One-pot, Additive-free Preparation of Functionalized Polyurethanes *via* Amine-thiol-ene Conjugation

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

Introduction

Facile synthetic and modification procedures of functionalized polymers have been the subject of extensive fundamental and applied research efforts during the last decade. The concept of 'click' chemistry[1-8] induced a transition towards 'on-demand' preparation of tailored polymeric

systems.[9] The toolbox of research labs is currently loaded with a variety of established 'click' reactions, offering ample possibilities for macromolecular design and synthesis. Moreover, the development and valorization of novel polymer materials with a broad range of applications (medicines,[10-13] electronics,[14-16] bioconjugation,[17-21] labeling,[22-26] etc.) significantly promoted interdisciplinary research. The elaboration of innovative procedures and the combination of existing reactions in multi-step one-pot sequences further exemplifies the scientific eagerness to study the possibilities and limitations of 'click' chemistry to the full extent.[27-28]

Polyurethanes (PUs) are an essential class of synthetic polymers that are world-wide applied on a large scale.[29] Large-scale production of these materials mainly relies on feeds of diisocyanates, diols and/or polyols in the presence of a catalyst. Despite the wide range of PUs available *via* step-growth polymerization, the lack of side-chain functionalities limits their scope. Therefore, methods leading to functionalized PUs equipped with reactive groups along their backbone remain of particular interest. These functional groups can be converted using 'click' chemistry, providing paths to unique materials with enhanced properties for high-end applications. The mainstream approach is to directly incorporate clickable side-groups in linear PUs during the polymerization process through the addition of a functionalized diol to the diisocyanate/diol mixture. In addition to the high intrinsic reactivity of diisocyanates, the reactive nature of the desired functional group mostly necessitates the use of protection/deprotection strategies, *e.g.* amine- and maleimide-containing diols are protected as the corresponding carbamate[30] and furan-adduct[31] prior to the polymerization. However, various functionalities have also been introduced directly as pendent groups in PUs by careful selection of the appropriate unprotected monomer diol: alkyne[32-36]-, alkene[37-39]-, hydroxyl[40]- and furan[41]-functionalized PUs are available

via this approach. Subsequent 'click' modification *via* copper catalyzed azide-alkyne cyclo-addition (CuAAC),[32-36] radical thiol-ene conjugation,[37-39] and thiol-maleimide conjugation[31] enabled the modular and efficient synthesis of tailored PUs. Similarly, the reactive moiety can be introduced through a functionalized diisocyanate, demonstrated by the synthesis of maleimide-functionalized copoly(urethane-urea)s.[42]

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

In 2011, we presented a promising accelerated protocol for the modular synthesis of polyurethane based materials, consisting of a one-pot *amine-thiol-ene* reaction of a stable AB'-monomer, containing an allyl and thiolactone unit connected by a urethane linkage. In this approach, a thiolactone entity serves as a thiol precursor (latent functionality). The thiolactone ring opens upon aminolysis (nucleophilic reaction) and the *in situ* generated thiol reacts with the allyl double bond in a radical photo-polymerization reaction.[43] However, conceptual issues directly related to the radical reaction in the one-pot process impede further extension of the scope of the methodology. Important to note is that some functional groups (*e.g.* furan,[44-48] double and triple bond), introduced *via* the amine, are incompatible with this radical environment. Additionally, the UV-curing happens upon decomposition of a photoinitiator (*e.g.*

DMPA), but model studies revealed that some amines (*e.g.* benzylamine) react with the formed radical fragments, thus limiting the use of a photoinitiator.

Therefore, 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, which is considered to be a breakthrough approach for the development of a direct, additive- and isocyanate-free synthesis strategy to obtain functionalized polyurethanes. 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.[49] The combination of the thiolactone-based strategy for the *in situ* generation of thiols and subsequent Michael addition undoubtedly broadens the scope of metal-free multi-step reactions for the design and synthesis of polymers.

Replacing the allyl double bond in the AB'-monomer with an acrylate function, allowing for the complete absence of radical species during the polymerization, would indeed be a step forward, although potential orthogonality issues render the conjugation procedure a fundamentally challenging two-step reaction sequence. Therefore, the chemoselective discrimination between both nucleophiles (amine *vs* the generated thiol) is the major focus when employing the nucleophilic amine-thiol-ene conjugation. Potential side reactions such as the aza-Michael addition[49] of the amine to the acrylate and disulfide formation are of primary concern.

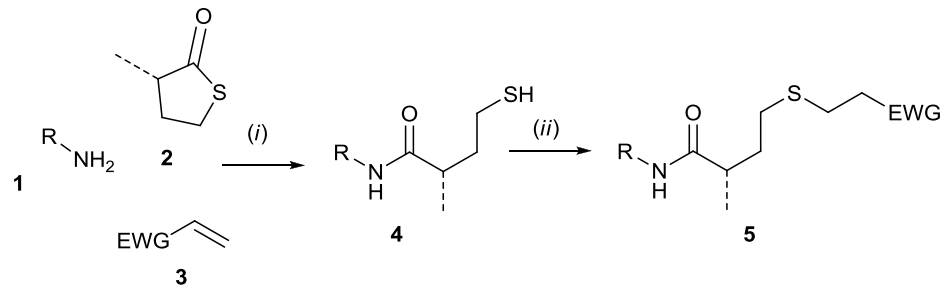
Prior to the design of a new AB'-monomer, model studies should reveal the feasibility of the anticipated one-pot two-step reaction. In a second stage, after the large-scale synthesis of a readily available AB'-urethane monomer, containing both an acrylate (A) and a thiolactone unit

(B'), several (multi)-functionalized PUs will be prepared by modular use of a variety of functional amines.

Results and discussion

Model and kinetic studies

The feasibility of the proposed amine-thiol-ene conjugation between an amine **1**, a thiolactone-containing compound **2** and a Michael acceptor **3** entirely relies on the selectivity of the conjugate addition (Scheme 1).

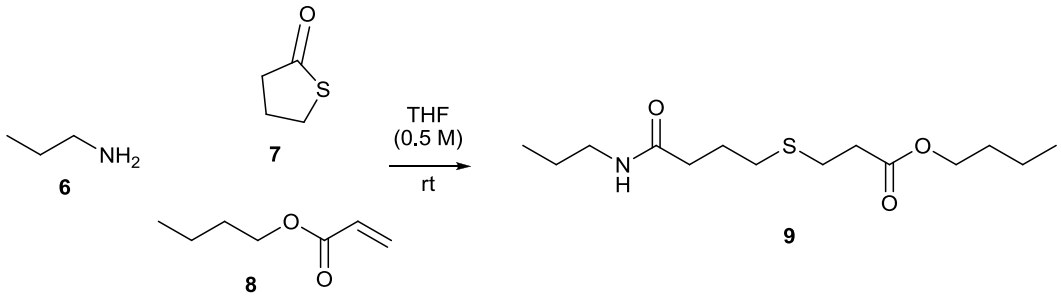


Scheme 1 – Nucleophilic amine-thiol-ene conjugation: aminolysis of the thiolactone ring (*i*), followed by thiol-Michael addition (*ii*). EWG = electron-withdrawing group.

Therefore, the selection of the reaction partners **1** and **3** is critically important. While maleimides react with both amines and thiols as Michael donor[49], acrylates are less reactive: at room temperature and without a catalyst, only secondary amines readily react with acrylates.[50] As a consequence, a reaction mixture of a primary amine, a thiolactone and an acrylate in the absence of any catalyst would result in the formation of the product **5**. The anticipated chemoselective discrimination between both heteroatomic nucleophiles (primary amine **1** and the intermediate thiol **4**) is based upon different reaction rates. The slow *aza*-Michael addition allows the

aminolysis of the thiolactone to precede while the subsequent thiol-Michael addition is known to be relatively fast.[51]

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. In a solution (in $CHCl_3$ or THF, 0.5 and 1 M respectively) of primary amine, thiol and acrylate, the consumption rate of the thiol and acrylate is identical (Scheme S 1 and Figure S 1). In a control experiment, only the amine and acrylate were mixed at room temperature. Whereas in the previous case the thiol was consumed in less than 15 minutes (1 M in THF), only a negligible conversion of the acrylate by aza-Michael addition was observed in the same time frame (Figure S 1). In a second model reaction, involving a thiolactone as latent thiol functionality, the kinetic profile of the reaction between *n*-propylamine **6**, γ-thiobutyrolactone **7** and *n*-butyl acrylate **8** was studied in detail (Scheme 2). It should be stressed that the reaction was performed at room temperature and under air atmosphere.



Scheme 2 – Model amine-thiol-ene conjugation between *n*-propylamine **6**, γ-thiobutyrolactone **7** and *n*-butyl acrylate **8**.

The 3D *online* FT-IR waterfall plot illustrates the decrease and increase of several $(C=O)_{stretch}$ absorption bands as a function of time (Figure 1a).

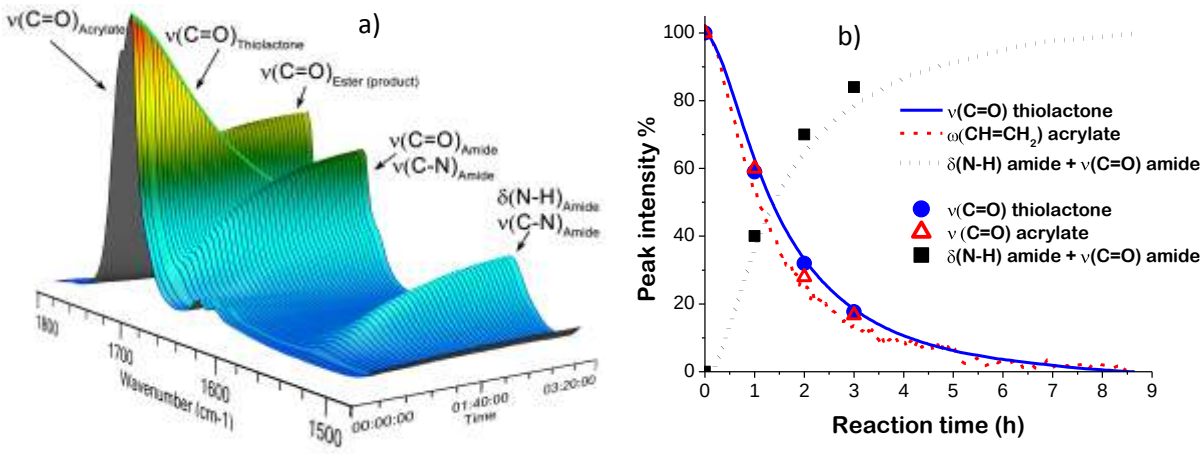
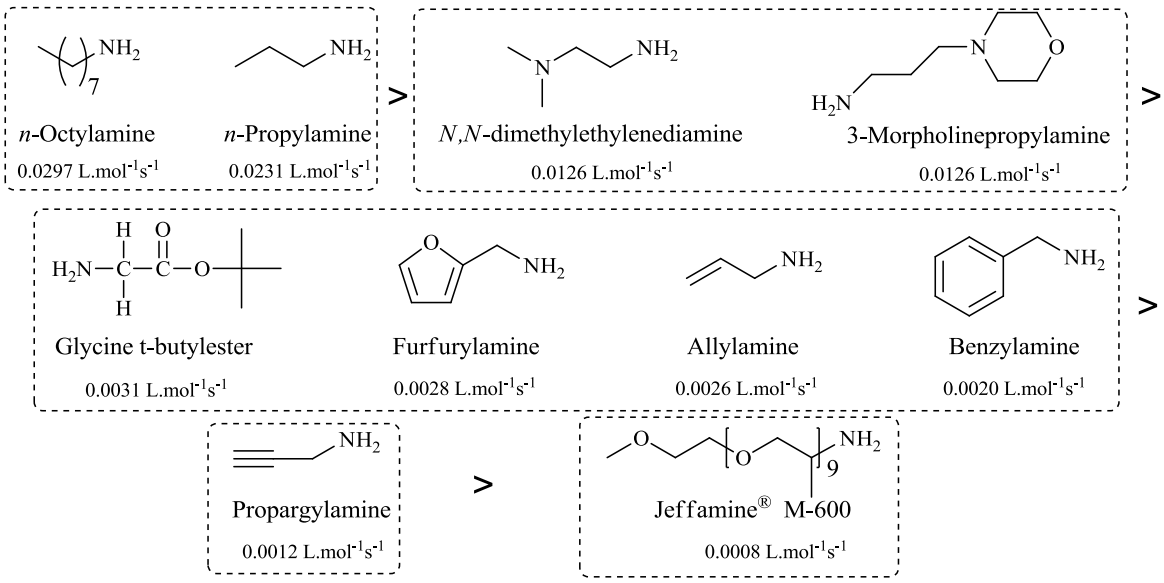


Figure 1 – *Online* monitoring of amine-thiol-ene conjugation between *n*-propylamine **6**, γ-thiobutyrolactone **7** and *n*-butyl acrylate **8**; (a) 3D FT-IR waterfall plot of $(C=O)_{stretch}$ absorption bands (1830 – 1490 cm^{-1}) and (b) FT-IR peak intensities as a function of time (kinetic curves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

Due to partial overlap of relevant bands in the IR spectrum (1830 to 1490 cm^{-1}, Figure S 2 and S 3, Table S 1), a deconvolution process was performed (Table S 2, Figure S 5 and S 6). In Figure 1b, the FT-IR peak intensities, reflecting the concentrations of the reactants **7** and **8** and the product **9** as a function of time, are shown. The decrease of the height of the thiolactone $(C=O)_{stretch}$ and the area of the acrylate $(CH=CH_2)_{wagging}$ vibrational bands have been used to establish the kinetic profile (Figure S 4). The formation of the amide (band area at 1540 cm^{-1}, $N-H_{scissoring}$ and $C-N_{stretch}$) is a good indicator for the consumption of **7**. For further confirmation, it is demonstrated that the area depletion of the deconvoluted thiolactone (C=O, 2 sub-bands at 1714 and 1698 cm^{-1}) and acrylate (C=O, at 1728 cm^{-1}) bands is strongly agreeing with the kinetic curves (Figure 1b). The major conclusion from this model study is that the aminolysis is the rate-determining step: the acrylate functions are consumed as fast as the thiolactone ones. With 1.1 eq. of *n*-propylamine compared to an equimolar mixture of thiolactone **7** and acrylate **8**, it takes 9 hours to reach 70% conversion (Figure S 7). The rate can be increased by adding more amine;

for example with a two-fold excess, the reaction is finished within 8 hours (Figure 1b). An LC-MS analysis of the reaction with 1.1 eq. of *n*-propylamine shows a clean mixture of starting materials and product **9**. Only a minor fraction of disulfide was detected (Figure S 8 c). Disulfide formation is more prominent at higher amine concentration (Figure S 8 d), indicating that the excess of amine should be limited. As the aminolysis step is rate-determining, a kinetic screening of the ring-opening of γ-thiobutyrolactone **7** in the presence of ten different (functional) primary amines was performed. Generally, the aminolysis of thiolactones can be described by second order kinetics.[52] Pseudo-first order conditions were established using a 50-fold excess of amine in THF. The conversion of **7** as a function of time has been monitored by GC analysis of periodically taken reaction samples (Figure S 9 and S 10). Rate constants are summarized in Scheme 3.

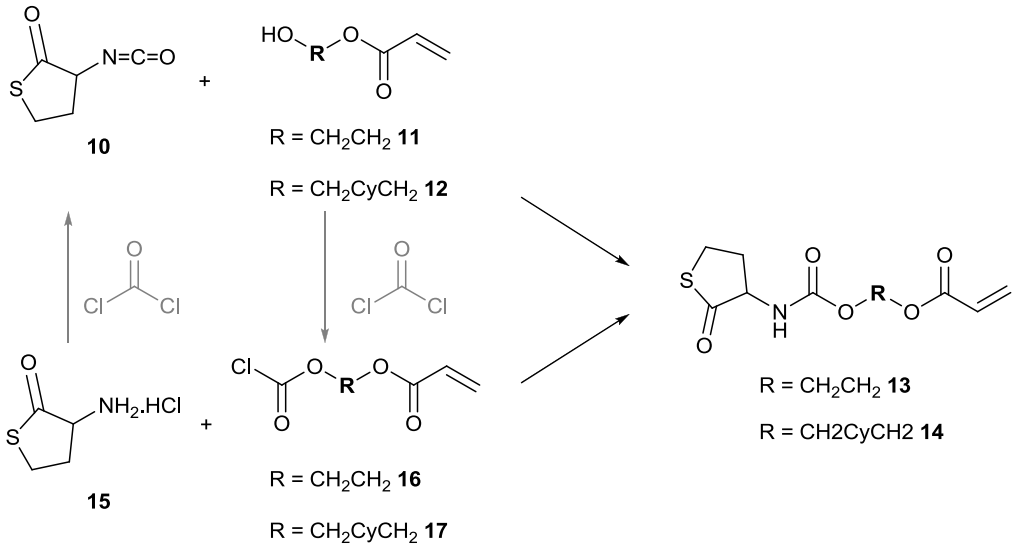


Scheme 3 – Rate constants of the aminolysis of γ-thiobutyrolactone **7** in the presence of different primary amines with indication of the relative reaction rates.

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

Monomer synthesis

The use of the above studied nucleophilic amine-thiol-ene conjugation in polymer synthesis demands a straightforward and scalable methodology for the synthesis of a stable monomer, containing an acrylate (A) and a thiolactone unit (B'). Upon aminolysis, this monomer forms a reactive thiol-acrylate, which will be consumed in the same medium by a conjugate addition. In order to synthesize such an AB'-monomer, two reaction routes have been explored (Scheme 4).



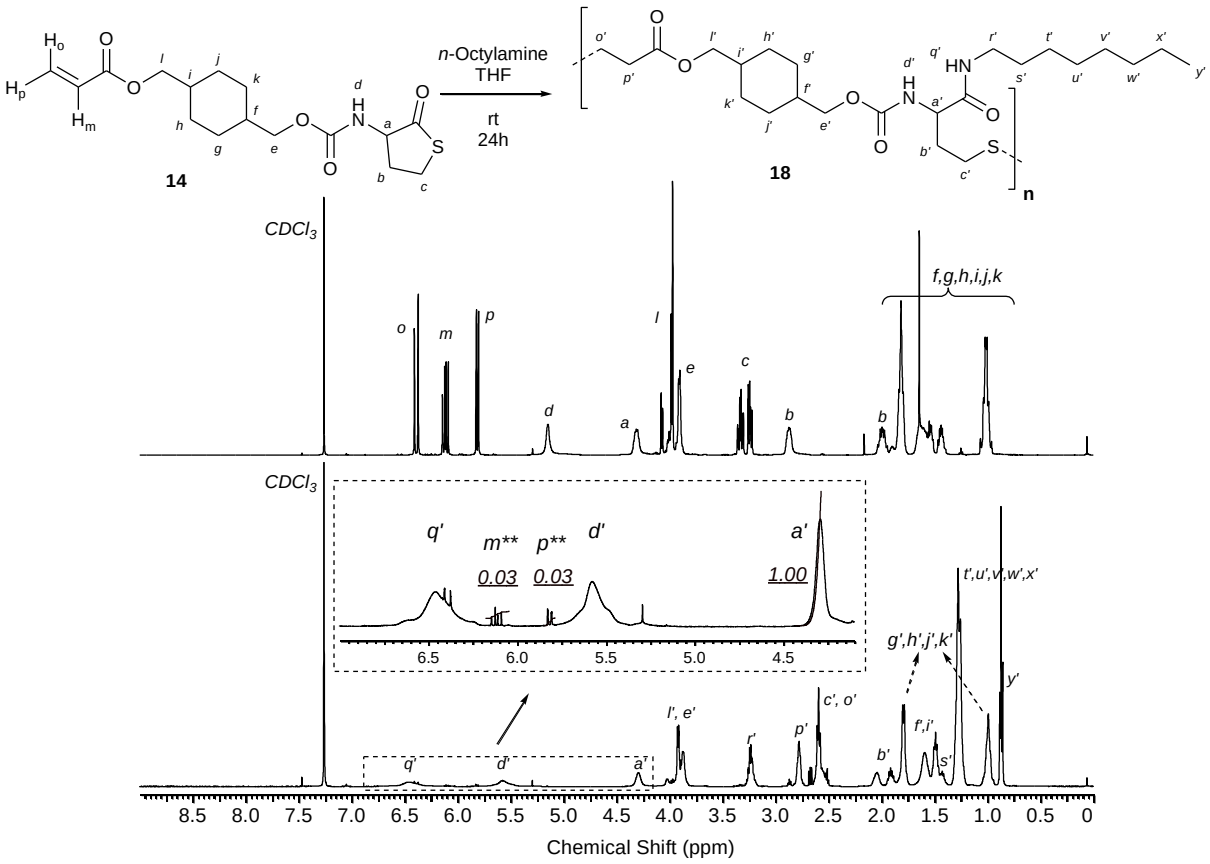
Scheme 4 – Two approaches for the synthesis of an AB'-monomer, containing on one hand a thiolactone and an acrylate group as reactive entities and on the other hand a stable urethane linkage.

In each case, a stable urethane bond connects the reactive entities. The first possibility relies on the Sn-catalyzed carbamate formation between α-cyanato-γ-thiolactone **10** [53] and an equimolar amount of a hydroxyl-functionalized acrylate. Two acrylates (2-hydroxyethylacrylate **11** and 1,4 -cyclohexanedimethanol monoacrylate **12**) have been converted to the respective monomers, **13** and **14**, with an isolated yield of 92%. The inherent instability of **13**, as a result of polyacrylate formation, requires radical inhibition, while **14** can be stored as a white powder for months at -20 °C without any inhibitor. A more scalable route consists of the phosgene treatment of the hydroxyl-functionalized acrylate **12** to render the chloroformate **17** and subsequent reaction of the latter with DL-homocysteine thiolactone **15** in the same reaction vessel. This procedure allows for the preparation of a relatively large amount (45 g) of the AB'-monomer **14** in a single batch with an overall isolated yield of 78% (Scheme S 3, Figure S 11 and S 12).

Polymerization by amine-thiol-ene conjugation

Although the thiol-Michael addition is generally regarded as a reversible reaction and therefore represents an elegant methodology for dynamic covalent chemistry,[54-56] thiol-acrylate conjugate addition has already been employed as the key step for the fabrication of functional polymer materials.[51,57-63] As a consequence, the polymerization *via* poly-addition of thiol-acrylates, originating from the aminolysis of AB'-monomers **13** and **14**, was studied in detail. 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.[64-65] Aminolysis of **13** at varying concentrations (0.25, 0.5 and 1 M) in THF resulted in a precipitate of low molecular weight (M_n ~ 2 kDa, determined by SEC). Precipitation could

be avoided in $CHCl_3$, but only oligomers were formed. Similar observations were made when changing the solvent to CH_2Cl_2 and *N*,*N*-dimethylacetamide. Repeating the same conditions, starting from monomer **14**, pointed out that poly-addition was most prominent in THF at 0.5 M: linear polymers with M_n of 12.0 kDa and $Đ$ of 1.69 were isolated by precipitation.



Scheme 5 – Aminolysis of AB'-monomer **14** with *n*-octylamine and the formation of polymer **18** by conjugate addition: ^{1}H-NMR spectra ($CDCl_3$, 500 MHz) of the monomer **14** (top) and the purified polymer **18** (bottom). Signals m^{**} and p^{**} (insert) designate two protons of the acrylate endgroup of polymer **18**. Spectral assignment of the 1D-^{1}H-NMR of polymer **18** was facilitated by 2D-NMR spectra (Figure S 13).

This optimized condition (a 0.5 M solution of **14** in THF at room temperature) was used for an *online* FT-IR study of the polymerization reaction (Table S 3 and Figure S 14 and S 15). Due to the overlapping of the urethane, acrylate and thiolactone C=O vibration bands, the aminolysis of

14 was followed by the increasing intensity of the amide vibrational band at 1683 cm^{-1}, whereas the conversion of the acrylate double bond was monitored by the acrylate scissoring vibration at 1409 cm^{-1}. Deconvolution and curve fitting of the obtained spectra in the region of 1800 – 1380 cm^{-1} were performed, such as for the model reaction (Table S 4 and Figure S 16). Again, a good agreement between the measured and deconvoluted band intensities was observed (Figure 2). Although the acrylate is mostly consumed after 3 h, only low-molecular weight polymer could be isolated from the reaction mixture at that moment. On the other hand, integration of the acrylate end-group in the ^{1}H-NMR spectrum of the polymer **18** after 24 h reaction time allowed for the determination of the DP (~ 33) and M_n (~ 15.5 kDa) (Scheme 5). The optimized conditions were subsequently applied as a general protocol for other (functional) amines as shown in Table 1.

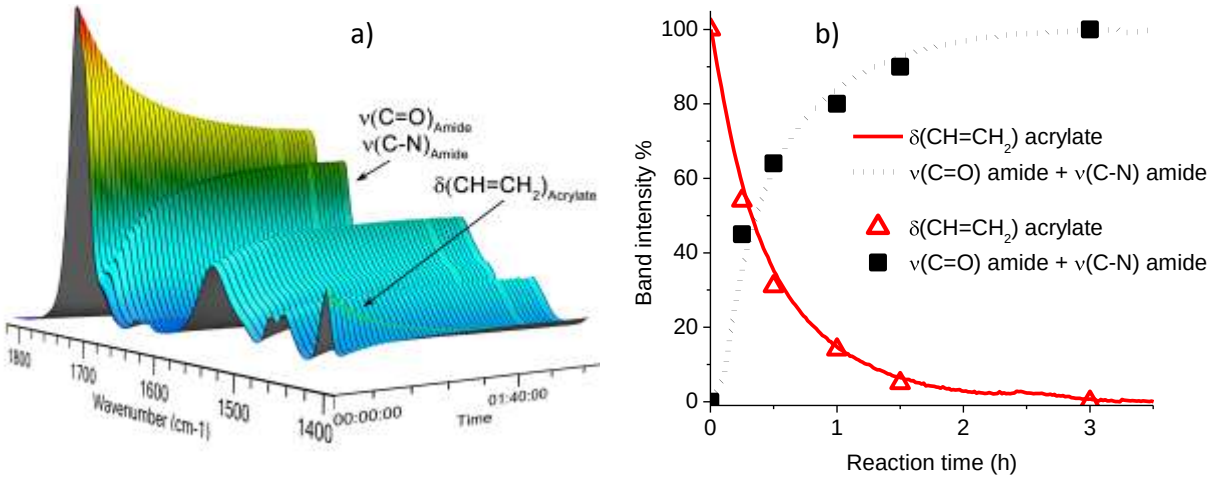


Figure 2 - *Online* monitoring of amine-thiol-ene conjugation (aminolysis and poly-addition) between octylamine and AB'-monomer **14**; (a) 3D FT-IR waterfall plot of $(C=O)_{stretch}$ absorption bands (1830 – 1360 cm^{-1}) and (b) IR peak intensities as a function of time (kinetic curves and deconvoluted data points).

Table 1 - Obtained molecular weight and dispersity by amine-thiol-ene reaction between (combined) primary amines and AB'-monomer **14**.

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

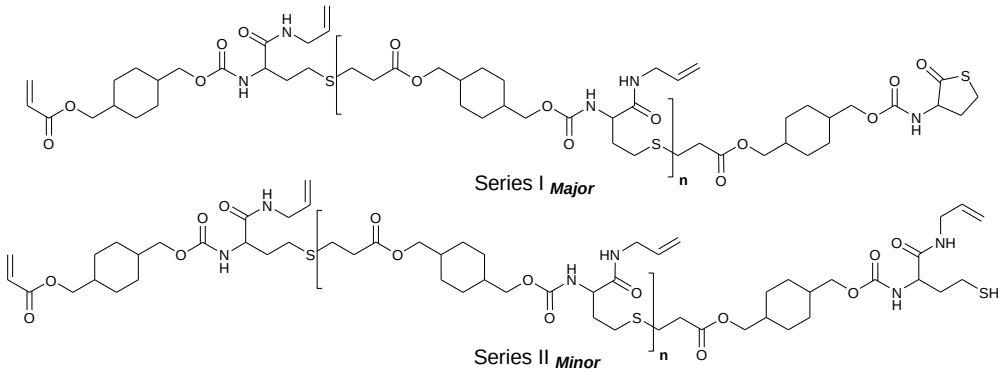
[a] Reaction conditions: entries *1* → *6*; monomer **14** in THF (0.5 M) at room temperature for 24 h in the presence of 1.1 eq. of amine; entries *7*, *8* and *9*; monomer **14** in THF (0.5 M) at room temperature for 24 h in the presence of 2 eq. of amine (1 eq. amine I and 1 eq. amine II);
[b] SEC, calibrated with PMMA standards, DMA as eluent (Figure S 17)
[c] Calculated from the integration of signals, specific for each individual amine, in the ^{1}H-NMR spectrum (Figure S 19, S 20 and S 21).

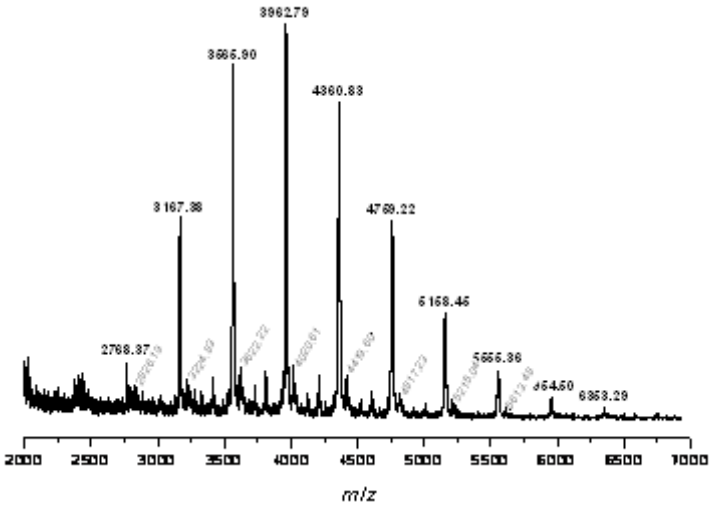
Of particular interest is the possibility to introduce double and triple bonds and reactive dienes (furan) without interference with the polymerization process (*entries 2*, *3* and *4*; Table 1). This renders the polymers accessible for further modification, without a protection and deprotection strategy being necessary. Other functionalities that were tested include a tertiary amine (*entry 5*) and a morpholine moiety (*entry 6*), enabling the synthesis of metal-complexing polymers.[66-68]

The presented strategy thus offers an easy-to-perform, one-pot method for the synthesis of functionalized PUs. Mixing the two ingredients (monomer **14** and the selected amine) at room

temperature without any additive or external trigger gives indeed access to a library of such polymers (Table 1).

MALDI-TOF analysis of a narrow-disperse fraction (Figure S 18) of allyl-functionalized polymer (Table 1, *entry 2*) confirms the structural build-up of the PUs and elucidates the nature of the end-groups (Figure 3).





	Series I *Major* [K-adduct]		Series II *Minor* [K-adduct]	
n	*calc.*	*exp.*	*calc.*	*exp.*
5	2769.22	2768.37	2826.28	2826.19
6	3167.41	3167.38	3224.46	3223.83
7	3565.59	3565.90	3622.65	3622.22
8	3963.78	3962.79	4020.84	4020.61
9	4361.97	4360.83	4419.03	4419.60
10	4760.16	4759.22	4817.21	4817.23
11	5158.34	5158.45	5215.40	5215.04
12	5556.53	5555.36	5613.59	5613.48
13	5954.72	5954.50	6011.78	--
14	6352.91	6353.29	6409.96	--

Figure 3 – MALDI-TOF analysis of the allyl-functionalized PU (Table 1, *entry 2*) including peak assignment.

Two series of signals can be readily assigned: the major distribution of peaks represents telechelic material bearing an acrylate and thiolactone entity as end-groups and a second minor series attributed to the corresponding thiol-acrylates. In both series, signals repeat each 398 Da,

i.e. the sum of the molecular weight of allylamine and monomer **14**. The minor series is shifted by 57 Da, exactly the molecular weight of allylamine. This MALDI-TOF analysis clearly demonstrates that there were no significant side reactions during the polymerization and again confirms that the aminolysis is rate-determining.

To extend the potential of this methodology and to demonstrate its versatility, experiments have been performed utilizing more than one amine, enabling the random incorporation of multiple functionalities. Reaction conditions were similar, except for the use of 2 eq. of amine (1 eq. of each amine compared to monomer **14**). The relative amount of the (functional) amines along the backbone after polymerization was calculated via integration of relevant signals in the ^{1}H-NMR spectra (Figure S 19, S 20 and S 21) and the values differ from the initial feed ratio. It was anticipated that the respective rates of aminolysis would have the greatest impact on the incorporation ratio. However, *entry 8* clearly demonstrates that two amines, being equally fast in the aminolysis reaction (Scheme 3), are incorporated in different amounts. The reactivity difference between the intermediate thiol-acrylates due to sterical factors most likely contributes significantly to this phenomenon. The results (*entries 7*, *8* and *9*) prove that different functionalities can be simultaneously incorporated along the PU backbone in a one-pot synthesis.

TGA-analysis of the obtained polymers (Table 1, *entries 1*, *2*, *4* and *9*) showed that these materials are thermally stable until 250 °C (Figure S 22).

Post-polymerization modification

Another appealing feature of this methodology is that, once the poly-addition has been completed, the reaction mixture essentially is a solution of the expected PU with a minor amount

of residual amine. Post-polymerization modification of the introduced functional group (*via* the primary amine), is thus possible in the same reaction medium. Two metal-free modification reactions were examined in this context: the radical thiol-ene reaction between 1-octanethiol and an alkene-containing polymer and the Diels-Alder reaction between *N*-methylmaleimide and a furan-containing polymer. Both polymers were synthesized by treatment of monomer **14** with allylamine (Table 1, *entry 2*) and, allylamine and furfurylamine (Table 1, *entry 9*), respectively. The disappearance of the distinct signals in the ^{1}H-NMR spectra and the apparent shift of the SEC traces indeed confirm the successful outcome of both modification reactions (Figure 4 and Figure S 23).

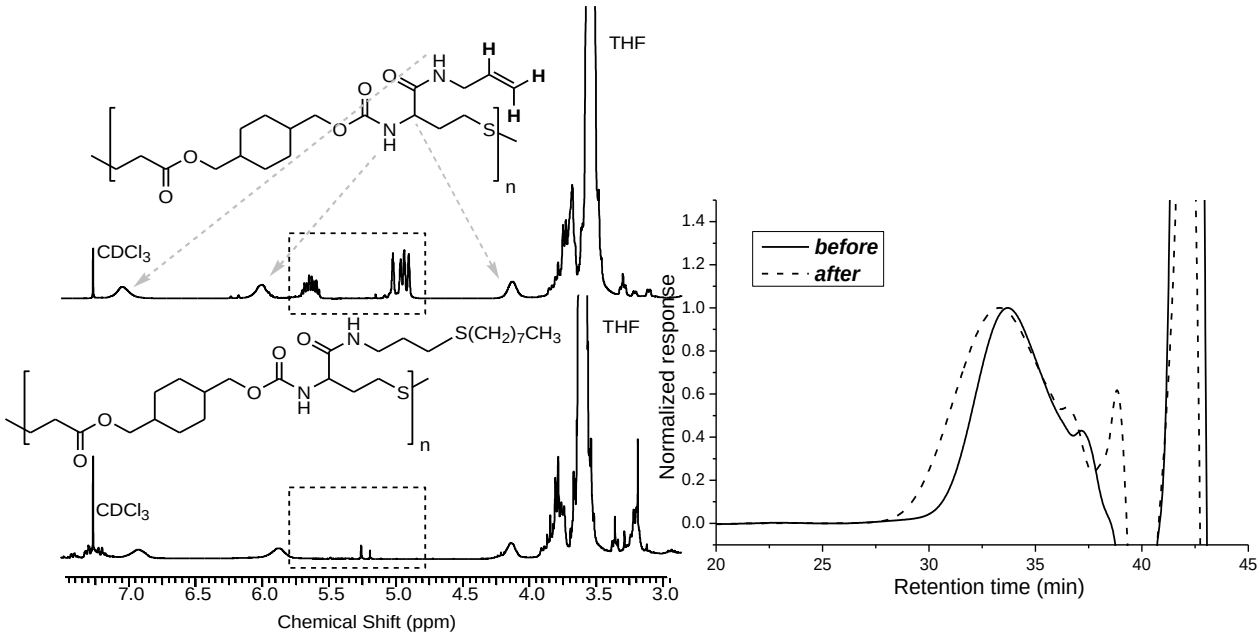


Figure 4 – Post-polymerization modification in the same medium of the allyl-containing PUs by radical thiol-ene conjugation with 1-octanethiol. (Left) Details of ^{1}H-NMR spectra ($CDCl_3$, 300 MHz) after poly-addition (*top*) and after subsequent thiol-ene modification (*bottom*) (Right) Corresponding SEC traces of reaction samples before and after thiol-ene modification.

Conclusions

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

Acknowledgement

Andreia Guimaraes is acknowledged for the MALDI-TOF analysis. All authors are thankful to Ghent University for financial support. F. G. thanks the Research Foundation-Flanders (FWO)

for the funding of her PhD fellowship. F. D. thanks the Institute for the Promotion of Innovation through Science and Technology in Flanders, Belgium (IWT) for the funding of his PhD fellowship. F.D.P. acknowledges the Belgian Program on Interuniversity Attraction Poles initiated by the Belgian State, the Prime Minister's office (P7/05) and the European Science Foundation – Precision Polymer Materials (P2M) program for financial support.

References

(1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* 2001, *40*, 2004.
(2) Hawker, C. J.; Wooley, K. L. *Science* 2005, *309*, 1200.
(3) Hawker, C. J.; Fokin, V. V.; Finn, M. G.; Sharpless, K. B. *Aust. J. Chem.* 2007, *60*, 381.
(4) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* 2007, *28*, 15.
(5) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* 2008, *29*, 952.
(6) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem., Int. Ed.* 2009, *48*, 4900.
(7) Sumerlin, B. S.; Vogt, A. P. *Macromolecules* 2009, *43*, 1.
(8) Golas, P.; Matyjaszewski, K. *Chem. Soc. Rev.* 2010, *39*, 1338.
(9) Barner-Kowollik, C.; Inglis, A. J. *Macromol. Chem. Phys.* 2009, *210*, 987.
(10) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* 2003, *8*, 1128.
(11) Hein, C. D.; Liu, X.-M.; Wang, D. *Pharm. Res.* 2008, *25*, 2216.
(12) van Dijk, M.; Rijkers, D. T. S.; Liskamp, R. M. J.; van Nostrum, C. F.; Hennink, W. E. *Bioconjugate Chem.* 2009, *20*, 2001.
(13) Veiseh, O.; Gunn, J. W.; Zhang, M. *Adv. Drug Delivery Rev.*, *62*, 284.
(14) Ciampi, S.; Le Saux, G.; Harper, J. B.; Gooding, J. J. *Electroanalysis* 2008, *20*, 1513.
(15) Hansen, T. S.; Daugaard, A. E.; Hvilsted, S.; Larsen, N. B. *Adv. Mater.* 2009, *21*, 4483.
(16) Huang, K.; Duclairoir, F.; Pro, T.; Buckley, J.; Marchand, G.; Martinez, E.; Marchon, J.-C.; De Salvo, B.; Delapierre, G.; Vinet, F. *ChemPhysChem* 2009, *10*, 963.
(17) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* 2010, *39*, 1388.
(18) Hoffman, A. S.; Stayton, P. S. *Prog. Polym. Sci.* 2007, *32*, 922.
(19) Nicolas, J.; Mantovani, G.; Haddleton, D. M. *Macromol. Rapid Commun.* 2007, *28*, 1083.
(20) Lutz, J.-F.; Boerner, H. G. *Prog. Polym. Sci.* 2008, *33*, 1.
(21) Lutz, J.-F.; Zarafshani, Z. *Adv. Drug Delivery Rev.* 2008, *60*, 958.

(22) Antos, J. M.; Francis, M. B. *Curr. Opin. Chem. Biol.* 2006, *10*, 253.
(23) Baskin, J. M.; Bertozzi, C. R. *QSAR Comb. Sci.* 2007, *26*, 1211.
(24) Hackenberger, C. P. R.; Schwarzer, D. *Angew. Chem., Int. Ed.* 2008, *47*, 10030.
(25) Weisbrod, S. H.; Marx, A. *Chem. Commun.* 2008, 5675.
(26) Best, M. D. *Biochemistry* 2009, *48*, 6571.
(27) Malkoch, M.; Thibault, R. J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. *J. Am. Chem. Soc.* 2005, *127*, 14942.
(28) Lundberg, P.; Hawker, C. J.; Hult, A.; Malkoch, M. *Macromol. Rapid Commun.* 2008, *29*, 998.
(29) Król, P. *Prog. Mater. Sci.* 2007, *52*, 915.
(30) Xie, Z.; Lu, C.; Chen, X.; Chen, L.; Hu, X.; Shi, Q.; Jing, X. *Eur. Polym. J.* 2007, *43*, 2080.
(31) Billiet, L.; Gok, O.; Dove, A. P.; Sanyal, A.; Nguyen, L.-T. T.; Du Prez, F. E. *Macromolecules* 2011, *44*, 7874.
(32) Fournier, D.; Du Prez, F. E. *Macromolecules* 2008, *41*, 4622.
(33) Fournier, D.; De Geest, B. G.; Du Prez, F. E. *Polymer* 2009, *50*, 5362.
(34) Billiet, L.; Fournier, D.; Du Prez, F. E. *Polymer* 2009, *50*, 3877.
(35) Basko, M.; Bednarek, M.; Billiet, L.; Kubisa, P.; Goethals, E.; Du Prez, F. E. *J. Polym. Sci., Part A: Polym. Chem.* 2011, *49*, 1597.
(36) Huang, J.; Xu, W. *J. Appl. Polym. Sci.* 2011, *122*, 1251.
(37) Ferris, C.; Violante De Paz, M.; Galbis, J. A. *J. Polym. Sci., Part A: Polym. Chem.* 2011, *49*, 1147.
(38) Ferris, C.; de Paz, M. V.; Galbis, J. A. *Macromol. Chem. Phys.* 2012, *213*, 480.
(39) Ott, C. *Polym. Chem.* 2012, *2*, 2782.
(40) Begines, B.; Zamora, F.; Roffe, I.; Mancera, M.; Galbis, J. A. *J. Polym. Sci., Part A: Polym. Chem.* 2011, *49*, 1953.
(41) Boufi, S.; Belgacem, M. N.; Quillerou, J.; Gandini, A. *Macromolecules* 1993, *26*, 6706.
(42) Gaina, C.; Gaina, V.; Ciobanu, C. *J. Appl. Polym. Sci.* 2009, *113*, 3245.
(43) Espeel, P.; Goethals, F.; Du Prez, F. E. *J. Am. Chem. Soc.* 2011, *133*, 1678.
(44) Burkey, T. J.; Griller, D.; Lunazzi, L.; Nazran, A. S. *J. Org. Chem.* 1983, *48*, 3704.
(45) Diart, V.; Roberts, B. P. *J. Chem. Soc.-Perkin Trans. 2* 1992, 1761.
(46) Paz, J. A.; Vega, R.; Rieumont, J.; Montero, L. A.; Alvarez, J. R. *Makromol. Chem., Theory Simul.* 1992, *1*, 99.
(47) Paz, J. A.; Rieumont, J.; Montero, L. A.; Alvarez, J. R. *Polymer* 1995, *36*, 5011.
(48) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* 1995, *60*, 7941.
(49) Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E. *Prog. Polym. Sci.* 2006, *31*, 487.
(50) Wu; Liu, Y.; He; Chung; Goh *Macromolecules* 2004, *37*, 6763.
(51) Hoyle, C. E. *Chem. Soc. Rev.* 2010, *39*, 1355.
(52) Garel, J.; Tawfik, D. S. *Chem. Eur. J.* 2006, *12*, 4144.
(53) Kraatz, U.; Wamhoff, H.; Korte, F. *Justus Liebigs Ann. Chem.* 1972, *758*, 177.

(54) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* 2002, *41*, 898.

(55) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* 2006, *106*, 3652.

(56) Maeda, T.; Otsuka, H.; Takahara, A. *Prog. Polym. Sci.* 2009, *34*, 581.

(57) Elbert, D. L.; Pratt, A. B.; Lutolf, M. P.; Halstenberg, S.; Hubbell, J. A. *J. Controlled Release* 2001, *76*, 11.

(58) Lutolf, M. P.; Tirelli, N.; Cerritelli, S.; Cavalli, L.; Hubbell, J. A. *Bioconjugate Chem.* 2001, *12*, 1051.

(59) Elbert, D. L.; Hubbell, J. A. *Biomacromolecules* 2001, *2*, 430.

(60) Tomasi, S.; Bizzarri, R.; Solaro, R.; Chiellini, E. *J. Bioact. Compat. Polym.* 2002, *17*, 3.

(61) Reddy, S. K.; Anseth, K. S.; Bowman, C. N. *Polymer* 2005, *46*, 4212.

(62) Rydholm, A. E.; Reddy, S. K.; Anseth, K. S.; Bowman, C. N. *Biomacromolecules* 2006, *7*, 2827.

(63) Shin, J.; Matsushima, H.; Chan, J. W.; Hoyle, C. E. *Macromolecules* 2009, *42*, 3294.

(64) Chan, J. W.; Hoyle, C. E.; Lowe, A. B.; Bowman, M. *Macromolecules* 2010, *43*, 6381.

(65) Li, G.-Z.; Randev, R. K.; Soeriyadi, A. H.; Rees, G.; Boyer, C.; Tong, Z.; Davis, T. P.; Becer, C. R.; Haddleton, D. M. *Polym. Chem.* 2010, *1*, 1196.

(66) Lindsay, D.; Sherrington, D. C.; Greig, J. A.; Hancock, R. D. *React. Polym.* 1990, *12*, 59.

(67) Hunter, T. C.; Price, G. J. *Analyst* 1995, *120*, 161.

(68) Price, G. J.; Clifton, A. A.; Burton, V. J.; Hunter, T. C. *Sens. Actuators, B* 2002, *84*, 208.