RAFT POLYMERIZATION

STUDY OF

THERMO-RESPONSIVE POLYMERS

Bachelor's degree final project

Degree of Chemistry

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Abbreviations

AIBN	2,2'-Azobis(2-methylpropionitrile)
AM	acrylamide
AN	acrylonitrile
ATRP	atom transfer radical polymerization
BHT	2,6-Bis(1,1-dimethylethyl)-4-methylphenol
CTA	chain transfer agent
DAD	diode-array detection
DCM	dichloromethane
DMP	2-{[(dodecylthio)carbonothioyl]thio}-2-methylpropanoic acid
DPT	dodecane 1-phenylethyl trithiocarbonate
EMP	2-{[(ethylthio)carbonothioyl]thio}-2-methylpropanoic acid
FRP	free radical polymerization
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
LCST	lower critical solution temperature
LRP	living radical polymerization
MA	methacrylate
MeHQ	p-methoxyphenol
MEOAc	oligo(ethylene glycol) methyl ether acrylate
MEO_2Ac	di(ethylene glycol) methyl ether acrylate
MEOMA	oligo(ethylene glycol) methyl ether methacrylate
Min	minutes
MMA	Methyl methacrylate
MPT	mercaptopropionic acid 1-phenylethyl trithiocarbonate
MWCO	molecular weight cut off
NMP	nitroxide mediated polymerization
NMR	nuclear magnetic resonance
PDI	polydispersity index
PNIPAM	poly(*N*-isopropylacrylamide)
RAFT	reversible addition-fragmentation chain transfer
RI	refractive index

SFRP	stable free radical polymerization
SS	standard solution
Sty	styrene
TLC	thin-layer chromatography
Vac	vinyil acetate

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1 Introduction

Smart materials represent one of the most exciting and emerging classes of materials. One of the main groups is based on polymers because they are of low cost and easily tailored concerning desired behaviour. The study of them as smart materials has been increased in the last two to three decades. Moreover, they have a wide range of applications due to his response to different kinds of stimuli, like the pH, radiation or temperature. Hence, they are used in the area of biotechnology, medicine and engineering.[1]

The simplest method to synthesize the polymers is the conventional free radical polymerization (FRP) since it does not require stringent process conditions and can be used for the (co)polymerization of a wide range of vinyl monomers[2]. However, the major limitation of FRP is poor control over some of the key elements of the process. It does not allow the preparation of well-defined polymers with controlled molecular weight, polydispersity, composition, chain architecture, and site-specific functionality. To avoid the limitations of FRP, in this study RAFT method has been used. [3]

RAFT processes are the most recent of the living/controlled free radical polymerization methodologies. This process has been frequently employed to successfully functionalize surfaces as well as micro- and nanoparticles, and this is of high importance for a range of applications. [3]

This study focuses on polymers that respond to temperature, an external stimulus that is easy to apply. This property makes them useful in a wide range of applications and consequently attracts wide scientific interest. Thermo-responsive polymers are used for biomedical applications including drug delivery, tissue engineering and gene delivery. [4]

2 Theoretical background

2.1 Temperature-responsive polymer

The so-called thermo-responsive polymers change their solvation state at a certain temperature.[1] These systems are not restricted to an aqueous solvent environment, but only the aqueous systems are of interest for biomedical applications. Many different classes of thermo-responsive polymers in aqueous solution are known, e.g. poly(vinyl ether)s, poly(*N*-vinyl amide)s, poly(ether)s and poly(oxazoline)s, but the most studied polymer is poly(*N*-isopropylacrylamide) (PNIPAm), which undergoes the changes in water at around 32°C from a hydrophilic state below this temperature to a hydrophobic state above it.[5]

The change in the hydration state reflects competing hydrogen bonding properties. Intra- and intermolecular hydrogen bonding of the polymer molecules are favoured compared to a solubilisation by water.[1]

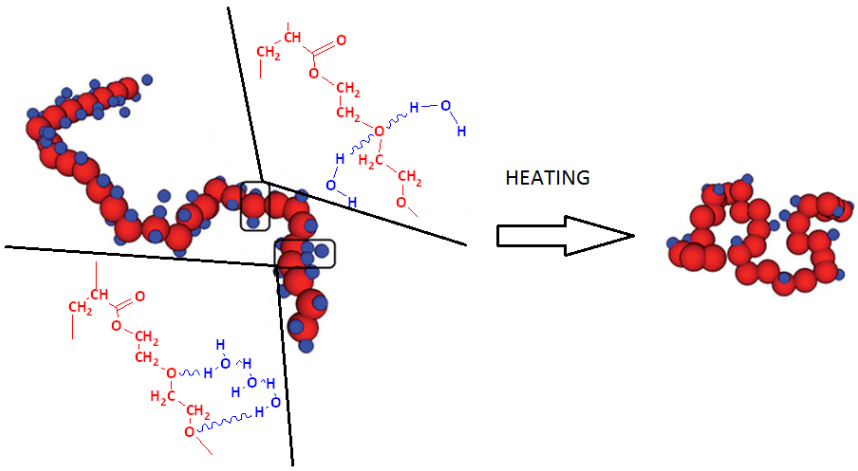


Figure 2.1-1 Schematic representation of the conformational change of MEOMA from a hydrated coil to a dehydrated collapsed globule. [6]

2.2 LCST and UCST behaviour

The lower critical solution temperature (LCST) is the critical temperature below which the components of a mixture are miscible for all compositions. Above LCST partial liquid immiscibility occurs. UCST behaviour is the other possibility, which means that the components are miscible above a critical temperature (UCST) and immiscible below it. [7]

The solubility of a polymer in aqueous solution is dependent on various factors such as molecular weight, temperature or addition of a co-solvent or additives. In the shown phase diagram of a polymer/solvent mixture vs. temperature, one can identify the critical solution temperature: the UCST or LCST.

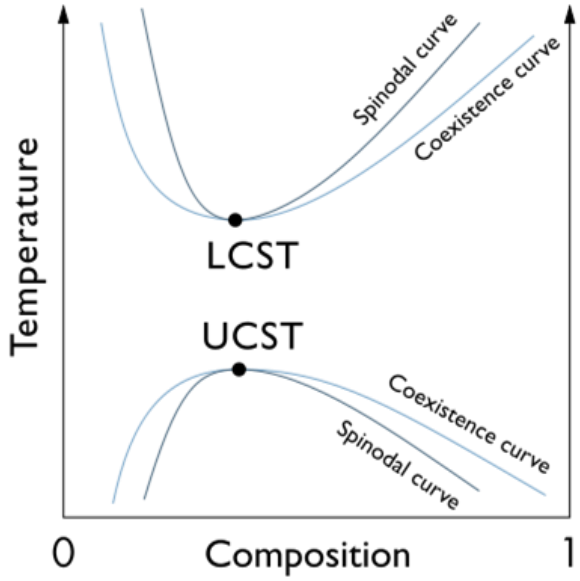


Figure 2.2-1 Temperature vs. composition plot of typical polymer binary solution phase behaviour including both an LCST and UCST. Composition = 1 means only (solid) polymer is present and composition = 0 means only solvent is present. [8]

The LCST is higher than the UCST, which means that there is a temperature interval where the polymer is completely miscible, and immiscible at both higher and lower temperatures.

The LCST of polymer solutions also depends on other factors, such as the polymerization degree, polydispersity, architecture and preparation. In the case of copolymers, it depends on his ratio as well as the hydrophobic of hydrophilic nature of the polymer.

2.3 Radical polymerization

The classification of polymerization reactions is based on the comparison of their mechanism. Free radical polymerization describes all polymerizations in which the propagating species is a free radical. It's the most widely practised method of radical polymerization, and is used for the preparation of polymers from monomers of the general structure $CH_2=CR_1R_2$. An example of this kind of monomers is the vinyl chloride, being R_1=H and R_2=Cl. The reaction can be divided in three stages: initiation, propagation and termination. [9]

Some advantages of radical polymerizations are the relative insensitivity to impurities, the moderate reaction temperatures and the multiple polymerization processes available. Some disadvantages related to the mechanism of free radical polymerization is the poor control of the molecular weight and the molecular weight distribution. This happens because the propagating radicals, produced by the addition of initiator, react with each other causing terminations. Hence, preparing well-defined polymers or copolymers is difficult. [10]

2.4 RAFT

Modern living radical polymerization (LRPs) techniques seek to compensate the limitations of the radical polymerizations, providing control over the molecular weight and the molecular weight distribution of a polymer. The control of molecular weight and molecular weight distribution has enabled access to complex architectures and site specific functionality that were previously impossible to achieve via traditional free radical polymerization[10].

These LRPs are classified in three different subgroups: stable free-radical polymerization (SFRP), most commonly nitroxide mediated polymerization (NMP), degenerative transfer polymerization, such as iodine transfer polymerization, or reversible addition-fragmentation chain transfer (RAFT), and metal mediated catalysed polymerization, such as atom transfer radical polymerization (ATPR). In order to extend the lifetime of the propagating chains, each of these methods relies on have a low concentration of active propagating chains that are unable to terminate.[11]

Among the existing LRP techniques, RAFT is probably the most versatile process[12] since it can be used with a large variety of monomers including (meth)acrylates, styrene,

(meth)acylamides, butadiene, and vinyl acetate; it is tolerant to a wide range of functional groups (e.g. OH, NR_2, COOH, $CONR_2$) and reaction conditions (bulk, solution, emulsion, miniemulsion, suspension); and it is simple to implement and inexpensive in relation to competitive technologies[13].

Another advantage of RAFT polymerization is the ability of modify the end groups of the polymer once it's synthesized, or before synthesize it, by modifying the end group of the RAFT agent (polymeranalogous reaction). It allows be able to change some property, such as LCST and elasticity.

2.4.1 CTA

RAFT agents, called chain transfer agents (CTA) are organic compounds possessing a thiocarbonylthio moiety. There are four classes of CTAs differing by the substituent group next to the thiocarbonyl functionality: dithioesters, trithiocarbonates, xanthates and dithiocarbamates (Figure 2.4-3).[14]

Substituents around the C=S group are labelled Z and R and can be tailored to suit the monomer used. The Z group should activate the C=S towards radical addition and stabilize the intermediate radical formed, whereas the R group should be a good free-radical leaving group and be capable of reinitiating free-radical polymerization. In general, given an appropriate choice of R group, trithiocarbonates are effective RAFT agents. [15]

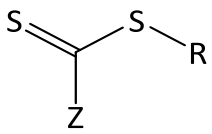


Figure 2.4-1 General RAFT agent structure (trithiocarbonate Z = SR, dithioester Z = alkyl or aryl, dithiocarbamate Z = NR_2, xanthate Z = O-alkyl, R = alkyl or H).[16]

As the RAFT mechanism proceeds by insertion of monomer units into the C=S bond, end-functionalised polymers can be easily achieved by incorporating the functional groups into the RAFT agent (groups R and Z).

In this project, four different CTA's were used, all of them belonging to trithiocarbonates: MPT= mercapto propionic acid 1-phenylethyl trithiocarbonate, DPT= dodecane 1-phenylethyl trithiocarbonate, DMP= 2-{[(dodecylthio)carbonothioyl]thio}-2-methylpropanoic acid, EMP= 2-{[(ethylthio)carbonothioyl]thio}-2-methylpropanoic acid.

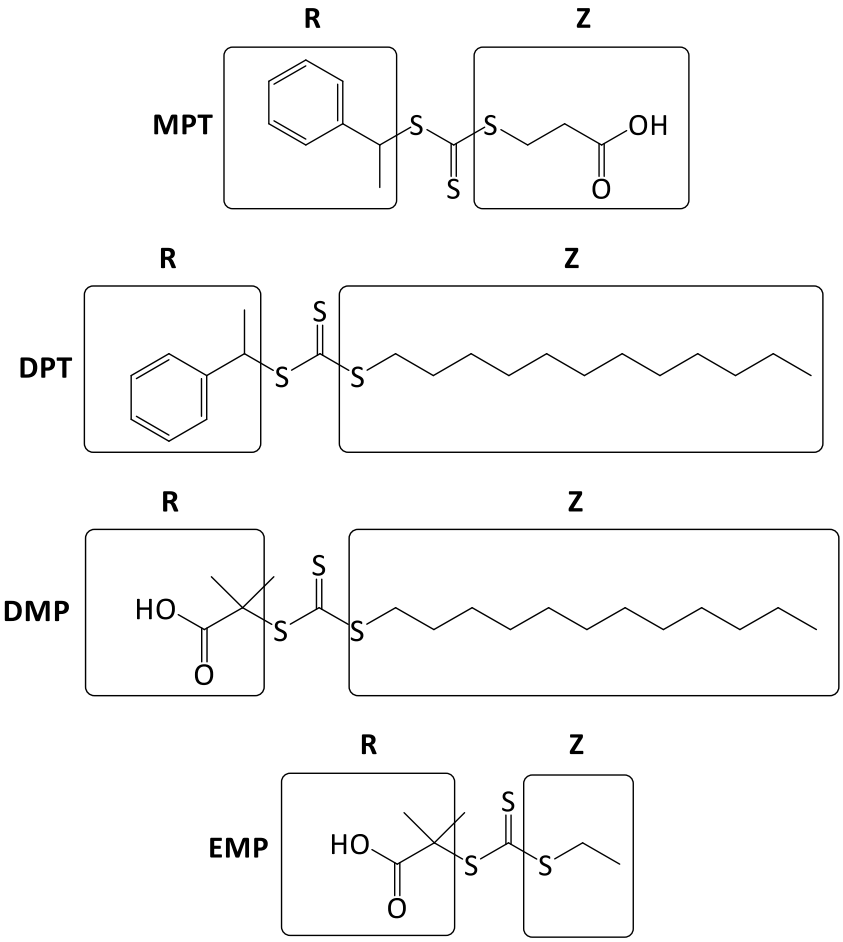
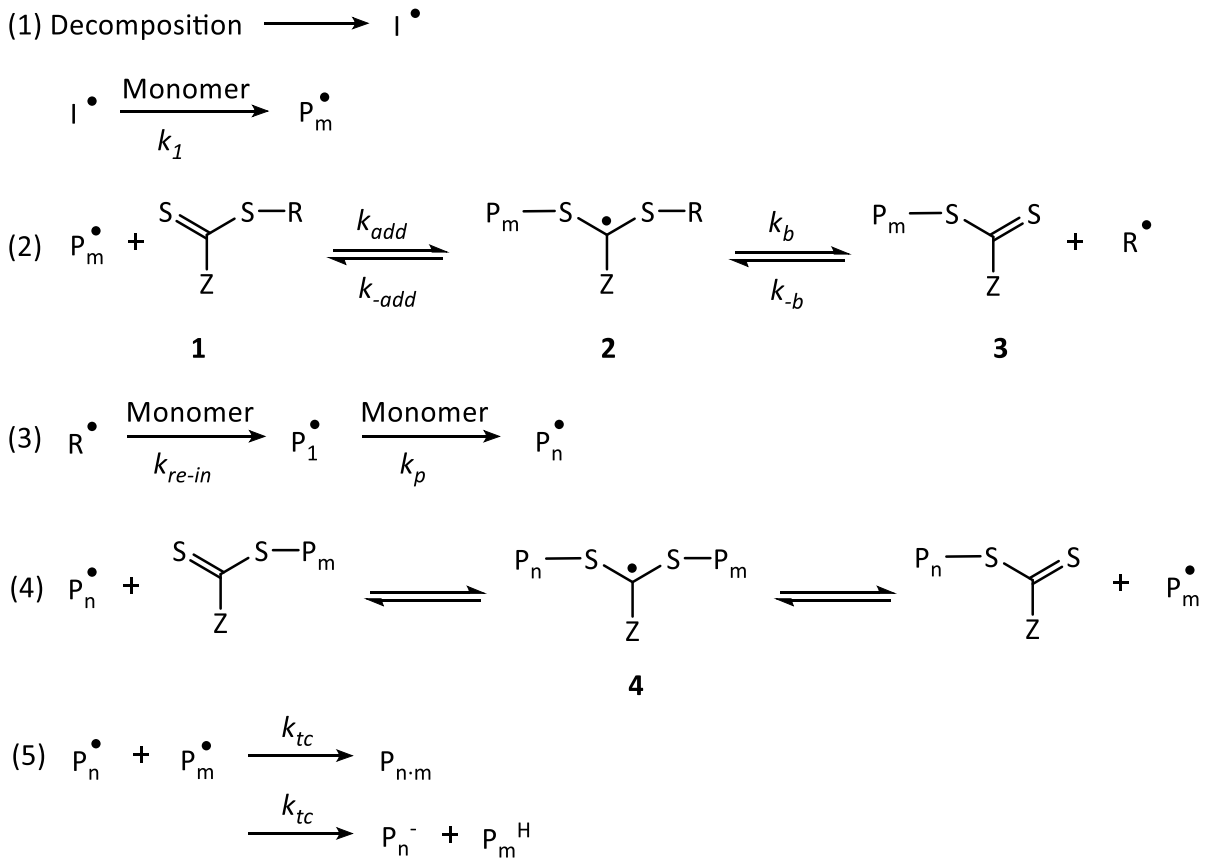


Figure 2.4-2 Different used CTAs.

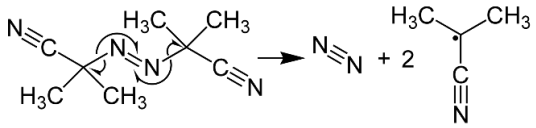
2.4.2 Mechanism of RAFT polymerization

The generally accepted mechanism for a RAFT polymerization is composed by five steps, which are the initiation, propagation, reversible chain transfer, reinitiation, chain equilibration and termination, showed below:



Scheme 2.4-1 Generally accepted mechanism for a RAFT polymerization.[17]

The thermal decomposition of radical initiators is the most widely adopted method of initiation, due to the commercial availability of such compounds. In this study, AIBN is used as initiator.



Scheme 2.4-2 Decomposition of the initiator AIBN.

The radical produced in the initiation step react with the RAFT agent **1** in a step of initialization (step 2). All of the RAFT agents are consumed in this step before any propagation commences. This is due to the highly reactive C=S bond of the RAFT agent, which means that radical addition is favoured over the addition to any of the double bonds that are present on the monomer. The radical intermediate **2** can fragment back to the original RAFT agent **1** and a radical or fragment to yield a RAFT agent **3** and a reinitiating radical. The structure of R should be such that it is a good reinitiating group. It should fragment at least as quickly as the initiator or polymer chains from the stabilized radical intermediate **1**. Following initialization, polymer

chains grow by adding monomer (step 3), and they rapidly exchange between existing growing radicals and the thiocarbonylthio group capped species **4** (step 4). The rapid interchange in the chain transfer step ensures that the concentration of growing radical chains is kept lower than that of the stabilized radical intermediates **4**, therefore limiting termination reactions. Although limited, termination reactions still occur via combination or disproportionation mechanisms (step 5)[17].

3 Objectives

The main objective of this study is to prepare thermo-responsive polymers using oligo(ethylene glycol) methyl ether methacrylate (MEOMA) as a monomer. The polymerization has to be via RAFT, in a controlled way. For that, we have to choose the correct CTA, and remove the inhibitors of the monomer (might effect in the polymerization).

First, the CTA has to be synthesized in the most pure way as possible, since is an important point to obtain the controlled polymerization. If the CTA is impure or contaminated with subproducts of the reaction, the polymerization will not work. To test if it is pure, it will be characterized by NMR.

Another important point is the assumption about if the inhibitors can affect or not in the polymerization. For that, some different methods and characterizations will be practiced.

Finally, several polymerizations will be done in order to synthesize the polymers with the desired properties.

4 Experimental part

4.1 Instruments

4.1.1 NMR

The ^{1}H-NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz) and samples were measured at room temperature. The chemical shift was specified in ppm, in deuterated chloroform. The ^{13}C-NMR spectra were recorded on a Varian 400 ASC (^{1}H-NMR). The spectra were analysed with the software ACD/1D NMR Processor.

4.1.2 GPC

For the analysis of the molar mass distribution an Agilent 1260 Infinity size exclusion chromatography (SEC) system equipped with an autosampler, an UV detector (λ = 280 nm) and a refractive index detector (RID) was used. A Gram 100 Å column and a pre-column with 5 µm particle size (Polymer Standard Service) was used at 60°C with dimethylacetamide (DMAc; containing 1 g/L LiBr) as eluent. The calibration line was recorded with PMMA standards. The flow rate of the systems was adjusted to 1 mL/min and 20 µL of the sample was injected.

4.1.3 HPLC

A HPLC device Agilent 1100 Series with DAD detector was used. A RP C18 column (150 x 4.6 mm) was used. The standard mobile phase was a gradient of acetonitrile and water, containing 0.05%of trifluoroacetic acid (0 min, 5% acetonitrile – 30 min, 100% acetonitrile L/L) with the flow rate of 1 mL·min^{-1}. The detector was operated at 214 nm. The column was set to at room temperature (21°C) and the injection volume was varied according the sample concentration.

4.2 Reagents and solvents

Destilled water was obtained from a MilliQ apparatus (specific electrical resistance of 18.2 MΩ·cm). AIBN (99%; Sigma-Aldrich, GHS-02[a], GHS-07[b]) was recrystallized from diethyl ether (technical grade; GHS-02, GHS-07). Dioxane (GHS-02, GHS-07, GHS-08[c]) was redistilled under argon atmosphere and sodium. Oligo(ethylene glycol) methyl ether methacrylate, Mn=300 g/mol or $MEO_{4/5}MA$ (Sigma-Aldrich, GHS-07). Oligo(ethylene glycol) methyl ether acrylate, Mn=480 g/mol or $MEO_{8/9}Ac$ (Sigma-Aldrich, GHS-08). Di(ethylene glycol) methyl ether acrylate, Mn=188 g/mol or MEO_2Ac (≥90%; Sigma-Aldrich, GHS-07). Carbon disulfide (≥99%; Merck, GHS-02, GHS-07, GHS-08). Mercaptopropionic acid (99%; Merck, GHS-05[d], GHS-06[e]). Triethylamine (GHS-02, GHS-05, GHS-06). (1-Bromoethyl)benzene (>95%; Acros, GHS-07). Hydrochloric acid (37%; Acros, GHS-05, GHS-07). Magnesium sulfate anhydrous (97%, Across). Dichloromethane (99.6%; Acros, GHS-07, GHS-08). Ethyl acetate (Sigma-Aldrich, GHS-02, GHS-07). Dodecanethiol (98%, Sigma-Aldrich, GHS-05, GHS-09[f]). α-Bromoisobutyric acid (Fluka, GHS-05). Hexane (technical grade, GHS-02, GHS-07, GHS-08, GHS-09). Ethanethiol (>99%, GHS-02, GHS-07, GHS-09) were used as recieved.

4.3 RAFT agent design and synthesis

4.3.1 Synthesis of MPT

A solution of mercaptopropionic acid (1.74 mL, 0.02 mol), triethylamine (5.58 mL, 0.04 mol), and carbon disulfide (3.63 mL, 0.06 mol) in chloroform (50 mL) was stirred for 3 hours at room temperature (22°C) under argon atmosphere, giving a yellowish solution that was stirred for another 24 hours with 1-bromoethylbenzene (2.73 mL, 0.02 mol). The stirring was stopped and the flask was opened to remove the remaining highly volatile carbon disulfide. The product was washed in a separation funnel twice with MilliQ water (50 mL), an aqueous solution of hydrochloric acid (50 mL, 1M) and again MilliQ water (50 mL). The organic phase was dried with magnesium sulfate, filtered and the solvent was removed in vacuum.

[a] Danger or Warning. Flammable
[b] Warning. Toxic cat.4, irritant cat. 2 or 3, lower systemic health hazards
[c] Danger or Warning. Systemic health hazards
[d] Danger or Warning. Corrosive cat. 1
[e] Danger. Toxic cat. 1-3
[f] Warning. Environment

The remaining yellowish oil was purified by column chromatography (SiO_2 – DCM/Ethyl acetate 6:1 v/v). The solvent was removed in vacuum. The residue was dried for several hours in high vacuum giving a yellowish oily compound.

Yield: 79%.

^{1}H-NMR$_{(CDCl3)}$: δ [ppm]= 7.25 (**a**, 5H, aryl), 5.25 (**b**, q, 1H, CH), 3.50 (**c**, t, 2H, CH_2), 2.75 (**d**, t, 2H, CH_2), 1.68 (**e**, d, 3H, CH_3).

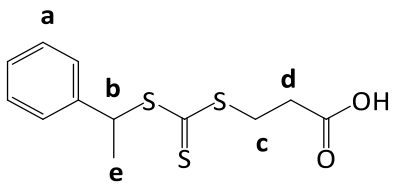


Figure 4.3-1 Molecular structure of MPT.

4.3.2 Synthesis of DPT

A solution of dodecanethiol (4 mL, 0.01 mol), and triethylamine (4.63 mL, 0.03 mol), in chloroform (20 mL) was stirred for 15 min at room temperature (22°C) under argon atmosphere. Then carbon disulfide (2 mL, 0.03 mol) was added and stirred for 3 hours, giving a yellowish solution that was stirred for another 24 hours with 1-bromoethylbenzene (2.3 mL, 0.01 mol). The reaction was stopped and the flask was opened to remove the remaining highly volatile carbon disulfide, and chloroform (30 mL, technical grade) was added. The product was washed in a separation funnel twice with MilliQ water (50 mL), an aqueous solution of hydrochloric acid (50 mL, 1M) and again MilliQ water (50 mL). The organic phase was dried with magnesium sulfate, filtered and the solvent was removed in vacuum. The residue was dried for several hours in high vacuum giving a yellowish oily compound.

Yield: Quantitative.

^{1}H-NMR$_{(CDCl3)}$: δ [ppm]= 7.25 (**a**, 5H, aryl), 5.26 (**b**, q, 1H, CH), 3.25 (**c**, t, 2H, CH_2), 1.68 (**d**, d, 3H, CH_3), 1.59 (**e**, quintet, 2H, CH_2), 1.18 (**f**, 16H, CH_2), 0.8 (**g**, t, 3H, CH_3).

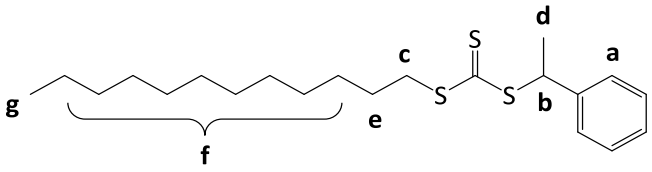


Figure 4.3-2 Molecular structure of DPT.

4.3.3 Synthesis of DMP

Dodecanethiol (4.5 mL, 0.02 mol) was added in a suspension of potassium phosphate tribasic monohydrate (4.35 g, 0.02 mol), in acetone (70 mL, technical grade) and was stirred for 30 min at room temperature (22°C). Then carbon disulfide (3.5 mL, 0.06 mol) was added and stirred for additional 30 min, changing the colour from yellow to orange. The solution was stirred for another 24 hours after adding α-Bromoisobutyric acid (2.74 g, 0.02 mol). In the next step hydrochloric acid (200 mL, 1M) was placed in the reaction flask to neutralize the basic pH and protonate the carboxylic acid group. In the further step, the solution was placed in an extraction funnel and DCM (150 mL) was added for 3 times. The product was extracted in the organic phase. The combined organic phases were treated with brine solution (100 mL) and washed three times with MilliQ water (100 mL). The solution was treated with magnesium sulfate, filtered and the solvent was removed in vacuum. The solid was recrystallized in hexane (5 mL, technical grade) yielding yellowish crystals.

Yield: 67%.

^{1}H-NMR$_{(CDCl3)}$: δ [ppm]= 3.28 (a, t, 2H, CH_2), 1.73 (b, s, 6H, $2CH_3$), 1.26 (c, q, 20H, $10CH_2$), 0.87 (d, t, 3H, CH_3).

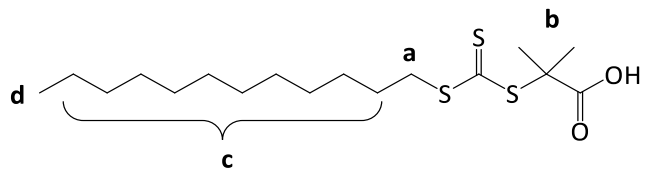


Figure 4.3-3 Molecular structure of DMP.

4.3.4 Synthesis of EMP

A suspension of ethanethiol (1.35 mL, 0.02 mol) and potassium phosphate tribasic monohydrated (4.35 g, 0.02 mol) in acetone (70 mL, technical grade) was stirred for 20 min at room temperature. Carbon disulfide (3.5 mL, 0.06 mol) was added and the yellow turning solution was stirred for another 30 min. α-Bromoisobutyric acid (2.74 g, 0.02 mol) was added and the mixture was stirred for 16 hours. An aqueous solution of HCl (200 mL, 1 mol/L) was added and the aqueous phase was extracted twice with dichloromethane (DCM; 150 mL). The combined organic extracts were washed with deionized water (75 mL) and a saturated aqueous solution of NaCl (brine; 75 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuum. The remaining oily residue was purified by column chromatography (SiO_2, n-hexane/ethyl acetate 2:1 v/v). The solvent was removed in vacuum and the residue was dried for several hours in high vacuum to obtain a solid and yellowish product that was recrystallized from hexane.

Yield: 55%.

^{1}H-NMR$_{(CDCl3)}$: δ [ppm]= 3.24 (**a**, q, 2H, CH_2), 1.73 (**b**, s, 6H, CH_3), 1.28 (**c**, t, 3H, CH_3).

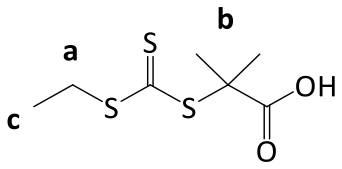


Figure 4.3-4 Molecular structure of EMP.

4.4 Polymerization

4.4.1 MEO$_{4/5}$MA RAFT polymerization [100:1:0.1]

The polymer synthesis (Scheme 4.4-1) was carried out in a 25 mL Schlenk tube (previously dried) which was charged with MEO$_{4/5}$MA (2 mL, $6 \cdot 10^{-3}$ mol), which was run through a basic alumina plug to remove the inhibitors, DPT as a CTA (22.79 mg, $6 \cdot 10^{-5}$ mol), AIBN as an initiator (10 µL of standard solution 3.22 M), and 10 mL of distilled dioxane, at room temperature (22°C) under argon atmosphere. After that, a freeze-thaw of the solutions were done in order to remove oxygen and the polymerization reaction was started at 70°C (decomposition

temperature of AIBN). After 18 hours, the polymer was precipitated in cold hexane in order to eliminate the remaining monomer. The polymers were analysed by GPC.

$$2\ mL\ OE_{4/5}GMA \cdot \frac{1.05\ g\ OE_{4/5}GMA}{1\ mL\ OE_{4/5}GMA} \cdot \frac{1\ mol\ OE_{4/5}GMA}{320.38\ g\ OE_{4/5}GMA} = 6.5 \cdot 10^{-3} mol\ OE_{4/5}GMA \quad (1)$$

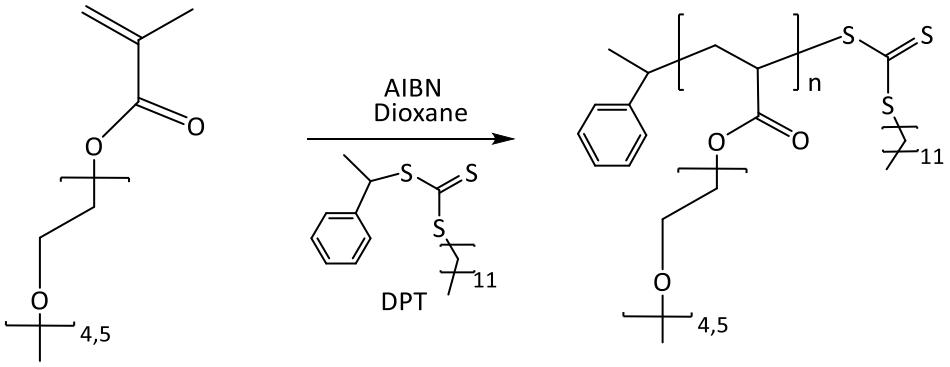
$$6.5 \cdot 10^{-3} mol\ OE_{4/5}GMA \cdot \frac{1\ mol\ DPT}{100\ mol\ OE_{4/5}GMA} \cdot \frac{350.62 \cdot 10^{3}\ mg\ DPT}{1\ mol\ DPT} = 22.79\ mg\ DPT \quad (2)$$

$$6.5 \cdot 10^{-3}\ mol\ OE_{4/5}GMA \cdot \frac{0.1\ mol\ AIBN}{100\ mol\ OE_{4/5}GMA} \cdot \frac{1}{2}^{g} \cdot \frac{164.21\ g\ AIBN}{1\ mol\ AIBN} = 5.33 \cdot 10^{-4}\ g\ AIBN \quad (3)$$

1 mL of standard solution of AIBN 3.22M was prepared (Equation 4 and 5) since the amount is too low to be weighted with precision.

$$1\ mL\ SS \cdot \frac{10^{6}\mu L}{10^{3}\ mL} \cdot \frac{5.33 \cdot 10^{-4}\ g\ AIBN}{10\ \mu L} = 0.5300\ g\ AIBN \quad (4)$$

$$0.53\ g\ AIBN \cdot \frac{1\ mol\ AIBN}{164.21\ g\ AIBN} \cdot \frac{1}{0.001\ L} = 3.22\ mol/L \quad (5)$$



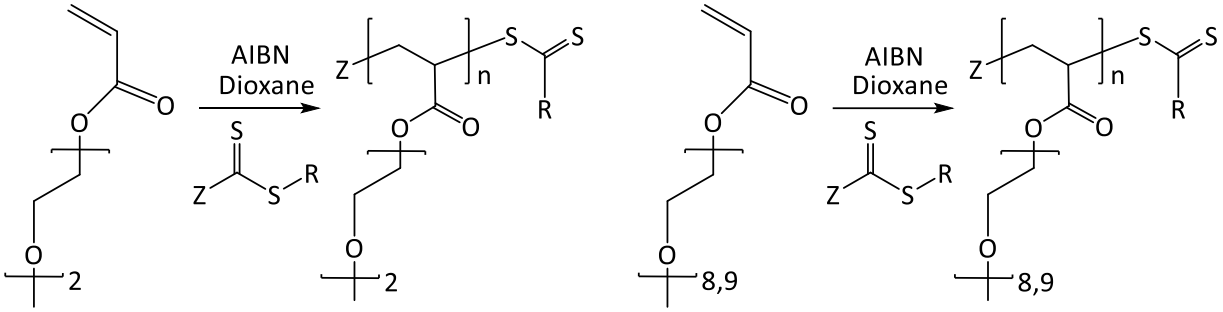
Scheme 4.4-1 RAFT polymerization reaction of $MEO_{4/5}MA$.

4.4.2 MEO_2Ac and $MEO_{8/9}Ac$ RAFT polymerization [50:1:0.1]

The polymer synthesis (Scheme 4.4-2) was carried out with the same method of the previous one (section 4.4.1). The corresponding amounts for each sample are presented in Table 4.4-1.

[g] Per each mol of AIBN, there are two radicals of initiator

MEO_2Ac and $MEO_{8/9}Ac$ were used as monomers [M], dried dioxane as solvent, and AIBN as initiator. All reactions were conducted at 70°C with a [M]/[CTA]/[AIBN] ratio of 50:1:0.1.



Scheme 4.4-2 RAFT polymerization reaction of MEO_2Ac (left) and $MEO_{8/9}Ac$ (right).

$$2\ mL\ OE_{8/9}GA \cdot \frac{1.09\ g\ OE_{8/9}GA}{1\ mL\ OE_{8/9}GA} \cdot \frac{1\ mol\ OE_{8/9}GA}{480\ g\ OE_{8/9}GA} = 4.54 \cdot 10^{-3}\ mols\ OE_{8/9}GA \quad (6)$$

$$4.54 \cdot 10^{-3}\ mol\ OE_{8/9}GA \cdot \frac{1\ mol\ CTA}{50\ mol\ OE_{8/9}GA} = 9.08 \cdot 10^{-5}\ mol\ CTA \quad (7)$$

$$4.54 \cdot 10^{-3}\ mol\ OE_{8/9}GA \cdot \frac{0.1\ mol\ AIBN}{50\ mol\ OE_{8/9}GA} \cdot \frac{1}{2} \cdot \frac{164.21\ g\ AIBN}{1\ mol\ AIBN} = 1.49 \cdot 10^{-3}\ g\ AIBN \quad (8)$$

1 mL of standard solution of AIBN was prepared (Equation 9 and 10) since the amount is too low to be weighted with precision.

$$1\ mL\ SS \cdot \frac{10^6 \mu L}{10^3\ mL} \cdot \frac{1.49 \cdot 10^{-3}\ g\ AIBN}{50\ \mu L} = 0.0298\ g\ AIBN \quad (9)$$

$$0.0298\ g\ AIBN \cdot \frac{1\ mol\ AIBN}{164.21\ g\ AIBN} \cdot \frac{1}{0.001\ L} = 0.18\ M\ AIBN \quad (10)$$

$$2\ mL\ DEGA \cdot \frac{1.016\ g\ DEGA}{1\ mL\ DEGA} \cdot \frac{1\ mol\ DEGA}{188.22\ g\ DEGA} = 1.08 \cdot 10^{-2} mols\ DEGA \quad (11)$$

$$1.08 \cdot 10^{-2}\ mol\ DEGA \cdot \frac{1\ mol\ CTA}{50\ mol\ DEGA} = 2.16 \cdot 10^{-4}\ mol\ CTA \quad (12)$$

AIBN stock solution previously calculate also was used for this polymerization (Equation 13 and 14)

$$1.08 \cdot 10^{-2}\ mol\ DEGA \cdot \frac{0.1\ mol\ AIBN}{50\ mol\ DEGA} \cdot \frac{1}{2} = 1.08 \cdot 10^{-5}\ mol\ AIBN \quad (13)$$

$$\frac{50}{4.54 \cdot 10^{-6}} = \frac{x}{1.08 \cdot 10^{-5}} \quad \Rightarrow \quad x = 118\ \mu L \quad (14)$$

Table 4.4-1. Polymerization conditions of MEO_2Ac and $MEO_{8/9}Ac$. [M]/[CTA]/[AIBN]= 50:1:0.1; 70°C; 20h.

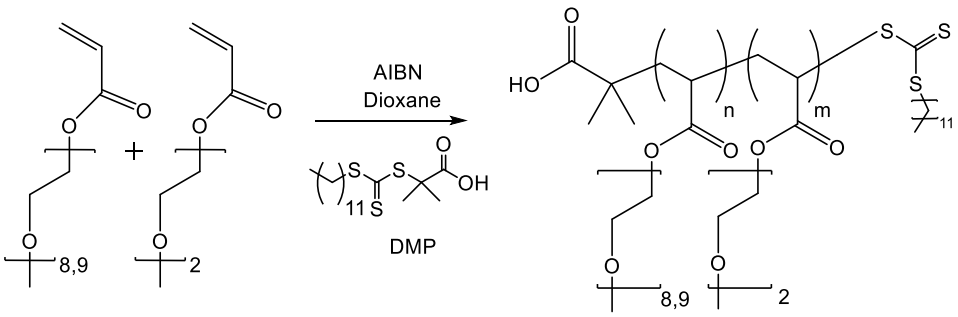
Monomer	mmols	CTA	mg CTA[a]	mmols CTA	mmol AIBN	µL AIBN SS[b]
$OE_{8/9}GA$	4.54	DMP	33.1	$9.08 \cdot 10^{-2}$	$4.54 \cdot 10^{-6}$	50
$OE_{8/9}GA$	4.54	MPT	26.0	$9.08 \cdot 10^{-2}$	$4.54 \cdot 10^{-6}$	50
$OE_{8/9}GA$	4.54	DPT	31.8	$9.08 \cdot 10^{-2}$	$4.54 \cdot 10^{-6}$	50
MEO2AC	10.80	DMP	78.6	$2.16 \cdot 10^{-1}$	$1.08 \cdot 10^{-5}$	118
MEO2AC	10.80	MPT	61.8	$2.16 \cdot 10^{-1}$	$1.08 \cdot 10^{-5}$	118
MEO2AC	10.80	DPT	75.6	$2.16 \cdot 10^{-1}$	$1.08 \cdot 10^{-5}$	118

[a] Calculate according to the molecular weight of the CTA's (DMP= 364.63 g/mol; MPT= 286.43 g/mol; DPT= 350.62 g/mol); [b] Standard solution of AIBN 0.18M

The determination of LCST was done dissolving each sample of polymer in water (1 % w/w) and light transmittance was measured with increasing the temperature.

4.4.3 MEO_2Ac and $MEO_{8/9}Ac$ RAFT co-polymerization

Different ratios of copolymer synthesis (Scheme 4.4-3) with DMP as CTA were carried out following the same procedure than the 4.4.1 section. The corresponding amount for each sample is presented in Table 4.2-2. To isolate the polymers, dialysis (molecular weight cut off, MWCO=1 kD) was performed because no solvent for precipitation was found.



Scheme 4.4-3 RAFT co-polymerization reaction of MEO_2Ac and $MEO_{8/9}Ac$.

$$9.08 \cdot 10^{-3}\ total\ mol\ monomer \cdot \frac{20}{100} = 1.81 \cdot 10^{-3}\ mol\ monomer \quad (15)$$

$$9.08 \cdot 10^{-3}\ total\ mol\ monomer \cdot \frac{40}{100} = 3.63 \cdot 10^{-3}\ mol\ monomer \quad (16)$$

$$9.08 \cdot 10^{-3}\ total\ mol\ monomer \cdot \frac{60}{100} = 5.44 \cdot 10^{-3}\ mol\ monomer \quad (17)$$

$$9.08 \cdot 10^{-3}\ total\ mol\ monomer \cdot \frac{80}{100} = 7.26 \cdot 10^{-3}\ mol\ monomer \quad (18)$$

$$9.08 \cdot 10^{-3} mol\ monomer \cdot \frac{1\ mol\ CTA}{50\ mol\ monomer} = 1.81 \cdot 10^{-4} mol\ CTA \quad (19)$$

$$9.08 \cdot 10^{-3} mol\ monomer \cdot \frac{0.1\ mol\ AIBN}{50\ mol\ monomer} \cdot \frac{1}{2} \cdot \frac{164.21 g\ AIBN}{1\ mol\ AIBN} = 1.49 \cdot 10^{-3}\ g\ AIBN \quad (20)$$

A standard solution of AIBN was prepared following the Equations 9 and 10.

Table 4.4-2 Co-polymerization conditions of MEO_2Ac and $MEO_{8/9}Ac$ with DMP as a CTA. [M]/[CTA]/[AIBN]= 50:1:0.1; 70°C; 40; $1.81 \cdot 10^{-4}$ mmol CTA; $9.08 \cdot 10^{-3}$ mmol AIBN.

Ratio MEO2AC/$OE_{8/9}GA$	mmols	mL MEO2AC	mL $OE_{8/9}GA$
20:80	1.81:7.26	0.33	3.19
40:60	3.63:5.44	0.67	2.40
60:40	5.44:3.63	1.00	1.60
80:20	7:26:1.81	1.34	0.80

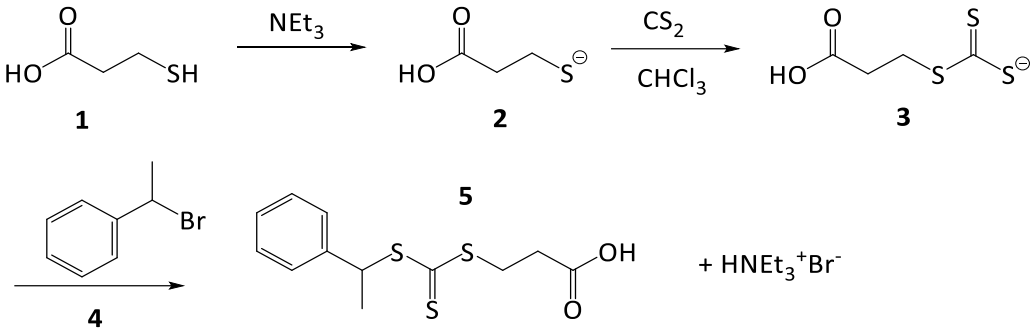
The determination of the LCST was measured following the procedure of the 4.4.2ç section.

5 Results and discussion

5.1 RAFT agent design and synthesis

The CTA mercapto propionic acid 1-phenylethyl trithiocarbonate (MPT) was synthetized using the synthetic route based on a procedure in the literature[18] shown in scheme 5.1-1. Thiol **1** was deprotonated with NEt_3. The resulting thiolate anion **2** added to the carbon disulphide to form the trithiocarbonate anion **3**. The latter one was converted by a nucleophilic substitution at the 1-bromoethyl benzene **4** to the respective trithiocarbonate derivate **5**.

The structure of the product was proven by ^{1}H-NMR spectroscopic analysis. Peaks at 7.25 ppm correspond to aromatic protons of the R fragment, while at 5.2 ppm (quartet) and 1.68 ppm (doublet) correspond to CH and CH_3 respectively or the other part of the R fragment. Peaks at 3.50 ppm (triplet) and 2.75 ppm (triplet) correspond to protons of the Z fragment, both CH_2.



Scheme 5.1-1 Applied synthetic route for MPT.

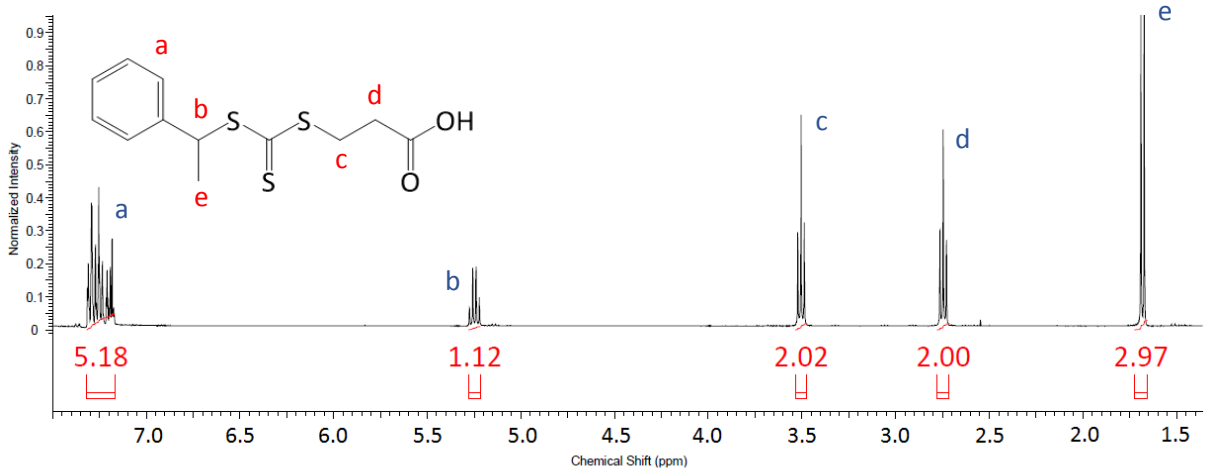
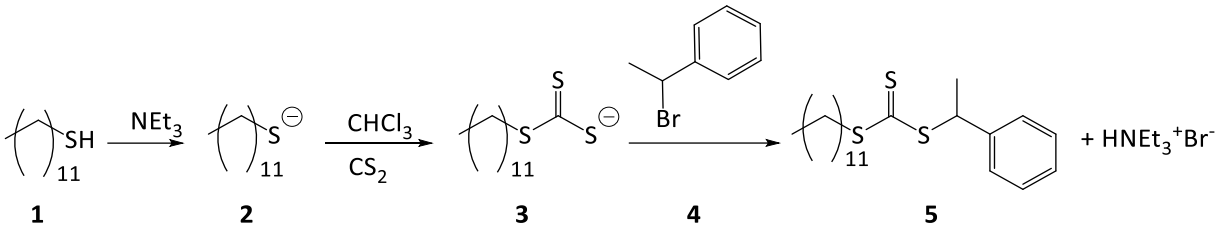


Figure 5.1-1 ^{1}H-NMR spectrum of MPT.

The CTA dodecane 1-phenylethyl trithiocarbonate (DPT) was synthetized using the same route for MPT.

The structure of the product was proven by ^{1}H-NMR spectroscopic analysis. Peaks at 7.25 ppm correspond to aromatic protons of the R fragment, while peaks at 5.26 ppm (quartet) and 1.68 ppm (doublet) correspond to the other part of the R fragment. Peaks at 3.25 ppm (triplet) correspond to protons of the Z fragment in α-position to the trithiocarbonyl group, and the peaks at 1.59 ppm (quintet) correspond to the protons in β-position to the trithiocarbonyl group. Peaks at 0.8 ppm (triplet) correspond to the terminal protons of the Z fragment, and the rest of protons correspond to peak at 1.18 ppm.



Scheme 5.1-2 Applied synthetic route for DPT.

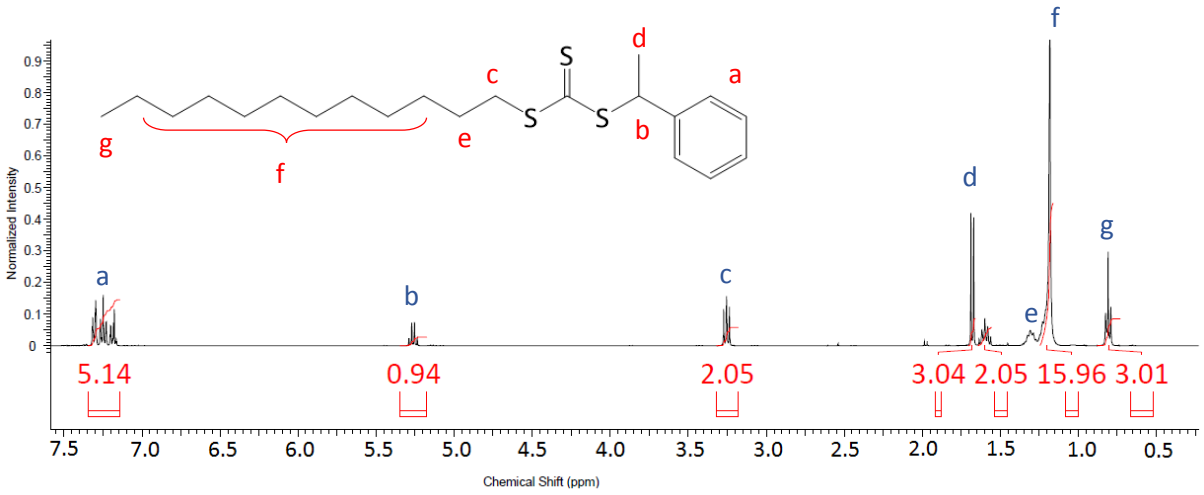
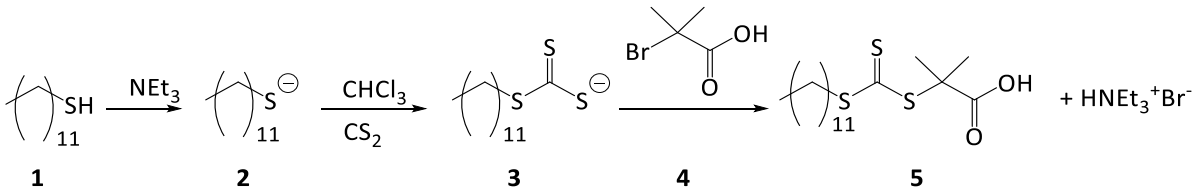


Figure 5.1-2 ^{1}H-NMR spectrum of DPT.

The CTA 2-{[(dodecylthio)carbonothioyl]thio}-2-methylpropanoic acid (DMP) was synthetized using the route as described for the MPT, but with α-Bromoisobutyric acid instead of 1-bromoethyl benzene.

The structure of the product was proven by ^{1}H-NMR spectroscopic analysis. Peak at 1.73 ppm (singlet) correspond of both CH_3 of the R fragment. Peaks at 3.28 ppm (triplet) correspond to protons in α-position to the trithiocarbonyl group of the Z fragment, while the peaks at 0.87 ppm (triplet) correspond to the terminal protons CH_3. The other protons of the Z fragment correspond to the peak 1.26 ppm (quadruplet).



Scheme 5.1-3 Applied synthetic route for DMP.

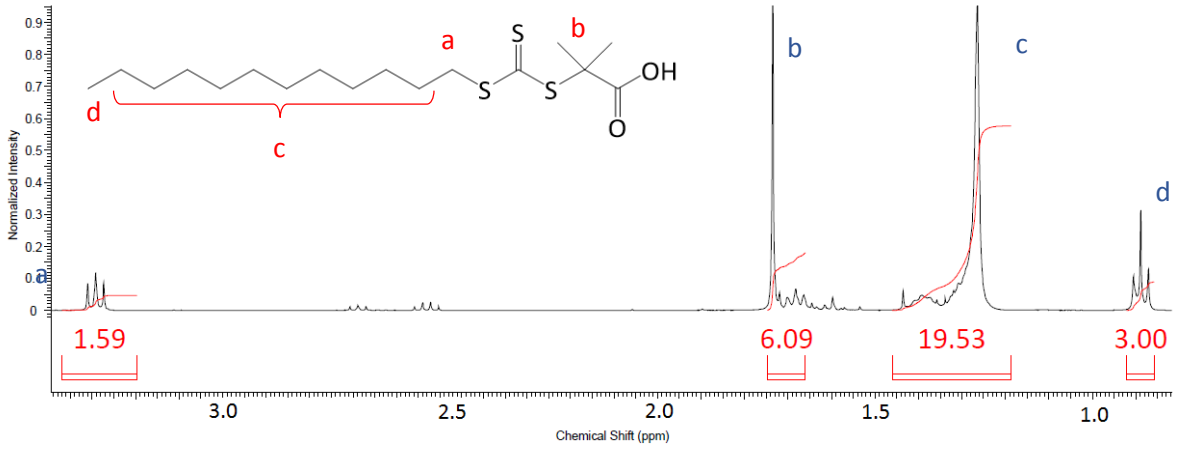
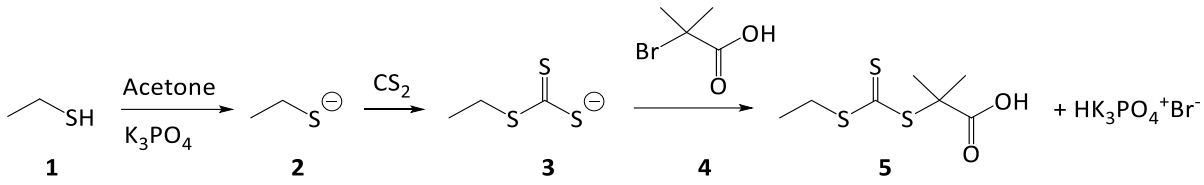


Figure 5.1-3 ^{1}H-NMR spectrum of DMP.

The CTA 2-{[(ethylthio)carbonothioyl]thio}-2-methylpropanoic acid (EMP) was synthetized using the route for the MPT, but with K_3PO_4 instead of NEt_3 as a base and with α-bromoisobutyric acid instead of 1-bromoethyl benzene.

The structure of the product was proven by ^{1}H-NMR spectroscopic analysis. Peaks at 1.73 ppm (singlet) correspond to both CH_3 of the R fragment. Peak at 3.24 ppm (quadruplet) correspond

to the protons from Z fragment in α-position of the trithiocarbonyl group, and peaks at 1.28 ppm (triplet) correspond to the terminal protons CH_3 of Z fragment.



Scheme 5.1-4 Applied synthetic route for EMP.

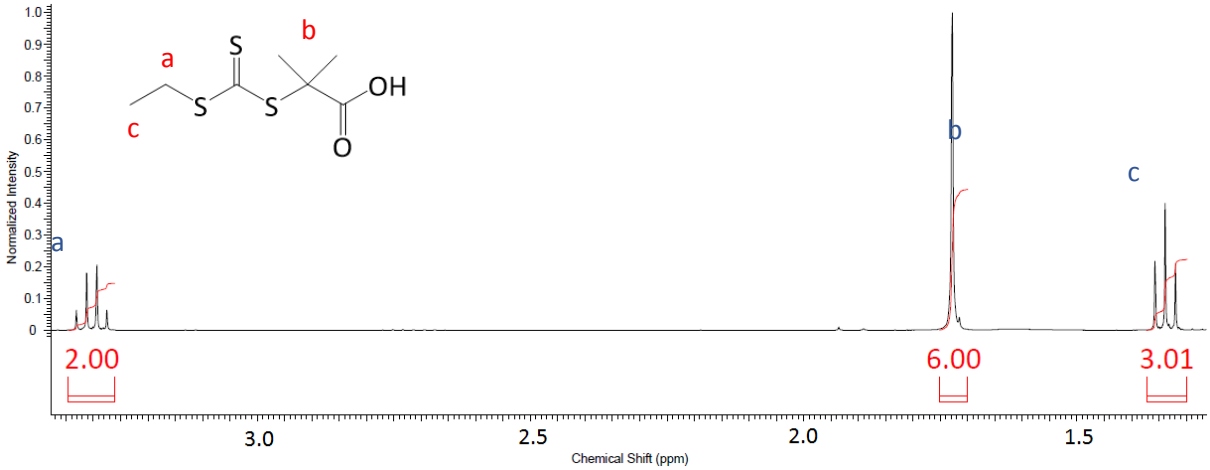


Figure 5.1-4 ^{1}H-NMR spectrum of EMP.

5.2 RAFT polymerization

$PMEO_{4/5}MA$ homopolymers were synthesized using DPT as a CTA. $MEO_{4/5}MA$ was used as a monomer [M], dried dioxane as a solvent, and AIBN as an initiator. All reactions were conducted at 70°C with a [M]/[CTA]/[AIBN] ratio of 100:1:0.1.

The calculated (theoretical) molar mass would be 30300 g/mol. The masses found were in the range between 184000 and 165000 g/mol, which is far beyond the separation limit of the chosen GPC-column. The polymerization was done three times.

One reason for this result could be the calibration method of the GPC instrument, which was done with polymethacrylate standards, a polymer which dissolves in dimethyl acetamide

completely different than MEOMA. But more likely an uncontrolled radical polymerization took place.

The control of the polymerization can be affected by several ways like, impurities, inhibitors or even by the used CTA. First, a wide study of the inhibitors of the monomers was done.

Small amount of MEHQ (100 ppm in $MEO_{4/5}MA$, 100 ppm $MEO_{8/9}Ac$ and 1000 ppm in MEO_2Ac) and BHT (300 ppm in $MEO_{4/5}MA$ and 100 ppm in $MEO_{8/9}Ac$) were in the monomers as inhibitors to prevent undesired polymerization during shipping and storage. Sometimes, retarders are also added. Both retarders and inhibitors react with initiator fragments or growing chains and terminate radicals.[19]

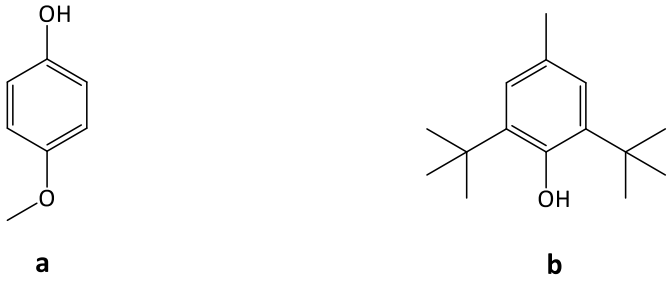


Figure 5.2-1 Current inhibitors in the monomer. a = MEHQ; b = BHT

Inhibitors are characterized by do stabilized free radicals. An effective inhibitor can be of the addition type, such as oxygen or quinine, where the radical adds to the component, or of the chain transfer type, such as the monomethyl ether of hydroquinone (MEHQ). [19] Because of their behaviour, they have to be removed before the polymerization is started.

First, they were determinate qualitatively by HPLC device. The two standard solutions were prepared adding 3 mg of inhibitor in each respective 25 mL volumetric flask. The volumes injected in the column were 5 µL. The standard mobile phase was a gradient of acetonitrile and water, containing 0.05% of trifluoroacetic acid (0 min, 5% acetonitrile – 30 min, 100% acetonitrile L/L) with the flow rate of 1 $mL \cdot min^{-1}$. The retention times were 8.1 for MEHQ and 25.3 for BHT.

Figure 5.2-5 shows the HPLC chromatogram of the unpurified monomer MEOMA at 214 nm. Clearly visible are the two inhibitors at 8.1 (MEHQ) and 25.3 min (BHT). The other peaks belong

to the mixture of oligomeric MEOMA. A molar weight ratio cannot be calculated from the peak because the aromatic inhibitors are much more sensitive of UV light than the MEOMA.

Several methods were tested in order to remove the inhibitors added to the used monomers:

- Silica gel column with diethyl ether as eluent. Previously, a study of the retention time of the inhibitors and monomer was done through TLC (Figure 5.2-2). HPLC analysis was practised for the determination of the inhibitors after the column. The results were not good because only one of the inhibitors was removed (MEHQ)
- Alumina plug without solvent. HPLC analysis was practised for the determination of the inhibitors after the plug. The results were good, since both monomers were removed. Hence, this method was chosen to eliminate the inhibitors before each polymerization. The advantage of this method in relation to the previous one, is that the monomer has not to be dried with vacuum after the process. Though, the disadvantage of this is the high waste of monomer since it also behaves as eluent.

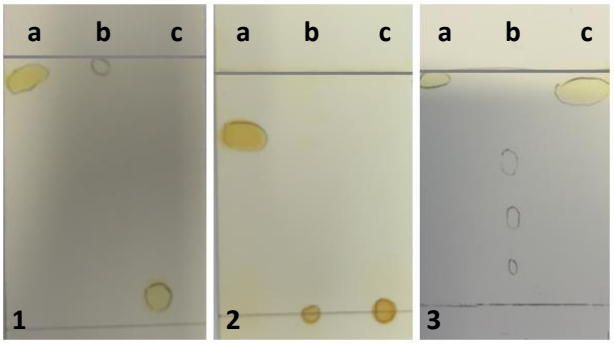


Figure 5.2-2 TLC of $MEO_{4/5}MA$. 1 = Toluene as an eluent, 2 = hexane as an eluent, 3 = diethyl ether as an eluent, a = solution of BHT inhibitor, b = solution of monomer, c = solution of MEHQ. Stained: iodine.

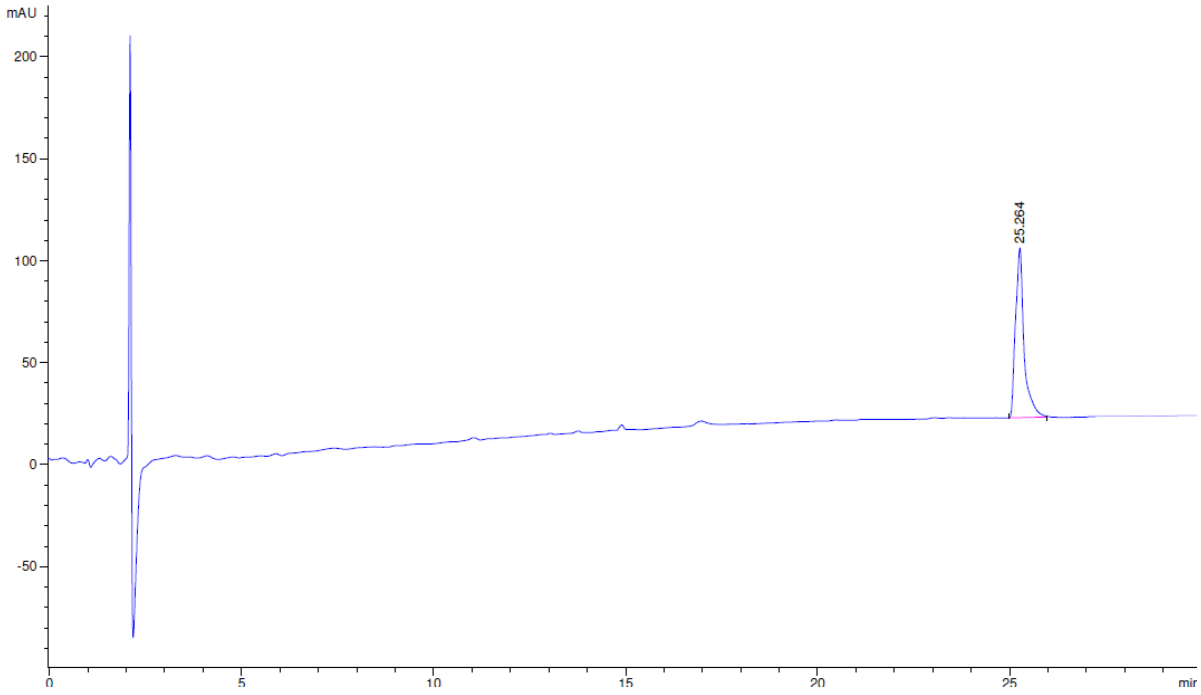


Figure 5.2-3 HPLC chromatogram of BHT. Retention time at 25.3 min.

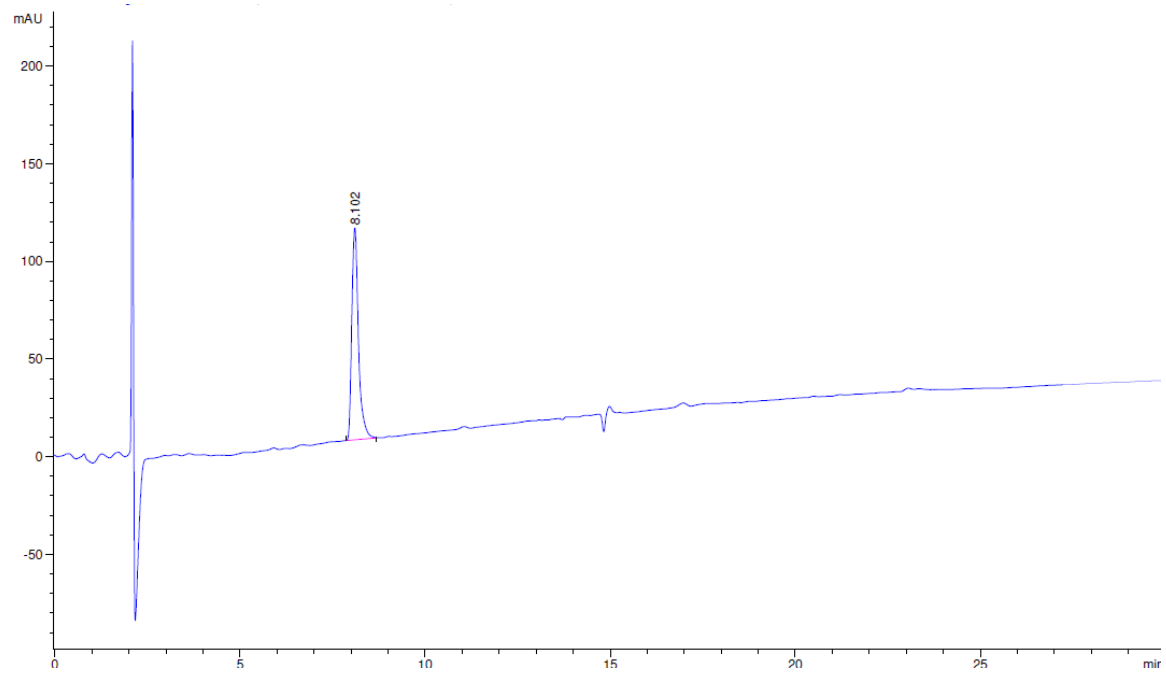


Figure 5.2-4 HPLC chromatogram of MeHQ. Retention time at 8.1 min.

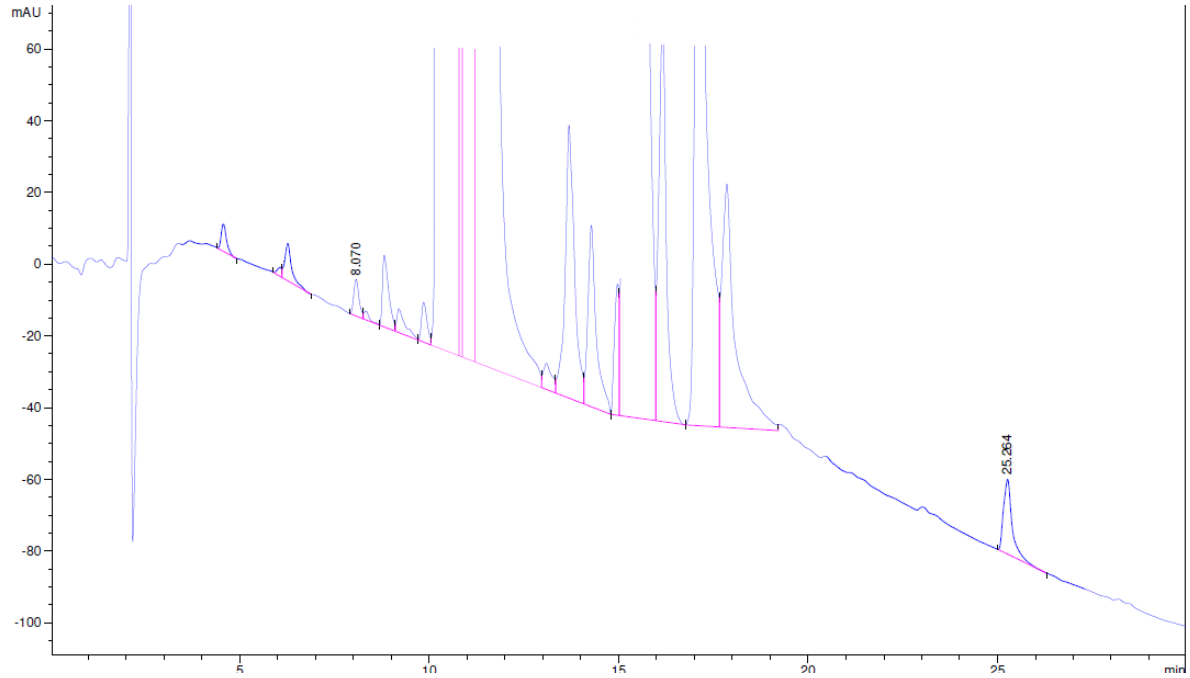


Figure 5.2-5 HPLC chromatogram of $MEO_{4/5}MA$.

Radical polymerization of $MEO_{4/5}MA$ was performed at 70°C with AIBN (0.05% M/M), dioxane for 18 hours, by silica gel column chromatography (sample 2), basic alumina plug (sample 3), and $MEO_{4/5}MA$ without any treatment (sample 1). The aim of this polymerization was see how much the inhibitors can affect. The polymers were isolated with cold hexane. As is shown in the table, the results obtained for the different samples are similar

Table 5.2-1 Results of the radical polymerization of $MEO_{4/5}MA$.

Sample	Yield (%)	Mn[a]	Mw[a]	Mw/Mn
1	51.4	$2.08 \cdot 10^5$	$2.78 \cdot 10^5$	1.3
2	62.0	$2.03 \cdot 10^5$	$2.78 \cdot 10^5$	1.3
3	47.9	$2.05 \cdot 10^5$	$2.80 \cdot 10^5$	1.3

[a] Molecular weight determinated by GPC

Then, a study of the CTA used was done. In several investigations, it was studied that the structures of the R and Z groups (described in theoretical background section) are of critical importance to start a polymerization. For the case or methyl methacrylates, the ability of a RAFT agent to carry out polymerization is highly dependent on the nature of the R group, whereas other monomers are more permissive with respect to the R group. Results of this

studies showed that only cumyl and cyanoisopropyl based R groups are able to react efficiently with methyl methacrylate monomers. [20]

The methyl methacrylates radicals formed in the first reaction step by the initiation are too stable to attack the thiocarbonyl bonds of the chosen CTAs.

Hence, a low rates of addition of monomer to the RAFT agent and a high rates of fragmentation of the radical occurs. Consequently, the polymerization looks like a conventional free radical polymerization because the concentration of radicals in the system is too high. [18]

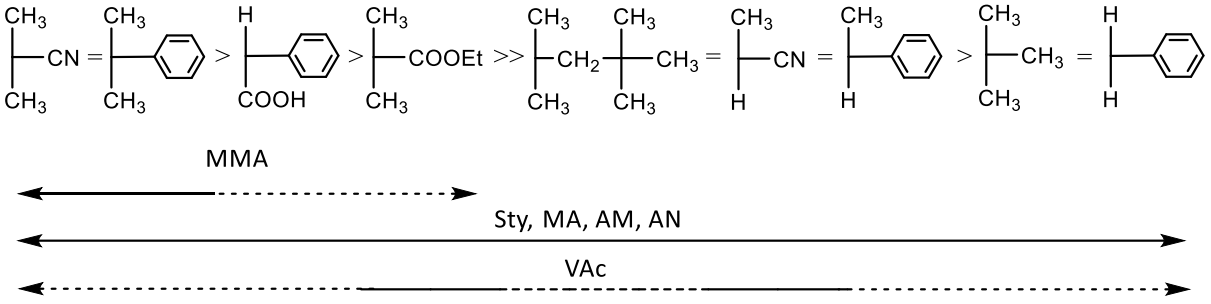


Figure 5.2-6 Guidelines for the section of R group substituents for various polymerizations. Fragmentation rate decrease from left to right. Dashed lines indicate partial control over the polymerization. MMA= methyl methacrylate, Sty= styrene, MA= methyl acrylate, AM= acrylamide, AN= acrylonitrile, Vac= vinyl acetate[21].

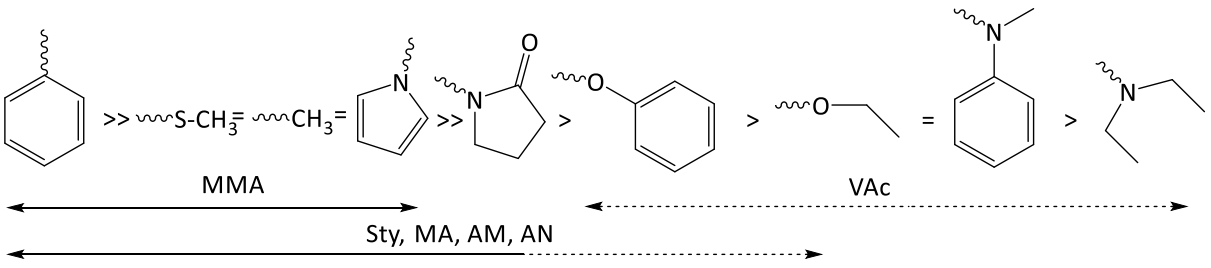


Figure 5.2-7 Guidelines for the selection of Z group substituents for various polymerizations. Fragmentation rates increase and addition rates decrease from left to right. Dashed lines indicate partial control over the polymerization. MMA= methyl methacrylate, Sty= styrene, MA= methyl acrylate, AM= acrylamide, AN= acrylonitrile, Vac= vinyl acetate

Consequently, the monomers used were changed from methyl methacrylate to methyl acrylate, which is more versatile to different CTA's. $PMEO_2Ac$ and $PMEO_{8/9}Ac$ were successfully synthesized with different end-groups using different CTA's.

The yields obtained differed between 29 and 71%. The molar masses obtained by GPC were not exactly as expected for the calculations (are not accurate because the monomers are a mixture of oligomers and an average molar mass is given by the supplier). Hence, RAFT of acrylates with these CTA's (DPT, DMP, MPT) lead to very well controlled polymers since these monomers have a very reactive propagating radical with low steric bulk that leads to fast polymerizations. RAFT polymerization of $PMEO_2Ac$ and $PMEO_{8/9}Ac$ always provided, independently from the CTA, good control of PDIs (M_w/M_n) ≈ 1.30.

A good control of the masses by the chosen CTAs and generally a controlled radical polymerization was obtained. The figure 5.2-8 shows the increase of M_n and M_w with time for $MEO_{8/9}Ac$ polymerization reaction with DMP as a CTA. At first, a steep slope shows that the molar masses increase fast with time. Then, the slope decreases.

The thermo-responsive polymer were characterized by cloud point, which the phase separation can be followed by turbidimetry. The LCST results obtained are very different depending on the monomer. In the case of $MEO_{8/9}Ac$ a high temperature (>97°C) is observed, while in the case of MEO_2Ac, the LCST is very low (<4°C).

Table 5.2-2 Synthetic conditions and results data of homopolymers[a].

	CTA	Yield (%)	M_n(theoretical)[c]	M_n(GPC)[d]	M_w/M_n[d]	LCST
$OE_{8/9}GA$	DMP	41	24300	7800	1.32	>97°C
$OE_{8/9}GA$	MPT	55	24300	7700	1.29	>97°C
$OE_{8/9}GA$	DPT	37	24300	9000	1.34	>97°C
MEO2AC	DMP	29	9700	6200	1.33	<4°C
MEO2AC	MPT	71	9700	5500	1.35	<4°C
MEO2AC	DPT	60	9700	6000	1.29	<4°C

[a]Target DP ≈ 50, [Mono : CTA : AIBN] = 50 : 1 : 0.1, 70°C, 20h. [c] Approximate theoretical molecular weight of homopolymers = target DP x $M_{Monomer}$ + M_{CTA}. [d]Determined by GPC (DMAc eluent and PMMA standards)

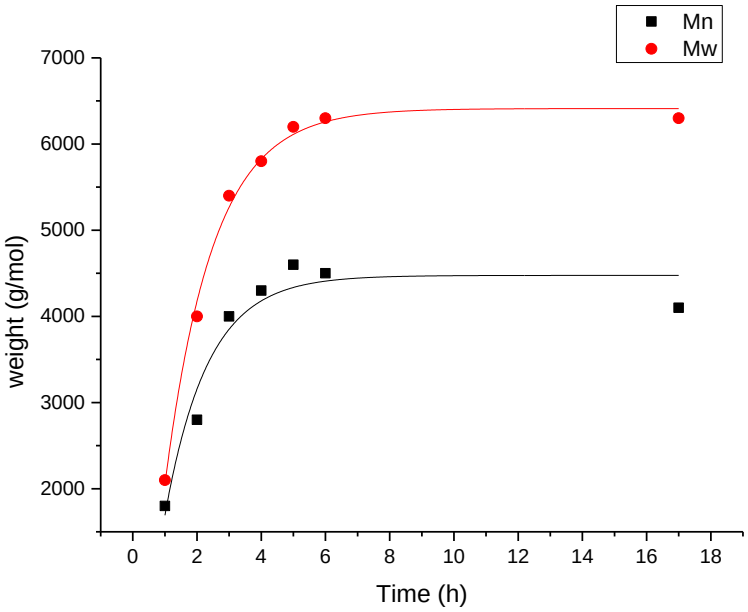


Figure 5.2-8 Plot with molar mass against time for $MEO_{8/9}Ac$ polymerization reaction with DMP as a CTA.

Depending on the required applications, it can be useful to have the possibility to tune the LCST of the thermo-responsive polymers. Especially thinking of biomedical applications, which the desired temperature turn is around 30-40°C.

Having the solubility behaviour of $PMEO_2Ac$ and $PMEO_{8/9}Ac$ in mind, a copolymer of both acrylates could show the desired thermo-responsive behaviour. Hence, copolymers containing different molar ratios of the acrylates were synthesized with DMP as CTA. All reactions were conducted at 70°C with a [M]/[CTA]/[AIBN] ratio of 50:1:0.1.

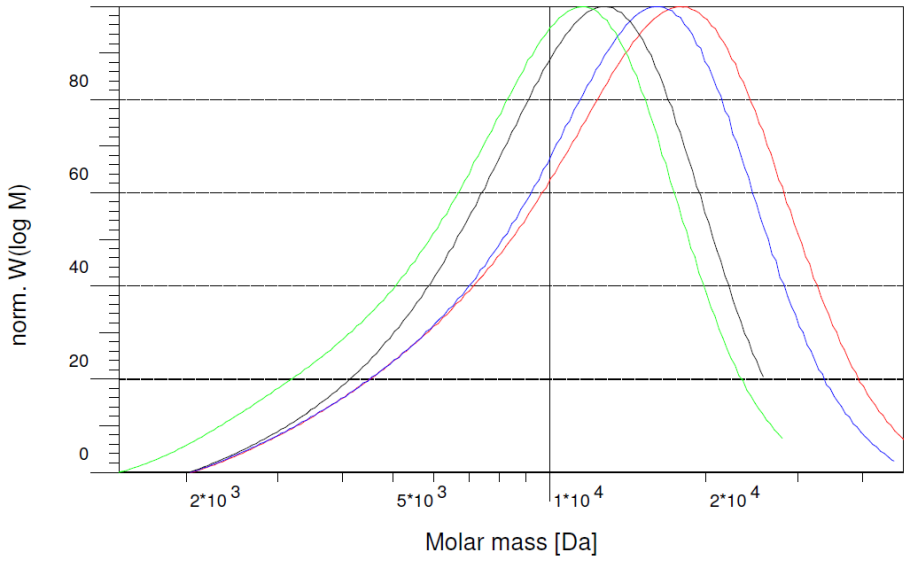
In general, only very small amounts of polymer were purified by dialysis. The molar masses obtained by GPC were not exactly the expected for the calculations. RAFT polymerization of $PMEO_2Ac$ and $PMEO_{8/9}Ac$ always provided a good control of PDIs (M_w/M_n) ≈ 1.40.

The effect of the ratio of the polymer concentration on the LCST is showed in Table 5.2-3 and Figure 5.2-9. For different concentrations of monomer, the range of LCST is changed.

Table 5.2-3 Synthetic conditions and results of thermo-responsive co-polymers P(MEO_2Ac-co-$MEO_{8/9}Ac$)[a].

MEO2AC	$OE_{8/9}GA$	Yield (%)	M_n(theoretical)[b]	M_n(GPC)[c]	M_w/M_n[c]	LCST
20	80	35	21446	11200	1.46	84-86°C
40	60	11	18529	10500	1.43	73-76°C
60	40	6	15611	8700	1.31	61-63°C
80	20	2	12693	7500	1.39	39-42°C

[a]Target DP ≈ 50, [Mono : CTA : AIBN] = 100 : 2 : 0.2, 70°C, 40h. [b]Theoretical molecular weight of homopolymers = target DP x $M_{Monomer}$ + M_{CTA}; Theoretical molecular weight of co-polymers = (target $DP_{OE8/9GA}$ x $M_{OE8/9GA}$) + (target DP_{MEO2AC} x M_{MEO2AC}) + M_{CTA}. [c] Molecular weight determined by GPC.



- P(MEO_2Ac-co-$MEO_{8/9}Ac$) 20:80
- P(MEO_2Ac-co-$MEO_{8/9}Ac$) 60:40
- P(MEO_2Ac-co-$MEO_{8/9}Ac$) 40:60
- P(MEO_2Ac-co-$MEO_{8/9}Ac$) 80:20

Figure 5.2-8 Comparison of the molecular weight distributions of copolymer samples by GPC. Refractive index (RI) was used as a detector.

Of both used monomers, $MEO_{8/9}Ac$ has a higher molecular mass, which means that the higher is the ratio of $MEO_{8/9}Ac$ in the polymer, the higher will be his molecular weight.

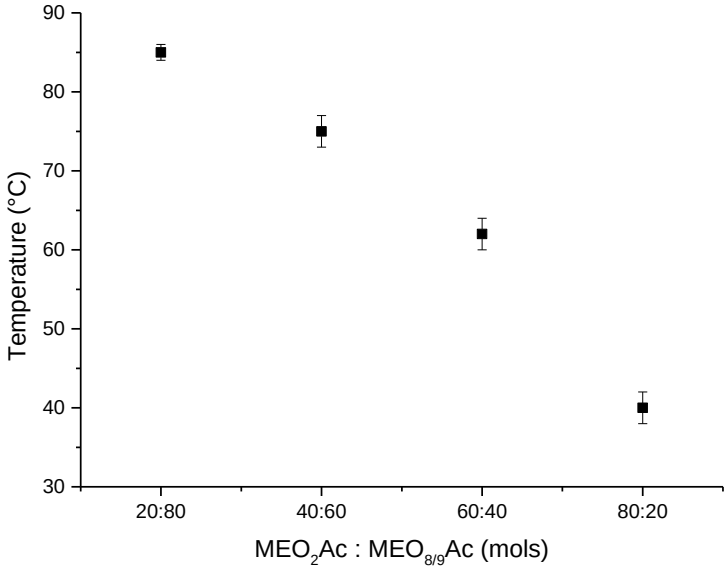


Figure 5.2-9 LCST Calibration curve of different rates of the copolymer P(MEO_2Ac-co-$MEO_{8/9}Ac$).

6 Conclusions

This work showed that the synthesized CTAs are not the proper to carry out the RAFT polymerization of MEOMA, the principal monomer which the investigation is interested in. At the beginning, this was not known and several test with the inhibitors were practised, since it was one of the assumptions to explain why the polymerization was not work.

After the test with the inhibitors, was demonstrated that they do not affect in the polymerization, concluding that either the CTAs or the monomer have to be changed.

The characterization of the CTAs was successfully done, giving good results since all of them were not impure or with subproducts of the reaction. Then, a change of the monomer was the next step, and was tested that the new kind of monomers (methacrylates) worked with the respective CTAs. Hence, the properties of the synthetized polymers was able to study.

7 References

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