerization of 2-Methylene-1,3,6-Trioxocane and Styrene Sulfonate Propyl Ester

In a representative experiment, MTC (549 mg, 4.2 mmol, 1.0 eq.), styrene sulfonate propyl ester (SSP, 959 mg, 4.2 mmol, 1.0 eq.) and the polymerization initiator azoisobutyronitrile (AIBN, 41.7 mg, 0.25 mmol, 0.06 eq.) were transferred into a pre-heated Schlenk flask under nitrogen atmosphere, to which 1.7 mL dry acetonitrile was added (**Scheme 1**a). The reaction mixture underwent three freeze-pump-thaw cycles and was heated to 70 °C. After a reaction time of 19 h, the reaction product was obtained as a yellowish solid. It was dissolved in chloroform and precipitated into hexane. The last two steps were repeated once. The product, PSSP-co-MTC, was a light-yellow powder (yield: 52%, 788.7 mg).

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.71 (m, 2H, 3- and 5-H), 6.70 (m, 2H, 2-and 6-H), 4.10 (m, 4H, 13- and 19-H), 3.81 (m, 2H, 10-H), 3.66 (m, 2H, 12-H), 2.15–1.16 (m, 9H, 7-, 8-, 9-, 20-, and 22-H), and 0.95 (br.s, 3H, 21-H) ppm. Further details and characterization data are found in Table S1 and Section S1.4.1 (Supporting Information).

2.2. Copolymerization of 2-Methylene-1,3,6-Trioxocane and Styrene Sulfonate Isobutyl Ester

In a representative experiment, MTC (276.2 mg, 2.1 mmol, 1.0 eq.), styrene sulfonate isobutyl ester (SSiB, 0.51 g, 2.1 mmol, 1.0 eq.) and the polymerization initiator AIBN (21.3 mg, 0.13 mmol, 0.06 eq.) were transferred into a pre-heated Schlenk flask under nitrogen atmosphere, to which 0.9 mL dry acetronitile was added (Scheme 1b). The reaction mixture underwent three freeze-pump-thaw cycles and was heated to 70 °C. After a reaction time of 2 h, the reaction mixture solidified, and the product was obtained as a yellowish solid. It was dissolved in chloroform and precipitated into hexanes. The last two steps were repeated once. The product, PSSiB-co-MTC, was a light-yellow powder (yield: 25%, 193.5 mg). ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.71 (m, 2H, 3- and 5-H), 6.71 (m, 2H, 2- and 6-H), 4.26–3.17 (m, 4H, 13- and 19-H), 3.77 (m, 2H, 10-H), 3.66 (m, 2H, 12-H), 2.66–2.02 (m,



Scheme 1. Copolymerization of 2-methylene-1,3,6-trioxocane (MTC) with a) styrene sulfonate propyl ester (SSP), b) styrene sulfonate isobutyl ester (SSiB), and c) styrene sulfonate sodium salt (SSNa). The numbering of the product atoms refers the NMR peak assignments (Figures S1 and S2, Supporting Information).

5H, 9-, 20-, and 22-H), and 0.92 (br.s, 3H, 21- and 23-H) ppm. Further details and characterization data are found in Table S1 and Section S1.4.1 (Supporting Information).

2.3. Copolymerization of 2-Methylene-1,3,6-Trioxocane and Styrene Sulfonate Sodium Salt

In a representative experiment, MTC (300 mg, 2.3 mmol, 1.0 eq.), styrene sulfonate sodium salt (SSNa, 475 mg, 2.3 mmol, 1.0 eq.), and the polymerization initiator AIBN (22.7 mg, 0.14 mmol, 0.06 eq.) were transferred into a Schlenk flask under nitrogen atmosphere, to which 2 mL DMSO were added (Scheme 1c). The reaction mixture underwent three freeze-pump-thaw cycles and was heated to 60 °C for 18 h. Next, the supernatant was decanted, and the precipitated reaction product was redissolved in water and precipitated into tetrahydrofurane. The last two steps were repeated until the monomer was near-quantitatively removed and the polymer was freeze-dried. The product, PSSNa-co-MTC, was a light-yellow solid (yield: 89 %, 707.9 mg).

^{1}H NMR (250 MHz, D_2O): $\delta = 7.55$ (d, $J = 2.2$ Hz, 2 H), 6.64 (d, $J = 2.7$ Hz, 2 H), 4.15–4.33 (m, $J = 35.7$, 9.0 Hz, 2 H), 3.68–3.86 (m, 2 H), 3.52–3.68 (m, 2 H), 0.67–2.01 ppm (m, 5 H). Further details and characterization data are found in **Table 1**.

2.4. Polymerization Kinetics

At defined time points, samples were taken from the reaction mixture using a syringe that had been previously flushed with nitrogen. The percentage of monomer conversion was calculated from NMR spectra of these samples using the integrals of the monomer peaks: The ratio of the respective monomer signal integral at a given time point, normalized to the solvent peak, was divided by the monomer signal integral at $t = 0$, normalized to the solvent peak, and subtracted from 1. Partially overlapping monomer signals were a problem in this procedure, as has been also described in the literature, therefore these results need to be treated with care.[12]

2.5. Degradation Studies

Two different degradation studies were performed—thin film degradation and degradation of polymer powder. 1) Thin film degradation. Silicon wafer pieces were pre-functionalized with benzophenone triethoxy silane as reported previously to make them hydrophobic.[13] PSSP-co-MTC was dissolved in chloroform at a concentration of 12 mg mL^{-1} and spin-coated onto the pre-functionalized wafer pieces (500 rpm, 100 rpm s^{-1}). The refractive index of the thus obtained layers was determined by ellipsometry (1.560 ± 0.019). They were then immersed into phosphate buffer (PBP, pH 7) or PBS with additional enzyme (0.2 mg mL^{-1} lipase from *Rhizopus oryzae*). The layer thickness was determined by ellipsometry at different time points. 2) Powder degradation. 50 mg of the copolymer PSSP-co-MTC were dispersed in 10 mL water, to which 2 mg lipase from *Rhizopus oryzae* were added. The suspension was brought to 37 °C, and 1 mL samples were taken at defined time points. The solvent was removed by rotary evaporation, and the polymer was redissolved in a

Table 1. Reagent amounts for the synthesis of PSSP-co-MTC, PSSiB-co-MTC, and PSSNa-co-MTC, respectively, and characterization data of the polymers obtained. The number average molar mass M_n and the polydispersity index (PDI) were determined by gel permeation chromatography (GPC, in DMF, 5 mg mL^{-1} LiBr, calibrated with polystyrene standards). The molar percentage of MTC repeat units was determined by ^{1}H-NMR spectroscopy.

Sample	MTC			AIBN			Sulfonate monomer				GPC results		^{1}H-NMR results
	n [mmol]	m [mg]	eq.	n [mmol]	m [mg]	eq.	Type	n [mmol]	m [mg]	eq.	M_n	PDI	% MTC
PSSP-co-MTC[a)]	4.2	549	1	0.25	41.7	0.06	SSP	4.2	959	1	49.2[e)]	2.1[e)]	22
PSSiB-co-MTC[b)]	2.1	276	1	0.12	21.3	0.06	SSiB	2.1	510	1	39.9[e)]	1.6[e)]	19
PSSNa-co-MTC[c)]	3.8	500	1	0.22	37.4	0.06	SSNa	3.8	792	1	83.1[f)]	11.3[f)]	18
PSSNa-co-MTC[d)]	5.4	700	2	0.32	52.5	0.06	SSNa	2.7	565	1	33.0[f]	2.8[f)]	9

[a)] Solvent: 1.7 mL dry acetonitrile; [b)] Solvent: 0.9 dry acetonitrile; [c)] Solvent: 2 mL acetonitrile:water 2:1 v/v; [d)] Solvent: 2 mL DMSO; [e)] GRAM columns, DMF, 5 mg mL^{-1} LiBr; f) MCX columns, 0.1 M phosphate buffer, pH 7.4.

suitable GPC eluent (*N,N*-dimethyl formamide, DMF) for analysis. 100 mg of the copolymer PSSNa-co-MTC were dissolved in either 20 mL PBS buffer or PBS with 0.2 mg mL^{-1} porcine pancreas lipase. In another set of experiments, 50 mg PSSNa-co-MTC was dissolved in 10 mL 3 molar NaOH. In either case, the reaction vessels were brought to 37 °C, and samples were taken at regular intervals. The solvent was removed by rotary evaporation, and the polymer was redissolved a suitable GPC eluent (0.1 M phosphate buffer, pH 7.4) for analysis.

3. Results

3.1. Study Design

The aim of this work was to obtain poly(styrene sulfonate) anions with hydrolysable ester groups as intended break points in the polymer main chain. As illustrated in Figure 1, we followed two synthetic pathways to obtain this kind of material. First, copolymers of 2-methylene-1,3,6-trioxocane (MTC) with different styrene sulfonate alkyl esters (propyl and isobutyl ester, respectively) were synthesized, which should then be deprotected by removal of the alkyl group to obtain the corresponding polyanion. The propyl ester (SSP) was chosen as a representative alkyl ester with medium hydrophobicity, the isobutyl ester (SSiB) had a similar hydrophobicity but a secondary alkyl group, which should come off more easily during thermal deprotection.[14] The expected advantage of synthesizing the target compound via these alkyl esters was that the charge-neutral polymers thus obtained (PSSP-co-MTC or PSSiB-co-MTC, respectively, Scheme 1) were organosoluble, which greatly simplified the molar mass determination by gel permeation chromatography (GPC), as well as the following film formation by spin coating for the degradation studies. The disadvantage was that the monomers had to be synthesized in two steps from styrene sulfonate sodium salt (SSNa), and that there was an additional deprotection step. In the second approach, MTC was copolymerized with the ionic monomer SSNa, which directly yielded the desired polyanion (PSSNa-co-MTC, Scheme 1). While the characterization of this copolymer required the use of aqueous GPC for analysis, which can be tricky for modified PSSNa, the second approach had the advantage that the polymer could be directly synthesized from the commercially available SSNa, and that the additional removal of the alkyl ester groups (the deprotection step) was avoided. It should be noted that calibrated GPC (in DMF, using polystyrene standards) was used in this study instead of GPC-MALLS, which would have given absolute molar masses, mostly because the polymer fragments obtained after hydrolysis were out of the measurement range of this method, among other issues (e.g., locally fluctuating dn/dc for copolymers).

3.2. Approach 1: Copolymers of 2-Methylen-1,3,6-Trioxocane and Styrene Sulfonate Alkyl Esters

3.2.1. Copolymerization of 2-Methylene-1,3,6-Trioxocane with Styrene Sulfonate Propyl Ester

Styrene sulfonate propyl ester (SSP) and 2-methylen-1,3,6-trioxocane (MTC) were obtained by literature procedures.[12] MTC was copolymerized with SSP in acetonitrile at 70 °C using azoisobutyronitrile (AIBN) as initiator. The comonomer ratio was 1:1. The product was analyzed by NMR spectroscopy. In the ^{1}H-NMR and ^{1}H,^{1}H-COSY NMR spectra of the reaction product PSSP-co-MTC, peaks corresponding to both the MTC and SSP repeat units were found (Figures S1 and S2, Supporting Information). The positions of these peak were comparable to those of the respective the homopolymers (Section S1.3.2, Supporting Information). By NMR peak integration, the overall MTC repeat unit content was estimated as 22%, i.e., the SSP to MTC ratio was 3.5:1. This is consistent with data from the copolymerization of MTC with styrene, where the MTC repeat unit content was 24%.[15] However, this conversion value also includes the MTC content of the homopolymer chains.[10] Separation of the MTC homopolymer from the copolymer with conventional methods (precipitation, trituration) was not complete.

3.2.2. Copolymerization of 2-Methylene-1,3,6-Trioxocane with Styrene Sulfonate Isobutyl Ester

Styrene sulfonate isobutyl ester (SSiB) was synthesized following literature procedures.[14] When MTC was added to SSiB, the

Table 2. Thermal characterization data of the poly(MTC), PSSP and PSSiB homopolymers, and the PSSP-co-MTC and PSSiB-co-MTC copolymers. The glass transition temperatures (T_g) were obtained by differential scanning calorimetry (DSC), polymer decomposition was analyzed by thermogravimetric analysis (TGA).

		Poly(MTC)	PSSP	PSSP-co-MTC	PSSiB	PSSiB-co-MTC
DSC: T_g [°C]		−46	137	50	179	35
TGA:*T* [°C]/Mass loss [%]	Alkyl		200	200	156	180
			15%	20%	5%	13%
	SO_2/SO_3		250–380	240–370	230–360	240–370
			38%	26%	38%	26%
	Aromatics		>380	370–650	>360	370–650
			30%	31%	34%	32%
	Backbone cleavage	360				

reaction immediately became dark red and viscous. In the ^{1}H-NMR spectra of the polymerization product (Figure S2, Supporting Information), additional peaks to the ones expected for the MTC and SSiB repeat units of the reaction product, PSSiB-co-MTC, were found. This hints at an undesired side reaction besides copolymerization, potentially an alkylation of the MTC monomer. By NMR peak integration, the MTC repeat units in the crude polymer were estimated as 19%, i.e., the SSPiB to MTC ratio was 4.3:1, but again a substantial amount of homopolymer was present that could not be separated.

3.2.3. Polymerization Kinetics of MTC and SSP

The polymerization kinetics of the SSP/MTC copolymerization was investigated by NMR and GPC analysis to determine the optimal reaction time for the target copolymers. First, the conversion over time was determined by monitoring the monomer consumption using ^{1}H-NMR spectroscopy (**Figure 2**a,b).

The data in Figure 2a show that reaction times >6 h were needed to drive the reaction to significant conversion of both monomers and indicates that SSP was consumed faster than MTC at an equimolar ratio, leading to predominantly SSP-rich polymer chains. At a MTC to SSP ratio of 2:1, the conversion of MTC was significantly faster than that of SSP (Figure 2b) until a plateau at around 50% conversion was reached (after 60 min), while the conversion of SSP continued to increase. This indicates profound reactivity differences between the two monomers. This was also observed, in a more quantitative way, in previous CKA copolymerization studies: for the copolymerization of styrene with MDO, Bailey et al. reported reactivity ratios of $r_{MDO} = 0.021$ and $r_{styrene} = 22.6$. In the here investigated case, both MTC and SSP preferred homopolymerization over copolymerization. The plot of molar mass over time (Figure 2c) does not have the expected plateau shape commonly found for free radical polymerizations, with M_n independent of the reaction conversion after an induction period. This is not surprising since the observed M_n development is an overlay of the formation of the copolymer and at least one of the homopolymers.

3.2.4. Polymer Characterization

The reaction products PSSP-co-MTC and PSSiB-co-MTC were studied by gel permeation chromatography (GPC), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) (**Figure 3**). The GPC elugrams (Figure 3a) contained one monomodal polymer peak in each case, with a slight tailing on the low molar mass flank of the curve. The number average molar masses and polydispersity indices (PDI) obtained are summarized in Table 1. The PDI of PSSP-co-MTC (2.1) was slightly higher than that of PSSiB-co-MTC (1.6), possibly because of more chain transfer, branching and cross-linking reactions. The thermal properties of the two copolymers, together with those of the respective homopolymers, are summarized in **Table 2**, and a representative DSC curve is shown in Figure 3c. The data show that every sample tested had a single glass transition temperature (T_g), and that the T_gs of the copolymers PSSP-co-MTC (50 °C) and PSSiB-co-MTC (35 °C) were in between those of the parent homopolymers (polyMTC: −46 °C; PSSP: 137 °C, and PSSiB: 179 °C). Since the NMR analysis confirmed the presence of MTC homopolymer in these samples, but only one T_g was detected, we can conclude that the homopolymer and copolymer chains are well miscible and formed a homogeneous blend. Such a phenomenon has been previously reported by Mushtaq et al. for polysulfone (PSU) and polyvinyl acetate (PVAc).[16] Polymer blend membranes that were prepared from PSU and PVAc showed a single T_g for all compositions, which is surprising given their rigid nature. Thermogravimetric analysis (TGA) was used to determine the onset of decomposition of each polymer, which is an important parameter for the intended removal of the ester groups. The poly(MTC) homopolymer was stable up to 360 °C, indicating that introduction of ester groups into the poly(styrene sulfonate) backbone would not compromise its thermal stability. For the PSSP-co-MTC and PSSiB-co-MTC copolymers, the first mass loss was observed at 200 and 180 °C, respectively, and was assigned to the loss of the sulfonate ester alkyl group. As expected, the isobutyl ester could be more easily cleaved than the propyl ester. However, the mass loss of the propyl ester was 20% (theoretical mass: loss 16%), while that of the isobutyl ester was only 13% (theoretical mass: loss 21%). Apparently, the above-mentioned alkylation side reactions during the synthesis of PSSiB-co-MTC, which most likely led to C—C bonds, also limited the possible mass loss. In the light of these side reactions, the characterization data for PSSiB-co-MTC that are presented here should be treated with care. The next significant mass loss (26% for both polymers, between 240 and 370 °C) corresponds to loss of the SO_3 fragment. Any mass loss observed at higher temperatures corresponds to loss of the aromatic fragments. An

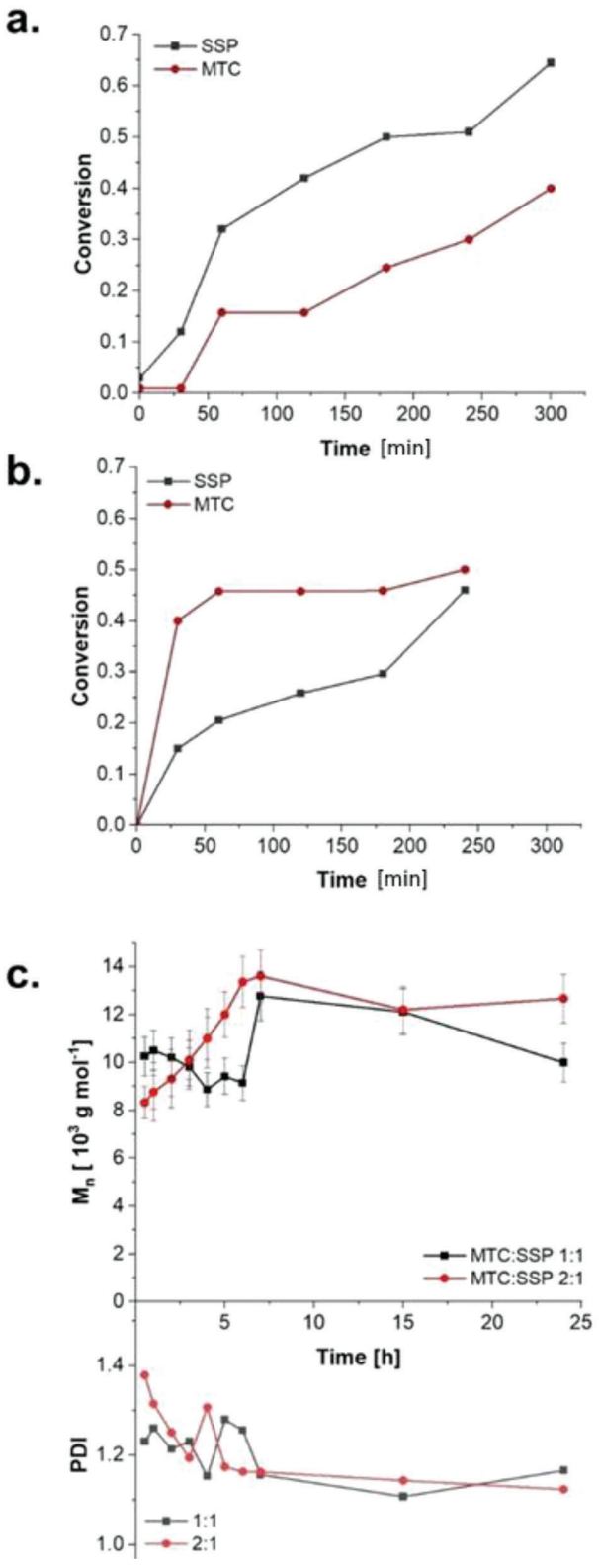


Figure 2. Polymerization kinetics of PSSP-co-MTC. a,b) Monomer conversion for a 1:1 and 2:1 monomer ratio, respectively, determined by ^{1}H NMR spectroscopy; c) Development of the molar mass M_n (upper graph) and PDI (lower graph) over time for copolymerizations with a MTC to SSP ratio of 1:1 and 2:1, respectively, determined by GPC.

isothermal TGA run (Figure 3d, at 150 °C) further confirmed that the isobutyl ester could be more easily cleaved than the propyl ester, however the process stagnated at a mass loss of 13% for ≈120 min, after which the polymer main chain decomposed.

Overall, the polymer characterization data confirm that PSSP-co-MTC and PSSiB-co-MTC could indeed be obtained. Originally, it was expected that PSSiB-co-MTC would be an intermediate from which the polyanionic target polymer could be obtained by thermal treatment. However, the observed side reactions and the incomplete thermal deprotection indicate that this was not a viable synthetic pathway, and PSSiB-co-MTC was therefore not be considered further.

3.2.5. Deprotection of PSSP-co-MTC

The thermal removal of the alkyl ester groups from the PSSP-co-MTC side chains, which seemed quantitative in the initial TGA measurement, was studied at different temperatures. For this, PSSP-co-MTC was placed in a vacuum oven and heated at 140 and 150 °C for 120 min. During these experiments, the sample turned black, which indicates structural decomposition. Afterward, the samples were weighed, and the mass loss was calculated (see Section S1.4.2, Supporting Information). In both cases, a mass loss of about 25% was obtained. NMR spectra were recorded before and after thermal treatment and normalized to compare signal intensities. The data show that not only the alkyl ester groups of the side chains were cleaved (signals at 4.2 and 3.7 ppm), but that also the signals from the MTC-repeat units nearly completely vanished. A new broad peak at 3.1 ppm hints at the formation of methyl groups after the sulfonate ester cleavage. Thus, the thermal deprotection of PSSP-co-MTC was also not possible. The alternative method, which is acid- or base-catalyzed deprotection, could not be used as it would likewise affect the ester group in the backbone.

3.2.6. Hydrolytic Degradation

Even though PSSP-co-MTC could not be thermally deprotected to a satisfactory extent, this polymer could be used as a model compound to study the hydrolysis rate of the MTC repeat units in a hydrophobic environment. For this, thin films of PSSP-co-MTC were cast onto functionalized silicon wafers carrying benzophenone groups,[13] which made the substrate more hydrophobic. For degradation, the thus formed films were immersed into phosphate buffer (PBS, pH 7 and physiological NaCl concentration, with and without lipase addition), and their layer thickness reduction over time was studied by ellipsometry (**Figure 4**a). In both cases, the film thickness (about 160 nm) stayed constant up to 12 days, and then decayed to less than 10 nm on day 17. This indicates bulk erosion of the hydrophobic film, i.e., the carbonyl ester groups in the material gradually dissociated until layer percolation failed and the entire material delaminated. As the enzyme could not penetrate the hydrophobic film, the degradation kinetics were the same with and without enzyme use. As pointed out by one of the reviewers, a control consisting of PSSP without carboxylate groups should have been used as a control experiment here to confirm the bulk degradation and exclude a simple delamination process. While this is very true, it seems unlikely that

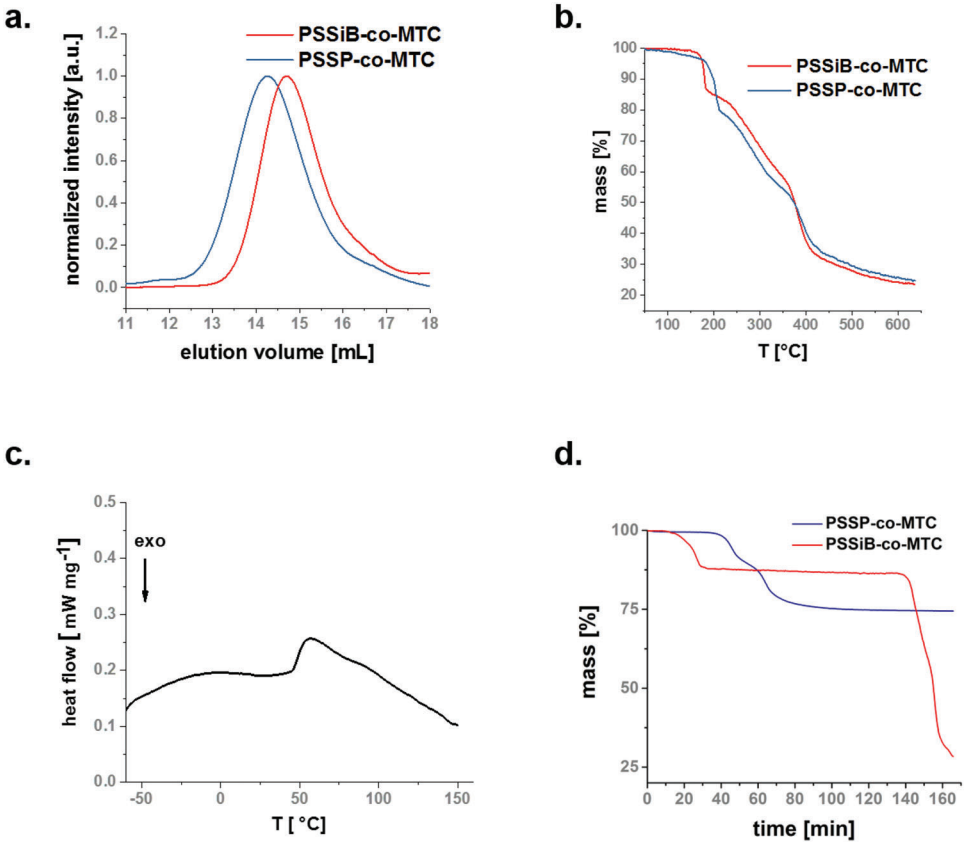


Figure 3. Characterization of PSSP-co-MTC and PSSiB-co-MTC: a) Gel permeation chromatography elugrams (RI detector); b) TGA curves from 50 to 650 °C (heating rate :10 °C min^{-1}); c) DSC curve of PSSP-co-MTC (heating rate 10 °C min^{-1}); d) isothermal TGA curves (150 °C for 120 min).

the layer would delaminate only after 12 days under these conditions, and not already within a few hours. Also, if the film cleanly delaminated from the substrate, there would not be a remaining thickness of about 10 nm. This remaining thickness hints at a loss of percolation within the film (i.e., cohesive failure, not adhesive failure).

Degradation of PSSP-co-MTC particles dispersed in aqueous solution was also studied. For this, copolymer powder was dispersed in aqueous solution at 37 °C (with additional enzyme). Samples were taken over 14 days and analyzed by GPC (Figure 3b). The first signs of degradation were observed after 2 days, when low molar mass peaks (oligomers) were found at an elution volume of 20–21 mL. Additionally, the molar mass of the main peak at 13–17 mL decreased over time, as shown in Figure 3c. These findings, i.e., slow but measurable degradation, further confirm the presence of hydrolysable ester groups in the back polymer bone. These results also confirm that the carbonyl ester groups hydrolyze within a few days, which further supports the bulk degradation argument for the film degradation.

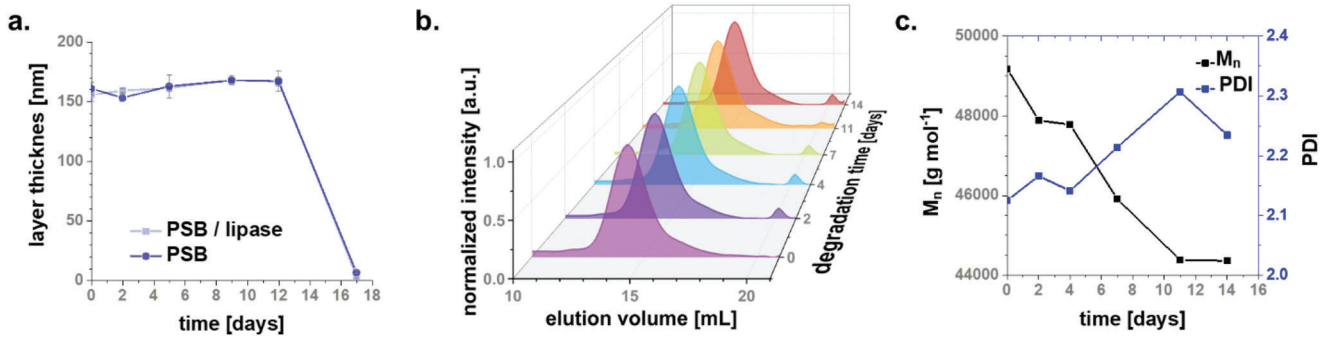


Figure 4. Degradation studies of PSSP-co-MTC. a) Polymer film degradation in phosphate buffer with and without additional enzyme: film thickness (determined by ellipsometry) versus degradation time; b) Degradation of polymer powder (dispersed in phosphate buffer) monitored by GPC; c) molar mass M_n and PDI of PSSP-co-MTC during hydrolytic degradation.

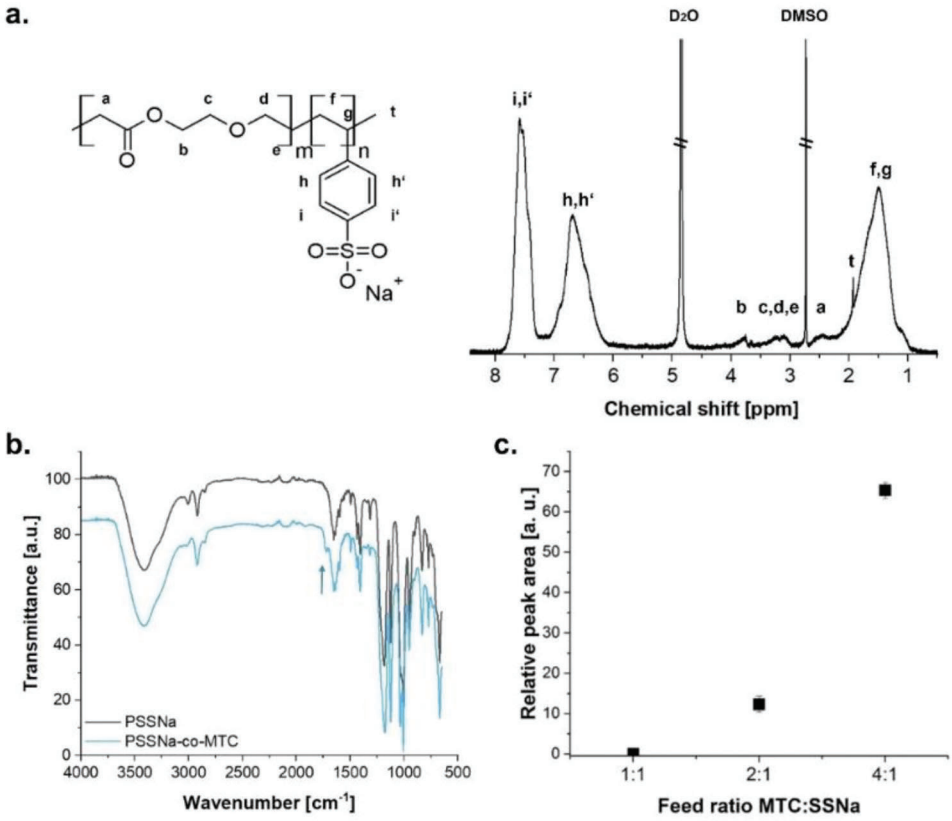


Figure 5. ^{1}H-NMR and FTIR analysis of PSSNa-co-MTC copolymers. a) Representative NMR spectrum of PSSNa-co-MTC. b) Representative FTIR spectra of PSSNa-co-MTC with 11% MTC content. The arrow corresponds to the carbonyl stretching vibration of the ester group in PSSNa-co-MTC. c) Relative peak areas of the C = O stretching vibration in the respective copolymers.

3.3. Approach 2: Copolymers of 2-Methylene-1,3,6-Trioxocane and Styrene Sulfonate Sodium Salt

3.3.1. Copolymerization of 2-Methylen-1,3,6-Trioxocane (MTC) with Styrene Sulfonate Sodium Salt

To obtain the desired poly(styrene sulfonate) anion with intended break points in the main chain, styrene sulfonate sodium salt and MTC were directly copolymerized via free radical polymerization. This method was chosen over controlled radical polymerization as, to our knowledge, the latter does not provide advantages in the sequence control in the batch mode.[17] These reactions were carried out in dimethyl sulfoxide (DMSO) (Scheme 1c) at a temperature of 60 °C. The crude polymer was purified by precipitation into ethyl acetate. In ^{1}H-NMR spectra of the purified product (example shown in **Figure 5**a), both the characteristic aromatic peaks of PSSNa and the aliphatic peaks of the MTC repeat units between 4.3 and 3.5 ppm were found. The percentage of MTC repeat units per PSSNa unit was determined by comparing the integral intensities of the aromatic PSSNa peaks between 8 and 6 ppm with the MTC repeat unit peaks between 3.7 and 2.5 ppm. For the purified PSSNa-co-MTC copolymer synthesized with a 1:1 monomer ratio, an amount of 2% MTC units was calculated. Before purification, the obtained crude product had 22% MTC units and a pronounced peak at 4.2 ppm, which is characteristic for the hydrogen atoms adjacent to an ester group between two MTC units, thus confirming the presence of MTC homopolymer. No such peak was found in the spectrum of the purified copolymer (Figure 5a), indicating the absence of MTC homopolymer. (At a total amount of 2% MTC repeat units, any neighboring MTC units in the copolymer should be below the detection limit of the method.) For the copolymerization of MTC with styrene, an MTC content of 24% had been reported.[18] Although it was not specified in this reference work if any MTC homopolymer was present, it seems reasonable to assume that this was the case, as these results resemble the data obtained for the crude product of this work.

When the SSNa to MTC ratio in this series of experiments was raised to 1:2, the amount of MTC repeat units in the copolymer increased to 7%, and to 11% for a ratio of 1:4. Thus, MTC incorporation did not increase much even at a significant excess of MTC. This result matches previous data for the copolymerization of the cyclic ketene acetal 2-methylene-1,3-dioxepane with styrene.[10]

The molar mass of the copolymers was analyzed by GPC (**Table 3**). The data show that the molar mass decreased with increasing MTC content. This trend was also observed in literature data.[10] A representative FTIR spectrum of a PSSNa-co-MTC copolymer with 11% MTC is shown in Figure 5b. The stretching vibration of the C = O ester group is found at 1731 cm^{-1} (arrow in Figure 5b),[19] the SO_2 group at 1183 cm^{-1}, and the aryl C–H signals at <3000 cm^{-1}.[19,20] Since the material was hygroscopic, a substantial water peak at 3425 cm^{-1} was also observed.

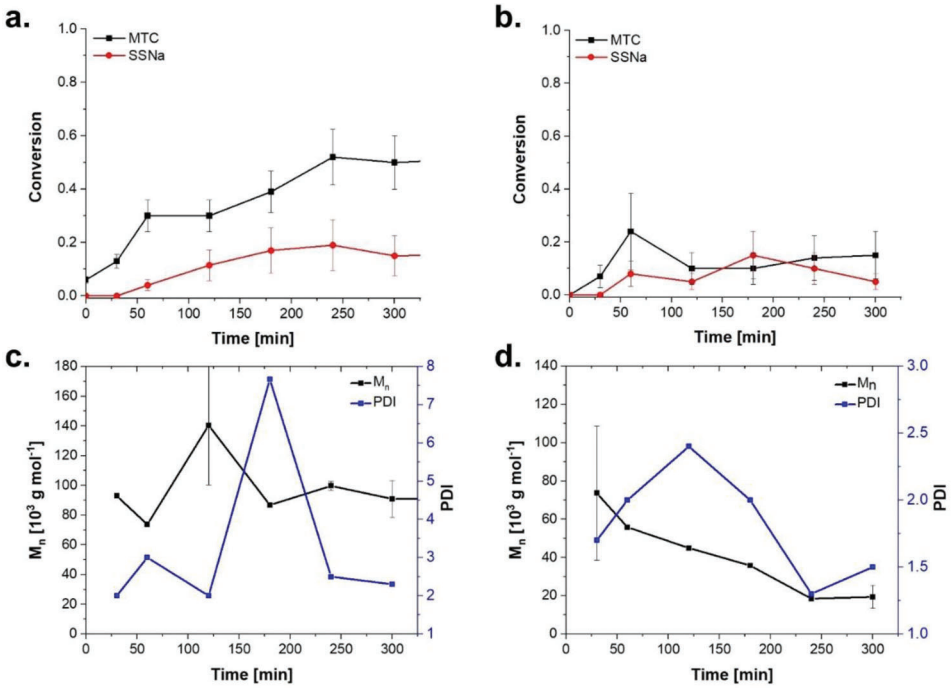


Figure 6. Polymerization kinetics of PSSNa-co-MTC. a) Conversion versus time at an equimolar comonomer ratio; b) conversion versus time for a 2:1 MTC to SSNa ratio. c) Molar mass of the formed polymer for a 1:1 MTC to SSNa ratio. d) Molar mass of the formed polymer for a 2:1 MTC to SSNa ratio. Error bars depict the measurement uncertainty.

Additionally, the relative peak area of the C=O stretching vibration at 1731 cm^{-1} was determined for the different monomer feed ratios to visualize the increasing incorporation of MTC (Figure 5c).

3.3.2. Polymerization Kinetics

The monomer conversion over time was monitored by NMR spectroscopy and GPC, as described for the corresponding alkyl ester copolymerizations (**Figure 6**, plots of conversion vs time for the MTC to SSNa ratios 1:1 and 2:1, respectively). Given the multitudinous possible sources of error in these data (sample homogeneity, calibration, signal to noise ratio, spectral overlap, etc.), we assumed an accumulated error of 5–20% and added theoretical error bars of 20%. The data show that the monomer conversion was slow but continuous at a 1:1 ratio, with MTC reacting faster than SSNa. At a higher MTC to SSNa ratio, the reaction was even more sluggish, indicating that MTC is a retarding agent for the formation of the target copolymer. The molar mass and PDI development for these reactions (Figure 6c,d) also indicate that more than one kind of polymer species formed, as the expected independence of M_n from conversion was not found. The PDI was very high, possibly due to back-biting and chain transfer reactions that led to branched polymers or cross-linking. These are well known problems encountered in batch copolymerization reactions of CKAs.[21]

Table 3. Characterization data for PSSNa-co-MTC copolymers. MTC content and SSNa conversion were determined by NMR spectroscopy. The number average molar mass M_n and the PDI were determined by GPC (MCX column, 0.1 M phosphate buffer, 1 mL min^{-1}).

MTC:SSNa ratio [%]	Content MTC [%]	Conversion SSNa [%]	M_n [kg mol^{-1}]	PDI
1:1	2	98	64	9
2:1	7	96	34	2.8
4:1	11	93	10	3

3.3.3. Polymer Characterization and Hydrolytic Degradation of PSSNa-co-MTC

The purified PSSNa-co-MTC copolymers were also analyzed by DSC and GPC. A representative DSC curve is shown in **Figure 7**a, and the results are summarized in **Table 4**. The DSC data showed that every sample tested had a single glass transition temperature (T_g), and that the T_gs of the copolymers PSSNa-co-MTC ($T_{g,\,2\%}$: 43.7 °C; $T_{g,\,7\%}$: 40.1 °C; $T_{g,\,11\%}$: 38.4 °C) were in between those of poly(MTC) (−46 °C) and the poly(styrene sulfonate) homopolymer (219 °C). With increasing MTC content, the T_g values also slightly decreased.

To estimate the number of MTC repeat units per polymer chain, the PSSNa-co-MTC copolymers were hydrolyzed and analyzed by GPC, and the molar mass of the hydrolysis products was compared to that of the parent copolymers (**Figure 8**). The GPC data of the intact copolymers indicate for the 1:1 ratio of PSSNa and MTC that the reaction was poorly controlled: the GPC curve was polymodal, and the PDI was as large as 11.3 (Figure 8a). Changing the MTC to PSSNa ratio to 2:1 significantly improved

Table 4. GPC analysis of PSSNa-co-MTC polymers and degraded oligomers, respectively.

			M_n of oligomers after degradation [kg mol^{-1}]	
	MTC content [%]	M_n[kg mol^{-1}]	Theoretical	Experimental
1:1	2	64	10	32
1:2	7	34	2.9	13
1:4	11	10	1.5	1.9

the reaction control, giving an almost monomodal GPC curve and a much lower PDI (2.8, Figure 8b). The degradation of PSSNa-co-MTC was studied in two different conditions (both at 37 °C): in phosphate buffer and in 3 M aqueous NaOH solution. For this, polymer powder was dissolved in each of these reaction media. After a given reaction time, the powder was recovered (removal of water by rotary evaporation, dissolution of the polymer in methanol), dried, and analyzed by GPC. In phosphate buffer, the molar mass decrease after 26 days was less than 5% (from 83 100 to 79 000 g mol^{-1}, data shown in Figure S6 and Section S1.4.3, Supporting Information). In NaOH, an almost instantaneous drop of the molar mass was observed, indicating that the ester groups could be readily hydrolyzed at the elevated pH value. For longer reaction times, only negligible further changes in the M_n were observed. The theoretical molar mass of the respective oligomers were calculated using the equation previously published by Jackson et al.,[10]

$$\text{Degraded oligomer } M_n^{\text{theoretical}} = \left(\left(\frac{\text{SSNa molar composition}}{\text{MTC molar composition}} \right) \cdot \text{SSNa}_{\text{Mnr}} \right) + \text{MTC}_{\text{Mnr}} \quad (1)$$

with SSNa_{Mnr} = molar mass of a styrene sulfonate repeat unit; MTC_{Mnr} = molar mass of a MTC repeat unit. Table 4 shows that there is a significant disparity between the theoretical and experimentally determined molar mass of the degraded oligomers for the comonomer ratios 1:1 and 2:1. However, at a comonomer ratio of 4:1, the theoretical and experimental values were matching very well (1.5 and 1.9 kg mol^{-1}, respectively). From this observation we can conclude that the incorporation of MTC into the polymer backbone at a 1:1 and 2:1 ratio is not uniform, and that long runs of SSNa repeat units exist in these copolymers that are not interrupted by MTC. It is also possible that in these copolymers, MTC is mainly attached to the PSS polymer chain ends. At a ratio of 4:1, this problem seems to be overcome, and MTC incorporation into the polymer backbone seems more regular. This effect has been previously reported for ring-opening copolymerization of MTC and MDO.[10] However, the elugram for the degraded oligomer obtained at the 4:1 ratio was bimodal, with a small fraction at lower elution volumes. This can be attributed to a small amount of PSSNa homopolymer still present even in the purified copolymer. As an 11% MTC content (obtained at a 4:1 ratio) was sufficient for the aim of this work, the PSSNa to MTC ratio was not further optimized.

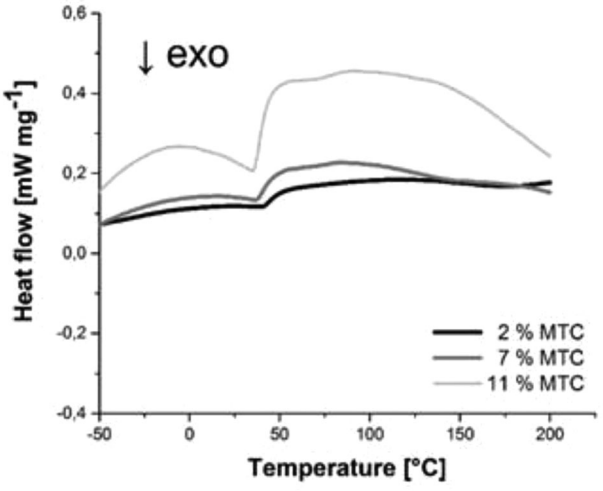


Figure 7. DSC thermograms of PSSNa-co-MTC copolymers.

4. Conclusion

In this work, we investigated the synthesis and degradation of copolymers of the cyclic ketene acetal MTC with styrene sulfonate alkyl esters, and with styrene sulfonate sodium salt. The data shows that copolymers with up to 11% MTC repeat units could be obtained at a MTC:SSNa ratio of 4:1, and that the PSSNa-co-MTC copolymers thus obtained were degradable by hydrolysis of the polymer main chain ester groups. Degradation of the corresponding PSSP-co-MTC esters proceeded much more slowly due to the poor solubility (and thus chemical availability) of these polymers when dispersed in aqueous medium. However, thin films made from this material could be completely delaminated from a substrate to which they were attached, indicating that the degradation proceeded by bulk erosion.

It has been previously reported that it is extremely difficult to control the ring-opening copolymerization of cyclic ketene acetals, and that it is likewise difficult to obtain copolymers from these monomers without structural defects such as cross-linking, branching and ring-retention, which all lead to a broadening of the molar mass distribution. The data presented here shows that these problems were also encountered in the PSSP-co-MTC and PSSNa-co-MTC systems. Yet for the PSSNa-co-MTC systems synthesized with a 4:1 MTC to SSNa ratio, the distribution of MTC repeat units in the main chain was relatively uniform, as indicated by the good match between the theoretical and experimental mass of the hydrolyzed oligomers. This indicates that the desired degradable poly(styrene sulfonate) anions were indeed obtained. So far, no other synthesis known to us leads to poly(styrene sulfonate) derivatives with main chain intended break points. From a molecular science perspective, the synthesis result is not fully satisfactory due to the lack of a better

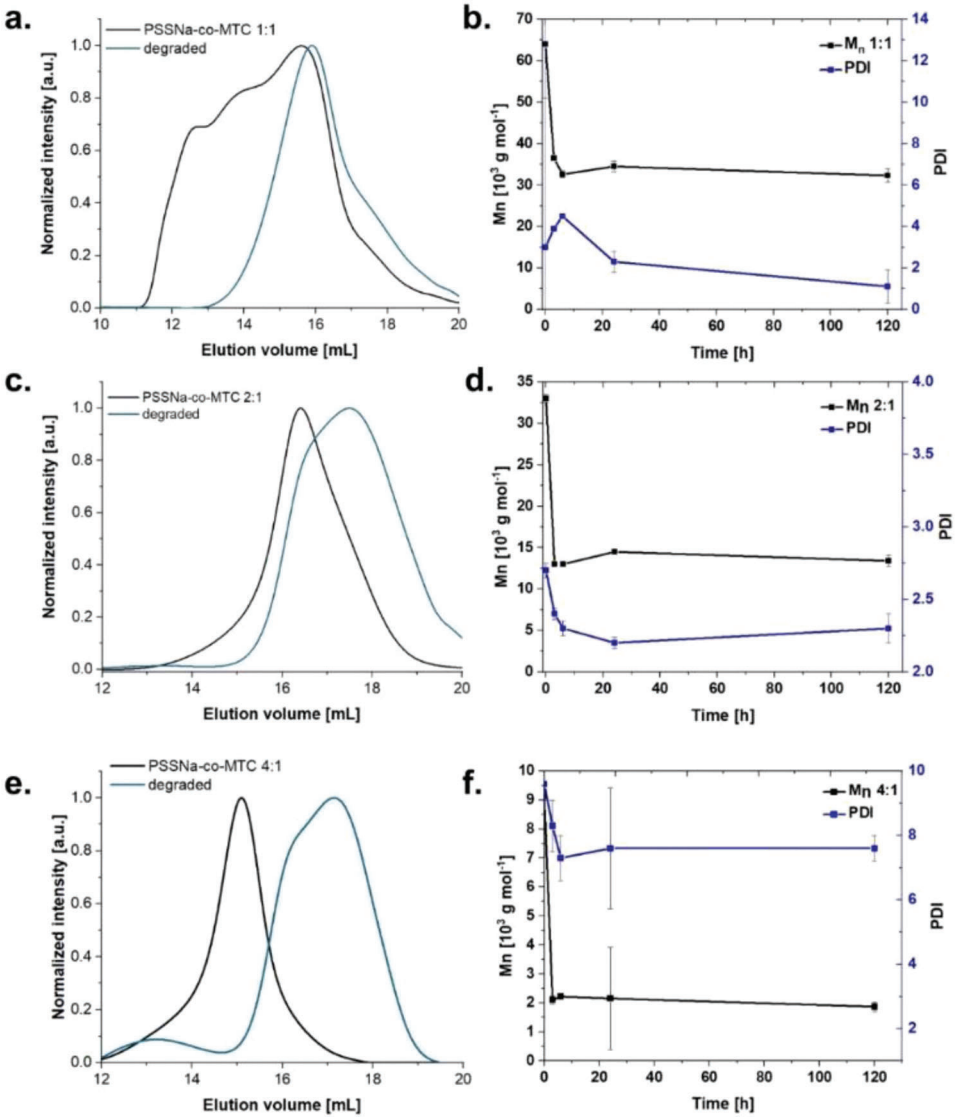


Figure 8. GPC characterization of PSSNa-co-MTC (showing the RI detector signal) before and after hydrolytic degradation in 3 M NaOH (conditions: PSS MCX column, 0.1 M phosphate buffer). a) Elugrams of PSSNa-co-MTC 1:1 (2% MTC) before and after degradation. b) Molar mass and PDI during the hydrolytic degradation of PSSNa-co-MTC 1:1 (2% MTC). c) Elugrams of PSSNa-co-MTC 2:1 (7% MTC) before and after degradation. d) Molar mass and PDI during the hydrolytic degradation of PSSNa-co-MTC 2:1 (7% MTC). e) Elugrams of PSSNa-co-MTC 4:1 (11% MTC) before and after degradation. f) Molar mass and PDI during the hydrolytic degradation of PSSNa-co-MTC 4:1 (11% MTC).

sequence control along the polymer chain. From a materials science perspective, these polyanions may very well do for applications in biomedical materials or sensors. As very recent work has shown for copolymerizations involving cyclic ketene acetals and vinylic monomers that semi-batch reactions yielded a better distribution and a higher percentage of degradable groups along the polymer backbone, future studies aimed at obtaining degradable poly(styrene sulfonate) should also adopt the semi-batch process.[11]

What is also important in this context is the finding that these polyanions hydrolyze very slowly under simulated physiological conditions. On the one hand, this guarantees sufficient stability for in situ applications, e.g., in vivo sensors. On the other hand, it has yet to be shown that full degradation of such a material at longer times is feasible, and that the resulting material can be either phagocytosed, or otherwise excreted. This, however, is best evaluated with a suitable animal model, and thus beyond the scope of the work here presented.

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.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords

degradation, PEDOT:PSS, poly(styrene sulfonate esters), poly(styrene sulfonate), polyanion

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