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Feature Article

One-pot multi-step reactions based on thiolactone chemistry: A powerful synthetic tool in polymer science

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ABSTRACT

One-pot multi-step reactions based on thiolactone chemistry emerged as a powerful tool to prepare tailor-made, multi-functionalized polymer architectures in a one-pot and elegant manner. This feature article highlights the most important features of this approach, demonstrated in various reactive systems including (bio-based) linear polymers, heterotelechelic polymers, polymeric networks and heterogeneous supports. This overview clearly reveals its remarkable versatility involving modular synthesis and double modification of polymers: thiolactones can be opened by a wide variety of functional amines and the released thiol can react with thiol 'scavengers' of choice.

Contents

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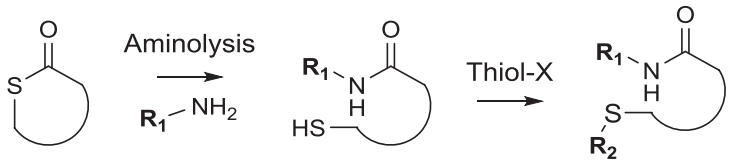

Fig. 1. A thiolactone entity as a latent thiol functionality: the thiol is released by nucleophilic ring-opening of the cyclic thiolester and subsequently a thiol-click can occur, incorporating R_1 and R_2 residues.

1. Introduction

During the last decade, robust and efficient organic reactions, generally denoted as 'click' chemistry [1], became indispensable tools for scientists active in synthetic macro- and supramolecular research groups [1b,2]. The decoration of polymeric materials with reactive functional handles and their subsequent post-polymerization modification (PPM) [3], ideally *via* 'click' chemistry, ultimately lead to a plethora of synthetic materials, covering many applications areas (electronics [4], bio-conjugation [5], labeling [6], medicine [7], etc.). The synergy between functionality and modularity is the key aspect of this popular approach [8]. Extensive method development resulted in a myriad of possible click-based reactions and, while some orthogonal reactions [9] are amenable to multi-step one-pot sequences, new paths to multi-functionalized materials via accelerated synthetic protocols became available [10].

Conjugation and modification reactions involving thiols are valuable metal-free alternatives to the heavily exploited copper assisted azide–alkyne cyclo-addition (CuAAC), the 'click' benchmark [11]. In addition to the nucleophilic nature of thiols in the presence of alkyl halides, epoxides, isocyanates and Michael acceptors, thiyl radicals readily react with double and triple bonds [12]. In order to solve some of the thiol-related issues (smell, shelf life and synthetic availability), the reactivity of a thiolactone (a cyclic thioester) as a latent thiol functionality has recently been explored by us in synthetic polymer science: the thiol is released by nucleophilic ring-opening (aminolysis) and subsequently reacts with a thiol 'scavenger' (Fig. 1).

This synthetic approach, based on the reactive mixture of an amine, a thiolactone and a thiol 'scavenger', has two particular attractive features compared to other efficient activated-ester chemistries, employed in polymer synthesis and PPM. First of all, no atoms are wasted as thiolactone chemistry results in 100% atom-efficient conjugation reactions. For example, although the reactivity of pentafluorophenyl esters [13] might be higher in an aminolysis reaction, it has the intrinsic disadvantage of releasing the corresponding phenol derivative as a side product. In comparison with azlactone-based reactions [14], another atom-efficient methodology, thiolactone chemistry enables double modification of polymer scaffolds. The first residue (R_1) originates from the used amine during the ring-opening, while a second entity (R_2) can be introduced via the subsequent thiol-X reaction (Fig. 1). In addition to the mentioned advantages, it is important to note that in some cases this double modification can be performed in a one-pot fashion leading to simplified experimental set-ups and thus accelerated, synthetic protocols.

After our pioneering research in 2011 [15], implementing thiolactones as functional handles for polymer synthesis, we and other groups further elaborated this approach, resulting in a large number of original research papers. Hence, the chemistry of thiolactones and its potential in polymer science will be reviewed in this contribution.

2. Chemistry of thiolactones: Reactivity and synthetic use of homocysteine-γ-thiolactone

Thiolactones are cyclic esters of mercapto-acids [16]. The most representative members of this class of sulfur-containing compounds are β-, γ- and δ-thiolactones, respectively four-, five- and six-membered rings (Fig. 2). α-Thiolactones generally are unstable intermediates [17] (except for α,α′-disubstituted analogs [18]). Additional structural classification distinguishes unsaturated and saturated thiolactones; only the latter will be further discussed.

The most widely used synthetic approach for the preparation of saturated γ- and δ-thiolactones is the direct lactonisation of the corresponding mercapto-acid [16,19]. The most important reactivity-related property of thiolactones is 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 [16a]. In addition to their different ring stability, a clear distinction regarding the reactive nature of lactones and thiolactones can be made: thiolactones only behave as acylating agents (ring opening via nucleophilic addition–elimination), in contrast to lactones displaying both acylating and alkylating activity (ring opening via nucleophilic substitution) [16a].

Due to the inherent ring strain, the susceptibility of thiolactones towards ring opening decreases with increasing ring size. In general, the stability of the ring increases with the number of substituents by steric congestion of the nucleophilic attack [16a]. Several nucleophiles for the ring opening can be considered: water, alcohols and amines are most prevalent. The hydrolysis and alcoholysis are only

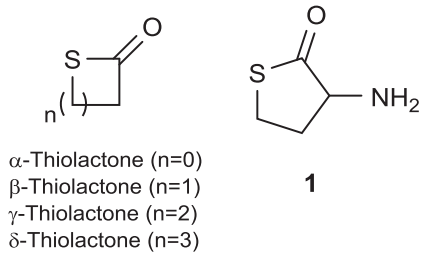

Fig. 2. General structure of saturated thiolactones and the chemical structure of homocysteine-γ-thiolactone **1**.

significant in basic medium, while aminolysis requires no additives. Aminolysis can thus be performed in aqueous medium, although hydrolysis is an important side reaction [16b,20]. 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 [16b,21]. Larger thiolactones are even susceptible to thiolysis via enzymatic ring-opening, yielding high-MW aliphatic polythioesters [22].

The most commonly used γ-thiolactone derivative is α-amino-γ-butyrothiolactone or homocysteine-γ-thiolactone **1**, a cyclic thioester of homocysteine (Fig. 2). Chemical preparation of **1** requires an acid-catalyzed intramolecular condensation of methionine [23] or homocysteine [24]. The thiolactone **1** absorbs UV-light (λ_{max} = 240 nm and $\varepsilon \sim 5000\ M^{-1}cm^{-1}$ in water). The low pK_a value of 6.67 for the amino group in **1** can be explained by the electron-withdrawing effects of the sulfur atom [25]. The hydrochloric acid salt of the racemate **1** is a white solid (mp 199–203 °C), stable at room temperature and readily available as a bulk chemical (low cost price). Under physiological conditions (pH 7.4, 37 °C), the thiolactone **1** has a half-life of 1 day [26].

Because of its dual aminoacyl-thioester character, homocysteine-γ-thiolactone **1** is susceptible for both nucleophilic (*vide supra*) and electrophilic attack. Self-condensation of two molecules **1** occurs in an attempt to obtain the free amino-group and mutual aminolysis (first intermolecular and second intramolecular aminolysis) takes place with the formation of the corresponding diketopiperazine adduct [16a]. Nevertheless, homocysteine-γ-thiolactone **1** is a quite valuable synthetic building block. Due to the intrinsic instability of the neutral homocysteine-γ-thiolactone **1**, an efficient reaction between the amino group in α-position and an electrophile is required. Amidation reactions are most frequently used: conjugation with acid halides [27], (*in situ*) activated carboxylic acids [27d,28] and anhydrides [29] enables the synthesis of homocysteine-γ-thiolactone derivatives. A carbamate linkage is formed by treatment with chloroformates [30]. Another important transformation reaction is imine formation, resulting from the condensation with aldehydes [25,31].

An important homocysteine-γ-thiolactone derivative is *N*-acetylhomocysteine thiolactone or citiolone **2** (Fig. 3), a commercial compound that was introduced as thiolating agent for proteins. This thiolation consists of the aminolysis of the water-soluble *N*-acetylhomocysteine thiolactone **2** by the ε-NH_2 groups of lysine residues [20a,32]. Thiolation of a large variety of macromolecular biochemical systems has been reported [27a,32b,33]. Citiolone **2** is also a drug

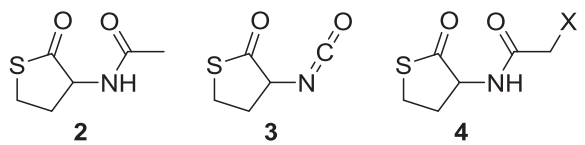

Fig. 3. Synthetic valuable building blocks, derived from homocysteine-γ-thiolactone **1**.

that is used as a mucolytic agent for the treatment of certain hepatic disorders [34]. In contrast to the reactivity of **2**, which fully relies on its acylating capacity, other noteworthy derivatives of homocysteine thiolactone **1** enable the incorporation of thiolactones in (macro)molecules. The primordial requirements are the conversion of the α-amino group of **1** into 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. For example, α-Isocyanato-γ-thiolactone **3** is obtained by phosgene treatment of homocysteine thiolactone **1**. In the presence of alcohols, amines or hydrazines, this isocyanate **3** is converted to the corresponding carbamates, urea and semicarbazides [35]. Other substrates susceptible for chemoselective nucleophilic attack are thiolactone-containing halides **4**. For example, *N*-(2-chloroacetyl)homocysteine thiolactone (**4**, X = Cl) reacts with thioglycolic acid, yielding erdosteine, a mucolytic agent for the treatment of bronchitis [36].

3. One-pot multi-step reactions based on thiolactones: Amine-thiol-ene conjugation

The combination of robust, efficient, and orthogonal conjugation chemistries, resulting in the development of several elegant one-pot, multi-step strategies, enables the implementation of accelerated synthetic protocols. As Malkoch et al. expressed the need to increase the range of available 'click' reactions that can be achieved without metal catalysts and to develop libraries of compatible reactions [10], the development of efficient one-pot processes based on metal-free conjugation chemistries in order to modify or prepare polymeric materials is of particular interest.

In addition to the fact that the commercial availability of thiols as starting materials is rather limited, thiols usually have an unpleasant smell and might have a poor shelf life due to oxidation reactions. Therefore, thiolactones are considered to be valuable thiol precursors, potentially resolving some of these thiol-related issues. First of all and most importantly, the thiolactone ring opening, resulting in the release of a free sulfhydryl group, can be achieved by the means of a wide variety of nucleophiles in an orthogonal way (*vide supra*). These latent thiols are not smelly and are recognized to be stable compounds. Moreover, thiolactone substrates can be subjected to one-pot multi-step reaction sequences.

This approach has been evaluated mainly by combining hydrolysis (or alcoholysis) and *S*-alkylation for the preparation of low-molecular-weight adducts. The lysis of thiolactones under basic conditions is often carried out in the presence of an alkylating agent. As a result of the high nucleophilicity of sulfur, *S*-alkylated compounds are the final products of these reactions [16b]. Methanolysis of homocysteine-γ-thiolactone hydrochloride **1** and subsequent alkylation by treatment with an alkyl halide in the same pot has been reported as a simple method for the synthesis of *S*-alkylhomocysteines **5** (Fig. 4 *top*) [37]. The basic hydrolysis of homocysteine thiolactone **1**, accompanied by

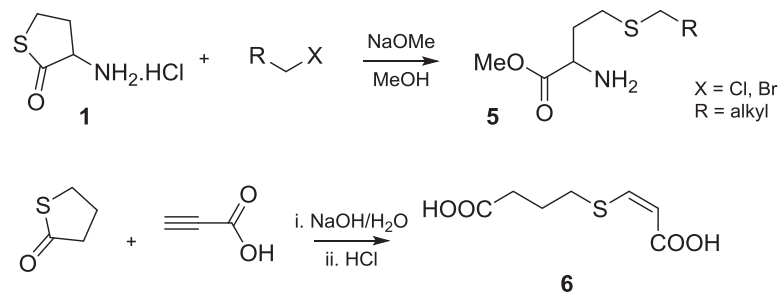

Fig. 4. Two examples of thiolactone-based two-step one-pot sequences; (*top*) methanolysis and *S*-alkylation of homocysteine-γ-thiolactone **1** enables the synthesis of *S*-alkylhomocysteines **5** and (*bottom*) treatment of γ-thiobutyrolactone with propiolic acid in basic aqueous medium generates the acrylic acid **6**.

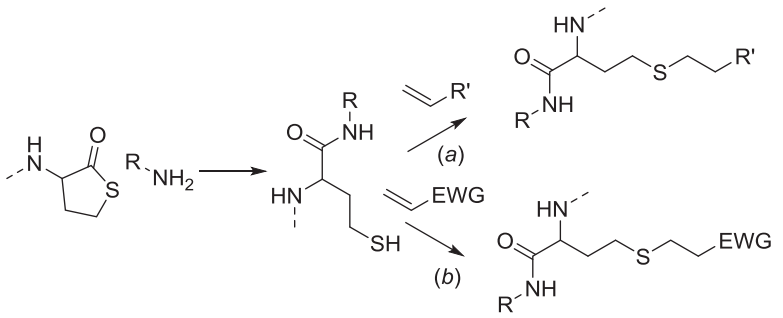

Fig. 5. Schematic depiction of the one-pot amine-thiol-ene conjugation: aminolysis of a thiolactone, followed by a thiol–ene conjugation. The *in situ* generated thiol can react according two distinct reaction pathways: (*a*) a *radical* (UV-initiated) or a *nucleophilic* (thiol-Michael) addition of a thiol to a double bond.

the alkylation of the thiol group, is the key step in the synthesis of several homocysteine derivatives [38]. Other combinations of two-step one-pot reactions have been explored. As a result of sequential hydrolysis and conjugate addition (thio-Michael addition), the reaction of γ-thiobutyrolactone with propiolic acid under basic conditions generates the corresponding acrylic acid **6** (Fig. 4 *bottom*) [39].

Aminolysis as a start of a one-pot multi-step reaction sequence based on thiolactones has the advantage over alcoholysis and hydrolysis since it does not require any additive to occur. However, it is not straightforward as in many cases, orthogonality issues would arise as a result of the reactive nature of amines. On the other hand, it provides the opportunity to introduce a functional group in the reaction product *via* the amine.

3.1. Amine-thiol-ene conjugation: Method development through in-depth model studies

Combination of thiolactone aminolysis with the addition of the generated thiol to a double bond in a one-pot fashion, the so-called *amine-thiol-ene conjugation*, introduced by us [15,40], has been recognized as a relevant extension of the popular thiol-ene chemistry. This simple, efficient, and modular linking process entails many attractive features, but prior its implementation in synthetic polymer science, we performed model studies to reveal its possibilities and limitations.

In Fig. 5, a schematic depiction of the amine-thiol-ene conjugation displays two distinct reaction pathways, originating from the nature of double bond as a reaction partner of the generated thiol. It is clear that this choice, either the *radical* (*a*) or the *nucleophilic* (*b*) thiol-ene reaction, greatly influences the set-up, potential side-reactions and outcome of the reaction. In any case, we consider the aminolysis to be rate-determining for the two-step process. Hence, the influence of the nature of the (primary) amine in the ring opening of thiolactones was studied. A kinetic screening (pseudo-first order conditions in THF) of the lysis of γ-thiobutyrolactone in the presence of ten different (functional) primary amines was performed [40]. Generally, the aminolysis of thiolactones can be described by second order kinetics [41].

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. The sterical constraints due to α-branching in Jeffamine® M-600 greatly decreases the reaction rate (Fig. 6). When applying the same reaction conditions, *i.e.* 50-fold excess of the nucleophile and neutral pH (no additives), other nucleophiles, like water, alcohols, thiols and anilines are not able to open the thiolactone ring. Another important observation during this study is the fact that in the presence of excessive amounts of amines, thiolactones are opened yielding the corresponding thiol, which readily dimerizes through disulfide formation. Although this side-reaction needs to carefully monitored during thiolactone-based synthetic endeavors, it can be a useful transformation in selected cases (*vide infra*).

The principal aim of our model studies is to assess the compatibility between the aminolysis and the subsequent

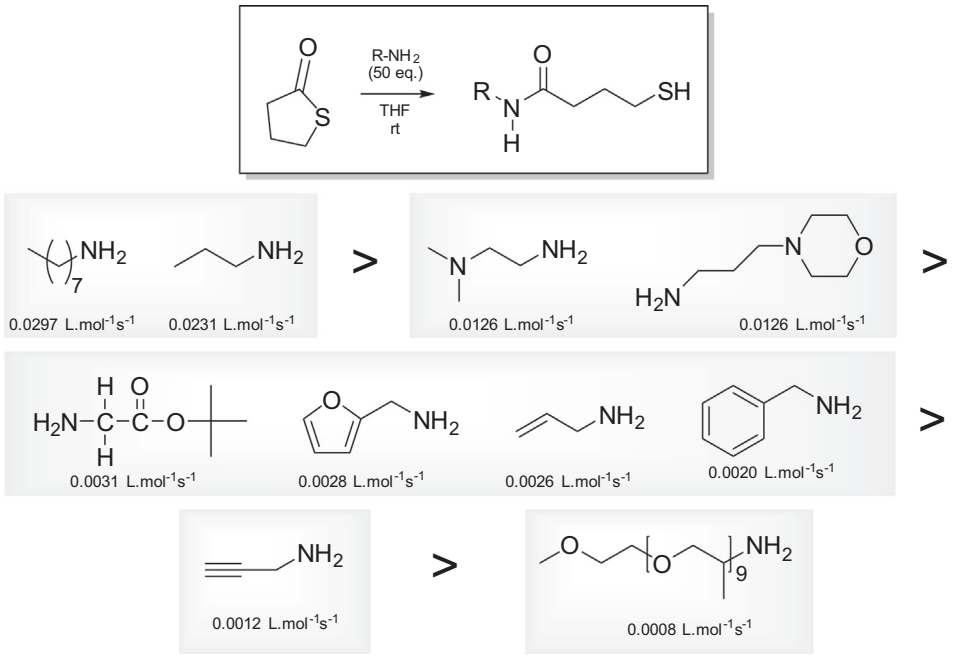

Fig. 6. Kinetic screening of the aminolysis of γ-thiobutyrolactone using pseudo-first order kinetics. Relative rate constants of the aminolysis of γ-thiobutyrolactone in the presence of different primary amines.

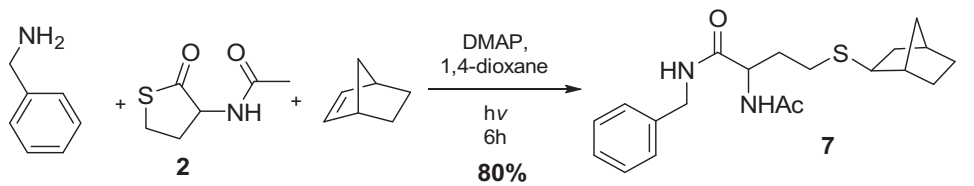

Fig. 7. Model amine-thiol-ene conjugation (*radical* thiol-ene): one-pot reaction between benzylamine, *N*-acetylhomocysteine thiolactone **2**, and norbornene under UV-irradiation.

thiol-click conjugation reaction of the *in situ* generated thiol. As mentioned before, we targeted to perform the amine-thiol-ene conjugation in a one-pot fashion, thus without intermediate purification of the thiol and without addition of chemicals during the process (everything present from the start).

The combination of thiolactone aminolysis and the *radical* thiol-ene process, which proceeds *via* a fundamentally different reaction mechanism has been performed on a mixture of benzylamine, *N*-acetylhomocysteine thiolactone **2** and norbornene as low-molecular-weight model compounds in order to master the reaction conditions (Fig. 7). The solution was irradiated by an external UV-light source, and 2,2-dimethoxy-2-phenyl acetophenone (DMPA) was selected as an efficient photoinitiator for thiol−ene conjugation [42]. An *online* ^{1}H NMR experiment pointed out that **2** was fully consumed after being in the presence of a twofold excess of benzylamine and 10 mol% of DMAP for 6 h. Furthermore, thorough LC–MS analysis of the reaction mixture obtained after the two-step reaction, revealed the formation of side products originating from the reaction between benzylamine and radical fragments of DMPA. However, using optimal conditions (no photoinitiator) and after a straightforward chromatographic purification, the model reaction yielded the conjugation compound **7** with an isolated yield of 80% (Fig. 7) [15].

Despite the successful model studies and polymerization reactions (*vide infra*), conceptual issues directly related to the radical reaction in the one-pot process partially impede extension of the scope of the methodology. Important to note is that some functional groups (*e.g.* furan [43], 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 [15].

Therefore, we aimed for 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. 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 [44]. 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 electron-rich double bond, like in an allyl or norbornenyl residue, with an acrylate function, allowing for the complete absence of radical species during the process, would indeed be a step forward, although potential orthogonality issues render the conjugation procedure a fundamentally challenging two-step reaction sequence. Hence, 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 [44] of the amine to the acrylate and disulfide formation are of primary concern.

The feasibility of the proposed *nucleophilic* amine-thiol-ene conjugation between an amine, a thiolactone-containing compound and a Michael acceptor entirely relies on the selectivity of the conjugate addition. Therefore, the selection of the reaction partners is critically important. While maleimides react with both amines and thiols as Michael donor [44], acrylates are less reactive: at room temperature and without a catalyst, only secondary amines readily react with acrylates [45]. 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 targeted conjugation adduct. The anticipated chemoselective discrimination between both heteroatomic nucleophiles (primary amine and the intermediate thiol) 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 [12c].

In order to confirm these hypotheses, a series of model reactions have been conducted, for which the reaction progress was monitored by *online* FT-IR analysis and LC–MS analysis (*offline*). The kinetic profile and outcome of the reaction between *n*-propylamine, γ-thiobutyrolactone and *n*-butyl acrylate was studied in detail (Fig. 8). It should be stressed that the reaction was performed at room temperature and under air atmosphere. The major conclusion from this model study is that, as was anticipated (*vide supra*), the aminolysis is the rate-determining step: the acrylate functions are consumed as fast as the thiolactones. With 1.1 eq. of *n*-propylamine compared to an equimolar mixture of thiolactone and acrylate, it takes 9 h to reach 70% conversion. The rate can be increased by adding more amine. For example with a twofold excess, the reaction is finished within 8 h. An LC–MS analysis of the reaction with 1.1 eq. of *n*-propylamine shows a clean mixture of starting materials and targeted product **8**. Only a minor fraction of disulfide was detected. Disulfide formation is more prominent at higher amine concentration, indicating that the excess of amine should be limited. The occurrence of the other suspected side-reaction, the aza-Michael addition between the primary amine and the acrylate, depends on the nature of the solvent. Trace amounts of the aza-Michael adduct is detected when performing the two-step reaction in $CHCl_3$ or THF, whereas in DMF, this reaction is more prominent.

3.2. Stepwise polymerization of AB′-type monomers via radical amine-thiol-ene conjugation

Encouraged by the successful model studies, implementation of the amine-thiol-ene conjugation, both the *radical* and *nucleophilic* version, was envisaged in synthetic polymer science. Consequently, several AB′ type monomers containing both a double bond and a thiolactone unit have been prepared. Upon aminolysis, this monomer forms a reactive thiol-ene, which will be consumed in the same medium in a step-wise poly-addition. It is clear that the nature of the introduced double bond will determine the reaction conditions and outcome of the two-step process. In any case, the use of the above studied amine-thiol-ene conjugation in polymer synthesis demands a straightforward and scalable methodology for the synthesis of a stable AB' monomer. An important aspect of this approach is the significant influence of the chemical linkage, like a urethane or an amide (*vide infra*), connecting the thiolactone and the double bond, on the final properties of the synthesized polymers.

Two different AB′-monomers, susceptible to *radical* amine-thiol-ene conjugation, have been synthesized and used in a photo-polymerization, yielding linear polymers with either a polythioether/polyurethane [15] or a polythioether/polyamide backbone [46].

A first AB' monomer, *N*-(allyloxy)carbonylhomocysteine thiolactone **9** has been synthesized in large amounts (>30 g) by treatment of homocysteine thiolactone **1** with allyl chloroformate, introducing the corresponding (allyloxy)carbonyl or alloc group, a popular amino-protecting group. Consequently, a stable urethane bond connects the reactive entities. In order to obtain high-molecular-weight polyaddition compounds in a radical photopolymerization of the corresponding AB (thiol-ene) monomer, the ratio between the involved functional groups should equal one. The aminolysis of the thiolactone in the monomer **9** should therefore reach full conversion. The *radical* amine-thiol-ene polymerization of **9** has been performed in the presence of two equivalents of different amines, respectively *n*-propylamine and ethanolamine (Fig. 9). In all cases, polyaddition occurs and after isolation of the obtained polymer, the SEC chromatograms display a

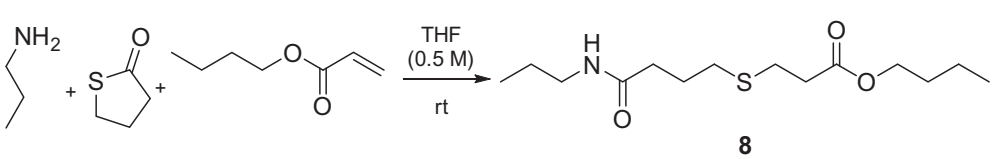

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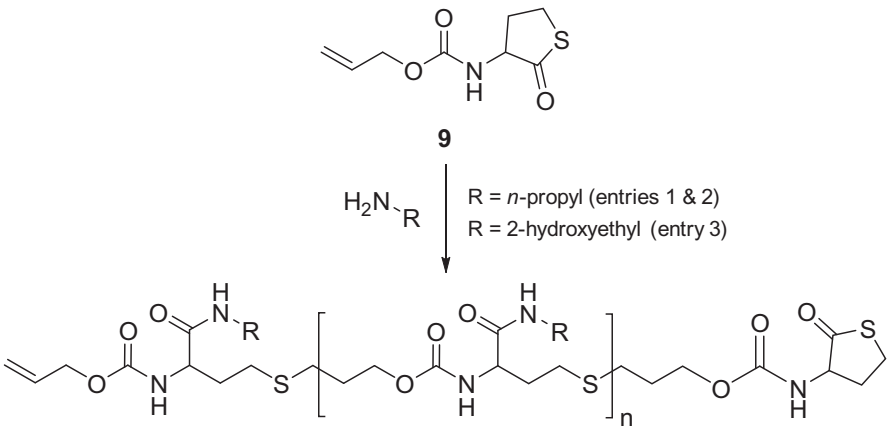
Fig. 8. Model amine-thiol-ene conjugation (*nucleophilic* thiol-ene): one-pot reaction between *n*-propylamine, γ-thiobutyrolactone and *n*-butyl acrylate.



Entry	R-NH_2	Initiator	T (°C)	Reaction time (h)	$M_{n,NMR}$ (kDa)	$M_{n,SEC}$ (kDa)	Đ
1	*n*-Propylamine	DMPA	40	0.5	3.8	4.2	1.9
2	*n*-Propylamine	AIBN	70	17	3.0	3.6	1.7
3	Ethanolamine	DMPA	40	1	7.8	22	1.6

Fig. 9. Stepwise radical polymerization of the monomer **9** in a one-pot process yielding a linear polymer with a polythioether/polyurethane backbone. The reaction conditions and analysis data of the obtained polymers are presented in the table.

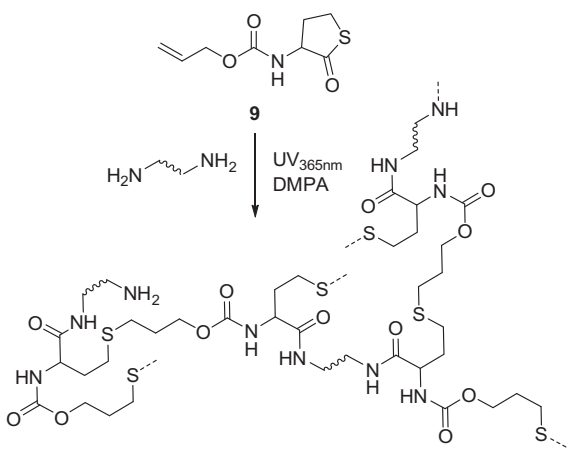


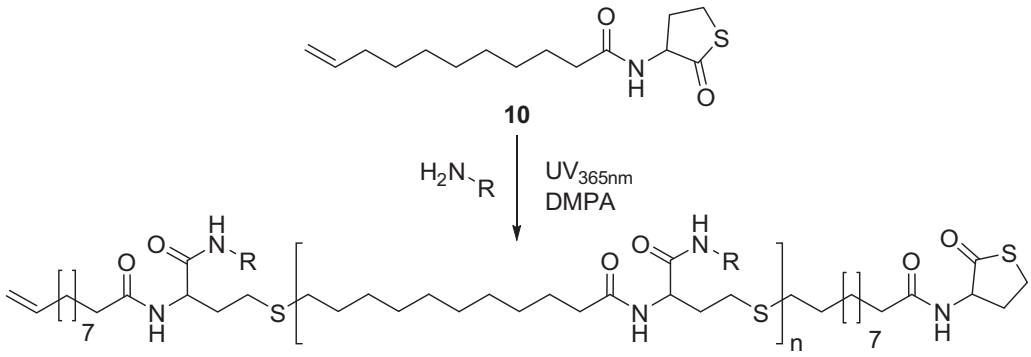
Fig. 10. Schematic depiction of the network formation: one-pot reaction between monomer **9** and a diamine cross-linker results in a polythioether/polyurethane network.

unimodal distribution, which allows for the determination of M_n and $Đ$. The quantification of M_n *via* end group analysis (double bond protons) in the ^{1}H NMR spectrum confirms the trends observed by SEC analysis. Interestingly, polymers with comparable chain length are obtained *via* the thermal initiated polymerization using AIBN (Fig. 9, *entry 2*) in comparison with the UV-initiated reaction (Fig. 9, *entry 1*) [15].

This mild and efficient one-pot polyaddition process yielded a polymer with a polythioether/polyurethane backbone and pendant hydroxyl groups (Fig. 9, *entry 3*). Indeed, under neutral conditions, hydroxyl functions are unable to open the thiolactone ring (*vide supra*) and alcohols do not interfere with radical thiol-ene reactions [12d]. 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 multi-functional amine does not interfere with either reactions in the one-pot multi-step process (aminolysis and *radical* thiol-ene), linear polymers can be obtained with direct introduction of side chain functional groups, prone to PPM [3].

To further extend the scope of this methodology in material science, polymer networks based on the AB′ type monomer **9** have been targeted. Polymer film formation occurs under UV-irradiation of a homogeneous reaction mixture of **9** and a diamine (Fig. 10). The choice of the diamine cross-linker regarding structure and molecular weight proved to be critical. While 1,6-hexanediamine was insoluble in the reaction mixture, the use of the more polar 4,9-dioxadodecanediamine as a cross-linker yielded a clear, non-tacky network film with good mechanical properties after UV-curing for 3 h. 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, as expected from the sluggish reaction of Jeffamine® M-600 in the aminolysis of γ-thiobutyrolactone (Fig. 6) [15].

In a second type of AB′ monomer, an amide linkage is foreseen to connect the thiolactone entity and the double bond. Upon aminolysis and subsequent UV-mediated thiol-ene conjugation, 10-undecenoyl thiolactonamide **10**, synthetically available in two steps on large scale, starting from the bio-based compounds undecenoic acid and homocysteine-γ-thiolactone **1**, is transformed into a linear polymer with a polythioether/polyamide backbone



Entry	R-NH$_2$	$M_{n,NMR}$ (kDa)	$M_{n,SEC}$ (kDa)	Đ	T_g^{DSC} (°C)
1	*n*-Propylamine	6.9	12.3	1.5	49.0
2	*n*-Butylamine	8.9	16.7	1.6	38.0
3	*n*-Hexylamine	8.5	15.3	1.5	25.0
4	*n*-Octylamine	10.3	19.3	1.5	18.0
5	2-Ethyl-1-hexylamine	2.0	6.7	1.5	-
6	*n*-Dodecylamine	7.8	11.0	1.4	14.0
7	*n*-Octadecylamine	6.9	9.1	1.2	5.0
8	Benzylamine	2.8	3.9	1.5	2.0
9	Ethanolamine	8.6	17.2	1.5	33.5
10	3-Morpholinopropylamine	12.2	12.3	1.6	24.0
11	*N*,*N*-Dimethylethylenediamine	6.2	1.4	1.4	-5.0
12	Cyclopropylamine	5.7	7.1	2.2	57.0
13	Pyrrolidine	8.9	8.1	1.5	22.0

Fig. 11. Stepwise UV-mediated radical polymerization of the 10-undecenoylthiolactonamide monomer **10** in a one-pot process, yielding a linear polymer with a polythioether/polyamide backbone. The analysis data of the obtained polymers are presented in the table.

(Fig. 11) [46]. The chemical structure of the obtained polymers includes two amides per repeating unit, rendering them fundamentally different from commercially available polyamides. Similar to the polyurethane synthesis from the AB′ monomer **9**, several pendent groups can be introduced via the amine.

Next to the outcome of the photopolymerization reaction (molar mass and Đ), the influence of the side chains with respect to the thermal and mechanical properties was studied. In all cases, the *radical* amine-thiol-ene conjugation of **10** yielded linear polymers of moderate DP and Đ, which can be attributed to the precipitation of the polymers during the reaction. In a first series of experiments (Fig. 11, entries 1 → 7), the carbon content of aliphatic amines was increased, yielding a library of structurally diverse polyamides. It is clear that the molar mass depends on the nature of the amine. This effect is most prominent when using two C-8 homologous amines with either a linear (*entry 4*) or a branched structure (*entry 5*) and can be attributed to sterical hindrance during the aminolysis.

Furthermore, the chemical compatibility of several amines towards the presented one-pot approach is confirmed because a variety of functional residues can be attached as pendant group to the backbone (Fig. 11, entries 8 → 13). Indeed, it has been demonstrated that the built-in functionality does not interfere with the radical amine-thiol-ene polymerization, enabling the attachment of an aromatic unit (*entry 8*), a hydroxyl function (*entry 9*), a morpholine moiety (*entry 10*) and a tertiary amine (*entry 11*). Access to polyamides with cyclic side-chain residues, originating from the use of a cyclic primary amine (*entry 12*) and a secondary amine (*entry 13*), is provided in similar manner. In terms of mechanical and thermal properties, there is clear correlation between the glass transition temperatures (T_g) of the polyamide and the number of carbons in the amine residue. As expected, the longer the aliphatic chain, the lower the T_g, due to an increased segmental mobility of the less packed polymer chains. Other parameters affecting the T_g are the decreased numbers of possible H-bonds (*entry 13* (22 °C) vs *entry 2* (38 °C)) and the decreased flexibility in the side-chain (*entry 12* (57 °C) vs *entry 1* (50 °C)).

The influence of the side chain is also demonstrated in the elasticity moduli of the polymers, determined via tensile testing. With an increasing number of carbon atoms in the polymeric side chain (Fig. 11, entries 1 → 7), the

E-modulus decreases and the elongation at break increases. Longer pendant 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.

The thermal stability of all the presented polyamides is determined by the presence of a sulfide in the backbone. Independent of the side-chain variation, degradation starts around 250 °C as analyzed with TGA.

A useful PPM of these diversely substituted polyamides is the (partial) oxidation of the sulfide linkages to their corresponding sulfoxides and sulfones. Evidence of this transformation was provided by in-depth MALDI-TOF MS and FT-IR analysis before and after the oxidation process. Oxidation conditions range from mild (7 days storage in unstabilized THF) to harsh (H_2O_2 and peracetic acid) options. The oxidation process gives rise to materials with different mechanical properties compared to the untreated polymer. In general, incorporating more oxygen atoms in the form of sulfoxides or sulfones renders the material more brittle [46].

Similar to the network formation by radical amine-thiol-ene conjugation of AB' monomer **9** and a diamine (Fig. 10), 10-undecenoylthiolactonamide **10** was successfully applied as starting monomer for the preparation of polymer networks. Different cross-linkers were tested, each time using equimolar amounts of amine compared to thiolactone units. Moreover, functional groups were incorporated in the polymer network by adding to the reaction mixture a monofunctional amine and reducing the amount of cross-linker. The incorporation of these functionalities (*eg.* benzyl, hydroxyethyl, etc.) was demonstrated with ^{1}H HR-MAS NMR spectroscopy. Depending on the used cross-linker and incorporated functionality, different mechanical properties were obtained [46].

The use of thiolactone-based reaction cascades for polymer synthesis is not restricted to the preparation of linear polymers or networks. Yan et al. demonstrated that a one-pot *radical* amine-thiol-yne reaction is the source of highly functionalized hyperbranched materials [47]. Their approach only required little adaptation of our presented method for the preparation of functionalized polyurethanes [15]. Indeed, analogous to the preparation of AB′ monomer **9**, a triple bond can be combined with a thiolactone through a urethane linkage, yielding an alkyne-containing A_2B' monomer **11**. When subjected to aminolysis, a thiol-yne containing intermediate (A_2B) is formed, which reacts further, forming a hyperbranched structure (Fig. 12). Noteworthy is the source of the UV-light, being natural sunlight, and complete absence of photo-initiators in the reaction. Due to these features, this approach qualifies as a sustainable manner for the synthesis of hyperbranched structures. The authors proved that sunlight is a necessary external stimulus, so a controlled exposure of sunlight to the reaction vessel provides straightforward manipulation of the reaction outcome. The consumption of thiols and the growth of hyperbranched polymers can be stopped and resumed in an 'on/off' approach. The reaction progress was monitored by ^{1}H NMR. In general, the obtained hyperbranched structures have moderated molecular weight (M_w = 12.0 → 22.0 kDa), relative low dispersity

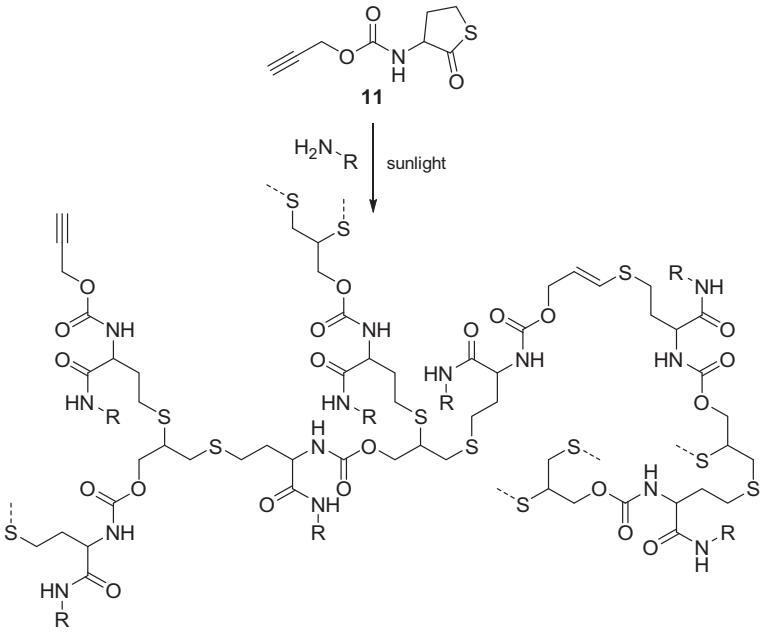


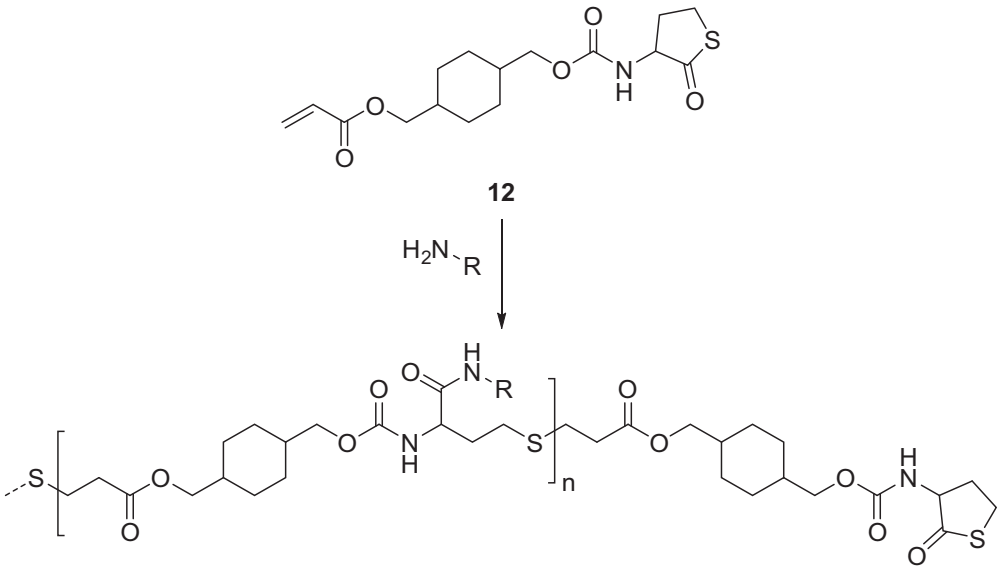
Fig. 12. Schematic depiction of the radical amine-thiol-yne conjugation: one-pot sunlight-mediated reaction between the alkyne-containing A_2B' monomer **11** and a primary amine results in a polythioether/polyurethane hyperbranched polymer.

($Đ$ = 1.62 → 3.3) and a high degree of branching (DB = 88 → 98%), mainly determined by the nature of the primary amine, used to open the thiolactone in **11**. In addition to the high number of unreacted terminal alkynes in the hyperbranched polymers, other functionalities can be introduced through the primary amine. For example, in order to improve their biocompatibility, PEG (M_n = 600 Da) and glucose were incorporated via their respective amines.

3.3. Stepwise polymerization of AB′-type monomers via nucleophilic amine-thiol-ene conjugation

In order to explore the above studied *nucleophilic* amine-thiol-ene conjugation in polymer synthesis, another stable AB′ monomer, containing an acrylate (A) and a thiolactone unit (B′), has to be devised and synthesized on a large scale. Upon aminolysis, this monomer forms a reactive thiol-acrylate, which will be consumed in the same medium by a conjugate addition [40].

In contrast to AB′ monomers **9**, **10** and **11**, all susceptible to *radical* amine-thiol-ene or amine-thiol-yne conjugation, combining an acrylate as reactive double bond and a thiolactone moiety as a thiol precursor in the same compound, is synthetically challenging. Our first choice was to combine the commercially available 2-hydroxyethyl acrylate with α-isocyanato-γ-thiolactone **3** (Fig. 3), but after its successful preparation and purification, the monomer could not be stored, even not for a short period and in the presence of a radical inhibitor, probably due to polyacrylate formation. However, when another hydroxyl-functionalized acrylate, 1,4-cyclohexanedimethanol monoacrylate, was used in the same reaction, AB′ monomer **12** (Fig. 13) could be prepared with an isolated yield of 92%. In this case, compound **12** can be stored as a white powder for months at −20 °C without any radical inhibitor present. A more scalable route consists of the phosgene treatment of the hydroxyl-functionalized acrylate to render the corresponding chloroformate and subsequent reaction of the



Entry	R-NH$_2$	$M_{n,SEC}$ (kDa)	Đ	Ratio (Amine I / Amine II)
1	*n*-Octylamine	12.0	1.7	-
2	Allylamine	5.3	1.6	-
3	Propargylamine	1.9	1.6	-
4	Furfurylamine	9.5	1.6	-
5	*N*,*N*-Dimethylethylene diamine	3.2	1.5	-
6	3-Morpholinepropylamine	7.6	1.7	-
7	*n*-Octylamine / *N*,*N*-Dimethylethylene diamine	8.8	1.7	49 / 51
8	Allylamine / Glycine *t*-butylester	6.8	1.7	72 / 28
9	Allylamine / Furfurylamine	8.4	1.5	58 / 42

Fig. 13. Stepwise additive-free polymerization of the AB′ monomer **12** in a one-pot process yielding a linear functionalized polyurethanes. The analysis data of the obtained polymers are presented in the table.

latter with DL-homocysteine thiolactone **1** in the same pot. This procedure allows for the preparation of a relatively large amount (45 g) of the AB′-monomer **12** in a single batch with an overall isolated yield of 78% [40].

Following the successful large scale preparation of monomer **12**, the polymerization via poly-addition of thiol-acrylates, originating from the aminolysis of **12**, was studied in detail by both ^{1}H NMR and *online* FT-IR analysis. 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 [12b,48]. This study revealed that poly-addition was most prominent in THF at 0.5 M and after stirring for 24 h at ambient conditions, linear polymers with an M_n of 12.0 kDa and $Đ$ of 1.7 were isolated by precipitation. The optimized conditions were subsequently applied as a general protocol for other (functional) amines (Fig. 13). Interestingly, linear poly(β-thioester)s prepared primary amine-catalyzed Michael addition reactions between 1,6-hexanediol diacrylate and 1,4-butanedithiol as A_2 and B_2 monomers, have similar moderate molecular weights [49].

Of particular relevance is the possibility to introduce double and triple bonds and reactive dienes (furan) without interference with the polymerization process (*entries 2*, *3* and *4*; Fig. 13). 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*).

The presented strategy thus offers an easy-to-perform, one-pot method for the synthesis of functionalized PUs. Mixing the two ingredients (monomer **12** and the selected amine) at room temperature without any additive or external trigger gives indeed access to a library of such polymers (Fig. 13), of which the structural build-up was confirmed by 2D-NMR and MALDI-TOF MS analysis. The latter clearly demonstrates that there were no significant side reactions during the polymerization and again confirms that the aminolysis is rate-determining as thiolactone end groups were most prominent.

In addition to the additive-free aspect of the *nucleophilic* amine-thiol-ene conjugation, another advantage over its *radical* counterpart is the improved tolerance towards functional amines, due to the mild reaction conditions and the complete absence of radical species. To extend the potential of this methodology and to further 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 **12**). 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, due to different consumption rate of both amines and derived thiol-acrylate intermediates. The results (*entries 7*, *8* and *9*, Fig. 13) prove that different functionalities can be simultaneously incorporated along the PU backbone in a one-pot synthesis. Another appealing feature of this methodology is that, once the poly-addition though amine-thiol-ene conjugation has been completed, the reaction mixture essentially is a solution of the expected PU with a minor amount of residual amine. PPM of the introduced functional group (via the primary amine), is thus possible in the same reaction medium. Two metal-free modification reactions were performed: the radical thiol-ene reaction between octanethiol and an alkene-containing polymer (*entry 2*) and the Diels–Alder reaction between *N*-methylmaleimide and a furan-containing polymer (*entry 9*).

3.4. Selective aminolysis of a multi-functional coupler

The reactivity of an AA′ type monomer **13** bearing a thiolactone and an ethylene carbonate was explored by Mommer et al. [96]. This multi-functional coupler **13** was synthesized from glycerol and homocysteine thiolactone **1**, two bio-based building blocks.

The reactivity of this bis-cyclic coupler towards primary amines was evaluated. At room temperature, the thiolactone moiety in **13** can be addressed selectively, leading to the formation of the corresponding thiol. The aminolysis of the cyclic carbonate results in the formation of a urethane bond and the release of a hydroxymethyl or a hydroxyl group, but it requires amine treatment at elevated temperature (Fig. 14). This selectivity enabled the versatile preparation of poly(amide urethane)s with pendant thioethyl and hydroxymethyl groups via aminolysis of **13** with a variety of diamines at different temperatures. The thiol and alcohol side chain functionalities can be converted in a post-polymerization treatment [50].

4. Double modular modification of thiolactone-containing polymers: Versatility and simplification

4.1. Polythiolactones as versatile precursors for polythiols and derived structures

Thiols are attractive sites for chemical modification and conjugation. However, their reactive nature renders direct incorporation into polymer systems very challenging. The interference of free thiols in most of the polymerization processes is a major issue, especially controlled/living polymerization reactions [51] suffer from thiol-induced side reactions. Thiols can react with (vinylic) monomers through radical or Michael additions and will also induce chain transfer reactions with propagating radicals [52].

Despite these issues, thiols have been introduced in linear polymers, both as pendant side chain functional handle and as reactive end group, the latter being most documented. Indeed, the aminolysis of the RAFT end group is a popular route towards (semi-) telechelics bearing a chain end thiol [53], which can subsequently be employed as a nucleophile in a thiol-bromo conjugation [54] and Michael addition [55] or as a thiyl radical in thiol-ene [55c,56] and thiol-yne [57] conjugation. In some cases, the aminolysis and modification preferentially occur in the same reaction medium (one-pot), avoiding the undesired oxidation to the corresponding disulfide that leads to bimodal polymer populations [55c].

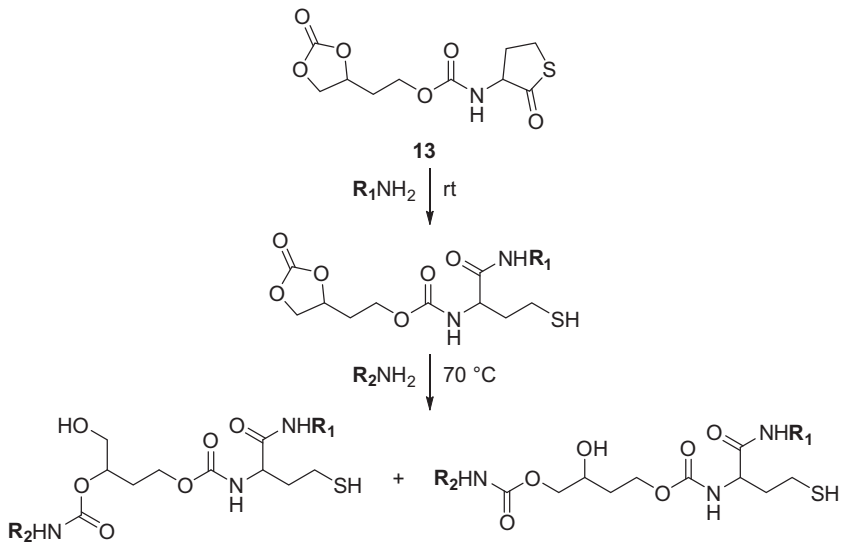


Fig. 14. Bis-cyclic monomer **13** with an ethylene carbonate and a thiolactone ring and the selective aminolysis reactions of both rings of the multifunctional coupler.

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-click reaction of choice. In general, there are two major issues regarding linear polymers with unprotected thiols. A first drawback is the interference of free thiols in the polymerization processes (*vide supra*). 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 along the backbone of linear polymers masked with different protecting groups [58]. Concomitant disulfide formation during and after deprotection is sometimes problematic, resulting in a polymer network [58e,58n]. In selected cases however, polyesters with pendant thiols have been prepared either via direct enzymatic [59] or chemoselective [60] polycondensation of unprotected thiol monomers, based on thiomalic acid.

Secondly, it should be stressed that the hard-to-avoid oxidative cross-linking of linear polythiols is a major hurdle to take, further hampering their more widespread use. 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 [61].

As introduced, thiolactones as functional handles along the backbone of a variety of linear polymers are sites along the linear backbone where a double modification/functionalization, a prime example of PPM, can occur: first, a wide variety of amines can be employed for the aminolysis, followed by a thiol-click reaction of choice (Fig. 15). These polythiolactones can thus serve as precursors for polythiols, thereby solving issues involving the preparation and long-term storage of polythiols.

The two main requirements enabling implementation of thiolactone chemistry for the purpose of PPM of linear narrow-disperse polymers are the straightforward preparation of reactive vinylic thiolactone-containing monomers and the subsequent controlled radical polymerization (CRP), ensuring clean incorporation of the thiolactone unit along the backbone. At first, we thus devised and synthesized two different types of vinylic monomers on large scale, one styrenic (*N*-(4-vinylbenzenesulfonyl) homocysteine-γ-thiolactone, **14**) [62] and the other acrylic (*N*-(acryloyl) homocysteine-γ-thiolactone, **15**) [63] (Fig. 16). In both cases, a stable linkage (a sulfonamide in **14** and an amide in **15**) avoids unwanted detachment of the thiolactone unit during PPM.

Next, the CRP of these thiolactone-containing monomers **14** and **15** was targeted. As there were no literature precedents on the compatibility of thiolactone in the presence of carbon-centered propagating radical systems, we adapted polymerization conditions guaranteeing the integrity of the thiolactone moiety. We deliberately avoided the use of metal-mediated CRP, in order to completely exclude transition metal residues throughout the process of monomer synthesis, CRP and PPM. Hence, reversible-addition fragmentation transfer (RAFT) [64] and nitroxide-mediated polymerization (NMP) [65] are the preferred polymerization techniques.

A first important observation is the lack of control and/or low conversions when attempting to homopolymerize either monomer **14** or **15**, as a result of solubility issues during the polymerization. Consequently, random copolymerizations of both monomers were performed.

Successful copolymerization of monomer **14** with styrene or methyl methacrylate (MMA), via RAFT or NMP, yields linear polymers with tunable thiolactone content (4–25%) and controlled molecular weight (M_n = 6.0 → 18.0 kDa), although dispersities are relatively high (~1.5) in the case of PMMA synthesized by NMP (Fig. 17) [62].

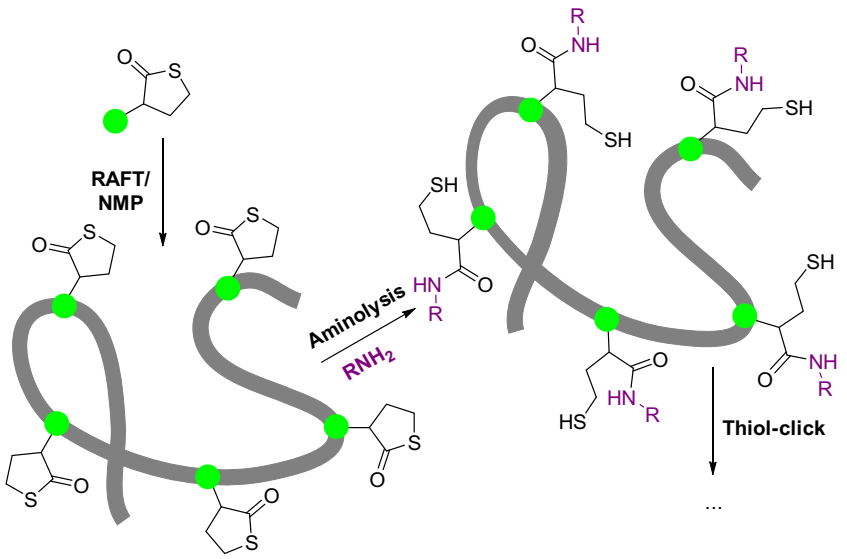


Fig. 15. Schematic depiction of double modification of pendant thiolactone moieties. After CRP (RAFT or NMP) of a stable vinylic thiolactone monomer, aminolysis of the linear poly(thiolactone) yields a linear polythiol, *i.e.* a reactive polymer scaffold for thiol-click modification.

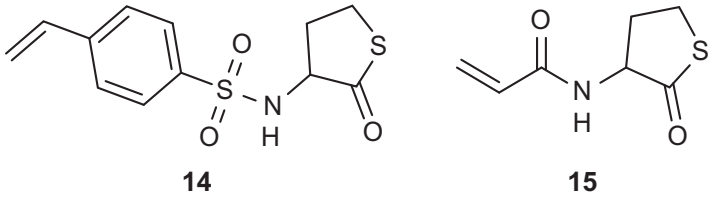


Fig. 16. Two different types of vinylic thiolactone-containing monomers: *N*-(4-vinylbenzenesulfonyl) homocysteine-γ-thiolactone **14** and *N*-(acryloyl) homocysteine-γ-thiolactone **15**.

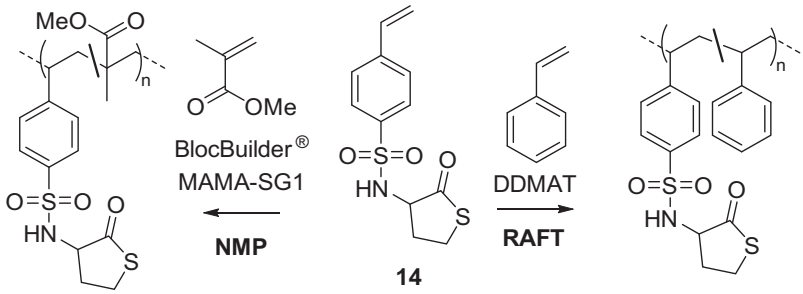


Fig. 17. RAFT of styrene and monomer **14**, and the NMP of MMA and monomer **14** yielding the respective random copolymers.

In an analogous manner, copolymers were produced by RAFT polymerization using monomer **15** as comonomer with *N*-isopropylacrylamide (NIPAAM) (Fig. 18). Thiolactone contents of the final polymers were determined via ^{1}H NMR spectroscopy and elemental analysis. The polymers used for the PPM exhibited thiolactone contents between 23 and 32 mol%, with molar masses in the range of 10–20 kDa and low dispersities ($Đ = 1.2 \rightarrow 1.3$) [63].

Although only narrow-disperse thiolactone-containing copolymers could be obtained, it has been demonstrated that thiolactones are compatible with radical polymerization conditions, using two different techniques (RAFT and NMP).

4.2. Double PPM of polythiolactones: Two-step batch process

The last stage is the double modification of the synthesized random copolymers (Figs. 17 and 18) using thiolactone chemistry. There are two approaches for the decoration of linear polythiolactones. On one hand, the PPM consists of two separate batch processes (aminolysis and thiol-click), with isolation of the polythiol, while on the other hand, the double PPM can be conducted in a one-pot manner, thus avoiding any intermediate purification. Both approaches have been investigated and the respective advantages and disadvantages were evaluated.

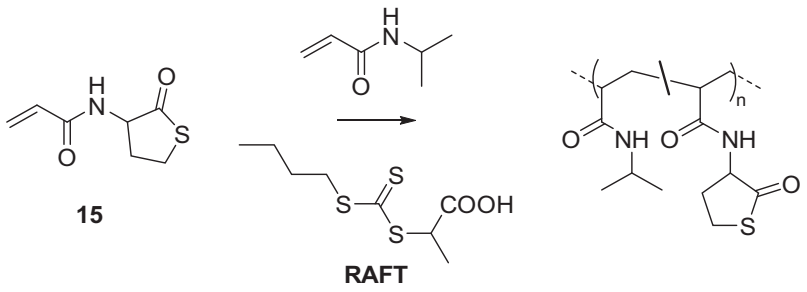


Fig. 18. RAFT copolymerization of NIPAAM and thiolactone-containing monomer **15**.

The first PPM approach was examined using the styrene-based polythiolactones (Fig. 17). In a first step, the aminolysis with a series of amines (benzylamine, *n*-propylamine, ethanolamine and Jeffamine® M-1000), generates thiols as pendant groups on the polymer chain [62]. Disulfide formation could be suppressed using an excess amount of low-molecular weight thiol (ethanethiol or octanethiol) as reducing agent. Acidic work-up before precipitation guarantees the formation of a series of polythiols. After isolation of these polythiols, conjugate addition (thiol-Michael reaction) with *N*-benzylmaleimide yields the double modified polymers. This result demonstrates that the thiols introduced on the polymer backbone can serve as functional handles for subsequent thio-click reactions, permitting a double modification of the polymer (Fig. 19). The reaction conditions are adapted during all stages of the process in order to completely suppress undesired disulfide formation. The low and constant dispersity of all linear polymers, as indicated by SEC analysis, is a proof of the success of this two-step batch approach. Similar results were obtained when starting the double modification sequence with thiolactone-containing PMMA [62]. The main disadvantage of this two-step approach is the laborious work-up procedure enabling the isolation of the polythiol without the formation of disulfides cross-links. However, these polythiols, once purified, can be stored in the dried state for longer periods (several months). The obtained polythiols are versatile scaffolds for further modification, using a variety of established conjugation reactions. Moreover, this approach is particularly advantageous over one-pot double PPM, when exploring thiol-X reactions that are not compatible with the aminolysis process, like the demonstrated thiol-maleimide conjugation.

4.3. Double PPM of polythiolactones: One-pot process through nucleophilic amine-thiol-ene conjugation

The second approach for double PPM has been performed using the polythiolactones, prepared by random RAFT copolymerization of NIPAAM and the thiolactone acrylamide monomer **15** (Fig. 18) [63]. Therefore, the respective copolymers were subjected to the additive-free *nucleophilic* amine-thiol-ene. A chloroform solution of the polythiolactone at a concentration of 10 wt% was treated with the desired acrylate, followed by addition of the primary amine. Both reagents were used in a fivefold excess with respect to the number of thiolactone units. In order to demonstrate the versatility of our concept, a variety of amine/acrylate combinations was used (Fig. 20).

In all cases a clear molecular weight shift was observed while a low dispersity ($Đ$) was maintained, which shows that side reactions such as disulfide formation are negligible. In other words, the released thiol groups are immediately trapped by the acrylate present in the solution. In addition to the performed SEC analysis, in-depth structural investigations of a selection of the modified polymers, using ^{19}F NMR (Fig. 20, *entry 2*) and 2D-NMR (*entry 10*),

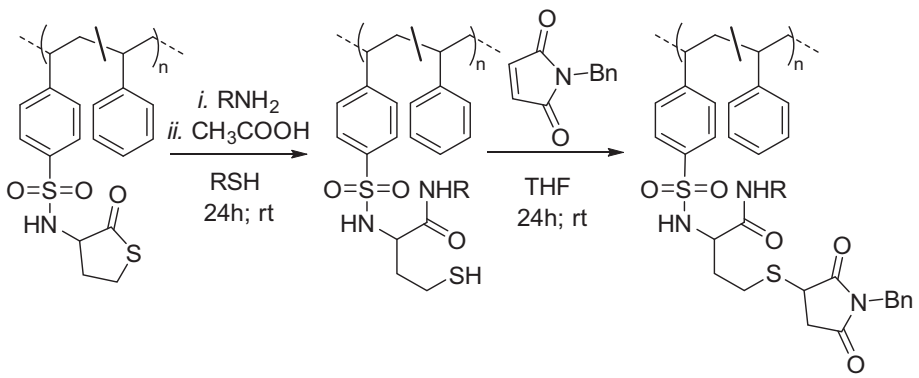
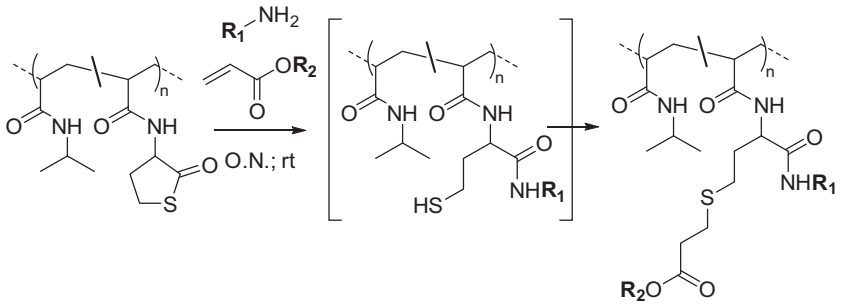


Fig. 19. Double PPM of thiolactone-containing linear polymers in a two-step approach. Nucleophilic ring-opening of pendant thiolactone moieties with an amine, generating polythiols. After intermediate purification, further modification with *N*-benzylmaleimide via a Michael addition reaction was performed.



Entry	Amine/Acrylate Combination	$M_{n,SEC}$ (kDa) [Đ]	
		Before PPM	After PPM
1	Benzylamine/ Methyl acrylate	6.4 [1.23]	7.0 [1.23]
2	4-Fluorobenzylamine/ 2,2,2-Trifluorethyl acrylate	6.4 [1.23]	8.3 [1.18]
3	Ethanolamine/ Hydroxyethyl acrylate	6.4 [1.23]	8.9 [1.21]
4	*n*-Octylamine/ Isobornyl acrylate	6.4 [1.23]	8.3 [1.20]
5	Ethanolamine/ Isobornyl acrylate	6.4 [1.23]	8.4 [1.22]
6	*n*-Octylamine/ Hydroxyethyl acrylate	6.4 [1.23]	8.0 [1.21]
7	Benzylamine/ 2-(2-Ethoxyethoxy) ethyl acrylate	6.4 [1.23]	7.3 [1.22]
8	*N,N*-Dimethyl-ethylenediamine/ 1-Ethoxyethyl acrylate	6.4 [1.23]	4.7 [1.23]
9	*n*-Propylamine/ Benzyl acrylate	6.4 [1.23]	7.7 [1.22]
10	Furfurylamine/ Benzyl acrylate	6.4 [1.23]	7.8 [1.22]
11	3-Morpholino-propylamine/ Methyl acrylate	10.9 [1.27]	12.5 [1.25]
12	*N,N*-Dimethyl-ethylenediamine/ Benzyl acrylate	10.9 [1.27]	6.0 [1.35]
13	*N,N*-Dimethyl-ethylenediamine/ 2-(2-Ethoxyethoxy) ethyl acrylate	10.9 [1.27]	9.0 [1.27]

Fig. 20. Double PPM of thiolactone-containing linear polymers in a one-pot approach using *nucleophilic* amine-thiol-ene conjugation. A solution of the polythiolactone is treated overnight with a primary amine and an acrylate at ambient conditions, yielding the corresponding double modified linear copolymer. The SEC data of the obtained polymers are presented in the table. Thiolactone content in the copolymer; entries 1 → 10: 25%; entries 11 → 13: 32%.

confirmed the near-quantitative double PPM. Furthermore, a successful functionalization was also achieved combining reagents of different hydrophilicity/hydrophobicity (*entries 3 → 6*).

Another important observation was the changed solubility properties of the modified copolymers, especially when a hydrophilic (*entry 3*) or a hydrophobic (*entry 4*) amine/acrylate pair was used. Furfurylamine (*entry 10*), 3-morpholinopropylamine (*entry 11*) or *N,N*-dimethylethylenediamine (*entries 8*, *12*, *13*) were tested as functional amines, giving pNIPAAm a multi-responsive character or providing the opportunity for further functionalization, as well as 1-ethoxyethyl acrylate (*entry 8*) as a protected carboxylic acid derivative [66] or 2-(2-ethoxyethoxy)ethyl acrylate (*entries 7* and *13*) introducing short ethylene glycol side chains to the polymer. In all cases, the modification was performed in chloroform but for example also peroxide-free THF could be used as reaction medium [63].

Encouraged by a successful application of the *nucleophilic* amine-thiol-ene conjugation in a one-pot double PPM approach, we additionally demonstrated that the degree of functionalization can be controlled through different substoichiometric amounts of the ring opening amine. This proved to be particularly interesting for tuning the LCST of the respective polymer. Indeed, in the selected case of double PPM with *N,N*-dimethylethylenediamine/2-(2-ethoxy ethoxy)ethyl acrylate (*entry 13*), the modification degree can be tuned, using different amounts of amine per batch. The tertiary amine residues can, upon protonation at a sufficiently low pH, cause an increased hydrophilicity of the polymer. Since the attachment of the acrylate to the polymer backbone depends on the prior aminolysis, the final polymers also bear varying amounts of 2-(2-ethoxy ethoxy)ethyl side chains. Consequently, a series of water soluble polymers showing an LCST depending on the pH and the degree of functionalization was obtained. Starting from a precursor polymer with a thiolactone content of 32 mol%, an increase of the degree of functionalization from 40% to 95% leads to a cloud point shift from 27 to 66 °C at pH equal to 7. Additionally, the polymer with the highest degree of functionalization (95%) exhibits a transition temperature of 35 °C at pH equal to 9 while it is still water soluble at 75 °C in acidic medium (pH = 5) [63].

The simplicity of the approach in terms of experimental set-up, together with the mild reaction conditions and the almost endless choice of amine/acrylate combinations, render the *nucleophilic* amine-thiol-ene conjugation a powerful and versatile PPM tool. The possibility for simultaneous introduction of chemical functionalities and solubility modulators provides paths to multi-functional tailor-made materials.

The unique character of this site-specific one-pot double modification approach should be highlighted. Very few PPM chemistries provide the opportunity of incorporating two residues at same site in a polymer. A noteworthy alternative is the three-step batch transformation of polymer-bound epoxides with sodium azide and subsequent CuAAC, introducing a first residue [67]. The generated hydroxyl functionality can be further modified.

4.4. One-pot double modification of thiolactone-containing nanostructures

One-pot double modification of thiolactones is not restricted to the described *nucleophilic* amine-thiol-ene conjugation. Monteiro and co-workers synthesized multifunctional nanostructures (worms and rods) with multiple chemical functionalities directly in water using a one-step RAFT-dispersion polymerization. The introduced functional handles originate from their presence in the R group onto the chain transfer agent (CTA). In the case of the thiolactone worms and rods, aminolysis with allylamine and subsequent one-pot scavenging of the released thiol using 2,2′-dipyridyl disulfide (thiol-disulfide exchange) in buffered aqueous solution results in the formation of the corresponding pyridyl disulfide and alkene functional nanostructures, allowing for further orthogonal reactions (Fig. 21) [68].

5. Aminolysis of thiolactones, followed by disulfide formation: Synthetic applications

A disulfide is a relatively stable, yet reversible covalent bond, able to (inter)connect a whole range of different substrates [69]. This inherent reversibility entails that it can be (re)formed or broken on the users' demand, generally under relatively mild conditions. Hence, it has been included in the dynamic covalent chemistry (DCC) toolbox [70] and it is essential in some covalent adaptable networks (CANs)[71] with self-healing capabilities [72].

However, undesired disulfide formation during thiol-click reactions and/or long-term storage of thiol-containing substrates is particularly concerning and was one of the initial arguments at the start of our thiolactone research. Although this unwanted secondary reaction can be completely avoided when employing one-pot thiolactone-based reactions, such as the *nucleophilic* amine-thiol-ene conjugation, it still requires careful monitoring. Sometimes the corresponding disulfide is the major adduct of a ring opening of the thiolactone precursor, especially in the absence of a thiol scavenger and in the presence of a larger excess of primary amine during the aminolysis (Fig. 6). At present, we still do not fully understand the parameters, influencing the disulfide formation degree during the aminolysis of a thiolactone, compromising the prevention, the prediction and the control of this event. However, we observed (a) that the amine concentration during the ring opening correlates with the extent of disulfide formation, (b) that disulfide formation was independent from the nature of the primary amine and (c) that it does not require additional oxidants to occur.

Based on these experimental observations, we explored the scope of the concomitant disulfide formation during the aminolysis of thiolactones as a useful synthetic method for the preparation of cyclic polymers [73]. In a first stage, we envisaged the synthesis of linear α,ω-heterotelechelic precursor via RAFT. The initial demand to design a thiolactone-containing CTA was therefore mandatory, providing the direct access to a thiol group at both α and ω polymer termini upon the treatment with an amine [53]. Then, the *in situ* produced thiol-telechelics can engage through a disulfide bonding in an intramolecular fashion to yield cyclic polymers, under high dilution and ambient conditions (open air, room temperature, without a need for a catalyst or any additive). Although there were reports on the

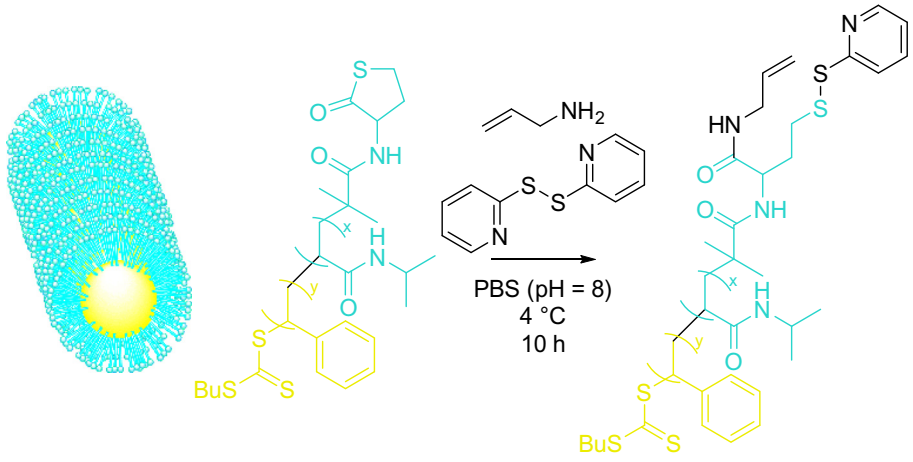


Fig. 21. One-pot double modification of thiolactone functional nanostructures (*left;* schematic cross-section) with allylamine and 2,2′-dipyridyldisulfide through aminolysis and disulfide exchange.

synthesis of cyclic polymers through RAFT polymerization and disulfide formation [74], the presented thiolactone/disulfide cyclization approach widens the range of possible unusual topologies that have practical implications to be manufactured by available synthetic methods. The reason for that primarily lays in the potential use of functionalized amines allowing the cycles to be equipped with desired functional groups for further topological upgrade. Another attractive feature, shared with a recent cyclization strategy using bromo-maleimide – thiol conjugation [75], is the fact that the required precursor end groups, *i.e.* the thiolactone and the dithiobenzoate (*vide supra*), are the direct result of the RAFT polymerization, omitting further end group modifications, like in most of the other ring-closure approaches [73d].

A thiolactone-containing dithiobenzoate **16** was synthesized in three steps on gram scale with an overall yield of 21%. Next, heterotelechelic linear polystyrene (PS) containing an α-thiolactone and an ω-dithiobenzoate group was synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization, mediated by CTA **16** (Fig. 22). Although the compatibility of thiolactone units with CRP was already demonstrated, [62,63] monitoring of the polymerization conditions was required as only at low conversions (ca. 25%), linear precursors with high end group fidelity (>95%) can be obtained [56,76]. Typically, narrow-disperse ($Đ$ = 1.1) heterotelechelic linear polystyrene with an M_n of ca. 4 kDa and a near-quantitative presence of both end groups was isolated [77].

The subsequent aminolysis reaction of this heterotelechelic precursor by slow addition of a primary amine (*n*-propylamine or ethanolamine) in a dilute solution (0.05 mM in CH_2Cl_2), which acts as a nucleophile for both the thiolactone and dithiobenzoate units, generated the α,ω-telechelic-dithiol under ambient conditions without the need for any catalyst or other additive (Fig. 22). The arrangement of thiols under a high dilution afforded cyclic PS through a disulfide linkage, evidenced by SEC, MALDI-TOF MS and ^{1}H NMR characterization. A series of cyclic polystyrene was obtained in high purity after concentration of the dilute reaction mixture and precipitation in methanol. Furthermore, employing ethanolamine, hydroxyl-functionalized cyclic PS was obtained, demonstrating the opportunity for the preparation of cyclic polymers with the pendant functionality of choice. Moreover, a controlled ring opening via either disulfide reduction or thiol/disulfide exchange enables easy and clean topology transformation, re-establishing the corresponding linear polymer and confirming the ring closure mechanism through disulfide formation [77].

6. Solid-supported thiolactones: Source of sequence-defined oligomers

All the thiolactone-based synthetic approaches presented so far occur either in solution or in a homogeneous reaction mixture. Implementation of these established protocols, exploiting the gathered knowledge on the chemical reactivity and selectivity of thiolactones during aminolysis and (one-pot) follow-up thiol-click reactions, in heterogeneous systems undoubtedly offers particularly interesting possibilities for the design of custom materials. Therefore, immobilization of a thiolactone moiety on a heterogeneous carrier, like a (metal) surface or a cross-linked bead, and subsequent modification through one of the above described methods was targeted.

The research field we specifically wanted to enter using solid-supported thiolactones was the area of control over the primary structure of functionalized oligomeric sequences. Today, an increased interest in and strong driver for fundamental research towards reliable sequence-controlled polymerization, enabling pre-programmed distribution of multiple functional groups along the backbone, encourages a growing number of research groups worldwide to contribute [78].

Pioneering efforts to control the primary structure (*i.e.* monomer sequence) of functionalized sequences have

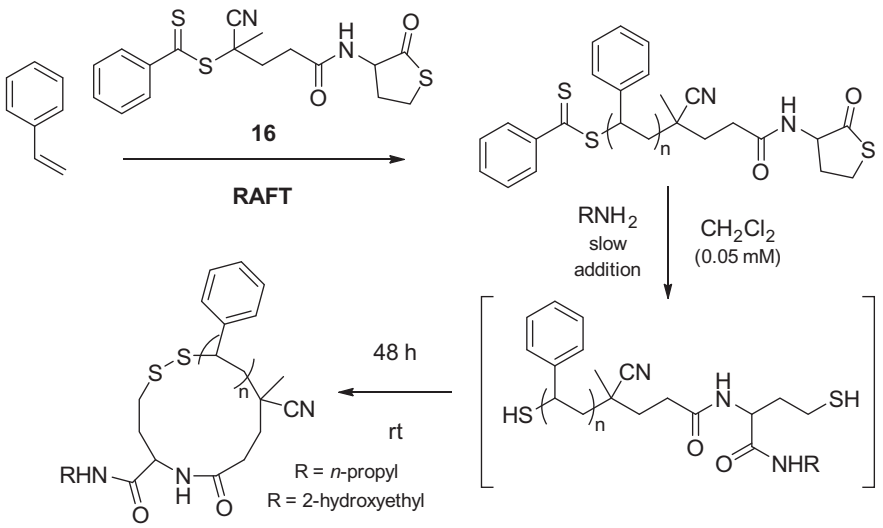


Fig. 22. Ring-closure approach for the preparation of cyclic polystyrene using RAFT and thiolactone/disulfide chemistry.

been based on several approaches, such as different reactivity ratios of vinyl monomers in CRP [79] and norbornenes in ring-opening metathesis polymerization (ROMP) [80], spatial prearrangement of monomers on a (macromolecular) template [81], the action of a small-molecule machine [82], controlled synthesis of multi-block copolymers in one-pot batch [83] or flow reactors [84]. Other attempts use (automated) sequential addition of building blocks on a solid [85] or liquid [86] support, leading to sequence control as a result of iterative coupling steps, omitting the need for pre-organization.

Application of the latter approach on a solid support currently remains the most versatile tool for controlling monomer sequence. Nevertheless, related protocols, established for peptide [87] and oligonucleotide [88] synthesis, also have less favorable characteristics. Indeed, they generally require the use of protecting groups and the restricted number of readily available building blocks, the so called 'monomer alphabet', equipped with the appropriate functional handle can further hamper the preparation of tailor-made functionalized sequences.

These drawbacks justify the development of an alternative coupling strategy for the controlled generation of sequence-defined multi-functionalized oligomers on solid support in a protecting group-free approach, inspired by the 'submonomer' synthetic protocol for the preparation of functionalized peptoids [89], *via* thiolactone-based chemistry.

Immobilization of a thiolactone unit on a solid support should enable chain extension after on-resin aminolysis, using a judiciously selected thiolactone building block, to reinstate the thiolactone functionality, *i.e.* the start of a next iterative reaction sequence (Fig. 23). This two-step aminolysis/chain extension protocol does not make use of any protecting groups. Furthermore, it relies on a single thiolactone-containing building block for chain extension, either *N*-(acryloyl) homocysteine-γ-thiolactone **15** or *N*-(2-bromoacetyl) homocysteine-γ-thiolactone **17**, respectively susceptible to thiol-bromo substitution and thiol-Michael addition. Most importantly, a myriad of functionalities can be introduced *via* the corresponding readily available amines [90].

As the repetitive aminolysis and chain extension steps occur in basic medium, an acid-labile linkage was foreseen for final cleavage from the solid support. Consequently, the carboxyl-functional thiolactone linker was coupled to a 2-chlorotrityl resin using standard conditions [91].

Aminolysis of the resin-bound thiolactone was performed by overnight treatment of the swollen resin with an excess of benzylamine, guaranteeing full thiolactone conversion. LC–MS analysis of the sample after acidic cleavage, revealed quantitative consumption of the thiolactone, but only the corresponding disulfide of the expected thiol could be identified (Fig. 24) [90].

After several failed attempts to avoid disulfide formation and to fully reduce the disulfide to the targeted thiol adduct, the synthetic strategy was adapted to consider the resin-bound disulfides, as stable intermediates. With respect to the two-step iterative protocol (Fig. 23), reduction of the disulfide by phosphine treatment followed by immediate *in situ* reaction of the generated thiol [92] with the next monomer building block is indeed an alternative for the proposed chain extension. However, these conditions were found not to be applicable when using building block **17** due to the incompatibility of a bromide leaving group with a tri-alkylphosphine. On the other hand,

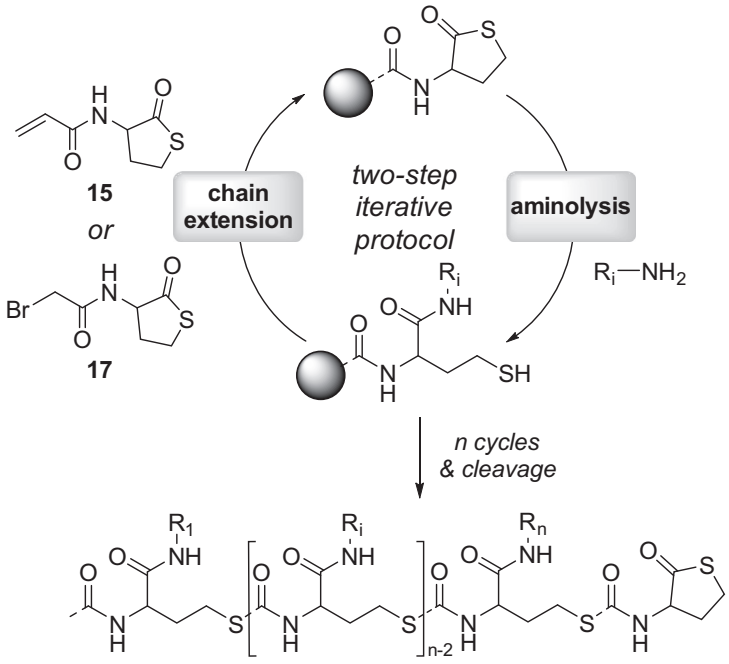


Fig. 23. Two-step iterative protocol for the synthesis of functionalized oligomers on solid support: aminolysis of the resin-bound thiolactone, followed by chain extension using a thiolactone-containing building block **15** or **17**.

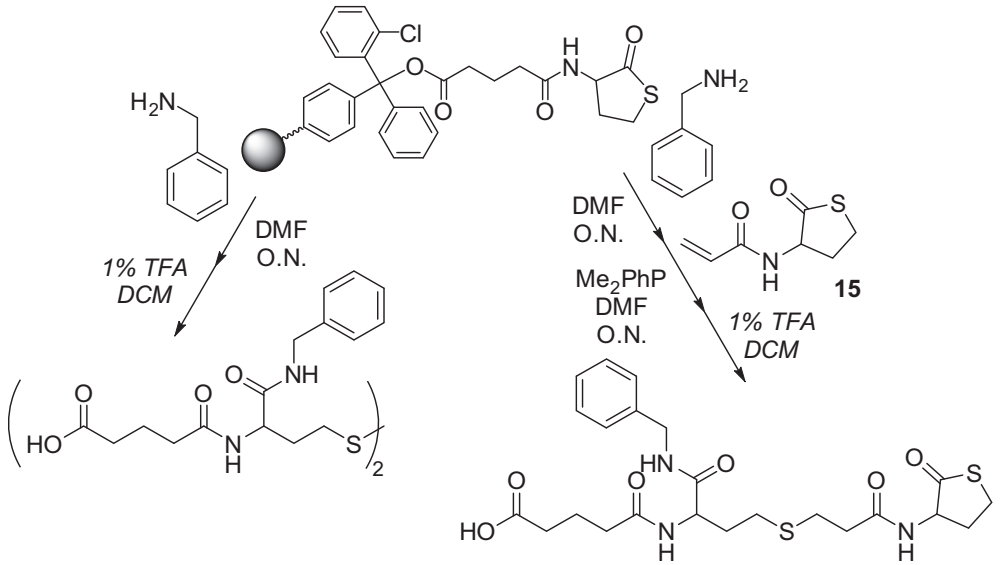


Fig. 24. Aminolysis and chain extension reactions starting from solid-supported thiolactones: (*left*) aminolysis of the resin-bound thiolactone with benzylamine results exclusively in the disulfide adduct and (*right*) aminolysis of the resin-bound thiolactone with benzylamine, followed by one-pot cleavage of the formed disulfide by phosphine treatment and chain extension *via* thiol-acrylamide conjugation.

considering chain extension *via* building block **15**, the phosphine reagent can fulfill a dual role: both as a reducing agent for the disulfide generated upon the aminolysis and as an efficient catalyst for the thiol-Michael addition [12b,48]. Cleavage of the resin-bound disulfide and Michael addition of the thiol to acrylamide **15** could indeed be successfully performed in the presence of an excess of Me_2PhP and building block **15**, as demonstrated by LC–MS analysis of the obtained conjugated product (Fig. 24) [90].

In order to further demonstrate the general potential of this methodology in terms of versatility and functional group tolerance, a small library of functionalized dimer sequences was prepared by 2 iterations of the elaborated two-step protocol (Fig. 23, $n = 2$). Different functional handles could consequently be incorporated in a single, longer oligomeric motif through application of extra aminolysis/chain extension cycles. As the consecutive overnight reactions in the current protocol render the overall process time-consuming, heating through microwave irradiation was successfully performed in order to significantly reduce the reaction times of both steps. This microwave-assisted protocol was applied for the preparation of trimer and tetramer sequences in good purity. Attempts to extend the tetramer to a multi-functionalized pentamer were partially successful, because side reactions become predominant. The structural build-up of the purified sequences was confirmed by HR-MS and *high-resolution* 2D-NMR (500 and 700 MHz) analysis, enabling full characterization of the obtained oligomeric species [90].

While the generated oligomers are small in size, reconstitution approaches could further allow the synthesis of larger chains, featuring designed and repetitive display of carefully selected and well-positioned functional entities [78c].

As an alternative to this solid-supported synthesis of sequence-defined oligomers, two recent methods based on chain elongation in solution have been reported. On one hand, the Passerini reaction, a multi-component reaction recently implemented in synthetic polymer science [93], in combination with radical thiol-ene addition was utilized, enabling the introduction of different side chains along the backbone [94], while on the other hand, thiolactones have been used in a sequential monomer addition protocol for the preparation of ABC-, CBABCD- and DCBABCDE-sequence copolymers [95]. In this approach, *N*-acetylhomocysteine thiolactone **2** was used to introduce thiol end groups in short unfunctionalized sequences (ABC-, CBABCD- and DCBABCDE) that were periodically polymerized by either *radical* thiol-ene or thiol-dibromomaleimide conjugation.

7. Conclusion and outlook

In summary, several thiolactone-based synthetic approaches for the preparation and modification of a variety of functionalized polymers have been established (Fig. 25).

Thiolactones are sensitive towards ring opening in the presence of amines and generally serve as thiol precursors in these conditions. The 100% atom efficient aminolysis can be followed by a thiol-click conjugation, offering the possible introduction of two residues: the first (R_1) originating from the ring opening amine and the second (R_2) from the thiol-X reaction. Extensive method development through dedicated model studies, focusing on the one-pot aminolysis of thiolactone units and subsequent thiol-click conjugation resulted in the elaboration of the amine-thiol-ene conjugation.

Both variants of this one-pot two-step reaction sequence, following either the *radical* or *nucleophilic* pathway, are applicable, although the *radical* version has some limitations due to orthogonality issues when using

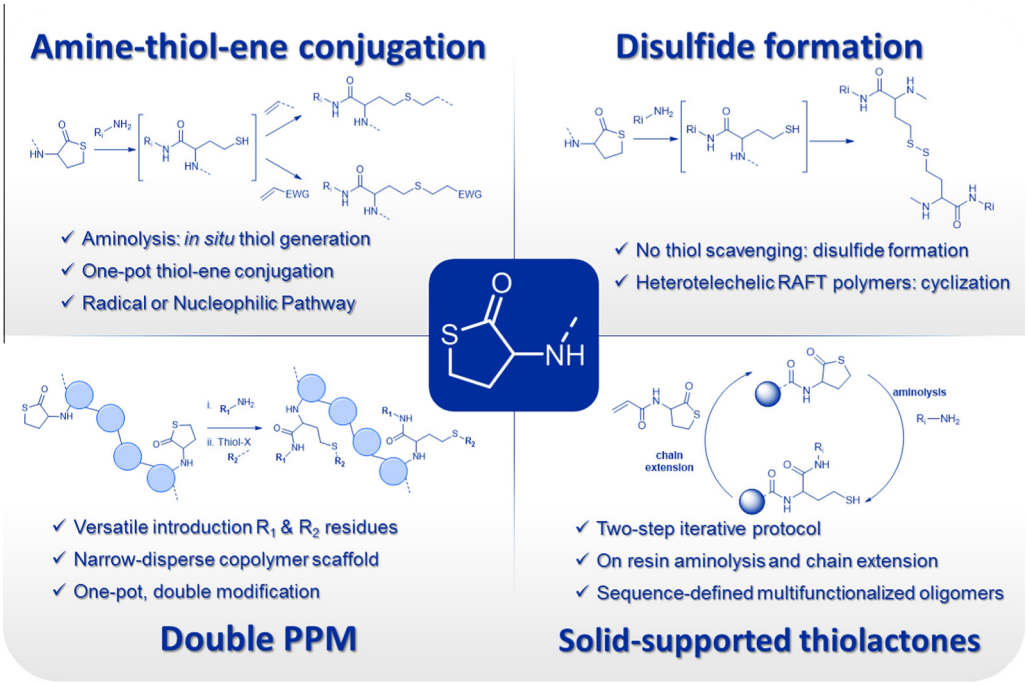


Fig. 25. Overview of thiolactone-based synthetic approaches for the preparation and modification of various functionalized polymers.

functionalized amines. A general approach to obtain thiolactone-containing compounds, enabling implementation of thiolactone chemistry in synthetic polymer science, consist of conversion of homocysteine-γ-thiolactone **1**, a bio-based commercially available building block. Two types of AB′ monomers, bearing both a thiolactone moiety and a reactive double bond (electron-rich or electron-poor), have been prepared, which were susceptible to polyaddition via thiol-ene (*radical* or *nucleophilic*) conjugation after aminolysis, finally yielding diversely substituted polyurethanes and polyamides (linear polymers and networks). In this context, the *nucleophilic* amine-thiol-ene conjugation is particularly attractive as this 100% atom-efficient polymerization is a very mild process, occurring at ambient conditions without any additive or external trigger.

In a second section, the double PPM of narrow-disperse thiolactone-containing linear polymers was discussed. First, two vinylic monomers (styrenic and acrylic), derived from **1**, were copolymerized using RAFT and NMP. At this stage, the compatibility of thiolactone units with radical polymerization conditions was demonstrated. Following successful CRP, the resulting polythiolactones, with varying thiolactone content and molecular weight, were subjected to double modification using two distinct approaches. On one hand, the PPM consists of two separate batch processes (aminolysis and thiol-click), with isolation of the polythiol, while on the other hand, the double PPM can be conducted in a one-pot manner, using a reactive mixture of a primary amine, an acrylate and a polythiolactone, thus avoiding any intermediate purification. Both approaches offer the possibility for double PPM of narrow-disperse polythiolactones, although the first approach requires more laborious work-up to isolate the polythiol without disulfide formation, but it offers the user more options for selecting the thiol-click in the second modification step. At this point we want to highlight again the scope of the *nucleophilic* amine-thiol-ene conjugation for double PPM as it proves to be a very straightforward and versatile method.

While developing these thiolactone-based synthetic methods, we recognized the general importance of disulfide formation as a side reaction during the aminolysis of a thiolactone ring, especially in the absence of a thiol scavenger. Although not fully mastered, we can influence the degree of disulfide formation to some extent, making it a useful and clean transformation. This knowledge was used to prepare cyclic polymers. CRP of styrene mediated by a designed thiolactone-containing CTA resulted in the synthesis of narrow-disperse heterotelechelic PS, having both reactive thiolactone and dithiobenzoate end groups. Upon aminolysis in a dilute medium, the linear precursor is transformed into an α,ω-dithiol, which cyclizes through disulfide formation. Topology transformation, from cyclic to linear, via scission of the disulfide bond offered further support for the proposed thiolactone/disulfide cyclization chemistry.

Finally, we established a two-step iterative protocol for the synthesis of multi-functionalized sequence-defined oligomers using solid-supported thiolactones. After immobilization of a thiolactone unit on a bead, a procedure through consecutive aminolysis and chain extension was investigated. Again, on-resin aminolysis results in the exclusive formation of the disulfide, an event which forced us to adapt the protocol. Indeed, in the second step of the cycle, the disulfide was cleaved using a phosphine and the released thiol was reacted with *N*-(acryloyl) homocysteine-γ-thiolactone **15** in a one-pot manner. This results in the reinstatement of the resin-bound thiolactone and thus the start of a next cycle. We demonstrated four successful

repetitions of the two-step iterative protocol, leading to sequence-defined oligomers having a unique backbone and various pendant residues by the use of a whole range of different functionalized amines during each aminolysis step in the cycle.

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 toolbox. Therefore, it will undoubtedly lead to many more applications, also in material science, in which the unique properties of the thiolactone functional handle, such as double modification, one-pot strategies and mild conjugation protocols, involving biomolecules, will attract the efforts of many more research groups worldwide.

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Prof. Filip Du Prez is since 1999 head of the Polymer Chemistry Research Group (www.PCR.UGent.be) at Ghent University in Belgium where 30 researchers are dealing with the design of functional polymer architectures and polymer materials, various types of (controlled) polymerization techniques and the development of new 'click' chemistries including thiolactone-based polymer chemistry. A couple of actual research domains are sequence controlled polymers, polymers from renewable resources, polymeric capsules and microparticles, self-healing materials, high performance coatings and step growth polymerization in combination with 'click' chemistry. He is author of about 190 peer-reviewed publications and patents (h-index 33), more than 10 book chapters and (co-) chairman of 10 (inter)national conferences on polymer chemistry related topics. In 2011 he co-edited a Wiley book on Complex Macromolecular Architectures. Since 2007 he is responsible for a large valorization consortium (Chemtech) in which two permanent business developers take care of the interface between the chemistry research at UGent and the chemical industry. In 2008, he had a Visiting Professor position at the CAMD Research Centre (UNSW, Sydney) and became co-editor of the Elsevier-journal European Polymer Journal.