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Limitations of Radical Thiol-ene Reactions for Polymer-Polymer Conjugation

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Abstract

In the current work, we report our findings on the use of radical thiol-ene chemistry for polymer-polymer conjugation. The manuscript combines the results from the Preparative Macromolecular Chemistry group from Karlsruhe Institute of Technology (KIT) and the Polymer Chemistry Research group from Ghent University (UGent), which allowed for an investigation over a very broad range of reaction conditions. In particular, thermal and UV initiation methods for the

radical thiol-ene process were compared. In the KIT group, the process was studied as a tool for the synthesis of star polymers by coupling multi-functional thiol core molecules with poly(*n*-butyl acrylate) macromonomers (MM), employing thermally decomposing initiators. The product purity and thus reaction efficiency was assessed via electrospray ionization mass spectrometry. Although the reactions with 10 or 5 equivalents of thiol with respect to macromonomer were successful, the coupling reaction with a one-to-one ratio of MM to thiol yielded only a fraction of the targeted product, besides a number of side products. A systematic parameter study such as a variation of the concentration and nature of the initiator and the influence of thiol to ene ratio was carried out for a one-to-one ratio of MM to thiol content. Further experiments with poly(styrene) and poly(isobornyl acrylate) containing a vinylic end group confirmed that thermal thiol-ene conjugation is far from quantitative in terms of achieving macromolecular star formation. In parallel, the UGent group has been focusing on photo-initiated thiol-ene chemistry for the synthesis of functional polymers on the one hand and block copolymers consisting of poly(styrene) (PS) and poly(vinyl acetate) (PVAc) on the other hand. Various functionalization reactions showed an overall efficient thiol-ene process for conjugation reactions of polymers with low molecular weight compounds (~90% coupling yield). However, while SEC and FT-IR analysis of the conjugated PS-PVAc products indicated qualitative evidence for a successful polymer-polymer conjugation, ^{1}H NMR and elemental analysis revealed a low conjugation efficiency of about 23% for a thiol-to-ene ratio equal to one. Blank reactions using typical thiol-ene conditions indicated that bimolecular termination reactions

occur as competitive side reactions explaining why a molecular weight increase is observed even though the thiol-ene reaction was not successful. The extensive study of both research groups indicates that radical thiol-ene chemistry should not be proposed as a straightforward conjugation tool for polymer-polymer conjugation reactions. Head-to-head coupling is a major reaction pathway, which interrupts the propagation cycle of the thiol-ene process.

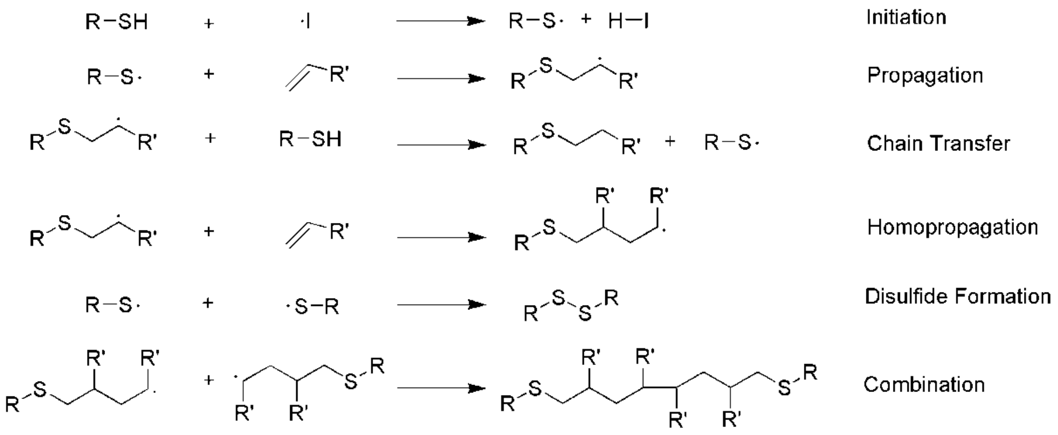
Keywords: Thiol-ene; Click Chemistry; Polymer-Polymer Conjugation; Star Polymer Synthesis; Electrospray Ionization Mass Spectrometry (ESI-MS); Block Copolymer

Introduction

The concept – or rather philosophy – of *click* chemistry, established by Sharpless not too long ago,[1] has rapidly triggered profound interest in the polymer community. Complex macromolecular products are often accessed via sequential chain extension of polymers prepared from multi-functional controlling agent cores[2-9] and the sequential chain extension process often does not proceed completely efficiently and thus residues of both the initial block as well as the second block can be formed. As a result, the product compositions of such macromolecular designs are often complex and difficult to purify. Also, sequential synthesis sets limitations to the choice of polymerizable monomers as the reactivity of the control agents towards the different blocks must be considered. The advent of the *click* philosophy has highlighted an efficient modular pathway to construct polymer materials enabling the synthesis of complex molecular architectures, including compositions that were previously inaccessible. There exist several excellent reviews on the topic and the underpinning details of *click* chemistry will not be reiterated here.[10-13] SANDY: PLEASE ADD REFERENCE HERE: Rhiannon K. Iha, Karen L. Wooley, Andreas M. Nystrm§, Daniel J. Burke, Matthew J. Kade and Craig J. Hawker, Chem Rev 2009, 109 (11), pp 5620–5686 It is sufficient to state that from the variety of *click* reactions available, the copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition[14] has proven to be the most popular method employed. Nevertheless, the use of a toxic metal catalyst, i.e. copper(I), remains a main drawback, especially for bio-related applications. Although a number of strategies have been developed to avoid the use of copper for azide-alkyne *click* reactions, it is often argued that at least in the near future these approaches will not be able to replace the copper(I) catalyzed coupling reaction.[13] To avoid the use of a copper catalyst, a number of alternative *click* strategies have been recently proposed,[15] and in particular (hetero) Diels-Alder cycloaddition reactions[7,16] as well as thiol-ene reactions[17-21] are becoming increasingly widespread. Among these, the thiol-ene radical addition reactions are believed to have significant potential to become as popular as the Cu(I)-catalyzed azide-alkyne *click* cycloaddition reaction, CuAAC, since the introduction of terminal alkene and thiol groups is straightforward and the coupling procedure can be conducted even without a catalyst in the presence of UV-light.[15] For example, this strategy has been employed as part of a facile method for the construction of various dentritic thioether structures,[22] where thiol-ene chemistry is used to functionalize the chain ends and to create a dentritic backbone. As a result, the potential of thiol-ene to be classified as a representative of the *click* class of reactions was recognized.

Thiol-ene coupling reactions are not new chemistry, but have been rather extensively studied over the last century,[23-25]and were described as early as 1926 by Braun and Murjahn.[26] While thiol-ene polymerizations are in use for the formation of networks[21,27] or for the purpose of controlling molecular weight in radical polymerizations, thiol-ene coupling is more recently also referred to as a *click* reaction.[28] Hoyle *et al.* have presented a detailed review on thiol-ene reactions from recent historical and on-going industrial perspectives, as well as discussing thiol-ene reactions in great detail as a newly rediscovered pathway to affording novel polymeric materials with specific properties.[29] Radical addition of thiols onto the vinyl double bonds of poly[2-(3-butenyl)-2-oxazoline], initiated by UV light has also been recently reported.[30]

When discussing conjugation via thiol-ene chemistry, it is important to distinguish radical thiol-ene from the catalyzed Michael addition of thiols onto vinyl groups, a reaction that has also been applied to polymeric compounds.[31-35-37] The present work does not focus on the Michael-type addition reaction but only on the thermally induced or UV light initiated thiol-ene coupling reaction involving radicals where no catalysts are employed. Radical thiol-ene coupling proceeds via a mechanism that is similar to that of a chain-transfer polymerization mechanism (see Scheme 1). In a first step, a thiyl radical is generated from a thiol functionalized molecule via hydrogen abstraction from an initiator-derived radical, which subsequently readily reacts with both electron rich and electron poor carbon–carbon double bonds. This reaction is referred to as propagation (not to be confused with the homopropagation of the chain growth mechanism in transfer polymerization). In the next step, the radical adduct abstracts a proton from another thiol, thus forming the reaction product and recovering a thiyl radical (chain transfer reaction). Frequently, side reactions have been observed.[38] It should be noted here, that in case thiol-ene chemistry shows significant side reactions, the whole process might not be considered to be a *click* reaction, as the occurrence of secondary reaction pathways is a direct contradiction to the *click* concept. Thus, thiol-ene may only serve as an efficient conjugation tool if such reactions can be largely avoided. One known side reaction is thiyl-thiyl radical coupling, which leads to disulfide formation; another is head to head coupling of the carbon centered radicals. These two reactions are arguably the most prominent reactions terminating the thiol-ene cycle, but in principle, any bimolecular spin-annihilation reaction can of course occur. Additionally, the step-mechanism of thiol-ene conjugation is in competition with the chain growth mechanism of a transfer polymerization if a (homo)polymerizable ene is used.



Scheme 1: Generalized radical thiol-ene *click* reaction – possible reaction pathways for the generated radicals.

In the past, several studies for a successful functionalization of polymers via radical-initiated thiol-ene conjugation with small molecules have been performed. However, no example exists where two polymer chains were coupled and even with the Michael addition type reaction, only few examples for such an attempt can be found in the literature to the best of our knowledge. This lack of (radical) thiol-ene chemistry as a tool for polymer conjugation was also most recently noted on by Sumerlin and Vogt.[39] One example of polymer-polymer conjugation has been presented by Li *et al.*, where a maleimide end group functionalized poly(*N*-isopropylacrylamide) was coupled to thiol end group functionalized poly(styrene) via a Michael addition reaction.[40] However, an excess of the thiol-functionalized poly(styrene) and its subsequent removal was required.

In the present work, we report our findings when performing polymer-polymer conjugation reactions using radical-initiated thiol-ene chemistry. Surprisingly, the thiol-ene approach was found to be relatively unsuccessful when targeting polymer-polymer conjugation reactions and only showed success to some extent, when polymers were functionalized with small molecules. Detailing why some reactions do not work is always challenging as ultimate proof might not be achievable. Still, we are convinced that such a report is mandatory in this case, as contrary to the impression given by a large number of papers, (radical) thiol-ene cannot be considered a *click*-type reaction for polymer-polymer conjugation chemistry.

Implications of the click concept for polymer conjugation reactions

The reason for the success of *click* chemistry within the polymer community lies in the fact that reactions that follow the *click* philosophy provide reaction pathways that would otherwise be inaccessible with conventional methodologies. Following the original definition by Sharpless[1] a *click* reaction must – among others requirements – proceed with a high thermodynamic driving force to allow for high yields and reasonable reaction times without the formation of problematic side products. The purification of the products should be facile and not require chromatographic separation. It is especially these requirements that make *click* chemistry so attractive for polymer chemists. When working with polymers, preparative chromatography is tedious if often not impossible. Reactions that proceed with close to 100 % selectivity and at the same time employ the starting materials in equimolar amounts allow for polymer-polymer reactions without the necessity of a product purification step (other than removing a potential catalyst or other additives). Without such reactions, modular approaches for the synthesis of complex macromolecules could not be taken.[41] In consequence, even though equimolar amounts of reactants are not strictly required from the original definition of *click* type reactions, it is the 'equimolarity feature' of efficient *click* reactions that causes their high value in polymer chemistry. Regardless, the click definition dictates that, if one reaction partner is used in excess, or if significant side products are formed during the reaction, that these components must be easily removable by non-chromatographic methods, that is recrystallization or distillation. When dealing with two polymeric reactants one can easily rule out distillation as a separation method. The analog to crystallization would be precipitation in the case of polymers. Thus, if one cannot use precipitation (or fractional precipitation for that matter) to separate the reaction product from excess starting material or byproducts, the original click definition is not fulfilled for a polymer conjugation reaction. It should be mentioned that when two polymer chains are coupled, the reaction product will always, at least partially, reflect the physical characteristics of the starting material. Thus complete separation based on solubility will always be hard to accomplish at best.

In the context of polymer conjugation, two requirements that directly follow from the original *click* philosophy can be defined, for which polymer reactions must be tested in order to assess their ability to serve for feasible modular transformations: (*i*) Endgroup transformation without any presence of significant side products and (*ii*) high conjugation efficiency when at least two polymer chains are coupled to each other, i.e. the completion of the reaction on a reasonable time scale without employing an excesses of one reaction partner. Violation of any of the above two requirements will inevitably lead to complex product mixtures that in the worst case are non-separable. Despite these strict requirements, there exist indeed very successful cases that fulfill the click criteria for polymer-polymer ligation [SANDY: PLEASE INSERT THESE REFERENCES HERE: Inglis, A. J.; Sinnwell, S.; Stenzel, M. H.; Barner-Kowollik, C. Angewandte Chemie Int. Ed. 2009, 48, 2411-241 AND Inglis, A. J.; Pierrat, P.; Muller, T.; Bräse, S.; Barner-Kowollik, C. Soft Matter 2010, 6, 82-84 AND Sumerlin, B. S.; Vogt, A. P. Macromolecules 2009, 43, 1-13 AND Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Angew. Chem.-Int. Ed. 2009, 48, 4900-4908] and would be unwise to state that the click criteria cannot be fulfilled in polymer conjugations.

In the current manuscript we have combined the results from two workgroups, the Preparative Macromolecular Chemistry group from the Karlsruhe Institute of Technology (KIT – Karlsruhe) and the Polymer Chemistry Research group from Ghent University (PCR – UGent). Both groups initially started their research tasks based on the encouraging results from other groups claiming *click*-status for (radical) thiol-ene reactions. While the synthetic targets were distinctly different in both research strands, the goal was identical, namely employing radical thiol-ene chemistry in a modular approach to link individual polymer chains. The combination of both projects allows for a study over a very broad range of reaction conditions using different thiols as well as enes in a joint effort. As the work was carried out entirely independently, the different synthesis strategies are outlined and discussed separately. The KIT group aimed for the synthesis of star polymers employing sequential radical thiol-ene coupling reactions using macromonomers and multifunctional thiols, while the UGent group aimed to couple two different polymer chains containing either thiol or ene functionalities to form block copolymers.

A joint discussion of the results from both groups will be found at the end of this paper where the results are put in context. Additionally, thermal and UV initiation methods will be compared with respect to thiol-ene chemistry as both groups employed different initiation methods. Evaluation of the efficiency of radical thiol-ene chemistry for polymer conjugation was judged based on the possibility to perform polymer endgroup modifications and polymer conjugation reactions without the presence of any side products.

Experimental

Materials

(*Karlsruhe*) Thiols with varying degrees of thiol functionalities were purchased from Sigma-Aldrich and used as received: 1-octanethiol (> 98.5 %), 1,4-butanedithiol (97 %), trimethylolpropane tris(2-mercaptoacetate) (tech.), and pentaerythritol tetrakis(3-mercaptopropionate) (PTMP) (97 %). AIBN (Sigma-Aldrich) was recrystallized twice from methanol, 1,1-azobis(cyclohexanecarbonitrile) (ACHN) (98%) (Sigma-Aldrich) was used as received, and hexyl acetate (97%) and butyl acetate (CHROMASOLV® Plus, for HPLC, 99.7 %) were used as solvent. *n*-butyl acrylate ≥ 99 %) (Sigma -Aldrich) was deinhibited over basic alumina before use.

(*Ghent*) Allyl alcohol ≥ (99%), 4 -(dimethylamino)pyridine (≥ 99%), Hünig's base - *N*,*N*-diisopropylethylamine (99.5%), bromoacetyl bromide ≥ (98%), O -ethylxanthic (96%), 2,2'-azobis(isobutyronitrile) (AIBN), dodecyl vinyl ether (98%), 1-dodecane thiol (≥ 98%) were purchased from Sigma-Aldrich and used as received. Vinyl acetate (VAc) (99+%, Sigma-Aldrich) was passed through a column of basic alumina to remove the inhibitor. Sodium dithionate ($Na_2S_2O_4$) (technical grade, 85%) (Sigma-Aldrich) was used as aqueous solution. 2,2-dimethoxy-2-phenylacetophenone (DMPA) (99%) and propylamine (98%) were purchased from Acros Organics and used as received. Styrene (St) (99%, extra pure) (Acros Organics) was passed through a column of basic alumina to remove the inhibitor. The chain transfer agent dibenzyl trithiocarbonate (DBTTC) was obtained from Arkema and used as received.

Sample Preparation

General procedure for thiol-ene reactions for the formation of star polymers from poly(butyl acrylate) macromonomer

Butyl acrylate macromonomer, BA MM, was synthesized via a facile method previously described.[42] No purification was necessary before the thiol-ene reaction could be performed. Samples were prepared as follows: AIBN (0.05 g mol^{-1}, 0.5 eq.) were added to macromonomer (100 mg, 0.055 mmol) in 2 mL butyl acetate solvent, and varied amounts of thiol compound (1-10 equiv.) were added. The mixture was degassed via the freeze-pump-thaw method, and then heated at 60 °C for 16 h with stirring, after which time the samples were quenched in ice water. Excess unreacted thiol compound and solvent were removed by drying in a vacuum oven at 30°C for 24 h. BA MM with a number average molecular weight of 1870 g·mol^{-1} and a polydispersity of 1.7 is obtained.

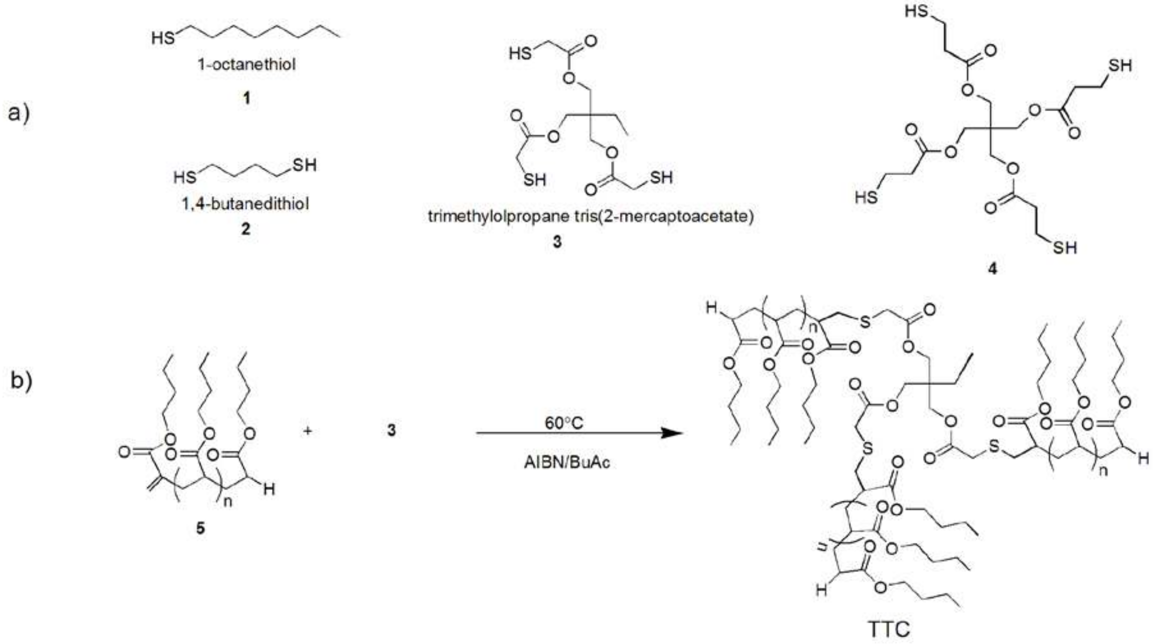
Typical procedure for thiol-ene reaction for block copolymer formation

A typical procedure is as follows (entry 2, Table 2). Thiol containing polystyrene (PS, 0.1 g , 3.33 x 10^{-5} mol, M_n = 3000 g·mol^{-1}, *PDI* = 1.20) and ene-containing poly(vinyl acetate) (PVAc, 0.06 g, 3.33 x 10^{-5} mol, M_n = 1800 g·mol^{-1}, *PDI* = 1.50) , (or low molecular weight compound in the case of functional polymers, respectively) and 0.2 equiv of photo-initiator 2,2-dimethoxy-2-phenylacetophenone (DMPA, 1.7 mg, 6.66 x 10^{-6} mol,) were placed in a three-necked round bottom flask and dissolved in minimal amounts of THF (0.6 mL) required to solubilize all components. The flask was sealed with a rubber septum and the reaction mixture was purged of oxygen by bubbling with N_2 for at least 30 min. The flask was irradiated in an oven equipped with a 365 nm UV lamp, and was positioned in a horizontal fashion, to ensure equal irradiation over the whole reacting mixture (distance between irradiation source and the flask ca. 20 cm). Irradiation time was 1 hour. The resulting functional polymers were precipitated three times in cold methanol while block copolymer were selectively precipitated in cold methanol.

Details on polymer characterization via NMR, SEC and ESI-MS and on the synthesis of the single polymer blocks can be found in the supplementary information accompanying the manuscript.

Results and Discussion (KIT)

If thiol-ene was a method that comes close in its efficiency to the well known *click* conjugation methods such as the copper catalyzed azide-alkyne coupling or (hetero) Diels-Alder reactions, then assembly of star molecules from specific core molecules with end-functional polymers should be feasible. Thus, in the KIT group we aimed for the synthesis of multi-arm acrylates from linear macromonomers with commercially available multifunctional thiols that are often used in the synthesis of polymer networks from traditional thiol-ene reactions (see Scheme 2).



Scheme 2: (a) Multifunctional thiols employed in the current study, (b) typical reaction performed

1.1 Synthesis of Butyl Acrylate Macromonomer

For the construction of complex molecular architectures, macromonomers are a convenient class of building blocks that are available for assembly. Linear macromonomers can be synthesized via a variety of methods.[43] Recently, we introduced a procedure to obtain pure macromonomers from auto-initiated acrylate polymerization at high temperatures.[42,44,45] As this method does not require any purification or post-modification steps and allows for high yields, we based our thiol-ene strategy mainly on this type of compound. In addition, the so-obtained macromolecules feature an unsaturated endgroup that can form relatively stable radicals upon addition of e.g. a thiyl radical, while not undergoing homopropagation due to steric reasons. This feature makes the poly(butyl acrylate) type macromonomer an excellent choice for thio ene conjugations: The double bond is relatively accessible and due to the 1,1 disubstituted nature combined with ester substituent, a relatively stable tertiary radical is formed upon radical addition, giving rise to a high driving force behind the addition reaction of the thiyl radicals to the ene. At the same time, no homopropagation can occur in contrast to similarily reactive enes like for example methyacrylates, which would readily form oligomers when monomer and thiol were employed in equimolar amounts. Also, acrylates show good solubility in most solvents so that solvent effects can largely be excluded and the choice of solvent is only limited with respect to radical transfer to solvent rates. As we have previously shown, butyl acetate does not show a high tendency to undergo radical transfer.

The mass spectrum of the starting butyl acrylate macromonomer (BA MM) that was employed is shown in the lower part of Figure 1 (for enlarged spectrum see Supplementary Information Figure S1). One major peak associated with structure **5** (see Scheme 2) can be found, corresponding to the macromonomer that is subsequently used as the ene in the thiol-ene reaction. Trace amounts of structures **6** and **7** can also be seen (for structures see supporting information), which correspond to a macromonomer molecule resulting from transfer to solvent, carrying a hexyl group (MM synthesis was performed in hexyl acetate solution) (**6**) and a saturated species (**7**) (all species that appear in the macromonomer are given in Scheme S1 in the supporting information section). The employed high temperature macromonomer synthesis[42] is clearly a very selective reaction, with over 95 % of the product constituting the required starting material structure for the thiol-ene reaction.[44] Thus, this starting material is compared to macromonomers prepared via classical controlled radical polymerization, of equally high overall functionality.

Alongside size exclusion chromatography, mass spectrometry is a powerful tool in investigations on the efficiency of *click* reactions as the product is directly observable from the spectra, even in cases where no change in the size distribution can be expected (for example, when conjugating a polymer chain with a small molecule) or where the elugram of the conjugated polymers is expected to be complex.[46] For observation of changes in polymer endgroups and conjugation points, no better analytical method exists to this date. This characterization approach is also especially useful for the present study where the macromonomers are conjugated via multi-thiol core molecules (see Scheme 2), thus leading to the formation of homopolymers with distinct topology. For coupling of the macromonomers with polymer chains of different type forming di-block copolymers, this technique is less appropriate, as the mass spectra of copolymers are far more complicated.

As previously shown,[47,48] mass spectra can be analyzed in a quantitative fashion if some prerequisites are fulfilled, i.e. when the ionization of the polymer does mainly depend on the backbone rather than on the endgroups. Hence, the occurrence of the saturated and therefore unreactive species **7** may be used to compare the product spectra from conjugation reactions under different reaction conditions. The saturated macromonomer product is not expected to – and indeed does not – participate in any reactions; therefore all spectra in the following discussion have been normalized with respect to the peak corresponding to **7** as a reference point.

1.2 Thiol-ene Reaction Conjugation of Butyl Acrylate Macromonomer and Trimethylolpropane tris(2-mercaptoacetate).

In a first step, the butyl acrylate macromonomer was reacted with a multifunctional thiol core molecule in a one-to-one ratio with macromonomer based on concentration of the complementary functionalities. The result from such a coupling reaction is depicted in Figure 1. Inspection of the mass spectrum reveals that most of the initial macromonomer is converted in the reaction and formation of some of the desired product **TTC** (**T**ri**T**hiol **C**oupling product) is observed. However, three additional products (denoted as **a**, **b** and **c** in the mass spectrum) are also observed, each in higher quantities than the desired reaction product. It can thus be concluded that the conjugation attempt, at least under the chosen conditions, was not successful. To evaluate if the reaction conditions were unreasonably chosen, further experiments were performed with an excess of thiol compared to ene, following conditions typically applied for thiol-ene reactions found in the literature. Following the procedure of Campos *et al.*,[18] reactions were carried out with 5-10 equivalents of thiol initiated by 0.5 eq. AIBN. Results for the trifunctional thiol species are presented in Figure 1 and results for the bifunctional thiol species are provided in the supplementary information (see Figure S3, Supplementary Information). With a 5-fold excess of thiol, almost quantitative conversion of the macromonomer into coupling products **DTC** (**D**i**T**hiol **C**oupling product, see Supplementary Information Scheme S1) or **TTC** (Scheme 1 and supplementary information Scheme S1), respectively, is observed. It should be noted that DTC and TTC both refer to different thiols as core molecules (difunctional thiol or trifunctional thiol) and not to the number of macromonomers attached as mass spectrometry cannot distinguish between the different DTC or TTC products (see below). Further raising the thiol content results in slightly improved yields, however, both reactions can be considered as successful transformations from the viewpoint of endgroup transformations. Very small amounts of side products are observed in all cases, underpinning the apparent efficiency of radical thiol-ene conjugations. Even though this result is encouraging, further analysis of the products is nevertheless disappointing. Alongside the mass spectra, Figure 1 also presents the resulting SEC traces of the reaction products. In all cases, no significant shift in molecular weight can be observed and the reaction products all have virtually the same molecular weight as the starting material. Such results are – judging from the overall good result from the mass spectrometric analysis – surprising only at first glance. The macromonomer employed in the reactions is produced from auto-initiated polymerization, i.e. its molecular weight is an exact multiple of the monomer molar mass. Thus, mass spectrometry is able to show the conversion of double bonds, but based on the obtained *m*/*z* it is impossible to elucidate how many arms of the core molecule have reacted. Addition of one macromonomer onto a core molecule results in isobaric species compared to addition of *n* macromonomers to the *n*-functional thiol. Thus, for the example of the DTC species, the reaction product where two macromonomers were attached to the original dithiol compound and the product where only a single macromonomer was conjugated to the dithiol appear, depending on the length of the macromonomer arm length, at the same *m*/*z* and are thus indistinguishable. Therefore, the results from mass spectrometry and SEC are not contradictory. As must be expected, the conversion of the alkene was successful, but due to the large excess of thiol, formation of star structures did not occur. Nevertheless, such experiments were mandatory to see if thiol-ene conjugation can be achieved under conditions reported in literature. These conditions can hence subsequently be used as a starting point for a systematic investigation to refine reaction conditions to match the needs of polymer-polymer conjugation.

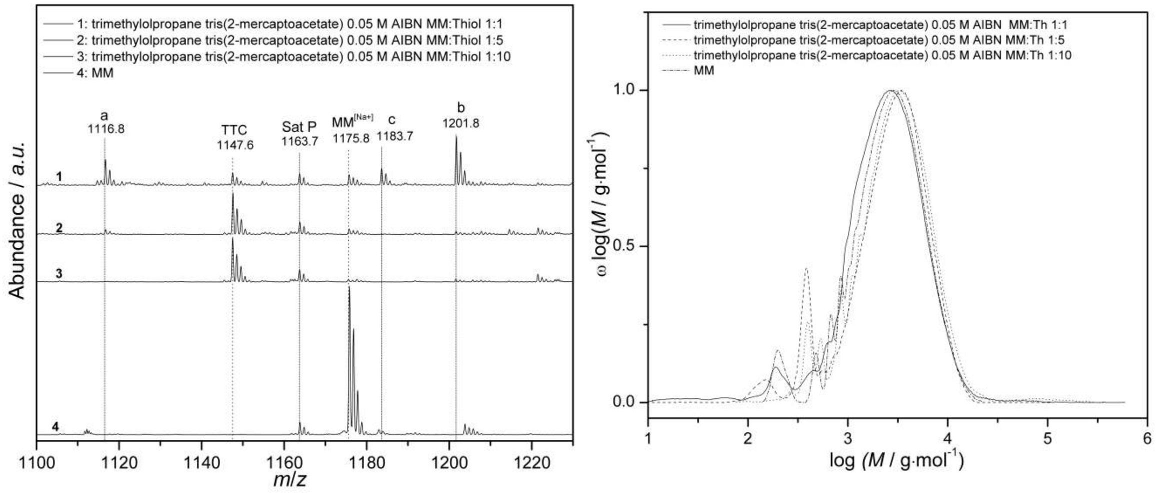


Figure 1 (l.h.s) Thiol-ene coupling reactions carried out with 5 and 10 equivalents of thiol with respect to MM end groups, employing trimethylolpropane tris(2-mercaptoacetate). Samples were heated for 16 h at 60 °C, in butyl acetate solution. (r.h.s) SEC elugrams of corresponding samples. SANDY: PLEASE RESIZE THE RIGHT HAND FIGURE TO THE SAME SIZE AS THE LEFT HAND ONE AND INSERT A SPACE BETWEEN LOG AND THE BRACKET ON THE Y-AXIS THIS HAS TO BE FIXED IN ALL MDW GRAPHS FROM US ALSO IN THE SI

If essentially pure star structures are targeted, the thiol-ene reactions must be carried out in a true 1:1 ratio of starting materials as only under such conditions it is assured that little starting material remains at the end of the reaction and that all individual chains have been assembled to larger structures. Slight excesses of the double bond-species may also be used, resulting in a product mixture of star polymers with some residual linear macromonomer chains. If the excess is small, i.e. in the order of a few percent only, such results might be tolerable from a materials point of view.

1.3 Thiol-ene Conjugation of Butyl Acrylate Macromonomer and 1-octanethiol

In order to optimize conditions for an equimolar conversion of thiol and ene, the system under investigation was switched to the more simple reaction of macromonomer with 1-octanethiol as this reduces the number of potential reactions and hence simplifies the interpretation of the mass spectra. If conditions can be identified under which such small monofunctional thiols can be conjugated onto a macromonomer in a 1:1 ratio, then one may proceed to more complex systems; a task that will be demonstrated to be unachievable under the studied conditions.

Reaction conditions were systematically varied to find optimum conditions for quantitative conversion of thiols. Reactions were carried out with variation in thiol to ene ratios (both excesses of thiol groups to macromonomer groups and vice versa were studied), and finally variation in the concentration and type of initiator were carried out. The initiator was varied from a concentration of $1.56 \cdot 10^{-3}$ to 0.5 mol L^{-1}, and the thiol was again reacted with macromonomer excesses ranging from 1 to 2 equivalents. Selected samples were carried out with excess macromonomer, ranging from 1.1 to 2 equivalents of macromonomer with respect to thiol ratio.

Figure 2 presents the mass spectra of the final product mixtures after a thiol-ene reaction between the butyl acrylate macromonomer with varying equivalents of macromonomer to 1-

octanethiol, initiated by 0.05 mol L^{-1} AIBN. All reactions employ a slight excess of macromonomer, as such conditions were deemed to be most likely to produce the target star product. Still, the attempt was to keep the excess of macromonomer as low as possible, as remaining, unreacted linear chains are difficult to remove from the resulting product mixture. Thus, large excesses are not practical when a pure end product is required, even though it would facilitate generation of the desired star structures when the multifunctional cores are used.

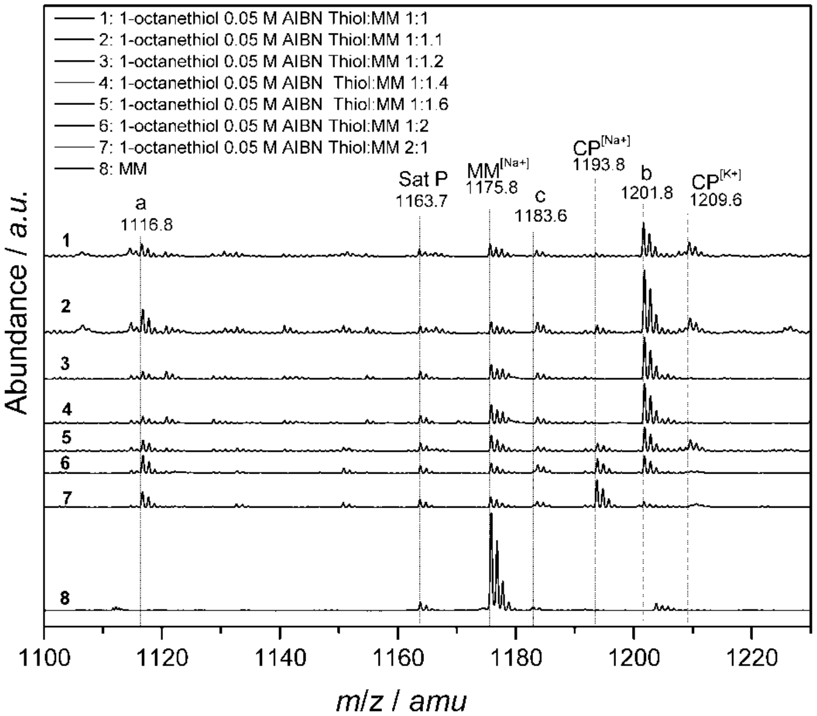


Figure 2: ESI-MS spectrum of the reaction between 1-octanethiol and butyl acrylate macromonomer showing one polymer repeat unit in the *m/z* range 1100 to 1230 g·mol^{-1} of the reaction mixture containing varying

ratios of thiol to ene endgroups, initiated by 0.05 M AIBN, after a reaction time of 16 h at 60 °C. The spectra have been normalized relative to the Sat P peak.

Inspection of Figure 2 indicates that under the applied reaction conditions very little, if any, macromonomer-thiol conjugate is formed. However, when an excess of 2 equivalents of thiol to 1 equivalent of macromonomer ene groups is employed, conversion to the desired conjugate product is achieved (over 50% of MM to the thiol-coupled species conversion is estimated).

Under all conditions, a number of side products do occur in the product spectra. Product **a** is a result of an AIBN radical reacting with a macromonomer chain to form an initiator fragment (i.e. cyano-isopropyl) terminated species. Identification of such a product in the reaction mixture is not surprising considering the large amounts of AIBN employed to initiate the thermal thiol-ene reaction; a concentration of 0.05 mol L^{-1} represents 0.5 equivalents in the reaction mixture. Small amounts of side product **c** can also be observed, the *m*/*z* value of which can be assigned to a macromonomer species carrying two initiator-derived fragments. The masses of both **a** and **c** are thus independent of the thiol employed. Another unidentified side product is found at 1201.8 Da, labeled **b**. This side product is possibly formed in a reaction resulting from the high concentration of AIBN. It should be noted that **b** is the main product observed under all conditions other than when 2 eq. of thiol are used, and therefore it is of critical importance to identify and/or minimize the extent of the reaction leading to **b**. To investigate its origin and to elucidate the reaction pathway by which it forms, further experiments were conducted with variations in the concentration of the employed AIBN initiator. Interestingly, under no conditions is (polymeric) disulfide observed, even though such coupling is known to occur in thiol-ene reactions. It may thus be concluded that once a thiyl radical has reacted with a macromonomer, the formed macroradical is unlikely to react with another thiyl radical but will almost certainly abstract a proton from any surrounding source (a coupling of a thiyl radical with primary initiator fragments can be excluded based on the mass spectra).

1.4 Variation of AIBN Initiator Concentration

Figure 3 presents the results of a series of experiments where the effect of initiator concentration on the resulting product mixture was explored, now using 1,4-butanedithiol as the conjugation point. AIBN has a half life of 10 h at 66 °C, and in the context of these experiments (having been conducted at 60 °C for 16 h), one would expect that the concentration of AIBN would affect the final product composition, since just under half of the AIBN is still present after the first 10 h of reaction. Figure 3 illustrates clearly that the initiator concentration is, within broad limits ($1.6\cdot10^{-3}$ $\text{mol}\cdot\text{L}^{-1}$ to $1.25\cdot10^{-2}$ $\text{mol}\cdot\text{L}^{-1}$), not a factor in determining the composition of the final product. The spectra are almost identical in all respects and following these observations, it was concluded that a minimum concentration of 0.05 mol L^{-1} AIBN is required for conversion of the macromonomer into – at least some amounts – of the desired conjugate product. In agreement with this observation, comparable trends in the product spectra are observed, when a variation of the thiol:MM ratio is performed according to Figure 2 at a lowered initiator concentration (for experimental results see supplementary information). Increasing the thiol:initiator ratio appears to be slightly beneficial, but the amount of side products being formed does not change significantly.

As no plausible structure can yet be assigned to species **b**, experiments were conducted using 1,1-azobis(cyclohexanecarbonitrile), ACHN, to investigate whether a change in initiator affects the positioning of **b** on the *m*/*z* axis, and to confirm whether the side products are a result of the particular initiator utilized (if **b** was formed upon reaction with initiator fragments, a shift in mass should be observed when changing the initiator). In fact, **b** is absent in the product spectra when ACHN is employed. However, as ACHN has a longer half life compared to AIBN, the change in initiator also caused a change in radical flux, the absence of **b** is thus indicative of an initiator-related origin of this product, but does not entirely prove this hypothesis. Nevertheless, the fact that **b** occurs at the same *m*/*z* regardless of the thiol employed also supports the hypothesis of this species being dependent on the type of initiator.

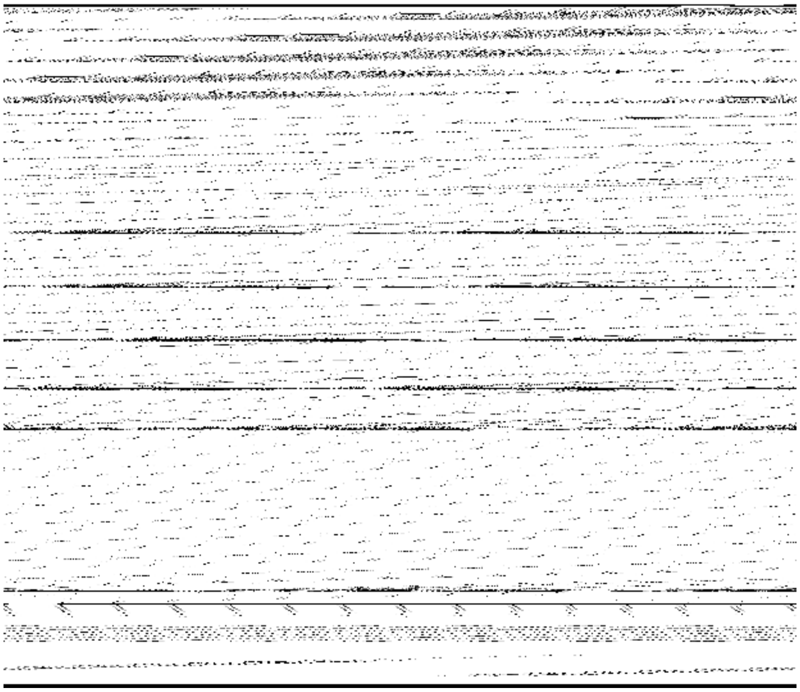


Figure 3: ESI-MS spectrum of the reaction between 1,4-butanedithiol and butyl acrylate macromonomer showing one polymer repeat unit in the *m/z* range 1100 to 1230 g·mol^{-1} of the reaction mixtures containing varying concentrations of AIBN initiator, after a reaction time of 16 h at 60 °C. The spectra have been normalized relative to the Sat P peak.

1.5 Excess macromonomer to thiol

As a final experiment, it was tested whether increasing the macromonomer content allows for synthesis of the desired products, even if the amount of leftover macromonomer after the reaction would not be tolerable. From a scientific point of view, it is however an important question whether an excess of alkene has similar benefits as an excess of thiol. Thus, reactions with the multifunctional thiols in a ratio of MM:thiol of 2:1 were performed. ESI-MS spectra can be seen in Figure 2, graph 7 (1-octanethiol); Figure S2(a) graph 7 (1,4-butanedithiol) and Figure S2(b), graph 6 (trimethyloylpropane tris(2-mercaptoacetate)). In such cases, a disappearance of the MM species cannot be expected when looking at the mass spectra and at best a one to one ratio of starting material to conjugation product can be envisaged. Analysis of the spectra immediately indicates that while the desired product is formed, large amounts of **a**, **b** and **c** are also formed in significant amounts, demonstrating the repeated failure of the procedure. It must however be noted that the analysis by ESI-MS may be misleading. If star-polymer assembly was indeed successful, significantly higher *m/z* values are reached and the reaction product might not be as clearly identifiable in the spectra due to the limited accessible molar mass range. As a consequence, the mass spectrometric data might overemphasize side products, which is supported by the apparent improvement in results for the difunctional thiol compared to the trifunctional thiol (where significantly higher masses are potentially formed). Therefore, the reaction products have also been subjected to SEC analysis to analyze the molecular weight of the product.

Figure 4 shows the SEC traces after reaction of a two times excess of macromonomer for the different thiols employed in this work. Although a slight shift in the traces is observed with increasing number of available arms on the core molecule, no significant increase in M_n of the samples can be observed. As mentioned above, a two-fold increase in molecular weight is not expected due to the leftover starting material. However, as SEC yields a weighted distribution, a clear shift of the distributions (with an increased polydispersity) should be seen if the star formation was indeed successful. Thus, the SEC results confirm the observation made by mass spectrometry: some star polymer product is formed as is evident by observation of a congruent species in the mass spectrum as well as the slight shift observed by chromatography. However, conversion of the macromonomer *and* of the thiol is far from complete and side products seem to be formed in at least similar numbers as the targeted structures.

To validate our results on a narrowly distributed polymer system, low PDI poly(isobornyl acrylate)s with a terminal vinyl function were prepared and subjected to radical thiolene coupling. These data can be found in the supporting information section accompanying this manuscript (Scheme S2 and Figure S4). The results remain – qualitatively – identical to those described above.

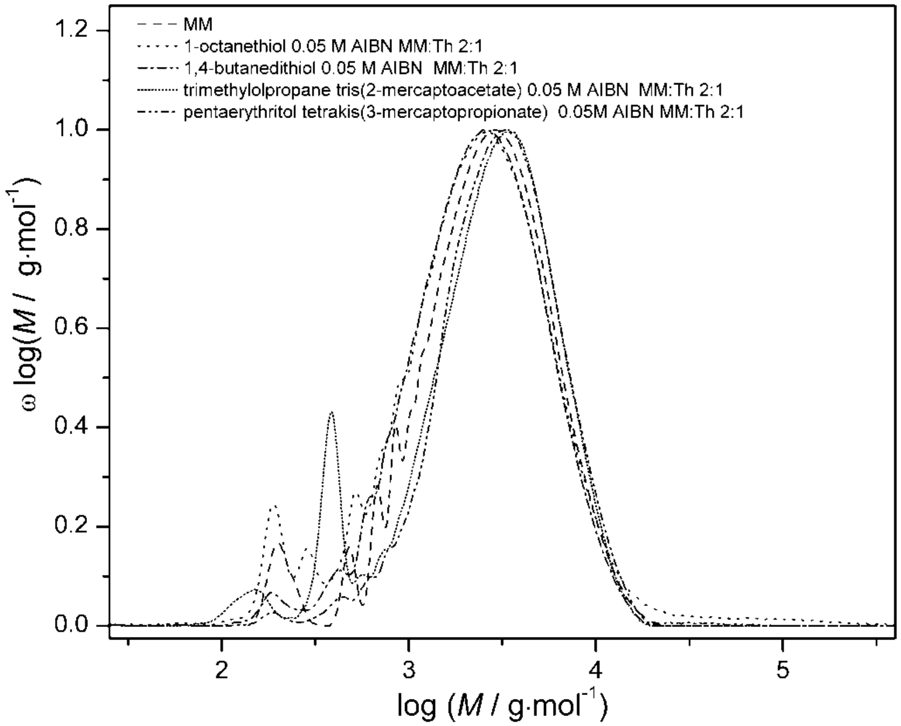


Figure 4: Molecular weight distributions of the starting macromonomer material, and product mixtures after the thiol-ene reaction with 1-octanethiol, 1,4-butanedithiol, trimethylolpropane tris(2-mercaptoacetate) and pentaerythritol tetrakis(3-mercaptopropionate). All samples were prepared using 0.05 M AIBN, and heated for 16 h at 60 °C, in butyl acetate solution, with the MM to thiol ratio as specified in the graph. One representative elugram was selected for each thiol studied as no significant shift was observed in any sample.

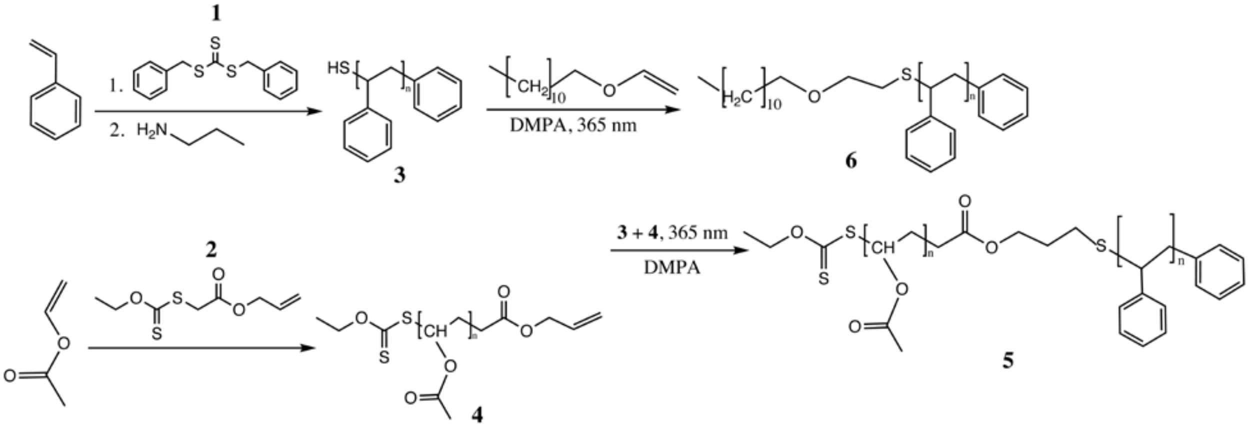
Results and Discussion (UGent)

Independently from the research efforts carried out by the KIT group in Karlsruhe, the UGent group has been focusing on photo-initiated thiol-ene chemistry for the synthesis of functional polymers and amphiphilic block copolymers consisting of a poly(styrene) (PS) and a poly(vinyl acetate) (PVAc) segment as a precursor of hydrophilic poly(vinylalcohol) PVA. Amphiphilic block copolymers have attracted great interest for a wide range of pharmaceutical, cosmetic, agricultural and biological applications, as a result of their unique solution and bulk properties (e.g. micellization, phase separation).[43,50] However, the copolymerization of VAc in a controlled fashion is all but straightforward, due to the high reactivity of its propagating radical.[51] Limited examples for the synthesis of PVAc-containing block copolymers have been reported, e.g. based on cobalt-mediated radical polymerization (CMRP),[52,53] reversible addition fragmentation chain transfer (RAFT) polymerization,[54] and strategies that combine ATRP and RAFT techniques.[55,56] Although the preparation of PVAc containing block copolymers has been accomplished, these approaches show a number of disadvantages. For instance, cobalt is a comparatively expensive catalyst, while utilizing a single polymerization technique such as RAFT restricts the choice of monomers to ones with similar radical reactivity. The range of monomers that could be copolymerized was extended by the combination of two polymerization techniques, yet the presence of residual homopolymer in the final product is hard to avoid because of either partial end group transformation of the macroinitiator or incomplete initiation of the second polymerization process. In fact, the most versatile way to synthesize a block copolymer is to conjugate two polymer segments via a powerful coupling method. The Cu(I)-catalyzed azide-alkyne *click* cycloaddition reaction (CuAAC) was found to be highly efficient for the modular synthesis of various block copolymers,[57,58] including PVAc-containing block copolymers.[59]

For these reasons, we aimed for the preparation of functional polymers as well as PS-*b*-PVAc block copolymers by UV initiated, metal-free thiol-ene chemistry. Our strategy consisted of the independent synthesis of well-defined PS and PVAc homopolymers via RAFT, bearing thiol and allyl functional groups respectively, and further post-polymerization conjugation reactions via thiol-ene radical addition reaction (see Scheme 3). It is noteworthy to state that – although we used photo-initiation in contrast to the thermally induced experiments carried out by the KIT group – the reaction proceeds via the same radical mechanism (Scheme 1). Moreover, Campos *et al.* reported that thiol-ene photo-coupling was found to proceed with higher efficiency, in a shorter time, and with higher tolerance to various functional groups in comparison with its thermal counterpart.[18] In the next section, functionalization of polymers via photo-initiated radical thiol-ene will be discussed first, as a model reaction and a preceding step to the modular synthesis of block copolymers.

2.1 Synthesis of thiol and ene containing polymers

A series of telechelic PS with various molecular weights containing a trithiocarbonyl end group were synthesized via RAFT polymerization (Scheme 4, **1**). After the precipitation of the polymer in cold methanol, the trithiocarbonate end group was reduced to a thiol via aminolysis at ambient temperature in the presence of propylamine as a nucleophile.[29] UV-Vis spectroscopy, employed to monitor the reaction progress, indicated that the maximum absorption at 320-350 nm (which corresponded to the trithiocarbonate moiety) disappeared after aminolysis (Scheme S5 Supporting Information), revealing a successful end group modification to the thiol group (Scheme 3, **3**). Dibenzyl trithiocarbonate (DBTTC) was selected as the transfer agent as it contains no functional groups, enabling the convenient detection of the incorporated functional groups during the subsequent functionalization reactions. Secondly, allyl terminated poly(vinylacetate) (PVAc-=) was prepared via MADIX/RAFT polymerization (Scheme 3, **2**) (see Supporting Information for reaction details).



Scheme 3: General strategy toward functional and block copolymers via radical thiol-ene chemistry

2.2 Synthesis of functionalized polymers

Initially, the above-mentioned PS-SH was functionalized with dodecyl vinyl ether to verify the coupling efficiency of the radical thiol-ene mechanism in polymer – low molecular weight compound conjugation reactions (Scheme 4, **6**). The vinyl ether double bond was chosen because of its high reactivity toward thiols.[29] Similarly to the conditions applied by Campos *et al.,*[18] PS-SH was functionalized using 5 times excess of dodecyl vinyl ether, in the presence of DMPA (Table 1, Entry 1-2). A minimal amount of THF to dissolve all components was used. After deoxygenation, the reaction was carried out at room temperature, by irradiating the reacting mixture with a 365 nm UV lamp for 1 hour. The functionalized polymer was subsequently purified three times by precipitation in cold methanol and analyzed by 500 MHz proton NMR spectroscopy (Figure 5). Appearance of a triplet signal at 0.88 ppm, attributed to the terminal –$\mathbf{CH_3}$ protons and a signal at 3.25 ppm attributed to the –OC$\mathbf{H_2}$- (methylene protons of the formed ether group), that were absent in the starting PS-SH polymer, indicate a successful functionalization. However, integrations reveal conjugation efficiencies of about 90 %. A loss of efficiency can arise from the RAFT process which gives rise to a fraction of dead polymer chains that only contain initiator fragments as endgroups, especially at high conversions. Additionally, it is known from the literature that S-S coupling cannot be completely suppressed during the aminolysis of the dithioesters,[9] thus 100% functionalization will never be achieved.

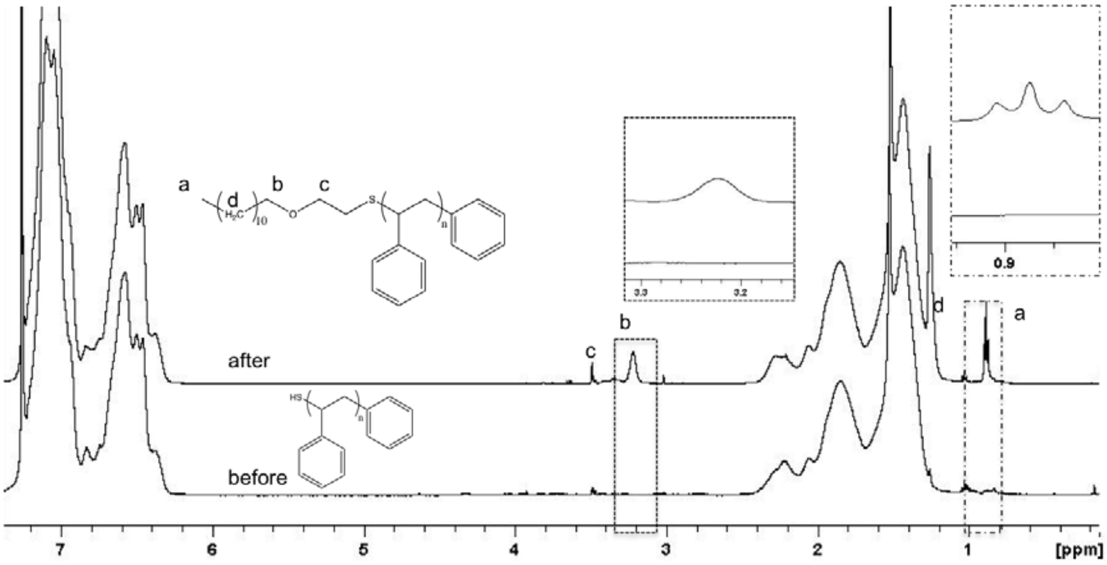


Figure 5: PS-SH spectrum before (bottom) and after functionalization (upper) with dodecyl vinyl ether; 5/1 thiol-to-ene ratio, 1 hour irradiation time (Table 1, entry 1)

In the same fashion, the functionalization of PS-SH with a range of other low molecular weight compounds (e.g. allyl ethyl ether, undecenoic acid, 1,4-butanediol vinyl ether) was carried out (Table 1, entries 3, 4 and 5), to introduce various functional groups (e.g. hydroxyl, carboxyl) at the polymer chain end. In the case of allyl ethyl ether and butanediol vinyl ether, similar conversions were obtained as in the previous experiments. On the other hand, when undecenoic acid was employed, conversion of only 30 % could be achieved, which is ascribed to the lower reactivity (by close to a factor of ca. 35) of the isolated double bond in comparison with the vinyl ether double bond.[29]

Table 1: Summary of the reaction conditions and results of functionalization of PS via thiol-ene reaction

Entry[a]	PS-SH (g/ mol)	Ene[b]	Initial ene eq.	Environment	Time (h)	Conv.[c] (%)
1	4.000	DVE	5	N_2	1	90
2	3.000	DVE	5	N_2	1	90
3	4.000	AEE	5	N_2	1	89
4	4.000	UDA	5	N_2	1	30
5	4.000	BDVE	5	N_2	1	80
6	4.000	DVE	5	air	1	77
7[d]	4.000	DVE	5	N_2	1	0
8	4.000	DVE	5	N_2	0.5	90
9[e]	4.000	DVE	5	N_2	4	88
10	4.000	DVE	1	N_2	1	89
11	4.000	DVE	2	N_2	1	89

[a]All reactions were performed in THF as a solvent, with 0.2 eq. of DMPA as photoinitiator (with respect to the thiol), irradiated under 365 nm UV light, unless mentioned different. [b] Abbreviations: DVE= Dodecyl vinyl ether, AEE= Allyl ethyl ether, UDA= Undecenoic acid, BDVE= 1,4-butanediol vinyl ether. [c]Calculated from ^{1}H NMR. [d] No photoinitiator added.[e] Reaction performed under sunlight.

2.3 Influence of irradiation source and oxygen

Thiol-ene photoreactions have been reported to be both relatively unaffected by oxygen[60] and rapidly accomplished even in the absence of a photo-initiator (by direct activation of the thiol).[61,62] Indeed, when functionalization was conducted without degassing the reaction solution, the reaction efficiency was still high with 77 % (Table 1, entry 6). However, when no photo-initiator was added, functionalization did not occur. (see Table 1, entry 7 in comparison with entry 1), demonstrating the inability of thiol functionalized polymers to self-generate free radicals, in contrast to the low molecular weight compounds.[61,62] Finally, lowering the irradiation time from 60 to 30 minutes resulted in similar functionalization yields, demonstrating that the reaction itself is relatively fast (Table 1, entries 8 and 1). Furthermore, as thiol-ene reactions may be typically initiated by UV-light close to the wavelength region of visible light (365 nm), it was expected that even sunlight could generate radicals in the reaction mixture, thus enabling polymer functionalization simply under irradiation by sunlight (Table 1, entry 9). Indeed, when a flask containing a deoxygenated reacting mixture was placed in bright sunlight for 4 hours, the reaction was shown to be as successful as under UV irradiation from a lamp (88 % degree of functionalization).

However, to truly judge the efficiency of thiol-ene chemistry in polymer functionalization, reactions using low molecular weight model compounds, one should use equimolar concentrations of the starting materials or – at a maximum – a two-fold excess in the initial ratio of PS-SH to dodecyl vinyl ether to avoid extensive purification steps (Table 1, entries 10 and 11). Following the typical procedure for UV initiated thiol-ene reactions and employing both a 1:1 and 1:2 thiol-to-ene initial ratio, PS-SH was successfully functionalized, with 89 % yield in the case of both 1:1 and 1:2 initial thiol-to-ene ratio demonstrating the relatively high efficiency for low molecular weight ene functionalization. This result is not directly in agreement with the observations made in the KIT group, where no significant increase in efficiency was observed when the ene content was increased, and only an excess of thiol allowed for improved conjugation. However, as will be shown below, a relatively large difference in reactivity (and thus conjugation efficiency) is observed for low molecular weight compounds in comparison to polymeric starting materials. As in the star assembly approach, only macromonomers were used (rather than small enes), and the above described high efficiencies are in contradiction with the results obtained from the thermally induced thiol-ene reactions.

2.4 Block copolymer synthesis

Thiol-ene chemistry has already been shown to be efficient in low molecular weight conjugation systems.[18] However, block copolymer synthesis via thiol-ene coupling reactions has not yet been reported. Table 2 summarizes the attempts to prepare PS-*b*-PVAc polymers by coupling PS-SH with PVAc containing an allyl end-group (PVAc-=) (see also Scheme 3, **5**).

Table 2: Summary of the reaction conditions and results of the thiol-ene coupling reaction between PS-SH and PVAc-=

Entry[a]	PS-SH/PVAc-=[b]	Time (h)	PS-SH	PVAc-=	conjugated product
			M_n/M_p/PDI[c]	M_n/M_p/PDI[c]	M_n/M_p/PDI[c]
1	1/1	1	4.000/4.500/1.18	1.800/2.200/1.50	5.600/6.300/1.17
2	1/1	1	3.000/3.400/1.20	1.800/2.200/1.50	4.500/5.200/1.20
3	5/1	1	3.000/3.400/1.20	1.800/2.200/1.50	4.100/4.800/1.26
4	5/1	5	3.000/3.400/1.20	1.800/2.200/1.50	3.900/4.400/1.23
5	1/1	1	5.800/6.700/1.27	1.800/2.200/1.50	7.000/8.200/1.19
6[d]	1/1	1	4.000/4.500/1.18	1.800/2.200/1.50	5.800/6.400/1.14
7	1/2	1	3.000/3.400/1.20	1.800/2.200/1.50	5.300/5.800/1.14
8	1/2	1	5.800/6.700/1.27	1.800/2.200/1.50	7.000/7.800/1.20
9[e]	1/1	1	3.000/3.400/1.20	1.800/2.200/1.50	3.700/3.800/1.26
10	-	1	3.000/3.400/1.20	-	4.400/5.400/1.23
11	-	1	-	1.800/2.200/1.50	2.700/3.000/1.37

[a] All reactions were performed in THF as solvent, with 0.2 eq. of DMPA as photoinitiator; under N_2 irradiated by 365 nm UV light.[b] Poly(styrene)/Poly(vinylacetate)= initial ratio. [c]Relative to polystyrene standards. [d] High dilution. [e]254 nm UV light.

Typically, PS-SH, PVAc-= and photo-initiator were dissolved in THF, and the reaction mixture was purged with nitrogen to remove oxygen and placed under the 365 nm UV light for 1h (Table 2, entries 1–2). After completion of the reaction, the excess of PVAc-= was removed by selective precipitation in cold methanol (given the relative composition of the targeted PS-b-PVAc, the conjugated polymer precipitates in methanol). The purified block copolymers were characterized by SEC, FTIR, ^{1}H-NMR and elemental analysis.

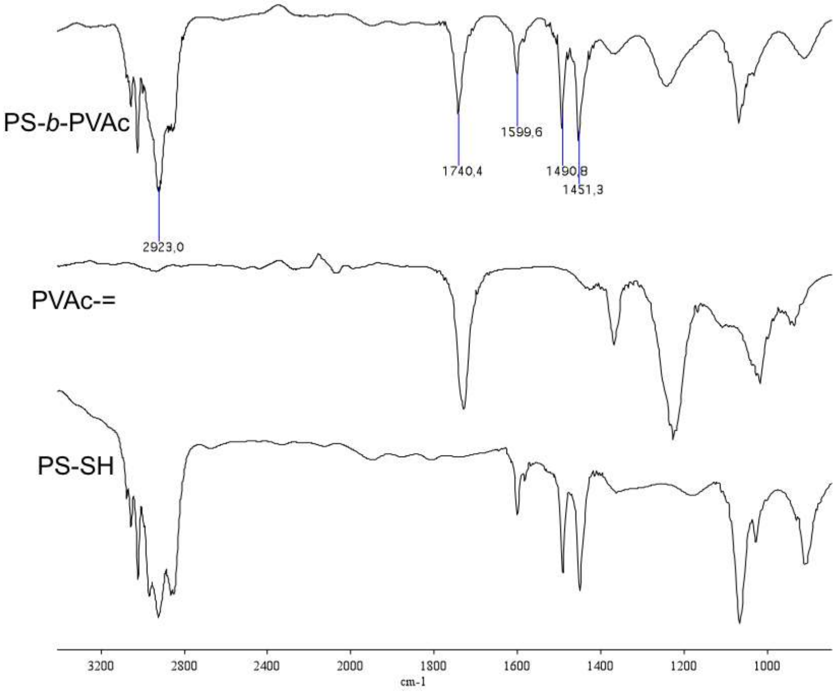


Figure 6: IR spectrum of PS-SH (bottom), PVAc-= (middle) and conjugated PS-*b*-PVAc (upper) (Table 2, entry 1)

The SEC traces of the purified block copolymer (PS-*b*-PVAc) showed a monomodal molecular weight distribution without any noticeable shoulder (see Figure 8c). The retention time of the final reaction product is clearly lower (thus evidencing higher molecular weight) than both starting polymers, indicating at first glance a successful polymer-polymer conjugation. In Table 2, the entries 1 and 2 show excellent agreement of peak molecular weight M_p and number average molecular weights M_n between the homopolymers and the corresponding block copolymers. Additionally, the starting polymers and the resulting conjugated blocks were analyzed by Fourier-transform infrared (FT-IR) spectroscopy. Figure 6 shows an overlay of the spectra of PS-SH, PVAc-= and PS-*b*-PVAc. The strong carbonyl band at around 1740 cm^{-1} is attributed to the PVAc segment, the benzene ring band vibrations to 1600, 1491 and 1451 cm^{-1}. The benzene ring double bond band at around 2923 cm^{-1} is attributed to the PS segment, suggesting the qualitative formation of PS-*b*-PVAc diblock copolymers.

Although SEC and FT-IR analysis provided qualitative evidence for a successful conjugation, further analysis of the block copolymer structures and formation efficiencies were performed. Therefore the block copolymers (Table 2, entry 1) were first analyzed via ^{1}H-NMR (500 MHz, $CDCl_3$), using an increased delay time to ensure quantitative analysis (Figure 7). Proton resonance signals of the PS segment appeared at 7.20-6.30 ppm (benzene ring), 1.84 ppm (-C**H**-) and 1.44 ppm (-C$\mathbf{H_2}$-); those of the PVAc block at 4.88 ppm (-C**H**-), 2.03 ppm (-C$\mathbf{H_3}$CO) and 1.84 ppm (-C$\mathbf{H_2}$-). Characteristic resonances of the PVAc backbone (-C**H**-) protons are well-separated from PS resonances. Hence, the ratio of integrals between PVAc backbone (4.88 ppm) and benzene ring (7.20-6.30 ppm) protons was calculated, surprisingly revealing a conjugation efficiency of only 25 %. As the choice of solvent may be critical for the solution properties of block copolymers and thus the NMR analysis,[63] d-dimethyl sulfoxide (DMSO), d-acetone and d-tetrahydrofuran (THF) were additionally tested as NMR solvents. However, regardless of the solvent employed, the calculated coupling yield did not differ from the result from where d-chloroform was used as the solvent.

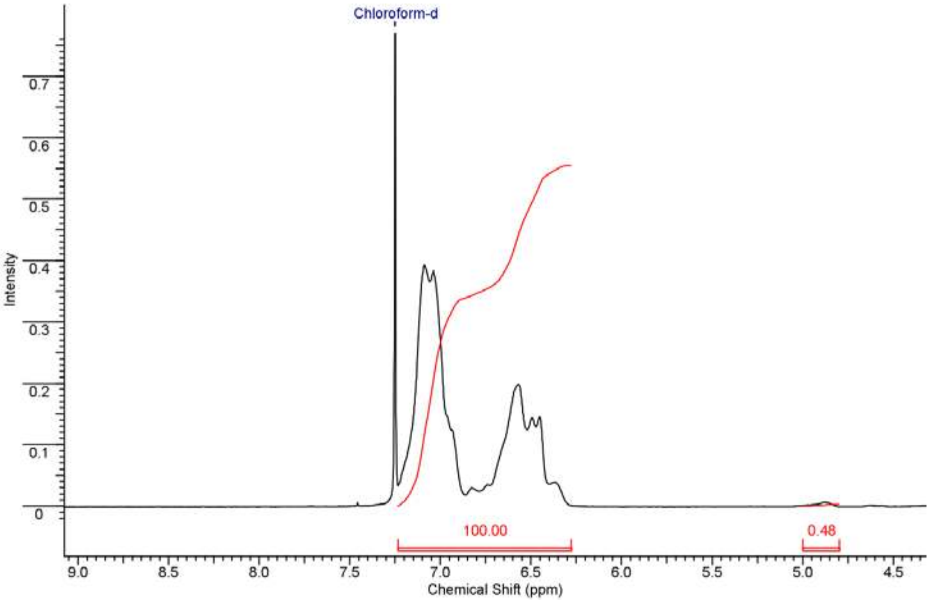


Figure 7: ^{1}H NMR spectrum of the product of thiol-ene coupling reaction (500 MHz, $CDCl_3$), Table 2, entry 1

To verify the results obtained by ^{1}H NMR analysis that are in conflict with the results from SEC and IR, elemental analysis was performed to determine exact carbon, hydrogen, oxygen and sulfur content of the purified product. The results obtained for the oxygen content are consistent with the ^{1}H-NMR results (3.3 % oxygen content measured compared to the theoretically expected 14 %, thus 23% of conjugation efficiency). These results then only allow for the conclusion that (radical) thiol-ene reactions are not efficient for polymer conjugation reactions, if a one to one thiol-to-ene initial ratio is used.

Although less interesting in view of an unavoidable post-conjugation purification step when an excess of one of the polymeric building block is used, additional experiments were performed with an excess of 5 equivalents of PS-SH in order to increase the efficiency of the conjugation reaction (Table 2, entry 3), yet the coupling efficiency remained the same. Moreover, with 5 eq. of PS-SH, longer irradiation time (5 hours instead of 1h; Table 2, entry 4), also did not improve the conjugation yield. Neither more diluted conditions (Table 2, entry 6), excess (2 eq.) of PVAc-= (Table 2, entries 7 and 8) nor the use of UV light with 254 nm wavelength instead of 365 nm (Table 2, entry 9) improved the conjugation yield significantly.

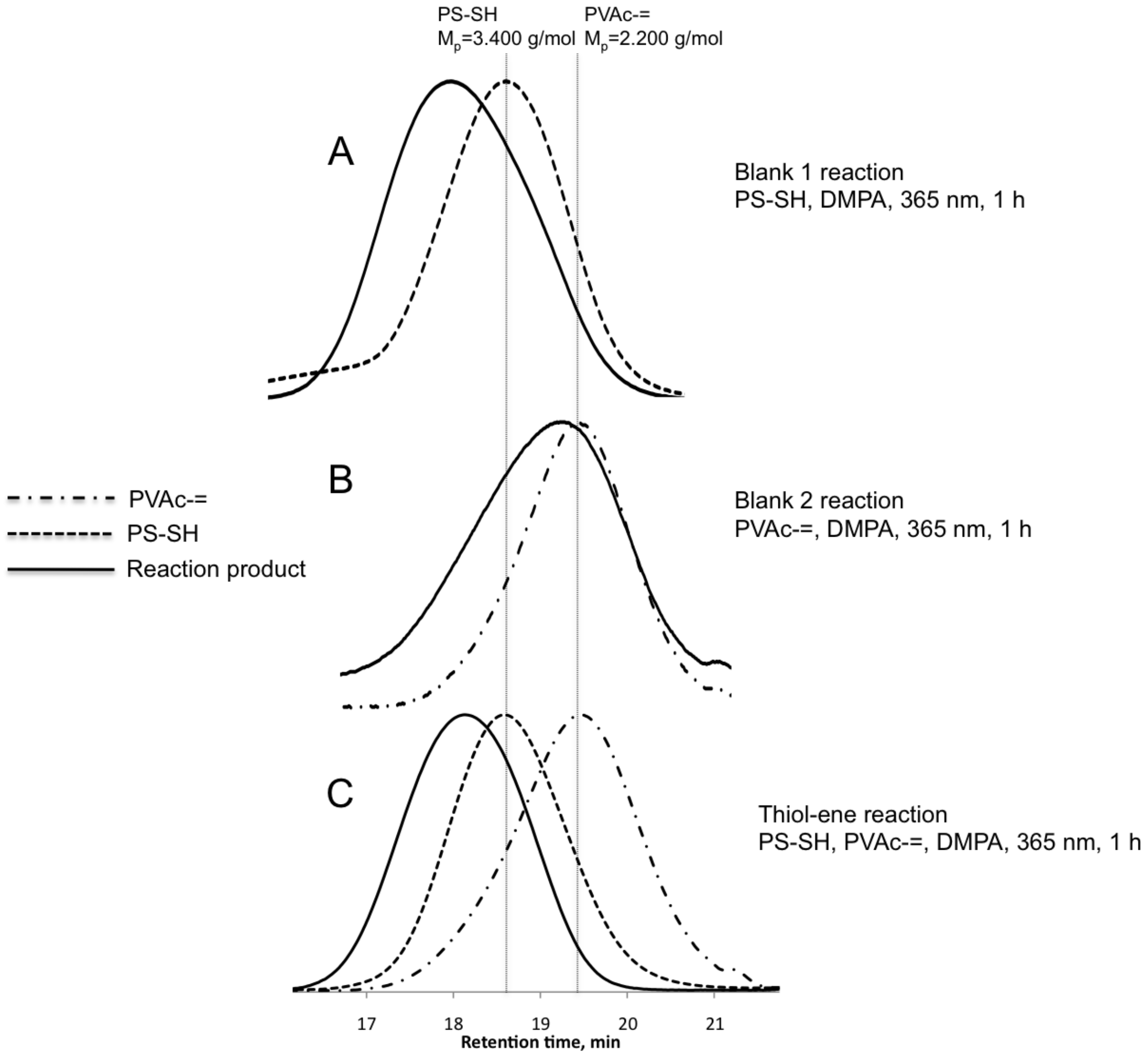


Figure 8: SEC traces of reagent(s) and reaction product: (A) PS-SH blank reaction (Table 2, entry 10); (B) PVAc-= blank reaction (Table 2, entry 11); (C) PS-SH/PVAc-= thiol-ene conjugation reaction under identical conditions (Table 2, entry 2).

To reveal the cause of the clear shift that was observed in SEC analysis, blank reactions were carried out. One blank reaction consisted of the application of the typical thiol-ene coupling conditions (irradiation time of 1h, DMPA photo-initiator present) to a reaction mixture only containing PS-SH (no PVAc-= was present). After 1 hour of irradiation time, a slight shift toward higher molecular weights was noticed in the chromatogram, which may be attributed to the formation of S-S species (see Figure 8a). In a similar blank reaction, PVAc= was irradiated (no PS-SH present). Similarly, a shift was observed toward higher molecular weight, strongly indicating bimolecular radical termination reactions (see Figure 8b). Thus, while the initial SEC analysis of the reaction product from the attempt to conjugate the PS-SH and PVAc-= blocks seemingly indicated a success of the reaction, closer analysis clearly reveals that the reaction was not at all successful and that the product mixture contains mostly random termination products. We conclude that coupling reactions via bimolecular termination reactions occur as competitive side reactions in thiol-ene polymer conjugation reactions of PS-SH and PVAc-=, underpinning that thiol-ene chemistry has severe limitations when targeting polymer-polymer conjugation reactions.

Joint Conclusions

The results from both groups are generally in good agreement with each other despite their relatively large difference in synthetic scope, starting materials and method of initiation employed. Even though the initial experiments undertaken in Ghent on first glance seem to indicate success of the reaction and are thus allegedly in disagreement with the results from Karlsruhe, both research strands come to the same conclusion when the conjugation product mixtures are characterized in in-depth. From all experiments carried out, it has become abundantly clear that both thermally and photo-chemically induced radical thiol-ene reactions are beset with considerable difficulties in reaching quantitative conversions when polymer-polymer conjugations are targeted. Neither variation of the initiator concentration (and type of initiator/initiation method), nor variation of the macromonomer to thiol concentration ratio or type of macromonomer, lead to optimized conditions of the reaction allowing for quantitative formation of the desired conjugation products. It seems that only a large excess of thiol allows for the formation of the targeted structures without significant amounts of side products.

In summary, it can be stated that:

(i) conjugation of a polymer with a small molecule counterpart works reasonably well, even if an excess of the low molecular weight compound must be used to achieve high conjugation efficiencies.

(ii) polymer-polymer conjugation largely fails if the starting materials are employed in (or close to) equimolar ratios.

(iii) the radical flux has only a limited effect on the outcome of the coupling reaction as a change in initiator concentration on one hand and a switch from dedicated UV-lamp irradiation towards sunlight as UV-source on the other hand did not have a decisive influence on the product.

(iv) the reason for failure in both research strands are qualitatively similar, i.e. head-to head coupling reactions that stop the propagation cycle of the thiol-ene process.

Generally, the similarity between thermal and photochemical initiation is not surprising. From a kinetic point of view, the applied radical source is more or less irrelevant as the competing reactions are chain stopping events vs. the propagation and the ene-addition reactions, thus comprising reactions that do not directly involve initiator fragments. Only one small difference exists, which might explain why frequently better conjugation efficiencies are observed from photochemical thiol-ene reactions. Ideally, the primary radicals would only abstract protons from the thiol. However, a fraction of the initiator fragments will add to the ene as a competitive side reaction, which in turn can start a thiol-ene reaction cycle, but finally leads to the formation of an undesired (non-conjugated) product. Thus, in principle, radical initiators should be employed that are comparatively slow in adding to the ene. For the photo-initiator DMPA it is known that its benzoyl fragment is a fast initiator whereas the second fragment might only be available for termination or proton abstraction, potentially aiding the overall process.[64] However, as only very limited data on initiation efficiencies are available to date, such a hypothesis remains speculative and an extensive experimental series would be required to confirm it. Regardless, as the initiation rate depends on the type of initiator and the ene (and of course the thiol with respect to the rate of proton abstraction), this implies that one needs to evaluate suitable initiators for each particular system, an approach that is not very promising if thiol-ene is proposed as a universal conjugation tool. Independent of the choice of initiator, an increase in the thiol to initiator concentration will have a beneficial effect, because transfer of the initiator fragment radicals onto a thiol will become more likely. In addition, termination of initiator fragments, as observed by ESI-MS, will occur to a lesser extent. The fact that functionalization of the chain ends via radical thiol-ene is largely successful, when the thiol is employed in excess, can be explained via this effect. For polymer-polymer conjugation, where the thiol concentration cannot be increased, a similar effect can only be reached by reducing the initiator concentration. This, however, also leads to a significantly reduced rate of reaction and unfeasibly long reaction times are required to reach full conversions while at the same time side reactions are not completely eliminated.

Any radical reaction proceeds to a certain extent with the formation of side reaction due to the high reactivity of the radicals and the sequential nature of the reaction. The termination reactions as observed in both the KIT and UGent research parts, appear to be unavoidable. Moreover, both cases show that it is not possible to suppress these side reactions to a sufficient degree if the thiol and ene compound are employed in equimolar ratios and in particular if polymeric starting materials are used. The somewhat better efficiencies that are observed for the coupling reactions with small molecules might indicate that the thiol-ene propagation reaction is subject to a diffusional control mechanism.

Ultimately, radical thiol-ene may only be used as a polymer conjugation tool if either the thiol or the ene is used in excess or if substantial side product formation is acceptable. Both approaches require tedious additional work-up procedures, which is a direct violation of the *click* concept.[1] Only for small molecules such purification may be easily performed (for example by precipitation or evaporation). Thus, radical thiol-ene is only effective if one can sacrifice efficiency and is satisfied with only partial conjugation, for example when grafting to surfaces or microspheres.[65]

Based on our findings as well as the definition of *click* chemistry, its implications and requirements for polymer-polymer conjugation, we therefore advise that *radical* thiol-ene conjugation chemistry should not be referred to as a *click* reaction. The criterion of a high reaction efficiency is clearly not fulfilled as a significant number of polymer byproducts must be expected when trying to conjugate two polymer blocks. Even if reaction conditions should exist under which successful polymer conjugation may be performed – even though we believe this is highly unlikely – the reaction clearly cannot serve as a general chemical tool. The *click* philosophy implies that the window of reaction conditions under which a reaction can be applied must be relative wide and this is certainly not the case for radical thiol-ene chemistry polymer conjugation.

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References

1 Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew. Chem., Int. Ed. Engl. 2001, 40, 2004-2021.

2 Unal, S.; Lin, Q.; Mourey, T. H.; Long, T. E. Macromolecules 2005, 38, 3246-3254.

3 Kadokawa, J.-i.; Kaneko, Y.; Yamada, S.; Ikuma, K.; Tagaya, H.; Chiba, K. Macromol. Rapid Commun. 2000, 21, 362-368.

4 Singh, R.; Verploegen, E.; Hammond, P. T.; Schrock, R. R. Macromolecules 2006, 39, 8241-8249.

5 Jo, Y. S.; van der Vlies, A. J.; Gantz, J.; Antonijevic, S.; Demurtas, D.; Velluto, D.; Hubbell, J. A. Macromolecules 2008, 41, 1140-1150.

6 Abraham, S.; Choi, J. H.; Ha, C.-S.; Kim, I. J. Polym. Sci., Part A: Polym. Chem. 2007, 45, 5559-5572.

7 Dag, A.; Durmaz, H.; Tunca, U.; Hizal, G. J. Polym. Sci., Part A: Polym. Chem. 2009, 47, 178-187.

8 Kaur, I.; Misra, B. N.; Gupta, A.; Chauhan, G. S. J. Appl. Polym. Sci. 1998, 69, 599-610.

9 Lima, V.; Jiang, X.; Brokken-Zijp, J.; Schoenmakers, P. J.; Klumperman, B.; Linde, R. V. D. J. Polym. Sci., Part A: Polym. Chem. 2005, 43, 959-973.

10 Lutz, J.-F. Angew. Chem., Int. Ed. Engl. 2007, 46, 1018-1025.

11 Angell, Y. L.; Burgess, K. Chem. Soc. Rev. 2007, 36, 1674-1689.

12 Moses, J. E.; Moorhouse, A. D. Chem. Soc. Rev. 2007, 36, 1249-1262.

13 Lutz, J. F.; Schlaad, H. Polymer 2008, 49, 817-824.

14 Johnson, J. A.; Finn, M. G.; Koberstein, J. T.; Turro, N. J. Macromol. Rapid Commun. 2008, 29, 1052-1072.

15 Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Angew. Chem., Int. Ed. Engl. 2009, 48, 4900-4908.

16 Sinnwell, S.; Inglis, A. J.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. Chem. Commun. 2008, 2052 - 2054.

17 Carioscia, J. A.; Lu, H.; Stanbury, J. W.; Bowman, C. N. Dent. Mater. 2005, 21, 1137-1143.

18 Campos, L. M.; Killops, K. L.; Sakai, R.; Paulusse, J. M. J.; Damiron, D.; Drockenmuller, E.; Messmore, B. W.; Hawker, C. J. Macromolecules 2008, 41, 7063-7070.

19 Campos, L. M.; Meinel, I.; Guino, R. G.; Schierhorn, M.; Gupta, N.; Stucky, G. D.; Hawker, C. J. Adv. Mater. 2008, 20, 3728-+.

20 Chen, G.; Amajjahe, S.; Stenzel, M. H. Chem. Commun. 2009, 1198-1200.

21 Cook, W. D.; Chen, F.; Pattison, D. W.; Hopson, P.; Beaujon, M. Polymer International 2007, 56, 1572-1579.

22 Killops, K. L.; Campos, L. M.; Hawker, C. J. J. Am. Chem. Soc. 2008, 130, 5062-5064.

23 Posner, T. Berichte der deutschen chemischen Gesellschaft 1905, 38, 646-657.

24 Mayo, F. R.; Walling, C. Chemical Reviews 1940, 27, 351-412.

25 Griesbaum, K. Angew. Chem., Int. Ed. Engl. 1970, 9, 273-287.

26 Braun, J. v.; Murjahn, R. Berichte der deutschen chemischen Gesellschaft (A and B Series) 1926, 59, 1202-1209.

27 Carioscia, J. A.; Stansbury, J. W.; Bowman, C. N. Polymer 2007, 48, 1526-1532.

28 Dondoni, A. Angew. Chem., Int. Ed. Engl. 2008, 47, 8995-8997.

29 Hoyle, C. E.; Lee, T. Y.; Roper, T. J. Polym. Sci., Part A: Polym. Chem. 2004, 42, 5301-5338.

30 Gress, A.; Volkel, A.; Schlaad, H. Macromolecules 2007, 40, 7928-7933.

31 Bickel, C. L. J. Am. Chem. Soc. 1950, 72, 1022-1023.

32 Wu, D.-C.; Liu, Y.; He, C.-B. Macromolecules 2008, 41, 18-20.

33 Liu, Y.-L.; Tsai, S.-H.; Wu, C.-S.; Jeng, R.-J. J. Polym. Sci., Part A: Polym. Chem. 2004, 42, 5921-5928.

34 Maraval, V.; Laurent, R.; Donnadieu, B.; Mauzac, M.; Caminade, A.-M.; Majoral, J.-P. J. Am. Chem. Soc. 2000, 122, 2499-2511.

35 Moszner, N.; Rheinberger, V. Macromol. Rapid Commun. 1995, 16, 135-138.

36 Mantovani, G.; Lecolley, F.; Tao, L.; Haddleton, D. M.; Clerx, J.; Cornelissen, J. J. L. M.; Velonia, K. J. Am. Chem. Soc. 2005, 127, 2966-2973.

37 Nurmi, L.; Lindqvist, J.; Randev, R.; Syrett, J.; Haddleton, D. M. Chem. Commun. 2009, 2727-2729.

38 Chan, J. W.; Yu, B.; Hoyle, C. E.; Lowe, A. B. Polymer 2009, 50, 3158-3168.

39 Sumerlin, B. S.; Vogt, A. P. Macromolecules 2009, asap article.

40 Li, M.; De, P.; Gondi, S. R.; Sumerlin, B. S. J. Polym. Sci., Part A: Polym. Chem. 2008, 46, 5093-5100.

41 Barner-Kowollik, C.; Inglis, A. J. Macromol. Chem. Phys. 2009, 210, 987-992.

42 Junkers, T.; Bennet, F.; Koo, S. P. S.; Barner-Kowollik, C. J. Polym. Sci., Part A: Polym. Chem. 2008, 46, 3433-3437.

43 Hadjichristidis, N.; Pitsikalis, M.; Iatrou, H.; Pispas, S. Macromol. Rapid Commun. 2003, 24, 979-1013.

44 Zorn, A.-M.; Junkers, T.; Barner-Kowollik, C. Macromol. Rapid Commun. 2009, in press.

45 Junkers, T.; Barner-Kowollik, C. Macromol. Theory Simul. 2009, 18, 421-433.

46 Barner-Kowollik, C. Macromol. Rapid Commun. 2009, 30, 1625-1631.

47 Koo, S. P. S.; Junkers, T.; Barner-Kowollik, C. Macromolecules 2009, 42, 62-69.

48 Günzler, F.; Wong, E. H. H.; Koo, S. P. S.; Junkers, T.; Barner-Kowollik, C. Macromolecules 2009, 42, 1488-1493.

49 Inglis, Andrew J.; Sinnwell, S.; Stenzel, Martina H.; Barner-Kowollik, C. Angew. Chem. 2009, 121, 2447-2450.

50 Castelletto, V.; Hamley, I. W. Polym. Adv. Technol. 2006, 17, 137.

51 Stenzel, M. H.; Cummins, L.; Roberts, G. E.; Davis, T. P.; Vana, P.; Barner-Kowollik, C. Macromol. Chem. Phys. 2003, 204, 1160-1168.

52 Debuigne, A.; Caille, J. R.; Willet, N.; Jerome, R. Macromolecules 2005, 38, 9488-9496.

53 Bryaskova, R.; Willet, N.; Debuigne, A.; Jerome, R.; Detrembleur, C. J. Polym. Sci., Part A: Polym. Chem. 2007, 45, 81-89.

54 Benaglia, M.; Chiefari, J.; Chong, Y. K.; Moad, G.; Rizzardo, E.; Thang, S. H. J. Am. Chem. Soc. 2009, 131, 6914-+.

55 Cui, L.; Tong, X.; Yan, X.; Liu, G.; Zhao, Y. Macromolecules 2004, 37, 7097.

56 Petruczok, C. D.; Barlow, R. F.; Shipp, D. A. J. Polym. Sci., Part A: Polym. Chem. 2008, 46, 7200-7206.

57 Opsteen, J. A.; van Hest, J. C. M. Chem. Commun. 2005, 57-59.

58 Van Camp, W.; Germonpre, V.; Mespouille, L.; Dubois, P.; Goethals, E. J.; Du Prez, F. E. React. Funct. Polym. 2007, 67, 1168-1180.

59 Quemener, D.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. Chem. Commun. 2006, 5051-5053.

60 Kharasch, M.; Nudenberg, W.; Mantell, G. J. Org. Chem. 1951, 16, 524-532.

61 Cramer, N. B.; Reddy, S. K.; Cole, M.; Hoyle, C.; Bowman, C. N. J. Polym. Sci., Part A: Polym. Chem. 2004, 42, 5817-5826.

62 Cramer, N. B.; Scott, J. P.; Bowman, C. N. Macromolecules 2002, 35, 5361-5365.

63 Bernaerts, K. V.; Fustin, C. A.; Bomal-D'Haese, C.; Gohy, J. F.; Martins, J. C.; Du Prez, F. E. Macromolecules 2008, 41, 2593-2606.

64 Szablan, Z.; Junkers, T.; Koo, S. P. S.; Lovestead, T.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. Macromolecules 2007, 40, 6820-6833.

65 Goldmann, A. S.; Walther, A.; Joso, R.; Ernst, D.; Loos, K.; Nebhani, L.; Barner-Kowollik, C.; Barner, L.; Müller, A. H. E. Macromolecules 2009, 42, 3707-3714.