





# Macromolecular metamorphosis of thermoplastic poly(thio)urethanes containing boronic acid esters

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## Abstract

Biodegradable thermoplastic polyurethanes (TPUs) are promising materials for vascular grafts, due to their excellent mechanical properties and the possibility to incorporate degradable moieties. Especially degradability is important in the field of tissue engineering (TE) or regenerative medicine, because the synthetic scaffold should be replaced by human tissue after a certain time. We synthesized thermoplastic polythiourethanes (TPTUs) based on degradable chain extenders and tested their mechanical, thermal and degradation characteristics. As soft-block we used polytetrahydrofuran (pTHF) and as hard-block the aliphatic hexamethylenediisocyanate (HMDI) in combination with a variety of chain extenders. The focus was set on the boronic acid-based dithiol 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB). As dithiol-based reference 1,2-bis(2-mercaptoethoxy)ethane (BMEE) was used and bis(2-hydroxyethyl)-terephthalate (BHET) as well-known ester-based reference chain extender. By using BDB as degradable chain extender we could accelerate the degradation rate in terms of mass erosion at 37 and 90°C compared to BHET-based TPUs. However, a strong increase in molecular weight was observed under degradation conditions. Further investigation by ATR-FTIR revealed a release of benzene-1,4-diboronic acid (BDAB) in the polymer. This leads to the formation of a hydroxy-terminated polyol, which then undergoes an intramolecular functional group metamorphosis with the thiourethane group to form a crosslinked polymer. BMEE-based TPTUs in contrast show excellent mechanical properties, even better than BHET-TPUs but a slightly lower mass erosion at 37 and 90°C.

## KEYWORDS

addition polymerization, biodegradable, biomaterials, mechanical properties, polyurethane

## 1 | INTRODUCTION

Cardiovascular diseases (CVD), reported as the primary cause of death in 2019 in the United States, accounted for nearly 900,000 deaths<sup>1</sup> and are also one of the main

causes of death worldwide.<sup>2,3</sup> This have resulted in a growing demand for vascular grafts to bypass or reconstruct aneurysms or occlusions.<sup>4</sup> Due to the complications of vascular harvesting, the frequent shortage of allogeneic grafts and the immunological rejection of

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animal vessels, it is essential to produce synthetic vascular grafts.<sup>2,3</sup> Currently, state of the art synthetic materials for vascular grafts are expanded polytetrafluoroethylene (ePTFE) and polyethylene terephthalate (PET).<sup>5</sup> Nevertheless, they are only suitable for blood vessels with a diameter larger than 6 mm. When used as small-diameter vascular grafts, these materials tend to cause occlusion and thrombosis<sup>6–8</sup> due to an imbalance of mechanical properties and poor endothelialization.<sup>9–11</sup> Therefore, a small-diameter tissue-engineered vascular graft (TEVG) needs to fulfill following requirements: The material must be biocompatible and able to induce a good healing response to minimize inflammation reactions. Furthermore, it would be advantageous if the TEVG is biologically active and allowing the formation of an endothelium and the infiltration of vascular smooth muscle cells (SMCs).<sup>12,13</sup> This would lead to a better integration into the vascular system. Moreover, similar mechanical properties to the native vessel are necessary to be able to withstand the dynamic forces without permanent deformation.<sup>14</sup> Finally, the implant must be compliant enough to be handled during surgery and strong enough to hold the sutures and should degrade completely to be replaced by human tissue in the end.<sup>9,15,16</sup>

As mentioned above, ePTFE and PET as implant material lead to a compliance mismatch between the native vessel and the implant.<sup>17</sup> This can be reduced by using thermoplastic polyurethanes (TPUs) as their mechanical properties are more similar to those of native blood vessels.<sup>5,18,19</sup>

The final properties of TPUs can be relatively easily fine-tuned due to their segmented structure of soft-blocks (amorphous) and hard-blocks (crystalline). Hydrogen bonds and Van der Waals interactions between the individual hard blocks lead to physical crosslinking of the polymer.<sup>5,20</sup> Through a two-step synthesis via a prepolymer (macrodiisocyanate), a chain extender (e.g., small molecular weight diol) can be incorporated, which are necessary to establish above mentioned segmented nature of TPUs.<sup>21</sup> Together with the diisocyanate, the chain extender forms the hard-block. By using a cleavable chain extender, hard-block degradable TPUs can be synthesized, and by using a cleavable macrodiol, soft-block degradable TPUs can be prepared.<sup>22</sup>

However, an improvement in mechanical properties usually results in poorer processability and slower degradation, or vice versa. Therefore, a new approach is presented here in which macromolecular metamorphosis is enabled by the use of thermoplastic polythiourethanes (TPTUs). The thiourethane group is transformed into a crosslinked or branched polyurethane by nucleophilic substitution of OH-terminated polymer species. The resulting crosslinked TPTU therefore has different mechanical

properties than the linear TPTU before metamorphosis (Figure 1).

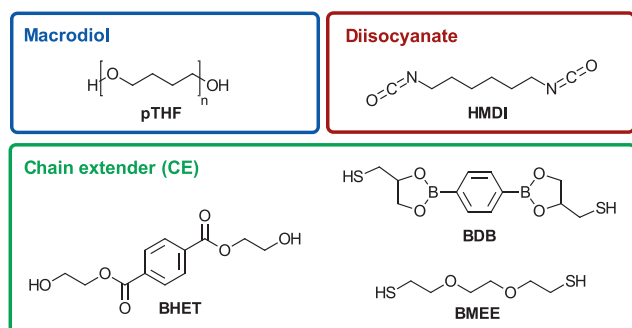
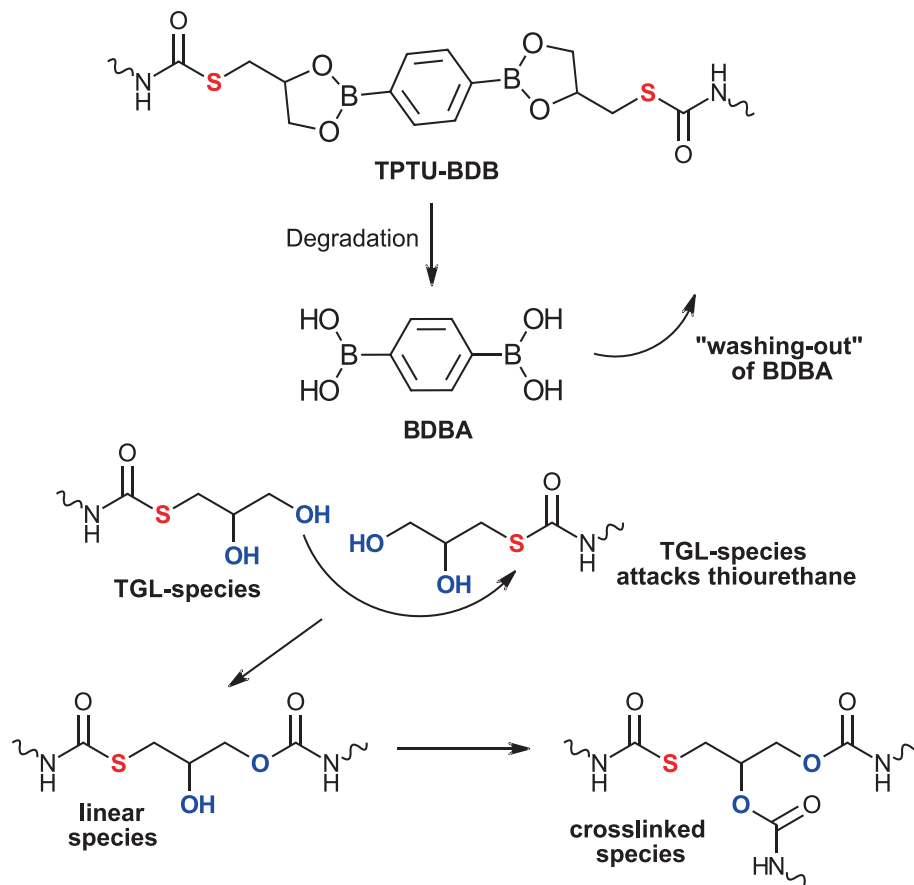
Generally, TPTUs exhibit excellent mechanical and physical properties and demonstrate biocompatibility.<sup>23</sup> In contrast to polyurethanes, TPTUs display higher crystallinity and flexibility because of the incorporated sulfur atoms.<sup>24,25</sup> Moreover, they exhibit fewer side reactions during synthesis compared to polyurethanes, such as the formation of allophanates and urethanes.<sup>26,27</sup> Furthermore, we incorporated a boronic acid ester-based chain extender into the polymers. Boronic acids are mild organic Lewis acids containing a trivalent boron atom substituted with one alkyl and two hydroxyl groups.<sup>28–30</sup> The replacement of hydroxyl groups with alkoxy or aryloxy groups is facile due to their lack of hydrogen donor capability, leading to the formation of boronic acid esters, also known as boronate esters or boronic esters.<sup>30–32</sup> Furthermore, boronic acids are able to form dynamic covalent bonds with diols such as 1-thioglycerol.<sup>28,33,34</sup> Due to the dynamic covalent bond it is possible to prepare self-healing polymers as Cash et al. showed previously.<sup>33</sup> The stability of the B–O bond, and therefore the equilibrium of the dynamic bond, is dependent on different factors such as the pH value of the solution, steric hindrance of the B–O bond and the acidity of the selected diol and boronic acid. Therefore, the equilibrium of the reaction can be shifted by changing these factors to the boronate ester or to the boronic acid favorable form.<sup>35–38</sup>

Boronic acids, classified as low toxicity, can be hydrolytically degraded to boric acid, which is recognized as an environmentally friendly compound. Their use does not lead to significant pH changes in the surrounding medium, thus reducing the risk of inflammatory reactions.<sup>32,39</sup> The research work of Sinaweil et al.<sup>40</sup> showed by means of cytotoxicity tests that the structurally analogous compounds 1,4-bis(4-vinyl-1,3,2-dioxaborolan-2-yl)benzene (VDB) and 1,4-bis[4-(allyloxy)methyl-1,3,2-dioxaborolan-2-yl]benzene (ADB) exhibit a sufficiently low toxicity towards fibroblast cells. Therefore, it can also be concluded that BDB has a comparably low toxicity and is therefore suitable as a chain extender molecule for TPUs for biomedical applications.

Thus, polymers containing boronate esters are not only interesting for hydrogels such as mentioned by Cash et al.,<sup>33</sup> they could be also promising materials for other parts of regenerative medicine such as vascular grafts.

Thus, we prepared TPTUs with enhanced mass erosion and the ability of macromolecular metamorphosis by introducing degradable boronic ester moieties into the hard block segment of the polymers (Figure 2). As hard block 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB)<sup>33,41</sup> was used in combination with hexamethylene-diisocyanate (HMDI). For comparison,

**FIGURE 1** Proposed macromolecular metamorphosis of TPTU-BDB by release of BDBA and the formation of crosslinks via an “intramolecular” reaction between hydroxy-terminated TGL-species (thioglycerol-species) and thiourethane moieties. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]



**FIGURE 2** Components used in the synthesis of TPU and TPTU include polytetrahydrofuran (pTHF) as macrodiol, hexamethylene diisocyanate (HMDI) and bis(2-hydroxyethyl) terephthalate (BHET), 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB) and 1,2-bis(2-mercaptoethoxy)ethane (BMEE) are used as chain extenders. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

another TPTU was synthesized based on 1,2-bis(2-mercaptoethoxy)-ethane (BMEE) as chain extender to investigate the influence of thiourethanes on the mechanical and degradation characteristics. As hydrolytic degradable ester-based chain extender, a TPU based on bis(2-hydroxyethyl)-terephthalate (BHET) was used as internal reference

material.<sup>19</sup> As benchmark material for mechanical characterization non-degradable Pellethane® 2363-80A (Pell) was used. Enhanced degradation of BDB based TPTU was demonstrated by in vitro degradation studies at 37°C and at accelerated degradation at 90°C in phosphate-buffered saline solution (PBS) for 10 weeks and evaluated gravimetrically and by molecular weight determination. The mechanical properties of the tested polymers are determined by tensile tests of solution cast polymer films. The molecular processes of TPTU-BDB during storage in PBS buffer solution are investigated in more detail using ATR-FTIR measurements, and hypotheses for the macromolecular metamorphosis of TPTUs are proposed.

## 2 | EXPERIMENTAL

### 2.1 | Materials and methods

All solvents and chemicals were purchased from Sigma-Aldrich, ABCR, Fluka or Fluorochem unless not noted otherwise and were purified by standard laboratory methods.<sup>42</sup> Polytetrahydrofuran (pTHF) ( $\bar{M}_n = 1000 \text{ g mol}^{-1}$ , confirmed by OH-Titration according to DIN 53240), bis(2-hydroxyethyl) terephthalate (BHET) (recrystallized

from water), tin(II) 2-ethylhexanoate ( $\text{Sn}(\text{Oct})_2$ ) and hexamethylenediisocyanate (HMDI) were all purchased from Sigma-Aldrich. Extra dry dimethylformamide (DMF, water content < 50 ppm) was purchased from Acros Organics.

Pellethane<sup>®</sup> (2363-80A, Pell) was obtained from Lubrizol (Cleveland, OH) and was used as benchmark material for all tested polymers. Before TPU and TPTU synthesis all chemicals were dried under reduced pressure (<0.1 mbar) at 90°C (pTHF) or at room temperature (chain extenders) and the residual water content (<50 ppm) was confirmed by Karl-Fischer titration.

## 2.2 | Synthesis

### 2.2.1 | Synthesis of 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB)

The synthesis of BDB was performed according to literature with minor modifications.<sup>41,43</sup> Therefore, 1-thioglycerol was freshly distilled immediately prior to synthesis. Subsequently, benzene-1,4-diboronic acid (6.00 g, 36.2 mmol, 1 eq.) and 1-thioglycerol (8.03 g, 74.2 mmol, 2.05 eq.) were dissolved in THF (160 mL) and deionized water (0.2 mL, 10.86 mmol, 0.3 eq.). Upon complete dissolution of all components, magnesium sulfate (10.00 g, 83.1 mmol, 2.3 eq.) was added slowly over a period of approximately 1 h. The reaction mixture is then stirred for 24 h at room temperature. Subsequently, the solution was filtrated to remove magnesium sulfate and dried under vacuum, resulting in a yellow powder. To further purify the powder, it was dissolved in toluene (200 mL). Any precipitated 1-thioglycerol was removed, and the product was recrystallized from toluene at 70°C (<sup>1</sup>H-NMR- and <sup>13</sup>C-NMR-spectra see supporting information, S1 and S2).

Yield: 9.27 g (29.9 mmol; 82.6%); Mp: 109.3–111.2°C; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 2.39 (2H, t, SH); 2.80 (4H, dd, CH<sub>2</sub>); 4.12 (2H, dd, CH<sub>2</sub>-O); 4.42 (2H, dd, CH<sub>2</sub>-O), 4.75 (2H, m, CH-O); 7.74 (4H, s, Ar-CH); <sup>13</sup>C-NMR (APT, 101 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 28.71 (-CH<sub>2</sub>-SH); 69.25 (CH<sub>2</sub>-O); 77.12 (CH-O); 133.84 (a, Ar-CH/Ar-C); GC-MS (DCM): 97.7%.

### 2.2.2 | Synthesis of thermoplastic poly(thio)urethanes (TPUs/TPTUs)

The synthesis of TPUs and TPTUs was conducted following established procedures.<sup>13</sup> Prior to the reaction, polytetrahydrofuran (pTHF) was dried under vacuum (<0.1 mbar) at 90°C for 24 h. Karl-Fischer titration confirmed a water content below 50 ppm. Hexamethylenediisocyanate (HMDI) was freshly distilled before use. Polytetrahydrofuran (5.0 g, 5 mmol, 1 eq.,  $\overline{M}_n = 1000 \text{ g mol}^{-1}$ ) was transferred to a three-necked round bottom flask and further dried for another 3 h. HMDI (1.68 g, 10 mmol, 2 eq.) was diluted in dry DMF (5 mL) and was added to pTHF at 60°C under argon atmosphere. Dry DMF (5 mL) was used in portions to rinse the syringe and transfer vessel. Stannous octoate ( $\text{Sn}(\text{Oct})_2$ , 0.05 mL, 0.2 eq.) was then added, and the mixture was stirred for 4 h at 60°C.

Subsequently, the chain extender (CE, 5 mmol, 1 eq.) dissolved in dry DMF (5 mL) was added to the reaction mixture at 60°C under argon atmosphere. For TPU-BHET-BDB with two CEs, BHET (2.5 mmol, 0.5 eq.) dissolved in dry DMF (2.5 mL) was added first. After a reaction time of 3 h the second CE, BDB (2.5 mmol, 0.5 eq.) dissolved in dry DMF (2.5 mL) was added (yield and used CEs for each polymer are listed in Table 1).

After each CE addition, the syringe and transfer vessel were rinsed with additional dry DMF (5 mL) in portions. Finally, the mixture was stirred overnight at the same reaction conditions. For purification, the polymer was precipitated in petroleum ether (800 mL) and dried under vacuum at 50°C, yielding a transparent to white powder.

## 2.3 | Characterization

### 2.3.1 | Karl-Fischer titration

Water content of solvents and pTHF was determined by an automated Karl-Fischer titration (Envirotech CA-21 moisture meter) using reagents and standards from Aquamicon (Mitsubishi Chemical Corporation).

	Yield/%	CE <sup>a</sup>	<i>m</i> CE/g	<i>n</i> CE/mmol
TPU-BHET	90.6	BHET	1.27	5
TPTU-BDB	87.6	BDB	1.55	5
TPU-BHET-BDB	85.1	BHET/BDB	0.64/0.78	2.5/2.5
TPTU-BMEE	82.4	BMEE	0.91	5

<sup>a</sup>Bis(2-hydroxyethyl) terephthalate (BHET), 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB), 1,2-bis(2-mercaptoethoxy)-ethane (BMEE).

**TABLE 1** Yields and chain extenders (CE) for TPU and TPTU synthesis.

### 2.3.2 | NMR-spectra

$^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were performed on a Bruker Avance FT-NMR spectrometer (400 MHz). Chemical shifts are reported in ppm. Deuterated chloroform ( $\text{CDCl}_3$ ) and deuterated Dimethyl sulfoxide ( $\text{DMSO}-d_6$ ) were purchased from Eurisotop. Calibration was done with non-deuterated solvents ( $\text{CHCl}_3$  at 7.26 ppm, DMSO at 2.50 ppm).

### 2.3.3 | Gas chromatography–mass spectrometry (GC–MS)

The purity of substances was determined using a Thermo Scientific Trace GC Ultra coupled with an ITQ 1100 MS and an AS 3000 auto-sampler.

### 2.3.4 | Gel permeation chromatography (GPC)

Determination of the molecular weights were performed on a Malvern Viscotek GPCmax VE2001 TDA system equipped with three columns (Styragel HR 0.5, HR 3 and HR 4 THF). As detectors, a Viscotek SEC-MALS 9 light scattering detector, a Viscotek TDA 305–021 RI + Visc detector, and a UV Detector Module 2550 for TDA 305 were used. Samples were prepared as syringe-filtered 2–3  $\text{mg ml}^{-1}$  THF-solutions spiked with 0.5  $\text{mg ml}^{-1}$  butylhydroxytoluol (BHT) as flow-marker. For all measurements, a flow rate of 0.8  $\text{mL min}^{-1}$  was used. Standard calibration was done with polystyrene standards between 480 and 44 k  $M_w$ . In the case of triple detection, the  $\text{dn/dc}$  value was determined by injecting the sample at five different injection volumes between 80 and 120  $\mu\text{L}$  and analyzing the slope of the signals. Data evaluation was performed using OmniSEC 5.12 from Malvern.

### 2.3.5 | Solution casting

For degradation studies and tensile tests, polymer films were prepared via solution casting. TPU solutions (10 wt % in hexafluoro-2-propanol, HFIP) were filled in a PTFE-mold ( $6 \times 4 \times 0.2 \text{ cm}$ ) and dried at room temperature for 2 days and afterwards under vacuum until constant mass was reached.

### 2.3.6 | Tensile testing

For mechanical testing specimens were punched of the solution casted polymer films (ISO 527, Typ 5B, bone-

shaped). Tensile tests were carried out on a Zwick Z050 universal testing machine with a strain rate of 50  $\text{mm min}^{-1}$ . Each polymer was tested at least in quadruplicates with a sample thickness between 20 and 40  $\mu\text{m}$ .

### 2.3.7 | Dynamic mechanical thermal analysis (DMTA)

To determine the glass transition temperature ( $T_g$ ), DMTA was conducted using a 2980 DMA V1.7B instrument by Anton Paar. The analysis was carried out at a frequency of 1 Hz and an amplitude of 1% between  $-100$  and  $50^\circ\text{C}$ . Dimensions of the samples: 20–40  $\mu\text{m}$  thickness, 2.3 mm broad and 9.3–12.2 mm length.

### 2.3.8 | ATR-FTIR

For ATR-FTIR measurements, a PerkinElmer Spectrum 65 FT-IR Spectrometer with a Specac Heated GoldenGate Controller was utilized. Measurements were conducted across the spectral range of 4000 and 600  $\text{cm}^{-1}$ , with 16 scans.

### 2.3.9 | Degradation, storage and incubation studies

Circular samples for degradation, storage and incubation experiments were punched out of solution casted polymer films with a diameter of 1 cm, a thickness of 40–60  $\mu\text{m}$  and a mass between 20 and 30 mg. Degradation studies were performed in PBS buffer solution ( $\text{pH} = 7.4$ ) at a constant temperature ( $37$  or  $90^\circ\text{C}$ ). The buffer solution was then decanted off and the sample was washed with deionized water. To remove absorbed salts, the samples were further immersed in distilled water for 3 h and then dried under vacuum until constant mass was reached. Measurements were made in triplicates.

## 3 | RESULTS AND DISCUSSION

Thermoplastic polyurethanes (TPUs) and thiourethanes (TPTUs), differing only in their chain extenders, were primarily investigated with regard to their mechanical properties and degradation behavior. As chain extenders (CEs) bis(2-hydroxy-ethyl) terephthalate (BHET), 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB), 1,2-bis(2-mercaptoethoxy)-ethane (BMEE), and a combination of BHET and BDB (50:50) were used.



### 3.1 | Synthesis of chain extenders and polymers

In this study, different TPUs and TPTUs were synthesized by two-step polymerization via the prepolymer method by variation of the chain extender. As macrodiol (MD) polytetrahydrofuran (pTHF,  $\overline{M}_n = 1000 \text{ g mol}^{-1}$ ) was used and hexamethylene-diisocyanate (HMDI) as diisocyanate (DI). The focus was on introducing a new boronate based chain extender 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB, Figure 3) to investigate the degradation behavior of boronate groups of thermoplastic poly(thio)urethanes.

For TPTUs, another dithiol was used as chain extender (CE) namely 1,2-bis(2-mercaptoethoxy)-ethane (BMEE) to investigate the influence of thiourethane groups in terms of degradation having about the same chain length. As additional reference material from literature TPU-BHET was synthesized with bis(2-hydroxy-ethyl) terephthalate (BHET) as carboxylic ester-based diol chain extender.<sup>19</sup> For all polymers, a component ratio of 1:2:1 was used (MD:DI:CE). Furthermore, TPU-BHET-BDB was prepared by mixing two chain extenders (BHET and BDB) in a molar ratio of 1:1 (1:2:0.5:0.5 – MD:DI:CE<sub>1</sub>:CE<sub>2</sub>).<sup>19</sup> The yield for all polymer syntheses was above 80% (Table 1). Pellethane® (Pell) was purchased as benchmark material (unknown ratio of pTHF), 4,4'-methyl-enediphenyl diisocyanate (MDI) and 1,4-butanediol (BDO). Figure 4 shows the two-step synthesis of TPUs and TPTUs.

### 3.2 | General characterization of polymers

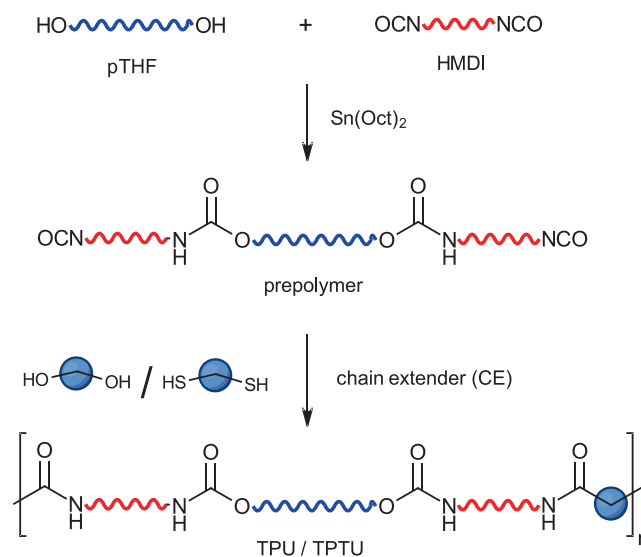
By means of <sup>1</sup>H-NMR spectroscopy, the component ratios between macrodiol, diisocyanate and chain extender (1:2:1) could be verified. Furthermore, the chain extender ratio of 1:1 at TPU-BHET-BDB could be confirmed with the same method (<sup>1</sup>H-NMRs of TPUs are shown in the Supporting information). Due to the constant used ratio, the theoretical hard block content for all polymers is in a narrow range between 34.2 to 39.3 wt% (Table 2), which was calculated by Equation (1). Nevertheless, the hard block content calculated via <sup>1</sup>H-NMR spectra (Supporting information, S3–S6) is lower. The reason for that could be an oligomerization between

diisocyanate and macrodiol in the prepolymer synthesis step and therefore, less chain extender could be incorporated in the second synthesis step as less isocyanate groups are available anymore.

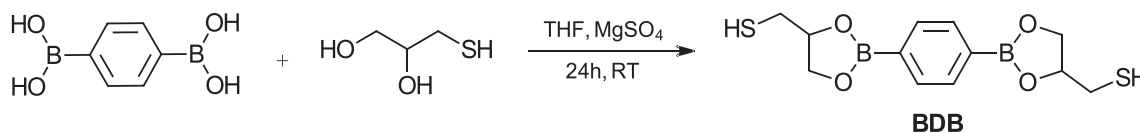
$$\frac{M(\text{CE}) + 2 \times M(\text{DI})}{M(\text{CE}) + 2 \times M(\text{DI}) + M(\text{MD})} = \% \text{HB} \quad (1)$$

Molecular weight and polydispersity were determined via GPC measurements in THF via triple detection method in a wide range between 6.4 to 62.2 kDa (Table 2). Especially, the very low  $\overline{M}_n$  values for TPTU-BDB (6.4 kDa) and TPU-BHET-BDB (13.7 kDa) are surprising because the observed viscosity of the polymer solutions after synthesis were comparable to them of the high  $\overline{M}_n$  polymers. Furthermore, the  $\overline{M}_n$  of the repeating units of TPUs and TPTUs are between 1.5 and 1.65 kDa, which means a derived low degree of polymerization (DP) of about 4 for TPTU-BDB.

Therefore, because only polymers with BDB as chain extender show such a low molecular weight, traces of residual water in the GPC solvent (THF) could lead to a hydrolysis of the B–O bond of the CE. This would result in a decreased molecular weight during measurement as a reformation of the B–O expected from the reaction



**FIGURE 4** Two-step synthesis of TPUs/TPTUs by using a chain extender (CE) with pTHF: HMDI: CE = 1:2:1. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/terms-and-conditions)]



**FIGURE 3** Synthesis of the chain extender 2,2'-(1,4-phenylene)-bis[4-mercaptan-1,3,2-dioxaborolane] (BDB).

**TABLE 2** Overview of synthesized polymers with different chain extenders, data from GPC measurements and mechanical properties.

Polymer	Ratio <sup>a</sup>	$\overline{M}_n/\text{kDa}^b$	$\overline{D}^c$	%HB <sub>th</sub> /wt% <sup>d</sup>	%HB <sub>cal</sub> /wt% <sup>e</sup>	$E^f/\text{MPa}$	$S^g/\text{MPa}$	$\epsilon_b^h/\%$	$T_g^i/^\circ\text{C}$
TPU-BHET	2:1:1	23.3	2.1	37.1	33.5	$31.0 \pm 1.4$	$14.1 \pm 0.7$	$1315 \pm 54$	−71
TPU-BHET-BDB	2:1:1/2:1/2	13.7	1.9	38.2	34.6	$38.9 \pm 2.8$	$6.1 \pm 0.2$	$263 \pm 9$	−67
TPTU-BDB	2:1:1	6.4	1.8	39.3	36.1	$69.8 \pm 5.5$	$10.4 \pm 0.7$	$507 \pm 72$	−64
TPTU-BMEE	2:1:1	62.2	2.1	34.2	32.8	$28.8 \pm 3.0$	$32.8 \pm 4.0$	$1746 \pm 73$	−56
Pellethane®	-	56.3	1.9	-	-	$14.2 \pm 0.3$	$25.2 \pm 1.2$	$1651 \pm 115$	−52

<sup>a</sup>Molar ratio DI:MD:CE (Diisocyanate:macrodiol:chain extender).<sup>b</sup>Number-average molar mass.<sup>c</sup>Dispersity.<sup>d</sup>Theoretical hard block content (%HB<sub>th</sub>).<sup>e</sup>Calculated hard block content from <sup>1</sup>H-NMR (%HB<sub>cal</sub>).<sup>f</sup>Elastic modulus  $E$ .<sup>g</sup>Tensile strength  $S$ .<sup>h</sup>Elongation at break  $\epsilon_b$ .<sup>i</sup>Glass transition temperature  $T_g$  obtained from the maxima of loss modulus curves.

equilibrium is not possible due to the low polymer concentration in the GPC sample ( $2 \text{ mg mL}^{-1}$ ), which is further diluted on the GPC column. Nevertheless, the Dispersity  $\overline{D}$  of all polymers is within a narrow range between 1.8 to 2.1 and therefore as expect at about 2.

Figure 6 shows FTIR spectra of TPTU-BDB and TPU-BHET. At  $\sim 3300 \text{ cm}^{-1}$   $\text{R}_2\text{—NH—}$  regions are shown. TPTU-BDB shows a sharper peak ( $\text{R}_2\text{—NH—}$ ) compared to the TPU-BHET. As previous studies<sup>8</sup> showed broader N—H peak indicates stronger hydrogen bond formation compared to sharper peak. Therefore, TPU-BHET is able to form stronger hydrogen bond interactions compared to TPTU-BDB. In the region of  $\sim 850$  and  $\sim 660 \text{ cm}^{-1}$  aromatic bands resulting from BDB and BHET could be identified. Furthermore, typical C—H bands between  $2950$  and  $2850 \text{ cm}^{-1}$  could be identified for both polymers. At the spectrum of TPTU-BDB, smaller bands at  $\sim 1320 \text{ cm}^{-1}$  and at  $\sim 1020 \text{ cm}^{-1}$  resulting from B—O and B—C are identified, which was also investigated for borates in a FTIR measurement study by Romanos et al.<sup>44</sup> Furthermore, molar ratios of MD:DI:CE (Table 2) were confirmed for all polymers via <sup>1</sup>H-NMR spectroscopy in DMSO-*d*<sub>6</sub> in NMR accuracy of  $\pm 5\%$  (Supporting information, S8–S11).

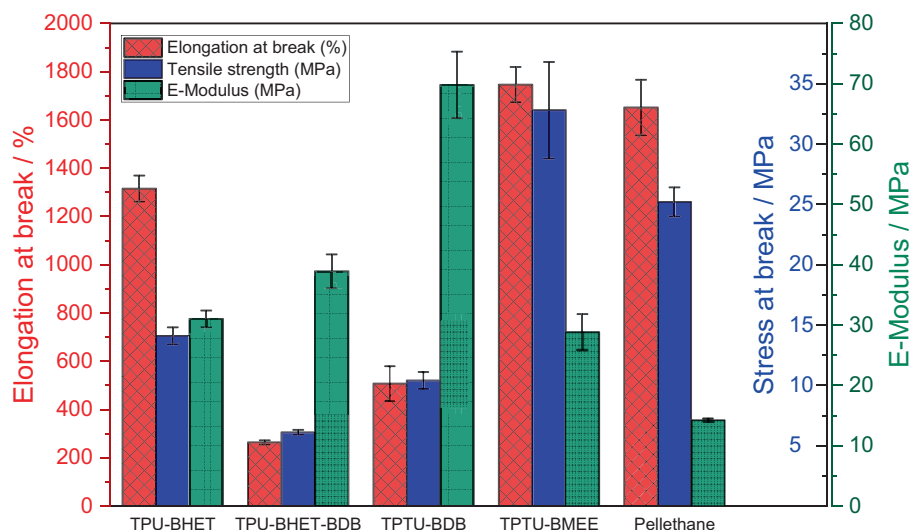
### 3.3 | Mechanical properties

With regard to the mechanical properties a vascular graft has to fulfill, it is important that it is sufficiently elastic to adapt to the changing blood pressure, but at the same time has sufficient strength. Thermoplastic polyurethanes and polythiourethanes consist of a flexible macrodiol, in our case polytetrahydrofuran (pTHF). This gives the material the necessary flexibility (soft-block). The hard-

block consisting of diisocyanate and chain extender increases the mechanical strength due to the formation of hydrogen bonds between the hard-blocks. This results in a physically crosslinked polymer. Thus, the formation of hydrogen bonds has a direct influence on the mechanical properties. Table 2 shows elastic modulus  $E$ , tensile strength  $S$ , elongation at break  $\epsilon_b$  and the glass transition temperatures ( $T_g$ ) of all tested polymers. Mechanical properties determined via tensile testing are furthermore shown in Figure 5. Both, tensile testing and DMTA measurements were performed with solution casted films. Representative stress–strain curves for each polymer are presented in the Supporting Information Section 4.

The  $T_g$  was determined by DMTA from the maximum of the obtained loss modulus curves (Supporting information, S7–S11). All  $T_g$ -values were far below  $0^\circ\text{C}$  as expected for a thermoplastic polymer as polyurethanes and polythiourethanes, which proves that all polymers are flexible at body temperature and therefore applicable as vascular grafts later on. The reference material Pell shows a relatively high  $T_g$  ( $-52^\circ\text{C}$ ) compared to TPU-BHET ( $-71^\circ\text{C}$ ) and TPTU-BDB ( $-64^\circ\text{C}$ ). The mixed BHET-BDB- based TPUs show  $T_g$ -values in between this range. TPTU-BMEE ( $-56^\circ\text{C}$ ) shows the highest  $T_g$  of the synthesized polymers nearly as high as Pell. The relatively high  $T_g$  of TPTU-BMEE was surprising because of its flexible structure. But due to the less bulky structure compared to BHET and BDB, the material is able to form more hydrogen bonds and therefore the  $T_g$  could increase.

As shown in Table 2 and Figure 5, Pell as benchmark material shows very good mechanical properties. Especially, the combination of high elongation at break, high tensile strength and relative low elastic modulus has to be highlighted. TPTU-BMEE shows even higher



**FIGURE 5** Comparison of elongation at break, tensile strength and elastic modulus of TPU-BHET, TPU-BHET-BDB, TPTU-BDB, and TPTU-BMEE with those of commercially available Pellethane. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.56429)]

elongation and tensile strength but also higher elastic modulus. It is known from literature that thiourethanes tend to be more flexible compared to urethanes and have a higher crystallinity,<sup>24,25</sup> which underlines the observed superior mechanical properties. Furthermore, BMEE moiety can form strong hydrogen bonds due to the two containing oxygen atoms per each molecule. In contrast to that, TPTU-BDB performed less favorably, although it is also a thiourethane. Due to its bulkier structure compared to BMEE, the BDB moiety can form hydrogen bonds less easily. Although, the chain extender BHET, which was used for the internal reference material TPU-BHET, has also a comparable bulky structure compared to BDB, TPU-BHET shows quite good mechanical properties.

Therefore, it can be assumed that BHET moieties easier form hydrogen-bond interactions compared to the BDB moiety. Surprisingly, TPU-BHET-BDB, which has a 1:1 mixture of BHET and BDB as chain extenders, shows the worst mechanical properties. The structural differences between both chain extenders could lead to a less favorable hard-block formation. Furthermore, the molecular weight has a direct influence on the mechanical properties. TPTU-BDB (6.4 kDa) and TPU-BHET-BDB (13.7 kDa) showed the lowest  $\overline{M}_n$ , while BMEE (62.2 kDa) showed the highest number-average molar mass (Table 2).

### 3.4 | Structural remodeling in simulated biological environment

To gain insight into the structural remodeling or metamorphosis of boronic acid ester based TPTU-BDB, polymer films prepared via solution casting were stored in PBS buffer solution (pH = 7.4) for 28 days to simulate a

biological environment. In addition, buffer solutions with pH = 5 and pH = 10 were used to find pH-dependent differences. After the samples were dried, the polymers TPTU-BDB and TPU-BHET were analyzed by ATR-FTIR spectroscopy.

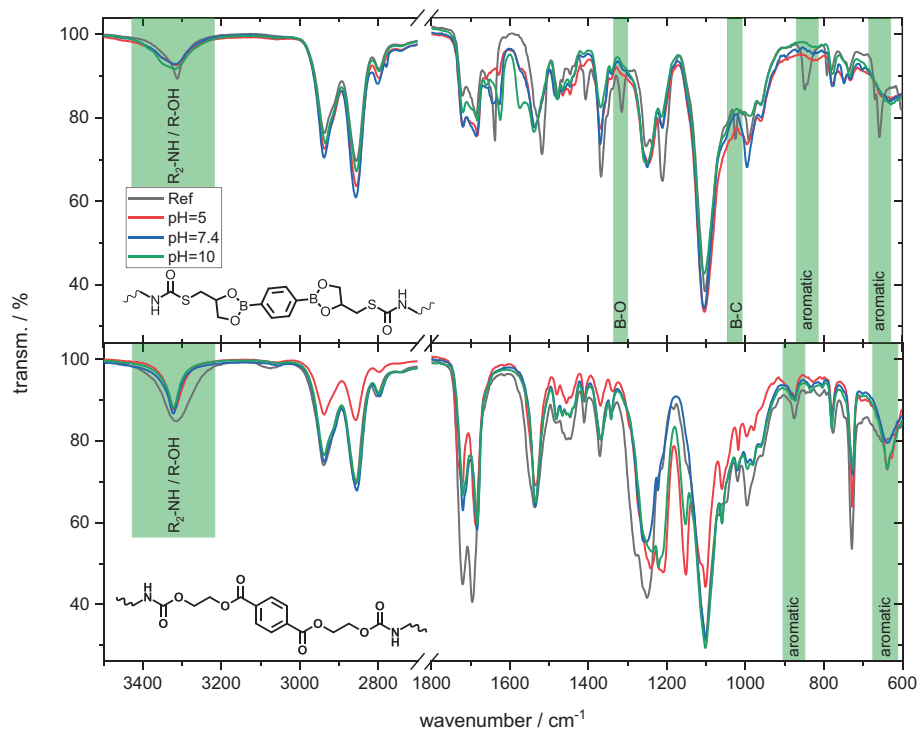
Figure 6 shows the FTIR spectra of TPTU-BDB and TPU-BHET before and after 28 days of sample storage at pH = 5, 7.4, and 10. The spectra show regions corresponding to  $R_2$ -NH and R-OH vibrations at about  $3300\text{ cm}^{-1}$ . Before storage in aqueous buffer solutions, TPTU-BDB shows a sharper peak in the  $R_2$ -NH region compared to the incubated samples, indicating the formation of OH groups due to an overlap of  $R_2$ -NH and R-OH vibrations. Aromatic bands originating from BDB are observed only at about  $850\text{ cm}^{-1}$  and  $660\text{ cm}^{-1}$  in the spectrum of TPTU-BDB before incubation, indicating a “washing out” of benzene-1,4-diboronic acid (BDDBA) during storage. This hypothesis is supported by Romanos et al.<sup>42</sup> who studied the IR bands of borates, in particular the B-O vibrations at about  $1320\text{ cm}^{-1}$  and the B-C vibrations at about  $1020\text{ cm}^{-1}$ , both of which were identified only in the spectrum of TPTU-BDB before storage in aqueous buffer solutions. In contrast, the FTIR spectra of TPU-BHET show no significant changes in the above regions. The aromatic bands at about  $850$  and  $660\text{ cm}^{-1}$  are observed at all pH values after 28 days of storage time.

### 3.5 | Degradation behavior

To get a further insight into the structural remodeling, the degradation characteristics in terms of mass erosion and molecular weight change of four different polymers were investigated (TPTU-BMEE, TPU-BHET, TPU-BHET-BDB, and TPTU-BDB). The benchmark material



**FIGURE 6** FTIR spectra of TPTU-BDB (Ref-top) and TPU-BHET (Ref-bottom) before incubation, as well as both polymers after 28 days of storage time at varying pH values (pH = 5, 7.4, and 10), were obtained within the spectral ranges of 3500–2700  $\text{cm}^{-1}$  and 1800–600  $\text{cm}^{-1}$ . [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



Pell was not analyzed in terms of degradation behavior because previous studies showed no evidence of degradation.<sup>13,19</sup> Degradation studies were performed for 70 days in phosphate-buffered saline solution (PBS 4×, pH = 7.4) at body temperature (37°C) and at elevated temperature (90°C) to accelerate the process of hydrolytic degradation. PBS solution was used in fourfold concentration (PBS 4×) because of a higher buffer capacity. The duration and temperature of the degradation experiments were chosen based on previous studies,<sup>8,13,19</sup> which showed that they are well suited for TPUs and provide an initial evaluation of the degradation behavior and the further process.

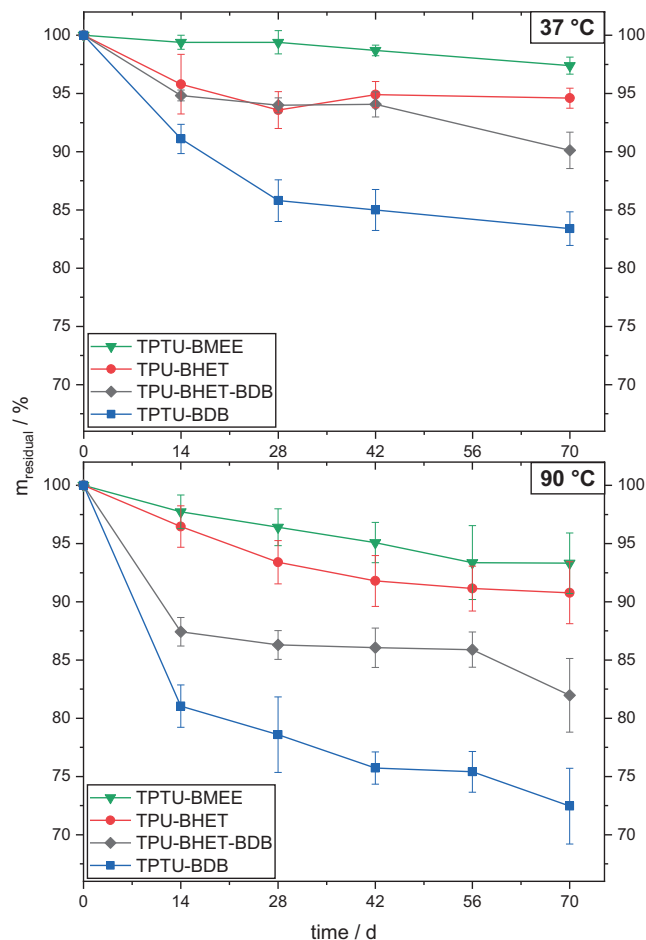
As expected, the ether based TPTU with BMEE as chain extender shows the lowest mass erosion at both temperatures (Figure 7) because no cleavable moieties are present in the molecule compared to BHET (ester) or BDB (B–O bond). After 70 days at 37°C about 97.5% of the original mass is still left compared to about 93% at 90°C. The ester cleavable TPU-BHET shows a bit faster degradation in terms of mass erosion compared to TPTU-BMEE. As expected, the fastest degradation is observed for TPTU-BDB. Because TPTU-BMEE shows very slow degradation, it can be assumed that the degradation of TPTU-BDB is caused of the cleavable B–O bond of the boronic acid ester, followed by a release of benzene-1,4-diboronic acid (BDDBA) as previous ATR-FTIR measurements showed. Furthermore, it can be seen that the washing out of BDDBA at 90°C mainly takes place in the first 14 days during degradation and

therefore the mass loss is highest during this period (Figure 7). Thereafter, the degradation rate of TPTU-BDB is very similar to that of TPU-BHET and therefore a similar further degradation process can also be assumed. Ehrmann et al.<sup>8</sup> showed that a higher degradation rate than for TPU-BHET would be desirable for use as vascular implants, which TPTU-BDB would fulfill.

In addition to the mass erosion, Figure 8 shows molecular weight change during degradation process in PBS buffer solution at 37 and 90°C. The number-average molar mass  $\overline{M}_n$  of the polymer before degradation acts as reference value (100%). After each time period  $\overline{M}_n$  was determined via GPC in triplicates via conventional calibration method. Figure 8 shows number-average molar mass changes at 37°C over a period of 70 days. TPTU-BMEE shows the smallest molecular weight decrease followed by TPU-BHET. In contrast to that for TPTU-BDB a constant increase of  $\overline{M}_n$  during 70 days is observed, resulting in even an absolute increase of molecular weight of ~16% compared to the starting point.

Since Figure 7 shows a decrease in mass, a possible explanation for this behavior could be macromolecular metamorphoses of hydroxy-terminated polymer species resulting from a release or “washing out” of BDDBA, as previously shown by ATR-FTIR spectroscopy. Therefore,  $\overline{M}_n$  would increase by a reaction of the hydroxy-terminated polymer species with the thiourethane group, leading to a branched or crosslinked polyurethane.

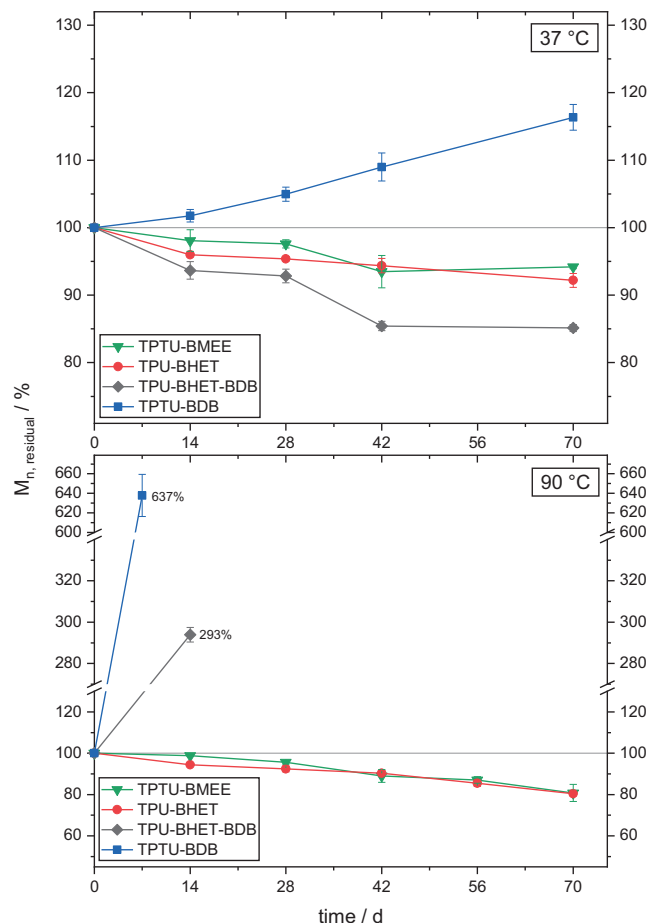
In contrast to TPTU-BDB, the mixed polymer TPU-BHET-BDB with a 1:1 ratio of the chain extenders BHET



**FIGURE 7** Residual mass  $m_{\text{residual}}$  in % of TPTU-BMEE, TPU-BHET, TPU-BHET-BDB, and TPTU-BDB in PBS buffer solution after exposure at 37 °C (top) and 90 °C (bottom), respectively. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.56429)]

and BDB shows the fastest and highest molecular weight decrease over 70 days, resulting in  $\sim 85\%$  of the original  $\overline{M}_n$ .

Further insights especially in the degradation behavior of TPTU-BDB gives the GPC degradation study at 90 °C (Figure 8). For TPU-BHET as expected a faster decrease of  $\overline{M}_n$  is observed at 90 °C. TPTU-BMEE shows nearly the same results as TPU-BHET. Compared to these results TPTU-BDB shows an extremely high increase of molecular weight during the first 7 days of  $\sim 640\%$ . Due to this surprising result a  $\overline{M}_n$  determination via triple detection was carried out for TPTU-BDB resulting in an increase of 440% after 7 days. For all other time points which were measured for TPTU-BMEE and TPU-BHET no GPC measurements were possible for TPTU-BDB due to insoluble specimens in any investigated solvents (Acetone,  $\text{CHCl}_3$ , DCM, dioxane, DMF, DMSO, ethyl acetate, EtOH, Hexafluoro-2-propanol, MeCN, MeOH, THF, water).



**FIGURE 8** The evolution of the number-average molar mass  $\overline{M}_n$  and its residual percentage with respect to the original  $\overline{M}_n$  before degradation were investigated for all polymers immersed in PBS buffer solution at 37 °C (top) and 90 °C (bottom), respectively. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/app.56429)]

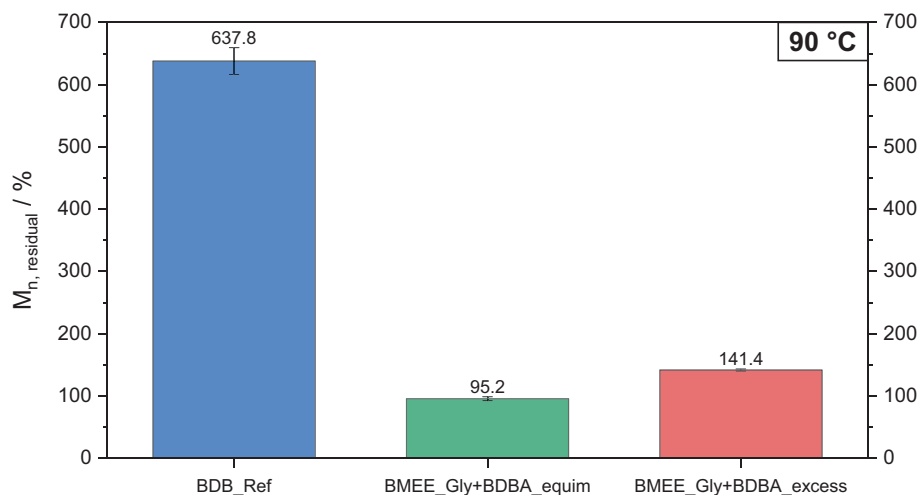
For TPU-BHET-BDB the increase of  $\overline{M}_n$  is also observed but only  $\sim 295\%$  after 14 days of degradation time. After 28 days until 70 days all samples were also insoluble as observed for TPTU-BDB in all above mentioned solvents.

In particular, the insoluble polymers of TPTU-BDB and TPU-BHET-BDB provide another indication that a reaction of the hydroxy-terminated polymer species with the thiourethane group is taking place, as insoluble cross-linked polymers would be formed.

Based on the observed release of benzene-1,4-diboric acid (BDAB) during degradation, as investigated by ATR-FTIR measurements, a plausible explanation for the insoluble nature of the sample and the substantial increase in molecular weight of TPTU-BDB can be inferred from the macromolecular metamorphoses shown in Figure 1.

To investigate possible side reactions of thiourethane groups with hydroxy groups<sup>45</sup> in the presence of

**FIGURE 9** Evolution of the number-average molar mass  $\overline{M}_n$ , expressed as a percentage of the original  $\overline{M}_n$  before degradation, over a period of 7 days for TPTU-BDB (BDB\_Ref), TPTU-BMEE with equimolar amounts of Gly and BDBA (center) and with an excess of Gly (600 eq.) and BDBA (40 eq.) relative to BMEE (CE). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]



benzene-1,4-diboronic acid (BDBA) during the degradation of TPTU-BDB, the thiourethane-based reference TPTU-BMEE was incubated in PBS buffer solution at 90°C for 7 days.

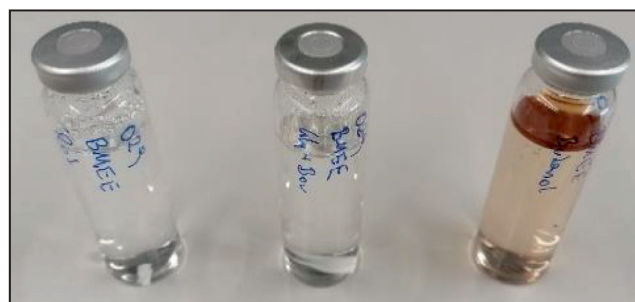
Equimolar amounts of BDBA and 1,2,3-propanetriol (glycerol, Gly) were also added. In addition, an excess of glycerol (600 eq. to CE) and BDBA (40 eq.) was added to another sample. Glycerol was included to show possible reactions of thiourethanes with hydroxy groups. Any resulting reaction would lead to the formation of cross-linked or branched polymer from the linear TPTU-BMEE, resulting in an increase in molecular weight or the formation of insoluble species with the trifunctional glycerol, which could also occur with the thioglycerol (TGL) species of TPTU-BDB (Figure 1).

Figure 9 shows the change in molecular weight  $\overline{M}_n$  of TPTU-BMEE after 7 days of degradation at 90°C with the addition of BDBA and Gly compared to TPTU-BDB.

A significant increase in molecular weight of approximately 40% was observed in the TPTU-BMEE sample with excess glycerol and BDBA, although still lower than that of TPTU-BDB.

It is evident that there is no identifiable increase in the molecular weight of TPTU-BMEE (95.2%) treated with equimolar amounts of Gly and BDBA compared to TPTU-BDB (637.8%).

The observation that this phenomenon was only visible with an excess of glycerol could be explained by the fact that Gly was dissolved in the buffer solution, whereas TPTU-BMEE was not dissolved. This allows only small amounts of Gly to penetrate into the sample (no intermolecular reactions). Conversely, with a large excess, the amount of Gly penetrating the polymer film is sufficient to allow reactions with thiourethane groups. In contrast, hydroxy-terminated TGL species in TPTU-BDB are able to react “intramolecularly” because the TGL is covalently bound to the polymer.



**FIGURE 10** TPTU-BMEE samples were degraded under different conditions: With an excess of 1-butanol (right), with glycerol and BDB (center), and without any additives after storage in PBS buffer solution (4×) at 90°C for 7 days. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

In addition, an excess of 1-butanol (600 eq. to CE) was added to TPTU-BMEE. This experiment clearly demonstrated that a reaction with alcohols was occurring, as evidenced by the brown color of the solution and the complete degradation of the polymer (Figure 10). Therefore, the hypotheses of a molecular weight increase of BDB-based polymers due to a reaction between hydroxy groups and the thiourethane moiety is underlined.

## 4 | CONCLUSION

In this study, we presented a novel boronic ester-based thermoplastic poly(thio)urethane elastomer (TPTU-BDB) using the chain extender 2,2'-(1,4-phenylene)-bis[4-mercaptopan-1,3,2-dioxaborolane] (BDB) that can undergo macromolecular metamorphosis in biological environments. TPTU-BDB showed improved degradation compared to other materials tested, although this resulted in slightly reduced mechanical properties that still remained within an acceptable range. In contrast, the use of the

ether-based dithiol BMEE as a chain extender resulted in polymers with excellent mechanical properties that even exceeded those of the reference material Pellethane®. However, the degradation rate of these materials was slower compared to TPTU-BDB and the ester-based reference polymer TPU-BHET.

Bulk erosion experiments and gel permeation chromatography (GPC) were performed to better understand the degradation behavior of these poly(thio)urethanes. During degradation, an increase in  $M_n$  was observed for both TPTU-BDB and TPU-BHET-BDB, suggesting that a macromolecular metamorphosis occurs when benzene-1,4-diboronic acid (BDBA) leaches out. This leaching process, confirmed by ATR-FTIR measurements, leads to the formation of hydroxy-terminated polymer species that can crosslink with the thiourethane moiety. Experimental model reactions using glycerol to simulate the presence of hydroxyl groups support this hypothesis.

Overall, thermoplastic poly(thio)urethanes based on boronic acid esters are very promising for vascular grafts, especially since previous studies have shown that boronic acids are low toxic and can be degraded to boric acid, thus minimizing the risk of inflammatory reactions.

## AUTHOR CONTRIBUTIONS

**Philip Schwarzl:** Data curation (lead); formal analysis (lead); investigation (equal); validation (equal); visualization (lead); writing – original draft (lead). **Thomas Koch:** Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); validation (supporting); writing – review and editing (supporting). **Robert Liska:** Conceptualization (supporting); formal analysis (supporting); funding acquisition (supporting); methodology (supporting); project administration (supporting); resources (supporting); supervision (supporting); validation (supporting); writing – review and editing (supporting). **Stefan Baudis:** Conceptualization (lead); data curation (supporting); formal analysis (supporting); funding acquisition (equal); investigation (supporting); methodology (lead); project administration (lead); resources (equal); supervision (lead); validation (equal); visualization (supporting); writing – original draft (supporting); writing – review and editing (lead).

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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