Polymer Technology Publication Series
Espoo 2003 No. 26

BRANCHED AND CROSSLINKED RESORBABLE POLYMERS BASED ON LACTIC ACID, LACTIDE AND ε-CAPROLACTONE

Antti Helminen

Dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the Department of Chemical Technology for public examination and debate in Auditorium KE 2 (Komppa Auditorium) at Helsinki University of Technology (Espoo, Finland) on the 19th of December, 2003, at 12 noon.

Helsinki University of Technology
Department of Chemical Technology
Polymer Technology

Distribution:
Helsinki University of Technology
Polymer Technology
P.O. Box 6100
FIN-02150 HUT, Finland
Tel. +358-9-451 2616
Fax. +358-9-451 2622
E-mail: helminen@polte.hut.fi

ISBN 951-22-6840-X
ISSN 0785-7144

Otamedia Oy
Espoo 2003

ABSTRACT

Branched and crosslinked degradable polyesters based on lactic acid, lactide and ε-caprolactone were prepared by utilizing different polymerization methods. Chain linking of hydroxyl telechelic lactic acid oligomers with 1,6-hexamethylene diisocyanate (HMDI) as a chain extender, yielded lactic acid based poly(ester-urethanes). When an excess of HMDI was used, polymers with broader molecular weight distribution and long-chain branching were obtained. Long-chain branching was confirmed by NMR and was seen in high shear thinning and melt strength in rheological measurements. Ring-opening polymerization of D,L-lactide, L-lactide and ε-caprolactone in the presence of stannous octoate and a co-initiator was employed as a method to prepare polyesters with controlled molecular structure. The initiation activity of different hydroxyl containing compounds was evaluated and new co-initiator compounds, polyglycerines, were shown to yield polylactides with up to 8 arms. Furthermore, by increasing the number of hydroxyls in the co-initiator, the polymerization rate increased and polylactides with higher molecular weight were obtained.

Crosslinked polymers with controlled molecular structure were prepared from end functionalized linear and branched polyester precursors. The effect of molecular architecture, *i.e.* branching, molecular weight and different monomer units in the precursors, on the curing and properties of the final networks was studied. Triethoxysilane and methacrylic double bond functionalization and polymerization of these moieties were utilized in the preparation of hydrolytically degradable networks with different properties. High strength was obtained with DLLA based networks, whereas the use of flexible CL/DLLA copolymers as network precursors yielded highly elastic crosslinked polymers with creep resistance.

In addition to the preparation and characterization, the degradability of the crosslinked polymers was evaluated. The polyester networks exhibited degradation similar to the corresponding thermoplastic polyesters. In general, the degradation occurred through bulk degradation where the mechanical properties of the polyesters deteriorated first and the mass loss followed. The degradation of the networks was enhanced by introducing labile anhydride bonds as weak linkages into the polyester network structure. This approach led to very rapidly degrading, crosslinked poly(ester-anhydrides) based on PCL, PDLLA, and PLLA. When a short PCL based precursor was used, the network showed characteristics of surface-erosion: the poly(ester-anhydride) network lost its mass and the dimensions of the specimen decreased at a steady rate over two days.

PREFACE

This work was carried out between 1999 and 2003 in the Laboratory of Polymer Technology at Helsinki University of Technology. The research was part of the National Technology Agency (TEKES) targeted research projects. Among these projects most work was carried out in the project “Biodegradable Fiber”. Part of the thesis was carried out in the Bio- and Nanopolymers Research Group of the Center of Excellence program funded by the Academy of Finland (CoE program code number 77317). The financial support from TEKES and Academy of Finland is gratefully acknowledged.

I would like to thank Professor Jukka Seppälä for his advice, interest and enthusiasm for my work, and for providing me the opportunity to work in his research group. I gratefully acknowledge my co-workers Dr. Janne Kylmä, Dr. Jukka Tuominen and Harri Korhonen for their contribution, invaluable comments and collective hard work. Other former and present members of the biopolymers group, especially Dr. Jaana Rich, are thanked for their help and thoughtful comments and discussions.

I wish to thank the personnel of the laboratory for creating a pleasant working atmosphere and for all the help I have received during the research. In particular, Jorma T. Hakala is thanked for his enthusiastic literature search. Arto Mäkinen and Eija Ahonen are acknowledged for the technical assistance. In addition, I am thankful to Dr. Kathleen Ahonen and Anton Rich for revising the language of the publications and the thesis.

All the participants in the research projects, especially in Biodegradable Fiber -project, and the members of the Bio- and Nanopolymers Research Group are thanked for widening my perspective in the field of polymers and biomaterials.

I would like to thank my parents for their support over the years. Finally my deepest gratitude belongs to my wife Jenni and our daughter Emmi for their love and support.

Espoo, November 2003

Antti Helminen

CONTENTS

LIST OF PUBLICATIONS

This thesis is based on the following six publications (Appendices I-VI), which are, throughout the summary, referred to by their Roman numerals.

I Helminen, A., Kylmä, J., Tuominen, J. and Seppälä, J. V., Effect of structure modification on rheological properties of biodegradable poly(ester-urethane), *Polym. Eng. Sci.* **40** (2000) 1655-1662.

II Korhonen, H., Helminen, A. and Seppälä, J. V., Synthesis of polylactide in the presence of co-initiators with different numbers of hydroxyl groups, *Polymer* **42** (2001) 7541-7549.

III Helminen, A., Korhonen, H. and Seppälä, J. V., Biodegradable crosslinked polymers based on triethoxysilane terminated polylactide oligomers, *Polymer* **42** (2001) 3345-3353.

IV Helminen, A., Korhonen, H. and Seppälä, J. V., Structure modification and crosslinking of methacrylated polylactide oligomers, *J. Appl. Polym. Sci.* **86** (2002) 3616–3624.

V Helminen, A., Korhonen, H. and Seppälä, J. V., Crosslinked poly(ε-caprolactone/D,L-lactide) copolymers with elastic properties, *Macromol. Chem. Phys.* **203** (2002) 2630-2639.

VI Helminen, A., Korhonen, H. and Seppälä, J. V., Crosslinked poly(ester anhydride)s based on poly(ε-caprolactone) and polylactide oligomers, *J. Polym. Sci. Part A: Polym. Chem.* **41** (2003) 3788-3797.

The author's contribution in the appended publications

Publication I: Antti Helminen carried out the experimental work, interpretation of the results and has prepared the manuscript together with Janne Kylmä and Jukka Tuominen.

Publication II: Antti Helminen and Harri Korhonen are jointly responsible for the research plan, experimental work, interpretation of the results, and the preparation of the manuscript.

Publications III-V: Antti Helminen has been in charge of the research plan, experimental work, and interpretation of the results and has prepared the manuscript with Harri Korhonen.

Publication VI: Antti Helminen and Harri Korhonen are jointly responsible for the research plan, interpretation of the results, and the preparation of the manuscript. Antti Helminen carried out the experimental work.

NOMENCLATURE

The following abbreviations are used in the overview.

^{1}H-NMR	proton nuclear magnetic resonance spectroscopy
^{13}C-NMR	carbon-13 nuclear magnetic resonance spectroscopy
BD	1,4-butanediol
BDI	1,4-butane diisocyanate
BD-Me$_2$	dimethacrylated butanediol
BOX	2,2’-*bis*(2-oxazoline)
CL	ε-caprolactone
DLLA	DL-lactide
DMA	dynamic mechanical analysis
DS	degree of substitution
DSC	differential scanning calorimetry
FTIR	Fourier transform infrared spectroscopy
HMDI	1,6-hexamethylene diisocyanate
IPTS	(3-isocyanatopropyl) triethoxysilane
LA	lactide
LLA	L-lactide
MAAH	methacrylic anhydride
MALDI-TOF	matrix assisted laser desorption/ionization - time of flight
MW	molecular weight
MWD	molecular weight distribution
NMR	nuclear magnetic resonance spectroscopy
PBS	phosphate buffer solution
PCL	poly(ε-caprolactone)
PDLLA	poly(DL-lactide)
PEG	poly(ethylene glycol)
PERYT	pentaerythritol (2,2-bis(hydroxymethyl)-1,3-propanediol)
PEU	poly(ester-urethane)
PGL(-06, -10)	polyglycerine(-06, -10)
PLA	poly(lactic acid) or polylactide
PLLa	poly(lactic acid) prepared by polycondensation of L-lactic acid
PLLA	poly(L-lactide)
PMAA	poly(methacrylic acid)
PPF	poly(propylene fumarate)
ROP	ring-opening polymerization
SAH	succinic anhydride
SEC	size exclusion chromatography
SnOct$_2$	stannous octoate

TMC		trimethylene carbonate
UV		ultraviolet
Postfix	-AH	anhydride
	-COOH	carboxylic acid terminated
	-OH	hydroxyl terminated

SYMBOLS

G'	storage modulus (Pa)
G''	loss modulus (Pa)
L_{CAP}	average caproyl sequence length
L_{LA}	average lactidyl sequence length
M_n	number average molecular weight ($g \cdot mol^{-1}$)
M_w	weight average molecular weight ($g \cdot mol^{-1}$)
SF	swelling factor
T_g	glass transition temperature (°C)
$\tan \delta$	loss tangent
η^*	complex viscosity ($Pa \cdot s$)

1 INTRODUCTION

1.1 General background

Resorbable and degradable polymers have been extensively studied throughout the last decades. Resorbable means that the material can be broken down and the degradation products are eliminated in the body.[1] In polymers, the resorbability is obtained mainly through enzymatic or non-enzymatic hydrolysis followed by the metabolism or excretion of the degradation products. The use of the term resorbable is limited to biomedical materials. When degradable polymers are used elsewhere, they should be denoted degradable or biodegradable, when the degradation is mediated by biological activity as in enzymatic hydrolysis.[1] The benefits of using resorbable or degradable materials are evident: biomedical materials implanted *in vivo* degrade after serving their purpose. This has been utilized in the preparation of controlled drug release systems and in orthopaedic implants and sutures. In bulk applications, the use of degradable polymers allows the preparation of totally biodegradable and compostable molded articles, films and packages.[2,3]

Degradable polymers can be obtained from a variety of sources. Many materials created in nature are biodegradable polymers. Trees and plants produce cellulose, lignin and starch, and chitin is abundant in shellfish and molluscs. These natural polymers are degradable, at least with the aid of suitable enzymes, but their processing, and thermal and mechanical properties set boundaries for their use. Biotechnology has been applied in the production of polyhydroxyalkanoates by fermentation from starch, whereas chemical synthesis offers routes to an unlimited number of different degradable polymers. Hydrolytically labile aliphatic polyesters comprise most of the synthetically manufactured degradable polymers.[4-7]

Lactic acid based polymers (PLAs) and their copolymers, especially with glycolide, are used and studied in both biomedical and bulk applications. For example, microparticles are used *in vivo* for targeted drug release and screws and pins are implanted for temporary support in orthopaedics. One of PLA's advantages is that the raw material, lactic acid can be derived from renewable resources, which makes PLA very attractive for the packaging sector. High-molecular-weight PLA is produced by the ring-opening polymerization (ROP) of lactide, cyclic dimer of lactic acid. ROP can be applied in the preparation of polyesters such as polyglycolide, polylactides of different stereo structures, polylactones such as poly(ε-caprolactone) and poly(δ-valerolactone), polycarbonates and a wide variety of copolymers. Chain extending of lactic acid oligomers prepared via polycondensation of lactic acid offers a different route to high-molecular-weight PLA.[3,4,8-12]

Synthetic degradable polymers are mostly linear and thermoplastic, and their properties are mainly tailored by changing the molecular weight, or by adding comonomers of different types, contents and distributions.[2,7] This thesis is focused on two other aspects of molecular architecture, namely branching and crosslinking. The preparation and properties of the branched and crosslinked resorbable polymers are covered, the intention being to explore the structure-property relations related to branching and crosslinking and to show the possibilities available with this type of structure tailoring.

1.2 Branched resorbable polyesters

Branching changes the properties of the resorbable polymers. Branched polymer contains more chain ends than its linear counterpart of equal molecular weight and the polymer chains are shorter. With the increasing number of terminal groups, their effect on the polymer properties is increased.[13] This can be seen in crystallinity, which decreases with increasing branching. The melting temperatures of the star-shaped poly(L-lactides) (PLLAs) are lower than for their linear analogues due to shorter chain length and the increase in the number of free chain ends disrupting the crystalline structure. PLLAs with up to 20 arms originating from poly(amidoamine) dendrimer have been reported to be completely amorphous before annealing. This is because the PLLA chains with molecular weight (MW) of 3000 $g\cdot mol^{-1}$ were unable to form crystallites when their chain movements were hindered in highly branched polymers.[14,15] In addition, the increasing number of hydroxyl end groups has been shown to lead to higher hydrophilicity and increased degradation rate in star-shaped polylactides.[14]

The radius of gyration for branched macromolecules is smaller than for linear polymers. Branching decreases the hydrodynamic volume of polymers, making their MW determination with SEC more complicated.[16,17] The inherent viscosity of the star-shaped polymers is lower than for corresponding linear polymers of equal MW. The melt viscosity is also lower for branched polymers, which can be utilized in processing at lower temperatures. This is especially beneficial for thermo-labile polymers such as polylactides. In the thorough investigation of the star-shaped PLAs' melt rheology by Dorgan and Williams,[18] the zero shear viscosity and the shear thinning were shown to increase with branching, since the MW of the branches was high enough for entanglements. The relaxation spectra showed that in the transition zone the linear and branched PLLA were nearly indistinguishable, whereas branching made a greater contribution to the polymer behavior in the terminal region. However, the flow activation was only modestly affected by the chain architecture.

Branched degradable polyesters are mainly synthesized by ring-opening polymerization of lactides or lactones, with stannous octoate ($SnOct_2$) and a polyol forming the actual initiator. Whereas linear polymers are obtained in ROP with mono- or difunctional alcohol, the use of a polyol yields highly branched structures. In general, the number of arms in the polymer corresponds to the number of hydroxyl groups in the polyol. The use of glycerol, trimethylolpropane, pentaerythritol, dipentaerythritol, sorbitol, mannitol, *myo*-inositol, sucrose, dendrimers and star-shaped poly(ethylene glycols) has been reported.[19-27] These co-initiators yield star-shaped structures as the branches arise from a single branching point. Comb-shaped polylactide has also been prepared, using linear macrocoinitiators with pendant hydroxyl groups.[28,29] Whether or not all the hydroxyl groups serve to co-initiate the growth of the polyester chain depends mostly on the position of the hydroxyl group and the ratio of monomers to the polyol. In general, primary hydroxyl groups are effective in co-initiating the polymerization, and the number of arms is increased by increasing the ratio of monomers to co-initiator.[21,30,31] A prerequisite for effective initiation activity is the solubility of the co-initiator into the monomers. The poor solubility of high melting point co-initiators, pentaerythritol, dipentaerythritol, *myo*-inositol and β-cyclodextrin has caused difficulties in polymerizations, as reported by Biela *et al.*[17] and Joziasse *et al.*[24]

Dendritic co-initiators derived from 2,2'-bis(hydroxymethyl)propionic acid (bis-MPA) derivatives yielded star-shaped poly(D,L-lactide) (PDLLA), PLLA and PCL with 2, 4, 6 or 12 arms, corresponding to the number of hydroxyls, accurate control of MW and narrow MWD (< 1.1). The hydrodynamic volume of the 12-armed polylactides was considerably lower than for polylactides with fewer arms, due to the more globular shape and conformation.[32] However, the use of poly(amidoamine) dendrimer with a greater number of hydroxyl or amine groups coinitiated the polymerization of fewer arms (16-21) than the number of hydroxyl or amine groups (32 or 28). This was attributed to the change in the density and distribution of coinitiating groups on the surface of dendrimer coinitiator and steric hindrance of attached polylactide chains.[14,26] In addition to star-shaped polymers, dendritic block copolymers have been synthesized by sequential ROP, functionalization and deprotection leading to radial geometry with different layers or generations of PLLA, PCL and various substituted polylactones.[33,34]

In addition to $SnOct_2$ and polyols used in the preparation of branched polyesters, spirocyclic tin initiators can be used in the preparation of branched PLLA, PDLLA, PCL, and poly(β-D,L-butyrolactone) by ROP. Using these initiators, star-shaped PLLAs with a high yield and a very narrow molecular weight distribution (1.04-1.13) were obtained.[15,35,36] Star-shaped PLA's have also been prepared by direct polycondensation of lactic acid with dipentaerythritol, leading to higher MW than in their linear counterparts.[37] Divergent polycondensation has been carried out to obtain resorbable glycerol and succinic acid or lactic acid based dendrimers of generations 1-4 corresponding to MW of 1300-10 700 $g \cdot mol^{-1}$ with MWD 1.02 at highest.[38,39] In addition to pure polyester dendrimers, dendritic-linear poly(ester-ethers) have also been prepared with PEG as the linear polyether block.[40]

All the methods described above were based on the divergent synthesis of branched polyesters propagating outwards from the core. However, branched polyesters have also been prepared by linking suitable polyester blocks. The "arm-first" method, in which the resorbable PCL chains were prepared first by ring-opening polymerization with functional aluminum alkoxides and the arms were then reacted with a multifunctional reagent to yield a three-armed polymer, was described by Tian *et al.*[41] Furthermore, the condensation of AB_2 or AB_4 macromonomers yielded hyperbranched PCL or block copolymers based on DLLA, CL and substituted CLs, as reported by Trollsås *et al.*[33,42-44]

1.3 Crosslinked resorbable polymers

Crosslinked polyesters and polyanhydrides comprise most of the crosslinked resorbable biopolymers. The properties of the networks are governed by the properties of the constituent monomers, but also by the crosslinking density, which is related to the distance between the crosslinking points. The tighter the crosslinking density, *i.e.* the shorter the chain length between the crosslinks, the higher the glass transition temperature and modulus.[45] Crosslinking has been used to obtain resorbable polymers with very high strength or with elastic properties.[46,47] Elastic networks recover after deformation because the crosslinks resist creep effectively. Water-soluble precursors can be used in the preparation of resorbable hydrogels.[48] The preparation of the crosslinked polyesters usually comprises several steps. The more complicated synthesis, as compared to the preparation of thermoplastic polyesters, can be seen as a possibility not only in structural tailoring but also in processing and crosslinking. By using liquid polyester precursors with low viscosity, even *in situ* curing can be applied in the formation of highly crosslinked networks.[49-51] In the following, the properties of the resorbable crosslinked polyesters and polyanhydrides are discussed, together with the methods for their preparation.

The dependence of the properties of the networks on their structure was shown with hard and rigid PDLLA networks crosslinked with isocyanates or with methacrylate functionalization by Storey *et al.*[45,52-54] A tensile strength of almost 70 MPa was obtained with the highest crosslinking density, and by increasing the size of the precursor triols from 960 to 2130 $g \cdot mol^{-1}$ the strength of the network decreased to about 50 MPa. A similar decreasing trend was also observed in tensile modulus and T_g.[45] By using CL or trimethylene carbonate (TMC) as a comonomer with DLLA in the precursors, the ductility of the networks was increased and networks exhibiting high break strains were obtained.[52] In PDLLA networks prepared by crosslinking of methacrylated triols, a tensile strength from 40 MPa to almost 80 MPa was observed.[53] The addition of TMC as a comonomer lowered the tensile modulus and strength and increased the break strain.[54] Anseth and co-workers[49,55] showed that the increase in CL/DLLA ratio made the networks more hydrophobic and thus more resistant to hydrolysis, when methacrylated liquid polyester diols were photocured to networks exhibiting a compressive modulus between 0.1-1.0 MPa. The results of cell seeding experiments suggested that these networks were cellularly compatible and promoted osteoblast attachment. Aoyagi *et al.*[56] prepared P(CL/DLLA) block copolymer networks with the aim of developing thermo-responsive membranes for drug delivery based on the phase changes of the PCL blocks. Permeation of indomethacin through the crosslinked membrane was controlled by reversibly changing the temperature between 20 and 40°C. Furthermore, the hydrophilicity of the polyester networks was controlled using acrylated poly(ether-ester) precursors containing PEG, poly(propylene glycol) or poly(tetramethylene glycol) as the ether block, or by copolymerization of monoacrylated PEG with acrylated polyesters. When the PEG content was high, the precursors were water-soluble and the final photocured networks showed water absorption of 80-95%.[48,57,58]

1.3.1 Networks crosslinked with double bonds

Acrylic, methacrylic, fumaric, maleic and itaconic double bonds have been utililized in the preparation of crosslinkable polyester precursors, which have subsequently been cured by thermal, redox- or photoinitiation to crosslinked polyesters.[30,31,49,59-62] Due to the good reactivity of acrylic and methacrylic double bonds, they have been commonly used in the preparation of resorbable networks. Acrylated or methacrylated poly(α-hydroxy acid) precursors have been prepared by functionalizing hydroxyl terminated oligomers with corresponding acid chloride[48,53-56,63] or by transesterification of high-molecular-weight PDLLA with diacrylate.[64] Networks from poly(propylene fumarates) (PPF) have been extensively studied for use as resorbable bone cements, as reviewed by Peter *et al.*[51] Crosslinkable and injectable compositions of PPF macromers, bioactive filler, porogen and *N*-vinyl pyrrolidone as reactive monomer have been cured at body temperature in the presence of crosslinking initiator. The crosslinking of PPFs has been enhanced by introducing acrylic or epoxy end groups into the oligomers.[46,65,66] Evaluation of the degradation products revealed that the double bond conversion of acrylic double bonds was significantly higher than the conversion of fumaric double bonds.[66] For other double bonds used in the crosslinking of polyesters, the itaconic double bond was shown to be much more reactive than the maleic double bond in thermal curing of functionalized PCL oligomers.[61]

Double bonds can also be located in the side chains or as pendant groups in the crosslinking of PLLA and PCL based network precursors. In one case, the poly(L-lactide-*co*-glycolic acid-*co*-L-serine) contained pendant hydroxyl groups, which were subsequently acrylated and the precursors then cured to glassy and transparent networks.[67] In another case, the pendant amino groups of poly(L-lactic acid-*co*-lysine) were grafted to poly(L-aspartic acid) side chains. The side chains contained carboxylic acid groups, which were partly reacted with methacrylic anhydride. By crosslinking, almost perfectly elastic hydrogels were obtained with swelling behavior controlled by the degree of methacrylation.[68]

Methacrylic double bonds have also been utilized in the preparation of another class of resorbable networks, crosslinked polyanhydrides. Methacrylation of carboxylic diacids such as sebacic acid, 1,3-*bis*(*p*-carboxyphenoxy) propane, or 1,6-*bis*(*p*-carboxyphenoxy) hexane, with methacrylic anhydride, yielded crosslinkable network precursors. These were photopolymerized *in situ* to surface-eroding and biocompatible crosslinked polyanhydrides targeted for orthopaedic applications or controlled release of active agents.[50,69,70] During the degradation of the photocured networks, the anhydride bonds were cleaved, leading to the formation of constituent diacids and water-soluble poly(methacrylic acid) (PMAA). The hydrophilic PMAA chains were characterized to low-molecular-weight oligomers with M_n between 500-3500 $g \cdot mol^{-1}$ by MALDI-TOF and ^1H-NMR, and thus they should not be accumulated in the body's circulatory system.[71] In a recent SEC study, the M_n of PMAA ranged from 58 000 to 410 000 $g \cdot mol^{-1}$,[72] which seems to contradict the earlier MALDI-TOF and NMR results reported by the same Anseth's group.[71] However, the biocompatibility responses in *in vivo* test of the networks and *in situ* curing were acceptable for an orthopaedic biomaterial.[73]

Similarly to crosslinked polyanhydrides, degradation of the polyesters crosslinked with double bonds yields α-hydroxy acids as the degradation products of the corresponding polyester blocks, but also hydrophilic low-molecular-weight polymers such as poly(acrylic acid) and poly(methacrylic acid) formed by the polymerization of the double bonds.[48,49,74] If these polymers are short enough, they should be excreted from the body by the kidneys similarly to low-molecular-weight PEG.[65,71] A threshold MW of 70 000 $g \cdot mol^{-1}$ for the passive excretion of hydrophilic polymers by kidneys has been stated.[65] The safety of using acrylated or methacrylated precursors in the formation of resorbable networks has raised some questions. Generally the networks have been well tolerated,[55,73] but Bruining *et al.*[75] reported that networks originating from dimethylamino ethyl methacrylate and a dimethacrylate crosslinker containing two carbonate groups were intrinsically cytotoxic. Timmer *et al.*[74] found dose-dependent cytotoxic response by characterizing *in vitro* cytotoxicity of the unreacted diacrylated PPF macromers and the degradation products of the networks. However, with dilutions, the acute cytotoxic response was lowered to an acceptable level. The well-cured networks showed no adverse effects when the extraction of toxic products was prevented by a high degree of curing and high crosslinking density.[74]

1.3.2 Other crosslinked polyesters

Other ways to prepare networks include the linking of polyester precursors using isocyanates, acid chlorides, epoxies, ethoxysilanes, and coumarin. In addition, networks can be obtained by direct polycondensation from the monomers or polyester precursors, using crosslinkers in the ROP, or by modifying polymers with peroxides or irradiation. The preparation of resorbable polyurethane networks is based on the reaction between hydroxyl groups of polyester polyols and at least difunctional isocyanate.[45,52,76-79] Even though many different isocyanates have been used in the network formation, only 1,4-butanediisocyanate and L-lysine diisocyanate (ethyl-2,6-diisocyanatohexanoate) are suitable as building blocks for resorbable polyurethanes, since the degradation products, 1,4-butanediamine and L-lysine are naturally present and not harmful to the human organ system.[45,76,80] Carboxylic acid chlorides can also be used as crosslinking agents for polyester oligomers in one pot synthesis.[36,81-84] Linear precursors were polycondensed with trimesoyl chloride, whereas at least trifunctional oligomers were cured with dichlorides such as sebacoyl or terephthaloyl chloride into degradable networks. The networks from random copolymers of CL and DLLA gave a nearly constant release of dexamethasone and 5-fluorouracil, controlled mainly by the hydrolytic degradation of the network.[84]

P(CL/DLLA) oligomers with cycloaliphatic-epoxy and glycidyl ester end groups were synthesized and suggested as precursors to resorbable networks.[85] In addition, the strength of the PPF networks was increased by using diepoxide functionalized PPF oligomers, even though the epoxide groups were known to be difficult to polymerize by radical initiation.[46] Furthermore, triethoxysilane functionalized PCL oligomers were utilized in the preparation of crosslinked hybrid organic-inorganic networks by Tian *et al.*[86-88] PCL oligomers functionalized with (3-isocyanatopropyl)triethoxysilane (IPTS) showed high incorporation into the sol-gel derived tetraethoxysilane based biocompatible network. The use of coumarin as photocurable group was reported in the crosslinking of liquid P(CL/TMC) oligomers by UV to thin films.[89-91]

A tough biodegradable elastomer, with degradation behavior resembling surface erosion with linear decrease in mechanical strength with mass loss, was synthesized by direct polycondensation of glycerol and sebacic acid.[47,92] With molar ratio 1:1, the crosslinking density was low and the MW between the crosslinks was over 18 000 $g \cdot mol^{-1}$. The polymer chains contained free hydroxyl groups, which contributed to mechanical properties by hydrogen bonding and made the polymer surface very hydrophilic.[47] Higher crosslinking density and the use of succinic acid, 1,12-dodecanedicarboxylic acid, 1,18-octadecanedicarboxylic acid or terephthalic acid in polycondensation of glycerol and sebacic acid led to transparent and flexible copolyester networks.[93] Degradable networks with low crystallinity and crosslinking density prepared by polycondensation of PCL-diols with multifunctional aromatic carboxylic acids, namely trimesic acid, pyromellic acid and mellic acid also exhibited elastic properties.[94]

The mechanical properties of polyesters have been significantly improved by using small amounts of crosslinkers, such as *bis*(ε-caprolactone-4-yl), 2,2-*bis*(ε-caprolactone-4-yl)propane, and spiro-*bis*-dimethylene-carbonate in the ROP of lactides, lactones and 1,5-dioxepan-2-one.[95-98] The crosslinkers contained two rings participating in the ROP. A high amount of crosslinker yielded networks with high crosslinking density and low swelling together with decreased crystallinity.[98,99] In addition, 1,2,7,8-diepoxyoctane has been used as a crosslinker in the ROP of cyclic adipic anhydride, yielding crosslinked poly(adipic anhydrides).[100]

Radical or irradiation crosslinking of high-molecular-weight polyesters has been shown to yield polymer networks. PLLA was crosslinked with dicumyl peroxide to achieve high gel contents. The backbone of PLLA was chemically changed in the crosslinking and the decomposition products of PLLA made the polymer ductile, exhibiting almost 200% elongation at break. On the other hand, electron beam irradiation was ineffective in the crosslinking of PLLA, causing polymer degradation and embrittlement.[97] Crosslinking of PCL by gamma rays improved its thermal stability, transparency and heat shrink property.[101] Electron beam radiation of poly(butylene succinate) increased the melt strength and foam stability,[102] whereas peroxide modification contributed to lower crystallinity, increased tensile strength and elongation in poly(butylene succinate) and poly(butylene adipate-*co*-succinate).[103,104]

1.4 Scope of the study

Resorbable and degradable polymers based on lactic acid, lactides and ε-caprolactone have been studied extensively in the Laboratory of Polymer Technology at Helsinki University of Technology.[105-112] In addition to ROP of lactides and/or ε-caprolactone, the chain extending of oligomers has been employed in the preparation of high-molecular-weight polyesters. This thesis explores new possibilities for tailoring these polyesters by branching and crosslinking and discusses the structure-property relations of resorbable polyesters related to this type of molecular architecture. The main target of the thesis work was to apply and develop techniques for the preparation of crosslinked and branched polyesters with different properties to be used in the development of future biomaterials.

The thesis discusses the work reported in the six appended publications. Branching and crosslinking form the two parts of the thesis. Branched polymers were prepared by using an excess amount of chain extender in the linking of PLA oligomers and the polymers were characterized by spectroscopy and rheological measurements as described in publication I. The preparation of highly branched polylactides with new co-initiator compounds, polyglycerines, by ROP has been reported in publication II. The molecular structure of the polymers was confirmed and the effect of these co-initiators on the polymerization of PLLA was studied.

Crosslinking was addressed in publications III-VI. Networks from linear and branched precursors were prepared and the effect of molecular architecture *i.e.* branching, molecular weight and different monomer units in the precursors, on the curing and on the properties of the final networks was studied. Triethoxysilane functionalization and crosslinking were applied in the preparation of resorbable polymers, as reported in publication III. In publications IV-VI the reported crosslinking was based on the commonly utilized polymerization of methacrylic double bonds. On the one hand, high strength was targeted in the preparation of DLLA based networks. On the other hand, highly elastic polymers and creep resistance were the properties sought when using flexible CL/DLLA copolymers as network precursors.

The degradability of the crosslinked polymers was reported together with their preparation in publications III-VI. In publication VI, the target was to enhance the degradation of polyester networks by introducing labile anhydride bonds as weak linkages into the network structure. This approach led to very rapidly degrading, crosslinked PCL, PDLLA, and PLLA based poly(ester-anhydrides).

2 BRANCHED POLYESTERS

Branched polyesters were prepared by two different polymerization methods. The first method employed comprised the polycondensation of lactic acid to poly(lactic acid) oligomers, which were chain linked to high-molecular-weight poly(ester-urethanes).[I] The other method, ring-opening polymerization of lactide and/or ε-caprolactone yielded oligomers and polymers with predicted molecular structure and molecular weight.[II,V] Branching can be used to tailor the flow properties of the polymers. In addition, branching increases the number and the effect of the end groups on the properties of the polymers, and the preparation of branched precursors opens up further possibilities in the network structure tailoring.

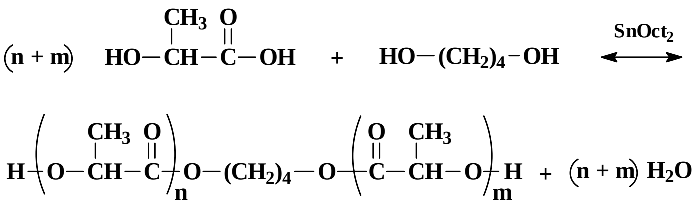
2.1 Lactic acid based poly(ester-urethanes)

Chain extending of lactic acid oligomers offers an alternative route to high-molecular-weight PLA.[12,109-112] In the conventional route to PLA, ROP requires lactide (LA) as a monomer. LA is the cyclic dimer of lactic acid and is formed from poly(lactic acid) oligomers by a back-biting reaction. The same oligomers can be used in the chain extending, producing high-molecular-weight PLA in a more straightforward manner without the need to cleave the formed PLA chains to lactide.[8,12] In the preparation of high-molecular-weight poly(lactic acids), the chain extending studied by our group utilizes the poly(lactic acid) oligomers formed by polycondensation and introduces bonds other than ester bonds into the polymer structure. These bonds are typically urethane bonds obtained by the chain linking of hydroxyl terminated oligomers with diisocyanate or oxamide bonds obtained by extending the carboxyl terminated oligomers with 2,2'-*bis*(2-oxazoline).[109,112] In addition, the combination of both isocyanate and oxazoline chain extending have been applied in the linking of oligomers containing both hydroxyl and carboxyl groups.[113,114]

As reported in publication I, lactic acid based poly(ester-urethanes) (PEU) were prepared from hydroxyl telechelic oligomers by chain linking with diisocyanate with the objective of modifying the rheological properties of the PEU. Rheological measurements are invaluable in the characterization of long-chain branching, as the other methods (NMR, SEC) start to lose their sensitivity with very low levels of branching. Even very rare branching can be seen in rheological measurements in increased zero-shear viscosity, increased shear thinning and high flow activation energy.[115] In addition, rheology becomes important when processing of the polymers is considered. Even though the melt behavior in processing is very complicated, rheological measurements at high shear rates can be used as a tool to estimate the processing behavior of a polymer.[116]

2.1.1 Polycondensation of lactic acid to OH-telechelic oligomers

Lactic acid based oligomers used in publication I had been prepared from L-lactic acid by polycondensation with $SnOct_2$ as a catalyst.[107,117] 1,4-Butanediol had been used in the preparation for molecular weight control and for hydroxyl termination of the oligomers (Figure 1). The properties of the oligomers are shown in Table 1. PLLa-2OH-A had been prepared in a pilot plant whereas a bench-scale reactor had been used in the preparation of PLLa-2OH-B. Even though the feed amounts were the same for both polymerizations, the oligomers differed from each other by the acid value and the amount of formed lactide monomer and butanediol in the oligomers. Acid value served as a measure of carboxyl end groups in the oligomers and a high acid value indicated a poor hydroxyl termination. Both of the oligomers used were totally amorphous, even though L-lactic acid was used as a monomer. This was due to racemization, which led to the formation of D-structures and loss of stereocontrol of poly(lactic acid) chains.[107]



$$(n+m)\ HO-\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-OH + HO-(CH_2)_4-OH \xleftrightarrow{SnOct_2}$$

$$H\left(O-\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}\right)_n O-(CH_2)_4-O\left(\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_3}{|}}{C}H-O\right)_m H + (n+m)\ H_2O$$

Figure 1. Polycondensation of lactic acid with 1,4-butanediol.

Table 1. Properties of the oligomers prepared by polycondensation of L-lactic acid.[I]

	SEC			*^{13}C-NMR*			*Titration*	*DSC*
Oligomer	***M_n*** *($g\cdot mol^{-1}$)*	***M_w*** *($g\cdot mol^{-1}$)*	***MWD***	***M_n*** *($g\cdot mol^{-1}$)*	***LA*** *(%)*	***BD*** *(%)*	***Acid value*** *($mgKOH\cdot g^{-1}$)*	***T_g*** *(°C)*
PLLa4-2OH-A	5300	11700	2.2	3900	2.0	1.5	3.7	36
PLLa4-2OH-B	4900	8900	1.8	3600	4.0	2.3	2.3	36

2.1.2 Chain extension of lactic acid oligomers with diisocyanate

The chain extension of hydroxyl telechelic lactic acid oligomers was utilized in the preparation of high-molecular-weight PLA. As shown in Figure 2, the linking of hydroxyl telechelic oligomers with diisocyanates was based on the reaction of OH-groups with isocyanates. In the preparation of lactic acid based poly(ester-urethanes), 1,6-hexamethylene diisocyanate (HMDI) has mainly been used as a chain extender.[106,109-111] However, PEU prepared with HMDI has shown an ecotoxicological effect in a recent biodegradation study by Tuominen *et al.*[118] When HMDI was substituted by 1,4-butane diisocyanate (BDI), no toxicological effect was detected and the poly(ester-urethane) degraded in a compost into nontoxic degradation products. Furthermore, the use of BDI and lysine diisosyanate have also been reported to be acceptable in the preparation of poly(ester-urethanes) and poly(urethane-ureas) for biomedical applications by Storey *et al.*[45] and Pennings and co-workers.[76,80] The preparation of PEU in publication I was based on the use of HMDI as a chain extender, but with current knowledge BDI could be used to substitute HMDI without major changes in the polymerization behavior.[118,119]

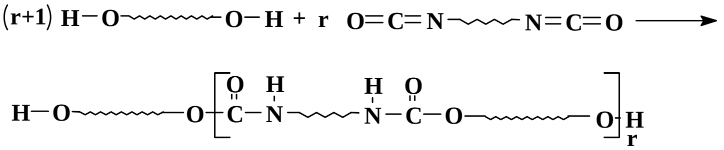


Figure 2. Chain extending of hydroxyl telechelic oligomers with diisocyanate.

Degradable, lactic acid based poly(ester-urethanes) were polymerized by chain linking of lactic acid oligomers. Different polymer structures were obtained by using different ratios of chain extender, HMDI, to the oligomers (NCO/OH ratio). The NCO/OH ratios used were from 1.05/1 to 1.35/1 (Table 2). By using a higher NCO/OH ratio, the higher M_w was obtained. This resulted a broadening of the MWD of the polymers, as the M_n was not as clearly increased with the amount of chain extender. The reason for broadening of the MWD was the formation of very large molecules with long-chain branching, confirmed by NMR and rheological measurements. As additional proof of the branching, the branching reactions eventually led to crosslinked polymers, if even higher ratios of NCO/OH were used.

Table 2. Properties of poly(ester-urethanes).[1]

	Polymerization			*SEC*			*DSC*
Polymer	***Oligomer***	***NCO/OH***	***Time*** *(min)*	***M_n*** $(g \cdot mol^{-1})$	***M_w*** $(g \cdot mol^{-1})$	***MWD***	***T_g*** *(°C)*
PEU-A-120	PLLa4-2OH-A	1.20	25	38 000	84 000	2.2	49
PEU-A-130	PLLa4-2OH-A	1.30	35	44 000	153 000	3.5	52
PEU-A-135	PLLa4-2OH-A	1.35	40	40 000	113 000	2.8	46
PEU-B-110	PLLa4-2OH-B	1.10	10	45 000	104 000	2.3	48
PEU-B-120	PLLa4-2OH-B	1.20	35	47 000	135 000	2.9	46
PEU-B-130	PLLa4-2OH-B	1.30	40	57 000	179 000	3.2	48

By comparing the M_n of the oligomers and polymers, it was found that the maximum extent of the linking reaction was about ten oligomer units. After that, the terminal groups became rare and their contacting each other was unlikely. The effect of the acid value of the oligomers was seen in the chain linking in the required NCO/OH ratio, polymerization time and in the molecular weights obtained. The oligomer PLLa4-2OH-A with higher acid value required a higher NCO/OH ratio and a longer time and the molecular weights obtained were smaller than those obtained using the oligomer PLLa4-2OH-B with a better hydroxyl termination. Thus the acid end groups in the oligomer impeded the chain linking reaction. Recently a method to reduce the acid value of the PLA oligomers by using 2,2'-*bis*(2-oxazoline) (BOX) was reported by Kylmä *et al.*[113] BOX reacted with carboxyl end groups and effectively reduced their amount.

The NMR analysis of the polymers gave insight into the progress of the linking reaction. In ^{13}C-NMR spectra, the resonance due to hydroxyl termination of the oligomers disappeared at an early stage of the polymerization and later on the resonance from the NCO group disappeared. During the polymerization with high NCO/OH ratio, previously uncharacterized peaks were formed close to the peaks originating from HMDI units and urethane linkage. These peaks were attributed to the branches in PEU, because they have not been characterized in linear PEUs with narrow MWD. The analysis of the ^{13}C-NMR results led to the conclusion that NCO terminated oligomers and polymers were formed with excess of diisocyanate and that later these reactive compounds formed the final polymers. The NCO terminated oligomers and polymers retained the reactivity of the isocyanates and they were able to react with urethane bonds leading to allophanates or by themselves in a self-addition reaction.[120] These are possible side reactions that would lead to branched poly(ester-urethanes) as shown in Figure 3. If these reactions were allowed to proceed even further with a higher ratio of NCO/OH, then polymers with insoluble portions were obtained and the polymers were partially or fully crosslinked. By crosslinking, the thermoplasticity of the PEUs was lost. The branching and crosslinking of PEU was in accordance with the findings of Kylmä and Seppälä,[111] who showed that an increase in the amount of diisocyanate in the chain linking of poly(lactic acid-*co*-ε-caprolactone) oligomers led to crosslinked structures. In addition, they proposed that excess isocyanate reacted with moisture, urethane and urea groups, leading to urea, allophanate, and biuret, respectively, as the side reactions in the preparation of PEU. The reactions in the chain linking of PLA oligomers have been covered in detail by Tuominen.[121]

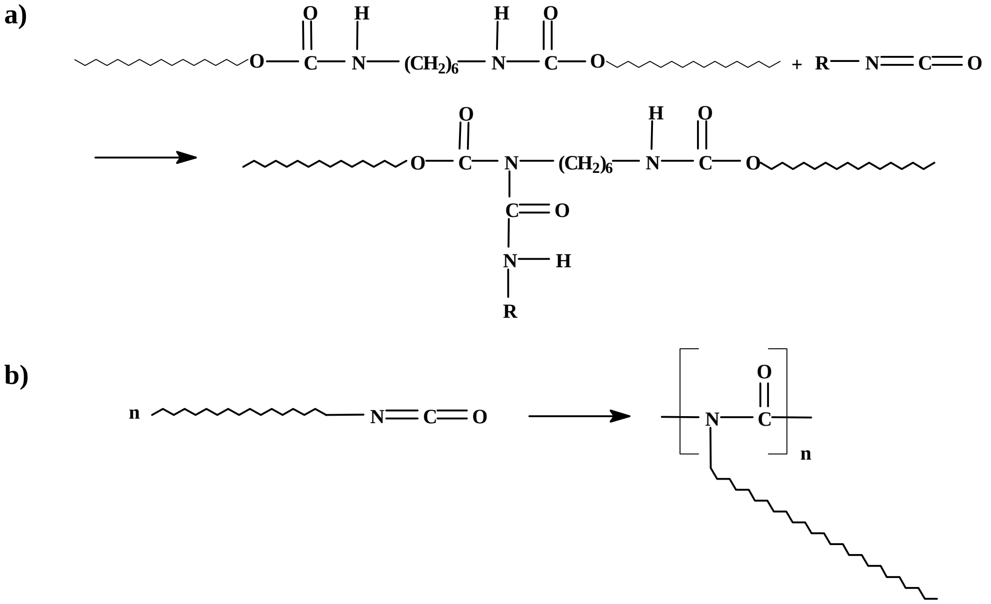


Figure 3. Formation of branches by (a) allophanate bonding or (b) isocyanate self-polymerization.

2.1.3 Rheological characterization

The rheological characterization was carried out with a dynamic rheometer giving information about the molecular structure of the polymers and with a capillary rheometer to extend the shear rate range. Prior to this study, the rheology of lactic acid based poly(ester-urethane) has been surveyed by Härkönen *et al.*[122,123] They reported that PEU is thermoplastic and can be processed with conventional processing equipment. In addition, the presence of long-chain branching was proposed as an explanation for the improved elasticity achieved in PEUs with broad molecular weight distributions. Recently, the rheological properties of polylactides have been studied extensively.[18,124-126] The molecular structure of lactic acid based poly(ester-urethanes) is close to the structure of polylactides. The main difference between PEU and PLLA is that PEU has an amorphous nature originating from the racemization of the lactic acid units during polycondensation and the introduction of urethane bonds into the molecular structure.

The PEUs with different molecular weight distributions were polymerized in order to evaluate and enhance the rheological properties for processing. In dynamic measurements complex viscosities at the lowest shear rate were highest for the sample with the broadest MWD, but the sample showed greatest shear thinning with the increasing shear rate. The higher viscosity level could be attributed to the increased M_w, in addition to the broad MWD and long-chain branching. The broadening of the MWD and long-chain branching are both known to increase the viscosity at low shear rates and increase the shear thinning,[116] and thus the effects were hard to distinguish from each other. As can be seen in Figure 4(a), the broadening of the MWD from 2.3 to 2.9 did not affect the storage and loss moduli (G' and G") and complex viscosity (η^*) as much as the further broadening to 3.2 obtained with the highest amount of chain extender used in the chain linking. This behavior suggests that as the MWD approaches 3 the long-chain branching starts to significantly affect the rheological behavior. In particular, this was seen in a higher storage modulus, which demonstrated the improved elasticity of PEU-B-130.

Capillary measurements supported the observations obtained with the dynamic rheometer. The capillary data (Figure 4(b)) showed that shear thinning was most pronounced for the samples with broad MWD, and the properties of PEU could be modified without visible deterioration of flow properties by varying the MWD of the polymer in a range between 2 and 3.5. The temperature dependence of the PEU can also be seen in Figure 4(b). The steady shear viscosity decreased by almost a factor of ten when the temperature was raised by 20°C. A similar change was detected in complex viscosity using the dynamic rheometer. Furthermore, the capillary data was used to correlate the behavior of PEU in extrusion coating of paper to its rheological properties and finally to molecular structure.[127]

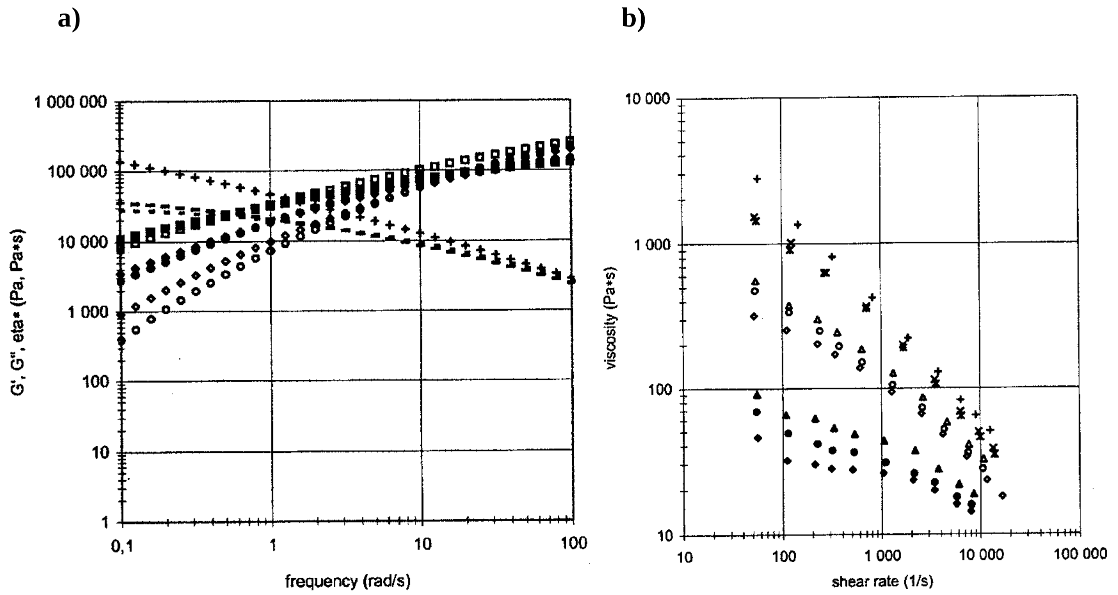


Figure 4. Characterization of PEU-B samples by (a) dynamic rheometer 120°C (PEU-B-110 (G' ○, G" ●, η* -), PEU-B-120 (G' ◇, G" ◆, η* –), and PEU-B-130 (G' □, G" ■, η* +)) and (b) capillary rheometer at different temperatures (viscosity of PEU-B-110 (140°C ✱, 160°C ◇, 180°C ◆), of PEU-B-120 (140°C ✕, 160°C ○, 180°C ●), and of PEU-B-130 (140°C +, 160°C △, 180°C ▲)).[1]

The poor thermal stability of PEU was a problem during rheological characterization. The high temperatures employed caused irreversible changes in the structure of the polymer, which can be seen in the collapse of complex viscosity and storage modulus. However, molecular weights measured by SEC did not show any significant change. The drop in G' and η*, accompanied by practically unaffected M_w, could be explained by degradation due to terminal cleavages in which small molecules such as lactide were formed. This was confirmed by ^{13}C-NMR, which revealed an increase in the lactide content in the polymer during the rheological characterization. These small molecules then served to lubricate the sample, with a marked effect on the rheological properties.

The rheological properties described above were lower than for corresponding polylactides[124,125] or for PEUs described by Härkönen *et al.*[122,123] However, PLLAs polymerized by the ring-opening polymerization of lactide had higher molecular weights and narrower MWD than PEUs obtained by chain extending. The exponential correlation of viscosity to M_w can be used to explain the difference between the PEUs and PLLAs. The higher viscosities in the earlier results with PEUs may be due to the effect of partially crosslinked polymers; some of the PEUs studied earlier had very broad molecular weight distribution curves[123] and, as shown in this study, crosslinking started as the MWD exceeded 3.5.

2.2 Polylactides and polylactones prepared through ring-opening polymerization

Ring-opening polymerization is a commonly used method to produce resorbable polyesters. The commonly used initiator, stannous octoate forms the actual initiating species with an alcohol[128-131] and by using a polyol as a co-initiator the molecular structure of the polymers can be controlled. With the ratio of co-initiator to monomer, the molecular weight of the polymers can also be controlled from oligomers to high-molecular-weight polymers. In addition to the homopolyesters, ROP has been used to produce copolyesters.[12] In the thesis, there were three different targets related to the preparation of branched polyesters by ROP. The first part deals with the initiation activity *i.e.* the number of hydroxyl groups initiating the polymerization in proportion to all hydroxyl groups in the co-initiator. This was evaluated for commonly used 1,4-butanediol and pentaerythritol, and two novel co-initiators, polyglyclycerines. The second part addresses the effect of co-initiators with different numbers of hydroxyl groups on the polymerization of high-molecular-weight PLLA. In the third part, star-shaped copolymers of DLLA and CL were prepared and characterized. Furthermore, the oligomers were subsequently used as precursors in the preparation of polyester networks with controlled molecular architecture.

2.2.1 Poly(D,L-lactide) oligomers with different numbers of arms

Different types of polyols were used as co-initiators with $SnOct_2$ to yield linear and branched polylactides (Figure 5), as reported in publication II. 1,4-butanediol (BD) contains two hydroxyl groups yielding linear oligomers and pentaerythritol (2,2-bis(hydroxymethyl)-1,3-propanediol, PERYT) is a star-shaped co-initiator with four primary hydroxyl groups. In addition to BD and PERYT, polyglycerines (polyglycerols from Daicel Chemical Industries, PGL-06 and PGL-10), were used as novel co-initiators with the aim of obtaining polyesters with even more branched structures than with PERYT. Polyglycerines are oligomers of glycerol with either 6 or 10 glycerol units on average. Thus they contain 8 or 12 hydroxyl groups, which theoretically can initiate the ring-opening polymerization and produce highly branched polymers. By using co-initiators with different numbers of hydroxyl groups, the aim was to systematically study the initiation activity of the co-initiators, but also to prepare oligomers with different numbers of arms to be used as network precursors.

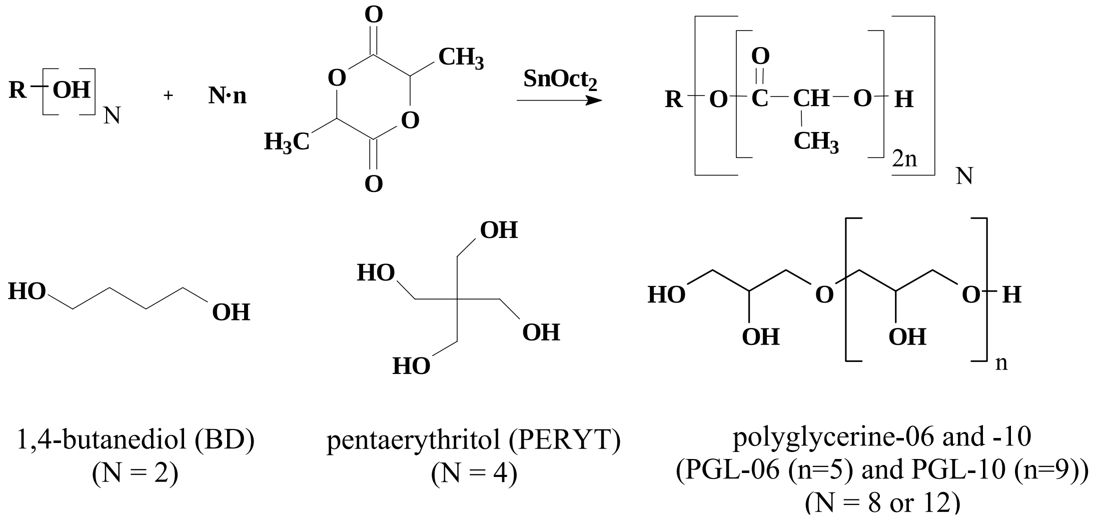


Figure 5. Ring-opening polymerization of lactide in the presence of co-initiators.

The polymerizations of D,L-lactide were carried out in bulk at 160°C for 3 hours in a batch reactor (Desing Integrated Technology) designed for agitation of viscous materials. The poor solubility of PERYT has caused non-quantitative co-initiation in some previous studies,[17,24] but no such problems were faced due to the use of a high polymerization temperature. The initiation activity of the co-initiators was evaluated from ^{1}H-NMR spectra by direct and indirect methods. In the direct method, the peak integral due to the methylene proton adjacent to the unreacted hydroxyl group in the co-initiator was compared with the peak integral of the methylene proton adjacent to the reacted hydroxyl group in the co-initiator.[21] The application of this method was successful for oligomers co-initiated with BD and PERYT. In the corresponding spectra, the above-mentioned peaks were distinct. This method yielded 2.0 initiating hydroxyl groups in BD, as predicted, and 3.7-3.8 in PERYT as shown in Table 3. Similar initiation activity has been previously reported for pentaerythritol.[21,31] According to Kim *et al.*[21], the initiation activity increased with increasing ratio of monomer to PERYT, and the formation of four-armed polymers occurred when the ratio of monomer to co-initiator reached 32. Lang and Chu[31] reported that in PCL oligomers prepared with PERYT all four possible structures were present when the monomer to co-initiator ratio was 5/1, *i.e.* PERYT co-initiated the growth of one, two, three and four polymer chains. By increasing the ratio to 40, the average number of initiating hydroxyls was over 3, but still some unreacted hydroxyls were present in the co-initiator core.

The indirect method for evaluating the initiation activity was based on the calculation of the average chain length of polylactide arms. The calculation of chain length was carried out with two different approaches; it was based on the ratio of either the hydroxyl proton or the terminal methine proton in the polylactide chain to methine protons in the polylactide chain. The average chain length was then compared with the theoretical chain length calculated with assumptions of full monomer conversion and the initiation of polymerization from all hydroxyl groups of the co-initiator. The assumption of full monomer conversion was shown to be valid, as the amount of lactide monomer in the oligomers was found to be 1.6-2.9% by

NMR. By comparing the number of initiating OH-groups in the BD and PERYT obtained by the direct and indirect method it seems that the direct method and indirect method based on the methine protons correlate well. Thus, the indirect method could also be used to evaluate the initiation activity of the co-initiators.

Table 3. Initiation activity of the hydroxyl groups in co-initiators.[II]

Co-initiator		***Initiating –OH***			
	Lactide / co-initiator	***Theoretical***	***Calculation via the characteristic peaks of co-initiator***	***Calculation via the ratio of measured to theoretical chain lengths***	
	(mol/mol)		$-C\underline{H}_2$-*OH* / $-C\underline{H}_2$-*O-polymer*	-O$\underline{H}$	-C$\underline{H}$-OH
BD	100/3	2	2.0	1.8	2.0
	100/5	2	2.0	1.9	2.0
	100/10	2	2.0	1.9	2.0
PERYT	100/5	4	3.8	3.4	3.4
	100/8	4	3.7	3.5	3.9
	100/12.5	4	3.7	3.5	3.8
PGL-06	100/1	8	-	6.2	9.9
	100/3	8	-	5.9	9.5
	100/5	8	-	4.0	8.0
PGL-10	100/5	12	-	8.3	11.1

The direct measurement of the initiation activity of the hydroxyl groups in polyglycerines was unsuccessful, as the co-initiators yielded broad peaks in the ^{1}H-NMR spectra and the peaks due to protons adjacent to the unreacted and reacted hydroxyl groups in the co-initiators could not be assigned. In addition, the peaks due to PGL overlapped partly with resonance of the terminal methine proton in the polylactide chain. Thus, the initiation activity calculated by comparing the peak integral of hydroxyl proton of terminal lactide unit to the peak integral of methine proton in the polylactide chain gave the most reliable results for PGLs. The initiation activity for PGL-06 was found to be 4.0-6.2 and for PGL-10 8.3. On average, the PGLs contained 8 and 12 OH-groups, of which 2 were primary and 6 or 10 secondary. It seems that the secondary OH-groups did not initiate the polymerization as efficiently as the primary OH-groups. This can be compared with the initiation activity of glycerol, which contains two primary and one secondary hydroxyl group. Lang *et al.*[30] showed that the initiation activity of glycerol approached 3 when the ratio of monomer to co-initiator was 40/1 in the ROP of CL. It can be concluded that a substantial proportion of secondary hydroxyl groups in polyglycerines took part in the initiation, and that their participation increased as the ratio of monomer to co-initiator increased, which is in accordance with the behavior of glycerol as co-initiator.

2.2.2 High-molecular-weight polylactides with different numbers of arms

The objective of the polymerizations reported in publication II was to evaluate systematically the effect of the number of the hydroxyl groups in the co-initiators on the polymerization rate and to optimize the polymerization time needed for the formation of high-molecular-weight polylactides. Previously, Joziasse *et al.*[24] have shown that the polymerization of star-shaped poly[(trimethylene carbonate)-*co*-(ε-caprolactone)] was faster than the polymerization of linear copolymer. The polymerizations of L-lactide to high-molecular-weight PLLA were carried out with SnOct$_2$ at 200°C. Co-initiators employed contained between 1 and 12 hydroxyl groups and benzoyl alcohol was used in addition to BD, PERYT and polyglycerines.

The preparation of high-molecular-weight polymers showed that the polymerization rate increased with the number of hydroxyl groups in the co-initiator, as shown in Figure 6. The initial slope of the molecular weight curve increased steadily from the polymerization where no co-initiator was used to the polymerization with polyglycerines. Along with the faster polymerization, higher molecular weight polymers were obtained.

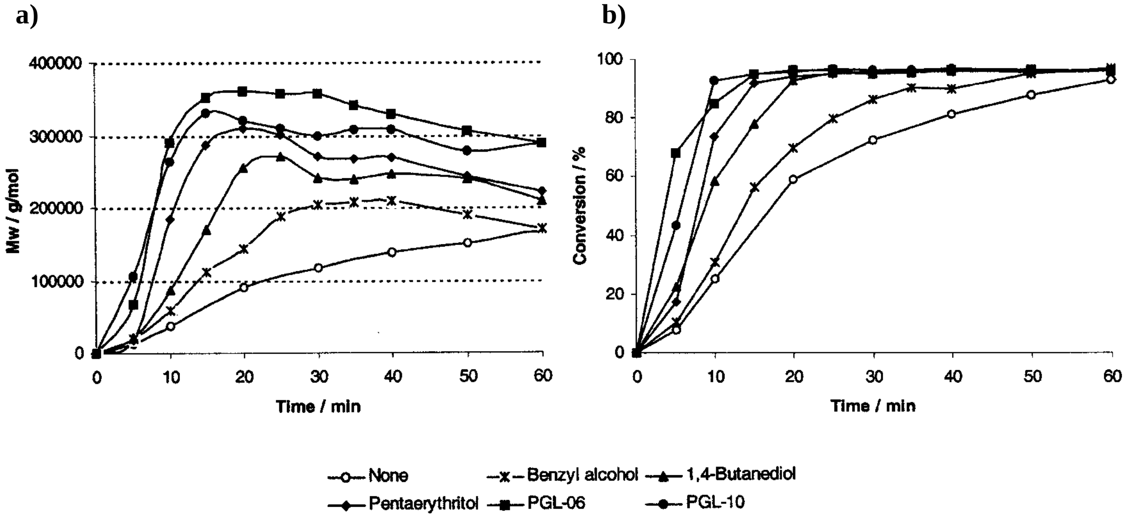


Figure 6. Dependence of (a) M_w and (b) conversion on time for different co-initiators.

Faster polymerization can also be seen in the monomer conversion shown in Figure 6(b). High hydroxyl group content in the polymer did not cause a drop in the conversion level or enhanced backbiting during extended polymerization, even though the hydroxyl groups have previously been reported to participate in backbiting reaction.[132,133] With time, all the co-initiators yielded conversions of about 95%, and the conversions stayed on the same level to the end of the polymerization. These results suggest that the hydroxyl content of the co-initiator affects the polymerization rate but not the monomer/polymer equilibrium.

The use of co-initiators with different numbers of hydroxyl groups yielded PLLA's with different numbers of branches. With the evaluated initiation activities of the co-initiators in mind, it is clear that highly branched polymers with a number of arms exceeding 6 and 8 were obtained with polyglycerines. With a higher number of arms the PLLA chains were shorter, which could be seen in the slightly lower melting temperatures (165-172°C) of the branched polymers in comparison with the linear ones (172-173°C).[II] This is in accordance with other studies in the highly branched PLLAs[14,15] and could be used as additional proof of increased branching in the high-molecular-weight poly(L-lactides).

2.2.3 P(CL/DLLA) copolymers

The ring-opening polymerization was also used in the preparation of star-shaped poly(ε-caprolactone/D,L-lactide) copolymers with theoretical molecular weights of 6 300-26 000 $g \cdot mol^{-1}$. The objective was to prepare oligomers of different sizes and chain stiffness to be used as network precursors. The rigidity of the polymer chains was altered by changing the comonomer ratio; polylactides are known to be hard and rigid, PCL is a tough, ductile polymer and the copolymer with an equal portion of the comonomers is rubbery.[108] The polymerizations were carried out in bulk at 160°C for 6 hours with pentaerythritol as a co-initiator. The oligomers were characterized by SEC and DSC in addition to NMR.

The results of the ^{13}C-NMR characterization of the oligomers are shown in Table 4. The amount of co-initiator and the monomer composition were altered in the polymerizations. Different oligomers are denoted with the CL/DLLA ratio, the amount of PERYT used in the preparation per 100 units of monomers and the number and type of the end groups. Due to the use of pentaerythritol as a co-initiator, the polymers had 4 OH-groups.[21,II] The amount of the co-initiator determined the molecular weight; the greater the amount of co-initiator the lower the molecular weight. In addition, narrow molecular weight distribution was obtained with the use of the co-initiator.[V] As shown in Table 4, the monomer composition evaluated by ^{13}C-NMR coincided well with the feed ratios, and the conversions of the monomers were high: no ε-caprolactone monomer residues were detected, indicating complete conversion for CL, and the conversion for DLLA was over 97%. Overlapping of the resonances prevented the use of ^{1}H-NMR in the determination of the molecular structure of the oligomers; thus ^{13}C-NMR was used in oligomer characterization.

The average sequence lengths of the caproyl and lactidyl units (L_{CAP} and L_{LA}) were calculated by the method of Kricheldorf and Kreiser[134] and compared with theoretical values for completely transesterified random structures in which a second mode of transesterification was allowed, *i.e.* the formation of lactyl units from lactidyl units.[135] The measured sequence lengths of the copolymers were close to the values of completely transesterified structures. In 50/50 mol-% copolymers, the average CL and DLLA blocks were 2.1 monomer units long or less, while for the completely transesterified structure the value was 1.5. Thus, it can be concluded that highly random copolymer structures were obtained. Moreover, the average lengths of sequences seemed to increase slightly with decreasing co-initiator content. In part, this could be due to the slower polymerization and transesterification rate with lower co-initiator content.

Table 4. Results of ^{13}C-NMR characterization of P(CL/DLLA) oligomers.[V]

Oligomer	*Theor.* **M_n**	*Composition*[a] **(^{13}C-NMR / In feed)**			*Conversion* **(^{13}C-NMR (%))**		*Average sequence length* **(^{13}C-NMR / Theoretical[b])**	
	(g·mol^{-1})	***CL***	***DLLA***	***PERYT***	***CL***	***DLLA***	L_{CAP}	L_{LA}
P(CL/DLLA30/70)-1-4OH	13 640	27.6/30	72.4/70	0.7/1.0	>99	97.6	1.4/1.4	3.4/2.8
P(CL/DLLA50/50)-0.5-4OH	25 950	47.3/50	52.7/50	-[c]/0.5	>99	98.0	1.9/1.5	2.1/1.5
P(CL/DLLA50/50)-1-4OH	13 040	47.9/50	52.1/50	1.1/1.0	>99	98.5	1.7/1.5	1.9/1.5
P(CL/DLLA50/50)-2-4OH	6 590	48.3/50	51.7/50	1.7/2.0	>99	98.3	1.6/1.5	1.8/1.5
P(CL/DLLA70/30)-0.5-4OH	24 760	68.2/70	31.8/30	-[c]/0.5	>99	98.4	2.9/2.2	1.4/0.9
P(CL/DLLA70/30)-1-4OH	12 450	68.2/70	31.8/30	1.2/1.0	>99	98.9	2.6/2.2	1.2/0.9
P(CL/DLLA70/30)-2-4OH	6 290	69.6/70	30.4/30	1.7/2.0	>99	98.7	2.4/2.2	1.2/0.9
P(CL/DLLA90/10)-1-4OH	11 850	92.0/90	8.0/10	0.5/1.0	>99	>99	6.3/5.5	0.8/0.6
P(CL/DLLA100/0)-1-4OH	11 550	100/100	-	0.7/1.0	>99	-	-	-

[a] units per 100 monomer units (CL + DLLA)

[b] sequence length for completely transesterified structure

[c] under detection limit

In all oligomers containing DLLA, terminal lactyl units (^{13}C-NMR: 66.7 ppm, ^{1}H-NMR: 4.33 ppm) rather than caproyl units (^{13}C-NMR: 62.3 ppm, ^{1}H-NMR: 3.61 ppm) were found by NMR. This is in accordance with the findings of Lang and Chu,[136] but the result differs from many of those reported earlier for copolymerizations of ε-caprolactone and lactide.[96,134,135,137-142] Lactide has been reported to polymerize more readily than ε-caprolactone, resulting in blockier structures with terminal caproyl units, and the conversion of CL has been lower than the conversion of LA. The differences in the polymerizations in publication V were probably due to the use of a high polymerization temperature, extended polymerization time, and effective agitation throughout the polymerization. These factors, in addition to the hydroxyl groups introduced from the co-initiator, all favor a high transesterification rate and the formation of highly transesterified structures.

3 CROSSLINKED RESORBABLE POLYESTERS

Crosslinked resorbable polymers present another class of biopolymers, in addition to the thermoplastics. By crosslinking, polymers with a new set of properties can be obtained. This part of the thesis focuses on the preparation of crosslinked resorbable polyesters from oligomers based on lactides, ε-caprolactone and their copolymers, and on the properties of the obtained polymer networks. Hydroxyl telechelic oligomers with different molecular architectures were functionalized with crosslinkable functionalities and subsequently crosslinked. The mechanical and thermal properties of the networks were addressed in order to explore the structure-property relations in the networks. In addition, the hydrolytic degradation of the polymer networks was examined.[III-VI]

3.1 Functionalization and crosslinking

Crosslinkable oligomers were obtained with different functionalization methods. In all cases, hydroxyl telechelic oligomers were used in the preparation of crosslinkable network precursors. The functionalizations employed and subsequent crosslinking reactions are presented in Figure 7. The first approach (A) included the synthesis of triethoxysilane functional network precursors and their crosslinking with acid catalyst.[III] The second approach (B) was to apply the reaction of methacrylic anhydride with hydroxyl terminated oligomers.[IV,V] The third route (C) was based on acid termination and subsequent methacrylation of carboxyl end groups by methacrylic anhydride, leading to the formation of anhydride bonds in the network precursors.[VI] Table 5 summarizes the functionalizations and crosslinkings performed. To explore the effect of the size and branching of the oligomeric network precursors on the curing and the properties of the networks, oligomers with different molecular architectures were used.

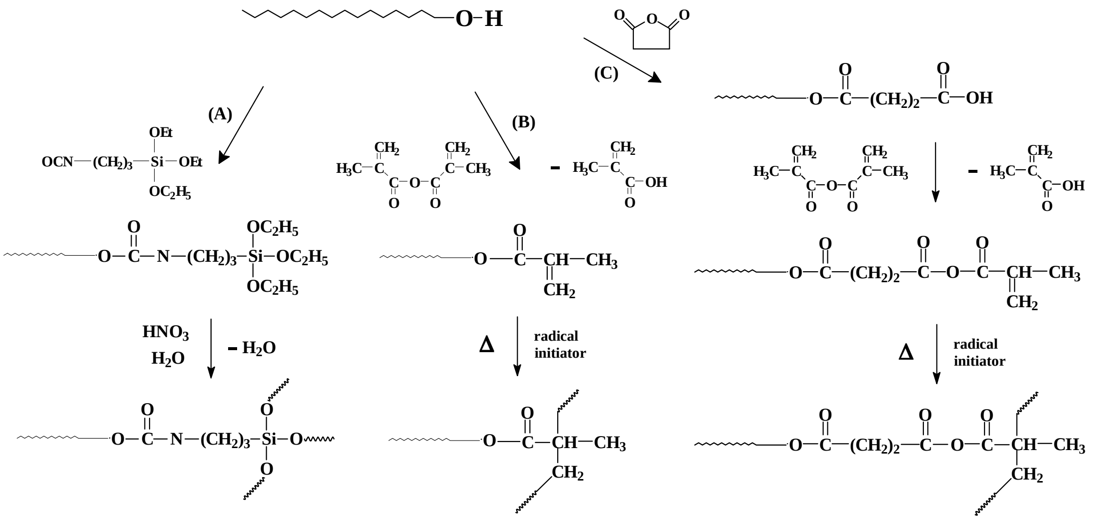


Figure 7. Functionalization and crosslinking reactions used in the thesis.

Table 5. Summary of the functionalization and crosslinking methods employed in the thesis.[III-VI]

		Functionalization			*Crosslinking*		
Functionalization	***Oligomer***	***T*** *(C°)*	***Time***	***DS*** *(%)*	***T*** *(C°)*	***Time***	***Gel content*** *(%)*
Alkoxysilane	PDDLA-OH	160	10 min	79 - 95	60 - 120	76 h	82 - 100
Methacrylation on –OH	PDDLA-OH	120	3 h	86 - 100	90	24 h	85 - 100
	P(CL/DLLA)-OH	160	3 h	> 95[a)]	90	24 h	90 - 98
	PCL-OH	160	3 h	> 95[a)]	90	24 h	97
Acid functionalization	PDLLA-OH	160	6 h	85 - 92	-	-	-
	PLLA-OH	160	6 h	88 - 93	-	-	-
	PCL-OH	160	3 h	98 - 99	-	-	-
Methacrylation on -COOH	PDLLA-COOH	60	24 h	92 - 98	120	1 h	N.A.
	PLLA-COOH	60	24 h	94 - 97	120	1 h	N.A.
	PCL-COOH	60	24 h	93 - 97	120	1 h	N.A.

[a)] not quantitatively measured due to relatively low amount of end groups.
N.A. not analyzed.

The functionalized oligomers were analyzed by SEC, ^{1}H- and ^{13}C-NMR, FTIR and DSC. The main features of the characterization were to confirm the proposed structures and to calculate the degree of substitution (DS) in the functionalized oligomers. Thermal properties of the network precursors were of importance, since they were used in the determination of the suitable crosslinking temperature range. The main principle in choosing the curing temperature was to use as low a temperature as possible, whilst ensuring that efficient curing was achieved.

Most of the characterizations available for polymers are carried out with polymer solutions. The crosslinked polymers are not soluble, and thus only the characterization methods not requiring solubility could be used. DSC was used to evaluate the increase in T_g accompanied with crosslinking. In addition, the possible enthalpy changes due to crystallinity or residual reactivity were evaluated. From the spectroscopic methods, FTIR was invaluable revealing the changes in reactive groups. Gel content measured by the extraction proved the formation of three-dimensional networks and swelling behavior revealed differences in crosslinking density.

3.1.1 Oligomers as building blocks for networks

Table 6 summarizes the molecular weights and the glass transition temperature of the linear and branched oligomers used in the preparation of polymer networks. The molecular architecture of the oligomers was controlled by the amount and type of co-initiator. Butanediol was used in the preparation of linear oligomers, star-shaped oligomers with four arms were obtained with PERYT and polyglycerines yielded oligomers with an even higher number of arms.[II] The amount of the co-initiator controlled the size of the oligomers. All together, three different monomers; D,L-lactide (DLLA), L-lactide (LLA) and ε-caprolactone

(CL), were used to prepare networks with different properties. For the summary of the thesis, the denotation of the oligomers was unified. The denotation shows the monomer(s) followed by the amount of co-initiator used and the number and type of the end groups. The OH-terminated oligomers were subsequently functionalized and used as network precursors.

Table 6. Properties of the hydroxyl telechelic oligomers.[II,V,VI]

		Theor.	*SEC*			*DSC*
Sample	***Co-initiator***	***M_n*** *($g\cdot mol^{-1}$)*	***M_n*** *($g\cdot mol^{-1}$)*	***M_w*** *($g\cdot mol^{-1}$)*	***MWD***	***T_g*** *(°C)*
PDLLA3-2OH	BD	4 890	8 200	10 600	1.3	38
PDLLA5-2OH	BD	2 970	5 100	6 300	1.2	30
PDLLA10-2OH	BD	1 530	2 500	3 200	1.3	19
PDLLA5-4OH	PERYT	3 020	4 000	5 400	1.4	34
PDLLA8-4OH	PERYT	1 940	2 800	3 300	1.2	27
PDLLA12.5-4OH	PERYT	1 290	1 700	2 200	1.2	13
PDLLA1-8OH	PGL-6	14 860	15 700	19 800	1.3	42
PDLLA3-8OH	PGL-6	5 260	5 400	6 600	1.2	30
PDLLA5-8OH	PGL-6	3 340	3 500	4 300	1.2	23
PDLLA5-12OH	PGL-10	3 640	3 000	3 700	1.2	18
PLLA5-2OH	BD	2 970	5 800	6 900	1.2	36
PLLA10-2OH	BD	1 530	2 700	3 100	1.2	22
PCL5-2OH	BD	2 370	5 200	7 200	1.4	-62
PCL10-2OH	BD	1 230	2 500	3 000	1.2	-66
P(CL/DLLA30/70)-1-4OH	PERYT	13 640	23 000	29 000	1.3	6
P(CL/DLLA50/50)-0.5-4OH	PERYT	25 950	39 000	51 000	1.3	-12
P(CL/DLLA50/50)-1-4OH	PERYT	13 040	21 000	26 000	1.3	-13
P(CL/DLLA50/50)-2-4OH	PERYT	6 590	11 000	14 000	1.3	-15
P(CL/DLLA70/30)-0.5-4OH	PERYT	24 760	41 000	56 000	1.3	-35
P(CL/DLLA70/30)-1-4OH	PERYT	12 450	22 000	28 000	1.3	-37
P(CL/DLLA70/30)-2-4OH	PERYT	6 290	11 000	14 000	1.4	-38
P(CL/DLLA90/10)-1-4OH	PERYT	11 850	24 000	31 000	1.3	-51
P(CL/DLLA100/0)-1-4OH	PERYT	11 550	23 000	31 000	1.3	-58

The theoretical M_n was calculated from the feed ratio of the monomer to the co-initiator and it was shown to correspond very well with the M_n calculated by end group analysis from the ^{13}C-NMR spectrum.[VI] The theoretical M_n was subsequently used in the calculation of the amounts of the functionalization agents used. By comparing the theoretical M_n with the M_n obtained by SEC, it is clear that SEC overestimated the molecular weights significantly for linear oligomers. The deviation from the actual M_n was due to the fact that polystyrene standards were used for calibration. With increasing branching, the hydrodynamic volume of the oligomers decreased when compared to linear oligomers with the same nominal M_n. This resulted in a smaller difference in the theoretical and measured M_n values in the branched oligomers than in their linear counterparts. The MWD was narrow for all polymerizations, leading to networks with rather uniform distances between the crosslinks. Furthermore, the length of the polyester arms seemed to control the T_g of the PDLLA oligomers, whereas the CL/DLLA ratio was dominant in determining the T_g of the P(CL/DLLA) copolymers.

3.1.2 Triethoxysilane functionalized oligomers

The reactions of alkoxysilanes were applied in the crosslinking of polyesters in publication III. First, alkoxysilane moieties were introduced into the hydroxyl terminated poly(D,L-lactide) oligomers by the reaction of isocyanate with an OH-group leading to a urethane bond. (3-isocyanatopropyl)triethoxysilane was used as the functionalization agent. Tian *et al.*[86] have reported the synthesis of triethoxysilane functionalized PCL oligomers with solvent and catalyst. The functionalized oligomers have been used with tetraethoxysilane as building blocks in solvent-based crosslinking of hybrid networks. However, in the chain linking of lactic acid oligomers, isocyanates have been shown to keenly react with hydroxyl groups at an elevated temperature.[109,I] The high reactivity was used in the functionalization of PLA oligomers with IPTS with the aim of avoiding the use and removal of solvents and catalysts.

A stoichiometric amount of IPTS was allowed to react with hydroxyl terminated oligomers at 160°C for 10 min. The reaction time at this temperature was sufficient to lead to degrees of substitution of 79-95% and with longer reaction times the possibility of premature crosslinking increased. The DS was analyzed by comparing the peak integrals due to the hydroxyl termination before and after the reaction in ^{1}H-NMR spectra. In addition to the loss of hydroxyl termination, the resonances characteristic of ethoxysilane groups were formed during the functionalization. By SEC, the functionalization was found to increase the molecular weights of the oligomers slightly, with one exception, but no crosslinking was observed. In general, the T_g of the PDLLA oligomers was decreased by triethoxysilane functionalization.

Crosslinking reactions of triethoxysilane-functionalized oligomers were comprised of the hydrolysis of alkoxysilanes to silanol groups and condensation of the silanols. The crosslinking was acid catalyzed and it was carried out at an elevated temperature. The above-mentioned reactions could be carried out at ambient temperature,[86,143] but in order to lower the viscosity of the functionalized oligomers and thus to facilitate mixing of the catalyst, the temperature was raised above the T_g of the oligomers. The increase in temperature also contributed to better removal of water in the condensation of silanols, leading to more efficient network formation. The functionalized oligomers were cured first for 4 hours at 60, 90 or 120°C, depending on the composition, and then post cured for an additional 72 hours at 90°C. Crosslinking typically yielded networks with high gel contents (94-100%). Finally, the success of network formation was seen in the mechanical properties of the samples. Early vitrification during curing made the samples practically insoluble and increased the T_g values, but the final mechanical strength was obtained only after the final curing.

3.1.3 Methacrylated oligomers

The concept of using oligomers with different molecular architectures as network precursors was also used with crosslinking chemistry other than that for alkoxysilanes. As reported in publications IV and V, methacrylic double bonds were introduced into the oligomers to make them crosslinkable through radical polymerization. In addition to the same PDLLA oligomers used in the networks based on alkoxysilane crosslinking, copolymers of D,L-lactide and ε-caprolactone were used in order to broaden the range of mechanical properties of the networks. Methacrylation was carried out with methacrylic anhydride (MAAH) instead of the commonly used methacryloyl chloride. Hydroxyl telechelic PDLLA oligomers were reacted with double the stoichiometric amount of MAAH at 120°C for 3 hours. PCL and P(CL/DLLA) oligomers had higher molecular weights and viscosity. Thus, a higher reaction temperature of 160°C was used. After the reaction, the PDLLA oligomers were purified by distillation, and PCL and P(CL/DLLA) oligomers by precipitation.

The hydroxyl groups of the oligomers were effectively end-capped to methacrylate groups according to ^{1}H- and ^{13}C-NMR. The degree of substitution ranged from 86-100%. In FTIR spectra, the hydroxyl absorbance disappeared and the double bond absorbance (1629 cm^{-1}) formed during functionalization. Premature polymerization of the double bonds during functionalization of the double bonds was ruled out by the fact that only a slight increase in M_n and M_w was observed and the MWD remained 1.2-1.3. In linear oligomers, the degree of substitution was 86-87%, but the highest DSs (close to 100%) were obtained with branched oligomers. This difference in the outcome of the functionalization was probably due to the high absolute amounts of MAAH serving also as a diluent in the functionalization of branched oligomers.

Crosslinking of the methacrylated oligomers was mainly carried out with thermal initiation. Dibenzoyl peroxide was used to initiate the crosslinking at 90°C, where all the functionalized oligomers were in the liquid state and the peroxide could be added to the reaction mixture. The curing time used was 24h. These curing conditions yielded polymer networks with gel contents ranging from 85-100% and the T_g of the networks increased significantly from the T_g of the oligomers. The branched oligomers were found to yield networks with higher gel contents. This could be attributed to the fact that the linear oligomers were not as completely functionalized with MAAH as their branched counterparts. In addition, the branched oligomers contained a higher number of crosslinkable double bonds and the corresponding networks were tightly crosslinked. In the crosslinking of branched oligomers it was not so crucial whether or not all the double bonds reacted in the curing, whereas in the linear oligomers both of the double bonds needed to react in order to contribute to crosslinking.

In order to carry out the crosslinking at a lower temperature, the viscosity of the reaction mixture was lowered with reactive monomer, as described in publication IV. Dimethacrylated butanediol (BD-Me_2) was chosen because it has a low viscosity and its structure is rather similar to the oligomers used. With 10 wt.% of BD-Me_2, curing was also feasible at 60°C and with 20 or 30 wt.% networks were also obtained at 37°C. By curing at 37°C high gel contents were achieved, but the polymers still contained reactive double bonds, as shown by the residual reactivity in the DSC scan. This was due to the fact that the curing temperature was lower than the T_g of the network. According to Burdick *et al.*[49], this reduces the mobility of the reacting species and makes the achievement of high conversions more difficult. The crosslinking initiator was chosen so that its reactivity was suitable at the desired temperature. The crosslinking was initiated by thermal initiation with dibenzoyl peroxide at 90°C, and by redox-initiation involving 2-butanone peroxide as initiator and cobalt naphthenate as promoter used at 60°C and 37°C. In addition, visible light was also used to initiate the polymerization. By using camphorquinone and ethyl-4-*N,N*-dimethylaminobenzoate, a network with high gel content (95%) was obtained at room temperature.

3.1.4 Acid functionalization followed by methacrylation

The structure of the crosslinked polyesters was modified by introducing hydrolytically labile anhydride bonds into the network precursors, and thus into the final polyester networks. In the preparation, the hydroxyl end groups of the PLLA, PDLLA and PCL oligomers were first converted to terminal carboxylic acid groups. This was carried out with 50% excess of the stoichiometric amount of succinic anhydride at 160°C. Different reaction times were used for different oligomers. PCL oligomers were functionalized in 3 h, because the terminal hydroxyl group in the PCL chain is a primary hydroxyl and thus its reactivity with cyclic anhydride is good.[144] The lactide-based oligomers, in which the terminal hydroxyl group is in the secondary position, required a longer reaction time of 6 h. Despite the shorter reaction time, the DS for functionalized PCL oligomers was 98-99%, while with polylactides a DS of 85-93% was reached. The higher reactivity of the hydroxyl groups connected to CL compared to the secondary hydroxyls in the terminal LA unit has been found previously in the functionalization of hydroxyl telechelic polyesters with maleic anhydride by Lang and Chu.[31,136]

Crosslinkable oligomers that contained anhydride bonds were formed from carboxylic acid functional oligomers with methacrylic anhydride, similar to the preparation of methacrylated diacids as precursors for crosslinked polyanhydrides and poly(ether-anhydrides).[50,145] In the functionalization, MAAH reacted with acid groups instead of hydroxyl groups. Substitution was carried out for 24 hours at 60°C with an excess of MAAH also serving as a solvent. After purification, the functionalized oligomers were characterized and the DS was found to be 92-98%. According to the NMR and FTIR, the network precursors contained anhydride bonds and crosslinkable methacrylate groups and the proposed structure was confirmed. The crosslinking was performed with dibenzoyl peroxide at 120°C. Curing changed the sticky or waxy oligomers to a hard polymeric specimen, showing considerable swelling behavior in CH_2Cl. In addition, the crosslinking increased the T_g.

3.2 Properties of crosslinked polyesters

The main focus of this thesis was to prepare crosslinked polymers with different properties in order to understand how the crosslinked structure affects the properties of the polymer. This part of the thesis addresses the effect of molecular architecture on the properties of the crosslinked polymers. PDLLA based networks were hard and rigid and were used to reveal the effect of the length of the polyester blocks between the crosslinks.[III,IV] The P(CL/DLLA) copolymers were elastic and showed how the comonomer ratio can be used to control both the mechanical and the degradation characteristics of the networks.[V]

3.2.1 Hard and rigid PDLLA based networks

PDLLA based networks prepared through alkoxysilane or methacrylate functionalizations retained the inherent mechanical properties of the thermoplastic PDLLA. They were hard and rigid, as shown in Table 7. The networks exhibited compressive yield strain from 4-8%, compressive yield strength of 18-120 MPa and modulus of 600-2800 MPa, depending on their molecular structure. For thermoplastic PDLLA, Grijpma *et al.*[146] have described rather ductile behavior with compressive strain of over 30% and a compressive stress over 100 MPa. In tensile testing, PDLLA mainly fails by crazing, but crazing is suppressed under compression and thus the brittleness of PDLLA observed in tensile testing is changed to ductile behavior under compression.[146] The results shown in Table 7 indicate that crosslinking increased the compressive modulus and lowered the compressive strain of the PDLLA.

Methacrylation as a functionalization method yielded crosslinked PDLLAs with higher strength and modulus than in networks obtained with the alkoxysilane functionalization. The methacrylated networks PDLLA5-2, PDLLA5-4, PDLLA5-8 and PDLLA5-12 were prepared with equal amounts of co-initiators, BD, PERYT, PGL-06 and PGL-10 respectively, containing different numbers of OH groups. By comparing them, the increase in branching of the oligomer can be seen to lead to higher compressive strength and modulus. This was due to the increase in reactive double bonds in the precursors and the resultant higher crosslinking density of the networks. In addition, the T_g was increased with branching due to the more restricted movement of the chain segments.

Table 7. Compressive and thermal properties of the crosslinked PDLLA prepared via triethoxysilane and methacrylic anhydride functionalization.[III, IV]

	Crosslinking based on alkoxysilanes				*Crosslinking based on methacrylation on -OH*			
	DSC	*Compressive testing*			*DSC*	*Compressive testing*		
Sample	T_g	***Yield strength***	***Modulus***	***Yield strain***	T_g	***Yield strength***	***Modulus***	***Yield strain***
	°C	*(MPa)*	*(GPa)*	*(%)*	°C	*(MPa)*	*(GPa)*	*(%)*
PDLLA5-2	43	18 ± 2	0.6 ± 0.2	4.1 ± 0.5	42	78 ± 2	1.8 ± 0.3	6.5 ± 0.4
PDLLA10-2	39	21 ± 4	0.6 ± 0.1	5.6 ± 0.7	40	72 ± 3	1.8 ± 0.1	5.2 ± 0.2
PDLLA5-4	52	81 ± 3	2.3 ± 0.1	4.4 ± 0.1	46	91 ± 5	2.0 ± 0.1	6.7 ± 1.0
PDLLA8-4	59	55 ± 3	1.8 ± 0.1	4.0 ± 0.2	49	120 ± 4	2.8 ± 0.1	5.0 ± 0.1
PDLLA12.5-4	-	-	-	-	51	107 ± 14	2.5 ± 0.2	5.5 ± 0.4
PDLLA3-8	66	71 ± 7	2.2 ± 0.2	4.0 ± 0.2	-	-	-	-
PDLLA5-8	64	51 ± 3	1.2 ± 0.1	7.5 ± 1.2	56	101 ± 8	2.6 ± 0.1	4.7 ± 0.3
PDLLA5-12	-	-	-	-	54	116 ± 3	2.4 ± 0.2	5.8 ± 0.3

By keeping the co-initiator content equal, increased branching reduced the length of the PDLLA blocks; in other words, the distance between the crosslinks was reduced. Storey *et al.*[45] have shown that the poly(ester-urethane) networks based on PDLLA triols with M_n of 1000-2000 g·mol^{-1}, had higher strength with decreasing M_n of the precursors. By comparing the networks PDLLA5-4 and PDLLA8-4, it can be seen that the compressive strength and modulus increased when the precursor M_n decreased from about 3000 g·mol^{-1} to 2000 g·mol^{-1}. However, a further reduction of precursor M_n and the PDLLA ester block length, as in PDLLA12.5-4, started to decrease the strength and modulus again when compared to PDLLA8-4. It seems that the mechanical properties were not solely a function of the distance between the crosslinks, but depended also on the inherent properties of the constituent lactide blocks, methacrylate blocks and the co-initiator units. In PDLLA12.5, the average length of the PDLLA block was very short (2.0 LA units), and the molar ratio of repeating units originating from methacrylic functionalization to lactide units was 50/100.

Overall, branched oligomers yielded networks with higher yield strength and modulus than the linear precursors. Networks from linear precursors have crosslinking points only originating from crosslinking sites, whereas the branched oligomers already contain crosslinking points in their structure in addition to the final crosslinking bonds formed during curing. The length between the crosslinks was equal to the length of the polyester arm in networks based on branched oligomers, but in networks based on linear precursors the length between the crosslinks was twice the length of the polyester arm. The longer distance between the crosslinking points was probably one of the reasons why the linear oligomers showed lowest compressive strength and modulus. Another factor contributing to this was the difference in the structure of the co-initiators. The BD used in linear oligomers is a linear four-carbon chain, producing inherently more flexible structures than pentaerythritol with four arms or polyglycerines with even more arms. This was seen in lower T_g of the networks prepared with

BD. In addition, the T_g of the networks prepared with BD decreased when shorter polyester precursors were used. Every precursor molecule contained one BD unit, and in shorter precursors the proportion of BD to DLLA units was higher. A similar trend in T_g has been found in networks containing oligo(ethylene glycol) and oligolactide blocks. Kricheldorf and Fechner[36] stated that the decrease in T_g with decreasing size of the precursors was probably attributed to a higher portion of oligo(ethylene glycol) blocks with inherently lower T_g.

The highest compressive strengths for networks based on the methacrylated oligomers were around 120 MPa in PDLLA8-4 and PDLLA5-12. PDLLA12.5-4 from methacrylated oligomers also gave a high strength of 107±14 MPa and its strength was further enhanced by the addition of dimethacrylated butanediol (BD-Me_2) as reactive monomer. The addition of 10 wt.% of BD-Me_2 was sufficient to increase the strength to 119±6 MPa, but further addition of reactive diluent was not found to increase the strength significantly further. The addition of reactive monomer increased the crosslinking density, contributing to the higher strength obtained. By using reactive monomer, the curing temperature could even be lowered to room temperature, but the compressive strength of the networks was found to decline with decreasing curing temperature. The decrease in compressive strength could be attributed to less efficient curing at lower temperatures due to the restricted movement of molecules. The higher curing temperatures allowed the crosslinking reactions to reach full conversion and high mechanical strength.

3.2.2 Elastic P(CL/DLLA) copolymer networks

In contrast to hard and rigid PDLLA based polymer networks, the range of mechanical properties achievable by crosslinking was extended to soft and elastic polymers by using P(CL/DLLA) copolymer precursors. The thermoplastic copolymers of ε-caprolactone and lactides have been extensively studied and their properties can be controlled by changing the stereoisomer of lactide and the content and distribution of the comonomers, in addition to the MW of the copolymers. The properties of block copolymers differ from those of random copolymers.[11] Even a small increase in average CL and LLA sequence lengths has been shown to increase the tensile strength by 100%.[137] The random copolymers of CL and DLLA with 55/45 molar composition have been shown to be very soft and even tacky.[108] In addition, they creep heavily, even at 37°C, due to their low T_g causing them to lose their form. However, these copolymers have been shown to have good diffusion properties and they have been described as promising candidates for controlled drug delivery by Rich *et al.*[147] As a crosslinked polymer, P(CL/DLLA) with 50/50 molar ratio has shown a nearly constant release of 5-fluorouracil and dexamethasone over several weeks, controlled mainly by the degradation of the matrix, as reported by Kricheldorf *et al.*[84]

The polymer networks prepared were based on star-shaped P(CL/DLLA) oligomers prepared with PERYT as co-initiator, as reported in publication V. The oligomers differed from each other by their molecular weight and CL/DLLA ratio. All the networks with their mechanical properties and the swelling factor (SF) describing the increase in sample volume when immersed in dichloromethane, are shown in Table 8. The SF of networks showed that lower molecular weight oligomers yielded networks with a higher crosslinking density, *i.e.* the distance between the crosslinks was smaller. The T_g values supported the swelling results by indicating a higher T_g for samples with a shorter distance between the crosslinkings, even though the corresponding precursors exhibited lower T_g values.

Table 8. Tensile properties, swelling factor and T_g of cured networks.[V]

	Tensile testing			*Swelling*	*DSC*
Sample:	***Modulus*** *(kPa)*	***Strength*** *(kPa)*	***Strain*** *(%)*	***SF***	T_g *(°C)*
P(CL/DLLA30/70)-1-4	5210 ± 160	9700 ± 1300	190 ± 20	3.4	16
P(CL/DLLA50/50)-0.5-4	250 ± 30	720 ± 140	350 ± 40	6.3	-7
P(CL/DLLA50/50)-1-4	640 ± 50	1120 ± 240	190 ± 30	4.2	-6
P(CL/DLLA50/50)-2-4	1430 ± 30	1350 ± 170	110 ± 10	2.5	-4
P(CL/DLLA70/30)-0.5-4	580 ± 10	1090 ± 40	260 ± 10	5.3	-32
P(CL/DLLA70/30)-1-4	1200 ± 40	1000 ± 60	100 ± 10	3.2	-30
P(CL/DLLA70/30)-2-4	2290 ± 50	1070 ± 170	50 ± 10	2.2	-27
P(CL/DLLA90/10)-1-4	1600 ± 80	1290 ± 180	100 ± 20	3.3	-53
P(CL/DLLA100/0)-1-4	25200 ± 8700	5100 ± 1100	80 ± 40	2.8	-55

By comparing the mechanical properties of the networks prepared with different sizes of the oligomers and 50/50 or 70/30 molar ratio of CL/DLLA, it can be seen that the tensile properties were also affected by the length of the copolymer blocks (Table 8); the increase in length decreased the tensile modulus and increased the maximum strain. This is also illustrated in Figure 8, showing the stress-strain curves for 3 copolymer networks with 50/50 molar ratio, differing only by their P(CL/DLLA) block length. By increasing the amount of pentaerythritol used in the oligomer synthesis, the precursors were smaller and networks with higher crosslinking density were obtained. This led to an increase in the tensile strength of the polymers and a decrease in the break strain. The increased crosslinking density was also accompanied by a greater slope in the stress-strain curve, which meant that tensile modulus was also increased. These results are in accordance with the findings of Storey *et al.*[45] with poly(ester-urethane) networks, where the effect of the polyester block length on the properties of the polymer networks has been discussed.

The ratio of CL/DLLA was found to have a pronounced effect on the properties of the networks, as shown in Figure 9. In general, the properties followed the trends of the thermoplastic P(CL/DLLA) copolymers. Crosslinked PCL showed properties rather similar to thermoplastic PCL, even though the crystallinity and the mechanical strength were not as high as in its linear counterpart. The PCL homopolymer network contained 20% of the crystalline phase. From the copolymer networks, only P(CL/DLLA-90/10)-1-4 contained a small amount of crystallinity, 6%. Even though crosslinking restricted the movement of molecules, there were still PCL blocks sufficiently long to crystallize. When the DLLA portion was increased to 50 mol-%, the networks showed higher strain values and decreased tensile strength and modulus. With a further increase in DLLA content in the copolymer networks, the stiffness of the polylactide chains started to increase the modulus and strength. The change was also observed in T_g, which increased from -55°C for PCL homopolymer to 16°C for P(CL/DLLA30/70)-1-4), according to the DSC scans. Similar trends in T_g and modulus on the CL/DLLA ratio in copolymer networks have been shown previously by Davis *et al.*[55] and Storey *et al.*[79]

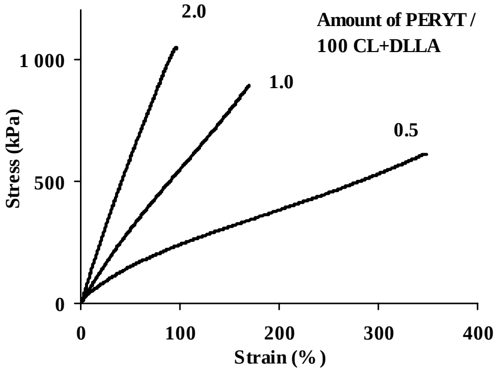


Figure 8. Stress-strain curves for copolymer networks prepared with different co-initiator amounts in the oligomer synthesis (CL/DLLA ratio 50/50 mol-%, under tension to failure).[V]

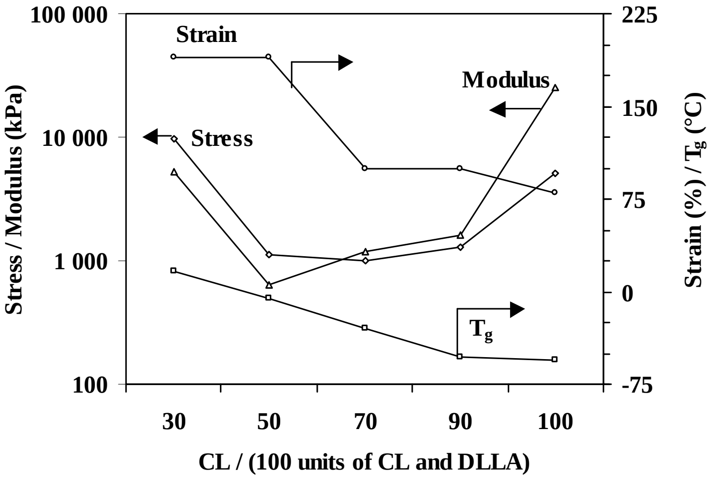


Figure 9. Tensile stress, modulus and strain at break and T_g of the polymer networks as a function of the amount of CL per 100 monomer (CL + LA) units.[V]

Characteristic features of the crosslinked polymers were the creep resistance and the lack of flow region above T_g, or after the melting of the crystalline segments. DMA showed that none of the networks exhibited viscous flow at high temperatures, whereas their thermoplastic counterparts are viscous liquids. Instead, the networks remained at the rubbery plateau throughout heating, from above the T_g to 130°C. At the plateau, the tan δ was 0.2-0.3, indicating that the storage modulus was 3-5 times as high as the loss modulus. This meant that the energy change required for displacement was mainly reversible.

The creep resistance was analyzed with tensile testing apparatus with two different experimental set-ups. In Figure 10, the results of a stress relaxation test for P(CL/DLLA100/0)-1-4 and P(CL/DLLA90/10)-1-4 (a) and of a cyclic tensile testing to 50% strain for P(CL/DLLA90/10)-1-4 (b) are shown. The stress relaxation test revealed a small change in relative stress immediately after the start of the experiment, but the change in stress relaxation flattened almost completely for the copolymer network with 90/10 CL/DLLA molar ratio. PCL homopolymer network showed some stress relaxation, but it still retained over 70% of the initial stress for almost 17 h measurement. After the measurement, the tested copolymer specimens recovered their original dimensions quickly. In crosslinked PCL, the recovery was not as fast and complete as with the copolymer network. The stress-strain behavior in cyclic tensile testing to 50% strain for P(CL/DLLA90/10)-1-4 was practically identical, despite the number of cycles. This clearly proved the elastic nature of the networks.

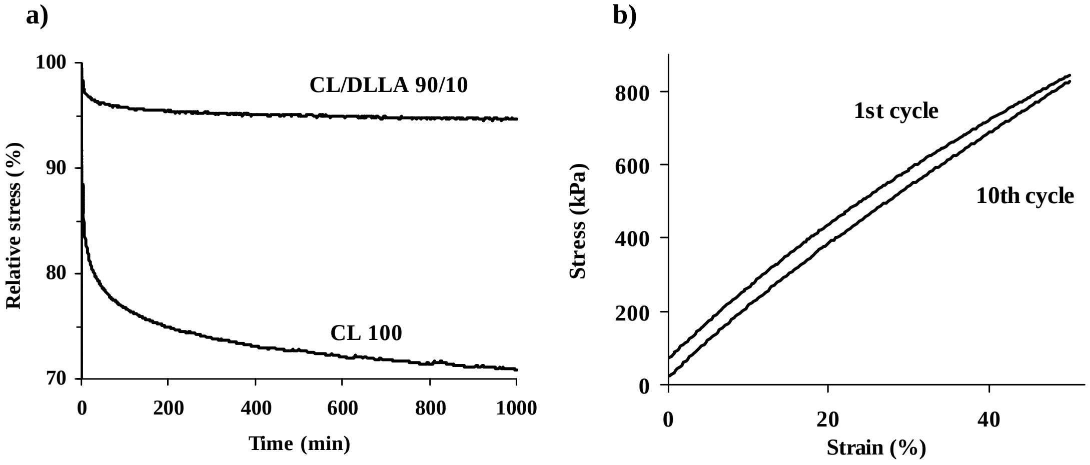


Figure 10. (a) Stress relaxation for two crosslinked P(CL/DLLA) (ratio of CL/DLLA shown above the curves, CL/DLLA 90/10 stretched to 50% strain and CL100 to 25% strain) and (b) cyclic stress-strain curves to 50% strain for P(CL/DLLA-90/10)-1-4.

3.3 Degradation of crosslinked polymers

The evaluation of the hydrolytic degradation is of importance when the preparation and characterization of degradable polymers are considered. Thus, in publications III-VI the degradation of the prepared networks was addressed. From the networks based on alkoxysilane functionalized PDLLA, the crosslinked polymer prepared with 100/5 of D,L-lactide to pentaerythritol (PDLLA5-4) was chosen as a representative sample. From the networks obtained with methacrylate functionalization, PDLLA12.5-4 was used in the hydrolysis study. It was prepared with and without reactive monomer (30 wt.%). As reported in publication V, all the copolymer networks were characterized, showing the differences in the degradation due to different polyester block length between the crosslinks and CL/DLLA ratio. Publication VI focused on enhancement of the degradation rate of the PCL, PDLLA and PLLA homopolyester networks by introducing anhydride bonds highly susceptible to hydrolytic degradation. All the degradation tests were carried out in a phosphate buffer solution (PBS) at pH 7.0 and 37°C. In addition to the water absorption and mass loss, changes in mechanical and thermal properties were monitored as a function of immersion time.

3.3.1 Mass loss and strength retention in polyester networks

The degradation tests of PDLLA based networks reported in publications III and IV are summarized in Figure 11, which shows a) the water absorption and remaining mass and b) compressive modulus and yield strength. The difference in the samples was in the functionalization used, the length of the PDLLA blocks and whether or not reactive monomer was used in the crosslinking of methacrylated oligomers.

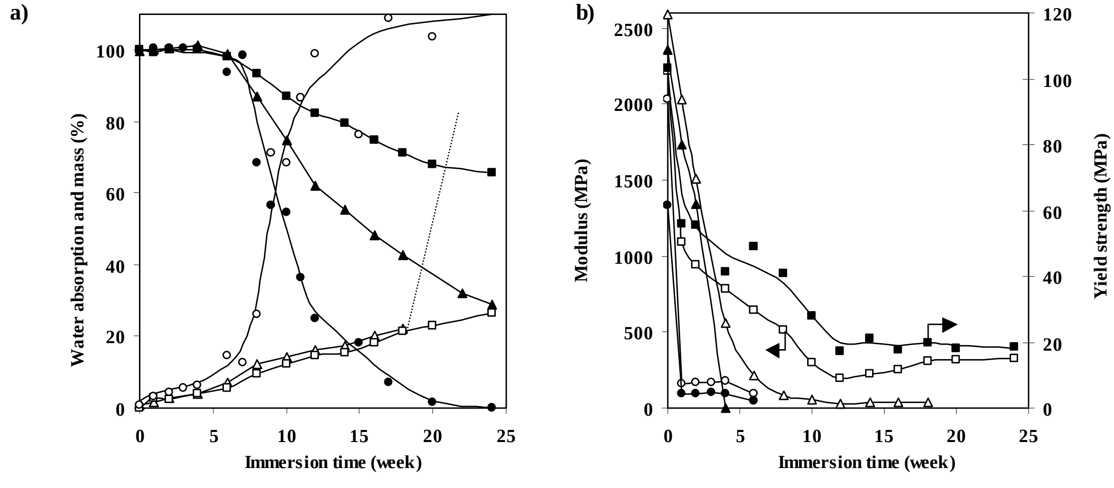


Figure 11. (a) Water absorption (open symbols) and remaining mass (closed symbols) and (b) compressive modulus (open symbols) and yield strength (closed symbols) for PDLLA5-4 crosslinked via triethoxysilane functionalization (●) and via methacrylation without reactive monomer (▲) and with 30 wt.% reactive monomer (■). The standard deviations ranged 1-5% in mass changes and 5-20% in mechanical properties.[III, IV]

All the PDLLA networks started to show mass loss after 6 weeks. After that, the network prepared with triethoxysilane functionalization exhibited the highest rate of degradation. The pronounced increase in mass loss after 6 weeks was accompanied by a sudden increase in water absorption. The networks prepared from methacrylated oligomers showed a steady increase in the water absorption up to 18 weeks, when the water absorption in PDLLA from methacrylated oligomer without reactive monomer abruptly increased. The addition of 30 wt.% of reactive monomer increased the resistance of the network to hydrolytic degradation, and even after one year the mass of the sample had declined only by 44%.

The strength retention of the above mentioned polymer networks during the hydrolysis test was followed by compressive testing of the specimen in the wet state. The polymer network prepared through alkoxysilane functionalization lost most of its strength during the first week in immersion, after absorbing 5% of water. It seems that water served as a plasticizer for this network. The networks prepared through methacrylate functionalization also started to lose their mechanical properties early in the hydrolysis, but the mechanical properties could be tested for 18 weeks. The stress-strain behavior of the immersed samples became more rubbery: the specimen showed no yield or break point and thus only the compressive modulus could be obtained. The addition of reactive monomer made the network more stable to hydrolysis, retaining part of its strength for one year.[IV]

It is clear that the degradation of the networks occurred through a bulk mechanism. The specimens absorbed water, which started to cause random chain scission of ester bonds in the polymer chain and the degradation was first seen in the drop in mechanical properties followed by increased water absorption and mass loss. In the network prepared with alkoxysilane functionalized oligomers, the degradation eventually led to hollow specimens because of the autocatalytic effect. This meant that the degradation proceeded with a higher rate inside the specimen than near the surface, due to acidic degradation products. This was first seen in decreased T_g values inside the specimen and finally in the hollow specimen.[III]

The effect of comonomer content and crosslinking density on the hydrolytic degradation was evaluated in publication V, where the mass changes and retention of the tensile modulus were monitored as a function of immersion time. In the copolymer networks, the copolymer ratio governed the degradation rate, as shown in Figure 12. Networks with high CL content showed practically no mass change during 12 weeks and their water uptake was low, whereas at the same time the network prepared with 70% of DLLA had lost almost 40% of its mass. The high lactide content in the copolymer corresponded to the increased mass loss and water absorption. The degradation of the CL rich networks was seen in their tensile modulus, which was lowered to almost half of the original modulus in 12 weeks, and in increased crystallinity. During the immersion at 37°C, the crystallinity started to increase and the shape of the melting endotherm changed, as shown in Figure 13. The new melting peak formed at 45°C, close to the melting endotherm of the PCL polymer blocks. It seems that immersion served as annealing for the networks, which increased the crystallinity. In addition, the degradation might have led to networks with slightly less restrictions for movement of the molecule segments and thus the PCL blocks could align more easily and form crystallites. Copolymer networks with a 50/50 ratio of CL/DLLA retained their shape, even though they lost their mechanical properties in 6 weeks. By comparing the form stability and retention of the modulus of the crosslinked copolymers with their linear counterparts, a marked improvement was achieved by crosslinking. Thermoplastic random P(CL/DLLA) copolymers with a similar molar ratio have been shown to creep heavily and their tensile properties could not be tested after immersion at 37°C.[148,149]

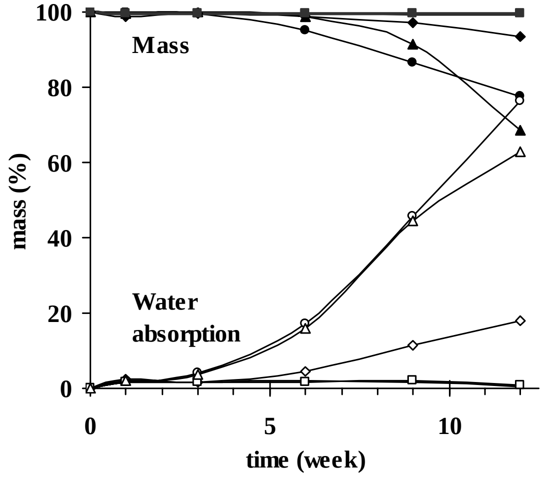


Figure 12. Water absorption (open symbols) and mass (closed symbols) for P(CL/DLLA)1-4 with ratio of CL/DLLA 100/0 (-), 90/10 (■), 70/30 (♦), 50/50 (●) and 30/70 (▲). The standard deviations were typically 1-5%.[V]

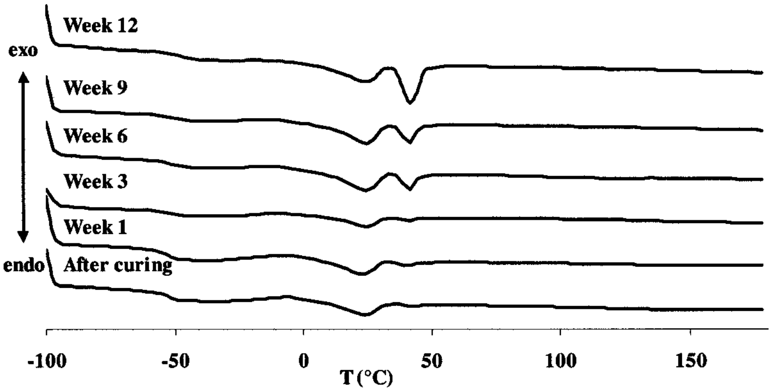


Figure 13. Melting endotherms of P(CL/DLLA-90/10)-1-4 before and after the hydrolysis.[V]

The networks with different lengths between the crosslinks differed in their degradation behavior. Networks with low crosslinking density, *i.e.* with long ester blocks, exhibited high water absorption and, as the crosslinking density was increased, the water uptake decreased. This could be related to the swelling behavior in an organic solvent, in which the decrease in crosslinking density led to greater swelling.[V] Surprisingly, the networks with low crosslinking density showed low mass loss in spite of high water absorption, since, in general, a high water uptake is related to a high degradation rate. It was suggested that this was due to the better diffusion of acidic degradation products out of the specimen showing high water absorption, which could lead to a less pronounced autocatalytic effect and thus slower degradation and mass loss.[V] There could also be a difference in the size, and thus in the solubility of the degradation products. The networks prepared with longer precursors could yield longer oligomers as their degradation products.

3.3.2 Enhanced degradation of crosslinked poly(ester-anhydrides)

The degradation of the polyester networks was enhanced by introducing anhydride bonds in the polymers. Anhydride bonds have been shown to be very susceptible to hydrolysis and the degradation of the polyanhydrides is governed by the hydrophobicity of the polymers. With hydrophobic monomers, even surface-eroding polymers have been obtained with degradation taking place either in hours, days or months, while hydrophilic poly(ether-anhydrides) have been reported to degrade through a bulk mechanism in few days.[50,145,150]

Crosslinked polylactide and poly(ε-caprolactone) based poly(ester-anhydride) networks degraded in a few days in PBS at 37°C. Crosslinked polylactide based poly(ester-anhydrides) absorbed water into the specimen during the first day and the anhydride linkages were cleaved. The degradation of the anhydride bonds was followed by the degradation and dissolution of the constituent oligomers. This type of degradation in two steps has been described in linear poly(ester-anhydrides) by Korhonen and Seppälä.[144] The rapid degradation of the crosslinked lactide based poly(ester-anhydrides) was due to the hydrophilicity of the polylactide oligomers, which allowed the water to penetrate into the polymer and cause hydrolysis of the anhydride bonds. Later on, the oligomers and their degradation products dissolved in the dissolution medium.

It is well known that poly(ε-caprolactone) is more hydrophobic than polylactides, and this was also observed with the poly(ester-anhydride) networks. The water absorption was lower in PCL based networks and the cleavage of the anhydride bonds took a longer time. PCL5-2-AH exhibited mass loss during the first days of dissolution, as shown in Figure 14, but after 4 days only oligomers insoluble in the dissolution medium were present. Further degradation of the PCL oligomers was not detected in two weeks, as the mass loss remained at the same level as after 4 days. In addition, the constituent oligomers tested did not show any mass loss or decrease in molecular weight in two weeks.

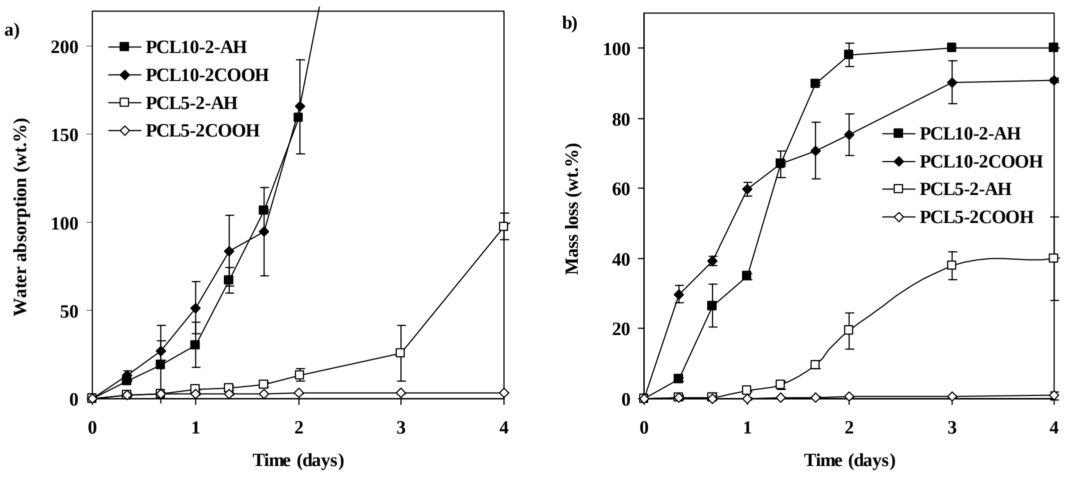


Figure 14. (a) The water absorption and (b) mass loss of the PCL based poly(ester-anhydride) networks and the corresponding COOH-terminated oligomers.[VI]

PCL10-2-AH eroded almost completely in two days with a rather steady rate of mass loss. The steady decrease in the sample dimensions is shown in Figure 15. According to FTIR, anhydride bonds were still present after 40 h of immersion when only 10% of the mass remained. This indicated that the degradation of PCL10-2-AH occurred mainly at the surface and, inside the sample, the polymer properties obtained by crosslinking remained. The corresponding waxy oligomers were also tested, with the result that they dissolved into the dissolution medium in two days. This shows that the oligomers in PCL10-2-AH were short enough for rapid dissolution from the surface after anhydride bond cleavage, but hydrophobic enough as polymers to restrict the water penetration into the structure.

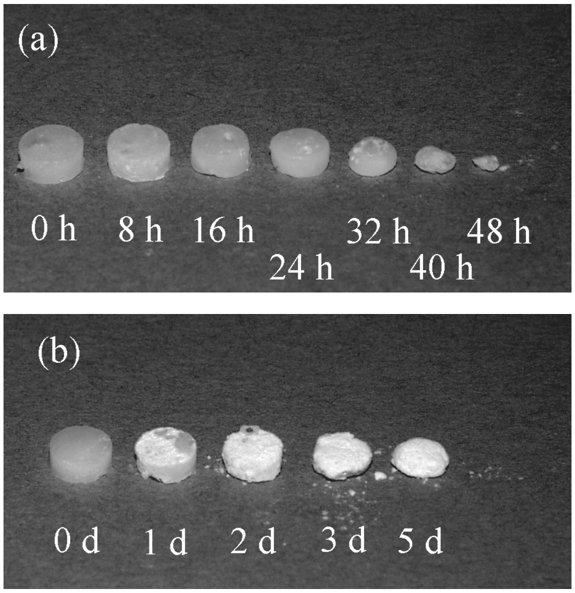


Figure 15. The disk degradation profiles for the PCL based poly(ester-anhydride) networks: (a) PCL10-2-AH, (b) PCL5-2-AH.[VI]

4 CONCLUSIONS

The main focus of the thesis was to prepare branched and crosslinked resorbable polyesters with a wide variety of properties. In addition, attention was paid to the structure-property relations in branched and crosslinked degradable polymers and possibilities that this type of macromolecular tailoring can offer. The work was based on the previous studies in our laboratory concerning the synthesis of degradable polymers by ring-opening polymerization, condensation polymerization and chain linking, and the applications of the degradable polymers mainly for biomedical uses. The major findings of the thesis are summarized follows:

Branched polyesters:

- Chain linking of hydroxyl telechelic lactic acid oligomers with diisocyanate created branches in the polymer backbone, when an excess of chain linking agent was used. The branches formed, accompanied with the broader MWD, enhanced the flow properties of the lactic acid based poly(ester-urethanes). The increased shear thinning and melt strength are beneficial in processing, especially in extrusion coating.
- The use of co-initiators with increasing number of hydroxyl groups increased the polymerization rate in the ring-opening polymerization and, by using polyglycerines as novel co-initiators, highly branched polylactides with a number of arms exceeding 8 were obtained. Rapid polymerization could be used in the preparation of high-molecular-weight polylactides in an extruder. In addition, the use of co-initiators enables tailoring of crosslinked networks with variable mechanical and degradation properties.

Crosslinked polyesters:

- Two different routes to resorbable polyester networks were applied. On the one hand, triethoxysilane functionalization and subsequent crosslinking were developed as a novel route to PDLLA based networks. On the other hand, methacrylated network precursors with different molecular architectures were prepared to expand the range of network properties from hard and rigid to soft and elastic.
- The networks based on methacrylated DLLA oligomers exhibited high compressive strength. The effect of the branching of the network precursors was systematically studied and it was found that the mechanical properties of the networks can be controlled by the number of arms in the constituent oligomer. Increased branching of the polyester precursor leads to networks with a higher crosslinking density accompanied by higher compressive strength and modulus. The crosslinked PDLLAs degraded through bulk degradation in a few months, but they lost their mechanical strength during the first weeks of the immersion.

- P(CL/DLLA) copolymers with highly random comonomer distribution yielded elastic networks. The mechanical, thermal and degradation properties of the networks were controlled mainly by the CL/DLLA monomer ratio, but also by the length of the copolymer blocks between crosslinks. By crosslinking, the form stability of the random copolymers with 50/50 molar ratio was enhanced significantly. The elasticity of the crosslinked polymers was confirmed with a stress relaxation test and cyclic tensile testing. The copolyester networks will be tested in applications of tissue engineering and controlled release of active agents.

- Novel poly(ester-anhydride) networks were prepared from PLLA, PDLLA and PCL oligomers by carboxylic acid termination, followed by methacrylation and curing. The networks typically exhibited a very rapid degradation to completion in four days. The poly(ester-anhydride) network PCL10-2-AH showed characteristics of surface erosion during degradation in two days. These networks with rapid degradation could be utilized in controlled drug release.

This thesis has been a part of ongoing research in the field of degradable polymers. The polymers were tailored mainly with biomedical applications in mind. The work continues in materials development, as in application development. Elastic copolymer networks have already been used in the preparation of porous matrices and composites for tissue engineering.[151] The composites have shown promising results in *in vitro* cell cultures and *in vivo* study is planned. Furthermore, the possibilities of these networks have been considered for the controlled release of active agents. The development of *in situ* curable network precursors and the enhancement of the degradation characteristics towards surface-erosion with steady degradation rate and controlled retention of mechanical properties, can be mentioned as the future challenges in the polymer synthesis related to this type of crosslinked polymer.

REFERENCES

1. Williams, D. F., *The Williams Dictionary of Biomaterials*, Liverpool University Press, Liverpool, UK, 1999, 343 pp.
2. Ikada, Y. and Tsuji, H., Biodegradable polyesters for medical and ecological applications, *Macromol. Rapid Commun.* **21** (2000) 117-132.
3. Amass, W., Amass, A. and Tighe, B., A Review of Biodegradable Polymers: Uses, Current Developments in the Synthesis and Characterization of Biodegradable Polyesters, Blends of Biodegradable Polymers and Recent Advances in Biodegradation Studies, *Polym. Int.* **47** (1998) 89-144.
4. Kost, J. and Goldbart, R., Natural and modified polysaccharides. In *Handbook of biodegradable polymers*, Domb, A. J., Kost, J. and Wiseman, D. M. (Eds.), Harwood Academic Publishers, Amsterdam 1997, pp. 275-289.
5. Doi, Y., Polyhydroxyalkanoates. In *Handbook of biodegradable polymers*, Domb, A. J., Kost, J. and Wiseman, D. M. (ed.), Harwood Academic Publishers, Amsterdam 1997, pp. 275-289.
6. Kobayashi, S. and Uyama, H., Biomacromolecules and Bio-Related Macromolecules, *Macromol. Chem. Phys.* **204** (2003) 235-256.
7. Okada, M., Chemical syntheses of biodegradable polymers, *Prog. Polym. Sci.* **27** (2002) 87-133.
8. Nieuwenhuis, J., Synthesis of Polylactides, Polyglycolides and Their Copolymers, *Clin. Mater.* **10** (1992) 59-67.
9. Lunt, J., Large-scale production, properties and commercial applications of polylactic acid polymers, *Polym. Degrad. Stab.* **59** (1998) 145-152.
10. Jacobsen, S., Degée, Ph., Fritz, H. G., Dubois, Ph. and Jérôme, R., Polylactide (PLA) – A New Way of Production, *Polym. Eng. Sci.* **39** (1999) 1311-1319.
11. Middleton, J. C. and Tipton, A. J., Synthetic biodegradable polymers as orthopedic devices, *Biomaterials* **21** (2000) 2335-2346.
12. Seppälä, J. V., Korhonen, H., Kylmä, J. and Tuominen, J., General Methodology for Chemical Synthesis of Polyester, in *Biopolymers Vol 3b Polyesters II – Properties and chemical synthesis*, Doi, Y. and Steinbüchel, A. (Eds.), Wiley-VCH, Germany 2002, pp. 327-369.
13. Lee, S.-H., Kim, S. H., Han, Y.-K. and Kim, Y. H., Synthesis and Degradation of End-Group-Functionalized Polylactide, *J. Polym. Sci. Part A: Polym. Chem.* **39** (2001) 973-985.
14. Cai, Q., Zhao, Y., Bei, J., Xi, F. and Wang, S., Synthesis and Properties of Star-Shaped Polylactide Attached to Poly(Amidoamine) Dendrimer, *Biomacromolecules* **4** (2003) 828-834.
15. Finne, A. and Albertsson, A.-C., Controlled Synthesis of Star-Shaped L-Lactide Polymers Using New Spirocyclic Tin Initiators, *Biomacromolecules* **3** (2002) 684-690.
16. Biela, T., Duda, A., Penczek, S., Rode, K. and Pasch, H., Well-Defined Star Polylactides and Their Behavior in Two-Dimensional Chromatography, *J. Polym. Sci. Part A: Polym. Chem.* **40** (2002) 2884-2887.

17. Biela, T., Duda, A., Rode, K. and Pasch, H., Characterization of star-shaped poly(L-lactide)s by liquid chromatography at critical conditions, *Polymer* **44** (2003) 1851-1860.

18. Dorgan, J. R. and Williams, J. S., Melt rheology of poly(lactic acid): Entanglement and chain architecture effects, *J. Rheol.* **43** (1999) 1141-1155.

19. Arvanitoyannis, I., Nakayama, A., Kawasaki, N. and Yamamoto, N., Novel star-shaped polylactide with glycerol using stannous octoate or tetraphenyl tin as catalyst: 1. Synthesis, characterization and study of their biodegradability, *Polymer* **36** (1995) 2947-2956.

20. Dong, C.-M., Qiu, K.-Y., Gu, Z.-W. and Feng, X.-D., Synthesis of Star-Shaped Poly(ε-caprolactone)-*b*-poly(DL-lactic acid-*alt*-glycolic acid) with Multifunctional Initiator and Stannous Octoate Catalyst, *Macromolecules* **34** (2001) 4691-4696.

21. Kim. S. H., Han, Y.-K., Kim, Y. H. and Hong, S. I., Multifunctional initiation of lactide polymerization by stannous octoate/pentaerythritol, *Makromol. Chem.* **193** (1992) 1623-1631.

22. Kim. S. H., Han, Y.-K., Ahn, K.-D., Kim, Y. H. and Chang, T., Preparation of star-shaped polylactide with pentaerythritol and stannous octoate, *Makromol. Chem.* **194** (1993) 3229-3236.

23. Grijpma, D. W., Joziasse, C. A. P. and Pennings, A. J., Star-shaped polylactide-containing block copolymers, *Makromol. Chem., Rapid Commun.* **14** (1993) 155-161.

24. Joziasse, C. A. P., Grablowitz, H. and Pennings, A. J., Star-shaped poly[(trimethylene carbonate)-*co*-(ε-caprolactone)] and its block copolymers with lactide/glycolide: synthesis, characterization and properties, *Macromol. Chem. Phys.* **201** (2000) 107-112.

25. Joziasse, C. A. P., Veenstra, H., Topp, M. D. C., Grijpma, D. W. and Pennings, A. J., Rubber toughened linear and star-shaped poly(d,l-lactide-*co*-glycolide): synthesis, properties and in vitro degradation, *Polymer* **39** (1998) 467-473.

26. Zhao, Y.-L., Cai, Q., Jiang, J., Shuai, X.-T., Bei, J.-Z., Chen, C.-F. and Xi, F., Synthesis and thermal properties of novel star-shaped poly(L-lactide)s with starburst PAMAM-OH dendrimer macroinitiator, *Polymer* **43** (2002) 5819-5825.

27. Choi, Y. K., Bae, Y. H. and Kim, S. W., Star-Shaped Poly(ether-ester) Block Copolymers: Synthesis, Characterization, and Their Physical Properties, *Macromolecules* **31** (1998) 8766-8774.

28. Breitenbach, A., Pistel, K. F. and Kissel, T., Biodegradable comb polyesters. Part II. Erosion and release properties of poly(vinyl alcohol)-*g*-poly(lactic-*co*-glycolic acid), *Polymer* **41** (2000) 4781-4792.

29. Tasaka, F., Ohya, Y. and Ouchi, T., Synthesis of Novel Comb-Type Polylactide and Its Biodegradability, *Macromolecules* **34** (2001) 5494-5500.

30. Lang, M., Wong, R. P. and Chu, C.-C., Synthesis and Structural Analysis of Functionalized Poly(ε-caprolactone)-Based Three-Arm Star Polymers, *J. Polym. Sci. Part A: Polym. Chem.* **40** (2002) 1127-1141.

31. Lang, M. and Chu, C.-C., Functionalized Multiarm Poly(ε-caprolactone)s: Synthesis, Structure Analysis, and Network Formation, *J. Appl. Polym. Sci.* **86** (2002) 2296-2306.

32. Atthoff, B., Trollsås, M., Claesson, H. and Hedrick, J. L., Poly(lactides) with controlled molecular architecture initiated from hydroxyl functional dendrimers and the effect on the hydrodynamic volume, *Macromol. Chem. Phys.* **200** (1999) 1333-1339.

33. Trollsås, M., Kelly, M. A., Claesson, H., Siemens, R. and Hedrick, J. L., Highly Branched Block Copolymers: Design, Synthesis, and Morphology, *Macromolecules* **32** (1999) 4917-4924.

34. Trollsås, M. and Hedrick, J. L., Dendrimer-like Star Polymers, *J. Am. Chem. Soc.* **120** (1998) 4644-4651.

35. Kricheldorf, H. R. and Fechner, B., Polylactones. LVIII. Star-Shaped Polylactones with Functional End Groups via Ring-Expansion Polymerization with a Spiroinitiator, *J. Polym. Sci. Part A: Polym. Chem.* **40** (2002) 1047-1057.

36. Kricheldorf, H. R. and Fechner, B., Polylactones. 59. Biodegradable Networks via Ring-Expansion Polymerization of Lactones and Lactides with a Spirocyclic Tin Initiator, *Biomacromolecules* **3** (2002) 691-695.

37. Kim, S. H. and Kim, Y. H., Direct Condensation Polymerization of Lactic acid, *Macromol. Symp.* **144** (1999) 277-287.

38. Carnahan, M. A. and Grinstaff, M. W., Synthesis and Characterization of Poly(glycerol-succinic acid) Dendrimers, *Macromolecules* **34** (2001) 7648-7655.

39. Carnahan, M. A. and Grinstaff, M. W., Synthesis and Characterization of Polyether-Ester Dendrimers of Glycerol and Lactic Acid, *J. Am. Chem. Soc.* **123** (2001) 2905-2906.

40. Carnahan, M. A, Middleton, C., Kim, J., Kim, T. and Grinstaff, M. W., Hybrid Dendritic-Linear Polyester-Ethers for in Situ Photopolymerization, *J. Am. Chem. Soc.* **124** (2002) 5291-5293.

41. Tian, D., Dubois, Ph. Jérôme, R. and Teyssié, Ph., Macromolecular Engineering of Polylactones and Polylactides. 18. Synthesis of Star-Branched Aliphatic Polyesters Bearing Various Functional End Groups, *Macromolecules* **27** (1994) 4134-4144.

42. Trollsås, M., Hedrick, J. L., Mecerreyes, D., Jérôme, R. and Dubois, Ph., Internal Functionalization in Hyperbranched Polyesters, *J. Polym. Sci. Part A: Polym. Chem.* **36** (1998) 3187-3192.

43. Trollsås, M., Atthoff, B., Claesson, H. and Hedrick, J. L., Hyperbranched Poly(ε-caprolactone)s, *Macromolecules* **31** (1998) 3439-3445.

44. Trollsås, M. and Hedrick, J. L., Hyperbranched Poly(ε-caprolactone) Derived from Intrinsically Branched AB_2 Macromonomers, *Macromolecules* **31** (1998) 4390-4395.

45. Storey, R. F., Wiggins, J. S., Mauritz, K. A. and Puckett, A. D., Bioabsorbable Composites. II: Nontoxic, L-lysine-Based Poly(ester-urethane) Matrix Composites, *Polymer Composites* **14** (1993) 17-25.

46. Domb, A. J., Manor, N. and Elmalak, O., Biodegradable bone cement compositions based on acrylate and epoxide terminated poly(propylene fumarate) oligomers and calcium salt compositions, *Biomaterials* **17** (1996) 411-417.

47. Wang, Y., Ameer, G. A., Sheppard, B. J. and Langer, R., A tough biodegradable elastomer, *Nature Biotechnology* **20** (2002) 602-606.

48. Sawhney, A. S., Pathak, C. P. and Hubbell, J. A., Bioerodible Hydrogels Based on Photopolymerized Poly(ethylene glycol)-*co*-poly(α-hydroxy acid) Diacrylate Macromers, *Macromolecules* **26** (1993) 581-587.

49. Burdick, J. A., Philpott, L. M. and Anseth, K. S., Synthesis and Characterization of Tetrafunctional Lactic Acid Oligomers: A Potential *In Situ* Forming Degradable Orthopaedic Biomaterial, *J. Polym. Sci. Part A: Polym. Chem.* **39** (2001) 683-692.

50. Anseth, K. S., Shastri, V. R. and Langer, R., Photopolymerizable degradable polyanhydrides with osteocompatibility, *Nature Biotechnology* **17** (1999) 156-159.

51. Peter, S. J., Miller, M. J., Yaszemski, M. J. and Mikos, A. G., Poly(propylene fumarate). In *Handbook of biodegradable polymers*, Domb, A. J., Kost, J. and Wiseman, D. M. (Eds.), Harwood Academic Publishers, Amsterdam 1997, pp. 87-97.

52. Storey, R. F. and Hickey, T. P., Degradable polyurethane networks based on D,L-lactide, glycolide, ε-caprolactone, and trimethylene carbonate homopolyester and copolyester triols, *Polymer* **35** (1994) 830-838.

53. Storey, R. F., Warren, S. C., Allison, C. J., Wiggins, J. S. and Puckett, A. D., Synthesis of bioabsorbable networks from methacrylate-endcapped polyesters, *Polymer* **34** (1993) 4365-4372.

54. Storey, R. F., Warren, S. C., Allison, C. J. and Puckett, A. D., Methacrylate-endcapped poly(d,l-lactide-*co*-trimethylene carbonate) oligomers. Network formation by thermal free-radical curing, *Polymer* **38** (1997) 6295-6301.

55. Davis, K. A., Burdick, J. A. and Anseth, K. S., Photoinitiated crosslinked degradable copolymer networks for tissue engineering applications, *Biomaterials* **24** (2003) 2485-2495.

56. Aoyagi, T., Miyata, F. and Nagase, Y., Preparation of cross-linked aliphatic polyester and application to thermo-responsive material, *J. Controlled Release* **32** (1994) 87-96.

57. Kim, B. S., Hrkach, J. S. and Langer, R., Biodegradable photo-crosslinked poly(ether-ester) networks for lubricious coatings, *Biomaterials* **21** (2000) 259-265.

58. Han, D. K. and Hubbell, J. A., Synthesis of Polymer Network Scaffolds from L-Lactide and Poly(ethylene glycol) and Their Interaction with Cells, *Macromolecules* **30** (1997) 6077-6083.

59. Storey, R. F., Wiggins, J. S., Mauritz, K. A. and Puckett, A. D., Bioabsorbable Composites. I: Fundamental Design Considerations Using Free Radically Crosslinkable Matrices, *Polymer Composites* **14** (1993) 7-16.

60. Han, Y. K., Edelman, P. G. and Huang, S. J., Synthesis and characterization of crosslinked polymers for biomedical composites, *J. Macromol. Sci.* **A25** (1988) 847-869.

61. Turunen, M. P. K., Korhonen, H., Tuominen, J. and Seppälä, J. V., Synthesis, characterization and crosslinking of functional star-shaped poly(ε-caprolactone), *Polym. Int.* **51** (2001) 92-100.

62. Tuominen, J., Kylmä, J., Seppälä, J. and Selin, J.-F., Biodegradable coating, WO 03/033563, 2001.

63. Mizutani, M. and Matsuda, T., Liquid acrylate-endcapped biodegradable poly(ε-caprolactone-*co*-trimethylene carbonate). I. Preparation and visible light-induced photocuring characteristics, *J. Biomed. Mater. Res.* **62** (2002) 387-394.

64. Coullerez, G., Lowe, C., Pechy, P., Kausch, H. H. and Hilborn, J., Synthesis of acrylate functional telechelic poly(lactic acid) oligomer by transesterification, *J. Mater. Sci.: Mater. Med.* **11** (2000) 505-510.

65. He, S., Timmer, M. D., Yaszemski, M. J., Yasko, A. W., Engel, P. S. and Mikos, A. G., Synthesis of biodegradable poly(propylene fumarate) networks with poly(propylene

fumarate)-diacrylate macromers as crosslinking agents and characterization of their degradation products, *Polymer* **42** (2001) 1251-1260.

66. Timmer, M. D., Jo, S., Wang, C., Ambrose, C. G. and Mikos, A. G., Characterization of the Cross-Linked Structure of Fumarate-Based Degradable Polymer Networks, *Macromolecules* **35** (2002) 4373-4379.

67. John, G. and Morita, M., Synthesis and Characterization of Photo-Cross-Linked Networks Based on L-Lactide/Serine Copolymers, *Macromolecules* **32** (1999) 1853-1858.

68. Elisseeff, J., Anseth, K. S., Langer, R. and Hrkach, J. S., Synthesis and Characterization of Photo-Cross-Linked Polymers Based on Poly(L-lactic acid-*co*-L-aspartic acid), *Macromolecules* **30** (1997) 2182-2184.

69. Muggli, D. S., Burkoth, A. K., Keyser, S. A., Lee, H. R. and Anseth, K. S., Reaction Behavior of Biodegradable, Photo-Cross-Linkable Polyanhydrides, *Macromolecules* **31** (1998) 4120-4125.

70. Burkoth, A. K. and Anseth, K. S., A review of photocrosslinked polyanhydrides: in situ forming degradable networks, *Biomaterials* **21** (2000), 2395-2404.

71. Burkoth, A. K. and Anseth, K. S., MALDI-TOF Characterization of Highly Cross-Linked, Degradable Polymer Networks, *Macromolecules* **32** (1999) 1438-1444.

72. Burdick, J. A., Lovestead, T. M. and Anseth, K. S., Kinetic Chain Lengths in Highly Cross-Linked Networks Formed by the Photoinitiated Polymerization of Divinyl Monomers: A Gel Permeation Chromatography Investigation, *Biomacromolecules* **4** (2003) 149-156.

73. Poshusta, A. K., Burdick, J. A., Mortisen, D. J., Padera, R. F., Ruehlman, D., Yaszemski, M. J. and Anseth, K. S., Histocompatibility of photocrosslinked polyanhydrides: A novel in situ forming orthopaedic biomaterial, *J. Biomed. Mater. Res.* **64A** (2003) 62-69.

74. Timmer, M. D., Shin, H., Horch, R. A., Ambrose, C. G. and Mikos, A. G., In Vitro Cytotoxicity of Injectable and Biodegradable Poly(propylene fumarate)-Based Networks: Unreacted Macromers, Cross-Linked Networks, and Degradation Products, *Biomacromolecules* **4** (2003)1026-1033.

75. Bruining, M. J., Blaauwgeers, H. G. T., Kuijer, R., Pels, E., Nuijts, R. M. M. A. and Koole, L. H., Biodegradable three-dimensional networks of poly(dimethylamino ethyl methacrylate). Synthesis, characterization and in vitro studies of structural degradation and cytotoxicity, *Biomaterials* **21** (2000) 595-604.

76. Bruin, P., Veenstra, G. J., Nijenhuis, A. J. and Pennings, A. J., Design and synthesis of biodegradable poly(ester-urethane) elastomer networks composed of non-toxic building blocks, *Makromol. Chem., Rapid Commun.* **9** (1988) 589-594.

77. Storey, R. F., Herring, K. R. and Hoffman, D. C., Hydroxy-Terminated Poly(ε-Caprolactone-*co*-δ-Valerolactone) Oligomers: Synthesis, Characterization, and Polyurethane Network Formation, *J. Polym. Sci. Part A: Polym. Chem.* **29** (1991) 1759-1777.

78. Kobayashi, H., Hyon, S.-H. and Ikada, Y., Water-curable and biodegradable prepolymers, *J. Biomed. Mater. Res.* **25** (1991) 1481-1494.

79. Storey, R. F., Wiggins, J. S. and Puckett, A. D., Hydrolyzable Poly(ester-urethane) Networks from L-Lysine Diisocyanate and D,L-lactide/ε-caprolactone Homo- and Copolyester Triols, *J. Polym. Sci. Part A: Polym. Chem.* **32** (1994) 2345-2363.

80. de Groot, J. H., de Vrijer, R., Wildeboer, B. S., Spaans, C. S. and Pennings, A. J., New biomedical polyurethanes ureas with high tear strengths, *Polymer Bulletin* **38** (1997) 211-218.

81. Kricheldorf, H. R., Synthesis of Biodegradable (Multi) block Copolymers, Star-shaped Polyesters and Networks Via Ring-expansion Polymerization, *Polym. Adv. Technol.* **13** (2002) 969-974.

82. Kricheldorf, H. R. and Stricker, A., Macrocycles. 13. Stannylated Glucose Glycosides as Cyclic Initiators of ε-Caprolactone and the Synthesis of Biodegradable Networks, *Macromolecules* **33** (2000) 696-701.

83. Kricheldorf, H. R. and Fechner, B., Polylactones. 51. Resorbable Networks by Combined Ring-Expansion Polymerization and Ring-Opening Polycondensation of ε-Caprolactone or DL-Lactide, *Macromolecules* **34** (2001) 3517-3521.

84. Kricheldorf, H. R., Fechner, B., Shikanov, A. and Domb, A., Polylactones. 57. Biodegradable Networks Based on A-B-A Triblock Segments Containing Poly(Ethylene Glycol)s – Synthesis and Drug Release Properties, *Biomacromolecules* **4** (2003) 950-955.

85. Storey, R. F. and Hickey T. P., New Epoxy-Terminated Oligoesters: Precursors to Totally Biodegradable Networks, *J. Polym. Sci. Part A: Polym. Chem.* **31** (1993) 1825-1838.

86. Tian, D., Dubois, Ph. and Jérôme, R., A new poly(ε-caprolactone) containing hybrid ceramer prepared by the sol-gel process, *Polymer* **37** (1996) 3983-3987.

87. Tian, D., Dubois, Ph. and Jérôme, R., Biodegradable and Biocompatible Inorganic-Organic Hybrid Materials. I. Synthesis and Characterization, *J. Polym. Sci. Part A: Polym. Chem.* **35** (1997) 2295-2309.

88. Tian, D., Dubois, Ph., Grandfils, C., Jérôme, R., Viville, P., Lazzaroni, R., Bredas, J.-L. and Leprince, P., A Novel Bidegradable and Biocompatible Ceramer Prepared by the Sol-Gel Process, *Chem. Mater.* **9** (1997) 871-874.

89. Matsuda, T., Mizutani, M. and Arnold, S. C., Molecular Desing of Photocurable Liquid Biodegradable Copolymers. 1. Synthesis and Photocuring Characteristics, *Macromolecules* **33** (2000) 795-800.

90. Matsuda, T. and Mizutani, M., Molecular Desing of Photocurable Liquid Biodegradable Copolymers. 2. Synthesis of Coumarin-Derivatized Oligo(methacrylate)s and Photocuring, *Macromolecules* **33** (2000) 791-794.

91. Mizutani, M. and Matsuda, T., Photocurable Liquid Biodegradable Copolymers: In Vitro Hydrolytic Degradation Behaviors of Photocured Films of Coumarin-Endcapped Poly(ε-caprolactone-*co*-trimethylene carbonate), *Biomacromolecules* **3** (2002) 249-255.

92. Wang, Y., Kim, Y. M. and Langer, R., *In vivo* degradation characteristics of poly(glycerol sebacate), *J. Biomed. Mater. Res.* **66A** (2003) 192-197.

93. Nagata, M., Machida, T., Sakai, W. and Tsutsumi, N., Synthesis, Characterization, and Enzymatic Degradation of Network Aliphatic Copolyesters, *J. Polym. Sci. Part A: Polym. Chem.* **37** (1999) 2005-2011.

94. Nagata, M., Kanechika, M., Sakai, W. and Tsutsumi, N., Biodegradable Network Elastomeric Polyesters from Multifunctional Aromatic Carboxylic Acids and Poly(ε-caprolactone) Diols, *J. Polym. Sci. Part A: Polym. Chem.* **40** (2002) 4523-4529.

95. Grijpma, D. W., Kroeze, E., Nijenhuis, A. J. and Pennings, A. J., Poly(L-lactide) crosslinked with spiro-bis-dimethylene-carbonate, *Polymer* **34** (1993) 1496-1503.

96. Grijpma, D. W. and Pennings, A. J., (Co)polymers of L-lactide, 1, Synthesis, thermal properties and hydrolytic degradation, *Macromol. Chem. Phys.* **195** (1994) 1633-1647.

97. Nijenhuis, A. J., Grijpma, D. W. and Pennings, A. J., Crosslinked poly(L-lactide) and poly(ε-caprolactone), *Polymer* **37** (1996) 2783-2791.

98. Palmgren, R., Karlsson, S. and Albertsson, A.-C., Synthesis of Degradable Crosslinked Polymers Based on 1,5-Dioxepan-2-one and Crosslinker of Bis-ε-caprolactone type, *J. Polym. Sci. Part A: Polym. Chem.* **35** (1997) 1635-1649.

99. Ryner, M. and Albertsson, A.-C., Tailored Mechanical Properties and Degradability of Polyesters by Controlled Molecular Architecture, *Macromol. Symp.* **175** (2001) 11-18.

100. Albertsson, A.-C. and Eklund, M., Short Methylene Segment Crosslinks in Degradable Aliphatic Polyanhydride: Network Formation, Characterization, and Degradation, *J. Polym. Sci. Part A: Polym. Chem.* **34** (1996) 1395-1405.

101. Darwis, D., Mitomo, H., Enjoji, T., Yoshii, F. and Makuuchi, K., Enzymatic degradation of radiation crosslinked poly(ε-caprolactone), *Polym. Degrad. Stab.* **62** (1998) 259-265.

102. Bahari, K., Mitomo, H., Enjoji, T., Yoshii, F. and Makuuchi, K., Radiation crosslinked polybutylene succinate) foam and its biodegradation, *Polym. Degrad. Stab.* **62**(3) (1998) 551-557.

103. Kim, D. J., Kim, W. S., Lee, D. H., Min, K. E., Park, L. S., Kang, I. K., Jeon, I. R. and Seo, K. H., Modification of Poly(butylene succinate) with Peroxide: Crosslinking, Physical and Thermal Properties, and Biodegradation, *J. Appl. Polym. Sci.* **81** (2001) 1115-1124.

104. Kim, D. J., Kang, H. J. and Seo, K. H., Peroxide Modification of Poly(butylene adipate-*co*-succinate), *J. Appl. Polym. Sci.* **81** (2001) 637-645.

105. Seppälä, J. V., Selin, J.-F. and Su, T., Menetelmä maitohappopohjaisen polyuretaanin valmistamiseksi, FI92592, 1994.

106. Seppälä, J., Härkönen, M., Hiltunen, K. and Malin, M., Biodegradable Thermoplastic Poly(ester-urethane), a presentation at MacroAkron '94, 35th IUPAC International Symposium on Macromolecules, Akron, July 11-15.1994.

107. Hiltunen, K., Härkönen, M., Seppälä, J. V. and Väänänen, T., Synthesis and Characterization of Lactic Acid Based Telechelic Prepolymers, *Macromolecules* **29** (1996) 8677-8682.

108. Hiljanen-Vainio, M., Karjalainen, T. and Seppälä, J., Biodegradable Lactone Copolymers. I. Characterization and Mechanical Behavior of ε-Caprolactone and Lactide Copolymers, *J. Appl. Polym. Sci.* **59** (1996) 1281-1288.

109. Hiltunen, K., Seppälä, J. V. and Härkönen, M., Lactic Acid Based Poly(ester-urethanes) : The Effects of Different Polymerization Conditions on the Polymer Structure and Properties, *J. Appl. Polym. Sci.* **64** (1997) 865-873.

110. Hiltunen, K., Seppälä, J. V. and Härkönen, M., Lactic Acid Based Poly(ester-urethanes) : Use of Hydroxyl Terminated Prepolymers in Urethane Synthesis, *J. Appl. Polym. Sci.* **63** (1997) 1091-1100.

111. Kylmä, J. and Seppälä, J. V., Synthesis and Characterization of a Biodegradable Thermoplastic Poly(ester-urethane) Elastomer, *Macromolecules* **30** (1997) 2876-2882.

112. Tuominen, J. and Seppälä, J. V., Synthesis and characterization of lactic acid based poly(ester-amide), *Macromolecules* **33** (2000) 3530-3535.

113. Kylmä, J., Tuominen, J., Helminen, A. and Seppälä, J., Chain Extending of Lactic Acid Oligomers. Effect of 2,2'-Bis(2-oxazoline) on 1,6-Hexamethylene Diisocyanate Linking Reaction, *Polymer* **42** (2001) 3333-3343.

114. Tuominen, J., Kylmä, J. and Seppälä, J., Chain Extending of Lactic Acid Oligomers. 2. Increasing of Molecular Weight with 2,2'-Bis(2-oxazoline) coupling, *Polymer* **43** (2002) 3-10.

115. Kokko, E., Metallocene-Catalyzed Ethene Polymerization: Long-Chain Branched Polyethylene, *Acta Polytech. Scand. Chem. Technol. Ser.* **290** (2002) 1-52.

116. Dealy, J. M. and Wissbrun, K. F., *Melt Rheology and its Role in Plastics Processing: Theory and Applications*, Van Nostrand Reinhold, New York 1990, 665 pp.

117. Hiltunen, K., Seppälä, J. V. and Härkönen, M., Effect of Catalyst and Polymerization Conditions on the Preparation of Low Molecular Weight Lactic Acid Polymers, *Macromolecules* **30** (1997) 373-379.

118. Tuominen, J., Kylmä, J., Kapanen, A., Venelampi, O., Itävaara, M. and Seppälä, J., Biodegradation of lactic acid based polymers under controlled composting conditions and evaluation of the ecotoxicological impact, *Biomacromolecules* **3** (2002) 445-455.

119. Rich, J., Tuominen, J., Kylmä, J., Seppälä, J., Nazhat, S. N. and Tanner, K. E., Lactic Acid Based PEU/HA and PEU/BCP Composites: Dynamic Mechanical Characterization of Hydrolysis, *J. Biomed. Mater. Res. (Appl. Biomater.)* **63** (2002) 346-353.

120. Dieterich, D., Grigat, E. and Hahn, W., Chemical and Physical-Chemical Principles of Polyurethane Chemistry. In *Polyurethane Handbook: Chemistry – Raw Materials – Processing – Applications - Properties*, Oertel, G. (ed.), Hanser Publishers, Munich, 1985, p. 7-41.

121. Tuominen, J., Chain Linked Lactic Acid Polymers: Polymerization and Biodegradation Studies, *Helsinki University of Technology, Polymer Technology Publication Series* **25** (2003) 1-54.

122. Härkönen, M., Hiltunen, K., Malin, M. and Seppälä, J. V., Properties and polymerization of biodegradable thermoplastic poly(ester-urethane), *J.M.S. – Pure Appl. Chem.* **A32** (1995) 857-862.

123. Härkönen, M., Hiltunen, K., Rantanen, T. and Seppälä, J. V., Effect of molecular weight distribution on the elasticity of melt of biodegradable poly(ester-urethane), *Annu. Transactions Nord. Rheol. Soc.* **3** (1995) 9-11.

124. Cooper-White, J. J. and Mackay, M., Rheological Properties of Poly(lactides). Effect of Molecular Weigth and Temperature on the Viscoelasticity of Poly(l-lactic acid), *J. Polym. Sci. Part B: Polym. Phys.* **37** (1999) 1803-1814.

125. Palade, L.-I., Lehermeier, H. J. and Dorgan, J. R., Melt Rheology of High L-Content Poly(lactic acid), *Macromolecules* **34** (2001) 1384-1390.

126. Lehermeier, H. J. and Dorgan, J. R., Melt Rheology of Poly(lactic acid): Consequences of Blending Chain Architectures, *Polym. Eng. Sci.* **41** (2001) 2172-2184.

127. Helminen, A., Kylmä, J. and Seppälä, J. V., The rheological properties of biodegradable poly(ester-urethanes) and their correlation with extrusion coating of paper, a poster presentation at 1999 Prague Meetings on Macromolecules: Rheology of Polymer Systems, Prague, Czech Republic, July 19-22, 1999.

128. Kowalski, A., Duda, A. and Penczek, S., Kinetics and mechanism of cyclic esters polymerization initiated with tin(II) octoate, 1, *Macromol. Rapid Commun.* **19** (1998) 567-572.

129. Kowalski, A., Duda, A. and Penczek, S., Mechanism of Cyclic Ester Polymerization Initiated with Tin(II) Octoate. 2. Macromolecules Fitted with Tin(II) Alkoxide Species Observed Directly in MALDI-TOF Spectra, *Macromolecules* **33** (2000) 689-695.

130. Duda, A., Kowalski, A. and Penczek, S., Polymerizations of ε-caprolactone and L,L-dilactide initiated with stannous octoate and stannous butoxide – a comparison, *Macromol. Symp.* **153** (2000) 41-53.

131. Kricheldorf, H. R., Kreiser-Saunders, I. and Stricker, A., Polylactones 48. $SnOct_2$-Initiated Polymerizations of Lactide: A Mechanistic Study, *Macromolecules* **33** (2000) 702-709.

132. McNeill, I. C. and Leiper, H. A., Degradation Studies of Some Polyesters and Polycarbonates – 2. Polylactide: Degradation Under Isothermal Conditions, Thermal Degradation Mechanism and Photolysis of the Polymer, *Polym. Degrad. Stab.* **11** (1985) 309-326.

133. Jamshidi, K., Hyon, S.-H. and Ikada, Y., Thermal characterization of polylactides, *Polymer* **29** (1988) 2229-2234.

134. Kricheldorf, H. R. and Kreiser, I., Polylactones. 13. Transesterification of poly(L-lactide) with poly(glycolide), poly(β-propiolactone), and poly(ε-caprolactone), *J. Macromol. Sci. – Chem.* **A24** (1987) 1345-1356.

135. Kasperczyk, J. and Bero, M., Coordination polymerization of lactides, 2. Microstructure determination of poly[(L,L-lactide)-co-(ε-caprolactone)] with ^{13}C nuclear magnetic resonance spectroscopy, *Makromol. Chem.* **192** (1991) 1777-1787.

136. Lang, M. and Chu, C.-C., Synthesis and Chemical Structural Analysis of Nitroxyl-Radical-Incorporated Poly(acrylic acid/lactide/ε-caprolactone) Copolymers, *J. Polym. Sci. Part A: Polym. Chem.* **39** (2002) 4214-4226.

137. Grijpma, D. W. and Pennings, A. J., Polymerization temperature effects on the properties of L-lactide and ε-caprolactone copolymers, *Polym. Bull.* **25** (1991) 335-341.

138. Vanhoorne, P., Dubois, Ph., Jerome, R. and Teyssie, Ph., Macromolecular Engineering of Polylactones and Polylactides. 7. Structural Analysis of Copolyesters of ε-caprolactone and L- or D,L-lactide Initiated by $Al(O^iPr)_3$, *Macromolecules* **25** (1992) 37-44.

139. Bero, M., Kasperczyk, J. and Adamus, G., Coordination polymerization of lactides, 3. Copolymerization of L,L-lactide and ε-caprolactone in the presence of initiators containing Zn and Al, *Makromol. Chem.* **194** (1993) 907-912.

140. Kasperczyk, J. and Bero, M., Coordination polymerization of lactides, 4. The role of transesterification in the copolymerization of L,L-lactide and ε-caprolactone, *Makromol. Chem.* **194** (1993) 913-925.

141. Bero, M. and Kasperczyk, J., Coordination polymerization of lactides, 5. Influence of lactide structure on the transesterification processes in the copolymerization with ε-caprolactone, *Macromol. Chem. Phys.* **197** (1996) 3251-3258.

142. Choi, E.-J., Park, J.-K. and Chang, H.-N., Effect of Polymerization Catalysts on the Microstructure of P(LLA-co-εCL), *J. Polym. Sci. Part B: Polym. Phys.* **32** *(*1994) 2481-2489.

143. Grankvist, B., Helminen, A., Vehviläinen, M., Ääritalo, V., Seppälä, J. and Linden, M., Biodegradable and bioactive hybrid organic-inorganic PEG-siloxane fibers. Preparation and characterization, *Colloid Polym. Sci.* (2003) in press.

144. Korhonen, H. and Seppälä, J. V., Synthesis of Poly(ester-anhydride)s Based on Poly(ε-caprolactone) Prepolymer, *J. Appl. Polym. Sci.* **81** (2001) 176-185.

145. Kim, B. S., Hrkach, J. S. and Langer, R., Synthesis and Characterization of Novel Degradable Photocrosslinked Poly(ether-anhydride) Networks, *J. Polym. Sci. Part A: Polym. Chem.* **38** (2000) 1277-1282.

146. Grijpma, D. W., Altpeter, H., Bevis, M. J. and Feijen, J., Improvement of the mechanical properties of poly(D,L-lactide) by orientation, *Polymer Int.* **51** (2002) 845-851.

147. Rich, J., Karjalainen, T., Ahjopalo, L. and Seppälä, J., Model Compound Release from DL-Lactide/ε-Caprolactone Copolymers and Evaluation of Specific Interactions by Molecular Modeling, *J. Appl. Polym. Sci.* **86** (2002) 1-9.

148. Malin, M., Hiljanen-Vainio, M., Karjalainen, T. and Seppälä, J., Biodegradable Lactone Copolymers. II. Hydrolytic Study of ε-Caprolactone and Lactide Copolymers, *J. Appl. Polym. Sci.* **59** (1996) 1289-1298.

149. Karjalainen, T., Hiljanen-Vainio, M., Malin, M. and Seppälä, J., Biodegradable Lactone Copolymers. III. Mechanical Properties of ε-Caprolactone and Lactide Copolymers after Hydrolysis *In Vitro*, *J. Appl. Polym. Sci.* **59** (1996) 1299-1304.

150. Kumar, N., Langer, R. S. and Domb, A. J., Polyanhydrides: an overview, *Adv. Drug Delivery Rev.* **54** (2002) 889-910.

151. Helminen, A., Meretoja, V., Närhi, T. and Seppälä, J., Porous matrices and composites from crosslinked P(CL/DLLA) copolymer, a poster presentation at 18th European Conference on Biomaterials, Stuttgart, Germany, October 1-4, 2003.