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Fast degradable blood vessel substitutes

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Institut für Angewandte Synthesechemie

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Abstract

In the last decades cardiovascular diseases have become the number one single cause of death throughout the world. Naturally the demand for substitute materials to replace failing tissue related to these diseases increased as well.
Vascular tissue engineering is a promising approach to meet these demands. Although there are synthetic materials available that can replace large diameter blood vessels, small diameter blood vessels of the same materials failed. Compliance and elastic mismatch as well as low hemocompatibility are considered to be the main reasons for failure.
Thermoplastic polyurethane materials (TPUs) might offer a new approach for designing small diameter vascular grafts.
This type of polymer usually shows good biocompatibility as well as elastomeric properties and usually can be processed from melt as well as from solution. The segmented configuration of these polyurethanes - consisting of a macrodiol, as flexible soft block, and a combination of diisocyanate and chain extender, as a rigid hard block - allows tuning of its final properties, such as mechanical properties and degradation, just by changing the building blocks.

The aim of this work was the synthesis of faster degrading TPUs compared to previously developed materials within our working group. These new materials were supposed to show soft block- and hard block degradability as well as suitable mechanical properties for the use in vascular tissue engineering and they should be processed by electrospinning.
To ensure highest possible biocompatibility the use of ester-based building blocks, which lead to acidic degradation products that can cause inflammatory reactions within the surrounding tissue, was supposed to be minimial.
In order to achieve this goal various polymers with either poly(tetrahydrofuran) or a new PEG-carbonate as soft block and combining them with different chain extenders including bis(2-hydroxyethyl)terephthalate, bis(2-hydroxyethyl)disulfide and newly synthesized thiazolidine compounds, ketals and organophosphates were prepared. As hard block only hexamethylene diisocyanate was used.
The higher hydrophilicity due to the ether moieties paired with the higher number of carbonate groups compared to already used polycarbonates and polyether soft blocks in the backbone of the polymer were expected to accelerate degradation with the chain extenders enhancing this effect.

The obtained materials were tested towards degradability and mechanical properties and compared to reference materials, to evaluate the most suitable polyurethane for the use in vascular tissue engineering.

Kurzfassung

Im Laufe der letzten Jahrzehnte entwickelten sich Herzkreislauferkrankung zur weltweit führenden Todesursache. Dadurch stieg auch die Nachfrage an Materialien zur/zum Behandlung/Ersatz von versagenden Blutgefäßen.
Tissue engineering von Blutgefäßersatzmaterialien ist ein vielversprechender Ansatz um diesen Bedarf zu decken. Obwohl Ersatzmaterialien für Gefäße mit großem Durchmesser erfolgreich eingesetzt wurden, schlugen die Versuche, diese Materialen für Gefäße mit kleinerem Durchmesser zu etablieren, fehl. Als mögliche Ursachen dafür werden fehlende Blutkompatibilität als auch zu unterschiedliche mechanische Eigenschaften gegenüber natürlichen Blutgefäßen angenommen.
Eine mögliche Lösung dieses Problems könnte der Einsatz von thermoplastischen Polyurethanen (TPUs) als innovatives Blutgefäßersatzmaterial liefern.
Diese Klasse von Polymeren zeichnet sich durch gute Biokompatibilität und gute mechanische Eigenschaften aus und kann dabei sowohl aus Schmelze als auch in Lösung verarbeitet werden. Der segmentierte Aufbau dieser Polymere – bestehend aus einem Makrodiol als flexiblem Softblock und eine Kombination aus einem Diisocyanat und einem Chainextender, als festem Hardblock – erlaubt es durch Änderung der verwendeten Ausgangsstoffe sowohl die mechanischen Eigenschaften als auch das Abbauverhalten zu beeinflussen.

Im Rahmen dieser Arbeit sollten Blutgefäßersatzmaterialien mit im Vergleich zu bisher in unserer Arbeitsgruppe entwickelter Materialien stark erhöhten Abbauraten entwickelt werden. Es sollten Materialien synthetisiert werden bei denen sowohl der Softblock als auch der Hardblock biologisch abgebaut werden kann. Um höchst mögliche Verträglichkeit zu gewährleisten, sollte weitestgehend versucht werden auf Bestandteile, die zu sauren Abbauprodukten und in Folge zu Entzündungsreaktionen des umliegenden Gewebes führen, zu verzichten.
Um dieses Ziel zu erreichen wurden neue Polyurethane durch Kombination von Polytetrahydrofuran oder eines Polyethercarbonats als Softblock mit verschiedenen Kettenverlängerern, darunter Bis(2-hydroxyethyl)terephthalat, Bis(2-hydroxyethyl)disulfid synthetisiert. Weiters wurde versucht neue Kettenverlängerer auf Basis von Thiazolidinverbindungen, Ketalen und Phosphorsäureestern zu synthetisieren. In allen Polyurethanen sollte Hexamethylendiisocyanat als Hardblock verwendet werden.

In der Folge wurden die hergestellten Polymere auf ihre Tauglichkeit für den Einsatz im Bereich des vaskulären Tissue Engineerings, durch Ermittlung der mechanischen Eigenschaften und des Abbauverhaltens, untersucht.

Introduction

1 The cardiovascular system

The human cardiovascular system consists of the heart, blood vessels and blood. The four-chambered heart (Fig.1) provides the whole body with nutrients, oxygen, etc. by pumping blood through a two- circular system which consists of arteries, capillaries and veins. Oxygen-poor blood is pumped out of the heart's right ventricle and travels through the pulmonary circuit to the lung, where the gas exchange from CO_2 to O_2 takes place (first circle). The oxygen-rich blood is then returned to the heart through the left atrium. Arteries transport the blood from the left atrium to the organs, while veins transport the oxygen-poor blood from the organs through a ventricle back to the heart (second circle).[1]

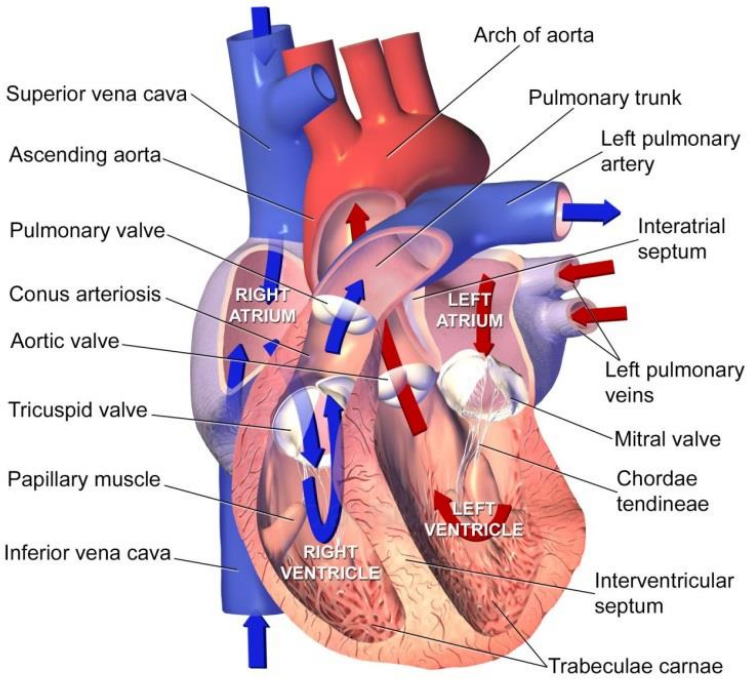


Figure 1: Anatomy of the human heart.[2]

Blood vessels are the second part of the circulatory system. Though there are three major types of blood vessels (arteries, capillaries, veins) their overall structure is very similar. They comprise of 3 different layers (Fig. 2).

The inner layer (*tunica intima*) consists of endothelial cells glued by a polysaccharide intercellular matrix that ensures blood flow.

The middle layer (*tunica media)* mostly consisting of smooth muscle cells is responsible for regulating the tonus. Between the second and third layer lays a thick elastic band (*membrana elastica externa*).

The outer layer (*tunica adventitia*) of blood vessels is mostly connective tissue but also contains fibrocollagenous networks and connects the blood vessel with the surrounding tissue.[1]

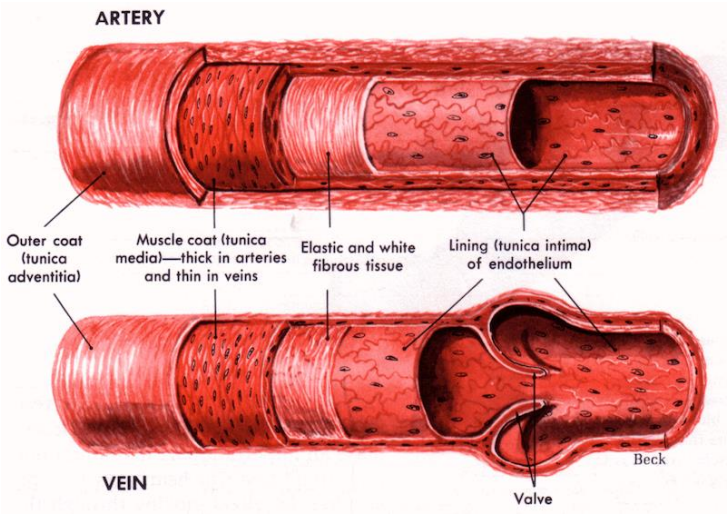


Figure 2: Structure of blood vessels[3]

2 Ischaemic heart disease and its treatments

Today WHO lists cardiovascular diseases (CVDs) as leading causes of death worldwide, with ischaemic heart disease (= coronary heart disease/ CHD) being the number one single cause of death in 2014.[4] (Fig. 3)

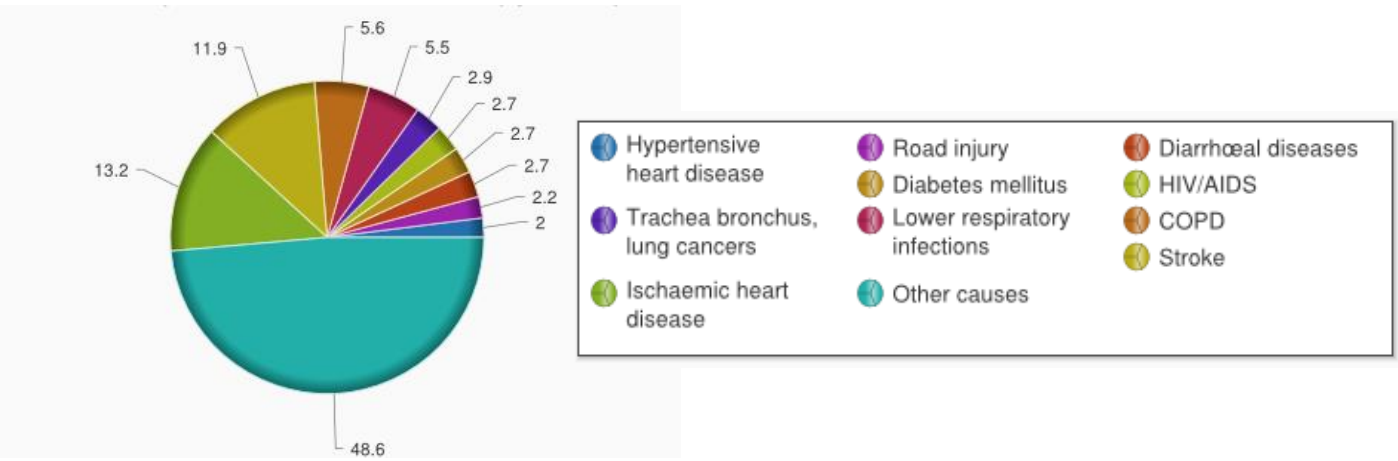


Figure 3: Percentages of the leading causes of death worldwide[5]

Generally CVDs are comprised of CHD, heart failure, cardiac arrest, ventricular arrhythmias and sudden cardiac death, rheumatic heart disease, transient ischaemic attack, ischaemic stroke, subarachnoid and intracerebral hemorrhage, abdominal aortic aneurysm, peripheral artery disease, and congenital heart disease. Ischaemic heart disease, which consists principally of CHD, is the predominant manifestation of CVD.[6]

The symptoms of CHD - including stable/unstable angina, nonfatal myocardial infarction, and coronary death - are direct results from an undersupply of the heart due to narrowings (atherosclerosis/thrombus) in the coronary arteries.[6,7]

Gaining a healthy lifestyle - proper nutrition, plenty of exercise/reducing overweight, quitting smoking and reducing stress - is in general the best prevention to avoid CHD.[7,8]

In advanced cases of CHD a recovery by a change in lifestyle isn't possible anymore and further measures have to be taken. These steps range from medication therapies to coronary angioplasty and stents to bypass surgeries and gene therapies.[7-9]

The main goal of these therapies is to resupply the heart with sufficient blood and therefore nutrients via the coronary arteries.

Drug therapies achieve this by reducing blood clotting, artery widening and simultaneously trying to reduce blood-cholesterol-levels to prevent further clogging (for details see B. Cohan et.al.[7]) by simply taking medication. Though this therapies can bring relieve for the mentioned symptoms in early stages of CHD they can't compensate for healthy arteries and a healthy lifestyle.

If drug therapies don't or can't show the desired results anymore, coronary angioplasty restores blood flow by mechanical flattening of the atherosclerotic plaque against the artery wall (Fig. 4): an empty balloon is inserted into the narrowed artery via catheter (A) and gets inflated and deflated several times (C,D). After removal of the balloon the blood vessel should be wide enough (E) to sustain sufficient blood flow. In some cases a stent has to be inserted afterwards to sustain the widening of the artery.

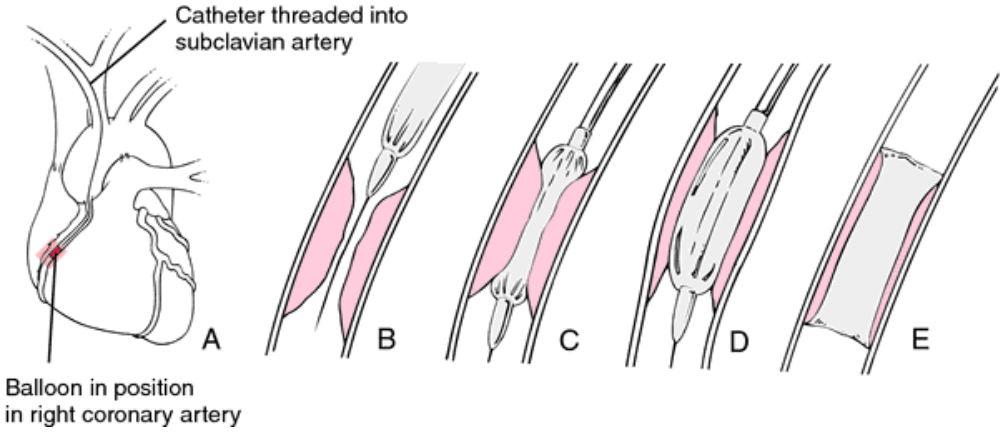


Figure 4: Principle of angioplasty[10]

If drug therapies and angioplasty aren't an option or in the case of a myocardial infarct the patient has to undergo a coronary bypass grafting surgery. By the usage of suitable artery or vein material it is possible to bypass the narrowed blood vessels by grafting them onto the coronary arteries to restore heart function. The most commonly used blood vessels for this procedure are the thoracic artery *(Arteria thoracica interna*) or the saphenous vein (*Vena saphena magna*) which are usually harvested from the patient (autografts). Donated tissue from humans (allografts) or animals (xenografts) is an option as well.

Though there has been made progress in treating CHD patients with gene therapies[9,11] to regenerate the coronary arteries, bypass grafting surgeries still are state of the art. But bypass surgeries suffer from several limitations as well. First of all autologous blood vessels are limited either due to previous surgeries or simple lack of healthy tissue. Donated tissue is always an option but immune response is very likely and immuno suppressants are necessary to avoid rejection of the tissue, which on the other hand can lead to non surgery related infections. Further donated tissue isn't always available especially in case of emergencies like myocardial infarction.

These limitations paired with the ever increasing number of CHD patients led to a search for alternative materials.

3 Tissue engineering (TE)

Tissue engineering is defined as an interdisciplinary field that applies the principles of engineering, materials science, and life sciences toward the development of biologic substitutes that restore, maintain, or improve tissue function.[12]

Tissue engineering (Fig. 5) starts by isolating specific cells and their growth on a three-dimensional biomimetic scaffold under controlled culture conditions. The construct is implanted at the desired site, and growth of new tissue into the scaffold is stimulated while it is degraded.[13] Usually three components are necessary to achieve this goal: (a) cells, (b) scaffolds to enable tissue ingrowth, and often with the addition of (c) growth factors.[14]

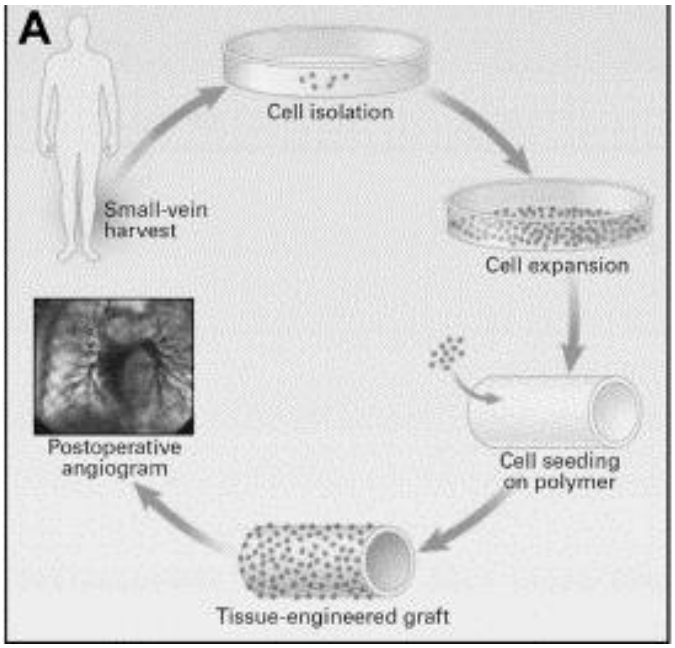


Figure 5: Principle of (vascular)TE[15]

The cell seeding of the graft can be performed in vitro (cellular tissue engineering) or in vivo as well (acellular tissue engineering).

In order to obtain fully regenerated tissue the scaffold has to show suitable architecture and has to be biodegradable as well as biocompatible. Further the scaffolds should be able to provide sufficient cell adhesion and should aid proliferation and expression of a specific phenotype. The physical structure of a scaffold on the other hand ideally controls cell function by regulating the

distribution/diffusion of nutrients and waste products whereas the scaffold surface chemistry affects cell adhesion, morphology and cellular activity.[16]

Today a large number of biomaterials (for further information see O'Brian[17]) is available which makes TE a powerful tool in treating a variety of medical conditions and might offer a possible solution to overcome today's limitations of treating CHD.

3.1 Vascular tissue engineering (VTE): goals and techniques

The overall goal of VTE lies in the production of an autologous tissue engineered vascular graft (TEVG) that is immunologically compatible, nonthrombogenic with the ability to grow and remodel.[18]

Numerous methods have been developed over the last decades and can be classified into *scaffold based* -, *scaffold free* approaches and *a combination of scaffold based and scaffold free methods*.

For each of these methods numerous examples can be found in literature.

The first example of a *scaffold free* TEVG was reported by Weinberg and Bell who cultured bovine endothelial cells (ECs), smooth muscle cells (SMCs) and fibroblasts, embedded them within a collagen matrix and formed them into a tubular structure.[19] L'Heureux et al. [20] refined this technique by shaping grafts from autologous smooth muscle cells.

Another quickly evolving *scaffold free* technique in TE/VTE is 3D bio-printing: cells and growth factors are printed layer by layer in phase-changing hydrogels/argarose gels to create grafts which mimic native tissue to a high degree.[21,22]

The *scaffold based* techniques are the classic TE approaches where a seeded / non seeded graft is implanted. The used materials range from natural to synthetic grafts and can be permanent as well as degradable. The procedures involved, differ depending on the used material. Decellularized scaffolds - as an example for natural scaffolds - are prepared by removal of immunologic responsive material (proteins, lipids, and nucleotide remnants) from non-autologous blood vessels (mostly from animals) by a combination of physical agitation, chemical surfactant treatment, and enzymatic digestion. Subsequently the remaining extracellular matrix (ECM) can be seeded with the patients' cells. [23-25]

In case of synthetic materials the incorporation of endothial cells into small diameter grafts is necessary to reduce thrombogenecity. The cell seeding occurs either in vitro by coating (chemical modification of the surface may be necessary to enhance cell adhesion) the surface of the graft with ECs or the graft is shaped/surface-modified in a way, that the cell adhesion can take place in vitro as well.

An example for the combination of scaffold *free and scaffold based approaches* is the bioreactor approach. During this process a synthetic, tubular non degradable scaffold is either implanted into the patient[26] (laboratory animal) or inserted into an artificial bioreactor[27] where native tissue can grow around the scaffold. After harvest and removal of the scaffold, the graft is ready for transplantation.

Each of these techniques has its advantages but suffers from various limitations as well. Methods using grown autologous tissue circumvent problems associated with response of the immune system but are expensive and time intensive procedures with the inability to treat emergencies. In addition they often lack the required mechanical properties.[28-30] Growing non autologous tissue has even more disadvantages as they might trigger an immune response as well.

Lack of control over ECM deposition and architecture, reports of progressive biodegradation, and the potential risk of viral transmission from animal tissue are limitations associated with decellularized scaffolds.[23-25]

Synthetic grafts on the other hand usually are easily available, are storage stable, have low production costs and provide the required mechanical properties. Non degrading materials like PET (Dacron) or Teflon (Goretex) however lack hemocompability in low diameter vascular grafts even when their surface is modified to enhance compability.[31,32]

Degrading materials therefore would avoid long term problems associated with hemocompability by leading to fully regenerated native tissue.

Requirements for degrading scaffolds however are very high. The ultimate goal is to synthesize a **biocompatible** (no immune response, inflammation and thrombus formation) material with suitable **mechanical properties** to withstand constant mechanical stress in form of blood pressure and tonus that can finally be processed into **porous** and **complex 3D structures** for better integration in physiological environment.[14,15]

4 Biodegrading materials in tissue engineering

To obtain fully regenerated native tissue the use of biodegradable materials is necessary.

In the beginning natural polymers like fibrin and collagen were considered the materials of choice because of their role as structure proteins in the human body and thus providing outstanding biocompatibility. But they never lived up to the expectations. Lack of the required mechanical properties[19,20] led to development of synthetic reinforced materials which could trigger immune response within the implantation site.[32] Therefore the main focus concerning natural biomaterials shifted towards decellularized scaffolds with their already mentioned drawbacks.[23-25,34]

Of course the lack of readily available natural biomaterials led to the development of synthetic alternatives as well.

Today the most commonly used synthetic biodegrading materials are polyesters which are known as degradable suture materials, but biocompatible and biodegrading polyanhydrides and polyurethanes are known as well.

4.1 Polyesters

Polyester-based degradable materials usually contain poly(lactic acid) *PLA*, poly(glycolic acid) *PGA*, poly(ε-caprolactone) *PCL*, poly(dioxanone) *PDO* or various copolymers of these compounds. (see Fig. 6)

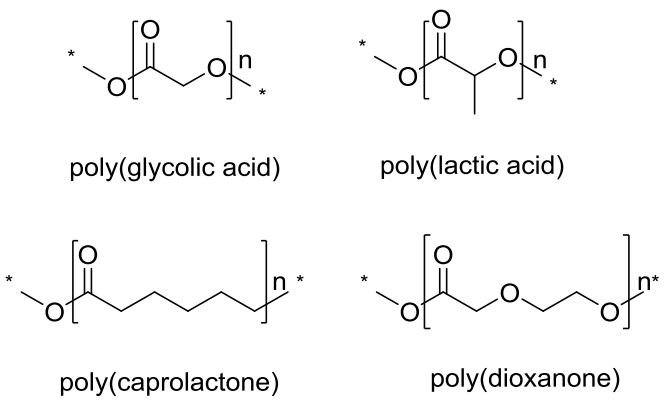


Figure 6: Polyesters used in biodegrading materials

Degradation occurs through hydrolysis of the ester bonds within the polymer forming acidic degradation products. In case of *PLA* and *PCL* the degradation products (glycolic acid or lactic acid) can be fully metabolized within the body. Though the degradation products of the other polyesters can't be metabolized they are not harmful either.

PGA is a partly crystalline polymer with up to 55% crystallinity that contributes to its high tensile modulus of around 12.5 GPa. It usually forms very stiff materials and is therefore in use as a bone replacement material. Its fast degradation and acidic degradation products however limit its biomedical applications.[35]

PLA like *PGA* is a crystalline polymer with around 37 % crystallinity. The degree of crystallinity depends on the molecular weight and the processing history of the polymer. It offers good tensile strength and a high modulus and is therefore used for the production of high strength fibers. Due to its additional methyl group *PLA* has a lower hydrophilicty than *PGA*. This fact in combination with its crystallinity leads to degradation rates of several years.[35]

Usually glycolic acid and lactic acid are co-polymerized to form amorphous, more readily degrading copolymers (*PLGAs*). They demonstrate good cell adhesion and proliferation making it a potential candidate for tissue engineering applications and were already processed into 3D scaffolds.[36,37] Their acidic degradation products however limit their use in VTE.

PCL is the polymer with the lowest hydrophilicity due to its relatively long aliphatic chain between the ester bonds. Degradation takes 2-3 years. It is a semicrystalline polymer which can be blended with a wide range of polymers. Due to its slow degradation it's usually copolymerized with lactic acid or glycolic acid.[35]

PDO is a colorless, semicrystalline polymer with relatively low hydrophilicity and therefore being a slow degrading polymer. Compared to *PGA* it has a very low tensile modulus of 1.5 GPa and loses its strength within 2 months. It takes around one year to fully degrade.[35]

Considering the drawbacks found in biodegradable polyesters, it was necessary to find more suitable materials to meet the high demands in VTE.

Their unique structure as well as their biocompatibility[34,38] makes polyurethanes the ideal candidates to fulfill the high requirements for degradable scaffold materials.

4.2 Segmented Thermoplastic Polyurethanes (STPUs)

STPUs are physically cross-linked polymers with elastomeric and thermoplastic properties which are synthesized by polyaddition-reactions.

They consist of alternating segments of so called soft blocks (a macrodiol) and hard blocks: either a low molecular weight diisocyanate (not chain extended STPU) or a combination of diisocyanate and low molecular diol/diamine/dithiol (chain extended STPU). Not chain extended STPUs are synthesized in a one shot process whereas in the case of chain extended STPUs a two-step process is required (see Fig. 7).

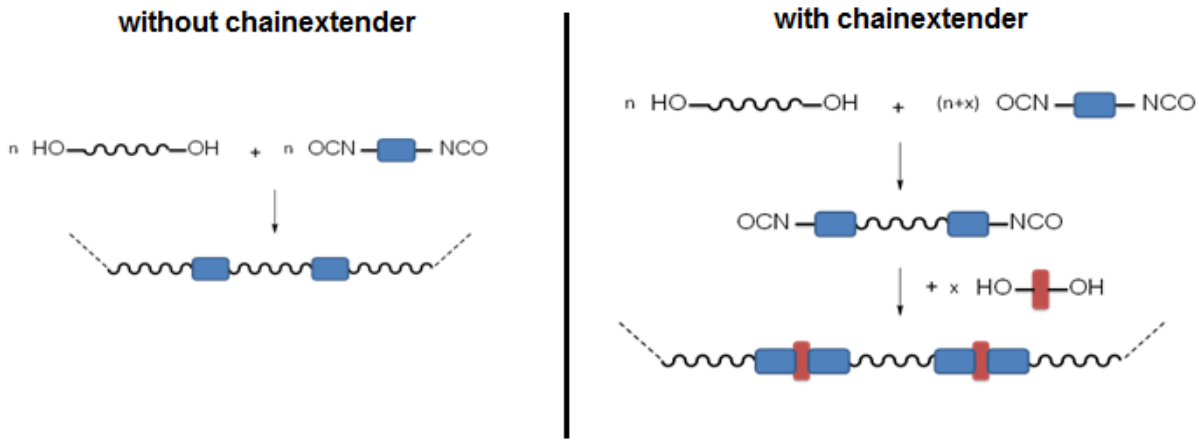


Figure 7: not chain extended (left) and chain-extended polyurethanes (right)

In the first step a prepolymer of the macrodiol and an excess of the isocyanate is formed. After the addition of the chain extender (diamine/diol/dithiol) a polyurethane-urea is formed in case of a diamine and a polyurethane/polyurethane-thiocarbamate is formed in case of a diol/dithiol.

Because of the step-growing mechanism and the water-sensitive nature of the diisocyanates, high purity compounds and water free reaction conditions are required.

Aggregation of the hard block segments, which is driven by H-bonding of the urethane-groups, leads to a physically cross-linked polymer. (Fig.8)

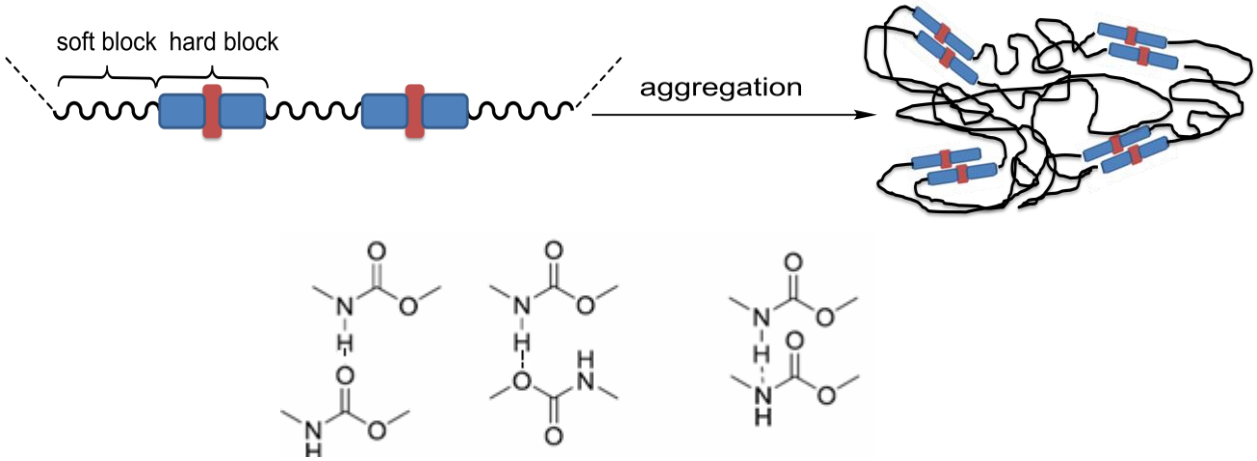


Figure 8: Aggregation of TPUs and H-bonding sites within the hard blocks

The result is a polymer with a hard, partly crystalline phase which provides the polymer with rigidity, and an amorphous, soft phase (macrodiol) which shows rubberlike properties.

The aggregation and final mechanical properties can be influenced by the choice and ratio of the used building blocks. Sterically demanding and non-symmetric isocyanates/chain extenders as well as functional groups (ether-, ester-, carbonate-moieties, organo-phosphates etc.) within the soft block can hinder aggregation and inhibit formation of crystalline moieties and usually lead to inferior mechanical properties compared to STPUs with aliphatic soft blocks and symmetric isocyanates/chain extenders. Choosing aromatic compounds as well as changing the molecular weight of the soft block and increasing the number of used building blocks (e.g. two different kinds of soft blocks/chain extenders etc.) allows further tuning of the properties. But homogeneity of the polymer may suffer severely and batch to batch variations might increase by involving too many compounds during synthesis.

4.2.1 Biodegradable STPUs

In order to achieve controlled biodegradability enzymatically[38-40] and/or hydrolytically[41] cleavable bonds have to be introduced into the backbone of the polyurethane. This can be done by using hydrophilic soft blocks like poly(ethylene glycols) and adding functional groups like disulfides, lipids, esters and carbonates to the hard block (hard block degrading TPUs) and/or the soft block (soft block degrading TPUs).

As already mentioned the scaffold has to fully degrade in order to achieve full regenerated native tissue. Naturally the overall mechanical properties have to stay constant throughout the process of degradation and regrowth of tissue, to avoid complications (see Fig. 9).

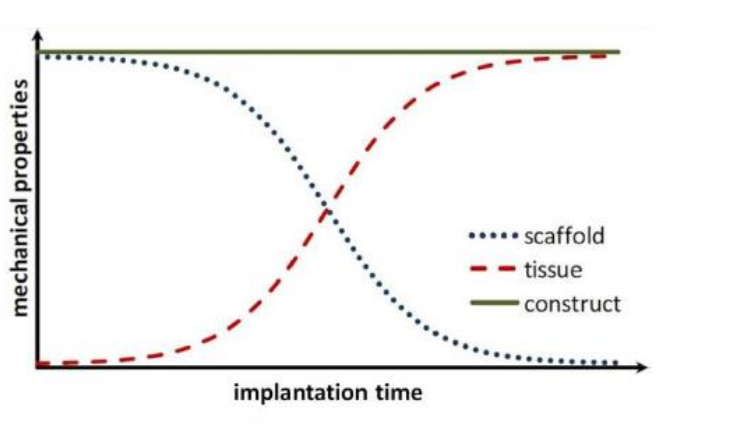


Figure 9: Ideal mechanical behavior of scaffold and tissue

The final degradation properties are determined by the composition of the polyurethane as well as by its molecular weight, polydispersity and crystallinity.[40] Generally hydrophilic polymers with a high number of cleavable functional groups degrade faster in a hydrophilic environment like the human body than hydrophobic polyurethanes with a low number of cleavable units and low molecular weight polyurethanes tend to degrade faster than their high molecular weight counterparts.

To complicate matters different polymers undergo different in vivo degradation processes that can also lead to failing grafts. A good overview of the involved processes is given by Cauich-Rodríguez et al.[42]

Degradation itself manifests via two mechanisms. (see Fig.10)

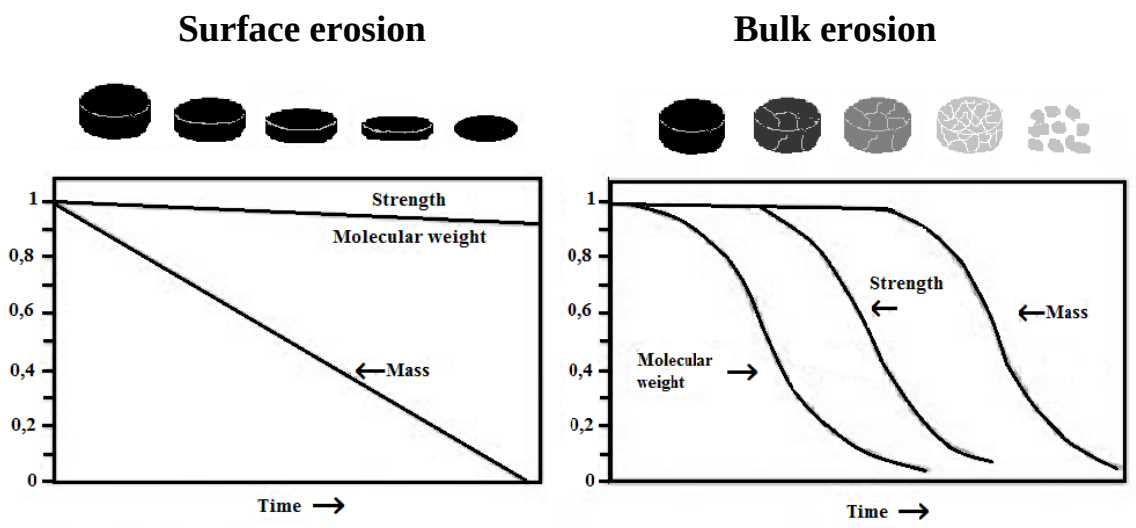


Figure 10: Differences between surface and bulk erosion[43]

On one hand there is surface erosion and like the name suggests the degradation and loss of mass and molecular weight only occurs on the surface of the polymer leaving inner parts of the polymer untouched.[44,45] Erosion and loss of mass and mechanical properties occurs gradually. On the other hand there is bulk erosion where the molecular weight of the polymer decreases homogeneously throughout the polymer.[44,45] At the beginning the chains are still too large to leave the bulk but the mass remains roughly the same. At a certain point the degradation products are small enough for diffusion which leads to a sudden loss of mechanical properties of the material. Further bulk erosion is enhanced under acidic conditions. Therefore polyester based materials with their acidic degradation products are prone to bulk erosion (autocatalytic bulk erosion).[45]

Generally surface erosion is preferred because it tends to be more predictable than bulk eroding materials but in case of porous materials like TEVGs both processes can go hand in hand.[44]

4.2.2 Processing of STPUs

Depending on their final mechanical properties, STPUs can be processed in various ways like extrusion, thermally induced phase separation and salt leaching/freeze-drying.[46] Remarkably STPUs, can be processed into fibers as well. Fibers can be obtained via melt spinning, wet spinning, dry spinning and electrospinning with electrospinning being the tool of choice in VTE.

Unlike the usual spinning techniques whose fibers can only be shaped by weaving or knitting and therefore yielding very symmetric structures that don't mimic the structure of the extracellular matrix, electrospinning allows a convenient production of irregular tubular structures of different kinds (see later) needed for VTE.

The process of electrospinning is visualized in Figure 11.

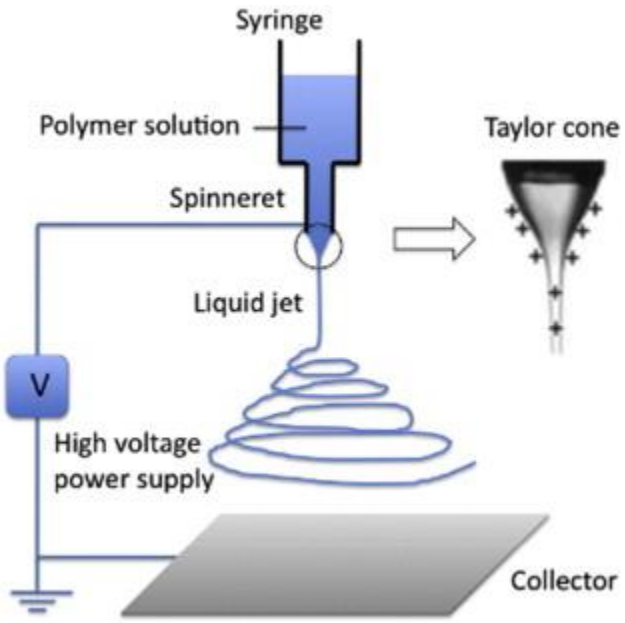


Figure 11: The principle of electrospinning[47]

A syringe fitted with a fine needle tip is provided with a polymer solution which is subsequently pumped through the needle tip. Between the needle tip and the collector an electric field is applied. When a small polymer droplet is exposed to said electric field the droplet stretches toward the nearest lower potential point and thereby forms a so called Taylor cone. At a certain point the electrostatic

forces overcome the surface tension forming the Taylor cone and a fiber jet is formed which is accelerated towards the collector. On the way from the needle tip to the collector the solvent gradually evaporates and ideally leaves pure polymer fibers at the collector. During the flight the fibers undergo random motions that yield random orientated fibrous networks. To obtain a tubular tissue engineered vascular graft (TEVG) a spinning and oscillating mandrel is used as a collector.

By changing parameters like polymer concentration, field strength, applying a second orthogonal electric field, rotational speed/ oscillation speed of the mandrel the structure (size, geometry and microstructure) of the final graft can be influenced in many ways.

Another specialty of this method is the ability to co-spin different materials, meaning that several materials could be spun simultaneously with several syringes present or that layered grafts can be obtained by successive spinning of different materials.

Objective

Low production costs, tunable mechanical properties, storage stability, low batch to batch variability and off the shelf availability are the main advantages of synthetic grafts for vascular tissue engineering (VTE).

Segmented thermoplastic polyurethanes (STPUs) are one of the most promising materials in the field of VTE as they can be crafted to provide good biocompatibility, degradability and mechanical properties. Further they can be processed via electrospinning[48] to provide fibrous networks that mimic the structure of native blood vessels to a large extent.

Based on the results of previous work in our research group, the goal of this diploma thesis was to provide a STPU material which meets the following requirements.

- significantly increased degradation rate
- capability to be processed via electrospinning
- mechanical properties that mimic native blood vessels

To achieve these goals a new diol-based soft block and chain extenders with hydrolytically cleavable moieties were supposed to be synthesized and finally merged into STPUs with the hidden agenda to synthesize them in a reasonable priced manner.

The soft block should contain a maximum of cleavable carbonate units whereas the main focus concerning new chain extenders laid on thiazolidine-diols but ketals and organophosphates were contemplated as well. Thus obtained polymers were supposed to be compared to materials containing the commercially available chain extenders bis(2-hydroxytethyl)terephthalate, bis(2-hydroxyethyl) disulfide and the previously in our working group used chain extender bis(3-hydroxypropyl)carbonate.

As reference materials, Reference D (pTHF1000/HMDI/DET) and the commercially available Pellethane (pTHF1000/MDI/BDO) should be used. Reference D was developed in our group and is known from previous works.[49] It can be electrospun and shows good mechanical properties, is biodegradable as well and is therefore deemed a good reference material.

To evaluate the suitability as possible material for VTE all materials should be tested towards their hydrophilicity, molecular weight, mechanical properties and degradability.

State of the art

Today a large number of different segmented thermoplastic polyurethanes (STPUs) are available for various applications ranging from the automobile industry, applications in sporting equipment to medical equipment as well as materials in tissue engineering.

The general structure of a STPU (see Fig. 12), however, is the same for all of these materials.

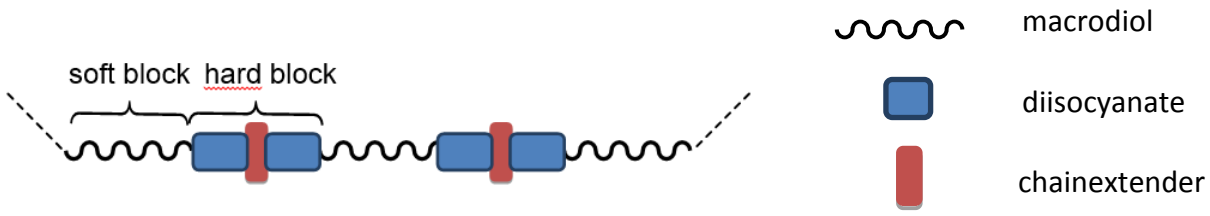


Figure 12: Structure of a chain extended STPU

They consist of alternating segments of soft blocks (a macrodiol) and hard blocks. The hard block is either a diisocyanate (not chain extended STPU) or a combination of a diiscocyanate with a low molecular weight diol/diamine/dithiol - called chain extender – as depictured in Fig. 12.

Depending on the used building blocks, the production of biocompatible, biostable/biodegradable materials with various mechanical properties is possible.

Biodegradable STPUs can be obtained if degradable moieties are incorporated into the backbone of the polyurethane. Such cleavable moieties can be esters, peptides, disulfides or carbonates. These bonds can either degrade enzymaticaly[38-40] or hydrolytically.[41]

Depending on the location of these functional groups within the STPU, *soft block degrading* or *hard block degrading* polyurethanes can be obtained. Of course it is possible to synthesize soft- and hard block degrading materials as well. As seen in Table 1, soft block degrading polyurethanes usually consist of a degradable macrodiol and a non-degradable hard block. Hard block degrading STPUs contain a non-degradable macro-diol as soft block and a degradable chain extender and/or hard block.

Table 1: degradation behavior of STPU building blocks

	soft block	chain extender	diisocyanate
soft block degrading STPU	degradable	non degradable	non degradable
hard block degrading STPU	non degradable	degradable	non degradable (or degradable)
soft/hard block degrading STPU	degradable	degradable	non degradable (or degradable)

The most commonly used soft blocks in soft block degrading polyurethanes are polyesters. Usually poly(lactic acid) *PLA*, poly(glycolic acid) *PGA*, poly(ε-caprolactone) *PCL*, poly(dioxanone) *PDO* or various copolymers of these polyesters (see Fig.13) are incorporated into polyurethanes to obtain biodegradability.[38,39,49] However, tested polyester-based STPUs led to inflammatory reactions when implanted, due to acidic degradation products.[38,39] Therefore the attention shifted towards carbonate based soft blocks as they don't form any acidic degradation products.[50] The most used soft blocks of this kind are poly(trimethylene carbonate) *pTMC*, poly(hexamethylene carbonate) *pHMC*, poly(butylene carbonate) *PBC* and poly(neopentyl carbonate) *pNPC*.[50-53] They are depictured in Figure 13.

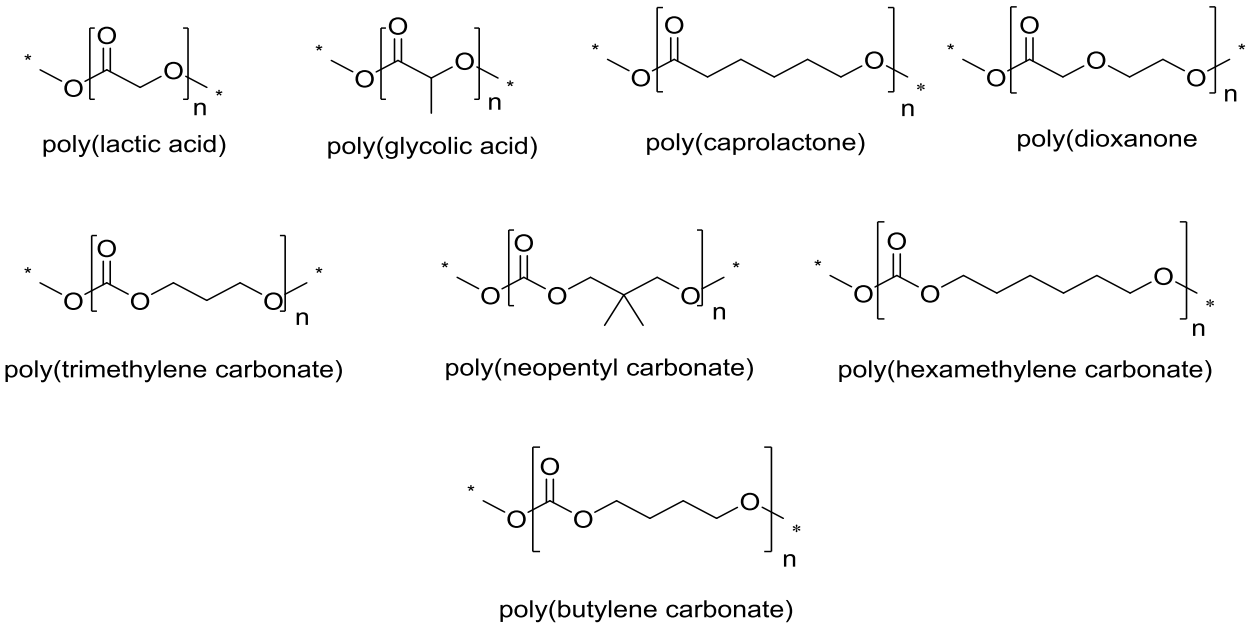


Figure 13: Common degradable soft blocks

Sobczak et al.[52] reported polycarbonates (*PC*) and poly(ester carbonate)s (*PEC*) containing STPUs for biomedical applications. They used macrodiols like *pTMC*, *pNPC* and two poly(ester carbonate)s like poly(caprolactone-trimethylene carbonate)diol and poly(caprolactone-neopentyl carbonate)diol. The toxicity of the polymers was evaluated as well, suggesting that the *PEC* or *PC* diols prepared might be applied for the synthesis of biomedical STPUs.
Zhou et al.[53] performed a number of detailed studies on the enzymatic degradation process of *PBC*, *pHMC*, and *PBC/pHMC* copolymers. They described a linear degradation process for all tested polymers, mainly influenced by the crystallinity of the polymers.

Hard block degrading polyurethanes on the other hand contain soft blocks made from hydrolytically stable poly(ethers) like poly(ethylene glycol) (*PEG*) or poly(tetrahydrofuran) (*pTHF*) of various molecular weights.[54,55] Poly(hexamethylene oxide) *PHMO* and poly(dimethylsiloxane) *PDMS* (see Fig. 12) have been used by Martin et. al.[56] to form biocompatible and biostable STPUs and therefore can be an option for hard block degrading materials as well. These soft blocks are depictured in Figure 14.

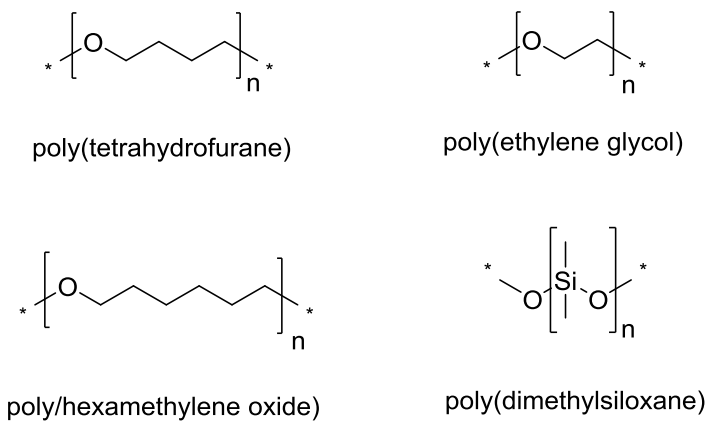


Figure 14: Common non degrading soft blocks

The choice of the used chain extender again is based on the wanted degradation behavior of the polyurethanes.

Soft block degrading polymers often contain aliphatic and therefore non degrading diols like 1,4-butane diol or ethylene glycol. The corresponding amines and dithiols can be used as well. (see Fig. 15)

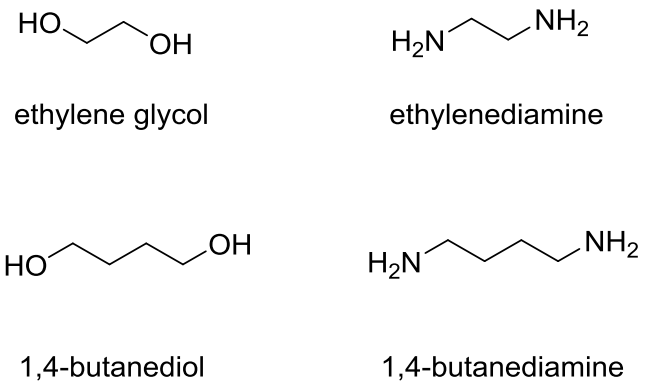


Figure 15: Common non degradable chainextenders

In case of hard block or soft/hard block degrading STPUs difunctional compounds with cleavable moieties like esters, carbonates and disulfides can be used. The use of commercially available bis(2-hydroxyethyl) terephthalate[48] and bis(2-hydroxyethyl) disulfide[57] (DHEDS) has been reported as well as the use of bis(3-hydroxypropyl) carbonate[58] and amino acids like L-glutamine and tyrosine[59] and esters like 3-hydroxypropyl 2-hydroxyacetate.[60]

Gunatillake et al.[60] compared the degradation of *PCL* based STPUs, containing either non-degradable (ethylene glycol) and ester based degradable chain extenders and observed a significantly increased degradation rates for STPUs containing ester based degradable chain extenders.

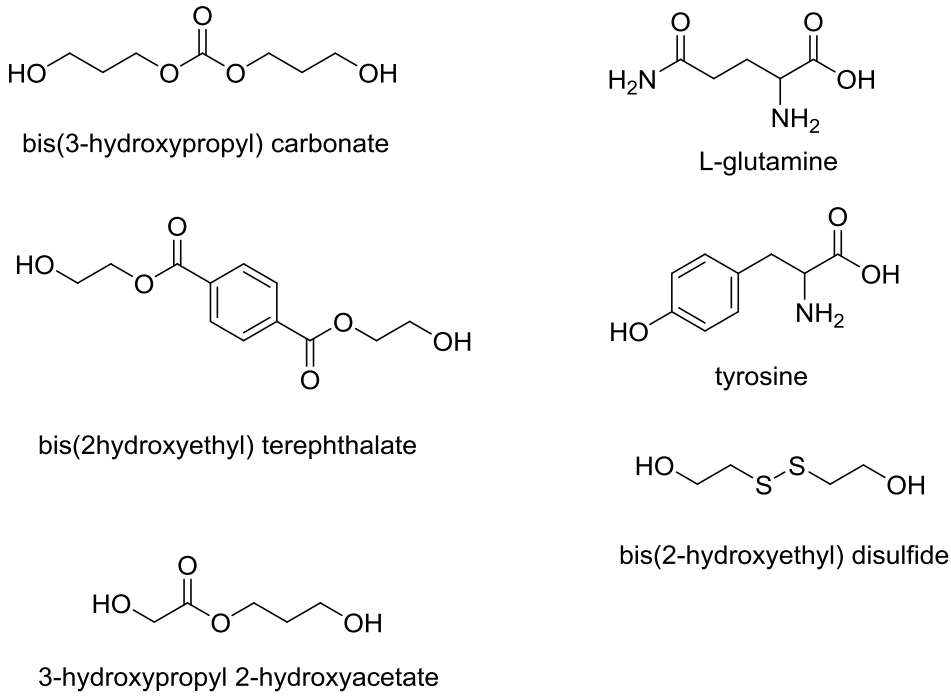


Figure 16: Degradable chainextenders for the use in STPUs

Skarja and Woodhouse[59] prepared amino acid (L-glutamine and tyrosine) chain-extended STPUs with various molecular weights based on *PCL* and *PDMS* and showed that these polymers underwent surface erosion by placing them in enzyme-mediated (but not buffer-mediated) solutions.

Zamora et al.[57] prepared various polyurethane copolymers by reacting various ratios of bis(2-hydroxyethyl) disulfide and 2,3,4-tri-O-benzyl-L-arabinitol or 2,3,4-tri-O-methyl-L-arabinitol with hexamethylene diisocyanate and showed that degradation of these polymers depended on the DHEDS content as well as the crystallinity of the polymers.

The diisocyanates in hard block degrading polyurethanes can either be degradable or non-degradable but literature mainly describes the use of non-degradable diisocyanates.[43,46,50-60] An example for a degradable diisocyanate is L-lysine ethylester diisocyanate which is reported to hydrolyze to the nontoxic L-lysine.[61] (see Fig.17)

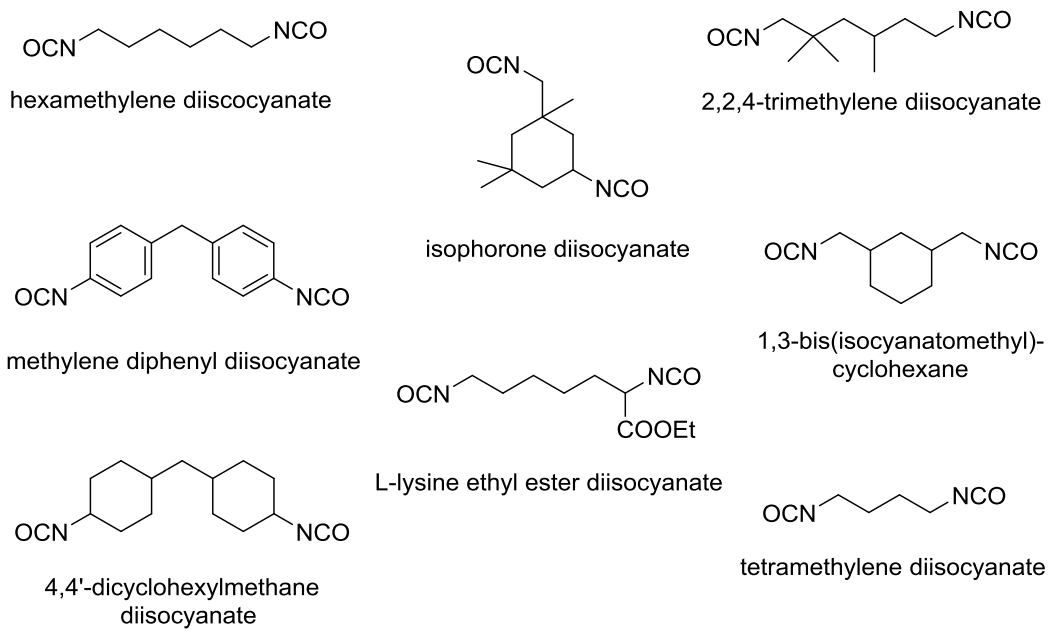


Figure 17: Degrading and non-degrading diisocyanates used for STPUs

But not every diisocyanate might be considered when it comes to biodegradable polymers. Beside the fact, that mechanical properties can be influenced by the choice of the molecule, toxic degradation products should be avoided to reduce risks of cytotoxicity, etc. Aromatic amines which derive from the corresponding aromatic diisocyanates like MDI - a widely used building block for polyurethanes - for example are known to be toxic/carcinogenic.

Results and Discussion

Today the most widely used degrading components (soft blocks and chain extenders) in segmented thermoplastic polyurethanes (STPUs) are ester based materials.[34-39,49-51,60,62] Beside their slow degradation rates, their acidic degradation products can limit the possible use of those materials in vascular tissue engineering (VTE). Our working group has developed a promising material which has proven to be biocompatible as well as biodegradable.[48] In vitro studies conducted with this material showed that the graft was fully replaced within one year in rats.[63] These results also indicated that a living system might be able to replace artificial grafts even faster.

In order to prove this thesis it was the goal of this work to synthesize new polymers with degradation rates of a few weeks. Because STPUs containing the well-established compounds (see “State of the art”) didn’t lead to the assumption of greatly increased degradation rates combined with outstanding biocompatibility, a new class of soft blocks should be developed. The focus of interest was laid on new polyether carbonate soft blocks with thiazolidine based chain extenders.

In case of the the poly(ether carbonate) faster degradation was expected due to more cleavable units and a higher hydrophilicity compared to already used soft blocks. (see Fig.18)

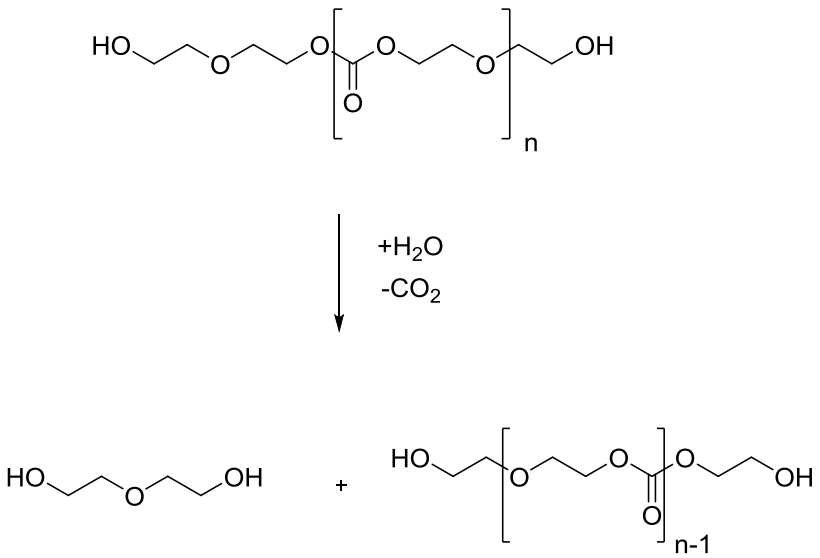


Figure 18: Hydrolysis of a poly(ether carbonate)

Thiazolidine based materials were of particular interest for three reasons:

a) they are known to be prone to hydrolysis.[64,65] (see Fig.19)
b) the hydrolysis rate can be influenced by modifying position 2 and 3 of the thiazolidine.[64]
c) Wathier et al. [66] were able to obtain thiazolidine cross-linked hydrogels which degraded within several weeks depending on the substitution of the thiazolidine.

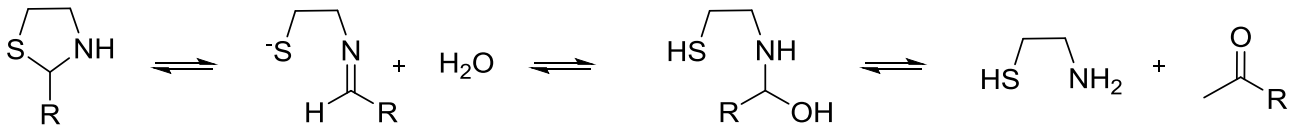


Figure 19: Hydrolysis of thiazolidines[67]

1 Poly(ether carbonate) soft blocks

1.1 Synthesis strategies for polycarbonates

Polycarbonates are versatile, thermoplastic, optically clear, tough and durable polymers. They are used in automotive industry as well as in the production of CDs/DVDs/Blu-rays and in electric and electronic devices.

Formally they contain a carbonate group as repetitive unit within the polymer (see Fig.20) and they can be described as esters of the carbonic acid.

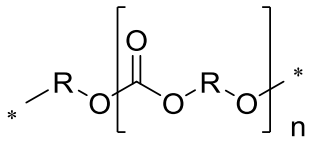


Figure 20: General structure of a polycarbonate

The two most common routes in industry to obtain polycarbonates are the Schotten-Baumann process and base-catalyzed two-step transesterification processes.[68]

In case of the Schotten-Baumann process polycarbonates are obtained by the reaction from a (sodium salt of a) diol with phosgene (see Fig.21)

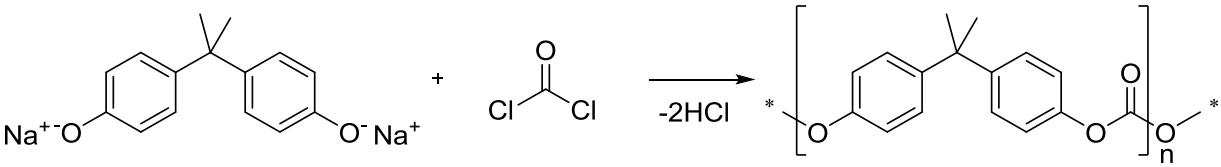


Figure 21: Polycondensation of bisphenol A and phosgene via Schotten-Baumann process

In case of the transesterification a diol reacts with a di-alkyl/aryl carbonate (see Fig.22).

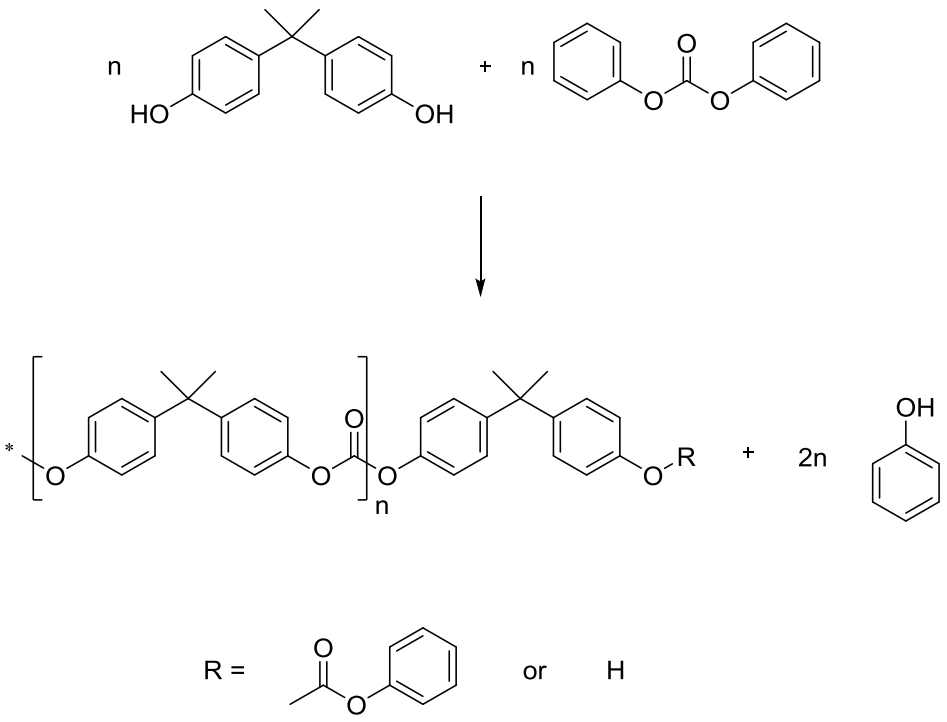


Figure 22: Polycarbonate synthesis by transesterification

Of course these processes are not strictly limited to bisphenols but generally these methods don't yield diols and therefore are not suitable for soft block synthesis. In case of the Schotten-Baumann process, the molecular weight is usually regulated by the addition of a monofunctional alcohol like p-*tert*-butyl phenol. Therefore the polymer chain usually is not hydroxy- terminated.[69] In case of the transesterification route the polymer is aryl/alkyl terminated. (see Fig. 22)

Another possibility to synthesize polycarbonates is the ring-opening polymerization (ROP) of cyclic carbonates such as trimethylene carbonate.

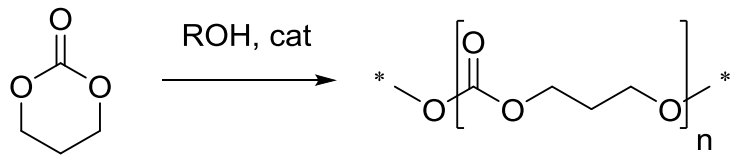


Figure 23: ROP of trimethylene carbonate

As depictured in Fig. 23, a catalyst and an initiator (often an alcohol) are required to enable this reaction.

This kind of reaction is usually catalyzed via organo tin compounds[70] or triethyl aluminium ($AlEt_3$)[71], but enzymatic catalysis has been reported as well.[72]

Generally this is a very versatile method as various cyclic carbonates can be used, which allows the tuning of the final properties of the polycarbonate.

In addition it is possible to obtain hydroxy-terminated polymer-chains if the starting agent is a diol, therefore making it the method of choice for soft block synthesis. (see Fig.24)

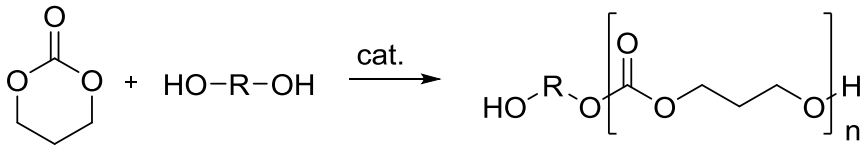


Figure 24: Synthesis of poly(trimethylene carbonate) diol

This method allows the synthesis of several polycarbonate diols like poly(trimethylene carbonate) diol pTMC, poly(hexamethylene carbonate) diol pHMC and poly(butylene carbonate) diol PBC, which already have been incorporated into STPUs.[50-53] (see State of the Art)

These materials however lack the desired fast degradation. Therefore in this thesis ethylene carbonate was polymerized to obtain a new class of more hydrophilic soft block for the synthesis of STPUs.

1.2 ROP of ethylene carbonate

Ring opening polymerisation of ethylene carbonate was reported by Vogdanis et al. who used various metal-based catalysts, such as alkoxides of tin and zirconium and anionic and cationic initiators (sec-butyllithium and methyl triflate) at temperatures between 100-170°C.[74] But instead of obtaining the homopolymer poly(ethylene carbonate) they reported the formation of the product poly(oxy-ethylene-*alt*-ethylene carbonate) due to partially decarboxylation.

As depictured in Fig. 25 the alcohol can either attack the carbonate-group (pathway A) or can attack the alkylene moiety of the ethylene carbonate (pathway B). In case of B the resulting terminal group is very unstable finally leading to decarboxylation. However, in both cases a diol is obtained.

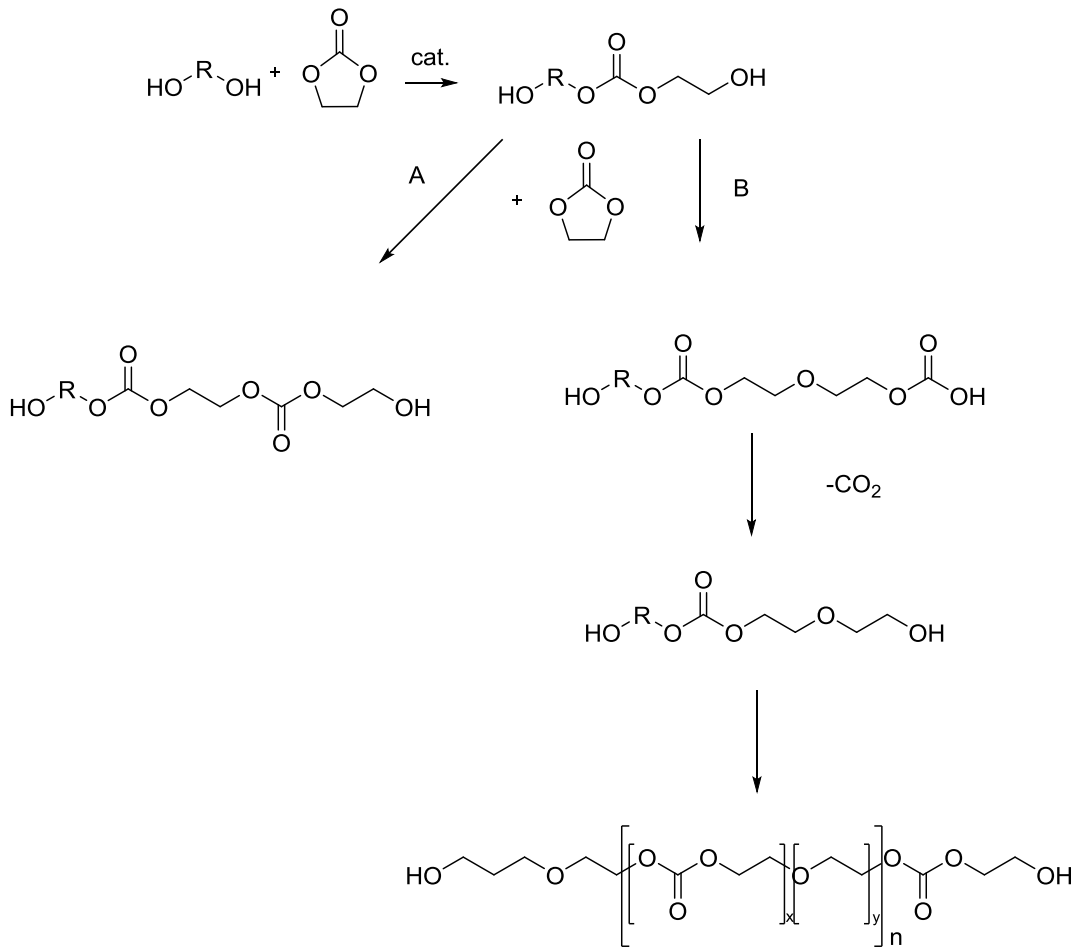


Figure 25: Proposed mechanism for the ROP of ethylene carbonate[69]

The reasons for the decarboxylation during ROP lies within the stability of the five membered ring of ethylene carbonate and the therefore required harsh reaction conditions of up to 170°C. Usually the attack on the carbonate group (pathway A) is more favorable as it is the most reactive site within a cyclic carbonate, therefore leading to homopolymers at moderate temperatures. (see ROP of TMC[52]) At temperatures of 170°C - which are required to polymerize ethylene carbonate - the attack on the alkylene group (Fig.25 pathway B) seems as likely as the attack on the carbonate group, therefore leading to the unstable carbonic acid end groups which then decarboxylate.[73,74]
The decarboxylation however wasn't deemed obstructive as the resulting polymer should still be more hydrophilic than already tested carbonate soft blocks due to additional ether groups.

The polymerization of ethylene carbonate was carried out under similar conditions that Vogdanis et al.[74] had reported, using 1,3-propanediol as initiator.
In a first step several catalysts were tested towards their aptitude for ROP of ethylene carbonate: the catalysts were $Ti(O^{i}iPr)_4$, K_2CO_3, $Zr(OBu)_4$, $Al(acac)_3$, dibutlyltindilaurate, $Sn(Oct)_2$ and $Sn(Oct)_2$ with a drop of NEt_3.
In a typical procedure EC was pulverized with mortar and pestle and dried over $CaCl_2$ for several days. It was polymerized in bulk with 1,3-propanediol as initiator with the ratio 100 : 1 : 0.5 for ethylene carbonate : diol : catalyst in all reactions at 170°C for 5 days under argon atmosphere. However, $Ti(OiPr)_4$, $Zr(OBu)_4$, $Al(acac)_3$ and dibutyltin dilaurate didn’t yield a polymer. ^{1}H-NMR confirmed the presence of non-reacted ethylene carbonate and 1,3-propanediol.
From the reactions with K_2CO_3, $Sn(Oct)_2$ without triethylamine and $Sn(Oct)_2$ with one additional drop triethylamine dark brown viscous liquids were obtained. They were confirmed to be poly(oxyethylene carbonate)s. Based on the viscosity of the products, the catalytic system $Sn(Oct)_2$ / triethylamine yielded the best result and therefore was used for further polymerizations.

In a second step poly(oxyethylene carbonate)s with molecular weights of approximately 1000g/mol and 2000g/mol should be synthesized in order to incorporate them in STPUs. Therefore the initiator concentration was varied, which should lead to different molecular weights.

The calculated ratios were 50 : 3 : 0.5 ($MW_{calculated}$ = 1500g/mol) for pEC1000 and 50 : 1.75 : 0.5 ($MW_{calculated}$ = 2500g/mol) for pEC2000.
After three days at 170°C (lower molecular weight polymers were reported to require shorter reaction times[69]) the obtained polymers were dissolved in DCM at room temperature and washed with cooled ~5% HCl. After evaporation of the solvent, the obtained polymers were dissolved in DCM and "precipitated" in *tert*-butyl methyl ether to decrease polydispersity which yielded dark brown, viscous polymers. Drying of the products was conducted in high vacuum at 70°C.

The molecular weights of the polymers were determined via the *p-toluenesulfonyl isocyanate (TSI) method* because the dark brown color made the determination of the hydroxyl number via DIN 53 240 impossible.
During this method, the diol is reacted with p-toluenesulfonyl isocyanate and dissolved in HPLC grade acetonitrile. The sample then is potentiometrically titrated with 0.1 N-tetrabutylammonium hydroxide (Bu_4NOH) solution using an autotitrator - pH electrode system.
Polydispersity was determined by size exclusion chromatography (SEC) using DMF as solvent.
As seen in Table 2 the obtained molecular weights were lower than the calculated molecular weights.

Table 2: calculated and obtained molecular weights and polydispersity

	calculated MW	**obtained MW**	**M_w/M_n**
pEC1000	1500g/mol	1220g/mol	1.3
pEC2000	2500g/mol	2037g/mol	1.6

This was expected due to increasing viscosity during reaction and decarboxylation. The reason why the difference in pEC2000 was higher than in pEC1000 may have lain in the bulk polymerization process. Increasing molecular weights usually go hand in hand with increased viscosities during polymerization which increases reaction times. Therefore a longer reaction time might have led

to a higher molecular weight polymer. However, the MW was in the required range, therefore not requiring longer reaction times.
Nonetheless, these results proved that the molecular weight can be influenced by changing the concentration of the initiator.

To gain information on the molecular weight distribution was of great interest because big differences in the molecular weights of the soft block chains might lead to inhomogeneous properties when incorporated into STPUs.
Whereas pEC1000 showed a relative homogeneous distribution with 1.3 (ionic polymerizations usually yield polymers with distributions around 1.1.) -which was a good result for a nonionic polymerization), pEC2000 with a distribution of 1.6 showed a value comparable by free radical polymerization (1.5 - 2).
Based on these results it can be concluded, that lower molecular weight poly(ether carbonate)s might be preferable over their higher molecular weight counterparts.

The amount of decarboxylation, that took place during polymerization, was of particular interest as well. A high number of carbonate units within the polymer would lead to faster *in vivo* degradation by enzymatic degradation. A high number ether groups on the other hand, would lead to a more hydrophilic polymer that would show increased water uptake which was expected to accelerate degradation even more. Therefore the distributions of carbonate and ether units of the obtained polymers were calculated.

The mol % carbonate groups can be calculated from the ^{1}H-NMR (see Fig. 26)

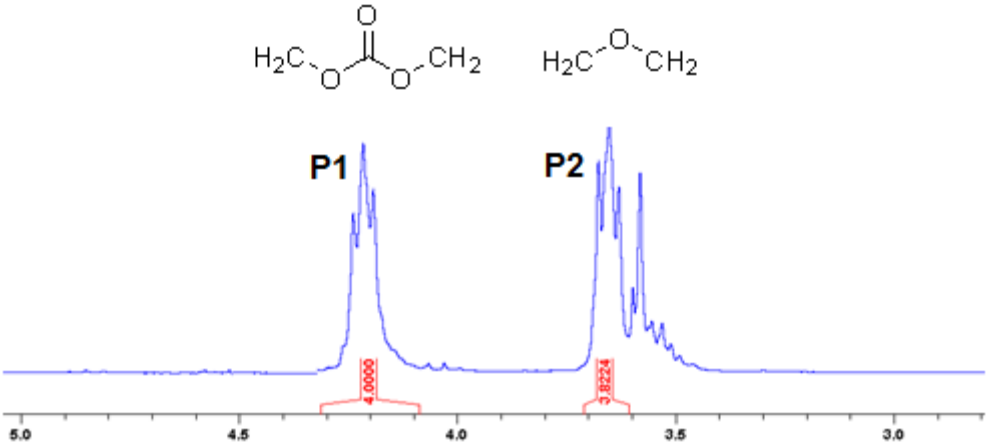


Figure 26: ^{1}H-NMR of pEC1000

by comparing the peak areas of the carbonate (P1) and ether signals (P2) using following equations:

$$\text{mol\% carbonate units} = \frac{\text{P1}}{\text{P1} + \text{P2}}$$

The number of carbonate units can be calculated according to:

$$\#\ carbonate\ units = \frac{M(polymer) * mol\%\ \ carbonate\ units}{M(ethylene\ carbonate) * 100}$$

Knowing the number of carbonate units and the polymer's molecular weight obtained from titration (TSI), the amount of ether groups can be calculated. Afterwards the mol % of both groups can be calculated. Prior to these calculations, the molecular weight of 3 CH_2 groups (from the initiator 1,3-propane diol) and the molecular weight of two H atoms from the hydroxyl-end groups have to be subtracted from the total polymer's molecular weight. Further the molecular weights can be calculated by:

$$MW = x\ (carbonate\ units) +\ y\ (ether\ units) +\ 3CH_2 +\ 2H$$

and compared to the obtained numbers of the TSI method.

As visualized in table 3 both polymers contain around 50mol% of ether and carbonate units.

Table 3: Distribution of ether and carbonate units and calculated MW

	pEC1000		**pEC2000**	
	mol%	#	mol%	#
H_2C-O-C(O)O-CH_2	51	6	50	11
H_2C-O-CH_2	49	8	50	13
	TSI	calculated	TSI	calculated
MW [g/mol]	1220	1164	2037	1974

.

These polymers contain around the same number of carbonate units like a pHMC with the same molecular weight but less carbonate units than pTMC. However the additional ether groups should lead to more hydrophilic STPUs than pHMC/pTMC-based STPUs nonetheless.

The calculated MW is in good correlation with the MW obtained via TSI method and is below the MW of one carbonate containing repeating unit. Hydroxyl number determination via TSI method therefore was deemed a good alternative to DIN 53 240.

In conclusion, poly(ether carbonate)s with varying molecular weights could be synthesized by changing the concentration of the initiator. The synthesis itself is simple in terms of reaction assembly, predictable, reproducible and doesn't require solvents during reaction.

2 Chain extenders

2.1 Development of thiazolidine based chain extenders

Thiazolidines are five membered rings which contain sulfur and nitrogen in position 1 and 3. (see Fig. 27)

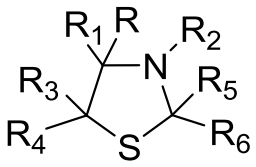


Figure 27: General structure of a thiazolidine

They are known for their use in penicilline-antibiotics[74] and as drugs to treat diabetes type II.[76]

In order to work as cleavable chain extenders in STPUs a thiazolidine requires at least two hydroxy/amino/thiol functionalities in position 2 and 4 or 5 to be able to react with a diisocyanate. As depictured in Fig.28, functional groups in position 4 and 5 would not lead to a scission of the polymer as the hydrolysis occurs at the C2-position.[64]

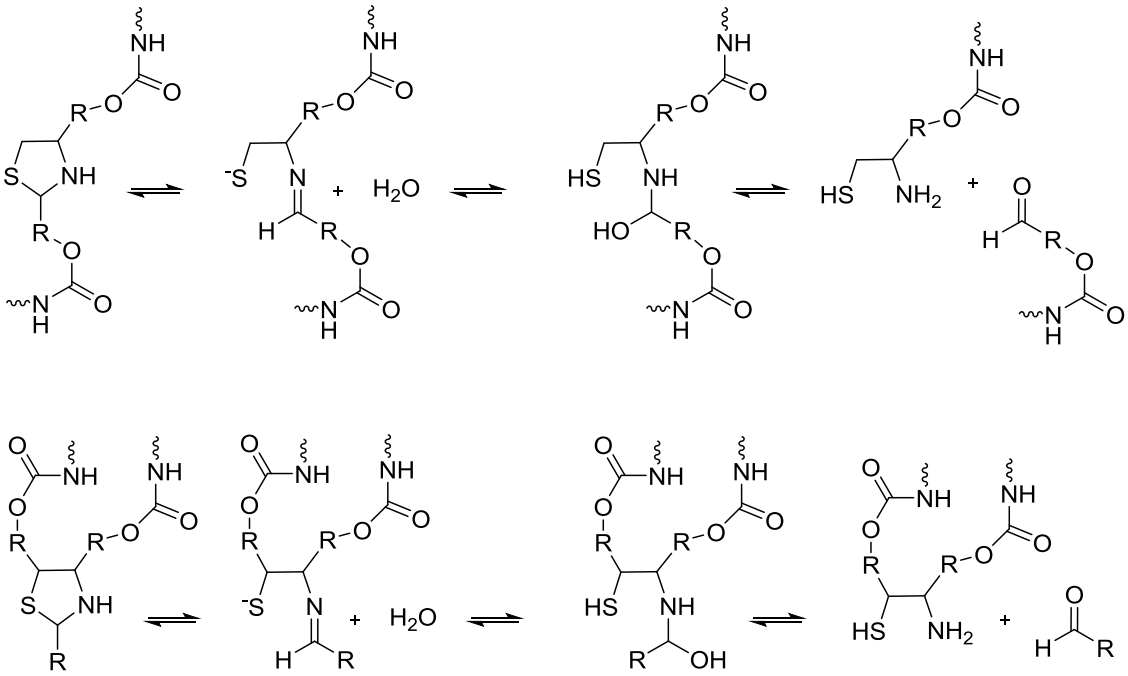


Figure 28: Hydrolysis of a 2,4-susbtituted (top) vs 4,5-substituted (bottom) thiazolidine incorporated in STPUs

Furthermore, the amine functionality must remain secundary to allow Schiff-base formation and thus degradation. But the free amine has to be protected prior to polyurethane synthesis to prevent possible cross linking via urea formation during STPU synthesis, which would lead to non-soluble polymers. Choosing a suitable protecting group therefore is crucial as thiazolidine derivatives are reported to hydrolyze very fast under strong acidic and alkaline conditions.[64,67] To avoid premature degradation of the polymer whilst removal of the protecting group, the protecting group is supposed to cleave under mild conditions. The dimethylethylcarbonyl (tboc) protecting group therefore seemed to be the most suitable choice as it can be easily removed under neutral to slightly acidic conditions.[77]

Additionally it was believed that a spacer between functional group and ring might be preferable for polyurethane synthesis. Big aliphatic spacers on the other hand should be avoided as they would lead to soft polymers. Additionally sterically hindering spacers like aryl or carboxyl groups at the C2 position should be avoided, as these groups are reported to hinder hydrolysis.[65]

So the task was to find a convenient and cheap synthesis route to obtain a small 2,4- or 2,5-substituted thiazolidine that can easily be modified into amines, alcohols or thiols with a short aliphatic spacer between the ring and the functional group.

A look in literature, however, revealed that synthesis of such a thiazolidine has not yet been reported. In fact only one synthesis of a difunctional thiazolidine has been found. Sriharsha et al.[78] reduced the N-protected thiazolidine-4-carboxylic acid-2-one to the corresponding diol. (see Fig.29)

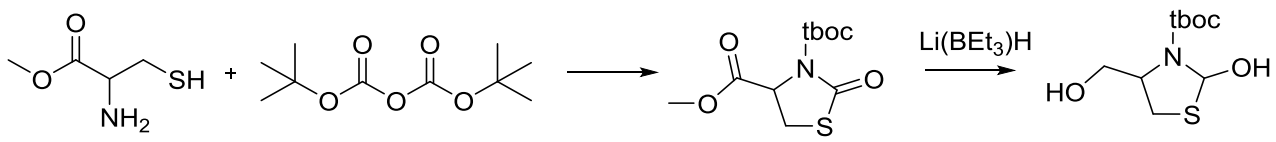


Figure 29: The synthesis of a N-protected thiazolidine-diol

However, lack of a spacer at the C2 position was believed to make it not a viable choice for STPU synthesis.
Derivatives with diamines, dithiols or aminothiols, hydroxythiols etc. have not been reported so far.

Starting with the lack of literature for suitable thiazolinde chainextender synthesis, new concepts had to be developed.
Generally thiazolidines can be synthesized by condensation of 2-aminothiols with a ketone/aldehyde[64,65,67] by hydration of thiazolines[75,79] or by synthesis of thiazolidinediones and their postmodification.[80] (see Fig. 30)

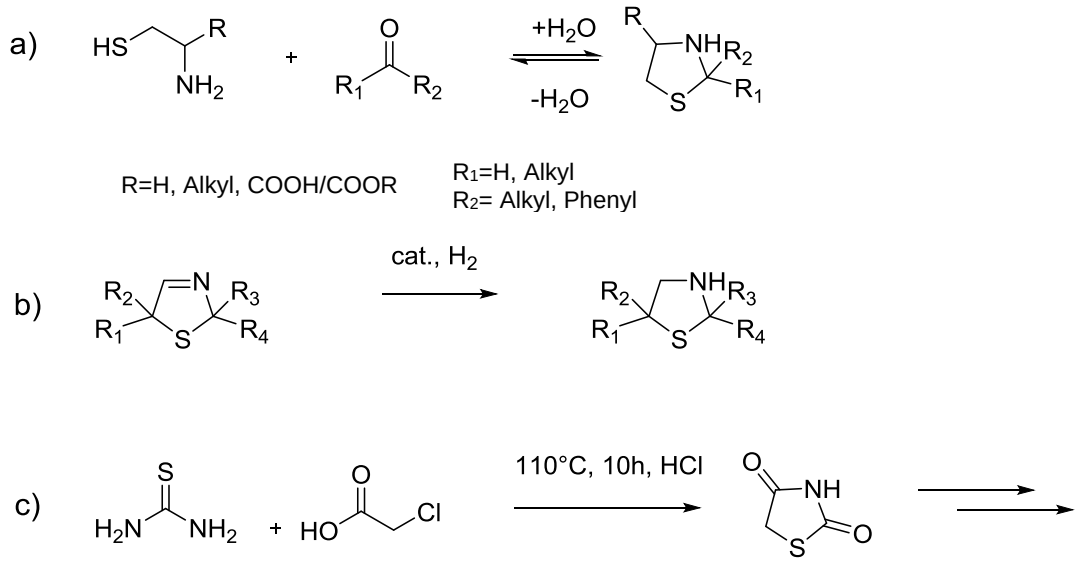


Figure 30: Synthesis routes for thiazolidines

These routes offered several possibilities to synthesize a suitable thiazolindine-chainextender (see Fig.31).

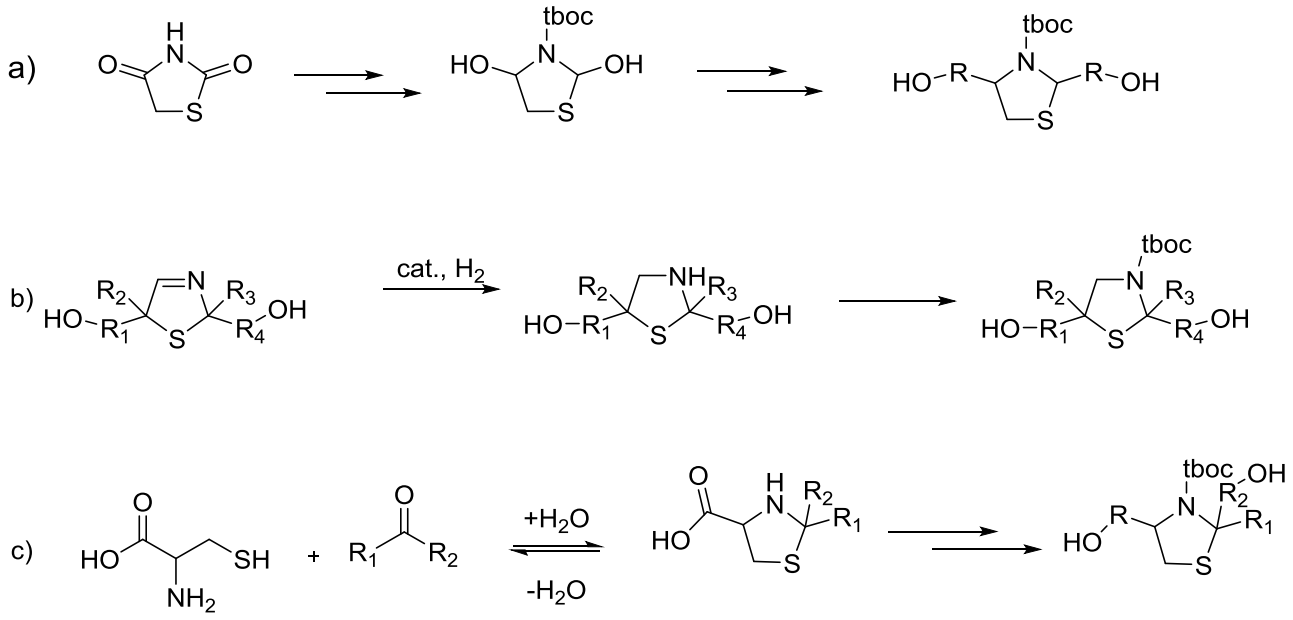


Figure 31: Possible routes for chain extender synthesis

The first idea was to simply reduce thiazolidindione (Fig.31, a). The resulting diol would have lacked the wanted spacer. Therefore further modification would have been necessary to obtain a suitable chain extender. The main reason why it was ruled out as a possible synthesis strategy was the fact that compared to the other routes, the reduction/modification of this dione has not yet been reported in literature.

The reaction pathway via thiazolines (Fig.31, b) seemed to be impractical as well. 3-Thiazolines are usually synthesized by Asinger(related)-reactions (see figure 31).[75,76,79,81-83]

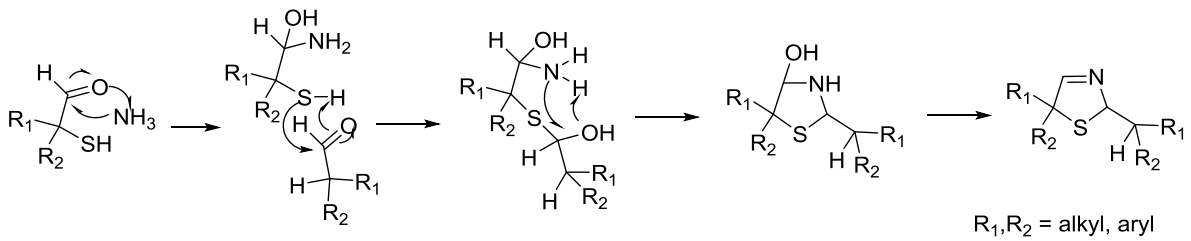
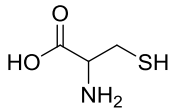
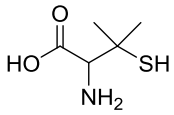
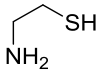
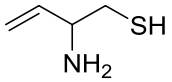
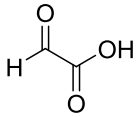
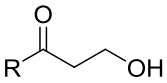
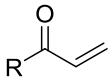


Figure 32: Synthesis of 3-thiazolines[83]

Of course it would have been possible to synthesize α-mercapto-carbonyl compounds that would allow modification before or after hydration of the thiazoline, but synthesis would have required additional synthesis steps. This contradicted the "easy-to-obtain" preliminary.

Therefore the condensation of 2-aminothiols with ketones/aldehydes and their post-modification (Fig.31, c) seemed to be the method of choice as literature reported numerous examples for synthesis and modifications of thiazolidines obtained by this route. But unfortunately no examples for suitable chain extender synthesis could be found. Furthermore this route has limitations as well.
First of all suitable and readily/cheap available 2-aminothiols are scarce and synthetic routes to obtain 2-aminothiols require additional synthesis steps without offering beneficial functional groups.[84-88] The same holds partially true for carbonyl compounds though several compounds are readily available not all of them might be considered.
Table 4 contains a list of compounds that were considered for the synthesis of a thiazolidine based chain extender.

Table 4: starting materials for thiazolidine condensation

2-aminothiols	available	modifiable
 cysteine	✓	✓
 penicillamine	✓	✓
 cysteamine	✓	—
 2-aminoprop-3-ene-1-thiol	—	✓
Carbonyl compounds		
 glyoxylic acid	✓	✓
 R=H, CH_3 R = CH_3 : 4-hydroxy-2-butanone R = H : 3-hydroxypropanal	✓	✓
 R = H, CH_3 R = CH_3 : methyl vinyl ketone R = H : acrolein	✓	✓

The most widely used and commercially available 2-aminothiols are cysteine, penicillamine and cysteamine. In case of cysteine and penicillamine modification is limited to the chemistry of the carboxylic acid group. Cysteamine is not suited for the synthesis of chain extenders due to lack of a beneficial functional group.

2-Aminoprop-3-ene-1-thiol was contemplated as well as it would offer room for modification, but additional synthesis steps would have been required, as it was not commercially available.

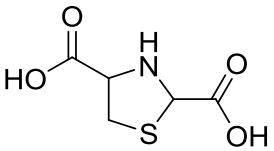
L-cysteine and penicillamine therefore were deemed the logical choice with a strong favor towards L-cysteine, as the two additional methyl groups on penicillamine were considered to have negative influence on the aggregation of a STPU.

Starting from L-cysteine several options regarding suitable condensation partners were available as depictured in table 4.

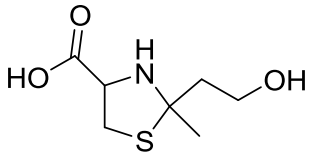
Glyoxylic acid, 4-hydroxy-butanone and 3-hydroxypropanal however were considered the logical choices. In case of glyoxylic acid the condensation reaction would yield a symmetric dicarboxylic acid which could lead to a symmetric chain extender. This could benefit the mechanical properties of a STPU. Further the modification of both sides would occur during the same reaction step, whereas in the case of acrolein/methyl vinyl ketone each side would require separate synthesis steps.

The use of 4-hydroxy-butanone and 3-hydroxypropanal would lead to slightly unsymmetrical molecules with offering the advantage of only having to modify one side of the molecule. As 2,2 disubstituted thiazolidnes were reported to undergo faster hydrolysis than monosubstituted thiazolidines, 4-hydroxybutanone was favored over 3-hydroxypropanal.

For these reasons the chain extender synthesis starting from 2,4-thiazolidinedicarboxylic acid and 2-methyl-2-hydroxyethyl-thiazolidine 4-carboxylic acid were considered the most promising synthesis routes. (see Fig. 33)



2,4-thiazolidinedicarboxylic acid



2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid

Figure 33: Starting compounds for chain extender synthesis

2.1.1 Attempted synthesis by reduction of 2,4-thiazolidinedicarboxylic acid and its derivatives

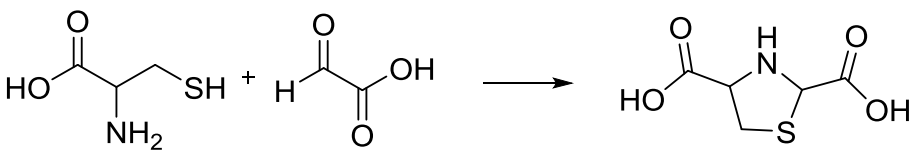
The synthesis of the chain extender starting from 2,4-dicarboxylic acid was considered to be one of the most promising routes, as the needed compounds are both cheap/easily available and formation of the di-carboxylic acid has been described several times in literature. Additionally it would only take 3 reaction steps to obtain a symmetric diol, which could benefit the final mechanical properties of a STPU.

The di-carboxylic acid was reported to be very stable under neutral conditions which led to the assumption that only the reduction at the C2 position to the corresponding alcohol would lead to a fast degrading compound.

Due to difficulties regarding the solubility/reactivity of the 2,4-thiazolidinedicarboxylic acid and lack of literature regarding the reduction of this compound, different reaction routes were tried.

2.1.1.1 Reduction of 2,4 thiazolidinedicarboxylic acid

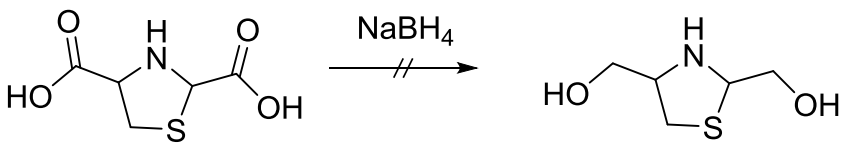
In a first step 2,4-thiazolidinedicarboxylic acid was synthesized according to literature[89] by stirring L-cysteine and glyoxylic acid at room temperature for several hours.



.

The pure product was obtained after filtration and washing with methanol.
This is a straight forward synthesis without any known side reactions and with good yields (up to 90%).

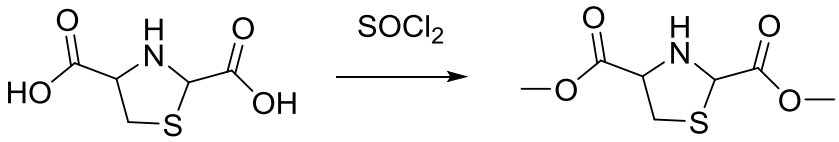
The reduction of the di-carboxylic acid however has not yet been reported in literature and therefore was carried out according to Saiz et. al.[90] who described the reduction of 2-phenyl-4-thiazolidinecarboxylic acid with $NaBH_4$ in dry methanol at 0 - 20°C.



2,4-Thiazolidinedicarboxylic acid was dissolved in dry MeOH and cooled to -5°C under inert atmosphere. $NaBH_4$ was dissolved in dry MeOH and was added drop wise to the stirred solution of the di-carboxylic acid.
The reaction was monitored by TLC but after 2 days, no reaction was observed.
The main problem during this reaction however was the poor solubility of the di-acid in methanol (and any other solvent beside DMSO) which obviously prohibited a reaction.
To check if a more reactive hydride would change the picture the more aggressive $LiAlH_4$ was used. The reaction temperature was adjusted to -15°C and the used solvent was dry THF (the dicarboxylic acid again didn't dissolve).
$LiAlH_4$ was dissolved in dry THF and cooled to -15°C under inert atmosphere. The di-acid was suspended in dry THF and slowly added to the hydride solution.
After several hours at -15°C again no reaction was observed and changing the temperature to room temperature didn't change the reactivity.
Because solubility seemed to be the main reason for the failed attempts the reaction was repeated with the corresponding 2,4-thiazolidinedicarboxylic acid - 2,4-dimethyl ester which should show better solubility.

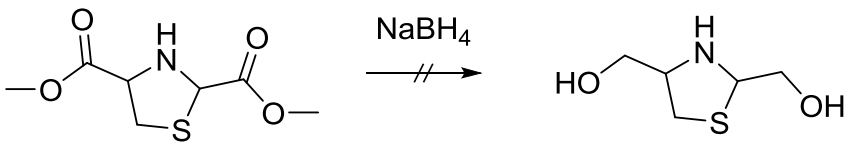
2.1.1.2 Reduction of 2,4-thiazolidinedicarboxylic acid 2,4-dimethyl ester

The esterfication was carried out according to literature by methylation of the acid groups via the Schotten-Bauman method.[91]



To a cooled suspension of dry methanol and di-acid $SOCl_2$ was slowly added. The yellow crystalline product was obtained in 50% yield by extraction with diethyl ether from water after destruction of the hydrochloride with $NaHCO_3$. GC/MS and TLC didn't show impurities so it was used without further purification. Usually the acid chloride is formed in a first step and the esterifying alcohol is added in a second step to avoid destruction of the thionyl chloride by the alcohol. In this case the di-acid seems to be more reactive than the alcohol.

The reduction of the di-ester again was conducted according to Saiz et. al.[90] with $NaBH_4$ in dry Methanol.



The di-ester was dissolved in dry MeOH and cooled to 0°C under inert atmosphere. Sodium borohydride dissolved in dry MeOH was added drop wise. Excess of the hydride was destroyed by adding 0,1M NaOH under subsequent cooling of the mixture. The precipitate was filtered off and washed with methanol. A product was obtained after extraction with DCM. Because the yield was very poor the previously obtained residue was subsequently washed with different solvents (MeOH, EtOH, AcN, DMSO, THF, EE) and the solvents were evaporated. The yield however couldn't be increased and the obtained product didn't resemble the target molecule

The reaction was monitored with GC/MS and TLC. Although some kind of reaction took place, the obtained product peaks did not indicate the formation of the wanted thiazolidine-diol. (see Fig.34)

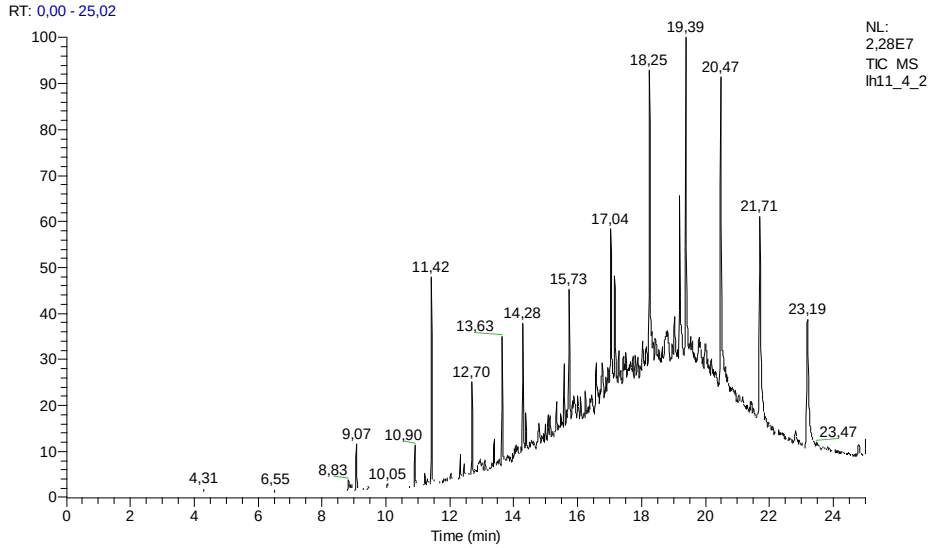


Figure 34: GC measurement after full conversion of the di-ester

Alkaline (0,1M NaOH) workup, yielded a very polar precipitate that resisted any attempt of dissolving and extraction with different solvents (MeOH, EtOH, AcN, DMSO, THF, EE). The small amount of product (<1%) didn't suffice for ^{1}H-NMR measurements.

Generally the workup was difficult because the yields were very poor and all attempts of increasing it (addition of additional base to the hydroxydic-residue and extraction with various solvents) failed.

Reasons for the failed synthesis can only be guessed as the reduction of acid functionalities is a standard procedure in organic chemistry.

The fact, that the GC/MS showed numerous peaks could have been an indication that there were several side reactions going on, or that the reaction products were too labile for GC/MS evaporation, therefore leading to a bigger number of detected molecules. Of course it is possible that the diol wasn't volatile enough for GC/MS measurements and that the obtained peaks simply showed side products.

It may however be possible that the diol was formed but was bound in form of boron esters (possibly oligomeric or polymeric aggregates, which form during

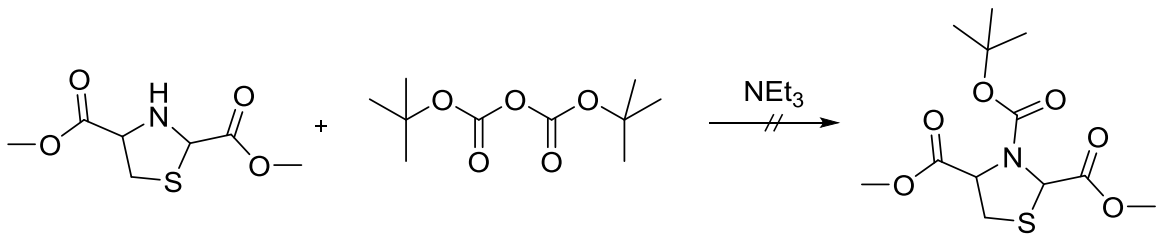
reduction with borohydrides) which could not be cleaved by the chosen work up. But it was possible as well that the resulting diol was extremely prone to hydrolysis.

Therefore the reaction was repeated several times with $NaBH_4$, $Ca(BH_4)_2$ and $LiAlH_4$ followed by different work ups including water, water alkaline, alcohol (methanol, isopropanol) and alcohol alkaline work ups, to see if different ways would lead to the desired product. But again the yields were very poor and formation of the diol couldn't be observed.

To eliminate the possibility of total hydrolysis during work up, the amino group was protected prior to reduction. The dimethylethylcarbonyl (tboc) protecting group was used for their reported easy removability under neutral conditions.

2.1.1.3 Reduction of N-protected 2,4-thiazolidinedicarboxylic acid and its derivatives

The tboc-protecting group was introduced according to Cremonesi et al.[92] who protected the 2,4-thiazolidinedicarboxylic acid, 4-methyl ester with di-tert-butyl dicarbonate in acetonitrile and triethyl amine at 70°C.
In a first experiment the 2,4-thiazolidinedicarboxylic acid, 2,4-dimethyl ester was favored over the dicarboxylic ester, as the dicarboxylic ester proved to be not soluble in acetonitrile therefore a reaction was not expected.



A mixture of 2,4-thiazolidinedicarboxylic acid, 2,4-dimethyl ester, di-tert-butyl dicarbonate and triethylamine in acetonitrile was refluxed for 7h. After evaporation of the solvent, the residue was dissolved in DCM and washed with a

cold 5% aq. HCl solution. After evaporation of the solvent a dark brown, oily liquid was obtained. GC/MS and TLC revealed formation of numerous products during synthesis. (see Fig.35)

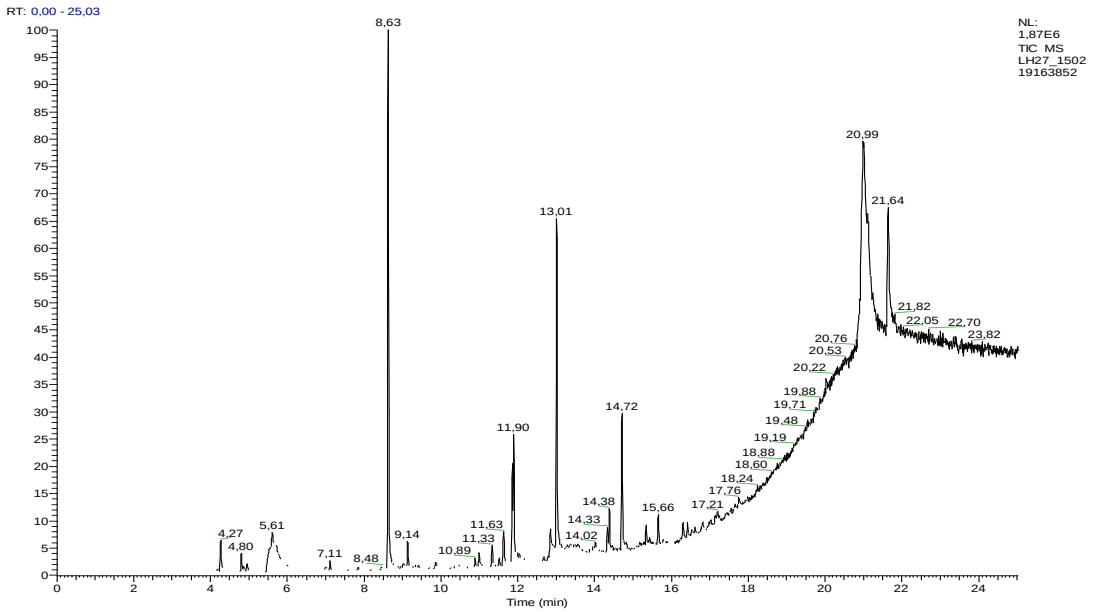


Figure 35: GC of the crude N-protected 2,4-thiazolidinedicarboxylic acid, 2,4-dimethyl ester

The product-peak could not be identified as none of the peaks resembled any expected fragmentation.

Examination of the ^{1}H-NMR of the crude product didn't indicate the formation of the wanted product either. (see Fig.36)

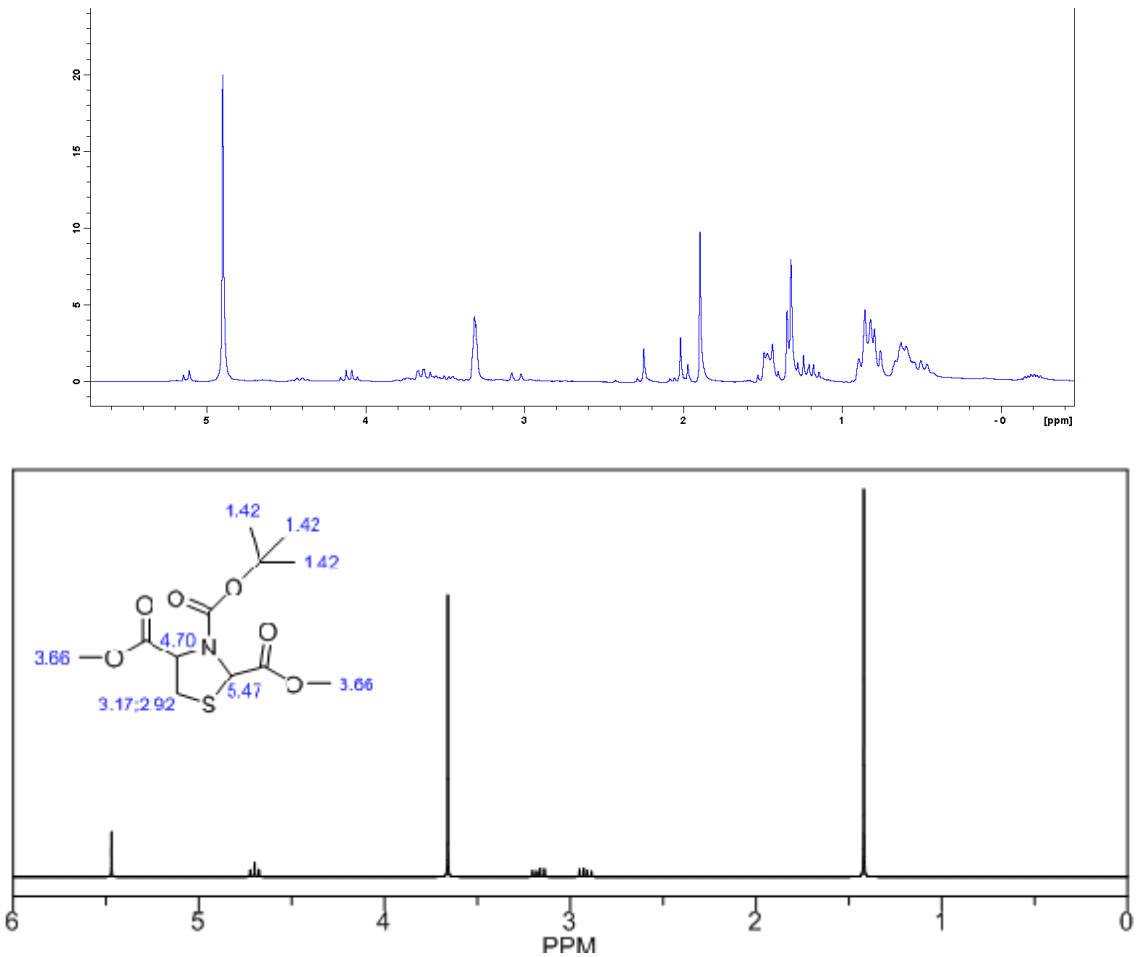
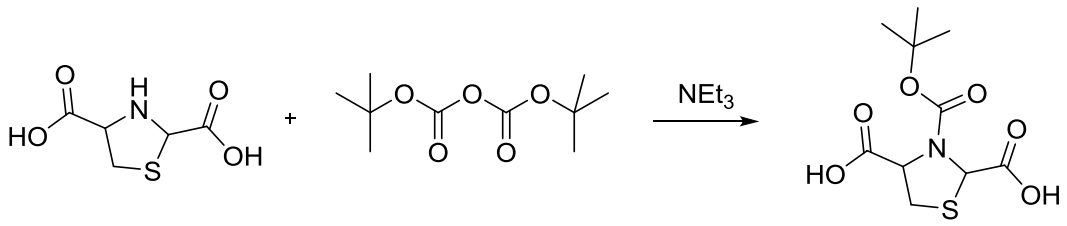


Figure 36: Relevant sector of the ^{1}H-NMR of the crude product and predicted spectrum of the target molecule

Most of all the lack of a prominent CH_3-peak which should result from the tert-butyl group implicated that synthesis failed. But generally the obtained signals didn't fit the expected product.
Attempts of gaining a separation to identify the obtained products failed as well.

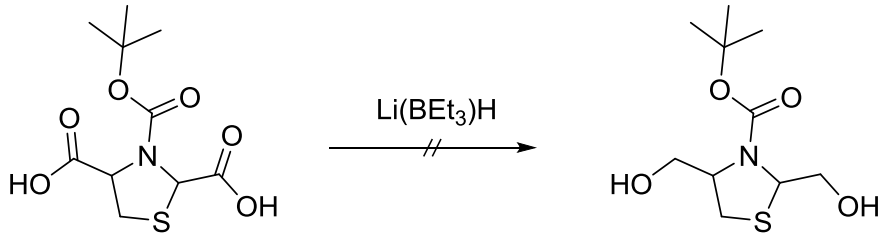
As it became clear that the wanted product hadn't been formed, the reaction was repeated with the di-carboxylic acid to test if a reaction would take place.



It turned out that the di-carboxylic acid dissolved without any problems under the used reaction conditions. After extraction from ~5% HCl aq. with DCM the pure product was obtained as orange solid in 97% yield.

The reasons for the failed synthesis of the N-protected 2,4-thiazolidinedicarboxylic acid, only can be guessed, as the obtained products couldn't be identified. The fact that the reaction with di-carboxylic acid worked, made it even more intriguing. Again it seemed that the dimethylester or its reaction product with the di-carbonate wasn't stable under the used reaction conditions leading to numerous products, as the GC/MS and ^{1}H-NMR suggested.

But as the reduction was supposed to work with the di-carboxylic acid as well as with the corresponding ester the synthesis was continued with the di-carboxylic ester.
In order to leave the protecting group untouched the reducing agent $Li(BEt_3)H$ was used, as proposed by Sriharsha et al.[77]



Thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl)ester was dissolved in dry THF under magnetic stirring and inert atmosphere. Superhydride solution was added drop wise to the cooled solution. Excess of the hydride was destroyed with 0,5M NH_3. After extraction with DCM and evaporation of the solvent a product was obtained. The crude product didn't resemble the target molecule.

Reaction monitoring via GC/MS indicated the formation of the wanted product during synthesis. (see Fig.37)

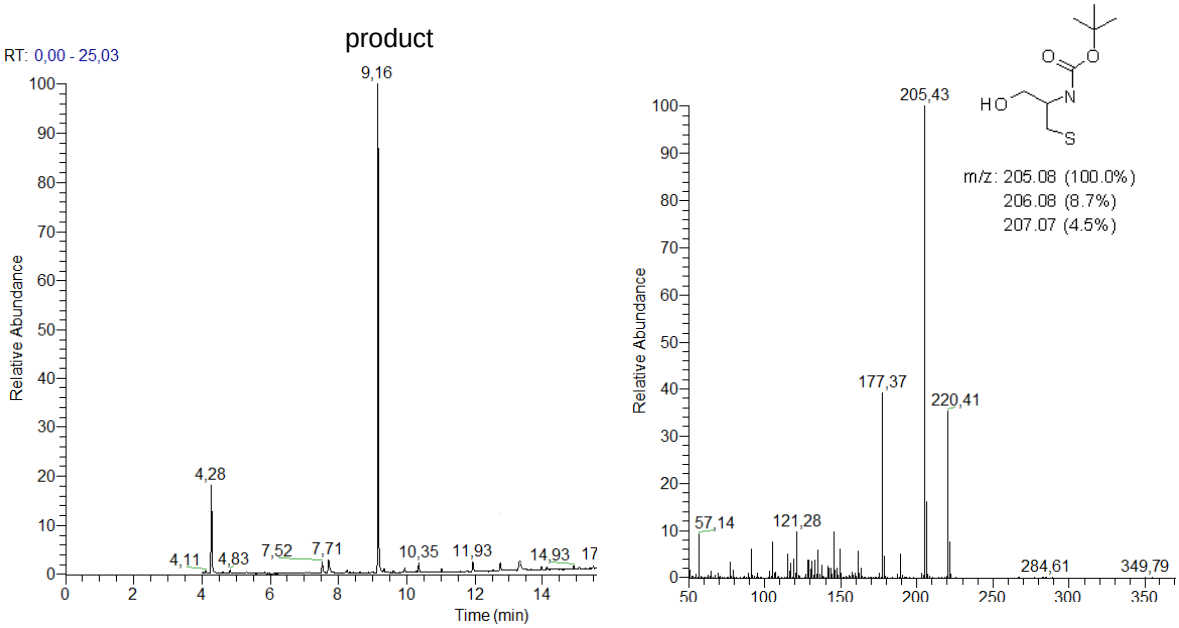


Figure 37: GC (left) and MS (right) during reaction

As seen in Fig. 37 two products (that were volatile enough for GC) were obtained. The fragmentation at 9.16min indicated the target molecule though no molecule peak was detected.

However after the addition of about 3mL NH_3 the peak at 9.16 disappeared and the peak at 4.28 increased. (see Fig.38)

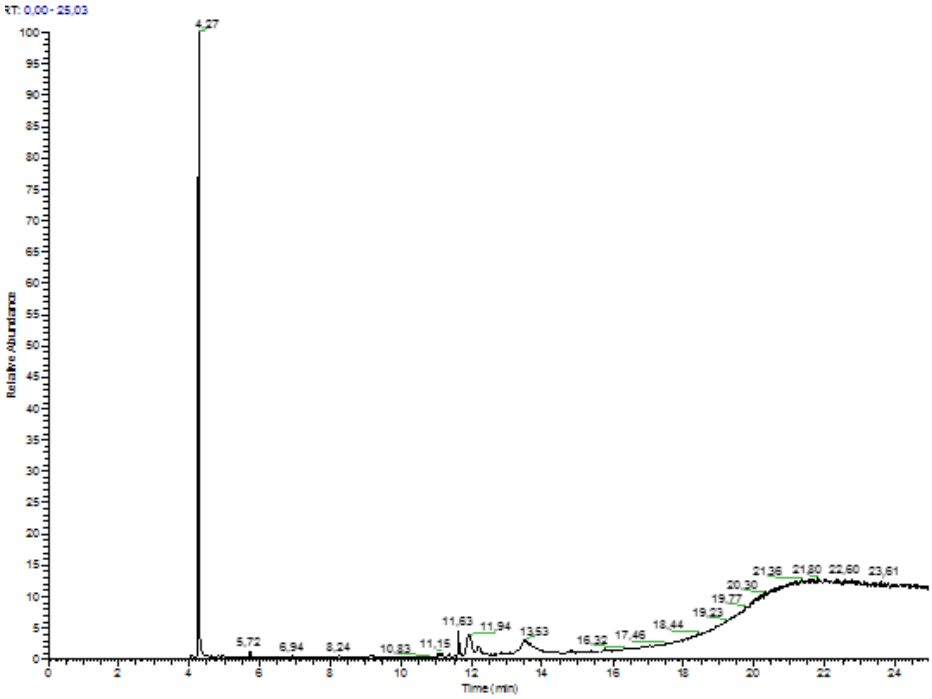


Figure 38: GC after addition of NH_3

This was surprising as it obviously showed, that the formed molecule seemed to be very labile. Although alkaline conditions should not have harmed the tboc protecting group and therefore inhibiting hydrolysis, a degradation took place nonetheless. The fragmentation of this signal was even more intriguing, as it couldn't be associated with a product that would have been expected from hydrolysis of the thiazolidine.

The reaction was repeated and the excess of hydride was destroyed with water but gave the same result.

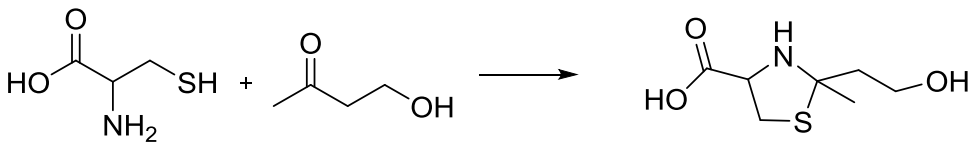
Even when the excess of hydride was destroyed with acetone the peak at 9.16min disappeared within 3 hours (under inert atmosphere) after finishing synthesis. All attempts of obtaining the firstly formed product failed due to the fast degradation of this product.

Reasons for this behavior are unknown and further examinations are necessary to explain it.

2.1.2 Attempted synthesis by modification of 2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid

Thiazolidine-chain extender synthesis starting from 2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid was the second most promising route to obtain a difunctional thiazolidine. The main advantage over starting from the 2,4-thiazolidinedicarboxylic acid was that only on side of the molecule had to be modified as the other side already carried a suitable group for STPU synthesis. The drawback was that synthesis of this compound had not been reported and its properties/ behavior during synthesis therefore were unknown.

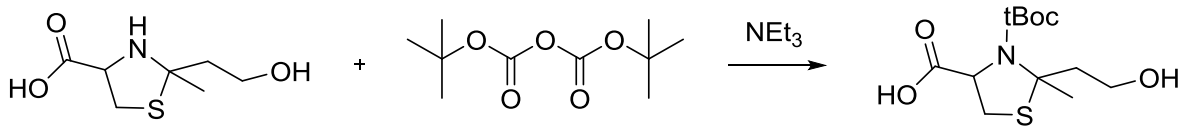
2.1.2.1 Reduction of 2-hydroxyethyl-2-methyl-2,4-dicarboxylic acid, 4-(2,2-dimethylethyl) ester



As the synthesis of 2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid had not been reported, the synthesis was at first conducted by stirring L-cysteine with 3-hydroxybutanone at room temperature in dry methanol under argon atmosphere for 24 hours. But no product was formed. Therefore the temperature was adjusted to 50°C in a second attempt, which gave a slightly yellow powder after 24h, after filtration and washing with dry methanol in 51% yield.

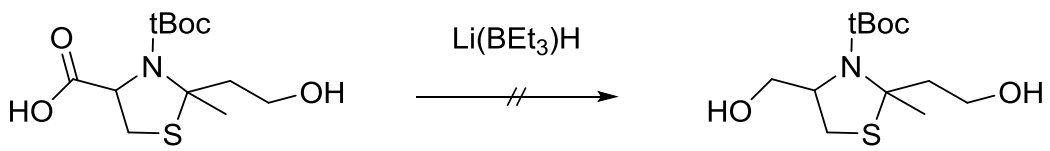
This product resisted any attempt of dissolving in deuterated solvents (d^6-DMSO, CD_3OD, D_2O) for ^{1}H-NMR measurements but IR suggested the formation of a ring-structure. Therefore derivatization of this product was required to verify formation of the target molecule.

Because 2,4-thiazolidinedicarboxylic acid showed comparable problems regarding solubility but could be reacted with di-tert-butyl dicarbonate, the same procedure was applied to the supposedly obtained 2-hydroxyethyl-2-methyl-2,4-dicarboxylic acid, 4(2,2-dimethylethyl) ester.



2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid and di-tert-butyl dicarbonate were stirred with triethyl amine at 70°C in acetonitrile for 7h. The residue obtained after evaporation of the solvent was dissolved in 5% HCl and extracted with DCM. After evaporation of the solvent the orange-red viscous liquid was purified by column chromatography (silica gel, DCM then EtOH) It turned out that only impurities could be eluted with DCM but not the target molecule. Therefore a polar solvent (in this case EtOH) had to be used. (Note of the author: For future purification attempts a reverse phase chromatography might be considered.) The product was obtained in 96% yield and its structure was confirmed by GC/MS and ^{13}C-NMR measurements.

After confirmed formation of the target molecule, the reduction was conducted according to Sriharsha et al.[78] with $Li(BEt)_3H$.



2-methyl-2(2-hydroxyethyl)-3,4-thiazolidinedicarboxylic acid, 3-(1,1-dimethylethyl)ester in dry THF was cooled to 0°C and the superhydride solution was added drop wise. After completed reaction excess of the hydride was destroyed with 0,5M NH_3. A crude product was obtained after extraction with DCM and evaporation of the solvent but couldn't be identified as the target molecule.

The reaction was monitored with GC/MS and the obtained spectrum was identical to the spectrum obtained during the reduction of the 2,3,4-thiazolidinetricarboxylic

acid, 3-(2,2-dimethylethyl) ester. (see Fig.39) Again some kind of degradation took place and the target molecule couldn't be obtained during/after work up.
The identical spectra of both reductions however only can be explained by a fragmentation of the target molecule during GC-evaporation. (see Fig. 39)

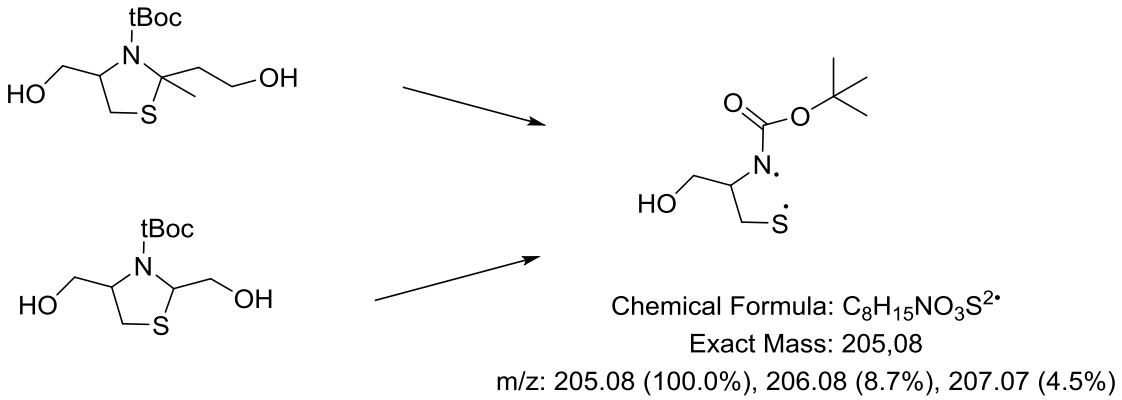
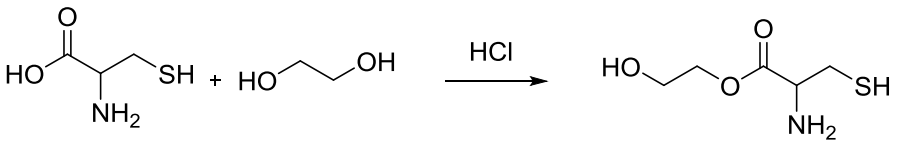


Figure 39: Possible fragmentation due to thermal stress during GC evaporation

Both molecules could form the same fragment (m/z = 205), which is detected during GC/MS analysis in both cases.
This result would confirm that the reduction worked at the C4-position and that the tboc protecting group wasn't attacked during reaction. But again the reasons for the degradation of the target molecule during work up remained unclear. For some reason the carboxylic group seemed to stabilize the thiazolidine ring in a way that the corresponding alcohol didn't/couldn't.

2.1.2.2 Esterification of L-cysteine

As it became clear that the wanted product couldn't be obtained via reduction of the carboxylic acid, an alternative idea occurred. If it would be possible to esterify L-cysteine with ethylene glycol, the resulting 2-hydroxyethyl ester could be reacted with 4-hydroxybutanone to yield a chain extender with circumventing the reduction, which obviously destabilizes the thiazolidine.
This reaction again was not reported in literature, allthough esterification of L-cysteine with monofunctional alcohols was reported several times using HCl as catalyst.[94,95]



L-cysteine, ethylene glycol and 3N HCl were refluxed for 18 hours. The cooled reaction mixture was subsequently poured into water and the ethylene glycol and/or its azeotrope with water was distilled off in high vacuum. The residue was mixed with THF and "recrystallized". The dark brown solid obtained after filtration resisted any attempt of dissolving in standard solvents under acidic, alkaline or neutral conditions.
The formation of the hydroxyethyl ester could not be confirmed.

In conclusion the synthesis of thiazolidine-based chain extenders was not successful. The reasons differ depending on the approach that was pursued.
In case of the reduction of 2,4-thiazolidinedicarboxyl acid the main problem derived from the non-dissolving properties in suitable solvents.
The biggest hindrance however seemed to be the stability of the obtained reduction products from the various N-protected/unprotected thiazolidines as the target molecule either couldn't be detected (reduction of 2,4-thiazolidinedicarboxylic acid, 2,4-dimethyl ester) or showed unexpected (non-hydrolysis based) degradation behavior in case of N-protected thiazolidines.

Searching for suitable alternatives to thiazolidines, other possible structures like organophosphates and ketals were considered for chain extender synthesis.

2.2 Development of organophosphate chain extenders

Organophosphates are esters of the phosphoric acid. Depending on the number of substituents mono-, di- and tri-substituted organophosphates are obtainable. (see Fig.40)

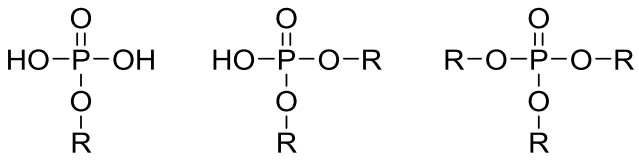


Figure 40: mono- , di- and tri-functional organophosphates

They can degrade by hydrolysis[96,97] as well as enzymatic degradation[97] which make them possible candidates for the use in biodegrading STPUs. In order to work as cleavable chain extender the organophosphate has to contain at least two hydroxy-, thiol- or amine-functionalities. (see Fig.41)

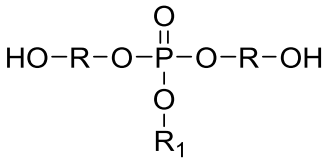
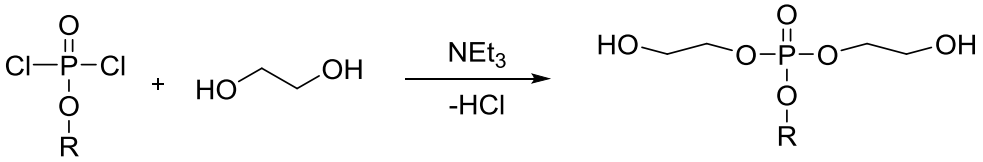


Figure 41: possible organophosphate chain extender

Literature provides a wide range of possible synthesis routes for various organophosphates but a diol/dithiol/diamine has not yet been reported.
The most straight forward synthesis route to obtain the desired difunctional chain extender was the reaction of phosphorodichloridic acid, ethyl ester with a diol.

2.2.1 Attempted synthesis by condensation of phosphorodichloridic acid, ethyl ester and ethylene glycol

The reaction was conducted according to Dworak et al.[99] who reacted phosphorodichloridic acid, ethyl ester with monofunctional alcohols using NEt_3 as an acid scavenger.



A mixture of phosphorodichloridic acid, ethyl ester and dry trimethylamine were dropped on cooled dry ethylene glycol at 0°C under inert atmosphere. Stirring was continued at room temperature for 6h. After filtering off the formed NEt_3*HCl the solvent was evaporated and the excess off ethylene glycol was distilled off in high vacuum. The residue was fractionated by high vacuum distillation and the product was analysed via ^{1}H-NMR. The product didn't fit the target molecule. The analysis suggested the formation of an oligomeric product as no hydroxy H-atoms could be identified in the ^{1}H-NMR.

Reasons for the failed synthesis may have lain in the high vacuum distillation at elevated temperatures possibly leading to polycondensation. Therefore alternative work ups were considered. Extraction of the target molecule with EE was not possible, column chromatography was ruled out as well, as the large excess of ethylene glycol (to prohibit polycondensation) turned out to be too much for lab scale equipment and precipitation wasn't an option as well, as the target molecule was considered a liquid.

2.3 Development of ketal-based chain extenders

Ketals are geminally arranged di-ethers with the general structure $R_2C(OR'_2)$. (see Fig.43)

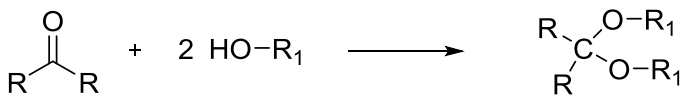


Figure 43: synthesis of a branched ketal

They reportedly are prone to hydrolysis[100] and therefore are possible candidates for the synthesis of biodegrading STPUs. For the possible use as chain extender the ketal again needs two hydroxy, amino or thiol functionalities. (see Fig. 44)

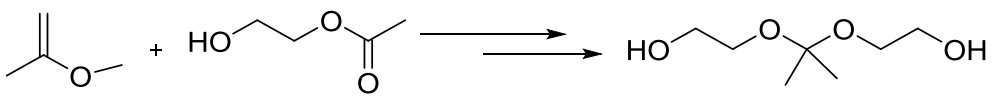
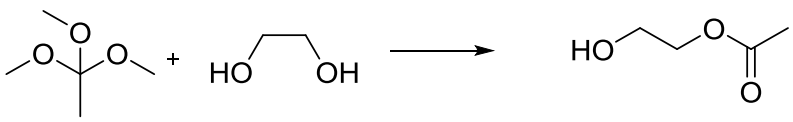


Figure 44: Synthesis of a possible ketal-based chainextender

Successful synthesis as depictured in Fig. 44 has been reported by Shenoi et al.[101]

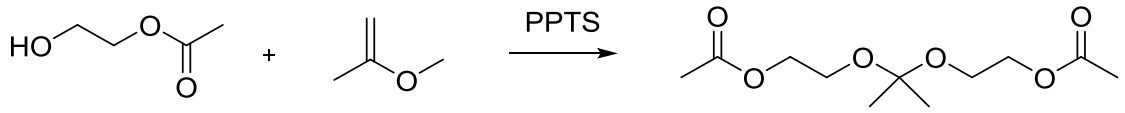
2.3.1 Synthesis of ethanol, 2,2'-[(1-methylethylidene)bis(oxy)]bis-, 1, 1'-diacetate

In a first step 2-hydroxyethyl acetate was synthesized by reacting trimethylorthoacetate with ethylene glycol.



Trimethylorthoacetate, ethylene glycol and p-toluenesulfonic acid in DCM were stirred at room temperature for 20h under inert atmosphere. The reaction was aborted by addition of water. The solvent was evaporated and the pure compound was obtained after flash chromatography in 90% yield.

In a second step the acetate was reacted with 2-methoxypropene to obtain the depictured ketal as reported by Shenoi et al.[101]



2-hydroxyethyl acetate and pyridinium p-toluenesulfonate (PPTS) were stirred under inert atmosphere for 15min. After addition of a 5A molecular and stirring for another 15min. 2-methoxypropene was added and the mixture was stirred at room temperature for 24h. The molecular sieve was filtered off and washed with dry THF. The solvent was evaporated under reduced pressure. A ^{1}H-NMR of the crude product indicated the formation of a degradation product of the desired ketal.

Reasons for this result remained unclear as the molecular sieve should have bound all water that happened to enter during the reaction and therefore prohibiting hydrolysis. NMR measurements were taken directly after obtaining the crude product. Additionally the NMR vessel was flushed with argon therefore the possibility of hydrolysis during NMR measurements were minimal.

3 Synthesis of the segmented thermoplastic polyurethanes (STPUs)

Like ordinary polyurethanes, STPUs can be obtained by polyaddition-reactions of diisocyanates with diols. The use of a high molecular weight diol as so called soft block allows the formation of a hard and a soft phase thus obtaining thermoplastic and elastomeric properties (see chapter "segmented thermoplastic polyurethanes"). The choice of building blocks determines the final properties of the polyurethane. Due to the large number of available diisocyanates, diols and macrodiols (see chapter “state of the art”) a large variety of polyurethanes with varying properties is available.

The goal of this work was to synthesize faster degrading STPUs with ideally comparable mechanical properties to previous synthesized STPUs and the possibility to process them via electrospinning. Further it was aimed to minimize the use of ester based materials which can lead to inflammatory reactions of surrounding tissue. The use of compounds forming toxic degradation products had to be avoided as well.

To reach this goal it was intended to incorporate a poly(ether carbonate) as a new class of degradable soft block into STPUs combined with different degradable chain extenders and the use of HMDI as hard block. To obtain comparable data, reference materials like Pellethane had to be used.

3.1 Purity of components

Due to the step-growing mechanism following Carothers law and therefore requiring exact ratios of the reacting groups, high purity compounds and solvents have to be used, to obtain high molecular weight polymers. In addition, water content plays a critical role as well as it reacts with isocyanates to form an amine and therefore changing the molar ratio of reacting groups.

HMDI was purified by vigreux distillation and storage stability was confirmed by GC-MS measurements. The water content of the dry DMF and the used soft blocks was measured by Karl Fischer titrations. Water contents below 250 ppm were considered sufficient. The macrodiols were dried in vacuum under magnetic stirring at elevated temperatures of ~90°C in high vacuum (10^{-2} mbar).

3.2 Reference materials

To obtain comparable data two different reference materials were used. As a non-degrading material the commercially available STPU Pellethane was used. It is an FDA approved material consisting of pTHF, MDI and 1,4-butanediol. The second reference material (Reference D) is a hard block degrading STPU developed within our working group[49] and consists of pTHF, HMDI and BHET.

The overall goal was to synthesize new materials within the molecular weight of Pellethane and mechanical properties matching these two materials. The degradation rate however was supposed to be drastically increased compared to Reference D.

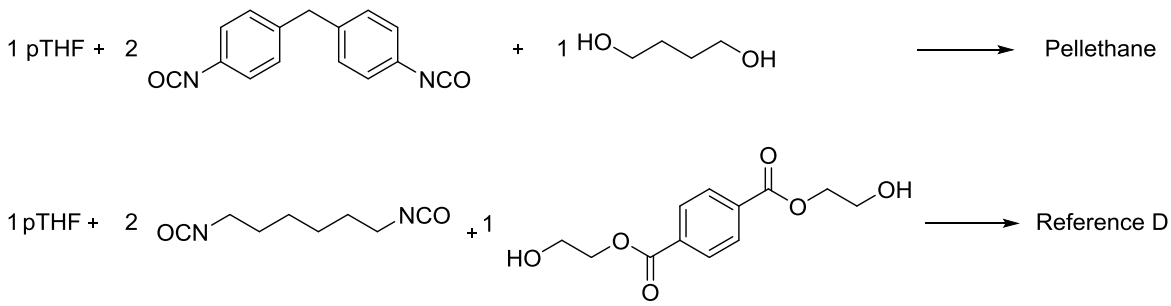


Figure 45: Reference materials

3.3 Preparation of the STPUs

The polyaddition reaction was carried out in a two-step process under inert (argon) atmosphere at 65-70°C using $Sn(Oct)_2$ as catalyst in dry DMF. (see Fig.46)

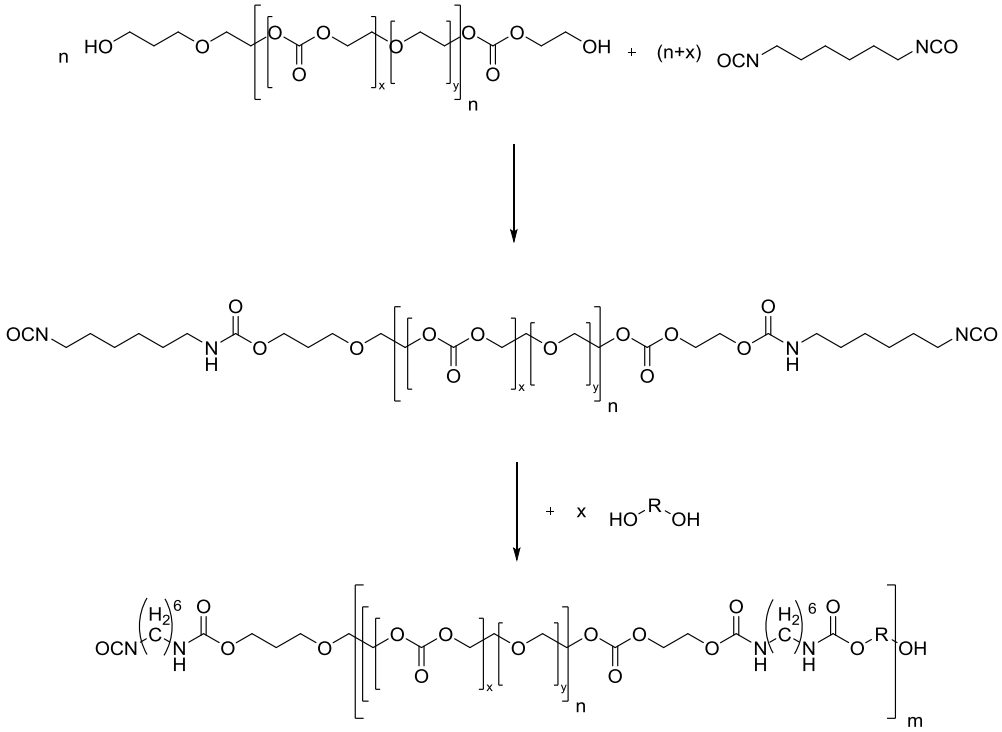


Figure 46: Preparation of a pEC-based STPU

The macrodiols (pTHF and pEC) were reacted with HMDI in a first step forming a prepolymer. After addition of a chain extender (BHET, BHPC, DHEDS; see Fig.47) the final polymer was obtained by precipitation in methanol and vacuum drying. BHET was used because it has already shown its ability to form biocompatible as well as biodegradable STPUs with good mechanical properties with the benefit of being commercially available.[48,63] DHEDS was used as a non-ester based material avoiding acidic degradation products and being commercially available. BHPC was used to provide the STPU with homogenous degrading properties, as a homogeneous degradation behavior might be favorable to sustain mechanical properties once implanted.

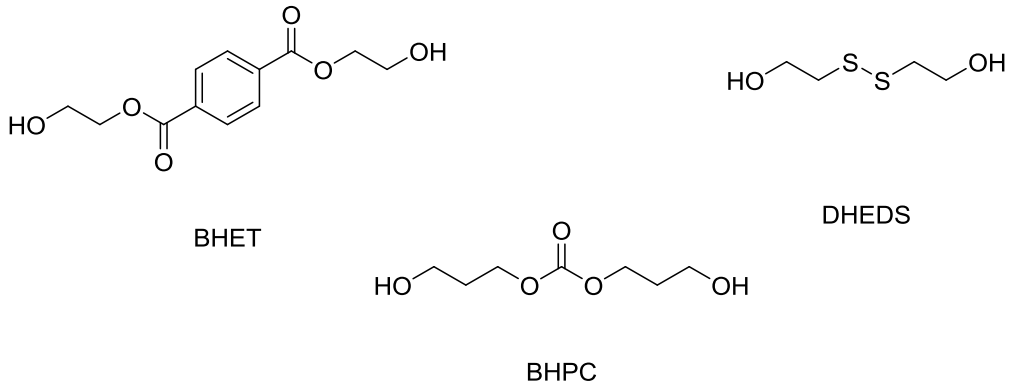


Figure 47: used chain extenders

To obtain STPUs with different mechanical properties different molecular weight soft blocks and various soft block / hard block ratios were used. Table 5 shows the used components and ratios.

Table 5: prepared STPUs

Monomers	Ratio	ID
pTHF : HMDI : BHET	1 : 2 : 1	Ref D
pTHF : HMDI : DHEDS	1 : 2 : 1	PU-pTHF-1
pTHF : HMDI : BHPC	1 : 2 : 1	PU-pTHF-2
pEC1000 : HMDI : DHEDS	1 : 2 : 1	PU-pEC1-S1
pEC1000 : HMDI : DHEDS	1 : 3 : 2	PU-pEC1-S2
pEC1000 : HMDI : BHPC	1 : 2 : 1	PU-pEC1-C1
pEC1000 : HMDI : BHET	1 : 2 : 1	PU-pEC1-T1
pEC2000 : HMDI : DHEDS	1 : 2 : 1	PU-pEC2-S1
pEC2000 : HMDI : DHEDS	1 : 2.5 : 1.5	PU-pEC2-S1.5
pEC2000 : HMDI : BHET	1 : 2 : 1	PU-pEC2-T1
pEC2000 : HMDI : BHET	1 : 2.5 : 1.5	PU-pEC2-T1.5
pEC2000 : HMDI : BHPC	1 : 2 : 1	PU-pEC2-C1
pEC2000 : HMDI : BHPC	1 : 2.5 : 1.5	PU-pEC2-C1.5

The pTHF-based STPUs were obtained in yields between 88-95% and showed promising rigidity.

PU-pEC1-S1 was obtained in 47% yield as a soft yellow polymer. Therefore the soft block / hard block ratio was increased to improve mechanical properties. This however gave a very brittle polymer in 78% yield.

PU-pEC1-C1 and T1 again yielded rigid white polymers in yields between 88-92%

The STPUs based on pEC2000 were first prepared in a 1:2:1 molar ratio but the yields were poor (below 50%) and the obtained polymers were too soft for further use. Therefore the amount of hard block was increased which yielded very brittle polymers that couldn't be used for mechanical testing.

4 Testing of the STPUs

4.1 Molecular weight

Molecular weight (MW) is of particular interest regarding degradable materials. Low molecular weight STPUs could degrade too fast and therefore lead to failing TEVGs. Although tuning of the MW is a way to tailor the properties to ones needs, high molecular STPUs usually show better mechanical properties than their low molecular weight counterparts.[101]

Reasons for a low molecular weight can be impurities, contaminations by water, inaccurate stoichiometric amounts of monomers and incomplete reaction due to high viscosity during reaction.

The molecular weight of the synthesized polyurethanes was determined via size exclusion chromatography in DMF. This method is based on calibration with standards like polystyrene or poly(methly metacrylate) thus providing relative numbers and therefore requiring reference materials. The obtained results were compared to Pellethane and reference D, as they have proven to show suitable mechanical properties in VTE.

Table 6 provides the obtained molecular weights of the synthesized STPUs.

Table 6: molecular weights of the STPUs

ID	**Pel**	**Ref.D**	**PU-pTHF-1**	**PU-pTHF-2**
M_n [kDa] / PD	**86.6 / 1.4**	**43.8 / 1.5**	20 / 1.7	43 / 1.6
ID	PU-pEC1-S1	PU-pEC1-S2	PU-pEC1-C1	PU-pEC1-T1
M_n [kDa] / PD	14 / 2.3	9 / 1.3	13 / 1.6	17 / 2.1
ID	PU-pEC2-S1	PU-pEC2-S1.5	PU-pEC2-T1	PU-pEC2-T1.5
M_n [kDa] / PD	19 / 1.4	20 / 1.7	4 / 1.6	6 / 1.4
ID	PU-pEC2-C1	PU-pEC2-C1.5		
M_n [kDa] / PD	6.4 / 1.7	9.2 / 1.5		

As can be seen the molecular weights and polydispersity differ greatly depending on the used soft block and chain extender. The pEC2000 containing polyurethanes yielded the lowest molecular weights in the range from 4-19kDa, whereas the pEC1000 containing polyurethanes show slightly higher molecular weights with 9-17kDa. The pTHF based STPUs are within the same range although Ref.D yielded the highest MW with 43.8kDa. The reasons for the low molecular weights of the pEC2000 based materials may be found in the very hygroscopic nature of this poly(ether carbonate) and its high viscosity making drying very difficult. Residual water however reacts with the diisocyanate to form amines that react with diisocyanates forming urea moieties. This side reaction shifts the molar ratio thus leading to lower molecular weights.
The same holds partly true for the pEC1000 containing STPUs with the difference that this soft block achieved slightly lower water contents after drying.
The reasons behind the differences between the pTHF containing STPUs on the other hand can't be explained satisfactory as the procedures were the same for all of them.

Based on the physical appearance of the obtained polymers PU-pTHF-1, PU-pTHF-2, PU-pEC-2 and PU-pEC-3 were selected for further testing.

4.2 Contact angle measurements

Contact angle measurement is a simple and sensitive method for determining the hydrophilicity (or hydrophobicity) of a surface. The contact angle correlates strongly with the polarity of a surface. Polar surfaces show lower contact angles than apolar surfaces. (see Fig.47)

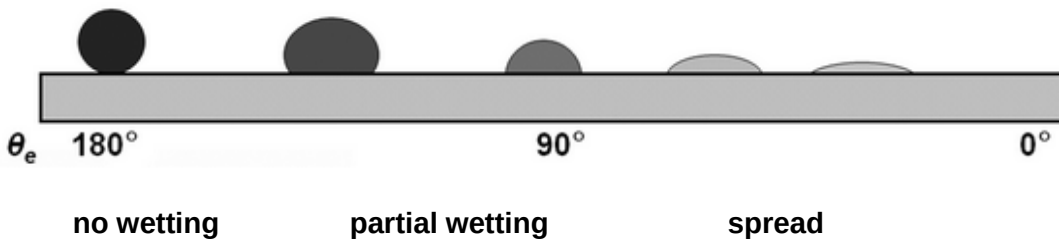


Fig. 47: Contact angle and wetting[103]

Polymer foils were prepared by dissolving the polyurethanes in DMF (about 10 % (w/w)) and pouring them into Teflon molds (60x40x2 mm3 cavity). The molds were dried at 35°C for a week and an additional week *in vacuo* at 35°C.
Teflon was used as a reference material, as it is a very hydrophobic material.

Table 7: Measured contact angles

Material	**θ_e [°]**
Teflon	106
Ref D	90
Pel	94
PU-pTHF-1	81
PU-pTHF-2	73
PU-pEC1-C1	52
PU-pEC1-T1	55

As expected all tested polyurethanes showed lower contact angles than Teflon (see table 6). The lowest contact angles were measured on the pEC-based

materials. This was a promising result as it was planned to obtain more hydrophilic polymers thus increasing degradation rates.

4.3 Degradation

To achieve fully regenerated native tissue in VTE the used scaffold materials (polymers) have to degrade in living systems such as the human body.

Degradation is achieved by incorporation of different cleavable moieties into the backbone of the polymer. Such cleavable moieties can be esters, peptides, disulfides or carbonates. These bonds can either degrade enzymaticaly[38-40] or hydrolytically.[41]

To prove the concept of degradability for the synthesized polyurethanes, round samples (d= 18 mm) of the solvent casted films with an average weight between 35 and 90 mg were placed in phosphate buffered saline (PBS) at a constant temperature of 90°C. These conditions of course didn't match those provided within biological systems but as some polymers take years to degrade, a higher temperature had to be used, to achieve rapid degradation.

Due to the lack of any enzymes in this set up, degradation only took place via hydrolysis.

The samples were removed after 10, 20 and 30 days cooled to room temperature, filtered, washed with distilled water and dried in vacuum.

The degradation was monitored by measuring the weight loss (see Fig.48) and the loss of molecular weight (see Fig.49) of the samples.

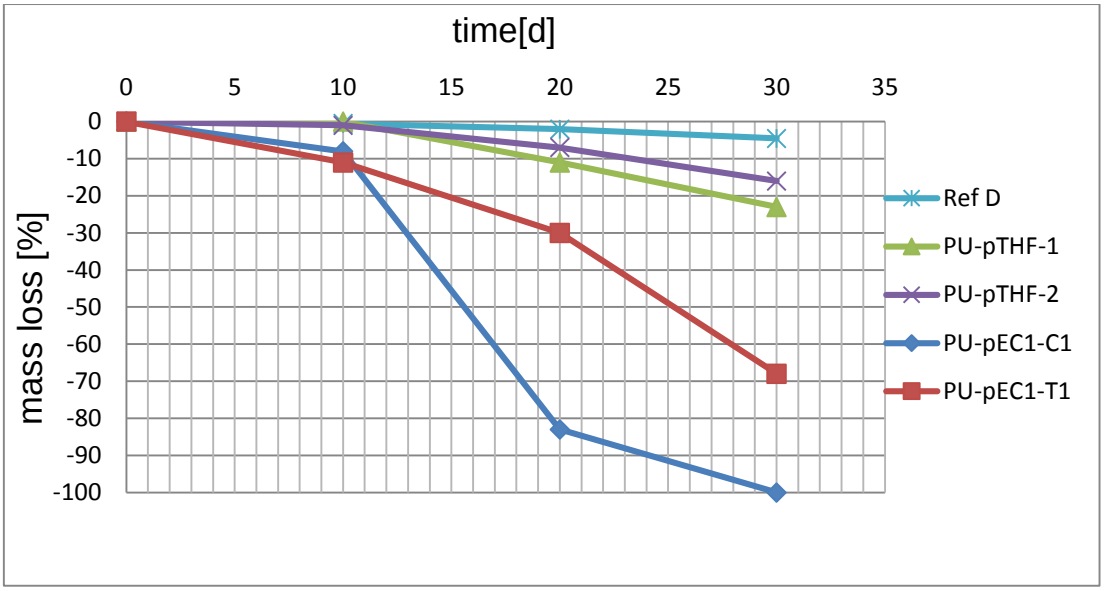


Figure 48: Mass loss of the polyurethanes in PBS at 90°C

As expected the non-degradable Pellethane showed no mass loss and was therefore not depictured in Figure 48.

As can be seen in Figure 48 the pEC-based materials degraded much faster than the pTHF-based materials (with PU-pEC1-C1 degrading within 30 days!) although it was expected that the ester containing PU-pEC1-T1 would degrade faster than the purely carbonate containing PU-pEC1-C1 as esters usually hydrolyze faster than carbonates.

The reason for this behavior might be found in the different molecular weights of the polymers. PU-pEC1-T1 with 17kDa had a higher molecular weight than PU-pEC1-C1with 13kDa thus allowing faster degradation. The same held partly true for the pTHF containing STPUs where Ref.D with the highest molecular weight degraded slower than PU-pTHF-1 and PU-pTHF-2.

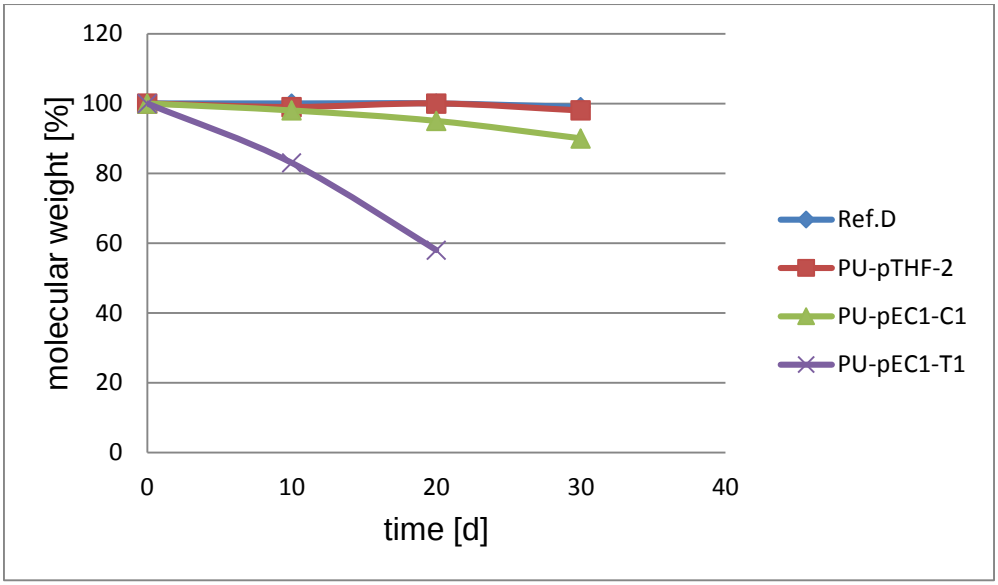


Figure 49: Loss of molecular weight for the STPUs in PBS at 90°C

The loss of molecular weight matched the expectations as well. The ester containing PU-pEC1-C1 showed gradual loss of molecular weight as time grew on implicating a bulk erosion mechanism (low mass loss at first but lower molecular weight and then fast loss of weight), whereas the rest didn't show significant loss of MW thus indicating surface erosion.

The degradation products of PU-pTHF-1 didn't dissolve in DMF for unknown reasons therefore the degradation mechanism couldn't be determined.

These results however were very promising as it showed that pEC containing STPUs degraded much faster than their pTHF containing counterparts with comparable molecular weight.

4.4 Mechanical Testing

The mechanical properties of the polyurethanes were determined by tensile tests on bulk samples. Tensile test specimens were punched from the solvent casted films (see contact angle measurements), measured and the tensile stress and tensile strain were determined.

While the sample is strained with constant velocity until it breaks, a stress-strain plot is recorded (see Fig.52).

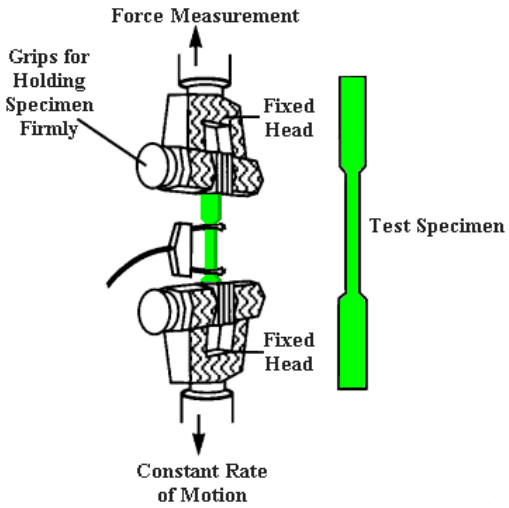


Figure 50: process of tensile testing[104]

For TEVGs three important parameters can be achieved by the stress-strain plot: the Young's modulus E [MPa], the tensile strength S [MPa] and the elongation at break ε [%]. They can be calculated by following equations:

$$\sigma = \frac{F}{A} \qquad \varepsilon = \frac{\Delta L}{L_0} * 100 \qquad E = \frac{\sigma}{\varepsilon}$$

σ = tensile stress [MPa]

F = tensile force [N]

A = initial cross section [mm^2]

ε = tensile strain [%]

ΔL = initial length

E = Young's modulus [MPa]

The Young's modulus describes the elastic properties of a material. The higher the Young's modulus the lower its elastic properties. For TEVGs this value should be low to ensure elastomeric behavior.
Tensile strength is the maximum tensile stress sustained by the test specimen during the tensile test. If values for the tensile strength are too low, problems during suturing and regarding the burst pressure will occur. In this case, the material is not suitable for the use of electrospun TEVGs.
Elongation at the break is a parameter describing the ductile properties of a material. It describes the ability of a material to deform under tensile strength.

The mechanical behavior of a STPU depend on the used building blocks, the ratio of the building blocks and molecular weight and the temperature whilst measuring. Temperature influences while testing of the materials can be neglected, as they were all tested at room temperature. But once implanted the mechanical behavior might change due to higher body temperature and vastly increased humidity.

Table 7: obtained mechanical testing data for the prepared polyurethanes

	E [MPa]			S [MPa]			E [%]		
Pel	14,1	±	1,3	51,9	±	4,8	1200	±	132
Ref D	15,8	±	3,4	32	±	8,1	951	±	208
PU-pTHF-1	26,6	±	2,6	4,1	±	0,4	28	±	2
PU-pTHF-2	29,4	±	5,9	8	±	1,3	142	±	9
PU-pEC-2	8	±	1,1	1,6	±	0,3	27	±	11
PU-pEC-3	49,6	±	4,8	4,7	±	0,9	30,5	±	6

As can be seen in Table 7 the mechanical properties of the new STPUs weren't in the range of Pellethane or Reference D and therefore are no possible candidates for VTE in the current state. The biggest problem however is the poor elongation at the break paired with non-elastomeric behavior (high Young's modulus) that rule them out as possible materials in VTE.

The main reasons for the poor properties probably was the low molecular weight of the prepared polymers. Gorna et al.[101] showed that there is a clear connection between molecular weight and mechanical properties of a polyurethane-elastomer. But the high polarity of the used poly(ether carbonate) might as well have hindered proper aggregation of the polymer thus leading to inferior mechanical properties.

In case of the pTHF based polyurethanes the lack of an aromatic system, that usually increases rigidity in a polymer, might have been an additional reason for inferior mechanical properties compared to Ref.D.

Summary

Cardiovascular diseases (CVDs) have become the leading causes of death worldwide with ischaemic heard disease (CHD) contributing to 13.2% to all deaths. Beside anti thrombotic drug therapies and percutaneous coronary interventions, coronary artery bypass surgeries are still state of the art for treating CHD. A limited amount of suitable autologous grafts and risks associated with allo-/xenografts led to a search for alternatives. The alternative therapeutic approach is the interdisciplinary field of vascular tissue engineering (VTE), uniting chemistry, material science, biology, and medicine to engineer vascular grafts. Beside the application of natural materials, which in most cases lacked the needed mechanical properties, and the use of in vivo grown cells as an autologous graft, the most promising approach in VTE lies within the use of synthetic materials. Conventional synthetic materials, like PET or PTFE, failed as small diameter blood vessels because of their low hemocompatibility and compliance mismatch leading to failing grafts. STPUs are particularly interesting, as a new material in VTE because of their unique structure consisting of a macrodiol, as flexible soft block, and a combination of diisocyanate and chain extender, as a rigid hard block. By changing the used building blocks this allows the production of biocompatible, elastomeric polymers which can be processed from melt as well as in solution, thus enabling them to be processed by electrospinning.

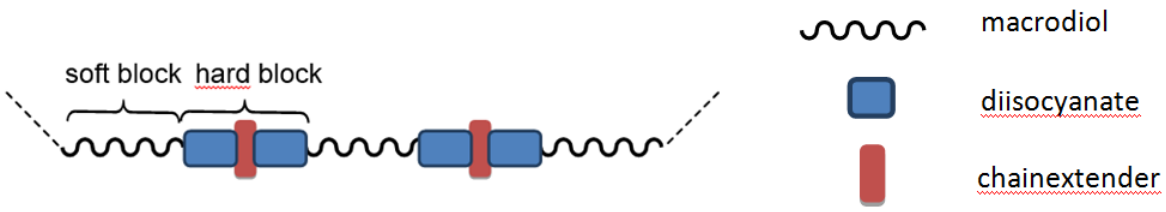


Figure 51: Structure of a STPU

Previous work in our institute developed a hard block degrading STPU by changing the building blocks of Pellethane (a FDA approved STPU), build up by pTHF as macrodiol, 4,4'-methylene diphenyl diisocyanate (MDI) and 1,4-butandiol as chain extender. To provide biodegradability MDI was replaced by the

aliphatic hexamethylene diisocyanate (HMDI) and a cleavable chain extender based on terephtalic ester was introduced to achieve degradability. This material was used as Reference D beside the reference material Pellethane.

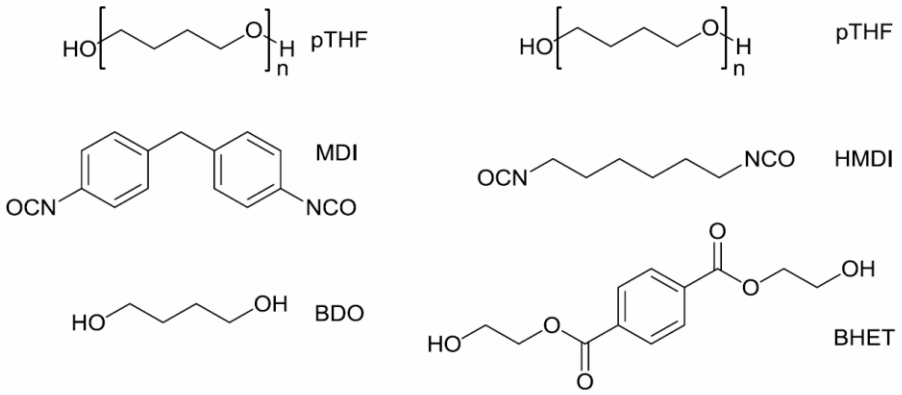
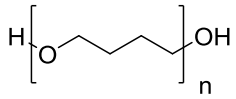


Figure 52: Monomers of Pellethane (left) and reference D (right)

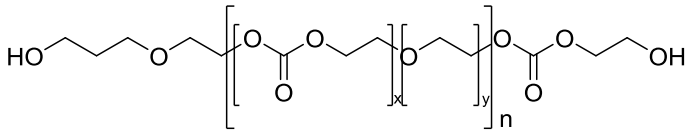
The goal of this work was to increase degradation rates significantly compared to Ref.D but sustaining biocompatibility as well as mechanical properties. Further the use of ester based materials should be minimized to avoid inflammatory reaction after implantation. Therefore the ester based chain extender BHET was replaced by various degradable chain extenders (BHPC, DHEDS, degradable thiazolidine /organophosphate/ketal based chain extenders were contemplated as well). To increase degradation further pTHF was replaced by a more hydrophilic and biodegradable poly(ether carbonate) in form of poly(oxy-ethylene-*alt*-ethylene carbonate).

Because the synthesis of thioazolidine-, organophosphate- and ketal-based chain extenders failed only BHPC, BHET and DHEDS were used. To obtain comparable data STPUs containing pTHF as soft block were synthesized as well. This way, a series STPUs could be tested towards mechanical strength and degradation rates using Pellethane and Reference D as reference materials.

soft blocks

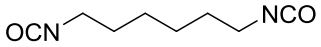


pTHF



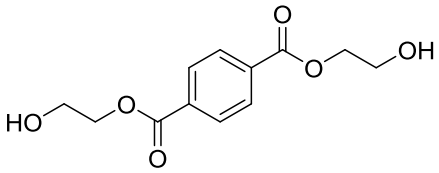
poly(oxy-ethylene-alt-ethylene carbonate)

hard block

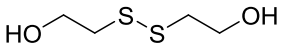


hexamethylenediisocyanate

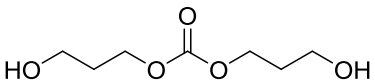
chainextenders



BHET



DHEDS



BHPC

Figure 53: Building blocks used for STPU synthesis

In conclusion the synthesis of the new more hydrophilic soft block poly(oxy-ethylene-*alt*-ethylene carbonate) with varying molecular weights and their incorporation into STPUs was successful. Drying of this polymer turned out to be a challenge due to its hygroscopic nature and its high viscosity. Final drying right before reaction in high vacuum at elevated temperatures did not suffice to ensure water free conditions during reaction. Water contents between 0.05w% - 0.1w% probably led to comparably low molecular weights of the final STPUs.

Degradation tests of these polyurethanes conducted in PBS at elevated temperatures indicated that the poly(ether carbonate) containing polyurethanes indeed provided significantly increased degradation rates compared to their pTHF containing counterparts.

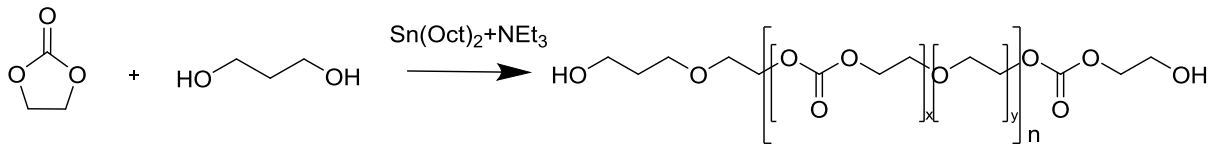
Mechanical testing showed inferior mechanical properties (low elasticity and low elongation at the break). The main reason for this results might have been the low molecular weights of these polyurethanes. Lack of an aromatic building block as well as hindered aggregation of the polyurethane-elastomer due to high polarity of the soft block might have played a critical role as well.

Experimental Part

1 Synthesis of a new carbonate based soft block

1.1 Ring opening polymerisation of ethylene carbonate[74]

Poly(ethylene carbonate) (MW ~ 1000)



	M [g/mol]	n [mol]	Eq.	amount
ethylene carbonate	88.06	1.13	1	100g
1,3-Propanediol	76.09	0.07	0.06	5.08g
tin(II)ethylhexanoate	404.87	0.01	0.01	4.6g
triethylamine	101.19	-	-	4 drops

All dried educts were placed into the reaction vessel under argon atmosphere and put into an oil bath at 170°C. After 36h of stirring at this temperature the mixture was allowed to cool to room temperature and was dissolved in 200mL DCM and washed three times with 30mL ~5% HCl. The organic layer was dried with Na_2CO_3 filtered and the DCM was evaporated. The polymer again was diluted with 50mL DCM and "precipitated" on 2L *tert*-butyl methyl ether. The ether was decanted and the residue was transferred in a 100mL flask. The solvent was evaporated and the product was dried with a rotavapor at 70°C (0,1mbar).
The molecular weight was determined with the TSI method (see page 81).

Yield: 42,1g of a mellow brown, honey like liquid (42%)

MW = 1220g/mol
^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.2 (t, 4H, CH_2-OC(O)O-CH_2), 3.6 (m, 4H, CH_2-O-CH_2)

Poly(ethylene carbonate) (MW ~ 2000)

	M [g/mol]	n [mol]	Eq.	amount
ethylene carbonate	88.06	1.25	1	110g
1,3-propanediol	76.09	0.04	0.03	3.35g
tin(II)ethylhexanoate	404.87	0.01	0.01	5g
triethylamine	101.19	-	-	4 drops

The reaction was conducted according to the procedure on page 80 with a reaction time of 120h.

Yield: 47,8g of a dark brown, honey like liquid (40%)

MW = 2037g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.2 (t, 4H, CH_2-OC(O)O-CH_2), 3.6 (m, 4H, CH_2-O-CH_2)

1.2 Determination of the hydroxyl number via TSI method

The necessary amount of sample was calculated by the following equation, with the expected #OH available from the table in DIN 53 240.

$$g\ sample = \frac{40}{expected\ \#OH}$$

The calculated amount of macrodiol was weighed into a 100mL beaker or Erlenmeyer flask and dissolved in 150mL HPLC grade acetonitrile to ensure sufficient immersion of the pH-electrode. The calculated amount of p-toluene sulfonyl isocyanate (TSI) (slight excess is recommended) was added and the solution was stirred for 5min. at room temperature. The excess of TSI was destroyed by addition of 1mL deionized water. Potentiometric titration was carried out with a 0.1N tetrabutylammonium hydroxide (Bu_4NOH) solution using an autotitrator - pH electrode system. The Bu_4NOH solution was prepared by diluting 100mL of 1M Bu_4NOH-methanol solution with 2-propanol to one liter. The 0.1N

Bu_4NOH was standardized by potentiometric titration against benzoic acid in methanol.

The hydroxyl number then can be calculated according to:

$$\#OH = \frac{(V_2 - V_1) * N * 56.1}{E}$$

V_2 Volume of Bu_4NOH at the second potentiometric endpoint
V_1 Volume of Bu_4NOH at the first potentiometric endpoint
N normality of the titrant solution
E original sample weight [g]

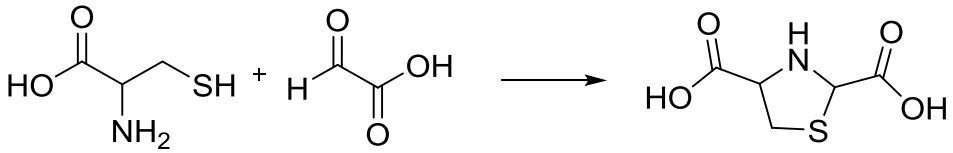
2 Developement of new chain extenders

2.1 Synthesis of thiazolidine-based chain extenders

2.1.1 Attempted synthesis by reduction of 2,4-thiazolidine-dicarboxylic acid and its derivatives

2.1.1.1 Reduction of 2,4-thiazolidinedicarboxylic acid

Synthesis of 2,4-Thiazolidinedicarboxylic acid[89]



	M [g/mol]	n [mmol]	Eq.	amount
L-cysteine	121.16	43	1.00	5.27g
glyoxylic acid	74.04	45	1.03	3.30g

L-cysteine and glyoxylic acid were weighed into the reaction flask and 100mL of methanol were added. The mixture was stirred at room temperature for 5-6h. The white precipitate was filtered off and washed with methanol. The solid was then dried in vacuo. The white powder was used for further reaction without any purification.

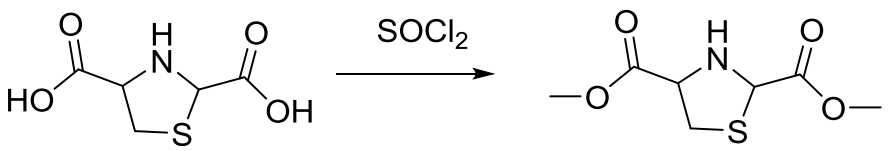
Yield: 6.9 g white powder (90%)

m.p. 183-184°C (Lit.[105]: 184-185°C)

^{1}H-NMR (200 MHz, $(CD_3)_2SO$): δ [ppm] = 4.86 (s, 1H, H_2), 3.8 (dd, 1H, H_5), 3.28 (dd, 1H, H_5), 2.7 (t, 1H, H_3)

2.1.1.2 Reduction of 2,4-thiazolidinedicarboxylic acid, 2,4-dimethyl ester

Synthesis of 2,4-Thiazolidinedicarboxylic acid, 2,4-dimethyl ester[91]



	M [g/mol]	n [mmol]	Eq.	amount
2,4-thiazolidinedicarboxylic acid	177.18	18	1	3.17g
thionyl chloride	118.97	83	4.6	6ml

2,4-Thiazolidinedicarboxylic acid was suspended in 50mL dry methanol and cooled with an ice bath. Freshly distilled thionyl chloride was added drop wise within 30min. and the temperature was raised to room temperature. After 16h of stirring at room temperature the mixture was heated to 90°C for one hour. After evaporation of the solvent the residue was dissolved in 80mL water and 80mL diethyl ether were added. Sodium carbonate was added under magnetic stirring until no further reaction (foaming) was observed. The phases were separated and the aqueous solution was extracted three times with 20mL of diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The yellow solid was dried in vacuo and was used without further purification.

Yield: 1.77g yellow crystals (49%)

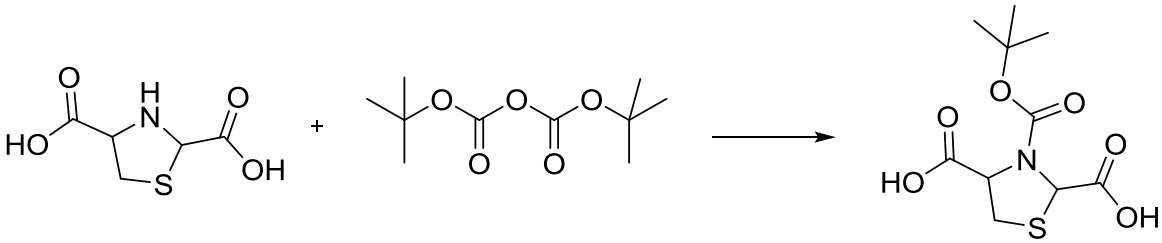
TLC (PE/EE 3:1): Rf = 0.33 / 0.44 (cis/trans)

m.p. 73-74°C (Lit.[91] = 70°C)

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.94 (s, 1H, H-2) 3.,81 (s, 3H, COOC$\underline{H_3}$) 3.80 (s, 3H, COOC$\underline{H_3}$) 3.30 (dd, 1H, H-5) 2.80 (t, 1H, H-3)

2.1.1.3 Reduction of N-protected 2,4-thiazolidinedicarboxylic acid and its derivatives

Synthesis of thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl)ester[92]



	M [g/mol]	n [mmol]	Eq.	amount
2,4-thiazolidinedicarboxylic acid	177.18	7.6	1	1.35g
di-tert-butyl dicarbonate	218.25	15.8	2	3.33g
triethylamine	101.19	15.8	2	2.1ml

A mixture of 2,4-Thiazolidinedicarboxylic acid, di-tert-butyl dicarbonate and triethylamine in 40 mL of acetonitrile was refluxed for 7h. After evaporation of the solvent, the residue was treated with 40 mL of a cold 5% aq. HCl solution and extracted three times with 15ml CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The product was used without further purification.

Yield: 1.91g orange, amorphous solid (95%)

m.p. decomposition above 112°C (Lit. -)

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 1.36 (s, 9H, C(C<u>H</u>$_3$)$_3$) 3.15 (d, 1H, H-5,); 3.39 (dd, 1H, H-5) 4.56 (m, 1H, H-4); 5.21 (s, 1H, H-2)

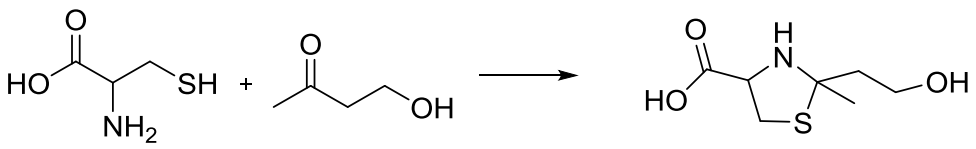
^{13}C-NMR (50 MHZ, $CDCl_3$): δ [ppm] = 28.0 (q, C(<u>C</u>H$_3$)$_3$); 32.5 (t, C-5); 59.7 (d, C-4); 62.4 (d, C-2); 82.3 (<u>C</u>(CH$_3$)$_3$); 170.4, 173.7, 174.3 (s, CO)

GC/MS (Acetone, EI, m/z): 265,18 (M); 146.1, 86.13, 59.15

2.1.2 Attempted synthesis by modification of 2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid

2.1.2.1 Reduction of 2-hydroxyethyl-2-methyl-4-thiazolidinecarboxylic acid derivatives

Synthesis of 2-methyl-2(2-hydroxyethyl)-4-thiazolidinecarboxylic acid[92]



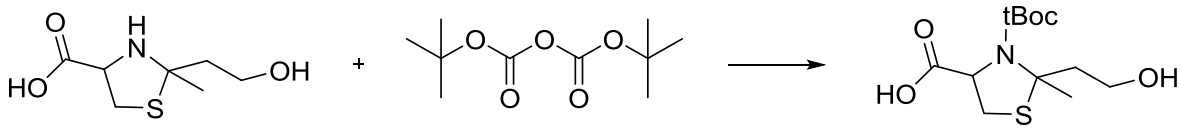
	M [g/mol]	n [mmol]	Eq.	amount
L-cysteine	121.16	8.3	1.00	1.00g
4-hydroxy-2-butanone	88.11	8.5	1.03	0.73g

L-cysteine and 4-hydroxy-2-butanone were placed in a flask and suspended in 40ml dry ethanol. The suspension was stirred at 50°C for 17h. The now slight yellow suspension was filtered and the filtrate was washed with methanol. The slight yellow solid proved to be insoluble in any deuterated solvent and made ^{1}H-NMR measurement impossible. This product was used for further reactions without purification.

Yield: 0.81g (51%) slight yellow powder

m.p. 171-173°C (Lit. -)

Synthesis of 2-methyl-2(2-hydroxyethyl)-3,4-thiazolidinedicarboxylic acid, 3-(1,1-dimethylethyl)ester



	M [g/mol]	n [mmol]	Eq.	amount
2-methyl-2(2-hydroxyethyl)-4-thiazolidinecarboxylic acid	191.27	4.2	1	0.81g
di-tert-butyl dicarbonate	218.25	8.2	2	1.79g
triethylamine	101.19	8.2	2	1.2ml

A mixture of 2-methyl-2(2-hydroxyethyl)-4-thiazolidinecarboxylic acid, di-tert-butyl dicarbonate and triethylamine in 25 mL of acetonitrile was refluxed for 7h. After evaporation of the solvent, the residue was treated with 15 mL of a cold 5% aq HCl solution and extracted three times with 10mL CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Impurities were removed by flash chromatography (DCM, silicagel) and the pure product was eluted with ethanol.

Yield: (96%) orange-red viscous liquid

TLC (EtOH): Rf = 0.53

n_D^{20} = - (Lit. -)

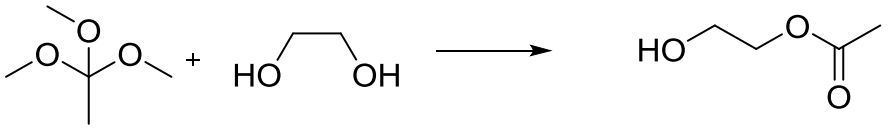
^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 9.65 (s, 1H, COO<u>H</u>) 5.25 (t, 1H, C<u>H</u>-COOH) 3.49 (t, 2H, CH_2-C<u>H_2</u>-OH) 3.22 (dd, 2H, S-C<u>H_2</u>) 2.55 (s, 1H, OH) 1.5 (s, 3H, CH_3) 1.44 (s, 9H, C(C<u>H_3</u>)$_3$) 1.21 (t, 2H, (t, C<u>H_2</u>-CH_2-OH)

^{13}C-NMR (50 MHZ, $CDCl_3$): δ [ppm] = 168 (s, <u>C</u>OOH), 155 (s, N-<u>C</u>OO), 84 (s, O-<u>C</u>(CH_3)$_3$) 80 (s, C2) 54 (s, C4) 43 (t, CH_2-<u>C</u>H_2-OH) 34 (t, C5) 32 (q, CH_3) 30 (q, O-C(<u>C</u>H_3)$_3$) 28 (t, <u>C</u>H_2-CH_2-OH)

2.2 Developement of ketal-based chainextenders

2.2.1 Synthesis of Ethanol, 2,2'-[(1-methylethylidene)bis(oxy)]bis-, 1,1'-diacetate

Synthesis of 2-hydroxyethyl acetate[101]



	M [g/mol]	n [mmol]	Eq.	amount
trimethylorthoacetate	120.15	77.5	1	10ml
ethylene glycol	62.07	60.0	0.8	3.3ml
p-toluenesulfonic acid	172.20	1.3	0.02	0.22g

Trimethylorthoacetate, ethylene glycol and p-toluenesulfonic acid were weighed into a flask which was flushed with argon. 75mL CH_2Cl_2 were added and the solution was stirred at room temperature for 20h. 1.4mL water were added and the mixture was stirred for 30min. The solvent was evaporated and the clear liquid residue was purified by flash chromatography (silica gel, $CHCl_3$:acetone = 9:1).

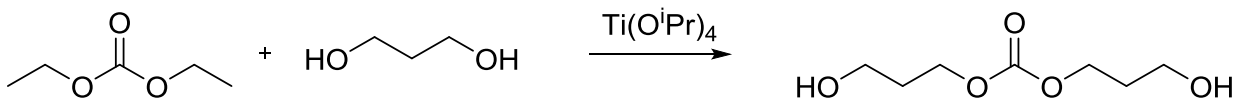
Yield: 5.6g clear liquid (90%)

TLC ($CHCl_3$:acetone 9:1): Rf = 0.48

n_D^{20} = 1.4235 (Lit.[106] = 1,4232)

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.93 (s, 1H, OH) 4.25 (t, 2H, C(O)O-C<u>H</u>$_2$) 3.58 (t, 2H, C<u>H</u>$_2$-OH) 2.1 (s, 3H, CH_3)

2.3 Synthesis of Bis(3-hydroxypropyl)carbonate (BHPC)[107]



	M [g/mol]	n [mmol]	Eq.	amount
diethyl carbonate	118.13	123	1	15g
propane-1,3-diol	76.1	738	6	58g
titanium(IV)isopropoxide	284.22	0.8	0.007	0.2ml

Propane-1,3-diol and diethyl carbonate were weighed into a flask and equipped with a distillation bridge and flushed with argon. The mixture was heated to 110°C and Ti(O*i*Pr)$_4$ was added. Part of Ti(O*i*Pr)$_4$ precipitated as TiO_2 due to residual water in the educts. After 4 h the temperature was increased to 170°C for another 48h. The mixture was then diluted with ethyl acetate and 5mL of water were added to fully precipitate the catalyst. The TiO_2 was removed by filtration and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and the solvent and propane-1,3-diol were distilled off. The product was further purified by column chromatography (silica gel, ethyl acetate).

Yield: 5.25g (24%)

TLC (EE): Rf = 0.37

n_D^{20}= 1.4542 (Lit.[107] = 1.4542)

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.23 (t, 4H, OCO_2-<u>CH_2</u>-CH_2) 3.66 (q, 4H, <u>CH_2</u>-OH) 2.83 (t, 2H, OH) 1.86 (p, 4H, CH2-<u>CH_2</u>-CH_2)

3 Synthesis of the Polyurethanes

3.1 Preparation of the building blocks

The purchased HMDI was purified by vigreux distillation at 131°C at $5*10^{-3}$mbar. The storage stability was confirmed via refractive index and GC-MS measurements. ((Et_2O, EI, m/z): 167.96 (M); 99.08; 85.06; 69.07; 56.04)

All purchased chain extenders were used without further purification and were dried and stored over $CaCl_2$ for several days. All liquid monomers were stored over molecular sieve (pore size 3Å).

The used poly-diols were dried in high vacuum at elevated temperatures under magnetic stirring (60-90°C /$5*10^{-3}$ mbar) for at least 4 hours directly before polymerization. To make sure that the reactions could be carried out under water free conditions all liquid reactants as well as the solvents and polyols were analyzed via Karl Fischer titration.

To confirm the molecular weight of the used macrodiols the hydroxyl number has been determined via TSI method. The hydroxyl number indicates the amount of mg KOH corresponding to the acetylated hydroxyl groups in 1g sample and allows the calculation of the molecular weight.

3.2 Synthesis of STPUs

General procedure:

The pre-dried soft blocks (pTHF, pEC) were weighed into a flask and dried at 90°C in high vacuum for at least four hours. The appropriate amount of hexamethylenediisocyanate was weighed into a dried transfer vessel and diluted with 5mL dry DMF and transferred to the reaction vessel via syringe. The transfer vessel and syringe were rinsed three times with 10mL dry DMF. Two drops of Tin (II)ethylhexanoate were added and the mixture was stirred at 65°C for 24h. The appropriate amount of dry chain extender was weighed into a transfer vessel and dissolved/diluted in/with 5mL dry DMF and transferred via syringe. The transfer vessel again was rinsed three times with 10mL dry DMF to ensure quantitative transfer. Additional 10mL dry DMF were added to the reaction mixture and stirring at 65°C was continued for another 24h. The mixture was allowed to cool

to room temperature and was diluted with 15ml DMF and precipitated in 10fold excess of methanol. The precipitate was filtered off and dried in vacuum.

Reference D

	M [g/mol]	n [mmol]	Eq.	amount
pTHF	1012	3.7	1	3.727g
HMDI	168.19	7.4	2	1.253g
BHET	254.24	3.7	1	0.941g

Yield: 4.97g (84%) white brittle polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 8.10 (d, 4H, Ar-H) 4.95/4.71 (m, 4H, NH) 4.50 (m, 4H, COO-CH_2-CH_2-OCON) 4.43 (m, 4H, COO-CH2-CH2-OCON) 4.05 (t, 4H, NCOO-CH2) 3.41 (t, 52H, CH_2-O) 3.13 (q, 8H, CH2-N) 1.61 (m, CH_2-CH_2-N / CH_2-CH_2-O) 1.30 (m, CH_2-CH_2-CH_2-N)
ATR-IR = 3321 cm^{-1} N-H st, 2940 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1} C=O…H-N st, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pTHF-1

	M [g/mol]	n [mmol]	Eq.	amount
pTHF	1012	4.2	1	4.267g
HMDI	168.19	8.4	2	1.418g
DHEDS	154.25	4.2	1	0.648g

Yield: 4.64g (73%) glassy white polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.53 (m, 4H, NH) 4.29 (m, 4H, NCOO-CH_2-CH_2-S) 3.43 (t, 55H, CH_2-O) 3.12 (m, 8H, CH_2-N) 1.88 (t, 4H, COO-CH_2-CH_2-CH_2-OCO) 1.43 – 1.20 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3354 cm^{-1} N-H, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pTHF-2

	M [g/mol]	n [mmol]	Eq.	amount
pTHF	1012	3.2	1	3.221g
HMDI	168.19	6.4	2	1.071g
BHPC	178.18	3.2	1	0.599g

Yield: 4.24g (87%) white brittle polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.53 (m, 4H, NH) 4.19 (m, 8H, OC(O)O-CH_2-CH_2-CH_2-O) 3.43 (t, 55H, CH_2-O) 3.12 (m, 8H, CH_2-N) 1.88 (t, 4H, COO-CH_2-CH_2-CH_2-OCO) 1.43 – 1.20 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3329 cm-1 N-H st, 2865 cm-1 OC-H st, 1737 cm-1 C=O st, 1715 cm-1 C=O st, 1642 cm-1 C=O…H-N st, 1242 cm-1 C-O st, 1094 cm-1 C-O st

PU-pEC1-S1

	M [g/mol]	n [mmol]	Eq.	amount
pEC	1220	3.9	1	4.790g
HMDI	168.19	7.8	2	1.321g
DHEDS	154,25	3.9	1	0.605g

Yield: 3.19 (47%) yellow soft polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 5.11 (2H, N-H) 4.88 (2H, NH) 4.29 (m, 4H, NCOO-CH_2-CH_2-S) 4.21 (t, 48H, CH_2-OC(O)O-CH_2) 3.6 (m, 50H, CH_2-O-CH_2) 2.86 (t, 7H, CH_2-S) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3354 cm^{-1} N-H st, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC1-S2

	M [g/mol]	n [mmol]	Eq.	amount
pEC	1220	2.1	1	2.578g
HMDI	168.19	6.3	3	1.041g
DHEDS	154,25	4.1	2	0.652g

Yield 3.35g (78%) white brittle polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 5.11 (2H, N-H) 4.88 (2H, NH) 4.29 (m, 4H, NCOO-CH_2-CH_2-S) 4.21 (t, 36H, CH_2-OC(O)O-CH_2) 3.6 (m, 34H, CH_2-O-CH_2) 2.86 (t, 10H, CH_2-S) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H st, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC1-T1

	M [g/mol]	n [mmol]	Eq.	amount
pEC	1220	2.9	1	3.577g
HMDI	168.19	5.8	2	0.986g
BHET	254,24	2.9	1	0.745g

Yield: 4.52g (85%) white polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 8.11 (s, 4H, Ar-H) 4.92 (s, 4H, NH) 4.50 (m, 4H, COO-CH_2-CH_2-OCON) 4.43 (m, 4H, COO-CH_2-CH_2-OCON) 4.27 (t, 52H, CH_2-OC(O)O-CH_2) 3.7 (m, 58H, CH_2-O-CH_2) 3.13 (t, 8H, CH_2-N) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC1-C1

	M [g/mol]	n [mmol]	Eq.	amount
pEC	1220	3.1	1	3.811g
HMDI	168.19	6.2	2	1.051g
BHPC	178.18	3.1	1	0.556g

Yield: 4.46g (81%) white polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.89 (s, 4H, NH) 4.27 – 4.1 (m, 50H, CH_2-OC(O)O-CH_2 (soft block) / CH_2-OC(O)O-CH_2 (chain extender) 3.7 (m, 45H, CH_2-O-CH_2) 3.13 (t, 8H, CH_2-N) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H st, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC2-S1

	M [g/mol]	n [mmol]	Eq.	amount
pEC	2020	1.7	1	3.504g
HMDI	168.19	3.4	2	0.581g
DHEDS	154,25	1.7	1	0.226g

Yield: 2.2g (51%) slight brown, soft polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 5.11 (2H, N-H) 4.88 (2H, NH) 4.29 (m, 4H, NCOO-CH_2-CH_2-S) 4.21 (t, 80H, CH_2-OC(O)O-CH_2) 3.6 (m, 106H, CH_2-O-CH_2) 2.86 (t, 6H, CH_2-S) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3354 cm^{-1} N-H, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC2-S1.5

	M [g/mol]	n [mmol]	Eq.	amount
pEC	2020	1.5	1	3.100g
HMDI	168.19	3.8	2.5	0.643g
DHEDS	154,25	2.3	1.5	0.353g

Yield: 3.41g (83%) gray powder

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 5.11 (2H, N-H) 4.88 (2H, NH) 4.29 (m, 4H, NCOO-CH_2-CH_2-S) 4.21 (t, 52H, CH_2-OC(O)O-CH_2) 3.6 (m, 64H, CH_2-O-CH_2) 2.86 (t, 6H, CH_2-S) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3354 cm^{-1} N-H, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-PEC2-T1

	M [g/mol]	n [mmol]	Eq.	amount
pEC	2020	1.9	1	3.753g
HMDI	168.19	3.8	2	0.623g
BHET	254,24	1.9	1	0.470g

Yield: 1,37g (28%) brown, soft polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 8.11 (s, 4H, Ar-H) 4.92 (s, 4H, NH) 4.50 (m, 4H, COO-CH_2-CH_2-OCON) 4.43 (m, 4H, COO-CH_2-CH_2-OCON) 4.27 (t, 80H, CH_2-OC(O)O-CH_2) 3.7 (m, 98H, CH_2-O-CH_2) 3.13 (t, 8H, CH_2-N) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC2-T1.5

	M [g/mol]	n [mmol]	Eq.	amount
pEC	2020	1.9	1	3.770g
HMDI	168.19	4.7	2.5	0.782g
BHET	254,24	2.9	1.5	0.707g

Yield: 4,15g (79%) brown, brittle polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 8.11 (s, 4H, Ar-H) 4.92 (s, 4H, NH) 4.50 (m, 4H, COO-CH_2-CH_2-OCON) 4.43 (m, 4H, COO-CH_2-CH_2-OCON) 4.27 (t, 58H, CH_2-OC(O)O-CH_2) 3.7 (m, 60H, CH_2-O-CH_2) 3.13 (t, 8H, CH_2-N) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC2-C1

	M [g/mol]	n [mmol]	Eq.	amount
pEC	2020	1.7	1	3.472g
HMDI	168.19	3.4	2	0.578g
BHPC	178.18	1.7	1	0.318g

Yield: 1.39g (37%) brown, soft polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.89 (s, 4H, NH) 4.27 – 4.1 (m, 104H, CH_2-OC(O)O-CH_2 (soft block) / CH_2-OC(O)O-CH_2 (chain extender) 3.7 (m, 96H, CH_2-O-CH_2) 3.13 (t, 8H, CH_2-N) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H st, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

PU-pEC2-C1.5

	M [g/mol]	n [mmol]	Eq.	amount
pEC	2020	2.1	1	4.211g
HMDI	168.19	5.3	2.5	0.891g
BHPC	178.18	3.2	1.5	0.559g

Yield: 2.43g (43%) brown, brittle polymer

^{1}H-NMR (200 MHz, $CDCl_3$): δ [ppm] = 4.89 (s, 4H, NH) 4.27 – 4.1 (m, 84H, CH_2-OC(O)O-CH_2 (soft block) / CH_2-OC(O)O-CH_2 (chain extender) 3.7 (m, 72H, CH_2-O-CH_2) 3.13 (t, 8H, CH_2-N) 1.43-1.26 (m, CH_2-CH_2-N / CH_2-CH_2-CH_2-N)
ATR-IR = 3312 cm^{-1} N-H st, 2984 cm^{-1} C-H st, 2857 cm^{-1} OC-H st, 1721 cm^{-1} C=O st, 1687 cm^{-1}, 1250 cm^{-1} C-O st, 1223 cm^{-1} C-N st

4 Testing of the STPUs

4.1 Contact angle measurement

Polymer foils with a thickness of 1-2µm were prepared by dissolving the polyurethanes in 5.2mL DMF (about 10 % (w/w)) and pouring them into Teflon molds (60x40x2 mm3 cavity). The molds were dried at 35°C for a week and an additional week *in vacuo* at 35°C.

Static contact angle measurements were performed at room temperature. A drop of water (5 µL) was dropped on the polymer surface and the contact angle was pictured via camera. The angle was measured via software of the model DSA 30S, Krüss.

4.2 Degradation studies

From the previously solvent casted films (thickness 1-2 µm), round samples with a diameter of 18 mm were punched. The weight of the samples was between 53 and 80 mg. The samples were placed in 15mL PBS at a constant temperature of 90°C for 10, 20 and 30 days. Composition of the PBS (pH: 7,4) NaCl: 8.01 g/L, KCL 0.20 g/L, Na2HPO4 * 2 H2O 1.78 g/L, KH2PO4 0.27 g/L. The cooled buffer was decanted off and the remaining sample was washed with distilled water. The washing included 2h of soaking in distilled water to remove absorbed buffer salt. Then the samples were dried in vacuum (constant weight). The degradation was determined by weight loss and molecular weight loss. Three samples were analyzed for each measuring point.

4.3 Mechanical testing

Tensile test specimens were punched from the previously solvent casted films according to ISO 527-1 type 5B. The specimens were applied in the tensile testing machine (Zwick Z050). The crosshead travel was used directly to determine the strain without the use of an extensometer. The strain was applied at a velocity of 50 mm/min to preload specimens with 0.1 N tension. At break of the material the measurement was aborted. For each polymer 4 specimens were measured.

Materials and Methods

All **Reagents and solvents** were purchased from Sigma-Aldrich, ABCR or Fluka in appropriate qualities.

For **thin layer chromatography (TLC)** aluminum foils, coated with silicagel 60 F254 from the company Merck were used.

For **column and flash column chromatography**, silicagel 60, from the distributor VWR was applied.

^{1}H-NMR (200 MHz) and **^{13}C-NMR (50 MHz)** spectra were measured with a BRUKER AC-E-200 FT-NMR- spectrometer. The chemical shift is displayed in ppm (s = singulett, d = duplett, t = triplett, q = quartett, m = multiplett).
Deutero-chloroform (CDCl3), deuterated DMSO (d6-DMSO) and deuterated methanol (MD_3OD) from the companies Aldrich and Eurisotop were used as a solvent.
ATR-FT-IR spectra were measured with a Perkin Elmer Spectrum 65 FT-IR spectrometer between 600 and 4000 cm-1.
Melting points were determined with a MPA100 OptiMelt automatic melting point system by SRS.

GC-MS runs were performed on a Thermo Scientific GC-MS DSQ II using a BGB 5 column (L = 30 m, d = 0.32 mm, 1.0 µm film, achiral) with the following temperature method (injection volume: 1 µL): 2 min at 80°C, 20°C/min until 280°C, 2 min at 280°C. MS spectra were recorded using EI ionization (70 eV) and a quadrupole analyzer.

SEC measurements were carried out on a Waters 515 HPLC-SEC system with three 7.3 x 300 mm Styragel columns (HR 0.5; HR 3; HR 4) equipped with a Waters 2410 RI detector. Flow rate was 1 ml/min at 40°C. Generally, polystyrene standards were used for calibration.

Titrations were performed potentiometrically on a 736 GP Titrino by the company Metrohm. As a reference electrode Metrohm Solvotrode 6.0229.010 (0.4 M tetrabutylammonium hydroxide in methanol) was used.

The **water content** was determined via an automated Karl Fischer titration device from METROHM.

Contact angle measurements were carried out on a Krüss DAS 30.

Tensile tests were measured on a Zwick Z050 tensile testing machine.

Abbreviations

BHPC	bis(3-hydroxypropyl)carbonate
DHEDS	bis(2-hydroxyethyl)disulfide
BHET	bis(2-hydroxyethyl)terephthalate
TE	tissue engineering
TEVG	tissue engineered vascular graft
HMDI	hexamethylenediisocyanate
pHMC	poly(hexamethylene carbonate)
pTMC	poly(trimethylene carbonate)
pTHF	poly(tetrahydrofurane)
PEG	poly(ethylene glycol)
STPU	segmented thermoplastic polyurethane
$Sn(Oct)_2$	tin(II)octoate
$Ti(O^iPr)_4$	titanium(IV)isopropoxide
MW	molecular weight
CVD	cardiovascular disease
CHD	coronary heart disease
VTE	vascular tissue engineering
ECM	extracellular matrix
PET	poly(ethylene terephthalate)
PLA	poly(lactic acid)
PCL	poly(ε-caprolactone)
PGA	poly(glycolic acid)
pNPC	poly(neopentyl carbonate)
PBC	poly(butylene carbonate)
MDI	4,4'-methylene diphenyl diisocyanate
tboc	dimethylethylcarbonyl protecting group

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