

# Synthesis and characterization of photo-crosslinked poly(carbonate anhydrides)

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**Abstract.** Biodegradable poly(carbonate anhydrides) based on poly(trimethylene carbonate) were synthesized by ring-opening polymerization. The hydroxyl-terminated oligomers were acid-functionalized with succinic anhydride and subsequently methacrylated to obtain photo-crosslinkable three-armed macromers with anhydride bonds. The degree of acid-functionalization was over 96%, and the degree of methacrylation was over 80%. The macromers were photo-crosslinked into networks at room temperature in a nitrogen atmosphere. In vitro degradation experiments in phosphate-buffered solution (pH 7.4) at 37 °C showed that the networks degraded rapidly with complete mass loss within 72 h. For networks prepared from the higher molecular weight, the presence of an alkenyl chain in the anhydride bond resulted in lower water uptake and consequently in a decrease in the degradation rate. The degradation mechanism of these networks showed characteristics of surface erosion.

**Keywords:** biodegradable polymers, poly(trimethylene carbonate), poly(anhydrides), polymer degradation, polymer networks

## 1. Introduction

Biodegradable and biocompatible polymers receive significant interest in the biomedical field for applications such as implants materials and drug delivery devices. Poly(trimethylene carbonate) (PTMC) is an amorphous polymer which has a low glass transition temperature of approximately  $-16\text{ °C}$  [1]. The mechanical properties of PTMC depend strongly on the molecular weight of the polymer [2]. Linear, non-crosslinked high molecular weight PTMC is a tough and flexible polymer that degrades via surface erosion *in vivo* without the release of acidic compounds [3, 4]. Due to its biocompatibility and biodegradability PTMC has potential for biomedical applications [5–12]. Non-crosslinked low molecular weight PTMC is soft and gummy with a low modulus and tensile strength. However, by photo-crosslinking methacrylate-functionalized low molecular weight

PTMC oligomers (macromers), networks that are creep resistant and have excellent mechanical properties can be prepared [13]. Due to these properties PTMC-based networks have been investigated for application as meniscus implants [14], microvascular networks [15], bone implants [16], intervertebral disk implants [17], and drug delivery devices [18]. By adjusting the molecular weight of the macromers used to prepare the networks, the mechanical properties can be tuned [13]. Additionally, the molecular weight of the macromers also influences the degradation rates of the networks [19]. In general, if the molecular weight of the macromers increases, so does the degradation rate. However, the rate of degradation is slow for networks prepared from macromers with molecular weights between 10 and 30 kg/mol, with a mass loss of only 0.5–3.7% in 36 weeks *in vivo* [19]. Crucially, the degradation appeared to take

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place via surface erosion. This allows the networks to obtain their mechanical strength during degradation, which is essential for load-bearing applications [1]. Previously, our group has reported on the preparation and characterization of photo-crosslinked poly(ester anhydrides) prepared from poly( $\epsilon$ -caprolactone) (PCL) and polylactide (PLA) [20–24]. Hydroxyl-terminated oligomers are acid-substituted with an anhydride compound to yield acid-terminated oligomers. The anhydride compound may be succinic anhydride or alkenyl succinic anhydrides containing 8–18 carbons in the alkenyl chain. Subsequent methacrylate-functionalization of these compounds results in crosslinkable macromers. Regular PCL networks, without anhydride bond, degrade very slowly [25, 26]. The addition of a labile anhydride bond results in networks that degrade much faster [21, 22], in 48 hours for the networks prepared with succinic anhydride to 64 to 72 hours for anhydrides containing an alkenyl chain with 12 or 18 carbons respectively. Increasing the macromer molecular weight also decreases the degradation rate [24].

Poly(ester anhydrides) networks are promising networks for drug delivery applications. While drug delivery with hydrophobic networks such as PTMC networks is possible, due to lack of microporosity and water uptake, the mesh size of the densely cross-linked network is the limiting factor in the drug release [27]. It is expected that the presence of succinic anhydride in the PTMC networks increases the water uptake and accelerates the degradation rate resulting in drug release with the polymer swelling and degradation as driving factors in the drug release. This would make PTMC-anhydride networks attractive materials for drug release applications. Also, developing PTMC-anhydride networks results in a material with tailorable degradation properties. Thus, the development of PTMC-anhydride networks is interesting not only for drug delivery but for the broader biomedical materials field in general.

Therefore, in this first study, a set of PTMC-anhydride networks with different succinic anhydrides was prepared and characterized by water uptake, degradation rate and type of erosion. To prepare these networks, low molecular weight macromers were chosen as (i) the degradation for those networks was expected to be faster, and (ii) the oligomer viscosity of these lower molecular weight macromers allows for similar synthesis without solvents.

## 2. Experimental

### 2.1. Materials

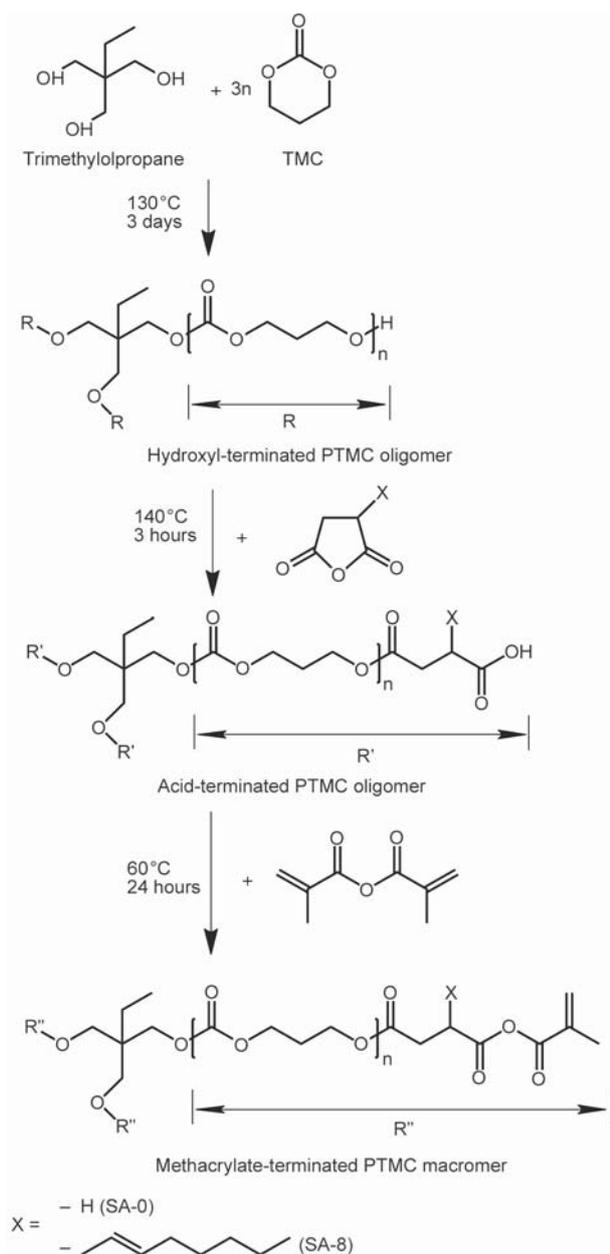
Trimethylene carbonate ( $\geq 99.0\%$ , TMC) was purchased from ForYou Medical Co. (China). Trimethylol propane (TMP), succinic anhydrides, methacrylic anhydride, hydroquinone, tin(II) 2-ethylhexanoate ( $\text{Sn}(\text{Oct})_2$ ) and d-chloroform were obtained from Sigma-Aldrich (USA). Chloroform was obtained from Merck (Germany) and TPO-L (Ethyl Phenyl (2,4,6-trimethylbenzoyl)phosphinate) was obtained from Carbosynth Limited (UK). Phosphate-buffered solution (PBS, pH 7.4) was purchased from Oy FF-Chemicals Ab (Finland). All chemicals were used as received.

### 2.2. Synthesis and characterization of PTMC-anhydride macromers

Three-armed hydroxyl-terminated PTMC oligomers were prepared by a 3-day ring-opening polymerization of TMC at  $130^\circ\text{C}$  under nitrogen atmosphere using TMP as initiator and  $\text{Sn}(\text{Oct})_2$  as catalyst. By adjusting the monomer to initiator ratio different molecular weights ( $M_n$ ) could be obtained. For each molecular weight, two out of three oligomers were acid-functionalized by a 3 h reaction of the hydroxyl groups with (alkenyl) succinic anhydride (3.09 mol/mol oligomer) at  $140^\circ\text{C}$ . To obtain photo-crosslinkable macromers, all oligomers are finally methacrylate-functionalized with methacrylic anhydride (7.5 mol/mol oligomer) in a 24 h reaction at  $60^\circ\text{C}$  in the presence of hydroquinone (0.1 wt% relative to the amount of monomer) preventing premature cross-linking. A reaction scheme of the preparation of photo-crosslinkable PTMC-anhydride macromers is shown in Figure 1.

The number average molar mass ( $M_n$ ) and monomer conversion of the oligomers, the degree of acid substitution, and degree of methacrylate functionalization were determined with  $^1\text{H}$  and  $^{13}\text{C}$  NMR (Brüker NMR Spectrometer AV III 400).

The thermal properties of the macromers were determined by differential scanning calorimetry (DSC) using a TA Instruments MT-DSC Q2000. Samples weighing 5–10 mg were heated from  $-90$  to  $100^\circ\text{C}$  at a rate of  $10^\circ\text{C}/\text{min}$  and subsequently cooled to  $-90^\circ\text{C}$  at a rate of  $10^\circ\text{C}/\text{min}$ . After 5 minutes at  $-90^\circ\text{C}$  a second heating scan to  $100^\circ\text{C}$  at a rate of  $10^\circ\text{C}/\text{min}$  was run, which was used to determine the glass transition temperatures ( $T_g$ ) of the macromers.



**Figure 1.** Reaction scheme of the preparation of photo-crosslinkable PTMC-anhydride macromers.

### 2.3. Network formation and characterization

To obtain photo-crosslinked networks, the liquid macromers were mixed with 5 wt% TPO-L photo-initiator and poured into cylindrical molds ( $d = 5$  mm,  $h = 2.5$  mm). The macromers were subsequently crosslinked at room temperature under nitrogen atmosphere in a self-made crosslink box for 30 min at 395–405 nm at an intensity of 1 mW/cm<sup>2</sup>. The obtained networks were post-cured under visible light for 40 minutes and then stored in vacuo.

The volume degree of swelling ( $q$ ) and gel content of the obtained networks were determined in triplicate at room temperature by swelling the networks

in chloroform for 24 hours. The values were calculated using Equations (1) and (2):

$$q = 1 + \frac{m_{\text{swollen}} - m_{\text{dry}}}{m_{\text{dry}}} \cdot \frac{\rho_p}{\rho_s} \quad (1)$$

$$\text{Gel content [\%]} = \frac{m_{\text{dry}}}{m_{\text{initial}}} \cdot 100 \quad (2)$$

where  $m_{\text{swollen}}$  is the mass of the swollen networks,  $m_{\text{dry}}$  the mass of the insoluble part of the networks after drying,  $m_{\text{initial}}$  the initial mass of the networks, and  $\rho_p$  and  $\rho_s$  are the densities of PTMC (1.31 g/cm<sup>3</sup>) and chloroform (1.48 g/cm<sup>3</sup>), respectively.

The thermal properties of the networks were determined by DSC, equally as previously described for the macromers. In addition, the thermal decomposition temperatures of the polymer networks were determined by Thermogravimetric Analysis (TA Instruments TGA Q500). Samples were heated from 30 to 600 °C at 10 °C/min under a nitrogen atmosphere. The hydrolysis of the networks in PBS (pH = 7.4) was performed by immersing the specimens in 10 mL (37 °C, shaking at 100 rpm) of PBS and recovery of the specimens at pre-determined intervals. For each time point, three parallel specimens were weighted and the thickness was measured before degradation. At recovery, the specimens were weighed again to determine the water-uptake. The specimens were then dried in vacuum until constant weight was achieved and the mass and thickness of the specimens could be determined. The water uptake was calculated using Equation (3):

$$\text{Water uptake [\%]} = \frac{m_{\text{wet}} - m_{\text{dry}}}{m_{\text{dry}}} \cdot 100 \quad (3)$$

where  $m_{\text{wet}}$  is the mass of the specimens at the moment of recovery from the buffer and  $m_{\text{dry}}$  is the mass of specimens after drying.

## 3. Results and discussion

### 3.1. Polymer synthesis and macromer analysis

The reaction scheme of the PTMC-anhydride polymerizations is shown in Figure 1. The synthesis of photo-crosslinkable PTMC-anhydride macromers consisted of three steps. First, three-armed hydroxyl-terminated oligomers were synthesized by ring-opening polymerization of TMC using TMP as initiator. By adjusting the monomer to initiator ratio, the molecular weight of the oligomer could be controlled. The targeted molecular weights were 900

and 2000 g/mol, hereafter called PTMC-900 and PTMC-2K, respectively. Second, the hydroxyl termination was converted into acid termination by a reaction with succinic anhydride or alkenyl succinic anhydride containing 8 carbons in the alkenyl chain. Third, the acid termination was changed to methacrylate termination by a reaction with methacrylic anhydride. The reaction conditions were derived from previous work on TMC syntheses and the preparation of poly(ester anhydrides) [13, 20, 28].

Table 1 gives an overview of the obtained oligomer molecular weights and monomer conversions, as determined by  $^1\text{H-NMR}$ . By comparing the area of the  $-\text{CH}_3$  peak of the TMP initiator at  $\delta$  0.92 ppm with the area of the PTMC methylene peak at  $\delta$  4.24 ppm the  $M_n$  of the oligomer could be determined. Besides, by comparing the PTMC methylene peak with the MC monomer peak at  $\delta$  4.45 ppm the conversion was calculated. The regular (non-acid-substituted) PTMC oligomers were directly methacrylate-functionalized. The degree of functionalization (DF) of these macromers was also determined by  $^1\text{H-NMR}$ . Methacrylate-functionalization was confirmed by the appearance of the H-signals of the  $\text{C}=\text{CH}_2$  groups at  $\delta$  5.58 ppm and  $\delta$  6.11 ppm. The degree of functionalization was calculated by comparing these peaks with the TMP initiator peak.

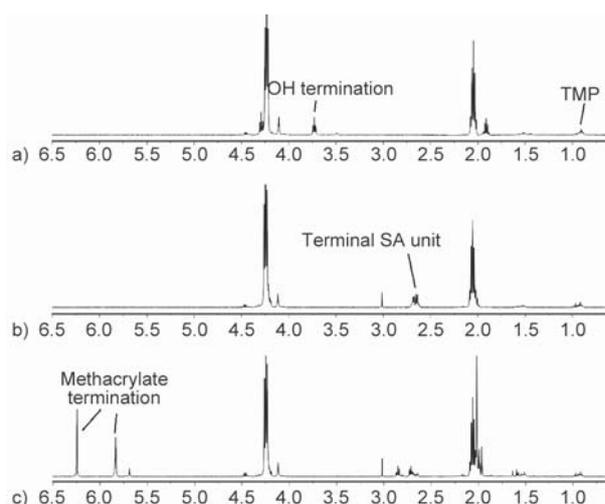
The acid functionalization of PTMC oligomers can be confirmed by  $^1\text{H-NMR}$  by the disappearance of the signals of the last  $\text{CH}_2$  group of the oligomer chain end at  $\delta$  3.7 ppm, as was previously described for acid-substituted lactide and caprolactone polymers [20]. The degree of substitution (DS) was shown to  $>96\%$  in all cases.

The quantitative analyses of the methacrylate functionalization of acid substituted oligomers are easier to be done by  $^{13}\text{C-NMR}$  [20]. Besides, we calculated the oligomer molecular weight. Table 1 gives an

overview of obtained results. To calculate the  $M_n$ , we compared the signal of the carbon of the TMP initiator at  $\delta$  7.2 ppm to the carbons of the repeating monomer unit at  $\delta$  28.0 and  $\delta$  64.3 ppm.

The degree of methacrylate functionalization was calculated by comparing the signal of the TMP initiator with the signal of the methacrylate that appears  $\delta$  163.1 ppm after functionalization. The DF of all macromers was  $>80\%$ . A complete overview of the results can be seen in Table 1, while Figure 2 shows the  $^1\text{H-NMR}$  spectra and Figure 3 the  $^{13}\text{C-NMR}$  spectra of typical PTMC-anhydrides. All obtained macromers were viscous liquids at room temperature.

The thermal properties of the obtained macromers were analyzed with DSC; an overview of the obtained  $T_g$ 's is shown in Table 1. The observed  $T_g$ 's of the regular PTMC macromers are slightly lower than those previously reported of similar molecular weights [13], but this is likely due to remaining methacrylic anhydride and methacrylic acid. There does not appear to



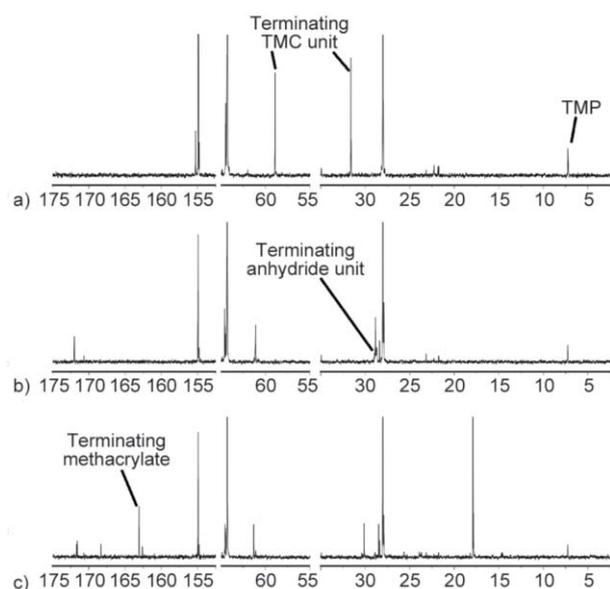
**Figure 2.**  $^1\text{H-NMR}$  spectra of (a) PTMC oligomer, (b) acid-substituted PTMC, and (c) methacrylated PTMC anhydride.

**Table 1.** Properties of PTMC and PTMC-anhydride macromers as determined by  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and DSC.

Macromer	$M_n$		Conv. [%]	DS [%]	DF [%]	$T_g$ (onset)	$T_g$ (mid-point) [°C]
	$^1\text{H-NMR}$ [g/mol]	$^{13}\text{C-NMR}$ [g/mol]					
PTMC-900	1000	–	99	–	79 <sup>a</sup>	–83	–82
PTMC-900-SA(0)	1000	1000	99	100	92 <sup>b</sup>	–79	–74
PTMC-900-SA(8)	1000	1000	99	100	99 <sup>b</sup>	–80	–77
PTMC-2K	2200	–	98	–	80 <sup>a</sup>	–69	–62
PTMC-2K-SA(0)	2100	2200	99	100	87 <sup>b</sup>	–65	–59
PTMC-2K-SA(8)	2200	2100	99	96	83 <sup>b</sup>	–71	–64

<sup>a</sup>DF determined by  $^1\text{H-NMR}$

<sup>b</sup>DF determined by  $^{13}\text{C-NMR}$



**Figure 3.**  $^{13}\text{C}$ -NMR spectra of (a) PTMC oligomer, (b) acid-substituted PTMC, and (c) methacrylated PTMC anhydride.

be a significant effect of the incorporation of an anhydride group in the macromer on the  $T_g$ .

### 3.2. Network formation and characterization

PTMC and PTMC-anhydride network cylinders were formed by photo-crosslinking the macromers using TPO-L as photo-initiator in a UV crosslinking box. After crosslinking, the cylinders were removed from the mold and characterized. An overview of the network properties is shown in Table 2. Network cylinders with gel contents between 92 and 100% were prepared. It should be noted that in initial experiments with networks prepared from two-armed macromers, maximum gel contents were not higher than approximately 70% (data not shown).

The degree of swelling in chloroform increased with the addition of the succinic anhydride to the macromer molecule structure. This is especially the case for the networks prepared with the higher molecular weight macromers. During the swelling process, the networks prepared from the lower molecular weight

macromers were prone to defragmentation due to the brittleness of these networks.

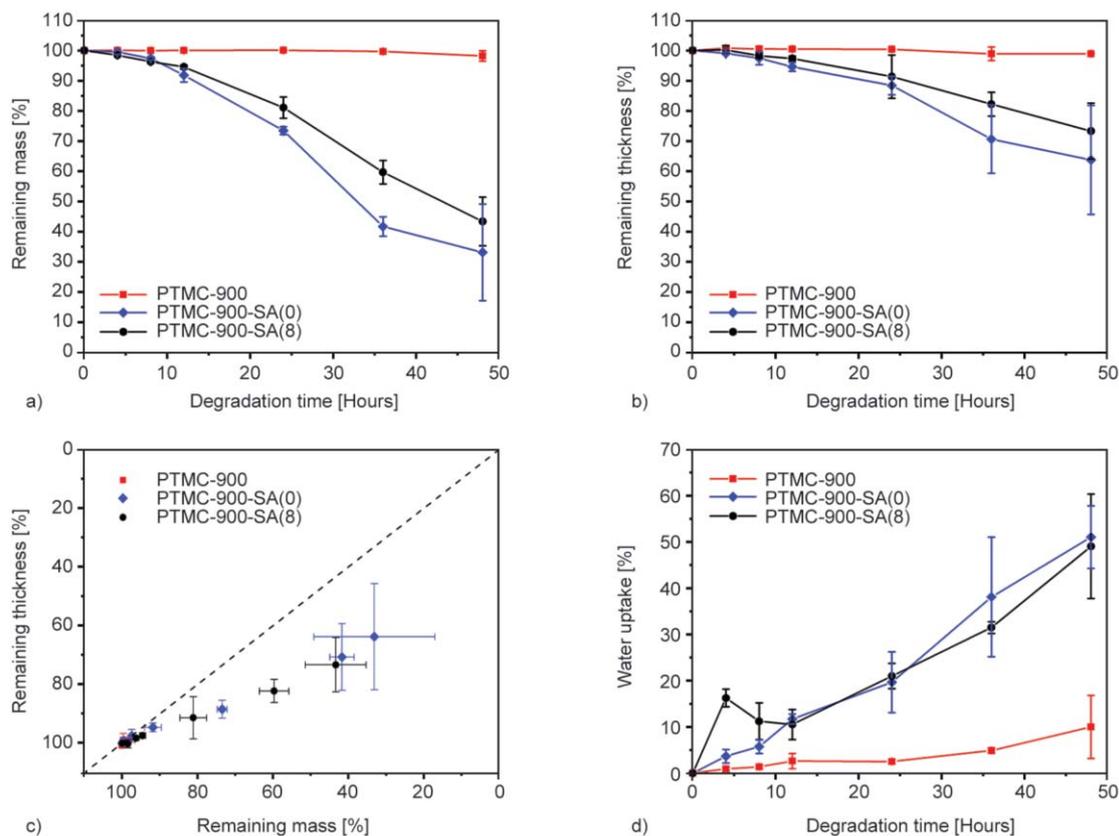
The glass transitions of the PTMC-2K and all three PTMC-900 networks could not be observed. This is likely due to the low molecular weight of the macromers, which results in densely crosslinked networks. As a result, the chain mobility of polymer chains in the networks is already strongly limited which means that the difference in mobility above and below the  $T_g$  is rather small and goes undetected. The  $T_g$ 's of PTMC-2K-SA(0) and PTMC-2K-SA(8) were close to the  $T_g$  of previously reported PTMC networks prepared from macromers with similar molecular weight [13]. The onset of the thermal decomposition temperatures of the polymer networks was between 267–301 °C.

### 3.3. Hydrolytic degradation of photo-crosslinked PTMC-anhydride networks

The *in vitro* hydrolytic degradation of photo-crosslinked PTMC-anhydride networks was investigated in PBS (pH 7.4) at 37 °C by determining the loss of mass and thickness of cylindrical samples over time. In addition, the water uptake of the samples was determined. Figure 4 shows the relative remaining mass and relative remaining thickness of the PTMC-900 networks in Figure 4a and Figure 4b respectively. As has been shown previously, regular PTMC networks do not show mass loss under this condition for this period [19]. The PTMC-900-anhydride networks, on the other hand, do show degradation with  $33.1\pm 16$  and  $43.3\pm 8\%$  average relative mass remaining after 48 hours for succinic anhydride and alkenyl succinic anhydride containing PTMC respectively. Besides, for both these samples a decrease in thickness is clearly noticeable. Further evidence of the decrease in thickness is shown in Figure 5. This indicates that these networks degrade via a surface erosion mechanism. Figure 4c shows that the mass is decreasing at a higher rate as compared to the thickness. If the degradation only proceeded from the top

**Table 2.** Properties of PTMC and PTMC-anhydride networks prepared by photo-crosslinking their respective macromers.

Network	Gel content [%]	Degree of swelling	$T_g$ (onset) [°C]	$T_g$ (mid-point) [°C]	$T_{\text{decomposition onset}}$ [°C]
PTMC-900	100±0.1	1.7±0.2	–	–	293
PTMC-900-SA(0)	100±0.1	1.9±0.1	–	–	280
PTMC-900-SA(8)	93±5.8	2.4±0.8	–	–	301
PTMC-2K	97±2.2	2.2±0.1	–	–	267
PTMC-2K-SA(0)	99±2.0	2.9±0.1	–11	–6	285
PTMC-2K-SA(8)	92±1.0	2.8±0.1	–15	–13	271



**Figure 4.** Degradation of PTMC-900-anhydride. (a) Relative remaining mass as a function of time. (b) Relative remaining thickness as a function of time. (c) Relative remaining thickness as a function of relative remaining mass. (d) Water uptake of the cylinders as a function of time.

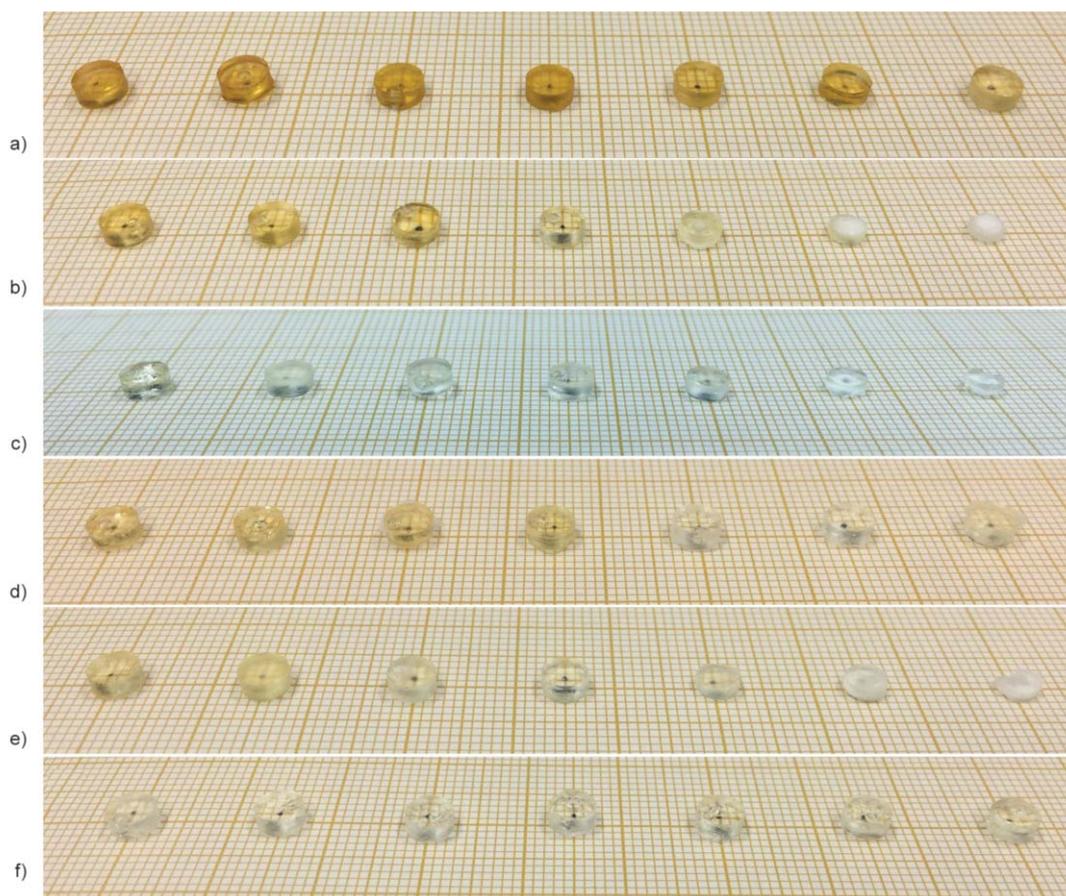
and bottom of the cylinders this rate would be equal [29], and the points would be shown on the dotted line in Figure 4c. The difference in rate indicates that these networks also loose mass elsewhere, likely on the side of the networks. Figure 4d shows that the water uptake of the PTMC-900-SA(0) is equal to that of PTMC-900-SA(8) which likely is the reason why the degradation of the PTMC-900-SA(8) has a similar degradation rate as PTMC-900-SA(0) while the additional alkenyl chain of the PTMC-900-SA(8) would be expected to significantly slow down the degradation rate [23].

Figures 6a and 6b show the relative remaining mass and relative remaining thickness of the PTMC-2K networks. Like the regular PTMC-900 networks, the regular PTMC-2K networks do not degrade. The PTMC-2K-SA(0) networks do show significant mass loss and loss of thickness in 48 h. As can be seen in Figure 6c, the decrease in mass is higher than the decrease in thickness, indicating that this network degrades similarly to the PTMC-900-SA(0) and PTMC-900-SA(8) networks. Figure 5 shows the loss of the thickness of vs. time. The PTMC-2K-SA(8)

networks do show a small loss of mass and thickness after 48 h but not enough to determine the degradation mechanism. Figure 6d shows that the water uptake of the PTMC-2K-SA(8) networks increases at a much slower rate than that of the PTMC-2K-SA(0) networks. This may be the reason the degradation of PTMC-2K-SA(8) networks is slower.

In preliminary experiments, the degradation products of the PTMC-anhydride network degradation in PBS were collected, dried in vacuum at 40 degrees, and used for NMR analyses. The degradation products showed the characteristic TMC peaks at  $\delta$  2.05 ppm and  $\delta$  4.25 ppm as well as the succinic anhydride peaks at  $\delta$  2.65 ppm. However, there were no methacrylate peaks visible at  $\delta$  5.58 ppm and  $\delta$  6.11 ppm indicating that the degradation products are acid-functionalized PTMC oligomers.

Some limitations concerning the above-described experiments and obtained results need to be discussed. First, the degradation experiments were only 48 h long. Experiments with longer timepoints were attempted, but for the fastest degrading networks the next time point of 72 hours could not be completed



**Figure 5.** Pictures of dried PTMC-900 (a), PTMC-900-SA(0) (b), PTMC-900-SA(8) (c), PTMC-2K (d), PTMC-2K-SA(0) (e), and PTMC-2K-SA(8) (f) networks exposed to PBS for (from left to right) 0, 4, 8, 12, 24, 36 and 48 h.

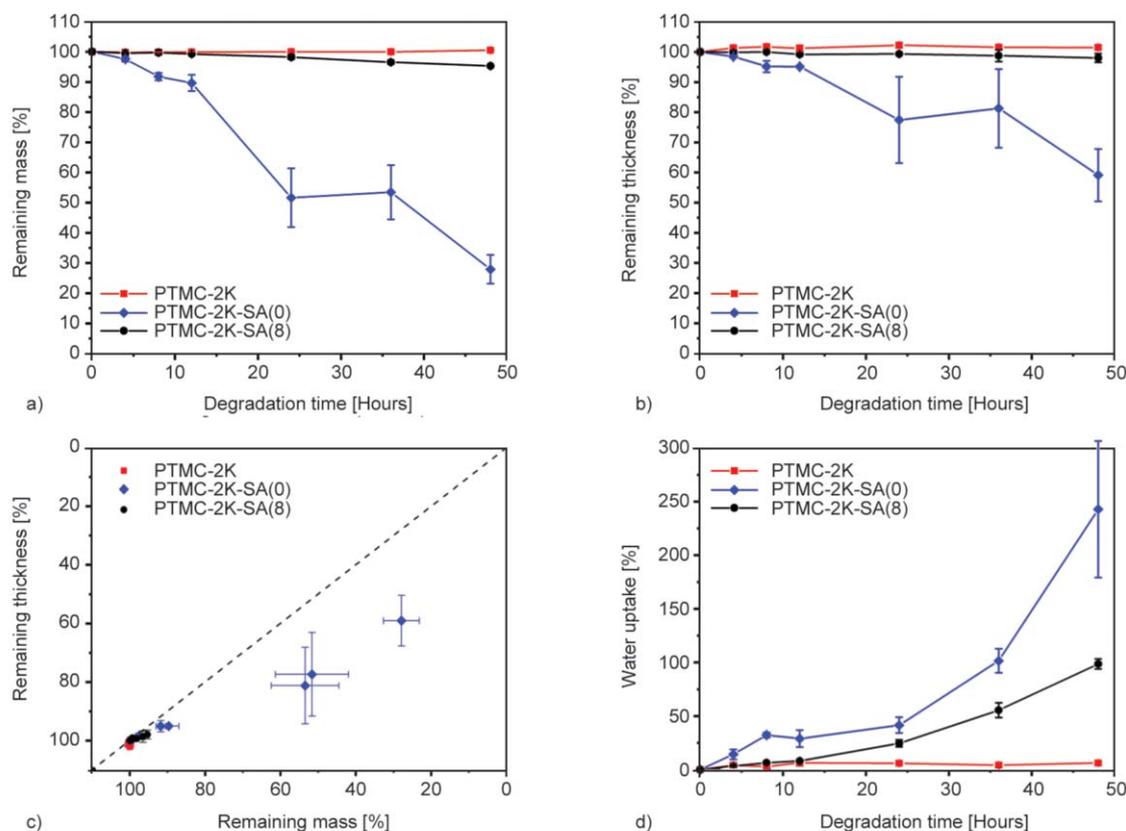
due to the networks being completely degraded somewhere between 48 and 72 h. Especially for networks prepared from PTMC-2K-SA(8) longer degradation times would be interesting to determine if the increase in water uptake will result in an increase in the rate of degradation. Longer degradation times can also be achieved by increasing the length of the alkenyl chains or the molecular weight of the macromers [23, 24].

Second, it has to be noted that the macromers were not purified after completion. These liquid macromers cannot be readily purified by precipitation in cold ethanol [13] and due to the low amounts of reagent used we chose not to remove excess methacrylic anhydride and formed methacrylic acid via elaborate vacuum distillation. However, the presence of methacrylic acid can accelerate the hydrolytic degradation as carboxylic acids increase the hydrophilic nature of their surroundings leading to an increase in the water uptake [30]. Polymer batches for follow-up experiments (*i.e.* for investigating the drug release or longer degradation times) should,

therefore, be purified to exclude the potential effect of the methacrylic acid.

Third, the pH of the PBS in the experiments was 7.4. However, the hydrolytic degradation of the anhydride-bond is base-catalyzed [31]. Therefore, degradation experiments in buffers with higher and lower pH should also be performed. For example, when considering drug delivery applications networks that degraded via hydrolytic anhydride-bond cleavage could potentially work as materials for orally administered colon drug-delivery as they can resist the acidic nature of the stomach.

The above-described results are encouraging as they show fast hydrolytically degradable PTMC networks can readily be prepared. However, it is also clear that for future applications several challenges remain. For drug delivery applications, polymer network degradation at more basic and acidic pH and the actual drug delivery characteristics remain to be investigated. Besides, the preparation and degradation of macromers of higher molecular weights and macromers with longer alkenyl chains can be considered.



**Figure 6.** Degradation of PTMC-2K-anhydride networks. (a) Relative remaining mass as a function of time. (b) Relative remaining thickness as a function of time. (c) Relative remaining thickness as a function of relative remaining mass. (d) Water uptake of the cylinders as a function of time.

For much higher molecular weights (*i.e.* 5000 g/mol and higher) it has to be considered that the viscosity of the acid-functionalized oligomers prior methacrylation is much higher than the viscosities of the low molecular weight oligomers used in this study, even at elevated temperatures. The reaction conditions may need to be adjusted to achieve a proper degree of functionalization. In addition, these macromers will be much more viscous, which may require the use of solvent and solvent extraction in network preparation.

#### 4. Conclusions

Photo-crosslinkable poly(trimethylene carbonate)-anhydrides were readily synthesized by the acid-functionalization of PTMC oligomers with (alkenyl) succinic anhydrides and subsequent methacrylate functionalization. The obtained PTMC-anhydrides were viscous liquids that could be photo-crosslinked to obtain solid networks. These networks were shown to be fast-degrading due to hydrolysis, with the degradation mechanism showing characteristics of surface erosion.

The here presented results open up a wide field of potential applications for the PTMC anhydrides. However, investigating the behavior of the networks under more acidic and basic degradation conditions, as well as longer degradation times by varying the macromer molecular weight and/or the length of the alkenyl chains of the anhydride group is needed to obtain more control over the degradation.

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