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Multistep reactions based on thiolactones for the synthesis of functionalized polymers

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Woord vooraf

Point n'est besoin d'espérer pour entreprendre, ni de réussir pour persévérer.

Onderzoek loopt niet altijd van een leien dakje. Meer zelfs, het gaat bijna per definitie gepaard met vallen en opstaan. Maar wanneer men doorzet, volgt de beloning in de vorm van wetenschappelijke voldoening. Ik bedank mijn vader, Prof. Eric Goethals, wie ik zo bewonder, om mij de beginselen van kritisch, wetenschappelijk denken bij te brengen. Om mij van kleins af aan te leren de dingen in vraag te stellen, maar ook om te relativeren. Deze basisprincipes hebben mij ertoe aangezet om chemie te studeren, en om uiteindelijk dit doctoraat te starten.

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Table of Contents

Chapter 1
General introduction, aim and outline

1.1. GENERAL INTRODUCTION AND AIM

The development and implementation of simplified and accelerated syntheses in macromolecular design has been a field of continuous research and will become even more important the coming decades. While striving to develop more advanced functional polymers, intended for high-end application materials, it is also important to assess the feasibility of a process. To meet these contradictory demands, *i.e.* the need for simplified synthesis strategies combined with increased complexity on a material level, a lot of work has been done to increase the efficiency of chemical processes.

The synthesis of different complex polymeric architectures in a straightforward manner is only possible when efficient reactions are available. Looking at the developments over the last 10 years, click chemistry has played a vital role in the synthesis of polymers with a complexity that was previously only reachable on a small scale, through complicated procedures and tedious work-ups. The main reasoning behind click chemistry is to follow nature's lead by using chemicals that are literally spring-loaded for a single trajectory, reacting exclusively with each other in a fast and efficient way. Kolb, Finn and Sharpless[1] defined a set of criteria for a reaction to be considered as a click reaction. For example, the given reaction has to be modular, wide in scope, result in high yields and may generate only inoffensive side-products. Reaction conditions have to be simple, using readily available starting materials and no or little amounts of benign solvents. A recent perspective from the own research group[2] denotes the recent advances in click chemistry in macromolecular science. An alternative set of requirements has been proposed for click reactions in macromolecular synthesis,[3] taking into account the different needs and perspectives for polymers (Figure 1-1). Besides the original criteria of modularity, chemoselectivity, single reaction trajectory and wideness in scope (in blue), some polymer-specific requirements are adapted and added to the definition (in green and green-blue).
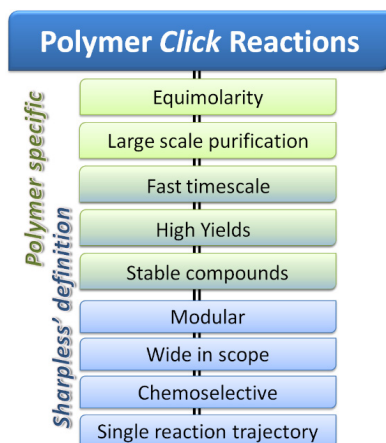
Figure 1-1. Requirements for click reactions involving one or more polymeric reagents (blue: originally defined by Sharpless; green and blue–green: adapted requirement related to synthetic polymer chemistry).[3]

The need for accelerated synthetic protocols and the role of click chemistry herein, has been documented by Malkoch et al.[4, 5] The protocols are based on executing several efficient modifications at the same time, whether or not dependent on each other. These one-pot multi-step approaches are especially attractive for the synthesis and post-polymerization modification of functionalized polymers, by reducing both synthetic and purification steps.

Developments in the field of polymer synthesis are often based on ways to increase functionality, by adding dedicated functional groups through efficient linking strategies. A lot of these methods are based on click chemistry.[6, 7] More recently, a lot of thiol-based chemistries have been used for this purpose,[8, 9] owing to the high reactivity of the mercapto-functionality.

The aim of this research project was to develop a method for the synthesis of **advanced polymeric structures** without the use of time-consuming protecting group strategies, based on the reaction between thiols and unsaturated carbon chains, denoted as **thiol-ene** or **thiol-yne** chemistry. Because of the disadvantages of working with thiols (*i.e.* unpleasant smell, limited commercial availability and instability due to oxidation reactions), there has been a continuous interest in the development of new ways to protect thiols, e.g. as disulfide, thiocarbonylthio-group or methanesulfonate. However, most of these methods require a protecting and a deprotecting step, which is unfavorable in terms of atom-efficiency and overall yield. The strategy herein presented, depicted in Scheme 1-1, is based on the use of a **thiolactone as a precursor for a thiol**, allowing for the direct introduction of a thiol, starting from stable amino compounds without the need for a subsequent deprotection step.
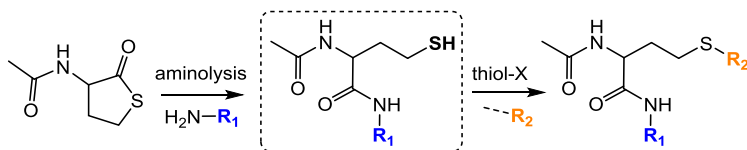
Scheme 1-1. Thiolactone strategy: a thiol is introduced by aminolysis of the thiolactone. In a next step, a thiol-X reaction is performed, which is achievable in the same reaction mixture.

Using thiolactones in polymer synthesis has a dual advantage: On one hand, it offers a chemoselective, atom-efficient way of generating thiols, while at the same time it is possible to introduce functionality *via* the amine. This one-pot amine-thiol-ene conjugation reaction was used for the synthesis and modification of diverse polymeric systems.

1.2. OUTLINE

Chapter 2 highlights the latest developments in thiol-based chemistries for polymer synthesis and functionalization. The reactivity of the thiol function relies on its ability to form reactive thiyl radicals as well as thiolate anions. An overview of the most commonly used reactions is given, classified according to which mechanism – radical or nucleophilic – is followed. Theoretical aspects are documented with dedicated examples. Especially radical and nucleophilic thiol-ene and thiol-yne addition reactions are important in the context of this work.

Chapter 3 addresses the use of protection strategies for thiols. Although thiol-based chemistry has gained importance in the synthesis of polymeric materials, there are some problems related to this functional group, which have to be kept in mind. Besides a usually unpleasant smell and limited commercial availability, thiols can act as chain transfer agent in radical polymerization processes and are prone to oxidation reaction, forming (undesired) disulfides. Therefore, a lot of effort has been undertaken to overcome these problems, by incorporating thiols in a masked state, or using protection groups. These methods can be atom efficient of non-atom efficient. A significant part of this chapter is giving a background on thiolactones as latent thiols, as this will be the central topic of this manuscript.

Chapters 4, 5 and 6 combine thiolactones with radical thiol chemistry. Interestingly, the thiolactone ring-opening and radical thiolation occur *via* fundamentally different mechanisms. It is shown that, although chemoselectivity issues have to be considered, these two processes can proceed simultaneously in the same reaction mixture.

Chapter 4 describes the *in situ* generation of thiols by nucleophilic ring-opening of a thiolactone with amines, followed by a UV-initiated radical thiol-ene reaction in a one-pot fashion. This versatile protocol has been evaluated for the accelerated synthesis of several types of polymeric architectures. After elaboration of a model amine-thiol-ene conjugation reaction, the readily available *N*-acetyl homocysteine thiolactone has been used as a compound to elegantly modify alkyne-containing polymers. A route based on a novel thiolactone-containing monomer, alloc-thiolactone, has been developed to successfully assemble functional, linear polyurethane-like polymers and polymer networks *via* a mild and straightforward radical photopolymerization process.

In **Chapter 5** a thiolactone derivative of 10-undecenoic acid was used as a renewable AB'-monomer for the one-pot synthesis of diversely substituted polyamide structures, containing amide moieties both in the polymer backbones and in their side-chains. Nucleophilic aminolysis of the thiolactone entity liberates a thiol, which further reacts in a stepwise thiol-ene photopolymerization reaction. Using different primary amines, several structurally diverse polymers, with physical properties dependent on the length and chemical identity of the side-chain, were obtained. Post-polymerization oxidation of the sulfide linkages in the polymer backbone to their corresponding sulfoxides and sulfones altered the material, with the degree of oxidation having an impact on the final mechanical properties. Furthermore, this polymerization procedure was applied for the synthesis of functional polymer networks.

Chapter 6 describes the combination of thiol-yne chemistry and thiolactone chemistry for the synthesis of hyperbranched polymers. In a first part, alkyne-thiolactone was synthesized as an A'B$_2$-type of monomer, where A' symbolizes a thiolactone unit and each π-bond of the alkyne group is a B unit. After aminolysis, an AB$_2$-monomer is generated. Through thiol-yne reaction, hyperbranched polymers were obtained, which could be characterized *via* NMR spectroscopy and SEC. Other A'B$_2$ and AB monomers were synthesized, one of them based on pTHF as a macromolecular precursor. The efficacy of a novel triflate initiator for pTHF was evaluated for this purpose.

Chapter 7 is different from the previous chapters, since radical processes are avoided. This offers the additional advantage of incorporating functional groups that are otherwise incompatible with radical processes. In this chapter, an isocyanate-free method for the synthesis of functionalized polyurethanes, based on amine–thiol–ene conjugation, was elaborated. *In situ* polymerization *via* Michael addition yields polyurethanes with a large variety of chemical functionalities. Side-chain functionality originates from the modular use of different amines, allowing for the introduction of

pendent functional groups along the polyurethane backbone. Model studies revealed the kinetic profile of this reaction sequence and excluded the occurrence of competing reactions, such as aza-Michael addition and disulfide formation.

Finally, **Chapter 8** describes the formation and modification of polymers with thiolactone handles in their side-chains. A proof for the double modification (aminolysis and subsequent thiol-X modification) of thiolactone units, incorporated in linear polymer scaffolds, was given. These polymers were prepared by either RAFT or NMP starting from a stable, readily available styrenic thiolactone monomer (St-TLa). Successful copolymerization of the latter with styrene (St) or methyl methacrylate (MMA) yielded linear polymers with varying thiolactone content (4–25%). Upon amine treatment, the ring-opening of the pendent thiolactones resulted in the formation of linear polythiols. Different primary amines were attached to the polymer backbone, while the Đs remained unchanged. The resulting polythiols are versatile scaffolds for further modification by various thiol-X reactions. In this respect, thiol–maleimide conjugation was used as a model reaction. NMR- and SEC-analyses revealed a near-quantitative double modification of thiolactone containing PS and PMMA by subsequent treatment with propylamine and *N*-benzylmaleimide.

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Abstract

Thiol-based chemistry has gained importance in polymer synthesis during the last years as a valuable alternative to the popular copper-catalyzed cycloaddition reaction between azides and alkynes. Thiols are easily transformed into their corresponding thiyl radicals or thiolate anions and are therefore versatile, reactive species. Many reactions involving thiols have therefore arisen as a means of performing efficient transformations on polymers. Two types of thiol-based reactions can be distinguished: nucleophilic and radical mediated processes. Especially the radical addition between a thiol and an alkene has played an important role in polymer synthesis and has often be denoted thiol-click chemistry. This chapter gives an overview of the currently used thiol-based chemistries in polymer synthesis, along with some dedicated examples.

Chapter 2
Thiol-X reactions in polymer chemistry

2.1. INTRODUCTION

Effective transformations on polymers are the topic of a great amount of research. Indeed, in contrast to organic synthesis, where efficient reactions are needed to increase overall yields, any transformation performed on a macromolecule must unavoidably be specific and high-yielding to obtain the (desired) fully reacted end-product. In this context, a lot of attention has been given to the click chemistry concept, for the first time presented by Sharpless, Kolb and Finn in 2001.[1] Click chemistry could (and should) be regarded a philosophy rather than a method, inspired by nature's ability to selectively join small molecules together, with the aim to gather a series of extremely efficient reactions which are applicable in both small- and large-scale applications. It was proposed that a reaction, in order to be of any meaning within this terminology, should meet certain strict criteria, all intended to simplify the overall reaction process. In their original article, the authors considered a range of reactions, emphasizing on the nucleophilic ring-opening of spring-loaded rings such as epoxides and aziridines and [3+2] alkyne-azide cycloadditions. Especially the copper-catalyzed Huisgen alkyne-azide reaction has had a great impact on polymer synthesis, because of its chemoselectivity and efficacy.[2-5]

Between 2001 and now, the amount of papers and reviews dedicated to the use of CuAAC click chemistry for the development of advanced materials, has increased progressively. However, the reaction requires the use of copper(I), and consequently ligands, for it to be able to proceed at room temperature. Together with the use of hazardous azide compounds, this is considered a drawback for certain applications, such as *in vivo* biological systems, electronic devices, … These considerations have motivated researchers to turn to other, metal-free chemistries,[6, 7] also exhibiting characteristics that fit partly in the click philosophy. The most prominent examples are the strain-promoted azide-alkyne cycloaddition reaction (SPAAC),[7] Diels-Alder reactions[8, 9] and reactions involving thiols.

Especially the latter have played an important role in the design of new functional materials, due to the versatility and the high reactivity of the thiol group. This reactivity originates from the specific

nature of the sulfur-atom, having a high electron-density and available d-orbitals. Both thiolate anions and thiyl radicals are readily formed and are considered "motivated" species for reaction, generally leading to high yields under relatively benign conditions. Essential when dealing with thiol-based chemistry, is the clear recognition that not all thiol structures behave equally. In a review by Hoyle et al, the thiol structures that are typically encountered are devided into four basic types:[10] alkyl thiols, propionate thiols, acetate (glycolate) thiols and aromatic thiols (Figure 2-1).
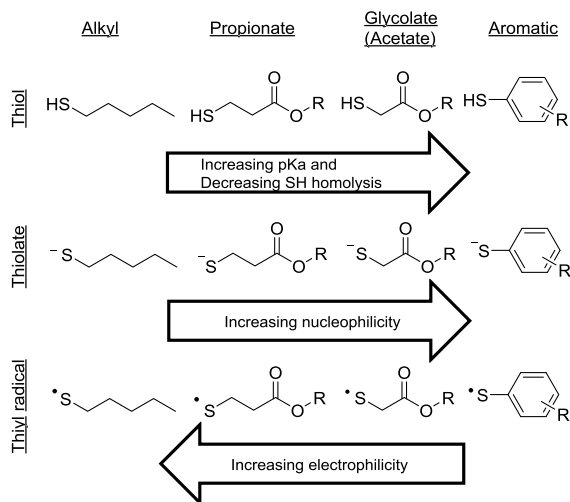
Figure 2-1. Structures of various thiol, thiolate and thiyl radical types.

In addition to these basic thiol types, Figure 2-1 also shows the corresponding thiolate anions and thiyl radicals. Arrows indicate the direction of increasing pK_a of the conjugate acids, the hydrogen abstractability by radicals, the nucleophilicity (thiolates) and electrophilicity (thiyl radicals). Due to the nature of these different thiol species and their corresponding thiolates and thiyl radicals, a variety of useful and readily available organic substrates becomes available for thiol-based reactions. Electron-rich enes and alkynes are used as substrates in radical reactions with thiyl radicals, whereas nucleophilic reactions with thiolate anions involve Michael additions to electron-poor enes, reactions with isocyanates, epoxides and halogens. Bowman et al.[10] referred to this set of reactions in their review as being a literal *toolbox* of efficient chemical reactions (Scheme 2-1). These reactions are indeed efficient, as they all proceed very rapidly, go to high conversions under mild reaction conditions and require little or no purification.
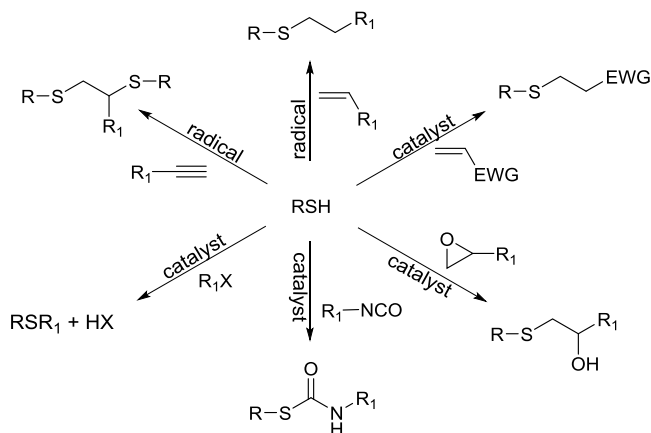
Scheme 2-1. Toolbox of efficient thiol reactions. EWG = electron withdrawing group. X = Br, I and R$_1$ = aliphatic or aromatic organic/bioorganic groups.

The constitution of this toolbox shows that thiols can undergo *many* successful reactions under mild reaction conditions. Although this is in fact a valuable property, the word *many* implies a restriction: they are susceptible to multiple simultaneous reactions. This limitation is generally acknowledged, but still several thiol-chemistries are frequently referred to as being thiol-click reactions. Here, we wish to point out again that, besides simplicity, the essential idea in click chemistry is to develop a set of efficient reactions, which should be thought of as "spring-loaded" for a single trajectory.[1] This means that click reaction components, although highly reactive, should also be chemoselective and orthogonal to a broad range of reagents, solvents and other functional groups. Even though an alternative set of parameters was suggested to revise the click conditions for polymer chemistry,[11] it was emphasized that the initial requirements of chemoselectivity/orthogonality, modularity and wideness in scope should not be put into question. The adaptation of the click concept to thiol-X chemistries is therefore, also in the field of macromolecular synthesis, unjustified. In the future content of this work, the term "click" will therefore be avoided when addressing thiol-based chemistry.

There are two basic types of thiol chemistries: those proceeding by radical processes and those that follow a nucleophilic pathway. The basic features of these reactions will be discussed in the following sections, illustrated by some recent representative examples of the implementation of these reactions in macromolecular design.

2.2. NUCLEOPHILIC THIOL REACTIONS

2.2.1. Thiol-epoxy reactions

Oxirane (or epoxide) ring-opening reactions are very reliable, stereospecific and nearly quantitative reactions. The paramount advantage of these S_N2-type reactions is the fact that competing elimination reactions are stereoelectronically disfavored, resulting in very high yields and product purity. The mechanism of the reaction is shown in Scheme 2-2. The reaction is catalyzed by a variety of strong bases, often tertiary amines, needed for the deprotonation of the thiol. Depending on the used catalyst, the reaction yields can vary significantly. Friguelli et al.[12] investigated the reaction of different oxiranes with thiophenol in bulk conditions, with the use of a Lewis or Brønsted acid catalyst. Also NaOH as a catalyst in water was used.[13]
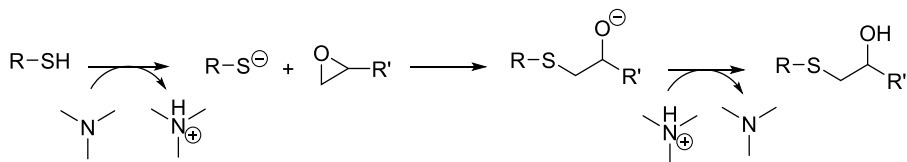
Scheme 2-2. Proposed mechanism for the base-catalyzed thiol-epoxy ring-opening reaction.

Thiol-epoxy reactions play a major role in various synthetic applications, for example in the development of biological and pharmaceutical compounds. Additionally, it is clear that the reaction has a distinct industrial relevance, being involved in the formation of adhesive, high performance coatings and composites. A particular, relatively new use of thiol-epoxy chemistry is its use as a two-component "self-healing agent". This means that both epoxy and its hardener mercaptan were microencapsulated. Once included in a traditional epoxy matrix, this two-component self-healing agent readily reacts when a crack proceeds in the material. This quickly initiates a healing process that allows the material to recover nearly fully, whilst only insignificantly affecting mechanical properties. The high efficiency of the thiol-epoxy reaction, even in the very restrictive conditions of the matrix, lies at the basis of these self-healing capacities.[14] Since then, this efficient chemistry has been implemented in various self-healing systems.[15, 16]

Thiol-epoxy reactions have also been used in other synthetic procedures, for example in the functionalization of epoxy supported bead surfaces. Reaction with dithiotreitol offered thiol and hydroxyl-functionalized beads. Next, model enzymes were attached to the surface through the thiol-

disulfide exchange reaction (Scheme 2-3). Also other functional groups could be incorporated using the same reaction.[17]
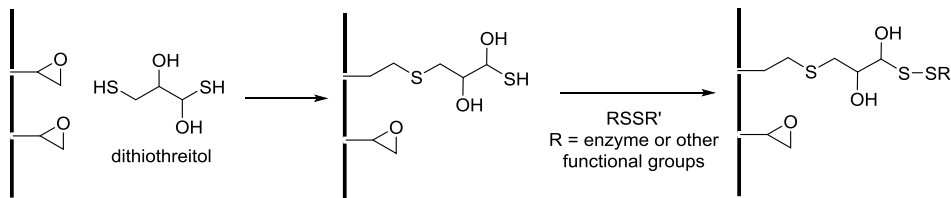
Scheme 2-3. Functionalization of support beads via initial thiol-epoxy reaction, followed by a disulfide-exchange reaction to efficiently link enzymes and other functional groups to the bead surface.

2.2.2. Thiol-isocyanate reactions

The base-catalyzed addition reaction of thiols to isocyanates has been known since the early 1940's as an efficient reaction that gives no byproducts. The kinetics of the reaction of primary and secondary thiols with phenylisocyanate indicate a fast reaction, while reactions with non-aromatic isocyanates proceed at lower rates. The mechanism of the anionic sequential chain-growth-step-growth process is depicted in Scheme 2-4. In a first step, the thiolate anion is generated through a catalytic amount of base, usually an amine. After atom-efficient addition, the proton abstraction in the second step readily regenerates the thiolate anion. Considering the low pK_a values of thiols relative to other typical organic protic species, this proton abstraction readily occurs. This also explains the observation that the thiol-isocyanate reaction proceeds rapidly and without side-products in the presence of water and alcohols. It is well-known that the reactivity of hydrogen-containing compounds such as alcohols, thiols, and primary or secondary amines towards isocyanates is proportional to the nucleophility of –OH, -SH and –NH$_2$, and the electron deficiency of the isocyanate carbon.
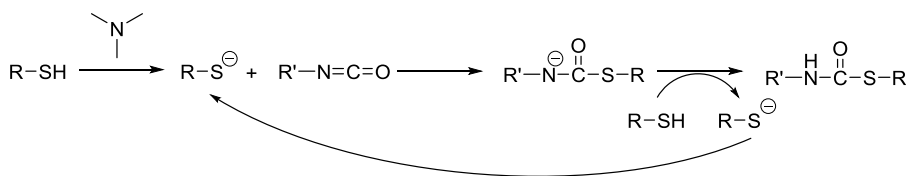
Scheme 2-4. Mechanism for the thiol-isocyanate reaction sequence.

The identity of the catalyst, the thiol acidity and the structure of the isocyanate all have a pronounced effect on the reaction kinetics.[18] The catalytic efficiency of tertiary amines is dependent upon the availability of the electrone lone pair, determined by both the basicity of the nitrogen and steric hindrance. Comparing different tertiary amines, it is observed that the reaction rate coefficients for DBN and DBU are significantly greater than for DABCO, DMAP, TEA, TBA and proton sponge, due

to the higher basicity of DBN and DBU (structures shown in Figure 2-2). The reaction is further influenced by the type of thiol, with lower pK_as increasing the rate of reaction since the formation rate of thiolate anions is promoted with lower pK_a values. The reactivity of isocyanates is affected by the electron deficiency of the carbon atom, in such a way that substituents stabilizing the positive character on the carbon atom enhance the isocyanate reactivity. In that respect, phenyl isocyanate showed a much higher reactivity towards thiophenol than hexyl isocyanate.[18]
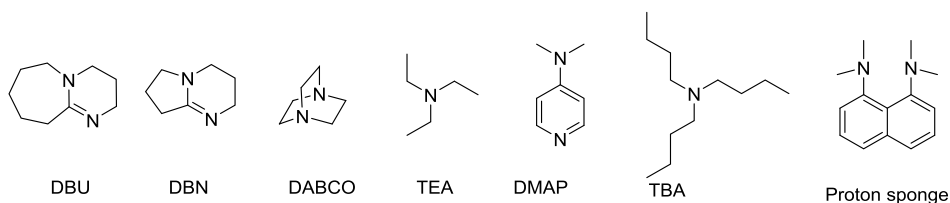
Figure 2-2. Molecular structures of tertiary amine catalysts.

Although thiol-isocyanate reactions (in the presence of low concentrations of mild catalysts) are much more efficient than the reaction of isocyanates with alcohols, the applications of polythiourethanes in industry are still limited compared to polyurethanes. The main industrial application of polythiourethanes is their usage as high refractive index optical materials.[19, 20] For example, difunctional methacrylates with thiourethane backbone groups and sulfide links were prepared by a thiol-isocyanate reaction. When polymerized, the resulting films produced highly refractive, scratch-resistant coatings on polythiourethane and polycarbonate optical plastic lens materials.[20]

Thiol-isocyanate reactions have been implemented in surface engineering, for example by incorporating functionalities onto a polymer brush surface.[21] Silicon substrates were first functionalized with a photoinitiator for the radical polymerization of 2-isocyanatoethyl methacrylate. The resulting isocyanate-containing polymer brushes could then serve as precursor for further functionalized materials, through the reaction with amines and thiols (Scheme 2-5a). Quantitative conversions were observed within minutes when using DBU as a catalyst, as observed by FT-IR spectroscopy. Sequential/area selective thiol-isocyanate brush modifications could be achieved using an elastomeric microcapillary patterning process, as shown in Scheme 2-5b. A lined-patterned PDMS stamp was used to create multifunctional, defined mictropatterned surfaces.
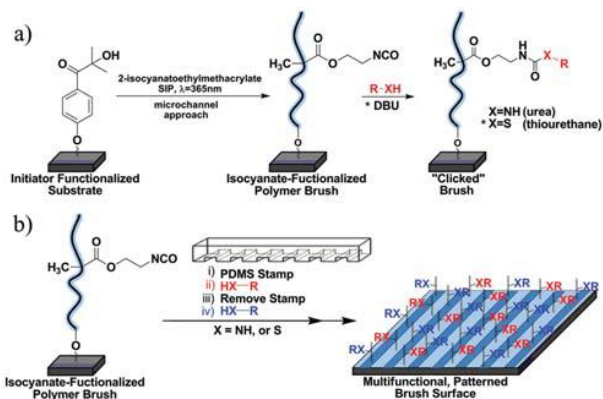
Scheme 2-5. a) Procedure for the surface-initiated photopolymerization of 2-isocyanatoethyl methacrylate and subsequent functionalization of the isocyanate moitie with amines or thiols. b) Patterning procedure for the isocyanate-containing polymer brush surfaces with sequential isocyanate reactions.

2.2.3. Thiol-halogen nucleophilic substitution reaction

Thiols can efficiently participate in nucleophilic substitution reactions with reactive substrates carrying good leaving groups. Therefore, thiol-halogen reactions have become one of the major thiol-X reactions. The reaction proceeds in the presence of organic bases such as trialkyl amines and generates halogenated salts, which are readily removed as precipitants. The most employed thiol-halogen S_N2 substitution reaction is the thio-bromo reaction, which has been called thio-bromo "click" due to its high reaction rates. Percec and coworkers[22] combined this nucleophilic substitution reaction for the synthesis of dendritic molecules with the acylation reaction with 2-bromopropionyl bromide. It was shown that multiarm dendritic polymers could be prepared with polyacrylate units connecting each of the branch units (Scheme 2-6).
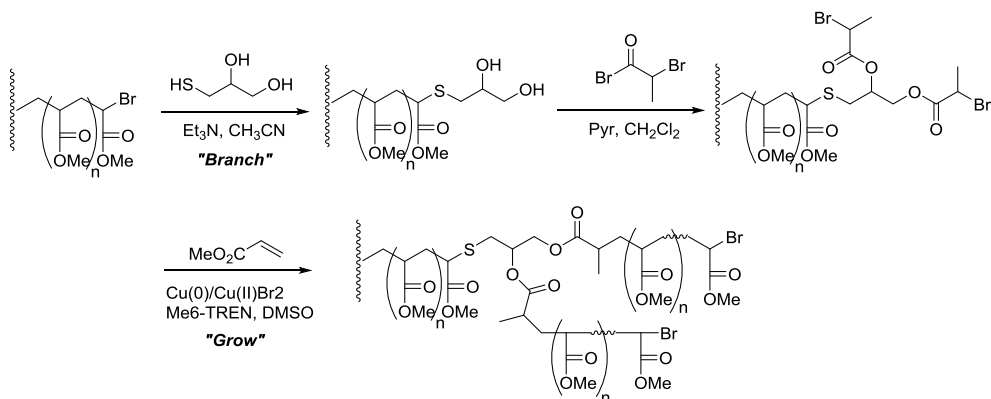
Scheme 2-6. Synthesis of bromo-terminated macromolecular dendrimers via thio-bromo and acylation reactions.

Also Davis et al.[23] used thio-bromo chemistry for the preparation of hyperbranched and multiblock polymers, through combination with RAFT chemistry.

Besides the thio-bromo reaction, the nucleophilic substitution reaction on the *p*-fluorine group of pentafluorophenyl moieties, has been used as an effective linkage strategy. For example, Becer et al.[24] prepared glycopolymers through the substitution reaction of a thiol-glucose unit with a pentafluorophenyl side group of the corresponding homopolymers and copolymers with styrene (Scheme 2-7). By following the reaction kinetics with ^{19}F NMR, the substitution reaction was shown to be nearly quantitative in the order of little over one hour. Also in another literature examples, thio-para-fluoro coupling has been used as a post-polymerization modification tool.[25]
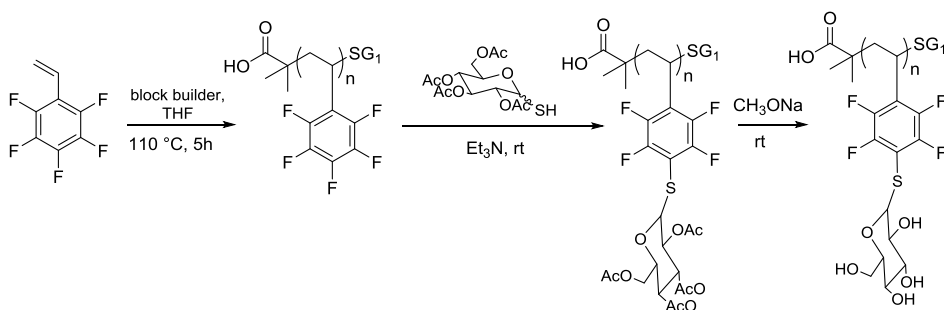
Scheme 2-7. Synthesis of glycopolymers using a thiol-halogen nucleophilic substitution reaction.

2.2.4. Thiol-Michael reactions

Probably one of the most promising and applicable efficient thiol reactions in polymer chemistry is the thiol-Michael reaction.[26] Generally, Michael additions involve the reaction of an enolate-type nucleophile in the presence of a catalyst to an α,β-unsaturated carbonyl. More specifically, the reaction is described as a special type of conjugate 1,4-addition in which the strong nucleophilic attack on the β-carbon of an α,β-unsaturated carbonyl results in a negatively charged enolate intermediate, that subsequently yields the Michael adduct, by protonating the catalyst. As illustrated in Scheme 2-8, the thiol-Michael reaction between a thiol and an electron-deficient vinyl group yields the thioether addition product, in the presence of a catalytic amount of base (e.g., an amine) or nucleophile.

The base-catalyzed pathway goes as follows: A thiol proton is abstracted by the action of a common base such as triethylamine, forming a thiolate anion together with a conjugate acid. The formed thiolate anion is a strong nucleophile, which initiates the addition to the electron-deficient β-carbon of the double bond, yielding an intermediate carbon-centered anion. Being a strong base, this anion can again abstract a hydrogen from the conjugate acid to yield the thioether as a product. The

base catalyst is thus regenerated in the process and the anionic propagation step has been shown to proceed rapidly in the absence of interference from protic sources such as water and alcohol.

a. Base-Catalyzed Mechanism
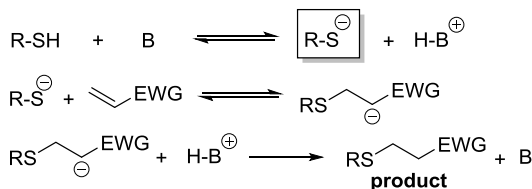
b. Nucleophile-Catalyzed Mechanism
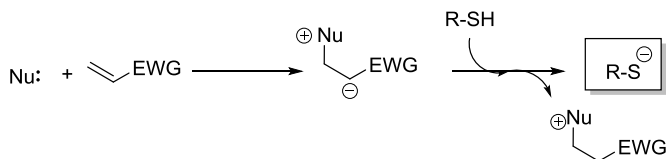
Michael-Addition Reaction Mechanism
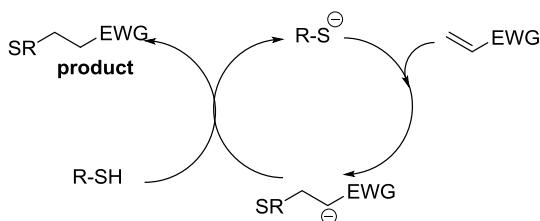
Scheme 2-8. The base and nucleophile catalyzed Michael addition reaction mechanism. The base catalyzed mechanism shows the hydrothiolation of an activated C=C bond *via* the addition of the anion across the electron-deficient beta-carbon of the ene, whereas in the nucleophilic pathway, the nucleophile undergoes conjugate addition to the activated C=C bond, generating the strong intermediate carbanion, which in turn deprotonates the thiol for subsequent thiol-Michael addition. EWG = electron-withdrawing group.

The reaction kinetics and yield of the base-catalyzed thiol-Michael reaction have been shown to depend on factors such as the strength and concentration of the base catalyst, the thiol pK_a, the steric accessibility of the thiol and the nature of the electron-withdrawing group. Other factors affecting the kinetics include the polarity and the pH of the solvent.

In the nucleophilic pathway (Scheme 2-8 **b**), the nucleophile itself does not catalyze the reaction. Instead, it reacts with the electron-deficient C=C bond to generate a strong base. Therefore, in this case, the kinetics are dependent on the nucleophilicity of the catalyst. Indeed, the higher the nucleophilicity of the catalyst, the larger the amount of active thiolate anion that can be generated. Especially phosphines have been used as nucleophilic catalysts, as it was shown that they catalyzed the reaction much more rapidly and efficiently in comparison with bases.[27-29] Li et al.[30] investigated the

thiol-Michael reaction with methacrylates as substrate, of which the carbon-carbon double bond generally shows a low reactivity under typical thiol-Michael addition reaction conditions. The researchers demonstrated that using dimethylphenylphosphine as a catalyst led to quantitative conversion of the reactants within less than an hour, while triethylamine or *n*-pentylamine required several hours to achieve high conversions.

Typical substrates for the thiol-Michael reaction include maleimides, vinyl sulfones, acrylates, acrylamides and methacrylates (Scheme 2-9). The order of reactivity is as follows:[31] maleimides > vinyl sulfones > acrylates/acrylamides > acrylonitrile > methacrylates/methacrylamides.

Scheme 2-9. Reactivity of commonly used substrates in thiol-Michael addition reactions.

Applications of the thiol-Michael addition reaction are numerous and found in different fields of material development. Thiol-acrylate systems have been used for the synthesis of dendrimers,[32, 33] modification of particles,[34] degradable hydrogels[35, 36] and block-copolymers. Recently, Pritchard et al.[37] demonstrated the formation of robust injectable hydrogels cross-linked *via* a Michael addition in aqueous media, exhibiting material properties resembling soft tissue. Thiol-maleimide type of reactions have been used most commonly in biological applications, primarily due to the selectivity in aqueous environments. The reactivity of maleimides is explained by two different factors: (i) the bond angle distortion and the ring strain, and (ii) the carbonyl groups being in the *cis*-conformation.

A recent, interesting contribution from Dove et al.[38] describes the (nucleophilic) thiol-yne Michael addition. Similar to the radical mediated thiol-yne reaction (*vide infra*), the thiols can in theory add twice across the triple bond, although the second addition is reported to be a lot slower than the first. This means that the single addition ene product can often be isolated in good yields, in contrast to the radical thiol-yne addition, where the second addition usually proceeds at a much higher rate. Use of the right catalyst (1,5,7-triazabicyclo[4,4,0]dec-5-ene, TBD) allowed for a full conversion of the single-reacted "ene" product (Scheme 2-10).

Scheme 2-10. Sequential addition of thiols to PEG-bispropiolate.

2.3. RADICAL THIOL CHEMISTRIES

In the last decade, radical reactions involving thiols have again taken an important role in the synthesis of (functional) polymeric materials. Two reactions will be discussed in this chapter: thiol-ene and thiol-yne reactions. Both the reactions occur via a chain-growth free radical polymerization process and achieve very rapid reaction rates and high conversions. Especially the radical addition of thiols to alkenes has gained renewed interest, the reaction's properties fitting well in the click chemistry philosophy. Whereas in the previous chapter, the reactivity of thiols was based on the ease of anion formation resulting from the thiol's pKa, the weak sulfur-hydrogen bond lies at the basis of the ease of thiyl radical formation. The strength of this sulfur-hydrogen bond is dependent on the thiol structure: Thiol propionate and thiol glycolate esters are more reactive compared to alkyl thiols, due to hydrogen bonding of the thiol hydrogen groups with the ester carbonyl (Figure 2-1).

2.3.1. Radical thiol-ene chemistry

There are several features associated with the thiol-ene reaction that make it particularly attractive, of which the most notable is the high conversion in short (seconds to minutes) timeframes. An illustrative review on thiol-ene polymerizations was given by Hoyle et al.[39, 40]
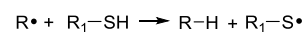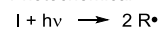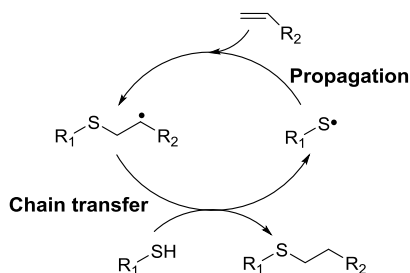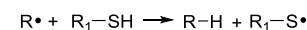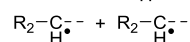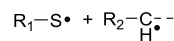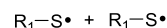
Figure 2-3. The radical-mediated thiol-ene reaction mechanism, with initiation, propagation and chain transfer, and termination processes.

Generally, the radical variant of the thiol-ene reaction is induced photochemically, proceeding *via* a typical chain process with initiation, propagation and termination steps (Figure 2-3). There are a number of ways of initiating thiol-ene reactions, photochemically or thermally, or by the use of redox initiators.[41] Yagci et al.[42] compared different thermal and photochemical initiators for thiol-ene coupling reactions, concluding that type I (cleavage type) photoinitiators such as DMPA gave the highest efficiencies. The structures of some typical radical initiators are shown in Figure 2-4. Moreover, it was shown that thiyl radicals can even be formed under sunlight,[43] or without photoinitiator.[44, 45]

Once formed, the thiyl radical initiates the chain process by inserting into the carbon-carbon double bond of the ene to give a carbon-centered radical. A subsequent hydrogen abstraction of a thiol group by this radical forms a thiyl radical, owing to the fact that thiols are good chain transfer agents, characterized by high chain transfer constants. Finally, as in any radical process, termination reactions occur by radical-radical coupling.

DMPA	Benzophenone	Camphorquinone	AIBN
type I photoinitiator	*type II photoinitiator*	*type II photoinitiator*	*thermal initiator*
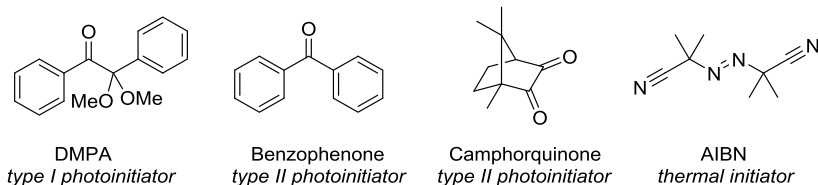
Figure 2-4. Molecular structures of some radical photo- and thermal initiators used in thiol-ene and thiol-yne chemistry. Type I photoinitiators: cleavage type; type II photoinitiators: hydrogen abstraction type.

The rate of the reaction is largely determined by the propagation to chain transfer ratio (k_p/k_{ct}). The alkene structures plays a dominant role, its reactivity being dependent on the extent of substitution. Highly substituted alkenes are less reactive than singly substituted alkenes. This is attributed to a reversible equilibrium in the propagation step, leading to a mixture of Z and E-substituted alkenes. Norbornene is different with the rates of free-radical addition of thiols being exceptionally high. This is explained by a combined effect of ring strain relief and the rapid hydrogen abstraction of the formed carbon-centered radical. The carbon-centered radicals that form when the thiyl radical is added to a methacrylate, styrene, or conjugated diene carbon-carbon bond are very stable and have inherently low hydrogen-abstraction rate coefficients, resulting in a slow chain transfer. The relative reactivity of some common alkene structures is depicted in Figure 2-5. The influence of the thiol structure on the reaction rate is assumed only to be of importance when the chain transfer is the rate-determining step.
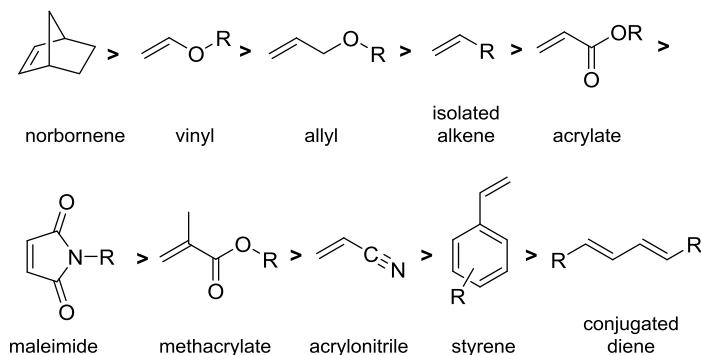
Figure 2-5. Relative reactivity of some general ene-structures used in radical thiol-ene chemistry.[39]

The widespread applications of thiol-ene chemistry in polymer and materials synthesis are documented in several recent reviews,[46, 47] owing to the continuous interest in this metal-free, efficient reaction. Some quite novel applications of thiol-ene reactions can be associated with RAFT polymerization, by virtue of the fact that the end-group originating from the chain transfer agent (CTA) can be regarded a latent thiol (see Chapter 3),[3, 48, 49] available for further modification on the polymer ω-chain-end. Modifications on the CTA also allow for the incorporation of functional groups at the α-chain-end. Stamenovic et al.[50] in our research group used this feature to synthesize a series of norbornenyl- and allyl- functionalized CTA's, including xanthates, dithiobenzoates and trithiocarbonates (Figure 2-6). Norbornene is the most reactive ene toward radical mediated thiol-ene chemistry, allowing to add additional functionality through a post-polymerization modification reaction on the polymer end group.
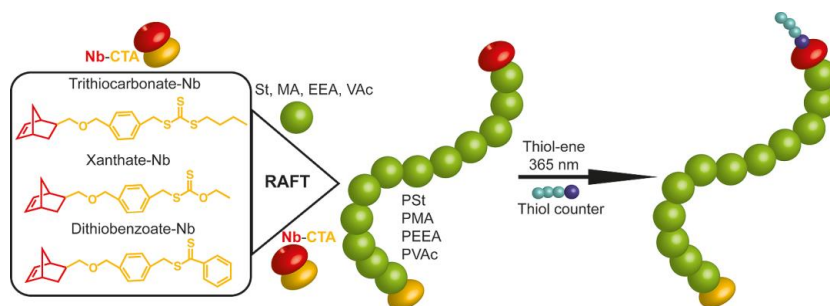
Figure 2-6. Norbornenyl- RAFT CTA's for the synthesis of norbornenyl-functionalized RAFT polymers, with subsequent thiol-ene functionalization.

Thiol-ene reactions have also been used for the synthesis of more complex structures, such as dendrimers, hyperbranched polymers and star polymers. For example, Antoni et al.[51] detailed a rapid procedure (everything done in a single day) for the synthesis of high molecular weight, well-defined 6th generation dendrimers *via* sequential radical thiol-ene and Cu-catalyzed alkyne-azide coupling reactions.

Although thiol-ene reactions have attracted more attention the last years as efficient linking strategy, it should be noted that historically, this type of reaction has shown its relevance mostly in the preparation of near-perfect networks and films, as exemplified by the work of Hoyle[39, 52-54] and Bowman.[55-57]

2.3.2. Radical thiol-yne chemistry

A complementary reaction to the above described thiol-ene reaction, is the radical thiol-yne addition reaction. Similar to the nucleophilic thiol-yne reaction, the triple bond has the ability to react with two equivalents of thiol, thus forming a double addition product with 1,2-regioselectivity. Mechanistically, the two separate thiol additions proceed in a similar manner to the thiol-ene reaction (Scheme 2-11). Again, a thiyl-radical is formed photochemically or thermally, which undergoes direct addition to the yne-bond, yielding the intermediate thioether vinyl radical. In the subsequent chain transfer step, the vinylthioether product is generated together with a new thiyl radical. A second thiyl addition to the vinylthioether (formally a thiol-ene reaction) yields the intermediate carbon-centered radical which undergoes a second chain transfer step, finally yielding the double addition thiol-yne product. Fairbanks et al.[58] showed that the subsequent thiol-ene reaction was approximately three times faster than the initial thiol-yne reaction.
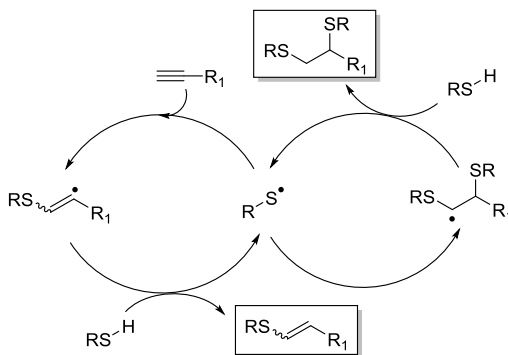
Scheme 2-11. Proposed mechanism for the double hydrothiolation reaction of terminal alkynes, under radical conditions.

A nice example of thiol-yne chemistry in polymer synthesis is its use as a straightforward manner of creating hyperbranched polymeric structures, making efficient use of the alkyne group as a double reaction site. Perrier et al.[59] describe the synthesis of a monomer containing both an alkyne and a thiol group. This monomer, a low-molecular weight bifunctional compound or a RAFT derived heterotelechelic polymer, can be regarded an AB_2 monomer, the alkyne being a reactive site where two addition reactions can take place (Scheme 2-12). Because of the fast second addition, a high degree of branching was obtained, leading to structures still having a lot of free alkynes, accessible for further modification reactions. The group of Perrier has done a lot of work on the synthesis of functionalized hyperbranched structures through thiol-yne chemistry.[59-62] The advantage of the thiol-yne reaction for the synthesis of hyperbranched structures was also evidenced in the work of Gao,[63] who used sequential thiol-ene and thiol-yne reactions to prepare these structrues in an A_2 + CB_2

approach. A dithiol (A$_2$) was first reacted with an acrylate(C)-alkyne(B$_2$) compound in a nucleophilic thiol-ene addition reaction. The resulting AB$_2$-monomer was subsequently reacted under UV-light to yield hyperbranched polymers with high molecular weights and broad polydispersities.
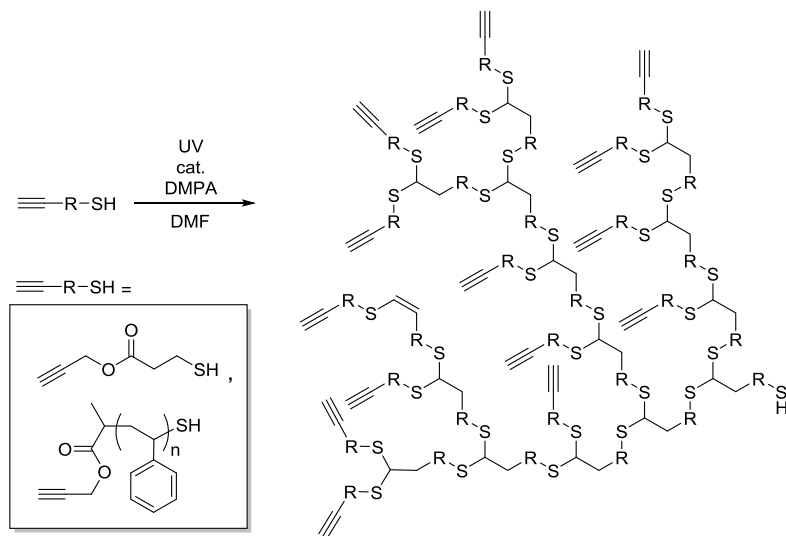
Scheme 2-12. Polymerization of a molecule containing an alkyne and a thiol functionality, leading to hyperbranched alkyne-functional polymers.

Voit et al.[64] have used thiol-yne chemistry for the synthesis of high-refractive index materials, making use of the selective thiol radical mono-addition to phenyl-acetylene derivatives. Using dithiols and tri-alkyne monomers, hyperbranched structures were obtained upon termal initiation with AIBN. The polymers are optically transparent and have high refractive indices.

2.4. CONCLUSION AND PERSPECTIVES

Thiol-based chemistries have become indispensable in the synthesis of highly functionalized, tailor-made polymers with different architectures. The reactivity of the thiol group enables both radical and nucleophilic reaction mechanisms with a variety of substrates. Due to this reactivity, most of these thiol-based reactions proceed rapidly with high conversions. Therefore, they have been found to be extremely useful for post-polymerization modification reactions, polymerization reactions and the preparation of cross-linked materials. The current trend towards sustainable development and green production processes has benefitted from the advances in the field of click chemistry, since click reactions are fundamentally 'green' due to the restrictive criteria to which they are bound. Although thiol-based chemistries do not fulfill all of these requirements, they have some advantages that fit well in the "click philosophy". The fact that all of the described reactions can proceed at ambient conditions, without the use of a metal catalyst, has demonstrated the utility of these reactions in biomedical applications. Moreover, the described reactions all proceed very rapidly. Nguyen et al.[65] in our research group have made a kinetic comparison of 13 different homogeneous thiol-X reactions, using online FT-IR. Besides comparing thiol addition reactions, also the reactivity of amines towards Michael substrates and isocyanates was evaluated. Michael acceptors showed to be more reactive towards thiols, whereas isocyanates react more rapidly with primary amines. Moreover, the used solvent had a considerable effect on base- and amine- catalyzed thiol-X reactions, whilst phosphine-catalyzed reactions were not significantly affected.

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Abstract

Reactions involving thiols have been extensively applied in many polymeric systems thanks to the reactive nature of the mercapto group, causing these reactions to be efficient and high-yielding. The amount of publications and reviews on the topic illustrates the rising importance of nucleophilic and radical thiol-ene, thiol-yne and other thiol-X chemistries. In view of orthogonality conflicts and considering the instability of thiols towards oxidation as well as their incompatibility with many polymerization processes, several strategies to protect thiols have been developed and optimized. Generally, a distinction can be made based on the atom-efficiency of the reactions as well as the mechanism triggering the thiol release. This chapter gives an overview of the advances in the use of protected thiols for macromolecular synthesis, with applications in polymerization or post-polymerization modification reactions, but also for the design of more complex structures. In all cases, it is essential that processes must not interfere with the latent thiol function until release is required.

Chapter 3
Protected thiol chemistries in macromolecular design

3.1. INTRODUCTION

Thiols exhibit a high reactivity towards a great amount of substrates. One could easily understand that this feature is hard to combine with the need for selectivity when multiple functional groups are present. In pure organic chemistry, protected group strategies are common practice, but macromolecular synthetic chemists are often reluctant when it comes to tedious work-up procedures while striving for the most economic and efficient way to afford the desired end-product. Nonetheless, a lot of work has been done to overcome thiol-related problems. Reflecting on both the importance and the shortcomings of thiol reactions, it is evident that many approaches have been developed to generate thiols on a polymer chain, whether present from the start in a masked state or introduced as a final work-up step. Depending on the application, a different strategy might be more applicable.

Numerous excellent reviews have been dedicated to the concept of click chemistry and applications in polymer chemistry, and more recently on the thiol-X concept (see chapter 2). However, together with the increased use of thiol-related chemistries in polymer science, the necessity for protected thiol strategies became increasingly more prevalent. Although many researchers have tackled this challenge by choosing a method applicable to their system, to the best of our knowledge, no review gathering these protected thiol techniques has appeared. The aim of this chapter is not only to give a comprehensive overview of the tools available to introduce thiols on a polymeric system, but in addition, to provide a guide that facilitates the selection of an appropriate strategy when working with protected thiols. A clear distinction will be made based on the atom-efficiency of the selected approaches. Indeed, depending on the application and purification methods, the release of (small) organic residues is a possible concern that has to be taken into account. Secondly, it is important to recognize that a thiol can be generated by either using protection-deprotection methods on a thiol of choice, or on the other hand, by using molecules that contain a thiol in a masked state. Before

describing general methods, some important issues regarding thiols in macromolecular synthesis will be discussed.

This chapter is aiming to provide an overview of the most common methods. Scheme 3-1 gives a summary of the classification that is made in this work. First, non-atom efficient strategies will be discussed. Incorporating thiols using one of these methods requires the use of a deprotection step, releasing a small molecule. On the other hand, atom efficient strategies allow for a direct incorporation of thiols in a one-step procedure.
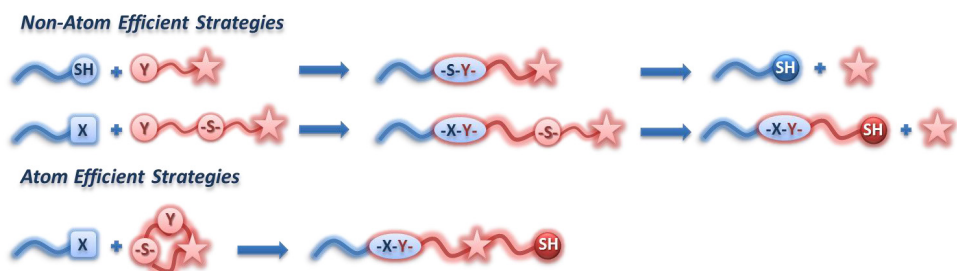
Scheme 3-1. Protected thiol strategies: Non-atom efficient processes, releasing a small molecule upon deprotection; and atom-efficient processes, where a single reaction step results in the formation of a thiol.

3.2. Thiol-related problems

The applicability and implementation of thiol-based chemistry, especially for large-scale purposes, is restricted due to a number of issues. Besides a dominant odor, especially in the case of low molecular weight thiols, a number of other problems regarding their reactivity are encountered. Also worth mentioning is that compared to other common reagents, such as alcohols and amines, the commercial availability of thiols is rather limited. This section is addressing some of the most common factors that synthetic polymer chemists have to take into consideration, such as the fact that thiols are excellent chain transfer agents and thus interfere in radical processes, and their susceptibility to oxidation.

3.2.1. Thiols as chain transfer agent

The concept of chain transfer by chain transfer agents in radical polymerizations has been described for the first time in the 1940's in the work of Mayo.[1] Polymeric radicals can, besides taking part in the propagation step, also react with each other and thus terminate the polymer chain growth. Not only the molecular weight, but also the rate of polymerization is consequently influenced. Chain transfer on the other hand, is the process that occurs when a polymer radical is terminated, while at

the same time a new radical is formed. This radical can in turn initiate a new chain (Scheme 3-2). In essence, this means that a radical is transferred from the polymer chain to another molecule, the so-called chain transfer agent. During the chain transfer step, the total radical concentration remains constant. Ideally, the newly formed radical has the same reactivity as the polymer radical and therefore does not alter the overall reaction rate. The presence of a chain transfer agent influences the polymerization by reducing the final average molecular weight of the polymer.
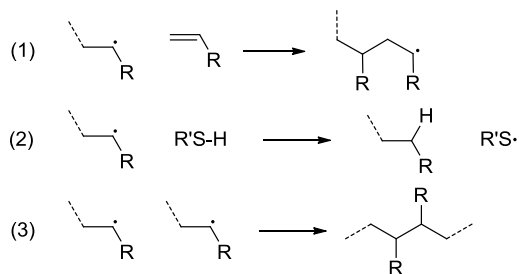
Scheme 3-2. Radical reactions in free radical polymerization. (1) Propagation, (2) Chain transfer to a chain transfer agent, in this example a thiol, and (3) Termination.

To evaluate the chain transfer, a chain transfer constant can be defined, which is a value dependent on the used monomer and the used chain transfer agent. This chain transfer constant C is defined as the rate constant for chain transfer divided by the rate constant of chain growth. The final average degree of polymerization can be calculated according to Equation 1.

$$\frac{1}{DP} = C \ \frac{[CTA]}{[M]} + \frac{1}{DP_0}$$

(1)

In this formula, [M] and [CTA] are the concentrations of monomer and chain transfer agent respectively, DP is the obtained average degree of polymerization and DP_0 is the average degree of polymerization in the absence of a chain transfer agent. If [M] = [CTA], the chain transfer constant represents the probability that any given radical undergoes chain transfer rather than growth by addition of monomer. This probability should be small if polymer formation is aimed for.

There are several chain transfer agents, but thiols are mostly documented.[2, 3] In fact, it can be understood quite easily that chain transfer lies at the basis of radical thiol-ene chemistry.[4] High chain transfer constants, and thus high rates of chain transfer, promote the formation of thiyl radicals, which can then further react with an ene with the formation of a thio-ether end-product.

Although thiols are industrially relevant as regulators in free radical polymerization reactions, it is impossible to achieve high molecular weights with larger quantities of chain transfer agent present.

The use of thiols in controlled radical polymerization reactions, such as Atom-Transfer Radical Polymerization (ATRP)[5] and Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization should be avoided and thus protection strategies become necessary. Actually, RAFT polymerization is a free radical polymerization based on chain transfer, reversibly mediated by a RAFT agent and leading to a high degree of control. RAFT agents as protected thiols will be further discussed in 3.3.2.1.

3.2.2. Disulfide formation

It is well-known that thiols are readily oxidized to disulfides and higher oxidation products by a variety of reagents, depending on the conditions.[6] On exposure to air, atmospheric oxygen can already generate disulfides, following a radical or ionic mechanism (Scheme 3-3). The ionic mechanism probably involves intermediate sulfenic acid, which cannot be isolated.[7] Moreover, autoxidation of thiols is known to be accelerated by bases.[8]
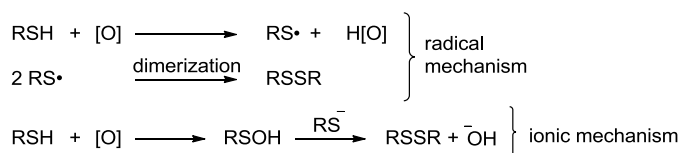
Scheme 3-3. Mechanisms of oxidation under air atmosphere.

Photo-oxidation is a second important way of producing disulfides. Thiols undergo photolytic cleavage quite easily, which results in the formation of a disulfide through radical recombination. Scheme 3-4 depicts the simple reaction scheme proposed for this reaction. This radical recombination is also a known side-reaction in radical thiol-ene processes and, unfortunately, it cannot easily be circumvented. Moreover, the easy formation of thiyl radicals is a problem in terms of shelf-life stability of thiol-ene mixtures. In many cases, stabilizers have to be added to a thiol-ene mixture to prevent "spontaneous" reaction. This is also in accordance with the observation of Bowman et al. that photoinitiated thiol-ene chemistry can proceed even in absence of radical initiators, such as DMPA or benzophenone.[9]
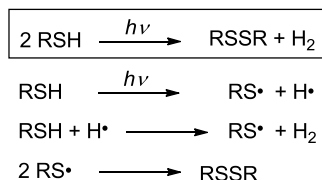
Scheme 3-4. Mechanism of the photo-oxidation of thiols.

Besides atmospheric oxygen, a number of other reagents can cause the oxidation of thiols to disulfides, although higher oxidation products are hard to avoid when applied. Examples are halogens (especially I_2), sulfoxides (such as dimethyl sulfoxide), metal ions, ... For a detailed overview of thiol oxidation techniques, the reader is referred to specialized literature.[6, 10, 11]

The equilibrium between thiols and disulfides plays an important role in many biological processes, for example in folding of proteins in living cells. The reaction has been exploited in peptide chemistry, since modification reactions on cysteine often rely on the formation of disulfide bridges. But also polymer chemists have used this linkage extensively, in vulcanization of natural rubbers, as coupling method, or as protecting group strategy. Although disulfide formation is undoubtedly a useful reaction, a major drawback is that the oxidation of thiols can occur (quite easily) at inappropriate timings, leading to unwanted side-products. Quite some examples exist in which the synthesis of polythiols is intended, but the final end-product is isolated as an insoluble cross-linked polymer network.[12] A correct use of protecting group strategies is therefore required to overcome these problems.

Finally, it is important to note that disulfide formation can be reversed by a number of reducing agents. This feature lies at the basis of using disulfides as protecting group strategy for thiols and will be discussed further in this chapter (3.3.1.1).

3.3. NON-ATOM EFFICIENT PROCESSES

In this section, a class of protected thiol strategies involving the release of a small molecule upon deprotection will be discussed. These are in other words non-atom efficient processes, which will be subdivided into two separate categories, based on the origin of the thiol. A first classification includes "thiol protection strategies". This kind of strategy is interesting when one wishes to protect a thiol of choice with the aim of releasing it at a later stage. In fact, this is in the spirit of pure organic synthesis, where functional groups are often protected to prevent reaction with other reactive groups. After the desired transformation has taken place, a deprotection step will result in the cleavage of the protecting group with release of the thiol. This is especially useful in those processes where the thiol is present from the start and has to survive the polymerization process. A second subdivision will cover "latent thiols" and is different from the previous since there is no choice of thiol possible. The thiol is introduced on the polymer starting from a precursor molecule that can be regarded as being a masked thiol. On addition of the right trigger, a thiol functionality is then generated.

3.3.1. Thiol protection-deprotection strategies

3.3.1.1. Disulfides

Disulfide bonds are covalent linkages, usually derived from the coupling reaction of two thiols. As described, disulfide formation by oxidation of thiols occurs easily by a whole range of oxidants, even atmospheric oxygen, and is consequently often regarded as a hard-to-avoid, unwanted side-reaction. Controlling the formation of disulfides is therefore of great interest and can be achieved by adjusting the pH, adding a redox reagent or applying the right protection group strategy. However, thanks to the reversibility of this oxidation reaction, the disulfide bond itself has become a useful protection group for thiols, applied in biochemistry as well as for the synthesis and/or modification of polymeric structures.[13]

Oxidation of thiols to disulfides can be achieved in numerous ways,[6] using peroxidic compounds, halogens, sulfoxides (such as DMSO), metal ions and molecular oxygen, catalyzed by different species. In some cases, precautions have to be taken to avoid over-oxidation to sulfoxides or sulfones. Disulfides as protected thiols are usually incorporated in polymers using disulfide-containing initiators or monomers, which are then used as functional handles for post-polymerization modification. Reduction takes place upon adding a reducing agent, liberating the protected thiol. Common reducing agents are phosphines, such as tributylphosphine, triphenylphosphine or *tris*(2-carboxyethyl)phosphine (TCEP), which are readily oxidized to their respective phosphine oxides (in the presence of water). Other frequently used reducing agents are thiols, the most regular being β-mercaptoethanol, dithiothreitol (DTT), or glutathione (Figure 3-1). Finally, it is worth mentioning that disulfides can also be cleaved photochemically,[14] allowing for example the synthesis of self-healing, photo-adaptable networks.[15]
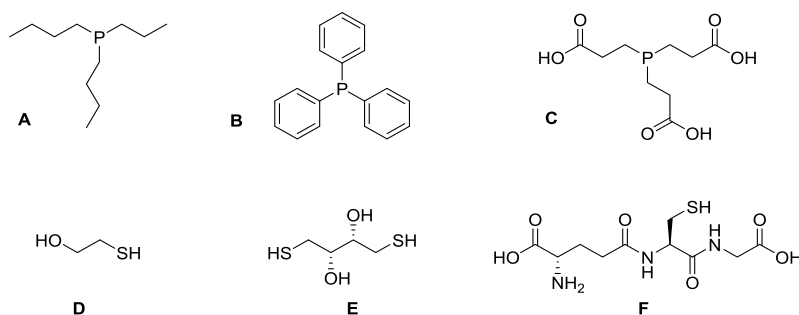
Figure 3-1. Frequently used reducing agents for disulfide reduction, usually phosphines and thiols: tributylphosphine (A), triphenylphosphine (B), TCEP (C), β-mercaptoethanol (D), DTT (E) and glutathione (F).

The reduction of disulfides is often realized through a thiol-disulfide exchange reaction, schematically depicted in Scheme 3-5 for the reaction in water.[16] The concentration of thiolate anions is determined by the pH of the medium and is an essential parameter for the reaction kinetics. It is important to note that the amount of added thiol (or reducing agent) determines whether the disulfide bonds are cleaved, exclusively forming thiols, or redistributed with the formation of (other) disulfides. Since the interconversion between thiols and disulfides is a key step in many biological processes, the reaction has been implemented in the development of advanced materials for controlled release.

$$R-SH + H_2O \rightleftharpoons R-S^{\ominus} + H_3O^{\oplus}$$

$$R-S^{\ominus} + R'-S-S-R' \rightleftharpoons R'-S-S-R + R'-S^{\ominus}$$

$$R'-S-S-R + R-S^{\ominus} \rightleftharpoons R-S-S-R + R'-S^{\ominus}$$

$$R'-S^{\ominus} + H_3O^{\oplus} \rightleftharpoons R'-SH + H_2O$$
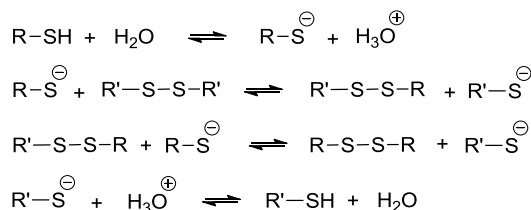
Scheme 3-5. Reaction scheme of thiol-disulfide exchange reaction in water.

Redox/thiol-sensitive polymers have indeed become an important class of stimuli-responsive materials due to their potential as drug carriers for controlled release.[17, 18] Disulfide containing polymers can be considered both redox and thiol-responsive because the S-S bond can be cleaved by numerous reducing agents, or undergo disulfide exchange in the presence of other thiols. Since the characteristic conditions of intracellular environments are mildly reducing due to the presence of significant concentrations of glutathione, disulfide links in polymeric systems can be cleaved upon entering the cell and specifically release bound pharmaceuticals. These redox/thiol-sensitive polymers are usually prepared by directly introducing disulfide groups into side chains or backbones using an appropriate monomer, cross-linker or initiator. Besides hydrogels and nanogels,[19, 20] redox-responsive disulfide containing polymers were used for the synthesis of hollow microspheres,[21] star polymers,[22-24] cyclic polymers[25] and micelles.[26, 27]

A very commonly used thiol-disulfide exchange system is the reaction of thiols with pyridyl disulfide (PDS) moieties (Scheme 3-6). The driving force for the reaction is the release of the chemically inert pyridine-2-thione group. This group has a characteristic UV-vis absorbance, which is particularly interesting, as it allows to monitor the reaction progress.[28]
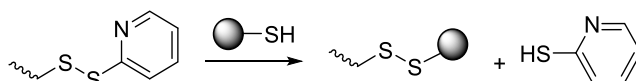
Scheme 3-6. Pyridyl disulfide as protected thiols: thiol-disulfide exchange reaction with the release of pyridine-2-thione.

Both the groups of Davis and Stenzel have investigated the combination of pyridyl disulfide groups with RAFT polymerization processes, starting from a pyridyl disulfide-labeled RAFT reagent.[29-32] It was shown that the PDS group is relatively stable during the RAFT polymerization process, but conversions have to be kept below 70% and moreover, low radical concentrations have to be used in order to avoid termination reactions originating from loss of pyridyl sulfonyl functionality.[31] In a post-polymerization modification reaction, the obtained RAFT polymers were reacted with thiol-containing moieties such as tripeptides, BSA, glutathione and 11-mercapto-undecanol. Alternatively, PDS-terminated macromolecules could be obtained by the reaction of dithiopyridyl disulfide with SH-terminated RAFT polymers, obtained after aminolysis of the RAFT end-group.[33] A recent publication of Hoogenboom and De Geest[34] uses PDS-terminated polymers for bioconjugation of polymers to bovine and avian serum albumin. The PDS group has not only been incorporated at the chain-end of polymers, but also as a reactive handle distributed along the backbone.[28] Furthermore, disulfide exchange reactions with pyridyl disulfide moieties have also been used for the synthesis of cross-linked nanogels as drug delivery platforms.[35, 36]

The conjugation of synthetic polymers with polypeptides and proteins is an established way of enhancing the properties of biomolecules and facilitating the establishment of polymer-based therapeutics. More specifically, the covalent attachment of PEG chains to a biomolecule has been investigated, as a way to increase solubility and stability. Many PEGylation approaches involve the use of amino-groups of lysine residues in the proteins. However, Haddleton et al.[37, 38] have described an alternative PEGylation strategy, using peptidic disulfide linkages as functional moieties to insert a reactive PEG (Scheme 3-7). Salmon calcitonin (sCT) was used as a model polypeptide, as it contains a disulfide bridge that can be reduced to yield reactive sulfhydryl functionalities.
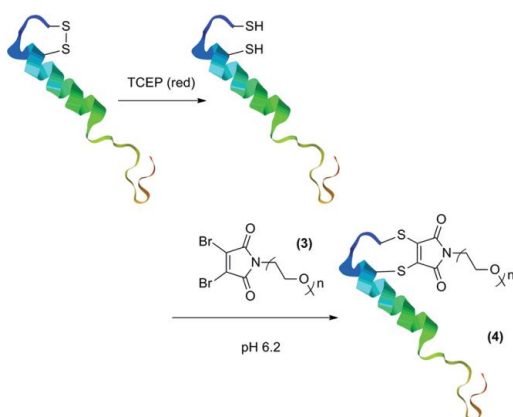
Scheme 3-7. sCT disulfide reduction using TCEP, followed by rebridging with a dibromomaleimide-functional PEG$_{5000}$ chain.

Disulfides can be incorporated in polymers through disulfide-containing initiators,[39] allowing for the degradation and possible end-functionalization of the polymer. If a difunctional initiator is used, reduction of the internal disulfide bond results in the formation of two thiol-functionalized linear polymer chains with half of the original molecular weight. Matyjaszewski et al.[40] pioneered the synthesis of a disulfide containing ATRP-initiator for the synthesis of reversibly cleavable polystyrene. The disulfide linkage could be reduced using DTT and be generated again through oxidation with FeCl$_3$. The same research group reported the ATRP of methyl, *tert*-butyl, and benzyl methacrylate using bis[2-(2-bromoisobutyryloxy)ethyl] disulfide as a difunctional initiator containing a disulfide link.[41] Mixtures of methyl methacrylate (MMA) and a difunctional methacrylate crosslinker containing an internal disulfide bond were then copolymerized by ATRP using the same initiator, giving rise to disulfide-cross-linked gels. Upon degradation, the gels were transformed into soluble, low molecular weight polyMMA fragments bearing thiol groups at the chain ends and along the backbone. Moreover, it was found in the same study that phosphines (in the presence of water), such as triphenylphosphine and tributylphosphine especially, are more efficient reducing agents than DTT for cleaving the disulfide bond. Besides ATRP initiators,[42, 43] also disulfide containing RAFT,[32, 44-46] NMP,[47] and ROP[48] initiators have been synthesized.

It should be noted that using disulfide links to incorporate sites of redox-sensitive degradation makes it possible to induce reversible cross-linking. This is an interesting feature especially in the development of covalent, adaptable networks,[49-51] which can exhibit self-healing capabilities.[15, 52, 53]

3.3.1.2. Photosensitive protection groups

Almost every functional group can be protected with a photo-labile protecting group and some excellent reviews have appeared on the subject.[54, 55] A major advantage of photodeprotection methods is the possibility to generate the desired functional group with spatial and temporal control. Interestingly, del Campo et al. have reported the orthogonal, wavelength selective deprotection of not less than seven surface-attached photoremovable groups, belonging to different families.[56] Similarly, the wavelength-selective release of thiols based on coumarinyl and 2-nitrobenzyl scaffolds has been described by Hagen et al.[57] Applications of the light-triggered release of thiols (and other functional groups) are mostly situated in the field of biochemistry and has been studied quite extensively in this context. For example, Smith and coworkers presented the patterned release of thiol functionalities on a surface, with the aim of attaching biologically active molecules to it.[58] In this way, they were able to attach DNA, biotin and peptides to a surface in a spatially controlled manner, while retaining their biological activities. Recently, photoreleasable thiol chemistry has been used for bioconjugation

purposes, allowing for the *in situ* PEGylation of maleimide-functionalized proteins and conjugation with quantum dot nanoparticles.[59]

The most commonly used photo-protection groups for thiols are phenacyl, benzoinyl, *o*-nitrobenzyl groups and coumarinyl groups. These groups are generally also useful for the protection of other functional groups, but they will be discussed here for thiols in particular.
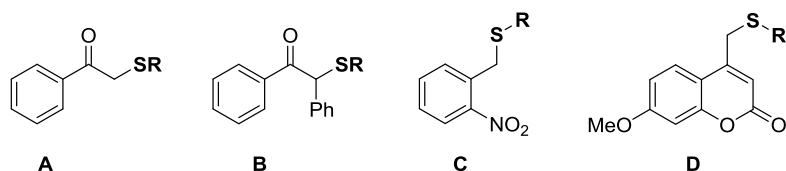
Figure 3-2. Overview of the most commonly used photo-protection groups for thiols: A. phenacyl; B. Benzoinyl; C. o-Nitrobenzyl and D. Coumarinyl.

o-Nitrobenzylic derivatives are well documented photolabile molecules and have been widely applied, despite some disadvantages. Scheme 3-8 shows the reaction pathway of the photorelease. The main photoreaction for *o*-nitrobenzyl substrates is believed to be the hydrogen transfer from the *o*-substituent to the nitro group, forming an aci-nitro tautomer in the ground state. This reaction is followed by an irreversible cyclization reaction. Ring-opening generates a thioacetal, which readily dissociates into a thiol and an aldehyde. It is shown that substituents on benzylic sites have a beneficial impact on the quantum yield,[54] whereas substituents on the aromatic ring are of interest when one wants to tune the absorbance, enhance solubility or anchor the group to a solid phase support.[60] The major disadvantage of *o*-nitrobenzyl photodeprotection is the release of a nitrosoaldehyde side-product, which absorbs incident light and operates as an internal filter. Moreover, this side-product easily undergoes a condensation reaction with amines to form stable imines.
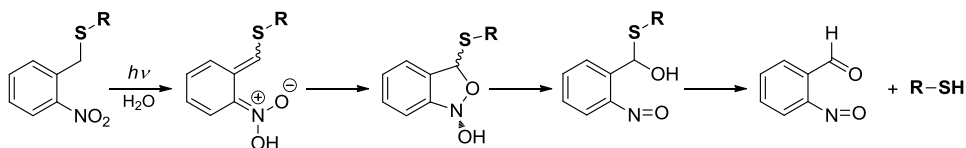
Scheme 3-8. Reaction mechanism for the photorelease of thiols from *o*-nitrobenzyl components.

Another class of photolabile protecting groups used to cage thiols, is derived from coumarin. Coumarins exhibit an increased stability and thanks to their fluorescent properties, it is possible to monitor reactions. Moreover, coumarin compounds can be used at higher wavelengths, a feature that is particulary interesting in biological applications. The photoreaction goes through a tight ion pair intermediate (heterolysis), whereby the coumarinylmethyl cation reacts quickly with nucleophiles or

solvent to generate a new stable product and a thiol (Scheme 3-9 **A**). Since thiols are poor leaving groups, the heterolysis step is more difficult and therefore they are often caged *via* a carbonate linkage. The hereby liberated thiocarbonic acid is unstable and undergoes decarboxylation with the release of the thiol (Scheme 3-9 **B**).
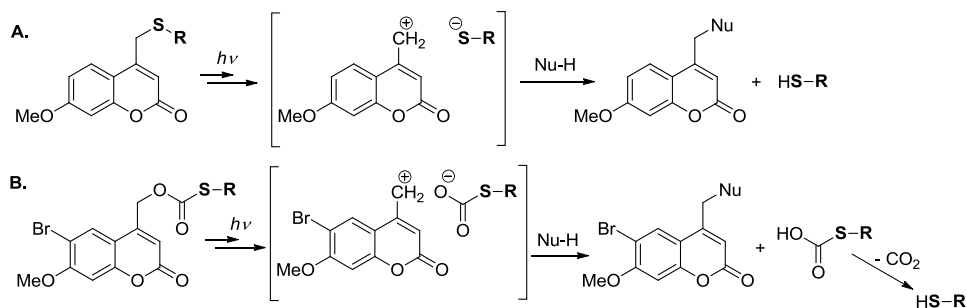
Scheme 3-9. A. Reaction scheme of the photodeprotection of coumarin-caged thiols. B. Decarboxylative photodeprotection of thiols.

A last class of photolabile protection methods suitable for thiols, are the aromatic ketones. Here, the center of photochemical reactivity is the carbonyl moiety. Several subclasses exist, based on the substituents. Scheme 3-10 shows the photoreaction of phenacyl compounds and benzoin compounds as examples. *S*-phenacyl xanthates for example are shown to undergo photoinitiated homolytic scission of the C-S bond to yield acetophenones and xanthic acids, in the presence of nucleophiles.[61]
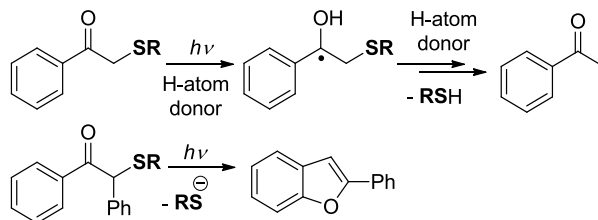
Scheme 3-10. Photoreaction of phenacyl (top) and benzoin (bottom) compounds.

Although *o*-nitrobenzyl groups have been implemented in polymer chemistry for the synthesis of photoresist materials,[62] and for the cleavage of polyuria capsules in our own research group,[63] it is only recently that the potential of these compounds as protection method for thiols has been exploited. Barner-Kowollik et al.[64] were able to synthesize (meth)acrylamide derivatives bearing UV-sensitive *o*-nitrobenzyl protected thiol groups. RAFT polymerization was employed to synthesize block copolymers possessing the protected thiol groups as a comonomer unit in one block, keeping the *o*-nitrobenzyl group intact during the polymerization process. The authors report the orthogonal double

deprotection and subsequent thiol-Michael addition, originating from aminolyzed RAFT thiocarbonylthio compounds (section 3.2.) and light-cleavable *o*-nitrobenzylthioether lateral groups (Scheme 3-11).
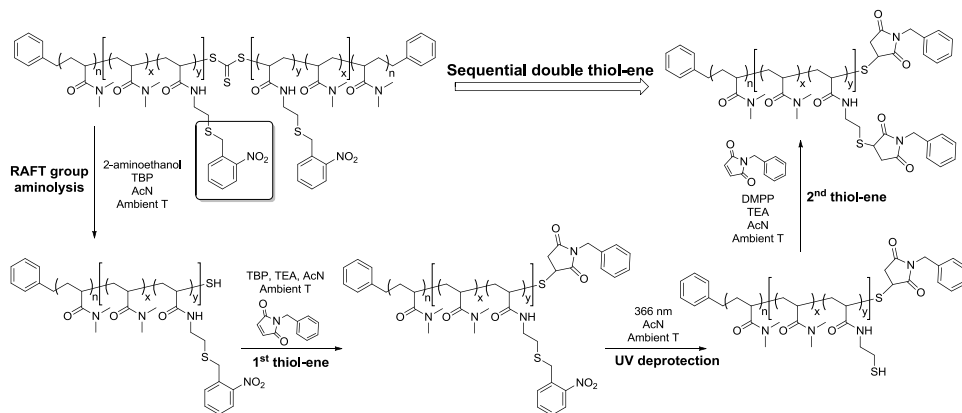
Scheme 3-11. Sequential deprotection/thiol–ene functionalization strategy applied to a RAFT polymerization-made block copolymer possessing the protected thiol groups as a comonomer unit in one block.[64]

Although interesting for polymer functionalization, surface modification remains the main field of interest for photolabile protection methods. The ability to pattern surfaces spatially and temporally is indeed a major benefit for the design of precision polymer materials.[65]

3.3.1.3. Thioethers and silyl-thioethers

In organic synthesis and solid phase peptide synthesis, thiol protection often relies on the use of thioethers as labile groups.[66, 67] The most frequently used thioethers are trityl, *S*-benzyl and substituted *S*-benzyl derivatives, such as the *p*-methoxybenzyl group (Figure 3-3). *n*-Alkyl thioethers are difficult to cleave and have therefore not often been used to protect thiols. *S*-benzyl thioethers are usually prepared easily through an S_N2 reaction with benzylchloride or benzylbromide in the presence of a base. However, cleaving these groups requires rather harsh reaction conditions, such as the use of strong acids or Na/NH$_3$, possibly affecting other functional groups and making this a less attractive strategy for the synthesis of more sensitive polymeric systems.
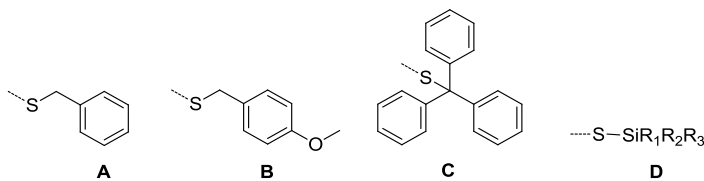
Figure 3-3. Thioether protection groups used in polymer synthesis: Benzyl thioether (A), *p*-methoxybenzyl thioether (B), trityl thioether (C), and trialkylsilyl thioether (D).

The triphenylmethyl (Trityl, Tr) group is another thioether protection reagent sometimes used in macromolecular design. For example, Endo et al.[68] document the use of a methacrylamide monomer derived from cysteine, which was protected with a trityl group, and polymerized in a free radical polymerization. After deprotection with HBr/CH$_3$COOH, the polymers became insoluble in any commercial solvent due to auto-cross-linking. However, when adding acetic anhydride, part of the deprotected thiols were transformed into thioacetate groups and thus crosslinking could be prevented. Schoenfisch et al.[69] used the trityl protection group to shield a thiol-containing monomer for the synthesis of functional polyurethanes. The thiols were recovered by reaction with TFA, after which they were converted in *S*-nitrosothiols, to serve as nitric oxide-releasing materials. Other examples include the synthesis of a trityl protected thiol polycarbonate[70] and the controlled radical polymerization (*via* NMP) of a styrenic trityl protected thiol.[71]

Finally, in the same way as for alcohols, the mercapto group can be protected with a silyl moiety, though the Si-S bond is weaker than the Si-O bond. Although this protection method has not been used very often, it is worth mentioning as being an extension to the other thioether protecting group strategies. Koeckelberghs et al.[72] synthesized poly(3-hexylthiophene)s having varying end-groups, amongst which was a thiol. This was achieved by preparing a protected thiol initiator, using a tri(isopropyl)silyl group. To remove the protecting group after polymerization, tri(butylammonium)fluoride was added in the presence of HCl, which resulted in the formation of a mixture of free thiols and disulfides.

3.3.2. Latent thiols

3.3.2.1. Thiols originating from the RAFT process and xanthates

Reversible Addition Fragmentation Transfer (RAFT) polymerization, described for the first time in 1998,[73] is a controlled radical polymerization technique (CRP),[74] which has been known to be one of the most versatile CRP techniques since it shows a high tolerance to a diverse range of monomers and functional groups.[75-77] In RAFT polymerization, small amounts of chain transfer agent (CTA) are used to

regulate the build-up of the molecular weight. These chain transfer agents can be subdivided into four classes: dithioesters, xanthates, trithiocarbonates and dithiocarbamates,[78] differing by the substituent group next to the C=S functionality (Figure 3-4). The substituents around the C=S moiety are labeled Z and R and influence the polymerization by facilitating the polymerization kinetics for certain well-defined classes of monomers (activated or non-activated). Moreover, the chemical modification of the Z and R groups allows for an easy incorporation of a wide range of functional groups at the polymer chain ends. Whereas Z influences the rates of addition and fragmentation by activating or deactivating the thiocarbonyl double bond , the free-radical leaving group R must be chosen such that the expelled radicals R• are capable of efficiently reinitiate the polymerization.

| dithiobenzoate | trithiocarbonate | dithiocarbamate | xanthate |
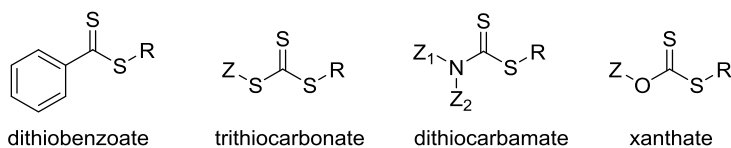
Figure 3-4. Four classes of chain transfer agents.

With respect to post-polymerization modification, it should be noted that all the classes of chain transfer agents mentioned above give rise to polymers containing a protected thiol moiety at their chain end. Indeed, RAFT polymers can be considered as macromolecular masked thiols. An interesting review by O'Reilly et al.[79] addresses the end group removal and subsequent modification of RAFT polymers. End group removal can be achieved using a free radical source, such as AIBN[74], or by thermal elimination, resulting in an unsaturated end group. The latter method requires temperatures typically ranging between 120-200 °C, which is a drawback if the polymer cannot withstand the thermolysis conditions. Both thermal elimination and exchange reactions with radicals lead to a polymer with a sulfur-free end group. However, as mentioned previously, the reactive CTA end groups also have the benefit that they can be transformed into a thiol end group, which can be subsequently used in a number of reactions. The reduction to a thiol can be achieved using a nucleophile, which is typically an amine, although also hydroxides and borohydrides have been used. A recent contribution of Wu et al.[80] demonstrates an alternative way of transforming the RAFT end group into a thiol, using sodium azide as nucleophile. The reaction was shown to be finished within 1 to 5 minutes, for several chain transfer agents and polymers. It was suggested that sodium azide acts as a versatile agent for end group modification, as it is not only able to cleave RAFT end groups, but also effectively converts the terminal halogen of ATRP polymers. In many cases, it is reported that the liberated thiols undergo inter-chain coupling reactions through disulfide bond formation, leading to higher molecular weight species.[81] A solution was found in the *in situ* reaction of the thiols with either acrylates,[82, 83]

maleimides,[84, 85] bromides[86] and sulfides. Alternatively, a reducing agent can be added to the solution, thus preventing oxidative coupling.

The mechanism and the kinetics of the nucleophilic reaction of amines with dithioesters has already been described in 1990[87], and a more recent contribution by Castro[88] explains the mechanism and the kinetics of the aminolysis of thioesters and thiocarbonates. As a consequence, the presence of primary and secondary amines in the reaction mixture should be avoided during the RAFT process, as it is likely that the CTA might be degraded and thus become inactive. Aminolysis has been the most widely used method of RAFT end group conversion, resulting in the formation of a thiol. Numerous literature examples make use of this efficient transformation, subsequently using the formed thiol in various follow-up reactions.[85, 89]

The use of the RAFT end group as an elegant thiol precursor was also demonstrated through the synthesis of cyclic polymers in our research group,[25] using RAFT and thiolactone-disulfide chemistry. For this purpose, a CTA was prepared containing a thiolactone functionality, which can be regarded a latent thiol as well (*vide infra*). Thus, polystyrene was obtained with a well-defined molecular weight and polydispersity, carrying a thiolactone at one and a dithiobenzoate at the other chain end. Upon aminolysis, the thiolactone moiety generates a free thiol (*vide infra*), while the dithiobenzoate is at the same time transformed into a thiol. This reaction is carried out under a high dilution (0.05 M), affording cyclic polymers after 2 days by oxidative disulfide coupling (Scheme 3-12). The authors show that the cyclic structures can be cleaved by disulfide exchange reactions or by adding a reducing agent (phosphines). Cyclization was proven by MALDI-TOF analysis, as well as SEC and ^{1}H NMR spectroscopy.
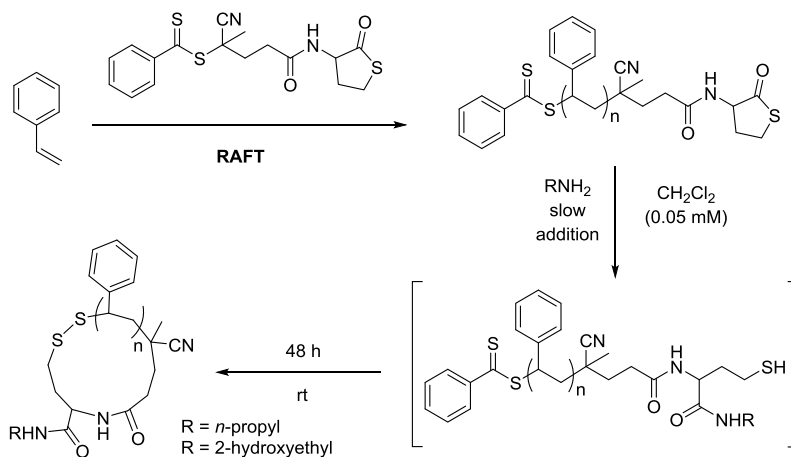
Scheme 3-12. Approach for the preparation of cyclic polystyrene using RAFT and thiolactone/disulfide chemistry.

The wide variety and synthetic possibilities of producing RAFT chain transfer agents, bearing extra functionalities, has created the potential to synthesize more advanced polymeric architectures. A prime example is the formation of hyperbranched structures, making use of the RAFT end-group as latent thiol, while a built-in alkyne functionality is primarily a double reaction site for thiols in the radical thiol-yne reaction. A lot of work on the combination of RAFT polymerization and thiol-yne chemistry has been done by Perrier et al.[90-93]

Dithiocarbonates, or xanthates, are common chain transfer reagents for the RAFT polymerization of non-conjugated monomers, such as vinyl acetate. Xanthates however can be implemented in such a way that they are inactive in the RAFT polymerization of activated monomers (e.g. acrylates or styrene). Nicolaÿ et al.[94] used this feature to synthesize polythiol copolymers from an *S*-alkyl-*O*-ethyl xanthate carrying methacrylate. It was shown that the thiol protecting group was fully compatible with the RAFT process. Deprotection was done by adding an amine under nitrogen atmosphere, with traces of reducing agent (tributylphosphine) added to the solution, to avoid disulfide formation during the process. The deprotection step was shown to be quantitative and yielded polythiol copolymers with different amounts of thiol incorporated on the polymer backbone.

The same research group evaluated the difference between different thiocarbonyl and thioester compounds as thiol protection group in both ATRP and RAFT polymerization (Scheme 3-13).[95] It was shown that dithiocarbamate moieties cannot be cleaved under mild aminolysis conditions. Moreover, dithiocarbamates led to significant side-reactions during the radical polymerization of acrylates, methacrylates and styrene. On the other hand, both thiocarbonyl and thioester moieties survived the radical polymerization without interfering in the process. Xanthates were shown to be more reactive towards aminolysis than thioacetates and led to quantitative conversions. Finally, the authors are confronted with disulfide formation during the storage of the formed polythiols and therefore recommend a one-pot deprotection and functionalization procedure instead of an intermediate purification step.
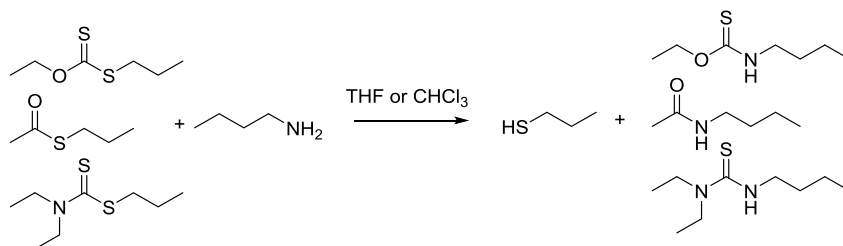
Scheme 3-13. Aminolysis of dithiocarbonates, dithiocarbamates and thioesters.

3.3.2.2. Thioesters

One of the most straightforward techniques to introduce thiols in polymer materials, consists of the deprotection of a thioester. The method has been used over the years for several applications, ranging from introducing thiols in polyurethanes for the covalent immobilization of biomolecules,[96] to the synthesis of functional microgels.[97] Deprotection is mostly done by a nucleophilic addition-elimination reaction, usually *via* aminolysis, alcoholysis, or hydrolysis. Most commonly, thioesters are found in the form of thioacetates and thiobenzoates, which are generally introduced in the polymer material *via* a nucleophilic substitution reaction using the potassium salt of the corresponding thioacids. Thioesters are mainly used as a source of sulfur, as a fast and straightforward way to introduce thiols in a masked state into polymers. In fact, it would also be possible to categorize this thiolation method under section 3.3.1., as there are a number of ways to form thioesters starting from a thiol precursor. Nevertheless, in most cases thioesters are not used to protect an existing thiol, but rather to easily incorporate thiols in the polymer, for instance, in a post-polymerization procedure.

For example, París et al.[98] prepared several (meth)acrylic polymers by ATRP, after which the bromide end group was transformed into a thiol in a two-step procedure (Scheme 3-14). In a first step, potassium thioacetate was used in a nucleophilic substitution reaction with the bromide end group, using a three-fold excess of thioacetate. The transformation into a thiol was subsequently achieved through hydrolysis in the presence of an alkene, allowing for the *in situ* consumption of the thiol when reacting in a radical thiol-ene addition. In this way, the researchers were able to attach a fluorescent moiety to the polymer chain end, which enabled the quantification of the thiol functionalization. From UV-vis absorption measurements, it was concluded that the modification reaction was nearly quantitative.
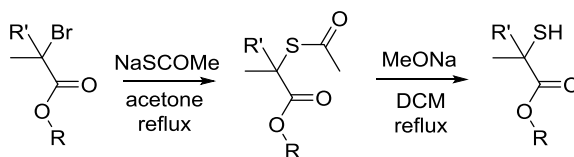
Scheme 3-14. Model reactions for the transformation of bromide groups into thiol groups.

Du Prez et al.[99] used thioacetates in the preparation of bio-sourced polythioethers. Starting from 10-undecenoic acid as a renewable resource, it was possible to prepare a new α-olefinic ω-thiol monomer. The preparation of this monomer occurred in a high-yielding four-step procedure (Scheme 3-15), starting with the reduction of the carboxylic acid functionality of the fatty acid to the corresponding primary alcohol. This alcohol was transformed into a good leaving group, using mesyl chloride, after which it could be reacted with potassium thioacetate, forming the thioester precursor.

Finally, deprotection with propylamine yielded the AB-monomer. This compound was shown to be stable when stored at -20 °C and no oligomers were observed after several months. Polymers were formed in bulk *via* a radical, stepwise polymerization reaction, generating polyethylene-like polyethers with molecular weights up to 40 kDa. An interesting observation was the increased disulfide concentration in the photochemically initiated polymer samples, compared to the thermally initiated ones.
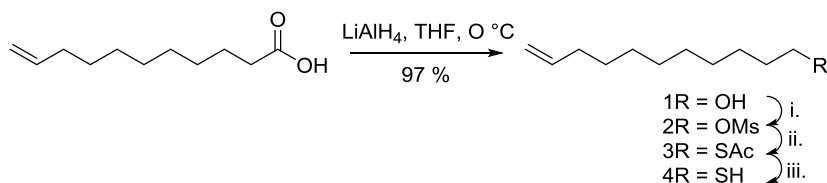
Scheme 3-15. Synthesis of an α-olefinic ω-thiol monomer from the bio-sourced 10-undecenoic acid.

Möller and coworkers[100] documented the synthesis of thiol functionalized poly(meth)acrylates, starting from modified MA or MMA monomers. These modification reactions were done *via* enzymatic transacylations with Novozyme 435® using 6-acetylthiohexanol and 6-benzoylthioxexanol, which were both prepared using potassium thioacetate and thiobenzoate. The authors observed significant transacylation side-products when synthesizing the thioacetate derivatives, whereas the approach using the benzoyl protected thiol gave rise to only one product. After removal of the enzyme from the monomer mixture, the monomer mixtures were polymerized through free radical polymerization in bulk, using AIBN as the initiator. Molecular weights up to 40 kDa were obtained. The removal of the protecting benzoyl groups was conducted using propylamine, after which the liberated thiol was subjected to a thiol-Michael addition reaction with methylacrylate. Interestingly, all reaction steps could be performed in a one-pot fashion without intermediate isolation or purification steps.

Alternatively, thioacetate groups can be added by using thioacetic acid as such.[101-103] The SH-group of thioacetic acid can be reacted in a radical or nucleophilic thiol-ene addition reaction, similar to the mercapto functionality.

3.3.2.3. Thiourea and thiodimethylformamide

Thiourea, a compound structurally similar to urea, is a widely used thiol precursor, produced yearly in kiloton scale. It is mainly used as a source of sulfur. Due to the high nucleophilicity of the sulfur atom, the compound reacts in a nucleophilic substitution reaction with halides.[104] The thus formed intermediate isothiouronium salt can be cleaved off *via* aminolysis or hydrolysis, with the formation of a free thiol and a guanidine salt or urea respectively (Scheme 3-16). However, due to its low solubility in common solvents for polymers, thiourea applications in the field of polymer synthesis remain rather limited.
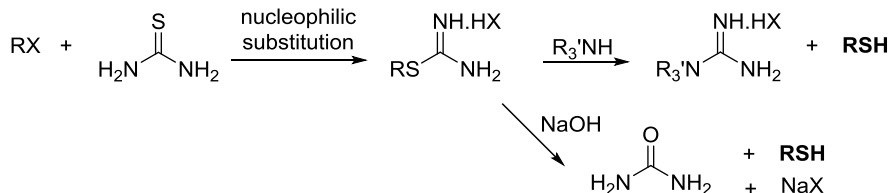
Scheme 3-16. Reactivity of thiourea with halide compounds, followed by aminolysis or hydrolysis, yielding free thiol compounds.

Braslau et al.[47] have employed thiourea in the synthesis of thiol-containing initiators for nitroxide-mediated polymerization. A benzyl chloride initiator was reacted overnight with thiourea in reflux conditions in ethanol to give the thiouronium salt. This salt was isolated as such and afterwards deprotected with sodium hydroxide in DMF to yield the initiator bearing a free thiol. This thiol-containing initiator was again protected as a tert-butyldimethyl silyl ether (*vide supra*) or as disulfide (*vide supra*) to be able to participate in the radical polymerization process. After the polymerization, deprotection and subsequent modification reactions could be performed. The same strategy was applied to prepare polymers with protected thiols in their side-chains.[71] Vinyl benzyl chloride was transformed into a benzylic thiol in a two-step synthesis, again using thiourea as the source of sulfur (Scheme 3-17). Whereas thiourea is a straightforward method of introducing thiols in a protected form, the generated thiouronium salts are not very suitable as protection group, because of their low solubility in most solvents. Therefore, after hydrolysis, the created thiol was again protected as a trimethylsilyl ether or a disulfide to facilitate the copolymerization reaction with styrene.
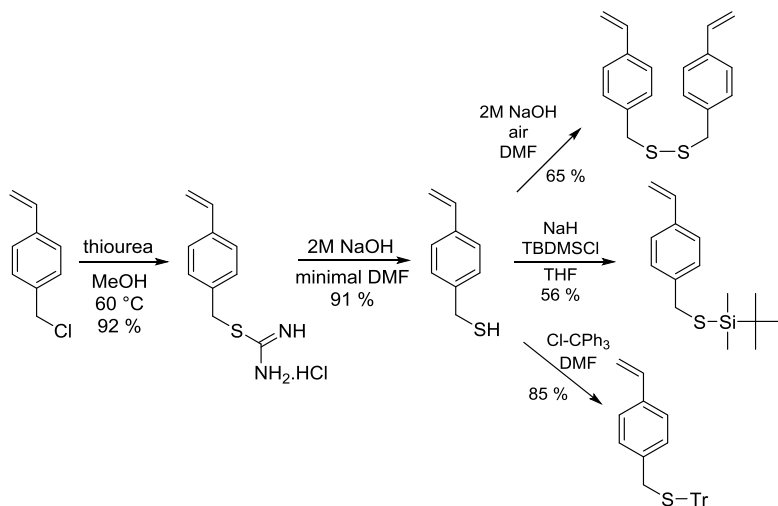
Scheme 3-17. Synthesis of protected thiol styrene monomers, using thiourea as a source of sulfur.

Substitution reactions on ATRP halide end groups, usually bromides, have been performed with various compounds, giving rise to new functional handles. Hilborn et al.[105] described the transformation of bromide end groups of ATRP prepared polystyrene using thiourea. In contrast to the synthesis procedure by Braslau et al., as described above, both the formation of the thiouronium salt and the hydrolysis were performed in the same reaction medium, without intermediate purification. A single reaction product, thiol end-functionalized polystyrene, was obtained with near-quantitative conversion. Yagci and coworkers[106] applied this one-pot synthesis strategy for the effective chemical modification of ATRP prepared polystyrene. The obtained thiol-end functional polymers were used to compare the efficiency of different initiator systems for thiol-ene reactions with allyl bromide, methyl acrylate and methyl methacrylate.

Because of the relatively low solubility of thiourea in common solvents, an alternative reagent, thiodimethylformamide (TDMF), is often used. The reactivity of TDMF is similar to thiourea, but the liquid compound is soluble in various organic compounds, including polymers. Moreover, it can be used as the reaction medium. Tsuda et al.[107, 108] described the use of this compound for the derivatization of chlorinated polystyrene. TDMF was also used by Matyjaszewski and Tsarevsky[40] for the preparation of polystyrene α,ω-dimercaptan. In this study, an ATRP prepared dibromo-terminated polystyrene was dissolved in TDMF (bubbled with nitrogen in order to avoid oxidative coupling of the eventually obtained thiols), and the reaction proceeded at 80 °C for 24 hours under nitrogen (Scheme 3-18). After methanolysis, the dithiol-terminated polymer was isolated and used for the preparation

of higher molecular weight polystyrene with internal disulfide bonds, which could be achieved by oxidation with $FeCl_3$.
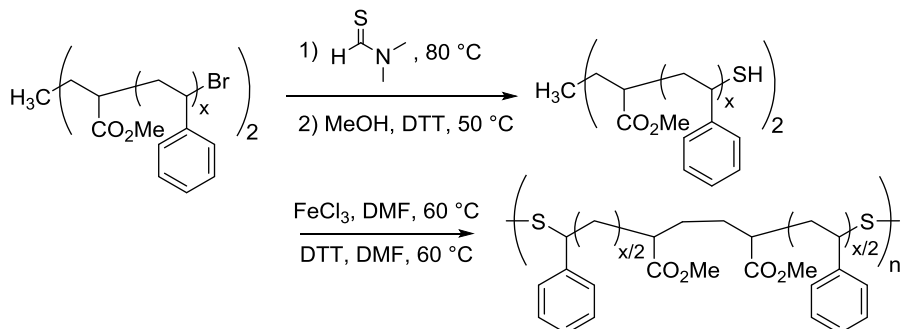
Scheme 3-18. Synthesis of polystyrene α,ω-dimercaptan, using TDMF, followed by oxidation.

3.3.2.4. Methanethiosulfonates

Methanethiosulfonates have been used primarily in biochemistry,[109-111] as a selective reagent in exchange reactions with free thiols, yielding unsymmetrical disulfides. Methanethiosulfonates contain a source of sulfur and are transformed into thiols quite easily by reaction with a strong base. Theato et al.[112] describe the ω-end group functionalization of RAFT polymers using methanethiosulfonates carrying an alkyne functional group. Butynyl methanethiosulfonate was prepared in a two-step procedure, by reacting chloro methylsulfonic acid with sodium sulfide, thus forming sodium methanesulfonate (Na-MTS). This was done following a synthesis procedure provided by Davis and coworkers.[113] Pure Na-MTS could be obtained in multigram scale. Na-MTS acts as a nucleophile and was employed in excess to react in a substitution reaction with the bromo group from butynyl bromide, yielding butynyl methanethiosulfonate, which was further used for polymer functionalization (Scheme 3-19).
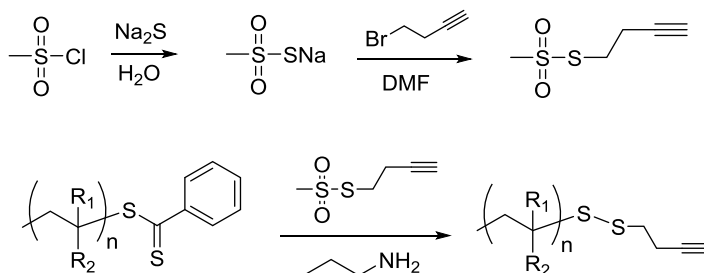
Scheme 3-19. Two-step synthesis of butynyl methanethiosulfonate and subsequent use for polymer modification of dithioester terminated RAFT polymers.

Five different polymers, including PS and PMMA, were prepared through RAFT polymerization, using different CTAs, and subsequently aminolyzed with *n*-propyl amine in the presence of *n*-butynyl methanethiosulfonate. This led to the formation of ω-alkyne functionalized polymers, coupled *via* a disulfide bridge. Successful transformation was proven by ^{1}H NMR spectroscopy and UV-vis measurements, showing a complete disappearance of the dithioester absorbance band. The obtained polymers were finally modified in a CuAAC click reaction on azide-functionalized glass surfaces, producing brushes along the surface.

As mentioned, sodium methanethiosulfonate is a nucleophile that can undergo nucleophilic substitution reactions with halogens. Davis and coworkers[114] made use of this reactivity to prepare polymeric methanethiosulfonates from ATRP polymers carrying a bromide end group (Scheme 3-20). Na-MTS was reacted in excess with respect to the bromide end group, yielding polymers with a masked thiol as a functional handle. Different post-polymerization reactions were evaluated. It was shown that the methanethiosulfonate end group successfully reacted with functional thiols, yielding functional disulfide-terminated polymers. Moreover, hydrolyzing the methanethiosulfonate groups under basic conditions at 70 °C gave rise to the formation of thiols, amenable to further thiol-ene reaction. For example, reaction with a fluorescein functionalized acrylate and a biotin modified maleimide could be performed in a one pot procedure.
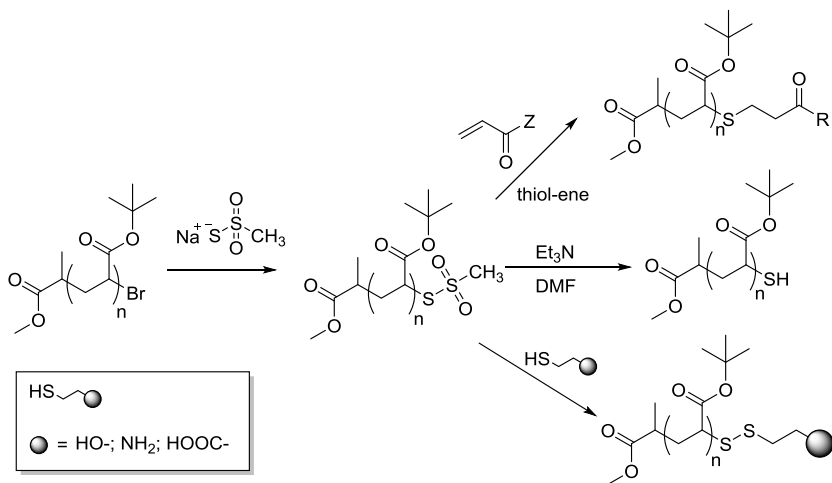
Scheme 3-20. Using sodium methanethiosulfonate, the ATRP halide end-group can be chemically modified and transformed in a subsequent functionalization step.

3.3.2.5. Sanger's reagent

In 1945, Sanger[115] used 2,4-dinitrofluorobenzene (now often referred to as Sanger's reagent) for the determination of free *N*-terminal amino acids in polypeptide chains, especially in insulin. Using the reagent in combination with other techniques, he was finally able to resolve the complete sequence of insulin. Being a reactive aryl halide, the compound can react with a whole range of nucleophiles, such as amines, sulfhydryls, and hydroxyls in a nucleophilic aromatic substitution reaction. Sanger's reagent has been used for the quantification of unreacted amines in dendronized linear polystyrenes,[116] and for the qualitative indication of amine presence in linear modified polystyrene.[117] Indeed, 2,4-dinitrobenzene compounds can be easily detected by UV absorbance measurements, and thus provide a quantification method for free amines.

Sanger's reagent has been utilized, to a smaller extent, as a strategy of introducing thiols in a masked state into polymers.[118] The protecting group can be quantitatively removed by 2-mercaptoethanol or other thiols, using mild conditions (pH = 8 at room temperature), releasing a free thiol.[119] Hilborn et al.[120] have used Sanger's reagent as a straightforward and mild technique of introducing thiols at the chain end of hydroxyl-terminated poly(ε-caprolactone) (Scheme 3-21). The incorporation of thiols was achieved in a post-polymerization modification, using a mercapto acetic acid protected with a 2,4-dinitrobenzyl group.[121] Coupling of this reagent through esterification with the hydroxyl end group of the polymer yielded the protected thiol polymer, which could be purified by simple precipitation. The extent of functionalization was shown to be 95-100%, demonstrated by ^{1}H NMR and UV-vis spectroscopy. Furthermore, the versatility of the method was proven by the preparation of thiol functional dendrons and thiol functional PEO. It should be noted that disulfide formation of the thiol end-functionalized polymers was observed in THF solution.
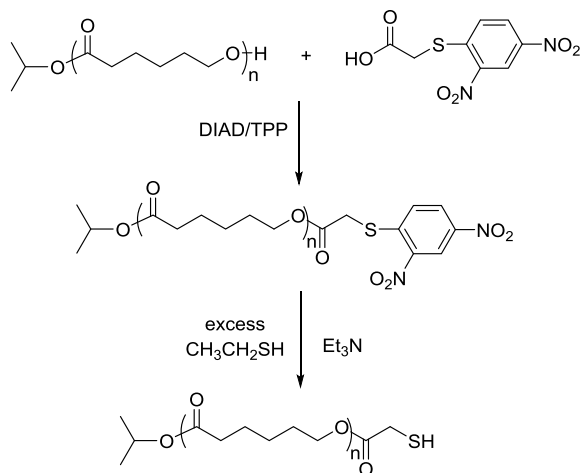
Scheme 3-21. Schematic overview of the introduction of a thiol functionality at the chain end of hydroxyl-terminated poly(ε-caprolactone) through the esterification with mercapto acetic acid, shielded with Sanger's reagent.

Extending the scope of the proposed method, initiators containing a protected thiol moiety based on Sanger's reagent were developed for both ATRP and ring-opening polymerization of methyl methacrylate or ε-caprolactone, respectively.[122] Adding mercaptoethanol to a solution of 2,4-dinitrofluorobenzene and triethylamine in chloroform yielded the ROP initiator (Scheme 3-22). Then, this product could be coupled with 2-bromo-2-methylpropionyl bromide to produce an ATRP initiator. The protection technique proved to be compatible with both polymerization methods. Deprotection was done as described before, using a large excess of free thiol.
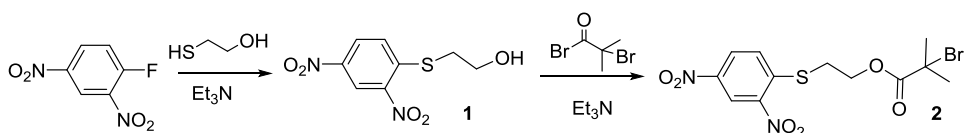
Scheme 3-22. Synthesis of ROP (1) and ATRP initiators containing a protected thiol in the form of Sanger's reagent.

3.4. ATOM EFFICIENT PROCESSES

For some applications (coatings, medicinal, …) it is of absolute priority to avoid small molecules leaking out of the system and certainly for these purposes, atom-efficient methods are very appealing. Moreover, atom-efficient methods are especially relevant in the context of green chemistry, since purification steps are limited and hence entire synthesis procedures can be optimized. Atom-efficient

ways to introduce thiols in polymer chains always imply the use of cyclic precursor molecules. In all of the described methods below, the sulfur atom is incorporated in a cyclic structure and a carbon-sulfur bond is broken upon adding an external trigger. It mostly concerns a nucleophilic addition-elimination procedure, leading to the opening of the ring structure and the release of a thiol.

3.4.1. Cyclic dithiocarbonates

Cyclic dithiocarbonates, similar to dithiocarbonates, can be regarded as latent thiols. A lot of work on this topic has been conducted by the research group of Endo. In 1995, the group published a first report on the selective synthesis of cyclic thiocarbonates, which had been a challenging task up to then.[123] The synthesis of these compounds is rather versatile, as it starts from carbon disulfide and a substituted oxirane, allowing for the formation of a large amount of differently substituted cyclic thiocarbonates. The yield of the reaction turned out to be dependent on the used solvent and the alkali metal halide as catalyst. The best results, giving only one regioisomer, were obtained using LiBr in THF as a solvent, at room temperature. Cyclic dithiocarbonates are interesting functional moieties in polymer materials since they react chemoselectively with amines, resulting in the formation of a thiol. Weaker nucleophiles, such as water and alcohols leave the ring-structure intact.
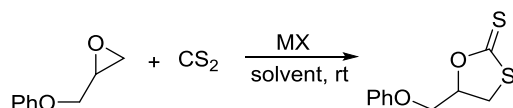
Scheme 3-23. Synthesis of cyclic dithiocarbonates, starting from substituted oxiranes and carbon disulfide.[123]

In a follow-up research, the authors investigated the implementation of these compounds in polymer synthesis. Incorporation of a cyclic dithiocarbonate onto a methacrylate monomer[124] allowed for the preparation of polymethacrylates with reactive handles in their side-chains. Indeed, reaction with butylamine and isopropyl amine afforded modified polymers, although gelation could not be avoided due to auto-oxidation of the liberated thiols. Moreover, the authors described the use of bifunctional cyclic dithiocarbonates in a polyaddition reaction with diamines, giving rise to polythiourethane structures.[125] After each ring-opening of the cyclic dithiocarbonate, a thiol is released along the backbone. Avoiding auto-oxidation of the formed polymers appeared to be impossible and therefore, prior to isolation, the thiols were reacted with acetic anhydride to yield the S-acetylated adduct.

More recently, the same research group investigated the synthesis of a norbornene monomer bearing a cyclic dithiocarbonate moiety (NB-DTC),[12] intended for the synthesis of reactive polynorbornene. The monomer was prepared starting from an epoxy-containing norbornene

precursor, by its reaction with carbon disulfide. NB-DTC underwent ring-opening methatesis polymerization catalyzed by a ruthenium carbene complex to give the corresponding polynorbornene. Kinetic studies revealed that when copolymerizing this monomer with 5-butyl-2-norbornene, a gradient-like polymer was obtained. The dithiocarbonate moiety in the side-chain was subsequently reacted with benzylamine to afford the corresponding thiourethane moiety having a free thiol group. The resulting product was a cross-linked polymer due to oxidative coupling.
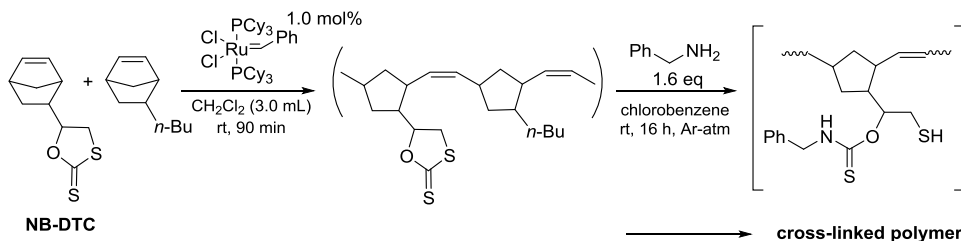
Scheme 3-24. A norbornene monomer, containing a cyclic dithiocarbonate (NB-DTC), polymerized *via* ROMP. Subsequent ring-opening with benzylamine yielded thiols in the side chain, which led to cross-linking.[12]

3.4.2. Ethylene sulfides

Oxiranes, or epoxides, are well-known compounds for their efficient reaction with nucleophiles, thus liberating hydroxyl groups. Also in polymer materials epoxides have been applied frequently, e.g. bisphenol-A diglycidyl ether in epoxy resins. Although ethylene sulfides, also referred to as thiiranes, are similar in structure and properties, their use in polymer synthesis is much less documented. Like most other low-molecular weight sulfur-containing compounds, ethylene sulfide also has an unpleasant smell. The three-membered cyclics are susceptible to nucleophilic ring-opening by nucleophiles, giving rise to the corresponding thiols in an atom-efficient way. Thiiranes can be synthesized in a number of ways, giving high yields. The synthesis of thiiranes can for example occur starting from 2-mercaptoethanols, using tetraalkyl orthocarbonates as cyclodehydrating agents to give the corresponding thiiranes in acid-catalyzed reactions, in aprotic solvents.[126] Other synthesis strategies consist of the transformation of oxiranes into thiiranes, for example by potassium thiocyanate in the presence of $LiClO_4$.[127]

Thiiranes can be polymerized by several mechanisms,[128] including living systems for the synthesis of well-defined polysulfides. However, their use as thiol precursor has been far less examined. Ethylene sulfide (ES) has been used for the chemical modification of cellulose[129], aiming at the synthesis of thiol-functionalized biopolymers capable of divalent metal cation complexation. A recent example by Rittschof and coworkers[130] describes how branched polyethyleneimine (BPEI) was coupled to a stainless steel surface, coated with dopamine (Scheme 3-25). Thiol groups were subsequently

produced on the surface by reacting the free amine groups with ethylene sulfide. The reason for this transformation is the wish to further functionalize through different modification reactions, such as thiol-epoxy, radical thiol-ene and thiol-Michael reactions.
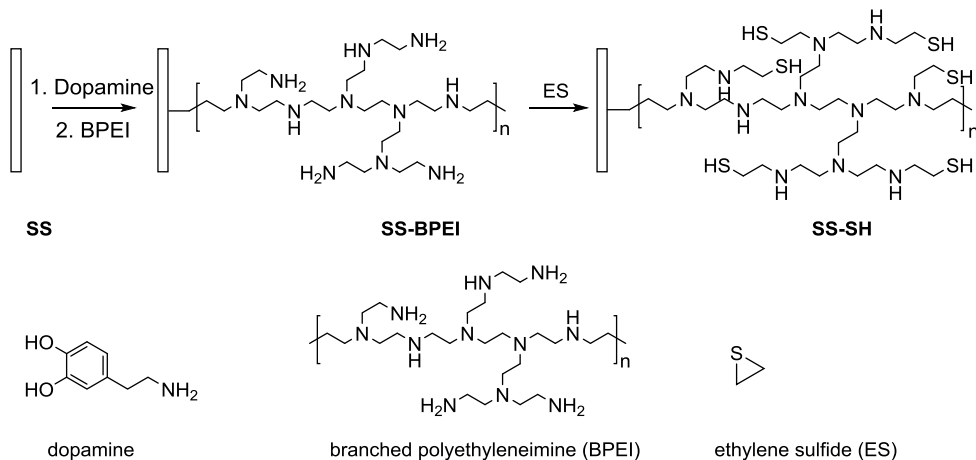
Scheme 3-25. Schematic illustration of the mercaptoethylation of branched polyethyleneimine coated stainless steel surface, prior to the functionalization reactions.[130]

3.4.3. Traut's reagent

A comparable reagent to thiolactones (see 3.5) is 2-iminothiolane, being a heterocyclic five-membered thioimidate. This compound was described for the first time by Traut[131, 132] in 1973 for the derivatization of peptides and is therefore often referred to as Traut's reagent. 2-Aminothiolane reacts spontaneously and selectively with primary amines in aqueous media at pH 7-9, although at higher pH values, it also reacts with hydroxyl groups, albeit at a much lower (1000-fold less) rate. Therefore, it has been used for peptide derivatization, for example through reaction with the *N*-terminus of a peptide of the ε-aminogroup of lysine, thus affording amidine bonds and a free thiol (Scheme 3-26), while leaving other nucleophilic species in the peptide unaffected. The compound has mainly been used to create thiols in biological systems as reactive handles for further modification or crosslinking reactions.
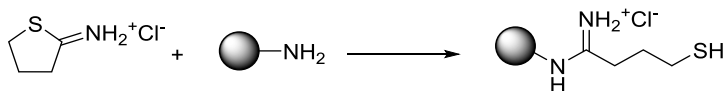
Scheme 3-26. Traut's reagent reacts with primary amines generating a free thiol.

Kataoka et al.[133] described the synthesis of environment-responsive block copolymer micelles with a disulfide cross-linked core, targeting an enhanced delivery of siRNA. In this study, the primary amines in poly(ethylene glycol)-*block*-poly(L-lysine) were reacted with 2-iminothiolan (Traut's reagent), generating mercaptopropyl groups through amidine bonds. These copolymers were subsequently used to form polyion complexes by mixing with siRNA, under reductive conditions (DTT). The thiol groups were afterwards oxidized with the formation of disulfide bridges, thus generating a core-crosslinked polyion complex system, which contributed to the stabilization of the otherwise unstable micelles. The release of siRNA was prompted in a reductive environment.

3.5. THIOLACTONES AS ATOM-EFFICIENT LATENT THIOL GROUP

3.5.1. Chemical structure and properties of thiolactones

Thiolactones are cyclic esters of mercapto-acids.[134, 135] The most representative members of this class of sulfur-containing compounds are β-, γ- and δ-thiolactones, respectively four-, five- and six-membered rings. α-Thiolactones, being strained three-membered ring compounds, are considered unstable (except for α,α-disubstituted analogues[136]) and are described as intermediates.[137] Additional structural classification distinguishes unsaturated and saturated thiolactones; only the latter will be discussed further. The most widely used synthetic approach for the preparation of saturated γ- and δ-thiolactones is the direct lactonisation of the corresponding mercapto-acid (Scheme 3-27).[134, 135, 138-144] Dehydration in diluted media is accelerated by heating and the use of an acid catalyst. Dehydrating agents like carbodiimides and phosphorus pentoxides enable the synthesis of β-thiolactones. In selected cases, cyclization of thiol-containing esters[145, 146] and amides[147, 148] similarly enables thiolactone formation.

n = 1 ; β-Thiolactone
n = 2 ; δ-Thiolactone
n = 3 ; γ-Thiolactone
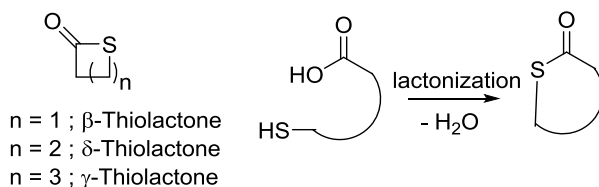
Scheme 3-27. General structure of saturated thiolactones and schematic depiction of the preparation of thiolactones by dehydration of mercapto-acids.

The most important reactivity-related property of thiolactones is the lysis of the ring by the action of a nucleophile. Thiolactones are more sensitive for ring opening than their corresponding lactones,

except for β-thiolactones.[134] In addition to their different ring stability, a clear distinction regarding the reactive nature of lactones and thiolactones can be made. Thiolactones are split by nucleophilic agents exclusively at the *S*-acyl bond (nucleophilic addition-elimination), whereas their oxygen analogues are opened by the same agents at either the *O*-acyl or *O*-alkyl (nucleophilic substitution) bonds. Thus thiolactones behave only as acylating agents, in contrast to lactones which have both acylating and alkylating activity (Scheme 3-28).[134]
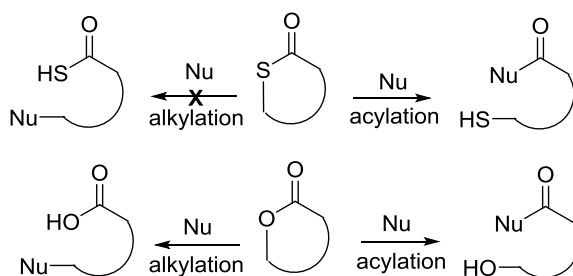
Scheme 3-28. General alkylation and acylation pathways for the ring opening of thiolactones (top) and lactones (bottom)

Due to the inherent ring strain, the susceptibility of thiolactones towards lysis decreases in following order: β- > γ- > δ-thiolactones. Generally, the stability of the ring increases with the number of substituents by steric congestion of the nucleophilic attack.[134]

Several nucleophiles for the ring opening can be considered; water, alcohols and amines are most prevalent. The hydrolysis and alcoholysis are only significant in basic medium, while aminolysis requires no additives. Aminolysis can thus be performed in aqueous medium, although hydrolysis is an important side reaction. The concomitant high pH-value should therefore be lowered by buffering the solution. Additionally, the hydrolytic opening can be suppressed in favor of aminolysis by using low temperatures, since the temperature coefficient of the rate of aminolysis is exceptionally small.[135, 149]

The use of other nucleophiles like thiols and carbanions for the ring opening is far less documented. β-Thiolactones can be opened by treatment with H_2S and Et_3N,[142, 150-153] while no reports on thiolysis of γ-thiolactones were found so far. Interestingly, ε-thiolactones (seven-membered thiol equivalent of caprolactone) and β-thiolactones can be polymerized in the absence of water and air to linear polymers by a base-catalyzed ring-opening reaction.[135, 154] This, however, requires high temperature and prolonged reaction times. Under these conditions, δ-thiolactones react sluggishly and γ-thiolactones are inert.

Stabilized carbanions like sodium dimethylmalonate[155] and ethyl lithiodiazoacetate[156-158] can open both γ- and δ-thiolactones. Hydride reduction of γ-thiolactones is a convenient way to prepare α,ω-hydroxyalkanethiols.[159, 160]

3.5.2. Structural features, synthesis and properties of homocysteine-γ-thiolactone
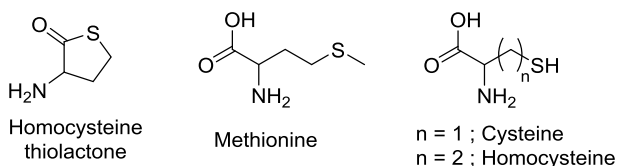
Figure 3-5. Chemical structures of homocysteine thiolactone, methionine, cysteine and homocysteine.

α-Amino-γ-butyrothiolactone or homocysteine-γ-thiolactone, a cyclic thioester of homocysteine, is a γ-thiolactone with a primary amine in the α-position (Figure 3-5). Homocysteine, a by-product of cellular methylation reactions on dietary methionine, is perhaps the most reactive amino acid in biological systems. Therefore, homocysteine and many of its *in vivo* formed metabolites, including homocysteine-γ-thiolactone, interfere with vital processes, rendering them a subject for intense biomedical and biochemical studies.[161]

Chemical preparation of homocysteine-γ-thiolactone requires an acid-catalyzed intramolecular condensation of methionine,[162] or homocysteine.[163] The thiolactone absorbs UV-light (λ_{max} = 240 nm and ϵ ~ 5000 $M^{-1}cm^{-1}$ in water). The low pK_a value of 6.67 for the amino group can be explained by the electron-withdrawing effects of the sulfur atom.[164] The hydrochloric acid salt of the racemate of homocysteine-γ-thiolactone is a white solid (mp 199-203 °C), indefinitely stable at room temperature and readily available. Under physiological conditions (pH 7.4, 37 °C), homocysteine-γ-thiolactone has a half-life of one day.[161]

3.5.3. Dual reactivity of homocysteine-γ-thiolactone

Because of its dual aminoacyl-thioester character, the reactivity of homocysteine-γ-thiolactone is of exceptional practical and theoretical interest. In fact, it is susceptible for both nucleophilic (*vide supra*) and electrophilic attack. Self-condensation of 2 molecules occurs upon deprotecting the amino-group. Mutual aminolysis (first intermolecular and second intramolecular aminolysis) takes place with the formation of 3,6-di-(β-mercaptoethyl)-2,5-dioxopiperazine. This dithiol readily polymerizes by disulfide formation (Scheme 3-29).[134]
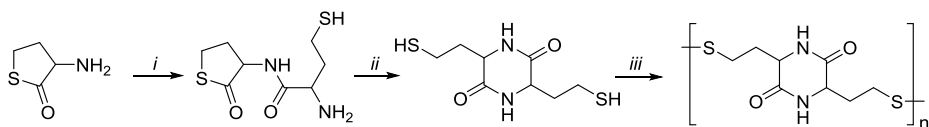
Scheme 3-29. Mutual aminolysis (an inter –(*i*), followed by an intramolecular (*ii*) reaction) of homocysteine-γ-thiolactone leads to diketopiperazine formation, which polymerizes by oxidative disulfide formation (*iii*).

Homocysteine-γ-thiolactone is a valuable synthetic building block. Due to the intrinsic instability of the neutral homocysteine-γ-thiolactone, an efficient reaction between the amino group in α-position and the electrophile is required to functionalize this compound. Amidation reactions are most frequently used: conjugation with acid halides,[165-168] (*in situ*) activated carboxylic acids[165, 169-174] and anhydrides[175] enables the synthesis of homocysteine-γ-thiolactone derivatives. A carbamate linkage is formed by treatment with chloroformates.[176] Another important functionalization reaction is imine formation, resulting from the condensation with aldehydes.[164, 177, 178] The remarkable reactivity of homocysteine-γ-thiolactone with aldehydes is most likely due to the low pK$_a$ value of the α-amino group, which is 2 – 3 units lower than the pK$_a$ values of amino acids. Alkylation reactions of the α-amino group are less common. Reductive amination is, however, reported to be a method to monoalkylate homocysteine-γ-thiolactone.[179]

3.5.4. Derivatives of homocysteine-γ-thiolactone
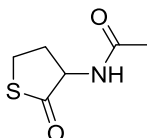
Figure 3-6. Chemical structure of *N*-acetylhomocysteine thiolactone.

The most commonly used homocysteine-γ-thiolactone derivative is *N*-acetylhomocysteine thiolactone or citiolone (Figure 3-6). This commercial compound was introduced as a thiolating agent for proteins. Thiolation consists of the aminolysis of the water-soluble *N*-acetylhomocysteine thiolactone by the ε-NH$_2$ groups of lysine residues and can be accelerated by the addition of silver ions (and imidazole[180]), allowing the reaction to proceed at physiologic pH.[149, 181, 182] Thiolation of a large variety of macromolecular biochemical systems has been reported.[166, 182-192] Citiolone is a drug used as a mucolytic agent for the treatment of certain hepatic disorders.[193] Besides its reactivity, which fully relies on its acylating capacity, other noteworthy derivatives of homocysteine-γ-thiolactone enable the incorporation of thiolactones in (macro)molecules, one of the starting points of this PhD research. The primordial requirements are the conversion of the α-amino group to a functional handle and, most

importantly, the conjugation to the reactive system of interest. Both steps should proceed while maintaining the integrity of the thiolactone ring. Several of these dual reactive compounds have been synthesized. α-Isocyanato-γ-thiolactone is obtained by phosgene treatment of homocysteine-γ-thiolactone. In the presence of alcohols, amines or hydrazines, this isocyanate is converted to the corresponding carbamates, urea and semicarbazides (Scheme 3-30).[194]
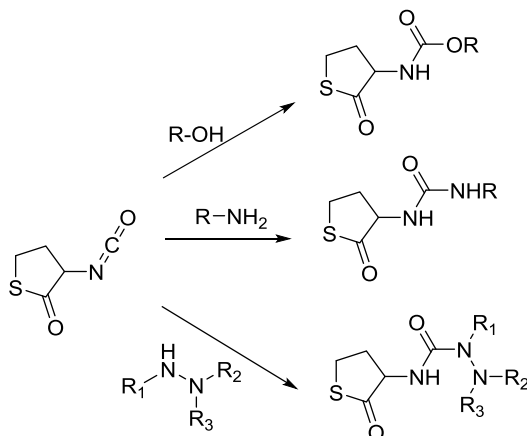
Scheme 3-30. Derivatization of α-isocyanato-γ-thiolactone by nucleophilc treatment.

3.6. CONCLUSION AND PERSPECTIVES

As a result of the continuous search for efficient reactions in the synthesis of tailor-made polymer materials, the importance of thiol-based chemistry has increased tremendously during the last decade. Thiols exhibit a high reactivity towards many substrates, which allows their use in diverse domains. On the other hand, this versatility in reaction possibilities also implies a lack of selectivity. This is witnessed when wanting to combine thiol chemistry with radical polymerizations, where thiols act as chain transfer agents. Moreover, thiols are sensitive to oxidation reactions, leading to the formation of disulfides in a usually uncontrolled manner. Other thiol related problems include their unpleasant smell and limited commercial availability. During the years, a lot of work has been done to overcome these thiol-related problems, by using thiol precursors in a masked state during the polymerization process, or by using latent thiols as a final work-up step. This chapter aimed at giving an overview of the techniques that have been used to introduce thiols in polymer materials, using thiol precursors. Some of these methods have been developed decades ago, also in other disciplines such as biochemistry, for the modification of peptides. The need for straightforward, fast and convenient protection methods for thiols has led to the revival of some of these methods and has crossed several

interdisciplinary barriers. There are several ways to introduce masked thiols into a polymeric material. Non-atom efficient processes include those methods whereby a small molecule is released upon deprotection. This can be achieved starting from a selected precursor thiol, which is protected prior to use. This is in the philosophy of pure organic synthesis. A typical example is the use of photolabile protection groups, which allows for a temporal and spatial control over thiol release. Also disulfides as a shielding method have been widely applied, often in combination with biochemical systems. Non-atom efficient processes can also be utilized with the aim of introducing a sulfhydryl group, without it being important which thiol is used. A prominent example is the end-group of RAFT prepared polymers, which can be reacted quite easily with a nucleophile (often an amine) to produce a thiol at the ω- chain end. Alternatively, atom efficient processes do not release side-products upon deprotection reactions, since it always concerns cyclic precursors. Thiolactone compounds for example are a class of latent thiols which have become more important, also in the context of one-pot multistep reactions.[195]

Indeed, one-pot multistep sequences and multiple functionalization reactions on polymers are the topic of a lot of current research. Thiol-based chemistry is playing an important role in the development of such functional materials. Also interdisciplinary research will continue to profit from the properties and possibilities of reactions involving thiols. Therefore, strategies for the selective release of thiols will remain an active field of research, and thus widen the opportunities for the precise design of dedicated and tailor-made materials.

3.7. REFERENCES

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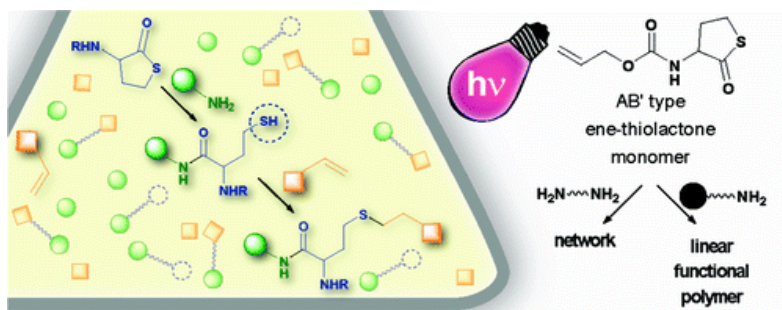
Abstract

This chapter describes the *in situ* generation of thiols by nucleophilic ring-opening of a thiolactone with amines, followed by a UV-initiated radical thiol-ene reaction in a one-pot fashion. This versatile protocol has been evaluated for the accelerated synthesis of several types of polymeric architectures. After elaboration of a model amine-thiol-ene conjugation reaction, the readily available *N*-acetyl homocysteine thiolactone has been used as modification procedure for alkyne-containing polymers. A route based on a novel thiolactone-containing monomer, alloc-thiolactone, has been developed to assemble functional, linear polyurethane-like polymers and polymer networks via a mild and facile radical photopolymerization process.

Chapter 4
One-pot multistep radical-induced synthesis of functional polymers

4.1. INTRODUCTION

Adding functionality on a polymer is usually achieved *via* post-polymerization modification reactions. However, transformations on polymers are often inefficient and can result in side-reactions on other functional groups, due to a lack of chemoselectivity. Therefore, efficient and specific reactions, which guarantee a successful modification, are highly desired. The abundant use of click chemistry in polymer synthesis is a reflection of that need. The fact that click reactions are, per definition, very reliable has led to their abundant use in one-pot multi-step sequences. For example, the *in situ* formation of azides has been studied, thus avoiding the dangers of handling these unstable compounds.[1-3] Apart from safety considerations, reducing the amount of reaction steps simplifies the complete procedure. Nowadays, metal-free methodologies that partly fulfill the set of click requirements[4] are eagerly developed and evaluated.[5] The radical or nucleophilic addition of a thiol to a double bond (thiol-ene chemistry[6-8]) has been recognized as a valuable metal-free alternative for the CuAAC due to some inherent click characteristics.

As Malkoch[9] et al. expressed the need to increase the range of available click reactions that can be achieved without the need of metal catalysts and to develop libraries of compatible reactions, our goal was to develop an efficient one-pot multi-step process based on metal-free radical thiol-ene chemistry, in order to modify or assemble polymers. Besides the fact that the commercial availability of thiols as starting materials is rather limited, thiols usually have an unpleasant smell and typically have a poor shelf life due to oxidation reactions. Therefore it can be advantageous to generate thiols *in situ* and convert them in a one-pot process.

Our investigation was inspired by a decades-old method for the introduction of sulfhydryl groups in natural proteins. This thiolation of proteins consists of the nucleophilic ring opening of the readily available *N*-acetylhomocysteine thiolactone (ACTL) by the ε-NH$_2$ groups of lysine residues (Chapter 3.5).[10, 11] We anticipated the ability to adapt this methodology and combine it with the radical thiol-

67

ene process in a one-pot fashion as a mild approach for the synthesis of polymeric architectures starting from stable amine containing compounds. Although the presented concept (Scheme 4-1) might not be broadly applicable due to the reactive nature of amines and radical species (orthogonality issues), this amine-thiol-ene conjugation as a simple, efficient and modular linking process is considered to be a relevant extension of the nowadays quite popular thiol-ene chemistry, especially in polymer science.
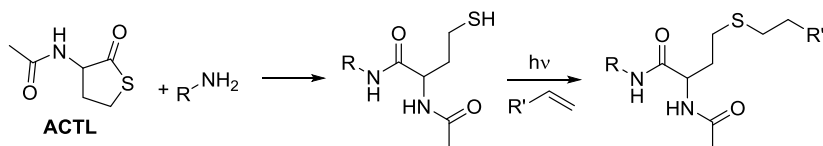
Scheme 4-1. General concept of the investigated metal-free one-pot reaction: nucleophilic opening of a thiolactone (aminolysis), followed by a radical thiol-ene conjugation.

4.2. MODEL STUDIES

Before applying the proposed strategy for the synthesis of novel polymer materials, model studies on low molecular weight compounds as well as on polymer systems are conducted, using ACTL as thiolating agent.

4.2.1. ACTL as model thiolactone compound

The most commonly used thiolactone derivative is *N*-acetylhomocysteine thiolactone (ACTL) or citiolone. As mentioned in Chapter 3, this readily available compound was introduced as a thiolating agent for proteins. The thiolation consists of the aminolysis of the water-soluble ACTL by the ε-NH$_2$ groups of lysine residues and can be accelerated by the addition of silver ions (and imidazole[12]), allowing the reaction to proceed at physiologic pH.[10, 11, 13] Thiolation of a large variety of macromolecular biochemical systems has been reported.[13-24] Moreover, citiolone is a drug used as a mucolytic agent for the treatment of certain hepatic disorders.[25] ACTL will be used here as a model compound to evaluate its applicability for polymer synthesis and modification.

4.2.2. Model study: low molecular weight compounds

As a first study, the one-pot two-step sequence was performed on low-molecular-weight model compounds in order to investigate the reaction kinetics and to analyze the composition of the obtained reaction mixture.

Benzylamine was treated with ACTL in the presence of 4-dimethylaminopyridine (DMAP) as a nucleophilic catalyst. In the initial reaction mixture, an excess of norbornene (ene-compound) was added to allow for the subsequent radical thiol-ene reaction. The reaction mixture was irradiated by an external UV-light source and 2,2-dimethoxy-2-phenyl acetophenone (DMPA) was selected as photo-initiator for thiol-ene conjugation (Scheme 4-2).
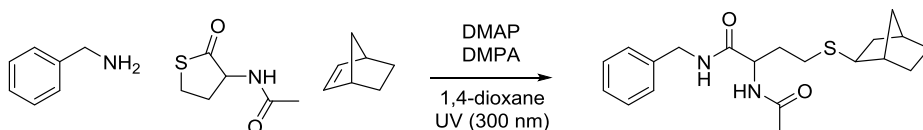
Scheme 4-2. Model amine-thiol-ene conjugation: one-pot reaction between benzylamine, *N*-acetylhomocysteine thiolactone and norbornene under UV-irradiation, using DMPA as photoinitiator.

Because of the extremely high reactivity of the norbornene double bond towards thiyl radicals, the first step of the reaction sequence was considered to be rate-determining. In an online ^{1}H-NMR experiment, the consumption of benzylamine was monitored by the decrease of the signal of the corresponding benzylic protons. This study pointed out that benzylamine was fully consumed after being in the presence of a two-fold excess of ACTL and 10 mol% of DMAP for 6 hours (Figure 4-1).
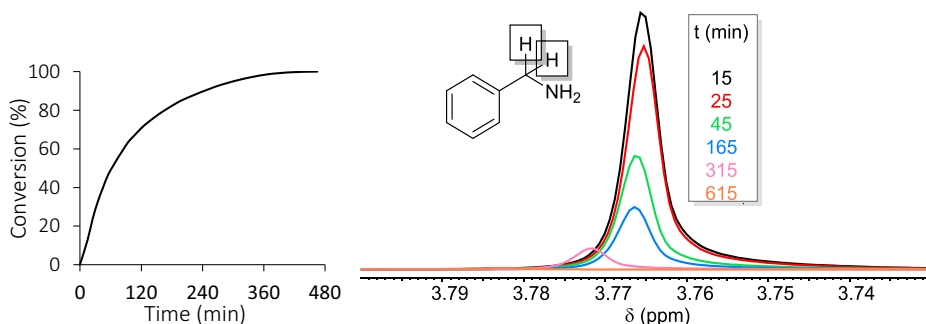
Figure 4-1. Aminolysis of *N*-acetylhomocysteine thiolactone: (left) Conversion of benzylamine as a function of time and (right) detail of the ^{1}H-NMR spectrum (500 MHz, 1,4-dioxane-d_8, 40 °C) representing the benzylic protons of benzylamine and their decrease in time.

A thorough analysis of the reaction mixture obtained after the two-step reaction was done via LC-MS analysis (Figure 4-2) and will be discussed in detail. In a first reaction step, benzylamine (BA) reacts with ACTL in the presence of dimethylaminopyridine (DMAP). From MS-analysis, it was concluded that during this step disulfides are being formed, besides the expected thiol (Entry 1). When the two-step reaction (ring-opening, followed by radical thiol-ene reaction with norbornene, NB) is performed in

the presence of DMPA as photoinitiator (Entry 2), different side-products are observed after 2 hours irradiation with UV-light of 300 nm. After column chromatography, the pure conjugate product could be obtained with a yield of 28 % (Entry 3). The side-products are identified as being reaction products between benzylamine and radical fragments of DMPA (Entry 4). The product indicated with an * did not ionize during MS and therefore, no structural information on this product could be obtained.

Using no photo-initiator and after chromatographic purification, the model conjugation reaction yielded the conjugation compound with an isolated yield of 80%. Table 4-1 shows the relative initial quantities of reactants in four different reactions, corresponding to the entries in Figure 4-2.

Table 4-1. Relative initial quantities of reactants/reagents in the model domino reaction. BA = benzylamine; NB = norbornene.

Entry	ACTL	BA	NB	DMAP	DMPA	Time (h)
1	2	1	-	0.2	-	2
2	2	1	1.2	0.2	0.1	2
3	-	1	-	-	0.1	3
4	2	1	5	0.1	-	6

The structure of the amine-thiol-norbornene reaction product, which is a mixture of diastereoisomers, was confirmed by NMR- and MS-analysis. An important general conclusion drawn from this model study is that the use of a photo-initiator should be limited because of the demonstrated interference between benzylamine and radical fragments of the photoinitiator (Entry 3). It is known that radical thiol-ene conjugation can be performed in the absence of a photoinitiator through irradiation with UV light or sunlight[26, 27]. No further efforts were undertaken to modify the radical initiation process as earlier reports showed that thermal initiators are generally less efficient than photo-initiators for radical thiol-ene conjugation[28] and that H-abstraction type photo-initiators such as benzophenone and thioxanthone react with amines with the formation of the corresponding imines.[29]
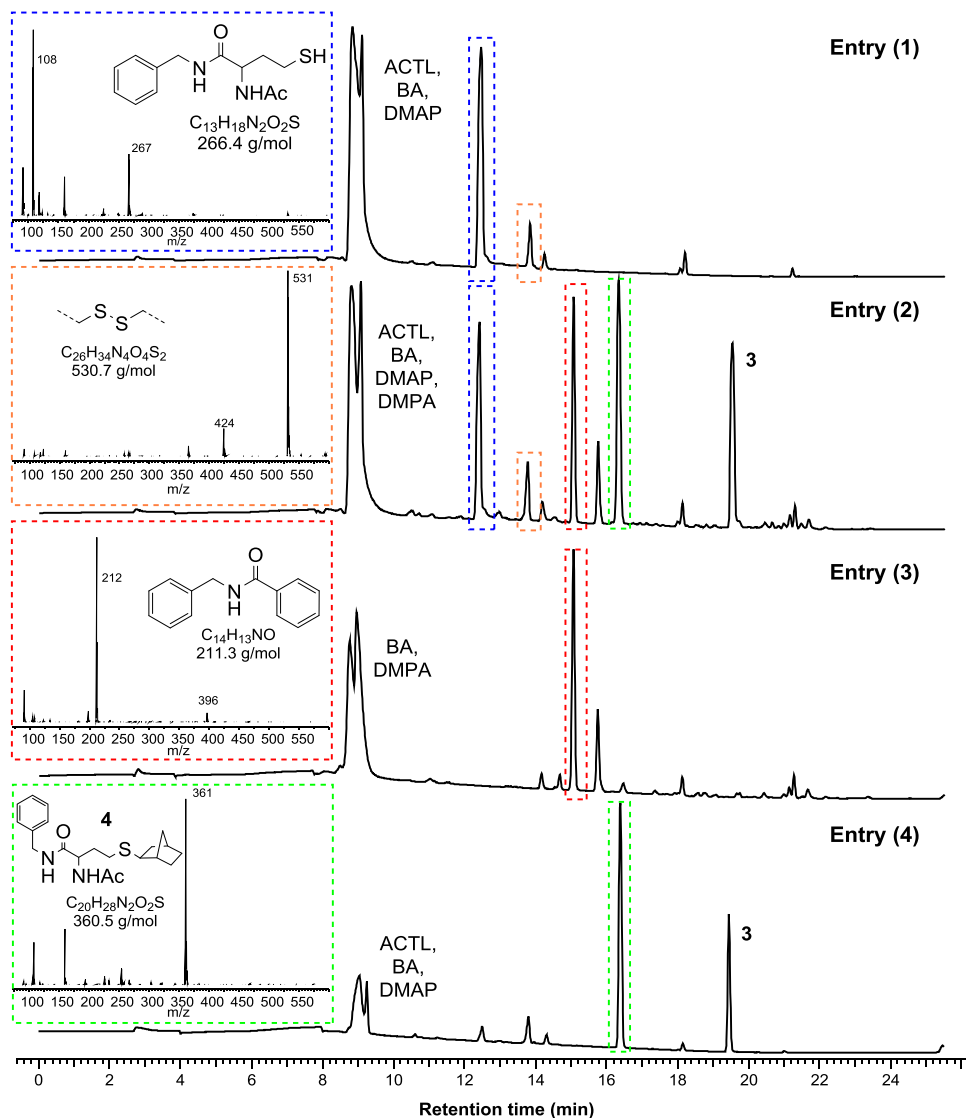
Figure 4-2. LC-MS analysis of the crude reaction mixtures, corresponding to entries (1) → (4) in Table 4-1. Inserts: ESI-MS spectra of relevant compounds of the model reaction.

4.2.3. Post-polymerization functionalization with ACTL

The above described two-step model reaction gave a total yield of 80%, which encouraged us to evaluate the use of ACTL as a thiolation agent for modifications on polymer substrates. Alkyne-functionalized polyesters, synthesized following a procedure by Billiet et al.,[30] were used for a thiol-yne addition reaction with the *in situ* formed thiol. The used polybutyleneadipate (PBAd) has an alkyne loading of 10.5% (Scheme 4-3).
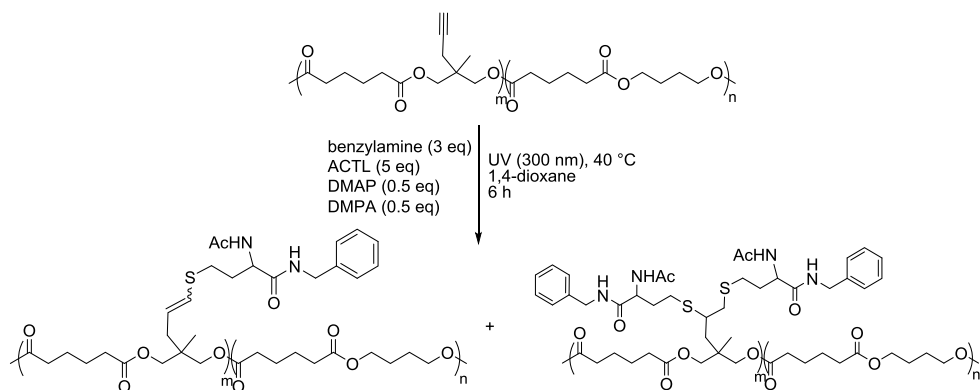
Scheme 4-3. Thiol-yne radical addition on PBAd-≡, using ACTL as thiolating agent for benzylamine.

An excess of benzylamine and ACTL were used to modify the alkyne-functionalized polybutyleneadipate (PBAd-≡). From SEC (UV-detection), it was concluded that benzylamine was successfully attached to the polymer. Indeed, the starting polymer substrate is UV-inactive (showing no SEC trace with UV-detection), while after modification with the UV-active benzylamine, a SEC trace is observed (Figure 4-3).
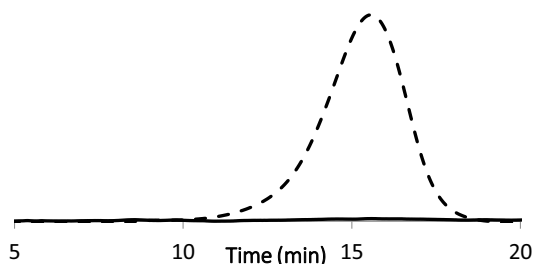
Figure 4-3. Overlay of SEC chromatograms (UV-detection, λ = 405 nm) of unreacted PBAd-≡ (solid line) and benzylamine-modified PBAd-≡ (dotted line).

^{1}H NMR analysis was used to determine the conversion of the reaction, as well as the relative amounts of formed thioether and dithioether. The conversion was calculated based on the ratio of the methyl protons (b) to the alkyne protons (d). The amount of dithioether was calculated by comparing the intensities of the double bond protons relative to the intensity of the amide protons (Table 4-2). Depending on the reaction times, the degree of functionalization is higher (Entry 1 vs. 2).
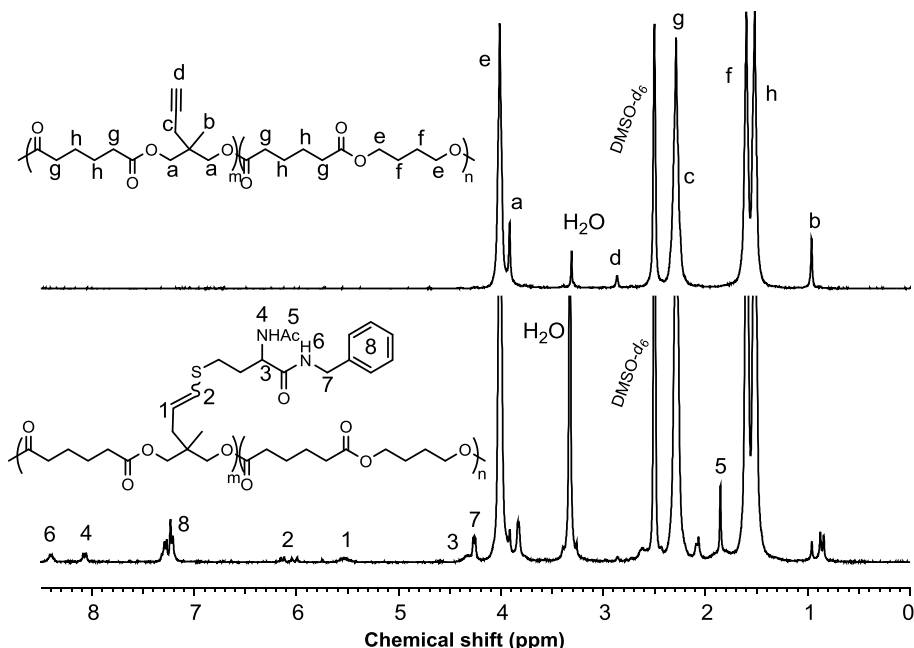
Figure 4-4. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of PBAd-≡ before and after modification with benzylamine. The double bond protons are used to calculate the relative amount of thioether and dithioether product.

The same reaction was repeated using Jeffamine® M-1000. This is a polyether (secondary) amine with a molecular weight around 800 g.mol^{-1}. An excess of amine and ACTL was added and the reaction was purified by precipitation. The reaction product was analyzed with ^{1}H-NMR and DOSY NMR (Diffusion Ordered SpectroscopY). DOSY differentiates between components based on their translational diffusion rates, and thus allows to interpret whether a polymer is functionalized, or if the NMR signals are originating from non-covalently linked molecules. From DOSY, it was clear that the Jeffamine signals had the same diffusion coefficient as the precursor polymer and therefore a successful modification was expected. The alkyne groups showed to be 100% consumed, although only 28 % was double modified with the formation of dithioether (Table 4-2; Entry 3).

Table 4-2. Conversion and relative amounts of thioether and dithioether, calculated from ^{1}H NMR (300 MHz).

Entry	Conversion (%)	% Thioether	% Dithioether	Time (hours)
1	15	80	20	2.5
2	63	89	11	6
3	100	72	28	16

4.3. MONOMER SYNTHESIS: ALLOC-THIOLACTONE

Scheme 4-4. Synthesis of Alloc-TL, by reacting homocysteine thiolactone with allyl chloroformate.

Encouraged by the successful model studies, we investigated the synthesis of a monomer containing both a double bond and a thiolactone unit. Similarly, Perrier et al.[31] reported on thiol-yne chemistry for the synthesis of hyperbranched structures using AB$_2$ type (macro)monomers, molecules bearing a thiol at the α chain-end of the molecule and an alkyne at the ω chain-end. In our case, as a thiolactone moiety can be considered as a precursor of a thiol functionality, the combination with a double bond results in an AB` type monomer. The valorization of the reactivity of this monomer, *N*-(allyloxy)carbonylhomocysteine thiolactone (Alloc-TL), upon aminolysis and subsequent UV-curing, would enable us to develop convenient and accelerated protocols for the synthesis of novel polymeric architectures. A scalable and high-yielding synthesis of the proposed ene-thiolactone monomer consisted of the treatment of homocysteine thiolactone with allyl chloroformate (Scheme 4-4), introducing the corresponding (allyloxy)carbonyl or alloc group, a popular amino-protecting group.

4.4. ONE-POT PHOTOPOLYMERIZATION

4.4.1. Linear polymers

Scheme 4-5. One-pot photopolymerization of Alloc-TL, being an AB'-monomer, using ethanolamine. The product is a polymer with a polyurethane/thioether backbone and pendent hydroxyl groups.

Radical (photo)polymerization reactions between a thiol and an alkene occur in a stepwise fashion (see chapter 2 for a theoretical description). Typically for stepwise polymerizations, a gradual increase of the molecular weight with increasing conversion is observed. In order to get high-molecular-weight polyaddition compounds, the ratio between the involved functional groups should equal one. The aminolysis of the thiolactone in the Alloc-TL monomer, generating the thiol, should therefore efficiently reach full conversion. When using benzylamine in the one-pot poly-addition reaction, polymer material could be identified by size-exclusion chromatography (SEC), but even after prolonged UV-curing, only low-molecular-weight material (M_n < 5 kDa) was formed, compromising the purification *via* precipitation and further analysis. On the other hand, in the presence of a two-fold excess of the nucleophile ethanolamine and a small amount of DMPA (5 mol%), the poly-addition occurred and after 1 hour of UV-curing, a white precipitate was obtained (Scheme 4-5).
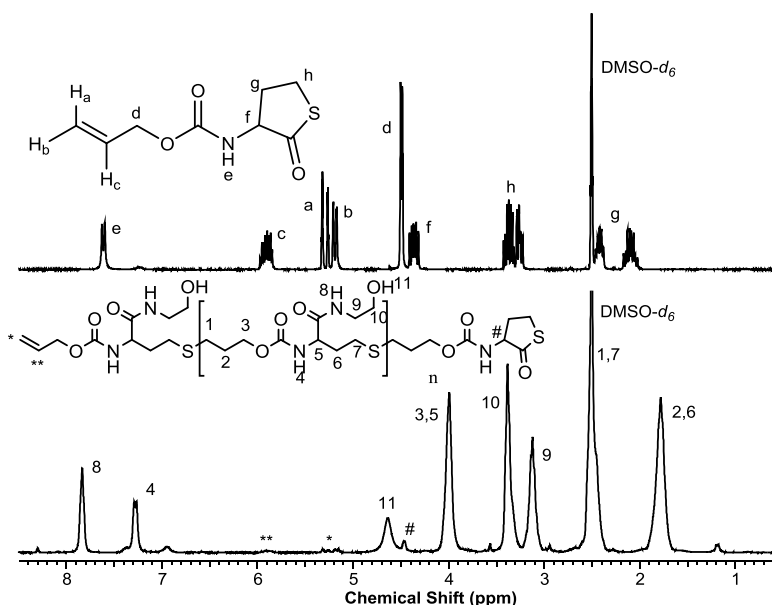
Figure 4-5. ^{1}H NMR Spectrum (300 Mhz, DMSO-d_6) and assignment of Alloc-TL (top) and the resulting polymer with polythioether/polyurethane backbone (bottom) and pendent hydroxyl groups.

The purified polymer was soluble in MeOH, DMSO, DMF and DMA and was analyzed by SEC and 1D- and 2D-NMR. The SEC chromatogram displayed a unimodal distribution with a polydispersity index (PDI) of 1.6 and M_n, determined via SEC, was 22 kDa. The quantification of M_n of the same polymer via endgroup analysis (double bond protons) in the ^{1}H-NMR spectrum (Figure 4-5) revealed a molecular weight of 7.8 kDa. The value obtained by SEC is rather qualitative, as the SEC-column is calibrated with PMMA standards, having a different hydrodynamic volume than the synthesized polymer. Moreover,

this polymer is more hydrophilic than PMMA, which also explains the shorter elution times on a hydrophobic column.

This mild and efficient one-pot poly-addition process yielded a polymer with a polythioether/polyurethane backbone and pendant hydroxyl groups. We deliberately selected the ambident nucleophile ethanolamine for the aminolysis: under neutral conditions, hydroxyl functions are unable to open the thiolactone ring[32] and alcohols do not interfere with radical thiol-ene reactions[8]. Standard synthetic methods for the synthesis of hydroxyl functionalized polyurethanes would certainly require a protection/deprotection strategy. Generalization of this reaction concept emphasizes the fact that, as long as the additional functional group of the multifunctional amine does not interfere with either reactions in the one-pot multistep process (aminolysis and radical thiol-ene), linear polymers can be obtained with direct introduction of side chain functional groups, prone to post-polymerization modification[33].

4.4.2. Polymer networks
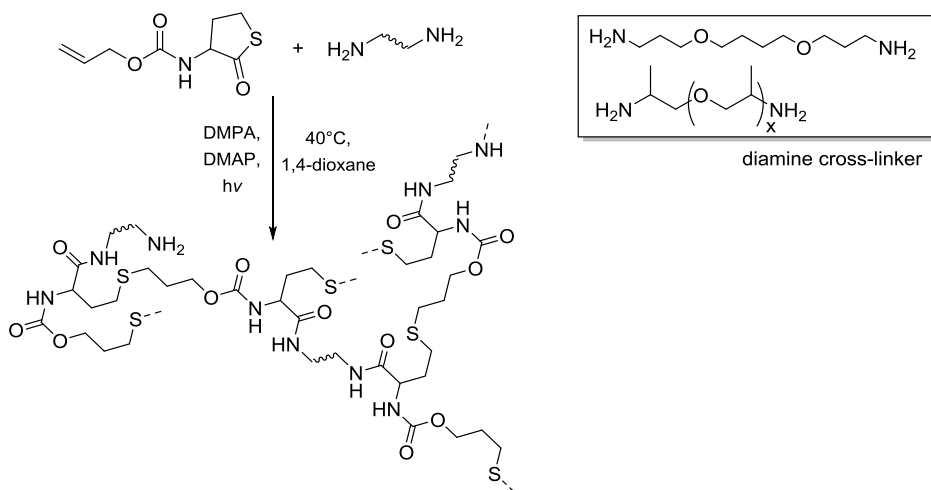
Scheme 4-6. Schematic depiction of the network formation: one-pot reaction between the Alloc-TL monomer and a diamine cross-linker results in a polythioether polyurethane network. Structure of 4,9-dioxadodecanediamine and Jeffamine® D series are shown.

To further extend the scope of this methodology in material science, polymer networks based on the AB′ type Alloc-TL were targeted. Anticipation of network formation was based upon treatment of this monomer with a diamine under similar conditions as described above (Scheme 4-6). Polymer film formation was expected by UV-irradiation of a homogeneous reaction mixture between 2 glass plates, separated by a thin silicone spacer.

The choice of the diamine cross-linker regarding structure and molecular weight proved to be critical. 1,6-Hexanediamine was insoluble in the reaction mixture. The use of the more polar 4,9-dioxadodecanediamine as cross-linker yielded a clear, non-tacky network film with good mechanical properties (not quantified, though high tensile strength was observed) after UV-curing during 3 hours. The use of the Jeffamine® D series (D-400, D-2000 and D-4000) as macromolecular cross-linkers was also attempted but poor film formation was observed, probably because the amine group is located on a secondary carbon atom, thus sterically hampering cross-linking.

4.5. CONCLUSION

In conclusion, we have demonstrated that a thiolactone entity can serve as a precursor for thiols in a one-pot amine-thiol-ene reaction: the thiolactone ring opens upon aminolysis and the *in situ* generated thiol reacts with a double bond, already present in the same pot. A model study was elaborated to master the reaction conditions. In order to valorize this reaction concept as an accelerated protocol in polymer synthesis, an AB′ type monomer, consisting of a double bond and a thiolactone moiety, was synthesized and used to successfully assemble functional, linear polymers and networks via a mild and facile radical photopolymerization process.

4.6. EXPERIMENTAL PART

4.6.1. Materials

1,6-Hexanediamine (Acros, 99.5+%), 2,2,4-trimethylpentane (iso-octane, Sigma Aldrich, HPLC), 2,2-dimethoxy-2-phenyl acetophenone (DMPA, Acros, 99%), 4,9-dioxadodecanediamine (Acros, 97%), 4-dimethylaminopyridine (DMAP, Aldrich, 99%), allyl chloroformate (Aldrich, 97%), benzylamine (Acros, 99.5+%), bicyclo[2.2.1]-2-heptene (norbornene, Fluka, ~97%), chloroform (Fisher Scientific, HPLC grade), dichloromethane (Sigma-Aldrich, HPLC), DL-homocysteine thiolactone hydrochloride (Fluka, ≥ 99%), DL-*N*-acetylhomocysteine thiolactone (Aldrich, 99%), ethanolamine (Fluka, ≥ 99%), ethyl acetate (Fluka, HPLC), Jeffamine® D-series (Huntsman) and methanol (Sigma Aldrich, HPLC grade) were used as received. 1,4-Dioxane (Acros, HPLC grade) was degassed (purged with Argon during 30 min) prior to use as a reaction solvent. Silicagel (ROCC, SI 1721, 60 Å, 40 – 63 μm) was used to perform preparative column chromatography, eluting with HPLC-grade solvents. The collected fractions were analyzed by thin layer chromatography (TLC-plates, Macherey-Nagel, SIL G-25 UV$_{254}$).

4.6.2. Methods

^{1}H- and ^{13}C-NMR (Attached Proton Test, APT) spectra were recorded in CDCl$_3$ (Eurisotop), DMSO-d_6 (Eurisotop) and 1,4-dioxane-d_8 (Aldrich) on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz.

An Agilent technologies 1100 series LC/MSD system equipped with a diode array detector and single quad MS detector (VL) with an electrospray source (ESI-MS) was used for classic reversed phase *LC-MS (liquid chromatography mass spectroscopy) and MS analysis*. Analytic reversed phase HPLC was performed with a Phenomenex C$_{18}$ (2) column (5 μ, 250 x 4.6 mm) using a solvent gradient (0 → 100% acetonitrile in H$_2$O in 15 min) and the eluting compounds were detected *via* UV-detection (λ = 214 nm).

FT-ATR-IR spectra were recorded on a Perkin-Elmer Spectrum1000 FTIR infrared spectrometer with pike-HATR module.

Size Exclusion Chromatography (SEC) was performed on a Waters instrument, with a refractive-index (RI) detector (2414 Waters), equipped with 3 Polymer Standards Services SEC serial columns (1 X GRAM Analytical 30 Å, 10 μm and 2 x GRAM Analytical 1000 Å, 10 μm) at 35 °C. Poly(methyl methacrylate) (PMMA) standards were used for calibration and N,N-dimethylacetamide (DMA), containing LiBr (0.42 g/mL) was used as an solvent at a flow rate of 1 mL/min. Molecular weight and polydispersity index were determined using the Empower software.

UV curing was performed by irradiation with 300 nm UV lamps (8 x 25 W) positioned in a metal cylindrical container.

4.6.3. Kinetic study of the aminolysis reaction *via* online ^{1}H-NMR

N-Acetylhomocysteine thiolactone (58 mg, 0.3643 mmol) and DMAP (2.2 mg, 0.0180 mmol) were dissolved in 1,4-dioxane-d_8 (600 μL) in an NMR tube. Iso-octane (20 μL) was used as an internal standard (reference peak at 0.90 ppm [C(CH_3)$_3$]). The reaction was started (t = 0) with the subsequent addition of benzylamine (20 μL, 0.1829 mmol). The reaction medium was sealed and from that moment on, the sample was analyzed every 10 minutes *via* ^{1}H-NMR spectroscopy (500 MHz at 40 °C) with a delay of 15 minutes for the first measurement. The consumption of benzylamine was monitored by the decrease of the signal of the corresponding benzylic protons in the ^{1}H-NMR spectrum (δ = 3.76 ppm). All spectra were calibrated according to the chemical shift of the solvent signal (1,4-dioxane-d_8, δ = 3.53 ppm).

4.6.4. Procedure and characterization of conjugation compound

To a solution of norbornene (861 mg, 9.146 mmol) in degassed 1,4-dioxane (6 mL) were sequentially added benzylamine (200 µL, 1.830 mmol), DMAP (22.4 mg, 0.183 mmol) and *N*-acetylhomocysteine thiolactone (582 mg, 3.658 mmol). The reaction medium was sealed and stirred during 6 hours at 40 °C while being cured by UV light. The reaction mixture was filtered over a short path of silica gel to quench the reaction, the silica was rinsed with EtOAc and the eluent was concentrated. Purification of the crude mixture by column chromatography (silicagel, EtOAc) yielded the conjugation compound (528 mg, 1.465 mmol, 80%) as a white solid.

$C_{20}H_{28}N_2O_2S$ (360.51 g/mol); ***m/z* (ESI-MS)** 361;

v_{max} / cm^{-1} 3313, 3258, 2950, 2868, 1649, 1546, 1452, 1369, 1287, 1070, 1029, 1016, 748, 705, 677, 596, 582, 544;

^{1}H-NMR (300 MHz, DMSO-*d6*, ppm) δ 8.43 (*t*, 1H), δ 8.06 (*d*, 1H), δ 7.35 → 7.27 (*m*, 2H), δ 7.27 → 7.15 (*m*, 3H), δ 4.40 → 4.15 (*m*, 3H), δ 2.66 (*m*, 1H), δ 2.48 → 2.33 (*m*, 2H), δ 2.19 (*m*, 1H), δ 2.12 (*m*, 1H), δ 2.03 → 1.26 (*m*, 9H), δ 1.25 → 1.05 (*m*, 4H);

^{13}C-NMR (75 MHz, DMSO-*d6*, ppm) δ 171.2 (C), δ 169.3 (C), δ 139.4 (C), δ 128.2 (CH), δ 127.0 (CH), 126.7 (CH), 52.0 (CH), 45.9 (CH), 42.0 (CH$_2$), 41.6 (CH), 38.5 (CH$_2$), 35.7 (CH), 35.0 (CH$_2$), 32.3 (CH$_2$), 28.3 (CH$_2$), 28.2 (CH$_2$), 27.7 (CH$_2$), 22.5 (CH$_3$)

4.6.5. Modification of PBAd-≡

PBAd-≡ (0.559 mmol; 1 g) is dissolved in 1,4-dioxane (10 mL). Benzylamine (1.676 mmol; 183 µL), ACTL (2.794 mmol; 0.445 g), DMAP (0.279 mmol; 34 mg) and DMPA (0.2794 mmol; 71.6 mg) are added under Ar-atmosphere. The reaction is stirred for 9 hours under UV-irradiation (300 nm) and samples are taken at dedicated times and precipitated in cooled MeOH. The same reaction is performed using Jeffamine ® M-1000 (1.397 mmol; 1.118 g), ACTL (1.397 mmol; 222 mg), DMAP (0.279 mmol; 34 mg) and DMPA (0.2794 mmol; 71.6 mg) (24 hours).

4.6.6. Synthesis of *N*-(allyloxy)carbonylhomocysteine thiolactone

DL-Homocysteine thiolactone hydrochloride (28 g, 0.1823 mol) was slowly added to a solution of NaHCO$_3$ (76.44 g, 0.91 mol) in H$_2$O/1,4-dioxane (1/1, 400 mL) and this mixture was stirred for 30 minutes. Allyl chloroformate (38.76 mL, 0.3644 mol) was added dropwise and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with brine (800 mL) and extracted with EtOAc (4 x 800 mL). The organic phase was dried (MgSO$_4$). The drying agent was

filtered and the resulting clear solution was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 98/2) to furnish the title compound (32.23 g, 0.1602 mmol, 87% yield) as a white solid.

C$_8$H$_{11}$NO$_3$S (201.24 g/mol); *m/z (ESI-MS)* 202, 174, 130, 113;

v$_{max}$ / cm^{-1} 3307, 1691, 1546, 1445, 1302, 1267, 1249, 1174, 1098, 1056, 925, 851, 778, 762, 686, 655, 615, 582, 557;

^{1}H-NMR (300 MHz, CDCl$_3$, ppm) δ 5.90 (*ddt*, 17.2, 10.4, 4.7 Hz, 1H), 5.30 (*m*, 1H), 5.29 (*ddd*, 17.2, 3.0, 1.5 Hz, 1H), 5.25 (*ddd*, 10.4, 2.6, 1.3 Hz, 1H), 4.57 (*dt*, 17.2, 5.6, 1.4 Hz, 2H), 4.32 (*m*, 1H), 3.28 (*m*, 2H), 2.83 (*m*, 1H), 2.01 (*m*, 1H);

^{13}C-NMR (75 MHz, CDCl$_3$, ppm) δ 205.1 (C), 156.2 (C), 132.6 (CH), 118.2 (CH$_2$), 66.2 (CH$_2$), 60.9 (CH), 32.0 (CH$_2$), 27.3 (CH$_2$).

4.6.7. Radical (photo)polymerization of Alloc-TL: linear polymer

A solution of *N*-(allyloxy)carbonylhomocysteine thiolactone (402 mg, 2 mmol) in 1,4-dioxane (1 mL) was treated with DMAP (49 mg, 0.4 mmol), DMPA (25 mg, 0.1 mmol) and ethanolamine (241 μL, 4 mmol) and irradiated with UV light during 1 h. The liquid fraction was decanted. The obtained white precipitate was rinsed with CHCl$_3$ (4 x 1.5 mL), dried, redissolved in MeOH (1.5 mL) and precipitated in cold CHCl$_3$ (15 mL). Decantation and drying yielded a white solid, which was subjected to analysis.

v$_{max}$ / cm^{-1} 3425, 2924, 1710, 1248, 1058;

M$_n$^{SEC} 22 kDa; PDI 1.6; M$_n$^{NMR} 7.8 kDa.

4.6.8. Radical (photo)polymerization of Alloc-TL: network film

A solution of *N*-(allyloxy)carbonylhomocysteine thiolactone (402 mg, 2 mmol) in 1,4-dioxane (1 mL) was treated with DMAP (49 mg, 0.4 mmol), DMPA (25 mg, 0.1 mmol) and 4,9-dioxadodecanediamine (204 mg, 1 mmol). The homogeneous reaction mixture was injected between 2 glass plates, separated by a silicon spacer (1 mm) and irradiated with UV light during 3 h (Figure 4-6). The obtained clear, yellow and non-tacky film was washed several times with 1,4-dioxane and dried.
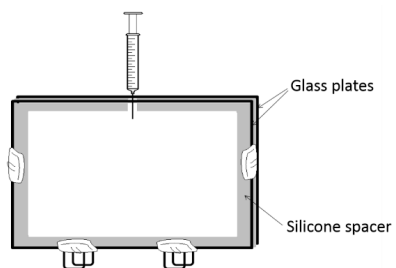
Figure 4-6. The homogeneous reaction mixture is injected between two glass plates, separated by a silicone spacer, prior to irradiation with UV-light.

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Abstract

A thiolactone derivative of 10-undecenoic acid was used as a renewable AB'-monomer for the one-pot synthesis of diversily substituted polyamide structures, containing amide moieties both in the polymer backbones and in their side-chains. Nucleophilic aminolysis of the thiolactone entity liberates a thiol, which further reacts in a stepwise thiol-ene photopolymerization reaction. Using different primary amines, several structurally diverse polymers, with physical properties dependent on the length and chemical identity of the side-chain, were obtained. Post-polymerization oxidation of the sulfide linkages in the polymer backbone to their corresponding sulfoxides and sulfones altered the material, with the degree of oxidation having an impact on the final mechanical properties. Furthermore, this mild and straightforward polymerization procedure was applied for the synthesis of functional polymer networks.

Chapter 5
Substituted Polyamides through Polymerization of Renewable Thiolactone Building Blocks

5.1. INTRODUCTION

Depleting resources, accompanied by increasing oil prices, are driving polymer industry towards the use of renewable feedstocks in order to achieve more sustainable production processes. Plant oils have already proven to be valid candidates for this purpose, as they are abundantly available world-wide at relatively low costs. Furthermore, plant oils and fatty acids can be converted into various useful monomers by straightforward modification reactions, often to serve as building blocks for polycondensation reactions.[1-5] For example, the modification of vegetable oils to polyols for the synthesis of polyurethanes has already been extensively reported[6] and fatty acid derived diols have been applied as monomers for the synthesis of linear polyurethane structures.[7] Kolb et al. prepared a series of polyesters and polyamides with varying side-chains, starting from fatty acid derived malonate esters.[8]

Sustainable development not only encompasses the use of renewable resources, but also implies the continuous search for optimized, efficient and environmentally friendly processing methods. Since its introduction in 2001, click chemistry has emerged as a green concept to couple chemicals together, strictly bound to requirements serving efficient procedures and lowering the impact on the natural environment.[9] A variety of synthetic procedures has since then been developed as valuable addition to this principle and many of them have played an important role in polymer synthesis.[10, 11] A reaction that has repeatedly been used for conjugation purposes in polymeric systems is the radical addition of a thiol to an unsaturated carbon-carbon bond.[12, 13] This chemistry, referred to as thiol-ene chemistry, has been known for over a century for the synthesis of thermoset materials, but has again gained importance during the last decade as a valuable metal-free alternative for the heavily exploited copper-catalyzed cycloaddition reaction between an azide and an alkyne (CuAAC).[13-15]

There are quite some examples in the literature describing the use of thiol-ene chemistry for the modification of fatty acid compounds, as the presence of double bonds in the aliphatic chain makes them ideal substrates for this reaction. Not surprisingly, 10-undecenoic acid (see Scheme 5-1), a fatty acid derived from castor oil by pyrolysis of its main constituent ricinoleic acid,[16] has come forth as one of the most promising compounds in this context. Indeed, the terminal alkene of 10-undecenoic acid is more reactive towards thiyl radicals than the more substituted internal alkenes of other fatty acids.[17] The polymerization of this compound using thiol-ene reactions can be achieved by either transforming it with a monofunctional thiol into a polycondensable monomer,[18-23] or by direct step-growth polymerization of derived α,ω-dienes with dithiols.[24-26] A prerequisite for the latter case is that both ene and thiol moieties have to be present in equimolar amounts in order to obtain sufficiently high molar masses. Nevertheless, by combining both functions in an AB-monomer, this stoichiometric requirement can be intrinsically fulfilled.[27] Two reviews on the use of thiol-ene chemistry for the modification of fatty acids to polymerizable compounds have recently been published.[28, 29]

Despite all the advantages of thiol-ene chemistry (metal-free, fast and high yielding), there are some thiol-related issues that have to be taken into account. Besides the fact that the commercial availability of thiols is rather limited, they usually have an unpleasant smell. Moreover, thiols are prone to oxidation reactions, affecting their shelf-life drastically. This is why research groups have been searching for ways to protect thiols, e.g. as thioacetate,[30] disulfide[31] or methanethiosulfonate.[32] However, these examples are based on a protecting/deprotecting strategy, which is unfavorable in terms of atom efficiency and overall yield. An alternative approach involves the use of stable precursor groups that can be regarded as latent thiols. For example, aminolysis of the thiocarbonylthio-group, resulting from the RAFT (Reversible Addition-Fragmentation Transfer) process, enables the formation of a thiol at the ω-end of the polymer chain.[33]

With the aim of synthesizing and modifying polymer materials through (protected) thiol chemistries, we developed a strategy that is based on the use of thiolactones as precursors for thiols,[34] inspired by a decades-old method for the introduction of sulfhydryl groups in natural proteins.[35] The strategy involves the nucleophilic ring-opening of a thiolactone (i.e. a five-membered cyclic thio-ester) by a primary amine, with the concurrent liberation of a thiol. Hence, the added value of this aminolysis reaction compared to other protection strategies becomes clear: it offers the opportunity of introducing a functional group of choice, provided that this functionality does not interfere with the ring-opening step. The combination of the thiolactone's dual function (releasing of a thiol and the incorporation of functionality through the amine) with a subsequent thiol-"click" reaction, was the starting point for the one-pot preparation of polythiols,[36, 37] functionalized polyurethanes,[38] cyclic polymers[39] and the synthesis of sequence-defined oligomers.[40]

One of the first commercialized polyamides from renewable resources is polyamide 11, manufactured under the trade name Rilsan® by Arkema. This polyamide is prepared through polycondensation of 11-aminoundecanoic acid, derived from castor oil, and finds its use in high-performance applications.[41] However, when wanting to explore new markets for polyamides by adding a functionality through substituents on their side-chains, one often has to turn to more complex synthetic pathways. A procedure carried out within our own research group consisted of the post-polymerization modification of alkyne-decorated polyamides *via* thiol-yne or CuAAC chemistry.[42]

In this chapter, we describe a straightforward, one-pot synthesis of functionalized polyamide structures, formed through step-growth thiol-ene polymerization of a renewable thiolactone derivative of 10-undecenoic acid. The chemical structure of the thus obtained polymers includes two amide bonds per repeating unit (one in both the main and side chain) and a thio-ether linkage, consequently making them fundamentally different from commercially available polyamides. Recently, polymers with multiple amides in their structural build-up were prepared by Kreye et al., who applied the Ugi four-component reaction for the synthesis of functionalized dienes as building blocks for thiol-ene and ADMET polymerization.[43]

In a first stage, the influence of the nature of the side-chains was studied with respect to thermal and mechanical properties. Next, post-polymerization oxidation was used to alter the properties of these materials at the level of the polymer main chain. Finally, this renewable monomer, combining a double bond and a thiolactone moiety, was applied as a starting material for the one-pot preparation of functional polyamide-based networks.

5.2. MONOMER SYNTHESIS

We targeted the preparation of a stable monomer containing both an unsaturated carbon-carbon bond and a thiolactone entity. Intended for a large-scale synthesis of polymer materials, this monomer had to be produced in considerable quantities, and should thus be derived from abundantly available and preferably renewable resources.
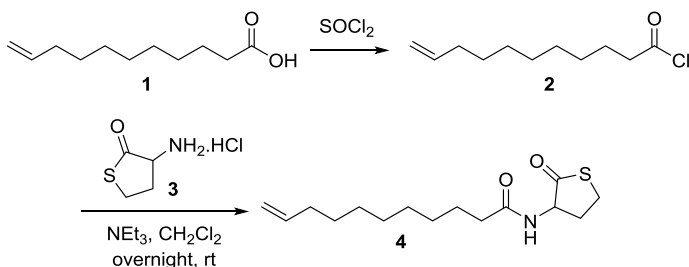
Scheme 5-1. Two-step synthesis of 10-undecenoyl thiolactonamide 4, starting from the renewable compound 10-undecenoic acid 1.

The synthesis of 10-undecenoyl thiolactonamide **4** proceeds in two steps (Scheme 5-1). 10-Undecenoic acid **1** was transformed in its corresponding acid chloride **2**, which subsequently can, after removal of the excess thionyl chloride, react with DL-homocysteine thiolactone **3** in the presence of triethylamine as a base. Both **1** and **3** are obtained from renewable resources and are readily available at relatively low cost. The product could be purified without the use of chromatographic methods. Instead, recrystallization from 2,2,4-trimethylpentane (iso-octane) delivered **4** on a large scale (> 50 g) as white crystals with an overall yield of 70 %. The purity of **4** was confirmed by LC-MS (ESI) and NMR spectroscopy (^{1}H (Figure 5-1) and ^{13}C.

5.3. POLYMERIZATION

10-Undecenoyl thiolactonamide **4**, an AB'-monomer linking both a double bond (A) and a thiolactone (B') moiety *via* an amide bond, can be considered as a precursor for an AB-type thiol-ene monomer. The thiol, which is generated through aminolysis of the thiolactone, will be able to react with the terminal ene function through radical thiol-ene addition, resulting in complex polyamide structures (Scheme 5-2).
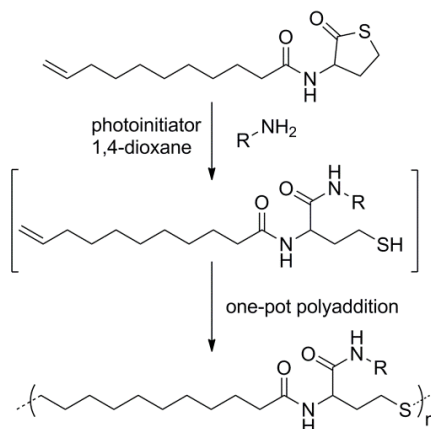
Scheme 5-2. One-pot stepwise photopolymerization of the 10-undecenoyl thiolactonamide monomer 4, yielding linear polyamide structures with adjustable side-chains.

It should be noted that this one-pot multi-step process is 100% atom efficient, has all reaction partners present from the start and that no intermediate purification is needed. Since radical (photo)polymerization reactions between a thiol and an alkene occur in a stepwise fashion, polymers of sufficient molecular weight will only be obtained when the aminolysis reaction (and thus the release of a thiol) reaches high conversions.

To define the reaction conditions that yield the highest molecular weights, a series of model reactions with octylamine as primary amine was conducted. These experiments revealed that the best results were obtained when using 1.1 equivalent of amine, 2,2-dimethoxy-2-phenylacetophenone (DMPA) as a photoinitiator in 1,4-dioxane as a solvent, after 5 hours of reaction time (Figure S3). The molecular weights when using azobisisobutyronitrile (AIBN) and camphorquinone as radical initiator were lower (Table 5-1), in accordance with the observations of Uygun et al.[44] The reaction temperature was set at 40 °C, the temperature induced by the UV-lamps.

Table 5-1. Molecular weight characteristics after polymerization using different initiators.

Initiator	Time (h)	$M_n{}^a$ (g.mol^{-1})	$M_w{}^a$ (g.mol^{-1})	Đ^a
AIBN	20	4300	5600	1,31
CQ	15	1900	2500	1,28
DMPA	5	4500	6100	1,37

^{a} SEC, calibrated with PS standards, THF as eluent.

With these reaction parameters, a series of polyamide structures with varying side-chains was synthesized by applying different aliphatic primary amines. These amines differ in the number of carbon-atoms in their alkyl chain, which are linear or branched. Table 5-2 gives an overview of the used amines and the corresponding molecular weight characteristics of the obtained polymers. In general,

the molecular weights and dispersities are rather low, because the polymers precipitate out of the reaction mixture after a certain amount of time, limiting their further growth. DMA as a solvent did not give rise to polymers with higher masses. Molecular weights were determined both *via* SEC and *via* end-group analysis (double bond protons, indicated with * and ** in the spectrum) in the ^{1}H NMR spectrum (Figure 5-1).
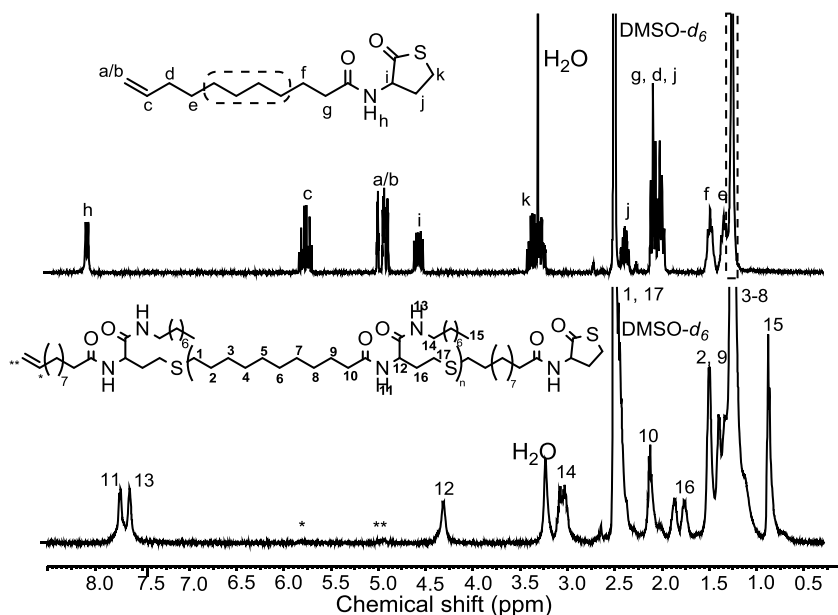
Figure 5-1. 500 MHz ^{1}H NMR- spectra (DMSO-d_6) of 10-undecenoyl thiolactonamide 4 (top) and the corresponding polyamide structure P8 (bottom), after ring-opening with octylamine and UV-irradiation.

Table 5-2. Overview of amines used for the polymerization of 4 and molecular weight characteristics of the corresponding polymers.

Entry	# of C	Amine	M_n^a (g.mol^{-1})	M_n^b (g.mol^{-1})	M_w^b (g.mol^{-1})	Đ^b
P1	0	Ammonia	1500	2700	4100	1.51
P2	1	Methylamine	5200	8500	16700	1.97
P3	2	Ethylamine	4700	7800	11300	1.45
P4	3	Propylamine	6900	12300	18400	1.50
P5	3	Isopropylamine	2600	4700	7100	1.52
P6	4	Butylamine	8900	16700	26500	1.59
P7	6	Hexylamine	8500	15300	22900	1.50
P8	8	Octylamine	10300	19300	29000	1.51
P9	8	2-Ethyl-1-hexylamine	2000	6700	9900	1.49
P10	12	Dodecylamine	7800	11000	15000	1.35
P11	18	Octadecylamine	6900	9100	10800	1.19

^{a} Calculated from end-group (double bond) protons in ^{1}H NMR spectra.
^{b} SEC, calibrated with PMMA standards, DMA as eluent.

The obtained molecular weights are clearly dependent on the amine structure. Ammonia is less nucleophilic than the other amines and therefore the aminolysis reaction will proceed less efficiently, leading to lower molecular weights. It is also observed that for branched amines (**P5**, **P9**), molecular weights are lower compared to the corresponding linear amines (**P4**, **P8**), an effect attributed to sterical hindrance.

	Series I [K-adduct]		Series II [K-adduct]	
n	*calc.*	*exp.*	*calc.*	*exp.*
4	1690.10	1690.65	1706.10	1706.56
5	2102.85	2103.28	2118.85	2119.44
6	2515.60	2516.04	2531.60	2532.17
7	2928.35	2928.90	2944.35	2944.92
8	3341.10	3341.83	3357.10	3357.91
9	3753.85	3754.18	3769.85	3770.61
10	4166.60	4167.44	4182.60	4183.12
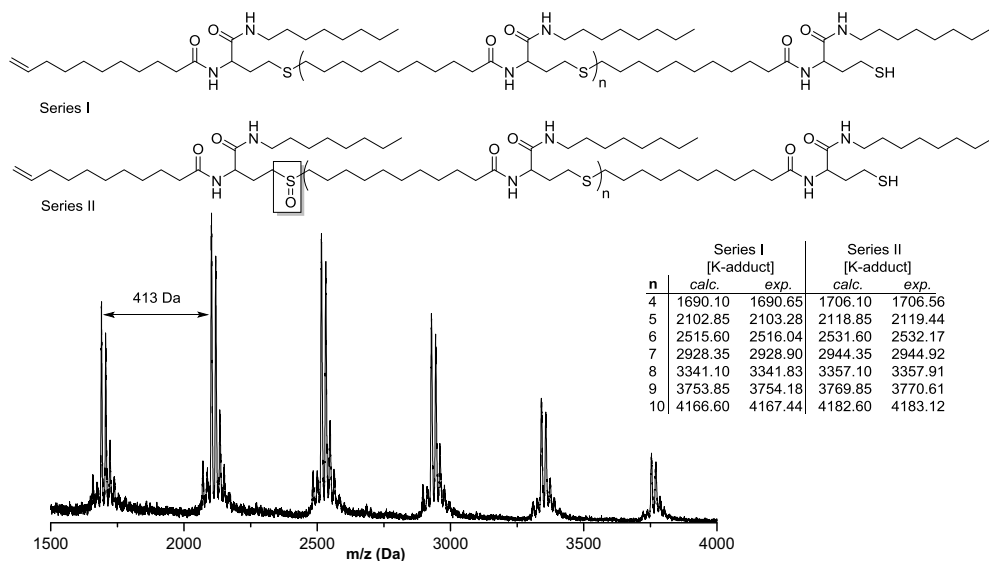
Figure 5-2. MALDI-TOF analysis of P8.

MALDI-TOF analysis was performed on **P8** to confirm the structural build-up of the polymers and to exclude the occurrence of possible side-reactions (Figure 5-2). Prior to this analysis, the polymer sample was separated into several narrow-disperse fractions by preparative SEC (Table 5-3).

Table 5-3. P8 is separated into 10 narrow-disperse fractions by preparative SEC.

Fraction	M_n^a (g.mol^{-1})	$Đ^a$
0	79100	1.47
1	32800	1.16
2	23200	1.07
3	17000	1.07
4	12800	1.06
5	9500	1.06
6	7000	1.08
7	4800	1.10
8	3100	1.14
9	1900	1.08
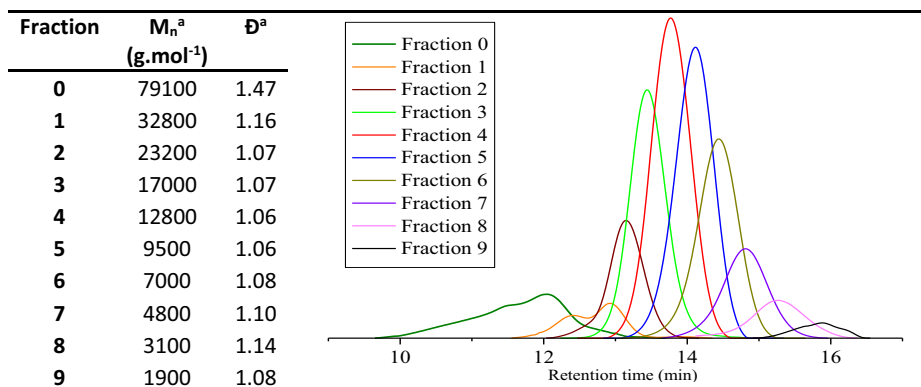
Two distinct series of signals are observed in the MALDI spectrum, separated from each other by 16 Da. In both series, signals are repeating each 413 Da, corresponding to the sum of the molecular weight of octylamine and the monomer **4**. The first distribution of peaks represents the expected heterotelechelic polymer bearing a double bond and a thiol functional group as end-groups, while the second series can only be explained by partial oxidation of the sulfur atoms in the main chain, expressed by the + 16 Da shift. Moreover, when looking more into detail, even a third and a fourth series with a mass difference of 16 Da can be distinguished, indicating further oxidation. Peroxides present in the used solvents (dioxane and THF) are the only oxidation source, of which the influence was proven by analyzing the same polymer sample in THF solution as a function of time. This generated more +16 Da peaks, limited in number by the amount of sulfides in the polymer chains. Anticipating the influence of the peroxides present in the used solvents, causing oxidation, the same sample was kept in a THF solution for a week and MALDI-TOF spectra were recorded as a function of time.

Figure 5-3 (A) is a detail of the thus obtained spectra, showing the mass peak at 1690 Da, corresponding to a DP of 4. Initially, two peaks are visible. After one day in THF-solution, the intensity of the first peak has decreased, while the intensity of the second has increased. Moreover, a third peak with again a mass difference of 16 Da appears. After one week, the detail in the MALDI-TOF spectrum consists of five peaks, each with a 16 Da mass difference and with the first two having a decreased intensity. Figure 5-3 (B) is the MALDI-TOF spectrum of a narrow-disperse fraction of the sample after one week. With increasing DP, it is observed that the amount of peaks increases. Indeed, an increasing amount of sulfide bonds in the polymer backbone gives rise to extra oxidation possibilities.
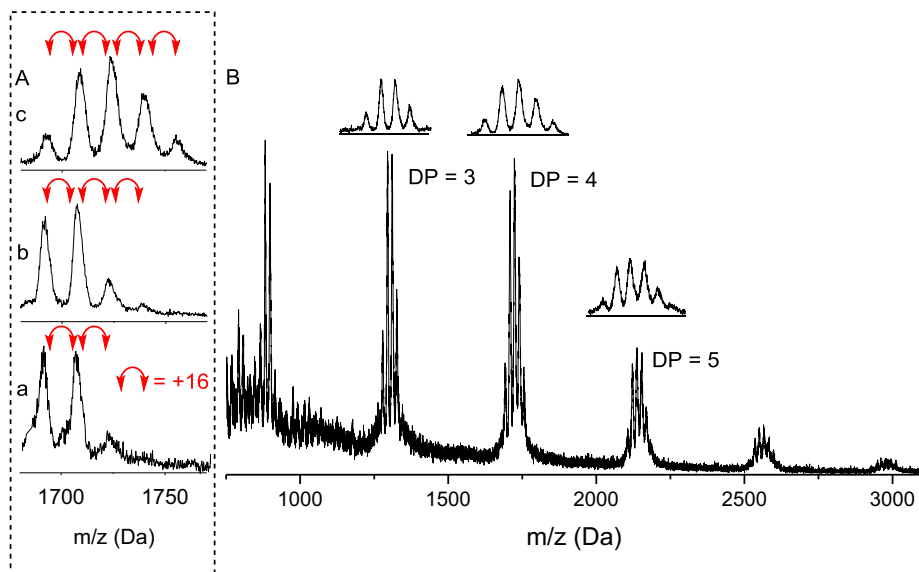
Figure 5-3. A) Detail of the MALDI-TOF spectra of a low molecular-weight fraction of P8, measured immediately after SEC separation (a), after one day in THF solution (b) and after seven days in THF solution (c). B) MALDI-TOF spectrum of the same fraction after one week in THF.

5.4. THERMAL AND MECHANICAL ANALYSIS

All the synthesized polymers are thermally stable up to at least 250 °C under air atmosphere (Figure 5-4), which is significantly less than commercially available polyamides such as Rilsan and Nylon 6, which typically start to degrade around 400 °C.[45, 46] However, similar degradation profiles are observed for polythioethers,[27] suggesting that the carbon-sulfur bond is the weakest linkage in the polymer structure.
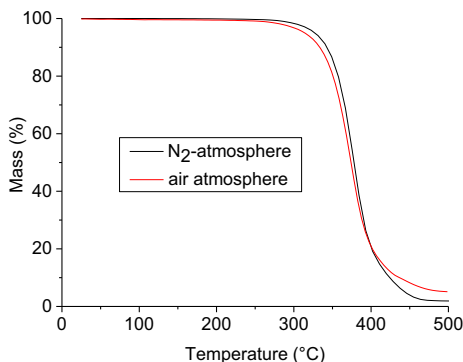
Figure 5-4. Thermograms of P8 (octyl side chain) in nitrogen and air atmosphere, obtained through TGA.

The polyamides all have a melting point around 90 °C, recorded *via* differential scanning calorimetry (DSC). Yet, this melting peak can only be observed in the first heating cycle of the DSC thermograms and does not appear in the second heating step (Figure 5-5), even after annealing. Recrystallization does not occur unless the polymer is dissolved and precipitated again, indicating that the process of crystallization is related to solubility and that once heated, side-chain conformational restrictions prevent the formation of crystallites, leading to an amorphous polymer.
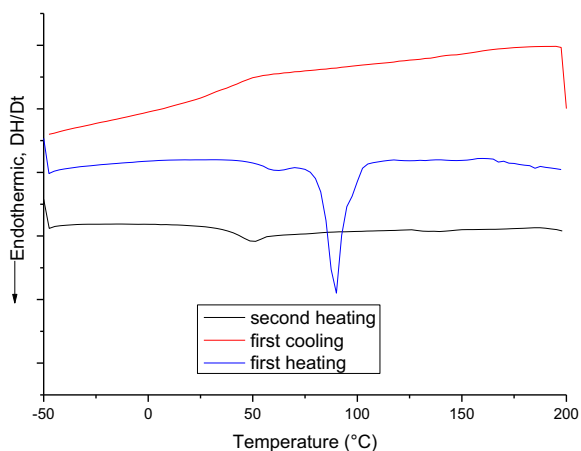
Figure 5-5. DSC thermogram of P4.

Glass transition temperatures of polyamide structures with linear side-chains, obtained from the second DSC heating scan, are shown in Figure 5-6 (A) and range from 5 to 50 °C. Polymers **P1-P3** are not taken into account, since their molecular weight is too low to provide a relevant glass transition. As expected, the number of carbons in the polymer side-chain affects the T_g: the longer the aliphatic chain, the lower the glass transition temperature. Indeed, longer side-chains result in a larger free volume and an increased segmental mobility of the less densely packed polymer chains.

The influence of the side-chain is also demonstrated in the elasticity moduli of the polymers, determined *via* tensile testing. **P1-P3** were brittle materials and could therefore not be subjected to mechanical testing. Figure 5-6 (B) shows the E-modulus and the elongation at break for the other polyamide structures with linear aliphatic side-chains. With an increasing number of carbon atoms in the polymeric side-chain, it is evidenced that the modulus decreases and the elongation at break increases. Longer pendent alkyl chains imply that the amide functions in the molecule are relatively more diluted, resulting in decreased polymer-polymer interactions and more flexible materials. Nevertheless, it is quite remarkable that polymers with molecular weights of about 10 kDa (and lower) give rise to materials with an elongation at break up to 1000 %. Generally, high molecular weights are necessary to ensure enough chain entanglements which give rise to such values. The additional

hydrogen bridges as a result of the presence of two nearby amide functions per repeating unit are believed to induce inter- and intramolecular interactions that compensate for the limited amount of chain entanglements.
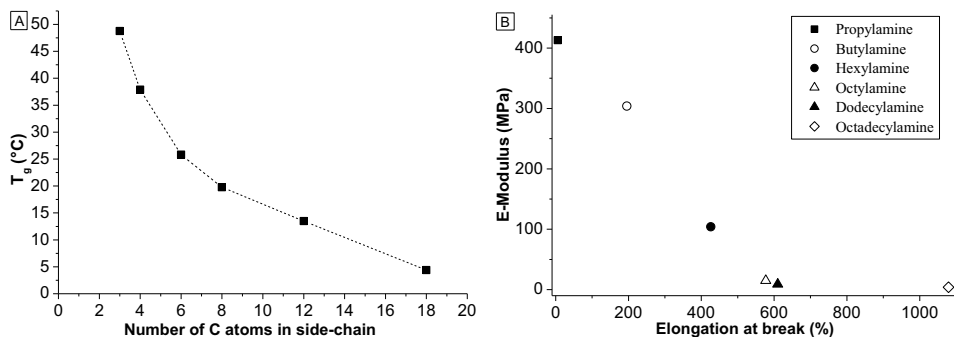
Figure 5-6. Influence of the length of the linear side-chain on T_g (A) and E-modulus and elongation at break, measured at room temperature (25 °C) (B).

5.5. POST-POLYMERIZATION MODIFICATION: OXIDATION

As evidenced from the MALDI-TOF analysis of **P8** (*vide supra*), partial oxidation of the sulfides in the main chain can occur because of the presence of peroxides in the used solvents. Therefore, a more controlled means of oxidation was performed using peroxides, aiming at the formation of sulfones. In a first reaction, a 35 % hydrogen peroxide solution was used in a chloroform/DMF mixture at 50 °C. A second, stronger oxidation method consisted of the use of peracetic acid under reflux conditions.

n	[K-adduct]		
	calc.	exp. (7 days)	exp. (H_2O_2)
0	1275.10	1275.78	/
1	1291.10	1291.67	/
2	1307.10	1307.67	/
3	1323.10	1323.66	1323.75
4	1339.10	1339.70	1339.71
5	1355.10	/	1355.65
6	1371.10	/	1371.69
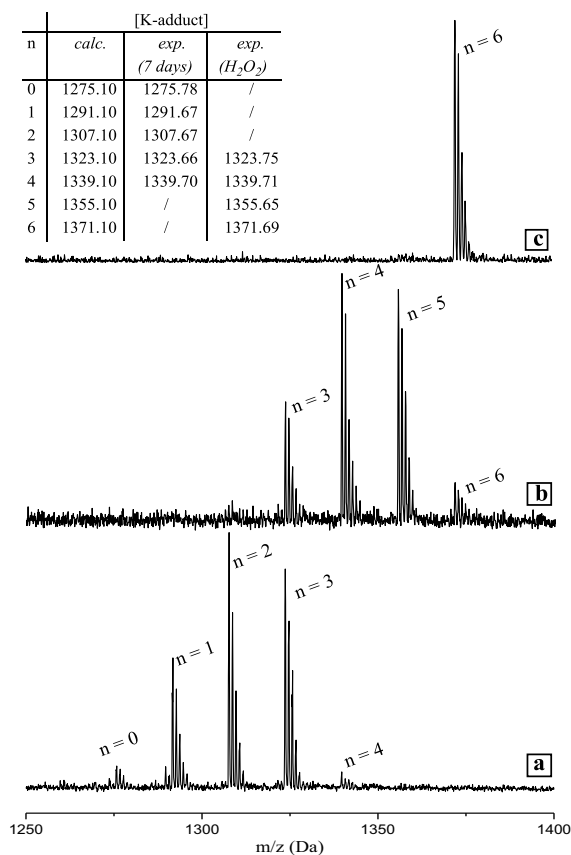
Figure 5-7. Detail of MALDI-TOF spectra of a narrow-disperse fraction of P8 **kept in THF solution for 1 week (a), after incomplete oxidation reaction with H_2O_2 (b) and after oxidation reaction with CH_3CO_3H (c). The amount of oxygen atoms (n) incorporated in the polymer increases with more oxidative conditions.**

Oxidation was followed by comparing the MALDI-TOF spectra of **P8** after one week in THF solution and after oxidation with hydrogen peroxide or peracetic acid. The samples were separated into narrow-disperse fractions using preparative SEC and only the low-molecular weight fractions were analyzed. Figure 5-7 is a detail of the MALDI-spectra, focusing at the polymer with a DP of 3 (m/z = 1277 Da). The maximum amount of oxygen atoms (n) incorporated in this polymer is 6, taking into account the fact that all free thiols will be transformed into disulfides in this oxidative environment. When kept in THF solution (non-distilled), it is evidenced that almost no thio-ethers are left in the polymer (n = 0). Instead, most of the sulfides are oxidized to sulfoxides (n ≥ 1) and to a lesser extent also to sulfones (n ≥ 2). The reaction with hydrogen peroxide further oxidized the product to sulfones, although also sulfoxides remain. Finally, when applying CH_3CO_3H as oxidant, the oxidation reaction is

complete, showing only one peak in the MALDI-spectrum with a maximum of 6 oxygen atoms incorporated (n = 6).
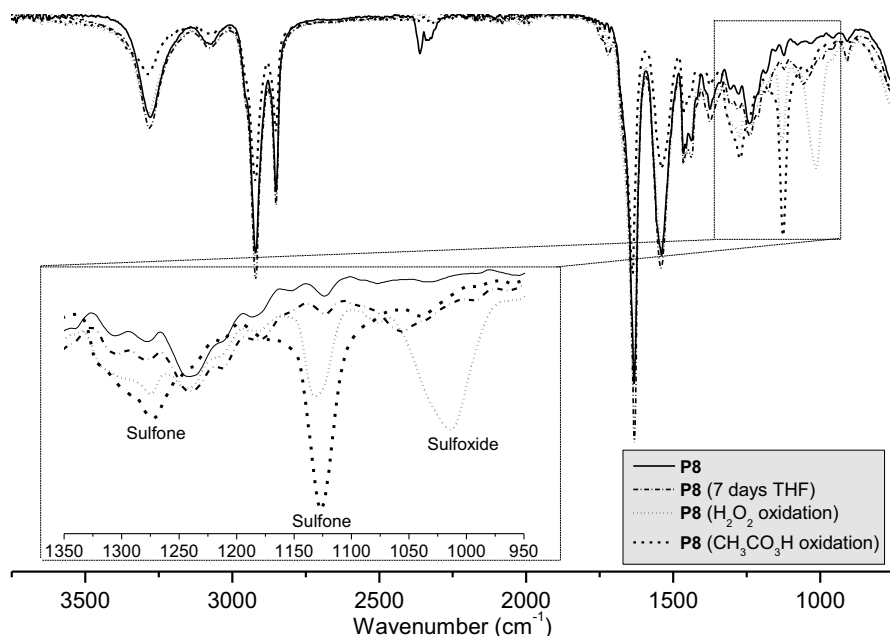
Figure 5-8. FT-IR spectra of P8, before and after oxidation processes.

Oxidation could also be monitored by FT-IR (Figure 5-8), as sulfoxides have specific IR stretch vibrations at 1050 cm^{-1} and sulfones at 1293-1285 cm^{-1} and 1148 cm^{-1}.[47] The absorption bands corresponding to sulfones and sulfoxides from oxidized **P8** have lower wavenumbers than these literature values due to hydrogen bonding, weakening the S=O bond. The observations from FT-IR confirm the MALDI-TOF experiments: when **P8** is reacted with H$_2$O$_2$, both absorption bands of sulfoxides (1017 cm^{-1}) and sulfones (1278 and 1134 cm^{-1}) are observed, while CH$_3$CO$_3$H treatment exclusively gives rise to sulfone bands in the IR spectrum. No significant oxidation is observed for the sample kept in THF for one week.

The oxidation process gives rise to materials with different mechanical properties compared to the starting product (Table 5-4). Indeed, incorporating more oxygen atoms in the form of sulfoxides or sulfones renders the material more brittle. Upon hydrogen peroxide treatment, the E-modulus of the original polymer **P8** increases almost five times and the elongation at break falls drastically. This effect is even more pronounced when the polymer is fully oxidized. When keeping **P8** in THF solution,

oxidation occurs to a lesser extent and the effect on the mechanical properties is consequently less pronounced.

Table 5-4. E-Modulus and Elongation at break of the untreated polymer P8, after one week in THF, after H₂O₂ oxidation and after CH₃CO₃H oxidation.

Entry	E-Modulus (MPa)	Elongation at break (%)
P8	15	580
P8 (7 days in THF)	20	510
P8 (H_2O_2 oxidation)	70	30
P8 (CH_3CO_3H oxidation)	110	10

5.6. FUNCTIONAL GROUP INCORPORATION

Altering the chemical nature of the polyamide structures can be achieved not only through post-polymerization modification procedures such as oxidation, but also by directly incorporating a functional group of choice. The advantage of making use of a thiolactone as a precursor for a thiol, is that it allows for the direct attachment of a group of interest while the step-wise thiol-ene polymerization proceeds. It is evident that the built-in functionality should not interfere with the polymerization process. For example, using allylamine or another unsaturated amine would lead to branching, whereas the use of diamines would lead to cross-linked structures (*vide infra*).

benzylamine   ethanolamine   3-morpholinopropylamine

cyclopropylamine   pyrrolidine   *N*,*N*-dimethylethylenediamine
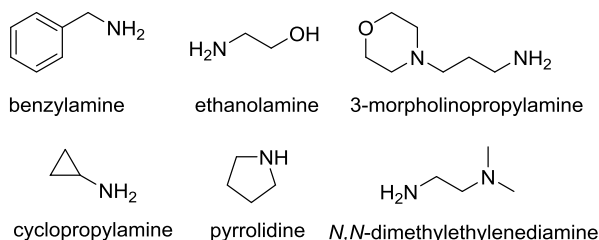
Table 5-5. Molecular weight characteristics of polymers using different amines (structures given above).

Entry	Amine	M_n^a (g.mol⁻¹)	M_n^b (g.mol⁻¹)	M_w^b (g.mol⁻¹)	Đ	T_g^c (°C)
P12	Benzylamine	2800	3900	5800	1.50	2.0
P13	Ethanolamine	8600	17200	24900	1.45	33.5
P14	3-Morpholinopropylamine	12200	12300	19800	1.61	24.0
P15	*N*,*N*-Dimethylethylenediamine	6200	1400	1900	1.35	-5.0
P16	Cyclopropylamine	5700	7100	15800	2.18	57.0
P17	Pyrrolidine	8900	8100	12100	1.49	22.0

[a] Calculated from end-group (double bond) protons in ¹H NMR spectra.
[b] SEC, calibrated with PMMA standards, DMA as eluent.

Table 5-5 gives an overview of polyamide structures (structures shown above the table) prepared using amines with a particular functionality, such as a morpholine moiety (**P14**), which enables the complexation of metals,[48] a tertiary amine (**P15**), a hydroxyl function (**P13**) and an aromatic group (**P12**).

Although **P17** and **P6** (Table 5-2) have similar molecular weights and exactly the same amount of carbons in their side-chain, the T_g of pyrrolidine-functionalized polymer **P17** is lower (22 °C) than the T_g of polymer **P6** (38 °C), which is decorated with pendent butyl groups. In contrast to the secondary amide formed through the reaction with butylamine, the reaction of pyrrolidine (five-membered cyclic secondary amine) with the thiolactone group produces a tertiary amide. This means that there is no possibility of hydrogen donation, which is reflected by a lower T_g. On the other hand, the T_g (57 °C) of **P16** (cyclopropylamine-functionalized) is higher than the T_g (50 °C) of **P4** (propylamine-functionalized). In this case, the linearity of the propyl group induces a higher flexibility, leading to a lower T_g.

The thermal stability of all these polyamide structures is again determined by the presence of a sulfur linkage in the polymer main chain. Independently of the side-chain variation, degradation starts around 250 °C as analyzed with TGA (same profiles as in Figure 5-4).

5.6.1. Influence of alcohols on the ring opening

To obtain even a higher amount of functionalization in a one-pot polymerization process without the need for post-polymerization modification, it was decided to aim for an increase in the amount of hydroxyl functions on the polymer chain. Therefore, the polymerization was now performed using amino-diols, such as 2-amino-1,3-propanediol and 2-amino-2-methyl-1,3-propanediol. However, remarkably, the dispersity of the obtained polymers by far exceeds the other values. Figure 5-9 shows the obtained SEC traces of the ethanolamine and 2-amino-1,3-propanediol polymers.
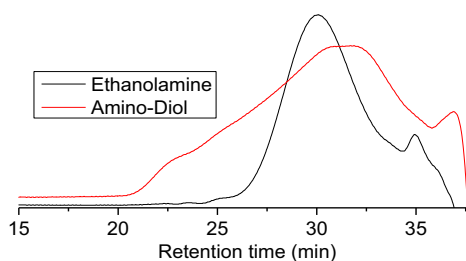

Figure 5-9. SEC traces of the polymers functionalized with ethanolamine and 2-amino-1,3-propanediol.

This observation suggests the occurrence of side-reactions giving rise to the formation of hyperbranched polymers. Although alcohols are reported not to be interfering with the nucleophilic ring-opening process, it should be kept in mind that in basic environment alcoholysis is an important side-reaction (Chapter 3).[49] To assess whether the alcohol functions indeed participate in the ring-opening, a model study on γ-butyrothiolactone was performed, using different reaction conditions (Scheme 5-3).

Five different reactions are performed, each time varying the reaction partners and analyzing the reaction mixture after 12 hours with LC-MS.
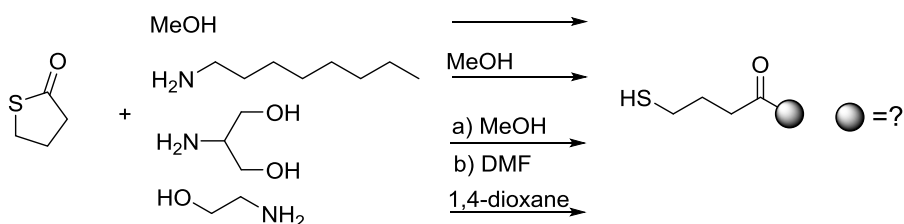
Scheme 5-3. Model reactions investigating the nucleophilic ring-opening of γ-butyrothiolactone.

An overview of the performed reactions is given in Table 5-6 and the results of the LC-MS measurements are depicted in Figure 5-10.

Table 5-6. Reaction conditions for the investigated model reactions.

	Solvent	Amine
1	Methanol	/
2	DMF	2-Amino-1,3-propanediol
3	Methanol	2-Amino-1,3-propanediol
4	Methanol	Octylamine
5	1,4-Dioxane	Ethanolamine

In a first experiment, it was investigated if MeOH as solvent is capable of opening the thiolactone ring in the absence of an amine (*i.e.* a base). Since only the starting thiolactone compound is found in the chromatogram, it is concluded that alcohols as such are not capable of opening the ring.

Next, the influence of the used solvent was evaluated through the reaction of γ-butyrothiolactone with 2-amino-1,3-propanediol. When the reaction proceeds in DMF, unreacted thiolactone is observed, besides ring-opened product. The reason for incomplete reaction can be found in the fact that the amine is located on a secondary carbon atom, leading to slower ring-opening. When the same reaction is performed in MeOH as solvent, the same reaction products are obtained. However, two

extra peaks are observed, corresponding with masses 487 Da and 589 Da (Figure 5-10.3). These can only be explained as being the reaction product of the hydroxyl-reacted compound. Since these side-products are not observed in DMF, it is concluded that the solvent plays a role in the mechanism, which has not been further investigated in this work.

A following reaction evaluates the reactivity of octylamine towards γ-butyrothiolactone in the presence of MeOH as solvent. From Figure 5-10.4, it can be concluded that the reaction went to completion without significant side-reactions. In other words, methanol does not interfere with the ring-opening process in the presence of an amine. Finally, ethanolamine was reacted with the model thiolactone in 1,4-dioxane as a solvent. Two different masses are detected, with two distinct LC-MS signals present per mass. In ^{13}C APT NMR, it is clear that besides the expected amide product, also ester is formed in lesser extent.

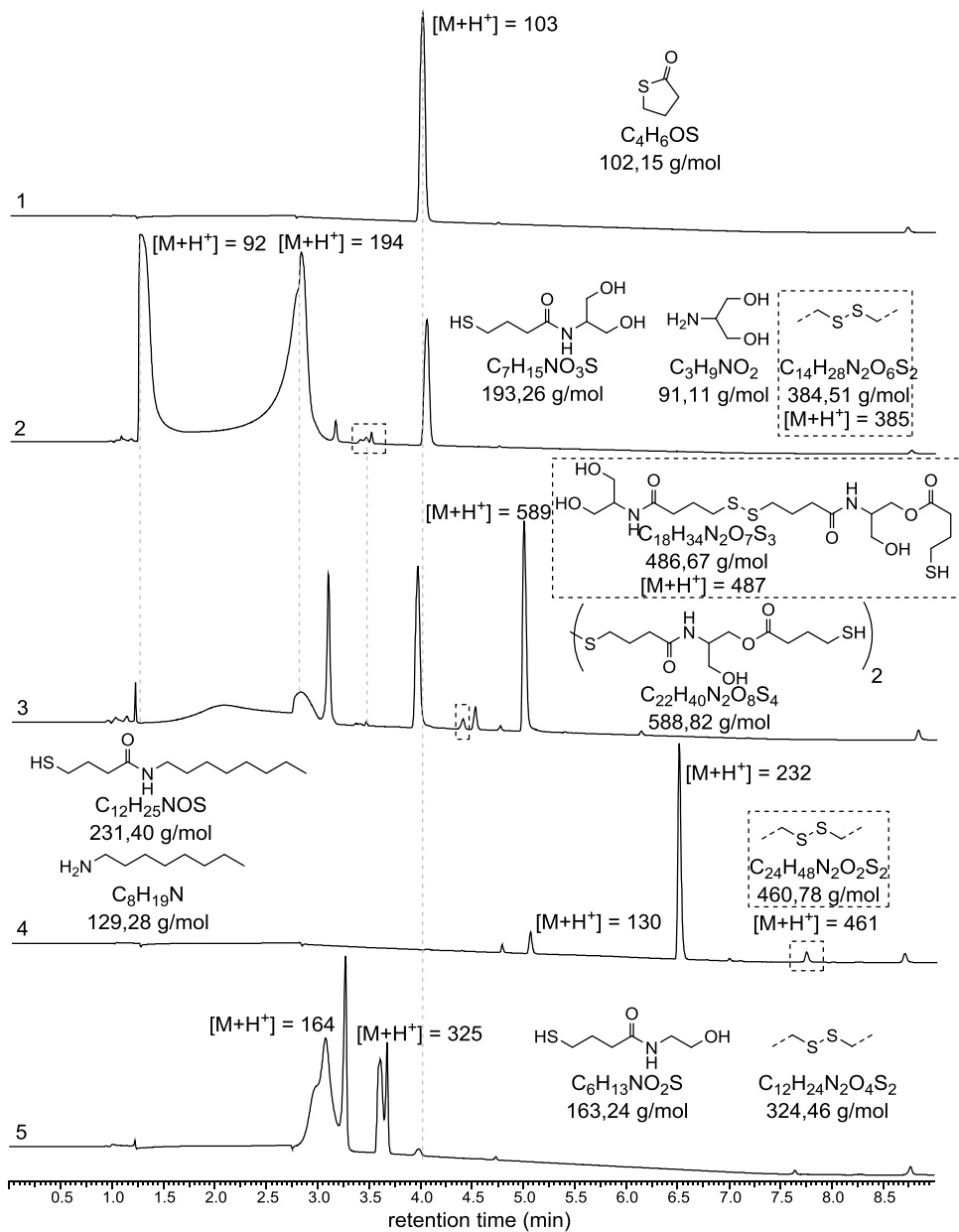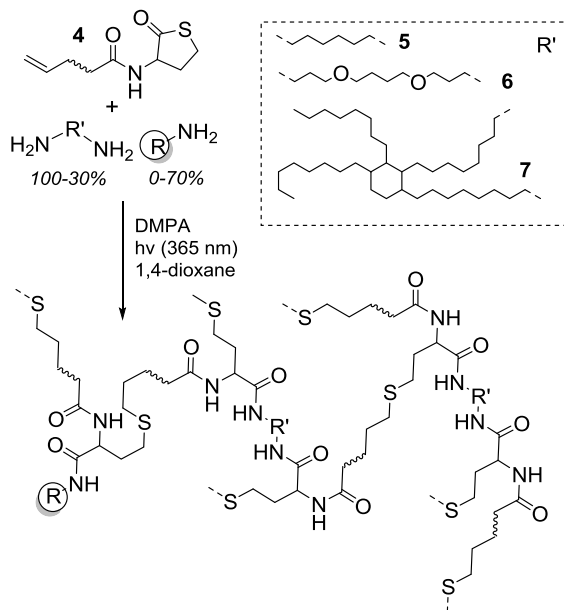**Figure 5-10. RP-HPLC traces of the different model reactions (gradient 0 -> 100% MeCN in 6 min, UV-detection (λ=214 nm)) with 1) γ-butyrothiolactone (MeOH), 2) γ-butyrothiolactone + 2-amino-1,3-propanediol (DMF), 3) γ-butyrothiolactone + 2-amino-1,3-propanediol (MeOH), 4) γ-butyrothiolactone + octylamine (MeOH) and 5) γ-butyrothiolactone + ethanolamine (1,4-dioxane).**

5.7. NETWORK FORMATION

Scheme 5-4. Schematic depiction of the one-pot network formation starting from the 10-undecenoyl thiolactonamide monomer 4 and a diamine cross-linker (5, 6 and 7). Monoamines may be added to the reaction mixture to incorporate functional groups (R) in the polymer networks.

Finally, 10-undecenoyl thiolactonamide **4** was applied as starting monomer for the preparation of polymer networks. Upon treatment with a diamine under similar conditions as described above, a cross-linked material is obtained (Scheme 5-4).

UV-irradiation of a homogeneous reaction mixture between two glass plates, separated by a silicone spacer, delivers these polymer networks as thin, non-tacky films with good mechanical properties. Different cross-linkers were tested, each time using equimolar amounts of amine compared to thiolactone units. 1,6-Hexanediamine **5** was poorly soluble in the reaction mixture and resulted in weak networks. However, the use of 4,9-dioxadodecanediamine **6** and priamine **7** as a cross-linker produced networks that exhibited different mechanical properties, illustrated by their E-moduli. Priamine **7**, being branched, generates networks with lower E-moduli and higher elongation at break compared to networks based on **6** (Table 5-7).

Table 5-7. Properties of the polymer networks prepared using different cross-linkers and monoamines.

Entry	Cross-linker	Monoamine	Soluble Fraction[a] (%)	E-Modulus (MPa)	Elongation at break (%)
N1	7	/	16	10	330
N2	6	/	5	81	60
N3	6	Ethanolamine	12	114	71
N4	6	Benzylamine	21	35	123
N5	6	Octylamine	23	50	152

[a] **Gravimetric determination after soxhlet extraction in CHCl$_3$ and drying of the samples.**

In a next step, functional groups were incorporated in the polymer network by adding to the reaction mixture a monofunctional amine and reducing the amount of cross-linker **6**. The network formation was performed with an initial mol fraction of monoamine of 30%. Higher amounts of monoamine (50% and 70%) lead to increased soluble fractions and therefore these conditions were less favorable for network preparation.

Remarkably, the mechanical properties of the obtained networks improve when adding ethanolamine to the reaction mixture (Table 5-7, **N3**). Both values of the E-modulus and elongation at break increase, which is attributed to a combination of the occurrence of additional hydrogen bridges and less chemical cross-links. This effect is hence not observed when applying benzylamine or octylamine.

Chemical analysis of polymer networks is often limited to surface analysis techniques. High Resolution Magic Angle Spinning (HR-MAS) NMR spectroscopy is a technique complimentary to regular liquid NMR spectroscopy that allows for the chemical and structural characterization of swollen polymer networks. These measurements were performed to obtain structural information of the polymer networks and to determine whether functionality was built in. Figure 5-11 shows an overlay of the ^{1}H HR-MAS spectra of **N4** (top) and **N5** (bottom).
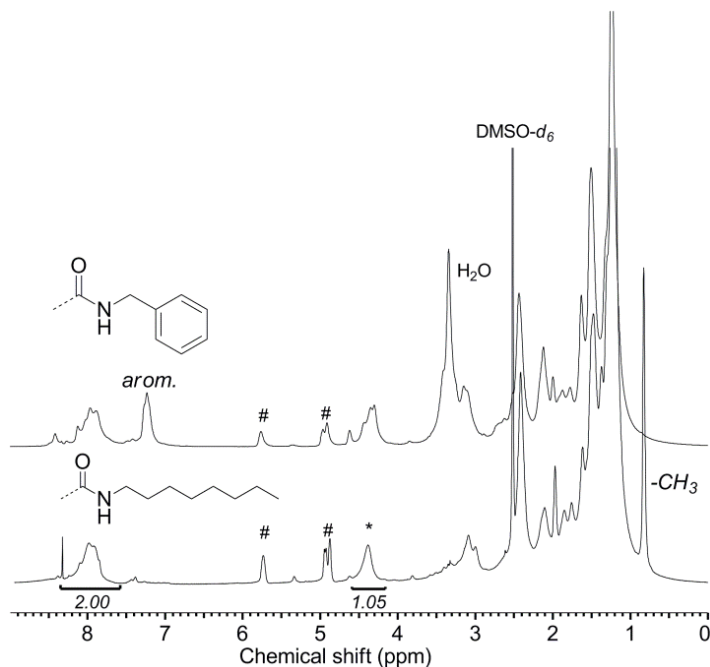
Figure 5-11. HR-MAS ¹H-NMR spectra (700 MHz, DMSO-*d₆*) of N4 **(top) and** N5 **(bottom).**

In both spectra, there are still double bond protons (#) visible, meaning that a limited mobility of the segments prevents full conversion. However, both functionalities (benzyl and octyl) were incorporated successfully, evidenced by the aromatic signals of benzylamine at 7.2-7.3 ppm and the protons of the –CH_3 group of octylamine at 0.8 ppm. In the bottom spectrum, the signal at 4.38 ppm (*) corresponds to the proton of the opened thiolactone, while no closed thiolactone rings can be observed. Integration of this signal compared to amide signals (7.8 ppm) confirms that the ring-opening reaction proceeded with near-quantitative conversion. This cannot be concluded from the top spectrum, where benzylic signals are overlapping in the same region.

5.8. CONCLUSION

Polyamide structures with diverse substituents on the polymer backbone were successfully synthesized starting from an AB'-monomer that contains both an alkene function (A) and a thiolactone moiety (B'). This monomer, based on the renewable compound undecenoic acid, was prepared on a large scale without the need for time-consuming work-up procedures. Nucleophilic ring-opening of the thiolactone with a series of different amines leads to the corresponding AB (B = thiol) monomer.

Subsequent free radical thiol-ene polymerization gave rise to a series of polyamide structures that also contain a sulfide linkage in their backbone. Diverse structures could be generated by altering the polymer side-chain through the applied amine, or by introducing functional groups that do not interfere with the polymerization process. Although the obtained molecular weights are limited with M_n-values ranging from 2 to 20 kDa, the materials show good mechanical properties as a result of hydrogen bonding. MALDI-TOF analysis confirmed the structural build-up of the polymers and revealed partial oxidation of the sulfides to sulfoxides, induced by peroxides in the used solvents. It was shown that this oxidation does not drastically alter the material properties, while full oxidation of the sulfides made the polymers more stiff and brittle. The same monomer was finally applied as starting material for the synthesis of polymer networks that could be decorated with functional groups. The successful incorporation of these functionalities was demonstrated with HR-MAS NMR spectroscopy. Depending on the used cross-linker and incorporated functionality, different mechanical properties were obtained.

In summary, this straightforward one-pot procedure allows for the synthesis of diverse functionalized polyamide structures, thanks to the dual function of the thiolactone moiety. Future research will focus on expanding this thiolactone approach to other bio-based compounds, allowing for a one-pot preparation of renewable, tailor-made polymers. Indeed, the research described in this chapter demonstrates the potential of thiolactones in combination with other bio-based resources to synthesize functionalized polymers in a more sustainable manner. Other bio-based sources (containing a double bond and a hydroxyl- or an acid function) are thought of, for example eugenol, to be transformed into biobased materials. Also thermoset materials, in the form of functional coatings, beads or films could be thought of. The ease with which the monomer structure can be varied allowed for the synthesis of polyamides in this case, but also polyurethanes are accessible (as shown in chapter 4 and 7).

5.9. EXPERIMENTAL SECTION

5.9.1. Materials

Acetonitrile ([75-05-8], ≥ 99.9 %), ammonia ([7664-41-7], 0.5 M solution in 1,4-dioxane), benzylamine ([100-46-9], ≥ 99 %), chloroform ([67-66-3], ≥ 99.8 %), cyclopropylamine ([765-30-0], 98 %), dichloromethane ([75-09-2]), 99.8 %), diethylether ([60-29-7], ≥ 99.9 %) 2,2-dimethoxy-2-phenyl acetophenone (DMPA) ([24650-42-8], 99 %), *N,N*-dimethylformamide ([68-12-2], 99.8 %), n-dodecylamine ([124-22-1], 98 %), ethanolamine ([141-43-5], ≥ 99 %), 2-ethyl-1-hexylamine ([104-75-

6], 98 %), n-hexane ([10-54-3], 95 %), isopropylamine ([75-31-0], ≥ 99.5 %), methanol ([67-56-1], 99.9 %), methylamine ([74-89-5], 2.0 M solution in THF), 3-morpholinopropylamine ([123-00-2]), *N,N*-dimethylethylenediamine ([108-00-9], ≥ 98.0 %), n-octadecylamine ([124-30-1], 99 %), n-octylamine ([111-86-4], 99 %), peracetic acid solution ([79-21-0], 36-40 wt% in acetic acid), n-propylamine ([107-10-8], ≥ 99 %), tetrahydrofuran ([109-99-9], 99 %), thionyl chloride ([7719-09-7], 99.7 %), γ-thiobutyrothiolactone ([1003-10-7], 98 %), triethylamine ([121-44-8], 99 %) and 10-undecenoic acid ([112-38-9], 98 %) were purchased from Sigma-Aldrich and used without purification. n-Butylamine ([109-73-9], 99.5 %), 1,4-dioxane ([123-91-1], ≥ 99 %), 4,9-dioxadodecanediamine ([7300-34-7], 97 %), DL-homocysteine thiolactone hydrochloride ([6038-19-3], 99 %), ethylamine ([75-04-7], 2.0 M solution in THF), 1,6-hexanediamine (124-09-4], ≥ 99.5 %), hexylamine ([11-26-2], 99 %), pyrrolidine ([123-75-1], 99 %), 2,2,4-trimethylpentane (iso-octane) ([540-84-1], 99 %) and hydrogen peroxide ([7722-84-1], 35% solution in water) were obtained from Acros Organics and used without purification. Chloroform D ([865-49-6], ≥ 99.8 %) and DMSO-*d6* ([2206-27-1], ≥ 99.8 %) were purchased from Euriso-top. Glacial acetic acid ([64-19-7], 99.8 %) was purchased from Fiers. Priamine ([68955-56-6]) was obtained from Croda. CH_2Cl_2 used for the monomer synthesis was distilled from CaH_2 prior to use. The reaction was followed by thin layer chromatography (TLC plates, Macherey-Nagel, SIL G-25 UV_{254}).

5.9.2. Methods

Nuclear magnetic resonance spectra were recorded on a Bruker AVANCE 300 (300 MHz) or a Bruker DRX 500 (500 MHz) spectrometer at 50 °C or at room temperature, depending on the solubility in DMSO-*d6*. *HR-MAS analyses* were performed on a Bruker Avance II 700 spectrometer (700 MHz). The samples were prepared as follows: dry material was cut into small pieces and put in a 4 mm rotor (80 µl). Next, solvent (DMSO-*d6*) was added to allow the material to swell. This removes most of the dipolar line broadening typically associated with the solid state, while residual line broadening caused by susceptibility differences can be handled by spinning at the magic angle. The sample was homogenized by stirring within the rotor. All ^{1}H NMR spectra were recorded using a HR-MAS probe equipped with a ^{1}H, ^{13}C, [119]Sn and gradient channel. Samples were spun at a rate of 6 kHz. To characterize the gels, 1D ^{1}H spectra were recorded. All spectra were measured with an acquisition time of 1.136 s in which 32768 fid points were obtained, leading to a spectral width of 20.6 ppm. For qualitative analysis 8 transients were summed up with a recycle delay of 2 s. For quantification, 32 scans were used with 30 s recycling delay to guarantee full relaxation of the signal.

Size-exclusion chromatography was performed on a Waters instrument with a RI detector (2414 Waters), equipped with 3 Polymer Standards Services SEC serial columns (1 x GRAM Analytical 30 Å, 10 µm and 2 x GRAM Analytical 1000 Å, 10µm) at 35 °C. DMA, containing LiBr (0.42 g.L^{-1}), was used as

eluent at a flow rate of 1 mL.min^{-1} and PMMA standards were used for calibration. Molecular weight and dispersity were determined using Empower software.

Preparative Size Exclusion Chromatography was performed on a Shimadzu instrument equipped with a LC-2OAT pump, a SIL-IOAF autosampler, an RID-IOA Differential Refractive Index Detector, a FRC-1OA Fraction Collector and a CBM-2OA PC Interface/System Controller. The LC solution software uses SEC software. The columns are from Shodex, more specifically a K-LG pre-column and a KF-2004 preparative column. A 9/1 THF/DMF mixture is used as eluent at a flow rate of 2.5 mL.min^{-1}.

MALDI-TOF mass spectrometry analyses were performed on an Applied Biosystems Voyager-DE STR instrument equipped with a nitrogen laser operating at 337 nm, pulsed ion extraction source and reflectron detector. The laser pulse width is 3 ns and the maximum power is 20 Hz. Spectra were recorded in the linear mode with an accelerated voltage of 19 kV and a delay of 100 ns. 100 Single shot acquisitions were summed to give the spectra and the data were analyzed using Data Explorer and Polymerix software. Samples were prepared by dissolving the matrix dithranol in the solvent (THF, 20 mg.mL^{-1}) and mixing with the polymer (1 mg.mL^{-1}) and potassium trifluoroacetate in acetone (15 mg.mL^{-1}), that has been used as cationizing agent.

Thermogravimetric Analyses were performed on a Mettler-Toledo TGA/SDTA851e instrument under both air and nitrogen atmosphere at a heating rate of 10 K.min^{-1} from 25 °C to 800 °C. The thermograms were analyzed using the STARe software from Mettler-Toledo.

Differential Scanning Calorimetry (DSC) analyses were performed with a TA Instruments 2920 Modulated DSC V2.6A, with a helium gas flush of 25 mL.min^{-1} and a nitrogen gas flush of 19 mL.min^{-1}. The samples were analyzed in TA sample pans which contained 5-10 mg of the sample. The glass transition temperatures were determined from inflection points in the second heating using the Universal V3.9A software from TA Instruments. Measurements were performed in a temperature range of -100 °C to 200 °C with a rate of 10 K.min^{-1}. *LC-MS* analyses were performed on an Agilent Technologies 1100 series LC/MSD system with a diode array detector (DAD) and a single quad MS. Analytical reversed phase HPLC-analyses were performed with a Phenomex Luna C18 (2) column (5 μm, 250 mm x 4.6 mm) and a solvent gradient (0 to 100 % acetonitrile in H$_2$O in 15 min). The eluted compounds were analyzed via UV detection (214 nm).

The mechanical properties were analyzed with a Tinius Olsen H10KT *tensile bench* with a load cell of 100 N, using flat dog bone type specimens with an effective gage length of 13 mm, a width of 2 mm, and a thickness of 1 mm. The tensile tests were run at a speed of 0.5 mm.s^{-1}. Test specimens were prepared by compression molding of thin sheets at 100 °C. After cooling, samples were cut from these

sheets using a Ray-Ran dog bone cutter. UV curing was performed by irradiation with 365 nm UV lamps (9 x 9 W) positioned in a metal cylindrical container.

5.9.3. Monomer synthesis: 10-undecenoyl thiolactonamide

10-Undecenoic acid **1** (292 mmol; 53.81 g) was dissolved in thionyl chloride (2.21 mol; 160 mL). The mixture was stirred under reflux conditions for 90 minutes after which thionyl chloride was evaporated and 10-undecenoyl chloride **2** was obtained as a brown oil. DL-Homocysteine thiolactone hydrochloride **3** (265 mmol; 40.71 g) was dissolved in dry dichloromethane (300 mL) and cooled to 0 °C, after which 10-undecenoyl chloride 2 (292 mmol; 59.19 g) was added dropwise to the solution. Triethylamine (184.73 mL) was slowly added to the reaction mixture and the reaction mixture was then allowed to reach room temperature and stirred for 24 hours. The solution was successively washed with a saturated $NaHCO_3$ solution (500 mL), 1 M HCl solution (500 mL) and brine (500 mL), after which the organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off and the resulting clear solution was evaporated under reduced pressure. The product was further purified by recrystallization from iso-octane. 10-Undecenoyl thiolactonamide **4** was obtained with 70 % yield as a white powder.

$C_{15}H_{25}NO_2S$ (283.43 g/mol^{-1}); ***m/z (ESI-MS)***: 284.1;

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 5.90 (s, 1H, NH), δ 5.82 (m, 1H, C=CH-), δ 4.97 (m, 2H, C=CH_2), δ 4.52 (quin, 1H, N-CH), δ 3.34 (m, 2H, S-CH_2), δ 2.99 (quin, 1H, S-C-CH_2), δ 2.25 (t, 2H, CO-CH_2), δ 2.05 (q, 2H, C=C-CH_2), δ 1.91 (sext, 1H, S-C-CH_2), δ 1.65 (quin, 2H, CO-C-CH_2), δ 1.31 (s, 10H, C=C-C-$(CH_2)_5$);

^{13}C-NMR (300 MHz, $CDCl_3$, ppm): 205.6 (C), 178.7 (C), 139.2 (CH), 114.1 (CH_2), 59.5 (CH), 36.4 (CH_2), 33.8 (CH_2), 32.2 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.6 (CH_2), 25.5 (CH_2); HR-MS (ESI): Expected 284.1606 Found 284.1681 [M+H]$^+$.

5.9.4. Polymerization: general protocol

The monomer **4** (7.06 mmol, 2 g) and 2,2-dimethoxy-2-phenyl acetophenone (DMPA) (0.98 mmol, 250 mg) were dissolved in 1,4-dioxane. 1.1 Equivalents of primary amine (7.76 mmol) were added. In case of dodecyl- and octadecylamine the reaction was performed in THF. The total volume of the mixture was calculated to be 10 mL. The clear reaction mixture was stirred for 5 h at 40 °C under UV-irradiation (365 nm). After this reaction time, a white precipitate was formed. The liquid fraction was decanted and the precipitate was then rinsed with methanol (4 x 15 mL) and diethylether (4 x 15 mL). Filtration and drying yielded a white solid, which was subjected to SEC and NMR analyses after drying under high vacuum.

5.9.5. Post-polymerization modification: oxidation

P8 (0.3 mmol, 3 g) was dissolved in 300 mL of a 2/1 chloroform/DMF mixture. Subsequently, glacial acetic acid (15 mL) and 35 % hydrogen peroxide (3 mL) were added. After two hours of reaction under reflux, the polymer was precipitated in cold hexane (2 L), filtered off and washed with a saturated Na_2SO_3 solution (4 x 800 mL) and water (2 x 400 mL). The polymer was dried under high vacuum.

A second procedure for the oxidation reaction was carried out as follows: **P8** (2.5 mmol, 2.5 g) was dissolved in 120 mL of a 2/1 chloroform/DMF mixture. Peracetic acid (36-40 wt% in acetic acid) (0.0375 mol, 7.15 mL) was added dropwise and the reaction was refluxed overnight. The polymer was then precipitated in cold hexane (1.2 L), filtered off and washed with a saturated Na_2SO_3 solution (4 x 600 mL) and water (2 x 600 mL). The polymer was dried under high vacuum.

5.9.6. Polymer network synthesis: general protocol

The monomer **4** (2.51 mmol, 710 mg) and DMPA (0.35 mmol, 88.6 mg) were dissolved in 1,4-dioxane (2.5 mL). Cross-linker **5**, **6** or **7** (1.25 mmol) was added and the homogeneous reaction mixture was injected between 2 glass plates, separated by a silicon spacer (1 mm) and irradiated with UV light during 2 h. The obtained polymer networks were purified by Soxhlet-extraction using chloroform as eluent.

Functionalized polymer networks were obtained in the same way, varying the amount of cross-linker and monoamine. Generally, 0.88 mmol of cross-linker was used and 0.75 mmol of monoamine to obtain a network with 30 mol% of functional amine incorporated.

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Abstract

This chapter documents on the synthesis of hyperbranched polymers, starting from thiolactone-containing precursor molecules. In a first part, alkyne-thiolactone was synthesized as an A'B$_2$- type of monomer, where A' symbolizes a thiolactone unit and each π-bond of the alkyne group is a B unit. After aminolysis, an AB$_2$-monomer is generated. Through thiol-yne reaction, hyperbranched polymers were obtained, which could be characterized *via* NMR spectroscopy and SEC. Other A'B$_2$ and AB monomers were synthesized, one of them based on pTHF as a macromolecular precursor. The efficacy of a novel triflate initiator for pTHF was evaluated for this purpose.

Chapter 6
# A'B₂ thiolactone building blocks for hyperbranched polymers

6.1. INTRODUCTION

Branched macromolecular structures occur in many shapes and sizes and numerous branched polymer "architectures" have been developed over the years.[1] Examples are star-like, ladder-like, brush- or comb-like polymers. In the 1980's, a new class of branching was developed with the introduction of dendritic polymers,[2] which is now recognized as one of the four classes of polymer architecture, after traditional types of linear, cross-linked, and chain-branched polymers. Hyperbranched polymers are a kind of dendritic polymers, lacking the extreme control which is usually found in their dendritic analogues. Indeed, unlike dendrimers, of which the synthesis relies on a tedious layer-by-layer build-up – giving rise to ideally branched, monodisperse structures, the branching in hyperbranched polymers occurs randomly. The preparation usually proceeds in a one-pot fashion, leading to heterogeneous products with a distribution in molar mass and branching.

In the last decades, dendrimers as well as hyperbranched polymers have attracted a lot of attention because of their recognized potential in applications such as drug-delivery vehicles, catalytic supports and viscosity modifiers.[3-6] Their interesting properties are owing to the branched architecture, as well as to their high number of functional end-groups. The synthesis of dendrimers has mostly attracted researchers with a strong organic background and led to perfectly designed nano-objects ideally suited for studying the influence of branching and functionality. Hyberbranched polymers on the other hand are much easier to synthesize and have therefore been considered for industrial applications.

The synthesis of hyperbranched polymers can be achieved using different approaches, going from bottom-up approaches (*i.e.* the polymerization of monomers), to top down methods (*i.e.* the degradation of networks) and middle upon (*i.e.* the modification of hyperbranched polymeric-precursor) syntheses. A lot of work has been conducted on the bottom-up polycondensation of AB₂ monomers, in which A and B are complementary functional groups.

Interestingly, Perrier et al.[7-9] have used the efficiency of the radical double addition reaction of a thiol to an alkyne for the synthesis of hyperbranched structures. A molecule bearing a thiol and an alkyne is an AB₂ type monomer, where A reacts with either of the B components. In this case, the thiol is the A unit, and each π-bond of the alkyne is a B unit. Both low-molecular weight monomers as well as polystyrene-based polymers, functionalized with an alkyne and a thiol, were used as AB₂ precursors for the synthesis of hyperbranched structures. Gao et al.[10] used sequential thiol-ene and thiol-yne chemistry for the synthesis of hyperbranched polythioether-ynes with a high degree of branching and a high molecular weight. It was shown by Fairbanks and coworkers[11] that the second thiol addition to the alkyne group proceeds faster than the first, which should result in a high degree of branching when an AB₂-type monomer is used. Therefore, the resulting polymers have a high amount of alkynes left, able to react in a CuAAC-type of click reaction.

However, the above introduced methodology, although leading to alkyne-functionalized structures, lacks versatility in the sense that functional groups can only be incorporated after polymerization. Thiolactones as precursors for thiols have the advantage that, upon ring-opening with an amine, also a functional group is included in an atom-efficient manner. This encouraged us to investigate the synthesis of a monomer containing an alkyne and a thiolactone unit. This monomer is essentially an A'B₂ monomer, with the thiolactone the being A' unit and each π-bond of the alkyne a B unit. This is expected to lead to highly functional, hyperbranched polymers (Scheme 6-1).
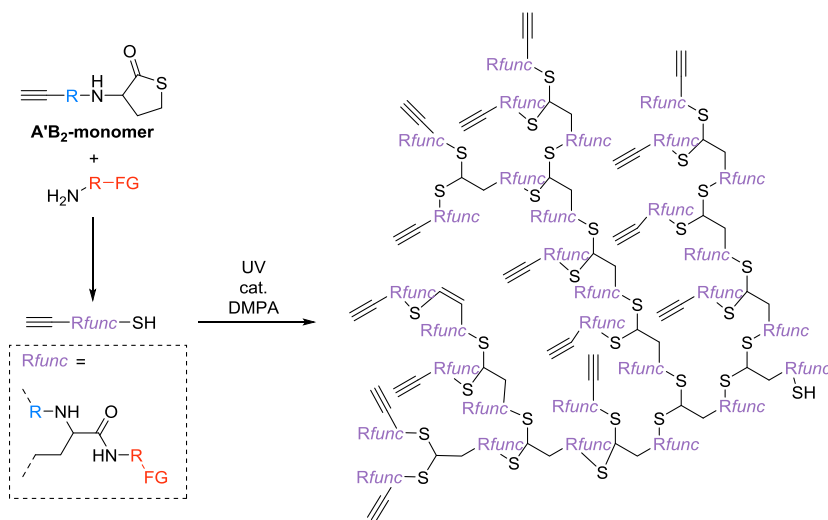
Scheme 6-1. General scheme for the polymerization of an A'B₂ type monomer, based on a thiolactone moiety as precursor for a thiol. Functional groups are incorporated *via* the amine and thiol-yne polymerization occurs upon UV-irradiation.

6.2. Monomer choice and synthesis

6.2.1. Alkyne-thiolactone
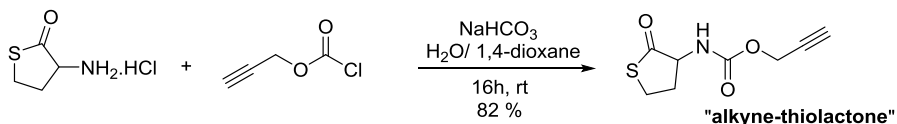
Scheme 6-2. Synthesis of "alkyne-thiolactone", a monomer containing an alkyne bond and a thiolactone moiety, coupled through a urethane bond.

We investigated the synthesis of a monomer containing both a triple bond and a thiolactone unit. In our case, as a thiolactone moiety can be considered a precursor of a thiol functionality, the combination with an alkyne bond results in an A'B₂ type monomer. The valorization of the reactivity of this monomer upon aminolysis and subsequent UV-curing, would enable us to develop a convenient method for the synthesis of hyperbranched polymeric structures. A scalable and high-yielding synthesis of the proposed alkyne-thiolactone monomer consisted of the treatment of homocysteine thiolactone with propargyl chloroformate (Scheme 6-2). The yield of this reaction was 82 % after flash chromatography and gave rise to a colorless oily product.

6.2.2. Alloc-thiolactone
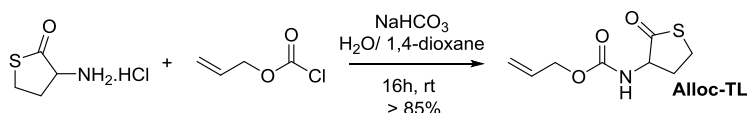
**Scheme 6-3. Synthesis of Alloc-TL, by reacting homocysteine thiolactone with allyl chloroformate.**

N-(allyloxy)carbonylhomocysteine thiolactone (Alloc-TL) was originally intended as a monomer for a new way of synthesizing functionalized polyurethane structures (Chapter 4). Indeed, this A'B monomer, where the thiolactone moiety is the A' unit and the double bond is the B unit, is transformed in the corresponding thiol-ene AB-monomer by treatment with an amine. Due to the presence of a urethane linkage, the photopolymerization gave rise to polythioether/urethane structures.

Although Alloc-TL is not a monomer of the type A'B₂, by ring-opening with a suitable, unsaturated amine, it can be transformed into an ABB' monomer, where A is the thiol, and B and B' are carbon-carbon π-bonds. A scalable and high-yielding synthesis of the proposed ene-thiolactone monomer

consisted of the treatment of homocysteine thiolactone with allyl chloroformate (Scheme 6-3), introducing the corresponding (allyloxy)carbonyl or alloc group, a popular amino-protecting group.

6.3. HYPERBRANCHED POLYMERS

6.3.1. Hyperbranched polymers based on alkyne-thiolactone
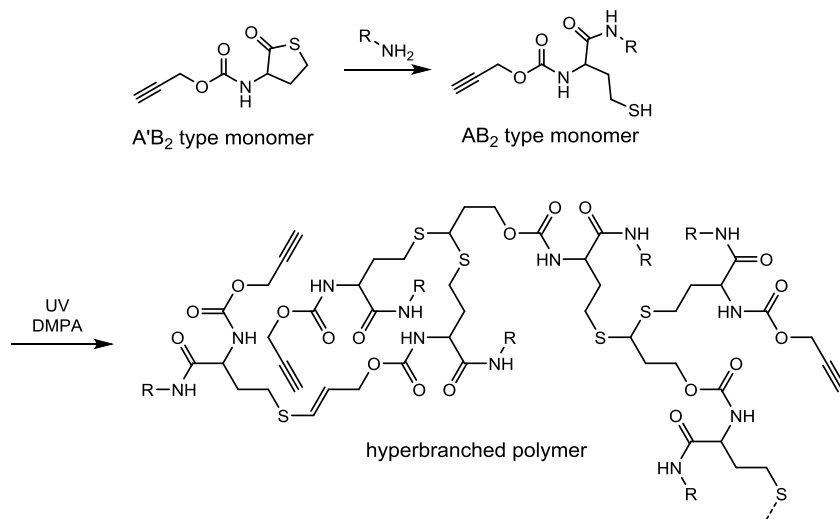
Scheme 6-4. Nucleophilic ring-opening of alkyne-thiolactone, followed by a thiol-yne reaction under UV-irradiation leading to hyperbranched polymers.

The reactivity of the alkyne-thiolactone monomer was investigated by a model reaction with propylamine. The formation of hyperbranched polymers was achieved using UV-light (365 nm), in the presence of DMPA as a photoinitiator. The total reaction can proceed (only under UV-irradiation) with all the reaction partners present from the start. In this case, the formed thiol would be able to react immediately with the alkynes present in the reaction mixture. Alternatively, the different reaction steps can be performed consecutively, making sure that the thiolactone has been fully converted in the corresponding thiol prior to thiol-yne addition.

In a first stage, it was attempted to perform the polymerization in a one-pot, two-step fashion: the two reaction steps are performed separately and consecutively. This means that alkyne-thiolactone was first allowed to react with propylamine, in the absence of UV-light. From LC-MS analysis, it was clear that, when using 2 equivalents of amine, the reaction was finished within 2 hours. After this first step, DMPA was added and the reaction was allowed to proceed under UV-irradiation.

The evolution of the molecular weight characteristics of the product, **HB1**, is followed as a function of time and the results are presented in Table 6-1. The dispersities of the obtained polymers are increasing with time and reach values up to 14, indicating the formation of hyperbranched polymers. When all reaction partners are present from the start, including UV-irradiation, a hyperbranched polymer with a slightly lower molecular weight is obtained (**HB2**, Table 6-1). This phenomenon could be explained by the relatively slow kinetics of the thiolactone ring-opening compared to the formation of radical fragments of DMPA. In what follows, an NMR study of the product resulting from a one-pot, two-step procedure is performed.

Table 6-1. Overview of the molecular weight characteristics of HB1 and HB2, for different reaction times.

Entry	Time (min)	M_n (g.mol^{-1})	M_w (g.mol^{-1})	Đ
HB1	20	5400	27600	5.1
HB1	60	6500	77100	11.9
HB1	120	7500	109600	14.7
HB2	60	5700	30300	5.4
HB2	120	5900	32000	5.5

In the analysis of hyperbranched stuctures, the degree of branching (DB) is one of the most important parameters because it is directly correlating with the density of the polymer structure and the number and location of the end groups. In contrast to dendrimers, which only possess dendritic (D) and terminal (T) units, hyperbranched polymers also have linear (L) units. In the case of the ideal statistical self-condensation of an AB₂ monomer, implying equal reactivity of all B groups and no side reactions, the number of linear units should be 50% and the dendritic units only 25%.

The ratio of structural units can be determined by NMR spectroscopy, as in Figure 6-1, showing the evolution of the ^{1}H-NMR spectrum at 5, 10, 30, and 60 minutes. A decrease of the signal at 4.6 ppm is observed, which is due to the reaction of the alkyne with the thiol, with the formation of a thioether and an alkene. Besides this, the increase of the signals at 4.3 ppm are due to the formation of a dendritic unit, meaning a fully reacted alkyne species. Over time, also signals originating from double bond protons are observed between 5 and 6.5 ppm, indicating the formation of linear species. The calculation of the DB for AB₂ type of polymers using the values for T, D and L was described in the 1990s by Webster et al.[12] and Fréchet et al.[13] as a function of the ratios of the dendritic (D), terminal (T) and linear (L) units, as shown in equation 2.

$$\text{Conversion} = \frac{L+2D}{D+T+L} \tag{1}$$

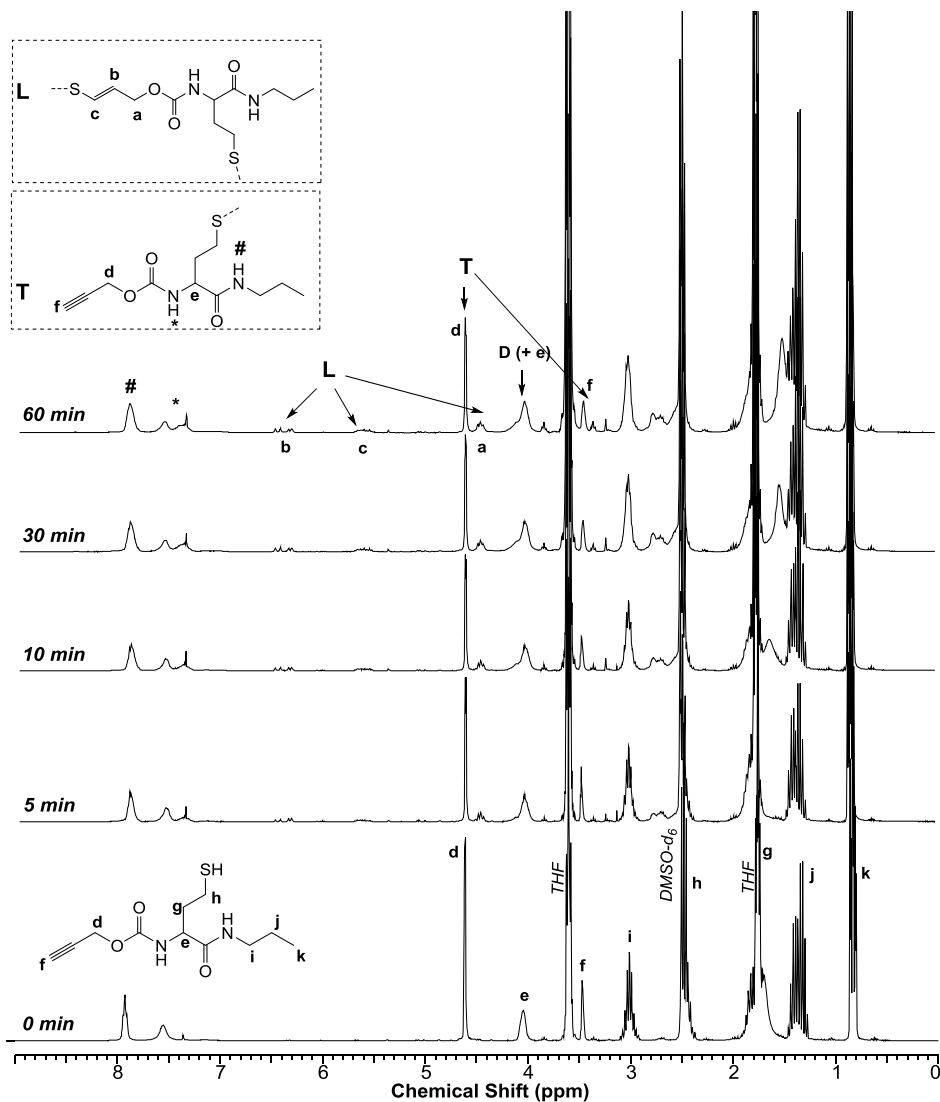$$\text{DB} = \frac{D+T}{D+T+L} \tag{2}$$

Figure 6-1. Overlay of the ¹H-NMR (300 MHz, DMSO-d_6) spectra of the reaction mixture, followed as a function of time, while being irradiated with UV-light. The spectrum at t = 0 min corresponds with the alkyne-thiolactone monomer, opened with propylamine after 2 hours of reaction.

The conversion of the thiols can be calculated from the NMR spectra, according to equation 1. The results are shown in Table 6-2. The conversion of the thiol groups already reached 88 % after 20 minutes. Interestingly, all the DB values are higher than 0.5, which should be the maximum value for a hyperbranched polymer made from an AB₂ monomer, in the case of equal reactivity of both the B

units. The reason for this high DB value is originating from the high amount of dendritic units (D), reaching up to 40% of all structural units. Even at low conversions, the DB is 0.89. This is a reflection of the fact that the first addition of a thiol to an alkyne is much slower than the addition to an alkene, meaning that both B units do not show equal reactivity.

Table 6-2. Calculated degree of branching (DB) and conversion of the hyperbranched polymers. (D, T and L denote the relative integration of the dendritic, terminal and linear units, resp.) Results obtained from Figure 6-1.

Time (min)	Conv (%)	DB	D	T	L
5	51.5	0.89	0.21	0.71	0.11
10	75.5	0.87	0.32	0.57	0.13
20	88.0	0.85	0.37	0.49	0.15
30	94.5	0.86	0.44	0.50	0.15
60	92.5	0.87	0.41	0.50	0.14

One of the advantages of combining a thiolactone moiety with an alkyne functionality, is the possibility of introducing extra functional groups *via* the used amine. This means that post-polymerization modification can be avoided and functionalization will be high. Besides propylamine, an experiment with ethanolamine was performed as proof of concept. In this way, hydroxylated hyperbranched polymers can be readily synthesized. Such kind of polymers have already been used in the synthesis of polyurethane networks, making use of not only the high amount of hydroxyl functions, but also the relatively low viscosity of the starting compounds. [14]

After 15 minutes of reaction, a white precipitate was formed. SEC analysis revealed that M_n: 5700 g mol^{-1}, M_w: 102 000 g mol^{-1} and Đ: 17.7. These results are indeed particularly interesting, because functionalized hyperbranched structures can be formed in a very short period of time (15 minutes only), without additional modification reactions being necessary. Finally, also *N,N*-dimethylethylamine as functional amine was used, leading to a low molar mass hyperbranched polymer with Mn: 1800 g.mol^{-1}, Mw: 4350 g.mol^{-1} and Đ: 2.41.

6.3.2. Hyperbranched polymers based on alloc-thiolactone
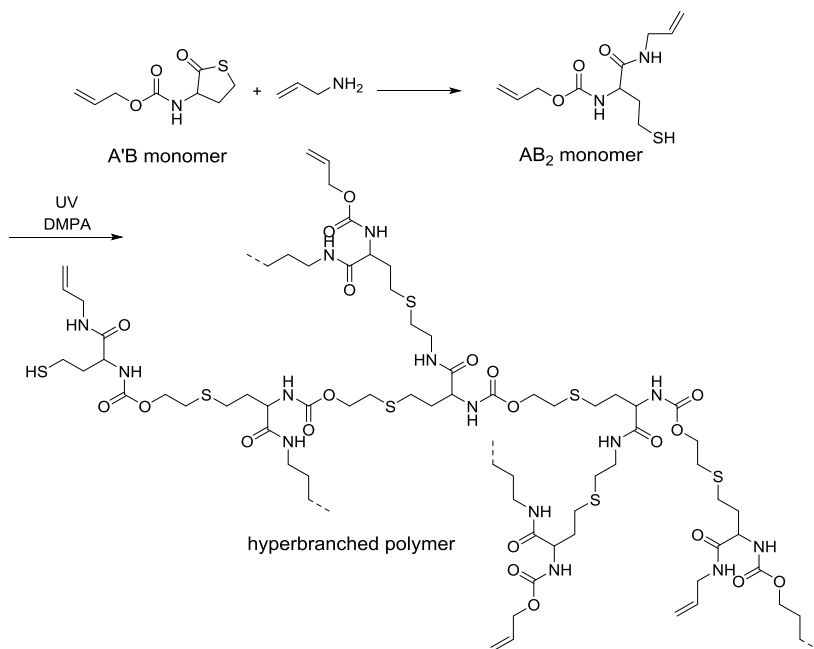
Scheme 6-5. Synthesis of hyperbranched polymers, starting from alloc-thiolactone, an A'B monomer. Using allylamine, the thiolactone ring is opened with the formation of an AB₂ monomer. DMPA was used as photoinitiator and 1,4-dioxane as the solvent.

Alloc-thiolactone is an A'B- monomer, containing both a thiolactone unit (A') and a double bond (B). This A'B-monomer can be converted into an AB₂-monomer by reaction of a double bond containing amine, such as allylamine, with the thiolactone: this generates a second double bond while at the same time a thiol is released. It can be argued that the obtained monomer is not really an AB₂-system, but rather an ABB' system. Indeed, the double bond introduced via allylamine is different from the alloc double bond. However, both are not considered to be activated double bonds and therefore we will assume that they exhibit similar reactivities. Upon UV-irradiation, a thiol-ene reaction occurs in the presence of a photo-initiator, leading to the formation of branched structures (Scheme 6-5). Similar to the polymerization of alkyne-thiolactone, the reaction proceeds in two steps: in a first step, allylamine is allowed to open the thiolactone ring, after which DMPA is added and the reaction is placed under UV-light.
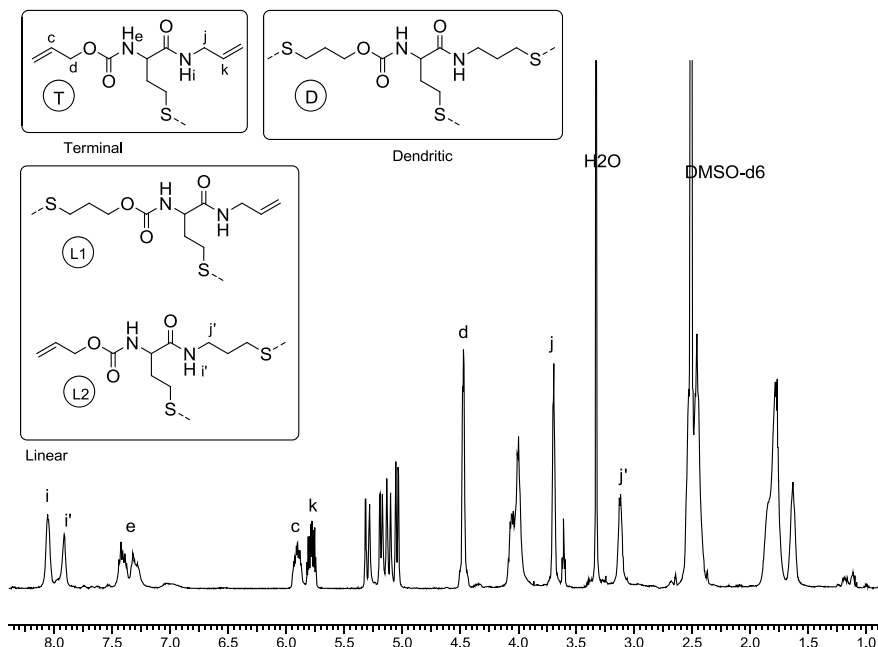
Figure 6-2. ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) of the reaction mixture of alloc-thiolactone, reacted with allyl-amine and placed under UV-irradiation (365 nm) for 1 hour. Inserts show the structures of terminal (T), dendritic (D) and different linear (L1 and L2) units.

Different units can be distinguished in the final product: 1 type of dendritic unit (D), 2 types of linear units (L1 and L2) and 1 type of terminal unit (T). Possible side-reactions (cyclization and disulfide formation) are not taken into account in the analysis. Figure 6-2 shows the ^{1}H-NMR spectrum of the hyperbranched polymer formation after 1h of reaction. The conversion of the thiols can be calculated from the intergration of the double bond protons c and k. The degree of branching, however, cannot be calculated, because it is not possible to differentiate between the dendritic units and the linear units, as was the case for alkyne-thiolactone.

The following conclusions can be drawn from NMR-spectra as a function of time (not shown):

- Signals j and d are decreasing at almost the same rate (d disappearing a bit faster than j), implying *equal reactivity of both alkene groups* (this allows us to conclude that there is branching).
- From integration of the signals corresponding to proton c and k, we can conclude that the *conversion of the thiol-groups is nearly 100% after 1h of irradiation*. The conversion of thiols is calculated based on the disappearance of double bonds. Only little disulfide formation is therefore expected.

The chromatograms obtained from size-exclusion chromatography showed a broad dispersity, in agreement with the formation of hyperbranched structures. Table 6-3 gives an overview of the molecular weight characteristics obtained after different irradiation times.

Table 6-3. Molecular weight characteristics of hyperbranched alloc-thiolactone polymer (reaction with allylamine).

Time (h)	M_n (g.mol^{-1})	M_w (g.mol^{-1})	Đ
1	6200	66000	10.5
2	6200	218000	35.2
3	6800	229000	33.3

The obtained polymers are structures carrying a high amount of double bonds, available for further modification. Although the proposed synthesis strategy, based on alloc-thiolactone, is a very straightforward and easy-to-perform method of preparing hyperbranched polymers, no other functional groups can be introduced from the start, as is the case for alkyne-thiolactone based hyperbranched polymers.

Both alkyne-thiolactone and alloc-thiolactone are low-molecular-weight precursor compounds for hyperbranched polymers. An interesting addition to this research consists of the replacement of these compounds with a macromolecular precursor, such as heterotelechelic pTHF. The motivation for this research is based on different arguments: 1) going from a linear to a hyperbranched polymer with the same molecular weight, viscosity is decreased due to a decrease in hydrodynamic volume. 2) Secondly, the physical properties of hyperbranched polymers are different from their linear analogues. For example, melting temperatures can be decreased by hyperbranching. 3) Finally, the presence of multiple chain-ends creates more reactive sites without extra chemical modifications being needed. This research was conducted in collaboration with Drs. Sofie Wallyn (PCR group).

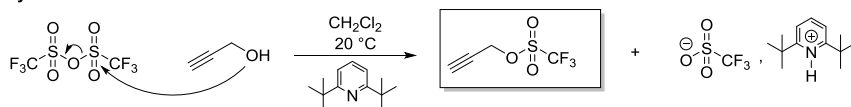# 6.4. HETEROTELECHELIC P(THF)

6.4.1. Introduction

Tetrahydrofuran (THF) is a monomer known for showing a living polymerization through a cationic ring-opening process (CROP).[15] It is an equilibrium polymerization leading to a final reaction mixture containing unreacted monomer. However, to obtain a certain molecular weight, the reaction should preferably be stopped before the equilibrium state is reached. Close to the equilibrium, the rate of polymerization becomes lower and thus side reactions are becoming more dominant (transfer to

polymer). This will lead to higher dispersities and a mixture of products. A great variety of initiators have been used for the polymerization of THF. Importantly, the initiation should be rapid and quantitative to have a high degree of control. The most useful initiators are strong alkylating reagents, such as trialkyloxonium ions and alkyl esters of strong acids such as fluorosulfonic or trifluoromethane sulfonic acid (triflic acid).[16]

The electrophilic cyclic oxonium functions, which are growing centres on the polymer chains, can react with nucleophiles to generate polyTHF with a certain end-group. The polymerization of THF initiated by triflic esters is generally accepted to have a high living character and has for that reason been chosen for the preparation of the desired macromolecular precursor.

Our interest consisted of generating a polyTHF macromolecular precursor, carrying an alkyne at one chain-end and a thiolactone moiety at the other, for the synthesis of hyperbranched structures. Perrier et al.[9] already synthesized heterotelechelic polystyrene with both an alkyne and a thiol, for the preparation of hyperbranched polymers. The reaction procedure is as follows (Scheme 6-6): An alkyne-functionalized triflic ester is synthesized by reaction of propargyl alcohol with triflyc anhydride (functionalized alcohols have been used often for the synthesis of functional initiators[17]). 2,6-Di-*tert*-butylpyridine is used as a non-nucleophilic proton trap to neutralize the liberated triflic acid. The hydroxyl-function of propargyl alcohol is thus substituted with a good leaving group, capable of initiating the cationic ring-opening of THF. Finally, termination is performed with a thiolactone-alcohol terminating agent.
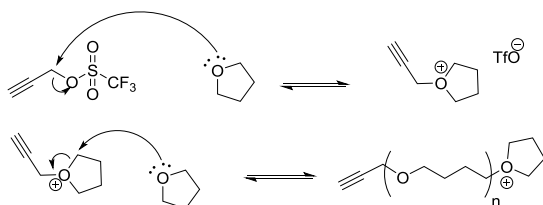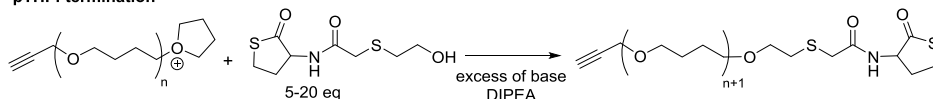

Scheme 6-6. Reaction mechanism for the synthesis of heterotelechelic polyTHF, starting from an alkyne-functionalized triflate ester. Termination is performed with an alcohol-containing thiolactone compound.

The thiolactone-alcohol compound was synthesized in the context of another research within the PCR group and was kindly provided by dr. Pieter Espeel. The synthesis consists of the substitution reaction of a brominated derivative of homocysteine thiolactone (Scheme 6-7), of which the synthesis is described in literature,[18] with mercaptoethanol.
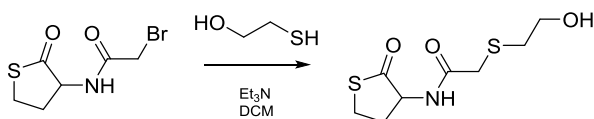
Scheme 6-7. Synthetic scheme for the preparation of a thiolactone-alcohol derivative.

This part will discuss the synthesis of heterotelechelic pTHF, having an alkyne and a thiolactone moiety at the chain ends, ≡-pTHF-TL, intended for the synthesis of hyperbranched structures. To evaluate the initiator efficiency, the reaction kinetics were examined for different initiator concentrations. Initiation should be fast in order to have a good control over molecular weight.

6.4.2. pTHF reaction kinetics

The polymerization of THF using propargyl triflate was followed as a function of time for different initiator concentrations: 0.014 M, 0.028 M and 0.054 M. Samples were taken at dedicated reaction times and quenched with MeOH.
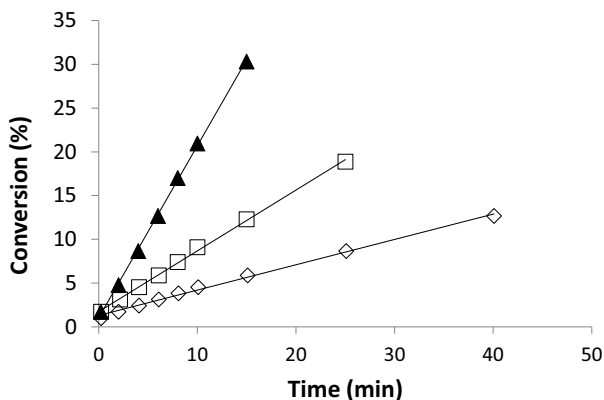
Figure 6-3. Time-conversion plots for the bulk polymerization of THF at 25 °C with different initiator concentrations. ▲: 0.054 M; □: 0.028 M; ◇: 0.014 M.

The time-conversion plots (Figure 6-3) of the bulk polymerization of THF with propargyl triflate at 25 °C show that, at low conversions, after a short period, an almost linear relationship is obtained for all initiator concentrations. These results indicate that the initiation reaction is completed in the early

stages of the polymerization. At higher conversions (>30 %), exchange reactions start to occur, resulting in a lack of control.
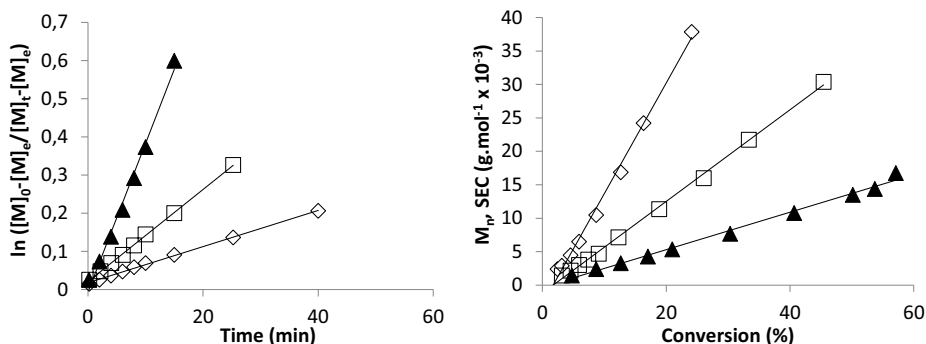

Figure 6-4. A. ln{([M]$_0$-[M]$_e$)/([M]$_t$-[M]$_e$)} as a function of time and B. M$_n$ (SEC, PS standards, THF as eluent) as a function of monomer conversion for the cationic ring-opening of THF at 25 °C, initiated by propargyl triflate, for 3 different initiator concentrations: ▲: 0.054 M; □: 0.028 M; ◇: 0.014 M; [M]$_0$ for ▲: 8.85 M; □: 8.99 M; ◇: 9.06 M; [M]$_e$=2.9 M.

Figure 6-4 A. shows first order kinetics for all initiator concentrations at low conversions, meaning that the concentration of active centres remains constant. Figure 6-4 B shows that M$_n$ evolves linearly with conversion until a certain value, in agreement with a fast initiated living polymerization. Moreover, when these results are compared with the results of Dubreuil et al.[16] for allyl triflate-initiated polymerization, it can be concluded that propargyl triflate has nearly exactly the same initiation characteristics as allyl triflate, which was found to be the best initiator in this study.

Table 6-4 gives an overview of some of the results of the obtained polymers after 15 and 40 minutes of polymerization, using different initiator concentrations. Dispersities were low in most cases, although at higher conversions, transfer reactions are known to occur, leading to higher dispersities. The through SEC obtained values for M$_n$ are higher than the M$_{n,th}$ values, which can be calculated according to the following formula:

$$M_n = \frac{([M]_0 - [M]_t)}{[In]} \times 72$$

This discrepancy however is easily explained by the use of polystyrene standards for calibrating the SEC instrument. Clearly, THF is a better solvent for polyTHF than for polystyrene, resulting in a maximal hydrodynamic volume of polyTHF compared to that of polystyrene. This explanation is further confirmed in paragraph 6.4.3., when comparing the masses from MALDI-TOF analysis after 15 minutes with the obtained M$_n$ values from SEC.

Table 6-4. Results for the cationic ring-opening polymerization of THF with different initiator concentrations.

Entry	[I]	Time (min)	Conversion (%)[a]	M_n, SEC (g.mol^{-1})[b]	Đ[b]
1	0.014	15	5,9	6500	1.13
2	0.014	40	12.7	16900	1.09
3	0.028	15	12,3	7100	1.12
4	0.028	40	26.1	16000	1.18
5	0.054	15	30,3	7700	1.15
6	0.054	40	50,1	13500	1.37

[a]Determined from ^{1}H-NMR spectroscopy.
[b]SEC with THF as eluent and calibrated with PS standards.

It can be concluded from these results that propargyl triflate (not described in literature yet) is a fast initiator for THF polymerization, leading to living polymers and thus to controllable molecular weight and dispersity.

6.4.3. Heterotelechelic pTHF and hyperbranching

Heterotelechelic pTHF can be formed by using a functional initiator and by terminating the reaction with a functional nucleophile, such as an alcohol. For this purpose, an alcohol-functionalized thiolactone compound was employed (Scheme 6-6). The polymerization, using an initiator concentration of 0.028 M, was terminated after 15 minutes, using 20 equivalents of the thiolactone compound, dissolved in dry DMF with DIPEA added as a proton trap. MALDI-TOF analysis shows a mass spectrum with peaks separated by 72 Da, with a good agreement between the theoretical, calculated values and the measured values (Figure 6-5). SEC analysis shows a M_w/M_n value of 1.26, showing a good control over the molecular weight. However, to our surprise, in the ^{1}H-NMR spectrum, only the propargylic end-group is visible, whereas no signals originating from the thiolactone moiety are observed. A possible explanation for this observation is that the formed pTHF structures are organized in micellar structures, shielding the thiolactone units in the NMR spectra. This hypothesis is confirmed by Dynamic Light Scattering (DLS), where hydrodynamic radii between 10 and 100 nm were observed, depending on the used solvent, indicating the formation of micelles.
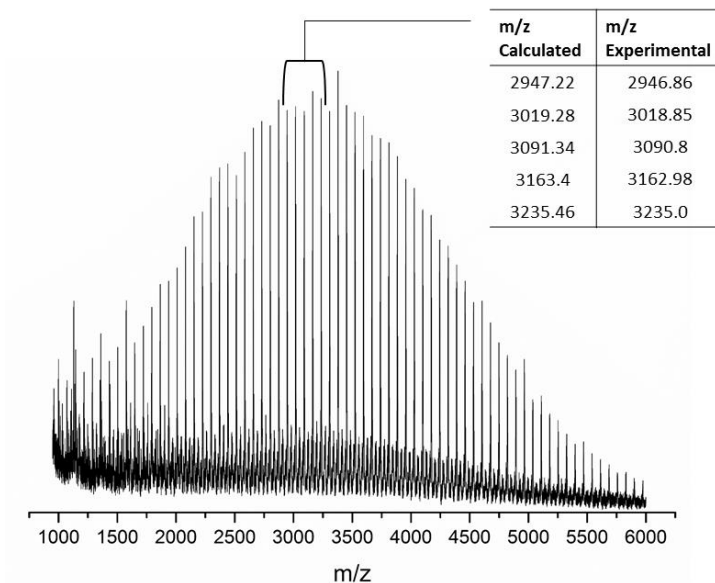
m/z Calculated	m/z Experimental
2947.22	2946.86
3019.28	3018.85
3091.34	3090.8
3163.4	3162.98
3235.46	3235.0

Figure 6-5. MALDI-TOF spectrum of ≡-pTHF-TL in linear mode.

The formation of hyperbranched structures was attempted by adding an amine (propylamine or ethanolamine) under UV-irradiation for 2 hours, in the presence of DMPA as a photoinitiator. However, SEC showed that the obtained polymers only doubled in molecular weight. There are two possible explanations for this observation:

- Due to the formation of micelles, the formed thiols (by aminlysis) are located closely to one other and are thus more likely to react with each other, forming disulfide bridges.
- Because of sterical restrictions, the formed thiols are able to react with the alkyne only once.

In the ^{1}H-NMR spectrum, no double bond protons are observed, which could lead to the conclusion that the first option is more likely (since addition to the alkyne would lead to the formation of an alkene). However, more detailed analyses should reveal the exact origin of these observations.

Attempts to disrupt the micellar structure (change of solvent, adding acid or salts) were unsuccessful. A proposed solution is to use a different end-capping thiolactone-containing compound, which would disfavor the formation of micelles. It can thus be concluded that the supramolecular ordening of the linear pTHF chains is of major concern when attempting to form hyperbranched structures.

6.5. CONCLUSION

Hyperbranched polymers were prepared starting from different precursor molecules. Alkyne-thiolactone is regarded as an A'B₂ monomer: The thiolactone (A') can be transformed into a thiol (A) through lysis with an amine. Upon UV-irradiation, this thiol is able to react with each of the π-bonds of the alkyne unit. The conversion as well as the degree of branching could be calculated from NMR spectra. The high degree of branching confirmed the observations of Fairbanks et al.,[11] showing that the second addition of a thiol to an alkyne proceeds faster than the first. This means that the obtained polymers have a high amount of alkyne functionalities left, which are available for further modification reactions. One of the major advantages of using a thiolactone-containing precursor molecule lies in the fact that functional groups can be incorporated from the start. This was demonstrated by using ethanolamine and *N,N*-dimethylaminoethylamine as functional amines.

Additionally, an AB₂-type of monomer was also generated by letting alloc-thiolactone react with allylamine. This resulted in a hyperbranched precursor, having two distinct double bonds (B₂) and a thiol unit (A). From NMR, it was clear that there was no significant difference in reactivity of the alkenes. Although it was clear from SEC that hyperbranched polymers were formed (high Đ), the degree of branching could not be determined from ¹H-NMR spectroscopy, since structural elucidation is rather complicated.

Finally, the synthesis of a macromolecular precursor was investigated. Using propargyl triflate, THF was polymerized *via* cationic ring-opening polymerization. Kinetic experiments revealed that this novel initiator leads to fast initiation and therefore a good control over the molecular weight and polydispersity was obtained. Termination with a hydroxyl-functionalized thiolactone moiety gave rise to heterotelechelic p(THF) and the structure of the polymer was confirmed by MALDI-TOF MS. However, the obtained structures were arranged in micelles (as was proven with DLS measurements) and it was concluded that because of this micellar arrangement, high molar mass hyperbranched polymers could not be formed.

6.6. EXPERIMENTAL PART

6.6.1. Materials

2,2-dimethoxy-2-phenyl acetophenone (DMPA, Acros, 99%), allyl chloroformate (Aldrich, 97%), chloroform (Fisher Scientific, HPLC grade), dichloromethane (Sigma-Aldrich, HPLC), DL-homocysteine thiolactone hydrochloride (Fluka, ≥ 99%), *N,N*-dimethylaminoethylamine (Aldrich, 96%), *N,N*-diisopropylethylamine (Aldrich, 99.5%), ethanolamine (Fluka, ≥ 99%), ethyl acetate (Fluka, HPLC), methanol (Sigma Aldrich, HPLC grade), propylamine (Aldrich, >99%), propargyl chloroformate (Aldrich, 96%), propargyl alcohol (Aldrich, 99%), trifluoromethanesulfonic anhydride (Aldrich, > 99%) and 1,4-dioxane (Acros, HPLC grade) were used as received. THF (Aldrich, >99%) was destilled over Na/benzophenone prior to use. 2,6-Di-tert-butylpyridine (TCI) was purified by destillation. Silicagel (ROCC, SI 1721, 60 Å, 40 – 63 µm) was used to perform preparative column chromatography, eluting with HPLC-grade solvents. The collected fractions were analyzed by thin layer chromatography (TLC-plates, Macherey-Nagel, SIL G-25 UV₂₅₄).

6.6.2. Methods

^{1}H- and ^{13}C-NMR (Attached Proton Test, APT) spectra were recorded in CDCl₃ (Eurisotop), DMSO-d_6 (Eurisotop) on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz.

An Agilent technologies 1100 series LC/MSD system equipped with a diode array detector and single quad MS detector (VL) with an electrospray source (ESI-MS) was used for classic reversed phase *LC-MS (liquid chromatography mass spectroscopy) and MS analysis*. Analytic reversed phase HPLC was performed with a Phenomenex C₁₈ (2) column (5 µ, 250 x 4.6 mm) using a solvent gradient (0 → 100% acetonitrile in H₂O in 15 min) and the eluting compounds were detected *via* UV-detection (λ = 214 nm).

Size Exclusion Chromatography (SEC) was performed on a Waters instrument, with a refractive-index (RI) detector (2414 Waters), equipped with 3 Polymer Standards Services SEC serial columns (1 X GRAM Analytical 30 Å, 10 µm and 2 x GRAM Analytical 1000 Å, 10 µm) at 35 °C. Poly(methyl methacrylate) (PMMA) standards were used for calibration and *N,N*-dimethylacetamide (DMA), containing LiBr (0.42 g/mL) was used as an solvent at a flow rate of 1 mL/min. Molecular weight and polydispersity index were determined using the Empower software.

UV curing was performed by irradiation with 365 nm UV lamps (9 x 9 W) positioned in a metal cylindrical container.

MALDI-TOF (Matrix-Assisted Laser Desorption and Ionization Time of Flight) mass spectrometry analysis was performed on an Applied Biosystems Voyager-DE STR instrument equipped with nitrogen laser operating at 337 nm, pulsed ion extraction source and reflectron detector. The laser pulse width is 3 ns and maximum power is 20 Hz. Spectra were recorded in the linear mode with an acceleration voltage of 17 kV and delay of 400 ns. 500 single shot acquisitions were summed to give the spectra and the data were analyzed using Data Explorer and Polymerix software. Samples were prepared by dissolving the matrix dithranol in the solvent (THF, 20 mg/mL), mixing with the polymer (2 mg/mL) and lithium bromide in THF (2 mg/mL) that has been used as cationizing agent.

Dynamic light scattering (DLS) was performed on a Zetasizer Nano-ZS Malvern apparatus (Malvern Instruments Ltd) using disposable cuvettes. The excitation light source was a He−Ne laser at 633 nm, and the intensity of the scattered light was measured at 173°. This method measures the rate of the intensity fluctuation and the size of the particles is determined through the Stokes−Einstein equation

$$d(H) = kT/3\pi\eta D \qquad (1)$$

where d(H) is the mean hydrodynamic diameter, k is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the dispersing medium, and D is the apparent diffusion coefficient. All samples were filtered through Millipore membranes with pore sizes of 0.2 μm prior to measurement.

6.6.3. Synthesis of "alloc-thiolactone"

DL-Homocysteine thiolactone hydrochloride (28 g, 0.1823 mol) was slowly added to a solution of NaHCO₃ (76.44 g, 0.91 mol) in H₂O/1,4-dioxane (1/1, 400 mL) and this mixture was stirred for 30 minutes. Allyl chloroformate (38.76 mL, 0.3644 mol) was added dropwise and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with brine (800 mL) and extracted with EtOAc (4 x 800 mL). The organic phase was dried (MgSO₄). The drying agent was filtered and the resulting clear solution was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH: 98/2) to furnish the title compound (32.23 g, 0.1602 mmol, 87% yield) as a white solid.

$C_8H_{11}NO_3S$ (201.24 g/mol); ***m/z* (ESI-MS)** 202, 174, 130, 113;

v$_{max}$ / cm^{-1} 3307, 1691, 1546, 1445, 1302, 1267, 1249, 1174, 1098, 1056, 925, 851, 778, 762, 686, 655, 615, 582, 557;

¹H-NMR (300 MHz, CDCl₃, ppm) δ 5.90 (*ddt*, 17.2, 10.4, 4.7 Hz, 1H), 5.30 (*m*, 1H), 5.29 (*ddd*, 17.2, 3.0, 1.5 Hz, 1H), 5.25 (*ddd*, 10.4, 2.6, 1.3 Hz, 1H), 4.57 (*dt*, 17.2, 5.6, 1.4 Hz, 2H), 4.32 (*m*, 1H), 3.28 (*m*, 2H), 2.83 (*m*, 1H), 2.01 (*m*, 1H);

¹³C-NMR (75 MHz, CDCl₃, ppm) δ 205.1 (C), 156.2 (C), 132.6 (CH), 118.2 (CH₂), 66.2 (CH₂), 60.9 (CH), 32.0 (CH₂), 27.3 (CH₂).

6.6.4. Synthesis of "alkyne-thiolactone"

NaHCO₃ (227 mmol; 19.11 g) is dissolved in a 1,4-dioxane/H₂O mixture (1/1) (100 mL). DL-homocysteine thiolactone (45.57 mmol; 7 g) is added dropwise. The reaction mixture is stirred for 30 minutes at room temperature. Propargylchloroformate (91.15 mmol; 8.89 mL) is added dropwise and the reaction mixture is stirred overnight at room temperature. The reaction mixture was diluted with brine (200 mL) and extracted with EtOAc (4 x 200 mL). The organic phase was dried (MgSO₄). The drying agent was filtered and the resulting solution was evaporated under reduced pressure. Flash column chromatography on silica gel (DCM/acetone 98/2) was performed to obtain the purified compound as a viscous, yellow oil.

C₈H₉NO₃S (199.2 g.mol⁻¹)

¹H-NMR (500 MHz, CDCl₃, ppm) δ   2.04 (*m*, 1H); 2.5 (*s*, 1H); 2.85 (*m* 1H); 3.29 (*m*, 2H); 4.35 (*m*, 1H); 4.72 (*dt*, 2H); 5.35 (*s*, 1H).

¹³C-NMR (75 MHz, CDCl₃, ppm) δ 205.1 (C), 156.2 (C), 132.6 (CH), 118.2 (CH₂), 66.2 (CH₂), 60.9 (CH), 32.0 (CH2), 27.3 (CH₂).

6.6.5. Alkyne-thiolactone: hyperbranching

In a first step, alkyne-thiolactone (1 mmol; 204.3 mg) is dissolved in THF and three freeze-pump-thaw cycles are performed to guarantee oxygen-free atmosphere. 2 Eq propylamine (2 mmol; 0.164 mL) are added. The reaction temperature is kept at 25° C. After 3 hours, a sample for LC-MS and NMR is taken. In a subsequent step, the same reaction mixture is placed under UV-irradiation (365 nm, 9 x 9W), after adding 2 wt% DMPA as photoinitiator (test experiment reveals that without photoinitiator nothing happens). The same procedure was also carried out with all reaction partners present from the start, as well as UV-irradiation.

6.6.6. Alloc-thiolactone: hyperbranching

Alloc-thiolactone (2 mmol; 402 mg) is dissolved in THF and three freeze-pump-thaw cycles are performed to ensure oxygen-free conditions. 1 equivalent of allylamine (2 mmol; 0.15 mL) is added and the reaction is placed at 40°C for 6h. A sample for LC-MS is taken to ensure all starting product is reacted. DMPA is added and the reaction is put under UV (365 nm). Samples for SEC and NMR are taken at dedicated time intervals.
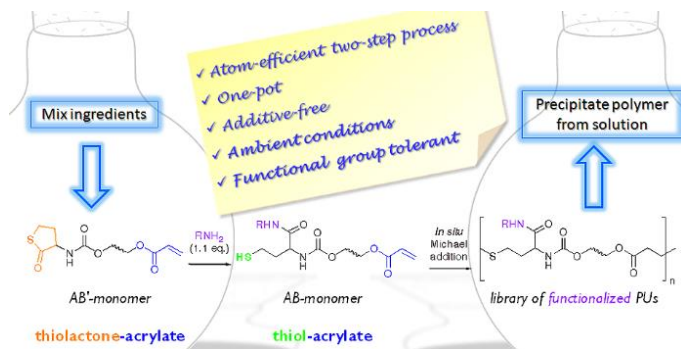
6.6.7. Heterotelechelic pTHF

In a flame-dried flask of 25 mL, 2.8 mL of dried CH_2Cl_2, 0.1 mL of DTBP (0.46 mmol) and 0.52 µL of Tf_2O (0.31 mmol) are added and stirred at 0 °C under nitrogen atmosphere. To this solution, 18 µL of propargyl alcohol (0.31 mmol) was added while stirring vigorously. The mixture was then stirred for 1 hour at 0 °C after which the temperature was set at 25 °C. Finally, THF (8 mL, 98 mmol) was added and the reaction was monitored by taking samples from the reaction mixture for analysis with SEC and ^{1}H-NMR.

The polymerization was carried out at 25 °C during a certain time and then terminated with a 20-fold excess of thiolactone-alcohol (1.45 g, 6.2 mmol) dissolved in 2.5 mL dried DMF with di-isopropylethylamine as protontrap (0.53 mL, 3.0 mmol). The formed salt was filtered off and the reaction mixture was evaporated under reduced pressure. Subsequently, the polymer was dissolved in CH_2Cl_2 and washed with ice-cold basic water (1M KOH). The water phase was extracted with CH_2Cl_2 (3x). After drying of the organic phase over $MgSO_4$ and evaporation of the solvent, the polymer was precipitated (dissolved in a minimal amount of THF) in pentane (cooled with liquid nitrogen). The obtained white precipitate was dried under reduced pressure to obtain a white powder.

6.7. REFERENCES

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✓ Atom-efficient two-step process
✓ One-pot
✓ Additive-free
✓ Ambient conditions
✓ Functional group tolerant

Mix ingredients

Precipitate polymer from solution

AB'-monomer   AB-monomer   library of *functionalized* PUs

thiolactone-**acrylate**   **thiol**-**acrylate**

Abstract

A straightforward, isocyanate-free method for the synthesis of functionalized polyurethanes, based on amine–thiol–ene conjugation, was elaborated. Aminolysis of a readily available AB'-urethane monomer, containing both an acrylate (A) and a thiolactone unit (B'), facilitates the preparation of various reactive thiol–acrylates. *In situ* polymerization *via* Michael addition proceeds under ambient conditions, yielding polyurethanes with a large variety of chemical functionalities. Side-chain functionality originates from the modular use of different amines, allowing for the introduction of pendent functional groups (e.g. double bond, triple bond, furfuryl, tertiary amine, morpholine) along the polyurethane backbone. Extensive model studies revealed the kinetic profile of this reaction sequence and excluded the occurrence of competing reactions, such as aza-Michael addition and disulfide formation. This mild onepot reaction requires no additives or external trigger and the obtained polyurethanes remain soluble throughout the process, enabling post-polymerization modification in the same reaction medium.

Chapter 7
# Functional polyurethanes *via* a thiolactone strategy

7.1. INTRODUCTION

Polyurethanes (PUs) are an essential class of synthetic polymers that are world-wide applied on a large scale.[1] Large-scale production of these materials mainly relies on feeds of diisocyanates, diols and/or polyols in the presence of a catalyst. Scheme 7-1 shows the general polyaddition reaction, as well as some common diisocyanates (MDI, TDI, HDI) and diol structures. For thermoset applications, often being the main goal for PU materials such as foams, polyols are used.
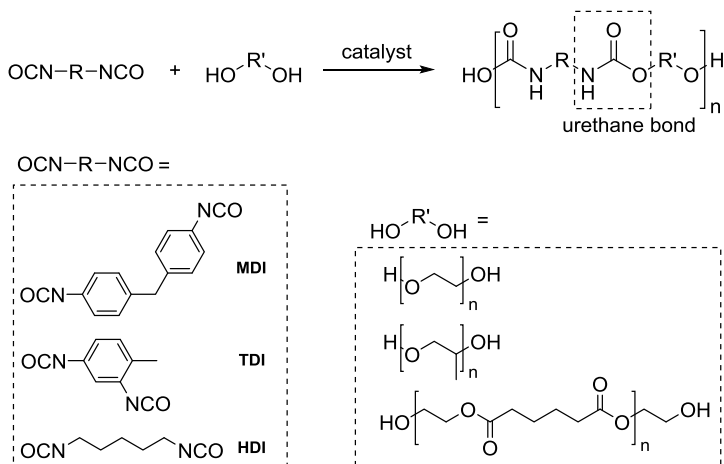
Scheme 7-1. General polyurethane synthesis starting from diisocyanates and diols, in the presence of a catalyst. Some common starting compounds are displayed.

Despite the wide range of PUs available *via* bulk step-growth polymerization, the lack of side-chain functionalities for further modification limits their scope. Therefore, methods leading to functionalized PUs equipped with reactive groups along their backbone remain of particular interest. These functional groups can be converted using 'click' chemistry, providing paths to unique materials

with enhanced properties for high-end applications. The mainstream approach is to directly incorporate clickable side-groups in linear PUs during the polymerization process through the addition of a functionalized diol to the diisocyanate/diol mixture. In addition to the high intrinsic reactivity of diisocyanates, the reactive nature of the desired functional group mostly necessitates the use of protection/deprotection strategies, *e.g.* amine- and maleimide-containing diols are protected as the corresponding carbamate[2] and furan-adduct[3] prior to the polymerization. However, various functionalities have also been introduced directly as pendent groups in PUs by careful selection of the appropriate unprotected monomer diol: alkyne[4-8]-, alkene[9-11]-, hydroxyl[12]- and furan[13]-functionalized PUs are available *via* this approach. Subsequent 'click' modification *via* copper catalyzed azide-alkyne cyclo-addition (CuAAC),[4-8] radical thiol-ene conjugation,[9-11] and thiol-maleimide conjugation[3] enabled the modular and efficient synthesis of tailored PUs. Similarly, the reactive moiety can be introduced through a functionalized diisocyanate, demonstrated by the synthesis of maleimide-functionalized copoly(urethane-urea)s.[14]

All methods mentioned above lack versatility as they generally only allow for the incorporation of one type of 'clickable' functional handle. Moreover, the absence of a general synthetic approach for the preparation of functionalized diols entails a requirement of dedicated multi-step synthesis of those diol monomers. Consequently, functionalized PUs differ not only in their reactive pendent moieties, but also in their backbone, compromising in-depth comparison of the material properties of the thus obtained materials and derivatives.

In Chapter 3, we presented a protocol for the modular synthesis of polyurethane based materials, consisting of a one-pot *amine-thiol-ene* reaction of a stable AB'-monomer, containing an allyl and thiolactone unit connected by a urethane linkage. In this approach, a thiolactone entity serves as a thiol precursor (latent functionality). The thiolactone ring opens upon aminolysis (nucleophilic reaction) and the *in situ* generated thiol reacts with the allyl double bond in a radical photo-polymerization reaction.[15] However, conceptual issues directly related to the radical reaction in the one-pot process impede further extension of the scope of the methodology. Important to note is that some functional groups (*e.g.* furan,[16-20] double and triple bond), introduced *via* the amine, are incompatible with this radical environment. Additionally, the UV-curing happens upon decomposition of a photoinitiator (*e.g.* DMPA), but model studies revealed that some amines (*e.g.* benzylamine) react with the formed radical fragments, thus limiting the use of a photoinitiator.

Therefore, the one-pot combination of the aminolysis of a thiolactone unit on one hand and a nucleophilic thiol-ene conjugation (Michael addition) on the other hand is considered to be a breakthrough approach for the development of a direct synthesis strategy to obtain functionalized

polyurethanes (see Scheme 7-2). The Michael addition between a nucleophile (such as thiol, amine or stabilized carbanion) and an activated double bond (eg. imidazole, acrylate, vinyl sulfone) is known to be an atom-efficient linking reaction. This versatile methodology is often the key step in polymer synthesis and conjugation, especially when complex macromolecular architectures are targetted.[21]
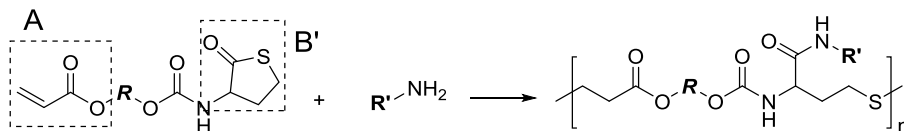
Scheme 7-2. General scheme representing the one-pot formation of functionalized polyurethanes, starting from an AB' type of monomer, without requiring additives.

The combination of the thiolactone-based strategy for the *in situ* generation of thiols and subsequent Michael addition undoubtedly broadens the scope of metal-free multi-step reactions for the design and synthesis of polymers. Replacing the allyl double bond in the AB'-monomer with an acrylate function, allowing for the complete absence of radical species during the polymerization, is considered to be a step forward. However, potential orthogonality issues render the conjugation procedure a fundamentally challenging two-step reaction sequence. Therefore, the chemoselective discrimination between both nucleophiles (amine *vs* the generated thiol) is the major focus when employing the nucleophilic amine-thiol-ene conjugation. Potential side reactions such as the aza-Michael addition[21] of the amine to the acrylate and disulfide formation are of primary concern. Prior to the design of a new AB'-monomer, model feasibility studies of the one-pot two-step reaction were performed. In a second stage, after the large-scale synthesis of a readily available AB'-urethane monomer, containing both an acrylate (A) and a thiolactone unit (B'), several (multi-)functionalized PUs and PU networks will be prepared by modular use of a variety of functional amines.

7.2. MODEL STUDY: AMINE-THIOL-ENE CONJUGATION
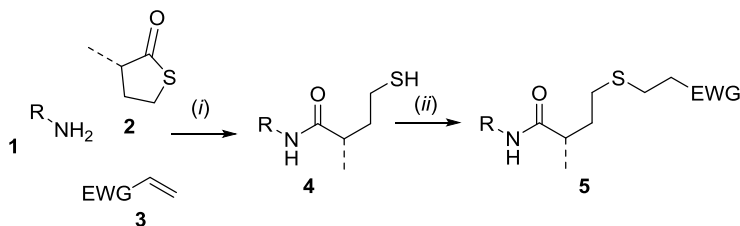
Scheme 7-3. Nucleophilic amine-thiol-ene conjugation: aminolysis of the thiolactone ring (i), followed by thiol-Michael addition (ii). EWG = electron-withdrawing group.

The feasibility of the proposed amine-thiol-ene conjugation between an amine **1**, a thiolactone-containing compound **2** and a Michael acceptor **3** entirely relies on the selectivity of the conjugate addition (Scheme 7-3). Therefore, the selection of the reaction partners **1** and **3** is critically important. While maleimides react with both amines and thiols as Michael donor[21], acrylates are less reactive: at room temperature and without a catalyst, only secondary amines readily react with acrylates.[22] As a consequence, a reaction mixture of a primary amine, a thiolactone and an acrylate in the absence of any catalyst would result in the formation of the product **5**. The anticipated chemoselective discrimination between both heteroatomic nucleophiles (primary amine **1** and the intermediate thiol **4**) is based upon different reaction rates. The slow *aza*-Michael addition allows the aminolysis of the thiolactone to precede while the subsequent thiol-Michael addition is known to be relatively fast.[23]

Simplified, following competing reactions could be proceeding at the same time:

[amine + thiolactone] vs [amine+ acrylate]

[acrylate + thiol] vs [acrylate + amine]

[acrylate + thiol] vs [thiol + thiol]

In order to confirm these hypotheses, a series of model reactions were conducted, for which the reaction progress was monitored by *online* FT-IR analysis. First however, a kinetic study of the aminolysis was conducted, in order to compare the relative reactivity of a series of amines towards the thiolactone moiety.

7.2.1. Aminolysis: comparison of the reactivity of amines
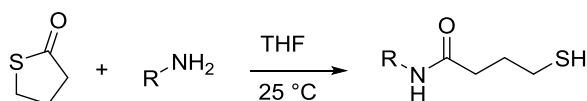
Scheme 7-4. Aminolysis of γ-thiobutyrolactone as a model reaction for the determination of the reaction rate.

The proposed two-step amine-thiol-ene conjugation starts with the *in situ* formation of a thiol through aminolysis, followed by nucleophilic thiol-ene addition. Since the aminolysis step is assumed to be rate-determining, a kinetic screening of the ring-opening of γ-thiobutyrolactone in the presence of fifteen different (functional) primary and secondary amines was performed (Scheme 7-4 and Figure 7-2). Generally, the aminolysis of thiolactones can be described by second order kinetics: the reaction order with respect to both the thiolactone and amine equals 1.[24] Pseudo-first order conditions were established using a 50-fold excess of amine in THF (equations 1-6).

$$-\frac{d[\text{thiolactone}]}{dt} = k_2[\text{thiolactone}][\text{amine}] \tag{1}$$

$$k_{obs} = k_2[\text{amine}](\text{pseudo} - 1\text{st order condition}) \tag{2}$$

$$-\frac{d[\text{thiolactone}]}{dt} = k_{obs}[\text{thiolactone}] \tag{3}$$

$$\int_{[\text{thiolactone}]_0}^{[\text{thiolactone}]_t} \frac{d[\text{thiolactone}]}{[\text{thiolactone}]} = -k_{obs}\int_0^t dt \tag{4}$$

$$\ln\frac{[\text{thiolactone}]_t}{[\text{thiolactone}]_0} = -k_{obs}t \tag{5}$$

$$k_2 = \frac{k_{obs}}{[\text{amine}]} \tag{6}$$

The conversion of γ-thiobutyrolactone as a function of time has been monitored by GC analysis of periodically taken reaction samples. Figure 7-1 depicts the results obtained from these off-line measurements. Rate constants are summarized in Figure 7-2. Stereo-electronic properties of the primary amines are the basis for the relative rate differences: aliphatic non-functional amines react faster than amines containing an inductive-withdrawing group, such as benzylamine or allylamine. The sterical constraints due to α-branching in Jeffamine® M-600 greatly influences the reaction rate. Cyclic, secondary amines, more specifically piperidine, piperidine and methyl piperazine were also analyzed. However, there was no correlation found with the 2nd order reaction kinetics, indicating a different mechanism in this case. Other secondary amines and tertiairy amines (diethylamine and triethylamine) did not react with γ-thiobutyrolactone.

The orthogonality of the reaction is proven by the fact that under the same reaction conditions (50-fold excess of the nucleophile and neutral pH), water, alcohols, thiols and anilines are not able to open the thiolactone ring.

The results shown in this kinetic study are of dual importance: first, possibilities and limitations of different aminolysis reactions are evaluated. Secondly, it gives an indication of the relative speed of polymerization using different amines, under the condition that the nucleophilic ring-opening is the rate-determining step (see 7.4.3). Finally, although in this study γ-thiobutyrolactone was used as a model compound, the same relative trend is expected for other thiolactone monomers.
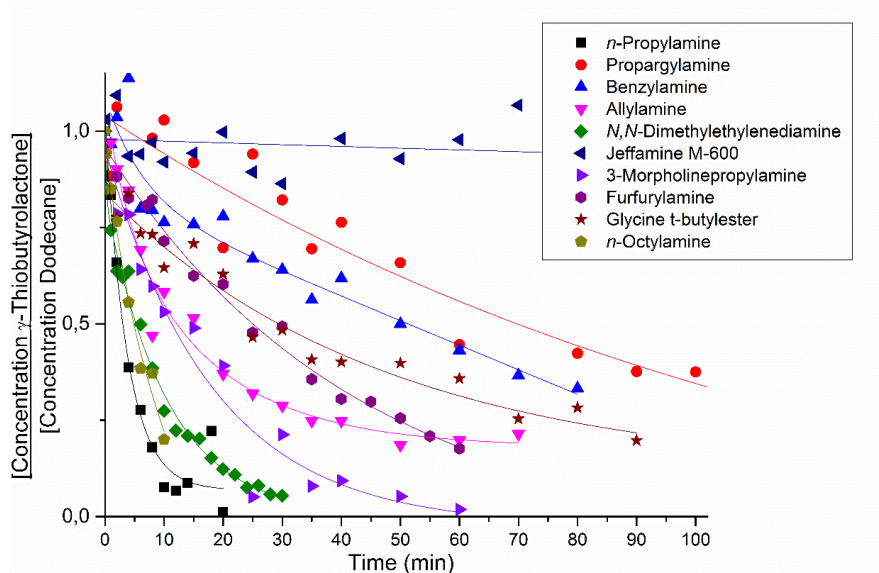
Figure 7-1. Decrease of thiolactone concentration as a function of time. k_{obs} can be calculated from the logarithmic thiolactone concentration as a function of time.
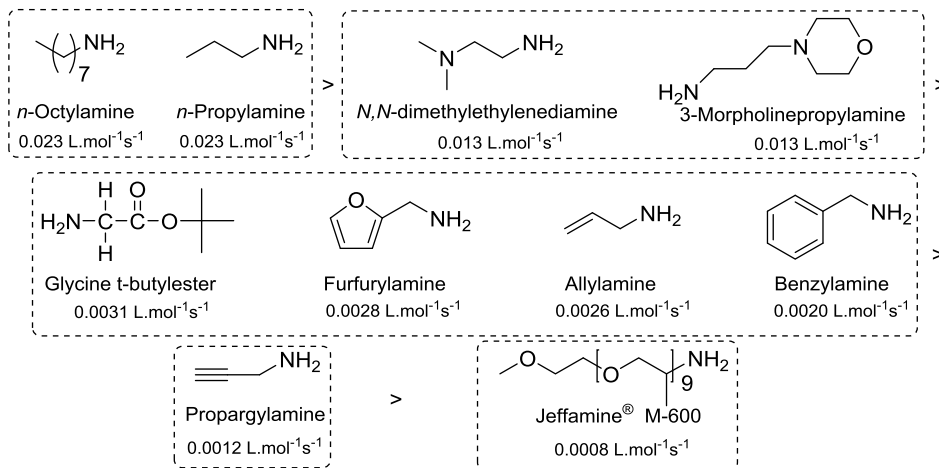

Figure 7-2. Rate constants of the aminolysis of γ-thiobutyrolactone in the presence of different primary amines with indication of the relative reaction rates.

7.2.2.Aza-Michael addition *vs* Thiol-Michael addition

The proposed one-pot two-step reaction, including the nucleophilic aminolysis of the thiolactone, and the subsequent nucleophilic thiol-ene addition to the acrylate, poses a fundamental question relating to selectivity. Indeed, the kinetic discrimination between aza-Michael addition and thiol-Michael addition is one of the factors in the one-pot two-step reaction that has to be taken into account. In theory, both nucleophiles could add to the electrophilic double bond, albeit with different reaction rates.
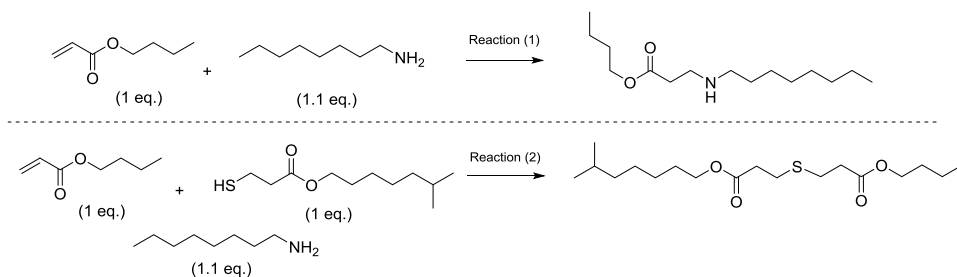
Scheme 7-5. Aza-Michael addition vs thiol-Michael addition. Two model reactions were performed for FT-IR online monitoring of the reaction progress. Reaction (1) is comprised of 1 eq. of *n*-butyl acrylate and 1.1 eq. of *n*-octylamine. Reaction (2) is comprised of 1 eq. of *n*-butyl acrylate, 1 eq. of IoMP and 1.1 eq. of *n*-octylamine.

To investigate whether one of those reactions is favored, a model study with an amine, a thiol and an acrylate is performed. In a solution (in CHCl$_3$ or THF, 0.5 and 1 M respectively; to assess the influence of concentration and solvent) of octylamine, isooctyl 3-mercaptopropionate (IoMP) and butylacrylate, the consumption rate of the thiol and acrylate were *online* monitored by FT-IR (Reaction 2 in Scheme 7-5 and Figure 7-3).

Figure 7-3 plots the decreases in the absorption intensity of the acrylate double bond wagging vibrations (987-968 cm^{-1}) and thiol SH stretching (2582 cm^{-1}), respectively.[i] The same study was done in 1M THF (Figure 7-3 a) and 0.5M CHCl$_3$ (Figure 7-3 b). In both cases, the solvent spectrum was subtracted to enhance the signal of the reaction species. During the reaction, the intensity of the C-H stretches (3000-2850 cm^{-1}) was constant, indicating that there was no change in intensity of the other bands due to solvent evaporation.

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[i] The conversion of the acrylate double bond was additionally confirmed by decreases in absorption intensity of the other acrylate CH=CH$_2$ vibrations, such as the twisting, scissoring and stretching ones at 814, 1409, 1638 and 1622 cm^{-1}, respectively, as well as shifts of the C=O ester stretching signal – originating from the ester signals of both *n*-butyl acrylate and IoMP – to a slightly higher wavenumber ascribed to the ester groups in the formed products.

From these graphs, it is clear that the consumption rate of the thiol and the acrylate is identical.
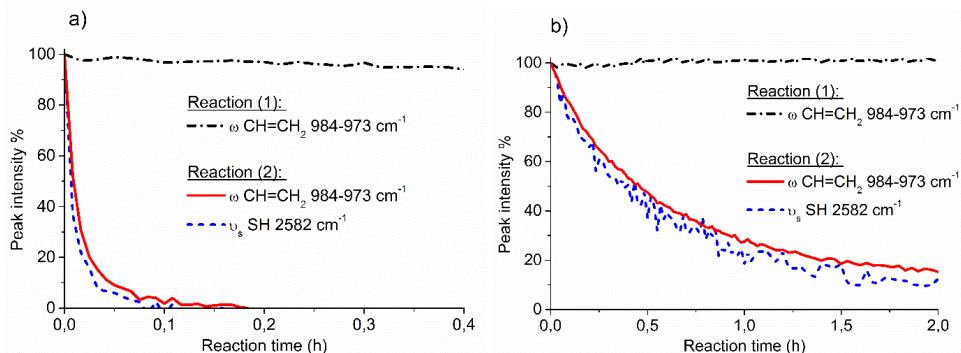

Figure 7-3. Aza-Michael addition vs Thiol-Michael addition. Two model reactions were performed in different solvents and concentrations: a) at a *n*-butyl acrylate concentration of 1 M in THF and b) at a *n*-butyl acrylate concentration of 0.5 M in CHCl₃. Reaction 1 involves the reaction between butyl acrylate and octylamine, whereas reaction 2 is the reaction between butyl acrylate, IoMP as thiol and octylamine (Scheme 7-5). Peak intensities of thiol and/or acrylate as a function of time reflect the kinetic profiles.

In a control experiment, only the amine and acrylate were mixed at room temperature. Whereas in the previous case the thiol was consumed in less than 15 minutes (1 M in THF), only a negligible conversion of the acrylate by aza-Michael addition was observed in the same time frame (Figure 7-3 a). Also in CHCl₃, the aza-Michael addition was not detectable.

From these experiments (reaction 1 and 2 in Scheme 7-5), a kinetic discrimination between aza-Michael addition and thiol-Michael addition can be concluded. Both nucleophiles react with a substantially different reaction rate, and will thus, most likely, not compete in a significant way.

7.2.3. Model amine-thiol-ene conjugation

In a second model reaction, involving a thiolactone as latent thiol functionality, the kinetic profile of the reaction between *n*-propylamine **6**, γ-thiobutyrolactone **7** and *n*-butyl acrylate **8** was studied in detail (Scheme 7-6). It should be stressed that the reaction was performed at room temperature and under air atmosphere. In other words, no special precautions were taken with respect to possible disulfide formation.
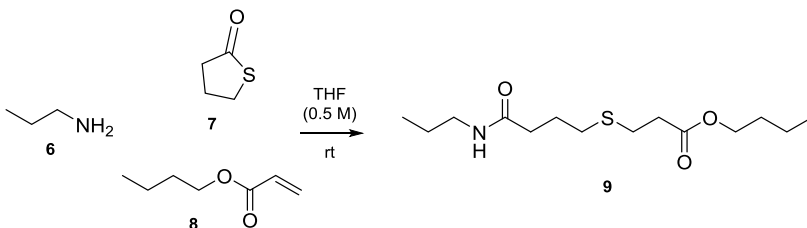
Scheme 7-6. Model amine-thiol-ene conjugation between *n*-propylamine 6, γ-thiobutyrolactone 7 and *n*-butyl acrylate 8.

An *online* FT-IR study of the model reaction was performed in order to monitor both reaction steps: the aminolysis and subsequent thiol-ene reaction. This study should reveal the occurrence of side-reactions. With the use of 1.1 eq. of *n*-propylamine, the reaction was not complete after 9 hours of measurement. Thus, in order to more easily deconvolute the FT-IR spectra (see further), 2 eq. of *n*-propylamine were used to speed up the reaction. Therewith, the reaction was complete after 8 h. FT-IR spectra of the reactants (see Scheme 7-6) with spectral assignments are shown in Figure 7-4 and listed in Table 7-1. A comparison of FT-IR spectra, again with assigned characteristic vibrational bands, recorded for the reaction at different reaction times (t = 0h, 1h and 8h), is shown in Figure 7-5.
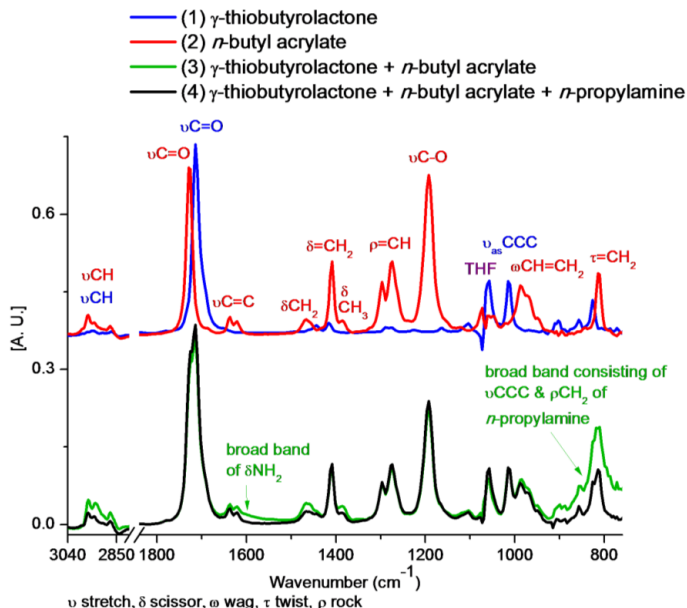

Figure 7-4. FT-IR spectra recorded for the reaction of *n*-butyl acrylate (1 eq.) with γ-thiobutyrolactone (1 eq.) in the presence of *n*-propylamine (2 eq.), at an acrylate concentration of 0.5 M in THF, at room temperature and under air condition: (3) prior to addition of *n*-propylamine, (4) right after addition of *n*-propylamine. For comparison, separate spectra of (1) γ-thiobutyrolactone and (2) *n*-butyl acrylate were recorded in the same solvent.

Table 7-1. Selected observed vibrational frequencies (cm⁻¹) and spectral assignments for the reaction of *n*-butyl acrylate with γ-thiobutyrolactone in THF in the presence of *n*-propylamine.

n-Butyl acrylate		γ-Thiobutyrolactone	
Wavenumber (cm⁻¹)	Assignment[a]	Wavenumber (cm⁻¹)	Assignment[a]
1728	ν(C=O)	1718	ν(C=O)
1638, 1622	ν(C=C)	1451	δ(CH$_2$)
1467	δ(CH$_2$)	1420	δ(CH$_2$)
1409	δ(=CH$_2$)	1294, 1278	ω(CH$_2$)
1386	δ(CH$_3$)	1224	τ(CH$_2$)
1297, 1278	ρ(=CH)	1165	τ(CH$_2$)
1190	ν(C-O)	1106	τ(CH$_2$)
987, 968	ω(CH=CH$_2$)	1015	ν$_{as}$(C$_4$-C$_3$-C$_2$)
814	τ(=CH$_2$)	911	ν$_s$(C$_4$-C$_3$-C$_2$)
		861, 826	ρ(CH$_2$)

n-Propylamine		Formed product	
Wavenumber (cm⁻¹)	Assignment[a]	Wavenumber (cm⁻¹)	Assignment[a]
1610	NH$_2$ symmetric	1737	ν(C=O) (ester)
1463	deformation	1678	amide I (νC=O, νC-N)
1390	CH$_2$ deformation	1540	amide II (δN-H, νC-N)
890-700	CH$_3$ deformation	1244	amide III
	CCC stretch, CH$_2$ rock,		
	NH$_2$ wag		

[a] **Assignments from reported vibrational studies[24-29] were compared to assign the bands observed in the experimental spectra. ν stretch, δ scissor, ω wag, τ twist, ρ rock.**

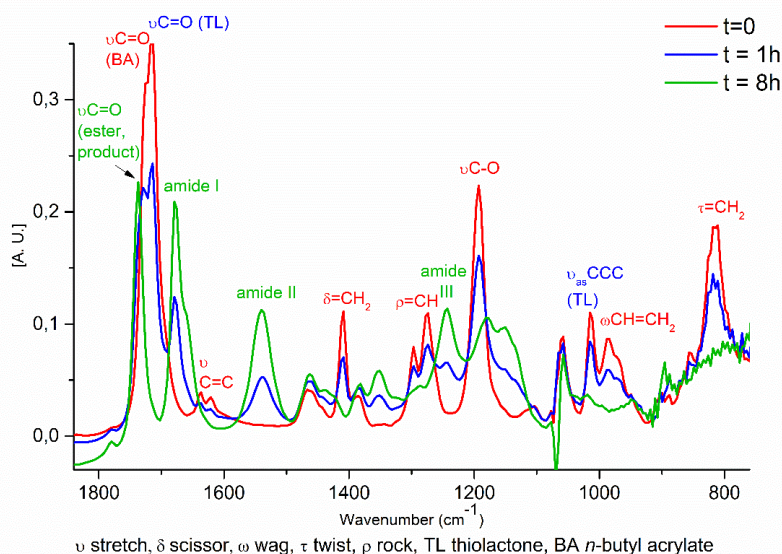υ stretch, δ scissor, ω wag, τ twist, ρ rock, TL thiolactone, BA *n*-butyl acrylate

Figure 7-5. FT-IR spectra as a function of reaction time recorded for the model reaction of butyl acrylate (1 eq.) with γ-thiobutyrolactone (1 eq.) in the presence of 2 eq. of *n*-propylamine, at an acrylate concentration of 0.5 M in THF, at room temperature and under air atmosphere.

Due to partial overlap of relevant bands in the IR spectrum, a deconvolution process was performed. For this deconvolution, the spectral region from 1830 to 1490 cm^{-1} with high signal-to-noise ratio was selected. The deconvolution was performed separately for each reagent, the product and eventually also the reaction mixtures at different reaction times. Examples of the fit results are shown in Figure 7-6, whereas Table 7-2 lists the band assignments and curve fit parameters of the FT-IR spectra in this region.
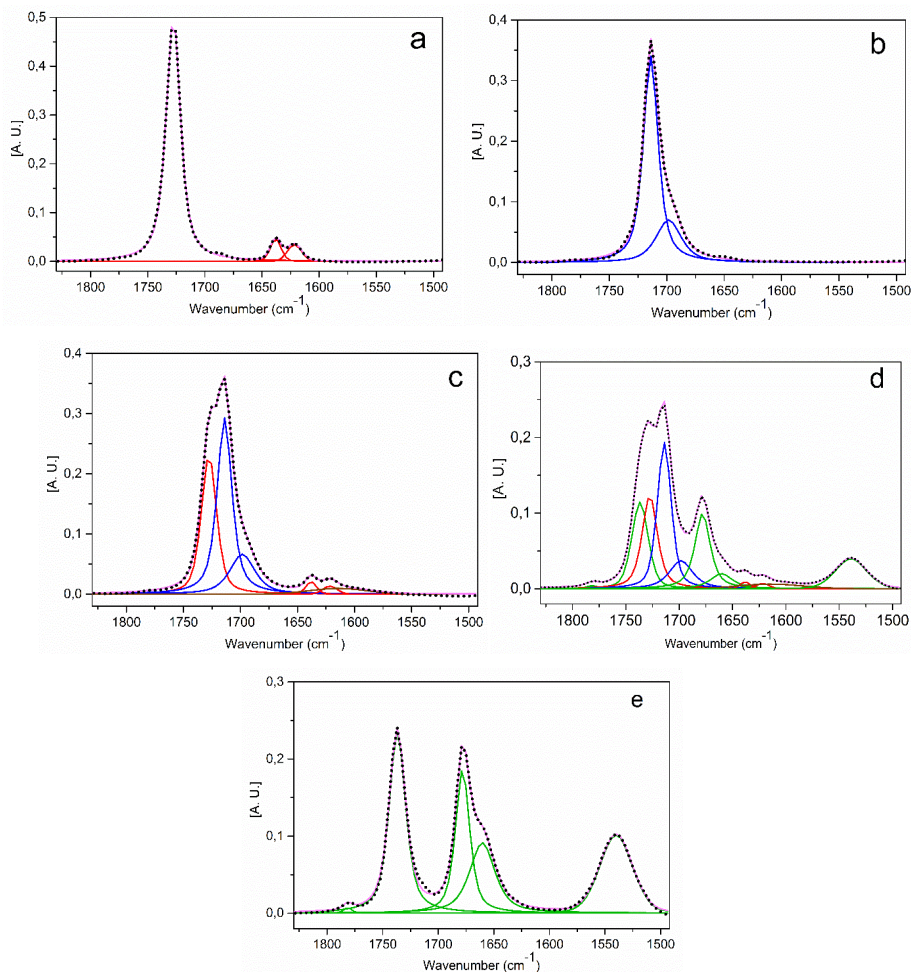

Figure 7-6. Curve fits of the FT-IR spectra measured in THF of (a) butyl acrylate, (b) γ-thiobutyrolactone, (c) the reaction mixture at t = 0, (d) the reaction mixture at t = 1 h, and (e) the formed product at t = 8 h. Reaction conditions: 1 eq. of butyl acrylate, 1 eq. of γ-thiobutyrolactone, 2 eq. of *n*-propylamine, acrylate concentration of 0.5 M in THF. The solid lines represent the fitted curves, while the dotted lines represent the measured spectra. In colors, red: butyl acrylate, blue: γ-thiobutyrolactone, brown: *n*-propylamine, green: product, pink: fitted sum spectra, and dotted black: measured spectra. See Table 7-2 for the deconvoluted band positions and assignments and curve fit parameters.

Table 7-2. Band assignments and curve fit parameters of the FT-IR spectra in the spectral region of 1830-1490 cm⁻¹ for the model reaction of *n*-butyl acrylate and γ-thiobutyrolactone with *n*-propylamine.

Vibration	Frequency (FWHH [b], Contour Shape) cm⁻¹ (cm⁻¹, f_G)
vC=O (product)	1782 (11-14, 0.81)
vC=O (product)	1737 (18, 0.64)
vC=O (*n*-butyl acrylate)	1728 (16-18, 0.40)
vC=O (γ-thiobutyrolactone)	1714 (15, 0.54)
vC=O (H-bonded, γ-thiobutyrolactone)	1698 (22, 0.30)
Amide I (product)	1678 (17, 0.28)
Amide I (more strongly H-bonded, product)	1660 (19-24, 0.20)
vC=C (*n*-butyl acrylate)	1638 (11, 0.80)
vC=C (*n*-butyl acrylate)	1622 (14, 10)
δNH₂ (*n*-propylamine)	1614 (73, 10)
Amide II [a]	1540 (34-35, 0.81)

[a] **The amide II vibration is constituted of different H-bonded vibrational sub-bands, but is deconvoluted for simplicity as one band.**
[b] **FWHH = Full Width at Half-Height**

A good agreement between the measured and deconvoluted peak intensities was observed (Figure 7-6). In Figure 7-7a, the 3D *online* FT-IR waterfall plot illustrates the decrease and increase of several (C=O)stretch absorption bands as a function of time. Figure 7-7b shows the FT-IR peak intensities as a function of time of both the kinetic curves and the different deconvoluted data points.
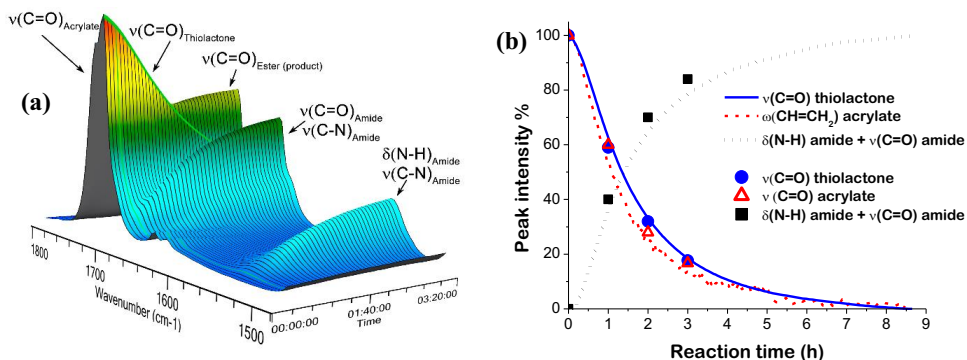

Figure 7-7. *Online* monitoring of amine-thiol-ene conjugation between *n*-propylamine 6, γ-thiobutyrolactone 7 and *n*-butyl acrylate 8; (a) 3D FT-IR waterfall plot of (C=O)stretch absorption bands (1830 – 1490 cm⁻¹) and (b) FT-IR peak intensities as a function of time (kinetic curves and deconvoluted data points).

The FT-IR peak intensities, reflecting the concentrations of the reactants **7** and **8** and the product **9** as a function of time, are shown. The decrease of the height of the thiolactone (C=O)stretch and the area of the acrylate (CH=CH₂)wagging vibrational bands have been used to establish the kinetic profile. The formation of the amide (band area at 1540 cm⁻¹, N-Hscissoring and C-Nstretch) is a good indicator for

the consumption of thiolactone **7**. It is thus demonstrated that the area depletion of the deconvoluted thiolactone (C=O, 2 sub-bands at 1714 and 1698 cm^{-1}) and acrylate (C=O, at 1728 cm^{-1}) bands is strongly agreeing with the kinetic curves (Figure 7-7b).

Finally, the reaction was also performed with 1.1 equivalents of amine. Figure 7-8 (a) shows curve fits of the FT-IR spectrum of the reaction mixture at t = 2 h for the reaction of n-butyl acrylate (1 eq.) with γ-thiobutyrolactone (1 eq.) in the presence of *n*-propylamine (**1.1 eq**.), at an acrylate concentration of 0.5 M in THF, at room temperature and under air atmosphere. The solid lines represent the fitted curves, while the dotted lines represent the measured spectra. The deconvoluted data points at t = 2 h in Figure 7-8 (b) were extracted from Figure 7-8 (b) and again demonstrate a strong agreement with the kinetic curves.
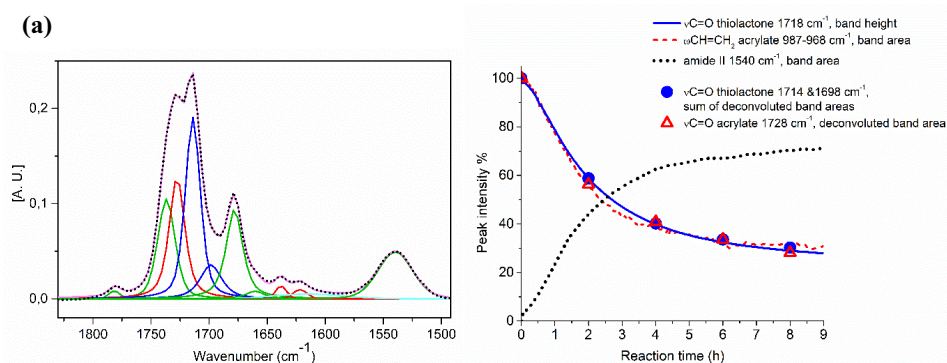

Figure 7-8. (a). Curve fits of the FT-IR spectrum of the reaction mixture at t = 2 h for the reaction of *n*-butyl acrylate (1 eq.) with γ-thiobutyrolactone (1 eq.) in the presence of *n*-propylamine (1.1 eq.), at an acrylate concentration of 0.5 M in THF, at room temperature and under air atmosphere. The solid lines represent the fitted curves, while the dotted lines represent the measured spectra. In colors, red: *n*-butyl acrylate, blue: γ-thiobutyrolactone, light blue: *n*-propylamine, green: product, pink: fitted sum spectra, and dotted black: measured spectra. (b). FT-IR band intensities as a function of reaction time for the same model reaction. The relative amide II band area corresponding to 100 % conversion was determined from a similar experiment but with 2 eq. of *n*-propylamine where the thiolactone group was fully converted (vide supra).

The major **conclusion** from this model study is that the aminolysis is the rate-determining step. Indeed, acrylate and thiolactone are consumed with the same rate: as soon as the thiol is formed, it will react with the acrylate. With 1.1 eq. of *n*-propylamine compared to an equimolar mixture of thiolactone **7** and acrylate **8**, it takes 9 h to reach 70% conversion (Figure 7-8). The rate can be increased with the amine concentration. For example with a two-fold excess, the reaction is finished within 8 h (Figure 7-7b).

7.2.4. LC-MS analysis: disulfide formation

Besides aza-Michael addition, a second side-reaction has to be taken into account. As elaborated in chapter 3, thiols are prone to oxidation reactions and often, certain precautions have to be taken to avoid thiol-thiol coupling. With the aim of forming polymers through amine-thiol-ene conjugation, disulfide formation as a side-reaction would significantly decrease the final molecular weight. An LC-MS analysis (Figure 7-9) of the reaction with 1.1 eq. of *n*-propylamine after 9 h (70% conversion) shows a clean mixture of starting materials and product **9**. Only a minor fraction of disulfide was detected (Figure 7-9 c). Disulfide formation is more prominent at higher amine concentration (Figure 7-9 d), indicating that the excess of amine should be limited. It was indeed reported that autoxidation of thiols is accelerated by bases.[25]
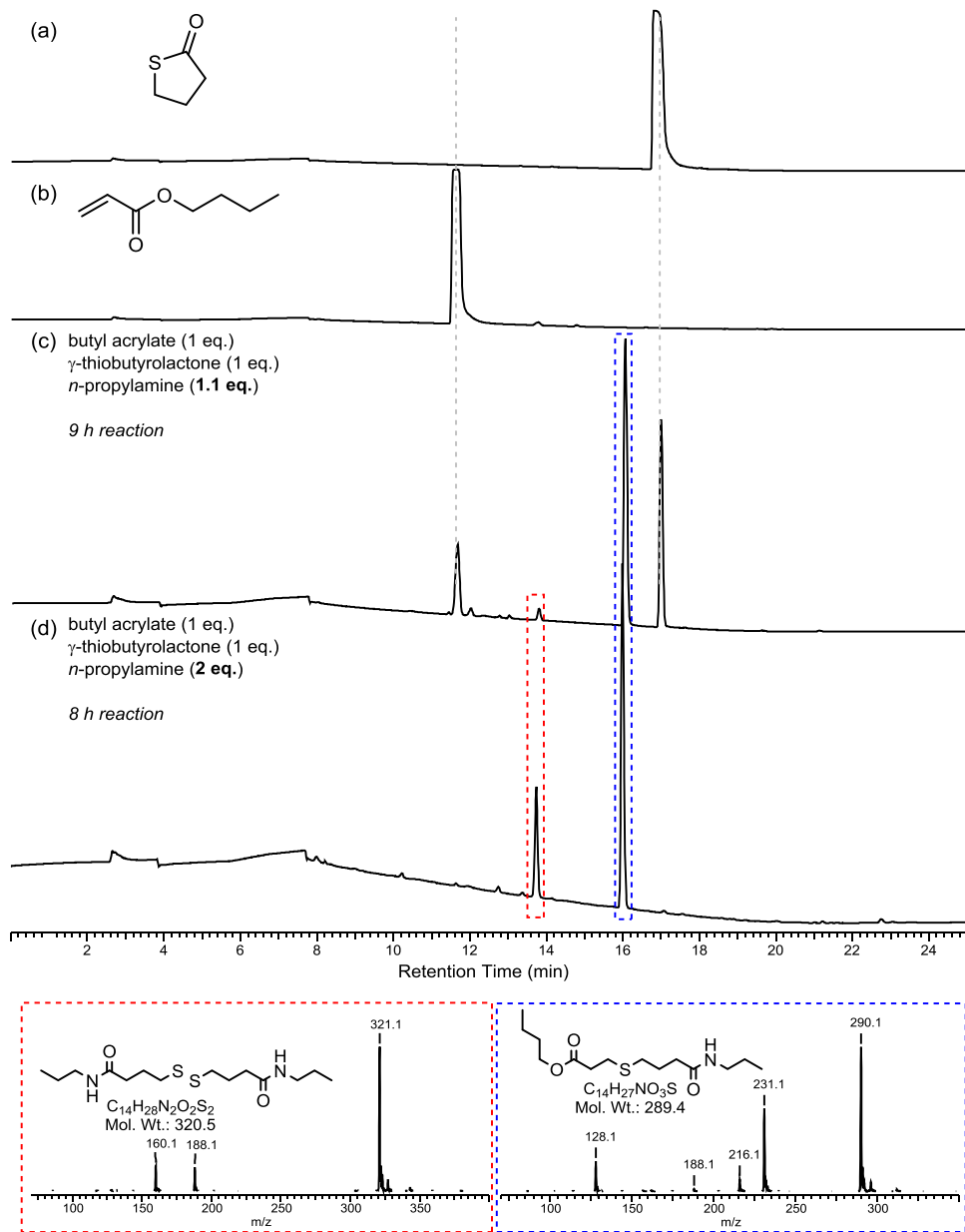
Figure 7-9. LC-MS analysis of the model reaction between butyl acrylate, γ-thiobutyrolactone and *n*-propylamine, at an acrylate concentration of 0.5 M in THF. Two different conditions were used; (c) 1.1 eq. of *n*-propylamine, 9 h reaction and (d) 2.0 eq. of *n*-propylamine, 8 h reaction. Inserts: ESI-MS spectra of relevant products of the model reaction.

7.3. MONOMER SYNTHESIS

The use of the above studied nucleophilic amine-thiol-ene conjugation in polymer synthesis demands a straightforward and scalable methodology for the synthesis of a stable monomer, containing an acrylate (A) and a thiolactone unit (B'). Upon aminolysis, this monomer forms a reactive thiol-acrylate, which will be consumed in the same medium by a conjugate addition. In order to synthesize such an AB'-monomer, two reaction routes have been explored (Scheme 7-7). In each case, a stable urethane bond connects the reactive entities, which will result after reaction in the formation of polyurethanes (paragraph 7.4).

The first possibility relies on the Sn-catalyzed carbamate formation between α-cyanato-γ-thiolactone 10 [26] and an equimolar amount of a hydroxyl-functionalized acrylate. Two acrylates (2-hydroxyethylacrylate 11 and 1,4 -cyclohexanedimethanol monoacrylate 12) have been converted to the respective monomers, 13 and 14, with an isolated yield of 92%. The inherent instability of 13, as a result of acrylate consumption, requires radical inhibition, while 14 can be stored as a white powder for months at -20 °C without added inhibitor. Monoacrylate 12 was chosen because of its higher solubility in common organic solvents (which will also have an influence on polymer solubility).

A more scalable route consists of the phosgene treatment of the hydroxyl-functionalized acrylate 12 to render the chloroformate 17 and subsequent reaction of the latter with DL-homocysteine thiolactone 15 in the same pot. This procedure allowed for the preparation of 45 g of the AB'-monomer 14 (see Scheme 7-9 for NMR spectrum with assignment of peaks) in a single batch with an overall isolated yield of 78%.
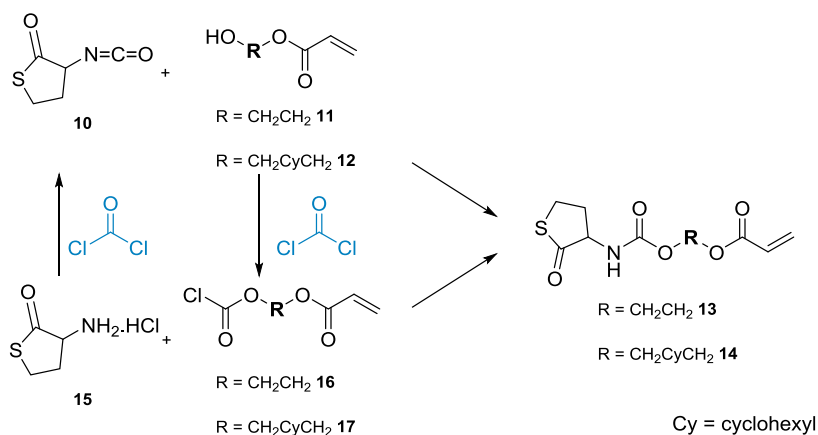
Scheme 7-7. Two approaches for the synthesis of an AB'-monomer, containing a thiolactone and an acrylate as reactive entities and a stable urethane linkage.

7.4. POLYMERIZATION BY AMINE-THIOL-ENE CONJUGATION

7.4.1. Optimization of polymerization parameters
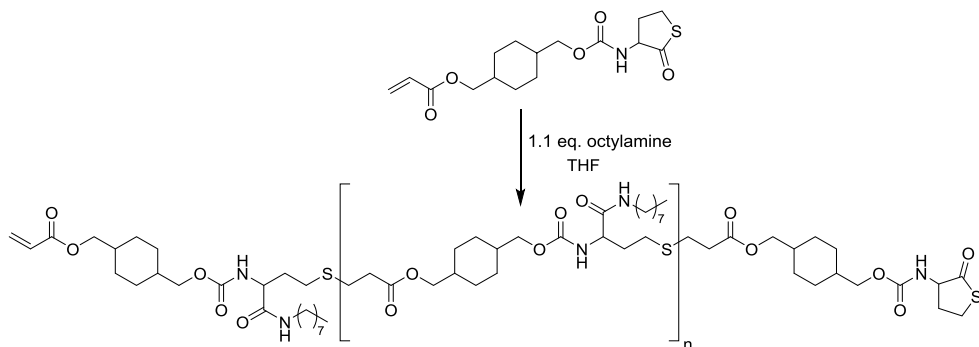
Scheme 7-8. Polymerization of monomer 14 in THF, using 1.1 equivalents of *n*-octylamine.

Although the thiol-Michael addition is regarded as reversible and therefore represents a methodology for dynamic covalent chemistry,[27-29] thiol-acrylate conjugate addition has already been employed as the key step for the fabrication of functional polymer materials.[23, 30-36] As a consequence, the polymerization *via* polyaddition of thiol-acrylates, originating from the aminolysis of AB'-monomers **13** and **14**, was studied in detail. The polymerization gives rise to a polymer with a urethane bond in the main chain, as a consequence of the monomer structure. Adding functional groups to the polymer is possible during polymerization through the amine. In fact, the polymerization can only start after adding the amine to the reaction mixture. A first screening of the reaction conditions (solvent and concentration) was performed in the presence of 1.1 eq. of *n*-octylamine, capable of a relatively fast aminolysis reaction (*vide supra*). The slight excess of amine potentially catalyzes the Michael addition after conversion of the thiolactone.[37, 38]

Aminolysis of monomer **13** at varying concentrations (0.25, 0.5 and 1 M) in THF resulted in a precipitate of low molecular weight (M_n ~ 2 kDa, determined by SEC). Precipitation could be avoided in CHCl₃, but only oligomers were formed. Similar observations were made when changing the solvent to CH₂Cl₂ and *N,N*-dimethylacetamide. Repeating the same conditions, starting from monomer **14**, pointed out that polyaddition was most prominent in THF at 0.5 M: linear polymers with M_n of 12.0 kDa and Đ of 1.69 were isolated by precipitation (Scheme 7-8).
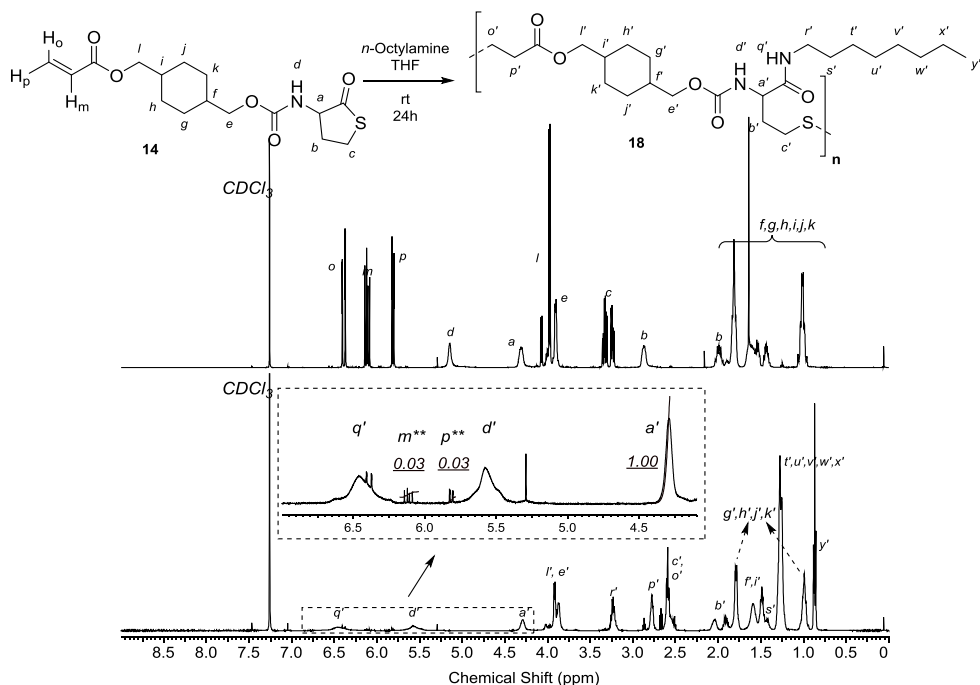
Scheme 7-9. Aminolysis of AB'-monomer 14 with *n*-octylamine and the formation of polymer 18 by conjugate addition: ^{1}H-NMR spectra (CDCl₃, 500 MHz) of the monomer 14 (top) and the purified polymer 18 (bottom). Signals m** and p** (insert) designate two protons of the acrylate end group of polymer 18. Spectral assignment of the 1D-^{1}H-NMR of polymer 18 was facilitated by 2D-NMR spectra.

Scheme 7-9 shows the ^{1}H-NMR spectrum of polymer **18** (bottom) after polymerization of monomer **14** (top) with *n*-octylamine. Spectral assignment was facilitated by 2D-NMR techniques. NMR analysis allows for the calculation of the molecular weight of the obtained polymer by integrating the acrylate end group protons in comparison to proton a' in the repeating unit.

7.4.2. FT-IR study of the polymerization

This optimized condition (a 0.5 M solution of **14** in THF at room temperature) was used for an *online* FT-IR study of the polymerization reaction. Figure 7-10 shows the FT-IR spectra of the starting compounds, while Table 7-3 gives an overview of the observed vibrational frequencies, with the corresponding spectral assignments.
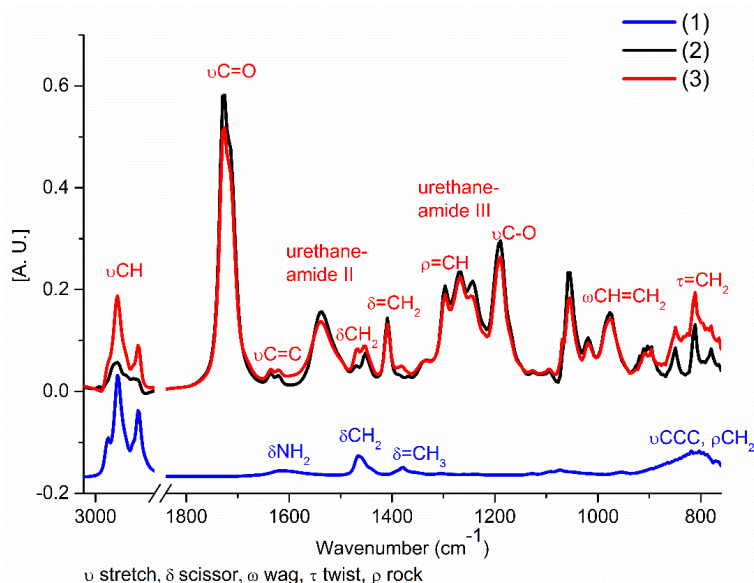
Figure 7-10. FT-IR spectra recorded for (1) neat *n*-octylamine and the reaction of 1 eq. of monomer 14 with 1.1 eq. of *n*-octylamine at a monomer concentration of 0.5 M in THF, at room temperature and under air atmosphere: (2) prior and (3) right after addition of *n*-octylamine.

Table 7-3. Observed vibrational frequencies (cm^{-1}) and spectral assignments for the reaction of 1 eq. of monomer 14 with 1.1 eq. of *n*-octylamine in THF.

Monomer 14 Wavenumber (cm^{-1})	Assignment[a]	*n*-Octylamine Wavenumber (cm^{-1})	Assignment[a]
1727-1713	ν(C=O) urethane, acrylate and thiolactone	1600	NH$_2$ symmetric deformation
1636, 1620	ν(C=C)	1465	CH$_2$ deformation
1537	urethane-amide II	1377	CH$_3$ deformation
1468, 1452	δ(CH$_2$)	910-700	CCC stretch, CH$_2$ rock, NH$_2$ wag
1409	δ(=CH$_2$)		
1380	δ(CH$_3$)		
1296, 1267	ρ(=CH)		
1244	urethane-amide III		
1187	ν(C-O)		
975	ω(CH=CH$_2$)		
810	τ(=CH$_2$)		

Formed polymer Wavenumber (cm^{-1})	Assignment[a]
1731	ν(C=O) (urethane & ester)
1680	amide I (νC=O, νC-N) of the amide bond formed
1537	amide II (δN-H, νC-N) of urethane and the amide formed
1240	amide III of urethane and the amide formed

ν stretch, δ scissor, ω wag, τ twist, ρ rock

[a] Assignments from reported vibrational studies[39-44] were compared to assign the bands observed in the experimental spectra.

Due to the overlapping of the urethane, acrylate and thiolactone C=O vibration bands, the thiolactone ring-opening of **14** (accompanied by amide bond formation) was followed by the intensity of the amide I vibrational band at 1680 cm^{-1}, whereas the conversion of the acrylate double bond was monitored by the scissoring acrylate vibration at 1409 cm^{-1}. Deconvolution and curve fitting of the spectra in the region of 1800-1380 cm^{-1} were performed in a similar manner to that for the model reactions (*i.e.* the reaction of *n*-butyl acrylate and γ-thiobutyrolactone and *n*-propylamine), in which curve fits were performed separately for each reagent and the final product and eventually for the reaction mixture at a certain reaction time.

The fit parameters (frequency, FWHH and contour shape) of the vibrations corresponding to the thiolactone and acrylate moieties of the monomer **14** were fitted based on the fit values of the *n*-butyl acrylate and γ-thiobutyrolactone model compounds. The fit parameters obtained from the fitting of the starting monomer and final polymer product were fixed during the fitting procedure. Table 7-4 shows the assignments and curve fit parameters of the deconvoluted bands. Examples of the fit results are shown in Figure 7-12. The areas of the deconvoluted amide I bands at 1682 and 1636 cm^{-1} and the scissoring acrylate vibration at 1409 cm^{-1} were chosen for estimation of the reaction conversions because these bands are well separated from the others, giving the most reliable fit values. However, it should be noted that there could be a certain error, although expected to be not significant, for the use of the area sum of the two fitted amide I bands as a measure for the amide group formation, due to possible different absorption coefficients of these bands as well as possible change in their content ratio during the reaction.
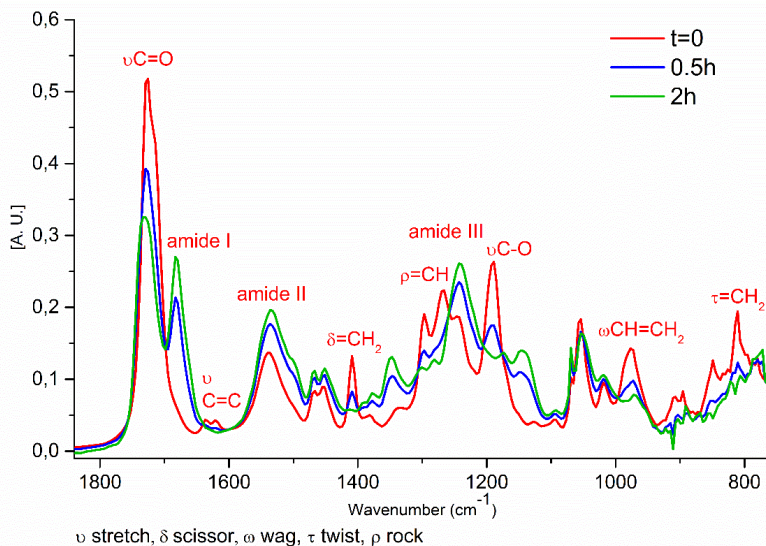
Figure 7-11. FT-IR spectra as a function of reaction time recorded for the reaction of 1 eq. of monomer 14 with 1.1 eq. of *n*-octylamine at a monomer concentration of 0.5M in THF, at room temperature and under air atmosphere.

Table 7-4. Band assignments and curve fit parameters of the FT-IR spectra in the spectral region of 1800-1380 cm^{-1} for the reaction of 1 eq. of the monomer 14 with 1.1 eq. of *n*-octylamine in THF.

Vibration	Frequency (FWHH[b], Contour Shape) cm^{-1} (cm^{-1}, f$_G$)
vC=O (ester of product)	1740 (17, 0.60)
vC=O (urethane)	1729 (19, 0.43)
vC=O (acrylate)	1728 (16, 0.40)
vC=O (ester of product)	1718 (15, 1)
vC=O (thiolactone)	1714 (16, 0.44)
vC=O (more strongly H-bonded, urethane and thiolactone)	1705-1704 (19-21, 0.7)
Amide I (product)	1682 (20, 1)
Amide I (more strongly H-bonded, product)	1666 (25, 0.61)
vC=C (acrylate)	1635 (10, 1)
vC=C (acrylate)	1621 (11, 1)
δNH$_2$ (*n*-octylamine)	1600 (66, 1)
Amide II[a] (urethane and amide bond formed in the product)	1537 (42, 1)
Amide II[a] (more strongly H-bonded)	1500 (30, 1)
δ(CH$_2$)	1469 (10-11, 1)
δ(CH$_2$)	1453 (22-27, 0.75)
δ(=CH$_2$)	1409 (11, 0.15)
δ(CH$_3$)	1380-1382 (18-22, 1)

[a] **The amide II vibration is contributed by both the urethane vibration and the amide bond formed as a result of the thiolactone ring-opening, but for simplicity is deconvoluted as one sum-band.** [b] **FWHH = Full Width at Half-Height.**
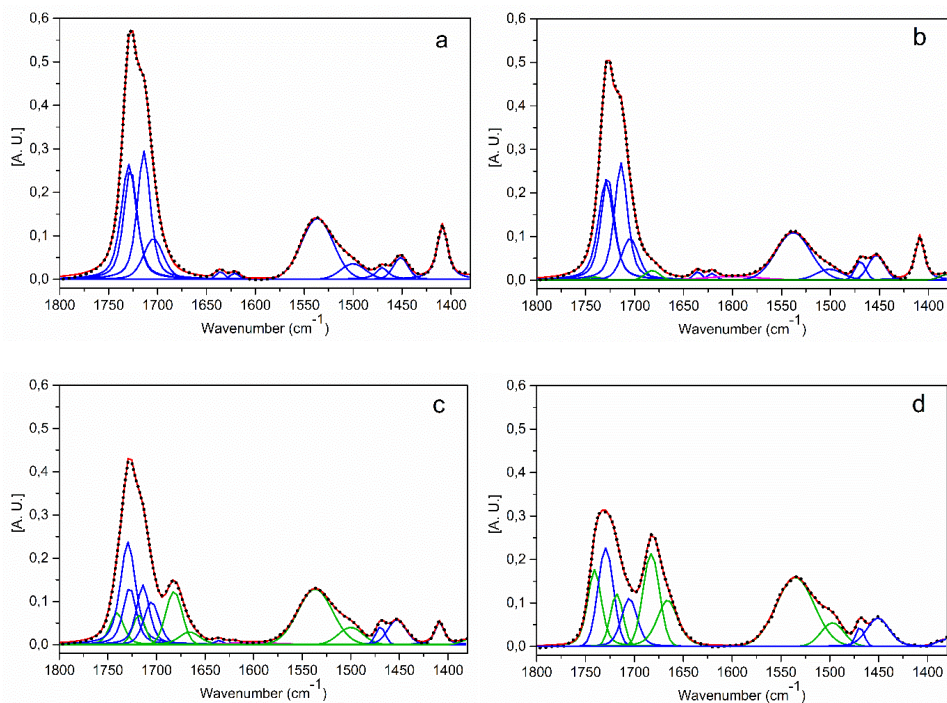
Figure 7-12. Curve fits of the FT-IR spectra measured in THF of (a) monomer 14, and of [monomer 14 + *n*-octylamine] reaction mixture at (b) t = 0, (c) t = 15 min, and (d) the polymer product at t = 3 h. Reaction conditions: 1 eq. of monomer 14, 1.1 eq. of *n*-octylamine, monomer concentration of 0.5 M, room temperature. The solid lines represent the fitted curves, while the dotted lines represent the measured spectra. In colors, blue: monomer 14, pink: *n*-octylamine, green: product, red: fitted sum spectra, and dotted black: measured spectra. See Table 7-4 for deconvoluted band positions and assignments and curve fit parameters.

In conclusion, a good agreement between the measured and deconvoluted band intensities was observed (Figure 7-13). Although the acrylate is mostly consumed after 3 h, only low-molecular weight polymer could be isolated from the reaction mixture. On the other hand, integration of the acrylate end-group in the ^{1}H-NMR spectrum of the polymer **18** after 24 h reaction time allowed for the determination of the DP (~ 33) and M_n (~ 15.5 kDa) (Scheme 7-9).

Figure 7-13. Online monitoring of amine-thiol-ene conjugation (aminolysis and polyaddition) between octylamine and AB'-monomer 14; (a) 3D FT-IR waterfall plot of (C=O)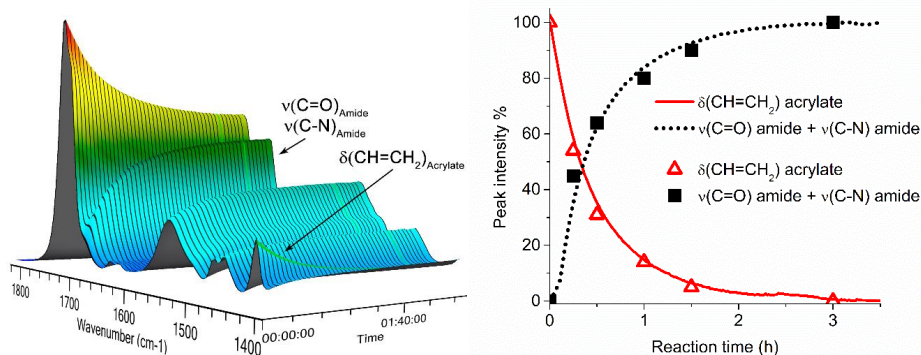 stretch absorption bands (1830 – 1360 cm^{-1}) and (b) IR peak intensities as a function of time (kinetic curves and deconvoluted data points).

7.4.3. Functionalized polyurethanes

Variation of the amine allows for the modular synthesis of functionalized polyurethanes. The proposed one-pot amine-thiol-ene conjugation has the advantage that any desired functionality can be introduced to the polymer, while all reaction partners are present from the start. The optimized conditions were applied as a general protocol for other (functional) amines as shown in Table 7-5.

Table 7-5. Obtained molecular weight and dispersity by amine-thiol-ene reaction between (combined) primary amines and AB'-monomer 14.

Entry[a]	Amine	M_n[b] (kDa)	M_w[b] (kDa)	Đ[b]	Ratio (Amine I / Amine II)[c]
1	*n*-Octylamine	12.0	20.3	1.69	-
2	Allylamine	5.3	8.7	1.63	-
3	Propargylamine	1.9	3.1	1.63	-
4	Furfurylamine	9.5	15.4	1.62	-
5	*N,N*-Dimethylethylene diamine	3.2	4.9	1.53	-
6	3-Morpholinepropylamine	7.6	13.0	1.73	-
7	*n*-Octylamine / *N,N*-Dimethylethylene diamine	8.8	14.7	1.67	49 / 51
8	Allylamine / Glycine t-butylester	6.8	11.4	1.67	72 / 28
9	Allylamine / Furfurylamine	8.4	13.0	1.54	58 / 42

[a] **Reaction conditions: entries 1 → 6; monomer 14 in THF (0.5 M) at room temperature for 24 h in the presence of 1.1 eq. of amine; entries 7, 8 and 9; monomer 14 in THF (0.5 M) at room temperature for 24 h in the presence of 2 eq. of amine (1 eq. amine I and 1 eq. amine II);**
[b] **SEC, calibrated with PMMA standards, DMA as eluent (Figure S 17)**
[c] **Calculated from the integration of signals, specific for each individual amine, in the ^{1}H-NMR spectrum.**

Of particular interest is the possibility to introduce double and triple bonds and reactive dienes (furan) without interference with the polymerization process (*entries 2*, *3* and *4*; Table 7-5). This renders the polymers accessible for further modification, without a protection and deprotection strategy being necessary. Other functionalities that were tested include a tertiary amine (*entry 5*) and a morpholine moiety (*entry 6*), enabling the synthesis of metal-complexing polymers.[45-47] The presented strategy thus offers an easy-to-perform, one-pot method for the synthesis of functionalized PUs. Mixing the two ingredients (monomer **14** and the selected amine) at room temperature without any additive or external trigger gives indeed access to a library of these polymers (Table 7-5). The values of the dispersities (Đ) are lower than theoretically expected (Đ = 2), because purification *via* precipitation removes a lower molecular weight fraction of the polymer.

MALDI-TOF analysis of a narrow-disperse fraction of allyl-functionalized polymer (Table 7-5, *entry 2*) confirms the structural build-up of the PUs and elucidates the nature of the end-groups (Figure 7-15). Preparative size-exclusion chromatography was performed to obtain this narrow-disperse fraction. The SEC-traces before and after preparative SEC are shown in Figure 7-14.
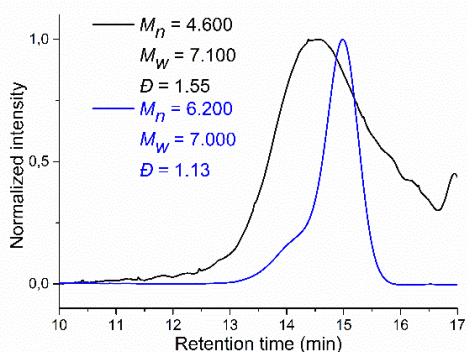
Figure 7-14. SEC traces (THF as eluent) of allyl-containing PU (Table 1, entry 2) before (black trace) and after (blue trace) preparative SEC. The narrow-disperse fraction was subsequently analyzed by MALDI-TOF.

In the MALDI-TOF spectrum, two series of signals can be readily assigned: the major distribution of peaks represents telechelic material bearing an acrylate and thiolactone entity as end-groups (Series I Major, Figure 7-15) and a second minor series attributed to the corresponding thiol-acrylates (Series II Minor, Figure 7-15). In both series, signals repeat each 398 Da, *i.e.* the sum of the molecular weight of allylamine and monomer **14**. The minor series is shifted by 57 Da, exactly the molecular weight of allylamine. This MALDI-TOF analysis clearly demonstrates that there were no significant side reactions during the polymerization and confirms that the aminolysis is the rate-determining step.

Series I *Major*
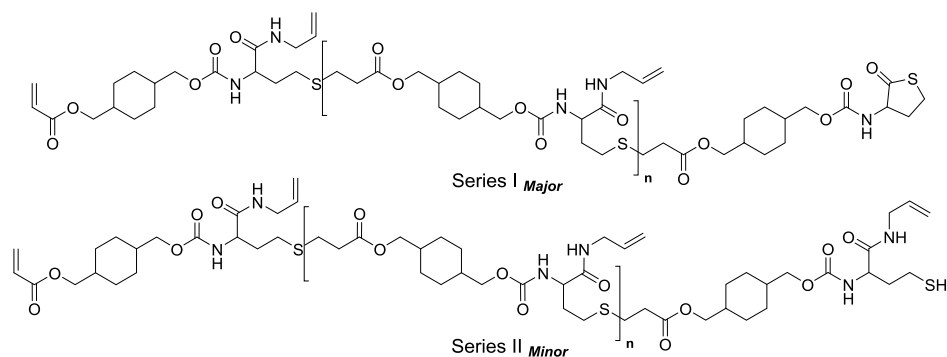
Series II *Minor*

	Series I *Major* [K-adduct]		Series II *Minor* [K-adduct]	
n	calc.	exp.	calc.	exp.
5	2769.22	2768.37	2826.28	2826.19
6	3167.41	3167.38	3224.46	3223.83
7	3565.59	3565.90	3622.65	3622.22
8	3963.78	3962.79	4020.84	4020.61
9	4361.97	4360.83	4419.03	4419.60
10	4760.16	4759.22	4817.21	4817.23
11	5158.34	5158.45	5215.40	5215.04
12	5556.53	5555.36	5613.59	5613.48
13	5954.72	5954.50	6011.78	--
14	6352.91	6353.29	6409.96	--
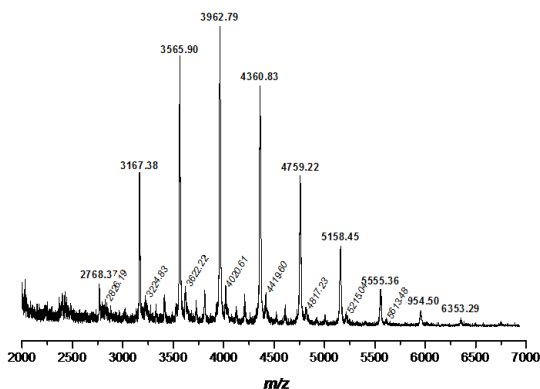
Figure 7-15. MALDI-TOF analysis of the allyl-functionalized PU (Table 7-5, entry 2) including peak assignment.

To extend the potential of this methodology and to demonstrate its versatility, experiments have been performed utilizing more than one amine, enabling the random incorporation of multiple functionalities. Reaction conditions were similar, except for the use of 2 eq. of amine (1 eq. of each amine compared to monomer **14**). The relative amount of the (functional) amines along the backbone after polymerization was calculated via integration of relevant signals in the ^{1}H NMR spectra and the values differ from the initial feed ratio. Indeed, depending on the chosen amines, the ratio of incorporation is expected to be different. Figure 7-16 shows the SEC trace (right) and ^{1}H NMR detail for the polymer (left), synthesized using a combination of *n*-octylamine and *N,N*-dimethylethylene diamine (Table 7-5, *entry 7*).

Figure 7-16. Synthesis of PUs having multiple functionalities along the backbone by treatment of monomer 14 with a combination of *n*-octylamine and *N,N*-dimethylethylene diamine (Table 7-5, *entry 7*). SEC trace (*bottom right)* and ¹H-NMR detail (CDCl₃, 500 MHz) including the integration of relevant signals determining the ratio of the incorporated amines (*bottom left*).
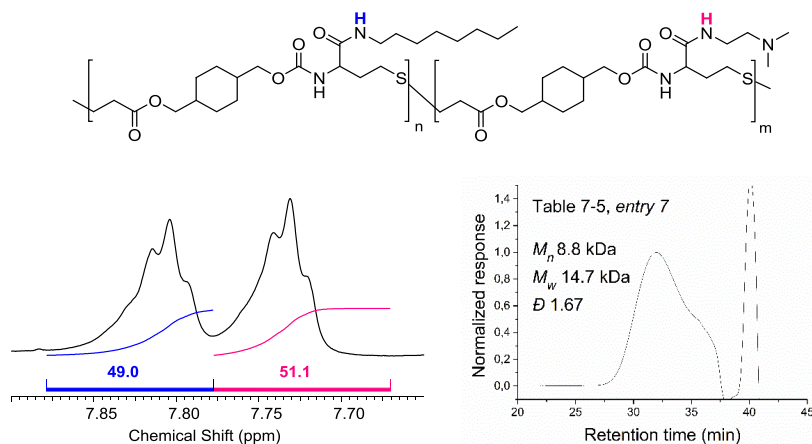
It was anticipated that the respective rates of aminolysis would have the greatest impact on the incorporation ratio. However, *entry 8* clearly demonstrates that two amines, being equally fast in the aminolysis reaction (Figure 7-2), are incorporated in different amounts. The reactivity difference between the intermediate thiol-acrylates as a result of sterical factors most likely contributes significantly to this phenomenon. Importantly, the results (*entries 7*, *8* and *9*) prove that different functionalities can be simultaneously incorporated along the PU backbone in a one-pot synthesis.

The obtained polymers (Table 7-5, *entries 1*, *2*, *4* and *9*) were thermally stable until 250 °C, measured with TGA.

7.5. POST-POLYMERIZATION MODIFICATION

Another appealing feature of this methodology is that, once the polyaddition has been completed, the reaction mixture essentially is a solution of the expected PU with a minor amount of residual amine. Post-polymerization modification of the introduced functional group (*via* the primary amine), is thus possible in the same reaction medium. Two metal-free modification reactions were examined in this context: on the one hand, the radical thiol-ene reaction between 1-octanethiol and an alkene-containing polymer and on the other hand, the Diels-Alder reaction between *N*-methylmaleimide and a furan-containing polymer. Both polymers were synthesized by treatment of monomer **14** with allylamine (Table 7-5, *entry 2*) and, allylamine and furfurylamine (Table 7-5, *entry 9*), respectively. The

disappearance of the distinct signals in the ^{1}H-NMR spectra and the apparent shift of the SEC traces indeed confirm the successful outcome of both modification reactions (Figure 7-17 shows the analyses for the thiol-ene modification, Figure 7-18 shows the ^{1}H-NMR analysis before after DA modification).
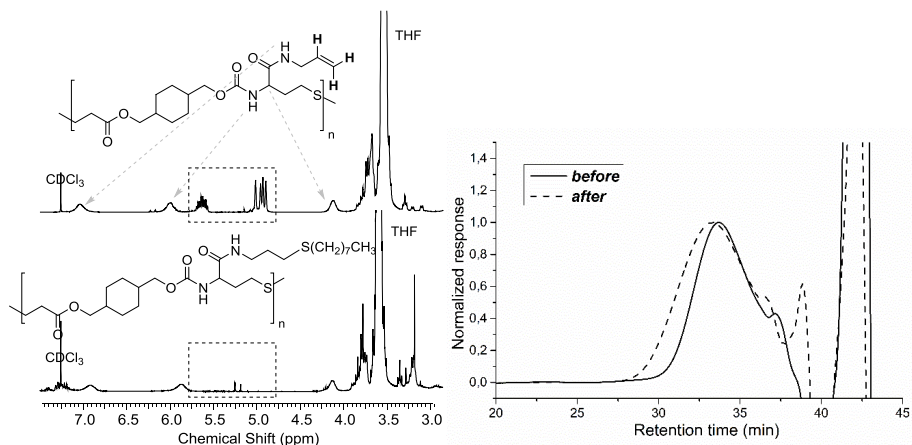
Figure 7-17. Post-polymerization modification in the same medium of the allyl-containing PUs by radical thiol-ene conjugation with 1-octanethiol. (Left) Details of ^{1}H-NMR spectra (CDCl$_3$, 300 MHz) after poly-addition (*top*) and after subsequent thiol-ene modification (*bottom*) (Right) Corresponding SEC traces of reaction samples before and after thiol-ene modification.

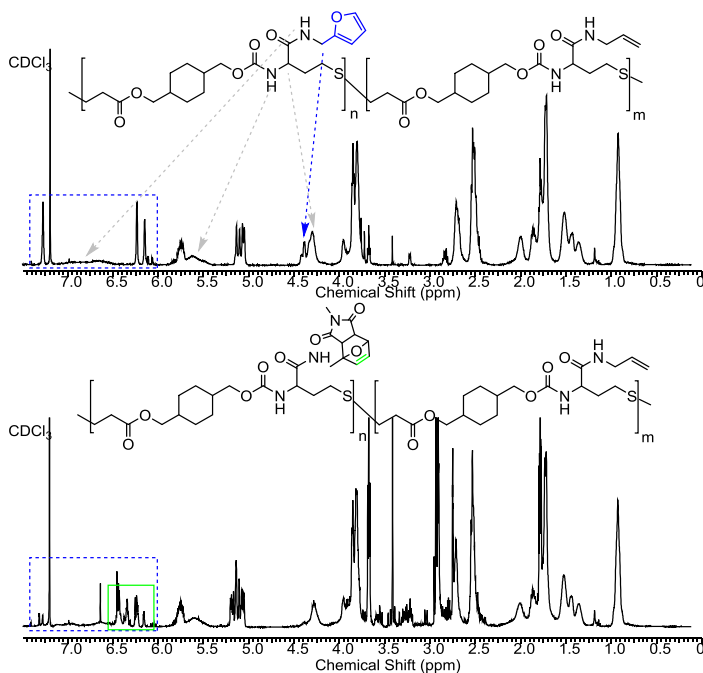**Figure 7-18. 1H NMR spectra (CDCl3, 500 MHz) before (*top*) and after (*bottom*) the post-polymerization modification in the same medium of the furfuryl-containing PUs by Diels-Alder reaction with *N*-methylmaleimide.**

7.6. POLYMER NETWORKS

By adding a cross-linker to a solution of monomer **14**, it is also possible to obtain polyurethane networks. The most important difference in the network formation, compared to the polymer networks described in chapter 3 and chapter 4, is the absence of radicals. The trigger for polymerization, and hence network formation, is the addition of a difunctional amine. An evident advantage is the fact that no additives have to be incorporated in the formulation. Interestingly, addition of a functional amine, together with the cross-linker, can yield functionalized polyurethane networks.
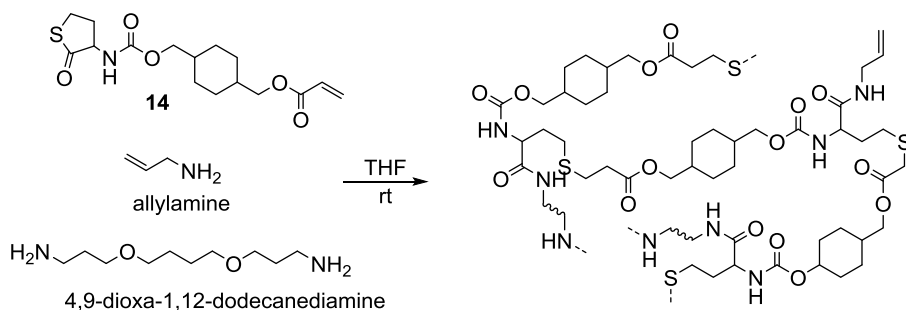
Scheme 7-10. Reaction scheme for the network formation, using allylamine as functional amine and 4,9-dioxa-1,12-dodecanediamine as cross-linker.

Polymer networks were obtained using allylamine as functional amine and 4,9-dioxa-1,12-dodecanediamine as a cross-linker. The components were mixed in a minimal amount of THF and injected between two glass plates separated from each other with a silicon spacer. After reaction, unreacted species were removed by Soxhlet extraction with chloroform. The mechanical properties of the networks were qualitatively evaluated through manual deformation and were of good mechanical quality when 50% or more cross-linker was used. Below that amount, the polymer films were sticky and fragile. The soluble fraction of the networks and their degree of swelling are presented in Table 7-6.

Table 7-6. Overview of the performed gravimetrical analyses to determine the soluble fraction and the degree of swelling of the different polymer networks. Used cross-linker: 4,9-dioxa-1,12-dodecanediamine.

Monomer	Functional amine	Cross-linker fraction (%)	Soluble fraction (%)[a]	Degree of swelling[b]
13	Propargylamine	50	32	125
13	/	100	3	90
14	Allylamine	50	12	100
14	/	100	8	85

[a] Gravimetrically determined through soxhlet extraction (8 hours) in chloroform
[b] Gravimetrically determined after swelling in chloroform (0.5 hours)

Chemical analysis of the polymer networks was possible using HR-MAS ^{1}H-NMR analysis. Figure 7-19 shows the ^{1}H-NMR spectra of the polymeric network, based on monomer **14**, functionalized with allylamine and for comparison reasons, the linear polymer also functionalized with allylamine (Table 7-5, *Entry 2*). The relevant peaks (double bond, urethane, amide), proving functionalization, are assigned. A rough estimation of the degree of functionalization is possible through the integration of the double bond protons compared to a signal of the polymer main chain. About 50 % of the amides is originating from allylamine, while the other 50 % is explained through cross-linking. Interestingly, monomer **13** was applicable for the formation of (functionalized) polymer networks (Table 7-6, *Entry 1 and 2*), whereas for the linear polymers, only low-molecular weight products could be isolated due to early precipitation during the reaction. Here, propargylamine was used to demonstrate the possibility to incorporate functionality.
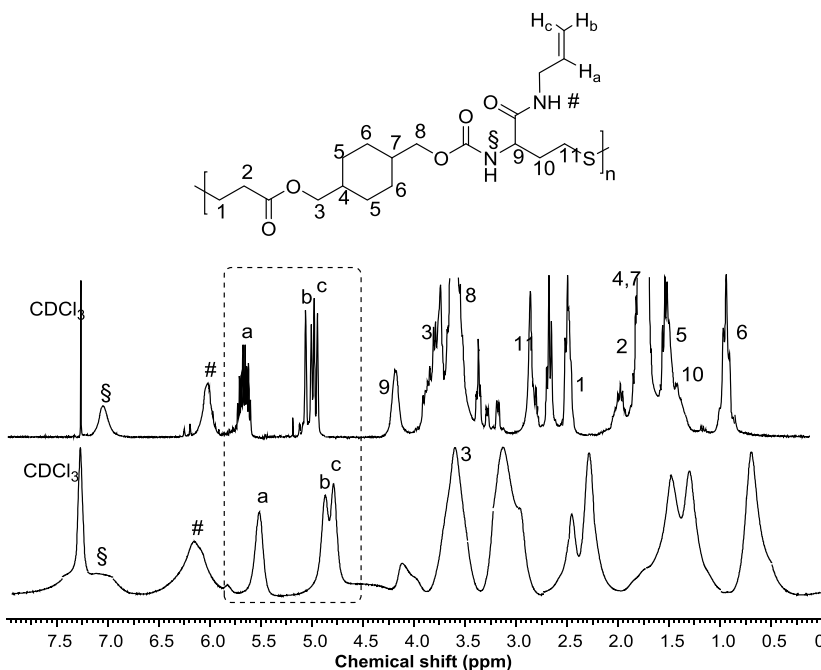

Figure 7-19. ^{1}H NMR spectra of polymer (top) and the HR-MAS ^{1}H spectrum of polymer network (bottom), in both cases using allylamine as a functional amine.

7.7. CONCLUSIONS

In conclusion, a straightforward procedure for the synthesis of functionalized PUs has been developed based on the nucleophilic amine-thiol-ene conjugation. Initial model studies, monitored via *online* IR, demonstrated that the aminolysis of a thiolactone in the presence of an equal amount of acrylate is a clean and atom-efficient two-step, one-pot conjugation reaction. This important observation encouraged us to explore this concept for the synthesis of functionalized PUs. After the large-scale synthesis of AB'-monomers, containing both an acrylate and a thiolactone moiety, several (functional) amines were employed to open the thiolactone group in the AB'-monomer. The resulting intermediate thiol-acrylate reacts *in situ* via Michael addition. This highly convenient procedure enabled the preparation of various (multi-) functionalized PUs. SEC-, NMR- and MALDI-TOF-analysis confirmed the structure of the PUs. The reaction does not require any additive or external trigger and proceeds at ambient conditions. As the obtained polymers remained soluble in the reaction mixture, the introduced functional groups (*e.g.* double bond or furan) served as functional handles for further tailoring through efficient post-polymerization modification in the same pot. Due to all these remarkable features, the nucleophilic amine-thiol-ene conjugation based on thiolactones is considered to be a powerful and elegant accelerated protocol for the synthesis and modification of functionalized materials. Therefore, its use is given the full attention in our laboratory and research towards functionalized coatings based on this concept is in progress.

7.8. EXPERIMENTAL SECTION

7.8.1. Materials

1,4-Cyclohexanedimethanol monoacrylate ([23117-36-4], 95 %) was kindly provided by Nippon Kasei. Glycine t-butylester ([6456-74-2], 97 %) and pyridine ([110-86-1], 99.5 %) were purchased from Alfa Aesar. Chloroform D ([865-49-6], $\geq$ 99.8 %) and DMSO-d_6 ([2206-27-1], $\geq$ 99.8 %) were purchased from Euriso-top. Jeffamine® M-600 was purchased from Huntsmann. DL-Homocysteinethiolactone hydrochloride ([6038-19-3], 99 %) and triethylamine ([121-44-8], 99 %) were purchased from Acros Organics. Allylamine ([107-11-9], $\geq$ 99 %), benzylamine ([100-46-9], $\geq$ 99.5 %), *n*-butyl acrylate ([141-32-2], $\geq$ 99 %), chloroform ([865-49-6], $\geq$ 99.8 %), dichloromethane ([75-09-2], $\geq$ 99.8 %), *N,N*-dimethylethylenediamine ([108-00-9], $\geq$ 98 %), dodecane ([112-40-3], $\geq$ 99 %), furfurylamine ([617-89-0], $\geq$ 99 %), diethylether ([60-29-7], $\geq$ 99.9 %), 2-hydroxyethylacrylate ([818-61-1], 96 %), isooctyl 3-mercaptopropionate (IoMP, [30374-01-7], $\geq$ 99 %), *N*-methylmaleimide ([930-88-1], $\geq$ 99.0 %), 3-morpholinopropylamine ([123-00-2], > 98 %), 1-octanethiol ([111-88-6], $\geq$ 98.5 %), *n*-octylamine ([111-86-4], 99 %), pentaerythritol tetrakis(3-mercaptopropionate) ([7575-23-7], > 95 %), phosgene ([75-44-5], ~ 20 % solution in toluene), propargylamine ([2450-71-7], 98 %), *n*-propylamine ([107-10-8], $\geq$ 99 %), tetrahydrofuran ([109-99-9], $\geq$ 99 %) and γ-thiobutyrolactone ([1003-10-7], 98 %) were purchased from Sigma-Aldrich and used without purification. Solvents (CH$_2$Cl$_2$ and pyridine) for the monomer synthesis were distilled from CaH$_2$ prior to use. Silicagel (ROCC, SI 1721, 60 Å, 40 – 63 μm) was used to perform preparative column chromatography, eluting with technical solvents. The collected fractions were analyzed by thin layer chromatography (TLC-plates, Macherey-Nagel, SIL G-25 UV$_{254}$).

7.8.2. Methods

^{1}H- and ^{13}C-NMR (Attached Proton Test, APT) spectra were recorded in CDCl$_3$ on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz. Chemical shifts are presented in parts per million (δ) relative to CHCl$_3$ (7.26 ppm in ^{1}H- and 77.23 ppm in ^{13}C-NMR respectively) or DMSO-d_6 (2.50 ppm in ^{1}H- and 39.51 ppm in ^{13}C-NMR respectively) as internal standard. Coupling constants (*J*) in ^{1}H-NMR are given in Hz. The resonance multiplicities are described as *d* (doublet) or *m* (multiplet).

An Agilent technologies 1100 series LC/MSD system equipped with a diode array detector and single quad MS detector (VL) with an electrospray source (ESI-MS) was used for classic reversed phase *LC-MS (liquid chromatography mass spectroscopy) and MS analysis*. Analytic reversed phase HPLC was

performed with a Phenomenex C_{18} (2) column (5 μ, 250 x 4.6 mm) using a solvent gradient (0 → 100% acetonitrile in H_2O in 15 min) and the eluting compounds were detected *via* UV-detection (λ = 214 nm).

High resolution mass spectra (HRMS) were collected using an Agilent 6220 Accurate-Mass time-of-flight (TOF) equipped with a multimode ionization (MMI) source.

Time-resolved *online ATR FT-IR* spectra were recorded on a React-IR 4000 Instrument (Mettler Toledo AutoChem ReactIR) equipped with a silicon ATR probe (SiComp, optical range 4400–650 cm^{-1}). For *online* monitoring, the silicon probe was introduced into a two-necked glass flask containing the reaction mixture and spectra were recorded every minute. The solvent spectrum was recorded at the reaction temperature and subtracted to enhance the signal of the reaction species. Curve-fittings of FT-IR spectra were performed using Bruker OPUS software (version 4.2). The parameters were optimized using a Levenberg–Marquardt algorithm.[48]

FT-ATR-IR spectra were recorded on a Perkin-Elmer Spectrum1000 FTIR infrared spectrometer with pike-HATR module.

GC-FID analyses were performed using a Hewlett Packard 5890 series II equipped with a Restek XTI-5 capillary column (30 mm x 0.25 mm, 0.25 μm film thickness of 5 % diphenyl and 95 % PDMS). The carrier gas (H_2) was used at a flow rate of 1.4 mL/min. After sample injection, the column oven was kept at 50 °C for 3 min, then heated until 240 °C at a rate of 20 °C/min and finally kept at 240 °C for 5 min.

Size Exclusion Chromatography (SEC) was performed using two different systems: (i) a Waters instrument, with a refractive-index (RI) detector (2414 Waters), equipped with 3 Polymer Standards Services SEC serial columns (1 X GRAM Analytical 30 Å, 10 μm and 2 x GRAM Analytical 1000 Å, 10 μm) at 35 °C. Poly(methyl methacrylate) (PMMA) standards were used for calibration and *N,N*-dimethylacetamide (DMA), containing LiBr (0.42 g/mL) was used as a solvent at a flow rate of 1 mL/min. Molar mass and dispersity were determined using the Empower software; (ii) a Varian PLSEC50plus instrument, using a refractive index detector, equipped with two Plgel 5 μm MIXED-D columns 40 °C. Polystyrene standards were used for calibration and THF as eluent at a flow rate of 1 mL/min. Samples were injected using a PL AS RT autosampler.

The preparative SEC setup consists of a Shimadzu LC-2OAT pump, a Shimadzu SIL-IOAF autosampler, a RID-IOA Differential Refractive Index Detector, a FRC-1OA Fraction Collector, CBM-2OA PC Interface/System Controller. Columns are from Shodex: a K-LG guard column and a KF-2004 prep column (elution 2.5 mL/min, THF, rt).

MALDI-TOF (Matrix-Assisted Laser Desorption and Ionization Time of Flight) mass spectrometry analysis was performed on an Applied Biosystems Voyager-DE STR instrument equipped with nitrogen

laser operating at 337 nm, pulsed ion extraction source and reflectron detector. The laser pulse width is 3 ns and maximum power is 20 Hz. Spectra were recorded in the linear mode with an acceleration voltage of 19 kV and delay of 100 ns. 100 single shot acquisitions were summed to give the spectra and the data were analyzed using Data Explorer and Polymerix software. Samples were prepared by dissolving the matrix dithranol in the solvent (THF, 20 mg/mL), mixing with the polymer (1 mg/mL) and potassium trifluoroacetate in acetone (15 mg/mL) that has been used as cationizing agent.

Thermogravimetric analysis (TGA) was performed with a Mettler Toledo TGA/SDTA851e instrument under air atmosphere at a heating rate of 10 °C/min from 25 to 800 °C. All curves are blank corrected (run with an empty pan under the same conditions).

7.8.3. Monomer synthesis
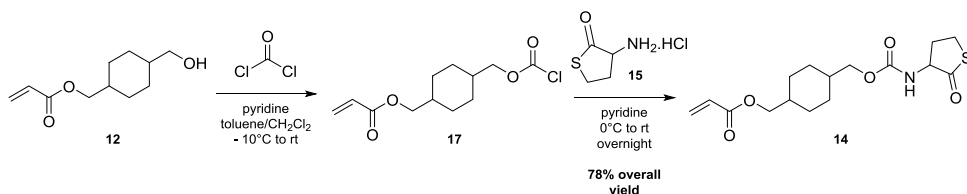
Scheme 7-11. One-pot two-step synthesis of the AB' monomer 14 from 1,4-cyclohexanedimethanol monoacrylate 12.

1, 4 – Cyclohexanedimethanol monoacrylate **12** (mixture of *cis/trans* isomers, ratio 18/82, 33.368 g, 167.8 mmol) was dried by azeotropic distillation in the presence of toluene, subsequently dissolved in CH_2Cl_2 (100 mL) and pyridine (13.54 mL, 167.8 mmol). In a well-vented fume-hood, a solution of phosgene (~ 20 % in toluene, 100.0 mL, 193 mmol) was diluted with CH_2Cl_2 (100 mL) in a 3-neck 1-L flask and cooled to -10 °C. The solution of 1, 4 – cyclohexanedimethanol monoacrylate **12** was then added dropwise to the phosgene solution, while maintaining the reaction temperature below 0 °C. A white precipitate was formed during the addition and afterwards, the reaction was allowed to reach room temperature within the next 2 h. The excess of phosgene was removed by bubbling argon through the reaction mixture (the outlet was passed through a saturated solution of $NaHCO_3$ to quench the unreacted phosgene). The solution of the formed chloroformate **17** was cooled to 0 °C and treated with pyridine (27.08 mL, 335.6 mmol) and DL-homocysteinethiolactone hydrochloride **15** (25.780 g, 167.8 mmol). The reaction mixture was allowed to reach room temperature overnight. The brown mixture was evaporated in the presence of 200 mL silicagel to dryness and directly purified by column chromatography (gradient elution: 100 % CH_2Cl_2 → CH_2Cl_2 / acetone: 95 / 5). The slightly coloured

fractions were concentrated, redissolved in a minimal amount of CH_2Cl_2 and precipitated in iso-octane, yielding the AB'-monomer **14** as a white solid with an overall yield of 78 % (45.10 g).

$C_{16}H_{23}NO_5S$ (341.4); **m/z (ESI-MS)** 342.1 [M+H]$^+$.

HRMS: [M+H]$^+$ Expected 342.1370, Found 342.1371; [M+NH$_4$]$^+$ Expected 359.1635, Found 359.1636.

^{1}H-NMR (500 MHz, CDCl$_3$, ppm) δ 6.38 (*dd*, 1H, 17.4, 1.5 Hz), 6.11(*dd*, 1H, 17.4, 10.5 Hz), 5.81 (*dd*, 1H, 10.4, 1.5 Hz), 5.14 (*br s*, 1H), 4.31 (*m*, 1H), 4.06$_{cis}$/3.97$_{trans}$ (*d*, 2H, 7.2$_{cis}$ / 6.5$_{trans}$ Hz), 4.01$_{cis}$/3.91$_{trans}$ (*m*, 2H), 3.33 (*ddd*, 1H, 12.1, 11.5, 5.1 Hz), 3.23 (*ddd*, 1H, 11.4, 7.0, 1.1 Hz), 2.87 (*m*, 1H), 2.00 (*m*, 1H), 1.83$_{cis}$/1.61$_{trans}$ (*m*, 2H), 1.81$_{trans}$/1.52$_{cis}$ (*m*, 4H), 1.42$_{cis}$/1.00$_{trans}$ (*m*, 4H).

^{13}C-NMR (125 MHz, DMSO-d_6, ppm) δ 205.6 (C), 165.5 (C), 156.2 (C), 131.4 (CH$_2$), 128.5$_{trans}$ / 128.4$_{cis}$ (CH), 68.9 (CH$_2$), 68.7$_{trans}$/66.7$_{cis}$ (CH$_2$), 59.8 (CH), 37.0$_{trans}$/34.3$_{cis}$ (CH), 36.6$_{trans}$/34.1$_{cis}$ (CH), 29.79 (CH$_2$), 28.2$_{trans}$/24.7$_{cis}$ (4 x CH$_2$), 26.32 (CH$_2$).

7.8.4. Polymerization: general protocol

The monomer **14** (341 mg, 1.0 mmol) was dissolved in THF (2.0 mL). The primary amine (1.1 mmol) was added at room temperature and the clear reaction mixture was stirred for 24 h at ambient conditions. The polymer was collected by precipitation in cold diethyl ether, washed with cold diethyl ether and cold methanol and dried prior to analysis.
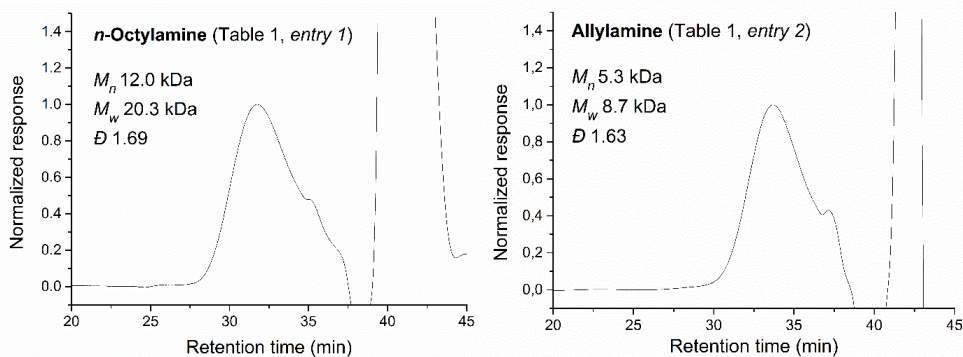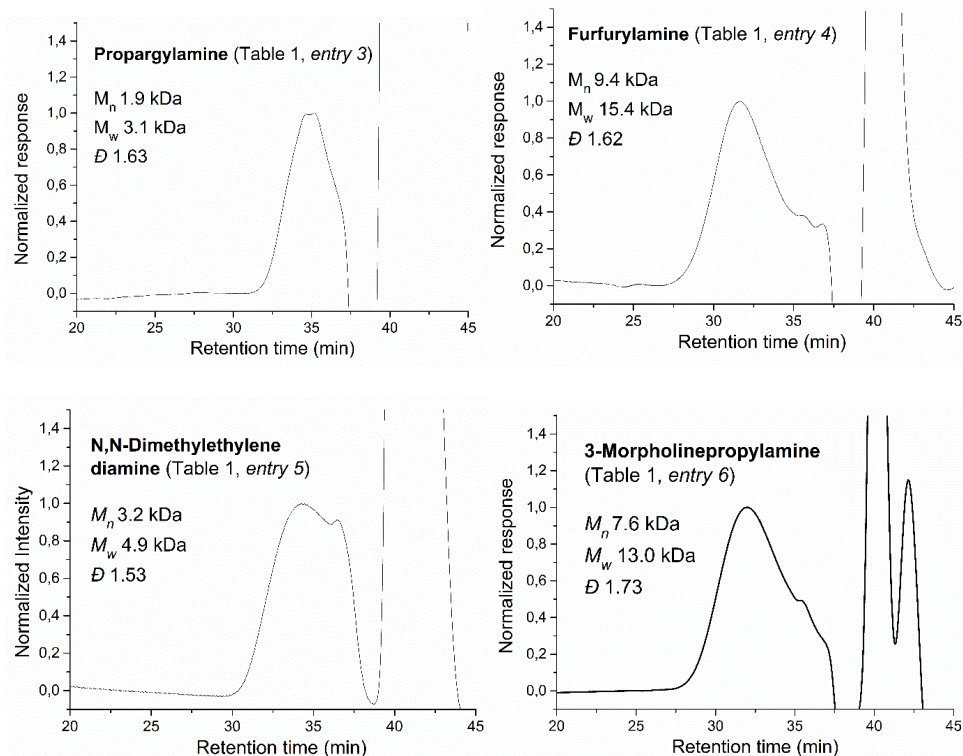
Figure 7-20. SEC traces and distribution analysis of the obtained polymers via treatment of monomer 14 with six primary amines (Table 7-5, entries 1→ 6).

7.8.5. Post-polymerization modification

7.8.5.1. Thiol-ene modification of allyl-containing PU

Monomer 14 (0.5 mmol; 170.7 mg) was dissolved in THF (1.0 mL). Allylamine (0.55 mmol; 0.038 mL) was added and the reaction mixture was stirred at room temperature for 24 h. A sample was taken from the clear reaction mixture for SEC- and ^{1}H-NMR-analysis. Consequently, thiol-ene modification was performed in the same pot by adding 1-octanethiol (1.0 mmol, 0.180 mL) and DMPA (0.04 mmol, 10.0 mg) as photo-initiator and irradiating UV-light (365 nm) for 5 h. Again, a sample was taken from the clear reaction mixture for SEC- and ^{1}H-NMR-analysis.

7.8.5.2. Furan-maleimide modification of furan-containing PU

Monomer 14 (1.0 mmol; 341.42 mg) was dissolved in THF (2.0 mL). Furfurylamine (1.0 mmol; 0.088 mL) and allylamine (1.0 mmol; 0.075 mL) were added and the reaction mixture was stirred at room temperature for 24 h. 500 µL was taken out of the reaction mixture and precipitated in 5 mL cold

Et$_2$O. The precipitate was then washed with cold MeOH (3 x 10 mL) and dried under vacuum. The purified sample was analyzed by SEC- and ^{1}H-NMR.

To the remaining 1.5 mL, *N*-methylmaleimide (1.5 mmol; 166.7 mg) was added. The reaction mixture was stirred at 50 °C for 5 h. 500 µL was again taken out of the reaction mixture and was precipitated in 5 mL cold Et$_2$O. The yellow precipitate was washed with cold MeOH (3 x 5 mL) and then dried under vacuum. The purified sample was analyzed by SEC- and ^{1}H-NMR.

7.8.6. Synthesis of polymer networks

Monomer **13** (0.5 mmol, 170.71 mg) was dissolved in 1mL THF. Propargylamine and 4,9-dioxa-1,12-dodecanediamine were added in different ratios (20 to 100% cross-linker). The reaction mixture was injected between two glass plates separated by a silicone spacer. After 24 hours, a cross-linked polymer film was removed and purified *via* soxhlet extraction with chloroform as eluent for 8 hours. The same procedure was applied for monomer **14**, using allylamine as functional amine in different amounts.

7.9. REFERENCES

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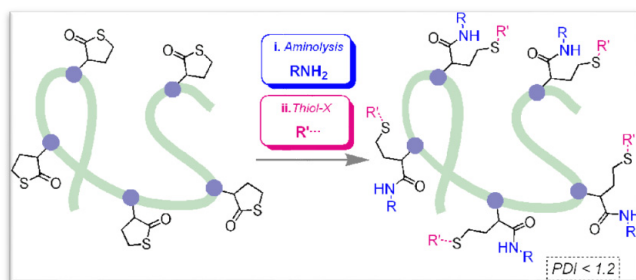
Abstract

A conceptual proof for the double modification (aminolysis and subsequent thiol-X modification) of thiolactone units, incorporated in linear polymer scaffolds, was elaborated. These polymers were prepared by either reversible addition–fragmentation chain transfer (RAFT) or nitroxide mediated radical polymerization (NMP) starting from a stable, readily available styrenic thiolactone monomer (St-TLa). Successful copolymerization of the latter with styrene (St) or methyl methacrylate (MMA) yielded linear polymers with varying thiolactone content (4–25%). Upon amine treatment, the ringopening of the pendent thiolactones resulted in the formation of linear polythiols. Different primary amines were attached to the polymer backbone, while the PDIs remained low. The resulting polythiols are versatile scaffolds for further modification by various thiol-X reactions. In this respect, thiol–maleimide conjugation was used as a model reaction.

Chapter 8
Double modular modification of thiolactone-containing polymers

8.1. INTRODUCTION

While the synthetic availability of various thiol end-capped polymers has been extensively documented, reports on the synthesis of macromolecules containing multiple thiols (polythiols) on their side chains are scarce. The strong interest in the development of such multi-thiol containing polymers finds its origin in the fact that they are potential substrates for the incorporation of various chemical functionalities via a thiol-X reaction of choice. Indeed, depending on the chemical environment and eventual application, a radical or nucleophilic reaction can be selected, producing either a non-cleavable (thio-ether from thiol-ene-, thiol-bromo- or thiol-epoxide-conjugation) or a cleavable (thio-carbamate from thiol-isocyanate-conjugation) linkage. However, there are two major issues regarding linear polymers with unprotected thiols. A first drawback is the interference of free thiols in both radical[1] and anionic polymerization processes. Consequently, reported synthetic routes towards polythiols require a protection/deprotection strategy, i.e. a detrimental approach in terms of atom efficiency and overall yield. A mercapto group can be incorporated as a *p*-methoxybenzyl thioether, a benzyl thioether, a thioacetate or a trityl thioether and can be deprotected by strong acid treatment,[2, 3],[4] Na/liquid ammonia reduction,[5] and aminolysis[6, 7]. A recent contribution reports the photodeprotection of thiol protecting groups based on UV-labile 2-nitrobenzyl moieties and subsequent thiol-ene modification of the released thiols.[8] In selected cases however, polyesters with pendent thiols have been prepared either via direct enzymatic[9] or chemoselective[10] polycondensation of unprotected thiol monomers.

Secondly, it should be stressed that the hard-to-avoid oxidative cross-linking of linear polythiols impedes their more widespread use. However, the thiol-disulfide conversion is reversible and various chemical agents are used for the scission of disulfide linkages, either via a thiol exchange or a reduction. Some elegant approaches toward synthetic polythiols are based on this reversibility. For example, Tsarevsky *et al.* employed a disulfide containing difunctional methacrylate as comonomer (cross-

linker) for the preparation of degradable PMMA-based gels by atom-transfer radical polymerization (ATRP). Treatment of the networks with tri-n-butylphosphine (Bu$_3$P) yielded a relatively narrow-disperse linear polythiol.[11]

Generally, thiols are incorporated in polymeric materials in a masked state (*vide supra*). Our research interest consists of the exploration of the reactivity of a thiolactone unit as a latent thiol functionality: the thiol is released by aminolysis (ring-opening) of the thiolactone and reacts *in situ* with a double bond in the same medium (thiol-ene conjugation). Endo and co-workers reported the synthesis of functional polymers based on another latent thiol moiety: a 5-membered cyclic dithiocarbonate group was introduced in linear poly(methacrylate)s[12] and poly(norbornene)s[13] as a masked thiol functionality. Similar to thiolactones, dithiocarbonates are sensitive to aminolysis, liberating thiols along the polymer chain. However, the stability of these dithiocarbonate monomers is an issue[12] and no attempts were reported so far to assemble linear polymers containing latent thiols, using controlled radical polymerization (CRP). Moreover, in all reported attempts,[12, 13] it proved to be impossible to preserve the linear nature of the polymer chains during the aminolysis of pendent cyclic dithiocarbonates, i.e. disulfide formation resulted in (partially) cross-linked materials.

Our two-fold aim was on the one hand to introduce thiolactone units as functional handles along the backbone of a variety of linear polymers and on the other hand to find a protocol that guarantees the long-term stability of the resulting polymers. It should be emphasized that pendent thiolactones are sites along the linear backbone where a double modification/functionalization can occur: first, a wide variety of amines can be employed for the aminolysis, followed by a thiol-based reaction of choice. As undesired disulfide formation, a possible side reaction during all stages of the process, would yield ill-defined polymer structures, reaction conditions will be adapted accordingly (Scheme 8-1). Interestingly, Keul et al.[14] have used a thiolactone-containing coupler monomer in combination with a diamine, to synthesize polyamides/urethanes with thiols as functional side-groups.

As controlled radical polymerization allows for the synthesis of well defined (co)polymers with tunable molecular weight, composition and topology,[15-18] a styrenic thiolactone containing monomer was synthesized from readily available materials and its stability (shelf life) and behavior in controlled radical (co)polymerization was examined. Once introduced as side chain functionalities, these thiolactone entities served as reactive handles for double functionalization (aminolysis and thiol-X), a prime example of post-polymerization modification.
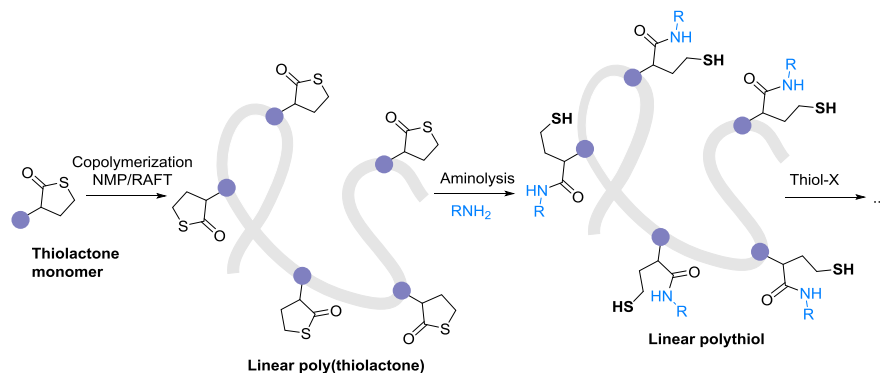
Scheme 8-1. Schematic depiction of double modification of pendent thiolactone moieties. After controlled radical copolymerization of a stable thiolactone monomer, aminolysis of the linear poly(thiolactone) yields a linear polythiol, i.e. a reactive polymer scaffold for thiol-X modification.

8.2. THIOLACTONE MONOMER SYNTHESIS: ST-TLA
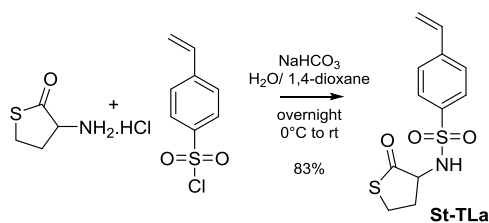
Scheme 8-2. Synthesis of styrene thiolactone monomer (St-TLa).

The synthesis of a thiolactone containing monomer started from the readily available homocysteine thiolactone hydrochloride. The most straightforward synthesis of a styrenic analogue is the reaction between homocysteine thiolactone and 4-vinylbenzenesulfonyl chloride, the corresponding sulfonyl chloride of styrene sulfonic acid. The stable sulfonamide linkage avoids unwanted detachment of the thiolactone unit during the post-polymerization modification (aminolysis and thiol-X). The one-step reaction and subsequent purification proceeded smoothly and was performed on 20 g scale, providing the styrene thiolactone monomer (St-TLa) as a white powder in 83 % yield (Scheme 8-2). The purified monomer was analyzed by LC-MS (ESI), HR-MS (ESI) and NMR (^{1}H and ^{13}C). Long-term stability of this monomer is not an issue: it is stable at room temperature without any special precautions. Moreover, ^{1}H-NMR of a solid sample of the monomer after heating for 24 h at 70 °C did not reveal any significant degradation. However, the solubility of the monomer is limited and as it is not soluble in styrene or MMA (at elevated temperature), a common solvent such as 1,4-dioxane or DMF is required for successful (co)polymerization.

Subsequently, two CRP techniques, namely RAFT [19, 20] and NMP[16], were employed as synthetic tools to obtain linear (co)polymers of the St-TLa monomer.

8.3. COPOLYMERIZATION OF STYRENE AND ST-TLA

8.3.1. RAFT Copolymerization of Styrene and St-TLa
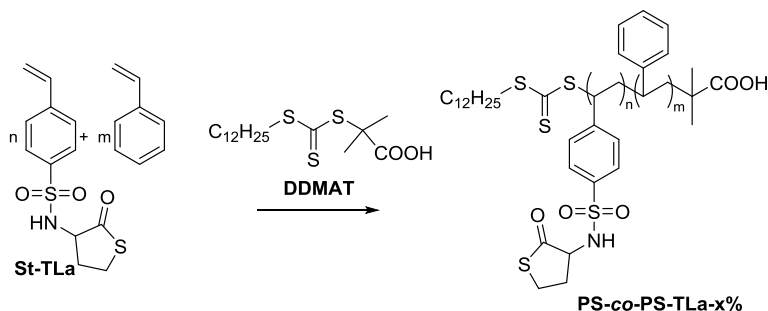
Scheme 8-3. RAFT copolymerization of styrene and St-TLa (targeted DP = 200, DDMAT/AIBN = 10, 70 °C, 12 h, molar percentage of St-TLa was varied from 0 to 20), yielding the copolymer PS-*co*-PS-TLa-x%.

RAFT polymerization has clearly demonstrated the ability to control the polymerization of a broad range of functional monomers. Considering this, the present work extends the use of a thiolactone-based styrene monomer to RAFT polymerization, allowing for the preparation of well-defined copolymers with adjustable thiolactone content, predictable molecular weights (MW) and low dispersity indices (Đ) (Scheme 8-3).

Table 8-1. Summary of the reaction conditions and results of the copolymerization of styrene and St-TLa. All experiments were performed at 70 °C, except for Entry 1 (80 °C).

Entry	$[M]_0/[CTA]_0$ /$[AIBN]_0$	Solvent, Conc/vol %	Time, h	[a]Conv., %		[b]M_n^{exp}, g.mol^{-1}	[b]Đ	St-TLa initial load, mol %	[c]St-TLa incorporated mol %
				St	St-TLa				
1	200/1/0.1	Dio[d] (7M)	6	-	19	11100	1.59	100	100
2	200/1/0.1	Dio (7M)	24	-	21	12400	1.28	100	100
3	200/1/0.1	Dio, 50	24	57	85	11700	1.10	10	13
4	200/1/0.1	Dio, 50	12	47	63	12500	1.10	20	25
5	200/1/0.1	Dio, 50	12	37	52	10800	1.10	10	13
6	200/1/0.1	Dio, 50	12	33	50	8200	1.10	5	7
7	200/1/0.1	Dio, 50	12	29	-	6400	1.09	0	-

[a] Calc. from ^{1}H-NMR, 300 MHz, CDCl$_3$; [b] SEC, THF as eluent; [c] calculated from the initial mol% load and conversion (Figure S5); [d] Dio: 1,4-dioxane.

Initially, the RAFT homopolymerization of St-TLa monomer was executed at 80 °C in anhydrous 1,4-dioxane (*Entry 1*, Table 8-1) with a lack of control as indicated by a relatively broad PDI value. On

the other hand, by lowering the temperature to 70 °C, polymers with a significantly lower Đ were obtained. However, limited conversions were achieved in both cases due to poor polymer solubility, causing an early phase separation in the reaction tube (Entry 2, Table 1). Hence, the RAFT copolymerization of styrene and styrene-thiolactone (St-TLa) was performed with various initial molar loads of St-TLa (e.g. 0, 5, 10 and 20 mol%, Table 8-1). The reactions were carried out in 1,4-dioxane, using AIBN as initiator and DDMAT as chain transfer agent (CTA), and the ratio of monomers to DDMAT to AIBN was 200:1:0.1, unless otherwise stated. A variety of reaction temperatures and solvent amounts were investigated, the optimal temperature being 70 °C with 50 vol% 1,4-dioxane.

Kinetic studies revealed a controlled polymerization process with a steady increase of both monomer conversions versus time, while the M_n of the copolymer linearly evolved with conversion, maintaining unimodal MW distributions and narrow PDI's (Figure 8-1).
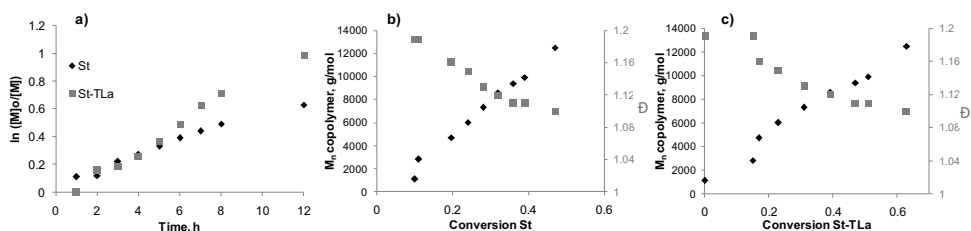

Figure 8-1. Copolymerization of styrene and St-TLa using DDMAT as CTA, at 70 °C, in 50 vol % 1,4-dioxane and with 0.1 equiv AIBN as the radical source, (St + St-TLa)/DDMAT = 200/1 (*Entry 4*, Table 8-1): straight kinetic plots (a); copolymer molecular weight and Đ evolution with monomer conversions (b and c).

In a first attempt, the homopolymerization of St was conducted and a conversion of 29 % was achieved within 12 h (*Entry 7*, Table 8-1). However, the RAFT copolymerizations utilizing St-TLa as comonomer resulted in St conversions that differed significantly compared to the homopolymerization case. Interestingly, when a higher initial load of St-TLa was employed, higher conversions of both St and St-TLa monomer were observed for the same polymerization conditions (*Entries 4*, *5*, and *6*, Table 8-1). This effect can be assigned to a promoted reactivity of the St-TLa propagating free radical.

Next, Figure 8-1 a shows that for a given St to St-TLa molar ratio initially present in the feed, the final conversion of St-TLa is always higher, albeit with an initial delay. This phenomenon is more prominent when the starting content of St-TLa is higher (e.g. 10 or 20 mol%). Therefore, the incorporation rate of the St-TLa monomer in the copolymer is increasing with monomer conversion, yielding a copolymer with a St-TLa content being more densely distributed as the growth of the copolymer chains is progressing. The minor difference in monomer reactivity however, allows to conclude the formation of a near-ideal random copolymer. The thiolactone content in the resulting copolymer was calculated based on the St-TLa monomer conversion and the initial load of St-TLa

monomer compared to styrene, using ^{1}H-NMR spectroscopy. Finally, the solubility of the obtained copolymers was investigated and although the proportion of the thiolactone moiety was high in some cases, all copolymers were soluble in common organic solvents. TGA-analysis of the PS-*co*-PS-TLa copolymers revealed that the copolymers degraded substantially at 350 °C, while the pure PS degraded at 400 °C.

8.3.2. NMP copolymerization of MMA and styrene-thiolactone
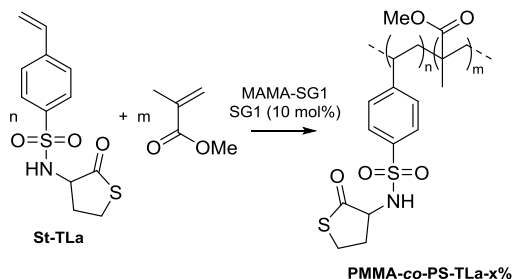
Scheme 8-4. NMP copolymerization of MMA and St-TLa (MAMA-SG1 (+10 mol% SG1), DMF = 25 vol%, 90°C, 3h) yielding the copolymer PMMA-co-PS-TLa-x%.

As NMP is recognized as being a versatile CRP-method for styrenic monomers, a series of experiments have also been performed with St-TLa. The copolymerization of St-TLa with MMA by NMP is shown in Scheme 8-4. It is known that MMA cannot be homopolymerized by NMP due to the large equilibrium constant (K)[21], which renders termination reactions excessive and stops the polymerization at low conversion (below 40%). However, Nicolas et al. proposed an alternative way to synthesize PMMA by NMP in a controlled manner[22]. They showed that the addition of a small amount of styrene (8.8 mol% or higher) lowered K sufficiently to obtain polymers with low Đ up to high conversion. Also, Lessard et al. were able to copolymerize MMA with 9-(4-vinylbenzyl)-9H-carbazole present in very low amount (1 mol%)[23]. In this respect, it has been investigated if the polymerization of MMA in the presence of St-TLa could be used to prepare TLa-functionalized PMMA for further modification (Table 8-2).

Table 8-2. Synthesis of PMMA-*co*-PS-TLa with different compositions by NMP[a]

Entry	St-TLa initial load, mol %	M_n (g.mol^{-1})	Đ	St-TLa incorporated, mol %[b]
1	3	14700	1.44	4
2	5	17800	1.48	7
3	10	17900	1.51	13

[a] Copolymerization conditions were as follows: initiator = MAMA-SG1 (+10 mol% SG1); DMF = 25 vol%; T = 90°C; t = 3h; theoretical M_n at 100% conversion = 20,000 g/mol. [b] Determined by ^{1}H-NMR.

Three experiments with 3 (*Entry 1*, Table 8-2), 5 (*Entry 2*, Table 8-2) and 10 mol% (*Entry 3*, Table 8-2) of St-TLa, initially present in the polymerization feed, were performed. Also in this case, the St-TLa loadings in the final polymers were higher than their initial amounts in the reaction mixtures, indicating that St-TLa is incorporated more favorably than MMA and that gradient-like copolymers are expected. This is in accordance with the outcome of the more detailed kinetic study of the RAFT copolymerization of styrene and St-TLa monomer (*vide supra*). The Đ's are close to 1.50, ascribed to a fraction of low molar mass products as a result of termination events. Nevertheless, the molar masses are similar and in accordance with the theoretical value of 20,000 g.mol^{-1} at 100% conversion from which it can be concluded that a small addition of St-TLa allows for a reasonably controlled polymerization of MMA by NMP. An initial amount of minimum 5 mol% of St-TLa is preferred to ensure a better control over the polymerization as a second low molar mass distribution was observed for PMMA-*co*-PS-TLa-4%.

The obtained series of copolymers with tunable thiolactone content were subjected to an extensive post-polymerization modification study.

8.4. DOUBLE MODIFICATION OF THIOLACTONE-FUNCTIONALIZED POLYMERS
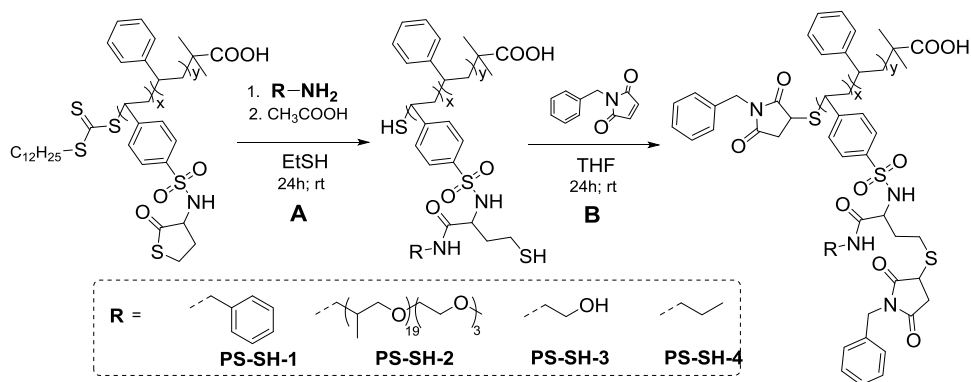
Scheme 8-5. Double modification reaction of PS-co-PSTLa. A. Nucleophilic ring-opening of pendent thiolactone moieties with an amine, generating polythiols. B. Modification of the polythiols with *N*-benzylmaleimide *via* a Michael-addition reaction.

8.4.1. Polythiols through post-polymerization modification

Copolymers of styrene and St-TLa (PS-*co*-PS-TLa-x%) were modified through reaction with a series of amines, generating thiols as pendent groups on the polymer chain. It is interesting to note that the amine not only functions as a nucleophile for the opening of the thiolactones, but also cleaves the

RAFT end group to produce a thiol. A challenge in the synthesis of thiol-containing polymers is to prevent disulfide formation (and eventually crosslinking) and thus maintain the narrow polydispersity of the precursor polymer, resulting from the RAFT process. Disulfide formation could not be suppressed using standard oxygen-free procedures and acidic work-up. However, it was possible to generate polythiols with a narrow dispersity when adding a reducing agent, in this case ethanethiol. Because of the ease of removal as a result of its low boiling point, this reducing agent was even used as solvent for the reaction. Acidic work-up before precipitation guaranteed the formation of polythiols (Scheme 8-5 A). With the intention to apply a general protocol for all experiments, 50 equivalents of amine were used in a 24 h reaction to ensure a full conversion of the thiolactone moieties.

First, three batches of PS-*co*-PS-TLa with different mol% of St-TLa (9, 13 and 25%) were transformed into the corresponding polythiols (PS-*co*-PS-TLa-x%-SH), using propylamine as nucleophile. It should be noted that when higher amounts of the thiolactone monomer were incorporated in the polymer, it became necessary to perform the reaction under oxygen-free atmosphere to prevent disulfide formation, even when using ethanethiol as (co-)solvent. If the reaction occurs without formation of disulfide bonds, the Đ of the polymer is expected to remain more or less constant, while a clear broadening of the SEC traces should be observed if disulfide coupling takes place. From SEC analysis, it can be seen that in all cases the shape of the chromatograms remains unimodal after reaction. However, tailing was observed at the low molecular weight range in the SEC traces of the sample with 13 and 25% St-TLa (Figure 8-2). Therefore, the molar mass values were lower than expected, as they should not decrease compared to the starting product. The reasons for this tailing are unclear at this point, although earlier observations of peak broadening during SEC analysis of unprotected, well-defined polyamines and polythiols are consistent with the present outcome. Nevertheless, ^{1}H-NMR analysis revealed complete reaction in all cases.
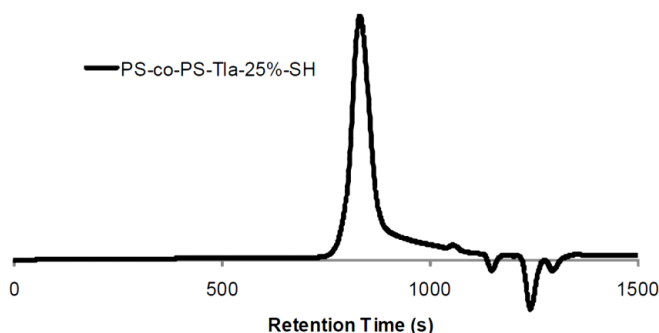

Figure 8-2. SEC trace of PS-co-PS-TLa-25%-SH reveals tailing at the low molecular weightrange (beyond the exclusion limit), compromising integration of the peak and thus adequate determination of the molar mass values.

Table 8-3. SEC results obtained after medication of different batches of PS-co-PSTLa, using propylamine as nucleophile.

Entry	M_n (g.mol^{-1})	M_w (g.mol^{-1})	Đ
PS-co-PSTLa-9%	7600	8500	1.11
PS-SH-4	7700	8700	1.12
PS-co-PSTLa-13%	11300	12600	1.12
PS-SH-5[a]	10800	12200	1.13
PS-co-PSTLa-25%	12000	14200	1.19
PS-SH-6[a]	11200	12600	1.12

[a] Tailing is observed and values obtained for M_n, M_w and Đ are thus not precise.

As an example, Figure 8-3 shows the ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) of PS-*co*-PS-TLa with 25 mol% St-TLa monomer incorporated before (bottom) and after (top) reaction with propylamine. The signals corresponding to the thiolactone protons clearly shift to other ppm values after ring-opening. Also, the proton signals from propylamine at 2.8 and 0.7 ppm become visible after reaction. While this is evidence for a (nearly) quantitative modification reaction, the unimodal shape of the corresponding size-exclusion chromatogram confirms that no disulfides were formed (see further; Figure 8-7). Similar spectra and results were obtained for other thiol loadings.
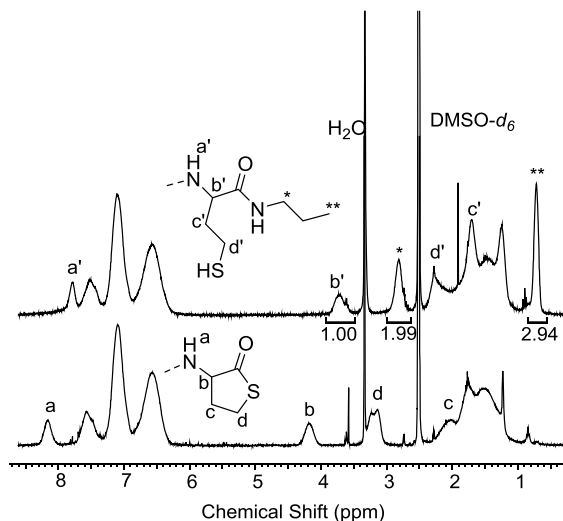

Figure 8-3. ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) of PS-co-PS-TLa-25% before (bottom) and after (top) reaction with propylamine.

Table 8-4. SEC[a] results obtained after the modification of PS-co-PS-TLa-9% (*Entry 1*) using different amines: benzylamine (*Entry 2*), Jeffamine M-1000 (*Entry 3*), ethanolamine (*Entry 4*).

Entry	Product	M_n (g.mol^{-1})	M_w (g.mol^{-1})	Đ[b]
1	PS-co-PS-TLa-9%	6700	7400	1.11
2	PS-SH-1	7000	7800	1.13
3	PS-SH-2	10700	13900	1.31
4	PS-SH-3	6400	7700	1.20

[a] **Eluent: THF; PS standards.**

In the previous experiments, propylamine was chosen as a means to generate thiols on the polymer backbone. On the other hand, one of the advantages for using a thiolactone, is the possibility to introduce functionalities or to alter the properties of the polymer *via* the amine. This benefit was exploited by using different amines as nucleophile. Table 8-4 gives an overview of the molecular weights and Đ's of PS-*co*-PS-TLa-9% before (*Entry 1*, Table 8-4) and after reaction with an amine, obtained by size-exclusion chromatography. When using benzylamine as nucleophile, the molecular weight of the polymer increases whereas Đ remains low (*Entry 2*, Table 8-4). Additional evidence of a successful modification is found in a clear shift of the signals assigned to the protons of the thiolactone in ^{1}H-NMR spectra (Figure 8-5 A). The thiol-functionalized polystyrene obtained when using Jeffamine® M-1000 (a polyetheramine with a broad molecular weight distribution around 800 g.mol^{-1}, as determined by ESI-MS) as nucleophile, still had a narrow dispersity, while M_n increased significantly (*Entry 3*, Table 8-4). This successful grafting of an oligomeric polyetheramine onto the polystyrene backbone via a thiolactone-amine conjugation experiment, was also witnessed in ^{1}H-NMR analysis (Figure 8-5 B).

The decrease in M_n observed with ethanolamine as nucleophile (*Entry 4*, Table 8-4) is attributed to the introduction of hydrogen bonds, decreasing the hydrodynamic volume of the polymer. ^{1}H-NMR analysis confirmed that the reaction occurred, since the signals originating from the thiolactone protons disappear after ring-opening (Figure 8-5 C).

Structure elucidation was further done by a Correlation Spectroscopy (COSY) and Heteronuclear Single-Quantum Correlation experiment (HSQC). Figure 8-4 gives an example for PS-co-PS-TLa-9%-SH after ring-opening with propylamine (similarly performed for each sample). It is interesting to note that, although disulfides are being formed quickly when dissolved, the obtained polythiols are stable as powder and can be kept as such.
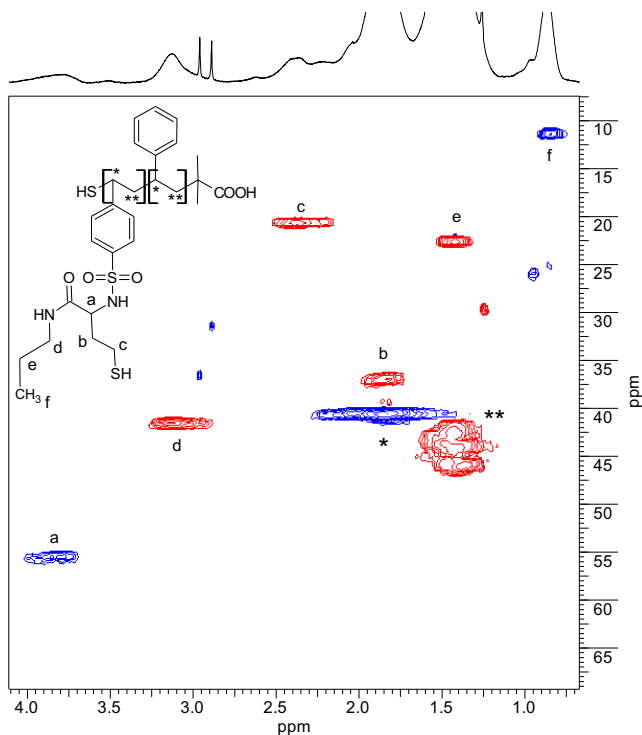
Figure 8-4. Detail of the HSQC spectrum (500 MHz, CDCl₃) of PS-co-PS-TLa-9%-SH (ring-opening with propylamine) with peak assignment of side chain (a - f) and backbone (* and **) non-aromatic atoms. Cross peaks in red represent methylene (CH₂) units, while the blue ones represent methine (CH) or methyl (CH₃) units.
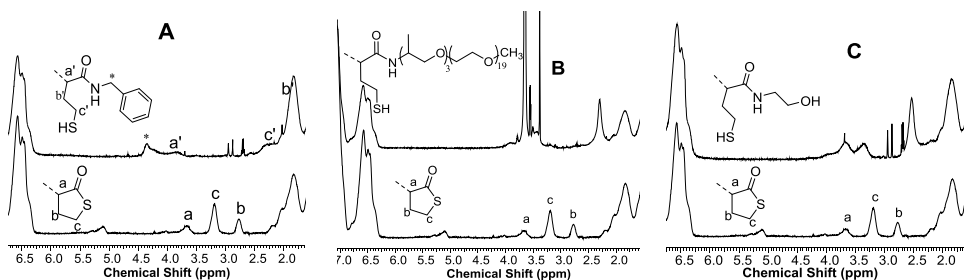
Figure 8-5. Overlay of the NMR spectra (300 MHz, CDCl₃; zoom of relevant area) of PS-co-PS-TLa-9% (bottom) and A. PS-SH-1 (benzylamine) (top); B. PS-SH-2 (Jeffamine® M-1000) (top) and C. PS-SH-3 (Ethanolamine) (top).

8.4.2.   Double modification of thiolactone-containing PS and PMMA

Finally, it was shown that the thiols introduced on the polymer backbone can serve as functional handles for subsequent thiol-X reactions, permitting a double modification of the polymer. For analysis purposes, a Michael reaction with *N*-benzylmaleimide was carried out. A 50-fold excess of maleimide was used to favor the thiol-maleimide coupling, which is performed in basic environment, conditions known to also encourage the formation of disulfides. Interestingly, the benzylic signals of *N*-benzylmaleimide are clearly distinguishable in ^{1}H-NMR-spectra at 4.6 ppm and hence the overall conversion can be calculated.
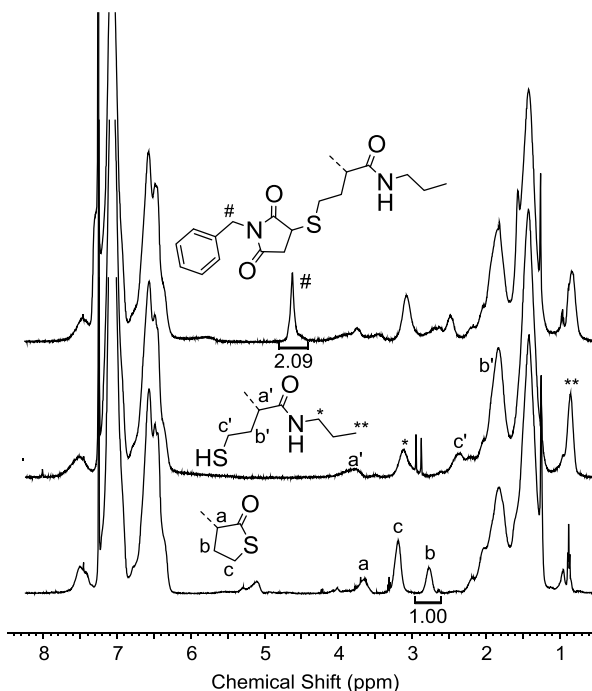
Figure 8-6. Overlay of ^{1}H-NMR spectra (500 MHz, CDCl₃) of PS-co-PS-TLa-9% (bottom), the reaction product after the first modification step with propylamine (PS-SH-4, middle) and the end product after the double modification with *N*-benzylmaleimide (PS-SH-4-MM, top). Integrations are relative to the aromatic signals and thus an estimation of the overall conversion was made.

Figure 8-6 shows an overlay of ^{1}H-NMR spectra (500 MHz, CDCl₃) of the starting product PS-*co*-PS-TLa-9% (bottom), the reaction product after the first modification step (middle) and the reaction product after double functionalization (top). After reaction with propylamine, the signals allocated to the thiolactone protons clearly shifted to other ppm values. Additionally, signals assigned to the protons of propylamine become visible at 3.2 and 0.7 ppm. When subsequently reacting this thiol-functionalized polystyrene with *N*-benzylmaleimide, a signal at 4.6 ppm appears. Integration of this

signal, relative to the aromatic signals originating from the original polymer and those introduced *via* the maleimide, shows that the double modification reaction was nearly quantitative. SEC analysis confirmed these results, since an increase in molecular weight is observed with every modification step, while dispersities remain low (Figure 8-7, Table 8-5).
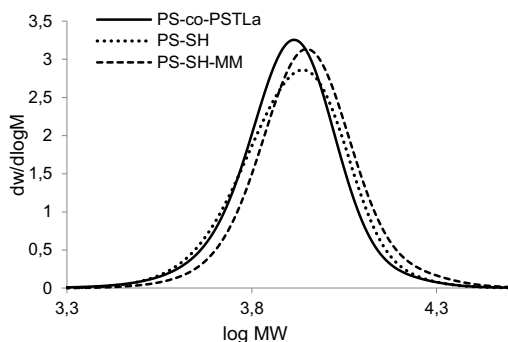

Figure 8-7. SEC traces of PS-co-PSTLa after reaction with propylamine and subsequent modification with *N*-benzyl maleimide.

Table 8-5. Results from SEC^a obtained before modification, after modification with propylamine and after double modification. SEC traces are shown in Figure 8-7.

Entry	Product	M_n (g.mol^{-1})	M_w (g.mol^{-1})	Đ
1	PS-co-PS-TLa-9%	7600	8500	1.11
2	PS-SH-4	7700	8700	1.12
3	PS-SH-4-MM	8500	9400	1.12

^{a} **Eluent: THF; PS standards**

Similarly, thiolactone-functionalized PMMA (PMMA-*co*-PS-TLa), synthesized *via* NMP, was reacted with propylamine to generate thiols on the polymer backbone. Again, ethanethiol was used as reducing agent and (co-)solvent (with THF) and reactions were performed under oxygen-free atmosphere to avoid disulfide formation. Different thiol loadings were obtained, starting from PMMA-*co*-PS-TLa with a varying amount of incorporated St-TLa monomer.

Table 8-6 gives an overview of the SEC results of the polymers before (*Entries 1, 3, 5*) and after (*Entries 2, 4, 6*) reaction with propylamine. In all cases, molecular weight increases after nucleophilic ring-opening of the thiolactone, while dispersities do not change significantly. Again, this is an indication of the absence of disulfides while ^{1}H-NMR analysis confirms that the molar mass increase can be ascribed to a nearly quantitative reaction.

Tabel 8-6. Overview of SEC[a] results obtained before and after (double) modification of a series of PMMA-co-PS-TLa with different mol% of thiolactone monomer (St-TLa) incorporated.

Entry	Product	M_n (g.mol^{-1})	M_w (g.mol^{-1})	Đ
1	PMMA-*co*-PS-TLa-4%	14650	21100	1.44
2	PMMA-*co*-PS-TLa-4%-SH	14900	22000	1.48
3	PMMA-*co*-PS-TLa-13%	17850	26850	1.51
4	PMMA-*co*-PS-TLa-13%-SH	18200	27450	1.51
5	PMMA-co-PS-TLa-7%	17750	26400	1.48
6	PMMA-co-PS-TLa-7%-SH	19950	29050	1.46
7	PMMA-co-PS-TLa-7%-SH-MM	24450	32150	1.31

[a] **Eluent: THF; PMMA standards**

The use of the thiol groups as functional handles was demonstrated through a double modification of PMMA-*co*-PS-TLa-7%, similar to the previous case, i.e. reaction with propylamine followed by *N*-benzylmaleimide (Scheme 8-6). After each modification step, the molar mass increases while Đ remains low (Table 8-6, *Entries 5-7*) and ^{1}H-NMR analysis confirms that the modification reaction proceeded with nearly quantitative conversion.
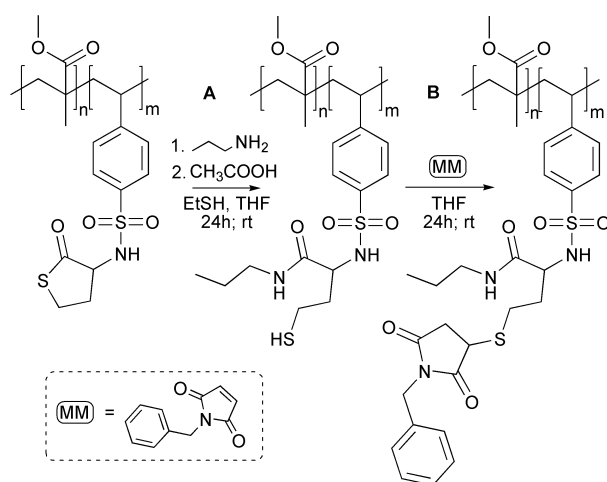
Scheme 8-6. Double modification of PMMA-co-PS-TLa. A. Nucleophilic ring-opening of thiolactone groups on the polymer backbone. B. Subsequent thiol-ene modification with *N*-benzylmaleimide.

8.5. CONCLUSION

In conclusion, a conceptual proof for the thiolactone approach as a synthetic tool for double, modular post-polymerization modification (aminolysis and thiol-X) was elaborated. The copolymerization of a stable thiolactone-containing styrenic monomer St-TLa, mediated by RAFT or NMP, yielded a series of linear polymers, based on styrene and MMA, with a tuneable content of pendent thiolactone units. These poly(thiolactone)s are precursors for narrow-disperse polythiols, given the fact that disulfide formation is completely suppressed. All reaction conditions were optimized in order to tackle this synthetic challenge. Aminolysis with various (functional) amines enabled us to produce polythiols with narrow PDI, even *grafting onto* modification with oligomeric Jeffamines proved to be successful. The subsequent thiol-X conjugation was demonstrated by the treatment of the obtained polythiols with *N*-benzylmaleimide, the ultimate evidence for the efficient double modification of pendent thiolactone moieties. Other thiol-based reactions could be performed in a similar way, starting from the same backbone.

The combination of controlled radical polymerization and double modification of an incorporated thiolactone ring is considered to be a powerful synthetic tool in polymer science as it provides routes towards reactive polymer scaffolds with more advanced structures (stars, block copolymers, ...). In a follow-up study, p(NIPAAm) polymers were synthesized, carrying thiolactones along the polymer backbone. It was also shown that the double post-polymerization modification was possible without intermediate purification, in a one-pot procedure.[24]

8.6. EXPERIMENTAL PART

8.6.1. Materials

N,N-Dimethylformamide (DMF) (Acros, HPLC grade), tetrahydrofuran (THF) (Aldrich, HPLC grade), isooctane (Aldrich, HPLC grade), dichloromethane (CH_2Cl_2) (Aldrich, HPLC grade), methanol (ChemLab, technical grade), propylamine (Aldrich, 98%), benzylamine (Aldrich, 99%), ethanolamine (Aldrich), Jeffamine M-1000 (Huntsman), *N*-benzylmaleimide (Aldrich, 99%), ethanethiol (Aldrich, 97%), homocysteïne thiolactone hydrochloride (Acros, 99%), $NaHCO_3$ (Roth, ≥ 99.5%) and pentane (technical grade) were used as received. S-1-dodecyl-S'-(α,α'-dimethyl-α''-acetic acid)trithiocarbonate (DDMAT)[25] and 4-vinylbenzenesulfonyl chloride[26] were prepared following a literature procedure. 2,2'-Azobis(isobutyronitrile) (AIBN) (Aldrich) was recrystallized twice from methanol. 1,4-Dioxane (Aldrich,

HPLC grade) was dried by distillation from Na/benzophenone. 3,7-Dioxa-4-aza-6-phosphanonanoic acid, 4,5-bis(1,1-dimethylethyl)-6-ethoxy-2,2-dimethyl-, 6-oxide (MAMA-SG1) and *N-tert*-butyl-1-diethylphosphono-2,2-dimethylpropyl nitroxide (SG1) were kindly supplied by Prof. Richard Hoogenboom (Ghent University). Both styrene (St) and methyl methacrylate (MMA) were stripped from inhibitor by passing over basic alumina before use. Silica gel (60 Å, 40 / 63 μm) was used as received from Rocc.

8.6.2. Methods

Size Exclusion Chromatography (SEC) analyses were performed on an Agilent (Polymer Laboratories) PL-SEC 50 plus instrument, using a refractive index detector, equipped with two Plgel 5 μm MIXED-D columns thermostated at 40°C. PS and PMMA standards were used for calibration. THF was used as eluent at a flow rate of 1 mL/min. Samples were injected using a PL-AS RT autosampler.

^{1}H- and ^{13}C-NMR (Attached Proton Test, APT) spectra were recorded in CDCl$_3$ (Eurisotop) and DMSO-d_6 (Eurisotop) on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz. Chemical shifts are presented in parts per million (δ) relative to CDCl$_3$ (7.26 ppm in ^{1}H- and 77.23 ppm in ^{13}C-NMR) or DMSO-d_6 (2.50 ppm in ^{1}H- and 39.52 ppm in ^{13}C-NMR) as internal standard. Coupling constants (*J*) in ^{1}H-NMR are given in Hz. The resonance multiplicities are described as *d* (doublet) and *m* (multiplet).

An Agilent technologies 1100 series LC/MSD system equipped with a diode array detector and single quad MS detector (VL) with an electrospray source (ESI-MS) was used for classic reversed phase LC-MS (liquid chromatography mass spectroscopy) and MS analysis. Analytic reversed phase HPLC was performed with a Phenomenex C$_{18}$ (2) column (5 μ, 250 x 4.6 mm) using a solvent gradient (0 → 100% acetonitrile in H$_2$O in 15 min) and the eluting compounds were detected *via* UV-detection (λ = 214 nm).

Thermogravimetric analysis (TGA) was performed with a Mettler Toledo TGA/SDTA851e instrument under air atmosphere at a heating rate of 10 °C/min from 25 to 800 °C.

8.6.3. Synthesis of Styrene-thiolactone monomer (St-TLa)

An ice-cooled solution of homocysteine thiolactone hydrochloride (16.38 g, 106.7 mmol) in H$_2$O/1,4-dioxane (240 mL, 1/1) was treated with NaHCO$_3$ (44.8 g, 533.3 mmol). After 30 min, a solution of crude 4-vinylbenzenesulfonyl chloride (128 mmol) in 1,4-dioxane (20 mL) was added at 0 °C and the mixture was stirred overnight at rt. The reaction mixture is diluted with brine (500 mL) and extracted with EtOAc (3 x 1 L). The organic phase was dried (MgSO$_4$). The drying agent was filtered and the resulting clear solution was evaporated under reduced pressure. The residue was purified by flash

column chromatography on silica gel (CH$_2$Cl$_2$/acetone: 98/2 → 95/5) to provide the title compound (25.27 g, 89.2 mmol, 83% yield) as a white solid.

C$_{12}$H$_{13}$NO$_3$S$_2$ (201.24 g/mol); *m/z (ESI-MS)* 202, 174, 130, 113;

HRMS (ESI): Expected 284.0409; Found 284.0405 [M+H][+], Expected 301.0675; Found 301.0629 [M+NH$_4$][+].

^{1}H-NMR (300 MHz, CDCl$_3$, ppm) δ 7.83 (*d*, 8.5 Hz, 2H), 7.53 (*d*, 8.4 Hz, 2H), 6.74 (*dd*, 17.6, 10.9 Hz, 1H), 5.88 (*d*, 17.6 Hz, 1H), 5.45 (*d*, 10.9 Hz, 1H), 5.19 (*d*, 2.8 Hz, 1H), 3.75 (*ddd*, 12.7, 6.8, 3.5 Hz, 1H), 3.25 (*m*, 2H), 2.85 (*m*, 1H), 2.06 (*m*, 1H);

^{13}C-NMR (APT, 75 MHz, CDCl$_3$, ppm) δ 204.0 (C), 142.6 (C), 137.9 (C), 135.4 (CH), 127.8 (CH), 127.1 (CH), 118.0 (CH$_2$), 62.1 (CH), 32.2 (CH$_2$), 27.7 (CH$_2$).

8.6.4. RAFT copolymerization of styrene and St-TLa

In a typical experiment, St-TLa (0.255 g, 0.9 mmol), styrene (1.83 g, 17.4 mmol), DDMAT (0.033 g, 9.2 x 10^{-5}mol), AIBN (1.5 mg, 9.1 x 10^{-6}mol) as thermal initiator ([M$_{St+St\text{-}TLa}$]$_0$/[CTA]$_0$/[AIBN]$_0$ = 200/1/0.1) and 1,4-dioxane as solvent were introduced in a Schlenk tube, which was degassed by three freeze-pump-thaw cycles, backfilled with nitrogen, sealed, and heated in an oil bath at 70 °C. To follow the polymerization kinetics, several aliquots at defined time intervals were withdrawn and subsequently characterized by ^{1}H-NMR and SEC in order to determine individual conversion of both monomers and molecular weight evolution, respectively. The final crude solution was precipitated in 10-fold excess of cold methanol, filtered, and dried under reduced pressure overnight, yielding the copolymer of styrene and St-TLa (PS-*co*-PS TLa-x%[2]), a slightly yellow fine powder.

8.6.5. NMP of MMA and St-TLa

In a typical experiment, for 3 mol % of St-TLa in the feed, 1.639 g (5.78 mmol) of St-TLa and 18.720 g (0.187 mol) of MMA monomers as well as 0.388 g (1.02 mmol) of MAMA-SG1 and 0.030 g (0.10 mmol) of SG1 were dissolved in DMF and stirred for at least 15 min to ensure complete homogenization of the mixture. The solution was then poured in a two-neck flask fitted with a septum and an argon connection. Subsequently, argon was bubbled through the mixture for 30 min. The flask was then immersed in an oil bath preheated at 90°C. After 3h, the reaction was quenched in an ice bath. The copolymer was separated from the reaction mixture by adsorption-based liquid

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[2] PS-co-PS-TLa-x%: copolymer of styrene and styrene-thiolactone with a thiolactone content of x mol%.

chromatography[27]: the crude reaction mixture was eluted over a silica gel column with a gradient of solvents (isooctane / THF from 1:1 to pure THF). The solvent was evaporated from the polymer fraction. The polymer was further redissolved in CH_2Cl_2 and precipitated in chilled pentane. The polymer (PMMA-*co*-PS-TLa-x%[3]) was subsequently filtered and dried under vacuum at 40°C for 12h. The monomer conversion was determined by ^{1}H-NMR analysis on crude samples dissolved in DMSO-d_6. Molecular weights were determined by SEC.

8.6.6.   Modification of thiolactone-functionalized polymers by aminolysis

In a typical experiment, 100 mg precursor polymer (PS-*co*-PS-TLa or PMMA-*co*-PS-TLa) was dissolved in 2 mL ethanethiol or in 2 mL ethanethiol/THF 1:1 (for PMMA-*co*-PS-TLa-13% and PS-*co*-PS-TLa-25%). 50 equivalents of amine (propylamine, benzylamine, ethanolamine, Jeffamine M-1000) were added and the reaction was stirred under Ar-atmosphere for 24 hours at room temperature. For PS-*co*-PS-TLa-13%, PS-*co*-PS-TLa-25% and all PMMA-*co*-PS-TLa's, the solution was introduced in a Schlenk-tube and three freeze-pump-thaw cycles were performed before adding the amine to the reaction mixture. 100 eq. of CH_3COOH compared to the initial amount of thiolactone were added before precipitating the reaction mixture in cooled MeOH for PS-*co*-PS-TLa or MeOH/H_2O (7:3) for PMMA-*co*-PS-TLa. The respective polythiols (PS-*co*-PS-TLa-x%-SH and PMMA-*co*-PS-TLa-x%-SH[4]) were obtained as a white powder, which was dried under vacuum for 24 hours.

8.6.7. Modification of polythiols with *N*-benzylmaleimide

N-benzylmaleimide (279 mg; 1.48 mmol) was dissolved in THF (1 mL) and triethylamine was added up to pH 9 (indicative value, measured with Merck pH indicator paper). The mixture was purged with Ar for 10 minutes. PS-*co*-PS-TLa-9%-SH (40 mg; 0.03 mmol of thiol groups) was added and the reaction was stirred for 20 h at room temperature. The reaction mixture was precipitated in a (8:2) solution of MeOH/H_2O and the powder was dried under vacuum for 24 h. For PMMA-*co*-PS-TLa-7%-SH, the same procedure was followed.

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[3] PMMA-co-PS-TLa-x%: copolymer of MMA and styrene-thiolactone with a thiolactone content of x mol%.

[4] PS-co-PS-TLa-x%-SH/ PMMA-co¬-PS-TLa-x%-SH : polythiol, originating from the aminolysis of a copolymer of styrene (or MMA) and styrene-thiolactone with a thiolactone content of x mol%

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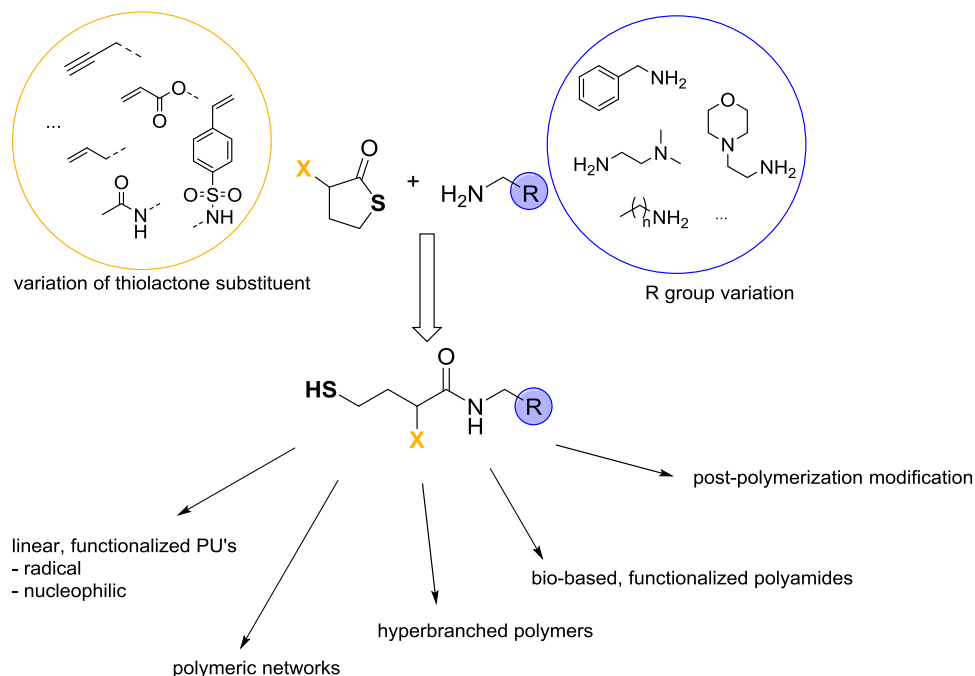
Chapter 9
General conclusion and perspectives

The aim of this work was to develop a new, straightforward synthetic procedure to speed up and simplify the synthesis of functional polymers, based on thiol-chemistry. Thiols have always been important in polymer chemistry, for example in the preparation of vulcanized rubbers and the formation of nearly perfect high-refractive index materials. More recently, thiol-based chemistry has gained importance in the development of functionalized materials and for the formation of polymers with an increased complexity.[1-6] Indeed, the emergence of efficient linking strategies, click chemistry in particular,[7, 8] has facilitated synthetic procedures and work-ups tremendously.

As a result of their high reactivity and their ability to react as thiyl radical as well as thiolate anion (Chapter 2), thiols have attracted a lot of attention in the synthesis of polymer materials, where the need for efficient reactions is very high. However, this reactivity towards a whole range of substrates directly implies a restriction: the chemoselectivity of a reaction is not always guaranteed. Moreover, thiols usually have a bad smell and are prone to oxidation reactions. In radical polymerizations, thiols are often used as chain transfer agents. Because of these reasons, the use of thiols often requires the use of protecting groups (Chapter 3), such as for example disulfides,[9] thiocarbonylthio groups[10] or methanethiosulfonates.[11] However, a lot of these methods require a protecting and a deprotecting step, which is unfavorable in terms of atom-efficiency and overall yield. The strategy explored within this PhD research is based on the use of a thiolactone as a precursor for a thiol, allowing for the direct introduction of a thiol, starting from stable amino-containing compounds without the need for a subsequent deprotection step (Scheme 9-1).[12]

Using thiolactones in polymer synthesis has a dual advantage: On the one hand, it offers a chemoselective, atom-efficient way of generating thiols, while at the same time it is possible to introduce functionality *via* the amine compound. This one-pot amine-thiol-ene conjugation reaction was used for the synthesis and modification of diverse polymeric systems.

variation of thiolactone substituent

R group variation

HS

X

O

N
H

R

post-polymerization modification

linear, functionalized PU's
- radical
- nucleophilic

bio-based, functionalized polyamides

hyperbranched polymers

polymeric networks

Scheme 9-1. Thiolactone strategy: a thiol is introduced by aminolysis of the thiolactone. In a next step, a thiol-X reaction is performed, achievably in the same reaction mixture. A great variety of amines can be used, as well as reactive "ene" or "yne" chemistry. The applications are numerous: ranging from hyperbranched, to functionalized linear polymers, to polymeric networks.

OVERVIEW OF THE RESULTS

In a first step of the research, the commercially available *N*-acetyl homocysteine thiolactone (ACTL) was used as a model thiolactone compound to assess the feasibility of the proposed one-pot amine-thiol-ene conjugation. One of the challenges was to perform both a nucleophilic and a radical process at the same time. Because of the successful model reaction between ACTL, benzylamine and norbornene as reactive "ene", the same model compound was used for the post-polymerization modification of alkyne-functionalized polymers. Finally, a monomer containing both a thiolactone and an ene was synthesized for the formation of linear polymers with a polythioether/polyurethane backbone, carrying functional groups in their side-chains. Moreover, the proposed strategy was also useful in the synthesis of polymer networks.

This first successful study encouraged us to investigate the synthesis of functionalized, bio-based polyamide structures. 10-Undecenoic acid was used as a biological precursor for the synthesis of an AB'-monomer, in which A symbolizes the carbon-carbon double bond and B' the thiolactone unit. These two units were connected through an amide linkage and polymerization gave rise to polyamide

structures, with amides that are present both in the polymer main chain as well as in their side-chains. An important observation was that, although the molecular weights of the obtained polymers were around 10 kDa and less, the E-moduli and elongation at break had values that are normally only observed for polymers with much higher molecular weights. This was attributed to the fact that two amide bonds are located closely to each other, leading to the formation of additional hydrogen bonds. Another observation was the spontaneous oxidation of the polymer backbone thioether linkage in THF. Oxidation could also be triggered using the appropriate oxidant.

Combining thiolactones with the radical thiol-ene and thiol-yne polymerization has finally resulted in the synthesis of hyperbranched polymers. Alkyne-thiolactone was synthesized as an A'B$_2$ monomer, containing a C≡C bond (B$_2$) and a thiolactone unit (A'). After aminolysis, a thiol is formed, thus generating an AB$_2$ monomer. Upon UV-irradiation, hyperbranched polymers were formed. The second thiol-addition to the carbon-carbon triple bond occurs faster than the first addition, leading to polymers with a high degree of branching, as calculated from ^{1}H-NMR data. Hyperbranched polymers could also be synthesized through thiol-ene polymerization, starting from the A'B monomer Alloc-thiolactone. In this case, allylamine was used to incorporate a carbon-carbon double bond. Again, after UV-irradiation, hyperbranched structures were obtained with broad dispersities (SEC). Structural characterization with ^{1}H-NMR spectroscopy is in this case less straightforward.

While the combination of thiolactone ring-opening with radical thiol chemistries proved to be successful in the synthesis of a diversity of polymer structures, the presence of radicals in the reaction medium impede further extension of the scope of the methodology. Important to note is that some functional groups (*e.g.* furan, double and triple bond), introduced *via* the amine, are incompatible with a radical environment. Additionally, the UV-curing happens upon decomposition of a photoinitiator (*e.g.* DMPA), but model studies revealed that some amines (*e.g.* benzylamine) react with the formed radical fragments, thus limiting the use of a photoinitiator. Therefore, the one-pot combination of the aminolysis of a thiolactone unit on one hand and a nucleophilic thiol-ene conjugation (Michael addition) on the other hand is considered to be a breakthrough approach for the development of a direct synthesis strategy to obtain functionalized polyurethanes. It was shown that the aminolysis of the thiolactone is the rate-determining reaction step, and that aza-addition was much slower than thiol-addition to the acrylate. Modular use of amines led to the formation of functionalized polyurethane structures.

Thiolactones can be regarded as sites where two reactions can take place. By incorporating them in polymers, it becomes possible to introduce multiple functional groups. Polymers with thiolactone handles in their side-chains were prepared starting from a Styrenic thiolactone monomer (St-TLA).

Polymers were prepared by either RAFT or NMP through copolymerization of the latter with styrene (St) or methyl methacrylate (MMA), yielding linear polymers with varying thiolactone content (4–25%). Upon amine treatment, the ring-opening of the pendent thiolactones resulted in the formation of linear polythiols. The formation of disulfides could be prevented by using ethanethiol as (co-)solvent. Different primary amines were thus attached to the polymer backbone, while the PDIs remained low. The resulting polythiols are versatile scaffolds for further modification by various thiol-X reactions. In this respect, thiol–maleimide conjugation was used as a model reaction. NMR- and SEC-analyses revealed a near-quantitative double modification of thiolactone containing PS and PMMA by subsequent treatment with propylamine and *N*-benzylmaleimide.

ONGOING RESEARCH AND GENERAL CONCLUSION

In the PCR group, ongoing research within a Marie-Curie EID project (SUSCOAT; PCR group as coordinator) is focussing on the development of functionalized coatings, using thiolactone monomers. Although thiol-ene chemistry has been used in coating industry, thanks to the improved adhesion as a result of low shrinkage, additional properties are hard to incorporate. The added value of thiolactone-ene monomers is the ease and the great variety with which functional groups can be integrated, also in polymeric networks. Using the appropriate amine, for example anti-bacterial, and in particular scavenging properties could be tuned. Another research using thiolactones, is aiming at the sequence-controlled synthesis of macromolecules on solid support. Indeed, expectations for the next generation of synthetic polymers included performance as single chains, ability to fold and self-regulate and the ability to sense specific molecules and/or catalyze reactions. Therefore, precisely functionalized linear polymers should exhibit sharply defined and tailored structure-activity relationships analogous to Nature's delicately engineered macromolecules. Other specific examples wherein thiolactone chemistry has been used, include the double modular modification of PNIPAAm,[13] the preparation of hollow, functionalized polymeric beads and the development of redox-responsive layers for the reversible release of functional molecules. Recently, the group of Tao[14] reported on a novel PEGylation method, using a "dansyl-thiolactone" compound. As a general conclusion and outlook, it can be stated that the versatility of the thiolactone approach in polymer science could be regarded as a breakthrough in the modern functionalization techniques. Therefore, it will undoubtedly lead to many more applications, also in material science, in which the unique properties of the thiolactone functional handle will attract the efforts of many more research groups world-wide.

SOME PERSPECTIVES…

It is clear that in this PhD research and in other parallel research lines within the PCR group, a new concept in synthetic polymer chemistry has been developed. A new family of monomers, based on the combination of a thiolactone and an unsaturated carbon-carbon bond has made it possible to target specific tailor-made polymers. The thus obtained versatility is demonstrated through the adaptation on the level of the *chemical* structure of the polymers. Although a lot of chemical variation is indeed accessible, future research should target modifications leading to materials with enhanced physical properties. It can be expected that by carefully chosing building blocks and amine triggers, the mechanical properties can be altered. With respect to stability, the fact that the formed thioether bond intrinsically limits the thermal resistance to about 200 °C, should be taken into account. Moreover, throughout this research, disulfide formation has always been a matter of concern. To some extent, it can be kept under control, but nevertheless, this issue is directly related to the nature of the thiol group and should therefore always be regarded as a possible side-reaction. As a final outlook, biobased polymeric materials should be considered as an opportunity that can be achieved with thiolactones. This was already briefly investigated in chapter 5, but one could think of more possibilities. In a world in which products from renewable raw materials become increasingly important, a catalyst-free and atom-efficient procedure based on a renewable compound indeed seems to fit extremely well.

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Chapter 10
Nederlandstalige samenvatting (Dutch summary)

Inleiding

Reeds geruime tijd is er een grote interesse in de ontwikkeling van op maat gemaakte polymeerarchitecturen voor de synthese van materialen met aangepaste eigenschappen. Efficiënte reacties zijn daarom noodzakelijk in de polymeersynthese. Een nieuwe evolutie kwam er door de implementatie van click-reacties voor de bereiding van gefunctionaliseerde materialen.[1-6] Een click-reactie moet voldoen aan specifieke voorwaarden: de reactie moet algemeen toepasbaar zijn, hoge opbrengsten zijn vereist en er mogen enkel onschadelijke nevenproducten worden gevormd die gemakkelijk kunnen worden verwijderd.[7, 8]

Behalve de zeer populaire koper-gekatalyseerde Huisgen 1,3 dipolaire cycloadditiereactie tussen een azide en een alkyn (CuAAC), zijn er de laatste jaren nieuwe efficiënte reacties geïntroduceerd die vooral interessant bleken te zijn omwille van het feit dat geen metaalkatalysator vereist is.[9, 10] Eén van de meest veelbelovende onder deze metaalvrije alternatieven is de additiereactie tussen een thiol en een alkeen, vaak benoemd met de term thiol-een (Schema 10-1).[11-15] De reactie heeft enkele aantrekkelijke kenmerken. Ze kan namelijk doorgaan onder een grote verscheidenheid aan reactiecondities. Een groot aantal "enen" en thiolen kunnen worden gebruikt voor de reactie, waarbij de reactiviteit afhankelijk is van het gebruikte thiol of alkeen. Een zeer belangrijk voordeel aan de reactie is dat ze meestal zeer snel doorgaat (ze kan afgelopen zijn in enkele seconden).
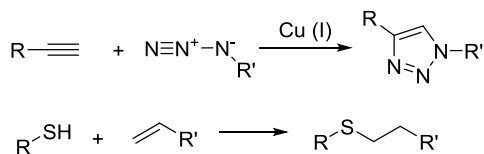
Schema 10-1. Schematische voorstelling van CuAAC (boven) en thiol-een additiereactie (onder), beide voorbeelden van efficiënte koppelingsreacties.

Thiolen zijn reactieve componenten, die gemakkelijk kunnen worden omgezet in thiyl radicalen, maar ook in thiolaat anionen. Deze reactiviteit heeft ertoe geleid dat een groot aantal thiol-gebaseerde reacties voorhanden zijn voor het efficiënt modificeren en synthetiseren van polymeerketens. De meest gekende zijn, naast de radicalaire thiol-een en thiol-yn additiereactie, [16, 17] aan aantal nucleofiele reacties met oxiranen,[18] isocyanaten,[19, 20] halogeenalkanen[21] en α,β-onverzadigde carbonylverbindingen (zoals acrylaten; thiol-Michael additie).[22-24] Dat thiolen veel succesvolle reacties kunnen ondergaan is op zich een voordeel, maar heeft wel als gevolg dat in veel gevallen de chemoselectiviteit in het gedrang komt. Bovendien hebben thiolen vaak een onaangename geur en zijn ze maar beperkt houdbaar omwille van mogelijke disulfide-vorming (oxidatie). Tot slot worden thiolen gebruikt als ketentransferreagentia in vrije radicalaire polymerisaties. Omwille van deze redenen is het veelal noodzakelijk om beschermgroepen voor thiolen te gebruiken. Enkele gekende voorbeelden zijn disulfiden,[25] thioesters (thioacetaten en thiobenzoaten)[26] en thioethers.[27]

DOELSTELLING
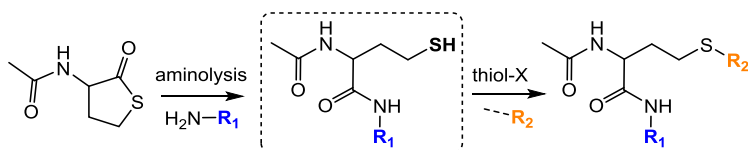
Schema 10-2. Thiolactonen zijn precursoren voor thiolen. Na nucleofiele ringopening kan het gevormde thiol worden omgezet in een vervolgreactie met een substraat dat al dan niet reeds aanwezig is in hetzelfde reactiemengsel.

Het doel van dit doctoraatsonderzoek was de synthese van verscheidene polymeerarchitecturen, gebaseerd op de reactie tussen thiolen en onverzadigde koolstof-koolstof bindingen, algemeen beschreven door de termen thiol-een en thiol-yn chemie. Centraal in het onderzoek staat het implementeren van thiolactonen als precursoren voor thiolen, voornamelijk om het gebruik van tijdsintensieve beschermstrategieën te vermijden. Thiolactonen zijn vijfringen die een thioëster bevatten en werden reeds in de jaren 50 gebruikt als methode voor het derivatiseren van amino-

eindgroepen in lysine-bevattende peptiden.[28, 29] De in dit werk toegepaste thiolactonstrategie laat toe om een thiol te genereren, startend van stabiele (en commercieel beschikbare) amines. De nucleofiele ringopening van het thiolacton leidt bovendien niet enkel tot de vorming van een thiol, maar ook in de covalente additie van een (functionele) groep via het amine. Deze eigenschap was een belangrijke toegevoegde waarde in dit onderzoek, aangezien het toeliet om op een eenvoudige manier functionalisatie van polymeren te verkrijgen, wat anders vaak tijdrovende en inefficiënte post-polymerisatie methoden vereist. Vervolgens kan het thiol in een volgende stap deelnemen in een reactie met een substraat dat al dan niet reeds aanwezig is in het reactiemengsel (Schema 10-2).

Belangrijk in deze meerstapsreactie is dat de sequentiële reacties, zijnde nucleofiele ringopening en thiol koppeling, met een hoog rendement doorgaan, opdat een hoge functionalisatiegraad wordt verkregen.

OVERZICHT

Radicalaire één-pot meerstapssynthese van functionele polymeren
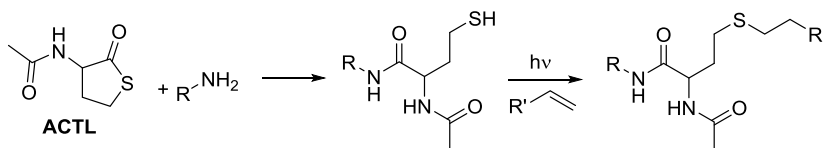

Schema 10-3. Algemeen concept van de onderzochte metaalvrije één-pot meerstapsreactie: nucleofiele ringopening van een model-thiolacton (ACTL) wordt gevolgd door een radicalaire additie van het thiol aan een alkeen.

Een eerste onderzoek, beschreven in hoofdstuk 4, had tot doel de mogelijkheden en beperkingen van thiolactonchemie te onderzoeken in een polymeerchemie context. Eerst werd een modelstudie met laag-moleculair-gewicht componenten uitgevoerd tussen een amine, *N*-acetyl homocysteine thiolacton (ACTL) en norborneen als reactief alkeen. Uit deze studie werd besloten dat de nucleofiele ringopening van het thiolacton de snelheidsbepalende stap is. Het laag-moleculair-gewicht thiolacton werd vervolgens gebruikt voor het modificeren van alkyn-gefunctionaliseerde polyesters, als alternatief op de koper-gekatalyseerde CuAAC reactie. Vervolgens werd een monomeer gesynthetiseerd, alloc-thiolacton, dat zowel een thiolacton als een alkeen bevat, verbonden door een urethaan binding. Op deze manier konden in een één-pot meerstapsreactie polyurethanen bereid worden die functionele groepen (o.a. hydroxyl-groepen) in hun zijketen bevatten. De methode werd

bovendien uitgebreid naar de synthese van polymere netwerken. Het algemeen concept van de één-pot meerstapssequentie wordt weergegeven in Schema 10-3.

Biogebaseerde polyamiden
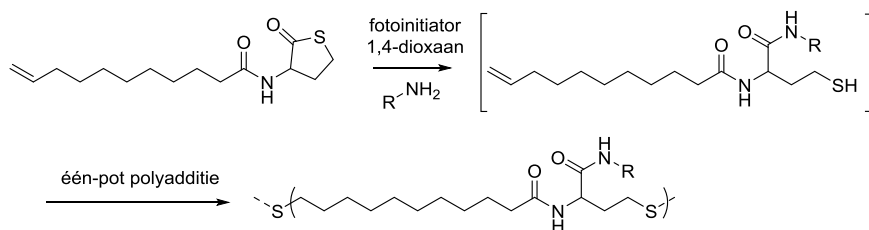
Schema 10-4. Uitgaande van thiolacton-gederivatiseerd undeceenzuur werden polyamide-achtige structuren met variërende zijketens gesynthetiseerd.

De combinatie van de nucleofiele ringopening van het thiolacton met de radicalaire vervolgreactie werd uitgebreid naar de synthese van polyamidestructuren met variërende zijketens (hoofdstuk 5). Hiertoe werd een nieuw monomeer gesynthetiseerd, uitgaande van 10-undeceenzuur als biogebaseerde grondstof. Een reeks alifatische amines met steeds langere zijketens werd gebruikt voor de ring-openingreactie. De gevormde polymeren bevatten amide bindingen in zowel de hoof- als in de zijketens en hadden moleculaire gewichten tot 10 kDa (Schema 10-4). De structuur van de polymeren, met twee amides die zo dicht bij elkaar liggen, leidt ertoe dat de mechanische eigenschappen van de gevormde polymeren beïnvloed worden. De E-modulus en breukrek bereiken waarden die normaal enkel geobserveerd worden voor polymeren met een hoger moleculair gewicht, en zijn bovendien afhankelijk van het aantal koolstofatomen in de amine-zijketen. Het eerste effect kan verklaard worden door de amide waterstofbruggen die het gebrek aan ketenverstrengelingen compenseren. Door een toenemend aantal koolstofatomen in de zijketen wordt het aantal amidebindingen relatief verdund, wat het tweede effect verklaart. Post-polymerisatie modificatie van de hoofdketen werd uitgevoerd door oxidatie. Op deze manier konden sulfonen en sulfoxiden gevormd worden, wat aanleiding gaf tot materialen die brosser waren. Er dient wel opgemerkt te worden dat oxidatie ook optreedt door de polymeren opgelost in THF of dioxaan te bewaren.

Hypervertakte polymeren
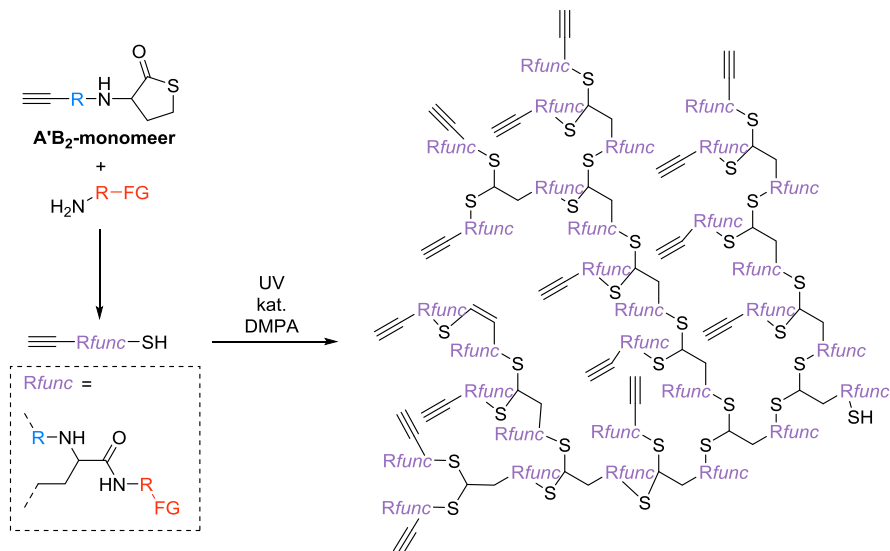
Schema 10-5. Algemeen schema voor de bereiding van gefunctionaliseerde hypervertakte polymeren uitgaande van een A'B₂-monomeer.

Thiolactonchemie in combinatie met radicalaire thiol-yn chemie werd onderzocht voor de synthese van hypervertakte polymeren (beschreven in hoofdstuk 6). Een monomeer met zowel een alkyn- als een thiolacton groep werd gesynthetiseerd als zijnde een A'B₂ monomeer. A' is hierbij het thiolacton, dat door reactie met het amine kan worden omgezet in een thiol (A), en elke π-binding van het alkyn is een B-eenheid. Reactie met een amine geeft aanleiding tot een AB₂ monomeer en, in het bijzijn van fotoinitiator en UV-licht, tot hypervertakte polymeren, gekenmerkt door een brede dispersiteit (Schema 10-5). Thiol-yn chemie werd reeds toegepast voor de synthese van hypervertakte structuren, maar het voordeel van de combinatie met thiolactonen ligt in de eenvoud waarmee functionele groepen kunnen worden ingebouwd in de structuur. Dit vereist met andere woorden geen post-polymerisatie modificatie. Bovendien werd ook het eerder vernoemde alloc-thiolacton gebruikt voor de synthese van hypervertakte polymeren. Hierbij moet een amine geïncorporeerd worden dat ook een dubbele binding bevat, zoals allylamine. Structuuropheldering van de gesynthetiseerde producten gebeurde aan de hand van NMR-spectroscopie en toonde aan dat de tweede additie aan het alkyn sneller gebeurt dan de eerste. Vervolgens werd heterotelechelisch polyTHF gesynthetiseerd, met een alkyngroep op het α-keteneinde en een thiolacton-groep op het ω-keteneinde. De vorming van hypervertakte structuren bleek minder vanzelfsprekend in dit geval, als gevolg van de vorming van micellaire structuren.

Thiolactonen en thiol-Michael additie
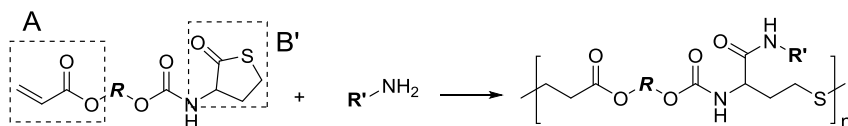
Schema 10-6. Algemeen schema voor de synthese van polyurethaanstructuren, startend van een thiolacton-bevattend AB'-monomeer en een (functioneel) amine. Hierbij zijn geen additieven vereist.

De combinatie van thiolactonchemie en radicalaire reacties met thiolen, houdt de beperking in dat bepaalde functionele groepen niet kunnen worden ingevoerd *via* het amine, zoals b.v. functionele groepen met onverzadigdheden. In een nieuwe benadering werden polyurethanen met functionele groepen op de zijketen bereid door een volledig nucleofiele amine-thiol-een conjugatie (hoofdstuk 7). De radicalaire thiol-een chemie werd vervangen door een nucleofiele thiol-Michael reactie, waarbij het gebruik van fotoinitiatoren en UV-licht vermeden kon worden. Het variëren van zijketens wordt gedaan door het modulair reageren van amines, waardoor op een isocyanaat-vrije manier en zonder vervolgreacties, functionele polyurethanen konden worden bereid in een één-pot meerstapsynthese (Schema 10-6). Modelstudies met online infra-rood metingen en LC-MS studies bevestigden dat het om een kinetische differentiatie ging: de additie van het thiol aan een acrylaat gaat veel sneller dan de additie van een amine aan een acrylaat. Disulfidevorming als nevenreactie is verwaarloosbaar.

Polythiolactonen als precursoren voor polythiolen
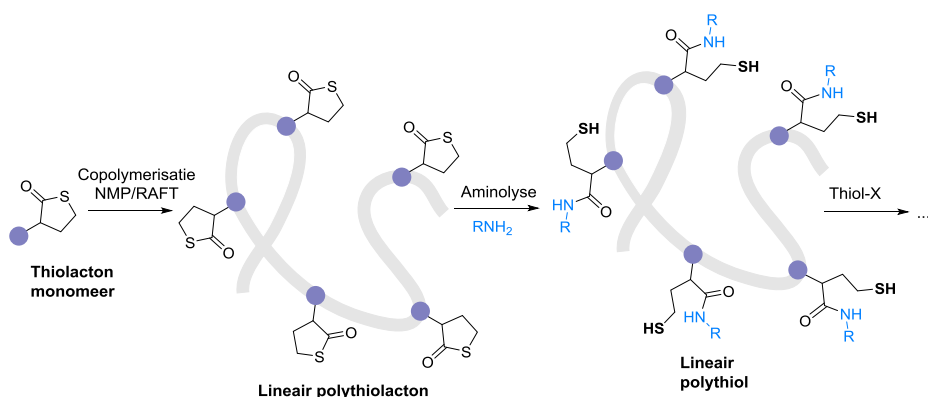
Schema 10-7. Schematische weergave van de dubbele modificatie van thiolacton-zijketens. Na de gecontroleerde polymerisatie (via RAFT of NMP) van een thiolacton monomeer, wordt een lineair poly(thiolacton) gevormd, dat na aminolyse kan omgezet worden in een lineair polythiol.

Tot slot werd aangetoond dat thiolactonen kunnen worden geïncorporeerd als zijketens op een macromolecule (hoofdstuk 8). Deze zijketens kunnen worden beschouwd als reactieve sites waar twee reacties kunnen plaatsvinden. Door nucleofiele ringopening met een amine wordt immers een thiol gevormd, dat vervolgens kan reageren in een thiol-X reactie (Schema 10-7). Startend van thiolacton-gederivatiseerd styreen (St-TLA) als monomeer, konden polymeren gevormd worden via RAFT of NMP polymerisatie. Lineaire polymeren met een variërende thiolacton hoeveelheid (4-25%) konden worden gesynthetiseerd door copolymerisatie met styreen (in het geval van RAFT) en MMA (in het geval van NMP). Door ringopening met een (functioneel) amine werden polythiolen gevormd. Disulfidevorming, en dus de vorming van polymeernetwerken, kon worden voorkomen door de reactie te laten doorgaan in ethaanthiol als (co-)solvent. Op deze manier was het mogelijk om verschillende gefunctionaliseerde polymeren te bereiden met lage dispersiteiten. De verkregen polythiolen werden vervolgens gefunctionaliseerd door middel van een thiol-maleïmide conjugatie. De efficiëntie waarmee de dubbele modificatie doorging werd aangetoond met NMR spectroscopie.

Conclusie

Algemeen kan gesteld worden dat de hier beschreven thiolactonstrategie toelaat om een grote waaier aan polymeermaterialen te bereiden, al dan niet gefunctionaliseerd. Als aanvulling op de gekende thiol-gebaseerde chemie in de functionalisatie van polymeermaterialen heeft de methode zich onderscheiden als een eenvoudig toepasbare manier om meerdere functionele groepen te incorporeren, zonder het gebruik van beschermstrategieën. In het hier beschreven onderzoek werden thiolactonen geïncorporeerd in monomeren voor de synthese van polyurethaan-achtige structuren (hoofdstuk 4) en biogebaseerde polyamiden (hoofdstuk 5). Dit gebeurde door een radicalaire thiol-een chemie. Vervolgens werd dit onderzoek uitgebreid naar de synthese van gefunctionaliseerde, hypervertakte polymeren (hoofdstuk 6). Ook werd het gebruik van radicalaire chemie omzeild door over te schakelen naar de nucleofiele thiol-Michael additie (hoofdstuk 7). Tot slot werden thiolactonen als reactieve sites op de polymeerhoofdketen ingebouwd (hoofdstuk 8).

Behalve de hier beschreven chemie, werd de veelzijdigheid van de thiolactonstrategie bewezen in tal van andere onderzoeken. In de eigen onderzoeksgroep worden op dit moment thiol-een gebaseerde netwerken ontwikkeld met behulp van thiolactonen, met als doel functionele groepen op een eenvoudige manier in te bouwen. Modificaties op polymeernetwerken kunnen als doel hebben antibacteriële eigenschappen te verkrijgen, of verontreiniging tegen te gaan. Dankzij het gebruik van thiolactonen, kunnen deze eigenschappen worden geïncorporeerd *tijdens* de synthese van de polymeerfilms. Ander onderzoek heeft geleid tot de sequentie-gecontroleerde synthese van

oligomeren,[30] zijketen-gefunctionaliseerd pNIPAAm,[31] polymere beads, … Ook in andere onderzoeksgroepen werden thiolactonen aangewend, onder meer als PEGylering methode[32] of als "coupler" monomeer voor de synthese van thiol-gefunctionaliseerde polymeren.[33]

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