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Dissertation

Strategies towards the synthesis of amphiphilic block copolymers *via* RAFT Polymerization

Ausgeführt zum Zwecke der Erlangung
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unter der Leitung von
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Kurzfassung

Die Reversible Addition Fragmentation Chain Transfer (RAFT)-Polymerisation, eine kontrollierte radikalische Polymerisationstechnik, ermöglicht die Herstellung verschiedener definierter Polymerarchitekturen mit niedrigen Dispersitätswerten aus einer Vielzahl an Monomeren. Dabei weisen insbesondere Blockcopolymere mit amphiphilem Charakter ein hohes Potenzial für den Einsatz in biomedizinischen Anwendungen (z. B. als Wirkstoffträgersysteme) auf. Im Rahmen der voeliegenden Arbeit wurden sowohl Homo- als auch Blockcopolymere ausgehend von verschiedenen Monomertypen mittels RAFT-Polymerisation hergestellt.

Im ersten Teil dieser Dissertation wurden Monomere aus der Gruppe der stärker aktivierten Laurylmethacrylat und N-Acryloylmorpholin, die zur Gruppe der `more activated monomers´ gehören als Bausteine ausgewählt. Der kontrollierte Charakter der RAFT Polymerisation mittels eines Trithiocarbonat basierenden RAFT-Reagenzes wurde untersucht, indem kinetische Studien der Homopolymerisationen durchgeführt wurden. Anschließend wurden amphiphile Blockcopolymere mit unterschiedlichen Gesamtmolekulargewichten hergestellt bei denen zum Teil funktionelle Monomere. die Möglichkeiten zur nachträglichen Modifizierung oder Fluoreszenzmarkierung bieten, copolymerisiert. Nach dem Entfernen der RAFT-Endgruppe wurden die Blockcopolymere weiter charakterisiert. Die kritische Mizellenbildungskonzentration wurde mittels Fluoreszenzspektroskopie bestimmt und STA-Messungen zeigten die thermische Stabilität der Polymere. Darüber hinaus wurde die Nichttoxizität der Blockcopolymere durch ein XTT-Array, welches von der Medizinischen Universität Wien durchgeführt wurde, nachgewiesen.

Der zweite Teil der vorliegenden Arbeit beschäftigte sich mit der RAFT-Polymerisation von Vinylestern, die der Gruppe der `less activated monomers´ zugeordnet werden können. Es wurde die RAFT-Polymerisation verschiedener kommerziell erhältlicher Monomere in Kombination mit zwei Xanthat-basierten RAFT-Reagenzien sowohl in Masse als auch in Lösung betrachtet. Dabei stellte sich heraus, dass unter den gewählten Reaktionsbedingungen nur eines dieser Reagenzien geeignet war. Außerdem wurde ein dualer Initiator, der sowohl als RAFT-Reagenz, als auch als Initiator für die Ringöffnungspolymerisation (ROP) dienen kann, hergestellt. Er wurde erfolgreich bei der RAFT-Polymerisation von hydrophoben Vinylestern und bei der ROP von Ɛ-Caprolacton eingesetzt. Die RAFT-Polymerisation eines synthetisierten, hydrophilen Vinylesters führte zu Polymeren mit bi- oder multimodaler Molekulargewichtsverteilung.

Abstract

Reversible Addition Fragmentation chain Transfer (RAFT) polymerization, a controlled radical polymerization technique, facilitates the preparation of well-defined polymer architectures showing low dispersity values from various types of monomers. Especially block copolymers with amphiphilic character show a high potential towards their usage in biomedical applications (e.g. drug carrier systems). Within this thesis, homopolymers as well as block copolymers of different types of monomers have been prepared by means of RAFT polymerization.

In the first part, monomers belonging to the group of more activated monomers, lauryl methacrylate and N-acryloyl morpholine, were chosen as building blocks. In order to evaluate the controlled character of the reactions using a trithiocarbonate based RAFT agent, kinetic studies of the homopolymerizations were conducted. Subsequently, amphiphilic block copolymers with different total molecular weights were prepared and, in some cases, functional monomers, offering possibilities for post-polymerization modification or fluorescent labeling, were incorporated. Finally, the RAFT end group was removed and the block copolymers were further characterized. Fluorescent spectroscopy was used to determine the critical micelle concentration and STA measurements revealed the thermal stability of the polymers. Additionally, the non-toxicity of the block copolymers was proven by an XTT array performed by the Medical University of Vienna.

The second part of the present work focused on the RAFT polymerization of vinyl esters, which can be assigned to the group of less activated monomers. Here, RAFT polymerization of different commercially available monomers in combination with two xanthate-based RAFT agents was tested in bulk and in solution. Thereby it turned out that only one was a suitable agent under the selected reaction conditions. In addition, a dual initiator, which can either serve as RAFT agent or as initiator for Ring Opening Polymerization (ROP) was prepared and tested. It was successfully applied in the RAFT polymerization of hydrophobic vinyl esters and in ROP of Ɛ-caprolactone. The RAFT polymerization of a novel hydrophilic vinyl ester led to polymers showing at least bimodal molecular weight distributions.

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Introduction

1 Block copolymers

Block copolymers (BCP) are built from at least two different monomers, whereat their arrangement in the polymer happens block-wise. Figure 1 shows different possibilities of how blocks can be arranged within a polymer.

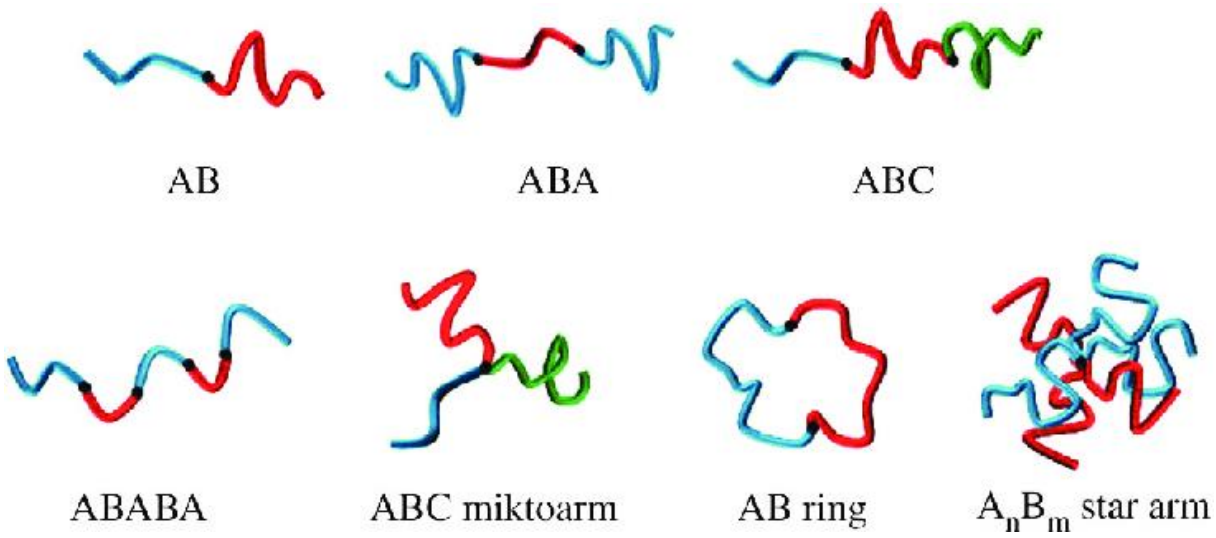


Figure 1: Possibilities for arrangement of block copolymers[1]

In principle, applications of block copolymers are based on the fact that the homopolymer blocks are able to self-organize in nanostructures, either in bulk or in solvents. A well-known usage of block copolymers can be found in thermoplastic elastomers (TPE), which are one of the oldest products based on different blocks and are widely used nowadays. Applications can be found in sealings, packing, toys, sports equipment, handrails and in general if haptic properties are of interest. TPEs comprise a soft and a hard component and their composition can vary from AB to multi-block copolymers.[2]

Another important example of block copolymers can be found in poloxamers, also known under the trade name “Pluronics” (BASF, 1973). Those materials are terpolymers (ABA-triblock copolymers) consisting of a hydrophobic poly(propylene oxide) block in the middle, attached to a hydrophilic poly (ethylene oxide) block on each end of the polymer chain. Due to the difference in solubility, these products show amphiphilic character allowing usage in various fields. Besides applications in the industrial field as detergents, lubricants or emulsifiers, they can also be used in cosmetics, food, paints and medical applications.[3]

In general, the synthesis of the aforementioned AB block copolymers is possible in different ways. Figure 2 depicts the four most prevalent synthetic pathways applicable for the preparation of such polymers with a narrow molecular weight distribution and a uniform composition. Syntheses of tri- or multi-block copolymers proceed in a similar matter. [4]

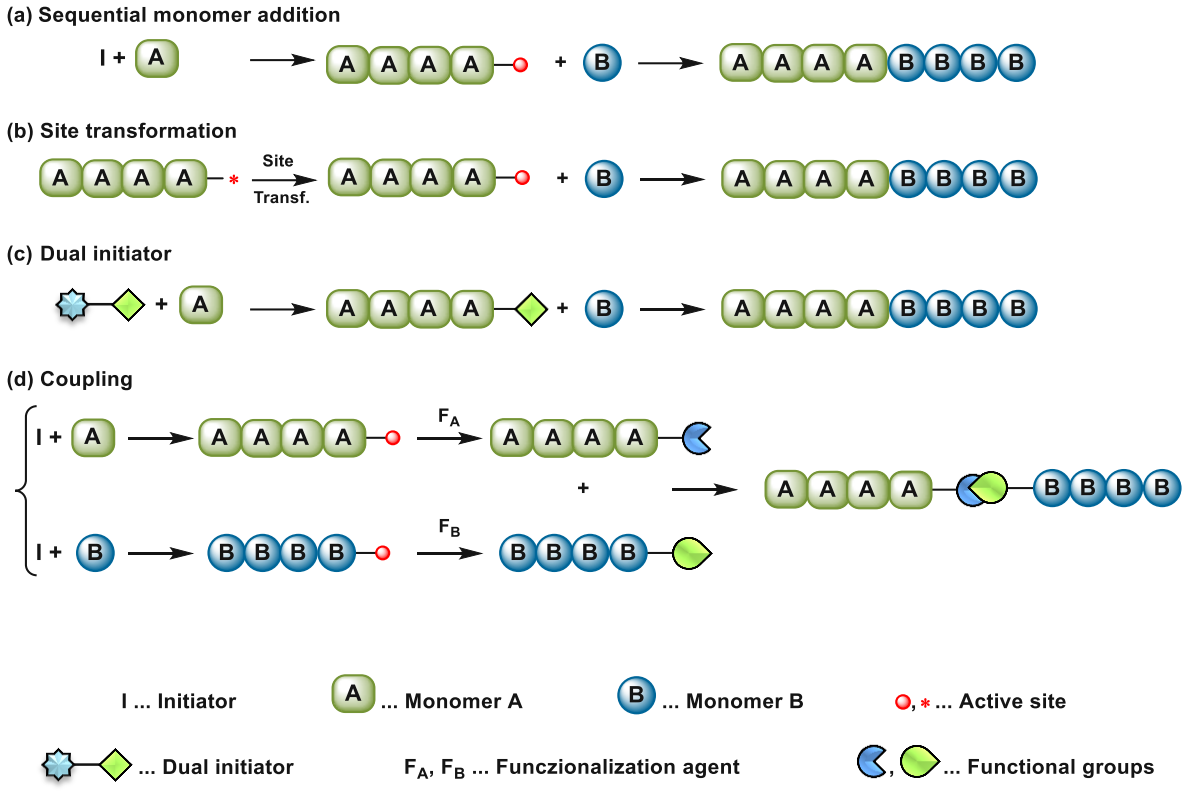


Figure 2: Schematic overview of various synthetic pathways towards the synthesis of block copolymers (drawn in dependence on Müller *et al.*[4])

One possibility for the synthesis of AB block copolymers is given by the sequential process **(a)**. Thereby, the first block is prepared from monomer A, and the active end group is then further used to generate the second block from monomer B.

Option **(b)** also proceeds in sequential manner, and is employed, if the chosen monomers are not polymerizable by using the same active end group. Hence, after the synthesis of the first block from monomer A a transformation reaction is necessary in order to change the active end group* into a suitable one ○ for the formation of the second block from monomer B.

Furthermore, the preparation of block copolymers is feasible by applying a dual initiator **(c),** which allows the polymerization of different monomers by means of diverse polymerization techniques. Here, the active species stays at the end of each propagating polymer chain. It has to be ensured that they are compatible and do not interfere with each other.

The fourth pathway **(d)** is based on the coupling of two homopolymers each equipped with highly reactive ω-functionalities .

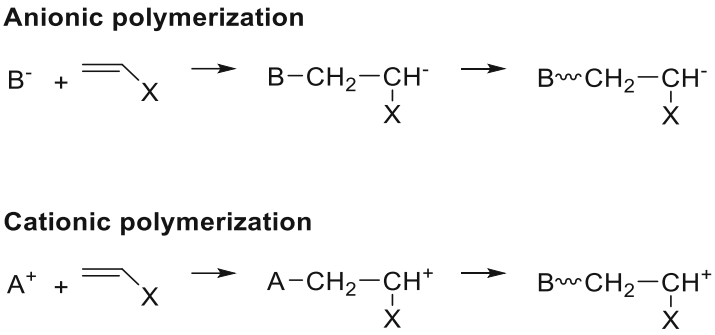
Polymerization techniques, which facilitate the syntheses of block copolymers via the above-mentioned pathways, show a living or controlled character. These methods include anionic/cationic polymerization as well as controlled radical polymerization techniques.[4]

2 Controlled Polymerization Techniques

Controlled polymerization techniques have their origin in the work of Michael Szwarc,[5,6] who first discovered "living anionic polymerization", which was a further development of the classical ionic polymerization.

2.1 Ionic polymerization

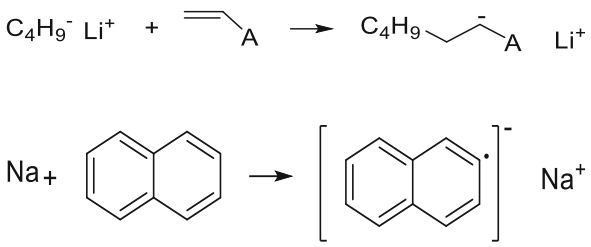
As indicated by the name, ionic polymerization is a chain growth reaction based on nucleophilic or electrophilic addition started by either anions or cations. Scheme 1 depicts the general mechanism of these two reaction types.



Scheme 1: General mechanism of anionic and cationic polymerization

Anionic polymerization requires monomers bearing an electron-withdrawing group, which provide the possibility to stabilize the carbanion formed by initiation. Examples are methacrylates and cyanoacrylates. Very important aspects are the choice and preparation of solvents, since traces of water or alcohols cause termination reactions. The same problem occurs when chlorinated solvents like chloroform are used. Additionally, in most cases low temperatures are necessary in order to control the reaction speed and to avoid side reactions. The absence of termination and transfer reactions enables the synthesis of well-defined polymers with low dispersity values. [4,7,8]

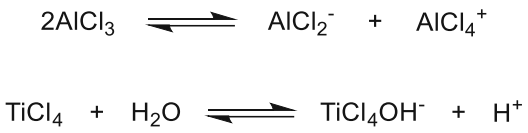
Initiation can be done by nucleophilic reagents or by electron transfer. The first-mentioned option uses ionic metal amides, alkoxides, hydroxides, phosphines, cyanides or amines. Very common is the usage of organometallic compounds such as butyl lithium or Grignard-compounds. The latter named possibility uses sodium in combination with naphthalene leading to the formation of a radical anion. Scheme 2 depicts these two initiation possibilities.



Scheme 2: Initiation possibilities in anionic polymerization

Under ideal conditions, no termination occurs in anionic polymerization processes, since molecules bearing the same charge cannot recombine. Hence, the polymer chain end group stays active even when all monomer is consumed and polymerization goes on if new monomer is added. Termination can occur due to impurities or by quenching in order to add functional groups to the polymer. Examples of this are addition of CO_2 or water, leading to COOH- or OH-end groups.

Ionic Polymerization can also proceed via a cationic process. Monomers suitable for cationic polymerization need substituents with electron-pushing effects, which enable stabilization of the carbenium ion. Isobutylene and vinyl ethers are monomers, which fulfill this requirement. Again, the purity and choice of the solvent are important, since even traces of water or alcohol can cause termination. Suitable solvents are chlorinated ones as well as toluene and benzene. Low temperatures are required in order to avoid unwanted side reactions like Friedel-Crafts-alkylation or deprotonation. Appropriate initiators for cationic polymerization can are Brønsted acids (e.g. perchloric acid) and Lewis acids (e.g. titanium tetrachloride). Some Lewis-acids show self-dissociation while others require the addition of water or alcohol whereby the acid then acts only as co-initiator. Scheme 3 depicts the different possibilities of initiation.[4,7,8]



Scheme 3: Initiation possibilities in cationic polymerization

As for anionic polymerization, termination between to growing chains is not possible due their identical charge. Nevertheless, resulting from high reactivity of the cations, different side reactions leading to either termination or transfer can occur.

Drawbacks of these ionic methods can be found in the request of stringent reaction conditions and limited monomer selection. It is essential that used components (monomer, initiator, solvent) are completely free of water, since this would cause termination reactions. Furthermore, often temperatures significantly below 0 °C are required. Hence, other options for the synthesis of well-defined polymers are of interest.

2.2 Controlled radical polymerizations

Besides his emphasis for anionic polymerization, Swarc also put a lot of effort in the research of radical polymerization[9-12], and thus contributed to the development of controlled radical polymerization (CRP) procedures. As well as in free radical polymerization (FRP), a broad variety of monomers is accessible via these techniques, and various reaction conditions can be applied.[13]

In literature these polymerization methods are also referred to as “living”, although this is only a characteristic of polymerization reactions where no transfer or termination of polymer chains occur.[5,14] In 2010 the International Union of Pure and Applied Chemistry (IUPAC) published a recommendation, in which these types of monomers are classified as “Reversible-Deactivation Radical Polymerization” (RDRP).[14]

2.2.1 Criteria for controlled polymerization

In order to classify a radical polymerization as a controlled process, it is necessary that certain criteria are fulfilled. First, a first-order-kinetic should be observed, meaning the polymerization rate $\mathbf{R_p}$, represented by the change of the monomer concentration **[M]** over time, should be a linear function dependent on the propagating constant $\mathbf{k_p}$ and the amount of propagating radicals $\mathbf{P^*}$ (see Equation 1). This fact arises on account of the insignificant number of

irreversible termination reactions and therefore constant concentration of the active species **[P*]**.[15,16]

$$R_p = \frac{-d[M]}{dt} = k_p[P^*][M] \qquad \textbf{Equation 1}$$

To show proof of this correlation, the natural logarithm of the ratio between the monomer concentration at the beginning of the polymerization $\mathbf{[M]_0}$ and the monomer concentration at any point in time **[M]**, is plotted against reaction time. According to Equation 2 this graph has to show linear behavior over time **t**, assuming a constant value for **[P*]** (see Figure 3).[15,16]

$$ln\frac{[M]_0}{[M]} = k_p[P^*]t \qquad \textbf{Equation 2}$$

The constant concentration of **[P*]** is based on the equilibrium between activation and deactivation processes. This is contrary to FRP, where this arises from the balance between initiation and termination. Figure 3 depicts the graph not only for the perpetual amount of active radicals **[P*]**, but also for deviations in both directions.

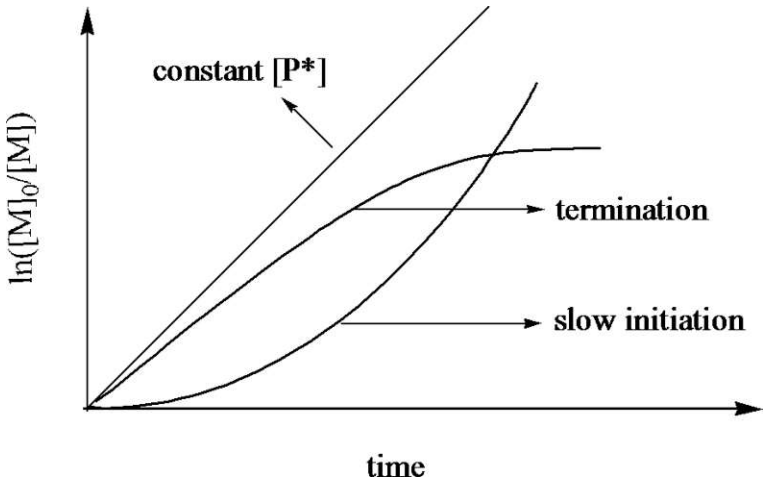


Figure 3: Possible evolutions of the logarithmic monomer concentration over time[16]

As already mentioned, the controlled polymerization is represented by the straight line in the diagram (constant **[P*]**), indicating initiation is fast.[15] If the initiation step is slowed down, the amount of radicals increases over time. This results in a soaring curve. On the contrary, a reduction in **[P*]**, caused by side reactions like termination, leads to a flattening of the curve. Additionally, it has to be mentioned, that this plot does not consider processes which have no

influence on the number of active radicals, like chain transfer processes or slow exchange reactions between active species.

As a second criterion for a CRP, the degree of polymerization **DP_n** and the molecular weight of the polymer, respectively, should be pre-determined by the initial concentration of monomer **$[M_0]$** as well as of controlling species **$[I_0]$** and have to show linear behavior referring to the monomer conversion, as can be seen from Equation 3.[15,16]

$$DP_n = \frac{M_n}{M_0} = \frac{\Delta[M]}{[I]_0} = \frac{[M]_0}{[I]_0} \cdot (conversion) \qquad \textbf{Equation 3}$$

This correlation is only valid if the quantity of polymer chains ia constant over the whole period of polymerization. To achieve this, the initiation has to proceed fast enough to start the growth of all polymer chains at the same time and to allow them to propagate as long as monomers are present. Furthermore, there should not be any transfer reactions leading to an increase of dispersity. Figure 4 depicts both, the ideal case of the increase in molecular weight over conversion, and the deviation thereof if slow initiation or side reactions (coupling or transfer) occur.

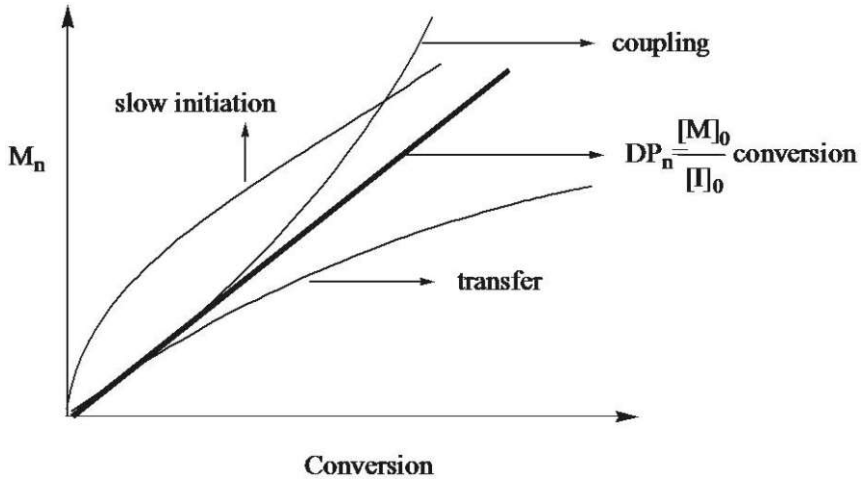


Figure 4: Possible evolutions of the molecular weight M_n in dependence on monomer conversion [16]

However, it has to be mentioned, that this graph does not consider termination reactions, as the amount of polymer chains stays the same. The curve is only affected if a significant number of coupling reactions happen, which leads to polymers with high molecular weights.

A third criterion for controlled radical polymerization is the possibility to obtain polymers with uniform chain length. Hence, polymers with a narrow molecular weight distribution and much

lower dispersity values compared to FRP are produced. This is exemplarily shown in Figure 5 for the polymerization of styrene via FRP and Reversible Addition Fragmentation-chain Transfer Polymerization (RAFT), respectively.

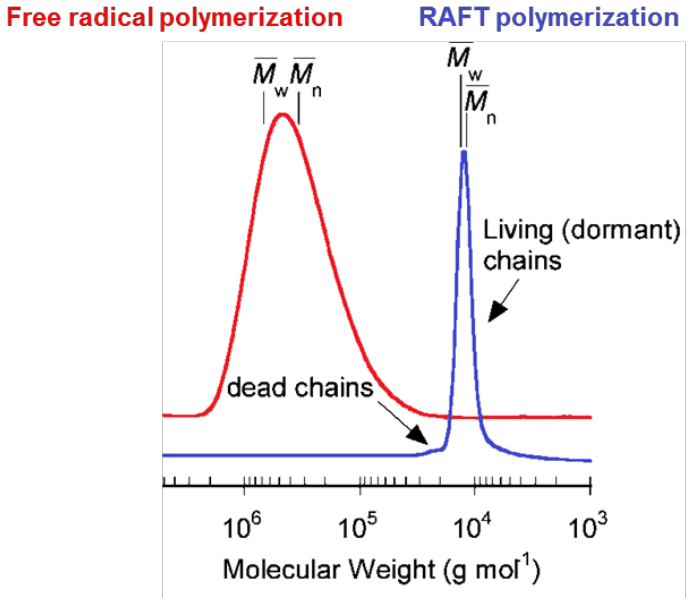


Figure 5: Typical SEC traces and resulting molecular weight distributions for the polymerization of styrene via free radical polymerization (red) and via RAFT polymerization (blue) (adapted from literature[17])

In order to realize this uniformity of the polymer chains, the initiation has to proceed fast compared to the propagation reaction, ensuring the concurrent growth of all chains. A homogenous growth of all chains is attained, if the interaction between different species is fast in relation to the rate of propagation. Additionally, transfer and termination are only present at an insignificant level and depropagation proceeds considerably slower than propagation to ensure irreversibility of the polymerization. Hence, if these requirements are fulfilled, a Poisson distribution is obtained (see Equation 4).

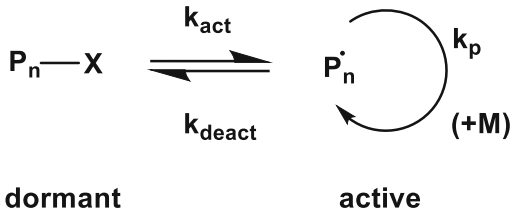
$$\frac{DP_w}{DP_n} = \frac{M_w}{M_n} = 1 + \frac{DP_n}{(DP_n + 1)^2} \cong 1 + \frac{1}{DP_n} \qquad \textbf{Equation 4}$$

Referring to Equation 4, the dispersity of the polymer $\mathbf{M_w/M_n}$, represented by the ratio between weight average molar mass $\mathbf{M_w}$ and the number average molar mass $\mathbf{M_n}$, should decrease with increasing degree of polymerization $\mathbf{DP_n}$. [15,16] For living radical polymerizations, this value should be less than 1.5.[18]

The forth criterion for CRP deals with the “living” character. As termination and chain transfer are very unlikely to happen, long-living polymer chains are obtained, still bearing their active end-functionality. So, as long as monomer is available, the chain growth continues even if new monomer is added. This gives the possibility to synthesize block copolymers consisting of two or more monomer types.[15,16]

2.2.2 Principles of controlled radical polymerization

In general all controlled radical polymerization techniques are based on the dynamic equilibrium between an active species, present at low concentration, and a large fraction of dormant species, which is unable to self-terminate or propagate.[19] Scheme 4 depicts the general mechanism of this process.

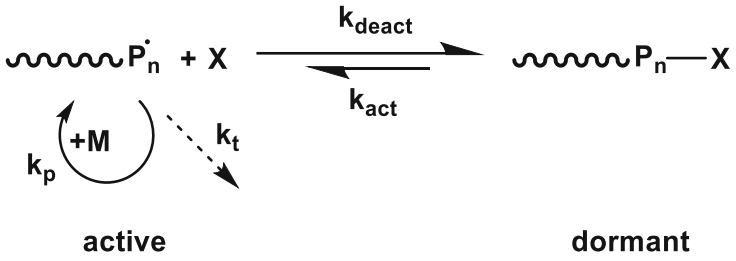


Scheme 4: General scheme of the reversible activation process in controlled radical polymerizations (according to Goto *et al.*[20])

The dormant species **P_n-X** is activated to give the active radical **$P_n^{\cdot}$**, which is then able to propagate. Thereby, the ratio between **$[P_n^{\cdot}]$** and **$[P_n$-X$]$** is usually less than 10^{-5}, meaning that the polymer chain is most of time present in the dormant state.[20] This condition can be reached either by a reversible activation/deactivation process based on the persistent radical effect (PRE), in which radicals are captured reversibly, or by a reversible transfer based degenerative transfer (DT).[13]

2.2.2.1 Persistent Radical Effect

The persistent radical effect (PRE), explained by H. Fischer,[21,22] describes a kinetic aspect, which leads to self-regulation in certain controlled radical polymerization systems. Thereby the growing polymer radical **$P_n^{\cdot}$** is captured rapidly by a stable radical **X** (with a rate constant of deactivation **k_{deact}**), and this results in the deactivation of the radical (Scheme 5), giving a dormant species **P_n-X**.[13]



Scheme 5: Principle of the deactivation/activation process as observed in polymerizations based on the persistent radical effect (PRE) (according to Braunecker et al.[13])

The (re)activation of the dormant species (with a rate constant of activation k_{act}) can then occur via heat/light triggered processes or by using a catalyst. Since the concentration of **X** increases over time due to the irreversible termination of $P_n^{\cdot}$ with another $P_n^{\cdot}$ radical (with a rate constant of termination k_t), the amount of radicals decreases, as well as the probability for termination reactions (with k_t). The growing polymer chains prevalently react with the persistent radical **X**, which is available at much higher concentrations (more than 1000 times), leadingto a shift of the equilibrium towards the dormant species P_n-**X**.[13]

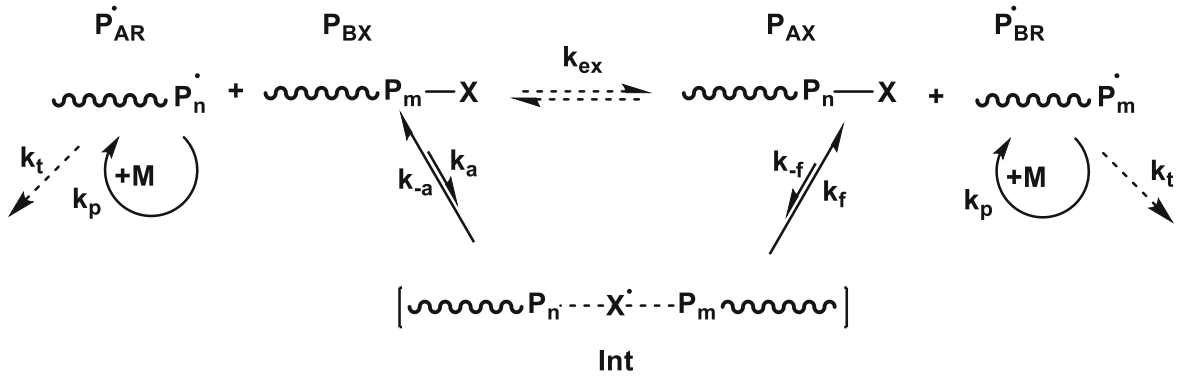
In contrast to free radical polymerization systems, where the constant amount of radicals is due to the equilibrium between initiation and termination, in PRE driven systems, the number of radicals is kept at the same level by the activation-deactivation process. PRE processes show a significant decrease of termination over time, since all polymer chains are short in the beginning, but become steadily longer.[23] Controlled radical polymerization techniques, which rely on the PRE, are stable free radical polymerization (SFRP) like nitroxide mediated polymerization (NMP), and atom transfer radical polymerization (ATRP).[13]

2.2.2.2 Degenerative Transfer

Controlled polymerizations, which do not proceed via the PRE, follow the degenerative transfer (DT) mechanism (see Scheme 6), which is based on the relocation of the active center between the active and the dormant species via a reversible chain transfer[24]. Therefore, several mechanisms are possible, but the thermodynamic neutral (dynamic) transfer has to proceed fast compared to propagation ($k_{ex} > k_p$) in order to obtain polymers with narrow molecular weight distributions and predetermined chain length[18].

These polymerizations allow the usage of conventional radical starters and the control of molecular weight is achieved by the addition of a transfer agent **R-X**. The exchange of the radical species is possible by transfer of the group/atom **X** or by an addition-fragmentation step. As shown in Scheme 6, this can succeed directly (characterized by the rate constant of exchange k_{ex}) or via a short-lived intermediate **Int** (characterized by the rate constants of addition k_a and fragmentation k_f). Thereby, the radical is transferred from the active polymer

chain $P^{\cdot}_{AR}$ to the dormant species P_{BX}, whereupon P_{AX} and $P^{\cdot}_{BR}$ are formed. It has to be noted, that the concentration of the dormant species P_{AX}/ P_{BX} has to be higher than that of the active species $P^{\cdot}_{AR}$/ $P^{\cdot}_{BR}$.[13]



Scheme 6: Principle of the degenerative transfer (according to Braunecker *et al.*[13])

As a key fact, in polymerizations, which are based on DT, the number of radicals is kept constant by the equilibrium between initiation and termination as in free radical polymerizations. [13] Nevertheless, techniques based on DT show a probability for termination throughout the whole polymerization, due to the constant formation of new polymer chains.[23]

The resulting degree of polymerization **DP** is defined by the molar ratio between the monomer **M** and the transfer agent **R-X** (see **Equation 5**).

$$\mathrm{DP} = \frac{[M]}{[R-X]} \qquad \textbf{Equation 5}$$

One example for polymerizations based on DT is iodine transfer polymerization.[13] Thereby, iodines are used to transfer the radical to the dormant species. However, the best-known type of such polymerizations is Reversible Addition Fragmentation-chain Transfer Polymerization (RAFT).

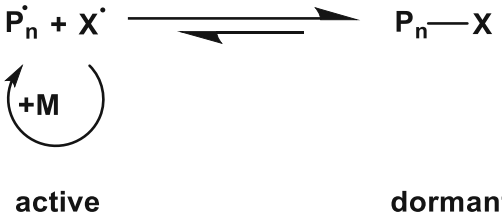
2.2.3 Comparison between conventional free and controlled radical polymerization

Concerning mechanism, selectivity (including chemo-, regio- and stereoselectivity), and the field of useable monomers, FRP and CRP show similar behavior. Nevertheless, according to Braunecker et al.[13] there are a few significant differences between those two polymerization techniques.

Due to the existence of a dormant species and recurring reversible activation in CRP, the polymer chains exist not only for about 1 second as in FRP, but for 1 hour or even longer.
Due to comparatively slow initiation in FRP processes, residual amounts of initiator stay in the reaction mixture if FRP is performed. On the contrary, the initiation usually proceeds fast in CRP processes, so that all chains start to grow simultaneously and along with this the control over the chain length of the resulting polymers becomes possible.
FRP leads to almost 100 % dead chain ends, whereas this amount is less than 10 % for CRP. With a few exceptions, like the preparation of low molecular weight polymers, FRP proceeds faster than CRP.
In FRP processes the amount of radicals is kept at the same level after a certain time since termination is compensated by initiation. In CRP a constant concentration of radicals is reached by the balance between the rate of activation and the rate of deactivation.
In general, termination in FRP is a reaction step between already long polymer chains and continually new formed chains. For CRP termination depends on the reaction kinetics. PRE processes show a significant decrease of termination over time, since all polymer chains are short in the beginning, but become steadily longer. Techniques based on DT show a probability for termination throughout the whole polymerization, due to the constant formation of new polymer chains.[23]

2.3 Techniques of controlled radical polymerizations

Nitroxide Mediated Polymerization (NMP) is the best known example of Stable Free Radical Polymerization (SFRP). It relies on the PRE, and to be more precise, the fundament is a dissociation-combination mechanism.[20,25] The active species $\mathbf{P_n}^{\cdot}$, which is able to propagate by adding to monomer molecules, and the capping molecule $\mathbf{X}^{\cdot}$ are generated by the homolytic bond cleavage of the dormant species $\mathbf{P_n\text{-}X}$ (see Scheme 7).[18]

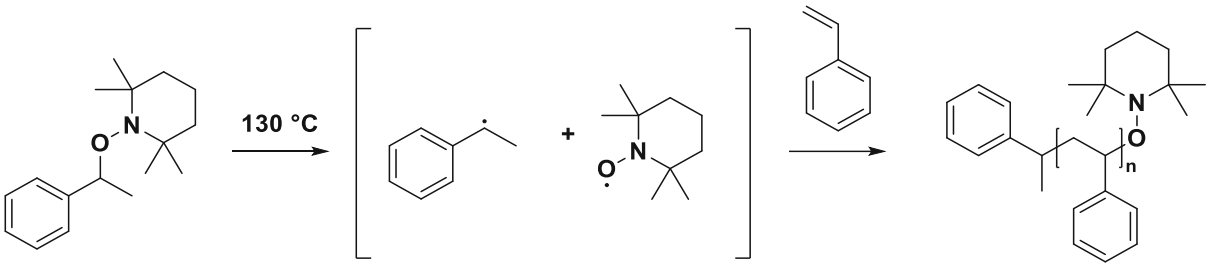


Scheme 7: Dissociation-combination mechanism as observed in NMP (according to D. Shipp[25])

This technique goes back to the usage of nitroxide radicals, which are stabilized due to resonance effects, as scavenger for radicals, whereas alkoxyamines are obtained. At elevated temperatures this reaction is reversible, and the active radical is again available.[26]

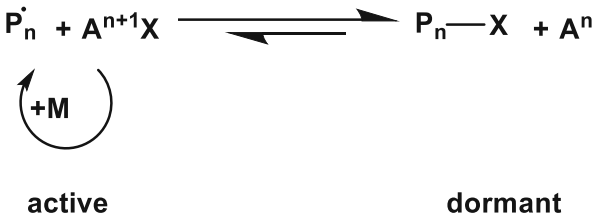
Hence, in NMP stable nitroxide radicals are used to control the formation of the dormant species and therefore keeping the amount of radicals at a low level.[27] Thereby, the initiation of the polymerization process is possible either in a bimolecular or unimolecular way. For the first option, a classical radical initiator (e.g. dibenzoyl peroxide) is used to generate an alkoxyamine from a nitroxide in an *in situ* process. The latter one uses an alkoxyamine as initiator, which decomposes into a reactive and a stable radical under high temperatures. It is also possible to use macromolecular alkoxyamines if block copolymers are desired.[28]

Nowadays, various nitroxides and alkoxyamines are known from literature. This enables the usage of this technique for the polymerization of different types of monomers[27,28] as well as for the synthesis of polymers with different architectures[26,29] (e.g. gradient[30,31]/statistical[32,33] copolymers, block copolymers,[34] graft[35] and star polymers[36]). Nevertheless, the best-known example is 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO). In Scheme 8 a NMP process is exemplarily shown for the preparation of poly(styrene) via a unimolecular initiation using S-TEMPO as initiating alkoxyamine.



Scheme 8: Preparation of poly(styrene) via a unimolecular induced NMP process using S-TEMPO as initiating alkoxyamine (referring to Hawker et al.[28])

Another RDRP technique, which relies on the PRE, is **Atom Transfer Radical Polymerization** (ATRP). It proceeds via an atom transfer mechanism as depicted in Scheme 9. Besides the fact, that a catalyst $\mathbf{A^n}$ (n represents the oxidation number) is involved in the homolytic cleavage of the dormant species $\mathbf{P_n\text{-}X}$, this process works analogously to dissociation-combination mechanism. Hence, this step is bimolecular and it results in the formation of the active $\mathbf{P_n}\cdot$ radical and oxidation of the used catalyst to give $\mathbf{A^{n+1}X}$.[18]



Scheme 9: Atom transfer mechanism as observed in ATRP (according to D. Shipp[25])

A proper catalyst system **A** for ATRP needs an oxidizable transition metal species $\mathbf{Mt^n}$, capable of expanding its coordination sphere, as well as a complexing ligand **L**, and a counterion with the ability to build an ionic or covalent bond to the metal center atom. Upon the homolytic cleavage of an alkylhalide **R-X** or $\mathbf{P_n\text{-}X}$, induced by the metal complex $\mathbf{Mt^n/L}$, and the addition of the generated halogenide radical $\mathbf{X}\cdot$ to the metal ion $\mathbf{Mt^n}$, a new, oxidized complex $\mathbf{Mt^{n+1}X/L}$ is formed. Additionally, the active radical $\mathbf{R}\cdot$ or $\mathbf{P_n}\cdot$ is released, which is then able to either start the polymerization or to propagate by adding to monomer molecules. [13,37]

Although various transition metals (e.g. Fe,[38,39] Mo,[40] Ni[41]…) have been successfully used in ATRP, copper turned out to be the most efficient one, since a broad variety of monomers is accessible and polymerization is possible in different environments.[13] The used ligands are usually nitrogen containing compounds like bipyridines[42] or pyridine imines[43]. The counterion is represented by a halide[37] (e.g. halogenated alkanes, benzylic halides) in most cases, though other possibilities (e.g. pseudohalides[44]) were successfully tested. As NMP, but to a higher extend, ATRP can be used for the preparation of different polymer architectures[37,45,46] (e.g. gradient copolymers,[47,48] block copolymers,[49] graft polymers,[50] star[51] and brush[52,53] polymers) from diverse types of monomers[37] (e.g. styrenes, (meth) acrylates, (meth) acrylamides…) under various reaction conditions (solution, bulk, heterogeneous systems).[37]

Reversible Addition Fragmentation chain Transfer polymerization (RAFT) is a rather young polymerization technique[54], which was established by the Australian CSIRO group [55,56] in 1998 and French researchers in 1999[57,58], whereat the last-mentioned group named this polymerization method MADIX (Macromolecular Design via the Interchange of Xanthates).

Since then, the interest in RAFT polymerization rose rapidly obvious from the steadily increasing number of publications on this topic up till now, as illustrated in Figure 6, including numerous review articles.[59-62]

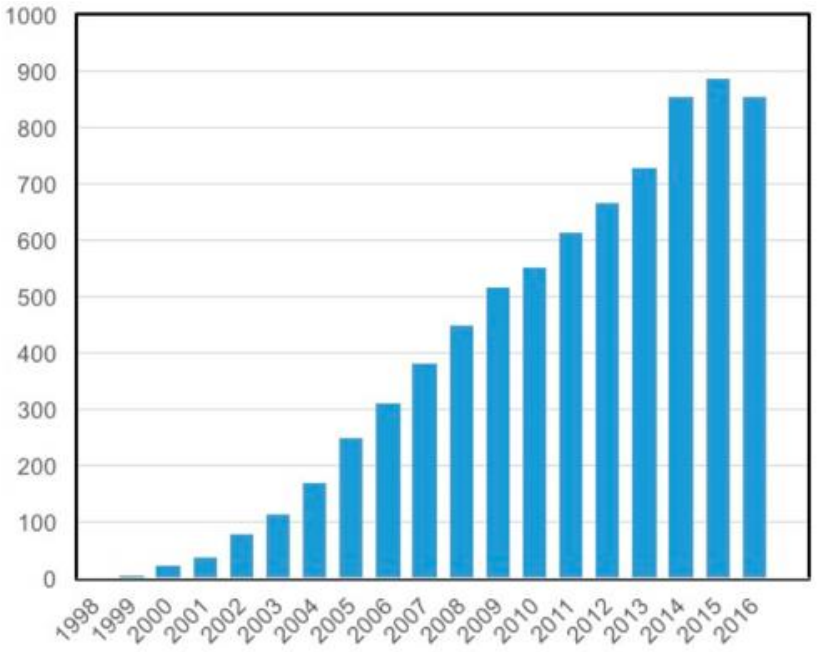


Figure 6: Number of publications on the topic of RAFT polymerization per year from 1998 up to 2016[63]

As other RDRP methods (NMP, ATRP), the RAFT technique offers many possibilities regarding reaction conditions and polymer architectures. Additionally, one of its big advantages over ATRP is the absence of any transition metals during the reaction. Compared to NMP, RAFT allows lower reaction temperatures, and a broader range of monomers is accessible.[64] In general, all common types of monomers and also less common monomers like ionic liquids[65,66] can be polymerized by means of RAFT polymerization under various reaction conditions. In literature reactions in the range from ambient temperatures up to 180 °C[67] and also at elevated pressure of up to 5 kbar[67,68] are reported. Furthermore, RAFT polymerization allows a broad variety of reaction media. Reactions can be performed either in bulk or in solution,[56] whereat organic solvents can be used as well as water.[15,69] In addition, less common solvents like supercritical carbon dioxide[70,71] or ionic liquids[72] have been applied as reaction media. Even polymerization in heterogeneous systems like in (mini) emulsion or dispersion is possible.[24,73]

Since this technique was used within this thesis, it is described in detail in the following chapter.

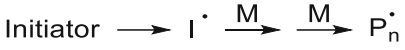
3 Reversible Addition Fragmentation chain Transfer Polymerization

3.1 RAFT Mechanism

As mentioned already in chapter 2.2.2.2, RAFT polymerization relies on a DT mechanism, characterized by an addition-fragmentation step. Besides the fact, that a RAFT agent/chain transfer agent is needed, the mechanism of the RAFT polymerization is similar to the one of free radical polymerization and consists of a few reaction steps, namely initiation, preequilibrium, reinitiation, main equilibrium and termination.

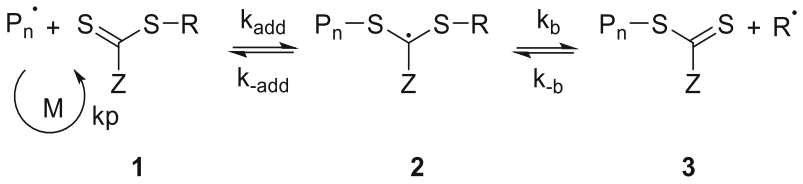
At the beginning of the reaction radicals have to be formed in order to start the polymerization. In general, this can be achieved by radicals from any source, although thermal initiators like azo compounds [e.g. 2,2′-azobis(2-methylpropionitrile) (AIBN), 4,4′-azobis(4-cyanopentanoic acid) (V-501)] are the most commonly used ones. Besides, redox and photo initiators or high-energy irradiation are suitable as well.[69,74]

Hence, an initiator molecule is homolytically cleaved to give radical **I**$^{\bullet}$, which can then add to the double bond of vinyl monomers. By continuing the addition of monomer molecules the polymeric radical **P$_n$**$^{\bullet}$ is formed (see Scheme 10).[62]



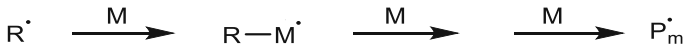
Scheme 10: Initiation step of a radical induced polymerization[62]

In the preequilibrium reaction step, which proceeds via the DT mechanism and is depicted in Scheme 11, the **P$_n$**$^{\bullet}$ radical adds to the sulfur of the C=S double bond in the thiocarbonyl-based RAFT agent **1**, and this leads to the formation of the intermediate radical **2**. Subsequently, this intermediate fragments into the dormant species **3** and the radical **R**$^{\bullet}$.



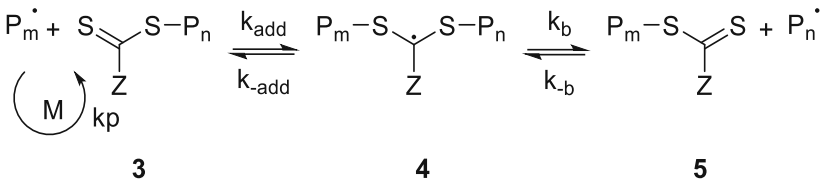
Scheme 11: Reversible chain transfer/propagation in RAFT polymerization [62]

After the fragmentation step reinitiation takes place, as the radical **R**• adds to the double bond of the monomer **M** and a new radical **R-M**• is formed**.** By subsequent addition of further monomer molecules the polymer racial $\mathbf{P_m}^{\bullet}$ is formed (Scheme 12).[62]



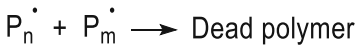
Scheme 12: Reinitiation step of a RAFT [62]

Subsequently, the radical $\mathbf{P_m}^{\cdot}$, formed in the reinitiation step, is able to react with the dormant species **3** to form again an intermediate radical **4**. As outlined in Scheme 13, the following fragmentation leads to a dormant species **5** and a newly released radical $\mathbf{P_n}^{\cdot}$, which is then once again able to propagate by adding further monomer units. This step of the RAFT process allows establishing the equilibrium between the propagating radicals ($\mathbf{P_n}^{\cdot}$ and $\mathbf{P_m}^{\cdot}$) and therefore the chance for all polymer chains to grow in the same extent is given. [62]



Scheme 13: Chain equilibration/propagation of a RAFT process [62]

In the same way as in a free radical polymerization process, it is possible that termination reactions occur during RAFT polymerizations by the reaction between two polymer radicals $\mathbf{P_n}^{\bullet}$ and $\mathbf{P_m}^{\bullet}$ and therefore the formation of dead polymer chains takes place (Scheme 14). Since the concentration of radicals is kept low during the whole polymerization by using only small amounts of initiator, this side reaction is very unlikely to happen and so the amount of unreactive chains is kept below 5%.[59]



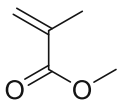
Scheme 14: Termination reaction in a RAFT polymerization [62]

3.2 About monomer reactivity - the MAM and LAM concept

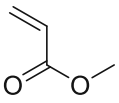
Depending on their substituents, vinyl monomers polymerizable by means of RAFT polymerization can be divided into two classes: “More Activated Monomers” (MAMs) and “Less Activated Monomers” (LAMs).

MAMs represent monomers where the double bond is either next to a carbonyl group, as for (meth) acrylates or acrylamides, or next to a nitrile group, as in the case of acrylonitrile. Also monomers containing aromatic rings attached to the double bond like styrenes or vinylpyridine, belong to this type of monomers.[75] In general, this type of monomer possesses highly reactive double bonds, but the resulting propagating radical shows lower reactivity towards the addition of further monomer units due to resonance stabilization of the radicals. This and some MAMs are depicted in Figure 7.

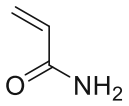
Resonance stabilization of acrylates



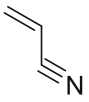
Methyl methacrylate



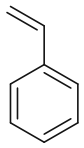
Methyl acrylate



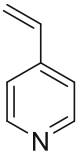
Acrylamide



Acrylonitril



Styrene



4-vinylpyridine

Figure 7: Chemical structures of monomers belonging to the group of MAMs

LAMs are monomers where the reactive double bond is the direct neighbor of a heteroatom (nitrogen, oxygen), which can also be part of a heteroaromatic ring system. Examples for such monomers are vinyl esters (e.g. vinyl acetate), N-vinylpyrrolidone or N-vinylcarbazole. Furthermore, monomers bearing a saturated carbon next to the double bond (e.g. diallyldimethylammonium chloride) belong to this class. Figure 8 illustrates the chemical structure of some LAMs. The reactivity of such molecules is oppositional to that of MAMs. Here, the monomers are rather unreactive, but the formed radicals show high reactivity towards addition reactions due to lack of resonance stabilization. [75]

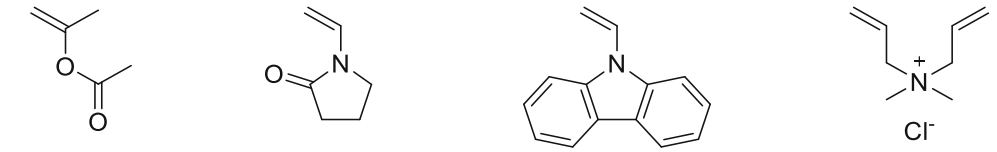


Figure 8: Chemical structures of monomers belonging to the group of LAMs

Thus, the varying reactivity of MAMs and LAMs has to be considered in the design and choice of an appropriate RAFT agent in order to obtain polymers with narrow molecular weight distributions.

3.3 RAFT Agent

The performance of controlled radical polymerizations always requires a specific molecule to control the reaction, and the molecular weight distribution, respectively. In the case of RAFT polymerization, the controlling part is called RAFT agent or chain transfer agent (CTA). The used CTAs are always thiocarbonyl compounds, which show the general structure RSC(=S)Z, including a reactive double bond, as well as a weak single bond (Figure 9).[54]

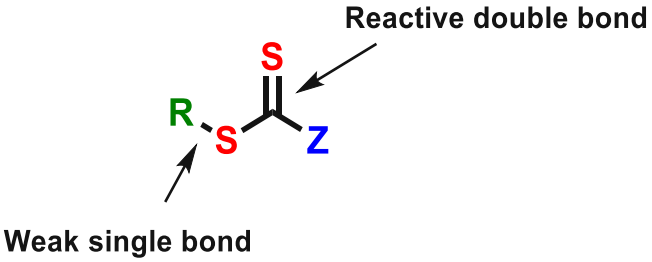


Figure 9: General structure of a RAFT agent (drawn according to Moad *et al.*[76])

Furthermore, the R and the Z-group can be varied in order to make the RAFT agent suitable for a specific monomer type (e.g. acrylates, acrylamides…) according to the MAM and LAM concept of more activated and less activated monomers.[75] Depending on the Z group, CTAs can be assigned to one of four general molecule structures (**Figure 10**).

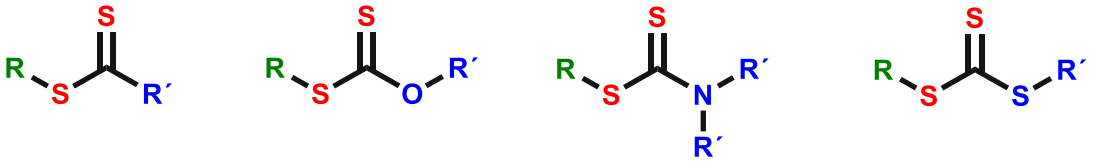


Figure 10: Possible structures of chain transfer agents (adapted from Smith et. al[54])

3.3.1 Role of the Z-group

The Z-group of the RAFT agent is responsible for the addition rate of the growing polymeric radicals $\mathbf{P_n}^{\cdot}$ / $\mathbf{P_m}^{\cdot}$ towards the C=S double bond of the CTA **1** or **3** (see Scheme 11). Furthermore, it defines the fragmentation rate of the intermediary formed radicals **2** and **4** into the dormant species **3** and **5** (see Scheme 13).

Dithioesters with a carbon next to the C=S double bond and trithiocarbonates with a sulfur atom as direct neighbor to the C=S bond show the highest reactivity for radical addition and are therefore more useful for stabilized radicals (e.g. (meth) acrylates). If xanthates or dithiocarbamates are used as CTAs, the activity of radical addition is significantly reduced. Therefore, they are suitable for less stabilized radicals (e.g. vinyl esters), what was proven by orbital calculations.[77] Considering the canonical forms of these types of molecules there is a possible negative polarization of the sulfur atom in the thiocarbonyl bond, as illustrated in **Figure 11**.

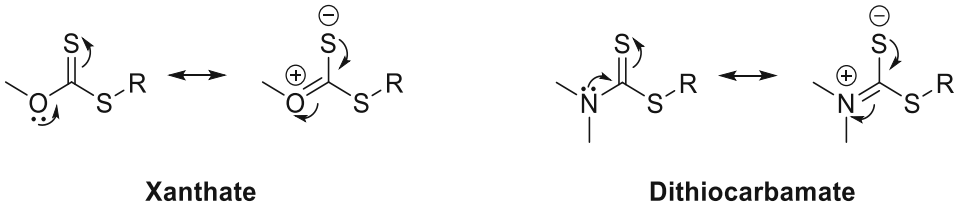


Figure 11: Canonical forms of xanthates and dithiocarbamates (according to Keddie et *al.*[75])

Since the lone pair of either the oxygen or the nitrogen atom is capable of interacting with the C=S double bond, the double bond character decreases, and therefore the CTA gets more stabilized in comparison to the intermediate radicals **2** or **4**. However, this effect does not occur if the nitrogen of the dithiocarbamate is included into an aromatic ring or if a carbonyl group is next to the nitrogen atom. Then a similar reactivity as for dithioesters or trithiocarbonates is achieved. The diverse reactivity in the dependence on the Z-group has to be considered when the type of monomer is chosen. MAMs require a highly reactive RAFT agent in order to give polymers with a narrow molecular weight distribution, since this ensures fast fragmentation and therefore retardation is improbable. LAMs on the other hand need less reactive CTAs, elsewise retardation or inhibition occurs.[75]

Figure 12 provides an overview of possible Z-groups for CTAs and their suitability for the different types of monomers. In general, the rate of addition decreases from left to right, whereas the rate of fragmentation increases in the same direction.[62]

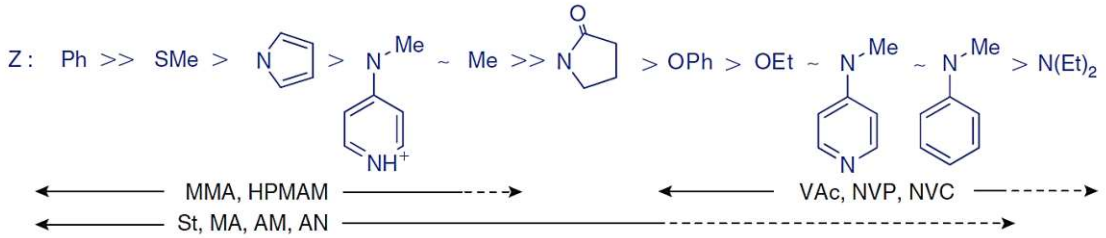


Figure 12: Suitability of various Z-groups for the RAFT polymerization of different types of monomers (methyl methacrylate (MMA), N-(2-hydroxypropyl) methacrylamide (HPMAM), vinyl acetat (VAc), N-vinylpyrrolidone (NVP), N-vinylcarbazole (NVC), styrene (St), methyl acrylate (MA), acrylamide (AM), acrylonitrile (AN))[62]

3.3.2 Role of the R-group

Compared to the polymeric radical $\mathbf{P_n}^{\cdot}$, the R-group has to show high capability of acting as a homolytic leaving group. Thus, the intermediate radical **2** (see Scheme 11) favors the fragmentation towards the dormant species **3** and the newly formed radical $\mathbf{R}^{\cdot}$. In succession, this radical must be capable to reinitiate the polymerization; elsewise retardation of the polymerization is likely to occur.[75] Figure 13 depicts various R-groups and their suitability for different types of monomer, whereat a decrease in fragmentation rates arises from left to right.[62]

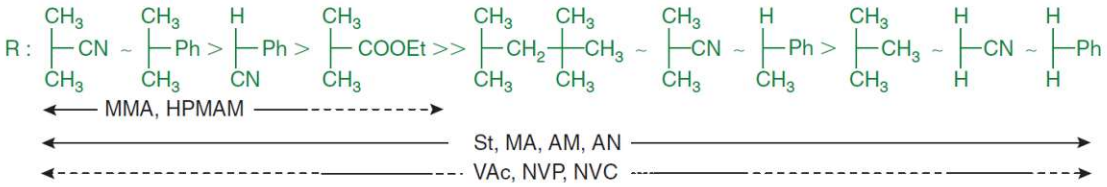


Figure 13: Suitability of various R-groups for the RAFT polymerization of different types of monomers (methyl methacrylate (MMA), N-(2-hydroxypropyl) methacrylamide (HPMAM), vinyl acetat (VAc), N-vinylpyrrolidone (NVP), N-vinylcarbazole (NVC), styrene (St), methyl acrylate (MA), acrylamide (AM), acrylonitrile (AN))[62]

3.4 Induction and Rate Retardation in RAFT polymerization

In some cases, an induction/inhibition period can be observed at the beginning of the RAFT polymerization. In this phase no polymerization occurs. The period of induction can vary from only minutes up to hours. This time can be determined from the plot of the logarithmic monomer concentration, $\ln([M]_0/[M])$, over time. Therefore, the straight line through the linear region of this graph is crossed with the x-axis, and the intersection point represents the induction time.[78] **Figure 14** depicts this for the polymerization of methyl acrylate using different concentrations of cumyl dithiobenzoate (CDB) as CTA.

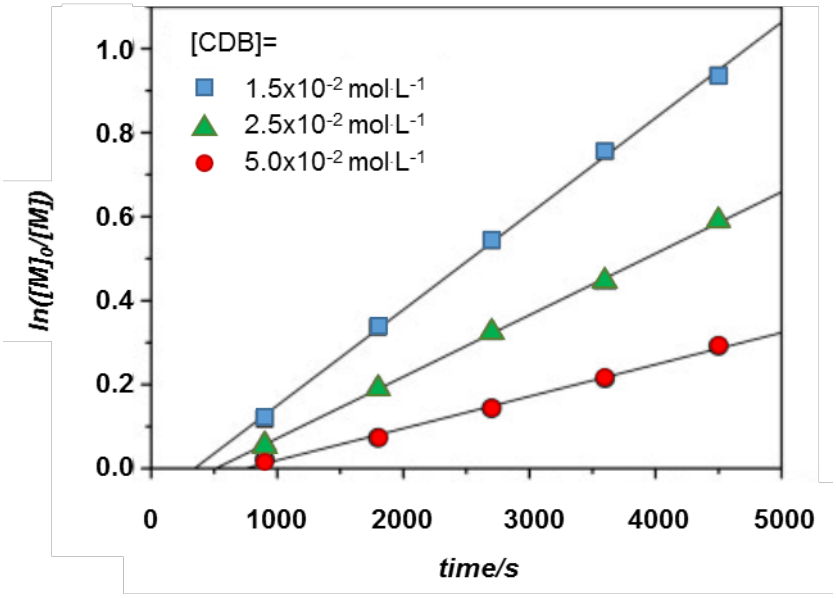


Figure 14: Induction and retardation in the polymerization of methyl acrylate using different concentrations of CDB (cumyl dithiobenzoate) as CTA (plot adapted from literature[79])

Rate retardation is another phenomenon, which is observed in RAFT processes and leads to a decrease in the polymerization speed or almost complete inhibition of the polymerization (see **Figure 14**). Although this effect may arise in any RAFT polymerization, it is most likely if dithiobenzoates are used as CTAs, since the aromatic Z-group stabilizes the intermediate radicals.[79,80]

In general, there are some factors that have to be considered in order to prevent retardation and/or inhibition within the RAFT polymerization process. First, the R-group of the CTA has to be chosen carefully (see 3.3.2), since retardation and inhibition occurs if reinitiation is not sufficiently fast. Besides, the R-group has to show good homolytic leaving behavior to limit or eliminate the induction period. Moreover, the choice of initiator plays a role. The radicals generated from the initiator molecule have to be better leaving groups than the propagating radicals in order to circumvent retardation or the formation of quite stable and unwanted byproducts of the CTA. In addition, reaction solutions should be degassed first and RAFT polymerizations should then be performed under inert gas atmosphere. While some RAFT polymerizations also work in the presence of air/oxygen, in most cases the presence of oxygen may result in rate retardation and/or an induction period, or even in damage of the RAFT agent.[79,80]

3.5 Modification and Removal of the RAFT end group

Due to the fact, that in a RAFT process the polymer is formed between the sulfur atom and the R-group, the thiocarbonylthio group of the RAFT reagent is still attached to the synthesized polymer after the polymerization is completed. Sometimes it might be of interest to remove or modify this group. Since the thiocarbonylthio group acts as a chromophore, the polymers are often colored. Depending on the used CTA this can range from violet to yellow [81]. Gradual decomposition of the polymers can cause bad smell due to the sulfur, which might be bothersome in some cases [82]. Furthermore, the sulfur containing group affects fluorescence, [83-85] which can become a problem in the usage of the polymers in photoactive applications[86]. When it comes to application in the biomedical field cytotoxicity has to be taken into account as well, although some literature indicates that thiocarbonyl endfunctionalized polymers show no cytotoxicity at all or only on a little scale.[87,88]

The chemistry of small molecules has taught us how such thiocarbonylthio groups react, and it was proven that most of the mechanisms are also applicable to polymers.[89,90] So in general, a broad variety of reactions can be used for the elimination of the RAFT end group[91]. Figure 15 provides an overview of these possibilities.

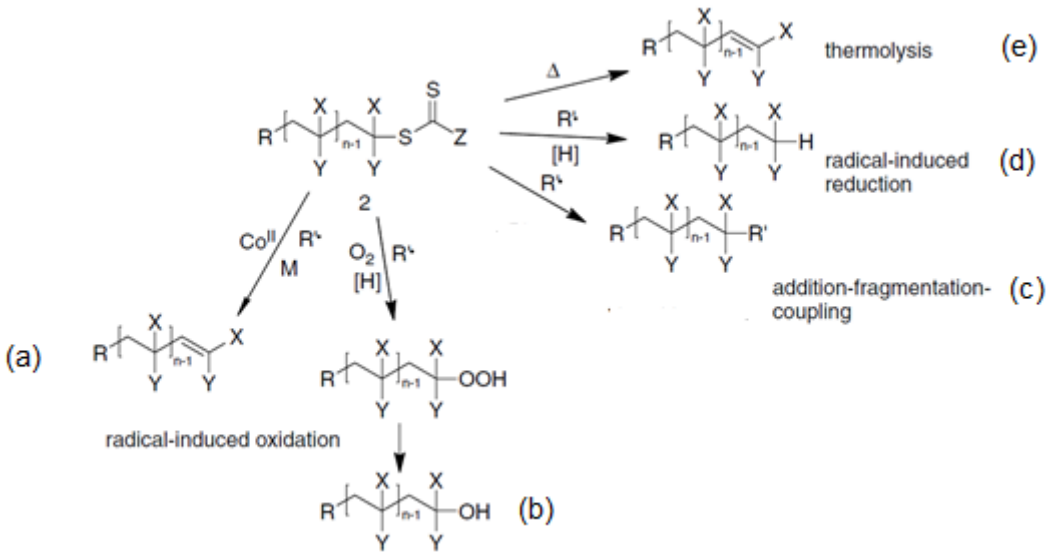


Figure 15: Overview of RAFT end group modification/removal[91]

(a) According to Soeriyadi *et al.*[92] the end group can be removed by adding cobalt (II) complexes to the reaction mixture to induce a catalytic chain transfer. [92] This leads to the formation of a double bond, giving the possibility to use the product as a macro monomer.

(b) Oxidation with agents like ozone, air or hydrogen peroxide can be performed, whereat thiolocarbonates,[93] hydroperoxy groups,[94] hydroxyl groups[95] or sulfines[96] are generated.

(c) Radical induced thiocarbonylthio elimination is possible by heating the polymer with a large amount of a radical initiator, like azobisisobutyronitrile (AIBN),[81,97] lauroyl peroxide (LPO) [81,82] or dibenzoyl peroxide (BPO)[82,98] to cause addition-fragmentation-coupling.

(d) Literature describes radical induced reduction as option to get rid of the sulfur containing end group by substitution with a hydrogen atom.[82]

(e) Thermolysis can be used to introduce a double bond at the end of the polymer chain if the RAFT agent is a dithioester[99] or a trithiocarbonate,[100] and a thiol group when xanthates[100] are used, respectively.

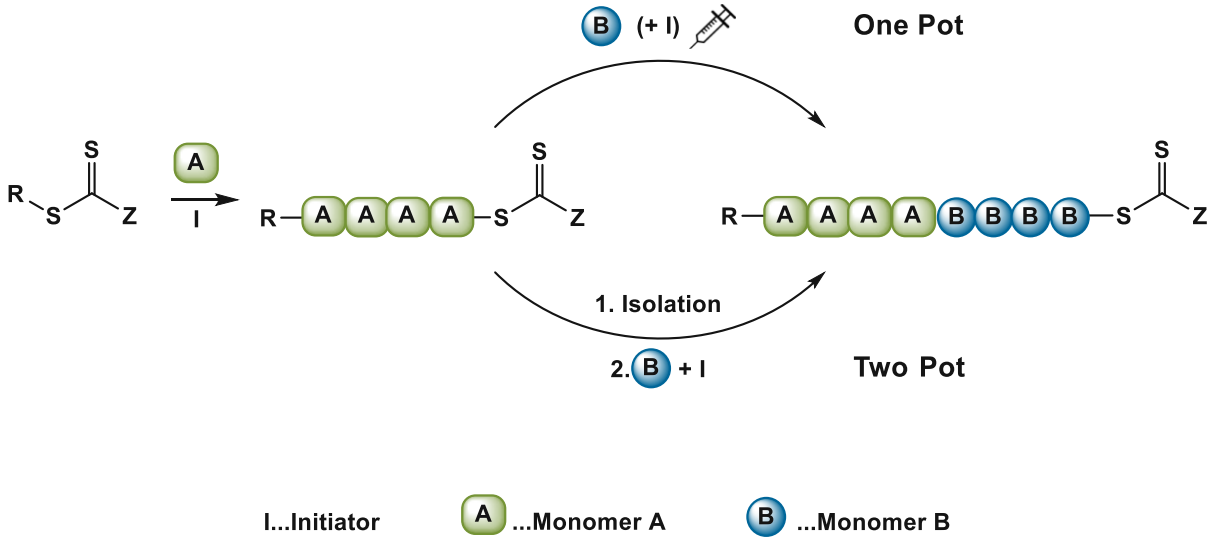
Additionally, there are possibilities to substitute the RAFT group in order to allow the preparation of block copolymers by using a second polymerization technique. These options will be described in the following chapter.

4 Synthesis of block copolymers involving RAFT polymerization

The synthesis of block copolymers involving RAFT polymerization can be done in different ways. On the one hand, all blocks can be generated via this technique, and on the other hand also a combination with other techniques is possible. In the following, different synthetic pathways applicable for the preparation of such polymers with a narrow molecular weight distribution and a uniform composition are described.

(a) Sequential monomer addition

One possibility for the synthesis of AB block copolymers is the sequential monomer addition process. Thereby, the first block is prepared from monomer A, and the active end group is then further used to generate the second block from monomer B.



There are two possibilities for the sequential synthesis of block copolymers via RAFT polymerization. The first option is a one pot synthesis, whereat the controlled polymerization of monomer A with a RAFT agent is started by an initiator **I**. Once the preparation of the first bock is completed, the second monomer B, and ,if necessary, again a small amount of initiator are directly added to this reaction mixture. The polymerization is stopped when the formation of the block copolymer is finished. Via this method not only diblock polymers, but also multi block (co)polymers can be prepared as reported by Gody *et al.*[101] They used (propanoic acid)yl butyl trithiocarbonate as CTA for the preparation of multiple blocks combining different monomers, namely N-isopropylacrylamide, N-hydroxyethylacrylamide, N-acryloylmorpholine and N,N-diethylacrylamide. Guimaraes *et al.*[102] also prepared multiblock copolymers in a one-pot reaction via RAFT polymerization from styrene and butyl acrylate with 2-(dodecylthiocarbonothioylthio)propionic acid as RAFT agent. Very recently, Carvente et

al.[103] published the multi block synthesis via RAFT polymerization from acrylamide, lauryl acrylate and N,N′-methylenebis (acrylamide) with S,1-dodecyl-S′-(α,α'-dimethyl-α"-acetic acid) trithiocarbonate as CTA.

However, some requirements have to be fulfilled to allow the preparation of block copolymers via this route. Besides the suitability of the active site for the second monomer, termination and transfer have to be marginal. In order to avoid irregularities in the composition of the propagating polymer, the crossover has to happen fast and in a quantitative way, whereby the order of added monomers has to be considered. Thus, the propagating radical of the monomer for the first block has to be a better or at least a similar leaving group as the propagating radical of the second monomer. So, for example, if a meth acrylate is used for the preparation of any of these blocks, it is necessary to start with this monomer.[104,105] Figure 16 provides an overview of the compatibility of different macro R-groups for various types of monomers for the preparation of block copolymers. Partial polymerization control is indicated by a dashed line.[106]

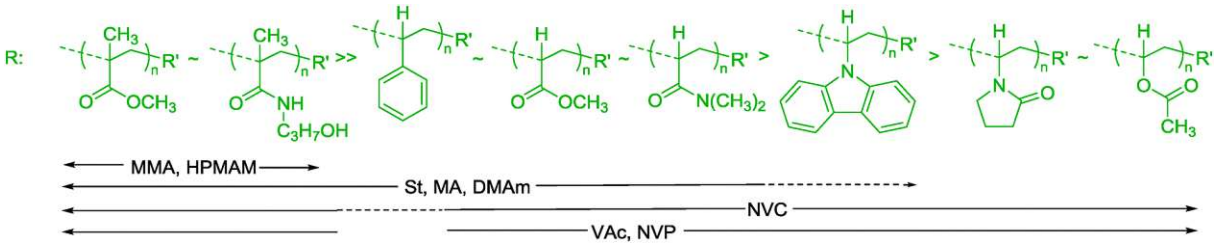


Figure 16: Overview of the suitability of macro R-groups of the RAFT agent for the preparation of block copolymers from various types of monomers (methyl methacrylate (MMA), N-(2-hydroxypropyl) methacrylamide (HPMAM), styrene (St), methyl acrylate (MA), N,N-dimethylacrylamide (DMAm), N-vinylcarbazole (NVC), vinyl acetate (VAc), N-vinylpyrrolidone (NVP))[106]

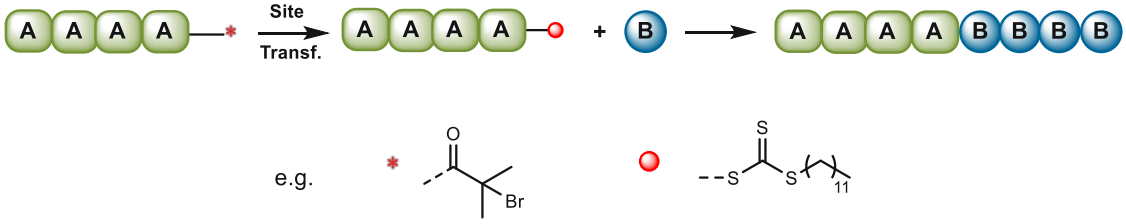
If the one pot pathway is not possible, the synthesis of block copolymers can be performed in a two-pot approach. For this purpose, the homopolymerization of monomer Ⓐ by using an initiator **I** and a RAFT agent is performed in the same way as in the one pot path. However, after the reaction is completed, the polymer is isolated (e.g. by precipitation) to give the so called macro RAFT agent, which can then be used for synthesis of the second block from monomer Ⓑ. It is also possible to prepare well defined block copolymers consisting of more than two blocks via this method.[107] Block copolymers from various types of monomers including (meth)acrylates, (meth)acryl amides, styrenics and vinyl monomers in combination with different RAFT agents are already known. [62,106] Subsequently, some of the recent examples from literature are summarized.

Pang et al. [108] prepared diblock and triblock copolymers comprising of styrene and methyl acrylate using 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid as CTA. They propose usage in direct self-assembly lithography as possible application. Block copolymers from

sucrose methacrylate and methyl methacrylate are reported by Marcilli *et al.*[109] applying *S*,*S'*-bis(*R*, *R'*-dimethyl-*R''*-acetic acid)-trithiocarbonate as the chain transfer agent. The obtained material shows potential for drug encapsulation or environmental remediation systems. pH- and thermoresponsive block copolymers from N-isopropyl acrylamide and 2-(dimethylamino)ethyl acrylate were synthesized by Giaouzi *et al.*[110] A similar polymer with potential application in biomedicine is poly(di-[ethylene glycol] methyl ether methacrylate)-b-poly(2-[diisopropylamino] ethyl methacrylate), which was prepared using 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl)] pentanoic acid as CTA. [111]

(b) Conversion of active site

Similar to the already described method **(a)**, option **(b)** also proceeds in sequential manner, and is employed, if the chosen monomers are not polymerizable by using the same active species.



After the synthesis of the first block from monomer A a transformation reaction is necessary in order to change the active site * into a suitable one o for the formation of the second block from monomer B . Since reaction conditions like temperature or solvent are usually different for each polymerization technique, the process is carried out in a two pot synthesis. Here RAFT can either be used for preparation of the first or the second block.

ATRP represents one option to be used together with RAFT polymerization. This allows the usually challenging preparation of block copolymers from MAMs and LAMs. The first block is generated by means of ATRP followed by a transformation reaction to obtain a macro-RAFT agent to synthesize a second block. To be precise, the bromine group is substituted by a xanthate group leading to the desired macroCTA. Petruczok *et al.*[112] combined tert-butyl acrylate and vinyl acetate and Hussain *et al.* [113] as well as Pavlovic *et al.* [114] used styrene and N-vinylpyrrolidone.

Chen et al.[115] prepared tetrablock copolymers via ATRP and RAFT polymerization, following another route. They synthesized a diblock from poly ethylene glycol and polystyrene followed

by a click chemistry site transformation to obtain a macroCTA for the subsequent generation of two additional blocks from N-isopropylacrylamide and 2-(dimethylamino)ethyl methacrylate by means of RAFT polymerization.

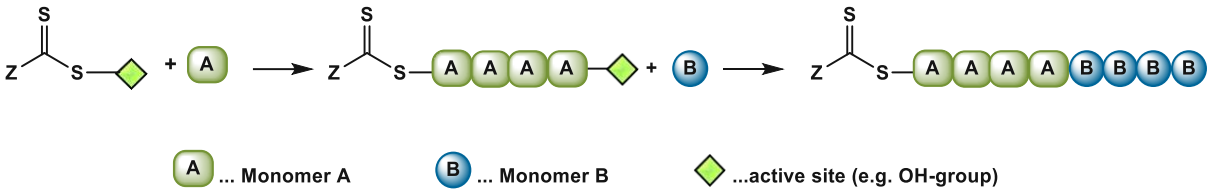
RAFT polymerization can also be combined with ionic polymerization techniques. Polyisobutylen was prepared by cationic living polymerization and the resulting polymer was further reacted with 4-cyano-4-(dodecylsulfanylthiocarbonylsulfanyl)pentanoic acid by transesterification to give a macro RAFT agent. This was then applied for the preparation of a second block from either methyl methacrylate or styrene,[116] oligo(ethylene glycol) methyl ether methacrylate[117] or amino acids.[118] Kumagai *et al.* [119] applied RAFT polymerization for the synthesis of the first block from methyl acrylate using S-1-isobutoxyethyl S′-ethyl trithiocarbonate as CTA. An in-situ transformation using tin tetrachloride allowed the subsequent preparation of an additional block from isobutyl vinyl ether via cationic polymerization. Zhang *et al.*[120] described a similar approach involving anionic polymerization of isoprene for the preparation of the first block. The active site of this polymer was then reacted with carbon disulfide and phenyl bromide to give a macro RAFT agent, which then served as controlling agent for the polymerization of styrene, N-isoproypylacrylamide or 2-hydroxyethyl acrylate.

Also, NMP can be combined with RAFT polymerization after exchange of the thiocarbonylthio group with a nitroxide, or *vice versa*. This process is called ESARA (Exchange of Substituents between (Macro) Alkoxyamines and (Macro)RAFT Agents) and was established by Favier *et al*.[121]

Schmid *et al*.[122] reported RAFT polymerization followed by ring opening polymerization (ROP). Polystyrene was prepared and then the RAFT end group was removed leading to a hydroxyl end group, which served subsequently as initiator for the ROP of ε-caprolactone. Additionally, the hydroxyl end group of polymers prepared by ROP can be either transformed to a RAFT agent via transesterification [123-125] [126] or converted to halogen end groups followed by reaction with a xanthogenate group.[127,128] Via this routes, various monomers have been polymerized including styrene, hydroxyethylmethacrylate, fluorinated monomers, N-isopropylacrylamide, N,N-dimethylaminoethyl methacrylate, N-vinylpyrrolidone, as well as lactic acid and ε-caprolactone.

(c) Dual initiator

The preparation of block copolymers is feasible by applying a dual initiator  , which allows the polymerization of different monomers by means of diverse polymerization techniques.



Here the active species remains at the end of each propagating polymer chain. It has to be ensured that they are compatible and do not interfere with each other. RAFT polymerization can be used for either preparation of the first or the following blocks. In some cases also simultaneous polymerization via two different mechanism is possible. Reviews by Pearson *et al.*[129] and Guo *et al.*[130] report various options involving RAFT polymerization and either ROP, ATRP or NMP.

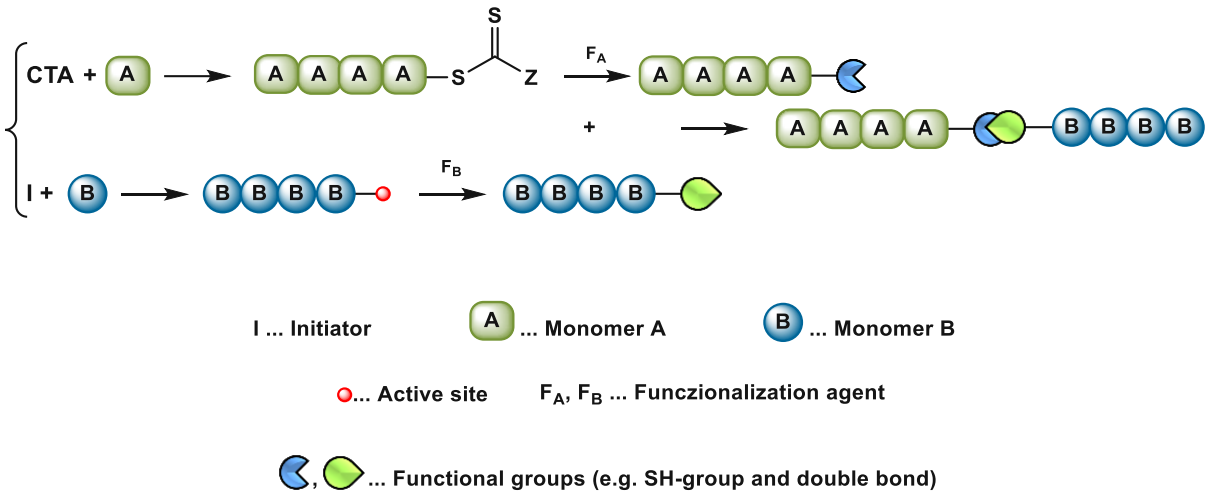
By far the most reported approach for this possibility is the combination of RAFT polymerization with ROP. In general, these molecules bear a hydroxyl group allowing starting ROP. The RAFT group can be based on dithioesters,[131-133] trithiocarbonates[133-140] and on xanthogenates.[140-146] Cyclic monomers for the ROP step include lactic acid, ε-caprolactone, 2-methyl-2-oxazoline or δ-valerolactone. Via this approach various monomers have been polymerized by means of RAFT polymerization. Examples are N-isopropylacrylamide, 2-ethylhexyl acrylate, methyl acrylate, N-vinylpyrrolidone, N-(2-hydroxypropyl) methacrylamide, vinyl acetate and vinyl chloroacetate.

Combination of RDRP techniques allows the preparation of block copolymers consisting not only, but also of MAMs and LAMs. Not much literature can be found on this topic, but dual initiators for RAFT polymerization and ATRP have been reported for agents based on xanthates[147-149] and trithiocarbonates.[150] The prepared polymers consist of combinations of methyl methacrylate, methyl acrylate styrene, vinyl acetate, N-vinyl carbazole and N-vinyl pyrrolidone.

Dual initiators allowing RAFT polymerization and NMP based on dithioester[151] and trithiocarbonate[152-154] have been reported by Thomas *et al*. Applying these initiator molecules, they polymerized various monomers including styrene, N-isoproyl acrylamide, acrylic acid, tert-butyl acrylate and p-styrenesulfonic acid sodium salt.

(d) Coupling reactions

The fourth pathway **(d)** is based on the coupling of two homopolymers each equipped with highly reactive ω-functionalities .



Therefore, it is necessary to remove the RAFT end group and transform it into a suitable functionality. This can be achieved be reacting the RAFT end group with nucleophiles such as thiols[155], hydroxides and amines[156,157] or with ionic reducing agents like boron hydrides[158,159] in order to generate a thiol end group. The obtained SH-group can then be further modified in many ways[91] (e.g. using click chemistry by thiol-ene addition to double bonds) to prepare block copolymers. Another possibility is to generate a vinyl bond at the end of the RAFT polymer and react it with a polymer bearing a Si-H end group.[160] If the Z-group of the RAFT polymer shows electron-withdrawing behavior, it is possible to perform a hetero Diels Alder reaction, enabling the subsequent preparation of block or star copolymers.[161-163]

5 Self-organizing structures generated from amphiphilic block copolymers

In general, self-organizing structures based on amphiphilic block copolymers can be used in the production of various nano- and microstructures, which find applications in different fields (e.g. material science, pharmacy…).[164]

The formation of such self-assembled structures requires the existence of a short-range force of attraction, as well as, a long-ranged repulsion. Parts **A** and **B** repulse each other, but because of the short-range interaction, it is not possible for them to separate. Hence, the most convenient way for them is to arrange in a way that the number of **A**/**B** contacts is at its minimum. Figure 17 depicts this schematically.[164,165]

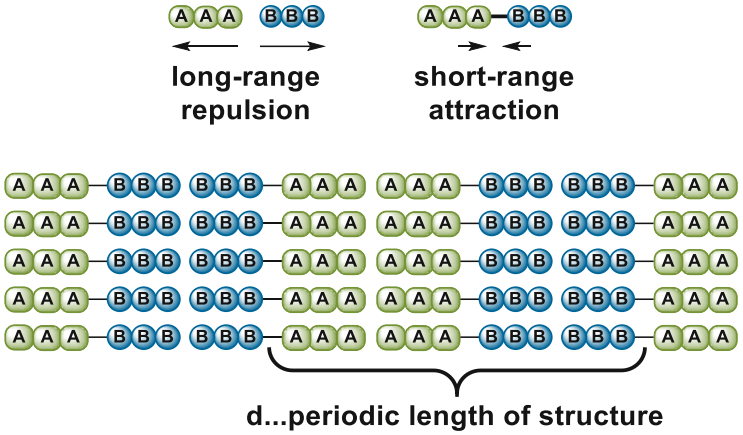


Figure 17: Long-range repulsion and short-range attraction leading to self-organization[164]

Due to the existence of these interactions, an interface between phases **A** and **B** is formed, as illustrated in Figure 18. Its shape represents the shape of the molecule, so that curved interfaces with a radius **R** are obtained if one part is smaller than the other one.

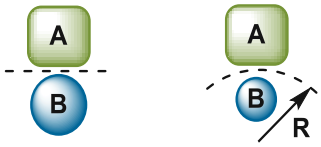


Figure 18: Interfacial curvature[164]

In block copolymers, these forces are represented by covalent bonds (short-range) and incompatibility due to hydrophobic and hydrophilic properties (long-range). If the soluble block in BCPs is large compared to the insoluble one, small curvature radii and therefore micelles shaped like a sphere are formed in solution. If the soluble part gets smaller, the shape of the self-organized structure changes towards a cylindrical micelle or a vesicle.[165]

Assemblies based on amphiphilic block copolymers, which consist of hydrophilic and hydrophobic parts and show the ability to form supramolecular aggregates in aqueous surrounding show a high potential as drug carrier systems. In recent years, big effort was put into the development of polymeric drug delivery systems in order to generate systems, which improve the activity as well as the specificity of active components, and decrease their toxicity by allowing targeted transport to diseased cells or organs at the same time.[166] Besides other possibilities,[167] RAFT polymerization is known to be a powerful tool for the preparation of such polymers.[168-171] In literature, examples for such drug carrier systems can e.g. be found for potential delivery systems of cancer therapeutics like paclitaxel or doxorubicin. Used building blocks are, for example, glycomonomers and amino acids[172], cellulose-based polymers[173], (meth)acrylamides like N-isopropylacrylamide[174] and N-(2-hydroxypropyl) methacrylamide[175].

However, as the concentration of these carriers in surrounding media gets really low when they are injected into the human body and circulate in the blood, it might be necessary to stabilize them in order to prevent unwanted dissociation.[176,177] Stabilization can be achieved by crosslinking of the generated micelles/vesicles either in the outer part (shell crosslinking, SCL[178]) or in the inner one (core crosslinking, CCL[179]). Figure 18 depicts exemplarily the formation and the subsequent SCL of an amphiphilic block copolymer micelle.

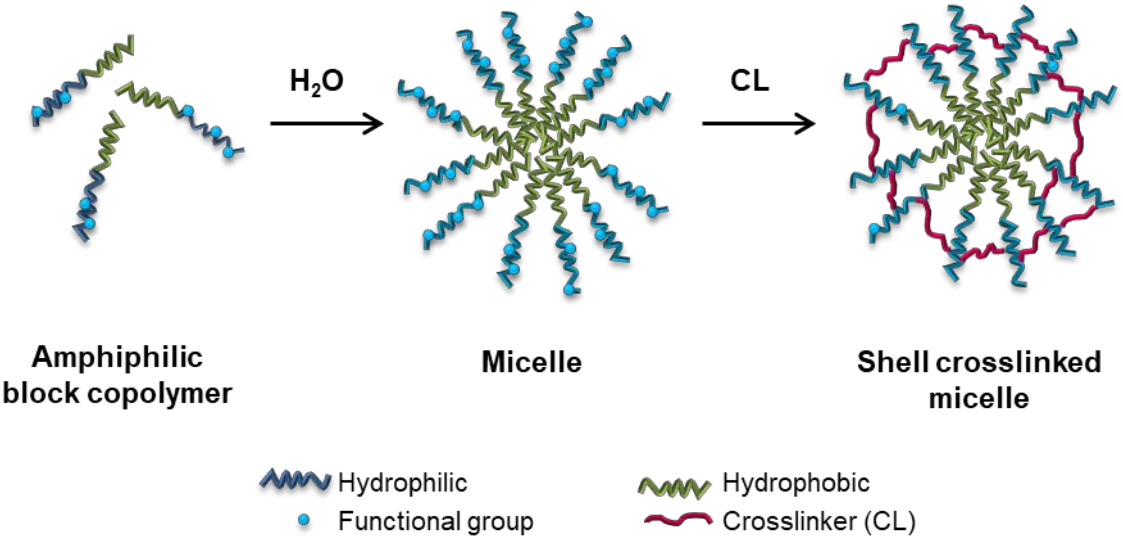


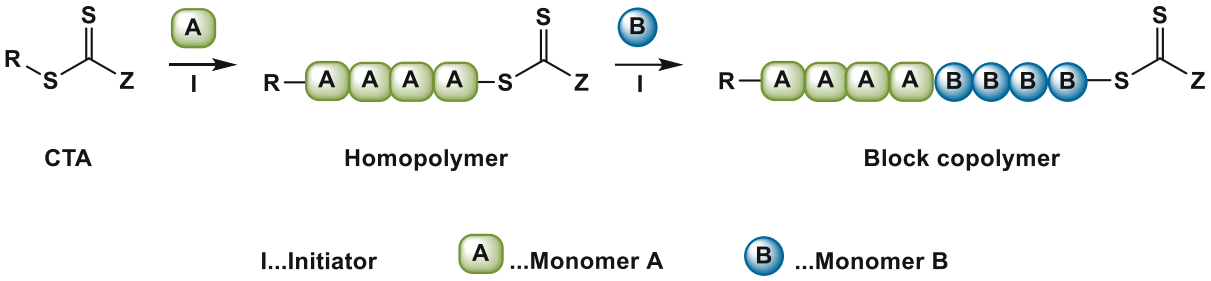
Figure 19: Formation of micelles in aqueous media and shell crosslinking (SCL)

For this purpose, various methods are known from literature, of which numerous are suitable for SCL as well as for CCL. However, it is necessary to perform SCL at very low polymer concentrations in order to avoid crosslinking of micelles among each other.[180]

Bifunctional reagents represent one option to achieve crosslinking.[176] Ester groups activated by N-hydroxy succinimide are highly reactive and form amides upon the reaction with amines. To use this option for crosslinking, one of these functionalities has to be incorporated in the polymer and the other one is applied as bifunctional linker.[181-184] Amines can further be used for this purpose, if they are reacted with aldehydes,[185,186] vinyl ketones,[187] imidates,[188] isocyanates[189] or carboxylic acids.[190,191] Hydroxy groups attached to the polymer backbone can be crosslinked either with divinyl sulfone[192] or with molecules containing benzophenone functionalities by application of UV light.[193] Furthermore, tertiary amines can be used together with iodines, like BIEE (bis(2-iodoethoxy)ethane),[194,195] as well as azides together with alkines.[195,196] Other possibilities are crosslinking via free radical polymerization,[197] photo-crosslinking,[198,199] polyelectrolyte complexation,[200] silicon chemistry[201,202] or reducible sulfides.[203]

Objective

Within this work, several strategies towards the synthesis of well-defined homo- and block copolymers should be investigated. RAFT polymerization is chosen as powerful tool to prepare different polymers at defined molecular weight.



Within the first part of this thesis, RAFT polymerization should be applied to investigate preparation of well-defined polymers from hydrophobic lauryl methacrylate (**LMA**) and hydrophilic N-acryloylmorpholine (**NAM**) in solution by conducting kinetic studies under various conditions. In following steps, amphiphilic block copolymers, which possess the ability to form micelles in aqueous media, should be synthesized and further investigated. ^{1}H-NMR spectroscopy should be applied to gather information about monomer conversion and for kinetic studies as well as for the analysis of the synthesized homo- and block copolymers. Additional information regarding the dispersity of the RAFT polymers should be obtained from SEC measurements. Fluorescent spectroscopy should be used to determine the critical micelle concentration of the generated amphiphilic block copolymers. Additionally, thermal stability and toxicity should be investigated.

The second part should deal with the RAFT polymerization of various highly biocompatible vinyl ester monomers, since their polymeric products deliver FDA approved polyvinyl alcohol as degradation product. First, kinetic studies of linear hydrophobic vinyl esters, namely, vinyl acetate (**VAc**), vinyl hexanoate (**VH**), and vinyl decanoate (**VD**), should be performed. Afterwards, the aforementioned vinyl esters as well as vinyl neo-nonanoate (**VN**) and vinyl chloroacetate (**VClAc**) should be investigated in combination with two different RAFT agents. Reactions in bulk as well as in solution should be performed using different amounts of initiator in order to see how monomer conversion and dispersity are affected by these parameters. A dual initiator bearing functionalities allowing RAFT polymerization as well as ring opening polymerization should be tested regarding its compatibility with chosen monomers. Again, ^{1}H-NMR spectroscopy and SEC measurements should be performed to obtain information about monomer conversion, molecular weight and dispersity of the polymers.

General Part A

RAFT polymers based on lauryl methacrylate and N-acryloylmorpholine

Figure 20 gives an overview of the monomers used to prepare hydrophilic and hydrophobic blocks.

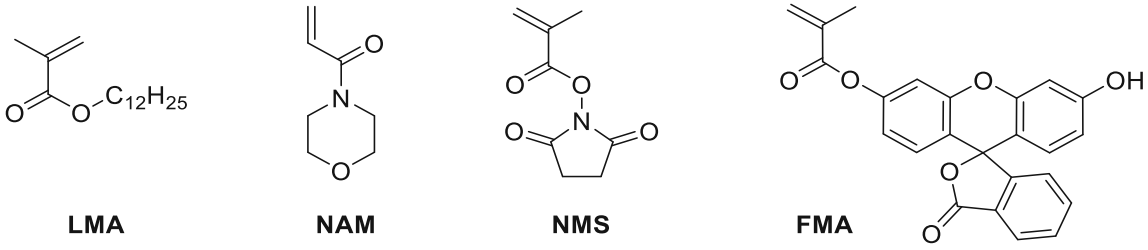


Figure 20: Overview of monomers used for the preparation of homo and (block) copolymers via RAFT polymerization

Lauryl methacrylate (**LMA**), a monofunctional and water insoluble monomer with a low volatility was chosen for the synthesis of the hydrophobic block based on preliminary results.[204] In general, applications of this monomer are polymeric coatings[205,206] or support material for liquid chromatography.[207] Furthermore, it shows good biocompatibility and therefore allows the usage for biomedical applications[208] and cosmetics.[209,210] Due to its long aliphatic chain, it provides the hydrophobicity that is needed to generate micelles in aqueous solution from amphiphilic block copolymers. Hence, Hemmelmann *et al*.[211] already used lauryl methacrylate for polymeric drug delivery systems, which are able to cross the blood-brain barrier.

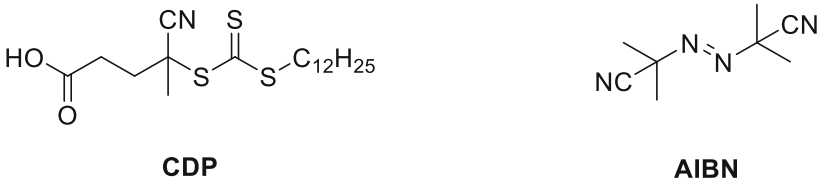
N-acryloylmorpholine (**NAM**), a bisubstituted acrylamide derivative, and its polymers are soluble not only in some organic solvents, but also in water.[107] Therefore, it is of high interest for the preparation of amphiphilic block copolymers. In general, this monomer can be used in a broad variety of applications like in cross-linked networks, which serve as polymeric support material in gel permeation chromatography[212] or in the synthesis of peptides from a gel-phase.[213] Furthermore, **NAM** is biocompatible and thus can be utilized for applications in the fields of biomedicine,[214,215] molecular biology[216] and drug delivery.[217]

Ferruti *et al*.[218] and Batz *et al*.[219] were the first to publish post modification of polymers generated from activated esters via nucleophilic substitution reactions. Since then, this method has become quite popular and is nowadays a frequently used technique.[220]

N-methacryloxysuccinimide (**NMS**) provides one possibility to add activated ester groups to the polymer backbone. However, Favier *et al.*[221] suggest solely copolymerization of this monomer, since the pure polymer can only be dissolved in DMSO or DMF. Furthermore, esters activated by NHS show a low potential toward hydrolysis,[222] and therefore of interest for applications in aqueous surroundings. As amines provide good affinity towards activated ester groups due to their nucleophilic character, this reaction can be performed in the presence of other functional groups like alcohols even when no protecting groups are used[220]. Modification of hydroxyl groups is achievable by NHS if no amino groups are present, but therefore higher temperatures and a catalyst (e.g. N,N-dimethylaminopyridin) are needed.[223] Examples for the usage of such NHS activated esters are crosslinking with diamines[181,183] or the attachment of active compounds (e.g. Methotrexate[224]). Addition of NHS groups to the polymer backbone was of interest for this work for a possible crosslinking of micelles with cystamine.

Fluorescein moieties can be used as marker molecules for imaging reasons.[224-226] These functionalities can be introduced via copolymerization of fluorescein-O-methacrylate (**FMA**). **FMA** was already used as comonomer in RAFT polymerization in order to allow imaging or detecting.[227-231]

Figure 21 depicts the chemical structure of the used RAFT agent and initiator.



CDP **AIBN**

Figure 21: RAFT agent and thermal initiator used within this thesis

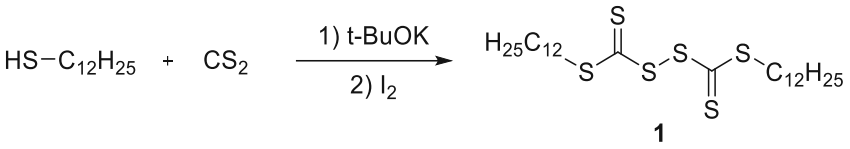
4-Cyano-4-[(dodecylsulfanylthiocarbonyl)-sulfanyl] pentanoic acid (***CDP***), which belongs to the group of trithiocarbonates, was chosen as RAFT agent. In general, this type of RAFT agents facilitate the preparation of polymers with narrow molecular weight distributions from MAMs.[75] ***CDP*** is well known to allow excellent control over the polymerization of methacrylates and at least good control over acrylate or acrylamide polymerization,[232] but was scarcely studied fo **NAM** and **LMA** so far.

Azobisisobutyronitrile (AIBN) belongs to the group of azo-initiators and is a classical thermal initiator for controlled radical polymerization.

A.1 Synthesis of the RAFT agent CDP

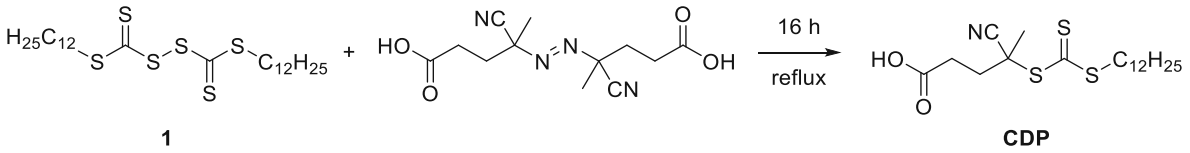
In literature the preparation of ***CDP*** is often described in three steps using sodium hydride.[233] In order to circumvent this hazardous chemical and to shorten the reaction time, the synthesis of ***CDP*** was performed in two steps as described by Farnham.[23]

First, bis(dodecylsulfanylthiocarbonyl)disulfide **1** was synthesized in one step as precursor for the trithiocarbonate based RAFT agent ***CDP***.



Dodecanthiol was left to react with carbon disulfide in the presence of potassium tert-butanolate. The following reduction by the addition of iodine led to the intermediate product **1,** which was received as a yellow-orange solid with a yield of 91%. It was used in the next synthesis step without further purification.

In the second step, the RAFT agent ***CDP*** was obtained via a radical induced process.



The precursor **1** was dissolved in ethyl acetate under inert gas atmosphere and 4,4'-azobis(4-cyanvalerianic acid) (V-501) was added in small portions in order to obtain ***CDP***. The raw product was recrystallized twice. ***CDP*** was obtained as a light-yellow powder (yield 41 %) and was then finally purified by column chromatography.

A.2 Syntheses of hydrophobic polymer blocks

A.2.1 Homopolymerization of lauryl methacrylate

LMA was already used in combination with ***CDP*** for the preparation of self-healing polymers,[234,235] ion-conducting block copolymers[236] and surfactants.[237] Furthermore, amphiphilic and self-assembling polymers were prepared from **LMA** using ***CDP***.[238-240] Prior to discussion of the results of the kinetic study of the homopolymerization of **LMA**, the analytical methods are described.

A.2.1.1 Determination of monomer conversion, molecular weight and dispersity

^{1}H-NMR spectroscopy was used to determine the monomer conversion and to calculate the theoretical molecular weight of the polymers. To allow this, naphthalene was added to the reaction mixture. Samples of 100 µl were withdrawn from the reaction mixture via a syringe before the start of the polymerization (for ^{1}H-NMR spectroscopy) and samples of 200 µL volume (^{1}H-NMR spectroscopy and SEC) were taken after the reaction was finished. If kinetic studies were conducted, samples were taken from the reaction mixture at regular intervals over the entire polymerization time. Those were immediately transferred into precooled vials to stop the polymerization. Afterwards they were stored at -18 °C until they were used for analytical measurements.

Since the monomer concentration was very low, all ^{1}H-NMR spectra were recorded with 256 scans at 200 MHz or with 16 scans at 400 MHz. For the evaluation of the monomer conversion, the decrease of the monomer signals compared to the constant naphthalene signals was used. In the following, this is exemplarily shown based on one RAFT polymerization of **LMA**. In Figure 22 the signals of the internal standard can be seen at about 7.8 ppm and at 7.4 ppm in the ^{1}H-NMR spectra, whereby the left signal was calibrated as 4 protons. The resulting signals from the double bond of the monomer appear at 6.0 ppm and 5.5 ppm. Figure 22 (a) depicts the spectra before the polymerization was started (t=0). It can be seen that the ratio between the signal of the internal standard and the monomer is roughly 1:2.

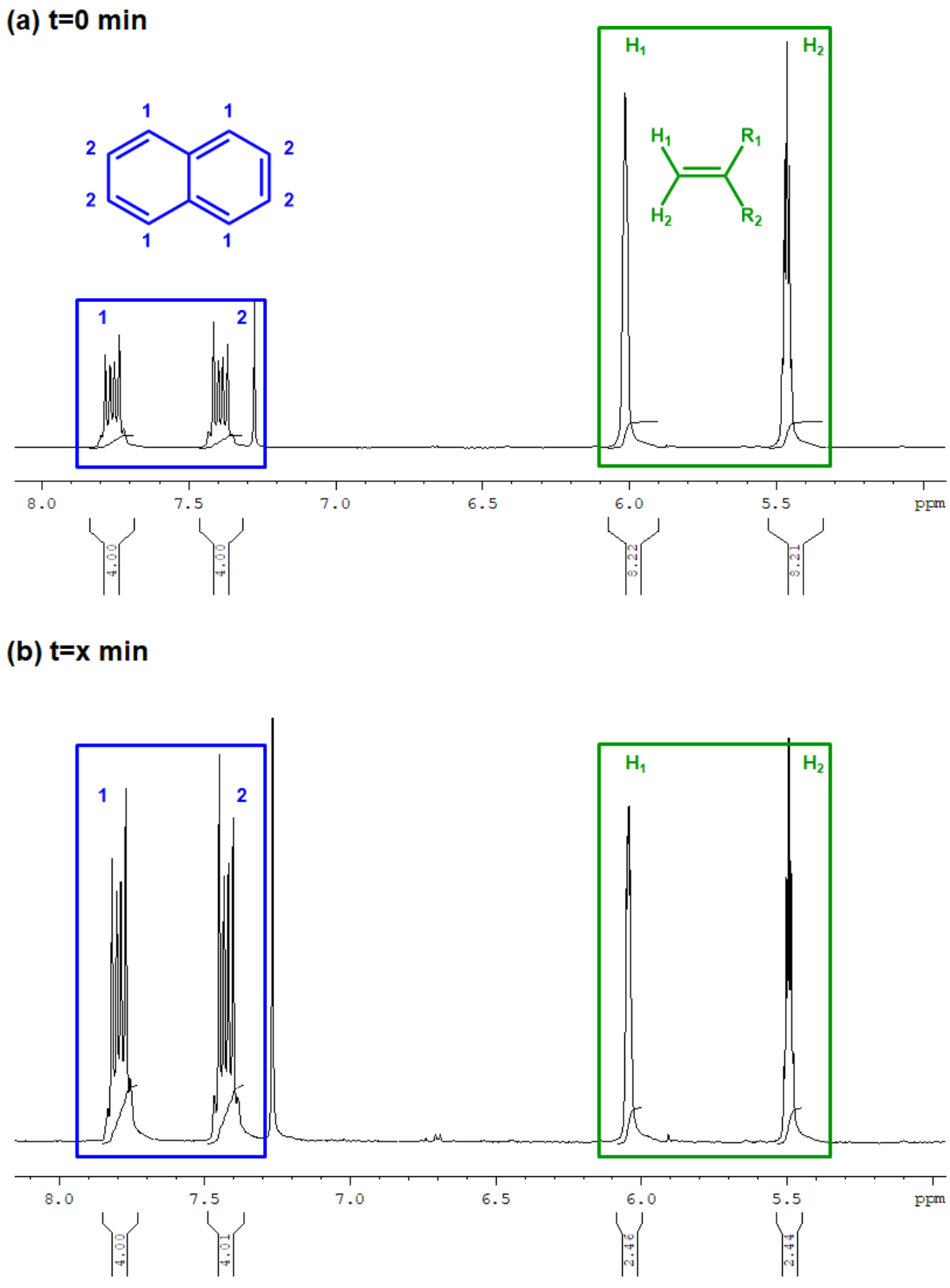


Figure 22: ^{1}H-NMR spectra of the reaction mixture containing LMA before the start of the polymerization (t=0) and after a certain time of polymerization (t=x)

As the conversion of the monomer proceeds within the course of the reaction, the intensities of the double bond signals decrease. In Figure 22 (b) a ^{1}H-NMR spectrum at a later

polymerization time (t=x) is depicted. Again, the naphthalene signal at 7.8 ppm was set to a value of 4. It can clearly be seen that the monomer signals decreased and the ratio between the signals from the standard and those from the monomer has changed to almost 2:1. The conversion of the monomer c_M can be calculated from the ratio between the signal intensities of the double bond (representing the monomer concentrations) by using Equation 6.[241]

$$C_M = 1 - \frac{Int_x}{Int_0}$$ **Equation 6**

C_M	Conversion of LMA at time t=x [ ]
Int_x	Integral of the (meth-)acrylate group at time t=x [ ]
Int_0	Integral of the (meth-)acrylate group at time t=0 [ ]

On the basis of the calculated conversion and the molar amounts of the used starting materials, it is possible to calculate the molecular weight of the polymer $M_{n,NMR}$ at every point in time. For this purpose Equation 7 was used.[242]

$$M_{n,NMR} = \left(\frac{[M]_0}{[CTA]_0} \cdot M_M \cdot C_M\right) + M_{CTA}$$ **Equation 7**

$M_{n,NMR}$	Calculated molecular weight of pLMA at a given conversion [g/mol]
$[M]_0$	Monomer concentration t=0 [mol]
$[CTA]_0$	CTA concentration at t=0 [mol]
M_M	Molecular weight LMA [g/mol]
M_{CTA}	Molecular weight CDP [g/mol]
C_M	Monomer conversion at t=x [ ]

Additionally to ^{1}H-NMR spectroscopy, size exclusion chromatography was used to determine the evolution of the molecular weight $M_{n,SEC}$ as well as the dispersity Đ of the synthesized polymers over time. It has to be noted that the molecular weight detected by SEC can significantly deviate from the molecular weight calculated from monomer conversion. This arises from the fact that the SEC was calibrated by using polystyrene standards and these standards do not show the same behavior as the synthesized polymers.

A.2.1.2 Kinetic study on the RAFT homopolymerization of lauryl methacrylate

Within this work, all RAFT homopolymerizations of **LMA** were performed at 90 °C over a period of 3 hours under inert gas atmosphere including the addition of naphthalene as an internal standard. ***CDP*** was used as RAFT reagent and azobisisobutyronitrile (AIBN) acted as thermal initiator. A molar ratio of 10:1 between the RAFT agent and the initiator was chosen. Preliminary experiments from S. Benedikt[204] suggested that the monomer conversion is limited to approximately 70 % under the selected reaction conditions. Presumably, this is caused by a decrease of polymer solubility in dioxane with increasing molecular weight leading to a compressed structure (e.g. coil) and therefore reduced accessibility. Therefore, the limited conversion was considered for the calculation of the starting monomer amount, in order to reach the desired molecular weight of the polymers. The monomer concentration was adjusted to 1.5 mol/L in dry dioxane for each polymerization.

The kinetic study for the preparation of poly lauryl methacrylate (**pL**) was conducted for a polymer with a target molecular weight of 14.3 kDa. Considering the limited monomer conversion of ~70 %, the expected molecular weight was 10 kDa. The starting materials (initiator, RAFT agent/macro RAFT agent, monomer and internal standard) were weighted into a penicillin flask. After the addition of dry solvent and sealing of the tubes with a rubber septum, the reaction mixture was purged with inert gas for at least 30 minutes in order to remove oxygen from the reaction solution. Then, the tubes were placed into a preheated aluminum block and left there for a predetermined period of time. The polymerizations were stopped by cooling down the tubes in an ice bath and the resulting polymers were precipitated in cold methanol. In order to perform the necessary analyses, samples were taken from the reaction mixture at regular intervals.

Table 1 shows the results from ^{1}H-NMR spectroscopy and SEC measurements.

Table 1: Results of the kinetic study of the RAFT homopolymerization of LMA using CDP as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa in dry dioxane ([M]=1.5 mol/L)

	pL			
Time [min]	**C_M [%]**	**$M_{n,\,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**
10	4	0.9	3.2	1.24
20	14	2.3	4.4	1.23
30	24	3.8	5.5	1.21
60	47	7.0	8.4	1.17
120	66	9.6	10.4	1.16
180	70	10.2	10.7	1.16

Figure 23 shows the monomer conversion in the course reaction time.

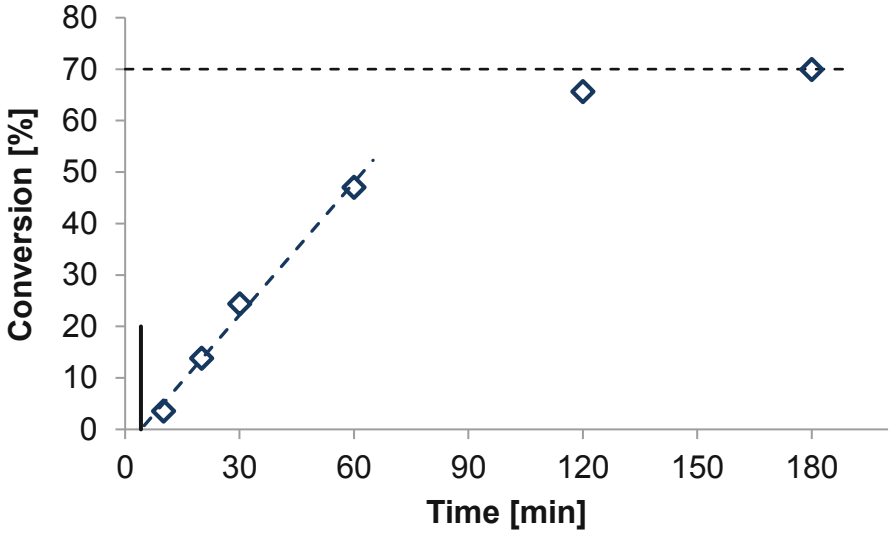


Figure 23: Monomer conversion of RAFT homopolymerization of LMA using *CDP* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa in dry dioxane ([M]=1.5 mol/L) in the course of reaction time

It can be seen that the polymerization proceeds quite fast in the first 60 minutes until a conversion of about 50 % is reached. Afterwards the curve flattens and converges towards the reported maximum conversion of approximately 70 %. This graph also shows the existence of an inhibition time. The intersection between the x-axis and the balance line through the linear region of the conversion was calculated and an inhibition time t_{inh} of 4 minutes was determined for the RAFT polymerization of **LMA**.

In order to classify a reaction as a controlled radical polymerization, the molecular weight of the polymer has to increase in a linear way with the monomer conversion. In Figure 24 the results of the homopolymerization of **LMA** are shown.

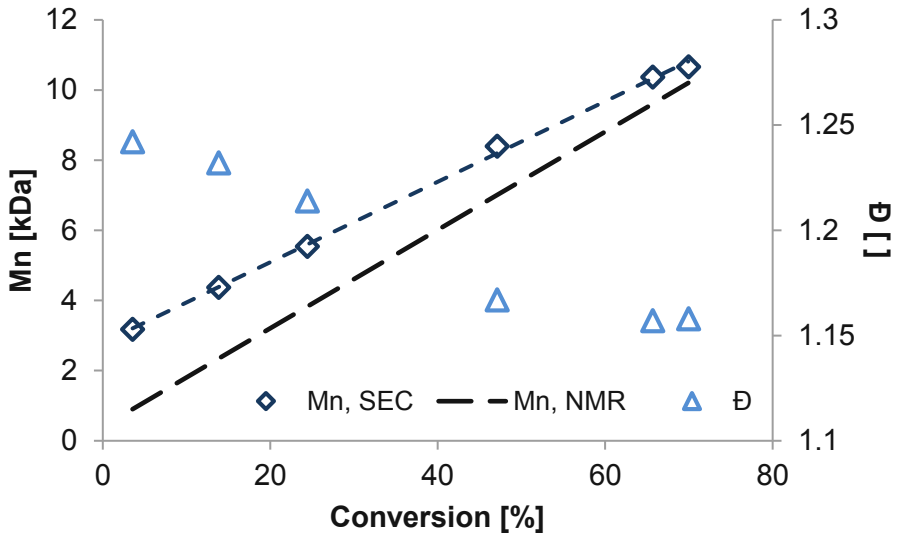


Figure 24: Correlation between molecular weight and dispersity and monomer conversion in RAFT homopolymerization of LMA using *CDP* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa in dry dioxane ([M] =1.5 mol/L)

$M_{n,\ NMR}$ calculated from Equation 7, is a linear function. The results obtained from the SEC measurements, $M_{N,\ SEC}$, showed a linear behavior as well. The discrepancy between those two datasets arises from the fact that polystyrene standards were used for the calibration of the SEC.

Additionally, the changes of the dispersity Đ during the polymerization can be observed in Figure 24. Even at the the beginning, Đ shows low values, which decrease slightly over time, reaching 1.16 at the end of the polymerization. In general, polymers generated via a controlled mechanism show dispersity values of 1.50 or less. In comparison to that, free radical polymerization leads to values above 2.00. The narrow molecular weight distribution of the synthesized p**L** indicates a controlled mechanism of the polymerization.

Figure 25 provides a closer look at the evolution of the molecular weight during the polymerization by comparing SEC spectra recorded from samples at different times.

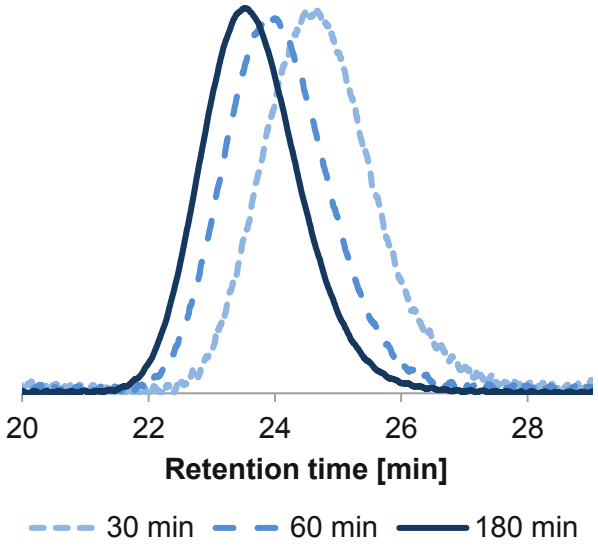


Figure 25: SEC spectra of the RAFT homopolymerization of LMA after 30, 60 and 180 minutes of reaction time

Over time, a clear shift of the polymer peak to lower retention time and therefore higher molecular weight is visible. Furthermore, it can be concluded that no terminated by-product or dead polymer chains were formed during the polymerization, as the peaks did not show any shoulders.

Another indicator for a controlled behavior is the reaction order. Therefore, it is necessary to calculate the natural logarithm (ln) from the ratio between the initial monomer concentration M_0 and the monomer concentration at the time the sample was taken M_x ($\ln([M]_0/[M]_x)$). Then, this value is plotted against the reaction time, and if the curve shows linear behavior, the radical concentration is assumed to be constant over time. This indicates that the polymerization is driven by a first order kinetic, and therefore displays a controlled character. The plot for the kinetic study of **LMA** is depicted in Figure 26.

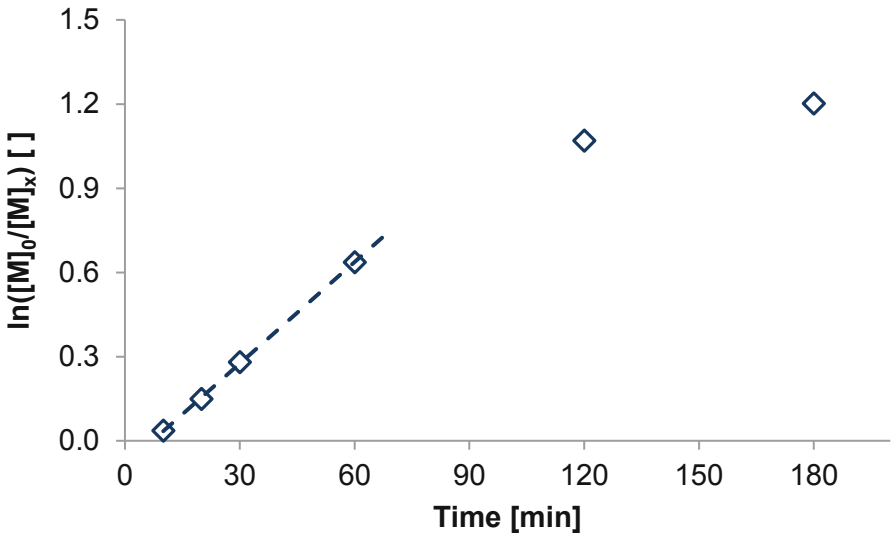


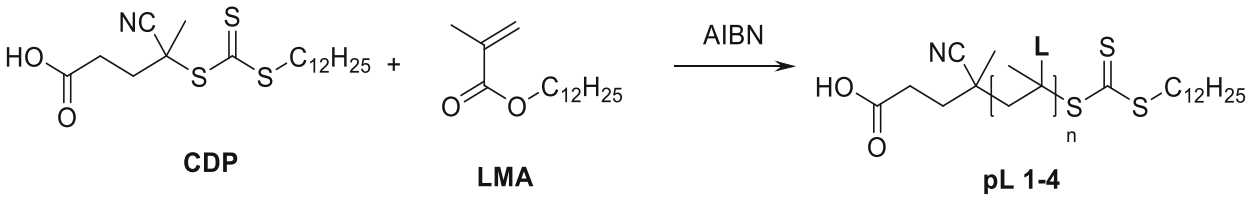
Figure 26: Pseudo first order plot of the RAFT homopolymerization of LMA using *CDP* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa in dry dioxane ([M]=1.5 mol/L)

A linear correlation between time and $\ln([M]_0/[M]_x)$ is not given for the whole polymerization, but within the first 60 min, a perfect linear course can be seen. The non-linearity might be due to the limited conversion of about 70 %.

It can be summarized that the polymerization of **LMA** with ***CDP*** as RAFT reagent and AIBN as thermal initiator proceeds in a controlled manner under the selected reaction conditions.

A.2.1.3 Preparation of homopolymers from lauryl methacrylate

LMA homopolymers with two different block lengths, 5 kDa and 10 kDa, were synthesized with a [CTA]:[I] ratio of 10:1 using the same procedure as described for the kinetic study, but samples were only withdrawn before the start of the reaction and after it was stopped.



CDP **LMA** **pL 1-4**

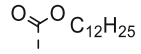
L= 

Table 2 summarizes values for monomer conversion, molecular weight and dispersity for those reactions.

Table 2: Results of the RAFT homopolymerization of LMA in dry dioxane using *CDP* as CTA and AIBN as initiator at 90 °C

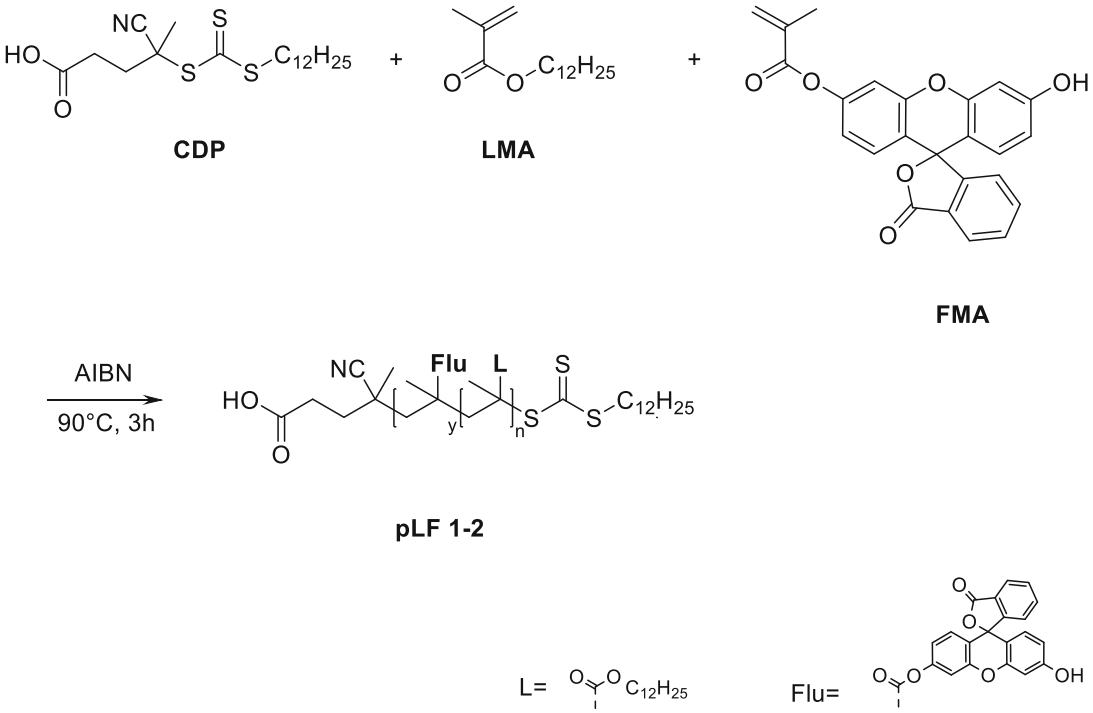
	$M_{n,target}$ [kDa]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
pL1	14.3	70	10.2	10.7	1.16
pL2	14.1	65	9.1	8.5	1.13
pL3	7.2	75	5.6	7.3	1.12
pL4	7.1	75	5.3	6.3	1.13

As shown in Table 2, the homopolymerization of **LMA** worked pretty well. Considering the expected conversions of about 70 %, the desired molecular weights were reached. The slightly increased conversion for polymers with a target molecular weight of 7.2 kDa is probably due to the better solubility of shorter polymer chains. Furthermore, the synthesized polymers show very satisfying dispersity values below 1.20.

In literature, the RAFT homopolymerization of **LMA** using ***CDP*** is scarcely reported, and mostly **LMA** was only polymerized with ***CDP***-based macro CTAs. Reactions have been performed in toluene at 70 °C for 4 hours leading to polymers with dispersity values in the range from 1.14-1.21 and a molecular weight between 5 and 10 kDa at monomer conversion rates of around 40%. The ratio between CTA and AIBN was thereby 8:1.[240] Enke *et al*.[235] conducted LMA homopolymerization in dimethylformamide at 70 °C for 19 h applying 4:1 as molar ratio between CTA and AIBN. This led to polymers with a dispersity of 1.16. Compared to those data, the here performed reaction led to polymers with dispersity values in the same range in shorter time and with less initiator. Thus, this synthetic pathway can be concluded as a suitable and effective one for the preparation of **pL** with ***CDP*** as RAFT agent. However, the monomer conversion is limited, a one-pot pathway for preparation of block copolymers is not feasible.

A.2.2 Introducing a fluorescent marker in the hydrophobic block

In addition to the **LMA** homopolymers hydrophobic blocks consisting of **LMA** and **FMA** were synthesized.



The content of **FMA** was 1 wt% with respect to the initial weight of **LMA** and 1.6 wt% under the consideration of **LMA**-conversion of about 70 %, respectively. The targeted molecular weight was 5 kDa and 10 kDa, again considering the limited conversion. These copolymerizations were performed under the same reaction conditions as the **LMA** homopolymerizations (90 °C, reaction time of 3 hours). The ratio between RAFT agent and initiator was again 10:1, dry dioxane was used as solvent and monomer concentration was 1.5 mol/L.

Monomer conversion was again calculated from ^{1}H-NMR data, but it was necessary to consider the conversion and the molar amount of each monomer. Equation 8 was used to calculate the overall conversion for these polymerizations.[221,242]

$$C_{total} = \frac{[M_1]_0 \cdot C_{M_{1,x}} + [M_2]_0 \cdot C_{M_{2\,x}}}{[M_1]_0 + [M_2]_0}$$ **Equation 8**

$C_{M\,y,x}$	Conversion of monomer y at t=x [ ]
C_{total}	Overall conversion at t=x [ ]
$[M_y]_0$	Concentration of monomer y at t=0

The molecular weight of the copolymers was calculated considering both, the conversion and the molar amount of each monomer. Since the amount of incorporated FMA was too low to determine it via ^{1}H-NMR spectroscopy, it was considered as 100%. Additionally, the molar mass of both monomers and the RAFT agent was taken into account, which led to Equation 9.[221]

$$M_{n,NMR} = \frac{[M_1]_0 \cdot M_{M_1} \cdot C_{M_1} + [M_2]_0 \cdot M_{M_2} \cdot C_{M_2}}{[CTA]_0} + M_{CTA} \qquad \textbf{Equation 9}$$

$M_{n,\,NMR}$	Calculated molecular weight of the copolymer at a given conversion [g/mol]
$[M_y]_0$	Concentration of the monomer at t=0 [mol]
$[CTA]_0$	Concentration of the RAFT agent at t=0 [mol]
M_{My}	Molecular weight of monomer y [g/mol]
M_{CTA}	Molecular weight of the RAFT agent [g/mol]
$C_{y,x}$	Conversion of monomer y at t=x [ ]

The results of these polymerizations are listed in Table 3.

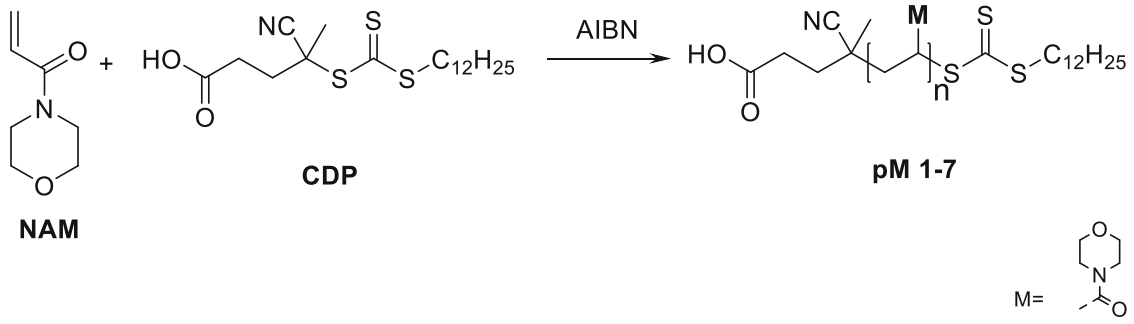
Table 3: Results of the RAFT copolymerization of LMA with 1 wt% FMA in dry dioxane using *CDP* as CTA and AIBN as initiator

	$M_{n,target}$ [kDa]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
pLF1	6.5	77	5.0	6.0	1.12
pLF2	14.2	68	10.1	10.4	1.15

These polymerizations also worked well and the expected monomer conversion of around 70% including the conversion of **FMA** was reached. The copolymers showed low dispersity values, indicating that their preparation also proceeded via a controlled mechanism, although **FMA** was added as a comonomer to the reaction mixture. The quantification of the fluorescein content will be discussed in chapter A.5.3.

A.3 Kinetic studies on the RAFT homopolymerizations of hydrophilic N-acryloylmorpholine

The RAFT polymerization of **NAM** has already widely been studied,[242-247] but ***CDP*** was hardly used as CTA in those experiments. Gaballa *et al.* used a macro CTA prepared from **NAM** and ***CDP*** for the preparation of glucose-responsive block copolymers in combination with pentafluorophenyl acrylate.[248,249] Additionally, a few attempts have been made with **NAM** and ***CDP*** in photopolymerization.[250-252]



Variation of temperature is supposed to influence the polymerization rate constants and therefore also the speed of polymerization. Hence, RAFT polymerizations at higher temperatures proceed faster and retardation should be reduced. Additionally, on the one hand more chains are initiated at high temperatures leading to a higher probability of termination accompanied by an increase in radical reactivity and thus, a loss of control expressed by increasing dispersity values. On the other hand, higher temperatures also lead to higher increase of the fragmentation rate constants compared to other constants, leading to a reduction of the lifetime of the intermediate radicals and therefore a reduction of side reactions.

Looking at the initiator concentration used for RAFT polymerization, at lower concentrations, an improvement of the dispersity is expected due to disfavoring of termination reactions since reactions only involving one radical species are favored. Thus, propagation and addition-fragmentation are preferred and polymers with narrower molecular weight distribution should be obtained. However, the concentration should be kept at a level where a sufficient rate of polymerization is enabled. Since dispersity and polymerization rates are influenced not only by one factor, the right balance between reaction parameters has to be found. [242,253,254]

Preliminary to the synthesis of the block copolymers, kinetic studies of the polymerization of **NAM** with ***CDP*** as RAFT reagent and AIBN as thermal initiator were conducted at three

different temperatures in order to obtain poly N-acryloyl morpholine (**pM**). Furthermore, the ratio between ***CDP*** and AIBN was varied.

A.3.1 Variation of temperature

In order to evaluate the influence of the reaction temperature, kinetic studies of RAFT homopolymerizations of **NAM** were performed at 70, 80 and 90 °C. All reactions were conducted at a molar ratio ***CDP***:AIBN of 10:1 and the monomer concentration was 1.5 mol/L in dry dioxane. The target molecular weight was 40 kDa. Samples were withdrawn during the polymerization process, allowing to evaluate the kinetics. As it was known from previous work[204,255] that the polymerization of **NAM** proceeds fast at 90 °C, the time intervals between the single samples were reduced compared to the other polymerizations within the first 30 minutes of the reaction.

Monomer conversion was derived from ^{1}H-NMR spectra according to Equation 6 and Equation 7 using monomer signals resulting from **NAM** at 6.44 ppm, 6.18 ppm and 5.60 ppm. Calculation was done separately for all signals, but since similar results were obtained, the average value was considered for further calculations.

Results of the analyses from RAFT polymerizations conducted at 70 °C and 80 °C are summarized in Table 4 and results of polymerizations at 90 °C in Table 5.

Table 4: Kinetic study of the RAFT homopolymerization of NAM at 70 °C and 80 °C, [CTA]:[I]=10:1, $M_{n,target}$=40 kDa

	pM2				pM3			
10:1	70 °C				80 °C			
Time [min]	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**
10	0	-	-	-	2	1.0	0.9	1.14
20	0	-	-	-	54	21.7	12.1	1.19
30	3	1.4	0.4	1.28	80	32.0	16.5	1.21
45	32	12.6	7.0	1.28	92	36.4	17.0	1.27
60	57	21.7	10.5	1.29	96	38.0	18.1	1.25
120	91	34.7	14.0	1.37	99	39.2	18.3	1.30
180	95	36.3	15.3	1.32	-	-	19.1	1.27
240	96	36.4	14.6	1.37	99	39.4	18.5	1.30
300	96	36.4	15.1	1.33	99	39.3	18.3	1.31
360	96	36.5	14.5	1.35	-	-	-	-

Table 5: RAFT homopolymerization of NAM at 90 °C, [CTA]:[I]=10:1, $M_{n,target}$=40 kDa

	pM1			
Time [min]	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**
5	1	0.7	-	-
7	1	0.8	-	-
9	3	1.5	0.7	1.15
12	36	14.6	8.3	1.24
15	67	26.7	13.0	1.30
20	84	33.4	14.0	1.38
25	91	36.3	14.2	1.45
30	95	37.8	14.0	1.43
60	98	39.2	14.3	1.46
120	99	39.5	14.0	1.47
180	99	39.4	14.4	1.47

It can be seen that the polymerization proceeded pretty fast at 80 °C, since almost full conversion of the monomer was reached within 60 minutes resulting in a polymer with a dispersity of 1.3. The polymerization was clearly slowed down by a decrease of temperature to 70 °C. Within the first 30 minutes of polymerization, almost no conversion took place. However, within three hours, almost complete monomer conversion was reached and the obtained polymers showed low dispersity (1.3) indicating a controlled polymerization process. At 90 °C the monomer is converted almost completely within 60 minutes leading to a polymer with a calculated molecular weight of 40 kDa. However, dispersity increases to 1.5.

The significant discrepancy between $M_{n,NMR}$ and $M_{n,SEC}$ can be easily explained by the fact that SEC in combination with a refractive index detection represents only a relative method. Apolar polymer standards based on polystyrene, which possess a different hydrodynamic volume than hydrophilic p**M,** were utilized to generate a calibration curve in THF. Thus, it gives the impression that polymers with relatively low molecular weight were obtained. Comparative measurements against polyethylene glycol standards, which show similar interactions with the solvent, were performed with water as eluent. Thereby the results showed molecular weights in the range of the ones calculated from the conversion received from ^{1}H-NMR spectroscopy. For a polymer with calculated molecular weight of 19.6 kDa a value of 18.5 kDa was obtained. Nevertheless, SEC analysis of the hydrophobic block and the BCPs is only possible in organic solvents. In order to maintain comparability between analytical data throughout the whole thesis, only values obtained from THF-based SEC measurements were used. Additionally, the focus in SEC spectra is on the shape and width of the peaks, which reflect the uniformity of

the polymer chains expressed by the dispersity value, thus the M_n values are of less significance.

Figure 27 shows the evolution of the monomer conversion in dependence on time at different temperatures.

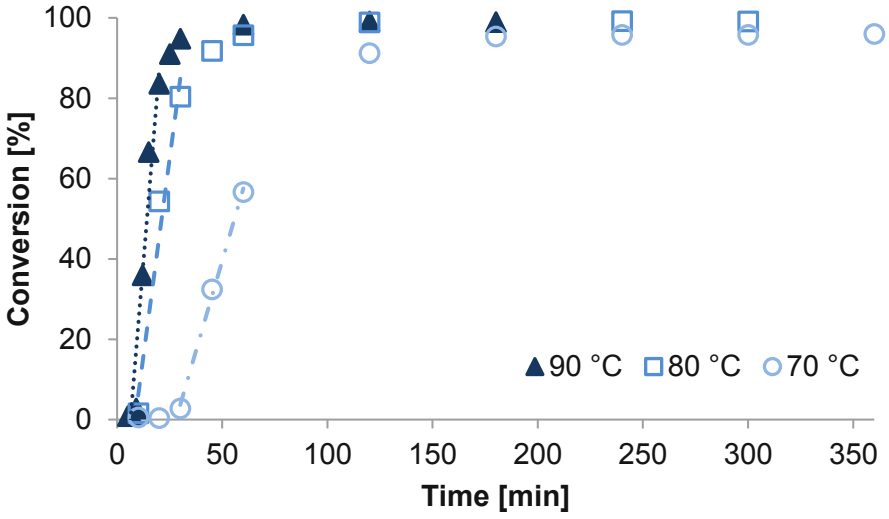


Figure 27: Monomer conversion in the course of time in the RAFT homopolymerization of NAM using *CDP* at a CTA-to-initiator ratio of 10:1 and an $M_{n,target}$ of 40 kDa at different temperatures

Here, the difference in reaction speed becomes obvious. The inhibition time t_{inhib} of these polymerizations was estimated from the linear region of these graphs at the beginning of each polymerization by calculating its intersection with the x-axis. The t_{inhib} was roughly 6 minutes at 90 °C, 9 minutes at 80 °C and 28 minutes at a temperature of 70 °C. So, additionally to the decrease in polymerization speed, indicated by a decrease in the slope of the aforementioned balance line, a significant increase in inhibition time becomes visible. Reactions at 80 °C and 90 °C showed a similar course, whereas the polymerization conducted at 70 °C showed explicitly a different behavior. In literature similar results can be found. Favier et al.[242] performed detailed kinetic studies on the RAFT polymerization of NAM using tert-butyl dithiobenzoate as RAFT agent initiated by AIBN in dioxane at 60 °C and 90 °C. By increasing the temperature, a significant increase of polymerization speed was visible. A conversion of 90% was reached within one hour instead of ten hours. This can be explained by the fact that higher temperatures lead to higher decomposition rate of the initiator as well as a rise of the fragmentation rate constant. Furthermore, they also observed a decrease in inhibition time if the polymerization was performed at higher temperature.

In order to proof the controlled character of the RAFT homopolymerization of **NAM**, which was indicated by the obtained low dispersity values, the criteria for a CRP were examined. As depicted in Figure 28, the molecular weight determined by SEC, $M_{n, SEC}$ and the dispersity, Đ, were plotted against monomer conversion. Only data in the region up to the first drawn sample with maximum conversion were considered.

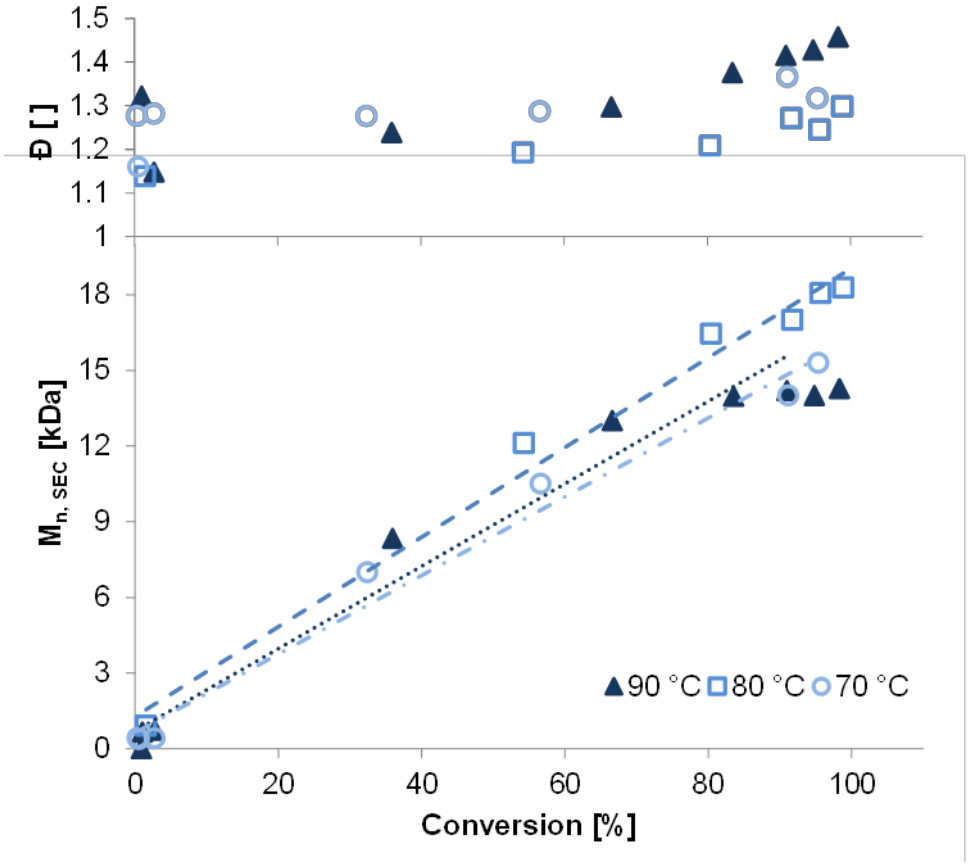


Figure 28: Correlation between molecular weight and dispersity with conversion of the RAFT homopolymerization of NAM using *CDP* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 40 kDa in dry dioxane ([M] =1.5 mol/L) at different temperatures

As required for a controlled polymerization, reactions at 70 °C and 80 °C showed a linear increase of the molecular weight with monomer conversion. In the case of the polymerization at 90 °C a linear course was not clearly recognizable. Regarding the dispersity, it becomes visible that higher temperature leads to higher values.

Finally, the reaction order of these polymerizations was examined. For this purpose, the natural logarithm of the ratio between the amount of monomer at the beginning of the reaction $[M]_0$ and the amount of monomer at different times $[M]_x$ was plotted against the reaction time. The resulting graphs are depicted in Figure 29.

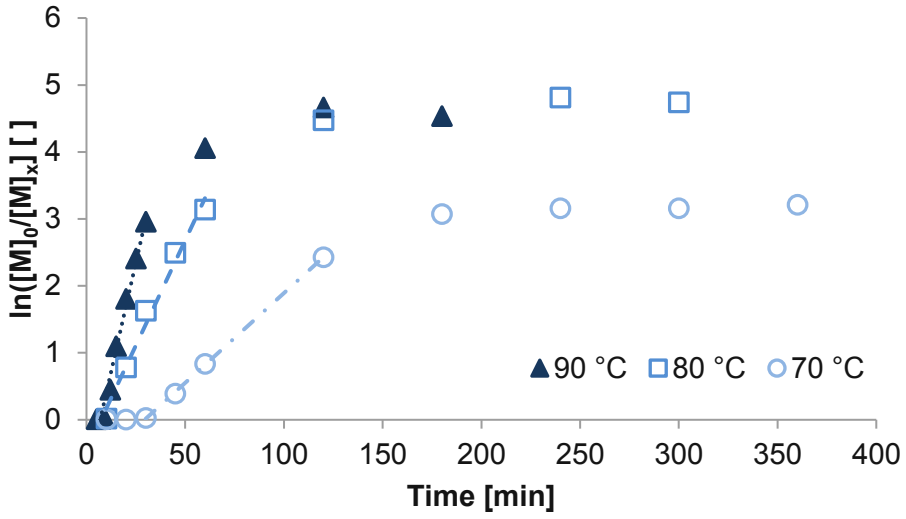


Figure 29: Pseudo first order plot for the RAFT homopolymerization of NAM using *CDP* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 40 kDa in dry dioxane ([M]=1.5 mol/L) at different temperatures

For all polymerizations a linear course of the graph can be seen at the beginning of the reaction. The curves flatten when almost full monomer conversion is reached.

Summing up, it can be concluded that ***CDP*** is a suitable CTA for the controlled polymerization of **NAM** by means of RAFT polymerization under the selected reaction conditions. The reactions proceed with almost complete monomer conversion within reasonable time and result in the formation of well-defined polymers.

As expected, the influence of temperature regarding the speed of polymerization becomes clearly visible. The difference between reactions performed at 80 °C and 90 °C is less significant than in the case of reactions at 70 °C. In regard of the dispersity, no significant difference is visible for 70 °C and 80 °C, but an increase to 90 °C leads to an increase of dispersity.

A.3.2 Variation of initiator concentration

In addition to the effect of temperature, the influence of the initiator concentration on the reaction rate and the uniformity of the resulting polymers was examined. For this purpose, polymerizations were carried out at 80 and 90 °C with molar ratios between ***CDP*** and AIBN of 15:1 and 20:1, and a targeted molecular weight of 20 kDa. Again, samples were withdrawn at different times and analyzed by ^{1}H-NMR spectroscopy and SEC. Since reactions at 70 °C proceeded quite slow, no experiments with lower amounts of initiator were performed at this temperature. Table 6 depicts the collected data sets of reactions proceeded with different [CTA]:[I] ratios at 80 °C.

Table 6: Kinetic study of the RAFT homopolymerization of NAM at 80 ° C, [CTA]:[I]=15:1 and 20:1, $M_{n,target}$=20 kDa

	pM4					pM5			
15:1	80 °C				**20:1**	80 °C			
Time [min]	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**	**Time [min]**	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**
16	0	-	-	-	**16**	0	-	-	-
20	0	-	-	-	**20**	0	-	-	-
30	41	8.4	5.8	1.17	**30**	49	10.1	6.8	1.15
45	80	16.2	9.6	1.17	**45**	84	16.9	10.3	1.15
60	91	18.2	10.5	1.17	**60**	93	18.7	11.2	1.16
120	97	19.4	10.9	1.19	**120**	98	19.6	11.4	1.17
180	97	19.5	10.6	1.21	**180**	99	19.8	11.3	1.18
240	98	19.5	11.7	1.18	**240**	98	19.7	11.8	1.18
300	98	19.6	11.0	1.18	**300**	98	19.7	11.0	1.19

Again, the RAFT polymerization of **NAM** proceeded fast. However, it is obvious that compared to a [CTA]:[I] ratio of 10:1, a reduction of the amount of initiator to 15:1 led to a slow-down of the reaction. Although the targeted molecular weight was reduced, it takes longer time to reach almost complete monomer conversion. Dispersity was reduced from 1.30 to 1.17. but it has to be considered that the molecular weight was lower. Comparative experiments at 80 °C with a target molecular weight of 20 kDa and [CTA]:[I] of 10:1 lead to polymers with a dispersity of about 1.20. Hence, it can be concluded that a reduction in amount of initiator does not lead to a significant improvement of the dispersity in this specific case. In order to check if a further increase of the [CTA]:[I] ratio has an a effect, experiments were performed at a ratio of 20:1 leading to the result that a further reduction does not show any effect on the reaction speed or the dispersity.

A different picture shows up for reactions performed at 90 °C at different molar ratios between CTA and initiator, as can be seen in Table 7.

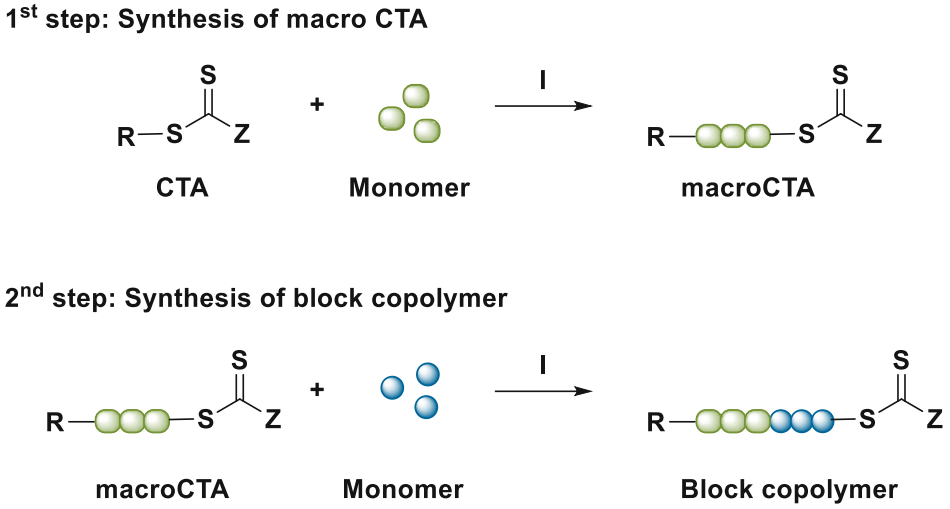
Table 7: Kinetic study of the RAFT homopolymerization of NAM at 90 °C, [CTA]:[I]=15:1 and 20:1, $M_{n,target}$=20 kDa

	pM6					pM7			
15:1	90 °C				**20:1**	90 °C			
Time [min]	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**	**Time [min]**	**C_M [%]**	**$M_{n,NMR}$ [kDa]**	**$M_{n,SEC}$ [kDa]**	**Đ [ ]**
12	88	17.8	10.5	1.21	**12**	49	10.3	7.3	1.16
18	96	19.4	11.1	1.22	**18**	84	17.2	10.4	1.20
22	98	19.7	11.1	1.23	**22**	90	18.3	10.9	1.20
26	98	19.9	11.1	1.24	**26**	94	19.1	11.1	1.22
30	99	20.0	11.0	1.25	**30**	96	19.5	11.3	1.22
60	100	20.1	11.0	1.26	**60**	99	20.1	11.2	1.25
120	100	20.1	11.0	1.26	**120**	99	20.2	11.4	1.23
180	100	20.2	11.1	1.25	**180**	100	20.3	11.3	1.24

Here, a reduction from 15:1 to 20:1 leads to a significant reduction in polymerization speed, although it has to be said that the reaction still proceeds fast and almost full monomer conversion is reached within one hour. In this case there is no change in dispersity in dependence on the initiator concentration.

A.4 Syntheses of amphiphilic block copolymers

Block copolymers were prepared in a two-step process as depicted in Scheme 15.



Scheme 15: Schematic illustration of the preparation of macroCTAs and subsequent synthesis of block copolymers

For the synthesis of the amphiphilic block copolymers (BCP), both types of the **LMA**-based hydrophobic blocks (with or without fluorescein moieties) were used as macro RAFT agent (mCTA). **NAM** was used as monomer to generate the hydrophilic block.

It was shown in previous works at the institute[204] that a block length ratio of 1:4 (hydrophobic : hydrophilic) provided the best results for this type of amphiphilic block copolymers concerning solubility. Therefore, the desired length of the second block was calculated from the molecular weight of the p**LMA** homopolymer, leading to targeted molecular weights of 25 kDa and 50 kDa, respectively.

When it comes to the analysis of the formed block copolymers, SEC can not only be utilized to determine the relative molecular weight and the dispersity Đ of the synthesized block copolymers, but also to check if an elongation of the polymer chain with the second monomer took place. Figure 30 exemplarily illustrates the shift of the peak maximum caused by the formation of a block copolymer.

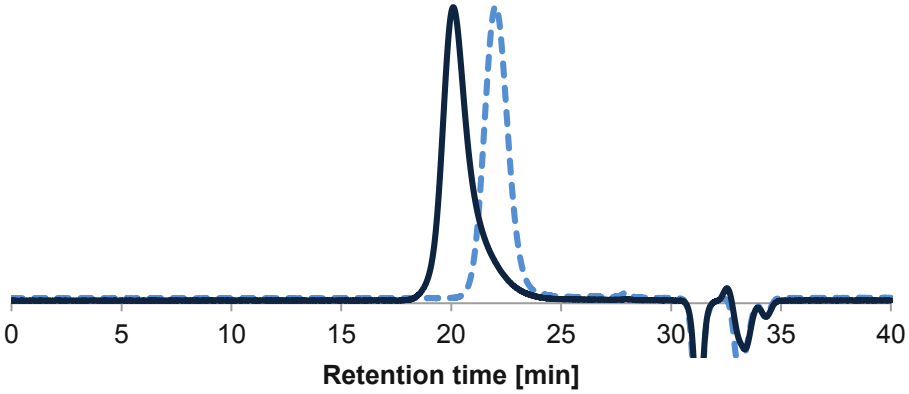


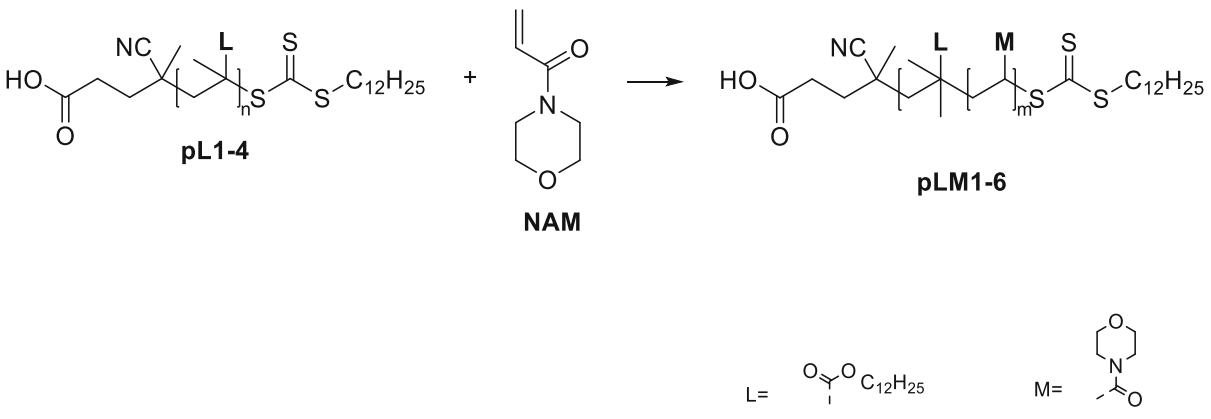
Figure 30: Example of SEC spectra of homopolymer (----) and block copolymer (——)

The graph clearly shows that in this case the block copolymerization was successful as the retention time of the polymer shifted from 22.01 minutes to 20.09 minutes. Only one narrow peak showed up in each spectrum, which indicates that no other homopolymer was formed during polymerization.

^{1}H-NMR spectroscopy was again used to determine monomer conversion and calculation of the molecular weight. Equation 6 and Equation 7 are used, whereby molecular weight and molar amount of ***CDP*** is replaced by the values for the corresponding macroCTA.

A.4.1 Block copolymerizations using pLMA as macro RAFT reagent

p**LMA** homopolymers with molecular weights of approximately 5 kDa and 10 kDa (pL1-pL4), respectively, were used as macro RAFT reagents to generate amphiphilic block copolymers in combination with **NAM.**



All these block copolymerizations were conducted in dry dioxane with an overall monomer concentration of 1.5 mol/L. The macroCTA-to-initiator ratio was 10:1 in all cases, but the temperature was varied. Reaction time was reduced in the case of higher temperature. The polymers were isolated by precipitation in cold methanol.

The formation of well-defined block copolymers can be clearly seen from comparing SEC curves of the initial macroCTA p**L** (**pL1**-**pL4**)) with molecular weights of approximately 5 kDa and 10 kDa and the resulting block copolymers p**LN** (pLM1-pLM6) with molecular weights of approximately 25 kDa and 50 kDa. Figure 30 shows SEC overlays from macroCTAs and block copolymers.

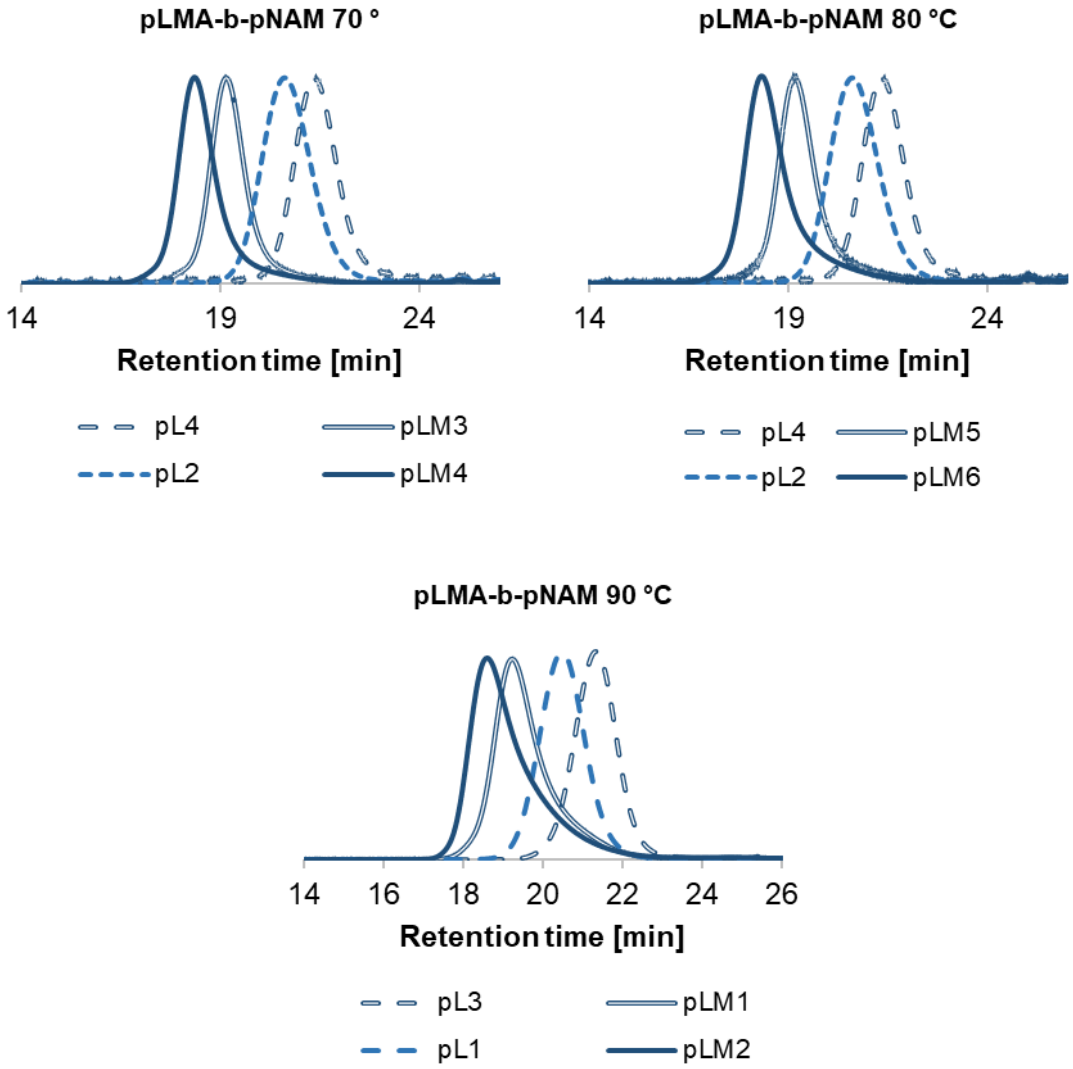


Figure 31: Overlays of SEC spectra obtained from reaction with pLMA as macroCTA and the resulting block copolymers at 70, 80 and 90 °C

In all cases, a significant shift of the polymer peak to lower retention time corresponding to higher molecular weight, is obvious. Since no shoulders to the peaks were visible, a controlled reaction is indicated. However, the increase in dispersity for polymers prepared at 90 °C is visible, since the peaks get broader at the bottom.

The obtained values from SEC as well as those from ^{1}H-NMR spectroscopy for these entire block copolymerizations including molecular weights and monomer conversion can be seen in Table 8.

Table 8: Results of the syntheses of block copolymers by using pLMA (LM1-LM4) as macroCTA in the polymerization of NAM at different temperatures

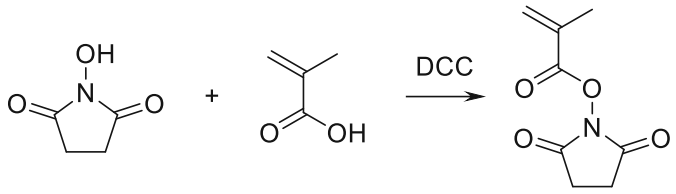
	T [°C]	**70**		**80**		**90**	
	t [h]	6.5		3		1	
	$M_{n,\,target}$ [kDa]	25	50	25	50	25	50
mCTA		**pL4**	**pL2**	**pL4**	**pL2**	**pL3**	**pL1**
	$M_{n,\,NMR}$ [kDa]	5.3	9.1	5.3	9.1	5.6	10.2
	$M_{n,\,SEC}$ [kDa]	6.3	8.5	6.3	8.5	7.2	10.6
	Đ [ ]	1.13	1.13	1.13	1.13	1.13	1.16
BCP		**pLM3**	**pLM4**	**pLM5**	**pLM6**	**pLM1**	**pLM2**
	C_M [%]	100	100	100	100	100	100
	$M_{n,\,NMR}$ [kDa]	26.6	45.5	26.6	45.8	27.5	51.3
	$M_{n,\,SEC}$ [kDa]	19.0	27.6	17.7	25.1	19.7	25.4
	Đ [ ]	1.16	1.23	1.21	1.30	1.29	1.38

Independent of the chosen temperature, all block copolymerizations proceeded with complete monomer conversion, merely the time varied. Well-defined amphiphilic block copolymers with dispersities in the range from 1.15 to 1.40 could be prepared. The dispersity increased with the total molecular weight of the block copolymers as well as with increasing reaction temperature.

A.4.2 Syntheses of functionalized block copolymers

A.4.2.1 Synthesis of N-methacryloxysuccinimide (NMS)

The monomer containing a NHS group, **NMS,** was synthesized via a Steglich esterification as described in literature.[218]



NMS

The esterification of freshly distilled methacrylic acid with N-hydroxysuccinimide was carried out in dry dioxane with N,N'-dicyclohexylcarbodiimide (DCC) as a coupling reagent. 0.8 mol% of butylated hydroxytoluene were added to the reaction mixture as an inhibitor to prevent unwanted polymerization of the methacrylate group. The synthesized product was purified by recrystallization from petrol ether and was obtained as white powder with a yield of 91%.

A.4.2.2 RAFT polymerizations

NMS was already used as comonomer within polymers prepared by means of RAFT polymerization.[181,183] Reactions with ***CDP*** as control agent can also be found in literature,[256,257] but not in combination with **NAM.**

In the same manner as preparation of block copolymer consisting of **LMA** and **NAM**, polymers with additional **NMS** as part in the hydrophilic block were synthesized. The amount of **NMS** was 10 wt% based on the total weight of monomer (8 mol% based on the molar amount of monomer). Dry dioxane was used as solvent and the monomer concentration was 1.5 mol/L. The targeted molecular weights were 25 kDa and 50 kDa and the ratio between macroCTA and AIBN was 10:1. The reaction temperature was set to 90 °C for a period of 3 hours. The polymer was isolated by precipitation in cold methanol.

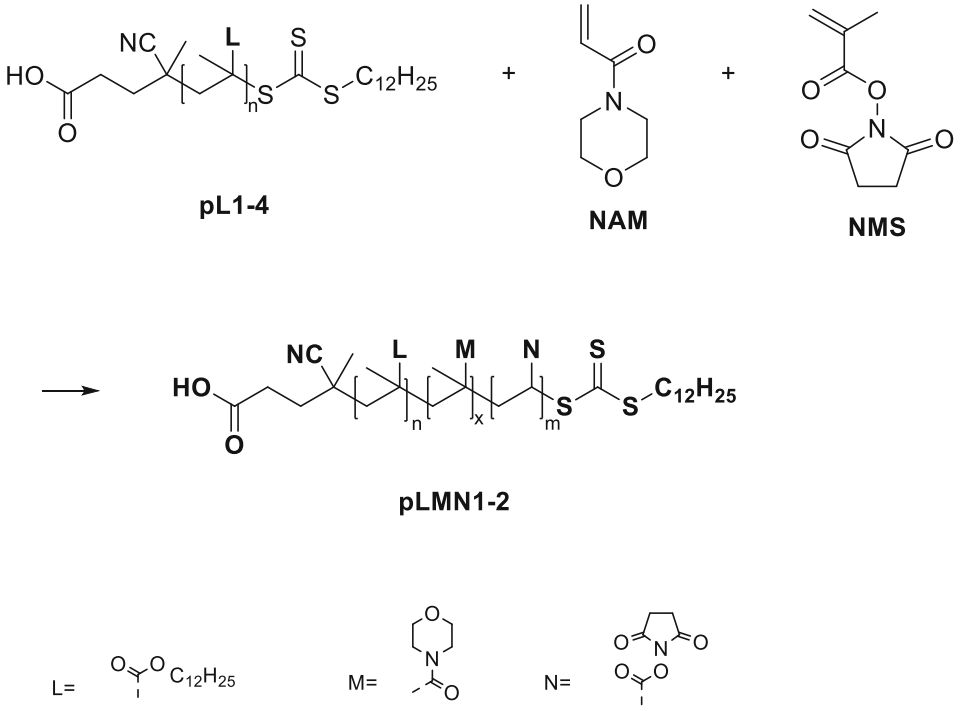


Table 9 summarizes the results of ^{1}H-NMR spectroscopy and SEC measurements. Figure 31 shows overlays of SEC traces.

Table 9: Results of the syntheses of block copolymers by using pL as macroCTA in the polymerization of NAM and NMS at 90 °C

	90 °C	pLMA-b-pNAM-c-pNMS	
	t [h]	1	
	$M_{n,\ target}$ [kDa]	25	50
mCTA		pL3	pL1
mCTA	$M_{n,\ NMR}$ [kDa]	5.6	10.2
mCTA	$M_{n,\ SEC}$ [kDa]	7.2	10.6
mCTA	Đ [ ]	1.13	1.16
BCP		pLMN1	pLMN2
BCP	C_M [%]	100	100
BCP	$M_{n,\ NMR}$ [kDa]	27.8	27.8
BCP	$M_{n,\ SEC}$ [kDa]	20.8	25.5
BCP	Đ [ ]	1.27	1.34

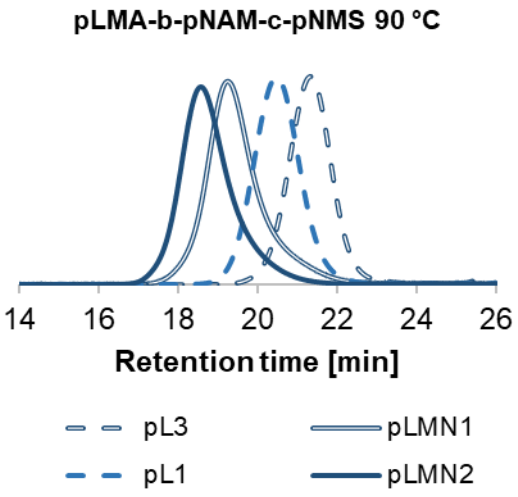
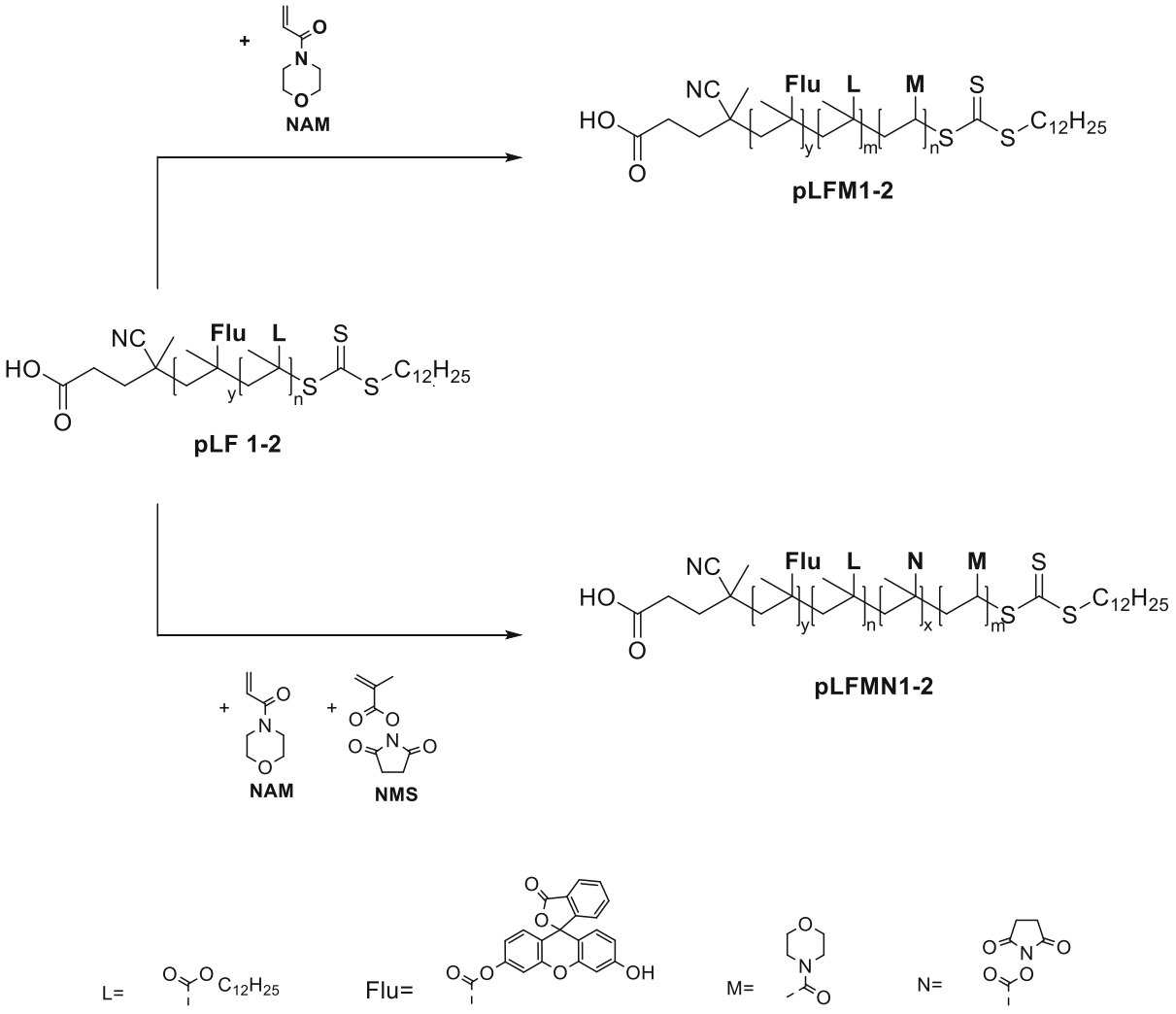


Figure 32: : SEC traces of the synthesized block copolymers by using pL as macroCTA in the polymerization of NAM and NMS at 90 °C

These polymerizations proceeded with full monomer conversion for both monomers. As it can be seen from the SEC spectra, only one peak, which shifted to shorter retention time and therefore higher molecular weight compared to macro CTA **pL1** and **pL3**, is visible for block copolymers **pLMN1** and **pLMN3**. This, in combination with the obtained dispersity values, suggests reactions proceeding in a controlled manner. As for polymerizations without **NMS** dispersity increases with molecular weight, but is still below 1.5. It can be concluded that the addition of **NMS** has no significant effect on the block copolymerization of **NAM** when **pL** is applied as macroCTA.

Besides p**LMA**, also p**LMA**-co-p**FMA** (p**LF1** and p**LF2**) was used as macroCTA for the preparation of amphiphilic block copolymers. The second block was made from **NAM** and in some polymers 10 wt% **NMS** were also introduced into the hydrophilic block. Here again, it was aimed to prepare block copolymers with a ratio between hydrophobic and hydrophilic part of 1:4 and molecular weights of 25 kDa and 50 kDa.



These block copolymerizations were performed in dry dioxane with an overall monomer concentration of 1.5 mol/L and a molar ratio between the macroCTA and the initiator of 10:1. All reactions were carried out at 90 °C over a period of 1 hour. The final products were isolated by precipitation in cold methanol.

Overlays of SEC traces obtained from the initial macroCTA p**LMA**-c-p**FMA** (p**LF1** and p**LF2**) and the resulting polymers p**LMA**-c-p**FMA**-b-p**NAM** (p**LFM1** and p**LFM2**) and p**LMA**-c-p**FMA**-b-p**NAM**-c-p**NMS** (p**LFMN1** and p**LFMN2**) are depicted in Figure 33.

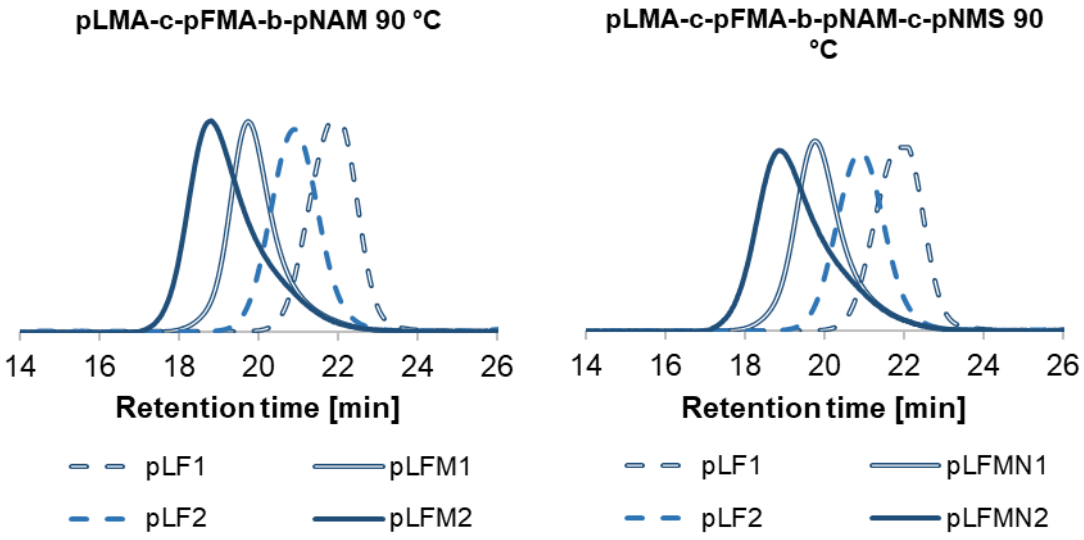


Figure 33: Overlays of SEC spectra obtained from pLMA-c-pFMA as macroCTA and the resulting block copolymers with NAM or NAM and NMS at 90 °C

An explicit shift of the SEC signal to lower retention time and, therefore higher chain length, is clearly visible. However, a slight peak tailing was visible for BCPs with a molecular weight of 50 kDa leading to higher dispersity values, as it also visible from the obtained data for these polymerizations, which are summarized in Table 10.

Table 10: Results of the syntheses of block copolymers by using pLMA-co-pFMA (LF1 and LF2) as macroCTA in the polymerization of NAM or the copolymerization of NAM and NMS

		pLMA-co-pFlu-b-pNAM		pLMA-co-pFlu -b-pNAM-co-pNMS	
	$M_{n,\ target}$ [kDa]	25	50	25	50
mCTA		**pLF1**	**pLF2**	**pLF1**	**pLF2**
	$M_{n,\ NMR}$ [kDa]	5.0	10.1	5.0	10.1
	$M_{n,\ SEC}$ [kDa]	6.0	10.4	6.0	10.4
	Đ [ ]	1.12	1.15	1.12	1.15
BCP		**pLFM1**	**pLFM2**	**pLFMN1**	**pLFMN2**
	C_M [%]	100	100	100	100
	$M_{n,\ NMR}$ [kDa]	25.1	50.1	25.2	50.1
	$M_{n,\ SEC}$ [kDa]	17.6	24.7	17.2	23.1
	Đ [ ]	1.24	1.47	1.27	1.50

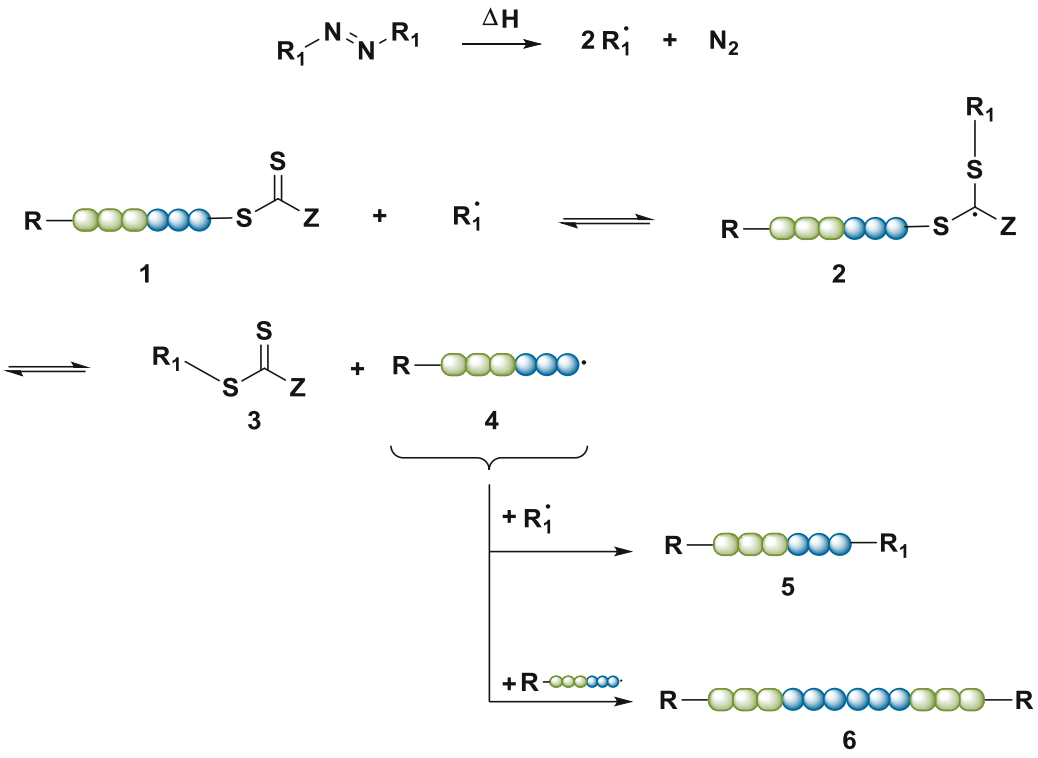
All reactions proceeded with complete monomer conversion within one hour and the synthesis of the amphiphilic block copolymers was successful, shown by a dispersity of 1.50 or less in all cases. As already indicated by the shape of SEC peaks, the uniformity of the polymer chains decreases if the molecular weight is increased. The increase in dispersity is slightly stronger than in the case of pure **pLMA** as CTA. However, since no bimodality of the peaks was apparent, a controlled polymerization process can be assumed. Thus, p**LMA**-c-p**FMA** was as well identified as suitable macroCTA for the RAFT polymerization of **NAM** and a mixture of **NAM** and **NMS**.

A.5 Removal of the RAFT end group

Due to the controlled character of the RAFT polymerization, the thiocarbonyl group of the RAFT reagent is still attached to the final product after the polymerization is completed. In some cases, it might be necessary to remove the RAFT end group due to undesired side effects.[87,88] Furthermore, the RAFT end group removal provides the possibility for modifications of the synthesized polymers. Besides the aforementioned reasons for the removal of the RAFT end group removal, also the hydrophobic character of the $C_{12}H_{25}$ residue needs to be considered. Since it is attached to the hydrophilic part comprising of **NAM**, the block copolymer might act as an ABC triblock copolymer[184] influencing its micelle formation properties.

A.5.1 Theoretical background

In general, different possibilities are available in order to remove the RAFT end group from the final polymers. Within this thesis the radical induced addition fragmentation coupling was chosen, since it is quite easy to perform and results in complete end group removal for many polymers.[91] In order to perform this reaction, a solution containing the polymer and a large excess of initiator (usually an azo-compound) is heated for a predefined period of time.[97] Scheme 16 shows the general mechanism of the radical induced end group removal via addition fragmentation coupling by using an azo initiator.



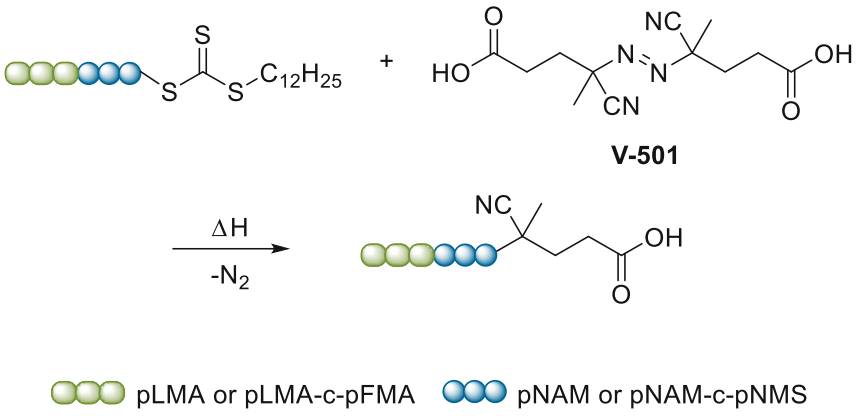
Scheme 16: General mechanism of the radical induced RAFT end group removal via addition fragmentation coupling with an azo initiator

It can be seen that this removal reaction shows the same steps as the traditional RAFT process. At the beginning of the reaction, the initiator forms two radicals $\mathbf{R_1}\cdot$ due to the rise in temperature. In the next step these radicals attack the C=S double bond of the (block) copolymer **1**, which leads to the formation of intermediate product **2**. The following fragmentation results in product **3** and the newly formed polymer radical **4**. Then, one possibility is the reaction between two of these molecules, which would lead to the formation of a triblock polymer **6**. However, on account of the large excess of initiator radicals the reaction between **4** and $\mathbf{R_1}\cdot$ is most likely to happen and therefore product **5** is generated.[91]

Besides the removal of the RAFT end group, this method also provides the possibility to recover the used CTA if the appropriate radical source is used.[97] Referring to Scheme 16, if $\mathbf{R_1}$ and **R** are the same, the RAFT agent will be obtained as product **3**. It can then be isolated by precipitating the polymer in a solvent in which the CTA is soluble. After filtering of the product, the solvent can be removed under reduced pressure to finally isolate **3**.

A.5.2 Procedure and results of the RAFT end group removal

The azo-compound 4,4′-azobis(4-cyanovaleric acid) (V-501) was used as the thermal initiator in order to substitute the sulfur containing end group with a 4-cyano pentanoic acid residue. The so introduced carboxylic acid functionality is not only hydrophilic, but als offers the possibility for further post modification of the polymer if needed.



The reaction was performed similar as described in literature.[97,184] The block copolymer was dissolved in dry dioxane at a concentration of 100 g/L and V-501 was added in a tenfold molar excess related to BCP. The resulting solution was then flushed with inert gas for about 30 minutes and was then put into a preheated thermoblock at 90 °C. After a period of 16 hours, the reaction was stopped by cooling down the tubes in an ice bath and the polymer was recovered by precipitation in pre-cooled methanol. The obvious color change from slightly yellow to clearly white, as shown in Figure 34, indicated that the removal of the RAFT end group had been successful.

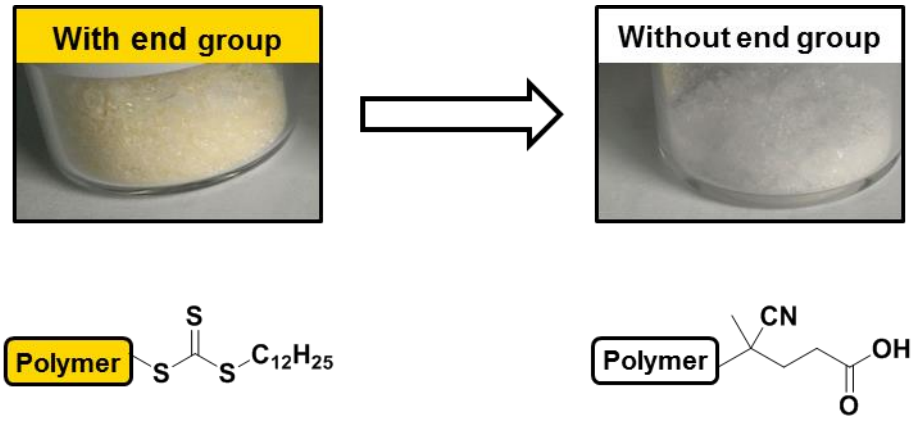


Figure 34: Color of the block copolymer before and after the removal of the RAFT end group

SEC measurements of the RAFT end group free polymers were done to gather information about the molecular weight and the PDI. Those values were compared with the data of the end group containing polymers in order to check effects on the dispersity or the molecular weight. Table 11 summarizes the results.

Table 11: Comparison of molecular weights and dispersity Đ obtained from SEC measurements performed before and after end group removal

With end group			Without end group		
BCP	**$M_{n,\,SEC}$ [kDa]**	**Đ [ ]**	**BCP**	**$M_{n,\,SEC}$ [kDa]**	**Đ [ ]**
pLM1	19.7	1.29	**pLM1-EG**	21.9	1.23
pLM2	25.4	1.38	**pLM2-EG**	30.4	1.25
pLM3	19.0	1.16	**pLM3-EG**	19.2	1.16
pLM4	27.6	1.23	**pLM4-EG**	29.5	1.17
pLM5	17.7	1.21	**pLM5-EG**	19.3	1.15
pLM6	25.1	1.30	**pLM6-EG**	28.2	1.21
pLMN1	20.8	1.27	**pLMN1-EG**	21.9	1.23
pLMN2	25.5	1.34	**pLMN2-EG**	27.6	1.34
pLFM1	17.6	1.24	**pLFM1-EG**	18.3	1.29
pLFM2	24.7	1.47	**pLFM2-EG**	27.0	1.34
pLFM3	17.2	1.27	**pLFM3-EG**	17.3	1.30
pLFM4	23.1	1.50	**pLFM4-EG**	29.0	1.31

The results show that the dispersity of the various polymers stayed unchanged or got slightly improved after the removal of the RAFT end group. However, taking a closer look at the

molecular weight measured via SEC, it is noticeable that this value increased for all polymers. Here, it has to be considered that these values were based on a calibration generated from measurements of polystyrene standards and thus, only relative molecular weights were obtained for the analyzed polymers. Since the hydrophobic end group was replaced by a hydrophilic one, chemical and physical characteristics were changed, leading to a different behavior during SEC analysis and to a relative molecular weight increase. However, since the molecular weight increased only slightly, combination between two block copolymers can be excluded.

Another characteristic, which indicates successful removal of the RAFT end group, is water solubility. Before performing this step, dissolving of the BCP proceeds very slowly or was even incomplete within two days. After the removing step, it took only few hours until complete dissolution.

A.5.3 Determination of the fluorescein content of amphiphilic block copolymers by UV/Vis spectroscopy

The exact determination of the fluorescein content of the block copolymers was performed by UV/Vis spectroscopy. Therefore, a dilution series of fluorescein methacrylate (**FMA**) in a 0.025 M Borax buffer solution (0.025 mol/L in water/methanol 1:3) at concentrations in the range from 1 µg/mL to 6 µg/mL was prepared in order to create a calibration curve (see Figure 35). This specific buffer system was chosen as it keeps the pH-value constantly at the slightly basic value of 8, which is important because fluorescein/fluorescein methacrylate starts to fluoresce in alkaline media. The measurements were conducted at a wavelength of 490 nm.

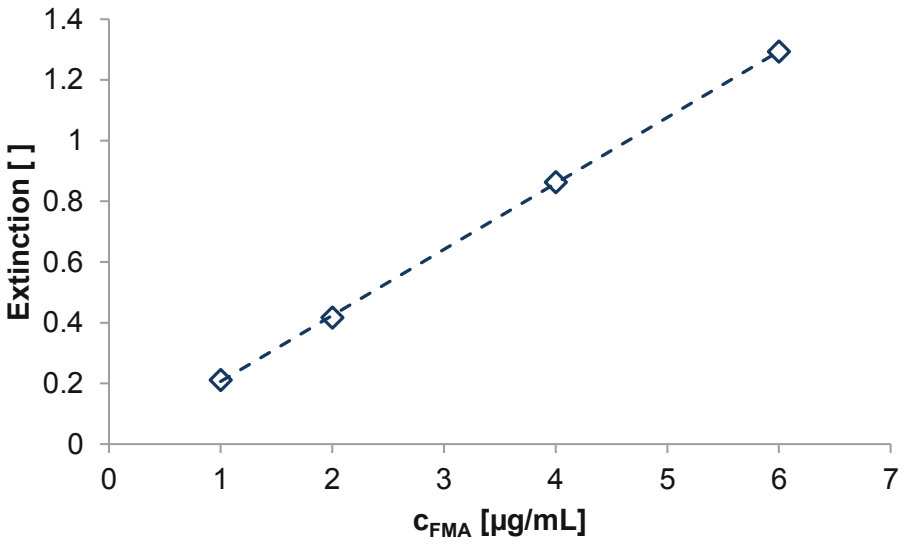


Figure 35: Calibration curve for the determination of the fluorescein content of the block copolymers by UV/Vis spectroscopy

Samples of the block copolymers were prepared at a concentration of ~1 mg/mL using the same borax buffer solution as for the calibration curve. UV/Vis spectroscopy measurements were performed and the resulting extinction signal was used to calculate the amount of fluorescein in µg/mL solution according to Equation 10.

$$c_{FMA} = \frac{E + 0.0112}{0.2175}$$ **Equation 10**

c_{FMA} Concentration of FMA in the solution [µg/mL]
E Extinction obtained from UV/Vis spectroscopy [ ]

In the next step, the percentage of weight of fluorescein based on the amount of polymer sample in the solution was calculated from the ratio between c_{FMA} and the concentration of the BCP solution. The obtained wt%-values are listed in Table 12.

Table 12: Results of the determination of the fluorescein content of the analyzed BCPs without RAFT endgroups in wt%

BCP	pLFM1-EG	pLFM2-EG	pLFMN1-EG	pLFMN2-EG
M_n [kDa]	25	50	25	50
Extinction [ ]	0.076	0.108	0.071	0.097
c_{BCP} [mg/mL]	0.97	0.99	1.02	1.02
Fluorescein [wt%]	0.042	0.056	0.037	0.049

It turned out that the fluorescein content was significantly lower than expected. Since 1.6 wt% was used in the initial polymerization of p**L**-co-p**F**, a value around 0.3 wt% would have been reached (considering the limited conversion of **LMA** and the total weight of the final block copolymer), if the used amount of **FMA** was completely incorporated into this block. However, the measurements were performed in a mixture of water and methanol in which the hydrophobic p**L**-co-p**F** block was not soluble, thus leading already to the formation of micelles. Since the fluorescein moieties are incorporated into the hydrophobic block, they were located in the core of the formed micelles and that could lead to masking of the fluorescence caused by the surrounding polymer along with reduction of the fluorescence. Nevertheless, the resulting signal showed enough intensity to be used as fluorescent marker in cell viability studies (see chapter A.6.3).

A.6 Properties of the synthesized block copolymers

A.6.1 Critical micelle concentration

Surfactants in aqueous media show the ability to form micelles, if a certain polymer concentration is exceeded. At low concentrations, the amphiphilic molecules are mostly on the surface, and the hydrophilic part is orientated towards the water. This continues until the complete surface is saturated. Afterwards the molecules start to form micelles, whereby the hydrophobic part is inside (see Figure 36). The concentration, which is necessary to generate micelles, is called critical micelle concentration (cmc).[258]

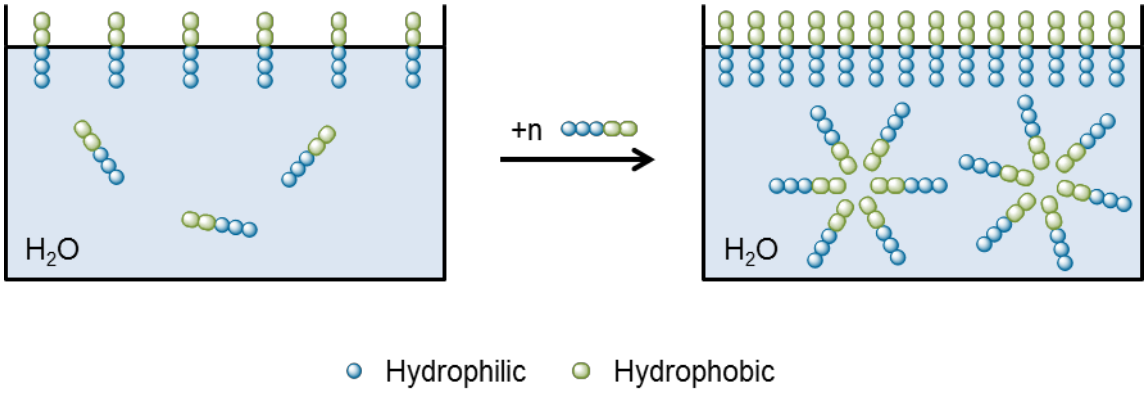


Figure 36: Micelle formation of amphiphilic block copolymers in aqueous media

In general, micelles based on amphiphilic block copolymers can be prepared in two ways. One option is the direct dissolution method, where the polymer is dissolved directly in water or other aqueous systems (e.g. phosphate buffer). The other possibility is the dialysis method. Here, the polymer is dissolved in a small amount of a water-miscible organic solvent and afterwards, the solution is dialyzed against water while stirring. Thereby, micelles are formed as the organic solvent is removed.[259] Within this thesis, the first mentioned method was chosen, in order to allow the preparation of solutions with exact concentration for the determination of the cmc values of the synthesized amphiphilic block copolymers.

Critical micelle concentrations were determined by fluorescent spectroscopy (FS) using pyrene as fluorescent dye. Pyrene can be used for this purpose since it delivers fluorescent spectra with characteristic fine structure in dependence on the polarity of the surrounding medium.[260,261] Raising the concentration of an amphiphilic polymer in the pyrene containing solution, leads to a higher intensity of the signals and, at the same time, a change of the fine structure. Figure 37 exemplarily depicts such fluorescent spectra recorded from aqueous block copolymer solutions with different concentrations of **pLM2-EG** without endgroups.

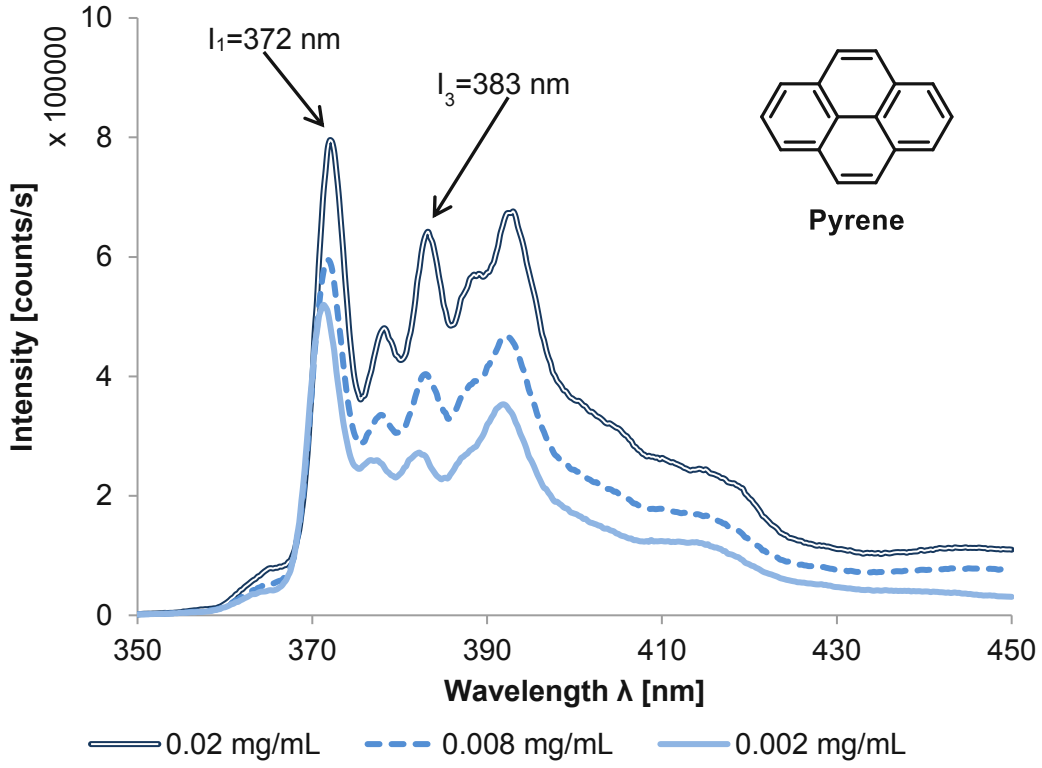


Figure 37: Fluorescence spectroscopy spectra of block copolymer pLM2-EG without end groups (solutions with different concentrations)

Emission lines at I_1=372 nm and I_3=383 nm are the ones needed for the determination of the cmc value. The peak at I_1 represents a forbidden transition, which is admittedly repealed for aromatic compounds in polar solvents (Ham-effect).[262] Therefore, its intensity changes clearly. On the other hand, peak I_3 is independent of the polar properties of the solvent. If the different graphs are compared, it becomes obvious that the relation between those two intensities changes in dependence on BCP concentration. Hence, the resulting I_1:I_3 ratio represents the degree of polarity of the medium, which surrounds the pyrene molecules. As pyrene is a highly apolar substance, it strives to get into the hydrophobic inner part of the formed micelles, whereby the I_1:I_3 ratio is affected. Based on this, Wilhelm *et al.*[263] developed a method to determine cmc via fluorescent spectroscopy.

In this particular case, fluorescent spectroscopy measurements of the samples were performed at an excitation wavelength of 336 nm. The resulting emission spectra were recorded in the range from 350-450 nm with a point distance of 0.25 nm and a dwell time of 1 second. The final spectra were obtained from the combination of three single measurements. Calculating I_1:I_3 ratios from these measurements and plotting them against the negative logarithm of the concentration of the dilution series prepared from the respective block

copolymer, results in a sigmoidal curve. A significant drop of this rate with higher polymer concentration can be observed. The cmc is then calculated by intersecting the straight line through the area of (almost) constant I_1:I_3-ratios at low polymer concentrations with the tangent in the inflection point of the S-shaped curve. Figure 38 depicts such a graph exemplarily for **pLM2-EG**.

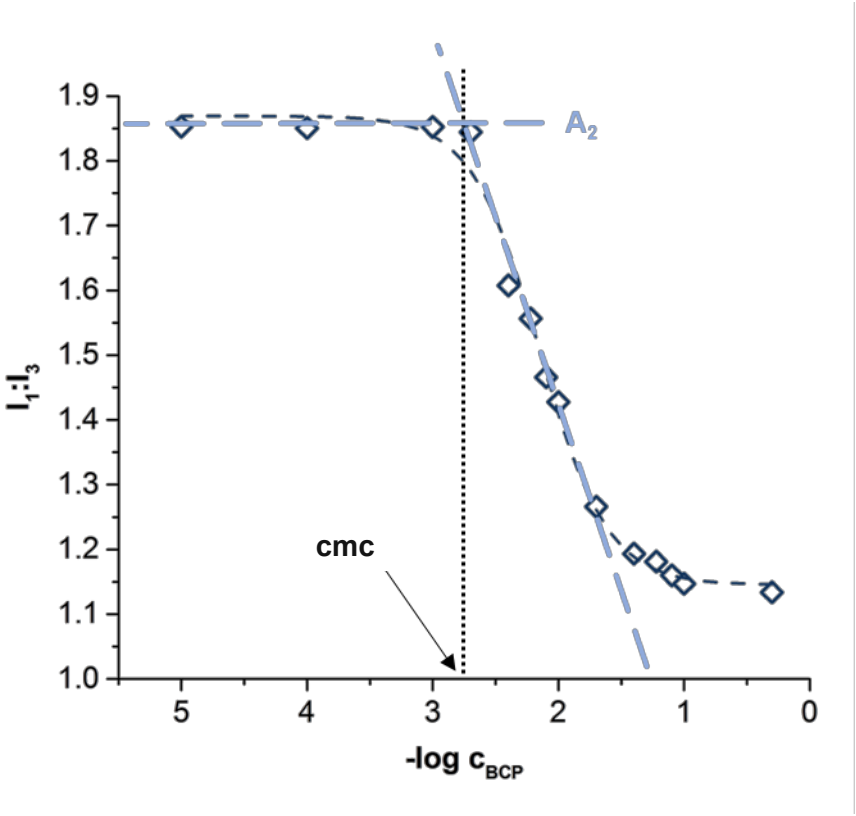


Figure 38: Example of a sigmoidal curve and the resulting straight lines of pLM2-EG used for the determination of the critical micelle concentration

In order to calculate the cmc values, the parameters A_1, A_2, x_0 and dx from the equation of the Boltzmann fit, which is obtained by the sigmoidal approximation (see Equation 11), are used.[264]

$$f(x) = A_2 + \frac{A_1 - A_2}{1 + e^{\frac{x - x_0}{dx}}}$$ **Equation 11**

A_1	Lower limit	x_0	Center of the sigmoid
A_2	Upper limit	d_x	Time constant

The tangent needed for the cmc determination was plotted through x_0 and $f(x_0)$ was calculated. In the next step, it was necessary to determine the slope k of the tangent, which is represented by the first derivative f´(x) (see Equation 12).[264]

$$f'(x) = \frac{(A_2 - A_1)e^{\frac{x-x_0}{dx}}}{dx(1 + e^{\frac{x-x_0}{dx}})^2}$$ **Equation 12**

A_1	Lower limit	x_0	Center of the sigmoid
A_2	Upper limit	d_x	Time constant

Thus, calculating f´(x_0) delivers the k value for the tangent through this point. The y-intercept was then derived by inserting x_0, f(x_0), and f´(x_0) respectively the slope k into a standard linear function f(x)=kx+d. Finally, to obtain the cmc, the so obtained tangent was intersected with the horizontal straight line through constant I_1:I_3-values, whereby the upper limit of the Boltzmann fit, A_2, was used as y-value.

Via this method, cmc values of block copolymers consisting of p**LMA** in the hydrophobic and p**NAM** and p**NAM**-c-p**NMS,** respectively, in the hydrophilic block, with total molecular weights of 25 kDa and 50 kDa, were estimated. Due to their fluorescing character, block copolymers bearing fluorescein moieties within the hydrophobic block could not be analyzed via this method.

Table 13 summarizes the values used for the calculation as well as the obtained cmc results.

Table 13: Values for cmc obtained by fluorescent spectroscopy for different amphiphilic block copolymers

		pLM1-EG	pLM2-EG	pLMN1-EG	pLMN2-EG
M_n [kDa]		25	50	25	50
Sigmoidal curve	**A_1**	1.11	1.15	1.11	1.16
	A_2	1.90	1.87	1.90	1.73
	x_0	2.31	2.15	1.65	2.35
	dx	0.22	0.27	0.39	0.22
cmc [µg/mL]		0.85	2.02	0.86	1.58

Comparing the results obtained for block copolymers with a molecular weight of approximately 25 kDa, it turned out that the incorporation of succinimide moieties had no influence on the resulting cmc. In general, the needed amount to reach micelle formation was quite low, but increased with growing molecular weight. However, values obtained for BCPs with roughly doubled molecular weight indicate an influence on cmc due to the activated ester groups. It

has to be mentioned that dissolving the polymer took longer time and complete dissolution was estimated by eye. Thus, some very small particles could have been still present, leading to a distorted concentration of the polymer solutions.

A.6.2 Thermal stability

Simultaneous thermal analysis (STA) combines the advantages of differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) and allows the determination of material data like glass transition temperature, degree of crystallinity or heat capacity. STA measurements were performed in order to examine the thermal stability of the synthesized amphiphilic block copolymers. This was of interest because the synthesized BCPs were also investigated regarding their cytotoxicity potential, where a preceding sterilization step at temperatures of up to 140 °C is required.

At the beginning, the sample was heated up to 100 °C within 10 minutes to get rid of possibly existing traces of water or other solvents and to erase the thermal history of the polymer. Over the following period of 15 minutes, the sample was cooled down to -100 °C. Subsequently, the specimen was heated up to 140 °C within 25 minutes and kept at this temperature for one hour. In the next 40 minutes the sample was heated to 500 °C, followed by a 40 minutes lasting cooling down to the starting temperature of 25 °C, where it was kept for half an hour.

Figure 39 exemplarily shows the TGA results for one of the analyzed block copolymers (**pLMN2-EG** with a molecular weight of 50 kDa).

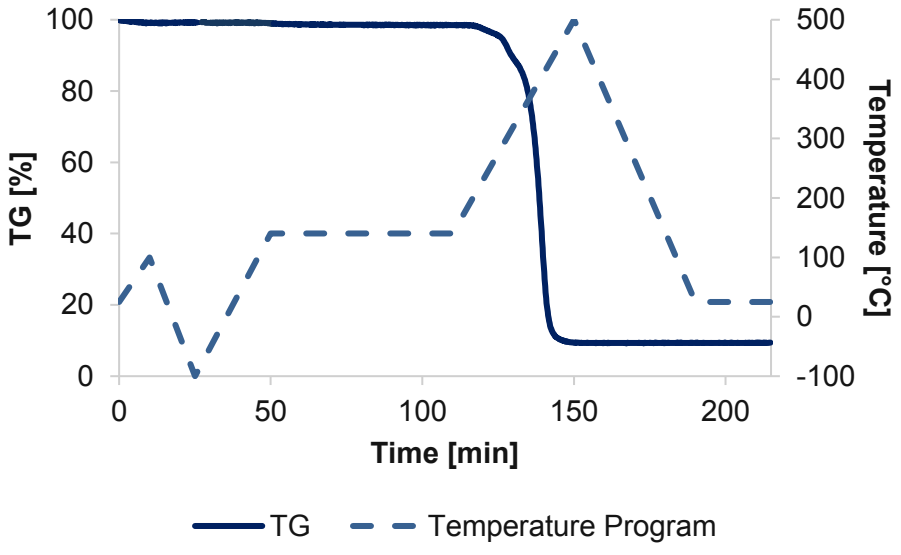


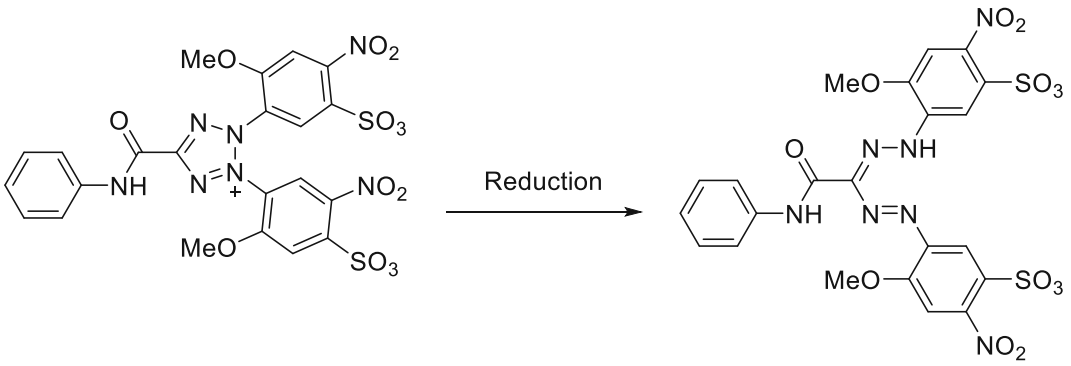
Figure 39: Thermogravimetric analysis of pLMA-b-pNAM-c-pNMS (pLMN2-EG) with a molecular weight of 50 kDa

During the first heating period no or only a marginal mass loss was observed, indicating a dry and solvent free product. Also, in the course of the second heating and the period of constant temperature at 140 °C no mass loss was observed and the polymer turned out to be stable at least until a temperature of 160 °C. Afterwards, the mass of the analyzed polymer started to decrease slowly until 400 °C are reached. Above this temperature, the decomposition of the sample proceeds quite fast, resulting in almost complete mass loss at the maximum temperature of 500 °C. The same measurement was performed for different block copolymers and similar results were obtained for all of them. Neither total molecular weight nor the presence or absence of the RAFT end group had an influence. Due to the thermal stability of the polymers, sterilization at 140 °C, which is required for in vitro-testing, is possible.

A.6.3 Cell viability

Tests regarding cell viability were performed at the Medical University of Vienna. In a first attempt, cell proliferation was tested by performing a Presto Blue ® assay. This utilizes the reducing character of viable cells to form a red and highly fluorescent species, which can then be detected via fluorescent measurement.[265] SaOs-2 (sarcoma osteogenic) cells were used and the tested block copolymer included fluorescein moieties. Unfortunately, no clear statement about the cell viability was feasible due to the interfering of the fluorescent signals from the polymer and the assay. In the course of this examination, it was tried to test the cellular uptake, but the same problem caused by the present fluorescein groups occurred.

In the second approach, the cell viability in the presence of the prepared amphiphilic block copolymers was tested by performing an XTT assay. 2,3-Bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilid salt (XTT) is utilized as detecting agent to estimate the number of living cells. As depicted in Figure 40, XTT can be reduced due to cellular effects to a water-soluble, orange formazan derivative, which can be detected by photometric methods.[266]



XTT **Formazan derivative**

Figure 40: Reduction of XTT to deliver an orange colored formazan derivative

In this particular case, human umbilical vein endothelial cells (HUVEs) were used to perform the assay and the tested polymer was an end group-free p**LMA**-b-p**NAM** (p**LM3-EG**) with a molecular weight of approximately 25 kDa. Prior to testing, the block copolymer was sterilized in an autoclave at 140 °C. Polymer solutions in endothelial cell growth medium were prepared at concentrations of 0.01 µg/mL, 1 µg/mL, 50 µg/mL and 100 µg/mL. Additionally, a control study without polymer solution was prepared for each concentration. Cell viability was then estimated via photometry at a wavelength of 450 nm. The results are graphically presented in Figure 41.

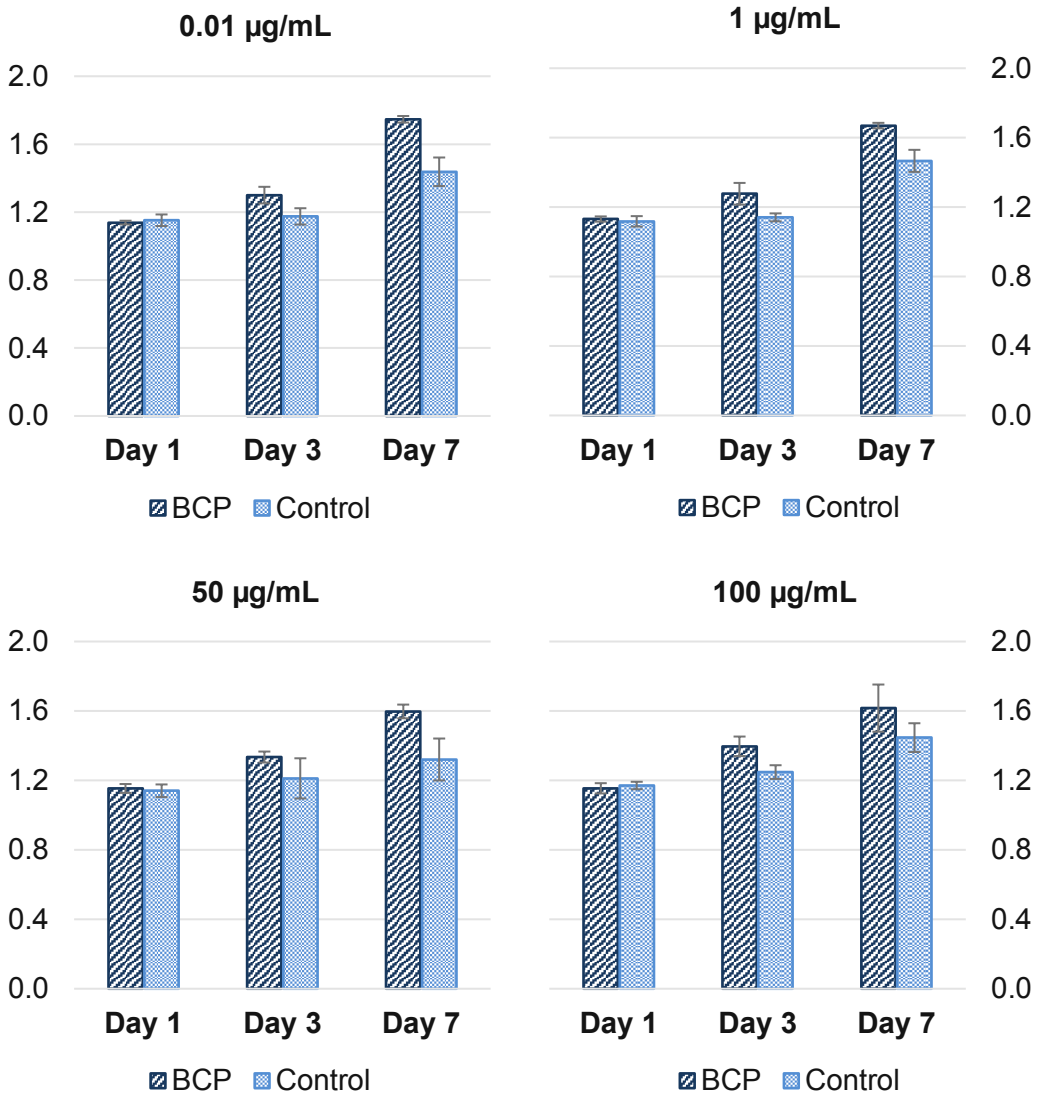


Figure 41: Results of the XTT assay of pLMA-b-pNAM (pLM3)

After one day, no significant difference in cell viability for all samples was observed. At day 3 and especially at day 7 a clear increase in number of living cells is recognizable. Thus, it can be concluded that the presence of the prepared amphiphilic block copolymer did not have any toxic effects on the surrounding cells.

General Part B

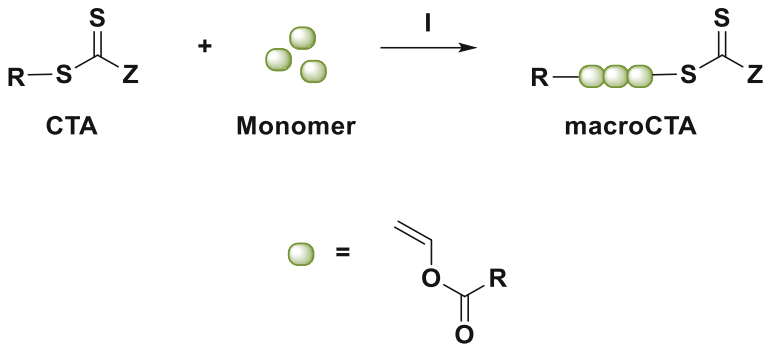
RAFT polymers based on vinyl esters

Vinyl esters are of high interest for medical applications as they give FDA (Food and Drug Administration) approved polyvinyl alcohol as degradation product[267] and show low cytotoxicity compared to (meth) acrylates.[268] However, the RAFT polymerization of this type of monomers was scarcely studied so far and only sparse literature is available on this topic.

In 2014, Harrison *et al*.[269] published a review article, revealing that RAFT polymerization of these monomers bears some difficulties, and that besides vinyl acetate only a few attempts to polymerize other vinyl esters (around 10) by this technique had been conducted. In general, the RAFT polymerization of vinyl esters is more challenging than the RAFT polymerization of monomers like (meth) acrylates or (meth) acrylamides, since they belong to the group of LAMs. Hence, the monomer itself shows low reactivity, contrary to the propagating radical, which is highly reactive. Unfortunately, this results in a higher feasibility of side reactions, and therefore the synthesis of polymers with narrow molecular weight distribution becomes more challenging.[269] Besides the possibility of reactions between propagating radicals and solvents, chain transfer to either the monomer or polymer[270] (inter- and intramolecular) can occur, resulting in the formation of branched polymers.[269] Another challenge is represented by the fact that no hydrophilic vinyl esters are commercially available, making it inevitable to synthesize them or to introduce hydrophilic groups after the polymerization process by, for example, hydrolysis of acetate groups.

B.1 RAFT polymerization of hydrophobic vinyl esters

Scheme 17 depicts schematically the preparation of well-defined polymers and macroCTAs, respectively, from vinyl esters.



Scheme 17: Schematic illustration of the preparation of macroCTAs from vinyl esters

B.1.1 Choice of monomers

The RAFT homopolymerization of various commercially available hydrophobic monomers should be examined. Linear vinyl acetate (**VAc**), vinyl hexanoate (**VH**) and vinyl decanoate (**VD**) as well as branched vinyl neo-nonanoate (**VN**) and chlorinated vinyl chloroacetate (**VClAc**) were chosen. Figure 42 depicts all the used monomers, whereof several have not been examined regarding their RAFT polymerization behavior so far.

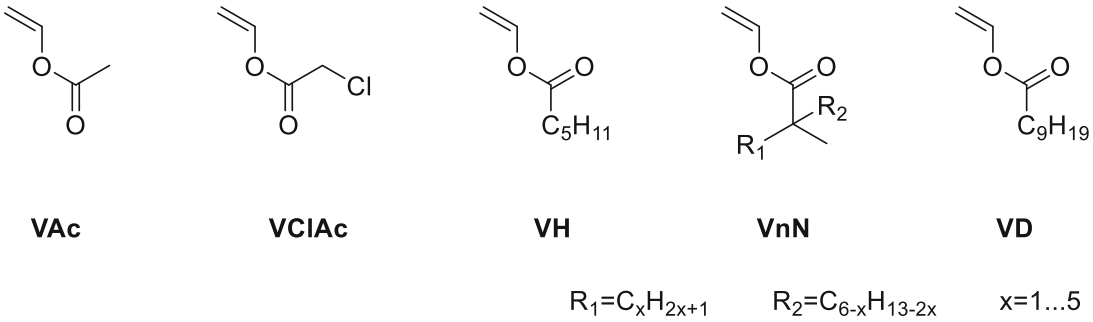


Figure 42: Overview of hydrophobic vinyl ester monomers investigated by RAFT polymerization

Vinyl acetate (**VAc**) is a highly volatile monomer, commercially available at low prices. It is used for various applications. Emulsions of polyvinyl acetate are used as adhesives, since they show good interaction with several materials (e.g. metal, porcelain, paper…), good color stability and are free of odor. Furthermore, vinyl acetate finds applications in various resins and (water-based) coatings, in textile industry (e.g. pigments) as well as in the production of flexible products (e.g. films, cable insulation…). Due to its chemical functionality, it is also used as intermediate or as co-monomer for various polymers. Additionally, it is applied in food industry for FDA conform packaging materials or for ink materials. [271]

Vinyl hexanoate (**VH**) is the commercially available vinyl ester of the saturated fatty acid hexanoic or caproic acid. So far, **VH** is seldom used in chemistry and only few literatures associated with this monomer is available. Up to now, it was applied to generate starch esters, which are interesting alternatives for conventional plastics based on petroleum, [272,273] or cellulose esters[274] via transesterification. Furthermore, **VH** was used in lipase catalyzed reactions to either give glucose-6-O-hexanoate,[275] which can be used for the preparation of glycolipids for applications in cosmetics, pharmaceutics or food industry. Additionally, **VH** could be applied for enantioselective acylation reactions by lipase catalysis.[276] The possibilities of **VH** to serve as monomer in photopolymerization-based additive manufacturing techniques, as well as its non-cytotoxicity, were evaluated and proven by Heller *et al.*[268] **VH** did not serve as monomer for other CRP-techniques like ATRP or NMP.

Vinyl decanoate (**VD**), the vinyl ester of capric or decanoic acid, a fatty acid, seems to be a promising monomer for the synthesis of amphiphilic block copolymers, since its long aliphatic chain provides the hydrophobicity needed for the water insoluble part of such materials. According to Heller *et al.*[268] vinyl decanoate shows no significant influence on cell viability and cell multiplication. Thus, this monomer can be classified as non-toxic and suitable for applications within the human body. Altogether, only few publications on **VD** are available. For example, so far, it was used as comonomer in polyvinyl acetate in order to modify alkali resistance,[277,278] as additive in the preparation of optical materials[279] or in cosmetic applications.[280,281] Furthermore, **VD** was used in different enzymatic transesterification reactions.[282,283]. ATRP or NMP of this monomer has not been reported in literature so far.

Vinyl neo-nonanoate (**VnN**) is a commercially available mixture of isomers of vinyl esters of different carboxylic acids with a branched C_8H_{17}-group next to the carbonyl carbon. According to Koch[284,285] such acids (also called Koch-acids or versatic acids) are obtained if olefins are reacted with carbon monoxide (CO) and H_2O under acidic conditions, whereby isomerization occurs and various isomers are formed. The respective vinyl esters, which are known as VeoVa™, vinyl versatate monomer or VV monomer, are then synthesized by reaction with acetylene. This type of monomer is substituted with a highly branched residue, leading to the absence of any hydrogen at the α-carbon. Therefore, it shows a high resistance towards hydrolysis under alkaline conditions. Furthermore, these monomers are UV resistant, non-hazardous and very hydrophobic.[286,287] Due to these properties, VV monomers are used as comonomer in the fabrication of polymers based on either vinyl acetate or acrylates and the resulting products are applied as paintings (e.g. glossy, water repellant, anti-corrosion) or coatings (e.g. automotive).[288,289]

The aforementioned characteristics, especially the harmlessness and the hydrolytic stability, make monomers like **VnN** of great interest for application in amphiphilic vinyl ester-based block copolymers, since partial hydrolysis under basic conditions is possible. This concept was already applied by Gu *et al.*[290] as well as by Nguyen *et al.*,[291] who used vinyl neo-decanoate in combination with vinyl acetate and vinyl pivalate, respectively, to generate block copolymers via RAFT polymerization. In a following step, polyvinyl alcohol was obtained as hydrophilic part by the partial hydrolysis of the acetate/pivalate block.

So far, this monomer was not used for ATRP or NMP and only one patent was filed on the RAFT polymerization of **VnN**, where it was used within an ABA triblock copolymer prepared in mini-emulsion for latex applications.[292] It was therefore of great interest to investigate the RAFT polymerization of **VnN** in more detail.

Vinyl chloroacetate (**VClAc**), the vinyl ester of chloroacetic acid, is available on the market at moderate prices. Due to the electron withdrawing effect of chlorine, this monomer is much more sensitive towards hydrolysis than vinyl acetate. According to Wuts[293] chloroacetate is hydrolyzed approximately 760 times faster than acetate under alkaline conditions. This is of interest for amphiphilic block copolymers, as a selective hydrolysis of the p**VClAc** block is possible to give water soluble and FDA approved polyvinyl alcohol, whereas the second block consisting of common vinyl esters (e.g. vinyl acetate) should stay unchanged.[294]

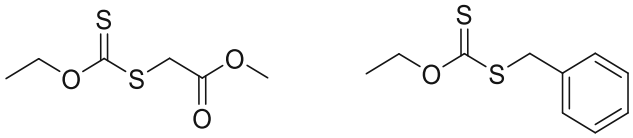
B.1.2 Choice of RAFT agents

When choosing a suitable RAFT agent for a specific polymerization, it is necessary to consider the type of used monomer (e.g. acrylates, acrylamides, styrenes, vinyl esters…). As already mentioned, vinyl esters belong to the group of less activated monomers (LAMs), but their radicals show high reactivity and therefore high affinity towards the addition to activated double bonds like the C=S double bond in RAFT agents. Using CTAs with Z-groups, which are able to strongly stabilize the formed intermediate radical, leads to retardation or inhibition of the polymerization of vinyl esters, since this impedes fragmentation, and therefore termination between intermediate radicals and either another intermediate species or a propagating radical is more likely to happen. Hence, trithiocarbonates or dithioesters, which are both known to control RAFT polymerizations of (meth) acrylates, (meth) acrylamides or styrenes, are not suitable for vinyl esters since they would cause inhibition.[295] However, less stable intermediate radicals and therefore, polymers with defined molecular weight and low dispersity are obtained if xanthates or dithiocarbamates are used to control the polymerization.[269] The general structure of RFAT agents suitable for vinyl esters is depicted in Figure 43.

Figure 43: General structure of RAFT agents suitable for vinyl esters

Since these agents contain oxygen and nitrogen with free electron pairs, respectively, they are able to reduce the double bond character of the C=S bond. It has to be noted, that dithiocarbamates with an aromatic Z-group (N-aryl) allow the preparation of polymers with narrower molecular weight distribution than in the case of CTAs bearing a N,N-dialkyl Z-group.[296]

Within this work, two xanthates were chosen as RAFT agents as they are easily accessible via straight-forward synthetic pathways. The used Z-group was selected based on the work of Stenzel *et al.,* [297] in which the influence of eight different xanthate substituents in the polymerization of vinyl acetate was examined, whereby the R-group stayed the same. The ethoxy group turned out to give the best results concerning low inhibition periods and low dispersity. Hence, methyl (ethoxycarbonothioyl)sulfanyl acetate (***MESA***), one of the most commonly used CTA for the RAFT polymerization of vinyl esters, was chosen for this work. As depicted in Figure 44, besides ***MESA*** also a second xanthate suitable for the RAFT polymerization of vinyl esters, namely S-benzyl O-ethyl carbonodithioate (***BED***), should be investigated in this thesis regarding their suitability for the RAFT polymerization of different vinyl esters.



MESA **BED**

Figure 44: Chosen RAFT agents for the controlled polymerization of vinyl esters

So far, ***MESA*** was mainly used for the thermally initiated RAFT polymerization of vinyl acetate (**VAc**) either in bulk,[297,298] or miniemulsion.[299,300] Furthermore, ***MESA*** served as CTA in the photo initiated polymerization of vinyl acetate in bulk[301,302] as well as in fluoroalcohols.[303,304] Some literature also reports the preparation of block copolymers consisting of **VAc** and vinyl pivalate,[305] t-butyl acrylate[306] or BMDO (5,6-benzo-2-methylene-1,3-dioxepane)[307] using ***MESA*** as RAFT agent. Besides, also the synthesis of polyethylene by means of RAFT polymerization with this CTA was reported in literature.[308]

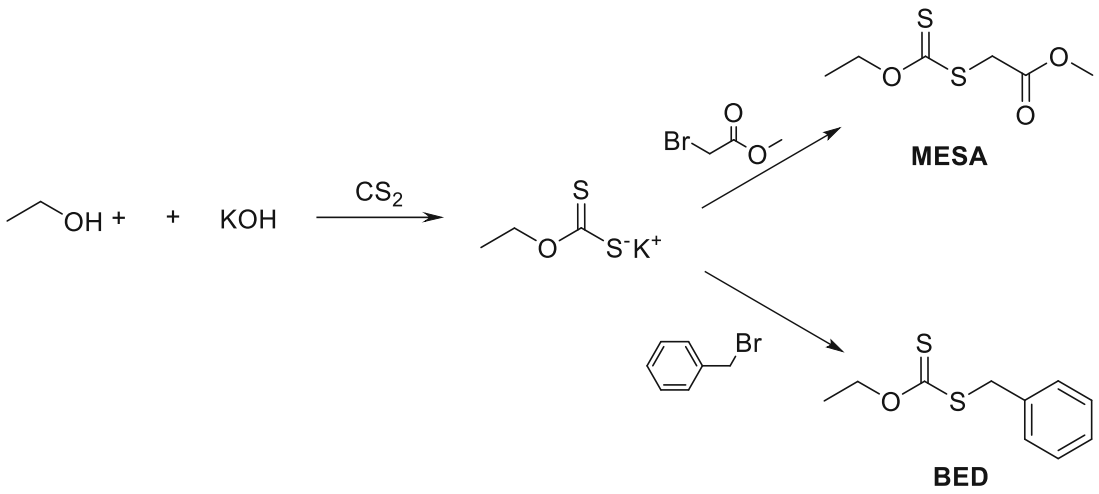
According to Harrisson *et al.*,[269] CTAs containing benzyl as R-group, should as well allow to control the molecular weight and the dispersity of polymers derived from vinyl esters.

In general, only a few groups investigated S-benzyl O-ethyl carbonodithioate (***BED***) as CTA, whereby a broad variety of different types of monomers was used. It was found that ***BED*** does not lead to satisfying results if applied in RAFT polymerization of a thiophene derivative (2,5-dibromo-3-vinylthiophene),[309] phenyl vinyl sulfide[310] or N-acryloyl-L-tryptophan,[311] since Đ values clearly above 2.0 were obtained. Furthermore, ***BED*** was tested in the RAFT polymerization of N-vinylpyrrolidone,[312-314] N-vinylcarbazole,[315,316] N-vinylphthalimide,[317] 2-methyl-N-vinylindole,[318] N-vinylcaprolactam,[319] different vinyl sulfonate esters[320] and methyl acrylate. [321] However, results were not completely satisfying, since obtained dispersities

ranged from 1.3 to 1.8. The only vinyl ester, which was successfully polymerized in a controlled manner using ***BED*** so far, is vinyl acetate. Beside its homopolmyer[322,323], copolymers with N-vinylpyrrolidone,[322] isopropenyl acetate[322] or N-vinylcarbazole were prepared. Furthermore, the synthesis of a block copolymer consisting of N-vinylpyrrolidone in the first and vinyl acetate in the second block was reported in literature.[314]

B.1.3 Synthesis of RAFT agents

The two chosen xanthates, namely ***MESA*** and ***BED***, were synthesized via a 2-step one-pot reaction according to literature.[297] Both CTAs possess the same Z-group (ethoxy), but different R-groups (methyl acetate or phenyl). Hence, different bromides had to be used for their syntheses.



For the preparation of ***MESA*** and ***BED*** in the first step potassium ethyl xanthate was prepared by dissolving potassium hydroxide in dry ethanol, followed by the slow addition of carbon disulfide as described by Stenzel *et al.*[297] In a second step, either methyl 2-bromoacetate[297] or benzyl bromide[312,324] was added in situ to obtain the desired products. ***MESA*** was then purified by filtering through basic aluminum oxide to obtain a yellow liquid with a yield of 80%. ***BED*** was received as slightly yellow liquid (61% yield) after purification by column chromatography.

B.1.4 Homopolymerization of hydrophobic vinyl esters

B.1.4.1 Determination of monomer conversion, molecular weight and dispersity

The conversion of the vinyl ester monomers was calculated from ^{1}H-NMR spectra. At defined time intervals during the polymerizations and at the end of each polymerization a sample of approximately 100 µL was withdrawn from the reaction mixture and quenched by cooling in an

ice bath. The samples were diluted with 600 µL of deuterated chloroform and ^{1}H-NMR spectra were recorded.

For analysis of RAFT polymers of vinyl esters, it is not necessary to use an internal standard as the signal from the polymer backbone can serve as reference signal. Figure 45 depicts the characteristic signals resulting from the double bond of a vinyl ester before (a) and in the course of the polymerization (b).

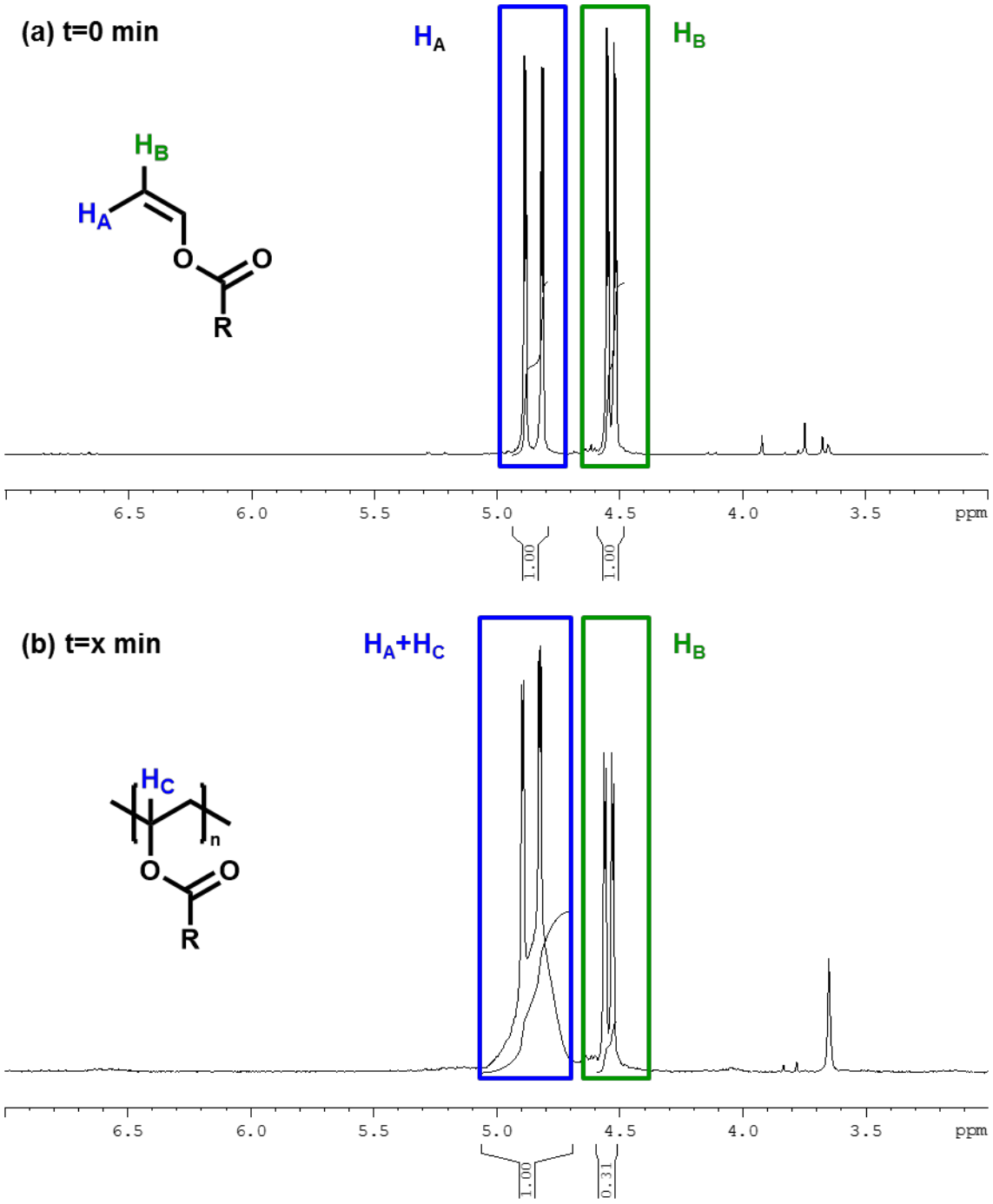


Figure 45: Typical ^{1}H-NMR spectra of a vinyl ester before, t=0, (a) and in the course of the polymerization t=x, (b)

At the beginning (t=0 min) the signal of the cis-proton **H_A** of the double bond can be seen at ~4.85 ppm and the signal of the corresponding trans-proton **H_B** appears at ~4.55 ppm. The ratio between these two signals is 1:1. While the polymerization proceeds, the intensity of **H_A** and **H_B** signals decreases as the monomer is consumed. A new signal **H_C** (also at ~4.85 ppm) is generated, resulting from the CH group of the polymer backbone. Thus, the signal at 4.85 ppm is the sum of the signal peaks of **H_A** and **H_C** (see Figure 45). As the decrease of the intensity of the **H_A** signal corresponds to the **H_C** signal increase, the integral of this peak stays constant. By comparing this integral to the integral of proton **H_B**, which represents the residue amount of monomer, the conversion can be calculated by using Equation 13.

$$C_M = Int\ (H_A + H_C) - Int\ (H_B) \qquad \textbf{Equation 13}$$

C_M	Monomer conversion at time t=x [ ]
Int (H_A+H_C)	Integral of the cis-proton and the proton resulting from the polymer backbone [ ]
Int (H_B)	Integral of the trans-proton [ ]

On basis of the monomer conversion C_M, the molecular weight of the resulting polymers can be calculated using Equation 7 (see chapter A).

Again, size exclusion chromatography was used to determine the relative molecular weight $M_{n,SEC}$ and the dispersity Đ of the synthesized vinyl ester based polymers. The withdrawn samples were dissolved in THF, filtered via a syringe filter and then analyzed at 40 °C at a flow rate of 1 mL THF per minute.

B.1.4.2 Kinetic studies of RAFT polymerizations of hydrophobic vinyl esters

In order to proof the controlled character, kinetic studies on the RAFT polymerizations were conducted with the vinyl esters **VAc**, **VH** and **VD** using ***MESA*** as CTA.

The needed amounts of all starting materials (initiator, RAFT agent and monomer) were weighted into reaction vials. Afterwards, the tubes were sealed with a rubber septum and the mixture was purged with argon for a minimum of 30 minutes to remove oxygen, which might lead to reaction inhibition. In the case of vinyl acetate, samples were frozen in liquid nitrogen prior to purging in order to prevent evaporation of the volatile monomer. Afterwards, the tubes were put into an aluminum block preheated to 60 °C and left there for 4 or 5 hours. The reactions were stopped by cooling in an ice bath and the samples were stored at -18 °C before analysis.

All kinetic studies with ***MESA*** as CTA were performed in bulk. The molar ratio between CTA and the initiator AIBN was 10:1 and the target molecular weight was 10 kDa. Samples for ^{1}H-NMR spectroscopy and SEC measurements were withdrawn via a syringe during the reaction. The results of those experiments are shown in Table 14, Table 15 and Table 16.

Table 14: Results of the kinetic study of the RAFT homopolymerization of VAc using *MESA* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa

Time [min]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
20	1	0.3	0.4	1.33
40	8	0.9	0.6	1.73
60	18	1.8	1.6	1.34
90	31	3.0	3.0	1.26
120	41	3.9	4.0	1.23
180	58	5.5	5.9	1.22
240	63	6.0	6.5	1.28

Table 15: Results of the kinetic study of the RAFT homopolymerization of VH using *MESA* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa

Time [min]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
20	8	0.7	0.5	1.22
40	22	1.7	1.5	1.35
60	41	3.0	2.7	1.31
120	71	5.0	4.8	1.35
180	83	5.9	5.5	1.44
240	88	6.2	5.7	1.47

Table 16: Results of the kinetic study of the RAFT homopolymerization of VD using *MESA* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa

Time [min]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
20	2	0.4	0.6	1.43
40	5	0.8	1.2	1.29
60	12	1.5	1.9	1.33
120	38	4.2	4.7	1.22
180	57	6.2	6.7	1.22
240	67	7.3	7.8	1.26

Figure 46 depicts the course of monomer conversion with time for the RAFT polymerization of **VAc**, **VH** and **VD** with ***MESA*** as CTA.

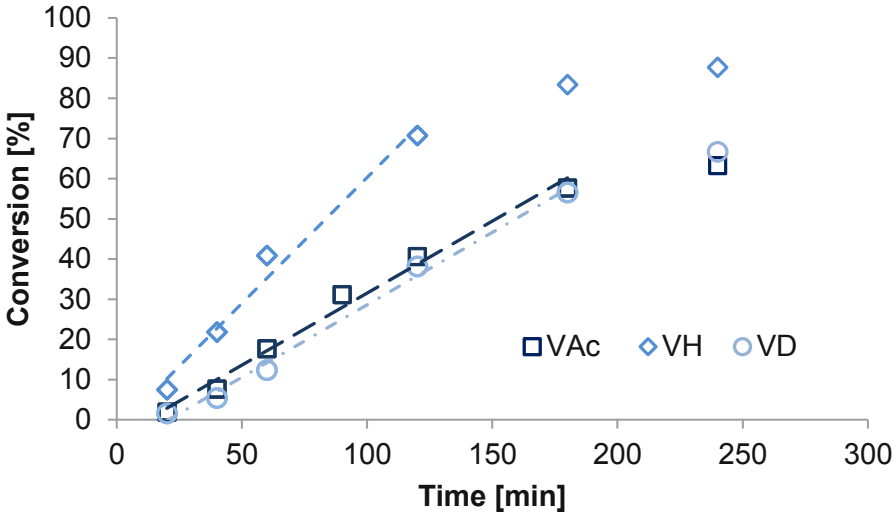


Figure 46: Time-dependent conversion of the RAFT homopolymerization of VAc, VH and VD using *MESA* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa

Despite the low conversion in the case of **VAc** (58% after 3 hours), the reaction slowed down due to the high viscosity of the reaction mixture. Furthermore, an inhibition period of 17 min could be estimated from the intersection of the linear region of the graph at the beginning of the polymerization (40 to 120 minutes) and the x-axis, whereby the conversion of 1% after 20 minutes was not considered. Stenzel *et al.*[297] published kinetic studies of **VAc** with ***MESA*** as CTA at 60 °C using AIBN as initiator and obtained a higher inhibition time of 51 min for a CTA-to-initiator ratio of 10:1, but it has to mentioned that they aimed at much higher molecular weights.

A linear relation can also be seen within the first two hours for the RAFT polymerization of **VH**. Afterwards, the graph flattens due to higher monomer conversion (83% after 3 hours). Those data points were not taken into account for determination of inhibition, which was graphically determined, leading to a result of roughly 4 minutes. Compared to **VAc**, viscosity of the reaction mixture is lower because of the longer side chains.

The monomer conversion of **VD** was constantly increasing over the whole duration of the polymerization process. After 4 hours a conversion of 67% was achieved, indicating lower reactivity of this monomer compared to **VH**. For determination of the inhibition time, the conversion after 20 minutes was not taken into account since only a value of 1.6% was obtained, which was within the inaccuracy limits of ^{1}H-NMR spectroscopy. Also, the data point at the end of the polymerization was omitted since a distinct flattening of the conversion curve

is visible. Inhibition period was again estimated in a graphical way leading to a result of 24 minutes of inhibition.

Figure 47 depicts the development of the molecular weight determined by SEC measurements ($M_{n,SEC}$), as well as values calculated from ^{1}H-NMR spectra ($M_{n,NMR}$), with increasing monomer conversion. Furthermore, the dispersity Đ of the polymer is shown as a function of the monomer conversion.

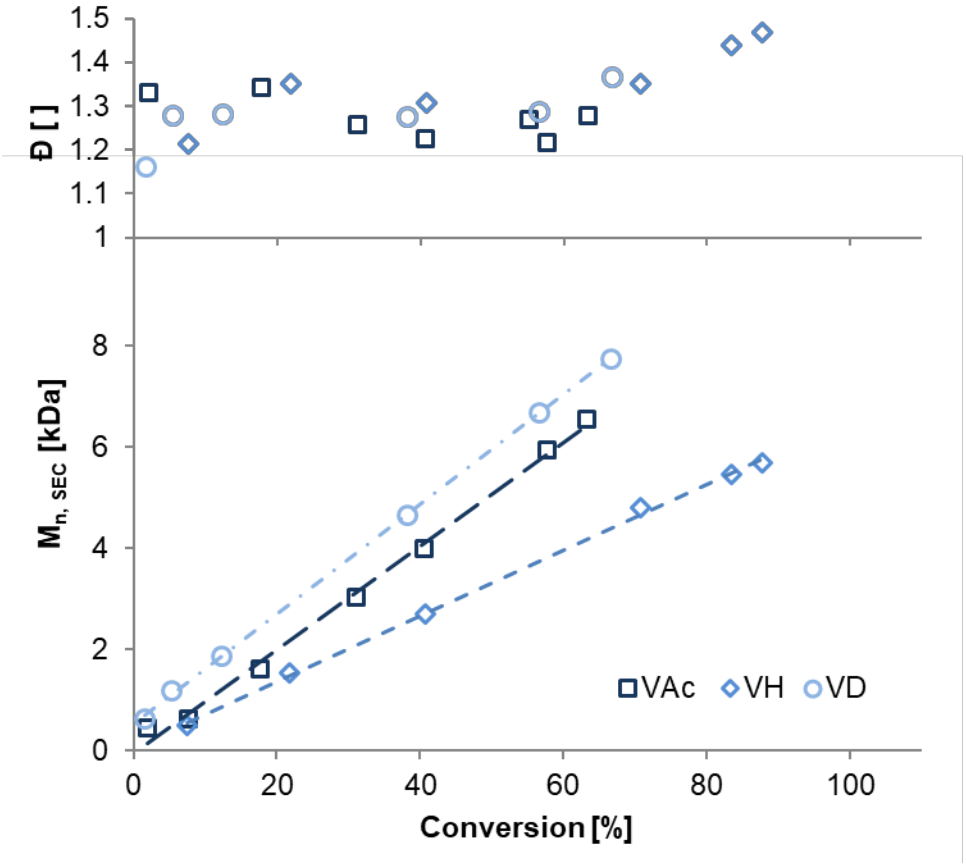


Figure 47: Course of molecular weight and dispersity with conversion for the RAFT homopolymerization of VAc, VH and VD using *MESA* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa

As can be seen, the molecular weight $M_{n,SEC}$ displayes a linear correlation with monomer conversion, which is one indicator for a controlled polymerization. Furthermore, the dispersity of the polymer stays below 1.35. up to conversion <70%. Even in the case of high monomer conversion (88% for **VH**) dispersity is <1.5. Finally, the reaction order was analyzed by plotting the logarithmic monomer concentration against the time, as can be seen in Figure 47. The data point obtained for a reaction time of 20 minutes for the polymerization of **VH** and **VD** was omitted due to the low monomer conversion at this point.

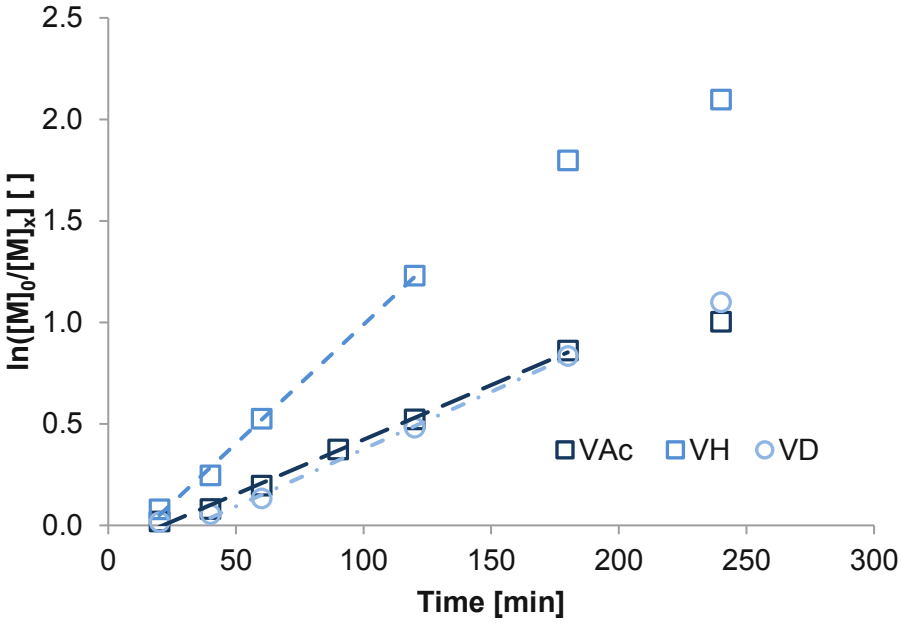


Figure 48: Pseudo first order plot conversion for the RAFT homopolymerization of VAc, VH and VD using *MESA* as CTA with a [CTA]:[I] ratio of 10:1 and a target molecular weight of 10 kDa

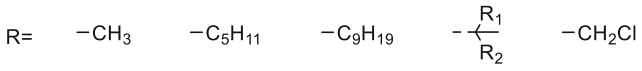
The plot shows good linear correlation within the first 180 minutes of the polymerization of **VAc**. Afterwards the slope of the graph declined, most probably due to the high viscosity impeding the mobility of the monomers. However, within the first 3 hours RAFT homopolymerization of **VAc** with ***MESA*** as CTA is driven by a first order kinetic.

The logarithmic monomer concentration $\ln[M_0/M_x]$ showed linear coherence with time over the complete polymerization process of **VH** and **VD** with ***MESA*** as CTA. This clearly shows that ***MESA*** is a suitable CTA for the polymerization of those vinyl ester monomers under the selected reaction conditions and that increasing length of the side chain does not have an influence.

B.1.4.3 Evaluation of the RAFT polymerization of various vinyl esters using MESA as CTA

RAFT polymerizations of all hydrophobic vinyl esters shown in Figure 42 were studied using ***MESA*** as CTA. In regard to the future syntheses of block copolymers, it was not only tried to polymerize vinyl ester by means of RAFT polymerization in bulk, but also in solution. The concentration of initiator was varied in order to find out the influence on polymerization speed and dispersity.

MESA



VAc **VH** **VD** **VnN** **VClAc**

$R_1=C_xH_{2x+1}$ $R_2=C_{6-x}H_{13-2x}$ x=1...5

B.1.4.3.1 Polymerization in bulk

For RAFT homopolymerizations of **VAc**, **VH**, **VD**, **VnN** and **VClAc** in bulk, ***MESA*** was used as CTA and AIBN acted as thermal initiator. Nearly all polymerizations were performed at 60 °C. An exception regarding initiator and temperature was made for **VClAc**. Since it was known from literature,[294] that AIBN is not a suitable initiator for the RAFT polymerization of this monomer, leading to long periods of retardation, 1,1'-azobis(cyclohexane-1-carbonitrile) (V-40) was used instead. The syntheses of these polymers were carried out at 80 °C, as it was found in literature, that in this specific case higher temperatures lead to lower dispersity values.[294]

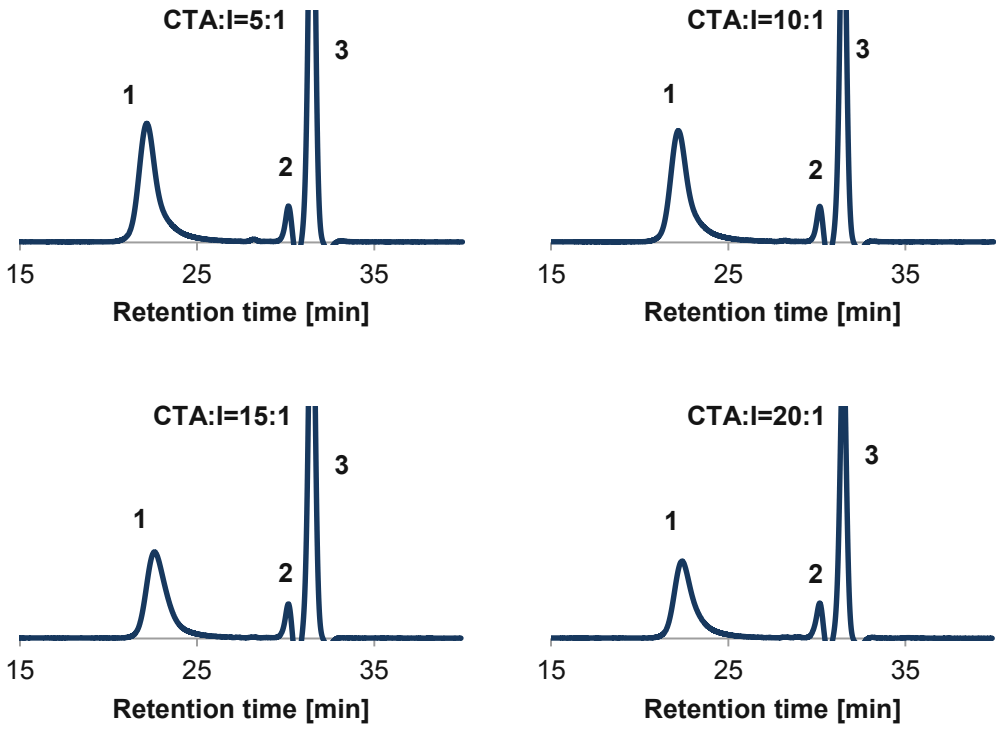
The targeted molecular weight was 5 kDa. The ratio between ***MESA*** and initiator was varied from 20:1 to 5:1 in order to investigate the effect on monomer conversion and on the dispersity of the resulting polymers. The procedure was the same as for kinetic studies, but samples for analyses (^{1}H-NMR spectroscopy and SEC) were only withdrawn at the end of the reaction. The reaction time was not fixed, since polymerizations without solvent lead to an increase in viscosity of the reaction mixture with growing degree of polymerization. The reactions were quenched as soon as the viscosity got obviously very high and stirring was not possible anymore. So, depending on the amount of AIBN and the monomer, reaction times ranged from 120 to 330 minutes. Reproducibility of the polymerizations was proven as every reaction was performed at least in duplicate. In Table 17 the results of these polymerizations are displayed.

Table 17: Results of RAFT homopolymerizations of various vinyl esters in bulk using *MESA as CTA* at different CTA-to-initiator ratios and a target molecular weight of 5 kDa

		[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]	Time* [min]
VAc	**pVAc-9**	5	77	3.8	3.5	1.27	140
	pVAc-10	10	71	3.5	2.2	1.20	250
	pVAc-11	15	67	3.5	2.7	1.21	330
	pVAc-12	20	62	3.1	3.0	1.24	330
VH	**pVH-9**	5	97	4.2	3.7	1.36	210
	pVH-10	10	95	4.7	3.7	1.39	220
	pVH-11	15	92	4.4	3.8	1.35	230
	pVH-12	20	83	4.1	3.4	1.33	240
VD	**pVD-9**	5	96	4.8	5.6	1.24	255
	pVD-10	10	95	4.8	5.5	1.23	285
	pVD-11	15	91	4.6	5.1	1.21	285
	pVD-12	20	86	4.3	5.3	1.18	285
VnN	**pVnN-9**	5	88	4.4	3.8	1.18	168
	pVnN-10	10	85	4.2	3.6	1.16	180
	pVnN-11	15	79	4.1	2.6	1.17	198
	pVnN-12	20	78	3.6	3.1	1.16	210
VClAc	**pVClAc-9**	5	83	4.1	4.2	1.35	120
	pVClAc-10	10	82	4.2	4.0	1.34	200
	pVClAc-11	15	84	4.2	4.0	1.36	265
	pVClAc-12	20	77	3.9	3.7	1.32	295

* Time until reaction mixture becomes too viscous for stirring

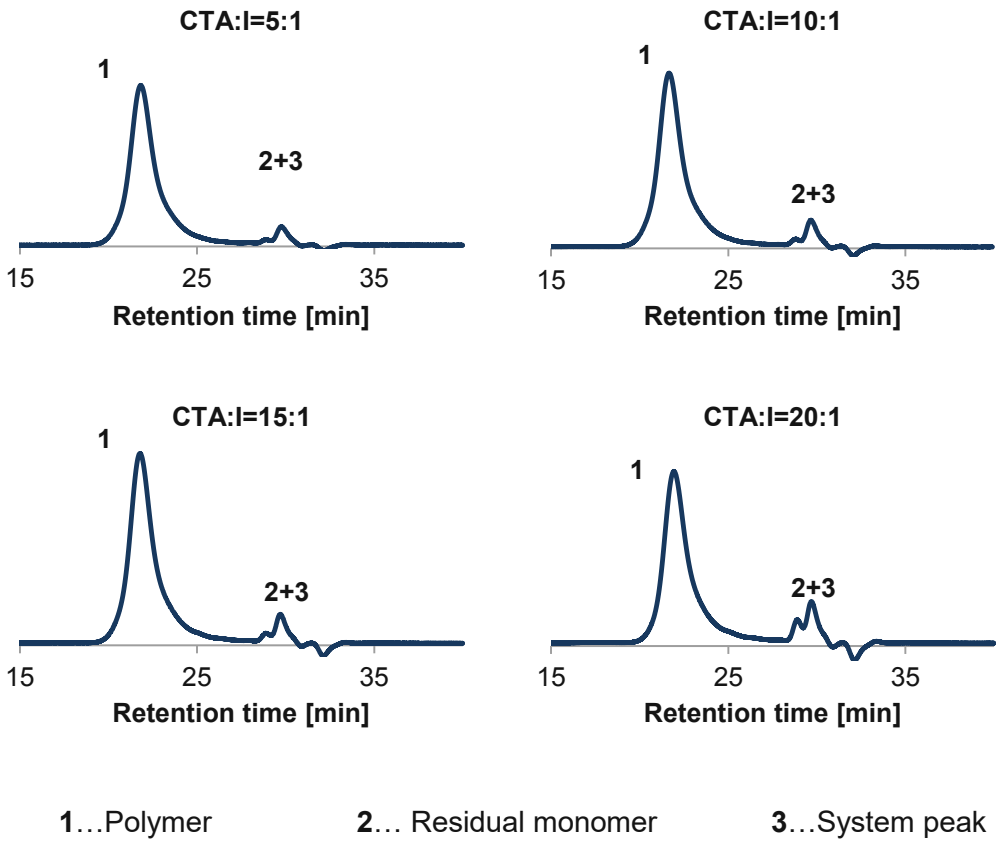
Polymerizations of **VAc** performed in bulk show conversions in the range from 62% to 77%. Lowest conversion is observed at the highest CTA:I ratio. In all cases, the dispersity is <1.27, dispersity values are similar and no peak shoulders are visible in SEC spectra (see left peaks in Figure 49), which indicates that the RAFT polymerization of **VAc** proceeded in a controlled manner under these reaction conditions.



1…Polymer **2**… Residual monomer **3**…System peak

Figure 49: SEC traces of RAFT homopolymerization of VAc with *MESA* as CTA in bulk using AIBN as initiator at different CTA-to-initiator ratios

Polymerizations of **VH** in bulk proceed relatively fast, leading to reaction times of maximal 4 hours. With high amounts of AIBN almost complete monomer conversion can be observed. Conversion decreases slightly with decreasing amount of AIBN. With the highest amount of initiator, a conversion of 83% is achieved. Chromatograms resulting from SEC analyses of RAFT polymerizations of **VH** in bulk are depicted in Figure 50.



1…Polymer **2**… Residual monomer **3**…System peak

Figure 50: SEC traces of RAFT homopolymerization of VH with *MESA* as CTA in bulk using AIBN as initiator at different CTA-to-initiator ratios

Besides low Đ-values (<1.4), also the shapes of these graphs indicate controlled polymerizations since no shoulders are visible. In all chromatograms only small amounts of residual monomer (peak **2)** are visible, which confirm the high conversion found by ^{1}H-NMR analyses.

Similar results were obtained for RAFT homopolymerizations of **VD** in bulk. All of them turned out to proceed well under the selected reaction conditions, as evidenced by high monomer conversion of up to 96% and dispersity values below 1.25 in all cases. Additionally, polymerizations proceeded quite fast as the reaction time was less than 5 hours for all reactions. Conversion decreased slightly with increased amount of initiator. Compared to **VH**, **VD** is less reactive as evidenced by longer reaction times needed to reach the same monomer conversion. This can be assigned to longer side chains of **VD**. Figure 51 illustrates the graphs resulting from SEC measurements.

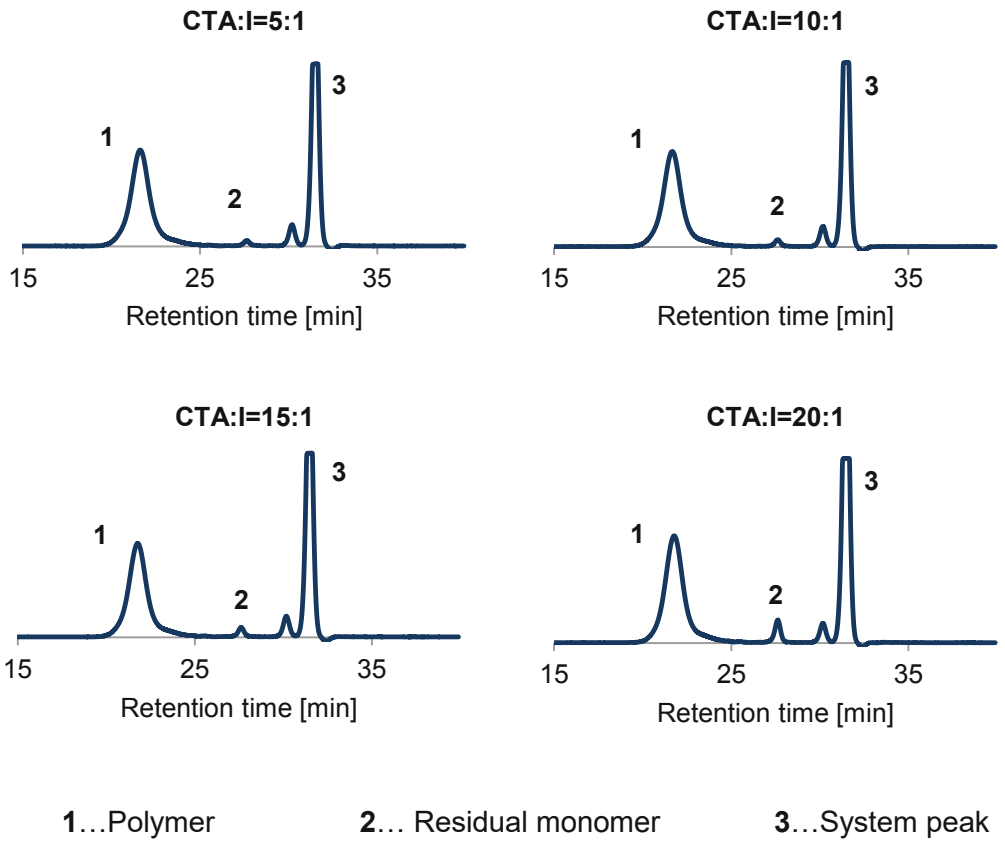
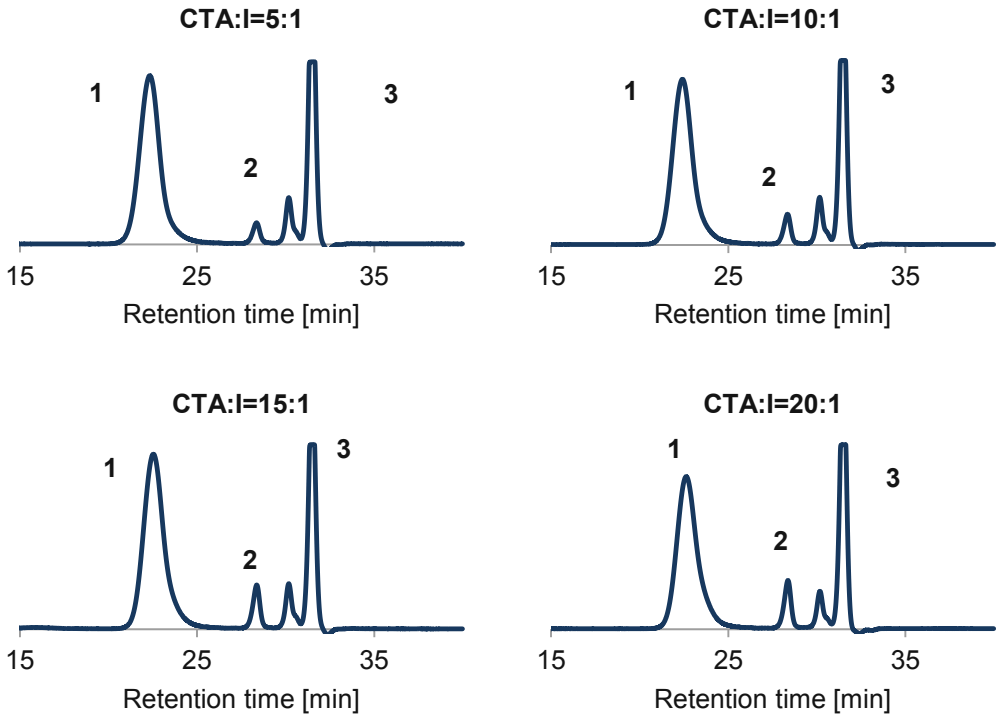


Figure 51: SEC traces of RAFT homopolymerization of VD with *MESA* as CTA in bulk using AIBN as initiator at different CTA-to-initiator ratios

Size exclusion chromatograms reveal narrow and well-shaped polymer peaks (**1a** and **1b**) without bimodality, implicating a controlled polymerization following the RAFT mechanism under the selected conditions.

Looking at the polymerizations of **VnN** conducted in bulk, the results show that all reactions proceed well and, again, monomer conversion decreased if the quantity of AIBN is reduced. The obtained values of conversion are in the range between 78 and 88%. Compared to **VH** and **VD** these values are lower and higher amounts of initiator are needed, but viscosity starts to increase at lower monomer conversion. Hence, it can be concluded that a high viscosity does not necessarily implicate almost full monomer conversion. The amount of initiator does not affect the dispersity of these polymers since the obtained values are all slightly below 1.20. Figure 52 depicts the SEC traces of all polymerizations of **VnN** in bulk.

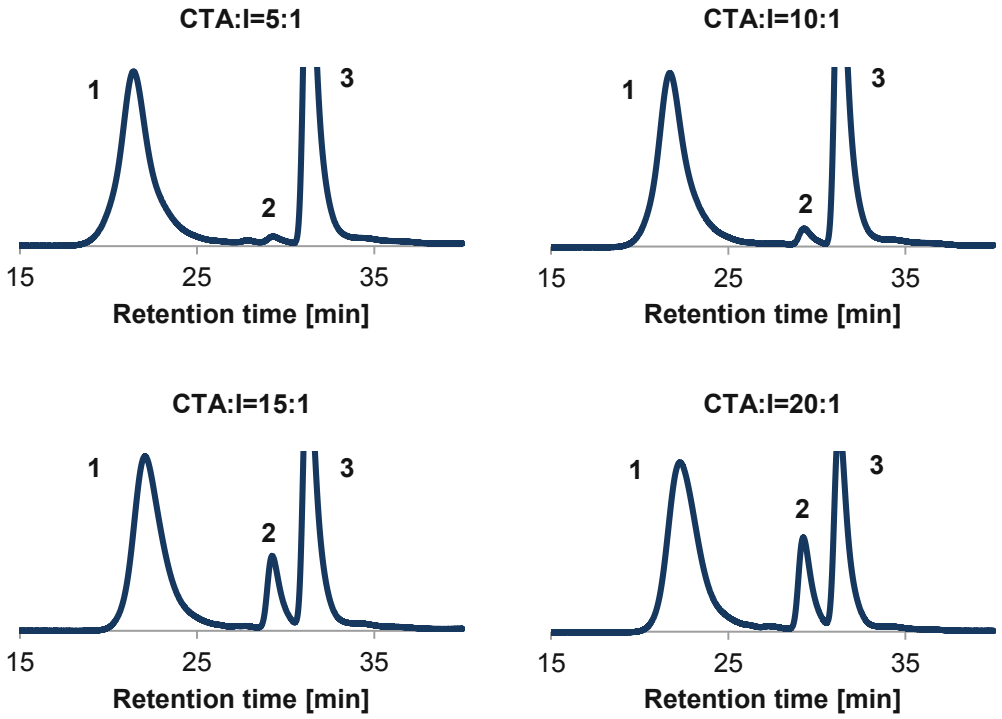


1…Polymer **2**… Residual monomer **3**…System peak

Figure 52: SEC traces of RAFT homopolymerization of VnN with *MESA* as CTA in bulk using AIBN as initiator at different CTA-to-initiator ratios

For all polymers very narrow and well-shaped peaks **1a** are visible in the chromatograms.

RAFT polymerizations of **VCIAc** with V-40 as initiator proceeded quite fast. Depending on the amount of initiator, monomer conversion of around 80% could be reached within 2-5 hours. Dispersity values are around 1.35 and therefore in the range of **VH**, but significantly higher than those of **VD** and **VnN** at similar monomer conversion. Figure 53 illustrates the chromatograms obtained from SEC measurements of all synthesized polymers from **VCIAc** in bulk.



1…Polymer **2**… Residual monomer **3**…System peak

Figure 53: SEC traces of RAFT homopolymerization of VClAc with *MESA* as CTA in bulk using V-40 as initiator at different CTA-to-initiator ratios

The absence of shoulders or bimodality of the peaks indicates a controlled polymerization.

In general, a tendency towards lower monomer conversion along with less initiator is recognizable, whereby for all monomers no significant influence on the dispersity is visible. Comparing results from RAFT polymerizations for **VH** and **VD**, it turns out that reactions proceed faster for **VH**, what was already indicated by the conducted kinetic studies (see chapter B.1.4.2). However, it can be seen that in this case the faster reaction results in higher dispersity values. Contrary to that, if branched **VnN** is used as monomer, reactions are speeded up compared to linear **VH** and **VD**. Another important factor was found in the viscosity of the reaction mixture, which limits monomer conversion as it affects the possibility of stirring the reaction mixture. Comparing linear monomers VH and VD, similar values for monomer turnover can be achieved until the solutions becomes too viscous. This indicates, that viscosity is not affected by the length of the side chains, but by the reaction speed. Looking at branched **VnN**, a different picture shows up. Due to the branched side chain, viscosity increases faster and sufficient stirring is not possible anymore at lower monomer conversion.

B.1.4.3.2 Polymerization in Solution

In addition to the reactions in bulk, RAFT polymerizations of the selected vinyl esters were also performed in solution at a monomer concentration of 5 mol/L in dry benzene. Again, the amount of initiator AIBN and V-40, respectively, was varied, while the quantity of RAFT agent stayed the same in order to reach a target molecular weight of 5 kDa. Polymerization time was 20 hours. Due to the presence of the solvent, viscosities of the mixtures were low enough for constant stirring. The reaction temperature was 60 °C for **VAc**, 70 °C for **VH**, **VD** and **VnN**, and 80 °C for **VClAc**. Reproducibility was shown by at least twofold performance of each reaction. Table 18 points out the collected results from ^{1}H-NMR spectroscopy and SEC.

Table 18: Results of the RAFT homopolymerizations of various vinyl esters in dry benzen using *MESA as CTA* at different CTA-to-initiator ratios and a target molecular weight of 5 kDa

		[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]	Time [min]
VAc	**pVAc-1**	5	45	2.4	1.4	1.18	1200
	pVAc-2	10	32	1.5	1.3	1.21	1200
	pVAc-3	15	20	1.1	0.8	1.27	1200
	pVAc-4	20	14	0.9	0.9	1.27	1200
VH	**pVH-1**	5	92	4.4	3.5	1.40	1200
	pVH-2	10	83	4.5	3.6	1.39	1200
	pVH-3	15	61	3.2	2.8	1.27	1200
	pVH-4	20	49	2.5	2.2	1.26	1200
VD	**pVD-1**	5	73	3.7	4.4	1.22	1200
	pVD-2	10	58	3.0	3.7	1.19	1200
	pVD-3	15	46	2.9	3.5	1.18	1200
	pVD-4	20	29	1.5	2.1	1.20	1200
VnN	**pVnN-1**	5	19	1.1	1.2	1.22	1200
	pVnN-2	10	n.c.	-	-	-	1200
	pVnN-3	15	n.c.	-	-	-	1200
	pVnN-4	20	n.c.	-	-	-	1200
VClAc	**pVClAc-1**	5	97	4.7	4.5	1.47	1200
	pVClAc-2	10	90	4.2	3.9	1.37	1200
	pVClAc-3	15	68	3.3	3.1	1.38	1200
	pVClAc-4	20	62	3.1	2.8	1.36	1200

n.c.= no monomer conversion

Polymerizations of **VAc** in dry benzene as solvent proceeded very slowly and monomer conversion of maximum 45% was reached within a period of 20 hours at a CTA-to-initiator-ratio of 5:1. This value decreased significantly with reducing the amount of initiator. In all cases low dispersity values <1.3. could be reached.

Figure 54 depicts the SEC traces obtained from these polymerizations.

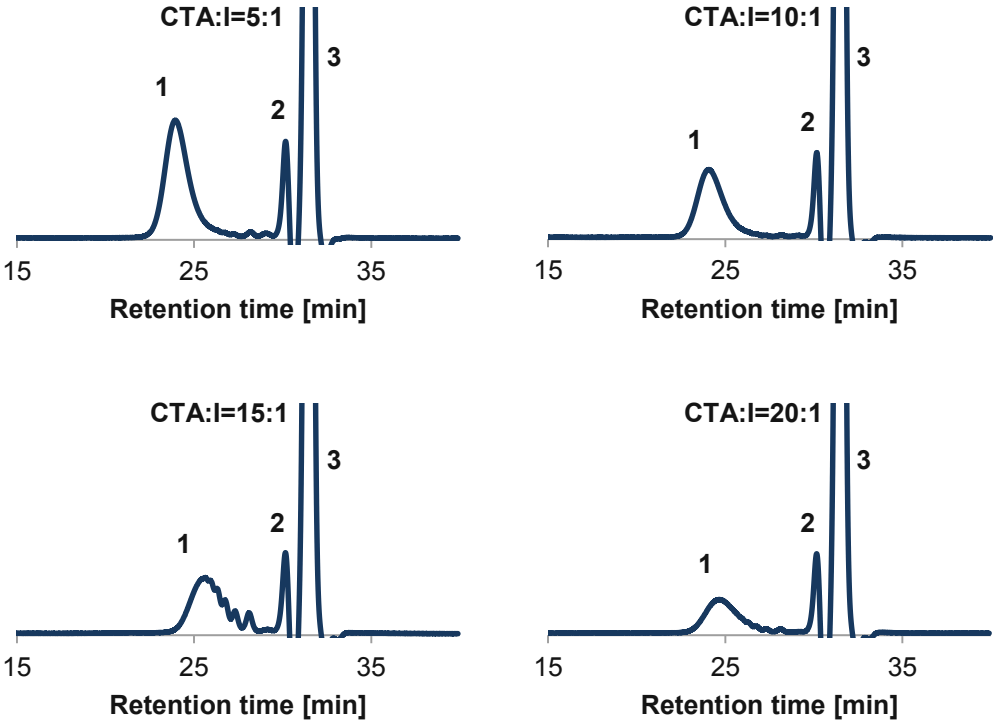


Figure 54: SEC traces of RAFT homopolymerization of VAc with *MESA* as CTA in dry benzene using AIBN as initiator at different CTA-to-initiator ratios

Dispersity values in Table 18 suggest that all these polymerizations delivered polymers with a narrow molecular weight distribution. However, taking a closer look at the shape of the polymer peaks **1a** in

Figure 54, a multimodal molecular weight distribution for CTA-to-initiator ratios of 15 and 20 is revealed. This can be explained by the low conversion and the resulting low molecular weight. Reactions carried out with higher amounts of initiator lead to narrow molecular weight distributions and well-shaped peaks in the SEC spectra indicating a controlled process.

Result of RAFT polymerizations of **VH** performed in solution show that monomer conversions of almost 50% up to more than 90% can be reached under these conditions. Dispersity values are in the range from 1.26 to 1.40 and the absence of any shoulders to the polymer peak in the SEC spectra (peaks **1a** in Figure 55) indicate a successful controlled polymerization of **VH.**

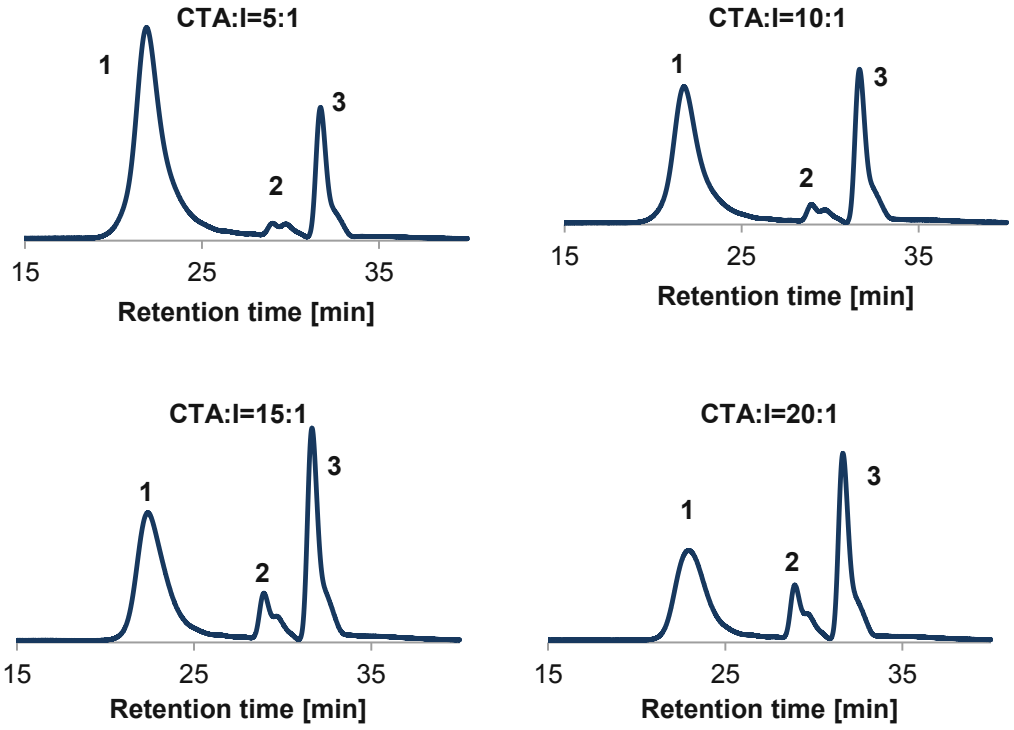


Figure 55: SEC traces of RAFT homopolymerization of VH with *MESA* as CTA in dry benzene using AIBN as initiator at different CTA-to-initiator ratios

RAFT homopolymerizations of **VD** in solution resulted in conversions between 29 and 73%. Again, conversion significantly decreased with increasing [CTA]:[I] ratio. Contrary to monomer conversion, where a significant effect of the initiator amount can be observed, dispersity is not affected. Dispersity values around 1.20 and the absence of any shoulders in the SEC curves indicate that the polymerizations proceed in a controlled manner (see Figure 56).

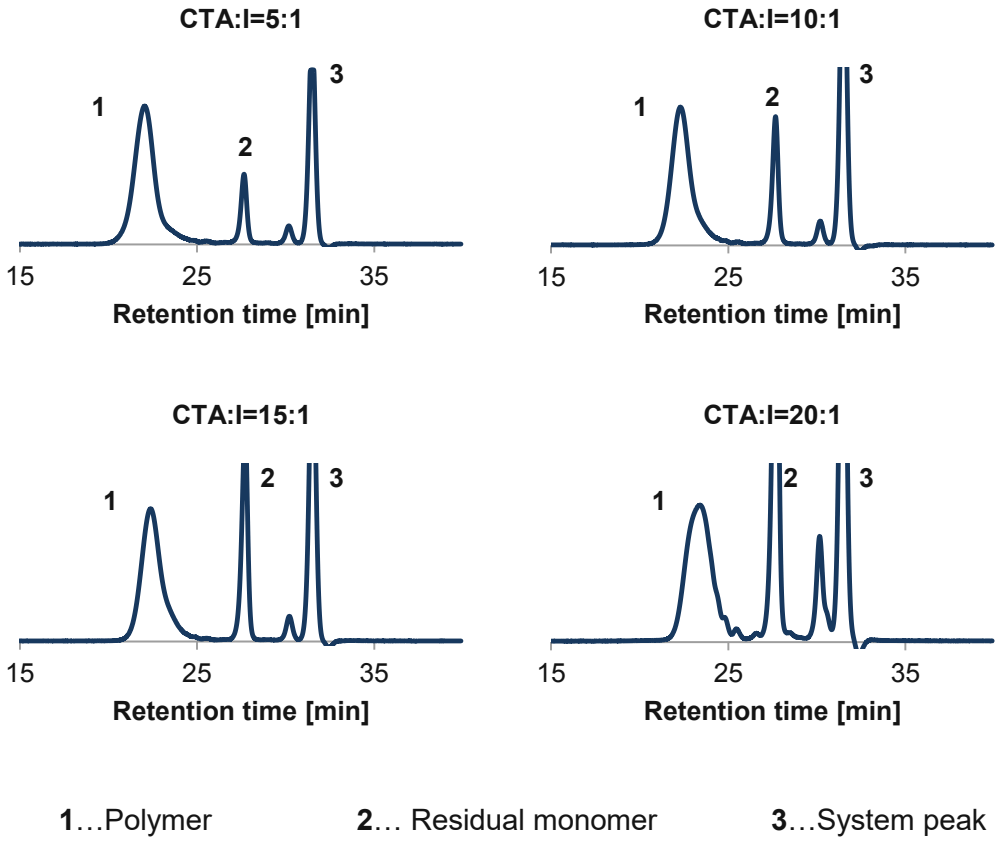


Figure 56: SEC traces of RAFT homopolymerization of VD with *MESA* as CTA in dry benzene using AIBN as initiator at different CTA-to-initiator ratios

RAFT polymerizations of **VnN** in solution show divergent results. At a CTA-to-initiator-ratio of 5:1 a monomer conversion of merely 19% is reached. When initiator amounts of 10 mol% or less (related to the amount of CTA) are applied, no monomer conversion can be observed after a polymerization time of 20 hours. SEC analysis of the 5:1 experiment revealed a peak with shoulders indicating a lack of control for this polymerization. Since this reaction proceedes very slowly, side reactions like chain transfer are more likely to happen, whereupon new chains are formed, having a lower molecular weight.

Also, in the case of RAFT Polymerization of **VClAc** monomer conversion decreases with the amount of initiator. Almost full monomer conversion can be observed at high initator concentrations. For CTA-to-initiator ratios of 5:1 and 10:1 phase separation was observed at the end of the polymerization. The sticky and highly viscous polymer was covered by a thin layer of liquid (probably a mixture of monomer and solvent). Consequently, monomer conversion was low (<70%). Dispersity values were in the range of 1.35 to 1.50. Figure 57 depicts the chromatograms obtained from SEC measurements of samples withdrawn directly from the reaction mixture after quenching.

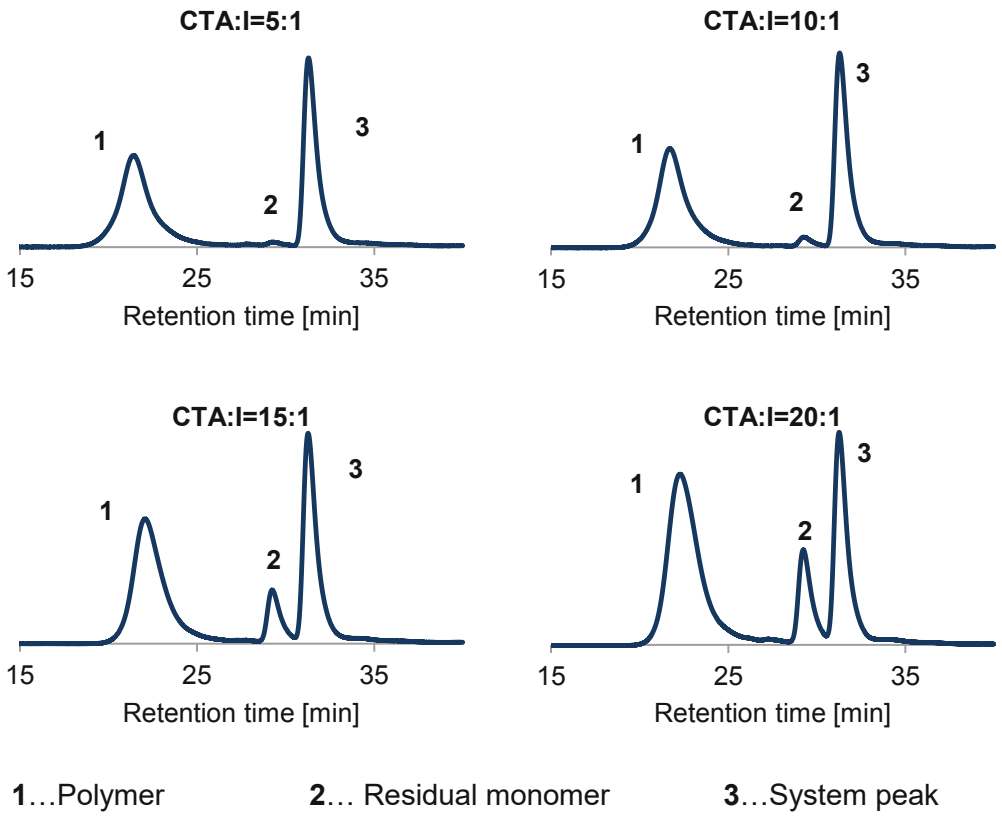


Figure 57: SEC traces of RAFT homopolymerization of VClAc with *MESA* as CTA in dry benzene using V-40 as initiator at different CTA-to-initiator ratios

The absence of shoulders and bimodality of the peaks **1** in the SEC traces indicate the controlled character of the polymerization under the selected reaction conditions.

A closer look at the RAFT polymerizations performed in solution reveals the following correlation (Figure 58).

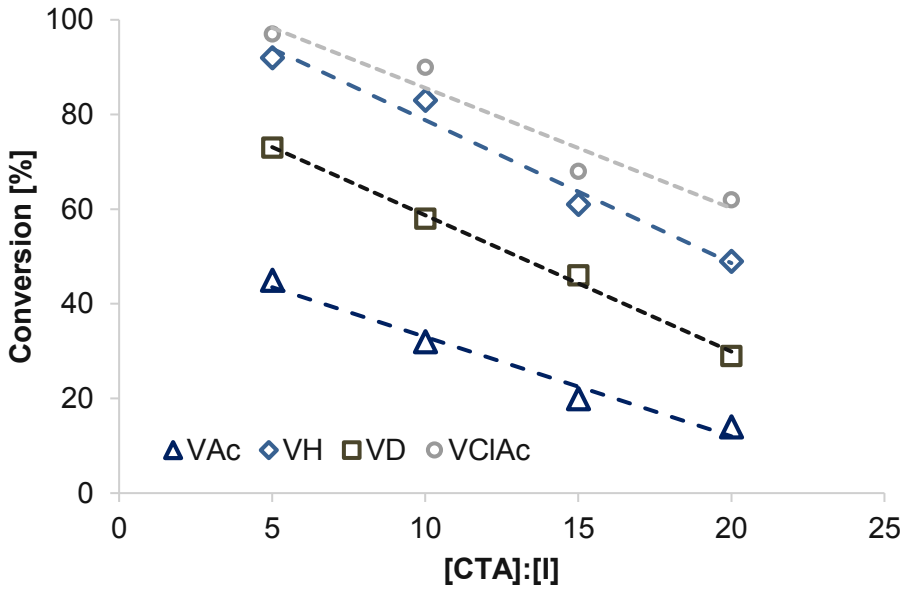


Figure 58: Correlation of monomer conversion of VAc, VH, VD and VClAc at different [CTA]:[I] ratios for reactions in solution

For all monomers, except **VnN** where the reaction only proceeds at high AIBN concentrations (not depicted), a linear correlation of the monomer conversion in dependence on the initiator amount is recognizable. In the case of **VAc**, extrapolation to a higher amount of initiator indicates that a change to a ratio of 2:1 will probably only lead to an increase of conversion of roughly 5% from 45% to 50%. Considering **VClAc** and **VH**, increasing the amount of initiator could lead to a reduction in reaction time. Nevertheless, there might also occur a worsening of dispersity leading to values above 1.5. For **VD** an increase to a ratio of 2:1 could lead to a conversion of around 82% instead of 73%. Since dispersity values are around 1.20, Đ should remain <1.5. Comparing **VH** and **VD**, it turns out that polymerizations of **VH** proceed faster than those of **VD**. This fact correlates with the results, which were found for polymerizations in bulk. Furthermore, it becomes obvious that polymerization speed is not only affected by viscosity, but also by the chemical structure of the monomers, to be precise, by the chain length of the linear side chains. Shorter side chains as for **VH** lead to higher polymerization speed compared to **VD**.

B.1.4.4 Comparison bulk and solution

RAFT homopolymerization of various hydrophobic vinyl esters in which ***MESA*** was used as CTA, yielded rather well-defined polymers. However, some significant differences were found depending on the used polymerization method (solution and bulk polymerization, respectively).

When choosing a specific type of reaction, it is necessary to consider its benefits, as well as its drawbacks.[325,326] By adding an inert solvent to a polymerization reaction mixture, as in case of a solution polymerization, the monomer concentration is decreased and therefore the process is slowed down, but polymers may show lower dispersity values. Furthermore, chain transfer to polymers and crosslinking are reduced, and at the same time, molar mass distribution gets narrower. Additionally, the viscosity of the reaction mixture is lowered, thus allowing a better transfer of heat and mass. This is an important fact, as especially in radical reactions, higher fluidity is desirable, since it prevents the undesired Trommsdorff effect. In contrast to that, polymerizations in bulk deliver pure polymers and proceed at higher reaction rates than those in solution. However, increase in viscosity during this process makes it more difficult to remove the polymerization heat. Thus, side reactions like chain transfer are more likely to happen. Additionally, the formation of polymers with a multimodal molecular weight distribution is promoted, not at least due to the gel effect.

In Table 19 the results of the experiments are summarized.

Table 19: Overview of monomer conversion and dispersity values for RAFT polymerizations using MESA as CTA in bulk and solution

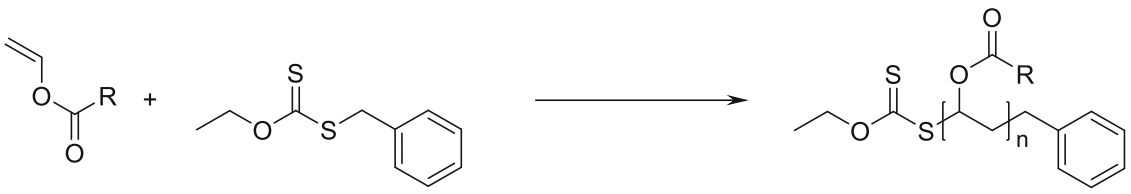
Monomer	[CTA]:[I]	C_M [%] bulk	C_M [%] solution	Đ [ ] bulk	Đ [ ] solution
VAc	5	77	45	1.27	1.18
	10	71	32	1.20	1.21
	15	67	20	1.21	1.27
	20	62	14	1.24	1.27
VH	5	97	92	1.36	1.40
	10	95	83	1.39	1.39
	15	92	61	1.35	1.27
	20	83	49	1.33	1.26
VD	5	96	73	1.24	1.22
	10	95	58	1.23	1.19
	15	91	46	1.21	1.18
	20	86	29	1.18	1.20
VnN	5	88	19	1.18	1.22
	10	85	n.c.	1.16	-
	15	79	n.c.	1.17	-
	20	78	n.c.	1.16	-
VClAc	5	83	97	1.35	1.47
	10	82	90	1.34	1.37
	15	84	68	1.36	1.38
	20	77	62	1.32	1.36

The conducted experiments show that RAFT polymerization is a complex topic and values are affected in different ways. Comparing monomer conversions for all polymerizations controlled by ***MESA***, the difference in reaction rate between reactions in solution and in bulk becomes obvious. As expected, reactions involving benzene as solvent lasting 20 hours, lead to partly significant lower turnover than bulk reactions within maximum five and a half hours, although in some cases higher temperatures were used. This can probably be assigned to lower rate constant resulting from lower monomer concentration. This effect is most evident in the polymerization of **VnN**. In bulk this polymerization was the fastest of all, but as soon as benzene is added as a solvent, there is a drastic decrease, so that no or only marginal conversion is achieved within 20 hours. Probably the fact that vinyl esters belong to the group of LAMs has an influence on the rate constant in solution and therefore on conversion.

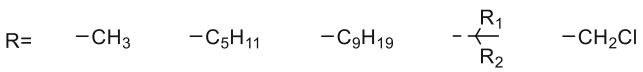
Contrary to the significant effect on the rate constant, dispersity is hardly effected by the addition of benzene. All values stayed in the same range below 1.5 as in bulk indicating also a controlled character of RAFT polymerizations in solution. Nevertheless, it has to be mentioned that these low values also for the reactions in bulk were probably ascribed to the small reaction volume of only a few milliliters, whereby the transport of heat was possible and therefore the Trommsdorff effect was unlikely to occur. For larger reaction volumes however, different results might be obtained with respect to this consideration.

B.1.4.5 Polymerization with BED as RAFT agent

Polymerizations with ***BED*** as CTA were performed using the same reaction parameters as for reactions with ***MESA***. Exceptions were made for the temperature, which was increased from 60 °C to 70 °C for reactions in bulk of **VH**, **VnN** and **VD**, since preliminary experiments showed no conversion at lower temperature.



BED



R=	$-CH_3$	$-C_5H_{11}$	$-C_9H_{19}$	$-\overset{R_1}{\underset{R_2}{C}}-$	$-CH_2Cl$
	VAc	**VH**	**VD**	**VnN**	**VClAc**

$R_1=C_xH_{2x+1}$ $R_2=C_{6-x}H_{13-2x}$ x=1...5

The ratio [CTA]:[AIBN] was again varied in the range from 5 to 20. The maximum time was set to 20 hours. Table 20 shows the results of all successful polymerizations. **VAc** could not be polymerized under the selected reaction conditions.

Table 20: Results of RAFT homopolymerizations performed in bulk using BED as CTA and AIBN and V-40, respectively, as initiator at different CTA-to-initiator ratios and a target molecular weight of 5 kDa

	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]	Time [min]
pVH-13	5	75	4.2	3.7	1.30	1200
pVD-13	5	64	3.3	2.7	1.26	1200
pVnN-13	5	15	0.9	0.9	1.20	1200
pVClAc-13	5	81	4.1	2.8	1.32	960
pVClAc-14	10	76	3.9	2.4	1.29	1135
pVClAc-15	15	36	1.9	1.6	1.26	1200

Reasonable monomer turnover (>60%) is possible for **VH** and **VD**, but high AIBN concentrations are necessary and a period of 20 hours is required. Similar results are obtained for **VClAc**. Here polymerization also occurs, if less initiator is used, but still, the reactions proceeded slowly. It is possible to prepare p**VnN** with ***BED*** as CTA, but only at very low monomer conversion. SEC measurements reveal that ***BED*** as CTA under bulk conditions leads to polymers with a narrow molecular weight distribution for **VH**, **VD** and **VClAc**, expressed by Đ-values around 1.30. Obtained SEC traces are displayed in Figure 59.

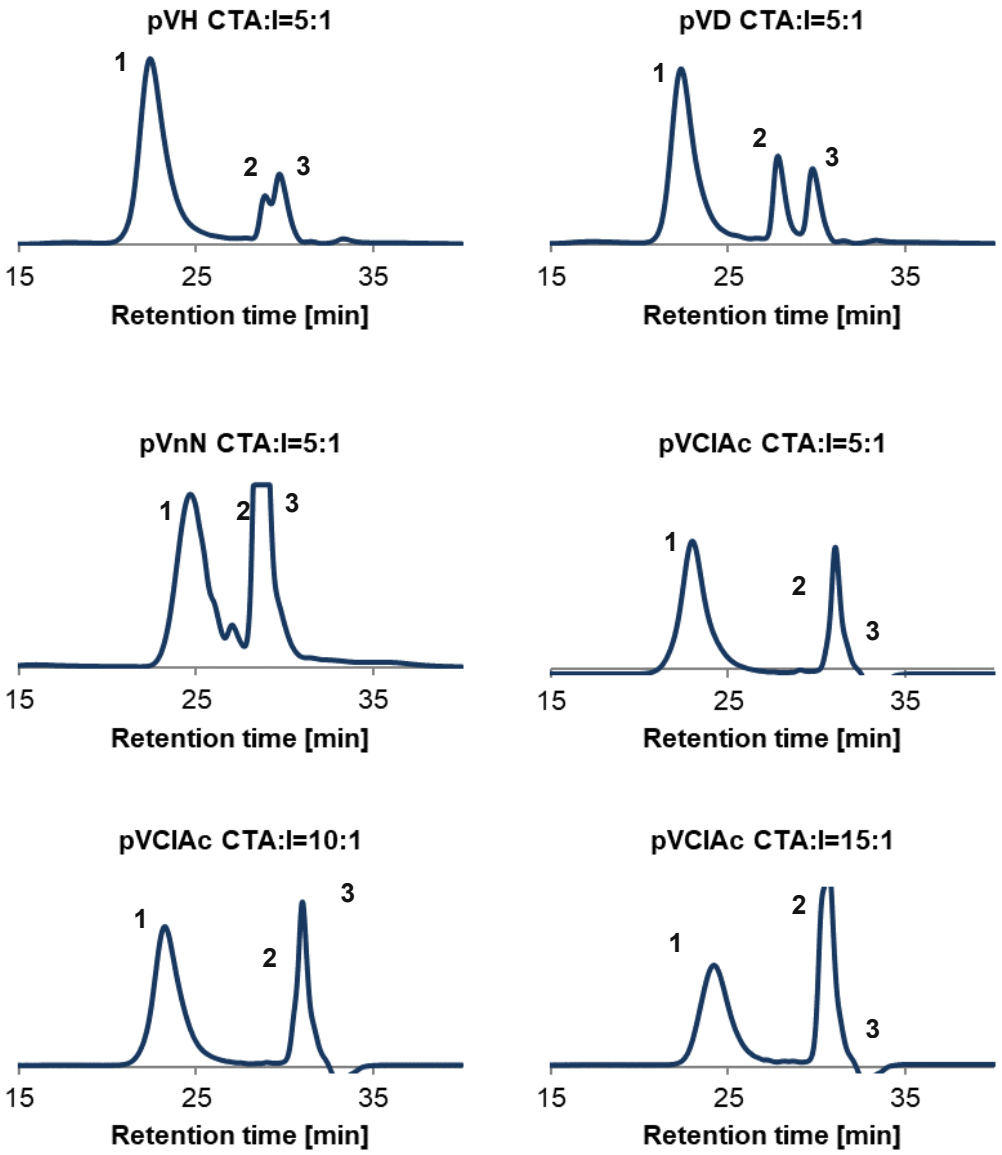


Figure 59: SEC traces of RAFT homopolymerization of VH, VD, VnN and VClAc with *BED* as CTA in bulk using AIBN as initiator at different CTA-to-initiator ratios

The absence of bimodality of the peaks in the case of **VH**, **VD** and **VClAc** indicated a controlled polymerization. In the case of **VnN** as monomer, a different picture is visible. Although the polymer peak shows a narrow molecular weight distribution, the peak has a shoulderin the range of lower molecular weights, indicating a bimodal distribution of the chain length. This is most probably a result of the low monomer conversion.

RAFT polymerizations utilizing ***BED*** as RAFT agent were as well performed in dry benzene at a monomer concentration of 5 mol/L. The reaction parameters were the same as for the

reactions performed with ***MESA*** and the reaction time was 20 hours. Table 21 provides an overview of the obtained results for **VH**, **VD** and **VClAc**.

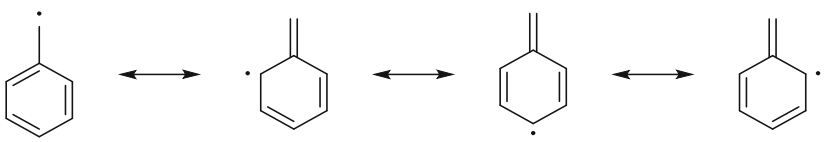
Table 21: Results of RAFT homopolymerizations performed in solution using BED as CTA and AIBN and V-40, respectively, as initiator at different CTA-to-initiator ratios and a target molecular weight of 5 kDa

	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]	Time [min]
pVH-5	5	14	0.9	1.0	1.26	1200
pVD-5	5	22	1.3	1.4	1.22	1200
pVClAc-5	5	80	4.1	2.8	1.40	1200
pVClAc-6	10	16	1.0	0.7	1.26	1200

It turned out that only few reactions worked under the selected reaction conditions. For **VAc** and **VnN** no monomer turnover occurs, for **VH** and **VD** only low values of 14% and 22%, respectively, are achieved at high initiator concentration. Similar monomer conversion is observed in the case of **VClAc**. Here, reasonable results of 80% are only reached, if a large amount of V-40 (CTA-to-initiator ratio of 5:1) is used. Ratios between CTA and V-40 of 10:1 and 15:1, respectively, only resulted in monomer conversion below 20%. Further reduction of the amount of initiator leads to total inhibition of the polymerization.

Although the dispersity for **pVH** was 1.26 and 1.22 for **pVD**, it has to be mentioned, that a shoulder at lower molecular weight is obvious in the SEC chromatogram (Figure 59). This is presumably due to the low conversion.

BED turned out to be a poor chain transfer agent for the RAFT polymerizations of different vinyl esters under the selected reaction conditions. One possible reason could be the stability of the benzyl radical, which is formed upon the fragmentation of the R-group. Since it includes a phenyl ring system bearing a delocalized π-electron system, which is able to stabilize the radical, it shows low tendency towards reinitiation of the polymerization process. Scheme 18 depicts the resonance structures of the generated benzyl radical.[327]



Scheme 18: Stability of benzyl radical[327]

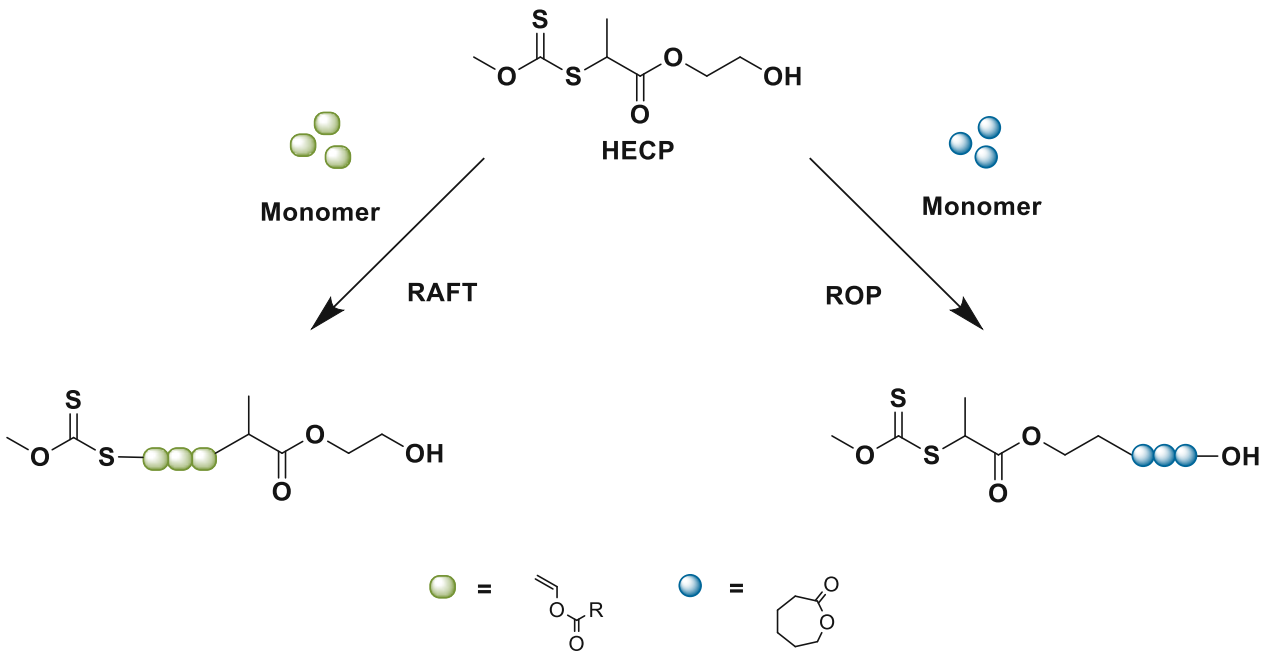
Additionally, this effect might be reinforced by the high stability of the used monomers since vinyl esters in general are rather unreactive. In most of these polymerizations, especially in

those performed in solution, no or only little conversion (less than 20%) was observed, indicating a preferred addition of the initiator-derived radicals to the reactive double bond of the RAFT agent leading to the fragmentation of the unreactive R-group. Thus, it seems, the reaction was not controlled but quenched by ***BED***. The only exception here was the RAFT polymerization of **VClAc**, where high conversion was also reached in the presence of a diluent. Presumably, this was due to the higher reaction temperature of 80 °C, since in general higher reactivity of the radicals can be expected at higher reaction temperatures. Improving the reaction towards higher monomer conversion by applying higher temperatures was also indicated by Congdon *et al.*[322] They reported the successful RAFT polymerization of **VAc** with ***BED*** in bulk at 68 °C reaching conversions up to 95% and dispersity values below 1.50. Nevertheless, it has to be mentioned, that water soluble 4,4′-azobis(4-cyanovaleric acid) (V-501) was used as initiator. Furthermore, 68 °C appears quite high for this reaction, since **VAc** itself has a boiling point of 72 °C and so evaporation of this highly volatile monomer might be a problem. Summing up, ***BED*** cannot be considered a suitable RAFT agent for vinyl esters that were investigated within this thesis.

B.2 RAFT polymerization using a dual initiator

Besides the possibility to generate all blocks of copolymers by one method, also the combination of polymerization techniques allows their synthesis. Besides RAFT polymerization, Ring Opening Polymerization (ROP) is also known to deliver polymers with defined molecular weights and narrow molecular weight distributions.[328] By combining these two polymerization techniques, it is not only possible to benefit from all their advantages, but also to broaden the field of useable monomers. Therefore, a dual initiator, which can either serve as RAFT agent for vinyl esters, as it bears a xanthate moiety, or as initiator for ROP due to the hydroxyl end group, was selected.

2-Hydroxyethyl 2-((ethoxycarbonothioyl)thio)propanoate (***HECP***) was chosen as RAFT agent for this study.



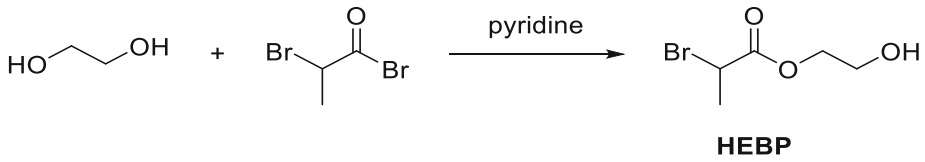
Scheme 19: Schematic illustration of the polymerizations possible by usage of dual initiator HECP

Until now, only sparse literature is available on this dual initiator. ***HECP*** was used to prepare block copolymers with narrow molecular weight distribution from ε-caprolactone by ROP in combination with RAFT polymerization of N-vinylpyrrolidone,[142,144] 3-Ethyl-1-vinyl-2-pyrrolidone,[144] vinyl chloroacetate,[143] N-vinylcaprolactam[141] and vinyl chloride.[145,146] Thereby a one-pot approach starting with ROP followed by RAFT polymerization or a two-step process starting with RAFT polymerization was used.

B.2.1 Synthesis of HECP

HECP was prepared by a two-step reaction via 2-hydroxyethyl-2-bromopropionate (**HEBP**) as described in literature.[149]

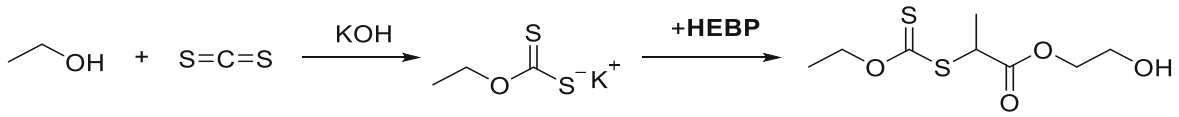
First, the precursor **HEBP** was prepared.



HEBP

The synthesis was performed by adding 2-bromopropionyl bromide (BPB) to ethylene glycol at low temperature, using pyridine as acid scavenger. The intermediate product **HEBP** was obtained as colorless liquid with a yield of 85%. Since no impurities from the corresponding dibromide from starting materials were visible in the ^{1}H-NMR spectrum, the raw product was used without further purification steps.

The dual initiator ***HECP*** was prepared by reaction of **HEBP** and potassium O-ethyl carbonodithioate.



HECP

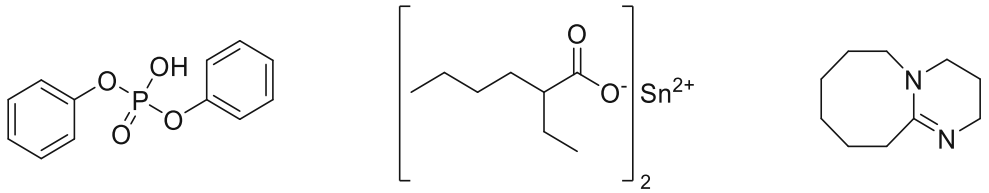
Primarily, the needed dithioate was prepared as described by Stenzel *et al.*[297] by dissolving KOH in dry ethanol and subsequent addition of carbon disulfide. Then the precursor **HEBP** was added to give the desired product ***HECP***. After purification via column chromatography, the product was obtained as slightly yellow liquid with a yield of 50%.

B.2.2 HECP as initiator for ROP - Proof of concept

In general, ROP techniques facilitate the preparation of polymers based on various cyclic monomers, like lactones, lactams, anhydrides, carbonates, olefins as well as others.[328] The mechanism can either be anionic, cationic or radical, whereby the ionic ones can also proceed via an activated monomer mechanism.[329]

Hydrophobic ε-caprolactone (**CL**) was chosen as monomer for first trials due to several reason: the monomer shows good biocompatibility, is already used in (bio) medical applications and this specific reaction is known to literature.[141-143]

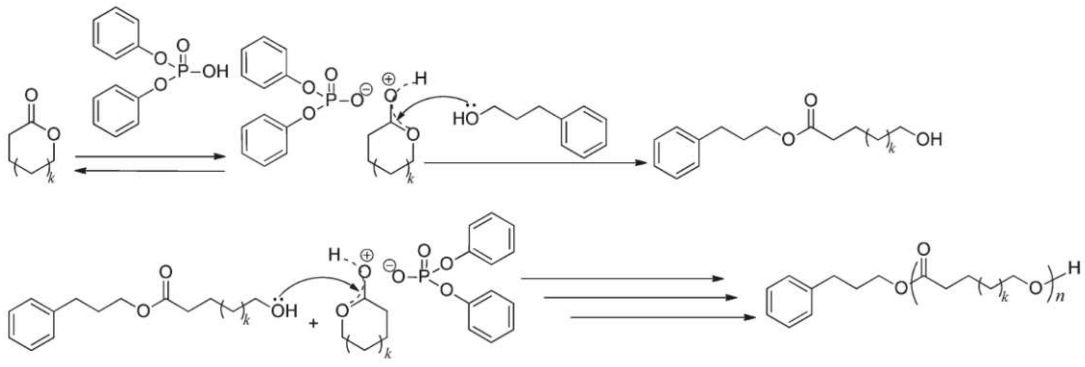
Three different commonly-known catalysts for ROP where chosen, namely diphenyl phosphate (DPP)[141-143], tin(II) 2-ethylhexanoate ($SnOct_2$) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) and tested regarding their suitability for the polymerization of **CL** initiated by ***HECP*** (see Figure 60).



DPP **Sn(II)Oct$_2$** **DBU**

Figure 60: Tested catalysts for the ROP of CL

The reaction with DPP as catalyst proceeds via an activated monomer mechanism, which is depicted in Scheme 20.



Scheme 20: Mechanism of the ring opening polymerization of ε-caprolactone using DPP as catalyst[330]

It turned out, that reactions with DBU at 60 °C led to no monomer conversion. According to literature, here a co-catalyst might be needed.[331,332] Polymerizations performed with $SnOct_2$ allowed the preparation of polymers, but the dispersity was around two and bimodality of the peaks in SEC curves was clearly visible (see Figure 61).

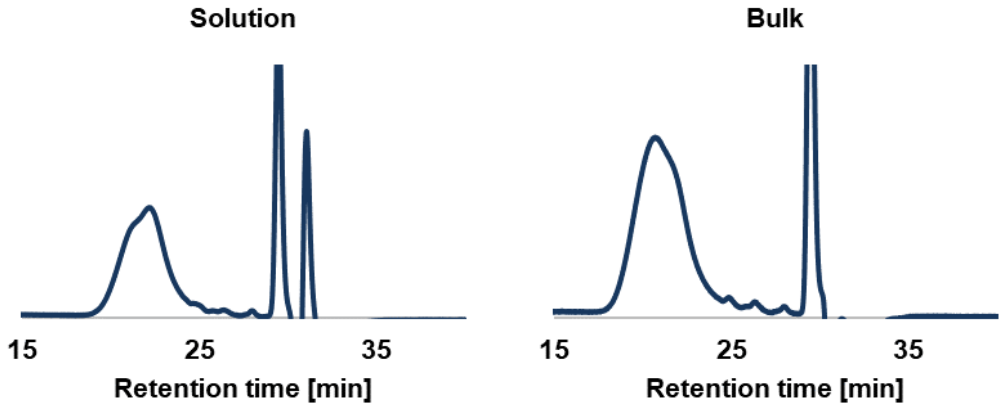


Figure 61: SEC traces of the ROP of CL with HECP as initiator and $Sn(Oct)_2$ as catalyst for a target molecular weight of 5 kDa performed in solution and bulk, respectively

Additionally, elevated temperature of 120 °C was needed, so $SnOct_2$ was not used in further experiments.

Polymerizations of **CL** with DPP in bulk (pCL-1) as well as in dry anisole (pCL-2) with a monomer concentration of 8.8 mol/L were performed similar as described in literature[141-143]. The ratio between catalyst DPP and initiator **HECP** was 1.5 and the targeted molecular weight was 23.0 kDa. The reaction time was 4 hours. Afterwards samples for SEC measurements were withdrawn from the reaction solutions. Table 22 gives an overview of the obtained results.

Table 22: Results of the ROP of CL with HECP as initiator and DPP as catalyst

		$M_{n,\ target}$ [kDa]	[M] [mol/L]	t [h]	$M_{n,SEC}$ [kDa]	Đ [ ]
Bulk	**pCL-1**	23.0	-	4	6.1	1.15
Solution	**pCL-2**	23.0	8.8	4	9.4	1.08

It turned out, that reaction in bulk delivers significantly lower molecular weight than reaction performed with a small amount of dry anisole. This might be due to sterical reasons, as the solvent increases mobility of the molecules and therefore chain growth is more likely to happen. At the same time, dispersity is somewhat lower. Figure 62 depicts the obtained SEC traces.

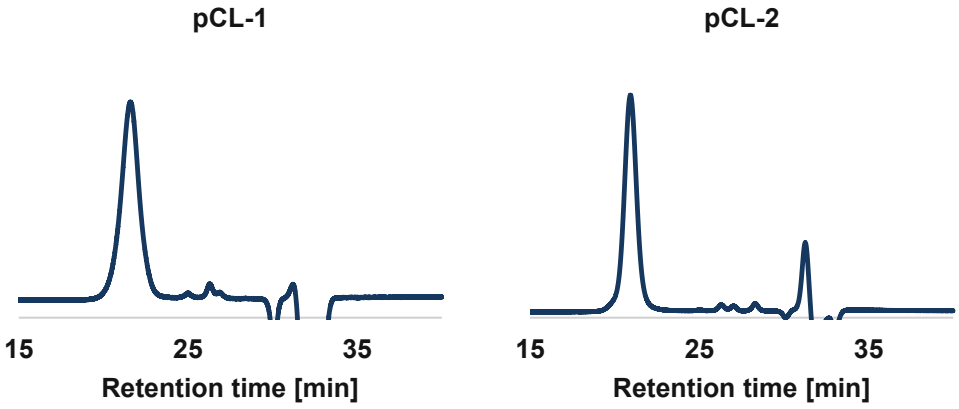
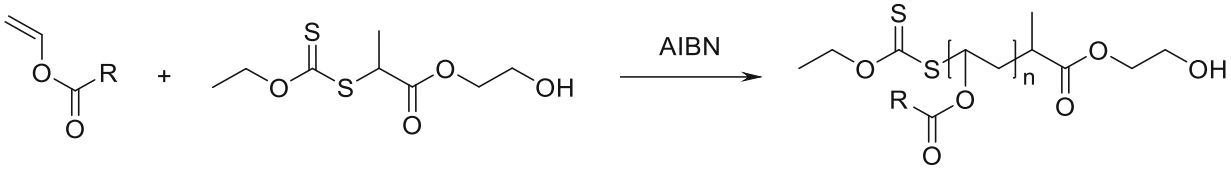


Figure 62: SEC traces of the ROP of CL with HECP as initiator and DPP as catalyst performed in bulk and solution, respectively

SEC curves show polymers with very narrow peaks and no shoulders are visible. The conducted reactions can be seen as a proof of concept, since they show that ***HECP*** fulfills its role as an initiator for ring opening polymerization.

B.2.3 Polymerization of hydrophobic vinyl esters using HECP as CTA

In order to proof the suitability of ***HECP*** as RAFT agent for vinyl esters, it was tested in a first series of experiments for the homopolymerization of hydrophobic **VH** and **VD** in bulk as well as in solution. Reactions in solution were performed in regards to future preparation of block copolymers. RAFT polymerization with ***HECP*** as CTA of both monomers was not reported in literature so far.



HECP **pVH 17-21** **pVD 17-28**

B.2.3.1 Polymerization of VD

Reactions in bulk were conducted at 60 °C and 70 °C, respectively, using different amounts of AIBN as initiator. The targeted molecular weight was 10 kDa and reactions were stopped after 5 hours by cooling down in an ice bath. Subsequently, samples from the reaction mixtures were analyzed by ^{1}H-NMR spectroscopy and by SEC. Table 23 summarizes the results.

Table 23: Results of the RAFT homopolymerization of vinyl decanoate in bulk using *HECP* as RAFT agent, and different CTA-to-initiator ratios at different temperatures

	T [°C]	[M] [mol/L]	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
pVD-23	60	bulk	5	48	5.0	6.2	1.16
pVD-24	60	bulk	10	-*	-*	6.1	1.15
pVD-25	60	bulk	15	n.c.	-	-	-
pVD-26	70	bulk	5	90	9.1	8.5	1.46
pVD-27	70	bulk	10	83	8.3	8.1	1.37
pVD-28	70	bulk	15	62	6.2	5.1	1.34

n.c.= no monomer conversion *Not determined

Polymerizations in bulk deliver satisfying values for monomer conversion. Even at 60 °C almost 50% conversion could be reached by using a large amount of AIBN. Although conversion for the polymerization with 10 mol% AIBN with respect to **HECP** was not determined by ^{1}H-NMR spectroscopy, the results obtained by SEC indicate a similar value. As expected, increasing the temperature to 70 °C, led to higher conversion. Turnover values in the range from 60% up to 90% could be reached. In general, a clear tendency towards higher

monomer conversion at higher temperatures and larger amounts of initiator is recognizable. Dispersity is not highly affected by the amount of initiator, but it is significantly increased if higher temperature are chosen for the reactions. Figure 63 shows the SEC curves obtained from the reactions conducted in bulk.

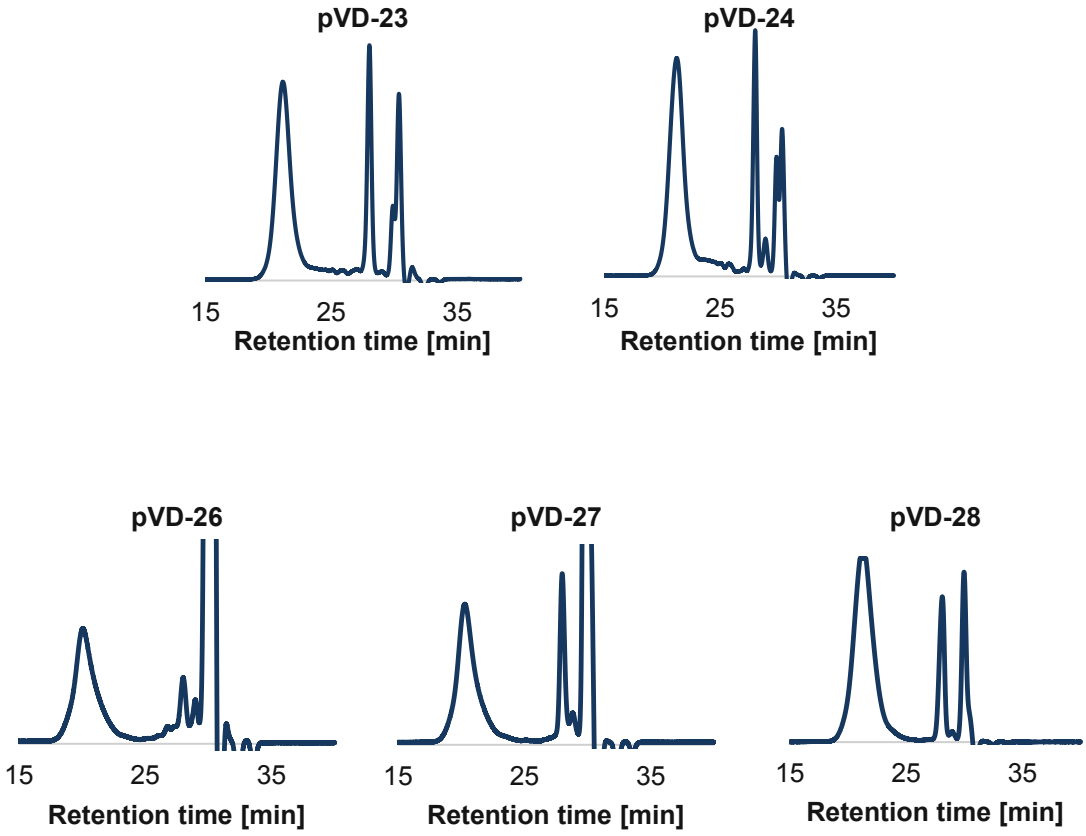


Figure 63: SEC traces of RAFT homopolymerization of VD with HECP as CTA in in bulk using AIBN as initiator at different CTA-to-initiator ratios and temperatures

The peaks in SEC graphs showed symmetrical shape without any shoulders. Especially p**VD**-23 and p**VD**-24 exhibited narrow molecular weight distribution at moderate monomer conversion. Also, the preparation of polymers p**VD**-26, p**VD**-27 and p**VD**-28 at 70 °C seemed to proceed in a controlled manner, albeit peaks get broader at this temperature. RAFT polymerizations of **VD** applying ***HECP*** in solution were performed in the same way as in bulk at different temperatures at varying initiator concentration and a targeted molecular weight of 10 kDa.16 wt% of dry anisole served as solvent which corresponds to a monomer concentration of 43 mol/L. The temperature was 60 °C or 70°C and the time was set to 18 hours. Table 24 summarizes the results obtained by ^{1}H-NMR and SEC analyses.

Table 24: Results of the RAFT homopolymerization of vinyl decanoate in dry anisole using *HECP* as RAFT agent, and different CTA-to-initiator ratios at different temperatures

	T [°C]	[M] [mol/L]	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
pVD-17	60	43	5	11	1.3	2.3	1.23
pVD-18	60	43	10	n.c.	-	-	-
pVD-19	60	43	15	n.c.	-	-	-
pVD-20	70	43	5	73	7.4	6.8	1.42
pVD-21	70	43	10	28	2.9	3.9	1.23
pVD-22	70	43	15	n.c.	-	-	-

n.c.= no monomer conversion

The RAFT polymerization of **VD** with ***HECP*** as CTA performed at 60 °C in solution led only to a very low monomer conversion of 11% at high amounts of initiator, although only a very little amount of anisole was used and reactions were left to proceed for 18 hours. By raising the temperature to 70 °C, the monomer turnover could be increased to 73% at the highest amount of AIBN, but at the expense of dispersity. Figure 64 shows the SEC traces obtained from the RAFT polymerizations of **VD** with ***HECP*** performed in solution.

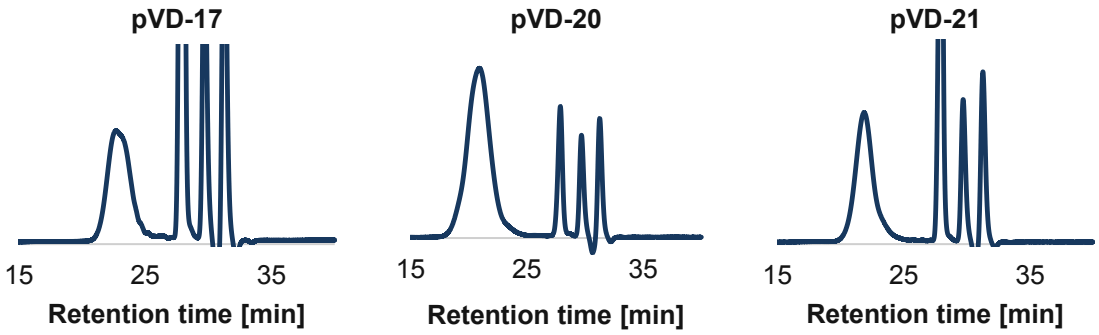


Figure 64: SEC traces of RAFT homopolymerization of VD with HECP as CTA in dry anisole using AIBN as initiator at different CTA-to-initiator ratios and temperatures

According to the shape of the SEC peaks, the polymerizations in anisole proceeded in a controlled manner, since the peaks showed symmetrical shape and no shoulders are visible. An exception might be p**VD**-17, where the peak maximum is less sharp, probably due to the extremely low monomer conversion of only 11%.

In order to obtain well-defined polymers at high monomer conversion, temperature should be kept low and reaction time has to be extended. It can be concluded that polymerizations should be performed in bulk and not in solution. This fact has to be considered when it comes to the synthesis of block copolymers.

B.2.3.2 Polymerization of VH

The RAFT homopolymerization of **VH** with ***HECP*** was tested in bulk and in solution (16 wt% dry anisole with respect to the amount of monomer). The high monomer concentration was chosen in accordance with literature.[149]

In a first attempt molar ratios between CTA and the initiator AIBN of 2 and 5 were chosen and the targeted molecular weight was quite high (35 kDa) for polymerizations in bulk. The temperature was 60 °C and the duration was 5 hours. Table 25 gives an overview of the data derived from ^{1}H-NMR spectroscopy and SEC measurements.

Table 25: Results of the RAFT homopolymerization of vinyl hexanoate using HECP as CTA in bulk at different CTA-to-initiator ratios at 60 °C

	$M_{n,target}$ [kDa]	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]	Time [min]
pVH-17	35.0	2	69	23.4	26.5	1.63	300
pVH-18	35.0	5	70	24.7	26.3	1.67	300

The polymerizations performed in bulk (p**VH**-17 and p**VH**-18) proceeded with a reasonable monomer conversion of almost 70% within 5 hours, but the dispersity of almost 1.70 indicated a lack of control over this reaction. Furthermore, no effect of the amount of initiator was observed - neither on monomer conversion nor on dispersity.

Subsequently, polymerizations were performed in solution at 60 °C whereby the targeted molecular weight was varied. Table 25 gives an overview of the data derived from ^{1}H-NMR spectroscopy and SEC measurements.

Table 26: Results of the RAFT homopolymerization of vinyl hexanoate using HECP as CTA in dry anisole at different CTA-to-initiator ratios at 60 °C

	$M_{n,target}$ [kDa]	[M] [mol/L]	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]	Time [min]
pVH-19	35.0	43	2	28	10.0	13.1	1.17	300
pVH-20	5.0	43	5	71	3.7	4.1	1.24	1100
pVH-21	7.5	43	5	69	4.9	4.3	1.31	1100

Adding a small amount of solvent led to a significant decrease in polymerization speed and monomer turnover was reduced by more than 50% within the same period. However, dispersity could be clearly reduced to a value below 1.20.

Since the polymerization in solution delivered a well-defined polymer, further reactions for polymers with lower molecular weight (5 and 7.5 kDa) were conducted, whereby the amount of initiator was reduced along with an increase in polymerization time to 18 hours. These results are as well observable in Table 26. Here, monomer conversions around 70% could be reached and resulting polymers (p**VH**-17 and p**VH**-18) showed low dispersity values around 1.30 or less. Figure 65 depicts SEC traces obtained from these polymerization reactions.

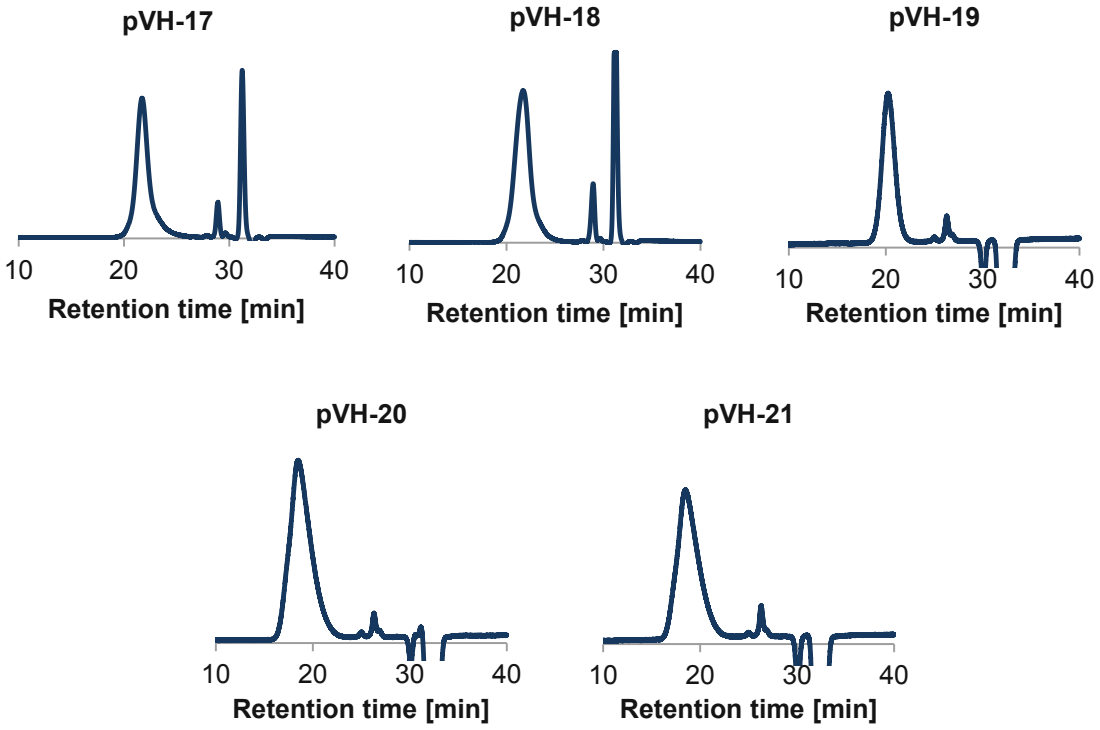


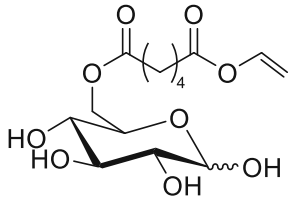
Figure 65: SEC traces of RAFT homopolymerization of VH with *HECP* in bulk and dry aniline using AIBN as initiator at different CTA-to-initiator ratios and different target molecular weights

In all cases, the resulting SEC peak maxima were sharp and the signals show no shoulders. However, SEC traces obtained from p**VH**-20 and p**VH**-21 showed broadening of the peaks at the bottom, indicating that under these conditions the reactions are not completely controlled by **HECP**. Therefore, ideally RAFT polymerization of **VH** with ***HECP*** should be performed in anisole with low amounts of AIBN, maybe even lower than 5:1 with only a low molecular weight. High molecular weights cannot be achieved with this system.

Comparing RAFT polymerizations in solution of **VH** and **VD** with ***HECP*** as CTA at 60 °C applying a AIBN-to-initiator ratio of 5:1, it can be seen that in the case of **VD** merely low monomer conversion can be reached under the selected reaction conditions. On the contrary, polymerization of **VH** leads to a monomer conversion of almost 50%. This indicates a higher reactivity and therefore higher reaction speed under these conditions. This fact was already found when other CTAs, namely ***MESA*** and ***BED***, were used to control the reactions.

B.2.4 Polymerization of hydrophilic monomers using HECP as CTA

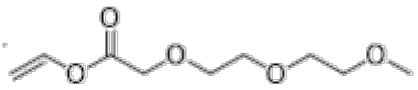
In general, no hydrophilic vinyl esters are commercially available. Therefore, it is necessary to synthesize them. There are different synthetic strategies to obtain vinyl esters: a very common approach is the transvinylation of vinyl acetate with an arbitrary carboxylic acid, catalyzed by salts of transition metals (e.g. palladium[333-335], mercury[336,337]). Furthermore, divinyl mercury[338] or phenylselenium ethanol[339], as well as, acetylene in combination with a catalyst (Fe, Mo, Mn, Re)[340] can be used to generate vinyl esters from the respective carboxylic acid. Starting from acid chlorides, mercuric diacetaldehyde or acetaldehyde together with pyridine[341] allow the preparation of vinyl esters. Moreover, ketenes can be used as starting materials to give vinyl esters upon reaction with acetaldehyde lithium enolate.[342] A further alternative especially for the preparation of divinyl esters is the application of enzymes (e.g. protease,[343-345] lipase,[346,347] proteinase[347]) which selectively catalyze the transesterification reaction of divinyl esters (e.g. divinyl succinate,[347,348] divinyl adipate,[346,347,349] divinyl sebacate[347,348]) with sugars (e.g. glucose,[343,348,350] mannose,[344,347] arabinose,[351] lactose,[345,347] sucrose[345,349]…). An example therefore is 6-O-vinyladipoyl-D-glucopyranose (VAG).



VAG

So far, the RAFT polymerization of **VAG** was scarcely published in literature. Albertin *et al.*[346] applied a CTA similar to ***MESA***, namely 2-thiopropionylsulfanyl-propionic acid methyl ester. However, the results reported for these reaction conditions showed quite low monomer conversion of only 15%. Bernard *et al.*[352] achived higher monomer conversion (35% within 9 hours, limited to 50%) using a 4-arm RAFT agent based on ***MESA***. Here, a higher monomer concentration of 2 mol/L was selected and the temperature was raised to 70 °C, and N,N-dimethylacetamide was used as solvent. Moreover, the copolymerization of **VAG** with N-isopropylacrylamide was examined by Sun *et al.*,[353] whereby well-defined copolymers were obtained. However, they used a trithiocarbonate as CTA, which is rather unknown to allow control over the polymerization of vinyl esters due to reactivity reasons. Other CRP methods were not applied for the polymerization of this monomer.

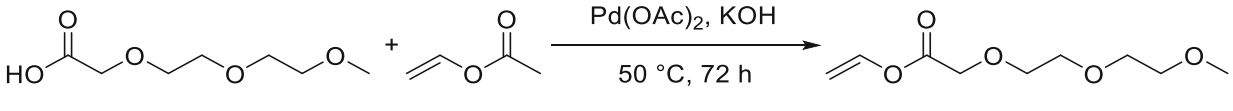
Since literature reports only low monomer conversion for VAG, it was aimed to find an alternative hydrophilic vinyl ester based on polyethylene glycol (PEG), which is known to be a FDA-approved, highly water soluble and biocompatible material,[354] and is widely used in various fields.[355,356] In drug delivery systems or targeted diagnostics, PEG is applied either by attaching via direct PEGylation[357,358] or within vehicles (e.g. micelles,[359,360] nanoparticles[361,362]). Furthermore, it is used in (bio) medicine,[363] tissue engineering[364] and cosmetics.[365,366] Hence, a PEG-like vinyl ester, namely vinyl 2-(2-(2-methoxyethoxy) ethoxy) acetate (**TOVE**), should be prepared, whereby a rather short hydrophilic chain was chosen to prevent problems caused by sterical hindrance due to long side chains.



TOVE

B.2.4.1 Synthesis of TOVE

The hydrophilic and water soluble vinyl ester **TOVE** was synthesized via a transition metal-catalyzed transesterification reaction in accordance with the work of Husár,[267] who described this synthesis route for a bifunctional vinyl ester.



TOVE

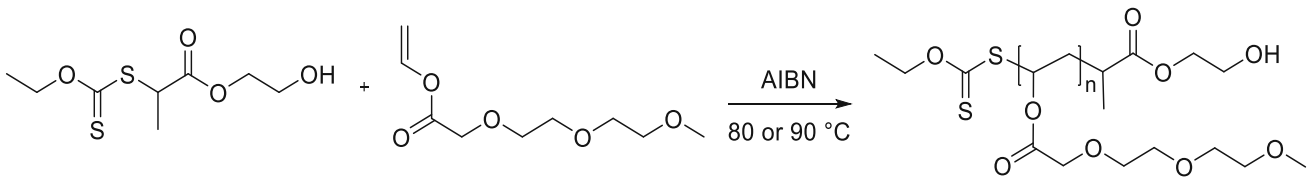
To a mixture of 2-(2-(2-methoxyethoxy)ethoxy)acetic acid in a large excess of vinyl acetate, palladium(II)acetate and potassium hydroxide were added as catalysts. The reaction mixture was then stirred at 50 °C for 3 days. The solid was filtered off and the product was extracted with ethyl acetate. Purification was performed by column chromatography and the monomer **TOVE** was obtained as slightly yellow liquid in a yield of 50%.

According to Thomas *et al.*[367], for this synthesis an increase in yield should be possible by adding small amounts of p-benzochinone (BQ, 1-3%) to the reaction mixture. BQ should re-oxidize the Pd(0)species, which is inactive, leading to Pd(II) and therefore to a re-activation of the reaction. However, the verification of this was not within the scope of this thesis.

B.2.4.2 RAFT polymerizations of TOVE

In literature no information about the polymerization of vinyl 2-(2-(2-methoxyethoxy) ethoxy) acetate (**TOVE**) is available.

The RAFT homopolymerization of **TOVE** with ***HECP*** as CTA was tested at different temperatures (80 °C and 90 °C), varying the monomer concentration in the range of 5 to 40 mol/L.



HECP **TOVE** **pTOVE 1-6**

The amount of AIBN was varied from 10 to 50 mol% with relation to the amount of CTA. The targeted molecular weight was 10 kDa and polymerizations were allowed to proceed over a period of 24 hours. After quenching the reactions by cooling down in an ice bath, samples were withdrawn and analyzed by ^{1}H-NMR spectroscopy and SEC.

Table 27: Results of the RAFT homopolymerization of vinyl 2-(2-(2-methoxyethoxy) ethoxy) acetate in dry anisole at different temperatures using *HECP* as RAFT agent, and different CTA-to-initiator ratios

	T [°C]	[M] [mol/L]	[CTA]:[I]	C_M [%]	$M_{n,NMR}$ [kDa]	$M_{n,SEC}$ [kDa]	Đ [ ]
pTOVE-1	80	5	2	42	4.7	2.4	1.52
pTOVE-2	80	5	5	41	4.2	2.7	1.51
pTOVE-3	90	5	2	57	6.1	3.9	1.61
pTOVE-4	90	5	5	56	5.7	3.0	1.63
pTOVE-5	90	5	10	27	2.9	2.2	1.48
pTOVE-6	90	40	2	72	6.0	4.1	1.88

Polymerizations of **TOVE** with **HECP** as CTA conducted at 80 °C proceeded only with monomer conversions of roughly 40% independent of the amount of AIBN, despite the quite high amounts of initiator and the long reaction time. Raising the temperature to 90 °C led to an increase in monomer turnover to almost 60%. In all cases, the obtained dispersity values indicated a lack of control over these polymerizations. Only for p**TOVE**-5 a dispersity of <1.50 could be reached, but with very low conversion of 27%. Figure 66 shows the SEC traces from these polymerizations.

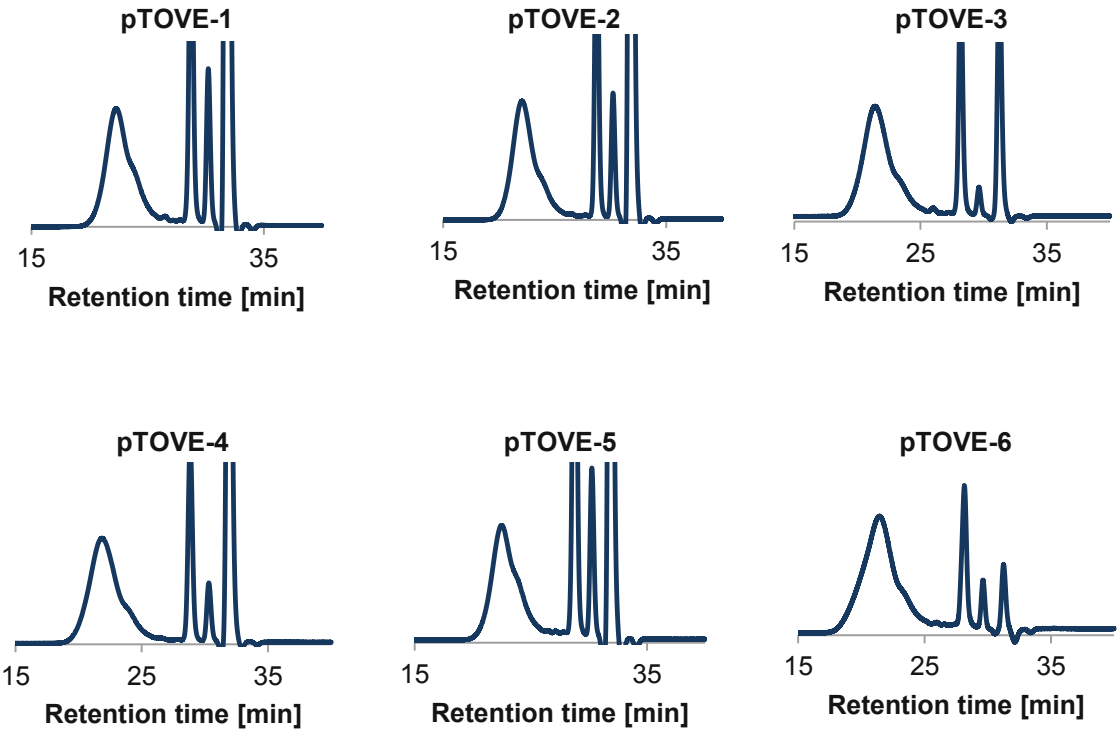


Figure 66: SEC traces of RAFT homopolymerization of TOVE with HECP as CTA in dry anisole using AIBN as initiator at different CTA-to-initiator ratios, temperatures and monomer concentrations

SEC traces clearly show that the polymerizations did not proceed in a controlled manner. All reactions delivered polymers with at least bimodal distribution of the molecular weight. The presumed cause therefore is that side reactions like H-abstraction took place, leading to chain transfer and thus branching and starting of new chains. Further attempts at 80 °C with different monomer concentrations and amounts of initiator AIBN led to similar results, and sometimes even worse dispersity. Additionally, it was tried to polymerize **TOVE** in a controlled manner by using ***MESA*** as CTA instead of ***HECP*** at 70 °C in bulk with a CTA-to-initiator ratio of 5:1. However, also under those reaction conditions, a bimodal molecular weight distribution was obtained at a monomer conversion of roughly 20% after 48 hours polymerization time.

Experimental Part A

RAFT polymers based on lauryl methacrylate and N-acryloylmorpholine

A.1 Synthesis of the RAFT agent CDP

The synthesis of 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)-sulfanyl] pentanoic acid (***CDP***) was performed in two steps as described by Farnham.[23]

A.1.1 Synthesis of bis(dodecylsulfanylthiocarbonyl)disulfide

First, bis(dodecylsulfanylthiocarbonyl)disulfide (**1)** was synthesized in one step.

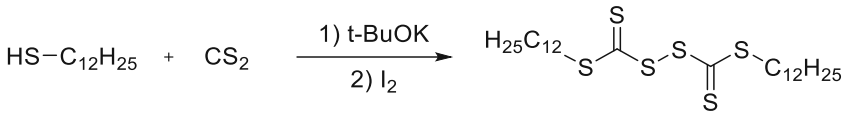


Table 28 summarizes the used amounts of educts.

Table 28: Educts used for the synthesis of bis(dodecylsulfanylthiocarbonyl)disulfide

	[g/mol]	[mmol]	[g]	[mL]	Eq
1-Dodecanethiol	202.40	35.9	7.27	-	1.0
Carbon disulfide	76.13	37.2	2.83	-	1.03
Potassium tert-butanolate	112.18	37.3	4.18	-	1.04
Iodine	253.80	18.8	4.77	-	0.5
Hexane	-	-	-	120	-
Tetrahydrofuran	-	-	-	35	-

1 equivalent potassium tert-butanolate in 120 mL hexane and 25 mL tetrahydrofuran (THF) was placed into a 3-necked flask with reflux condenser, septum and thermometer and the mixture was then stirred at 5 °C (ice-water-bath) for 5 minutes. Afterwards 1 equivalent 1-dodecanethiol was slowly added, whereby a white emulsion was generated. After stirring the mixture for 30 minutes at 5 °C, 1 equivalent of carbon disulfide was added dropwise over a period of 15 minutes. Since this led to the formation of a solid, yellow foam, the magnetic stirrer

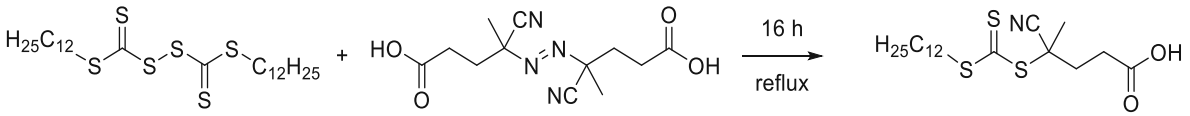
was replaced by a mechanical one and the stirring was continued for 4 hours at room temperature. This was followed by the dropwise addition of 0.5 equivalents iodine dissolved in 10 mL THF via a syringe over a period of 15 minutes. After stirring the mixture for another 20 hours, it was dissolved in hexane, washed with cold saturated NaCl solution (1x100 mL), thiosulfate solution (1x100 mL) and again with cold saturated NaCl solution (1x100 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed in vacuum. The product was dried in vacuum overnight and the yellow oil was then crystallized at 4 °C.

Yield ($C_{26}H_{50}S_6$): 9.09 g yellow-orange solid (yield: 91%)

^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) 3.28-2.68 (m, 4H, -S-C**H**$_2$-), 1.68 (quin, 4H, - S-CH_2-C**H**$_2$-), 1.43-1.17 (m, 36H, -C**H**$_2$-), 0.87 (t, 6H, -C**H**$_3$, J= 6.26 Hz)

A.1.2 Synthesis of 4-cyano-4-[(dodecylsulfanylthiocarbonyl)-sulfanyl] pentanoic acid

CDP was obtained via a radical induced process.



[555.05] **1** [280.28] [403.66] **CDP**

Table 29 shows the used amounts of educts.

Table 29: Educts used for the synthesis of 4-cyano-4-[(dodecylsulfanylthiocarbonyl)-sulfanyl] pentanoic acid

	[g/mol]	[mmol]	[g]	[mL]	Eq
Disulfide 1	555.07	16.2	9.00	-	1.0
V-501	280.28	27.6	7.73	-	1.7
Ethyl acetate	-	-	-	85	-

1 equivalent disulfide **1** was placed into a 250 mL 3-necked flask, equipped with a reflux condenser and a thermometer, and dissolved in 85 mL ethyl acetate. The solution was first purged with argon for 15 minutes in order to remove dissolved oxygen, then heated to reflux and kept there for 2 hours under argon atmosphere. Afterwards, V-501 was added in small portions under argon counter flow. After stirring the reaction solution for 16 hours under reflux,

it was cooled down to room temperature and the solvent was removed in vacuum. The residue was recrystallized from hexane, whereat the solid was filtered off, washed with water and then again recrystallized from petrol ether. After drying under high vacuum ^{1}H-NMR analysis still showed traces of educt 1, so that another recrystallization step in diethyl ether was necessary.

Yield ($C_{19}H_{33}NO_2S_3$): 5.36 g yellow solid (yield: 41%)

2 g oft he obtained product were finally purified by column chromatography (PE:EA 1:1)

Yield ($C_{19}H_{33}NO_2S_3$): 1.02 g yellow solid (51% of raw product)

R_f (PE:EA 1:1)= 0.75

^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) 3.31 (t, 2H, -S-C**H**$_2$-, J=7.41 Hz), 2.72-2.34 (m, 4H, -C**H**$_2$-C**H**$_2$-COOH), 1.87 (s, 3H, -C-C**H**$_3$), 1.68 (quin, 2H, -S-CH$_2$-C**H**$_2$-, J=7.41 Hz), 1.42-1.20 (m, 18H, -C**H**$_2$-), 0.87 (t, 3H, -CH$_2$-C**H**$_3$, J=7.02 Hz)

A.2 Syntheses of hydrophobic polymer blocks

A.2.1 Homopolymerization of lauryl methacrylate

A.2.1.2 Kinetic study on the RAFT homopolymerization of lauryl methacrylate

The kinetic study of the RAFT homopolymerization of **LMA** was performed according to the following procedure. First, the initiator AIBN was weighted into a penicillin flask. This was followed by the addition of the (macro)CTA, the monomer(s) and the internal standard naphthalene. After addition of dry solvent (dioxane), a stirring bar was added, and the tubes were sealed with a rubber septum. After complete dissolution of all components, the reaction mixture was purged with argon for at least 30 minutes in order to replace oxygen to avoid inhibition, whereat at the beginning the gas volume above the solution was purged and afterwards the solution itself. The polymerization was started by immersing the tube into a preheated aluminum block and was stopped after a certain period of time by cooling down the tube in an ice bath.

Samples of 200 µL were withdrawn before the reaction was started, after it was stopped and at several points in time with a syringe, which was purged with argon. All samples were immediately cooled in an ice and stored at -40 °C until further usage.

Table 30 summarizes the reaction parameters, molar ratios of the educts and results for the kinetic study of the RAFT polymerization of **LMA**. Exact amounts of the reactants can be seen from Table 31.

Table 30: Reaction parameters and molar ratios of the educts for the kinetic study of the RAFT polymerization of LMA

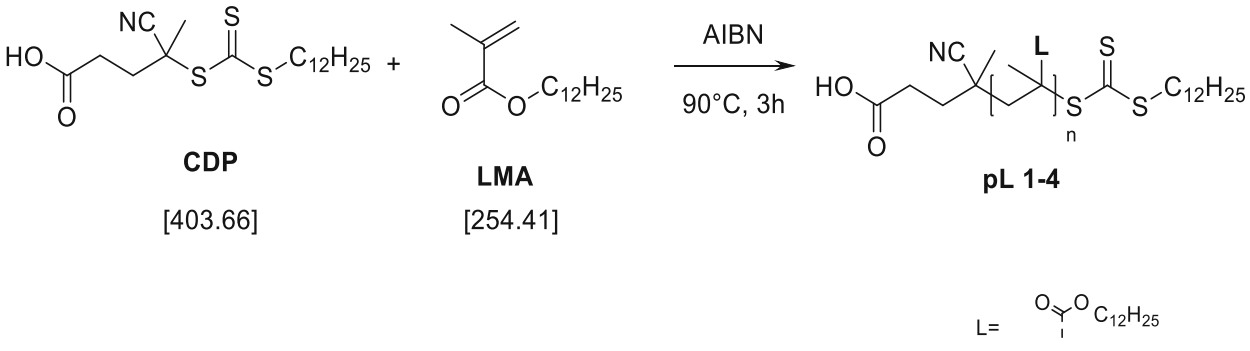
	pL
Temperature [°C]	90
Time [min]	180
[M]:[CTA]	55
[CTA]:[I]	10
[M]:[Std]	8
$c_{Monomer}$ [mol/L]	1.5
$M_{n, NMR}$ [kDa]	10.2
$M_{n, SEC}$ [kDa]	10.7
Đ [ ]	1.16

Table 31: Initial weights and molar amounts of educts for the kinetic study of the RAFT polymerization of LMA

	pL	
	[g]	**[mmol]**
LMA	2.86	11.2
	[mg]	**[mmol]**
CDP	82.4	0.20
AIBN	3.4	0.021
Naphthalene	180.0	1.40
	[mL]	
Dioxane dry	7.5	

A.2.1.3 Preparation of homopolymers from lauryl methacrylate

Hydrophobic polymers from LMA were prepare according to the general polymerization procedure as described before (A). Samples were withdrawn before the reaction was started and after it was stopped. Cold methanol was used to recover polymers by twofold precipitation.



CDP [403.66]

LMA [254.41]

pL 1-4

Table 32 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT polymerizations of **LMA**. Exact amounts of the reactants can be seen from Table 33.

Table 32: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of LMA

Polymer	pL1	pL2	pL3	pL4
Temperature [°C]	90	90	90	90
Time [min]	180	180	180	180
[M]:[CTA]	55	55	27	27
[CTA]:[I]	10	10	10	10
[M]:[Std]	8	8	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5	1.5	1.5
$M_{n,\,NMR}$ [kDa]	10.2	9.1	5.6	5.3
$M_{n,\,SEC}$ [kDa]	10.6	8.5	7.3	6.3
Đ [ ]	1.16	1.13	1.12	1.13
Yield [g]	1.65	1.92	1.82	1.76
Yield [%]	56	93	60	83

Table 33: Initial weights and molar amounts of educts of the RAFT polymerizations of LMA

	pL1		pL2		pL3		pL4	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
LMA	2.86	11.2	2.00	7.9	2.86	11.2	2.00	7.9
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
CDP	83.2	0.20	59.0	0.15	171.4	0.43	123.0	0.30
AIBN	3.3	0.020	2.6	0.016	7.0	0.043	5.0	0.030
Naphthalene	180.0	1.40	125.0	0.98	189.8	1.48	124.9	0.98
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Dioxane dry	7.5		5.2		7.5		5.2	

A.2.2 Introducing a fluorescent marker in the hydrophobic block

RAFT polymerizations of **LMA** with fluorescent marker FMA were performed according to the general polymerization procedure. Thereby the amount of **FMA** was 1 wt% with respect to the initial weight of **LMA.**

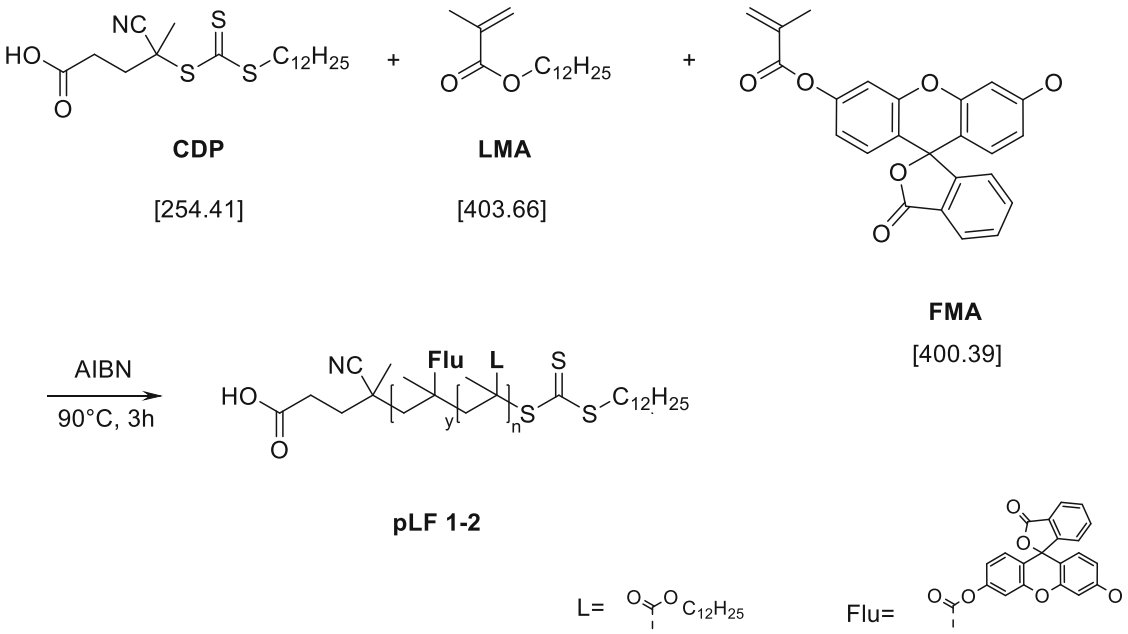


Table 34 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT polymerizations of **LMA** and **FMA**. Exact amounts of the reactants can be seen from Table 35.

Table 34: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of LMA and FMA

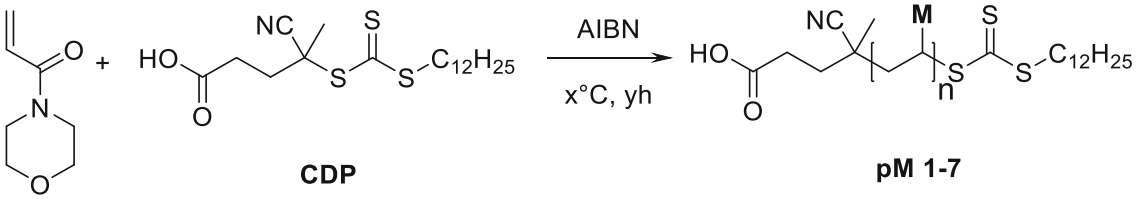
Polymer	pLF1	pLF2
Temperature [°C]	90	90
Time [min]	180	180
[M]:[CTA]	27	55
[CTA]:[I]	10	10
[M]:[Std]	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5
$M_{n,\,NMR}$ [kDa]	5.0	10.1
$M_{n,\,SEC}$ [kDa]	6.0	10.4
Đ [ ]	1.12	1.15
Yield [g]	1.45	1.98
Yield [%]	48	65

Table 35: Initial weights and molar amounts of educts of the RAFT polymerizations of LMA and FMA

	pLF1		pLF2	
	[g]	[mmol]	[g]	[mmol]
LMA	2.86	11.3	2.86	11.3
	[mg]	[mmol]	[mg]	[mmol]
FMA	27.8	0.07	28.2	0.07
CDP	173.2	0.40	84.2	0.20
AIBN	6.83	0.041	3.37	0.02
Naphthalene	184.3	1.44	181.7	1.41
	[mL]		[mL]	
Dioxane dry	7.5		7.5	

A.3 Kinetic studies on the RAFT homopolymerizations of hydrophilic N-acryloylmorpholine

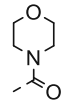
N-acryloylmorpholine (**NAM**) was chosen as monomer for the preparation of the hydrophilic block.



NAM [141.17]

CDP [403.66]

pM 1-7

M= 

x=70, 80 or 90 y=3 or 5

A.3.1 Variation of temperature

All reactions were performed following the general polymerization procedure as described in A. Samples were withdrawn before and during the reaction. Table 36 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT polymerizations of **LMA** at different temperature. Exact amounts of the reactants can be seen from Table 37.

Table 36: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of LMA at different temperatures

Polymer	pM1	pM2	pM3
Temperature [°C]	90	70	80
Time [min]	180	360	300
[M]:[CTA]	280	280	280
[CTA]:[I]	10	10	10
[M]:[Std]	8	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5	1.5
$M_{n,\,NMR}$ [kDa]	39.4	36.5	39.3
$M_{n,\,SEC}$ [kDa]	14.4	14.5	18.3
Đ [ ]	1.47	1.35	1.31

Table 37: Initial weights and molar amounts of educts of the RAFT polymerizations of LMA at different temperatures

	pM1		pM2		pM3	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
NAM	2.00	14.2	1.01	7.1	1.00	7.1
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
CDP	20.5	0.05	10.8	0.03	10.3	0.03
AIBN	0.9	0.005	0.4	0.002	0.5	0.003
Naphthalene	224.9	1.75	113.8	0.89	110.3	0.86
	[mL]		**[mL]**		**[mL]**	
Dioxane dry	9.4		4.7		4.7	

A.3.2 Variation of initiator concentration

All reactions were performed following the general polymerization procedure. Samples were withdrawn before and during the reaction. Table 38 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT polymerizations of LMA at different initiator concentrations. Exact amounts of the reactants can be seen from Table 39.

Table 38: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of LMA at different initiator concentrations

Polymer	pNAM-4	pNAM-5	pNAM-6	pNAM-7
Temperature [°C]	80	80	90	90
Time [min]	300	300	180	180
[M]:[CTA]	139	139	139	139
[CTA]:[I]	15	20	15	20
[M]:[Std]	8	8	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5	1.5	1.5
$M_{n,\,NMR}$ [kDa]	19.6	19.7	20.2	20.3
$M_{n,\,SEC}$ [kDa]	11.0	11.0	11.1	11.3
Đ [ ]	1.18	1.19	1.25	1.24

Table 39: Initial weights and molar amounts of educts of the RAFT polymerizations of LMA at different initiator concentrations

	pNAM-4		pNAM-5		pNAM-6		pNAM-7	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
NAM	1.00	7.1	1.00	7.1	1.01	7.1	1.01	7.1
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
CDP	20.6	0.05	20.5	0.05	20.6	0.05	20.5	0.05
AIBN	0.6	0.003	0.6	0.003	0.6	0.004	0.5	0.003
Naphthalene	112.8	0.88	117.1	0.91	112.7	0.88	125.7	0.98
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Dioxane dry	4.7		4.7		4.7		4.7	

A.4 Syntheses of amphiphilic block copolymers

General procedure (see A) was used to prepare the block copolymers and the final products were obtain by precipitating the polymer in cold methanol twice. Samples were withdrawn before the reaction was started and after it was stopped.

A.4.1 Block copolymerizations using pLMA as macro RAFT reagent

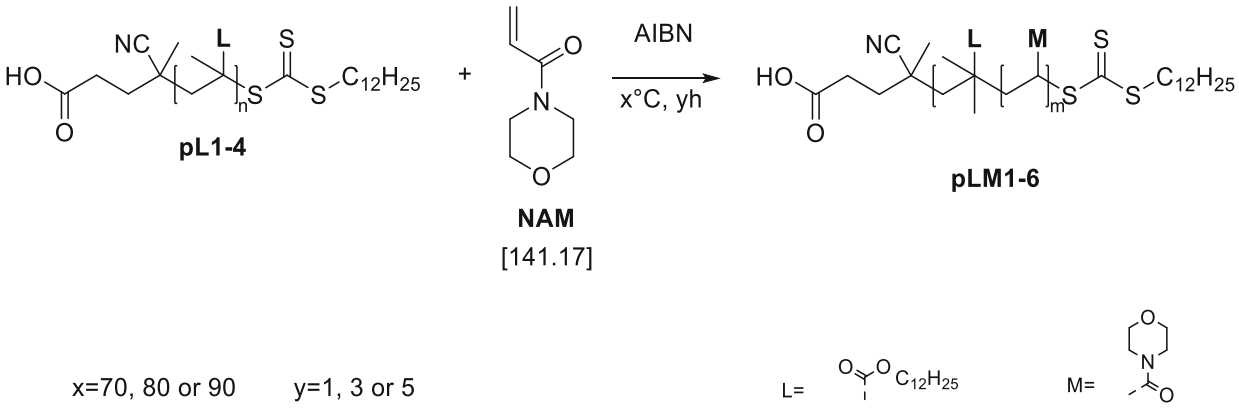


Table 40 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT blockcopolymerizations of **NAM** with p**LMA** as macro RAFT agent. Exact amounts of the reactants can be seen from Table 41 and Table 42.

Table 40: Reaction parameters and molar ratios of the educts of the RAFT block copolymerizations of NAM with pLMA as macro RAFT agent

Polymer	pLM3	pLM4	pLM5	pLM6	pLM1	pLM2
Temperature [°C]	70	70	80	80	90	90
Time [min]	6.5	6.5	3	3	1	1
[M]:[mCTA]	150	260	150	260	159	286
[mCTA]:[I]	10	10	10	10	10	10
[M]:[Std]	8	8	8	8	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5	1.5	1.5	1.5	1.5
$M_{n,\,NMR}$ [kDa]	26.6	45.5	26.6	45.8	27.5	51.3
$M_{n,\,SEC}$ [kDa]	19.0	27.6	17.7	25.1	19.7	25.4
Đ [ ]	1.16	1.23	1.21	1.30	1.29	1.38
Yield [g]	0.86	0.51	0.80	1.08	1.84	1.98
Yield [%]	69	41	64	86	73	79

Table 41: Initial weights and molar amounts of educts of the RAFT block copolymerizations of NAM with pLMA as macro RAFT agent

	pLM3		pLM4		pLM5			
mCTA	pL4		pL2		pL4			
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
NAM	1.00	7.1	1.00	7.1	1.00	7.1		
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
mCTA	250.5	0.05	250.4	0.03	249.8	0.05		
AIBN	0.8	0.005	0.5	0.004	0.8	0.005		
Naphthalene	115.1	0.90	116.6	0.91	117.9	0.92		
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Dioxane dry	4.7		4.7		4.7			

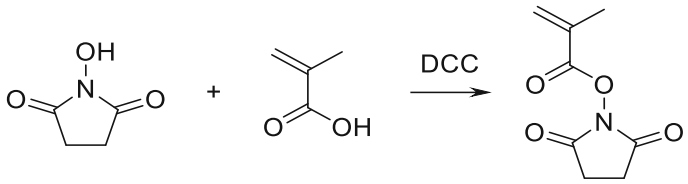
Table 42: Initial weights and molar amounts of educts of the RAFT block copolymerizations of NAM with pLMA as macro RAFT agent

	pLM6		pLM1		pLM2			
mCTA	pL2		pL3		pL1			
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
NAM	1.01	7.2	2.00	14.1	2.00	14.1		
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
mCTA	250.1	0.03	515.0	0.09	500.0	0.05		
AIBN	0.5	0.003	1.4	0.008	1.0	0.006		
Naphthalene	112.2	0.88	264.0	2.10	229.0	1.79		
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Dioxane dry	4.7		9.0		9.0			

A.4.2 Syntheses of functionalized block copolymers

A.4.2.1 Synthesis of N-methacryloxysuccinimide (NMS)

N-Methacryloxysuccinimide (NMS) was synthesized via a Steglich esterification as described in literature. [368]



NMS

[115.09] [86.09] [183.16]

Table 43 shows the used amounts of educts.

Table 43: Educts used for the synthesis of N-methacryloxysuccinimide

	[g/mol]	[mmol]	[g]	[mL]	Eq
N-Hydroxysuccinimide	115.09	8.7	1.00	-	1.0
Methacrylic acid	86.09	8.7	0.75	-	1.0
DCC	206.33	8.7	1.79	-	1.0
BHT	220.35	0.07	0.0153	-	0.008
Dioxane abs.	-	-	-	15	-

1 equivalent N-hydroxysuccinimide in 15 mL were placed into a 50 mL round bottom flask and cooled to 0 °C with an ice bath. Afterwards 1 equivalent freshly distilled methacrylic acid and in succession1 equivalent DCC were slowly added. After DCC was added, the formation of a white precipitate could be observed. After stirring the reaction mixture for 2 hours at 0 °C, it was warmed to room temperature. Then BHT was added and stirring was continued for 16 hours. The white solid was filtered off and the solvent was then removed under reduced pressure. Finally, the obtained product was purified by recrystallization from petrolether.

Yield ($C_8H_9NO_4$): 1.45 g white solid (91% yield)

^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm): 6.41 (s, 1H, C**H**$_2$-R), 5.88 (d, 1H, C**H**$_2$-R), 2.86 (s, 4H,R- C**H**$_2$-C**H**$_2$-R), 2.05 (s, 1H, C**H**$_3$-R)

A.4.2.2 RAFT polymerizations

All polymerizations were performed according to the general polymerization procedure. Hereby, either pure p**L** or p**LF** was used as macro RAFT agent.

Table 44 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT blockcopolymerizations of **NAM** and **NMS** with p**L** as macro RAFT agent. Exact amounts of the reactants can be seen from Table 45.

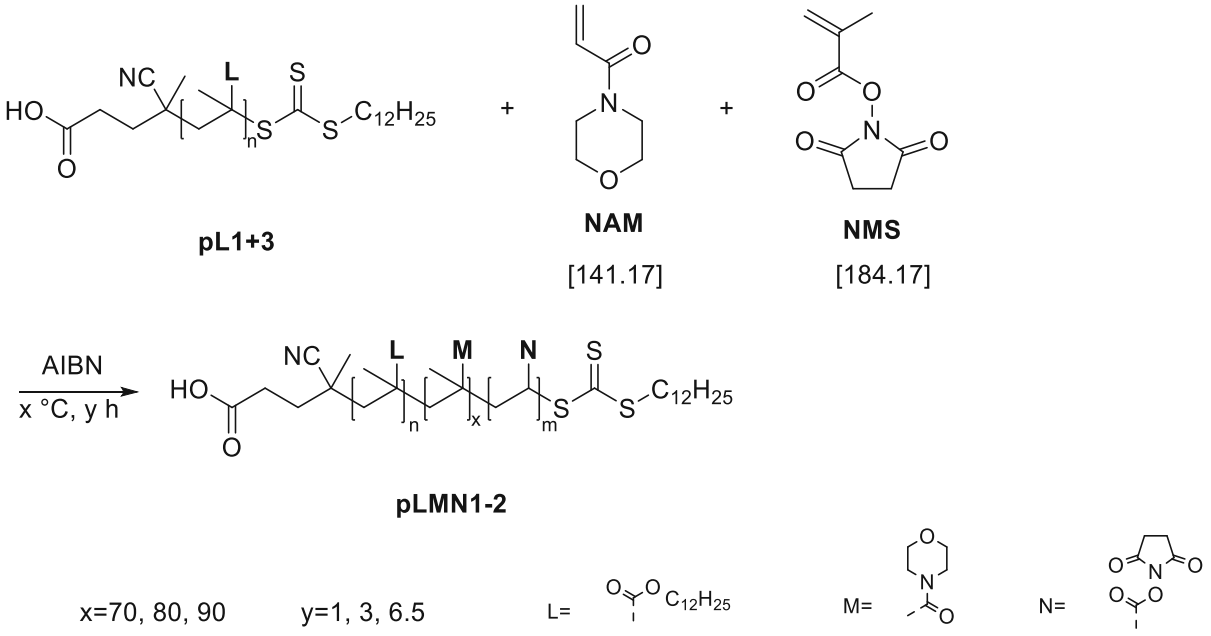


Table 44: Reaction parameters and molar ratios of the educts of the RAFT block copolymerizations of NAM and NMS with pL as macro RAFT agent

Polymer	pLMN1	pLMN2
Temperature [°C]	90	90
Time [min]	60	60
[M]:[mCTA]	156	280
[mCTA]:[I]	10	10
[M]:[Std]	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5
$M_{n,\,NMR}$ [kDa]	27.8	49.2
$M_{n,\,SEC}$ [kDa]	20.8	25.5
Đ [ ]	1.27	1.34
Yield [g]	1.73	1.51
Yield [%]	69	60

Table 45: Initial weights and molar amounts of educts of the RAFT block copolymerizations of NAM and NMS with pL as macro RAFT agent

	pLM6		pLM1	
mCTA	pL3		pL1	
	[g]	**[mmol]**	**[g]**	**[mmol]**
NAM	1.81	12.8	1.81	12.8
	[mg]	**[mmol]**	**[mg]**	**[mmol]**
mCTA	508.0	0.09	504.0	0.05
AIBN	1.7	0.010	0.05	0.007
NMS	203.0	1.11	203.0	1.11
Naphthalene	133.0	1.82	224.0	1.75
	[mL]		**[mL]**	
Dioxane dry	9.0		9.0	

Table 46 summarizes the reaction parameters, molar ratios of the educts and results of the RAFT blockcopolymerizations of **NAM** and of copolymerozation of **NAM** and **NMS** with p**LF** as macro RAFT agent. Exact amounts of the reactants can be seen from Table 47.

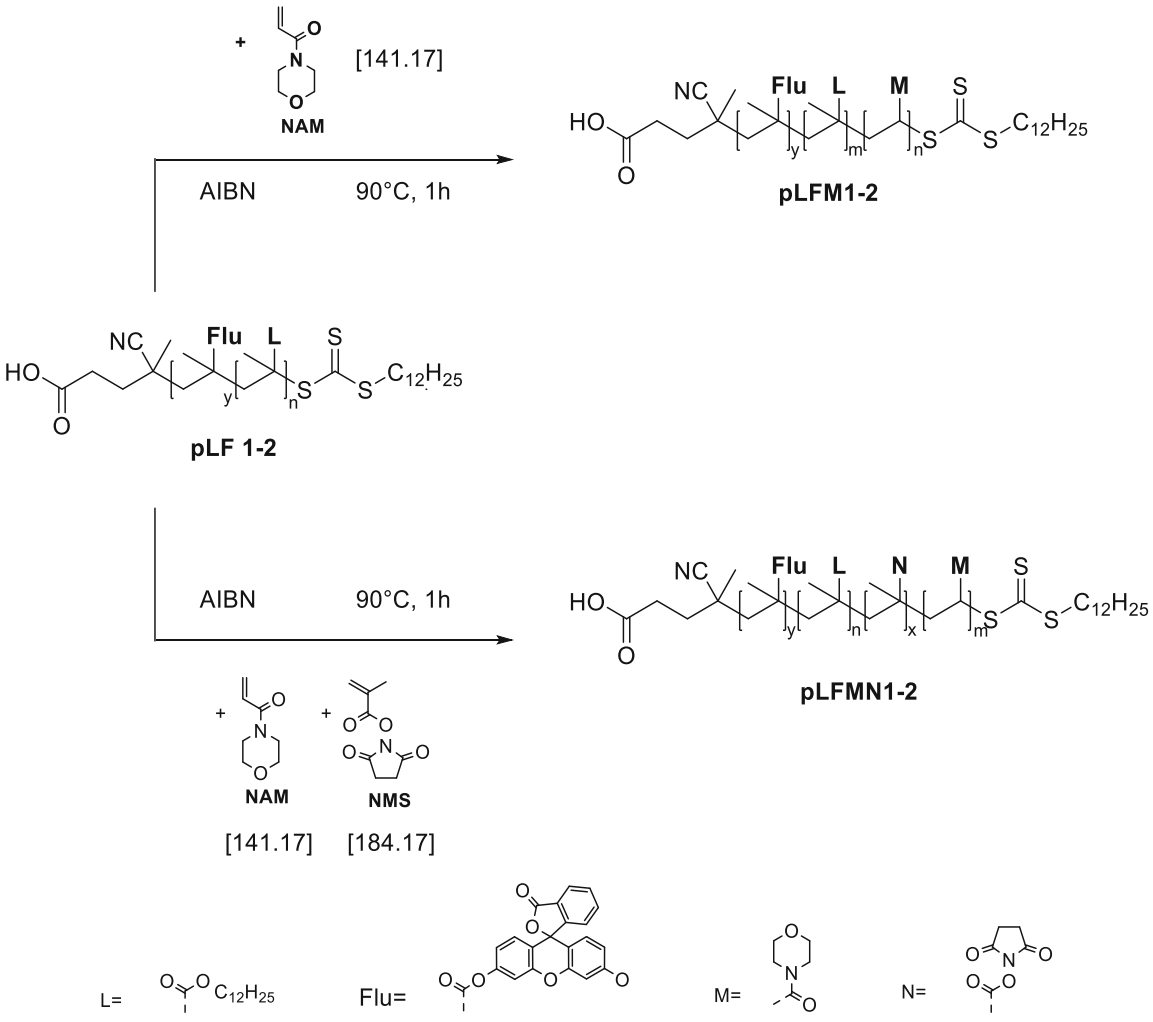


Table 46: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of NAM or NAM and NMS with pLF as macro RAFT agent

Polymer	pLFM1	pLFM2	pLFMN1	pLFMN2
Temperature [°C]	90	90	90	90
Time [min]	60	60	60	60
[M]:[mCTA]	142	284	139	280
[mCTA]:[I]	10	10	10	10
[M]:[Std]	8	8	8	8
$c_{Monomer}$ [mol/L]	1.5	1.5	1.5	1.5
$M_{n,\ NMR}$ [kDa]	25.1	50.1	25.2	50.1
$M_{n,\ SEC}$ [kDa]	17.6	24.7	17.2	23.1
Đ [ ]	1.24	1.47	1.27	1.50
Yield [g]	1.78	2.81	1.88	1.96
Yield [%]	71	72	75	78

Table 47: Initial weights and molar amounts of educts of the RAFT block copolymerizations of NAM or NAM and NMS with pLF as macro RAFT agent

	pLFM1		pLFM2		pLFMN1		pLFMN2	
mCTA	pLF1		pLF2		pLF1		pLF2	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
NAM	2.00	14.2	2.00	14.2	1.80	12.8	1.81	12.9
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
mCTA	503.0	0.10	508.0	0.05	499.0	0.10	505.0	0.05
AIBN	1.6	0.010	1.0	0.006	1.7	0.010	1.0	0.006
NMS	-	-	-	-	200.0	1.09	204.0	1.11
Naphthalene	235.0	1.83	229.0	1.79	222.0	1.73	220.0	1.72
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Dioxane dry	9.0		9.0		9.0		9.0	

A.5 Removal of the RAFT end group

A.5.2 Procedure and results of the RAFT end group removal

In order to remove the RAFT end group, BCP and V-501 as radical source were weighted into a penicillin flask and dissolved in dry dioxane at a concentration of 0.1 g/mL. Afterwards, the tubes were sealed with a rubber septum and the solutions were purged with inert gas for at least 30 minutes. The so prepared samples were immersed into a preheated aluminum block at 90 °C and left there for 16 hours. Reactions were stopped by cooling down in an ice bath and polymers were recovered by twofold precipitation into cooled methanol.

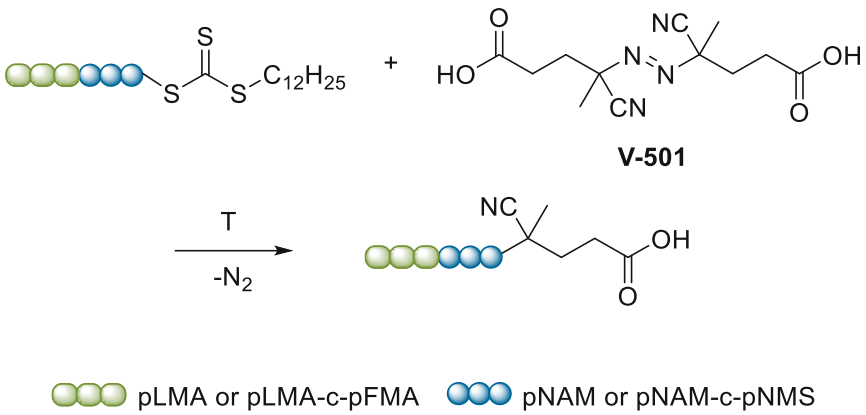


Table 48, Table 49 and Table 50 show the initial weights for these reactions.

Table 48: Initial weights of the RAFT end group removal of pLM1 – pLM4

Polymer	pLM1	pLM2	pLM3	pLM4
BCP [g]	0.51	0.50	0.30	0.50
BCP [µmol]	19	19	7	11
V-501 [mg]	53	31	18	31
V-501 [µmol]	188	110	66	109
Dioxane dry [mL]	5	5	3	5

Table 49: Initial weigths of the RAFT end group removal of pLM5, pLM6, pLMN1 and pLMN2

Polymer	pLM4	pLM5	pLMN1	pLMN2
BCP [g]	1.00	1.00	1.00	1.00
BCP [µmol]	40	20	40	20
V-501 [mg]	115	58	124	65
V-501 [µmol]	410	207	442	232
Dioxane dry [mL]	10	10	10	10

Table 50: Initial weights of the RAFT end group removal of pLFM, pLFM2, pLFMN1 and pLFMN2

Polymer	pLFM1	pLFM2	pLFMN1	pLFMN2
BCP [g]	1.00	1.00	1.00	1.00
BCP [µmol]	40	20	40	20
V-501 [mg]	112	57	128	58
V-501 [µmol]	400	203	457	207
Dioxane dry [mL]	10	10	10	10

Experimental Part B

RAFT polymers based on vinyl esters

B.1 RAFT polymerization of hydrophobic vinyl esters

B.1.3 Synthesis of RAFT agents

B.1.3.1 Synthesis of methyl (ethoxycarbonothioyl)sulfanyl acetate (MESA)

The synthesis of ***MESA*** was performed in a two-step-one-pot reaction as described by Stenzel *et al.* [297]

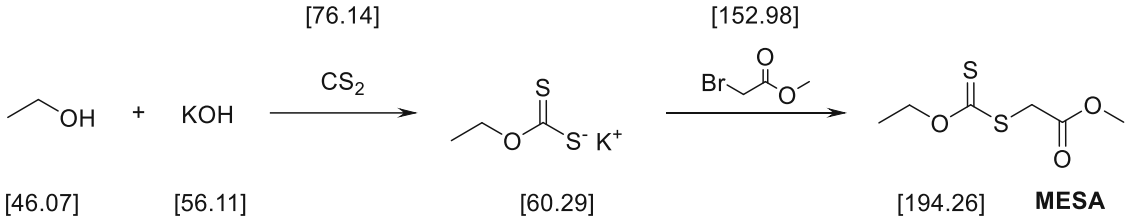


Table 51 summarizes the used amounts of educts.

Table 51: Educts used for the synthesis of methyl (ethoxycarbonothioyl)sulfanyl acetate

	[g/mol]	[mmol]	[g]	[mL]	Eq
Ethanol dry	46.07	343.0	15.80	20.0	6.9
Potassium hydroxide	56.11	50.0	2.81	-	1.0
Carbon disulfide	76.14	165.0	12.60	10.0	3.3
Methyl 2-bromoacetate	152.97	50.0	7.60	4.7	1.0

In a 50 mL 3-necked flask, equipped with reflux condenser, septum and dropping funnel, 1 equivalent potassium hydroxide were dissolved in 20 mL of dry ethanol. Afterwards, 3.3 equivalents carbon disulfide were added via a dropping funnel, whereupon the solution turned yellow and a white, voluminous precipitate was formed. After 5 hours stirring at room temperature, 1 equivalent methyl 2-bromoacetate were added via a syringe and stirring was continued for another 18 hours. Then, the precipitate was removed by filtration, washed with small portions of dry ethanol and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of diethyl ether and then filtered over basic aluminum oxide. After removing the solvent in vacuum, the product was obtained as yellow liquid.

Yield ($C_6H_{10}O_3S_2$): 7.73 yellow liquid (80% calculated yield)

^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm): 4.53 (q, 2H, -O-C**H**$_2$-CH_3, J=7.12 Hz), 3.81 (s, 2H, -S-C**H**$_2$-CO-), 3.63 (s, 3H, -O-C**H**$_3$), 1.31 (t, 3H, -O-CH_2-C**H**$_3$, J=7.12 Hz)

B.1.3.2 Synthesis of S-benzyl O-ethyl carbonodithioate (BED)

The synthesis of ***BED*** was done via two steps in an in-situ process. Thereby, the preparation of potassium-O-ethyl xanthogenate was carried out as described by Stenzel *et al.*[297] and the second step was carried out in dependence on McDowall *et al.*[312] and Ladavière *et al.* [324].

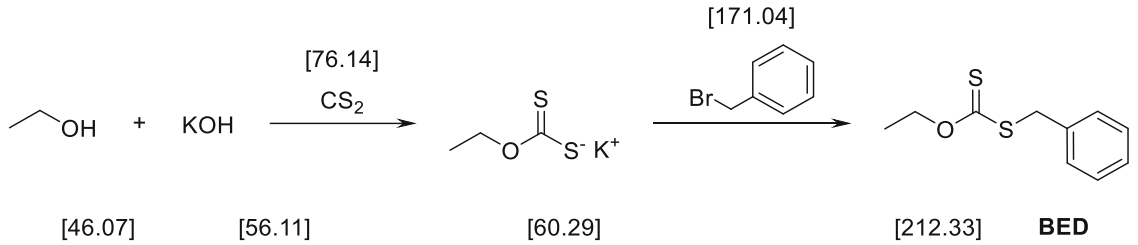


Table 52 summarizes the used amounts of educts.

Table 52: Educts used for the synthesis of S-benzyl O-ethyl carbonodithioate

	[g/mol]	[mmol]	[g]	[mL]	Eq
Ethanol dry	46.07	343.0	15.80	20.0	6.9
Potassium hydroxide	56.11	50.0	2.81	-	1.0
Carbon disulfide	76.14	165.5	12.60	10.0	3.3
Benzyl bromide	171.04	50.0	8.55	5.9	1.0

In a 100 mL 3-necked flask with reflux condenser and dropping funnel, 1 equivalent of potassium hydroxide was dissolved in 20 mL of dry ethanol under slight heating up to 50 °C. After complete dissolution, 3.3 equivalents of carbon disulfide were added slowly via the dropping funnel at this temperature, whereupon the solution turned yellow and a white, voluminous precipitate was observed. Hence, 10 mL of dry ethanol were added to ensure stirring of the solution. After five hours, heating was removed and the reaction mixture was cooled down with an ice bath. Then 1 equivalent benzyl bromide was added dropwise by what the color of the solution changed to slightly yellow. Following, the reaction mixture was left to warm to room temperature and stirring was continued for 14 hours. Reaction control was done by TLC (PE:EA 45:1), and as it showed residues of benzyl bromide, the mixture was heated to 50 °C and stirred there for another 4 hours. Again, reaction was controlled by TLC. For the work up, the solution was filtered in order to remove the precipitate, and the solvent was

removed under reduced pressure. Afterwards, 150 mL diethyl ether were added and solution was washed with brine (3x150 mL). The organic layer was dried over sodium sulfate and the solvent was evaporated to yield 9.28 g of a yellow liquid. The crude product was then purified by column chromatography using petrol ether as solvent. After the impurities have been completely eluted, the solvent was changed to pure ethyl acetate. The product-containing fractions were pooled and solvent was removed under reduced pressure to give a yellow liquid.

Yield ($C_{10}H_{12}OS_2$): 6.50 g yellow liquid (61% calculated yield)

R_f (PE)= 0.28

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.42-7.24 (m, 5H, -S-CH_2-**Ph**), 4.67 (q, 2H, -O-C**H**$_2$-CH_3, J=7.15 Hz), 4.39 (s, 2H, -S-C**H**$_2$-Ph), 1.44 (t, 3H, -O-CH_2-C**H**$_3$, J=7.02 Hz)

B.1.4 Homopolymerization of hydrophobic vinyl esters

B.1.4.2 Kinetic studies of RAFT polymerizations of hydrophobic vinyl esters

All polymerizations were performed using the following standard procedure. The needed amounts of initiator, RAFT agent and monomer were weighted into a penicillin flask, and solvent was added if required. Then, a magnetic stirring bar was added to the mixture and the tubes were sealed with a rubber septum. All reaction solutions were purged with inert gas for at least 30 minutes. An exception was made is vinyl acetate was used as monomer. Since it is highly volatile, reaction mixtures were frozen with liquid nitrogen and purged with inert gas while thawing. This was repeated not less than three times. Afterwards, polymerizations were started by placing the flasks into a preheated aluminum block and they were left there for a certain period. Reactions were stopped by cooling down the tubes in an ice bath. Finally, samples were withdrawn with a syringe, purged with argon, for analysis via ^{1}H-NMR and SEC. The samples were stored at -40 °C until further usage for analyses. If reactions were utilized to gather information about reaction kinetics, samples were also withdrawn during the polymerization process.

Table 53 summarizes the reaction parameter and molar ratios. In Table 54 the initial amounts of the educts are shown.

Table 53: Reaction parameters for the kinetic studies of the RAFT polymerizations of VAc, VH and VD in bulk using MESA as CTA

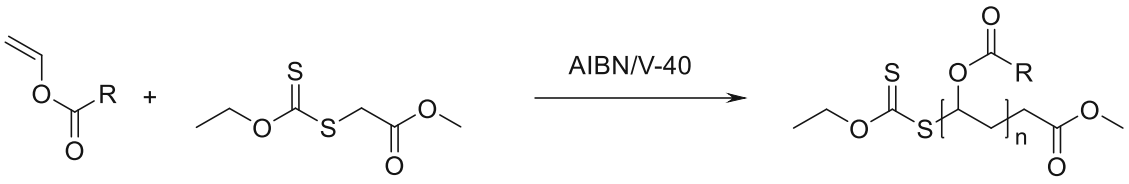
Polymer	pVAc	pVH	pVD
Temperature [°C]	60	60	60
Time [min]	300	240	240
[M]:[CTA]	115	55	50
[CTA]:[I]	10	10	10
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk

Table 54: Initial weights and molar amounts of educts for the kinetic studies of the RAFT polymerizations of VAc, VH and VD in bulk using MESA as CTA

	pVAc		pVH		pVD	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VAc	2.00	23.2	-	-	-	-
VH	-	-	3.01	21.1	-	-
VD	-	-	-	-	3.00	15.1
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
MESA	42.6	0.22	79.4	0.41	55.0	0.30
AIBN	3.3	0.020	7.0	0.042	4.8	0.029

B.1.4.3 Evaluation of the RAFT polymerization of various vinyl esters using MESA as CTA

The RAFT polymerizations were performed following the standard procedure either in bulk or solution.



MESA

[194.26]

R= $-CH_3$ $-C_5H_{11}$ $-C_9H_{19}$ $-\overset{R_1}{\underset{R_2}{\leftarrow}}$ $-CH_2Cl$

VAc **VH** **VD** **VnN** **VClAc**

[86.09] [142.20] [198.31] [184.28] [120.53]

$R_1=C_xH_{2x+1}$ $R_2=C_{6-x}H_{13-2x}$ x=1...5

B.1.4.3.1 Polymerization in bulk

Table 55 summarizes the reaction parameter and molar ratios for the polymerizations of **VAc** in bulk. In Table 56 the belonging initial amounts of the educts are shown.

Table 55: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VAc in bulk using MESA as CTA

Polymer	pVAc-9	pVAc-10	pVAc-11	pVAc-12
Temperature [°C]	60	60	60	60
Time [min]	140	250	330	330
[M]:[CTA]	56	56	56	56
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk	bulk
c_M [%]	77	71	67	62
$M_{n,\,NMR}$ [kDa]	3.8	3.5	3.5	3.1
$M_{n,\,SEC}$ [kDa]	3.5	2.2	2.7	3.0
Đ [ ]	1.27	1.20	1.21	1.24

Table 56: Initial weights and molar amounts of educts of the RAFT polymerizations of VAc in bulk using MESA as CTA

	pVAc-9		pVAc-10		pVAc-11		pVAc-12	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VAc	1.00	11.7	1.00	11.7	1.02	11.8	1.01	11.8
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
MESA	41.3	0.21	41.7	0.21	40.5	0.21	41.6	0.21
AIBN	6.8	0.041	3.4	0.021	2.3	0.014	1.7	0.010

Table 57 summarizes the reaction parameter and molar ratios for the polymerizations of **VH** in bulk. In Table 58 the belonging initial amounts of the educts are shown.

Table 57: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VH in bulk using MESA as CTA

Polymer	pVH-9	pVH-10	pVH-11	pVH-12
Temperature [°C]	60	60	60	60
Time [min]	210	220	230	240
[M]:[CTA]	34	34	34	34
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk	bulk
c_M [%]	97	95	92	83
$M_{n,\,NMR}$ [kDa]	4.2	4.7	4.4	4.1
$M_{n,\,SEC}$ [kDa]	3.7	3.7	3.8	3.4
Đ [ ]	1.36	1.39	1.35	1.33

Table 58: Initial weights and molar amounts of educts of the RAFT polymerizations of VH in bulk using MESA as CTA

	pVH-9		pVH-10		pVH-11		pVH-12	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VH	1.00	7.0	1.00	7.0	1.01	7.1	1.01	7.1
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
MESA	47.1	0.24	43.3	0.21	43.4	0.22	41.6	0.21
AIBN	6.8	0.041	3.4	0.021	2.3	0.014	1.8	0.011

Table 59 summarizes the reaction parameter and molar ratios for the polymerizations of **VD** in bulk. In Table 60 the belonging initial amounts of the educts are shown.

Table 59: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VD in bulk using MESA as CTA

Polymer	pVD-9	pVD-10	pVD-11	pVD-12
Temperature [°C]	60	60	60	60
Time [min]	285	285	285	285
[M]:[CTA]	24	24	24	24
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk	bulk
c_M [%]	96	95	91	86
$M_{n,\,NMR}$ [kDa]	4.8	4.8	4.6	4.3
$M_{n,\,SEC}$ [kDa]	5.6	5.5	5.1	5.3
Đ [ ]	1.24	1.23	1.21	1.18

Table 60: Initial weights and molar amounts of educts of the RAFT polymerizations of VD in bulk using MESA as CTA

	pVD-9		pVD-10		pVD-11		pVD-12	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VD	1.02	5.2	1,00	5,0	1,02	5,1	1,01	5,1
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
MESA	41.1	0.21	40.4	0.21	41.0	0.21	40.5	0.21
AIBN	6.7	0.041	3.4	0.021	2.4	0.015	1.7	0.010

Table 61 summarizes the reaction parameter and molar ratios for the polymerizations of **VnN** in bulk. In Table 62 the belonging initial amounts of the educts are shown.

Table 61: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VnN in bulk using MESA as CTA

Polymer	pVnN-9	pVnN-10	pVnN-11	pVnN-12
Temperature [°C]	60	60	60	60
Time [min]	168	180	198	210
[M]:[CTA]	26	26	26	26
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk	bulk
c_M [%]	88	85	79	78
$M_{n,\,NMR}$ [kDa]	4.4	4.2	4.1	3.6
$M_{n,\,SEC}$ [kDa]	3.8	3.6	2.6	3.1
Đ [ ]	1.18	1.16	1.17	1.16

Table 62: Initial weights and molar amounts of educts of the RAFT polymerizations of VnN in bulk using MESA as CTA

	pVnN-9		pVnN-10		pVnN-11		pVnN-12	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VnN	1.00	5.4	1.00	5.4	1.00	5.4	1.00	5.4
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
MESA	40.9	0.21	41.5	0.21	40.0	0.21	45.1	0.23
AIBN	6.7	0.041	3.5	0.021	2.4	0.015	1.8	0.011

Table 63 summarizes the reaction parameter and molar ratios for the polymerizations of **VClAc** in bulk. In Table 64 the belonging initial amounts of the educts are shown.

Table 63: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VClAc in bulk using MESA as CTA

Polymer	pVClAc-9	pVClAc-10	pVClAc-11	pVClAc-12
Temperature [°C]	80	80	80	80
Time [min]	120	200	265	295
[M]:[CTA]	40	40	40	40
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]				
c_M [%]	83	82	84	77
$M_{n,\,NMR}$ [kDa]	4.1	4.2	4.2	3.9
$M_{n,\,SEC}$ [kDa]	4.2	4.0	4.0	3.7
Đ [ ]	1.35	1.34	1.36	1.32

Table 64: Initial weights and molar amounts of educts of the RAFT polymerizations of VClAc in bulk using MESA as CTA

	pVClAc-9		pVClAc-10		pVClAc-11		pVClAc-12	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VClAc	1,0	8,4	1,01	8,4	1,01	8,4	1,00	8,3
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
MESA	41.1	0.21	43.3	0.22	41.0	0.21	39.8	0.20
AIBN	10.2	0.042	5.1	0.021	6.4	0.014	2.5	0.010

B.1.4.3.2 Polymerization in Solution

Table 65 summarizes the reaction parameter and molar ratios for the polymerizations of **VAc** in solution. In Table 66 the belonging initial amounts of the educts are shown.

Table 65:Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VAc in solution using MESA as CTA

Polymer	pVAc-1	pVAc-2	pVAc-3	pVAc-4
Temperature [°C]	60	60	60	60
Time [min]	1200	1200	1200	1200
[M]:[CTA]	56	56	56	56
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	5	5	5	5
c_M [%]	45	32	20	14
$M_{n,\,NMR}$ [kDa]	2.4	1.5	1.1	0.9
$M_{n,\,SEC}$ [kDa]	1.4	1.3	0.8	0.9
Đ [ ]	1.18	1.21	1.27	1.27

Table 66: Initial weights and molar amounts of educts of the RAFT polymerizations of VAc in solution using MESA as CTA

	pVAc-1		pVAc-2		pVAc-3		pVAc-4	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VAc	1.00	11.6	1.00	11.6	1.00	11.6	1.01	11.7
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
MESA	40.9	0.21	46.3	0.24	40.4	0.21	44.2	0.23
AIBN	6.9	0.042	3.6	0.022	2.3	0.014	1.8	0.011
	[mL]		[mL]		[mL]		[mL]	
Benzene dry	2.3		2.3		2.3		2.3	

Table 67 summarizes the reaction parameter and molar ratios for the polymerizations of **VH** in solution. In Table 68 the belonging initial amounts of the educts are shown.

Table 67: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VH in solution using MESA as CTA

Polymer	pVH-1	pVH-2	pVH-3	pVH-4
Temperature [°C]	70	70	70	70
Time [min]	1200	1200	1200	1200
[M]:[CTA]	34	34	34	34
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	5	5	5	5
c_M [%]	92	83	61	49
$M_{n,\,NMR}$ [kDa]	4.4	4.5	3.2	2.5
$M_{n,\,SEC}$ [kDa]	3.5	3.6	2.8	2.2
Đ [ ]	1.40	1.39	1.27	1.26

Table 68: Initial weights and molar amounts of educts of the RAFT polymerizations of VH in solution using MESA as CTA

	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VH	1.01	7.1	1.07	7.6	1.00	7.1	1.00	7.1
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
MESA	43.3	0.22	40.0	0.21	40.2	0.21	42.0	0.22
AIBN	6.8	0.042	3.4	0.021	2.2	0.013	1.7	0.011
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Benzene dry	1.4		1.4		1.4		1.4	

Table 69 summarizes the reaction parameter and molar ratios for the polymerizations of **VD** in solution. In Table 70 the belonging initial amounts of the educts are shown.

Table 69: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VD in solution using MESA as CTA

Polymer	pVD-1	pVD-2	pVD-3	pVD-4
Temperature [°C]	70	70	70	70
Time [min]	1200	1200	1200	1200
[M]:[CTA]	24	24	29	24
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	5	5	5	5
c_M [%]	73	58	46	29
$M_{n,\,NMR}$ [kDa]	3.7	3.0	2.9	1.5
$M_{n,\,SEC}$ [kDa]	4.4	3.7	3.5	2.1
Đ [ ]	1.22	1.19	1.18	1.20

Table 70: Initial weights and molar amounts of educts of the RAFT polymerizations of VnN in solution using MESA as CTA

	pVD-1		pVD-2		pVD-3		pVD-4	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VD	1.01	5.1	1.00	5.1	1.24	6.2	0.99	5.0
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
MESA	41.0	0.21	40.6	0.21	40.9	0.21	43.6	0.22
AIBN	6.9	0.042	3.5	0.021	2.3	0.014	1.7	0.010
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Benzene dry	1.0		1.0		1.0		1.0	

Table 71 summarizes the reaction parameter and molar ratios for the polymerization of **VnN** in solution. In Table 72 the belonging initial amounts of the educts are shown.

Table 71: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VnN in solution using MESA as CTA

Polymer	pVN-1
Temperature [°C]	70
Time [min]	1200
[M]:[CTA]	26
[CTA]:[I]	5
$c_{Monomer}$ [mol/L]	5
c_M [%]	19
$M_{n,\,NMR}$ [kDa]	1.1
$M_{n,\,SEC}$ [kDa]	1.2
Đ [ ]	1.22

Table 72: Initial weights and molar amounts of educts of the RAFT polymerizations of VnN in solution using MESA as CTA

	pVN-1	
	[g]	[mmol]
VnN	1.00	5.4
	[mg]	[mmol]
MESA	42.3	0.22
AIBN	6.8	0.041
	[mL]	
Benzene dry	1.1	

Table 73 summarizes the reaction parameter and molar ratios for the polymerizations of **VClAc** in solution. In Table 74 the belonging initial amounts of the educts are shown.

Table 73: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VClAc in solution using MESA as CTA

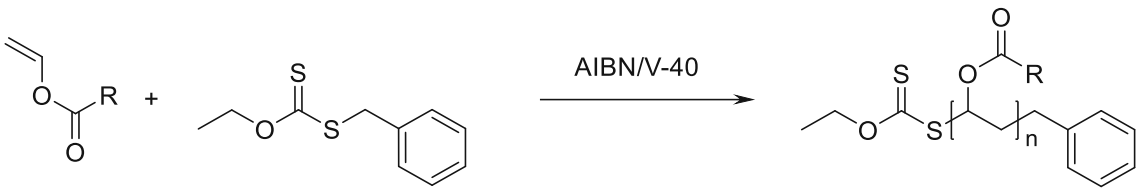
Polymer	pVClAc-1	pVClAc-2	pVClAc-3	pVClAc-4
Temperature [°C]	80	80	80	80
Time [min]	1200	1200	1200	1200
[M]:[CTA]	40	40	40	40
[CTA]:[I]	5	10	15	20
$c_{Monomer}$ [mol/L]	5	5	5	5
c_M [%]	97	90	68	62
$M_{n,\,NMR}$ [kDa]	4.7	4.2	3.3	3.1
$M_{n,\,SEC}$ [kDa]	4.5	3.9	3.1	2.8
Đ [ ]	1.47	1.37	1.38	1.36

Table 74: Initial weights and molar amounts of educts of the RAFT polymerizations of VClAc in solution using MESA as CTA

	pVClAc-1		pVClAc-2		pVClAc-3		pVClAc-4	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VClAc	1.01	8.4	1.00	8.3	1.00	8.3	1.01	8.4
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
MESA	42.4	0.22	44.2	0.23	41.8	0.22	42.00	0.22
V-40	10.2	0.042	5.1	0.021	3.4	0.014	2.6	0.010
	[mL]		[mL]		[mL]		[mL]	
Benzene dry	1.7		1.7		1.7		1.7	

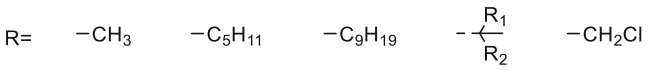
B.1.4.4 Polymerization with BED as RAFT agent

The polymerizations were carried out as described in the general polymerization procedure.



BED

[212.33]



	VAc	VH	VD	VnN	VClAc
	[86.09]	[142.20]	[198.31]	[184.28]	[120.53]

$R_1=C_xH_{2x+1}$ $R_2=C_{6-x}H_{13-2x}$ x=1...5

Table 75 summarizes the reaction parameter and molar ratios for the polymerizations of **VH**, **VD** and **VnN** in bulk. In Table 76 the belonging initial amounts of the educts are shown.

Table 75: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VH, VD and VnN in bulk using BED as CTA

Polymer	pVH-13	pVD-13	pVnN-13
Temperature [°C]	70	70	70
Time [min]	1200	1200	1200
[M]:[CTA]	34	24	26
[CTA]:[I]	5	5	5
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk
c_M [%]	75	64	15
$M_{n,\,NMR}$ [kDa]	3.9	3.3	0.9
$M_{n,\,SEC}$ [kDa]	2.6	2.7	0.9
Đ [ ]	1.30	1.26	1.20*

Table 76: Initial weights and molar amounts of educts of the RAFT polymerizations of VH, VD and VnN in bulk using BED as CTA

	pVH-13		pVD-13		pVnN-13	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VH	1.00	7.0	-	-	-	-
VD	-	-	1.00	5.0	-	-
VnN	-	-	-	-	1.01	5.5
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
BED	43.8	0.21	44.5	0.21	45.0	0.21
AIBN	6.8	0.041	6.9	0.042	6.9	0.042

Table 77 summarizes the reaction parameter and molar ratios for the polymerizations of **VClAc** in bulk. In Table 78 the belonging initial amounts of the educts are shown.

Table 77: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VClAc in bulk using BED as CTA

Polymer	pVClAc-13	pVClAc-14	pVClAc-15
Temperature [°C]	80	80	80
Time [min]	960	1135	1120
[M]:[CTA]	40	40	40
[CTA]:[I]	5	10	15
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk
c_M [%]	81	76	36
$M_{n,\,NMR}$ [kDa]	4.1	3.9	1.9
$M_{n,\,SEC}$ [kDa]	2.8	2.4	1.6
Đ [ ]	1.32	1.29	1.26

Table 78: Initial weights and molar amounts of educts of the RAFT polymerizations of VClAc in bulk using BED as CTA

	pVClAc-13		pVClAc-14		pVClAc-15	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VClAc	1.00	8.3	1.00	8.3	1.00	8.3
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
BED	44.1	0.21	44.1	0.21	44.8	0.21
V-40	10.2	0.042	5.0	0.021	3.4	0.014

Table 79 summarizes the reaction parameter and molar ratios for the polymerizations of **VH**, **VD** and **VClAc** in solution. In Table 80 the belonging initial amounts of the educts are shown.

Table 79:Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VH. VD an VClAc in solution using BED as CTA

Polymer	pVH-5	pVD-5	pVClAc-5	pVClAc-6
Temperature [°C]	70	70	80	80
Time [min]	1200	1200	1200	1200
[M]:[CTA]	34	24	40	40
[CTA]:[I]	5	5	5	10
$c_{Monomer}$ [mol/L]	5	5	5	5
c_M [%]	14	22	80	16
$M_{n,\,NMR}$ [kDa]	0.9	1.3	4.1	1.0
$M_{n,\,SEC}$ [kDa]	1.0	1.4	2.8	0.7
Đ [ ]	1.26	1.22	1.40	1.26

Table 80: Initial weights and molar amounts of educts of the RAFT polymerizations of VH. VD an VClAc in solution using BED as CTA

	pVH-5		pVD-5		pVClAc-5		pVClAc-6	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VH	1.00	7.1	-	-	-	-	-	-
VD	-	-	1.00	5.0	-	-	-	-
VClAc	-	-	-	-	1,01	8,4	1,01	8,4
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
BED	43.5	0.20	45.6	0.22	44,4	0,21	44,2	0,21
AIBN	6.8	0.041	6.9	0.042	-	-	-	-
V-40	-	-	-	-	10,2	0,042	5,1	0,021
	[mL]		**[mL]**		**[mL]**		**[mL]**	
Benzene dry	1.4		1.0		1.7		1.7	

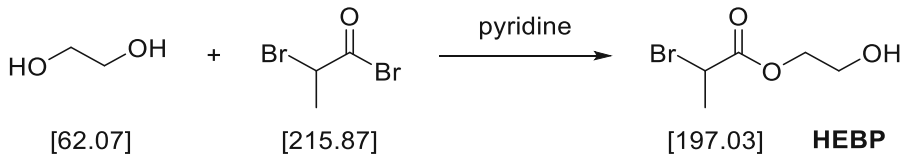
B.2 RAFT polymerization using a dual initiator

B.2.1 Synthesis of HECP

The dual initiator was synthesized in a two-step reaction as described in literature. [149]

B.2.1.1 Synthesis of 2-hydroxyethyl-2-bromopropionate

The precursor 2-hydroxyethyl-2-bromopropionate (**HEBP**) was prepared in a one-step reaction.



[62.07] [215.87] [197.03] **HEBP**

Table 81 summarizes the used amounts of educts.

Table 81: Educts used for the synthesis of 2-hydroxyethyl-2-bromopropionate

	[g/mol]	[mmol]	[g]	[mL]	Eq
Ethylene glycol	62.07	441	27.37	-	50.7
2-Bromopropionyl bromide	215.87	8.7	1.88	-	1
Pyridine	79.10	9.1	0.72	0.71	1.05
THF dry	-	-	-	15.0	-

Ethylene glycol was dissolved in 10 mL of dry THF in a 50 mL 3-necked round bottom flask, equipped with thermometer, drying tube and stirring bar, and cooled down to 0 °C. Then 2-bromopropionyl bromide diluted in 5 mL of dry THF was added via a dropping funnel over a period of 15 minutes and the reaction mixture was stirred at this temperature for one hour. Afterward the solution was allowed to warm to room temperature and stirring was continued for another 16 hours. After complete conversion, as proven by TLC (PE:EA 4:1), the mixture was poured into 80 mL acidified water (pH=2) and was then extracted with dichloromethane (6x10 mL). The combined organic layers were washed with brine and dried over sodium sulfate. After the solvent was removed in vacuum, HEBP was obtained as slightly yellow oil. HEBP was further used without conducting any purification steps.

Yield ($C_5H_9BrO_3$): 1.47 g slightly yellow oil (85% yield)

R_f (PE:EA 4:1)= 0.14

^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm): δ 4.37 (q, 1H, -C**H**-Br, J = 6.92 Hz), 4.23 (t, 2H, -C**H$_2$**-O-R, J = 4.72 Hz), 3.79 (t, 2H, -C**H$_2$**-OH, J = 4.73 Hz), 2.92 (s, 1H, -O**H**), 1.77 (d, 3H, -C**H$_3$**, J = 6.92 Hz)

B.2.1.2 Synthesis of 2-hydroxyethyl 2-((ethoxycarbonothioyl)thio)propanoate

The dual initiator 2-hydroxyethyl 2-((ethoxycarbonothioyl)thio)propanoate(**HECP**) was prepared in two steps in an one-pot reaction.

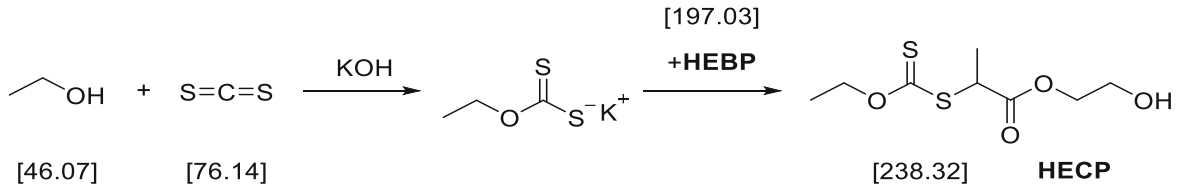


Table 82 summarizes the used amounts of educts.

Table 82: Educts used for the synthesis of 2-hydroxyethyl 2-((ethoxycarbonothioyl)thio)propanoate

	[g/mol]	[mmol]	[g]	[mL]	Eq
Ethanol dry	46.07	85.6	3.95	5.0	11.4
Potassium hydroxide	56.11	7.5	0.42	-	1.0
Carbon disulfide (CS_2)	76.14	25	1.88	1.5	3.3
HEBP	197.03	7.5	1.47	-	1.0

Potassium O-ethyl carbonodithioate was prepared *in situ* from dry ethanol (EtOH), potassium hydroxide (KOH) and carbon disulfide (CS_2) and left to react with HEBP without further purification. Therefore, KOH was dissolved in 5 mL of dry EtOH and CS_2 was slowly added, whereby a yellow precipitate was formed. Additional 5 mL EtOH were added in order to dissolve the solid and the solution was warmed to 40 °C. After stirring for 5 hours, HEBP dissolved in 5 mL dry THF was added and stirring was continued for 12 hours at room temperature. The formed solid was removed by filtration and the filter cake was washed with EtOH repeatedly. After the solvent was removed under reduced pressure, the residue was dissolved in DCM, washed with brine and dried over sodium sulfate. DCM was then removed by rotary evaporation to give 1.17 g yellowish, oily liquid. Following, the crude product was purified via MPLC (42 g silica gel, PE:EA 4:1) and ***HECP*** was obtained as yellowish oil.

Yield ($C_8H_{14}O_4S_2$): 0.90 g yellowish oil (50% yield)

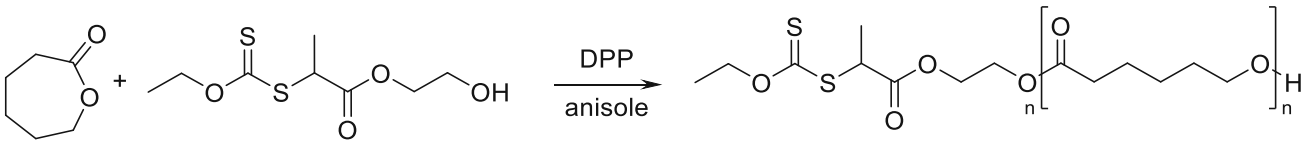
R_f (PE:EA 4:1)= 0.20

GC-MS (DCM): m/z 237.81 (M), 220.94, 194.85, 176.93, 148.94, 131.02, 117.04, 99.05, 88.01, 73.04, 59.01

^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 4.61 (q, 2H, -O-C**H$_2$**-CH_3, J = 7.12 Hz), 4,39 (q, 1H, -S-C**H-**CH_3, J = 7.42 Hz), 4.26 (m, 2H, -CH_2-C**H$_2$**-O-R), 3.81 (m, 2H, -C**H$_2$**-OH), 2.3 (br s, 1H, -O**H**), 1.57 (d, 3H, -CH-C**H$_3$**, J = 7.43 Hz), 1.40 (t, 3H, -CH_2-C**H$_3$**, J = 7.12 Hz)

B.2.2 HECP as initiator for ROP - Proof of concept

Reactions were performed similar as described in literature.[143] ε-caprolactone (CL), diphenyl phosphate (DPP) and HECP were weighted into a penicillin flask and purged with argon. Polymerizations were started by warming to 30 °C. After a predetermined period, the reactions were stopped by adding a solution of 4-dimethylamino pyridine (DMAP) in dry anisole (c=0.09 g/mL) and polymers were recovered by precipitation in cold petrol ether.



[114.14] [238.32] **HECP** **pCL 1-2**

Reaction parameters and molar ratios can be seen from Table 83 and initial weights and molar amounts are summarized in Table 84.

Table 83: Reaction parameters and molar ratios of the educts for the ROP of CL sing HECP

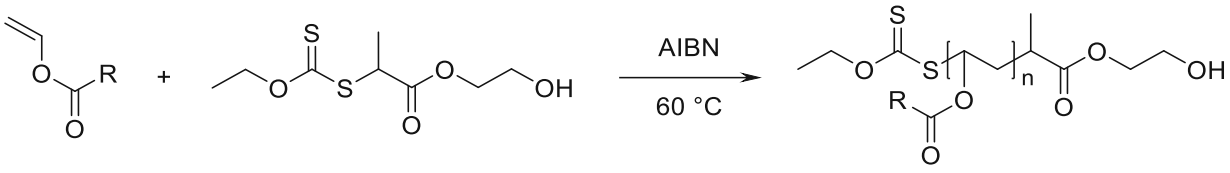
Polymer	pCL-1	pCL-2
Temperature [°C]	30	30
Time [min]	240	240
[M]:[HECP]	200	200
[DPP]:[HECP]	1.5	1.5
$c_{Monomer}$ [mol/L]	bulk	8.9
$M_{n.\ SEC}$ [kDa]	6.1	9.4
Đ [ ]	1.15	1.08

Table 84: Initial weights and molar amounts of educts for the ROP of CL sing HECP

	pVH-5		pVD-5	
	[g]	[mmol]	[g]	[mmol]
CL	3.76	33.0	3.76	33.0
	[mg]	[mmol]	[mg]	[mmol]
HECP	39.3	0.17	39.3	0.17
DPP	61.7	0.25	61.7	0.25
	[mL]		[mL]	
Anisole dry	-		3.7	

B.2.3 Polymerization of hydrophobic vinyl esters Using HECP as CTA

The RAFT polymerizations were performed following the general polymerization procedure as described in A.



R= C_5H_{11} C_9H_{19} **HECP** **pVH 17-20** **pVD 17-28**

[140.20] [198.31] [238.32]

B.2.3.1 Polymerization of VD

Table 85 summarizes the reaction parameter and molar ratios for the polymerizations of **VD** with ***HECP*** in bulk. In Table 86 the belonging initial amounts of the educts are shown.

Table 85: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VD in bulk using HECP as CTA

Polymer	pVD-23	pVD-24	pVD-26	pVD-27	pVD-28
Temperature [°C]	60	60	70	70	70
Time [min]	300	300	300	300	300
[M]:[CTA]	50	50	50	50	50
[CTA]:[I]	5	10	5	10	15
$c_{Monomer}$ [mol/L]	bulk	bulk	bulk	bulk	bulk
c_M [%]	48	-*	90	83	62
$M_{n,\,NMR}$ [kDa]	5.0	-*	9.1	8.3	6.2
$M_{n,\,SEC}$ [kDa]	6.2	6.1	8.5	8.3	8.1
Đ [ ]	1.16	1.15	1.46	1.37	1.34

Table 86: Initial weights and molar amounts of educts of the RAFT polymerizations of VD in bulk using HECPas CTA

	pVD-23		pVD-24		pVD-26		pVD-27		pVD-28	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VD	1.00	5.0	1.00	5.0	1.00	5.0	1.00	5.0	1.01	5.1
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
HECP	24.4	10.24	24.4	10.24	24.4	10.24	24.4	10.24	24.9	10.45
AIBN	3.3	0.020	1.7	0.010	3.3	0.020	1.7	0.010	1.2	0.007

Table 87 summarizes the reaction parameter and molar ratios for the polymerizations of **VD** with ***HECP*** in solution. In Table 88 the belonging initial amounts of the educts are shown.

Table 87: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VD in solution using HECP as CTA

Polymer	pVD-17	pVD-20	pVD-21
Temperature [°C]	60	70	70
Time [min]	1080	1080	1080
[M]:[CTA]	50	50	50
[CTA]:[I]	5	5	10
$c_{Monomer}$ [mol/L]	43	43	43
c_M [%]	11	73	28
$M_{n.\,NMR}$ [kDa]	1.3	7.4	2.9
$M_{n.\,SEC}$ [kDa]	2.3	6.8	3.9
Đ [ ]	1.23	1.42	1.23

Table 88: Initial weights and molar amounts of educts of the RAFT polymerizations of VD in solution using HECP as CTA

	pVD-17		pVD-20		pVD-21	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
VD	2.00	10.1	2.00	10.1	2.00	10.1
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
HECP	48.9	20.52	49.0	2.56	48.9	20.52
AIBN	6.7	0.041	6.7	0.041	3.4	0.021
	[mL]		[mL]		[mL]	
Anisole dry	0.23		0.23		0.23	

B.2.3.2 Polymerization of VH

These reactions were conducted as described in the general procedure (see A). Table 89 summarizes the reaction parameter and molar ratios for the polymerizations of **VH** with ***HECP*** in solution and bulk. In Table 90 the belonging initial amounts of the educts are shown.

Table 89:Reaction parameters and molar ratios of the educts of the RAFT polymerizations of VH in solution and bulk using HECP as CTA

Polymer	pVH-17	pVH-18	pVH-19	pVH-20	pVH-21
Temperature [°C]	60	60	60	60	60
Time [min]	300	300	300	1100	1100
[M]:[CTA]	245	245	245	34	51
[CTA]:[I]	2.1	5	2.1	5	5
$c_{Monomer}$ [mol/L]	bulk	bulk	43	43	43
c_M [%]	69	70	28	71	69
$M_{n,\,NMR}$ [kDa]	23.4	24.7	10.0	3.7	4.9
$M_{n,\,SEC}$ [kDa]	265	26.3	13.1	4.1	4.3
Đ [ ]	1.63	1.67	1.17	1.24	1.31

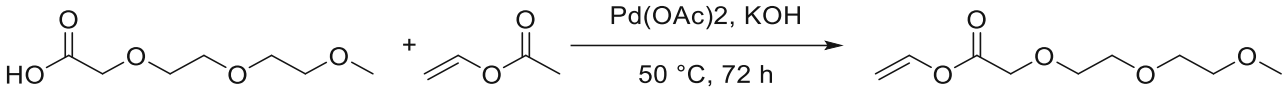
Table 90: Initial weights and molar amounts of educts of the RAFT polymerizations VH in solution and bulk using HECP as CTA

	pVH-17		pVH-18		pVH-19		pVH-20		pVH-21	
	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
VD	3,70	26,0	3,70	26,0	3.70	26,0	3.01	21.1	3.01	21.1
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
HECP	26.0	0.11	25.0	0.10	25.6	0.11	147.5	0.62	107.6	0.45
AIBN	8.2	0.050	3.5	0.021	8.2	0.050	20.4	0.125	13.6	0.083
	[mL]		**[mL]**		**[mL]**		**[mL]**		**[mL]**	
Anisole dry	-		-		0.6		0.5		0.5	

B.2.4 Polymerization of hydrophilic monomers using HECP as CTA

B.2.4.1 Synthesis of TOVE

The hydrophilic and water soluble vinyl ester vinyl 2-(2-(2-methoxyethoxy)ethoxy)acetate (**TOVE**) was synthesized in dependence on literature[267] via a palladium-catalyzed transesterification reaction.



[178.18] [86.09] [204.22] **TOVE**

Table 91 summarizes the used amounts of educts.

Table 91: Educts used for the synthesis of vinyl 2-(2-(2-methoxyethoxy)ethoxy)acetate

	[g/mol]	[mmol]	[g]	[mL]	Eq
2-(2-(2-methoxyethoxy) ethoxy)acetic acid	178.18	28.1	5.00	-	1.0
Vinyl acetate	86.01	673.5	57.93	-	24.0
$Pd(OAc)_2$	224.51	2.1	0.47	-	0.075
KOH	56.11	1.4	0.08	-	0.1

A mixture of 1 equivalent 2-(2-(2-methoxyethoxy) ethoxy)acetic acid. 23.8 equivalents vinyl acetate. 0.075 equivalents $Pd(OAc)_2$ and 0.1 equivalents KOH was prepared in a 100 mL round bottom flask equipped with a reflux condenser and a drying tube filled with $CaCl_2$. It was heated to 50 °C and stirred there for 89 hours. Since thin layer chromatography (PE:EA 1:1) showed complete conversion of the acid. the solution was filtered and 50 mL ethyl acetate were added. The organic phase was washed with H_2O (2x50 mL). dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified via MPLC (PE:EA 1:1. pure EA at the end) and was then obtained as slightly yellow liquid.

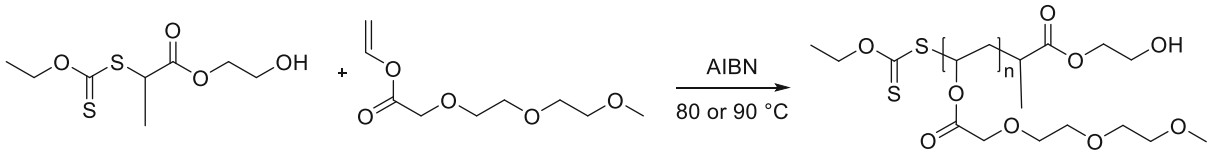
Yield ($C_9H_{16}O_5$): 2.88 g slightly yellow liquid (50% yield)

R_f (PE:EA 1:1)= 0.36

^{1}H-NMR ($CDCl_3$. 200 MHz): δ (ppm) 7.29 (dd. 1H. H_2C=C**H**R. J_1=6.26 Hz. J_2=13.89 Hz). 4.90 (dd. 1H. $\mathbf{H_{cis}}$H=CHR. J_1=1.76 Hz. J_2=13.89 Hz). 4.62 (dd. 1H. $\mathbf{H_{trans}}$H=CHR. J_1=1.56 Hz. J_2=6.26 Hz). 4.25 (s. 2H. -C(=O)-C$\mathbf{H_2}$-O-). 3.68 (m. 8H. -O-C$\mathbf{H_2}$-C$\mathbf{H_2}$-). 3.35 (s. 3H. -O-C$\mathbf{H_3}$)

B.2.4.2 Polymerizations

TOVE was polymerized by means of RAFT polymerization using HECP as CTA using the general polymerization procedure (see A).



[238.32] **HECP** [204.22] **TOVE** **pTOVE 1-6**

Table 92 summarizes the reaction parameter and molar ratios for the polymerizations of **TOVE** with ***HECP***. In Table 93 and Table 94 the belonging initial amounts of the educts are shown.

Table 92: Reaction parameters and molar ratios of the educts of the RAFT polymerizations of TOVE in solution using HECP as CTA

Polymer	pTOVE-1	pTOVE-2	pTOVE-3	pTOVE-4	pTOVE-5	pTOVE-6
Temperature [°C]	80	80	90	90	90	90
Time [min]	1440	1440	1440	1440	1440	1440
[M]:[CTA]	50	50	50	50	50	50
[CTA]:[I]	2	5	2	5	10	2
$c_{Monomer}$ [mol/L]	5	5	5	5	5	40
c_M [%]	42	41	57	56	27	72
$M_{n,\,NMR}$ [kDa]	4.7	4.2	6.1	5.7	2.9	6.0
$M_{n,\,SEC}$ [kDa]	2.4	2.7	3.9	3.0	2.2	4.1
Đ [ ]	1.52	1.51	1.61	1.63	1.48	1.88

Table 93: Initial weights and molar amounts of educts of the RAFT polymerizations of TOVE in solution using HECP as CTA

	[g]	**[mmol]**	**[g]**	**[mmol]**	**[g]**	**[mmol]**
TOVE	0.20	1.0	0.20	1,02	0,21	1,0
	[mg]	**[mmol]**	**[mg]**	**[mmol]**	**[mg]**	**[mmol]**
HECP	5.0	0.02	4.6	0,02	4,8	0,02
AIBN	1.7	0.010	0.7	0,004	1,8	0,011
	[mL]		**[mL]**		**[mL]**	
Anisole dry	0.2		0.2		0.2	

Table 94: Initial weights and molar amounts of educts of the RAFT polymerizations of TOVE in solution using HECP as CTA

	pVD-17		pVD-20		pVD-21	
	[g]	[mmol]	[g]	[mmol]	[g]	[mmol]
TOVE	0.21	1.0	0.20	1,0	0,21	1,0
	[mg]	[mmol]	[mg]	[mmol]	[mg]	[mmol]
HECP	5.3	0.02	5.0	0,02	6,2	0,03
AIBN	0.7	0.004	0.4	0,002	1,7	0,010
	[mL]		[mL]		[mL]	
Anisole dry	0.2		0.2		0.02	

Materials, devices and analyses

Reagents and solvents were – unless noted here – used as received. **LMA** and **NAM** were distilled under reduced pressure. In order to remove inhibiting MEHQ, **VAc** was destabilized by filtration over basic aluminum oxide prior to use. **VH**, **VD** or **VnN** (20 g) were washed with 1 N sodium hydroxide solution (100 mL) twice, dried over sodium sulfate and distilled under reduced pressure. **VClAc** was stirred over CaH_2 at room temperature for 16 hours, filtered and distilled under reduced pressure.

For thin layer chromatography (TLC) aluminum foils, coated with silicagel 60 F254 from the company Merck were applied.

Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). The silica gel chromatography was performed with a Büchi MPLC-system equipped with the control unit C-620, fraction collector C-660, and UV-photometer C-635.

All 1H-NMR spectra were recorded with a Bruker Avance 200 MHz device or a Bruker Avance 400 MHz device. The chemical shift was reported in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet on doublet, bs = broad singlet). The solvent used was deuterated chloroform (CDCl3, 99.5 % deuteration).

GPC measurements were performed with a Waters GPC using three columns connected in series (Styragel HR 0.5, Styragel HR 3 and a Styragel HR 4) and a Waters 2410 RI detector. The samples were diluted with THF, filtered via Acrodisc® CR 13 mm syringe filter with 0.2 µm PTFE membrane and injected into the measurement vials. Generally, polystyrene standards were used for calibration. Analysis was the done at 40 °C at a flow rate of 1 mL THF per minute.

Fluorescent spectroscopy measurements were performed on a FSP920 fluorescent spectrometer from company Edinburgh Instruments. Spectra were evaluated with F900 software.

UV-VIS spectroscopy was performed with a UV-1800 SCHIMADZU UV spectrometer.

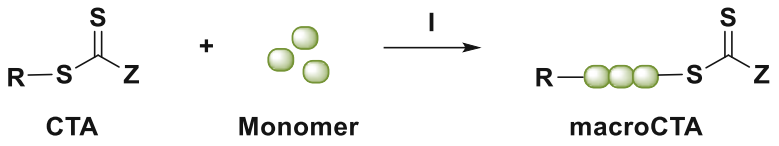
DSC/TGA measurements were performed on a NETZSCH STA 449F1 Jupiter der Firma NETZSCH and data were recorded and evaluated with the software STA 449F1, Version 1-414/6.

Summary

The aim of this work was to evaluate strategies towards the synthesis of amphiphilic block copolymers by means of Reversible Addition Fragmentation chain Transfer (RAFT) polymerization, a technique, which facilitates the preparation of well-defined polymers with narrow molecular weight distribution from a broad range of monomers without using any metal containing catalysts.

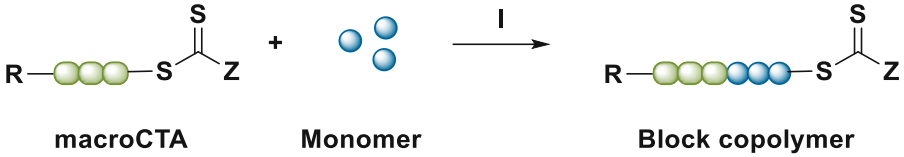
In the first part, amphiphilic block copolymers were synthesized in a two-step process and investigated. Before that, the homopolymers of the hydrophilic and hydrophobic block were prepared and analyzed.

1st step: Synthesis of macro CTA



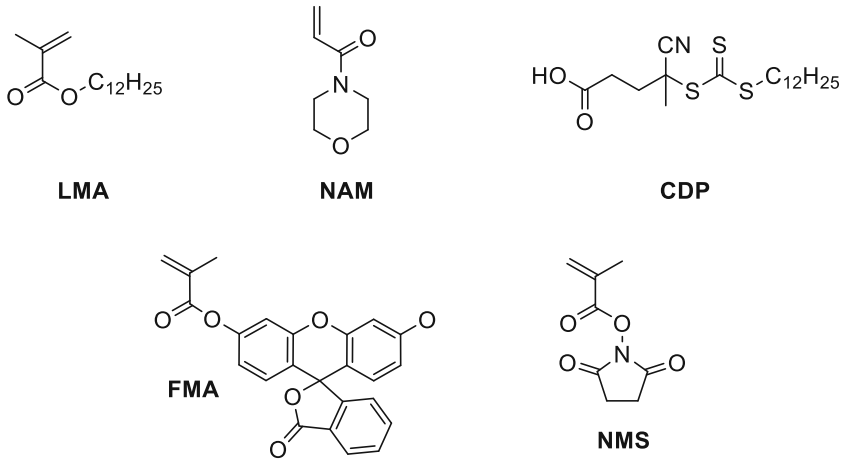
CTA Monomer macroCTA

2nd step: Synthesis of block copolymer



macroCTA Monomer Block copolymer

Monomers belonging to the group of more activated monomers (MAMs) were utilized and the thermal initiator AIBN acted as radical source.



LMA NAM CDP

FMA NMS

Hydrophilic N-acryloyl morpholine (**NAM**) and hydrophobic lauryl methacrylate (**LMA**), were chosen to be investigated. 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)-sulfanyl] pentanoic acid

(***CDP***), a trithiocarbonate-based RAFT agent was synthesized and subsequently utilized to control homopolymerizations of the aforementioned monomers. Afterwards, p**LMA** acted as macroCTA for the syntheses of well-defined block copolymers in combination with **NAM**. Additionally, macro CTAs including small amounts of fluorescein-O-methacrylate (**FMA**), a fluorescent marker, were prepared and as well used to generate block copolymers. ^{1}H-NMR spectroscopy and size exclusion chromatography (SEC) were used to determine monomer conversion, molecular weight and dispersity of the polymers.

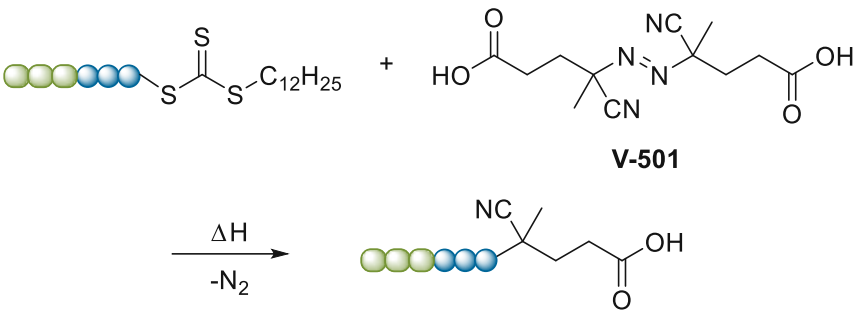
It was conformed that ***CDP*** is a well-suited CTA for the preparation of hydrophobic p**LMA** under the selected reaction conditions, meaning a temperature of 90 °C and a CTA to initiator ratio of 10:1. Polymers with narrow molecular weight distribution, indicated by a dispersity below 1.20, could be obtained at monomer conversions around 70%. Independently of the target molecular weight, no higher monomer turnover could be reached, probably due to reduced solubility in the used solvent dioxane. Furthermore, the controlled character of this reaction was proven by conducting a kinetic study. Regarding the copolymerization of small amounts of **FMA,** no effect on dispersity or monomer conversion was observed.

In the next step, the RAFT homopolymerization of hydrophilic **NAM** with ***CDP*** as CTA was investigated in detail. Therefore, kinetic studies at different temperatures (70, 80 and 90 °C) and CTA-to-initiator (10:1, 15:1 and 20:1) were conducted. It turned out that all these reactions proceed in a controlled manner, but effects of the temperature became obvious. Reducing the temperature from 90 °C to 80 °C scarcely influences the speed of polymerization, but a further reduction to 70 °C leads to a significantly slower polymerization process. Dispersity is improved, if lower temperatures are chosen. Variation of the amount of initiator showed no effect on dispersity, but at 90 °C a decrease in reaction speed is visible if less AIBN is used. Nevertheless, in all cases polymers with a dispersity below 1.50 were obtained.

In the following steps, p**LMA** was applied as macroCTA in the preparation of block copolymers with a dispersity below 1.40 in all cases. Here, again the reaction temperature was altered (70, 80 and 90 °C) resulting in BCPs with lower dispersity values at lower temperatures. As expected, at the same time the polymerization process was slowed down. In some polymers synthesized N-methacryloxysuccinimide (**NMS**), which was prepared in the course of this thesis, was copolymerized within the hydrophilic block to offer the possibility of post modification of the resulting products if needed. In the same way as p**LMA** also p**LMA**-c-p**FMA** served as macro CTA for the polymerization of **NAM** or a mixture of **NAM** and **NMS**.

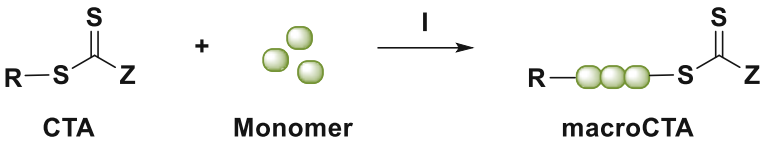
After the RAFT polymerization process is completed, the sulfur-containing group is still attached to the final product, causing color and may reveal toxic effects in some cases. Hence,

this group was removed via a radical induced process using a large excess of 4,4′-azobis(4-cyanovaleric acid) (V-501) as radical source.

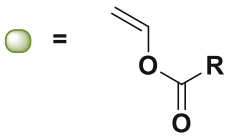


This step resulted not only a change in color from slightly yellow to white, but also a clear improvement of water solubility. Performing size exclusion chromatography of the polymers before and after the removal, allowed to exclude high amount of termination between polymeric radicals, since molecular weight and dispersity stayed almost unchanged and no product with high molecular weight was visible in the obtained spectra. Further analysis of the block copolymers was done by UV/Vis spectroscopy in order to examine their fluorescein content and by fluorescent spectroscopy was applied to determine their critical micelle concentration. Obtained CMC values increased with higher total molecular weight of the amphiphilic block copolymers. The incorporation of **NMS** had no significant influence on the CMC. In preparation for toxicity testing of the prepared amphiphilic block copolymers, their thermal stability was tested via simultaneous thermal analysis (STA), since sterilization was meant to be done in an autoclave at 140 °C. Thereby it turned out that decomposition of the polymers started at temperatures around 160 °C, indicated by significant mass loss, leading to the conclusion that sterilization is possible at 140 °C. Finally, cell viability tests were performed at the Medical University of Vienna applying an XTT assay. The obtained results showed no toxic effect on the used HUVE cells, since their viability stayed the same as for the control sample or was even slightly improved.

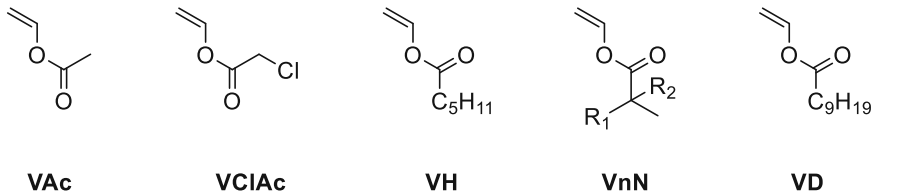
The second part of this thesis dealt with the preparation of polymers based on vinyl esters, which belong to the group of less activate monomers (LMAs), by means of RAFT polymerization. This type of monomer is of high interest for applications within the human body as it gives FDA approved polyvinyl alcohol as degradation product and shows less toxicity compared to (meth) acrylates. However, the RAFT polymerization of vinyl esters was not intensively studied so far.



CTA Monomer macroCTA

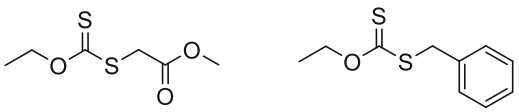


Within this work, different linear hydrophobic vinylesters namely vinyl acetate (**VAc**), vinyl hexanoate (**VH**), vinyl decanoate (**VD**), were investigated. When it comes to preparation of amphiphilic block copolymers, selective hydrolysis represents and option. Therefore, also easy-hydrolyzable vinyl chloroacetate (**VClAc**) and hydrolytically stable vinyl neo-nonanoate (**VnN**) were polymerized. Xanthate-based CTA methyl (ethoxycarbonothioyl)sulfanyl acetate (***MESA***) was synthesized and its suitability as CTA for the different vinyl esters, was tested. Additionally, S-benzyl O-ethyl carbonodithioate (***BED***), a CTA also based on a xanthate, but possessing a different leaving group, was prepared and investigated. Reactions were performed in bulk as well as in solution (5 mol/L in dry benzene) and the amount of initiator was varied. Tested CTA-to-initiator ratios were 5:1, 10:1, 15:1 and 20:1. Analytical data (monomer conversion, molecular weight and dispersity) were obtained from ^{1}H-NMR spectroscopy and SEC.



VAc **VClAc** **VH** **VnN** **VD**

$R_1=C_xH_{2x+1}$ $R_2=C_{6-x}H_{13-2x}$ x=1...5



MESA **BED**

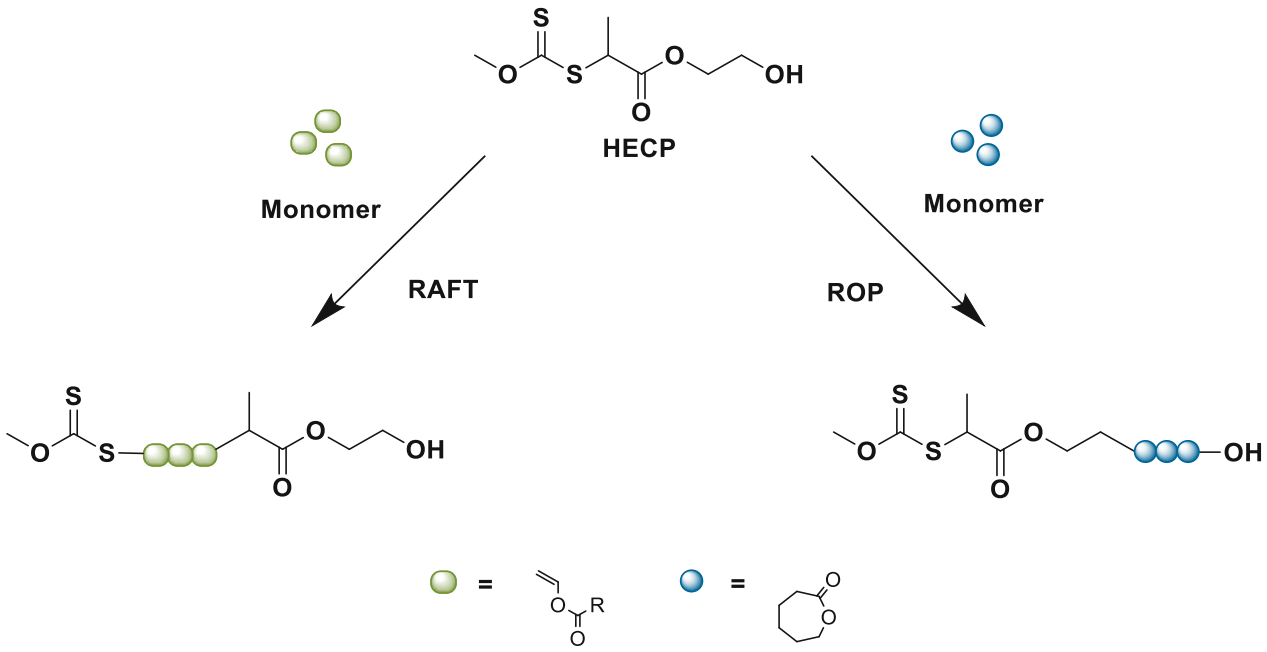
The following Table gives an overview about monomer conversion and dispersity values of the conducted RAFT homopolymerizations, which led to conversions above 60%. They show good

potential for the preparation of uniform macro RAFT agents, which would be suitable for further BCP preparation.

	MESA				*BED*			
	Solution		**Bulk**		**Solution**		**Bulk**	
	c_M [%]	**Đ**	**c_M [%]**	**Đ**	**c_M [%]**	**Đ**	**c_M [%]**	**Đ**
VAc	-	-	62-77	< 1.30	-	-	-	-
VClAc	62-97	< 1.5	73-83	< 1.40	80	1.40	36-81	~1.30
VH	61-92	≤ 1.40	83-97	< 1.40	-	-	75	1.30
VnN	-	-	78-88	< 1.20	-	-	-	-
VD	29-73	~1.20	86-96	< 1.25	-	-	64	1.26

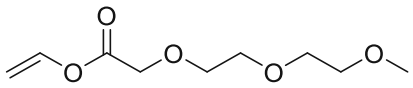
Besides **VAc**, none of the investigated monomers was polymerized via RAFT polymerization using ***MESA*** or ***BED*** as chain transfer agent so far. Within this thesis, it could be demonstrated that ***MESA*** facilitates the preparation of homopolymers with narrow molecular weight distribution under the selected reaction conditions. Especially, reactions in bulk deliver polymers with low dispersity values at high monomer conversion.

An additional approach towards the synthesis of block copolymers was investigated by using a dual initiator 2-hydroxyethyl 2-((ethoxycarbonothioyl)thio)propanoate (***HECP***), which is able to serve as CTA as well as initiator for ring opening polymerization (ROP).



It was proven that ***HECP*** facilitates the preparation of well-defined polymers from Ɛ-caprolactone. Additionally, ***HECP*** served successfully in the RAFT homopolymerization of **VD** and **VH**.

In regard to the need of a hydrophilic part for the preparation of amphiphilic block copolymers, an ethylene glycol based vinyl ester, vinyl 2-(2-(2-methoxyethoxy)ethoxy)acetate (**TOVE**), was synthesized.



TOVE

RAFT polymerizations of this monomer showed no satisfactory results, since dispersity values were above 1.50 and SEC peaks showed shoulders indicating non-uniform polymer chain length.

Summing up, it can be concluded that the RAFT homopolymerization of **LMA** and, more detailed, of **NAM** was studied within this thesis, whereupon good results were obtained. Followed by the preparation of amphiphilic block copolymers from these two building blocks. RAFT end groups were successfully removed and the resulting products showed no toxic effect on tested cells. Quite contrary, an increase in cell growth was observed, what allows the assumption that this block copolymers could also be used to increase cell growth upon request. Though, more testing has to be done to enable a precise statement in this regard.

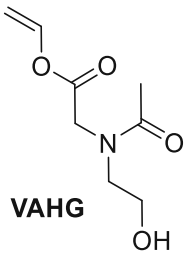
In respect to the application of the prepared block copolymers as drug carrier systems, ongoing experiments should deal with the detailed examination of the micelles. Here, one big task will be the crosslinking with diamino linkers (e.g. cysteine or hexamethylene diamine) and the subsequent evaluation of the thereof resulting effects. Another interesting part will be studying of rather medical questions. First, it has to be figured out, if active substances can be incorporated into these specific micelles and at which amount. Furthermore, cellular uptake of those aggregates and finally the release of enclosed drugs have to be tested.

Considering vinyl ester, it can be said that under the selected reaction conditions, ***MESA*** is clearly to favor over ***BED***, since polymers with satisfying dispersity values and at the same time, reasonable conversion can be derived from all monomers. However, as far as reaction volumes do not become too large and the Trommsdorff effect is negligible, polymerization in bulk is preferred for macroCTAs, as much shorter reaction times are needed as for reactions

in solution. When it comes to the preparation of block copolymers, solubility of them in the chosen monomer for a second block has to be considered. Thus, then a solvent and longer reaction times might be inevitable.

As a conclusion, within this thesis, a solid foundation for the ongoing research on the RAFT polymerization of vinyl esters and the subsequent preparation of block copolymers was laid. It was possible to prepare macro RAFT agents successfully from various hydrophobic vinyl esters (**VAc**, **VClAc**, **VH**, **VnN** and **VD**) applying ***MESA*** as CTA. The next step should be the examination of the synthesis of block copolymers, especially amphiphilic ones in order to obtain potential materials for drug carrier systems. Since there is almost no literature available on the synthesis of such block copolymers based on vinyl esters, attempts can be made based on the herein reported results. First, it will be necessary to conduct experiments to find out, if reactions should be done in bulk or solution and in which solvent. Here, the solubility of the macro CTA in the monomer for the second block plays a decisive role.

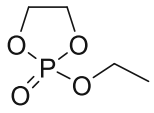
Additionally, it is necessary to find suitable hydrophilic vinyl ester monomers, which can be combined with the already testes hydrophobic ones. Here, different options are conceivable. Besides further investigation of already prepared PEG-based **TOVE**, monomers based on oxazoline, like vinyl N-acetyl-N-(2-hydroxyethyl)glycinate (**VAHG**) would be an option.



VAHG

A route towards the synthesis of this molecule was already described by Uyama *et al.*[369] RAFT polymerization of this monomer was not reported so far. Hence, this will be another challenge in upcoming research.

Extensive studies have to be done on the ***HECP***-initiated ROP of either Ɛ-caprolactone (**CL**) or other cyclic monomers. Especially hydrophilic monomers are of interest, since they can be combined with the already successfully polymerized hydrophobic monomers **VH** and **VD**. One possibility for such a monomer can be found in phosphorous-containing structures like 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (**EP**).



EP

Polymers based on phosphoesters like **EP**, so called polyphosphoesters (PPE), are of high interest for applications within the human body (e.g. for drug delivery,[370] dental applications,[371] tissue engineering[372]). Biodegradation of such materials is possible *via* hydrolysis or enzymatic processes. Furthermore, they are hemocompatible and their structures show high similarity to nucleic acids. [373] Possible synthetic pathways for this monomer are reported in literature by Clément *et al.*[374] as well as by Wen *et al.*[375] This monomer was already used for the preparation of drug carrier systems as described by Wen *et al.*[376] and Cheng *et al.*[377]

Abbreviations

AIBN	Azobisisobutyronitrile
$[CTA]_0$	CTA concentration at t=0
$[CTA]_0$	Concentration of the RAFT agent at t=0
$[M]_0$	Monomer concentration t=0
$[M_y]_0$	Concentration of monomer y at t=0
$[M_y]_0$	Concentration of the monomer at t=0
AM	Acrylamide
AN	Acrylonitrile
ATRP	Atom Transfer Radical Polymerization
BCP	Block copolymer
BED	S-benzyl O-ethyl carbonodithioate
BMA	Butyl methacrylate
BPO	Dibenzoyl peroxide
BSPA	3-Benzylsulfanylthiocarbonylsufanylpropionic acid
CDB	Cumyl dithiobenzoate
CDP	4-Cyano-4-[(dodecylsulfanylthiocarbonyl)-sulfanyl]pentanoic acid
CDP	4-Cyano-4-(phenylcarbonothioylthio) pentanoic acid
C_{ges}	Overall conversion at t=x [ ]
CL	ε-caprolactone
c_M	Monomer conversion at time t=x [ ]
c_M	Monomer conversion
$C_{M\,y,x}$	Conversion of monomer y at t=x [ ]
$conc_M$	Monomer concentration
CRP	Controlled radical polymerization
CTA	Chain transfer agent
C_x	Monomer conversion at t=x [ ]
$C_{y,x}$	Conversion of monomer y at t=x
Đ	Dispersity
DCC	N,N'-Dicyclohexylcarbodiimide
DMAm	N,N-Dimethylacrylamide
DP_n	Degree of polymerization
DT	Degenerative transfer
EG	end group
ESARA	Exchange of Substituents between (Macro)Alkoxyamines and (Macro)RAFT Agents
FMA	Fluorescein-O-methacrylate
FRP	Free radical polymerization
GTP	Group Transfer Polymerization
HEBP	2-hydroxyethyl-2-bromopropionate
HECP	2-Hydroxyethyl 2-((ethoxycarbonothioyl)thio)propanoate
HEMA-PCL	2-hydroxyethyl methacrylate-poly(ε-caprolactone)
HPMAM	N-(2-Hydroxypropyl) methacrylamide
Int_0	Integral of the (meth-)acrylate group at time t=0 [ ]
Int_x	Integral of the (meth-)acrylate group at time [ ]
IUPAC	International Union of Pure and Applied Chemistry

k_{act}	Rate constant of activation
kDa	Kilo Dalton
k_{deact}	Rate constant of deactivation
LAM	Less Activated Monomer
LMA	Lauryl methacrylate
LPO	Lauryl peroxide
MA	Methyl acrylate
MADIX	Macromolecular Design via the Interchange of Xanthates
MAM	More Activated Monomer
M_{CTA}	Molecular weight CTA [g/mol]
M_{CTA}	Molecular weight of the RAFT agent [g/mol]
MESA	methyl (ethoxycarbonothioyl)sulfanyl acetate
min	Minute
M_M	Molecular weight monomer [g/mol]
MMA	Methyl methacrylate
M_{My}	Molecular weight of monomer y [g/mol]
$M_{n\ ,\ NMR}$	Theoretical molecular weight at a given conversion [g/mol]
$M_{n,\ NMR}$	Molecular weight calculated from ^{1}H-NMR spectroscopy measurements
$M_{n,\ NMR}$	Calculated molecular weight of the copolymer at a given conversion [g/mol]
$M_{N,\ SEC}$	Molecular weight obtained by size exclusion chromatography
NAM	N-Acryloylmorpholine
NIPAM	N-Isopropylacrylamide
NMP	Nitroxide Mediated Polymerization
NMR	Nuclear magnetic resonance
NMS	N-Methacryloxidesuccinimide
NVC	N-Vinylcarbazole
NVP	N-Vinylpyrrolidone
pL	poly (lauryl methacrylate)
pLF	poly (lauryl methacrylate)-co-(fluorescein-O-methacrylate)
pLFM	poly (lauryl methacrylate)-co-(fluorescein-O-methacrylate)-block-poly (N-acryloyl morpholine)
pLFMN	poly (lauryl methacrylate)-co-(fluorescein-O-methacrylate)-block-poly (N-acryloyl morpholine)-co-poly (N-Methacryloxidesuccinimide)
pLM	poly (lauryl methacrylate)-block-poly (N-acryloyl morpholine)
pM	poly (N-acryloyl morpholine)
PRE	Persistent radical effect
RAFT	Reversible Addition Fragmentation-chain Transfer
RDRP	Reversible-Deactivation Radical Polymerization
ROMP	Ring-opening metathesis polymerization
ROP	Ring Opening Polymerization
SEC	Size exclusion chromatography
SFRP	Stable Free Radical Polymerization
St	Styrene
t	Time
tBAAm	tert-butyl acrylamide
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl
THF	Tetrahydrofuran
t_{inh}ib	Inhibition time

TOVE	Vinyl 2-(2-(2-methoxyethoxy) ethoxy) acetate
TPE	Thermoplastic elastomer
TUW	Technische Universität Wien
UV/Vis	Ultra violet/visible
V-501	4,4′-Azobis(4-cyanopentanoic acid)
VAc	Vinyl acetate
VClAc	Vinyl chloroacetate
VD	Vinyl decanoate
VH	Vinyl hexanoate
VnN	Vinyl neo-nonanoate

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Curriculum vitae

Curriculum Vitae DIPL.-ING. MARIA SCHACHNER, MSC

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Professional Experience

06/2021 – to date	**Bodo Möller Chemie Austria GmbH, Gertrude-Fröhlich-Sandner Straße 2, 1100 Vienna** Account Manager Additives
04/2017 – 05/2021	**Plastoplan Kunststoffhandel GmbH, Lichtblaustraße 6, 1220 Vienna** Head technical department, head testing laboratory Sax Polymers, material development
10/2016 – 03/2017	**Plastoplan Kunststoffhandel GmbH, Lichtblaustraße 6, 1220 Vienna** Technical department, head testing laboratory Sax Polymers, material development
03/2012 – 04/2016	**Institute of Applied Synthetic Chemistry, Division of Macromolecular Chemistry, Technische Universität Wien, Getreidemarkt 9, 1060 Vienna** University assistant
08/2007 – 09/2016	**BS-Modelshop GmbH, Gutheil-Schoder-Gasse 8, 1100 Vienna** Post processing of plastic parts, office work
2009 & 2010	**„Austrian Summer Scholars Program"** Planning and organization, supervision on location
09/2004 – 06/2007	**Volkstheater Wien, Neustiftgasse 1, 1070 Vienna** Audience service
07/2004	**Satel Film GmbH, Linzer Straße 375, 1140 Vienna** Office work

Education

03/2012 – to date	**Doctoral programme in Engineering Sciences: Technical Chemistry** Technische Universität Wien Research topic: RAFT polymerization; synthesis and characterization of polymers
09/2010 – 06/2014	**Master's degree program International Business and Engineering** UAS Technikum Wien Graduation with Master degree (MSc) Thesis "Leasing als Mittel zur Wachstumsfinanzierung in kleinen und mittleren Unternehmen"
24/06-18/08/2013	**Short term Research Stay in the Research group of Prof. Dr. Katja Loos** Zernike Institute for Advanced Materials, Department of Polymer Chemistry, University of Groningen, The Netherlands Working on enzymatic synthesis of sugar-based monomers

04/2010 – 02/2012	**Master programme Technical Chemistry - Synthesis** Technische Universität Wien Graduation with Master degree (Dipl.-Ing.), Thesis “Synthese polymerer Wirkstoffträgersysteme mittels RAFT Polymerisation”
2008/2009/2010	**Austrian Summer Scholars Program** 6 weeks at Miami University, Oxford, Ohio (USA)
10/2004 – 04/2010	**Bachelor programme Technical Chemistry** Technische Universität Wien Graduation with Bachelor degree (BSc)
09/1996 – 06/2004	**Realgymnasium Perau Villach and Realgymnasium Diefenbachgasse, Wien XV** Graduation with Matura

Additional Education

07-09/2019	**IPMA Level D** Certified Project Management Associate
23-24/03/2017	**Workshop WIFI Wien** “Von der Kollegin zur Vorgesetzen“
12/05/2015	**Workshop** “Keine Krise bei Konflikten - Konflikte erkennen und lösen”
11-12/11/2014	**Workshop** “ Erfolgreich positionieren - im universitären und beruflichen Umfeld ”
01-02/04/2014	**Workshop** “Selbstpräsentation in Schlüsselpositionen”
09/2005	**Driver´s license** (B)
06/2003	**Language Study Travel** (1 week) in Barnstaple, Great Britain
2001/2002	**ECDL** “European Computer Driving Licence“
07/2000	**Language Study Travel** (2 weeks) in Eastbourne, Great Britain

Languages

German	Native Speaker
English	Fluent

Conference Contributions-Poster Presentation

26/05-29/05/2015	P2M Final meeting, Lacanau, France
24/09-28/09/2012	ESF Research Networking Programme on Precision Polymer Materials (P2M), San Feliu de Guixols, Spain
19/11-21/11/2012	5th Biomaterialsymposium, Vienna, Austria
09/10-12/10/2011	4th Joint ESAO IFAO Congress, Porto, Portugal

Conference Contributions-Oral Presentation

08/07-11/07/2015	International Symposium on Frontiers in Biomedical Polymers (FBPS), Riva del Garda, Italy
03/04-05/04/2013	Austrian - Slovenian Polymer Meeting - ASPM 2013, Bled, Slovenia