Thiolactone chemistry, a versatile platform for macromolecular engineering

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Abstract

Thiolactones are often described as latent thiols. They can be ring-opened by hydroxy or amine groups releasing thiols, which can further react with a large variety of functional groups. Based on this one-pot cascade reaction, versatile and powerful tools have been developed for macromolecular engineering. This review covers the different uses of γ-thiobutyrolactones in polymer chemistry either as thiolation agents, as linkers, as ring-opening polymerization monomers, as reactant in stepwise polymerization, as components of initiating systems, or as functional handles for double post-modification reactions.

Keywords: cascade reaction, double post-modification reaction, ring-opening, polymerization thiolactone chemistry, macromolecular engineering.

Abbreviations

AIBN: azobisisobutyronitrile

AROP: anionic ring-opening polymerization

ATRP: atom transfer radical polymerization

BEMP: 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

DABCO: 1,4-diazabicyclo[2.2.2]octane

DBTL: dibutyltin dilaurate

DBU: 1,8-diazabicyclo(5.4.0)undec-7-ene

DMA: dimethylacrylamide

DMAP: 4-diméthylaminopyridine

DMPA: 2,2-dimethoxy-2-phenyl acetophenone

DMF: dimethylformamide

DTT: dithiothreitol

EDC: 1-ethyl-(3-3-dimethylaminopropyl) carbodiimide hydrochloride

EGE: eugenol glycidyl ether

HEA: hydroxyethylacrylamide

HTL: homocysteine thiolactone

LCST: lower critical solution temperature

MADIX: macromolecular design via the interchange of xanthates

MALDI TOF: matrix assisted laser desorption ionization - time of flight

MeCN: acetonitrile

NHTL: *N*-acetyl homocysteine thiolactone

NHS: *N*-hydroxysuccinimide

NIPAM: *N*-isopropylamide

NMP: nitroxide mediated polymerization

PAM: polyacrylamide

PDEAEMA: poly(2-(diethylamino)ethyl methacrylate)

PDSEMA: poly(pyridyldisulfide ethylmethacrylate)

PDMS: polydimethylsiloxane

PEO: poly(ethylene oxide)

PPEGMA: poly(poly(ethylene glycol) methacrylate)

PVP: polyvinylpyrrolidone

RAFT: reversible-addition fragmentation chain transfer

ROP: ring-opening polymerization

TBL: γ-thiobutyrolactone

TEA: triethylamine

Tg: glass transition temperature

TLA: thiolactone acrylate derivative

TlaAm: *N*-(acryloyl) homocysteine-γ-thiolactone, thiolactone acrylamide

VGE: vanilin glycidyl ether

Introduction

Lactones have been widely studied and used in macromolecular chemistry over the past decades. In particular, numerous recent review papers are giving a general overview of the ring-opening polymerization (ROP) of lactones.[1, 2] Other reviews are focusing on specific lactone families, such as macrolactones,[3] γ-butyrolactones[4-6] and α-unsaturated γ-butyrolactones,[6] or are dealing with various synthetic pathways, including as metal-catalyzed,[7] rare earth metal initiated,[8] organo-catalyzed,[9] enzymatic,[10] and stereoselective[11] ROP. Comparatively, thiolactones have been scarcely used in macromolecular chemistry because of their low polymerizability. The polymerizations of β-propiothiolactone,[12] δ-thiovalerolactone,[13] and ε-thiocaprolactone[13, 14] have been only sporadically reported since the sixties. However, due to a growing interest for sulfur-containing polymers in various application areas, including optics, coatings, heavy-metal recognition and medical technology,[15, 16] thiolactones have been increasingly investigated over the last decade in polymer science. This renewed interest has arisen with the seminal work of the group of Du Prez on the use of γ-thiolactones in polymer chemistry.[17] In this review, we will exclusively focus on five-membered ring thiolactones (also called γ-thiobutyrolactone or γ-thiolactones), which are the most commonly used in

the macromolecular field. It is worthy to note that a large number of the thiolactone derivatives discussed here were prepared from D,L-homocysteine thiolactone (HTL). HTL is a renewable chemical derived from homocysteine or methionine amino acids, and is commercially-available at relatively low cost. Contrary to γ-butyrolactone, for which the homopolymerization has already been published despite the low strain energy of its five-membered ring,[4] the homopolymerization of monocyclic γ-butyrolactone has never been reported. Even if this lack of polymerizability was detrimental to the synthesis of polythioester by anionic ring-opening polymerization (AROP), thiolactones are often regarded as latent thiols which can be released by nucleophilic ring-opening in a 100% atom-efficient way, making subsequently possible to benefit from a large toolbox of efficient thiol-X reactions.[18] They offer opportunities to circumvent the drawbacks related to the direct use of thiols (e.g. unpleasant smell, limited commercial availability, tendency to oxidation, and low shelf life) or encountered by conventional protecting/deprotecting strategies (e.g. low atom efficiency, purification step and low overall yield). Therefore, one-pot (multistep) reactions based on the versatile thiolactone chemistry became the starting point for various synthetic strategies in macromolecular synthesis. The incorporation of a large variety of sulfur-based chemical functionalities (thiols, thioethers, disulfides or thioesters) is made possible by the polymerization process or by post-modification reaction. The sulfur atom incorporation takes places within the main chain, on the lateral substituents or at the polymer chain ends. In addition, thiolactone chemistry enables the versatile design of various architectures, such as dendrimers[19] or 3D networks.[20]

In 2015, two reviews dealing with the use of γ-thiolactones in macromolecular chemistry were published by Du Prez *et al.* These reviews mainly focus on polyaddition based on one-pot multi-step thiolactone reactions and on the double modification of thiolactone-containing polymers.[21, 22] In this review, we intend to give an overview of γ-thiobutyrolactones derivatives in macromolecular chemistry including their use as thiolation agents, linkers, (co)monomers in ROP processes, comonomers in the formation of polymer repeat units by cascade reactions, components of the initiating systems, or functional handles for double post-modification reactions. The various reaction conditions described in the literature will be presented, and the recent advances will be emphasized. In

addition, the use of thiolactones for the synthesis of periodic copolymers and sequence-defined macromolecules will be discussed.

A. Thiolactone as thiolation agent

Thiol chemistry is a powerful and widely used tool in macromolecular science, which currently remains highly investigated in the fields of polymer synthesis[23] and peptide chemistry.[24] The generation of thiols on macromolecules is always a challenging task and many approaches have been developed.[25] A one-step 100% atom-efficient strategy involving γ-thiolactone as a masked thiol has been developed more than 60 years ago for the thiolation of proteins.[26] The thiol is released by the nucleophilic ring-opening of the thiolactone ring according to an addition-elimination mechanism. Up to now, primary amines and alcohols are by far the most commonly encounter chemical functionalities acting as nucleophiles in this reaction. It is worth noting that hydroxyl functions are unable to open the thiolactone under neutral conditions and require the presence of a base or an enzymatic catalyst.[27] On the contrary, primary amines are more nucleophilic than alcohols and can open thiolactone rings without the presence of catalyst.

A.I. Reaction between thiolactone and amine-bearing macromolecules

A.I.1. Primary amine pendant groups

A.I.1.a. Peptide and protein thiolation

A high plasma level of homocysteine is a known risk factor for several diseases, such as neurogenerative or cardiac diseases.[28] It turns out that extracellular homocysteine is enzymatically converted *in vivo* in *N*-homocysteine thiolactone, which can react with the ε-amino groups of protein lysine residues under physiological conditions and generates a thiol moiety on the surface of the protein (Figure 1). This modification of biological proteins, a process called *N*-homocysteinylation, is detrimental to their function and increases oligomerization through disulfide bridge formation.[29-31] For the first time in 1956, Benesch *et al*. mimicked this reaction using *N*-acetylhomocysteine thiolactone to introduce thiol groups in natural proteins in biochemistry.[26] This atom economical technique

enabling the preparation of thiol-containing peptides and similar ones were patented,[32, 33] after which *N*-acetyl homocysteine thiolactone (NHTL) was used for the thiolation of numerous amine-containing natural compounds. Interestingly, NHTL, also medically called citiolone, is commercially-available at relatively low cost.

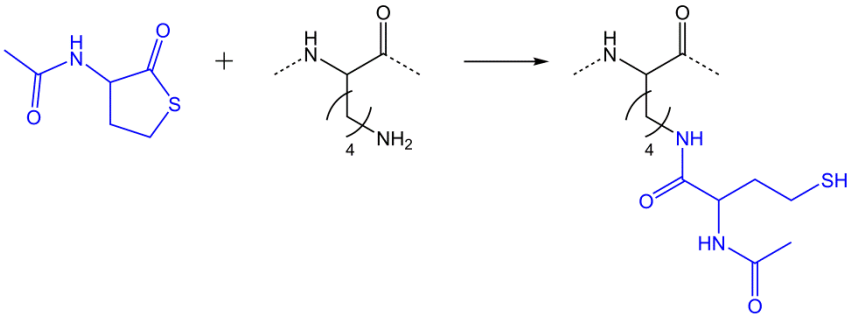

Figure 1. Modification of a peptide lysine residue by *N*-acetyl homocysteine thiolactone.

Klotz *et al.* showed that the thiolation of gelatin with *N*-acetylhomocysteine thiolactone is catalyzed in the presence of imidazole.[34] The thiolation of **gelatin** was carried out in degassed sodium-carbonate buffer at pH=10 at 40 °C under inert argon atmosphere using an excess of NHTL.[35] Thiolated gelatins have subsequently been used to prepare reversible gelatin-based hydrogels,[35] gelatin hydrogel for tissue engineering[36, 37] or for high definition 3D bioprinting.[38, 39] Thermo-responsive hybrid hydrogels based on poly(2-oxazoline) and thiolated gelatin have also been recently prepared by the group of Hoogenboom.[40] Thiol groups have also been introduced on collagen by reacting lysine side-chain amino groups with γ-thiobutyrolactone in EtOH/PBS at room temperature for 24 hours.[41] Around 60% of the total lysines were functionalized with -SH groups. In addition, various acidic derivatives of homocysteine thiolactone have been used to introduce thiol functionalities into various proteins.[42] The **albumin** lysine residues were reacted with *N*-substituted homocysteine thiolactone. Interestingly, under physiological conditions, the reaction proceeded site-specifically on the lysine residues having the lowest pKa (only three of the 59 protein lysine residues).[28, 43-45] Chubarov *et al*. synthesized *N*-trifluoroacetylhomocysteine thiolactone (TFA-tHcy) and *N*-perfluorinated thiolactone. Due to their water-solubilities, these fluorine-labeled homocysteine thiolactones are suitable for ^{19}F labeling of proteins under mild conditions. In particular, they were reacted with human serum albumin, generating

a fluorine-labeled macromolecular probes that could be used as tags for ^{19}F magnetic resonance imaging.[43, 45]

Polylysine acetate has been thiolated at room temperature with TBL in an aqueous solution at pH = 9.[46] The thiol groups generated during the thiolactone ring-opening have been concomitantly oxidized in order to generate S-S cross-linking between the polypeptide chains. Up to 30% of the ε-amino groups could be functionalized.

Overall, it was shown that the steric and electronic properties of the amine highly affect the rate of thiolactone aminolysis. Low aminolysis rates were observed for residues with bulky side chains, which strongly limited the use of thiolactone in amide synthesis.[47] Burdick and coworkers demonstrated that the addition of a silver catalyst at pH>7 led to an efficient thiolation of several amino-functionalized (bio)macromolecules using *N*-acetylhomocysteine thiolactone.[48] And recently, Lin and coworkers developed a method involving tandem activation of the thiolactone by silver-DABCO pair allowing an efficient reaction with sterically hindered residues such as valine, proline, isoleucine and leucine with high yields. An unprecedented range of thiol-containing amino acid residues or oligopeptides was synthesized and could be used afterwards for the modification of bioactive compounds by thiol-X chemistry.[49]

A.I.1.b. Chitosan thiolation

In addition to peptides and proteins, the thiolation of various amino-containing oligo- and polysaccharides, in particular chitosan, has been studied.[50-52] The dissolution of chitosan in lactic acid followed by its reaction with homocysteine thiolactone in the presence of imidazole as catalyst was poorly efficient.[52] The amino lateral substituent of HTL acted as competitor of the chitosan primary amino groups, resulting in low substitution degrees. Therefore, HTL was replaced by NHTL in the following research works.[53] In addition, Ferris et al. demonstrated the need to work in a buffered medium allowing a partial and equilibrated protonation of chitosan primary amines.[54] The protonated amines allows the dissolution of chitosan, while neutral nucleophilic amines are needed for the efficient aminolysis of the thiolactone ring. Thus, the thiolation of chitosan was carried out at 25°C at

pH=6.0 in an aqueous buffer solution of 2-(*N*-morpholino)ethanesulfonic acid (MES) for 48 h in the dark and under inert atmosphere.[54] Thiolated chitosan has found multiple applications, for example as a bioadhesive polymer in drug delivery,[55] or to generate oil core-polymer shell microcapsules[53] Thiolated aminocellulose was demonstrated as an efficient medium in affinity chromatography.[51] Finally, the thiolation of an amino-containing **oligonucleotide** was also carried out using *N*-acetyl homocysteine thiolactone in a sodium phosphate buffer at pH=8.0.[56]

A.I.2. Primary amine end-groups

Thiolactone chemistry was also used to introduce a thiol group at the end of amino end-functionalized macromolecules. At first, **polyethyleneimine** and its derivatives were thiolated.[57-59] The functionalization was performed in water at room temperature using TBL,[57] in dichloromethane at room temperature using NHTL,[58] or in DMF at 55°C with a bis-thiolactone.[59] Thiol functionalized PEI were adsorbed onto the surface of gold nanoparticles in order to reduce their toxicity[58] or coated *in situ* on carbon nanotubes in the preparation process of high-performance Li-S batteries.[59] PEG-PEI were also thiolated using BTL at room temperature in water at pH 5-6.[60] The amino end groups of poly(oxyethylene-co-oxypropylene) (Jeffamine) were converted into thiol by a reaction with NHTL in chloroform in the presence of DMPA (as photoinitiator) and readily photografted *in situ* on unsaturated macromolecular derivatives, such as poly(3-hydroxyoctanoate)-co-(3-hydroxyundecenoate)[61] or polyphosphazene.[62]

Zhao *et al.* synthesized a thiolactone derivative with a fluorescent moiety (dansyl thiolactone) by the coupling reaction of dansyl chloride with HTL in the presence of TEA (Figure 2).[63] Then, a multifunctional PEG derivative containing both fluorescent and protein-reactive groups at the chain end was prepared by the reaction of an amino terminated methoxy poly(ethylene glycol) with dansyl thiolactone and 2,2′-dithiodipyridine as thiol scavenger.

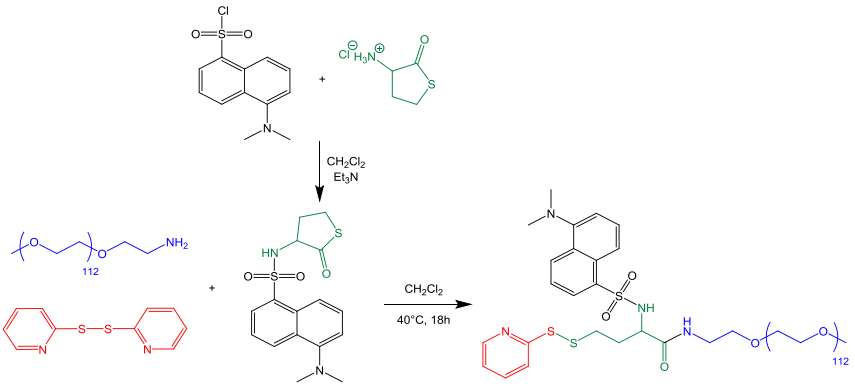

Figure 2. Synthesis of fluorescent protein-reactive PEG derivative.[63]

Destarac and coworkers developed a xanthate-mediated route to functional γ-thiolactones.[64] These thiolactones were used to functionalize amino-terminated poly(ethylene oxide) and amino-terminated polydimethylsiloxane in the presence of acrylates playing the role of thiol scavengers. Very recently our group benefit from the properties of the thiolactones to develop a one-pot, two step method to efficiently initiate the AROP of propylene sulfide using primary amine / γ-thiolactones as initiating system in the presence of BEMP superbase[65] allowing the synthesis of well-defined α,ω-heterotelechelic poly(propylene sulfide)s (Figure 3).[66]

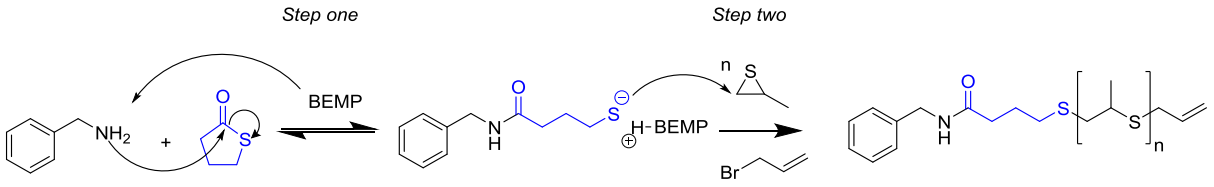

Figure 3. AROP of propylene sulfide initiated using benzyl amine / BTL as initiating system in the presence of BEMP superbase.[66]

A.II. Reaction between thiolactone and alcohol-bearing macromolecules

Martinelle and coworkers performed the thiolation of hydroxy end-terminated polycaprolactone and of polypentadecalactone using γ-thiobutyrolactone in the presence of *Candida antarctica* Lipase B (CALB) as catalyst (Figure 4).[67-69] More than 90% thiol functionalization were obtained by this simple process. Very recently, BTL was used to introduce an ester linker between an hydroxy initiating compound and a polythioether chain.[66]

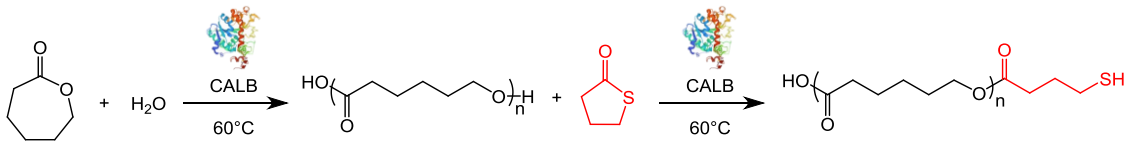

Figure 4. CALB-catalyzed caprolactone polymerization and subsequent thiolation with BTL.[69]

The group of Albertson studied the thiolation of hemicellulose using γ-thiobutyrolactone.[70] In the absence of a catalyst, hemicellulose hydroxyl groups are not sufficiently strong to undergo the 1,2-nucleophilic addition leading to the ring-opening of the thiolactone ring. Therefore, a non-nucleophile strong base (NaH) was added in DMSO, at room temperature and under N_2 to deprotonate the hydroxy groups and thus, enhance their nucleophilicity and their reactivity toward the thiolactone. Thiolated hemicellulose with a degree of substitution equal to 0.16 were obtained and subsequently reacted under various click reaction conditions, yielding hemicellulose-based hydrogels.[70] Low thiolation rate (up to 6%) were also obtained by reacting poly(vinyl alcohol) with γ-thiobutyrolactone under extreme conditions: 30 w% sulfuric acid in DMSO at 90°C and under argon for 3 days.[71] The lipase-catalyzed reaction of hydroxy groups appeared to be more efficient. Langer and coworkers performed the γ-thiobutyrolactone ring-opening thiolation of ethoxylated polyols using CALB-immobilized on acrylic resin reaching up to 80-85 % functionalization rate of the hydroxy groups.[72]

Finally, besides primary amines and alcohols, *N*-acetyl homocysteine thiolactone was also reacted with the hydrazide groups of hydrazido sepharose in $NaHCO_3$ to introduce thiol groups.[73] However, the efficiency of the coupling was not precisely evaluated.

B. Introduction of thiolactone functional group on macromolecules

The introduction of thiolactone groups into macromolecules is of particular interest due to the rich and varied chemistry of these chemical moieties. First, thiolactones can serve as a chemically-activatable reaction handle for the introduction of multiple thiol functionalities into macromolecules. Latent thiols prevent the inherent drawbacks of free thiols as already mentioned in the introduction and the thiol is

released when necessary by the addition of primary amines. Secondly, thiolactone ring is one of the few handles allowing double post-polymerization modification of polymers, as it has already been highlighted by Du Prez and coworkers in 2015.[74] These functionalizations are easy to perform under mild conditions. In this chapter, we intend to give a comprehensive overview of the strategies available to introduce thiolactone rings on a polymeric system as lateral substituents or as end-groups. These protocols can be classified in two main categories: the thiolactone can be introduce either by the polymerization process or by post-functionalization of pre-existing functional polymer chains.

B. I. Introduction of thiolactone during the polymer synthesis

The polymerization of thiolactone-bearing thiolactone monomers or the use of thiolactone-containing initiators in controlled polymerization processes are complementary pathways to introduce thiolactone moieties on macromolecules. It should be noted that the direct use of thiol-bearing monomers or initiators is almost impossible because free thiols strongly interfer with numerous polymerization processes, in particular radical and ionic polymerizations. Different polymerization techniques have been reported to date for the use of thiolactone containing monomers within the polymerization. In most cases, radical polymerization techniques have been employed but metathesis or stepwise polymerization processes were also reported.

B.I.1. Polymerization of thiolactone-containing monomers.

B.I.1.a. Radical polymerization of thiolactone-containing monomers.

Thiolactone moieties are fully compatible radical mechanism. Therefore, numerous thiolactone-bearing vinyl monomers (Figure 5) have been (co)polymerized by free or controlled radical polymerization methods leading to polymers with pendant thiolactone moieties.

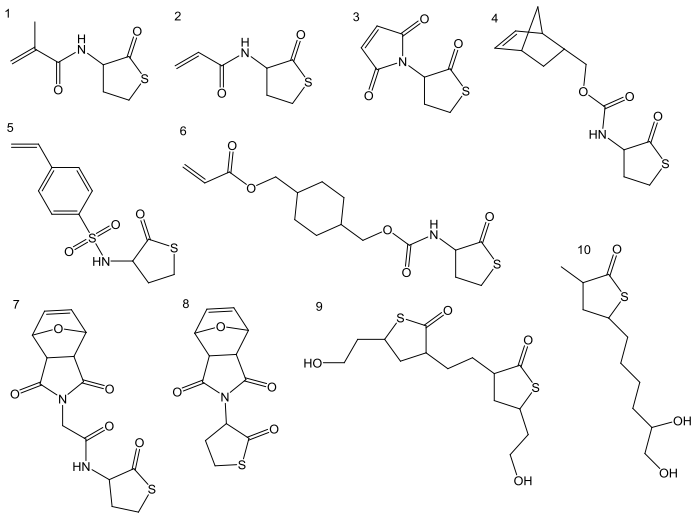

Figure 5. Monomers used for the synthesis of thiolactone-bearing polymers.

Free radical polymerization

Kitano *et al.* reported the first radical copolymerization of *N*-methacryloyl-D,L-homocysteine thiolactone (Figure 5.1) with lipids-derived monomers initiated by potassium peroxydisulfate at 60°C in order to prepare homocysteine-containing polymerized liposomes.[75] Later, polyacrylamide chains bearing thiolactones (PAM-TL) have been synthesized by free radical polymerization of *N*-(acryloyl) homocysteine-γ-thiolactone (Figure 5.2) initiated by AIBN in DMF at 70°C,[76] or by micro-wave assisted surface-initiated radical polymerization.[77] PAM-TL were successfully applied in industrial waste-water for capturing Ag(I), due to the highly selective and highly effective adsorption ability of thiolactones toward Ag(I).[76] Alternatively, PAM-TL brush surfaces were modified with amines and functional acrylates or maleimides in DMSO in the presence of TEA at room temperature, in order to prepare various multifunctional polymer surfaces.[77] A thiolactone-functionalized maleimide (Figure 5.3) was synthesized by Rudolph *et al.* and polymerized by free radical polymerization using either AIBN as initiator in THF at 70°C or Lucirin TPO in dichloromathane/or in the bulk under UV irradiation.[78] In addition, free radical copolymerization of thiolactone-containing norbornene monomer (Figure 5.4) and methyl acrylate were carried out using AIBN as initiator at 80°C in butyl acetate for 3 hours.[79]

Controlled radical polymerization

Reversible-addition fragmentation chain transfer (RAFT) is the most commonly used controlled radical polymerization technique for polymerization of thiolactone-derived monomers. In 2012, the group of Du Prez synthesized a thiolactone-containing styrene monomer (Figure 5.5). Due to solubility issues, the homopolymerization of this monomer was poorly controlled and only low conversions were obtained. Therefore, it was copolymerized with styrene at 70°C in DMSO in the presence of AIBN as initiator and a trithiocarbonate chain transfer agent.[80] Copolymer with a tunable content of thiolactone units, molar masses up to 18 kg/mol and dispersities around 1.5 were obtained. *N*-(acryloyl) homocysteine-γ-thiolactone (Figure 5.2) has been copolymerized with different monomers under classical RAFT polymerization conditions (e.g.: AIBN as initiator, trithiocarbonate chain transfer agents, in dioxane at 65-70°C): *N*-isopropylamide (NIPAM),[74, 81-83] dimethylacrylamide (DMA),[84-86] NIPAM/DMA,[74] *N*-hydroxyethylacrylamide (HEA)[87] and n-butyl acrylamide.[88] Copolymers with dispersity values between 1.1 and 1.4 and molar masses up to 30 kg.mol^{-1} were obtained. These copolymers typically contained between 5 and 30% of thiolactone units. The homopolymerization of *N*-(acryloyl) homocysteine-γ-thiolactone (Figure 5.2) was also carried out by RAFT in DMF, which solubilizes both monomer and homopolymer.[89] More complex polymer architectures were also prepare: PDEAEMA-b-P(NIPAM-st-TlaAm) block copolymer,[90] PPEGMA-b-P(NIPAM-st-TlaAm) block copolymer,[91] or double hydrophilic block copolymers (DHBC).[92] Another interesting monomer, maleimide thiolactone (Figure 5.3), was synthesized by Rudolph *et al.*[78] This monomer was copolymerized with styrene and NIPAM via controlled radical polymerization using AIBN as initiator and a trithiocarbonate chain transfer agent in dioxane at 70°C. In the case of styrene comonomer, strictly alternating copolymers were obtained.

Besides RAFT, two other controlled radical polymerization techniques have also been reported. Thiolactone-containing styrene monomer (Figure 5.5) was copolymerized with methyl methacrylate under NMP conditions using MAMA-SG1 blockbuilder in the presence of SG1 in DMF at 90°C for 3 hours.[80] A series of copolymers with a tunable thiolactone content (up to 13%) were obtained. A thiolactone-containing acrylate derivative (Figure 5.6) was copolymerized with n-butyl acrylate by ATRP.[93] Statistical copolymers and poly(*tert*-butyl acrylate-b-*n*-butyl acrylate-co-TLA)s

having up to 20% thiolactone units were prepared. Recently, methyl methacrylate and a thiolactone-containing styrene monomer (Figure 5.5) were copolymerized by surface-initiated ATRP from a regenerated cellulose membrane.[94] Pre-functionalization of silica particles with the ATRP initiator were used to initiate the copolymerization of HEA and TLAam.[95]

B.I.1.b. Ring-opening metathesis polymerization of thiolactone-containing monomers

Two thiolactone-bearing oxanorbornene monomers (Figure 5.7 and 5.8) were synthesized by the group of Durmaz and copolymerized with butyl-functionalized oxanorbornene monomer by ring-opening metathesis polymerization using the first generation Grubbs catalyst at room temperature.[96] The resulting polymers had the expected number-average molar masses (around 10-12 $kg.mol^{-1}$) and relatively narrow dispersities (1.21 to 1.35).

B.I.1.c. Step-growth polymerization of thiolactone-bearing monomers

Well-defined polyurethanes containing side-chain and in-chain thiolactone groups have been recently synthesized by polyaddition using a chain extension method. To this end, two different thiolactone-functionalized diols (Figure 5.9 and 5.10) were reacted with isocyanate–telechelic urethane prepolymers of different chain lengths, resulting in polyurethanes bearing thiolactone groups either within or along the polymer backbone and with different densities of functionalization.[97]

B.I.2. Chain-end functionalization with thiolactone moieties (thiolactone-containing initiators)

The introduction of reactive thiolactone handles at the end of a polymer chain is also of particular interest as it will allows subsequent double modification under mild conditions. Thus, diverse thiolactone end-functionalized polymers have been prepared via various strategies. Copper-mediated controlled radical polymerization was carried out using a thiolactone containing initiator for the synthesis of various polymers, such as polystyrene or polybutylacrylate (Figure 6.A). High thiolactone-end-group fidelities was demonstrated by MALDI ToF analyses.[98] Monteiro and

coworkers synthesized a γ-thiolactone functional RAFT agent and used it for NIPAM RAFT polymerization at 60°C in DMSO (Figure 6.B).[99] The resulting poly(NIPAM) macro chain transfer agents were subsequently used in RAFT-Mediated Emulsion Polymerization of styrene in water to directly produce multifunctional worms and rods. More recently, the group of Destarac developed various thiolactone-containing mediators for reversible-deactivation radical polymerization: bromo-containing ATRP initiators, xanthates for RAFT/MADIX polymerization and SG1-based alkoxyamine for NMP (Figure 6.C and 6.D).[100] All these agents were used for the successful syntheses of thiolactone end-functionalized polymer chains.

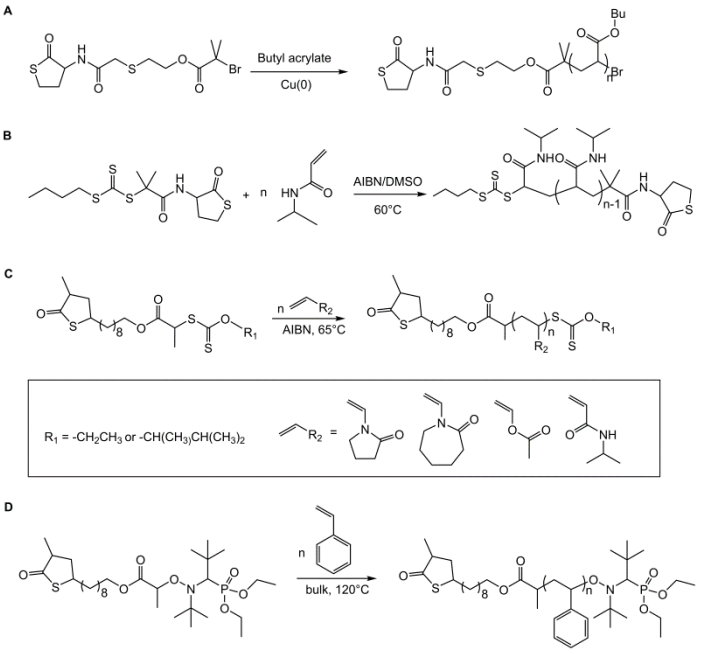

Figure 6. A) Thiolactone-containing ATRP initiator for the polymerization of n-butyl acrylate;[98] B) Thiolactone-containing chain transfer agent for the RAFT polymerization of NIPAM;[99] C) Thiolactone-containing chain transfer agent for the RAFT-MADIX polymerization of various vinyl monomers;[100] D) Thiolactone-containing alkoxyamine initiator for the polymerization of styrene.[100]

B.II. Synthesis of thiolactone-bearing structures via post-modification approach.

Another approach to incorporate thiolactone moieties into a macromolecule structure is the postmodification of other functional groups using coupling reactions.

Homocysteine thiolactone was reacted with poly(γ-glutamic acid) in the presence of 1-ethyl-(3-3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) in water at pH = 6 (Figure 7.A).[101] Unfortunately, the presence of side-products resulting from a possible secondary coupling between the amine group of one homocysteine thiolactone and the thiolactone of another one was not assessed. The resulting thiolactone grafted poly(glutamic acid) have degrees of substitution up to 54% and were cross-linked with cysteine grafted ε-polylysines to form hybrid polypeptide hydrogels.

Alternatively, α-isocyanato-γ-thiolactone was reacted with various hydroxy end-functionalized polymer chains, such as PEO, polycaprolactone and polydimethylsiloxane, in the presence of dibutyl laurate as catalyst (Figure 7.B).[20, 98] Quantitative end-capping was demonstrated by MALDI ToF spectroscopy and NMR analyses. Recently, natural pullulan in dried DMSO was reacted overnight at 65°C with α-isocyanato-γ-thiolactone. The hydroxy group in C6 position is sterically less hindered and more reactive and thus was preferentially functionalized.[102] Biocompatible hydrogels were then prepared in PBS without addition of a catalyst by a click-like reaction of thiolactones with diamines and/or amine-containing biological substrates, such as gelatin or GHK oligopeptides.

An azide-bearing thiolactone was reacted in DMF with a polyester possessing electron-deficient triple bonds in the main backbone, through metal-free cycloaddition reaction (Figure 7.C).[103] The resulting thiolactone-functional polyesters is a promising platform for the preparation of novel polymeric materials by means of thiol-Michael addition reaction. The reverse pathway has been used by Phan et al. to introduce a thiolactone end-group on a azide end-functionalized poly(sulfobetaine).[104]

Thiolactone-containing polymeric ionic liquid were obtained by the quaternization of poly(1-vinylimidazole) with a bromo thiolactone derivative and then used as blend with PVP to prepare nanofiber mats by electrospinning, the presence of the thiolactone units allowing easy orthogonal double post-functionalization by aminolysis followed by thiol–alkene “click” reaction (Figure 7.D).[105]

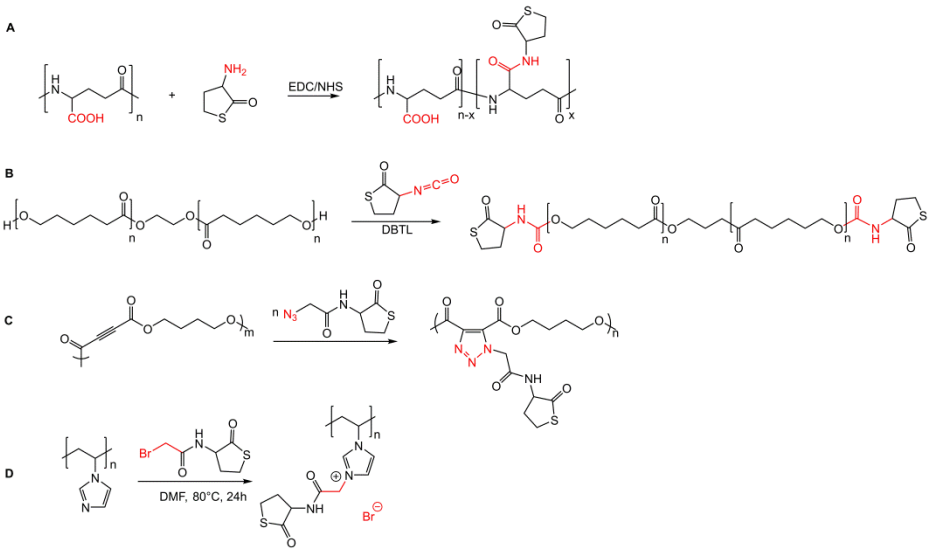

Figure 7. Different post-modification strategies to introduce thiolactone moieties on polymers. A) Carboxylic acid - amine condensation;[101] B) reaction between alcohol and isocyanate;[98] C) Alkyne - azide cycloaddition reaction;[103] D) alkylation of imidazole with bromide derivative.[105]

B. III. Double modification reactions of thiolactone moieties

Thiolactone substituents provide multiple possibilities for chemical modifications. They are susceptible to double modifications. Thiolactones are active esters, which react readily with various nucleophilic functional groups. However, to the best of our knowledge, only primary amines have been used for the nucleophilic attack of thiolactone-functional macromolecules. Thiols released by the ring-opening exhibit a high reactivity toward a large variety of substrates (Figure 8). First, thiols are able to be added to unsaturated bonds to give sulfides (or thioethers). Depending on the reaction conditions and on the nature of the double bond, the mechanism can be nucleophilic or radical mediated. The most used process is the Michael-type nucleophilic addition of thiols to activated olefins (electron-poor double bonds or "Michael acceptor"). Electron-rich enes are used as substrates in radical reactions with thiyl radicals, and can be initiated by UV irradiation or radical initiators. Secondly, compounds containing a disulfide bridge are able to undergo disulfide exchange reactions with thiols. Finally, other nucleophilic reactions with thiolate anions are possible, such as reactions with isocyanates, epoxides and halogens. It is worth noting that the double modification reactions were according to a one-pot strategy in the vast majority of cases. However, a two-step pathway was

occasionally adopted with the intermediary purification of the thiol-containing macromolecules. The aims of this part is to provide an overview of this powerful double post-polymerization toolbox.

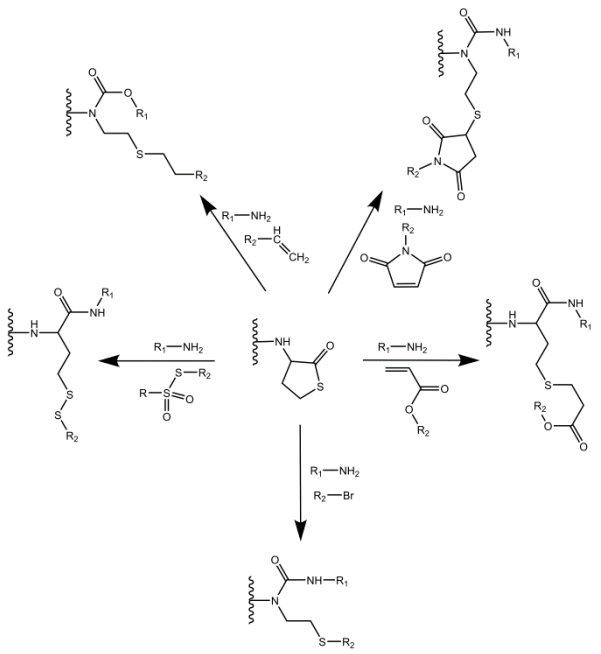

Figure 8. Most common strategies for thiolactone double modification.

B.III.1. Amine / thiol−ene double post-polymerization reaction

B.III.1.a. Thiolactone double modification using amine / Michael addition

The thiol-Michael addition is an organic reaction between a thiol and an alkene compound bearing an electron-withdrawing substituent. This efficient and versatile type of reaction has received significant attention in material chemistry.[106] Among the diverse electron withdrawing activating groups that enable the nucleophilic addition of thiol anion to olefins, acrylates were the most commonly used Michael acceptors.

Acrylates as Michael acceptors.

In 2013, The group of Du Prez introduced one-pot cascade double functionalization reaction between thiolactone-bearing polyacrylates synthesized by RAFT, primary amine molecules and acrylates.[74] After the ring-opening of the thiolactone by a primary amine, the released thiol groups were instantly trapped by acrylate compounds present in the reaction mixture. It should be notice that amine groups

can also slowly react with acrylates according to an aza-Michael mechanism.[107] The groups of Du Prez and Möller separately investigated these potential orthogonality issues and performed model reactions with γ-thiolactones in the presence of primary amines and acrylates. A high kinetic selectivity in favor of the reaction between thiol and acrylate groups was demonstrated and no significant traces of aza-Michael adducts could be detected.[108, 109] This ring-opening/Michael post-polymerization modification of thiolactone-bearing polymers has been reported many times since then. In the majority of cases, the double modification proceeded in a quantitative manner with low molar mass primary amines and acrylates, under mild conditions, without the presence of any catalyst but in the presence of reactant excess.[74, 78, 89, 105] As evidenced by MALDI ToF analyses, this double modification strategy was also successfully applied to thiolactone end-terminated polymers (PEO and polycaprolactone) and to the synthesis of midchain functionalized block copolymers via polymer-polymer conjugation (Figure 9).[98]

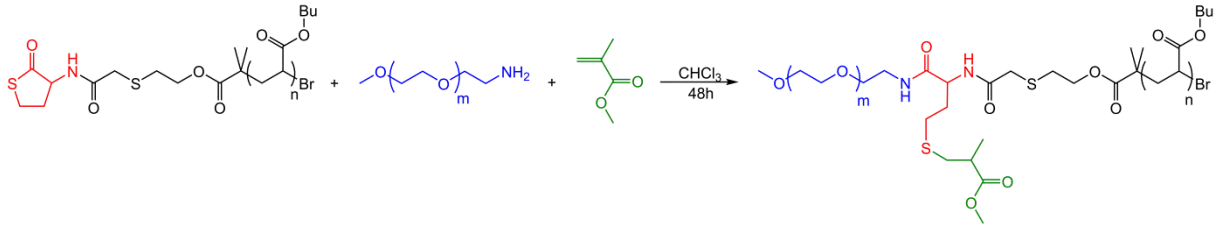

Figure 9. Synthesis of midchain functionalized polycaprolactone-*block*-PEO copolymers via polymer-polymer conjugation.[98]

When the double modification is carried out in the presence of both primary amine and acrylates compounds, aminolysis is the rate-determining step.[22] Some authors reported the influence of the amine bulkiness on the yield of the ring-opening reaction: partial functionalization for bulky amines (e.g. benzyl- or octylamine) while propyl- or allylamine reacted quantitatively.[93] Similarly, Baysak *et al.* demonstrated that an increase of the steric hindrance of the carbon atom in alpha position of the primary amine strongly decreased the efficiency of the ring-opening reaction, as expected by the decrease of the amine nucleophilicity. The efficiency of the amino compound was evaluated as follows: butylamine ≈ hexylamine > allylamine ≈ benzylamine > cyclohexylamine >> tert-butylamine.[96, 103] Except for the highly sterically-hindered tert-butylamine, it was however possible to reach quantitative amidation by increasing the number of equivalents of amino compounds or the

reaction time.[103] Moderate functionalization value was found when furfurylamine was used probably due to a reduced nucleophilicity of the amine in the presence of the electron-rich furfuryl group.[96] These results are in good agreement with the rate constants determined by Espeel et al.[108] of the model aminolysis of BTL in the presence of different primary amines: $k_{propylamine} > k_{N,N\text{-}dimethylethylenediamine} > k_{tert\text{-}butylamino\ acetate} \approx k_{furfurylamine} \approx k_{allylamine} \approx k_{benzylamine} > k_{propargylamine} > k_{Jeffamine\ M\text{-}600}$.

In addition, the thiolactone accessibility had also a strong influence on the yield of the double post-functionalization reaction. For polymer chains having a high density of lateral thiolactone moieties, the maximum double modification rate was more limited. For example, only 60 % of conversion could be reached for the double modification of poly(styrene-*alt*-maleimide thiolactone) alternating copolymers.[78] Moreover, Baysak *et al.* showed that the farther the thiolactone moieties are from the main backbone, the higher is the yield of their reaction with amine and methacrylate compounds.[96]

Interestingly in a paper of Reese *et al.*, the double post-polymerization modification of poly(acrylamide-homocysteine thiolactone) brushes was performed with 4-bromobenzylamine and 1H,1H-perfluoro-*N*-decyl acrylate using either sequential or one-pot strategies, enabling a comparison of both pathways.[77] Interestingly, the functionalization rate of the second step was higher in the case of the one-pot strategy (59% aminolysis conversion, 74% thiol-Michael conversion) than in the case of the sequential process (54% aminolysis conversion, 11% thiol-Michael conversion). The authors assumed that the one-pot process enabled both reactants to readily diffuse into the brush resulting in a more efficient double conjugation.

This double modification strategy enables the synthesis of well-defined macromolecules and various architectures. The possibility to control the degree of functionalization enabled to prepare polymers with finely tuned properties, such as poly(NIPAAm)-based polymers with various cloud points,[74] or a variety of new polymeric ionic liquid.[89] Amphiphilic graft and toothbrush copolymers were also synthesized by reacting poly(n-butylacrylamide-co-thiolactone acrylamide) with propylamine and voluminous acrylate-end-terminated PEO.[93] Silicone-based 3D-networks were generated by the reaction of thiolactone end-functionalized PDMS with diamine and diacrylate monomers.[20]

Finally, thiolactone-bearing polymers were used to coat acrylamide- and amino-functional surfaces. Various thiolactone containing copolymers (poly(DEAEMA)-block-poly(NIPAM-st-TlaAm), poly(DEAEMA)-block-poly(NIPAM-st-TlaAm)) were ring-opened with diverse alkylamines, followed by thiol-ene coupling reactions with acrylamide-coated magnetite nanoparticles (MNP). The coated nanoparticles were used in controlled drug release and bio-conjugation.[90] Interestingly, the degree of hydrophobicity of the coated nanoparticles can be tuned by using primary amines with various alkyl chain lengths, thus influencing the nanoparticles self-assembly properties in water. A similar strategy was used to prepare a range of new HPLC stationary phases by immobilizing thiolactone-containing thermoresponsive copolymers on aminopropyl-silica in the presence of various acrylate compounds in THF or dioxane,[83] or for the preparation of mixed-mode membrane absorbers.[94]

Other types of Michael acceptor

Double modifications by aminolysis and subsequent thiol click reaction have also been performed with other type of Michael acceptor, such as methacrylates[94] or maleimides.[80] However, it is worth mentioning that primary amines can react with maleimides.[110] Therefore, when maleimides are used, a two-step reaction protocole is required. The polythiols has to be isolated and then, reacted with maleimides.

B.III.1.b. Thiolactone double modification using amine / radical thiol-ene addition

Thiolactone-containing polymer chains could also be double post-functionalized by reaction with a primary amine followed by a radical thiol-ene reaction with an allyl group. Radical thiol-ene addition have low activation energy and therefore, can be performed under mild conditions. Such a process was used to prepare polymeric ionic liquid using ionic liquid bearing an allyl group[89] or to graft β-1-O-allyl galactose tetra-acetate on polyacrylamides in order to obtain polymer GM1 mimics.[87]

B.III.1.c. Thiolactone double modification using amine / thiol-disulfide interchange reactions

The thiol groups released from the thiolactone rings during the aminolysis reactions were also reacted with different scavengers, such as thiosulfonates,[97, 100] or pyridyl-disulfide compounds[92] in order to generate disulfide bonds by thiol-disulfide interchange reactions. Unlike Michael acceptors, these scavengers do not react with amine groups, reducing the need of reactant excess. In addition, this new disulfide bond can be cleaved in the presence of a reducing agents. Destarac and coworkers performed the double post-functionalization of different TL-terminated polymers using an amine−thiol−thiosulfonate reaction. For example, TL-polyNIPAM was reacted with benzylamine and methylmethanethiosulfonate in THF at 30°C for 3 days.[100] The total double modification was proven by MALDI-ToF analysis. The same group used amine/thiosulfonates reactions to double post-modify polyurethanes containing side-chain or in-chain thiolactone groups (Figure 10).[97] If both localization could be modified, in-chain thiolactones were less reactive than side-chain thiolactones due to higher steric hindrance.

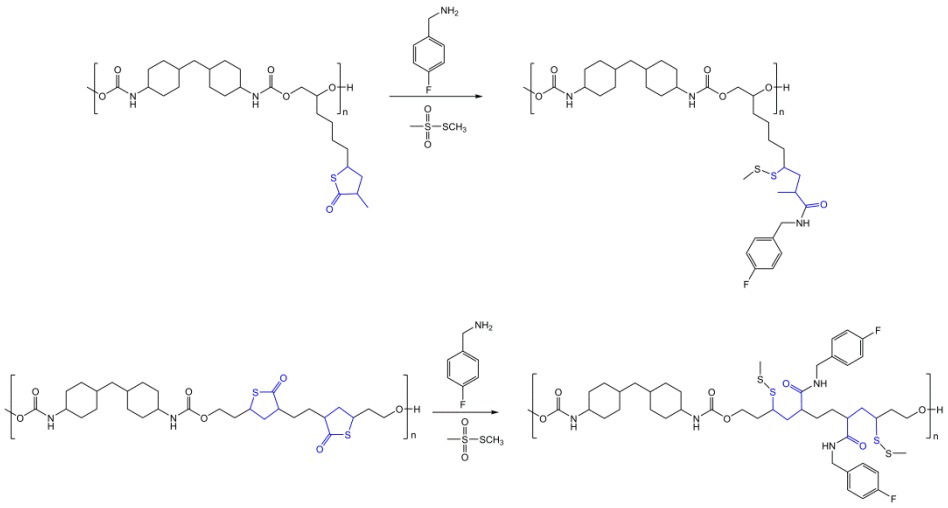

Figure 10. One-pot double post-polymerization modification reactions of thiolactone-containing polyurethanes.[97]

A striking example of the usefulness of the double modifications is the labeling of double hydrophilic block poly(meth)acrylates bearing thiolactone lateral substituents with a pH-sensitive naphthalimide-based amine derivative and a rhodamine B pyridyl-disulfide derivative.[92] The thiolactone chemistry

enabled the covalent attachment of both fluorescent probes on the same repeating units. The double modification induced a close proximity between both fluorophores (donor and acceptor) enabling non-radiative energy transfer (FRET), which stops if the redox-responsive disulfide linkage connecting rhodamine B to the polymer chain is cleaved by a reducing agent. γ-thiolactone functional worms and rods were produced by RAFT-Mediated Emulsion Polymerization in water using a thiolactone functional macro-RAFT transfer agent.[99] The thiolactone at the surface of the nano-objects were subsequently converted to allyl and pyridyl disulfide groups for further orthogonal reactions.

The group of Demoustier-Champagne used the double modification of poly(DMA-coTlaAm) for the coating and functionalization of gold surfaces. Instead of using thiosulfonates or pyridyl-disulfide compounds, they directly used functional thiols to generate the disulfide bond. Parts of the generated thiols were used for the formation of stable sulfur-gold bonds, and the remaining thiol groups were reacted with thiol-containing functional/active molecules, such as fluorophore, enzyme, bioadhesive or bioactive peptides.[84-86] Similarly, the free thiols formed after the ring-opening reactions of thiolactone groups of various copolymers were used to coat amino-functionalized magnetite nanoparticles and cross-linked the polymer chain through disulfide bonds in order to induce the formation of magnetite nanoparticles clusters.[91]

B.III.1.d. Thiolactone double modification using amine / nucleophilic reaction with halogen derivatives

A thiolactone-containing polyacrylamide was modified in a one-pot two-steps process. First it was reacted in chloroform with n-alkyl amines at room temperature and then 2-bromoethyl tetra-O-acetyl-mannopyranoside was added at 60°C to prepare glycopolymers.[82] The double post-functionalisation proceeded with high efficiency in a near-quantitative manner. However, this reaction has some drawbacks: the reactions proceeded in the presence of triethylamine and tris(2-carboxyethyl) phosphine to respectively neutralize the generated HBr prevent cross-linking caused by the oxidation of thiols to disulfides. The resulting amphiphilic graft copolymers have self-assembly properties,

affording glycopolymer-based nanoparticles. Interestingly, the size of the amine residue controlled both the size and the morphology of the particles.

B.III.1.e. Double modification of thiolactones in the presence of primary amine and thiol-scavenger containing polymers

Thiolactone double modification reactions were also used in a slightly modified strategy in which the polymer is bearing thiol scavenger groups and thiolactone molecules are used as linker. For example, thiolactone-functionalized drug molecules (e.g. with paclitaxel) were reacted with *N*-(3-aminopropyl)-imidazole and poly(ethylene glycol)-block-poly(pyridyldisulfide ethylmethacrylate) (PEG-PDSEMA) in the presence of TEA in order to synthesize imidazole-containing block copolymer prodrugs (Figure 11).[111] These amphiphilic copolymers self-assembled in water into drug-loaded micellar nanoparticles. The presence of imidazole groups and disulfide bonds provide pH and glutathione responsiveness for tumor acidity-promoted cellular internalization and intracellular drug release. Recently, the post-modification of acrylate-end-functionalized polyisobutylene was carried out with the commercially-available *N*-acetylhomocysteine thiolactone and various primary amine in the presence of DBU.[112]

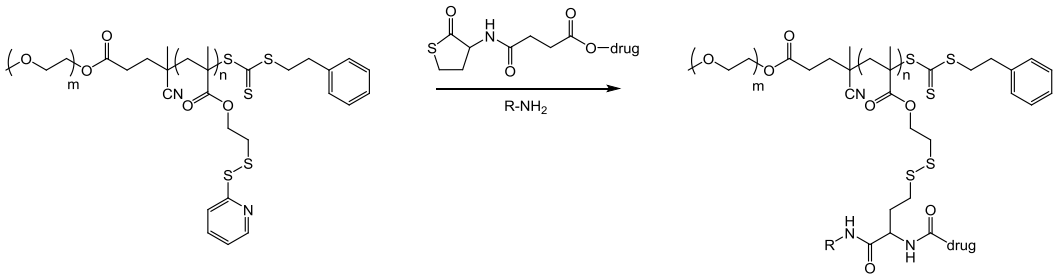

Figure 11. Synthesis of varying block copolymer prodrugs via thiolactone chemistry reaction among thiolactone-functionalized drug molecules, functional moiety-containing amines, and PEG-PDSEMA.[111]

C. Thiolactone derivatives used as monomers

In this chapter, thiolactones actively participate in the generation of polymer main chains, either as heterocyclic monomers in ring-opening polymerization or as reactant in multi-step stepwise polymerization.

C.I. γ-thiolactones as (co)monomers in ring-opening polymerization

The ring-opening polymerization of thiolactone was less studied than the ROP of lactones. The polymerizations of 4-, 6- and 7-membered thiolactones (β-propiothiolactone,[12] δ-thiovalerolactone,[13] and ε-thiocaprolactone[13, 113]) have been occasionally reported since the sixties. More recently, the controlled ring-opening polymerization of β-thiolactone derived from cysteine has been achieved,[114] DNA-mimicking polythioesters were prepared by controlled ROP of δ-thiolactone monomer, [115] and well-defined poly(ε-thiocaprolactone) were achieved by organocatalyzed ROP in the presence of thiourea[113] or by lipase-catalyzed ROP.[116] Nevertheless, to the best of our knowledge, the homopolymerization of monocyclic γ-thiolactones have never been reported due to their ring stability. Only recently, Lu and coworkers succeeded to homopolymerize a 4-hydroxyproline-derived γ-thiolactone to produce a fully recyclable polythioester.[117] The higher ring strain of the bridged bicyclic monomer allows the ROP to proceed even at room temperature. The introduction of bridged rings improve polymerizability of the thiolactone and the crystallinity of the polythioesters. Similarly, a bridged bicycle thiolactone, 2-thiabicyclo[2.2.1] heptan-3-one ([2.1.1]BTL) enabled the facile synthesis under mild conditions of polythioesters with very good thermomechanical properties.[118] In addition, these polymers can be easily depolymerized and reused: full chemical recyclability. The copolymerization of substituted γ-thiolactones with trimethylene carbonate has been reported by Destarac and co-workers allowing the preparation of poly(carbonate-co-thioester)s.[119] However, the percentage of thiolactone incorporation remained limited, less than 10 mol%. The ring-opening copolymerization of γ-thiobutyrolactone with non-polymerizable epoxides initiated by quaternary onium salts was reported by Nishikubo and co-workers.[120] Strictly alternating poly(ester-alt-thioether)s were obtained but with high dispersities and low molar-mass control. A good control of the alternating ring-opening copolymerization of thiolactones and epoxides was recently achieved using alcohol-phosphazene bases as initiating systems (Figure 12).[121] A strict alternating character was observed even when highly reactive epoxide monomers were used. The prepared poly(ester-alt-thioether)s are promising materials due to the presence of both cleavable ester groups and reactive oxygen species-sensitive thioether groups in each repeating unit of the main backbone. Despite the presence of a

weakly acidic amide group in the structure of commercially-available bio-based *N*-acetyl homocysteine thiolactone, the use of benzyl alcohol-BEMP as initiating system allowed its alternating copolymerization with various epoxides.[122] Well-defined copolymers were synthesized. It is noteworthy, that these NHTL-based copolymers have significantly higher Tg compared to similar stuctures prepared with γ-thiobutyrolactone. This result can be explained by the presence of acetamido lateral substituents in each repeating unit and the establishment of intermolecular H-bonding. The alternating ring-opening copolymerization of NHTL was also performed with epoxides derived from eugenol or vanillin, two bio-based aromatic alcohols, resulting in a series of fully renewable poly(ester-alt-thioether)s.[123] In the case of vanillin glycidyl ether, the synthesis of copolymers bearing one aldehyde function every repeating unit without any protection-deprotection step has to be highlighted, even if obtained *Mn* remained currently limited. Poly(NHTL-alt-EGE) and poly(NHTL-alt-VGE) scaffolds are reactive platforms that could be further functionalized using a wide range of mild chemical reactions.

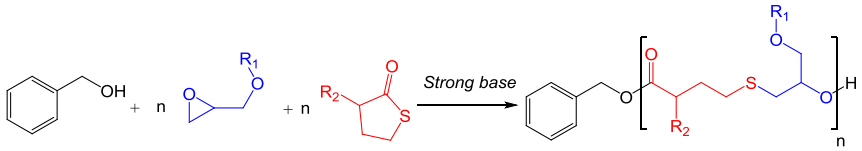

Figure 12. Alternating ROP of γ-thiobutyrolactone and epoxides using benzyl alcohol in combination with a strong base as the initiating system.[121]

C.II. Thiolactone-based multi-step reactions for polymer synthesis

Since the seminal paper of Espeel and coworkers in 2011,[17] the thiolactone chemistry has been used to synthesize a large range of multi-functional polymers by stepwise polymerization. These one-pot multi-step polymerizations are efficient tools that enables the generation of polymer backbones containing various combination of functional groups (thioether, ester, carbamate, disulfide...) and bearing various lateral substituents. In the first part, we introduce the polymers for which the main chain is obtained by thiol-X chemistry, resulting in the incorporation of the sulfur atoms in the

polymer backbone, mainly as thioether or as disulfide. In the second part, the main chains are formed by the reaction of the thiolactone rings and amine groups, resulting in sulfur-containing lateral substituents.

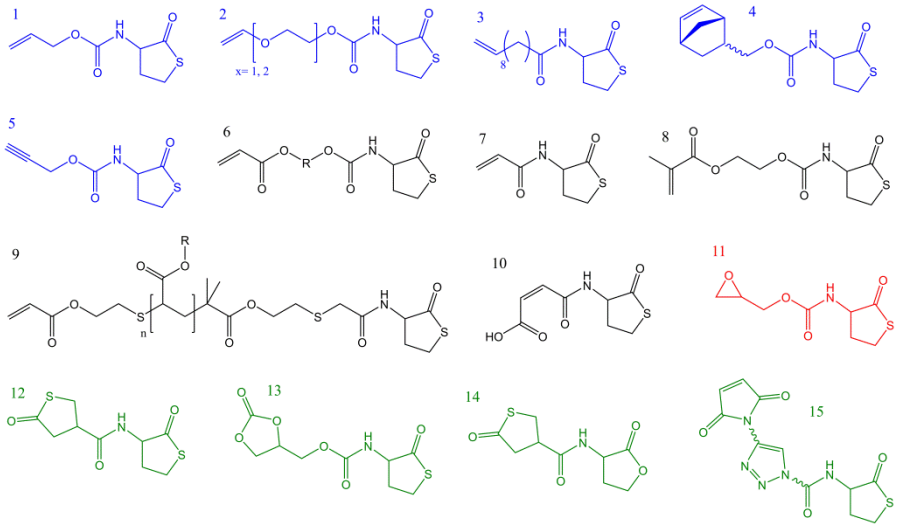

Figure 13. Thiolactone-containing difunctional monomers used in stepwise polymerizations.

C.II.1. Thiolactone-based stepwise polymerization: Sulfur atom incorporated in the main polymer chain

Various strategies have been developed to prepare a variety of multi-functional backbones, in which sulfur atoms are integrated in the repeating unit of the main chain. We propose the following classification.

The ***AB+C-->A'B*** strategy (Figure 14) requires the synthesis of a AB monomer containing both a thiolactone ring (A) and a thiol scavenger functional group (B). Polymers are obtained through the nucleophilic attack by an amine (C) of the thiolactone ring, which *in situ* generates a thiol group (A') able to react further with the thiol scavenger of the monomer.

The ***2A+BB+CC-->A'A'+BB*** strategy (Figure 19.B) does not require the preliminary synthesis of a thiolactone functional AB monomer. In this case, thiolactones (A) are reacted with diamines (CC) to generate dithiols (A'A'), which undergoes a stepwise polymerization in the presence of another difunctional monomer bearing suitable thiol scavenger functionalities (BB).

In the ***A+BC-->A'B*** strategy (Figure 17), a thiolactone (A) reacts with a compound containing both a primary amine group and a thiols scavenger moiety (BC) to generate a difunctional monomer containing both a thiol and a thiol scavenger (A'B), which immediately undergoes a stepwise polymerization.

In all these approaches, various type of thiol-X chemistry have been used to perform the polyaddition of the *in situ* generated monomers.

C.II.1.a. Polyaddition based on radical thiol-ene chemistry

A mild and efficient one-pot cascade reaction process was first published by the group of Du Prez in 2011 for the synthesis of polyurethanes. In this paper, AB-monomer, containing an allyl and a thiolactone unit connected by a urethane linkage (Figure 13.1), was reacted with a primary amine in order to generate an allyl- thiol-containing A'B monomer. The latter was subsequently used in stepwise radical thiol-ene photopolymerization yielding polyurethane structures that also contain a thio-ether linkage in their backbone (poly(urethane-thioether), Figure 14.A).[17] Different nature of polymer backbones can be generated by changing the chemical nature of the linker between the carbon-carbon double bond and the thiolactone ring in the A'B monomer. Poly(polyether-urethane-thioether) were prepared using an AB monomers containing both vinyl ether and thiolactone groups connected through a poly(ethylene oxide) linker (Figure 13.2).[124] A similar polyaddition procedure was applied for the synthesis of diversely substituted polyamide structures using a fully renewable thiolactone amide derivative of 10-undecenoic acid (AB monomer, Figure 13.3).[125] The obtained polymers have original chemical structures including two amide bonds and one sulfide linkage per repeating unit. The choice of the primary amines for the aminolysis reaction strongly affects the polymer physical properties, such as Tg[125] or LCST,[124] by varying the length and chemical nature of the lateral substituents. In addition, (functional) networks were obtained by using diamine compounds.[17, 125] Cross-linked film with good resistance and transparency properties were prepared by the reaction under UV of thiolactone-containing monomers (Figures 13.1 and 13.3) with various diamines and polyamines.[126] The amine thiol-ene polymerization was also successfully applied to a

thiolactone monomer with substituted norbornene moieties leading to new linear polyurethane having bridged bicyclic norbornane in its backbone.[79]

The previous amine thiol-ene polymerizations were typically conducted in weakly polar solvents (1,4-dioxane or THF) using 2,2-dimethoxy-2-phenyl acetophenone (DMPA) as photoinitiator under UV irradiation et 365 nm.[17, 79, 124, 125] 4-dimethylaminopyridine (DMAP, 5 w%) was used as nucleophilic catalyst for the aminolysis by Du Prez and coworkers in their pioneering work[17] but this catalyst was not used in the following papers. It can be noted that the properties of the polymers were modified by post-polymerization oxidation of the thioether linkages to their corresponding sulfoxides and sulfones.[125] The degree of oxidation strongly influenced the mechanical properties: full oxidation of the sulfides made the polymers stiffer and more brittle.

Yan et al. synthesized a thiolactone combined with an alkyne group through a carbamate linkage (Figure 13.5). This A_2B-type monomer was subjected to aminolysis and subsequent radical thiol-yne polyaddition generating hyperbranched materials.[127] The triple bond was able to react twice with thiols without any photoinitiator and under sunlight irradiation.

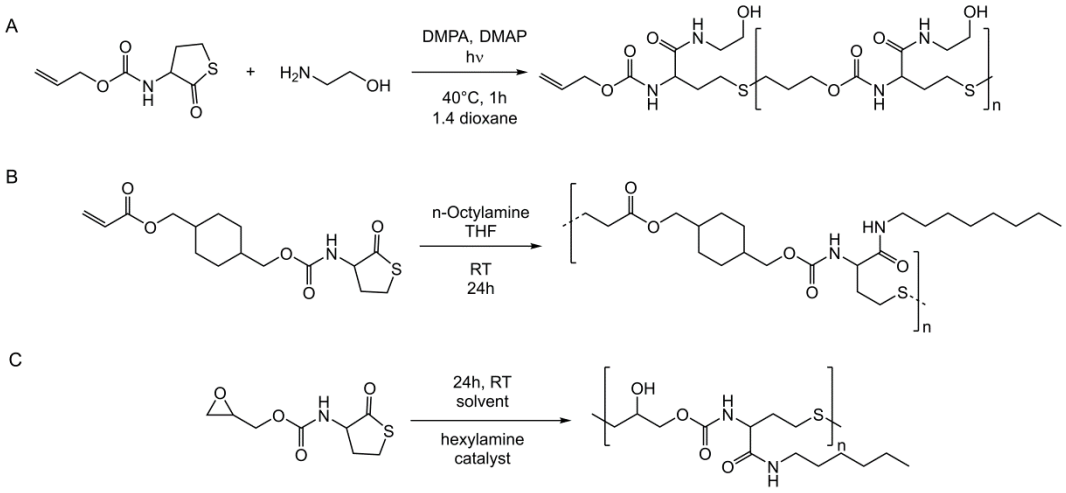

Figure 14. Stepwise polymerizations of various thiolactone derivatives in a one pot process according to a AB+C-->A'B strategy: radical thiol-ene addition,[17] Michael addition[108] and thiol-epoxy step growth reactions.[128]

C.II.1.b. Polyaddition based on nucleophilic thiol-ene chemistry (Michael addition)

The scope of the previous process remains limited due to the radical nature of the polyaddition, which precludes the presence on the primary amine of common functional groups, such as double and triple bonds or furfuryl groups. Other drawbacks are the presence of photo-initiator and the sensitivity of the some primary amines to radicals. Therefore, Espeel et al. proposed to replace the allyl double bond in the AB monomer with an acrylate function (Figure 13.6).[108] The electron deficient acceptors nature of acrylate double bonds allows a nucleophilic addition mechanism for the step-growth polymerization in the presence of oxygen and the complete absence of radical species during the polymerization. This one-pot combination of TBL aminolysis and subsequent thiol-(meth)acrylate addition was used to prepare numerous functionalized poly(ester-urethane-thioether)s (Figure 14.B),[108, 129] and poly(amido-thioether).[129] It should be noted that this process is remarkably versatile and tolerant to post-functionalizable moieties, such as double, triple bonds or reactive dienes. However, aza-Michael addition of the amine to the Michael acceptor is a potential side reaction. Therefore, the chemoselective discrimination between both nucleophiles (amine and thiol) has to be clearly evaluated.

Driessen et al. were also able to synthesize acrylate and thiolactone end-functionalized AB macromonomers (Figure 13.9).[130] A thiolactone-containing ATRP initiator was synthesized using a one pot, two-step protocol and used to initiate the Cu(0) polymerization of isobornyl acrylate. After full conversion, the bromine end-group was transformed into an acrylate, yielding an heterotelechelic thiolactone-acrylate end-functionalized poly(isobornyl acrylate).[130] The previous macromonomer was used to prepare a precision functionalized multi-segmented block copolymers via the nucleophilic ring-opening of the thiolactone unit by a primary amine and consecutive thiol-Michael addition. Interestingly, this strategy yielded a library of polymer chains, with functionalities equally spaced across the backbone. Figure 13 shows the various (meth)acrylate-containing thiolactone monomers that were used in this alternative strategy. These polymerizations based on Michael addition were typically conducted under mild conditions at room temperature in weakly (THF) to highly polar

solvents (DMSO) in the absence of any additive/catalyst.[108, 130] One paper reported that dimethylphenylphosphine (DPP) is an efficient catalyst for thiol-(meth)acrylate Michael addition in DMSO.[129] It is worth noting that the choice of the primary amine allowed the introduction of numerous substituents ranging from PEG chains to reactive handles.

The Michael addition between nucleophilic thiols and activated double bonds is not limited to (meth)acrylate groups but can also be carried out with other chemical groups, such as acrylamides, maleimide or *N*-maleamic acid. Stimuli-responsive poly(amido thioether)s with various pK_a and hydrophobic content or with tunable LCST and UCST behaviors have been synthesized using acrylamide thiolactone (Figure 13.7) and different amines.[129, 131, 132] The resulting polymers were used to stabilize oil-in-oil emulsions.[131, 132] Likewise, precisely alternating polyampholytes with poly(amido thioether) backbones have been obtained by the ring-opening in the presence of primary amines and the subsequent nucleophilic Michael polyaddition of N-maleamic acid functionalized homocysteine thiolactone monomer (Figure 13.10).[133] The reaction was carried out in water at room temperature in the presence of $NaHCO_3$ (basic catalysis). Redox-responsive nanogels were prepared by the reaction of PSBs functionalized with terminal groups of furan-maleimide adducts and thiolactone with cystamine as cross-linker in the presence of DMPA and under UV irradiation (Figure 15).[104]

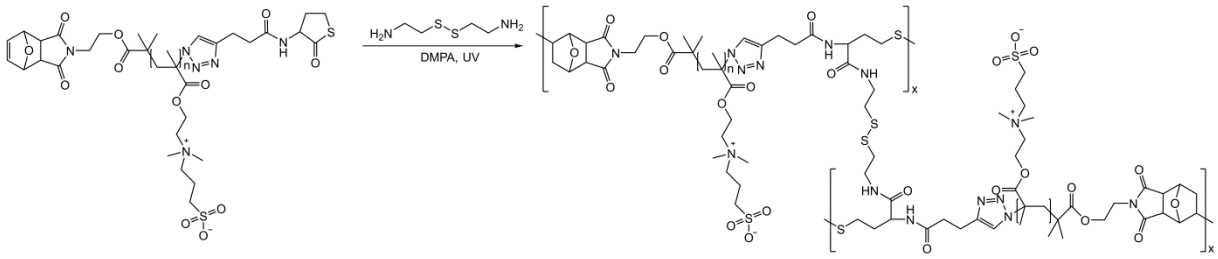

Figure 15. Synthesis of redox-responsive nanogels via thiol-ene reaction.[104] Copyright 2020. Reproduced with permission from Elsevier.

C.II.1.c. Polyaddition based on thiol-epoxy reaction

The group of Möller reported the reaction of a carbamate-linked epoxy-thiolactone (AB bis-cyclic monomer, Figures 13.11) with hexylamine to yield poly(urethane-thioether)s with pendant hydroxyl

groups (Figure 14.C).[128] It should be noted that if the ring-opening of the thiolactone is fast and the presence of a basic catalyst is not mandatory, the polyaddition process as the epoxy thiol active A'B monomer has to be carried out under basic conditions. The efficiencies of different bases (DMAP, DBU and LiOH) were tested on the whole one-pot two-step process. DMAP was detrimental to the thiolactone ring-opening kinetics and a poorly efficient catalyst for thiol–epoxy polymerization reaction of the bis cyclic monomer. In the presence of DBU, the polyaddition is catalyzed but the rate constant of the thiolactone ring-opening is lower than without a catalyst. When DBU is used, both the thiolactone ring-opening as well as the polyaddition reaction are catalyzed. Eventually, LiOH was the most efficient in catalyzing both the thiolactone ring-opening and the polyaddition. Polymerizations were performed in different solvent (THF, DMF, MeCN, MeCN/H_2O); for all tested conditions, the number-average molar masses are limited (max 4300 g/mol) and (cyclic) oligomers are present. As expected, the replacement of the monoamine compound by PEG diamine enabled the preparation of hydrogels. Interestingly, Möller and coworkers demonstrated in a second paper that amino acids lithium salts were able to react and open at room temperature the thiolactone ring of an epoxy-containing thiolactone monomer, *in situ* generating a thiol- epoxy- AB monomer, which immediately underwent a base-catalyzed thiol-epoxy polyaddition.[134] A series of functional poly(thioether-urethane)s with amino acids in the side chain was synthesized and used to prepare nanoparticles through polyelectrolyte complexation.

C.II.1.d. Polyaddition based on thiol-cyclocarbonate reaction

Very recently, the group of Detrembleur used the S-alkylation of thiols with cyclocarbonates (Figure 16) according to a *2A+BB+CC-->A'A'+BB* strategy.[135] Diamino compounds, *N*-acetylhomocysteine thiolactone and tri-cyclocarbonates were mixed together in DMSO at 80°C in order to build self-blown polyhydroxyurethane foams. Amine groups rapidly ring-opened the thiolactone ring releasing thiol groups. Simultaneously, two competitive ring-opening reactions of the cyclocarbonates were observed; that is, the acylation of the amine to form hydroxyurethane linkages and the alkylation of

the thiol soft nucleophile with concomitant CO_2 generation. Reactions were performed in the presence or in the absence of DBU. In contrast to the hydroxyurethane, the formation of the thioether was strongly accelerated in the presence of DBU. This one-pot process enabled the preparation of flexible to rigid foams with open-cell morphology. Interestingly, the foams can be easily recycled into films or structural composites by thermal treatment, thanks to the dynamic nature of the hydroxy urethane linkages.

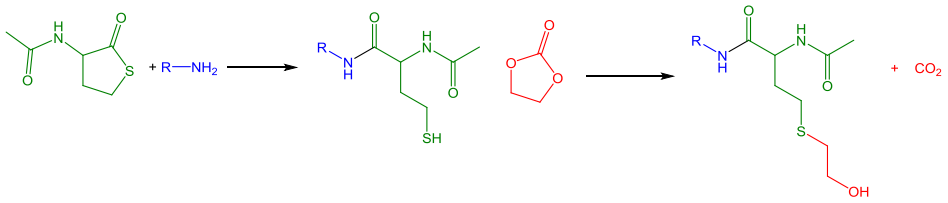

Figure 16. NHTL aminolysis and decarboxylative S-alkylation by cyclic carbonate.

C.II.1.e. Polyaddition based disulfide exchange reaction

The group of Thayumanavan proposed another versatile cascade polymerization method (*A+BC-->A'B strategy*) based on thiolactone ring-opening chemistry and a thiol exchange reaction in order to prepare disulfide containing polyamides.[136] Various functionalized homocysteine thiolactones are ring-opened by the amino group of pyridinyl disulfide ethylamine generating a thiol that is further captured in situ by another pyridinyl disulfide ethylamine via a thiol exchange reaction (Figure 17). This technique enables the synthesis of poly(amide-disulfide)s which can be degraded under UV or redox conditions or in the presence of enzymes. However, we can notice that pyridinethione is released making it less atom efficient than the previous cascade reaction pathways.

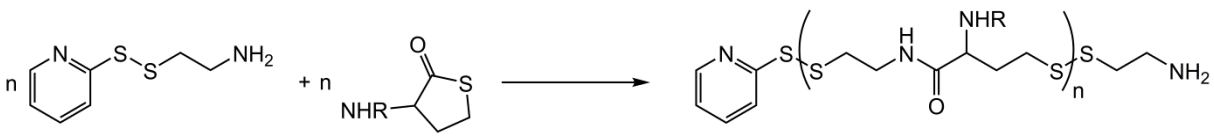

Figure 17. Step-growth polymerization based on thiolactone ring-opening chemistry and thiol exchange reaction in order to prepare disulfide-containing polyamides according to a *A+BC-->A'B strategy*.[136]

C.II.2. Thiolactone-based stepwise polymerization: Sulfur-atom as polymer lateral substituent

In all the previous examples of polymers prepared by stepwise polycondensation, the sulfur atom was embedded into the backbone. In this last part, original polymers bearing sulfur-containing lateral substituents were synthesized by the polyaddition of diamines (CC) with either a bis-thiolactone AA or with a hetero bisfunctional coupler AB bearing one thiolactone and another amine-reactive moiety.

C.II.2.a. Bisthiolactone + diamine

In 2014, the group of Möller used an AA+BB strategy resulting in polymer chain on which the thiol groups are present as lateral substituents.[137] A bis(thiolactone) AA-type monomer (Figure 13.12) was reacted with different BB-type diamine comonomers to form polyamides with thiol groups in the side chains. Dithiothreitol (DTT) was added to prevent cross-linking of the resulting thiol polymers. In a second step, the thiol moieties can be reacted with acrylate via thiol-Michael addition at room temperature to produce various functional polyamides (Figure 18.A). The lateral thiol groups generated by the thiolactone ring-opening could also be used in a cross-linking strategy if diacrylate compounds are used (AA + BB + CC). Silicone-based amphiphilic co-networks were prepared at room temperature by curing thiolactone end-functionalized PDMS, diamine and commercially-available PEG diacryates yielding a range of transparent elastomers.[20]

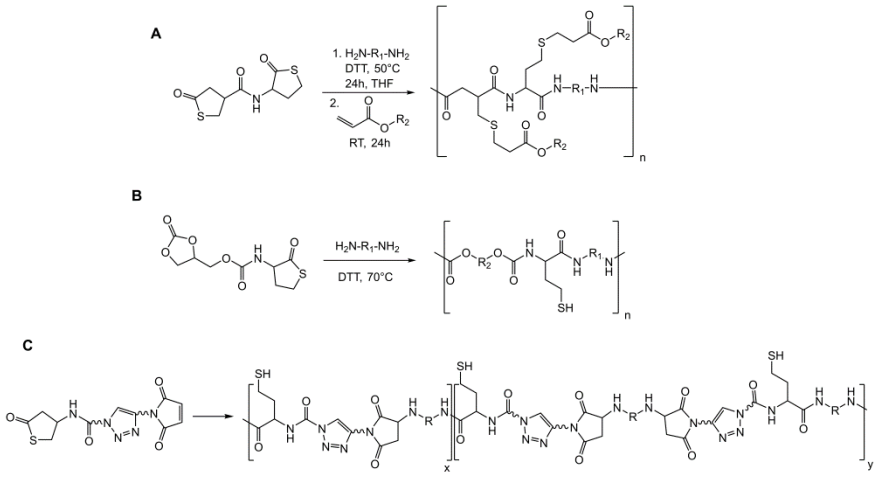

Figure 18. Polyadditions between diamines and: A. bislactones;[137] B. thiolactone/cyclocarbonate coupler;[138] C. thiolactone/maleimide coupler.[139]

C.II.2.b. Thiolactone / Amine-reactive group difunctional coupler + diamine

Difunctional thiolactone monomers composed of two chemically-different reactive heterocycles were involved in stepwise polymerizations. The polymerization of cyclocarbonate-functionalized (Figure 13.13) or lactone-functionalized thiolactones (Figure 13.14) with diamine compounds resulted in poly(amide urethane)s and polyamides with hydroxy group and thiol side groups, (Figure 18.B).[138, 140] Interestingly, for both couplers, the thiolactone ring can be addressed selectively under mild reaction conditions. Thus, poly(amide urethane)s or polyamides with alternating diamine building blocks can be obtained by sequential addition of two different diamines to the coupler.[138] At an elevated temperature (70-90 °C in DMF or in the bulk), both cycles of the coupler are converted.

The group of Yang developed a thiolactone-maleimide difunctional monomer (Figure 13.15), which was reacted with diamines to generate poly(amide-imide)s having pendant thiols (Figure 18.C).[139] They demonstrated that the Michael addition between the amines and the maleimides was quantitative and much faster than the ring-opening of the thiolactones, explaining the absence of the byproduct from the thiol–maleimide Michael addition. Additionally, the water-solubility of the polymers was significantly enhanced by PEGylation via a thiol–methacrylate Michael addition. Thiolactone-maleimide difunctional monomer was also used in the one-pot synthesis of soluble and fluorescent aliphatic hyperbranched poly(amide-imide) with solvent-dependent emission.[141]

D. Sequence-controlled polymers

Sequence regulation of polymers is one of the trending topic in polymer chemists. Recent works have shown that thiolactone chemistry is a powerful tool for synthesizing sequence-controlled polymers, such as periodic copolymers or sequence-defined polymers.[142]

D.1.Periodic copolymers

As defined by IUPAC, a periodic copolymer is a copolymer consisting of macromolecules comprising more than two species of monomeric units in regular sequence.[143] These periodic polymers could be prepared in one-pot processes via the combination of various quantitative and highly selective reactions. Here, we aim to provide an overview of the reaction combinations that include the ring-opening of a thiolactone.

Hong and coworkers reported a 3-component cascade polymerization (2A+BB+CC→A'A'+BB strategy) based on simultaneous ring-opening of thiolactone and thiol-Michael addition reactions (Figure 19.B.1.).[144] Various thiolactone derivatives, dimethacrylates and diamines were reacted in THF under mild conditions at 45 °C for 48 h yielding periodic copolymers (-$[BABC]_n$-) with high molar masses (up to 50 $kg.mol^{-1}$). Similarly, amino-telechelic PDMS (BB) were reacted with functional thiolactones (A) to *in situ* generate dithiol macromonomers (A'BBA'), which immediately polymerized with PEG diacrylate (CC) to generate PEG- and PDMS-containing poly(amido-ester-thioether).[64] The previous protocol was slightly modified by replacing di(meth)acrylates by allyl methacrylate (Figure 19.B.2).[145] In that case, the thiols released by the ring-opening of the thiolactone can readily react with the electron-deficient methacrylate groups but are not able to react with the electron-rich allyl groups. Only after the ring-opening and the Michael addition reactions are completed, the polymerization is carried out by radical thiol-ene addition under UV-irradiation yielding -$[BABC]_n$- periodic copolymers.

Other strategies required the sequential addition of the monomers. You and coworkers prepared an -$[ABC]_n$- periodic copolymers using the following sequence of reactions: in a first step cysteamine is reacted with and allyl methacrylate according to a thiol-Michael addition, then in a second step, NHTL is added to the reaction mixture leading to the nucleophilic attack and the ring-opening of the thiolactone to generate a thiol- allyl-terminated derivative, which is finally polymerized by radical thiol-ene polyaddition under UV (Figure 19.A).[146] More complex sequences were also developed. -$[CBABCD]_n$- copolymers were prepared using different sequence of reactions, such as Michael addition, thiolactone ring-opening, thiol/bromomaleimide substitution (Figure 19.C.1);[146] or TL ring-opening / thiol-Michael addition and amino-yne click reactions (Figure 19.C.2).[147] -$[DCBABCDE]_n$-

copolymers were synthesized according to the following reaction order: thiol-Michael addition, TL ring-opening, thiol/bromoamide substitution reaction and aza-Michael addition (Figure 19.D).[146, 148]

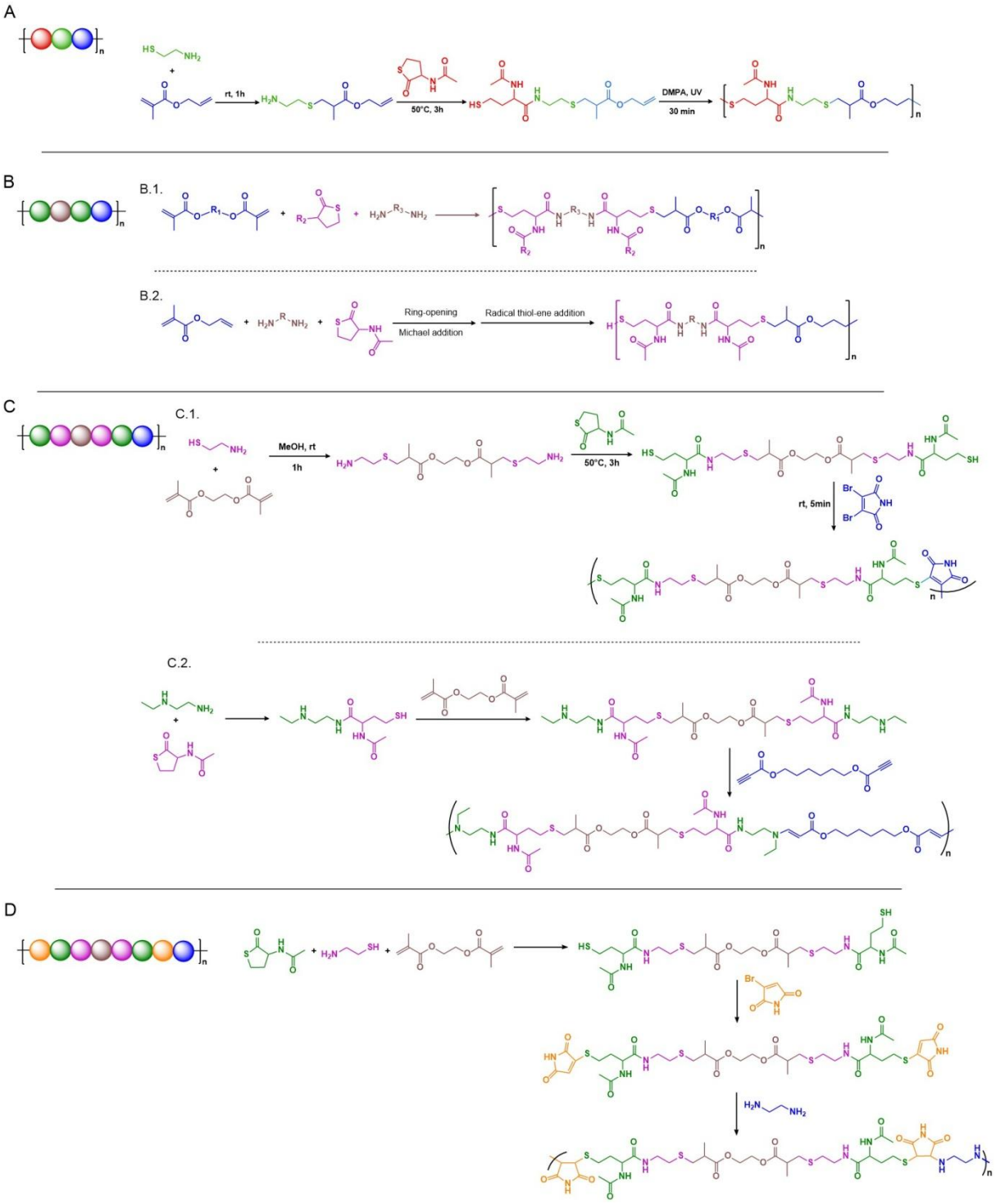

Figure 19. Different strategies using thiolactone chemistry for the synthesis of periodic macromolecules.[144-148]

-[ABCD]$_n$- periodic copolymers were prepared using **two consecutive multicomponent reactions** in one pot.[149] First, NHTL was reacted in DMF with *N*,*N*-dimethyldipropylenetriamine in the presence of triethylamine (nucleophilic ring-opening of NHTL and subsequent thiol-Michael addition) in order to generate a propargyl- secondary amine-containing derivative. In a second time, p-toluenesulfonyl azide and CuCl were added to the reaction mixture enabling the polymerization at 70 °C according to a Cu catalyzed azide-alkyne-amine coupling (Figure 20.A.). This technique was also used to prepare polymers with more complex morphologies, such as hyperbranched and core-shell polymers). [149]

-[DCBABCDE]$_n$- periodic copolymers were prepared by the same group using two consecutive multicomponent reactions in one pot.[150] First, the reaction of 1 equivalent of diamine compound with 2 equivalents of thiolactone and the subsequent thiol-Michael addition with 2 eq. of propargyl methacrylate in order to generate a dipropargyl derivative. In a second time, 1 eq. of phenyl diamine (or diol), 4 eq. of p-toluenesulfonyl azide and CuCl are added to the reaction mixture enabling the polymerization at 70 °C according to a Cu catalyzed azide-alkyne-diamine (or diol) coupling (Figure 20.B.).

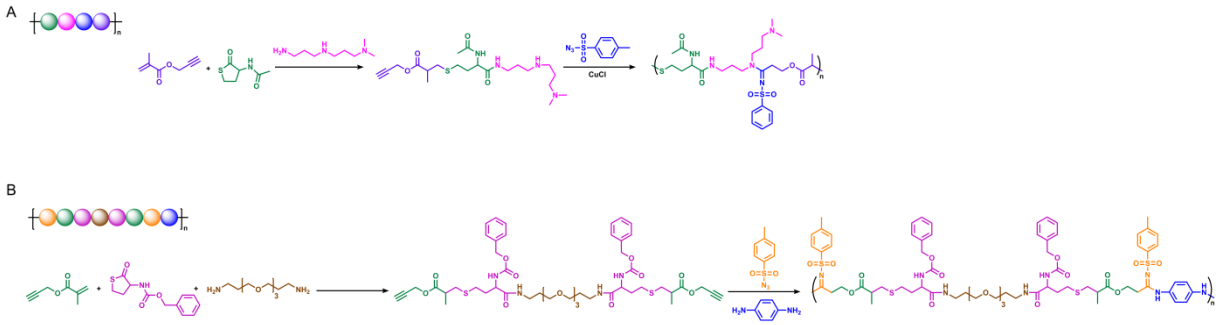

Figure 20. Synthesis of -[ABCD]$_n$- and -[DCBABCDE]$_n$- periodic copolymers by sequential multicomponent reactions.[149, 150]

D.2. Sequence-defined copolymers

The thiolactone chemistry has also been used by the group of Du Prez to synthesize sequence-defined polymers using different protective group-free two-step iterative protocols on a solid support. The first

protocol was published in 2013 and started with a thiolactone immobilized on a solid support (Figure 21.A).[151] The first step of the iterative sequence was the ring-opening of the thiolactone by a primary amine and the concomitant release of a thiol. Then, after several washing, *N*-acryloyl homocysteine-γ-thiolactone was added and reacted with the thiol group according to a thiol-Michael addition mechanism in order to introduce a new thiolactone moiety at the end of the chain enabling to start a new iterative reaction sequence. In this protective group-free approach, the functionality originates from the use of various commercially-available primary amines in the first step and the second step corresponds to the chain extension through the use of a single thiolactone-containing building block for the chain extension. However, this strategy has drawbacks, such as an inevitable disulfide formation, which required to be *in situ* reduced just before the chain extension reaction. In addition, only very short functional sequences (up to tetramers) could be obtained with high purity. An improved two-step protocol was published by the same group in 2016 (Figure 21.B).[152] The first step of the iterative sequence consists of the nucleophilic attack and ring-opening of the thiolactone by an amino alcohol (ethanolamine or 4-amino-1-butanol). The released thiol immediately reacted with an acrylic compound according to a thiol-Michael addition mechanism, thus preventing the formation of disulfides and enabling to introduce a wide set of functionalities. The chain extension is done in the next step by reacting α-isocyanato thiolactone with the alcohol moiety introduced via the aminolysis reaction. Highly pure decamers could be synthesized. This protocol was then transfer to an adapted peptide synthesizer, enabling faster decamer syntheses (33 h vs 3-5 days). However, it should be noticed that the decamers prepared by the automated approach were less pure than the one obtain by the conventional method. This second iterative strategy was optimized for polar conditions and used to synthesize PEGylated 5-mers precision oligomers using a TentaGel© PAP resin.[153]

Various adaptations were also introduced to this second strategy. In order to increase the diversity of lateral side-groups, ethyl thioacrylate was used instead of acrylate and the iterative protocol was adapted by adding an additional post-functionalization step by substitution of the thioester side-group with any chosen primary amine in the presence of thiophenol as catalyst.[154] It should be noted that the reaction between primary amine and thioacrylate aza-Michael addition is faster than the thiolactone

ring-opening, therefore these reactions were performed separately in two-steps and dimethylphenylphosphine was added to the reaction mixture to avoid disulfide formation. Pure octamers were successfully synthesized. Alternatively, alkyl halides have been used for the introduction of side-chains functionalities instead of acrylic compounds.[155] This approach was used with enantiopure thiolactone building blocks in order to prepare stereocontrolled and sequence-defined oligomers (up to high-purity undecamers).[155] In 2022, Reith and al. performed the chain extension and the thiolactone restoration via a carbodiimide coupling with a carboxylic acid-containing thiolactone building block.[156] In the same paper, the use of 3-amino-1,2-propanediol and acetonide acrylate enabled the preparation of mikto-arm star-shaped macromolecules.[156]

The alcohol moiety, which is required for the chain extension reaction with α-isocyanato thiolactone, was alternately introduced by using hydroxyethylacrylamide.[157] In this case, primary amines were used as the functional handles. This strategy was used with an automated synthesizer to prepare rather large amount (at the gram scale) of sequence-defined structures (up to nonamers).

The previous strategies have a common limitation associated with the introduction of a single coding monomer per synthetic cycle. To address this issue, a dual-encoding strategy was recently developed, in which the thiol generated by the nucleophilic attack of various functional primary amine on the carbonyl group of the thiolactone ring was reacted with an epoxide enabling to simultaneously introduce both an additional functional side-group and an alcohol moiety required for the chain extension (Figure 21.C).[158] As a result, two functional groups are introduced per synthetic cycle, thus considerably increasing the number of coding possibilities.

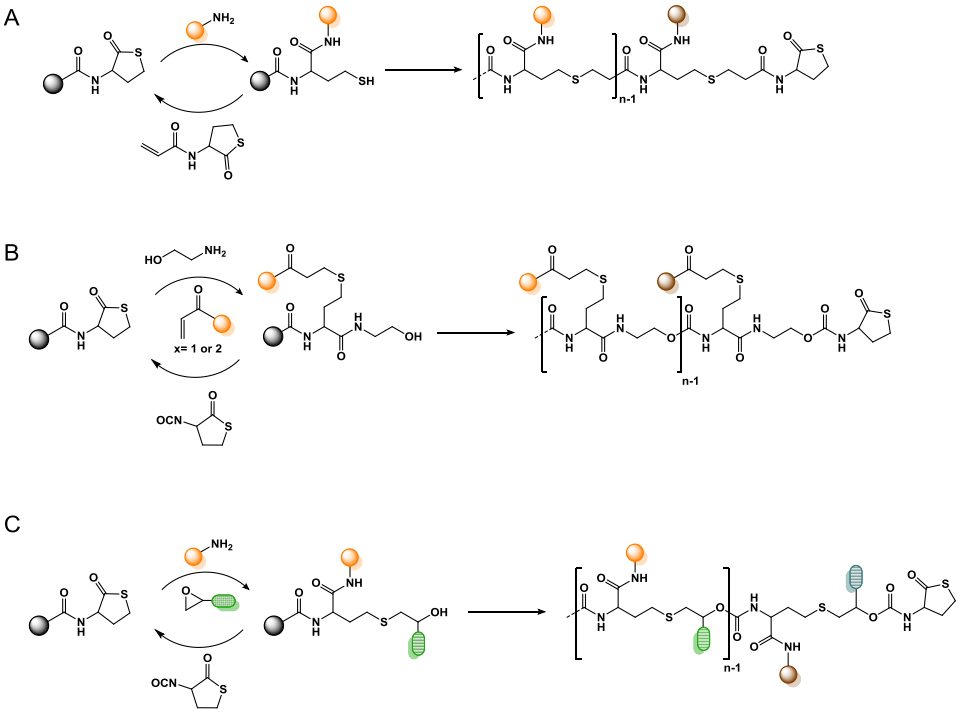

Figure 21. Different strategies based on thiolactone chemistry for the synthesis of sequence-defined macromolecules.[151, 152, 158]

Conclusion and perspectives

In summary, the use of γ-thiolactones in polymer chemistry has recently gained considerable interest. The double modification of γ-thiolactones by nucleophilic substitution followed by thiol-X chemistry advantageously enabled the facile design of various multi-functional macromolecules. The latent thiol character of thiolactones combined with the tremendous variety of nucleophilic amine-containing molecules and the versatility of thiol-X chemistry provide a powerful toolbox to polymer chemists. Easy to implement protocols were used in all steps of polymer chain synthesis: initiation, propagation, termination and post-modification. The use of thiolactone monomers for ring-opening (co)polymerizations or multistep polyadditions enables the preparation of a large range of original polymers incorporating various combination of chemical moieties into their backbones. The ring-opening copolymerization of γ-thiolactones and their derivatives with epoxides afforded an opportunity to circumvent the low polymerizability. It would certainly be interesting to enriched the variety of chain structures and properties of resultant sulfur-containing polymers by extending the

copolymerization to other cyclic monomers and the polyadition to other nucleophilic groups. In addition, the synthesis of polymers with high molar mass by ROP or polyaddition remains a challenge.

The functionalization of polymer chains with thiolactone moieties is also more and more considered. Indeed thiolactone handles opens nearly endless possibilities of polymer chain double post-polymerization modifications. Thiolactone chemistry was applied on rational design and controlled synthesis of various macromolecular architectures, including multi-block copolymers, graft copolymers, 3D-networks, hybrid materials and macrocycles. It is also worth noting that various thiolactone-based synthetic approaches toward sequence-defined polymers have been recently developed.[159]

The demand for "greener" materials is definitely growing in the society: macromolecular science is required to create environmental-friendly monomers and polymers via sustainable pathways. Thiolactone chemistry present many advantages to address this challenge. No atoms are wasted as thiolactone chemistry results in 100% atom-efficient conjugation reactions. The reactions are mainly carried out under mild conditions. Recent papers reported the use of monomers based on renewable compounds.[122, 125] In addition, the design of self-immolative polymers is currently a very active field of polymer science.[160-162] Thioesters can be cleaved under mild conditions and did not induce side-reactions. Polythioester materials derived from the bridged bicyclic BTL are promising chemically recyclable polymers with high performance properties, that match the ones of commodity plastics.[118]

In addition, some properties of the thiolactone chemistry have not yet been fully exploited and offer favorable opportunities for future research. The redox properties of the sulfur-containing moieties, the influence of the tacticity, and the degradation properties remain largely under-investigated. Synthetic pathways have been recently developed toward new functional (bis)thiolactones, enabling the future design of original functional materials.[119, 163, 164] Finally, few hybrid materials have been prepared by combining the thiolation of peptides/proteins with polymer synthesis.

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