α, ω End Group Functionalization of RAFT Polymers Based on Pentafluorophenyl Esters and Methane Thiosulfonates

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Contents

Abbreviations V
Introduction 1
- Views and Visions 1
- Designing Functional Polymers: A Motivation for End Group Chemistry 1
- Interests in End Group Functionalized Polymers 3
- Polymerization Techniques: From Anionic to RAFT 4
- Literature Approaches to Functional End Groups in the RAFT Process 5

References 9
Scope of this work 15
Results 17
- α End Group 17
- ω End Group 19
- Hetero-Telechelic Polymers 21
- Summary and Conclusions 24

Publications

P1 Synthesis of Reactive Telechelic Polymers Based on Pentafluorophenyl Esters 29

P2 A Method for Obtaining Defined End Groups of Polymethacrylates Prepared by the RAFT Process during Aminolysis 41

P3 Versatile ω-End Group Functionalization of RAFT Polymers Using Functional Methane Thiosulfonates 49

P4 Hetero–Telechelic Dye–Labeled Polymer for Nanoparticle Decoration 63

P5 Synthesis of Hetero-Telechelic α, ω Bio-Functionalized Polymers 71

P6 Synthesis of Hetero-Telechelic α, ω Dye Functionalized Polymer by the RAFT Process and Energy Transfer between the End Groups 81

List of Publications 95
Acknowledgement 97

Abbreviations

AIBN	azobisisobutyronitrile
ATRP	atom transfer radical polymerization
AuNP	gold nanoparticle
CTA	chain transfer agent
DEGMA	diethylene glycol (monomethyl ether) methacrylate
DMF	dimethylformamide
DTE	dithioester
FRET	fluorescence (Förster) resonance energy transfer
GPC	gel permeation chromatography
HSQC	hetero-nuclear single-quantum coherence
IR	infrared
LCST	lower critical solution temperature
LMA	lauryl methacrylate
MMA	methyl methacrylate
MTS	methane thiosulfonate
NBD	7-nitro-2,1,3-benzoxadiazole
NIPA(m)	*N*-isopropyl acrylamide
NIPMA(m)	*N*-isopropyl methacrylamide
NMP	nitroxide mediated polymerization
NMR	nuclear magnetic resonance
NP	nanoparticle
OG	Oregon Green
PBS	phosphate buffered saline
PEG	poly(ethylene oxide)
PFP	pentafluorophenyl
QD	quantum dot (semiconductor NP)
RAFT	reversible addition-fragmentation chain transfer
S	styrene
SAM	self-assembled monolayer
SPR	surface plasmon resonance
T4	thyroxin
TCSPC	time correlated single photon counting
THF	tetrahydrofuran
TLC	thin layer chromatography
TR	Texas Red
TTC	trithiocarbonate
UV-vis	ultra-violet and visible (light)

Introduction

Views and Visions

A one-word summary of the achievements of chemistry in the twentieth century could be: polymers. An everyday life has become unthinkable without synthetic commodity polymers such as polyethylene, polypropylene, nylon or polystyrene, or commonly, "plastics". The ease of producing materials with tunable mechanic properties explains the broad spreading of polymeric materials throughout construction engineering, packaging industry, transportation including space travel, and many other fields of technology.

While the fundamental research on many customary plastic products has already passed its zenith, nine years into the twenty-first century, functional polymers are conquering research fields on alternative energy or biotechnology and pharmacy. Semiconducting polymers are being explored for the construction of efficient solar panels and light emitting displays. Polymer pharmaceutics are drugs bound to a polymer that is intended to selectively find diseased cells. Many of the modern applications and aims rely on improved synthetic techniques to produce functionalized polymers that can create interfaces between organic materials and inorganic or biological components, thus enabling the combination of the advantages from each part of science.

Looking ahead, enthusiastic researchers draw visions of solar cells printed onto textiles and of hope to cure cancer based on polymers carrying functional groups and hybrid systems including functionalized polymers. With a global energy crisis approaching and the perpetual threat of new lethal diseases, pursuing such objectives seems to be the right thing to do.

The possibility to investigate novel functional polymers, however, relies on synthetic methods to construct such materials. Accordingly, there is a need to explore novel synthetic techniques leading to well-defined functional polymers easier, more accurate and with a broader range of possibilities than before. It arises the question of how and where to best install functional groups into a polymer; of a polymerization procedure and a polymer architecture.

Designing Functional Polymers: A Motivation for End Group Chemistry

Concerning the architectural design of a functional linear polymer chain, there are two principal possibilities: (1) functional groups incorporated into monomeric units and thus located along the polymer backbone or (2) functional groups specifically positioned at the two end groups of a polymer chain.

1. Groups statistically distributed along the polymer backbone

The first approach has extensively been investigated. Activated esters, such as pentafluorophenyl (PFP) esters[1] proved to be very successful candidates for reactive polymers and are easily accessible through monomers such as PFP-acrylate, PFP-methacrylate[2] or PFP-vinyl benzoate.[3] They react with primary and secondary amines under very mild conditions to form the respective amides. In many cases, it is not de-

sired to convert every monomeric unit with the same functional amine (often, a direct polymerization of the respective amide monomer could be easier), but to statistically convert the activated units with different amines. The purposes of groups thus inserted can be to provide solubility, to act as anchor groups for inorganic nanoparticles[4,5] such as quantum dots,[6-14] to target biological materials or to bear fluorescent dyes[6,7] or pharmaceutically active drugs.[15-17] Some of these groups are most efficient if present only in very low concentrations, such as fluorescent dyes, running the risk of quenching effects.

Incorporating multiple functionalities along a polymer backbone has however several drawbacks. If different groups, such as amines, to be installed into the polymer show different reactivities toward the reactive polymer, it becomes difficult to control the exact percentage of incorporation of each group. Even if different reactivities can be ruled out or compensated, the incorporation of functional groups is statistical and the exact amount especially of diluted functionalities per polymer chain is subject to strong variations. The intramolecular distance between two functional groups is ill-defined. If there is an effect of neighboring groups during the conversion of the reactive polymer, domains differing in local composition are formed and the statistical estimations about concentration or average distances between functional groups fail. Additionally, the physical properties, such as solubility, extent of swelling, conditions causing chain collapses and insolubility, relations between molecular weight and size, or glass transition temperature are ill-defined for polymers consisting of different statistically distributed side residues.

2. Functionalization of both End Groups

The second approach, functionalization of the end groups of a polymer and especially the incorporation of two different functionalities onto the α and the ω end groups, poses a more considerable synthetic challenge and is less examined. However, there are distinct advantages compared to the statistical incorporation of functional groups.

Through end group functionalization, defined 1:1 attachments of a polymer and another molecule can be realized. As a (linear) polymer chain has exactly two end groups, quantitative conversion of each yields a very defined number of functionalities per chain. The average distance between two functional end groups is defined through the end-to-end distance of the polymer chain. This can either be determined through light scattering experiments or can be estimated from tabulated relations between size and molecular weight. The polymer chain itself is not modified by the end group manipulation and thus retains its solubility behavior and its physical properties. This may be exploited to externally control the end-to-end distance through solvent and / or temperature and thus to control the average distance between the two functional groups. Generally, α, ω hetero-telechelic polymers can be applied to build up ABC structures, where A and C are arbitrary groups and B is a polymer chain that mediates solubility and has a defined end-to-end distance, which depends on external parameters.

Because of these advantages, there is not only an academic interest in finding improved methods for an independent α, ω functionalization, but there are also application interests and research possibilities connected to α, ω functionalized polymers.

Interests in End Group Functionalized Polymers

Defined 1:1 assemblies are especially important in biotechnology, where conjugates consisting of exactly one peptide and one polymer are desired in order to improve activity and stability of proteins[18,19] or to create stimulus responsive polymer-protein conjugates.[20-26]
Hetero-telechelic polymers may be applied for the synthesis of di- or multiblock copolymers or as cross-linkers for polymer networks.[27]

Polymers with one functional end group are used for synthesizing polymer brushes on surfaces by a grafting-to technique.[28-35] Stimulus responsive polymeric surfaces are of great interest for applications in microfluidics.[36] If also the opposite end group bears a functionality, this group is tethered to the surface, while having a defined distance and maximum mobility. For analytical biochemistry, planar gold surfaces are of interest, enabling the detection of proteins and other analytes through surface plasmon resonance (SPR). A hetero-telechelic polymer could be interesting for bio-functionalization where a targeting group could be present in a small concentration on a surface that prevents non-specific binding of an analyte protein. For biosensors and chip-based bioassays, often multilayers of biological components are constructed, requiring building blocks with two specific binding sites.[40-43] It would be of considerable interest to include telechelic synthetic polymers in these constructions, exploiting the advantages of polymers, such as flexible functionalization or stimulus responsive behavior.

Energy Transfer between the End Groups

Apart from planar gold surfaces, also the modification of metal or semiconductor nanoparticle (NP) surfaces is of interest. Polymers are promising materials, as hybrid materials combining the solubility, processability and functionality of the polymeric shells and the unique optical and electrical properties inherent to the NP can be obtained.[12-13] Semiconductor NP (QD) are used as bio-labels[13,44,45] and as energy donors in biological[46-48] and optoelectronic[49-51] research. Gold nanoparticles (AuNP) have an intense plasmon oscillation, that can accept fluorescence excitation energy through quenching.[52-54] As the energy transfer efficiency is highly dependent on the distance between NP and chromophore,[53,55] there is a high scientific interest in fine-tuning this distance.[55-60] A straightforward polymer architecture would be a hetero-telechelic polymer with an anchor group at one end and a fluorescent dye at the other.

Because of the high distance dependence of the FRET efficiency, FRET is a very useful tool for the investigation of molecular arrangements and processes on a nanometer scale.[61-66] It can be quantified by several techniques such as time-resolved fluorescence measurements.[67-69] Many mathematical models and simulations on the evaluation of such spectroscopic data for various theoretic setups have been presented.[70-74] The huge potential of FRET to investigate molecular architectures on a nanometer scale thus relies on the synthetic success of placing fluorescent dyes precisely at strategic locations of molecules. If a polymer chain is equipped with two fluorescent dyes capable of FRET, invaluable information on end-to-end distance[67,75-84] and especially the behavior of isolated polymer chains during a lower critical solution temperature (LCST) transition could become accessible.

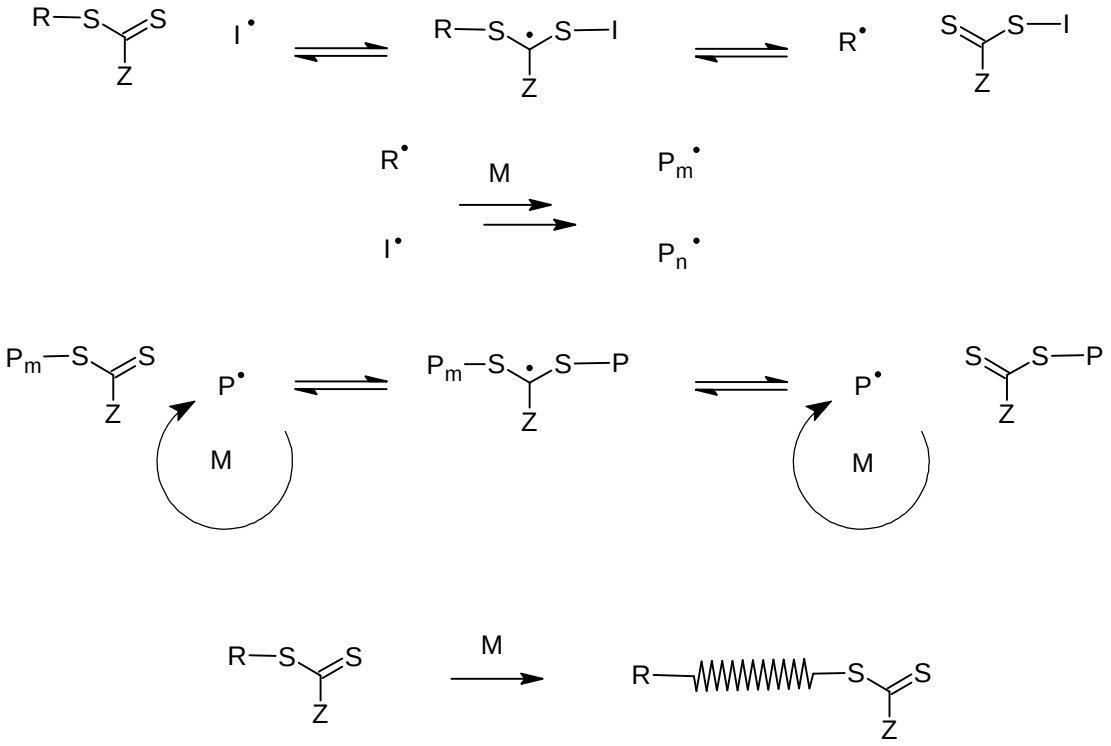
In order to obtain well-defined hetero-telechelic polymers, promising synthetic techniques need to be explored and, if necessary, extended.

Polymerization Techniques: From Anionic to RAFT

For several decades, anionic polymerization was the most successful method for preparing hetero-telechelic (vinyl based) polymers.[85-87] The synthesis involved a functionalized anion for initialization and the addition of an adequately modified electrophile for termination. As long as no terminating agent is added, the terminal anion stays intact ("lives") and allows for the formation of diblock copolymers through addition of a second monomer as soon as the first has been completely consumed. Anionic polymerization is thus also termed living polymerization. However, due to the high reactivity of carbon anions, anionic polymerizations are very intolerant toward functional groups and require an absolute absence of protic solvents. Many functional end groups, including many fluorescent dyes or groups with biological uses are thus not applicable.
The end of the twentieth century saw the beginning and steady rise of controlled radical polymerization. Most prominent are atom transfer radical polymerization (ATRP),[88,89] nitroxide mediated polymerization (NMP)[90] and reversible addition fragmentation chain transfer (RAFT) polymerization.[91] Compared to a free radical polymerization, termination processes such as recombination or disproportionation of two radicals are artificially suppressed. In ATRP and NMP, equilibria between a dormant and an active (radical) species reduce the concentration of radicals. In RAFT, radicals are passed on and shared between chain transfer agents. Whereas in a free radical polymerization each radical initiator gets the chance of initiating a polymer chain, in RAFT, the propagation mechanism is initiated and controlled by the chain transfer agents. As in all three methods the propagating species are radicals, less restrictions apply to the polymerization conditions and a broader range of reactions becomes available for the functionalization of polymers – including the end groups.

The success of RAFT polymerization in many different fields can be followed in several reviews.[92-104] It is probably the most promising technique for the preparation of hetero-telechelic polymers.[105-106] Chain transfer agents (CTAs) mediating the RAFT process are usually dithioesters or trithiocarbonates with two functional groups, although also carbon based CTAs have been described. In the following, the mechanism is briefly described for a dithioester CTA. According to the denotation of Chiefari et al.,[91] the two functional groups are termed leaving group *R* and activating group *Z* and fulfill specific purposes. The same steps apply to a trithiocarbonate (or xanthate); here, the first atom of the group decoded with *Z* would be a sulfur (or oxygen).

The RAFT mechanism[107-110] starts with a fragment of a radical initiator, such as a cyano-propyl-radical originating from AIBN, attacking the dithioester. The *Z* group has the purpose to stabilize the resulting carbon-based radical and encourage its formation through addition of the initiator fragment. The *R* group is chosen to stabilize an *R*-based radical and is often designed to resemble the monomers intended for polymerization. The following fragmentation is thus directed into expelling the *R* group, which starts the polymerization. The terminal radical of the propagating chain may then add onto another dithioester moiety, setting free its *R* group (or an already formed polymer chain) in turn, thus transferring the radical.
In summary, the polymer chain is inserted between the *R* group and the dithioester (DTE), resulting in the structure *R*(α)–polymer–DTE–*Z*(ω). The RAFT process thus has a great potential in producing hetero-telechelic polymers. The trick is to employ suitable *R* and *Z* groups which enable installing the desired end groups either before or after polymerization, but which do not influence the polymerization mechanism.



The RAFT mechanism.[107-110] *Initiation, propagation, and equlibria providing chain transfer. I: initiator fragment, e.g. cyanopropyl radical; M: monomer; P: polymer chains. The bottom schematics show the overall reaction providing polymers with defined R and dithioester-Z end groups.*

Literature Approaches to Functional End Groups in the RAFT Process

In this chapter, methods to modify either the *R* or the *Z* group of chain transfer agents are discussed separately. Generally, a combination of two suitable methods may be employed to create a hetero-telechelic polymer.

1. Modification of the *R* /α Group

In RAFT, propagating chains are initiated by the *R* fragments and are thus covalently linked to the *R* groups by a C-C bond. The modification of a CTA to include a functional or reactive *R* group is thus a very common and expedient way to introduce a certain α end group.

Among others, CTAs with dye,[111,112] dopamine,[113] PEG,[114] poly ethylene,[115] terpyridine,[116] bipyridine,[117] poly(methyl silsesquioxane),[118] galactose,[119] biotin,[120,121] pegylated lysine[122] or C18 alkyl chain[123] *R* groups have been designed and employed for polymerization. Reactive *N*-hydroxysuccinimide (NHS) ester,[119] acid,[124] azide,[26,125-128] alkynyl[126,129-131] or (protected) amine[105] α end groups have allowed polymer modifications through post-polymerization reactions.

2. Modification of the *Z* /ω Group

The Z group is not directly attached to the polymer chain, but linked to it via the dithioester or trithiocarbonate. The modification of the *Z*/ω group is more challenging compared to the *R*/α group. Synthetic attempts toward hetero-telechelic α, ω functionalized polymers thus rely on a powerful method for ω functionalization in the first place and a compatible method for the α end group.

The synthesis of CTAs with a modified *Z* group as prospective reactive or functional ω end group can be complex and is not very common. Alternatively, several methods to replace the dithioester or trithiocarbonate with a functionality are in use.

2.1 *Z*-Group Functionalization

CTAs with C18 alkyl chain,[123,132] azide,[133] fluorescent dye,[134] triphenylamine[135] or pyridyl disulfide[23,128,136,137] *Z*-groups have been published.

Bulmus and Davis have elegantly exploited the RAFT mechanism to produce α, ω hetero-telechelic polymers with two orthogonally reactive end groups (azide and pyridyl disulfide).[128] Pyridyl disulfides[138] (along with alkyl thiosulfates (Bunte salts)[139] and alkyl methanethiosulfonates (MTS))[140-142] are reagents with an electrophilic sulfur atom which undergo very selective exchange reactions with free thiols yielding unsymmetrical disulfides. Disulfides are very stable toward air, water and other nucleophiles. They may be biologically or chemically reduced, making polymers containing molecules attached via disulfide bond possible candidates for drug delivery.[143]

A major drawback of functionalizing the *Z* group, however, is, that the dithioester or trithiocarbonate link between the ω end group and the polymer chain is not very stable. Both groups are easily decomposed in contact with radicals,[144] heat or nucleophiles,[105,145] including water at elevated pH.[146] The group of Barner-Kowollik has recently shown that even storage in cyclic ethers such as THF can cause dithioester decomposition through peroxide oxidation.[147] Additionally, it may be disadvantageous to locate a fluorescent dye beyond a dithioester or trithiocarbonate, because these groups are also chromophores and may interfere with dyes through quenching or exciplex formation.[148,149]

2.2 Removing the dithioester(DTE) / trithiocarbonate (TTC)

Several methods, such as thermolysis or reduction with stannanes,[105,145] to eliminate the terminal RAFT-agent have been put forward. As these methods completely remove any functionality from the ω terminus, they do not play any role for the creation of α, ω hetero-telechelic polymers and are only mentioned for completeness.

2.3 Replacing the DTE / TTC

2.3.1 Addition of Thiol onto Unsaturated Bond after Aminolysis

A different strategy towards ω-functionalized polymers is to make use of a terminal thiol which may be released from polystyrene derivatives and poly[(meth)acrylamides] prepared by the RAFT process by aminolysis.[27,150-155] Thiol terminated polymers have not only found extensive use in producing self-assembled monolayers on metal surfaces, such as gold nanoparticles,[150-152] but they are also widely used for end group conjugation.[27,153-155] Very popular is the reaction of the terminal SH group with maleimides[27,153,155-157] or acrylates[153] via Michael addition or with iodoalkanes[157-158] through nucleophilic substitution. Using this approach, poly(*N*-isopropylacrylamide) (PNIPA) with pyrene,[155,157,158] hydroxyl[153,157] or maleimide[27] end groups or poly(methyl methacrylate) (PMMA) with hydroxyl end groups[156]

have been synthesized. However, releasing a thiol by aminolysis and subsequent conjugation has several drawbacks:
(i) Maleimides do not exhibit a very strong selectivity towards thiols but also undergo Michael addition of amines.[159] Thus, a two-step reaction is often employed; first, a polymer with terminal SH groups is prepared by aminolysis. After purification from the excess of amine, a functional maleimide can be added in a second step.[155]
(ii) The terminal thiols are prone to oxidation by oxygen. The resulting polymer-polymer disulfides do not undergo conjugation reactions, which makes it mandatory to work under inert atmosphere or add reducing agents to prevent disulfide formation.
(iii) Quantitative synthesis and purification of terminal thiols fails for poly[(meth)acrylates] because the initially formed SH group backbites into the penultimate monomer unit resulting in a thiolactone,[160] thus maleimide conjugation is not quantitative[156] or even impossible with poly[(meth)acrylates].

2.3.2 Reaction with an Excess of Diazo-Initiator

Perrier et al.[144] presented a versatile method to recycle the chain transfer agent by reacting polymers obtained from a RAFT polymerization with an excess of AIBN or different diazo-initiators. Thereby, radicals cleave the bond between the ultimate repeating unit and the sulfur atom and saturate both emerging radicals with the radical fragments from the initiator. This method also allows the introduction of functional groups, which previously need to be installed into the diazo derivative. Such groups need to be stable toward elevated temperature and radicals.
It may however occur that double molecular weight products (supposably through radical-radical addition of two polymer chains) are formed.[161] Although the complete removal of terminal dithioester is apparent through the loss of the typical absorbance from the polymer, some authors[121,144] do not address the end group conversion, i.e. the percentage of incorporation of the new end group. Recently, problems to obtain functionalized end groups with certain polymers by the use of diazo compounds have been reported.[145,162]
The Maynard group has utilized a diazo-initiator carrying a protected maleimide to replace the trithiocarbonate end group with a bio-reactive functionality.[121,163] In combination with a biotin-functionalized *R* group, hetero-telechelic bio-functionalized polymers could be obtained. The deprotection step of the maleimide via retro Diels-Alder reaction however required harsh conditions that caused cleavages of ester bonds.[121] Poly[(meth)acrylates], such as poly[ethylene glycol methacrylates] are thus not eligible for this approach.

2.4 Diels–Alder Addition of Dienes onto DTE

The groups of Barner-Kowollik and Stenzel have recently presented the addition of dienes onto the thiocarbonyl double bond of diethoxyphosphoryldithioformate and pyridin-2-yldithioformate end groups of polystyrene via a hetero-Diels-Alder reaction. The reaction yielded dithioketal cyclohexenes in very high yields and also allowed the formation of 2-, 3- and 4-arm stars.[163-170]

3. Summary

Incorporation of functional or reactive groups, which do not interfere during polymerization, into the *R* group of a CTA is a common and expedient method for modification of the α end group.
A modified Z group may be retained as ω end group, but will be connected to the polymer chain via a very labile link. Terminal thiols, which may be released by aminolysis, undergo side reaction on poly[(meth)acrylates], circumventing a reaction with a maleimide or similar reagent. Side products may also be formed during exchange of the terminal RAFT agent with a modified diazo-compound. End groups installed by this method need to survive heat and radicals and may need harsh conditions for deprotection, thus excluding poly[(meth)acrylates] from eligible polymers.

In order to find a versatile synthetic access to stable, highly functionalized hetero-telechelic polymers including poly[(meth)acrylates], there is the need of developing improved methods for the modification of terminal dithioesters.

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Scope of this work

The scope of this dissertation is to investigate suitable methods to synthesize α, ω hetero-telechelic polymers by the RAFT process. Contrary to methods discussed in the introduction, a versatile concept that is applicable for poly[(meth)acrylates] is intended. Methods should thus be probed on various methacrylates, for instance the stimulus responsive poly[diethylene glycol monomethyl ether methacrylate], but also on polystyrene and poly[*N*-isopropyl acrylamide]. Generally, methods enabling very high end group conversions and ideally no side-products (such as double molecular weight polymers) should be found and optimized. The concept should especially allow the use of fluorescent dyes with high brightnesses and photostabilities, thus exclude approaches in which the dithioester or trithiocarbonate stays intact and possibly interferes with the terminal chromophores by quenching. As fluorescent dyes may only be available in very small quantities, reactions and purifications on a micro-scale need to be applicable.

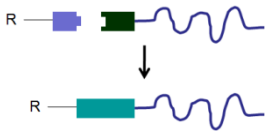
End groups capable of coordinating to metal and semiconductor surfaces need to be investigated in order to allow nanoparticle decoration. Defined hetero-telechelic polymers carrying a dye and a suitable anchor group should then allow to space fluorescent dyes at a defined distance from nanoparticles, to be investigated spectroscopically.

Especially the possibility to prepare α, ω hetero-telechelic dye-labeled polymers, which have up to now not been synthesized by a controlled radical polymerization technique, is of interest. A goal is to bring about fluorescence resonance energy transfer (FRET) between the end groups of single polymer chains and thus to establish access to spectroscopic methods to study polymer conformation.

A successful concept may then also be extended to further end groups, e.g. with biological uses or such providing additional means of modifying the end groups.

Results

α End Group



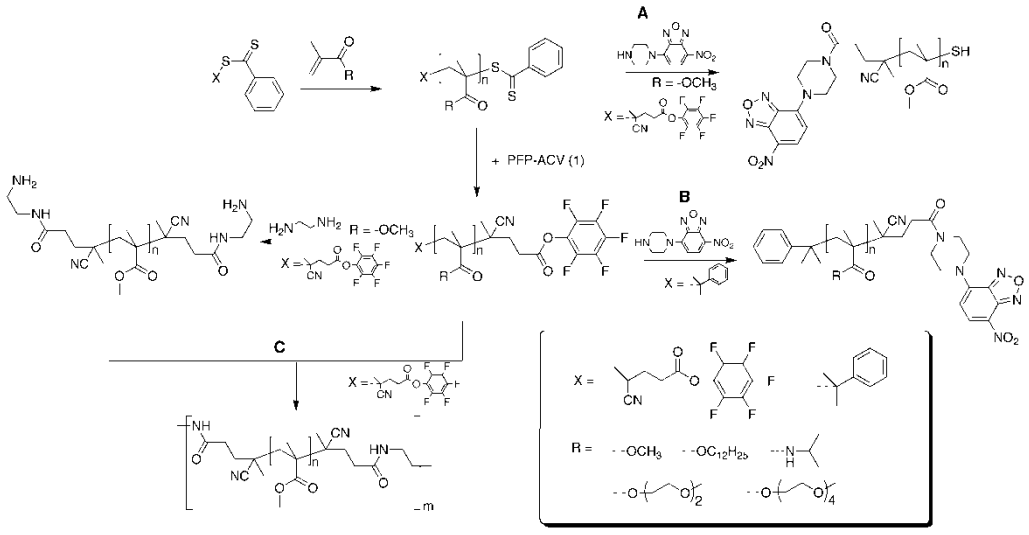
Activated Ester α End Groups

Pentafluorophenyl esters had previously been shown to be stable during a RAFT polymerization, to be highly reactive toward primary and secondary amines and to have the advantage of simple analysis through ^{19}F NMR measurements. Here, a CTA containing a PFP activated ester at the *R* group was synthesized. Accordingly, polymers with a PFP α end group could be obtained. Various methacrylate monomers were polymerized with very high conversions, low polydispersity indices and with good control over the molecular weight. In addition, various diblock copolymers were synthesized. To avoid side reactions by aminolysis, the ω-terminal dithioesters were removed through reaction with an excess of AIBN, leaving the α-terminal PFP ester intact. The PFP esters could then be reacted with the dye NBD carrying a secondary amine in over 80% yields, confirming the presence and high reactivity of the PFP α end group. α-PFP esters thus proved to be a very advantages means of introducing functionalities into polymer chains.

Further synthesis:

The synthesis of the PFP-CTA afforded a PFP modified diazo compound as an intermediate product, which was also employed to replace the ω dithioesters. Accordingly, (homo-) telechelic polymers with activated PFP esters at both end groups were obtained and used for the preparation of multi-block copolymers.

P1: Roth, P. J.; Wiss, K. T.; Zentel, R.; Theato, P. *Macromolecules*, **2008**, *41*, 8513–8519



Look-Out

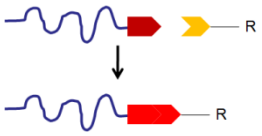
In a related project, stimulus responsive poly[diethylene glycol methacryate] (PDEGMA) derived from the PFP-CTA was used for the conjugation with the two amine-functionalized chain ends of a collagen-like peptide, resulting in a polymer-*b*-collagen-*b*-polymer triblock, which was used to study temperature dependent self-assembly.

Wiss, K. T.; Ohm, D. K.; Roth, P. J.; Kiick, K. L.; Theato, P. *Macromolecules* **2009**, **DOI:** 10.1021/ma900417n

In a different cooperation, homo-telechelic poly[ethylene glycol methacrylates] prepared from the PFP-CTA and the PFP modified diazo compound were functionalized with azobenzene end groups. This provided the possibility to influence the LCST of the polymer chains through isomerization of the end groups by irradiation.

Jochum, F. D.; Roth, P. J.; Theato, P. *Macromolecules* **2009**, *submitted*

ω End Group



1. Defined ω End Group on Poly[methacrylates] for Attachment to Gold Surfaces

As discussed in the introductory part, a substantial problem during the isolation of terminal thiols, (e.g. for subsequent maleimide conjugation) is that on PMMA and other poly[(meth)acrylates], side reactions such as backbiting occur. For polystyrene and poly[*N*-isopropylacrylamide] on the other hand, the successful preparation of terminal thiols has enabled self-assembled monolayers (SAMs) on planar gold and also the encapsulation of AuNPs.

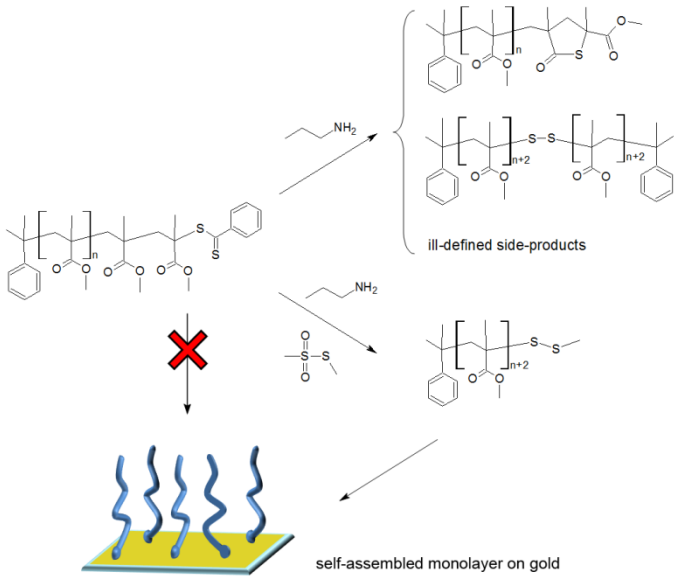
The cardinal idea developed here was to introduce a highly thiol reactive species during aminolysis that would not undergo considerable side reactions with the amines. Instead, an efficient scavenging of the *in situ* formed thiols was intended to prevent any formation of side products. As reagent, methyl methane thiosulfonate (methyl MTS) was investigated. It may easily be attacked by thiols, expelling methane sulfinic acid and forming a methyl disulfide. Amines increase the hydrolysis with water but do not harm the MTS reagent.

Accordingly, aminolysis of PMMA-DTE in the presence of 20 equiv. of methyl-MTS gave terminal methyl disulfides in quantitative yields. Side products were not detected. As was expected from an (unsymmetrical) disulfide, SSMe-terminated PMMA and PDEGMA formed stable SAMs on planar gold surfaces and could stabilized AuNP during synthesis in a two-phase system. A terminal methyl disulfide group is thus an alternative to a terminal thiol, especially in cases when the latter causes difficulties to obtain.

P2: Roth, P. J.; Kessler, D.; Zentel, R.; Theato, P. *Macromolecules* **2008**, *41*, 8316-8319
Method for AuNP synthesis:
Roth, P. J.; Theato, P. *Chem. Mater* **2008**, *20*,1614-1621

Look-Out

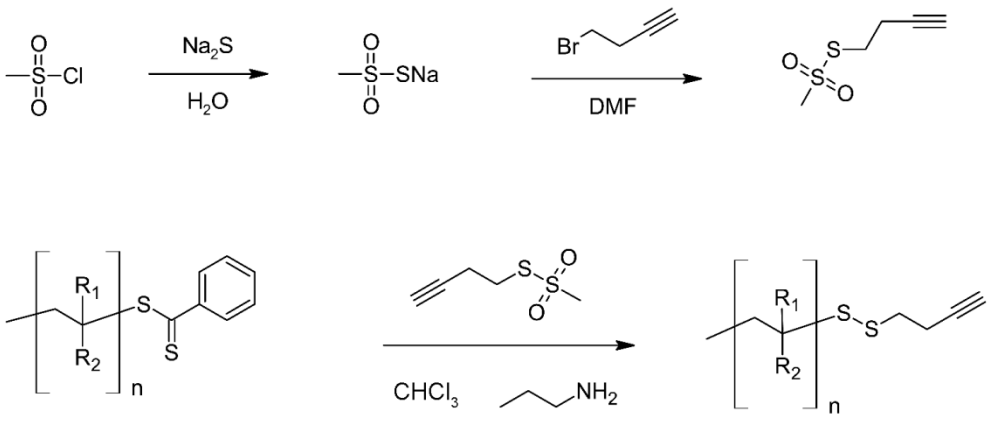
The experiments on attachment of terminal methyl disulfides onto metal surfaces laid the groundwork for the later on decoration of nanoparticles with dye-labeled polymers.



2. Variable ω End Group Functionalization

As described above, aminolysis of a terminal PMMA-dithioester in the presence of methyl-MTS produced terminal methyl disulfides. Next, this synthetic concept was extended to introduce functional end groups onto various polymers. As exemplary reagent, an acetylene functionalized MTS reagent was synthesized in two steps. Three poly[methacrylates] PMMA, PLMA, and PDEGMA, and PNIPA and PS with ω dithioesters, but with different α end groups, were subjected to butynyl-MTS / n-propyl amine. Reactions were performed at room temperature and without inert atmosphere. The acetylene group served the purpose of easy analysis through NMR spectroscopy. ^{1}H and ^{1}H /^{13}C HSQC spectra confirmed the quantitative installation of the butynyl end group into the polymers. Double molecular weight side products were not observed with any polymer.

The MTS method thus presents a powerful alternative to introduce ω functionalities onto RAFT polymers under very mild conditions with quantitative yields. The method is likewise successful for poly[methacrylates], polystyrene and poly[acrylamides], and is independent of the *R* group of the CTA the polymer was derived from. Functional MTS reagents can easily be obtained starting from functional alkyl bromides.



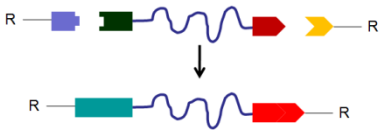
Further chemistry

The terminal functionalities are connected to the polymer chain via disulfide bonds. This connection is very stable in the absence of radicals or reducing agents, but may be selectively cleaved upon demand. To demonstrate this, the acetylene-terminated polymers were attached onto an azide functionalized glass surface via "click" chemistry (2+3 dipolar Huisgen cycloaddition of azide to acetylene). The covalent attachment of the polymers could be seen from the water contact angles of the surfaces, which assumed values typical of the attached polymers. After immersing the glass slides into a solution of dithiothreitol (a selective reducing agent for disulfides), all glass slides exhibited the same contact angle, independent of the polymer prior attached to it, suggesting a complete removal of the polymer brush.

Generally, this approach creates the possibility, to attach a functional onto an end group via click chemistry and to remove it by a complementary reduction. Two of the polymers employed, PNIPA and PDEGMA, have an LCST in water. Accordingly, water contact angles increased significantly above LCST, showing that the polymer brush could (reversibly) be collapsed on the surface through an external stimulus.

P3: Roth, P. J.; Kessler, D.; Zentel, R.; Theato, P. *J. Pol. Sci. A*, **2009**, *47*, 3118-3130

α, ω Hetero-Telechelic Polymers



1. Dye-Labeled Polymers for Decoration of AuNP and QD

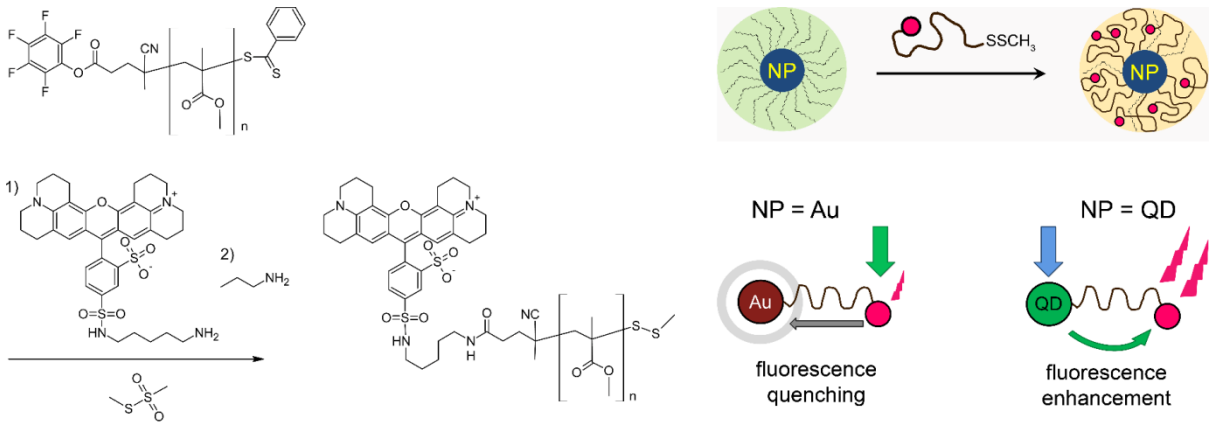
With concepts established for each end group, the route to hetero-telechelic polymers was the combination of α PFP esters and functional MTS reagents for ω disulfide formation.

Accordingly, a one-pot reaction was conducted to convert PFP-PMMA-DTE into TR-PMMA-SSMe using Texas Red (TR) cadaverine and methyl-MTS. For this reaction, the MTS reagent and TR cadaverine were added first and allowed to react. PFP esters are highly reactive toward amines and usually react to completion with 1 equivalent within about 20 minutes. DTE on the other hand usually require an excess of amines and several hours to react completely. It was thus assumed, that TR cadaverine would attach to the α PFP ester, instead of being wasted to aminolyze the DTE. For the latter reaction, n-propyl amine was injected into the reaction after 16 hours. The analysis of the product polymer indicated that the assumption was correct. The polymer was highly colored indicating a successful reaction at the α end group. In contrast to a polymer with DTE end group, the product formed a SAM on planar gold in an SPR experiment, indicating that also the installation of ω methyl disulfide had been successful.

Nanoparticle Functionalization

As discussed in the introduction, AuNP can act as energy acceptors and thus quench the fluorescence of nearby chromophores. Quantum Dots, on the other side, are often employed as energy donors in biological and optoelectronic research. Here, TR-PMMA-SSMe was used to replace native ligands on the NP surfaces with the SSMe end group and thus space the dye from the NP according to the length of the polymer. QD with easy replaceable oleic acid ligands as prepared by the group of Prof. Char (SNU, Korea) were used. To facilitate ligand exchange on AuNP, oleyl amine ligands were chosen over thiol ligands in the synthesis of AuNP. The NP-PMMA-TR hybrids were soluble in DMF, contrary to the oleyl-stabilized NP, thus indicating a successful surface modification. No aggregates were found for AuNP or QD after polymer encapsulation. As expected, the fluorescence of TR tethered to AuNP was quenched and the fluorescence of TR tethered to QD was enhanced. The distance of dyes to QD was estimated from the energy transfer efficiency and was in good agreement with the end-to-end distance of the polymer calculated from the molecular weight. Compared to polymers with statistically distributed dyes and anchors, the hetero-telechelic geometry thus allowed a defined attachment of dyes onto NP.

P4: Roth, P. J.; Kim, K.-S.; Bae, S. H.; Sohn, B.-H.; Theato, P.; Zentel, R. *Macromol. Rapid. Commun.* **2009**
DOI: 10.1002/marc.200900254



2. α, ω Bio-Target-Labeled Polymers for Conjugation of Two Different Proteins

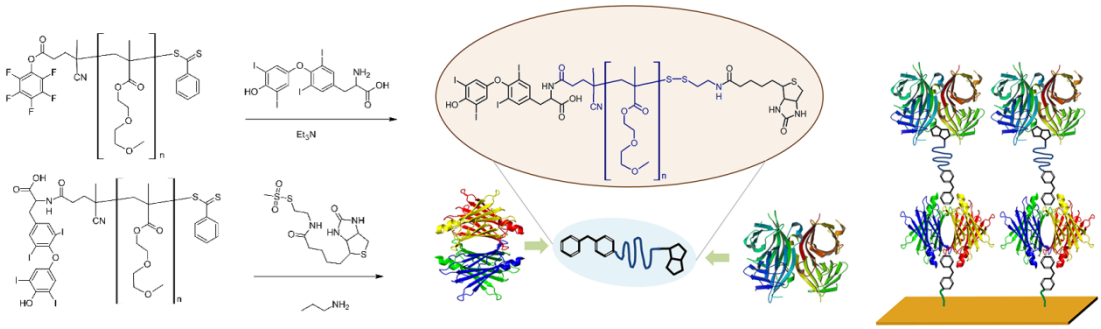
In this project, α PFP esters were combined with an aminolysis of the ω DTE in the presence of a functionalized MTS reagent. The reaction was carried out in two steps. Analysis of the intermediate product confirmed that PFP esters may completely be converted in the presence of DTE which are not aminolyzed. The retained DTE were then converted into disulfides in the next step. Thus, the use of α PFP esters and ω MTS chemistry creates a novel pathway toward polymers with two functionalized end groups. The high reactivity and selectivity of each chemistry also allows complex molecules to be introduced as end groups:

As MTS reagent, *N*-biotinylaminoethyl methanethiosulfonate was used. Biotin specifically targets streptavidin. As amine, the thyroid hormone thyroxin (T4) was used. Thyroxin has an amine group and is recognized and bound by its transport protein transthyretin; also if the amino group has been modified. The polymer was the methacrylate PDEGMA, which is soluble in water at room temperature. Very high end group conversions were obtained. Double molecular weight materials or other side products were not found.

Protein Conjugation

T4-PDEGMA-Biotin was next used for protein conjugation. First, buffered solutions of streptavidin, transthyretin and the polymer were mixed. As streptavidin has four binding sites for biotin and transthyretin has two binding sites for thyroxin, a micro gel was formed, as monitored by light scattering. Tissue engineering makes use of such protein / polymer networks. As discussed in the introduction, polymeric adapters for connecting two different proteins are also interesting for subsequent protein immobilizations on surfaces. Accordingly, a disulfide carrying T4 moieties was designed and self-assembled on a planar gold surface. Next, buffered solutions of transthyretin, then T4-PDEGMA-Biotin, then streptavidin were brought in contact with the gold surface. SPR measurements showed the subsequent immobilization and the successful binding of the polymeric end groups to the proteins. If the polymer was omitted, no attachment of streptavidin onto the transthyretin-covered surface occurred.

P5: Roth, P. J.; Jochum, F. D.; Zentel, R.; Theato, P. *Biomacromolecules* **2009**, *in preparation*



Look-Out

The specific binding of transthyretin onto the T4 labeled disulfide was used as a reference during the specific immobilization of proteins onto reactive surface coatings based on polysilsesquioxanes.

Kessler, D.; Roth, P. J.; Theato, P. *Langmuir* **2009**, **DOI:** 10.1021/la901878h

3. α, ω Dye -Labeled Polymers and Energy Transfer Between the End Groups

With α PFP esters and ω MTS chemistry successfully applied to produce a hetero-telechelic poly[methacrylate] with very high end group conversions, these methods were next used to equip a low molecular weight PDEGMA with two fluorescent dye end groups in order to enable energy transfer. As energy donor, Oregon Green was used, which was purchased with a primary amine. As energy acceptor, Texas Red-2-sulfonamidoethyl methanethiosulfonate (TR-MTS) was used. The synthesis of the hetero-telechelic polymer proceeded in two steps, affording a donor-only labeled intermediate product. As a reference, also an acceptor-only labeled polymer was synthesized, this time in a one-step synthesis, where n-propyl amine replaced the α PFP ester and set free the ω thiol, which then attacked TR-MTS. For work-up, thin layer chromatography was used, which could successfully separate free dyes and dye-labeled polymers on a microgram scale.

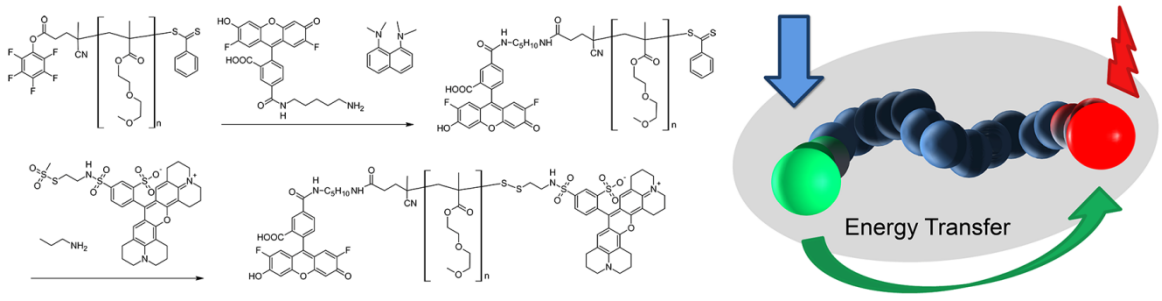
The end group conversions were lower than was expected from the previous projects, probably due to steric hindrance and solubility issues of the dye reagents. Still, the mild conjugations methods allowed the use of high-performance dyes and afforded the desired donor / acceptor end group labeled polymer.

Spectroscopy

Fluorescence spectroscopy confirmed the presence of both dye end groups on polymer chains. A comparison of the donor / acceptor labeled polymer with the two one-dye-only references suggested, that energy transfer between the end groups was occurring, as was intended. Although singly labeled polymers were present, selective donor excitation and selective acceptor emission detection allowed to sort out the polymer chains with both dyes. Time-correlated single photon counting was used to determine the time constant of energy transfer, as well as the average distance between both dye end groups. This was in good agreement with the end-to-end distance obtained from light scattering before the end group attachment.

With the successful synthesis of a polymer with two dye end groups and an effective means of analysis, this work opens the possibility of investigating stimulus dependent chain end-to-end distances on single polymers. This may help to answer the question, to what extent a single (infinitely diluted) chain would undergo a lower critical solution transition.

P6: Roth, P. J.; Haase, M.; Fischer, K.; Basché, T.; Theato, P.; Zentel, R. *Macromolecules* **2009**, *in preparation*

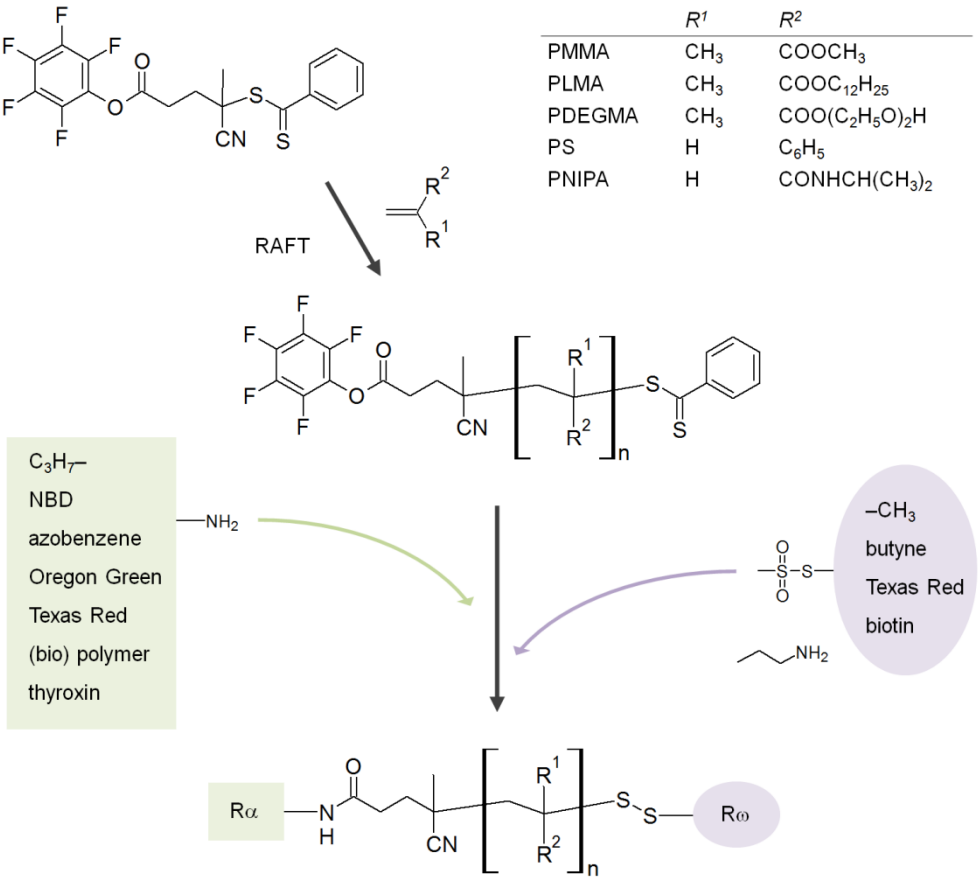


Summary and Conclusions

For α end group functionalization, a CTA with an activated PFP ester was synthesized. It allowed the introduction of inert propyl amides, of light responsive diazo compounds, of the dyes NBD, Texas Red, or Oregon Green, of the hormone thyroxin or allowed the formation of multiblocks or peptide conjugates. Conversions were usually between 80% and quantitative.

For ω end group functionalization, problems of other techniques were overcome through an aminolysis of the dithioester in the presence of a functional methane thiosulfonate (MTS), yielding functional disulfides. These disulfides were stable under ambient conditions and could be cleaved on demand. Using MTS chemistry, terminal methyl disulfides (enabling self-assembly on planar gold surfaces and ligand substitution on gold and semiconductor nanoparticles), butynyl disulfide end groups (allowing the "clicking" of the polymers onto azide functionalized surfaces and the selective removal through reduction), the biotarget biotin, and the fluorescent dye Texas Red were introduced into polymers. Conversions were usually quantitative, except for Texas Red, due to low solubility of the Texas Red MTS reagent.

Both end groups, PFP ester and DTE are reactive toward amines. If a step-wise conversion of the end groups is desired, the α PFP amidation needs to be performed under mild conditions, e.g. absence of excess of nucleophiles, so as not to harm the DTE. This way, polymers tethering fluorescent dyes to AuNP and to QD, polymers spacing two different fluorescent dyes, and polymers with biological end groups as protein adapters were synthesized.



	R^1	R^2
PMMA	CH_3	$COOCH_3$
PLMA	CH_3	$COOC_{12}H_{25}$
PDEGMA	CH_3	$COO(C_2H_5O)_2H$
PS	H	C_6H_5
PNIPA	H	$CONHCH(CH_3)_2$

The fact that both end groups are reactive toward amines may however also be exploited for simple one-pot reactions converting both end groups. In research beyond the scope of this dissertation, MTS reagents with C16 alkyl chains, carboxylic acids, terminal olefins and perfluorinated chains were synthesized and used in one-pot reactions with different amines which formed both the prospective α end groups and aminolyzed the ω DTE. This way, a library of polymers with different α and ω end groups was easily obtained and was used to study the influence of end groups on the LCST of the polymers.

As the MTS end group conversion works equally well on acrylate, acrylamide and styrene based monomers, an amine as α end group, an MTS reagent as ω end group, and a polymer spacer can thus each be chosen from a pool of "building blocks", which can then be assembled into a defined material with novel properties.

PFP esters and MTS chemistry should, however, not be understood as an inseparable couple. Here, this particular combination was put to great use. MTS chemistry, as a powerful approach to functionalize the dithioester end groups of RAFT polymers, may also be employed independent to any functionality at the α end group, be that for instance a complementary "clicking" functionality, an inorganic component such as poly(methyl silsesquioxane), or an end group with no particular interest at all.

Concluding, a versatile concept to synthesize α, ω end group functionalized RAFT polymers was presented. The synthesis is based on activated pentafluorophenyl esters and aminolysis of dithioesters in the presence of functionalized methane thiosulfonates. The usefulness of the concept was demonstrated on various examples, with application interests ranging from biochemistry to optoelectronics. As well-defined functional materials could easily be obtained, the synthetic approaches presented here are also promising methods for research and applications beyond this dissertation.

Publications

Synthesis of Reactive Telechelic Polymers Based on Pentafluorophenyl Esters

Roth, P. J.; Wiss, K. T.; Zentel, R.; Theato, P. *Macromolecules*, **2008**, *41*, 8513–8519

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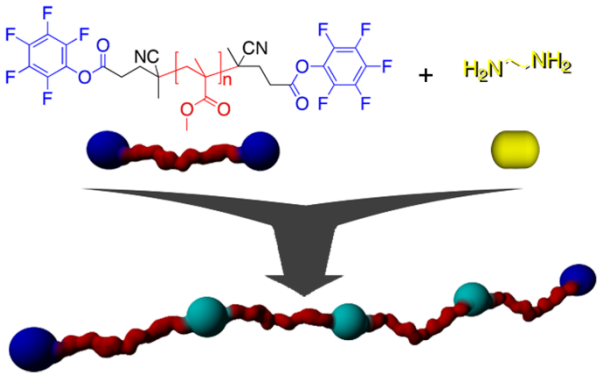


Abstract

A diazo initiator and a chain transfer agent (CTA), both containing a pentafluorophenyl (PFP) activated ester, were synthesized. In a RAFT polymerization using the functionalized chain transfer agent (PFP-CTA), methyl methacrylate (MMA), diethyleneglycol monomethylether methacrylate (DEGMA), polyethyleneglycol monomethylether methacrylate (PEGMA) and lauryl methacrylate (LMA) could successfully be polymerized into homopolymers and diblock copolymers with good control over molecular weight, very high conversions and narrow molecular weight distributions. Polymers derived from the PFP-CTA possessed an activated ester at the α-end of the polymer chain, which could be reacted with amines with high conversions. The terminal ω-dithioester group of each polymer chain could quantitatively be removed by treating the polymer with an excess of AIBN, leaving the α-PFP ester functionality intact. Accordingly, the pentafluorophenyl ester diazo compound could successfully be employed to functionalize RAFT polymers with a PFP ester at their ω-end. As a consequence, functionalization of both end-groups was possible and lead to telechelic polymers, exhibiting an active ester at both ends of the polymer chain. As an example, a high molecular weight PMMA was prepared by polycondensation with ethylene diamine.

Introduction

Polymers carrying reactive functional groups have been receiving an increasing amount of attention: Post-modifications of reactive polymers with a large variety of reagents have been carried out leading to smart materials with adjustable LCSTs[1] or multidentate ligands for the encapsulation of quantum dots,[2,3] titania nanorods[4] and other inorganic nanoparticles.[5-7] Such hybrid materials are interesting in material development and in optoelectronic research. Also, reactive polymers may be employed for surface modifications.[8] Monomers containing reactive sites such as activated esters,[9-11] acetals,[12-13] azides,[14] oxazolones,[15] acid azides[16] or protected acetylenes[17] may be converted by free radical or controlled radical polymerization techniques into polymers or block copolymers containing a high number of chemically addressable groups.

A synthetically different challenge is the introduction of functional end groups into a polymer, which was synthesized by a radical polymerization. The linear chain of this polymer then acts as a spacer between the α and the ω end groups of that specific polymer chain. Polymers with one functional endgroup may be used for bioconjugates,[18-21] precursors for diblock copolymers,[22] or for synthesizing polymer brushes on surfaces by a grafting-to technique.[23,24] A variety of methods to obtain end group functionalized polymers by nitroxide mediated polymerization (NMP),[25] atom transfer radical polymerization (ATPR)[26-32] or reversible addition fragmentation chain transfer polymerization (RAFT)[18-22, 33-38] have been reported. Telechelic polymers, i.e. polymers that feature the same functional group at both chain ends are of interest as precursors for multi-block-copolymers or as crosslinkers in polymer networks. Synthetic strategies to produce hydroxy,[39] carboxylic acid,[36,39] thiol [40-42] or amine[43] carrying telechelic polymers have been published.

The RAFT polymerization[44] uses a dithioester chain transfer agent (CTA) and thus results in polymer chains that carry a CTA residue on their α end and a dithioester at their ω terminus. These dithioesters are very promising for a subsequent polymer end group functionalization. A large number of differently functionalized CTAs have been reported. Bathfield et al.[18] performed a dicyclohexyl carbodiimide (DCC) coupling of 2-(phenylthiocarbonylthio)propanoic acid with *N*-hydroxysuccinimide (NHS) and used the resulting NHS-activated CTA for biofunctionalization prior to polymerization of *N*-acryloylmorpholine. These authors also used the activated CTA succesfully for the polymerization of *N*-acryloylmorpholine without amidation of the activated ester and also reported the synthesis of a different NHS activated CTA derived from azobis-(4-cyanovaleric acid) which was coupled with DCC / NHS. Zheng and Pan[45] synthesized the same CTA by DCC / NHS coupling of 4-phenylthiocarbonylthio-4-cyanovaleric acid and used it as a precursor for the synthesis of polymeric stars carrying 8 or 16 dithioesters groups. An acid chloride precursor trithiocarbonate was presented by Jesberger et al. and was used for the synthesis of a multifunctional RAFT agent.[46]

Common post-modification reactions of the ω-dithioester are aminolysis,[35,38,47] thermolysis or reduction with borohydride or stannane.[35,38] Perrier et al.[36] presented a method to recycle the chain transfer agent by reacting the polymer obtained from a RAFT polymerization with an excess of AIBN. Thereby, radicals cleave the bond between the ultimate repeating unit and the sulfur atom and saturate both emerging radicals with a cyanopropyl radical.

Herein, we describe the synthesis of a new chain transfer agent, pentafluorophenyl-[4-(phenylthiocarbonylthio)-4-cyanovalerate], via esterification of azobis-(4-cyanovaleric acid). While sharing a similar reactivity towards amines as the known NHS esters,[48] pentafluorophenyl (PFP) esters have the advantage of being easily analyzed by ^{19}F NMR spectroscopy. The PFP activated CTA was employed for the controlled polymerization of methyl methacrylate (MMA), diethyleneglycol monomethyl-ether methacrylate (DEGMA), polyethylene glycol monomethylether methacrylate (PEGMA), lauryl methacrylate (LMA) and *N*-isopropyl methacrylamide (NIPMA) yielding polymers and block copolymers with one chemically addressable PFP end-group. By using bis(pentafluorophenyl) azobis-(4-cyanovalerate), the dithioester end groups could be completely removed and replaced with an PFP activated residue yielding reactive telechelic polymers with PFP activated esters at both ends.

Experimental Section

Materials. All reagents were purchased from Acros, Aldrich, or Fluka and used as received unless stated otherwise. Tetrahydrofuran (THF) was distilled from sodium / potassium. Carbon disulfide was distilled from potassium permanganate. Dichloromethane was distilled from phosphorpentoxide. Dioxane was distilled from sodium. The monomers methyl methacrylate (MMA), diethyleneglycol monomethylether methacrylate (DEGMA), polyethylene glycol monomethylether methacrylate (PEGMA) and lauryl methacrylate (LMA) were distilled from calcium hydride.

Dithiobenzoic acid. This compound was synthesized in analogy to a literature procedure.[49] Briefly, 9.3 ml of dry THF and 7.5 mL of a 2 M phenylmagnesiumbromide solution in THF (15 mmol) were heated to 40°C in a nitrogen atmosphere. 2.06 g (27 mmol) of carbondisulfide were then slowly injected through a septum. After stirring for 45 minutes at 45°C, it was poured onto a mixture of 110 g of ice and 50 mL of concentrated hydrochloric acid. The violet mixture was then extracted several times with diethyl ether; the organic phases were combined and dried over magnesium sulfate. After evaporation of the solvent 2.10 g (91%) of a violet li-quid of characteristic odor were obtained.

Dithiobenzoic acid disulfide. 2.07 g (16.33 mmol) of iodine were dissolved in 40 ml of diethylether and 2.10 g (13.61 mmol) of dithiobenzoic acid were added. The mixture was stirred overnight and was then washed with an aqueous solution of sodium carbonate and subsequently with an aqueous solution of sodium sulfite to eliminate the excess of iodine. The organic phase was dried with magnesium sulfate, and the solvent was removed. After drying in high vacuum, the product became a red solid (1.12 g, 54%) with almost no smell.

Bis(pentafluorophenyl) azobis-(4-cyanovalerate) (PFP-ACV, 1). 10.0 g (35.7 mmol) of azobis-(4-cyanovaleric acid), 15.8 g (85.8 mmol) of pentafluorophenyl, 29.1 g (271.3 mmol) of 2,6-lutidine and 207 mL of dry dichloromethane were combined in a round bottom flask equipped with a stir bar and a septum in an argon atmosphere. The mixture was cooled to 0°C and 22.5 g (107.1 mmol) of trifluoroacetic anhydride were added dropwise through the septum. The reaction was allowed to warm to room temperature over night. The mixture was then extracted three times with 100 mL of water each, reaching neutral pH after the third extraction. The organic phase was dried over magnesium sulfate and the solvent was removed in light vacuum at 30°C. The raw product was dissolved in dichloromethane and precipitated into cold hexane to remove remaining lutidine. After two consecutive precipitations from dichloromethane into hexane, 12.9 g (59%) of product were obtained which were pure as confirmed by NMR and IR spectroscopy. ^{1}H NMR, 300 MHz, $CDCl_3$, δ = 3.00 - 2.48 (m, 8 H, CH_2), 1.78, 1,73 (2 s (cis, trans), 6 H, CH_3); ^{13}C NMR, $CDCl_3$, δ = 167.5 (O*C*O), 142.6, 141.4, 139.5, 138.1 136.2 (weak, *C*F), 117.0 (*C*N), 71.7 (*C*CN), 32.7 (OCO-CH_2-*C*H_2), 28.3 (OCO-*C*H_2); 23.9 (*C*H_3); ^{19}F NMR, $CDCl_3$, 376 MHz, δ = -152.88 (d, 4 F, J = 15 Hz), -157.56 (t, 2 F, J = 21 Hz), -162.20 Hz (t, 4 F, J = 19 Hz); IR 2929 cm^{-1} (w, CH), 1766 cm^{-1} (s, C=O), 1517 cm^{-1} (s, PFP), 1398 cm^{-1} (m), 1292 cm^{-1} (m), 1097 cm^{-1} (s), 987 cm^{-1} (s, PFP), 908 cm^{-1} (m).

Pentafluorophenyl-(4-phenylthiocarbonyl-thio-4-cyanovalerate) (PFP-CTA, 2). 2.17 g (7.08 mmol) of dithiobenzoic acid disulfide, 6.50 g (10.61 mmol) of bis(pentafluorophenyl) azobis-(4-cyanovalerate) (**1**) and 40 mL of ethyl acetate were combined in a round bottom flask with stir bar and condenser. Argon was bubbled through the mixture for 20 minutes and the top of the condenser was equipped with a balloon filled with argon to ensure absence of oxygen. The mixture was refluxed for 16 hours. The solvent was removed and the residue was purified by column chromatography with chloroform as eluent. 5.49 g (87%) of spectroscopically clean product was obtained. ^{1}H NMR, 300 MHz, $CDCl_3$, δ = 7.91 (d, 2 H, J = 7.8 Hz, *o*-Ar), 7.57 (t, 1 H, J = 7.5 Hz *p*-Ar), 7.39 (t, 2 H, J = 7.8 Hz, *m*-Ar), 3.08-3.01 (m, 2 H, O=C-CH_2), 2.80-2.70 (m, 1 H, O=CH2-C*H*H), 2.59-2.49 (m, 1 H, O=CH2-CH*H*), 1.97 (s, 3 H, CH_3); ^{13}C NMR, $CDCl_3$, δ = 219.7 (S*C*S), 167.8 (O*C*O) 144.3 (*ipso*-C_6H_5), 142.7, 139.4, 136.3, 134.4 (weak, *C*F), 133.2 (*para*-C_6H_5), 128.6 (*meta*-C_6H_5), 126.7 (*ortho*-C_6H_5), 118.2 (*C*N), 45.5 (*C*CN), 32.9 (OCO-CH_2-*C*H_2), 29.1 (OCO-*C*H_2); 24.2 (*C*H_3); ^{19}F NMR, $CDCl_3$, 376 MHz, δ = -152.88 (d, 2 F, J = 19 Hz), -157.69 (t, 1 F, J = 23 Hz), -162.28 Hz (t, 2 F, J = 21 Hz); IR 2927 cm^{-1} (w, CH), 1785 cm^{-1} (s, C=O), 1516 cm^{-1} (s, PFP), 1445 cm^{-1} (w), 1101 cm^{-1} (s), 990 cm^{-1} (s, PFP), 866 cm^{-1} (m), 761 cm^{-1} (m), 686 cm^{-1} (m); elem. anal.:

theor. C 51.23, H 2.72, N 3.14, S 14.4; found C 50.76, H 2.59, N 3.02, S 14.31.

4-Nitro-7-piperazin-1-yl-2,1,3-benzoxadi-azole (NBD-Amine). This compound was synthesized according to a literature procedure.[50]

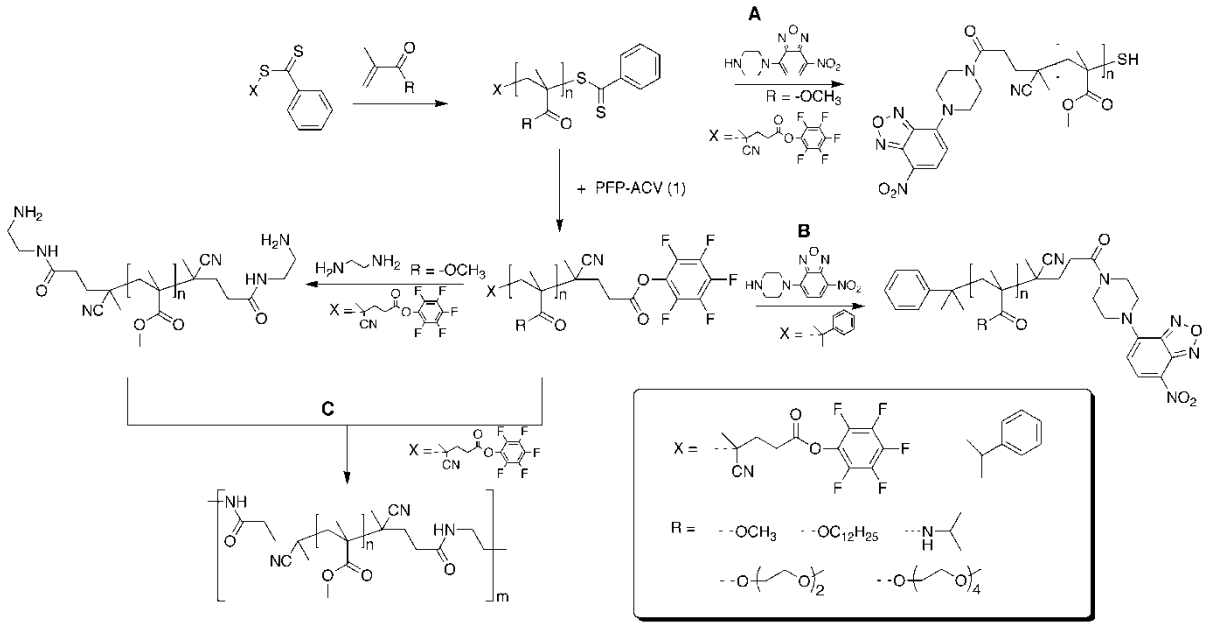
Diethyleneglycol monomethylether methacryate (DEGMA synth.). This monomer is commercially available but contains traces of a cross-linker leading to high molecular weight shoulders. Synthesis of the monomer led to a higher purity. Diethyleneglycol monomethylether (Fluka, >99%) was subjected to a column chromatography using ethyl acetate / isopropanol 2:1 as eluent. 6 g (50 mmol) of purified diethyleneglycol monomethylether, 5.30 g (52.5 mmol) of triethylamine and 150 ml of dry dichloromethane were combined in a round bottom flask equipped with a stir bar and a septum. After cooling the mixture to 0°C, 5.75 g (55 mmol) of methacryloyl chloride were added drop-wise and the reaction allowed to warm to room temperature over night. The reaction was then washed several times with water, the organic phase was dried and the solvent was evaporated. The crude product was distilled over calcium hydride. To ensure a high purity, only the middle fraction of the distillation (boiling point 57°C – 60°C at 9.7×10^{-2} mbar; 2.8 g, 30%) was used for polymerization.

***N*-Isopropyl methacrylamide (NIPMA).** In a round bottom flask 85 ml of dry dichloromethane, 9,65 ml (112.7 mmol) of isopropylamine and 16.63 ml (118.3 mmol) of triethylamine were combined in an argon atmosphere and the mixture was cooled to 0°C. 12 mL (124 mmol) of methacryloyl chloride were then added drop-wise. The reaction was allowed to warm to room temperature overnight. Precipitated ammonium salts were removed by succion filtration and the filtrate was extracted with water several times. The organic phase was dried and the solvent was evaporated to give 13 g (91%) of crude product, which was recrystallized from hexane yielding 8.7 g (61%) of pure monomer.

General RAFT polymerization procedure. All RAFT polymerizations followed the same general procedure. An example is given: 4 mL (21.68 mmol) of commercial diethyleneglycol monomethylether methacrylate distilled over calcium hydride, 483 mg (1.08 mmol) of PFP-CTA (**2**), 44.4 mg (270,9 mmol) of AIBN and 6 ml of freshly distilled dioxane were combined in a Schlenk flask. The mixture was degassed by three freeze-pump-thaw cycles and the flask was refilled with argon. It was then heated in a stirred oil bath set to 75°C for 13 hours. The polymer was precipitated from diethyl ether / hexane and dried in vacuum. The yield was almost quantitative. For diblock copolymers, a RAFT polymer was used as a macro-CTA instead of the PFP-CTA. Molecular weights and polydispersities are given in table 1.

PMMA polymerized in the presence of cumyl dithiobenzoate. The chain transfer agent was synthesized according to a literature procedure.[47] 1.6 mL (15 mmol) of methyl methacrylate, 88.2 mg (0.32 mmol) of cumyl dithiobenzoate and 12.8 mg (0.078 mmol) of AIBN were added to a Schlenk-tube and oxygen was exchanged with nitrogen by five freeze-pump-thaw cycles. The polymerization was carried out at 75°C for 21 hours. The polymer was purified by precipitation into methanol from THF for three times to yield 1.39g (88%) of cumyl-PMMA-dithioester. M_n (GPC) = 8.9 k g/mol; PDI (GPC) = 1.10.

General procedure for reaction of PFP-polymer with NBD-Amine. In a typically experiment, 2 µmol of PFP end-functionalized PMMA were dissolved in 5 mL of dioxane and a solution of 10 µmol of NDB-Amine in 3 mL of dioxane was added. The mixture was stirred for 1 day at 50°C. After concentrating the solution by removing most of the solvent, the polymer was precipitated from methanol several times until the methanol remained colorless. The absence of unreacted dye was confirmed by GPC using a UV-Vis detector set to 475 nm.



***Scheme 2**. Overview of reactions described in detail in the text.*

General procedure for dithioester removal. In a typical run, a polymer containing a dithioester end group and 20 equivalents of the diazo compound (AIBN or PFP-ACV **1**) were dissolved in dry dioxane. 12 ml of dioxane were used for 10 mmols of diazo component. The mixture was heated to 80°C for 2.5 hours. Then, the polymer was precipitated three times in methanol (PMMA) or diethyl ether / hexane (1:1) (poly[ethyleneglycol methacrylate]). A ^{1}H NMR spectrum showed no remaining residues of the azo compound.

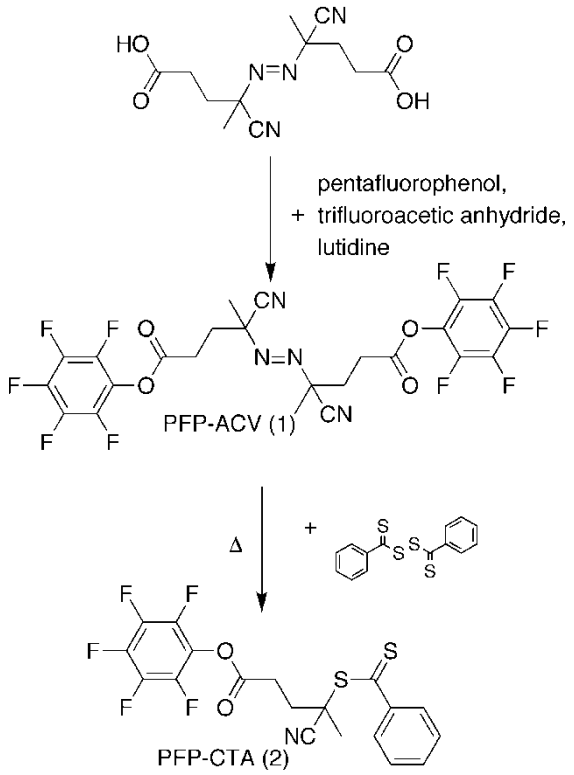
A sample of α-PFP-PDEGMA after AIBN treatment was analyzed by ^{19}F NMR: $CDCl_3$, 376 MHz, δ = -153.01 (m, 2 F), -157.92 (m, 1 F), -162.38 Hz (m, 2 F).

Treating α-cumyl-PMMA with PFP-ACV (**1**) yielded α-cumyl-PMMA-ω-PFP (**6**), which was analyzed by ^{19}F NMR: $CDCl_3$, 376 MHz, δ = -153.02 (m, 2 F), -157.68 (m, 1 F), -162.39 Hz (m, 2 F)

Formation of multiblock PMMA. Telechelic PMMA, exhibiting PFP end groups, was synthesized by reacting α-PFP-PMMA with an excess of PFP-ACV as described above. To ensure an accurate 1:1 ratio of amines and active esters in the polycondensation reaction with ethylene diamine, first a sample of telechelic PMMA was reacted with an excess of ethylene diamine to give telechelic PMMA exhibiting amine end groups: 150 mg of 14.8 k g/mol PFP-PMMA-PFP was dissolved in 1 ml of THF and 100 equivalents of diethylamine were quickly added. The mixture was stirred over night at 40°C, then the polymer was precipitated three times in methanol and dried in vacuum. 20 mg of telechelic PMMA and 20.2 mg of telechelic PMMA (Scheme 2C) were dissolved in 0.6 ml of THF and a drop of triethylamine was added. The mixture was stirred over night at 40°C. A longer reaction time did not increase the conversion, oligo-PMMA was obtained in quantitative yield, Mn (GPC) = 70 k g/mol, PDI (GPC) = 1.44.

Results and discussion

The scope of the present study is to prepare telechelic polymers that possess an activated ester at both end-groups. In order to reach this goal, we combined several individual techniques that had recently been presented to prepare either α end group functionalized polymers[18,45,46] or ω end group functionalized polymers[36] synthesized by a radical polymerization technique. As our former investigations had shown, the pentafluorophenyl ester is a very versatile and reactive functionality [10] and we favored it as the activated ester of choice for the present study. Accordingly, a pentafluorophenyl ester azo initiator was synthesized first.



Scheme 1. *Synthesis of a pentafluorophenyl (PFP) active ester functionalized diazo initiator (**1**) in a one-step reaction and conversion into a PFP functionalized chain transfer agent (**2**).*

In a second step, this azo initiator was converted into a pentafluorophenyl ester functionalized chain transfer agent, which should be capable to control a reversible addition-fragmentation chain transfer (RAFT) polymerization. Scheme 2 shows the roles of both of these two new compounds for the preparation of telechelic active ester polymers.

Synthesis of a pentafluorophenyl ester azo initiator. In contrast to the common methods of synthesizing a PFP ester by either activation of the acid with DCC or by a two-step reaction via an acid chloride, we investigated a one-step reaction to synthesize bis(pentafluorophenyl) azobis-(4-cyanovalerate) (PFP-ACV **1**) from azobis-(4-cyanovaleric acid) (ACVA) using trifluoroacetic anhydride (TFAA) to activate the acid (scheme 1). TFAA is known to react with pentafluorophenol under mild conditions to give pentafluorophenyl trifluoroacetate, which is a commercial, effective, one-step reagent to create PFP esters,[51] although expensive. TFAA also reacts with carboxylic acids under mild conditions [52] to form a mixed anhydride, which is susceptible to alcoholysis. Thus, a reaction composed of a carboxylic acid, TFAA and pentafluorophenol yielded the desired PFP ester under mild conditions. In the experiment we added 2,6-lutidine to scavenge the trifluoroacetic acid generated during the reaction. After stirring the components overnight at room temperature, pure PFP-ACV (**1**) could be obtained by simple precipitation into cold hexane. The yield was moderate (59%), however, the product was pure and did not contain any mono-functionalized azo-compound side product as could be seen from ^{1}H NMR, ^{19}F NMR and the bands of IR spectroscopic data (see supporting information). The acid precursor showed a prominent O-H band above 3000 cm^{-1} and a carbonyl absorption at 1702 cm^{-1}, while the ester product was lacking the O-H band, only exhibiting a weak C-H band just below 3000 cm^{-1}; the carbonyl peak had completely shifted to 1785 cm^{-1}, indicating the presence of an active ester, and the product spectrum also contained the characteristic aromatic peak also to be seen in a spectrum of pentafluorophenol centered at 1500 cm^{-1} and 990 cm^{-1}.

Synthesis of a pentafluorophenyl ester functionalized chain transfer agent. From PFP-ACV (**1**), a PFP functionalized chain transfer agent PFP-CTA (**2**) was synthesized via radical reaction with dithiobenzoic acid disulfide (scheme 1). Reaction at 77°C for 16 h resulted in PFP-CTA (**2**) in 87 % yield after purification by column chromatography. This synthesis is well established for the diazo acid derivative ACVA and we were able to apply it with equally good results for our modified azo initiator PFP-ACV.

Synthesis of polymers with a PFP ester at the α-position. PFP-CTA could successfully be used to polymerize various methacrylates, such as MMA, DEGMA, PEGMA and LMA, under RAFT polymerization conditions. The RAFT polymerization of *N*-isopropyl methacrylamide (NIPMA) resulted in a very low yield and low molecular weight polymer. Polymerizations of methacrylates, however, proceeded with a very accurate control over the molecular weight, near quantitative monomer conversions and narrow molecular weight distributions. Table 1 lists polymers and block copolymers derived from PFP-CTA (**2**). In the case of DEGMA, both the monomer available from Aldrich and a homemade monomer were used. The commercial monomer seemed to contain trace amounts of a cross-linker, presumably diethyleneglycol dimethacrylate, which

Table 1. *List of polymers and diblock copolymers derived from the PFP functionalized chain transfer agent.*

Entry	1st Monomer	M_n[h] [g/mol]	PDI[h]	2nd Monomer	M_n [g/mol] diblock	PDI diblock
1	DEGMA com.	4 k	1.12			
2	DEGMA[a] com.[b]	5.5 k	1.09	PEGMA	25 k	1.31
3	DEGMA com.	8 k	1.14	NiPMA	9 k	1.11
4	DEGMA com.	9 k	1.14			
5	DEGMA com.	10 k	1.18	LMA	16 k	1.18
				MMA	20 k	1.19
6	DEGMA com.	25 k	1.34			
7	DEGMA synth.[c]	2.8 k	1.08	NiPMA	3.4 k	1.09
8	DEGMA synth.	21 k	1.12	NiPMA	22 k	1.10
9	DEGMA synth.	41 k	1.19	NiPMA	43 k	1.16
10	PEGMA[d]	25 k	1.18			
11	NiPMA[e]	3.0 k	1.17			
12	LMA[f]	8 k	1.06	PEGMA	20 k	1.14
13	LMA	22 k	1.06			
14	MMA[g]	3.6 k	1.08	PEGMA	15 k	1.18
15	MMA	14.8 k	1.18			

[a] Diethyleneglycol monomethylether methacrylate, [b] commercially avaiable monomer containing trace amounts of a crosslinker, [c] synthetic monomer made from purified diethyleneglycol monomethyl ether [d] polyethyleneglycol monomethylether methacrylate. NMR analysis showed that each monomer contained about 4 ethylenglycol units, [e] N-isopropylmethacrylamide, [f] lauryl methacrylate, [g] methyl methacrylate, [h] molecular weights (given in g / mol) and PDIs were determined by GPC analysis.

caused polymers to have a slight shoulder towards higher molecular weights and thus, broader molecular weight distributions such as M_w/M_n = 1.34 at 25 k g/mol (table 1, entries 1-6) were obtained. However, polymerization of the homemade monomer synthesized from carefully purified diethyleneglycol monomethylether yielded high molecular weight polymers with considerably smaller molecular weight distributions, such as M_w/M_n = 1.19 at 41 k g/mol (table 1, entries 7-9).

Polymers derived from PFP-CTA (**2**) carried an activated ester at their α-group, which could be shown by ^{19}F NMR (figure 1, graph c). In order to address the terminal activated ester, a sample of PFP-PMMA (table 1, entry 15) was reacted with 4-nitro-7-piperazin-1-yl-2,1,3-benzoxadiazole (an amine functionalized NBD) (scheme 2A). The obtained polymer was intensely orange colored and a GPC measurement with the UV-Vis detector set to the absorption maximum of the NBD dye (475 nm) indicated that the polymer was colored and that any excess of dye had successfully been removed from the sample by several precipitation steps (figure 2). As the amine functionalized dye was employed in excess, the ω-end-group of the polymer was converted into a thiol[35,38] or a thiolactone by backbiting.[47] The GPC curve of the dye func-tionalized PMMA was very slightly shifted towards higher molecular weights, however, no peak of twice the molecular weight was observed, indicating that no disulfide coupling had occurred under these conditions.

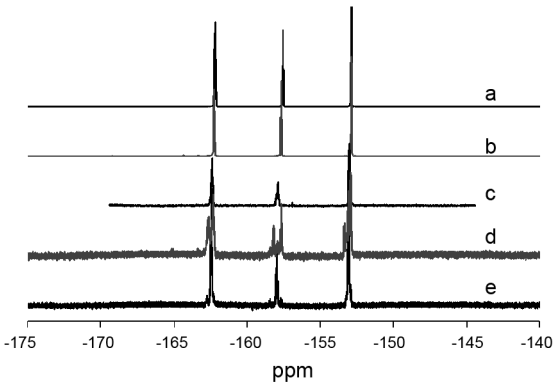


Figure 1. *^{19}F NMR spectra of (a) pentafluorophenyl ester functionalized azo initiator PFP-ACV (**1**), (b) pentafluorophenyl ester functionalized chain transfer agent PFP-CTA (**2**), (c) α-pentafluorophenyl ester functionalized poly(diethylenglycol monomethylether methacrylate) derived from PFP-CTA after dithioester removal with AIBN, (d) ω-pentafluorophenyl ester functionalized PMMA obtained by reacting the dithioester terminated polymer with an excess of PFP-ACV and (e) telechelic α, ω pentafluorophenyl ester functionalized PMMA obtained from combining the use of the modified CTA (**2**) and end-group exchange with an excess of (**1**).*

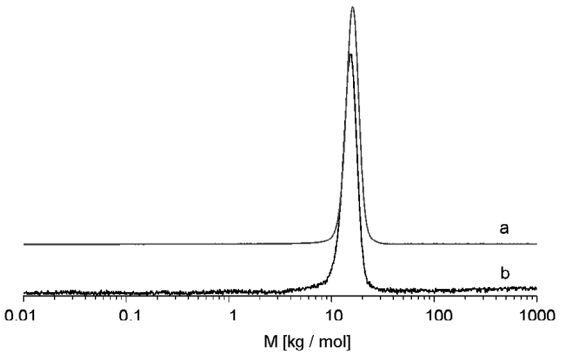


Figure 2. *Reaction of an α-PFP ester functionalized polymer with a functional dye: Gel permeation chromatograms of α-pentafluorophenyl ester functionalized PMMA (table 1, entry 15) (line b) and after reaction with NBD-amine (scheme 2, route A) (line a). For the measurement of the NBD-functionalized polymer, the UV-Vis detector was set to the absorption maximum of the dye, indicating that no free dye at low molecular weight elution was present.*

The molecular weight of the employed polymer was determined by two methods: First, by GPC analysis using a light scattering detector and the known value for dn/dc of 0.085 ml/g for PMMA and second, by end group analysis. The absorbance of the dithioester end group of PFP-PMMA (table 1, entry 15) was measured and compared with a calibration curve of the concentration dependent absorbance of PFP-CTA (see supporting information). From the GPC / light scattering measurement a molecular weight of 14.8 k g/mol could be calculated, whereas the dithioester end-group analysis resulted in a molecular weight of 14.4 ± 0.7 k g/mol. The difference of these values being less than 3 % indicates that nearly all the polymer chains carry the dithioester end-group and thus, analysis of its absorbance is a valid approach for determination of the molecular weight.

In order to analyze the conversion of the PFP end-group with amine functionalized NBD, the absorbance of the NBD functionalized PMMA was measured and compared with a calibration curve of the concentration dependent absorbance of NBD-Amine (see supporting information). In combination with the molecular weight, a conversion of the PFP ester end-group of 83.6% (using GPC / light scattering data) and 81.4 ± 4.0 % (using dithioester absorbance data) could be calculated. These values are in very good agreement with end-group conversion presented in the literature, for example, a conversion of 80.1 ± 2.6 % for a cysteamine end capped polymer that had been reacted with an activated ester dye was reported.[19] It should be noted that the non-quantitative conversion may result from i) PFP esters not being present at the α-end-group; for instance by polymer chains that had been initiated by AIBN, ii) alcoholysis / hydrolysis of the PFP esters during precipitation or storage, or iii) an incomplete reaction with the chromophore due to a small concentration of the polymer end groups.

Synthesis of polymers with a PFP ester at the ω-position. To introduce a pentafluorophenyl ester end-group at the ω position, the dithioester end group had to be exchanged in a reaction described in detail by Perrier et al.[36] Similar to the conditions reported there, we treated the dithioester-terminated polymer (PFP-PMMA, table 1,entry 15) in a first model reaction with 20 equivalents of AIBN, resulting in a quantitative replacement of the dithioester by a cyano-propyl group originating from AIBN. The GPC traces of the resulting polymers did not differ from those of the dithioester containing polymers, demonstrating that no polymer-polymer radical coupling had occurred. However, if the temperature exceeded 80°C during the reaction, then a high-

er molecular weight shoulder at twice the molecular weight was found, probably caused by the high concentration of radicals during the reaction. The PFP ester at the α end group was not harmed by this treatment, as the ester is stable towards radicals and elevated temperature in the absence of nucleophiles. Clearly, the ^{19}F NMR spectra of polymers obtained after the exchange reaction still showed the typical PFP ester signals (figure 1, graph c). As this showed, an exchange reaction allows for an independent derivatization at the ω end of RAFT polymers, and accordingly we next investigated the use of the PFP functionalized azo initiator PFP-ACV (**1**) during the end group exchange reaction. For this, a sample of PMMA was polymerized with cumyl dithiobenzoate resulting in a polymer terminated in a dithioester but not containing any fluorine. This cumyl-PMMA-dithioester was reacted with 20 equivalents of PFP-ACV (**1**) at 80°C for 2.5 hours and the resulting polymer PMMA-ω-PFP was precipitated 3 times into methanol to remove any low molecular weight side products (see scheme 2). The UV-Vis spectrum of PMMA-ω-PFP showed that the absorbance of the dithioester centered at 302 nm had vanished, suggesting a complete removal of the dithioester end group and complete replacement with the PFP ester carrying residue as was shown for exchange reactions with other diazo compounds by Perrier et al.[36] (see supporting information). GPC traces recorded before and after the treatment with PFP-ACV did not show any differences showing that no side reactions had occurred that have an influence on the molecular weight or the molecular weight distribution (see figure 3, curves a and c). A ^{19}F NMR spectrum taken of the product showed three distinct peaks that are typical for a PFP ester, indicating that the PMMA had been functionalized with a pentafluorophenyl active ester at its ω-position (see figure 1 d). Reacting the polymer with NBD-amine yielded a colored PMMA and a GPC trace was recorded using a UV-Vis detector set to 475 nm, the absorbance maximum of the NBD dye (figure 3, curve b). This measurement clearly showed that the polymer had been functionalized with the dye, as there is a strong signal of the detector and the unmodified polymer has no absorbance at this wavelength. It can also be seen that all unreacted dye had successfully been removed by precipitation for there is no low molecular weight signal of the UV-Vis detector.

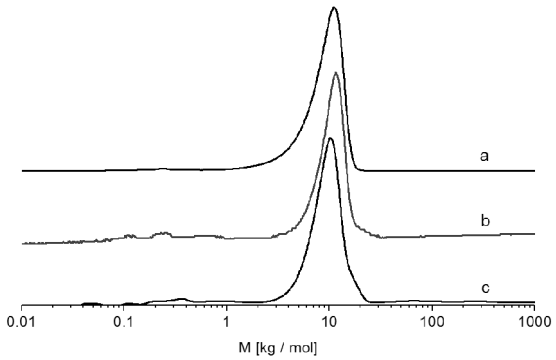


Figure 3. *Reaction of α-cumyl, ω-dithioester PMMA with an excess of PFP-ACV (**1**) and functionalization with a functional dye (scheme 2, route B): Gel permeation chromatograms of (a) α-cumyl, ω-pentafluorophenyl ester PMMA, (c) after removal of the dithioester by replacing it with PFP-cyanovalerate and (b) after reaction with NBD-amine. For this measurement, the UV-Vis detector was set to the absorption maximum of the dye, indicating that no free dye at low molecular weight elution was present.*

Synthesis of telechelic polymers. The experiments described above showed, that we could incorporate pentafluorophenyl esters at either the α position of a polymer chain utilizing a pentafluorophenyl ester functionalized chain transfer agent, or at the ω terminus of a polymer chain by treating a polymer containing a dithioester with a pentafluorophenyl ester functionalized azo compound. The latter reaction progresses via a radical mechanism and is thus independent of the nature of the α-group of the polymer chain. We therefore took advantage of the pentafluorophenyl ester functionalized azo compound and the pentafluorophenyl ester functionalized chain transfer agent in one synthesis and prepared a telechelic polymer containing pentafluorophenyl esters at both its α and ω ends (see scheme 2). For this purpose, PFP-PMMA (table 1, entry 15) with a molecular weight of 14.8 k g/mol was reacted with a 20-fold excess of PFP-ACV (**1**) to yield the polymer PFP-PMMA-PFP. The quantitative removal of the dithioester was again monitored by the disappearance of the absorption band at 302 nm. GPC traces showed only a very slight shift towards higher molecular weights of the telechelic polymer PFP-PMMA-PFP in respect to the precursor polymer PFP-PMMA. The ^{19}F NMR spectrum of PFP-PMMA-PFP showed three peaks (see figure 1, graph e). The difference of the chemical environment of

the α end group and the ω end group (tail vs. head connection to monomers) was not sufficient to result in separate signals.

Polycondensation of telechelic polymers. One of the many uses of telechelic polymers is that they can be used in polycondensation reactions yielding multiblock polymers. As an example, we used the telechelic polymer PFP-PMMA-PFP to prepare a multiblock homo-polymer with ethylene diamine (see scheme 2, route C). In such a polycondensation reaction, the exact 1:1 ratio of reactive groups is essential to achieve a high conversion. For this reason, the telechelic polymer PFP-PMMA-PFP was first reacted with an excess of ethylene diamine yielding the telechelic polymer NH_2-PMMA-NH_2 featuring amine groups at the α position and the ω position of the polymer chain. This polymeric diamine was then allowed to react with the telechelic polymer PFP-PMMA-PFP overnight at 40°C. A longer reaction time did not result in an increase of the conversion. The resulting multiblock homo-PMMA was analyzed by GPC (figure 4). Line *a* represents the precursor PMMA with a molecular weight of 14.8 k g/mol, whereas line *b* is the signal of the product of the polycondensation of the PFP-PMMA-PFP with the respective polymeric diamine, with a resulting molecular weight of 70 k g/mol. The multiblock homo-polymer still contained some homo-polymer chains, probably due to a small fraction of precursor PMMA, which did not exhibit a pentafluorophenyl ester at both α and ω positions. Further, a shoulder at double molecular weight could be seen. The main peak however comprised molecular weights up to over 100 k g/mol implying that the PMMA chains consisted of at least six or more single building blocks. This was only possible if α, ω-difunctional polymer chains had been present in the polycondensation reaction. The overall conversion of the polycondensation was probably limited due to several reasons: i) a very low concentration of reactive groups with proceeding reaction, ii) a low mobility of the larger chains and iii) an imprecise 1:1 ratio of reactive groups. Compared to other synthetic routes that had been reported on the formation of multiblock homo-polymers, our method yields very high molecular weight multiblock homo-polymers. For example, You et al.[42] reported multiblock homo-polymers by oxidative coupling of different telechelic polymers featuring thiol groups at the α- and ω-position of the polymer chain. Their multiblock homo-polymers consisted of 7 to 13 single building blocks, which were of much lower molecular weight (2.5 k g/mol to 3.5 k g/mol).

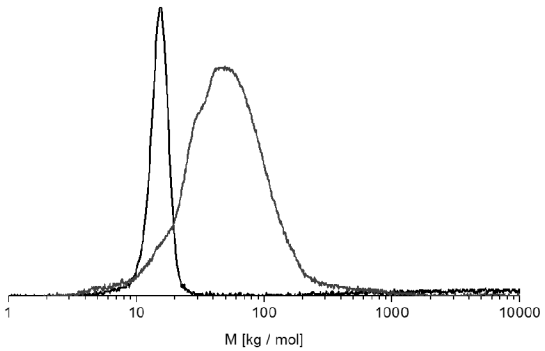


Figure 4. *Reaction of telechelic PFP-PMMA-PFP with a diamine to form multiblocks homopolymers: Gel permeation chromatograms of a single PMMA buidling block (curve a) and of the multiblock homopolymer obtained from reacting α-PFP, ω-PFP PMMA with ethylene diamine (scheme 2, route C) (curve b). The molecular weight and PDI of the precursor PMMA are 14.8 k g/mol and 1.18, whereas the multiblock homopolymer had an avarage weight of 70 k g/mol with a PDI of 1.44.*

Considering main applications of telechelic polymers such as formation of multiblocks and use as crosslinkers, our PFP functionalized polymers are very promising compared to existing hydroxyl, carboxylic acid or thiol terminated polymers as they may be addressed under mild conditions with high conversions and also have the great advantage of being easily characterized with ^{19}F NMR spectroscopy.

Conclusion

A simple synthesis of a pentafluorophenyl (PFP) functionalized azo initiator, bis(pentafluorophenyl) azobis-(4-cyanovalerate) by way of a one-step esterification with trifluoroacetic anhydride as activating agent was described. From this compound, a PFP-functionalized chain transfer agent (CTA) was synthesized, which could polymerize methacrylates effectively producing polymers carrying one active ester per chain. The use of PFP esters has the advantage of elegant analysis trough ^{19}F NMR spectra, which could show that the α PFP ester is not harmed by removal of the dithioester by treatment with an

excess of azo initiator. By using the PFP functionalized azo compound we were able to incorporate active esters at the ω-terminus of RAFT polymers thus allowing active ester functionalization at either the α end of methacrylate polymers or at the ω end, or at both ends of a polymer chain together to give telechelic PFP esters. Both the α and the ω PFP esters could be addressed with a secondary amine with high conversion. Telechelic PMMA could successfully be employed in a polycondensation with ethylene diamine. As PFP esters may also be conjugated with a manifold variety of compounds of arbitrary molecular weight ranging from inorganic compounds to biologically active molecules, these procedures broaden the possibilities of modern polymer architecture and the development of novel functionalized materials.

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Supporting Information Available. IR spectroscopic data following the synthesis of PFP-ACV, a UV-Vis absorbance calibration curve of the CTA dithioester and absorption measurements of PMMA-dithioester for calculation of the molecular weight, determination of NBD conversion through a UV-Vis absorption calibration curve and UV-Vis data showing the complete removal of the dithioester end group by exchange reaction with PFP-ACV. This material is available free of charge at http://pubs.acs.org.

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A Method for Obtaining Defined End Groups of Polymethacrylates Prepared by the RAFT Process during Aminolysis

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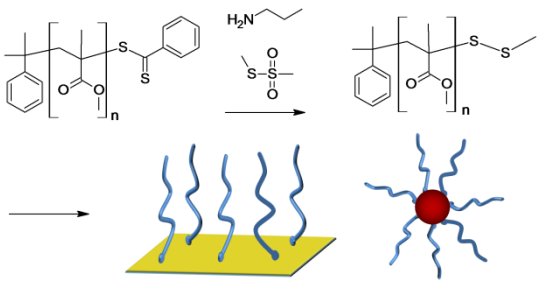


Abstract.

Aminolysis of the thiocarbonylthio end-group of poly(meth)acrylates that have been prepared by a RAFT polymerization leads – in contrast to polystyrenes and poly(meth)acrylamides – to the formation of thiolactones by backbiting. We found that the addition of methyl methanethiosulfonate during the aminolysis of a polymethacrylate suppresses this thiolactone formation and results in the formation of a terminal methyl disulfide even in the presence of oxygen. The terminal methyl disulfides could successfully be employed to create self-assembled monolayers on a gold surface and for stabilization of gold nanoparticles.

Reversible addition fragmentation chain transfer (RAFT) polymerization[1] is a very versatile controlled radical polymerization technique. The use of thiocarbonylthio chain transfer agents (CTA) yields polymers terminated with a dithioester, which is sensitive towards radicals, nucleophiles, temperature, and reducing agents. Thus, many postpolymerization methods may be employed to modify this dithioester end group. By thermolysis or reduction[2,3] the dithioester group may be removed, whereas treatment with an excess of a diazo compound allows for the introduction of functional end-groups.[4,5] Very popular is the aminolysis of the dithioester end group, however, the products of this procedure depend very much on the chemical structure of the polymer. Polystyrene and derivatives and poly [(meth)acrylamides] yield terminal thiols (or symmetrical disulfides if oxygen is present).[6-12] These end groups are particularly interesting for producing self assembled monolayers (SAMs) on gold surfaces[13,14] which find applications in biochemistry,[15-17] catalysis,[18,19] nanotechnology[20] and microelectronics.[21-24] Further, thiol terminated polystyrene,[25] polystyrene derivatives[6] and several poly[(meth) acryl-amides][6-8] have been used to encapsulate gold nanocrystals; and thiol terminated poly[(meth)acrylamides] have been used for end group modifications[9,10] and fluorescent labelling.[11,12] Poly[(meth) acrylates] however suffer from the great drawback that the aminolysis affords the desired terminal thiol only in low yields.[26-28] It has been reported that reduced polymers with an H end group, a double molecular weight material even in the absence of oxygen[26,27] and other ill-defined products[26] are produced. Quantitative analysis of a thiol end group such as with Ellman's reagent[9] is only rarely presented. Xu *et al.*[28] investigated the aminolysis of polymethacrylates in the absence of oxygen in greater detail, providing evidence that the resulting polymer bears a terminal thiolactone which is obtained by backbiting of an initially formed thiol into the penultimate monomer unit. Although being a defined polymer end group, this thiolactone cannot be employed for conjugation or for surface modifications, very much in contrast to a thiol end-group. Also the native dithioester end groups have been investigated for adsorbing onto a gold surface by Duwez et at.,[29] however, they could only obtain a grafting density of 0.013 chains /nm² which is very low compared to literature values for terminal thiols grafted to gold nanoparticles such as 0.94 chains /nm² for polystyrene[30] or 1.8 to 3.6 chains /nm² for poly[N-isopropyl acrylamide].[8]

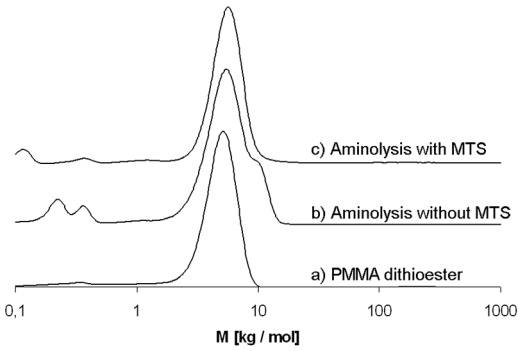
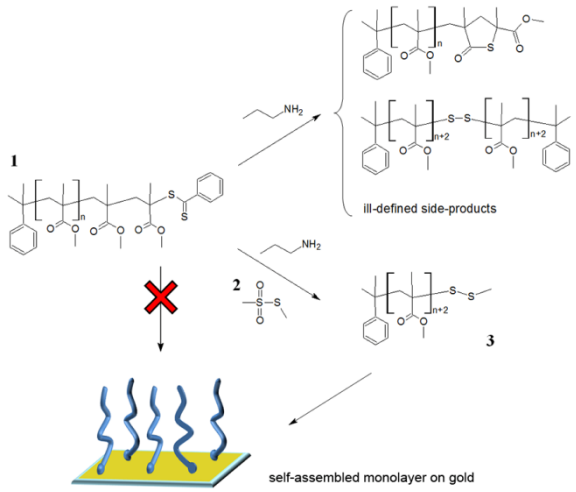


***Figure 1**. Gel permeation chromatograms of PMMA (a) with dithioester end-group (**1**), (b) aminolyzed with 10 equivalents of n-propylamine without inert atmosphere and (c) aminolyzed with 10 equivalents of propylamine after addition of 20 equivalents of MTS without inert atmosphere (**3**).*

In this communication, we investigate the effect of methyl methanethiosulfonate (MTS, **2**) during the aminolysis reaction of polymethacrylates that have been prepared by RAFT polymerization with the goal of producing a defined polymethacrylate end group capable of producing a dense SAM on a gold surface. MTS reacts quickly and selectively with thiols to yield the respective methyl disulfides. Amines increase the hydrolyzation rate but do not attack the sulfur atoms themselves. Thus, methanethiosulfonates have found intensive use in selective[31] labeling of cysteine groups for the determination of structure and function of ion channel,[32] receptor[33] and membrane[34] proteins. We expect thiols that are released by aminolysis from the polymer dithioester end group also to react with MTS and to prefer this reaction over the competing reactions of thiolactone formation and oxidation to symmetrical polymer-polymer disulfides by oxygen.

As a model compound we synthesized a short polymethylmethacrylate (PMMA) (**1**) (M_n = 3900 g/mol, M_w/M_n = 1.08) using cumyl dithiobenzoate as chain transfer agent.[35] First, we subjected it to 10 equivalents of *n*-propylamine in THF in the presence of oxygen.[36] After 3.5 hours, the pink color had vanished and a gel permeation chromatography (GPC) analysis showed a bimodal product distribution (see Fig.1 a and b), probably composed of a thiolactone and a polymer-polymer disulfide caused by oxygen oxidation (see upper part of scheme 1).



Scheme 1. Overview of aminolysis products of PMMA. *The aminolysis of the dithioester of polymethacrylates is known to produce product mixtures[26-28] such as a thiolactone by backbiting of a terminal thiol[28] or a symmetrical polymer-polymer disulfide of double molecular weight by oxygen oxidation (see Fig. 1b). In the presence of MTS (**2**) however, only terminal methyl disulfides are formed. In contrast to the native dithioester terminated polymers, the methyl disulfide terminated polymers form stable self-assembled monolayers on a gold surface.*

A polystyrene with M_n = 1170 g/mol aminolyzed under the same conditions completely transformed into the double molecular weight material,[35] suggesting that the oxygen concentration was high enough for complete oxidation. An aminolysis of PMMA was repeated under the same conditions, this time in the presence of 20 equivalents of MTS.[37] The resulting polymer (**3**) was then analyzed by GPC, UV-Vis spectroscopy and NMR. The GPC peak of (**3**) (Fig. 1c) had the same shape and position as the signal of the starting PMMA (**1**) (Fig. 1a). No peak of double molecular weight was found, suggesting that thiols formed by aminolysis found a more preferable reaction pathway than being oxidized although oxygen was present. The pink dithioester color had vanished from the MTS aminolysis reaction after 3.5 hours and the precipitated polymer was colorless. UV-Vis measurements showed that the characteristic dithioester absorbance peak centered at 302 nm had completely vanished for the polymer that was treated with amine and MTS.[35] ^{1}H, ^{13}C and HSQC-NMR spectra were measured of both the reactant (**1**) and the product (**3**) polymers and are shown in figure 2. The ^{1}H-NMR spectrum of (**1**) (Fig. 2A) showed exactly the same signals as discussed in detail in the literature[28] and we could attribute the peaks accordingly. Both end groups were clearly visible in the ^{1}H-NMR. The aromatic signals of the cumyl α group, (denoted *b*, *c*, *d*) appeared in the spectra of both polymer (**1**) and polymer (**3**) (see Figure 2A and B, respectively), whereas the three distinct signals of the dithiobenzoate ω end group (labeled *j*, *k*, *l*) vanished completely after amine / MTS treatment. Most interesting was a single methylene proton signal of the ultimate monomer unit (denoted *a* in figure 2), which gave rise to a set of signals at 2.40 to 2.70 ppm well detached from the rest of the methylene group resonances. All signals of this proton were shifted upfield to 2.35 - 2.58 ppm due to the end group conversion. The terminal methyl group of polymer (**3**) (denoted *i* in Fig. 2B) gave rise to a broad singlet positioned at 2.31 ppm. By comparing the integrals of the single backbone hydrogen (1 H) and the terminal methyl group (3 H) a quantitative end group conversion can be assumed within the accuracy of the NMR evaluation (Fig. 2C). Further evidence of the complete transformation could be obtained from ^{13}C and HSQC NMR measurements. The latter are shown in fig. 2D (polymer **1**) and fig. 2E (polymer **3**). The shift of the ultimate methylene group protons *A* and *B* through the MTS / amine reaction can be seen as well as the appearance of the $SSCH_3$ group signal. For reference, interpreted ^{13}C NMR spectra of both polymers are given in the supporting information.

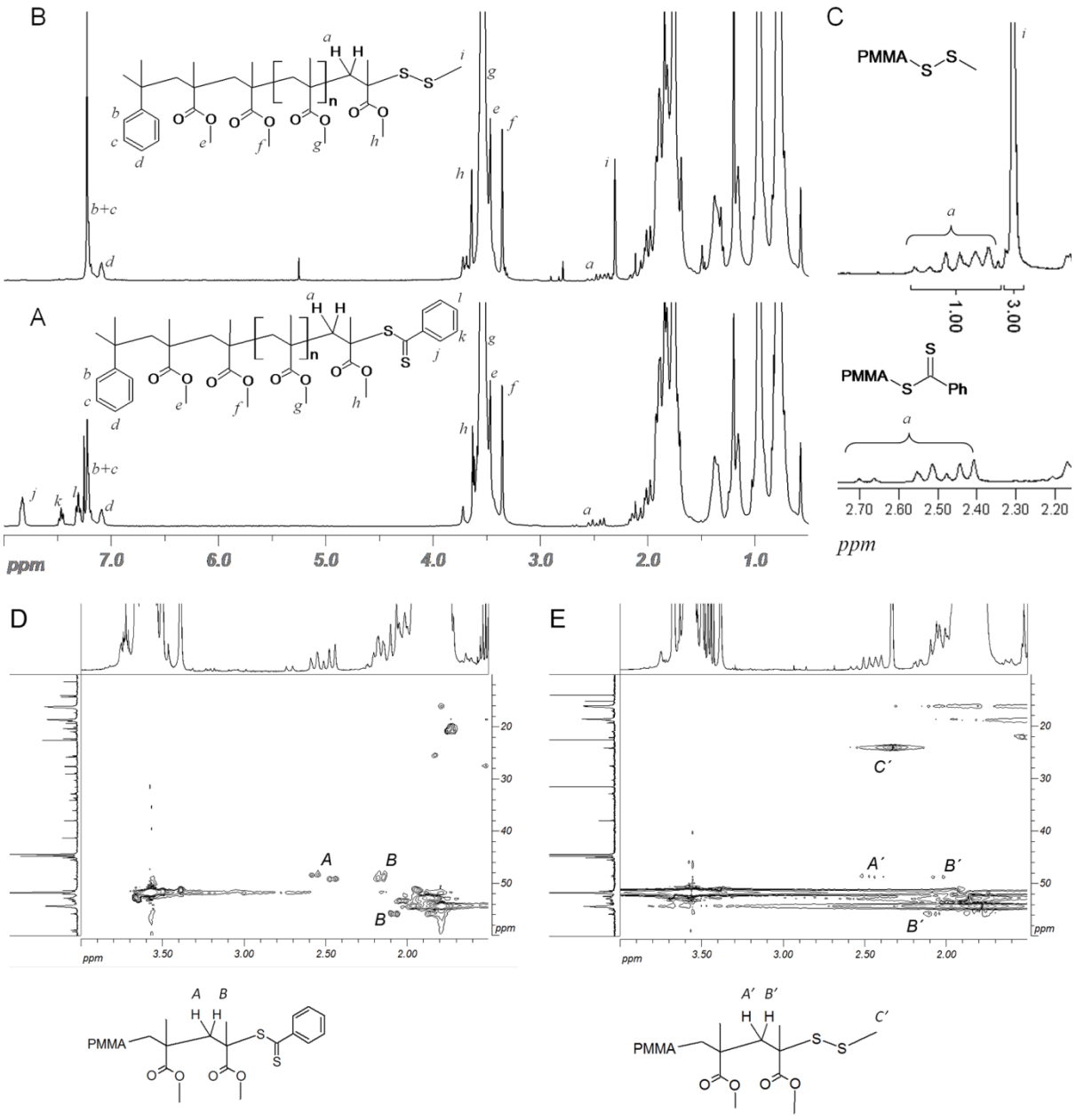


***Figure 2**. 400 MHz ^{1}H-NMR spectra ($CDCl_3$, internal signal at 7.24 ppm used as reference) of (A) the starting PMMA with dithioester end-group (**1**) and (B) the product of aminolysis with MTS (**3**). Part (C) is an enlarged region showing the single proton denoted a and the methyl end-group with integrals. HSQC spectra of polymers (**1**) (part D) and polymer (**3**) (part E) show the shift of the methylene protons denoted A and B and the appearance of the distinct signal of the terminal methyl group.*

Organic disulfides are very stable in air, towards water and nucleophiles and bind strongly to gold surfaces forming the SAMs as the corresponding thiols.[38] We therefore expected the methyl disulfide terminated polymer would show a stronger affinity towards gold surfaces and therefore result in better SAMs than the dithioester terminated polymers. We compared the self-assembly of polymers that differed only by their end group (dithioester versus methyl disulfide) on a gold surface by surface plasmon resonance (SPR) measurements. PMMAs (**1**) and (**3**) were measured in 0.1 mg / ml ethyl acetate solution. We also prepared a set of poly(ethyleneglycol monomethylether methacrylate) (PDEGMA)[39] (M_n = 5900 g/mol, M_w/M_n = 1.09) exhibiting dithioester and methyl disulfide termini[35] and compared their self-assembly behavior on gold surfaces by SPR using ethanol as solvent. The results are shown in figure 3. After an initial overshoot which was probably caused by chains adsorbing onto the

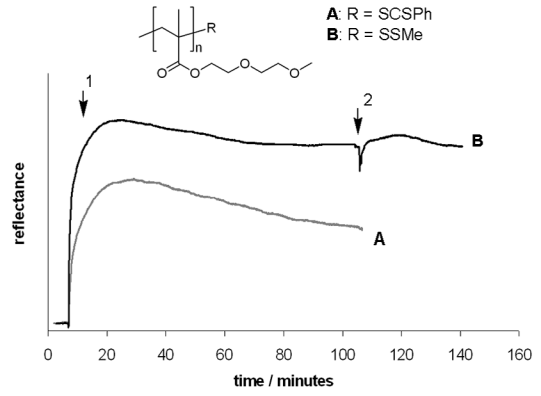


***Figure 3**. Reflectance versus time from SPR measurements of the starting poly[diethyleneglycol monomethylether methacrylate] (PDEGMA) with dithioester end group (curve A) and of PDEGMA with methyl disulfide end group (curve B). Both samples were measured in 0.1 mg / ml ethanol solutions. Position 1 marks the injection of solutions into the cell. Layer thicknesses before position 2 were 1.93 nm (A) and 3.23 nm (B). At position 2, the surface was washed with pure ethanol. After washing, the self-assembled PDEGMA-SSCH$_3$ film had a thickness of 3.22 nm. Layer thicknesses were calculated using ε_{real} = 2.25 for all organic layers.*

surface and then rearranging into a denser, more ordered packing, the $SSCH_3$-terminated PDEGMA reached a reflectance plateau implying that a stable SAM had been formed. Washing with pure solvent could not remove the adsorbed polymers. The dithioester terminated polymer also adsorbed onto the gold surface, however, after an overshoot the reflectance showed a steady decrease suggesting that the polymer desorbed from the surface again and no dense SAM was formed.[29] Similar results were obtained for PMMAs (**1**) and (**3**)[35] SAMs from asymmetric disulfides are known to phase separate upon annealing by S-S bond cleavage[40] and we therefore analyzed both PDEGMA-$SSCH_3$ and PMMA-$SSCH_3$ covered surfaces by AFM before and after annealing them at 100°C for 8 hours. The measurements revealed a smooth polymer coverage and no influence of annealing for both PMMA and PDEGMA.[35] It is likely that only PMMA-sulfyl groups remained attached to the gold surface with methyl thiols or methyl disulfides being desorbing into the solution again, similar to the results discussed for asymmetric disulfides in the literature,[38] thus producing the same monolayer that would have been obtained from a theoretical PMMA-SH. We also used the disulfide terminated PMMA to prepare polymer encapsulated gold nanoparticles using a two phase reduction of auric acid in the presence of PMMA-$SSCH_3$[41] resulting in particles of 5 ± 2 nm diameter, which were characterized by UV-Vis and TEM.[35]

In conclusion, we presented a simple modification of the aminolysis of polymethacrylates prepared by the RAFT process overcoming the problems of thiolactone and side product formation. The method uses the high reactivity of methyl methanethiosulfonate towards thiols, thus favoring methyl disulfide formation even in the presence of oxygen. The transformed disulfide end group showed a higher affinity towards a gold surface than the dithioester end group and could successfully be employed for encapsulation of gold nanoparticles. This method enables polymethacrylates to be grafted onto metal surfaces and also opens new routes to end group functionalization of RAFT polymers.

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Supporting Information Available. Experimental details for the synthesis of PMMA, PDEGMA and polystyrene with dithioester termini, GPC analysis of polystyrene aminolysis with and without MTS, UV-Vis data following the disappearance of the dithioester absorbance with amine / MTS treatment, ^{13}C NMR spectra of PMMA with SCSPh and $SSCH_3$ end groups, SPR data of PMMA with $SSCH_3$ and SCSPh end-groups adsorbing onto a gold surface, AFM images of PMMA-$SSCH_3$ and PDEGMA-$SSCH_3$ covered surfaces before and after annealing and experimental details, UV-Vis absorbance and TEM images of gold nanoparticles obtained from PMMA-$SSCH_3$. This material is available free of charge at http://pubs.acs.org

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[35] see supporting information for details

[36] To a 6 mM solution of 3.9 k PMMA-dithioester (**1**) in THF 10 equivalents of *n*-propylamine were added and the mixture was stirred at room temperature for 3.5 hours. No inert atmosphere was used. The polymer was precipitated from methanol several times to completely remove low molecular weight substances.

[37] To a 6 mM solution of 3.9 k cumyl-PMMA-dithioester (**1**) in THF 20 equivalents of MTS (**2**) were added and after 1 minute 10 equivalents of *n*-propylamine were added and the mixture was stirred

at room temperature for 3.5 hours. No inert atmosphere was used. The polymer was precipitated from methanol several times to completely remove low molecular weight substances.

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Versatile ω-End Group Functionalization of RAFT Polymers Using Functional Methane Thiosulfonates

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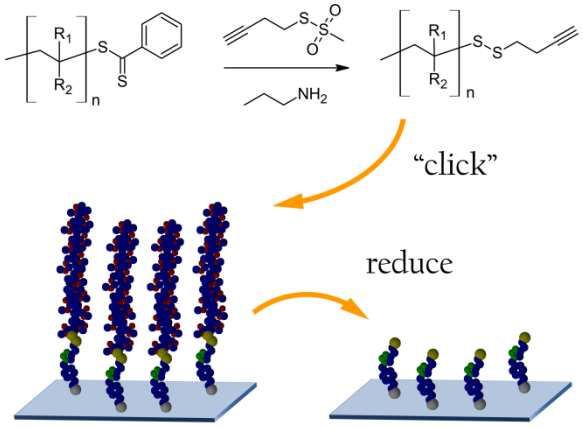


Abstract.

Five different polymers, poly[methyl methacrylate] (PMMA), poly[lauryl methacrylate] (PLMA), poly[diethylene glycol methacrylate] (PDEGMA), poly[*N*-isopropylacrylamide] (PNIPA) and poly[styrene] (PS) prepared by the RAFT process and thus terminated with dithioesters were aminolyzed in the presence of *S*-3-butynyl methane thiosulfonate (MTS), which was synthesized in two steps. Analysis of the polymers by 2-D NMR, UV-vis absorbance, and gel permeation chromatography revealed them to quantitatively carry acetylene end groups connected with disulfide bridges, indicating that functional MTS reagents can be employed for end group functionalization of RAFT polymers. This versatile method is of advantage compared to conjugations with functional maleimides, where isolation of terminal thiols is often required but inexpedient for poly[(meth)acrylates] because their terminal thiols may undergo backbiting and thus avoid conjugation. The acetylene terminated polymers were bound to an azide functionalized glass surface in a Cu (I) catalyzed cycloaddition. The modified surfaces exhibited water contact angles corresponding to the polarity of the attached polymers. In the case of the stimulus responsive polymers PNIPA and PDEGMA, the surfaces showed temperature dependent contact angles. The disulfide bond connecting the polymers to the surface could be selectively cleaved and resulted in all surfaces having the same contact angle, independent of the nature of the polymer prior attached to the surface.

Introduction

Reversible addition fragmentation chain transfer (RAFT)[1] polymerization is a very versatile polymerization technique to produce well defined polymers, block copolymers, polymer stars[2] and other complex polymer architectures.[3] Functional polymers with one or more reactive groups per repeating unit,[4,5] end group functionalized (hetero-) telechelic polymers,[6-10] (multi-) stimulus responsive materials,[11-13] organic-inorganic hybrid systems[14-16] or conjugates with bioactive molecules[10,17-19] demonstrate the huge success of the RAFT polymerization and may be followed in many reviews that have appeared over the past few years.[20-22] In RAFT, chain transfer agents (CTAs) are used that most commonly consist of a dithioester or a trithiocarbonate carrying an activating group Z and a leaving group R.[1] As a consequence of the polymerization mechanism, the monomers are inserted between the R group and the dithioester or trithiocarbonate. Both R and Z are retained as polymer end groups, the α- and ω-end group, and the polymer thus has the general structure R-Polymer-DTE-Z, where DTE abbreviates dithioester but may also be a trithiocarbonate or similar group. Introduction of functionalities at the α-end group can very easily be achieved by modifying the R group of the CTA used in the RAFT process. Following this R-approach, polymers with azide,[23,24,25] alkynyl,[24,26-28] dye,[29] biotin,[30] a galactose derivative, [31] *N*-hydroxysuccinimid[31] or pentafluorophenyl ester[9] end groups, as well as polymer stars originating from multifunctional chain transfer agents have successfully been synthesized.[2] The dithioester or trithiocarbonate is retained at the ω-end group of a polymer chain and remains reactive towards radicals,[7] heat or nucleophiles,[21,32] including water at a high pH.[33] The strong absorbance of dithioesters has been shown to interfere with other chromophores through exciplex formation and quenching.[34] Thus, several methods to completely remove the sulfur containing end groups from a polymer, such as reduction with stannanes or thermolysis, have been reported.[21,32]

A strategy towards ω-functionalized polymers, however, is to make use of a terminal thiol which may be released from polystyrene derivatives and poly[(meth)acrylamides] prepared by the RAFT process by aminolysis.[35-41] Thiol terminated polymers have not only found extensive use in producing self-assembled monolayers on metal surfaces, such as gold nanoparticles,[34-37] but they are also widely used for end group conjugation.[38-41] Very popular is the reaction of the terminal SH group with maleimides[6,38,39,41,42] or acrylates[38] via Michael addition or with iodoalkanes[42,43] through nucleophilic substitution. Using this approach, poly(*N*-isopropylacrylamide) (PNIPA) with pyrene,[41-43], hydroxyl[38,42] or maleimide[39] end groups or poly(methyl methacrylate) (PMMA) with hydroxy end groups[6] have been synthesized. However, releasing a thiol by aminolysis and subsequent conjugation has several drawbacks: (i) Maleimides do not exhibit a very strong selectivity towards thiols but also undergo Michael addition of amines.[44] Thus, a two-step reaction is often employed; first, a polymer with terminal SH groups is prepared by aminolysis. After purification from the excess of amine, a functional maleimide can be added in a second step.[41] (ii) The terminal thiols are prone to oxidation by oxygen. The resulting polymer-polymer disulfides do not undergo conjugation reactions, which makes it mandatory to work under inert atmosphere or add reducing agents to prevent disulfide formation. (iii) Quantitative synthesis and purification of terminal thiols fails for poly[(meth)acrylates] because the initially formed SH group backbites into the penultimate monomer unit resulting in a thiolactone,[45] thus maleimide conjugation is not quantitative[6] or even impossible with poly[(meth)acrylates].

A different method of introducing ω-functionalities that works for both polystyrene, polyacrylamides and poly[(meth)acrylates] is to synthesize a chain transfer agent that contains a functional Z group which is retained as polymer ω end group. Using this Z-approach, polymers with terminal octadecyl chains,[46,47] azides[48] or fluorescent groups[49] have been synthesized. Bulmus, Davis and co-workers synthesized several trithiocarbonate CTAs containing a pyridyl disulfide moiety as the Z group.[10,18,19,50] This functional group is stable under the polymerization conditions[19] and provides an ω end group, which can be reacted with various thiols yielding unsymmetrical disulfides. Disulfides are very stable toward air, water and other nucleophiles. They may be biologically or chemically reduced, making polymers containing

molecules attached via a disulfide bond possible candidates for drug delivery.[51]

Along with alkyl thiosulfates (Bunte salts)[52] and alkyl methanethiosulfonates (MTS),[53-55] pyridyl disulfides[56] are reagents with an electrophilic sulfur atom. All three kinds of reagents undergo very selective exchange reactions with free thiols yielding unsymmetrical disulfides and are therefore widely used in organic synthesis and biochemistry. Their high selectivity toward thiols versus amines and other nucleophiles makes this thiol chemistry complementary to both activated esters, which react easily with amines but not thiols; and also to click-chemistry,[57] the copper (I) catalyzed cycloaddition of an azide to an acetylene. In fact, both pairs of reactivities, i.e. pyridyl disulfide and activated esters;[58] and pyridyl disulfide and azides[10] have been employed and selectively conjugated in the same polymer chains.

The Z-approach, which may be independently used in addition to an R-approach, shows elegantly the versatility of the RAFT process in producing very well defined materials and thus the combination of both approaches leads directly to hetero-telechelic polymers,[10,46]. However, compared to an aminolysis and subsequent maleimide conjugation, only polymers derived from special Z-functionalized CTAs are eligible for post-polymerization modifications such as a click reactions[48] or disulfide exchanges.[10,18,19,50] Also, the reactive dithioester or trithiocarbonate moiety remains positioned in between the polymer chain and the functionalized ω group, making the highly defined material susceptible towards all kinds of nucleophiles, radicals, heat or even trace amounts of peroxides in cyclic ether solvents.[59]

We recently showed that methyl methanethiosulfonate (MTS) can be added to an aminolysis of PMMA prepared by the RAFT process to prevent thiolactone formation.[60] The thiols released at the polymer end group preferred the reaction with MTS over the competing side reactions even if oxygen was present, thus terminal methyl disulfides were formed. In the present study, we investigate whether this reaction may also be employed to introduce functional ω end groups into RAFT polymers. Compared to the method by Bulmus and Davis, we do not synthesize a CTA containing a thiol reactive site but we make use of the thiol that we in situ release from the terminal dithioester and react it with a small molecule, which contains a thiol reactive site – MTS – in one step. Such a reactive moiety can be introduced into a small molecule through nucleophilic substitution of a halogen. Also, a wide variety of MTS reagents are commercially available. As the introduction of terminal methyl disulfide groups proceeded in a one pot room temperature reaction without inert atmosphere, we expect the reactions with functionalized MTS reagents to proceed similarly and to work on poly[(meth)acrylates] as well as polystyrenes and poly[(meth)acrylamides].

The scope of the present paper is to synthesize a functional MTS reagent and show that various polymers, poly[methyl methacrylate] (PMMA), poly[lauryl methacrylate] (PLMA), poly[diethylene glycol methacrylate] (PDEGMA), poly[*N*-isopropylacrylamide] (PNIPA) and poly[styrene] (PS) which were derived from different common chain transfer agents, could be modified at their ω–end groups with near quantitative yields. As example for a functionality, an alkynyl moiety was chosen because of its easy detection via NMR and because this approach allows further end group manipulations by click chemistry. We subsequently clicked the acetylene-terminated polymers onto an azide-functionalized surface enabling analysis through water contact angle measurements. We could then successfully remove the polymers from the surface again by reducing the disulfide bonds. This method is a simple but effective alternative to other approaches to functional ω end groups of RAFT polymers.

Experimental Section

Material and Methods. All reagents were obtained from Acros, Aldrich, or Fluka and used as received unless stated differently. THF was distilled from sodium / potassium. Toluene was distilled from sodium. CuBr was washed several times with glacial acetic acid.

Contact angles were measured of advancing water drops. Values given were averaged from at least eight measurements. Generally, the standard deviation of these values was below 2 degrees. NMR data was obtained on a 400 MHz FT-spectrometer from Bruker. The chemical shifts relative to TMS are given in ppm. Molecular weights obtained from GPC measurements are polystyrene equivalents.

Chain Transfer Agents. In this study, polymers derived from four different CTAs were employed. Pentafluorophenyl-(4-phenylthio-carbonylthio-4-cyanovalerate) (PFP-PCV) was synthesized as previously described.[9] Cumyl dithiobenzoate (cumyl-DTB), benzyl dithiobenzoate (benzyl-DTB) and 4-phenylthio-carbonylthio-4-cyanovaleric acid (PCVA) were synthesized according to literature procedures.[21]

Sodium Methane Thiosulfonate 1. Sodium methane thiosulfonate was synthesized according to a literature procedure.[61] Briefly, 39 g (0.3 mol) of sodium sulfide hydrate (60-63%) were dissolved in 113 mL of deionized water at 60°C. The solution was cooled to 0°C, and 34.5 g (0.3 mol) of methanesulfonyl chloride was added drop wise. The mixture was heated to reflux for 18 hours, turning yellow, and then brown. A precipitate was removed by filtration and the solvent was removed. The combined solids were extracted several times with ethanol. Upon removing the ethanol, 18 g (45%) of sodium methane thiosulfonate were obtained. ^{1}H NMR (D_2O), δ = 3.38. ^{13}C NMR (D_2O) δ = 54.5.

***S*-But-3-ynyl Methane Thiosulfonate 2.** Sodium methane thiosulfonate **1** (2.86 g, 21.3 mmol) was dissolved in dry DMF (28 mL) and a solution of 4-Bromo-but-1-yne (1 mL, 1.42 g, 10.65 mmol) in dry DMF (2 mL) was added. The mixture was stirred overnight at 40 °C. Precipitated sodium bromide was removed by filtration. DMF was removed in vacuum and the residue was extracted with diethyl ether several times. Upon removal of the solvent, spectroscopically pure product (1.38 g, 79 %) could be obtained as a viscous liquid. ^{1}H NMR ($CDCl_3$) δ = 3.32 (s, 3 H, CH_3); 3.26 (t, 2 H, S-CH_2); 2.65 (2 H, td, S-$CH_2C\mathit{H}_2$), 2.06 (t, 1 H, CCH). ^{13}C NMR ($CDCl_3$) δ = 80.75 (*C*CH); 70.99 (*C*CH); 50.93 (S-CH_2); 34.95 (CH_3); 19.92 (S-$CH_2\mathit{C}H_2$).

Polymers 3a-3e. Polymerization was carried out as previously described.[9] For a short (2.2K g/mol) PMMA, a ratio for monomer:cumyl-DTB:AIBN of 6:1:0.1 was chosen. Molecular weights and PDIs determined by GPC are given in table 1.

General procedure for end-group modification 4a-4e: All polymers were functionalized according to the same general procedure: To a 42 mM solution of dithioester terminated polymers **3a-3e** in chloroform first 20 equiv. of butynyl-MTS **2** were added, then 50 equiv. of n-propyl amine were added under vigorous stirring. The reaction mixture was stirred overnight at room temperature, turning first orange then yellow within a few hours. The resulting polymers **4a-4e** were purified by several consecutive precipitations into diethyl ether (PDEGMA, PNIPA), methanol (PLMA, PS) or diethyl ether / hexane (1:1) (PMMA). Yields of purified polymers were: PDEGMA (61%), PLMA (79%), PNIPA (70%), PS (45%), PMMA (21%). The low yield of the latter two polymers may be attributed to the low molecular weights (PS 1170 g/mol; PMMA 2200 g/mol), which generally causes purification problems. The obtained products were however spectroscopically clean. The complete absence of excess reagent could be verified by the absence of a UV absorbance band centered at 293 nm. Data is discussed in detail in the text below.

4-Vinylbenzyl Azide 5. 4-Vinylbenzyl chloride (10 g, 65.52 mmol) was dissolved in 200 mL of acetone and cooled to 0 °C. Sodium azide (6.55 g, 100 mmol) dissolved in 25 mL of water was added and the mixture was stirred for 24 h. Cold water was added to the suspension and it was extracted three times with cold toluene. The organic phases were dried (magnesium sulfate) and the solvent was removed. 9.92 g (95 %) of a clear liquid was obtained. A proton NMR measurement showed a complete shift of the benzylic CH_2 group from 4.55 ppm to 4.32 ppm indicating that the complete substitution had yielded a pure product. ^{1}H NMR ($CDCl_3$) δ = 7.38 (m, 4 H, Ar-H); 6.73 (dd, 1 H, Ar-C*H*CHH); 5.78 (dd, 1 H, Ar-CHCH*H*); 5.39 (dd, 1 H, Ar-CHC*H*H); 4.32 (d, 2H, Ar-CH_2N_3).

4-(Azidomethyl)-phenylethyl-(dimethyl)-chlorosilane 6. 4- Vinylbenzyl azide **5** (2 g, 14 mmol), dimethylchlorosilane (2.65 g, 28 mmol), platinum/charcoal (10 mg) and 20 mL of toluene were combined in an argon atmosphere and stirred for 5 days at 40 °C. The catalyst was filtered off and the solvent and excess of hydrosilane and other volatile side products were removed in vacuum. 3.09 g (87%) of a light yellow liquid were obtained. ^{1}H NMR ($CDCl_3$) δ = 7.38 (m, 4 H, Ar-H); 4.31 (d, 2H, Ar-CH_2N_3), 2.49 (m, 2 H, Ar-CH_2-CH_2-Si), 0.64 (m, 2 H, Ar-CH_2-CH_2-Si), 0.35 (s, 6 H, Si-CH_3).

Azide functionalized glass slides 7. Glass slides were first rinsed with a detergent solution, then rinsed thoroughly with deionized water and activated in oxygen plasma for 20 minutes. They were then immersed into a 1 wt % solution of 4-(azidomethyl)-phenylethyl-(dimethyl)-chlorosilane **6**

in THF overnight. After self-assembly of the chlorosilanes, the slides were thoroughly washed with THF to remove all unbound materials and were dried in vacuum at 40°C for 24 hours.

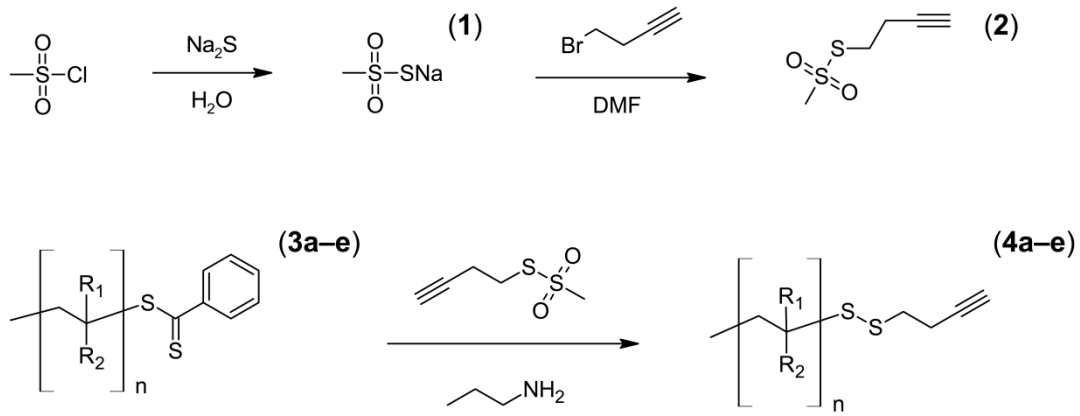
General procedure for surface click reaction 8. Very flat flasks with a ground neck and a vacuum outlet were used for surface reactions as they allowed a small volume of solution to cover the slide entirely. Generally, 10 mg of CuBr was added to the flask, 7 mL of a 20 mM solution of acetylene terminated polymers **4a-4e** in freshly distilled THF and the azide functionalized glass slide **7** were added. The ground neck was sealed with a septum and the outlet connected to a vacuum line and the flask was degassed by 4 freeze-pump-thaw cycles, refilling with argon each time. Then, pentamethyltriethylenetriamine (PMDETA, 26.2 µL) dissolved in 1 mL of freshly distilled THF was injected through the septum and the flask was lightly shaken to ensure dissolution of the catalyst. The mixture turned very light green and was let sit at room temperature overnight. The glass slides were removed from the flask and consecutively immersed and let sit into 3 beakers containing fresh THF, then they were rinsed thoroughly by pouring fresh THF over them for several minutes. The slides were then dried in vacuum at 40°C for 24 hours. Contact angles are given in table 1 and figure 5.

General procedure for reduction of disulfide bonds 9. To remove the polymers that had been attached through click chemistry by reducing the disulfide bonds, the glass slides were immersed into a 0.1 M solution of dithiothreitol in chloroform and let sit for 48 hours. After that, the slides were first washed with chloroform, then with THF and dried in the same way described above. Contact angles are given in table 1 and figure 5.

Results and Discussion

For showing that functional ω-end groups of RAFT polymers may be introduced in a single step by adding a functionalized methane thiosulfonate (MTS) to the aminolysis, we first synthesized an MTS molecule featuring a butynyl residue (**2**). This functional group was chosen as an example because it allows for analysis through NMR and more importantly, it provides the possibility of subsequently performing click chemistry[57] at the polymer end group. Click Chemistry, or the copper(I) catalyzed 1,3 dipolar cycloaddition of an acetylene to an azide is a very versatile tool because it proceeds under very mild conditions and with very high yields and thus, both triple bonds and azides have become very popular moieties in the synthesis of functional polymers. Azides[62] and alkynes[63,64] have been introduced into monomeric units and subsequently used for attaching a functionalized counterpart. Initiators for atom transfer radical polymerization (ATRP)[65] containing both azides[66] and protected acetylenes[67] have been reported on. The substitution of terminal halides from polymers prepared by ATPR with azides has led to a wide variety of polymer end group functionalizations by click chemistry and architectures such as photocleavable stars[68] could be realized. Modular approaches to di-[67] and triblock[69] copolymers using telechelic azide / acetylene terminated polymers have been described by van Hest and co-workers. For RAFT, several azide functionalized chain transfer agents have been synthesized and successfully employed for attaching various acetylenes[23-25] including biomolecules[10,17] to the polymer α end groups and for synthesizing hetero-arm stars[70]. Also, CTAs with an alkyne R-group have been synthesized and used for the preparation of diblock copolymers,[24,26] surface modifications[27,28] or tadpole shaped copolymers[71] by click chemistry. A terminal ω azide via a Z-approach was presented by Zhu and co-workers and used for attaching a fluorescent dye.[48] Especially the complex systems such as diblocks or stars rely on the very high conversion of this cycloaddition even at polymer end groups. However, click chemistry at the ω-end group of RAFT polymers by replacing the dithioester has – to the best of our knowledge – not been presented yet. These works also contributed to our decision to choose an acetylene as an example of a functional group to be introduced via MTS chemistry.

Synthesis of Butynyl-MTS. The synthesis of butynyl-MTS **2** proceeded in two steps (scheme 1). First, sodium methanethiosulfonate (Na-MTS, **1**) was synthesized by reacting chloro methylsulfonic acid with sodium sulfide according to a literature procedure.[61] Pure Na-MTS could be obtained on a multi-gram scale. In the second step, Na-MTS was employed in excess as nucleophile to replace a bromide from a butynyl residue. Dry DMF could be



Scheme 1. *Two step synthesis of butynyl methane thiosulfonate and its role during the aminolysis of dithioester terminated polymers.*

used as solvent for both reactants, resulting in a precipitation of the side product sodium bromide as the reaction progressed over 24 hours. For workup, NaBr was removed by filtration, DMF was removed in vacuum, and the residue was extracted with diethyl ether, leaving behind the excess of Na-MTS, which is not soluble in diethyl ether. The product obtained after removing the solvent was pure and contained only trace amounts of DMF, as could be seen from ^{1}H and ^{13}C NMR spectroscopy, and was used for polymer modifications without any further workup. Butynyl-MTS **2** is soluble in many organic solvents with polarities ranging from methanol to toluene and will also dissolve in a 1:1 methanol / water mixture (hydrolysis will eventually occur) and in a 2:3 diethyl ether / hexane mixture. This broad range of solubility made it very easy to find suitable solvents or solvent mixtures to precipitate various polymers including very short polymer chains, which often exhibit purification difficulties.

Polymer functionalization. Five different polymers **3a-3e**, including the three poly[methacrylates] PMMA, PLMA and PDEGMA; polystyrene and poly[*N*-isopropylacrylamide] which had been synthesized from different CTAs (table 1) were aminolyzed with n-propyl amine in the presence of butynyl-MTS (scheme 1). Whereas the cumyl and benzyl α groups of the polymers are not effected by the amine / MTS treatment, the acid α group originating from PCVA will reversibly be deprotonated and the pentafluorophenyl (PFP) activated ester end group will be transformed into the n-propyl amide during aminolysis.[72] A propyl amide α group will hardly change the polymer's size, solubility or other of its properties compared to a PFP ester or acid end group, but this approach offers the possibility of doing chemistry on both end groups and encourages the use of a functional amine to perform both the replacement of the PFP ester and the aminolysis of the dithioester. Activated ester and electrophilic sulfur chemistry have been shown to be complementary and not to effect each other.[58] However, within this paper we want to focus on the method and the successful manipulation of the ω-end group. For the end group reactions, chloroform was used as solvent for all polymers. To 1 equiv. of polymers **3a-3e** 20 equiv. of butynyl-MTS **2** were added first, and after one minute 50 equiv. of n-propyl amine were injected. No degassing or inert atmosphere was employed. Reactions were typically stirred overnight at room temperature and afterwards the polymer was precipitated several times to ensure a complete removal of excess of MTS agent and of low molecular weight side products. The resulting triple bond terminated polymers **4a-4e** were analyzed by gel permeation chromatography (GPC), UV-vis spectroscopy, and NMR.

***Table 1**. Overview of polymers, the chain transfer agents they were derived from, molecular weights and polydispersity indices of dithioester terminated polymers **3a-3e** and after exchange with butynyl disulfide end groups **4a-4e**, and water contact angles of glass slides with polymers clicked onto them **8a-8e** and after reduction with DTT **9a-9e**.*

	Polymer	CTA used	Dithioester End Group (**3**)		Acetylene End Group (**4**)		Contact Angles on Surface [°]		
			M_n [g/mol]	PDI	Mn [g/mol]	PDI	Polymer (**8**) T=20°C	40°C	Reduced (**9**)
a	PMMA	Cumyl-DTB[1]	2,200	1.10	2,600	1.07	80	---	65
b	PDEGMA	PFP-PCV[2]	10,200	1.17	11,500	1.17	30	61	64
c	PLMA	PFP-PCV	10,300	1.10	10,400	1.10	99	---	65
d	PS	Benzyl-DTB[3]	1,170	1.09	1,400	1.10	85	---	69
e	PNIPA	PCVA[4]	6,600	1.16	7,300	1.18	73	90	64

1) Cumyl dithiobenzoate;
2) Pentafluorophenyl-(4-phenylthiocarbonylthio-4-cyanovalerate)
3) Benzyl dithiobenzoate
4) 4-Phenylthiocarbonylthio-4-cyanovaleric acid

Polymer Analysis. The results of the GPC measurements are summarized in table 1 and exemplarily, the elution curves of PDEGMA **3b** and **4b** are shown in Figure 1. For all polymers, the MTS / amine treatment had the same effect on the molecular weight distributions: whereas the shape and the width of the peaks stayed the same, all signals were slightly shifted towards a higher molecular weight. We attribute this shift to the polymer coiling differently around its new end group and its therefore adopting a slightly higher volume, although the actual molecular weight of the butynyl disulfide end group (117 Da) is lower than the native phenyl dithioester end group (153 Da). It should be noted here, that the increase in molecular weight was still well below a signal corresponding to a double molecular weight material, and that no peak or shoulder of such a material appeared in the products **4a-4e**. This can also be seen from the polydispersity indices that remained as low as the ones of the starting polymers **3a-3e**. If butynyl-MTS had not been added to the reaction mixture, the oxygen present in the reaction would have caused a (partial) formation of polymer-polymer disulfides, which would have been easy to detect with GPC, as already published recently.[6,45,60] The absence of a double molecular weight peak for all polymers thus suggests that a different reaction pathway – one offered by the MTS reagent – was followed compared to an aminolysis without the MTS reagent.

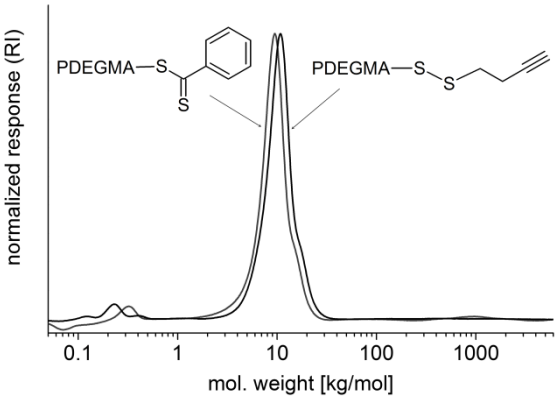


***Figure 1**. Gel permeation chromatograms of PDEGMA **3b** with dithioester terminus and PDEGMA **4b** with butynyl disulfide end group.*

UV-vis measurements showed a complete disappearance of the prominent dithioester absorbance band centered at 302 nm for all polymers **4a-4e**. As an example, the measurements of PLMA **3c** and **4c** are shown in figure 2. The reagent butynyl-MTS **2** also showed a weaker absorbance around 293 nm, which made UV-vis spectroscopy a useful tool to also monitor the complete removal of the excess of MTS reagent by precipitation (see supporting information).

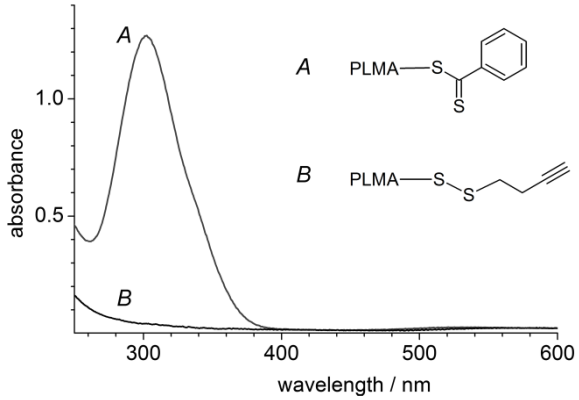


***Figure 2**. UV-vis spectra of PLMA **3c** before and PLMA **4c** after dithioester removal by aminolysis in the presence of butynyl-disulfide to be seen by the complete disappearance of the characteristic dithioester absorbance centered at 302 nm.*

Figures 3A and 3B show the ^{1}H NMR spectra of PMMA **3a** and **4a**. Both end groups are clearly visible. The aromatic region of PMMA **3a** shows both the signals of the cumyl α-end group and of the phenyl dithioester ω-end group. The *para* proton of the cumyl group, denoted *a*, was used as reference for integration as it is not effected by the MTS / amine reaction at the other end group. Between 2.78 and 2.42 ppm in spectrum A appears a multiplet, which arises from one of the two methylene group protons of the ultimate monomer unit, denoted *b*. The splitting of these signals and the difference between the two protons of this methylene group occur because of tacticity.[45] Integration of this signal group was equivalent to one proton, suggesting a very high telechelic functionality, i.e. a quantitative presence of the terminal dithioester, which is primarily responsible for the downfield shift of proton *b*. It has been reported that the percentage of polymer chains deficient of a terminal dithioester increases with an increasing molecular weight due to side reactions.[73] One should, however, also allow a certain error of a few percent of the NMR integration method. In the spectrum of PMMA **4a** (see Figure 3B) the integral of the para cumyl proton *a* was again set to 1.00. This curve is now clearly devoid of aromatic phenyl dithioester peaks. Instead, two new resonances arise as broadened triplets positioned at 2.78 and 2.53 ppm. The first, being caused by the methylene group adjacent to the newly installed disulfide bond (labeled *c*) has an integration value of exactly 2.00 protons. The signal resulting from the neighboring methylene group (*d*) overlaps with the peaks of the proton of the ultimate methylene group within the polymer (now called *b'*). It can however be seen that an upfield shift has occurred to the latter resonances as they now reach down to 2.38 ppm and their upper end can just made out at 2.59 ppm. We found the same shift when we introduced terminal methyl disulfide groups into PMMA.[60] The observed integration value of 3.00

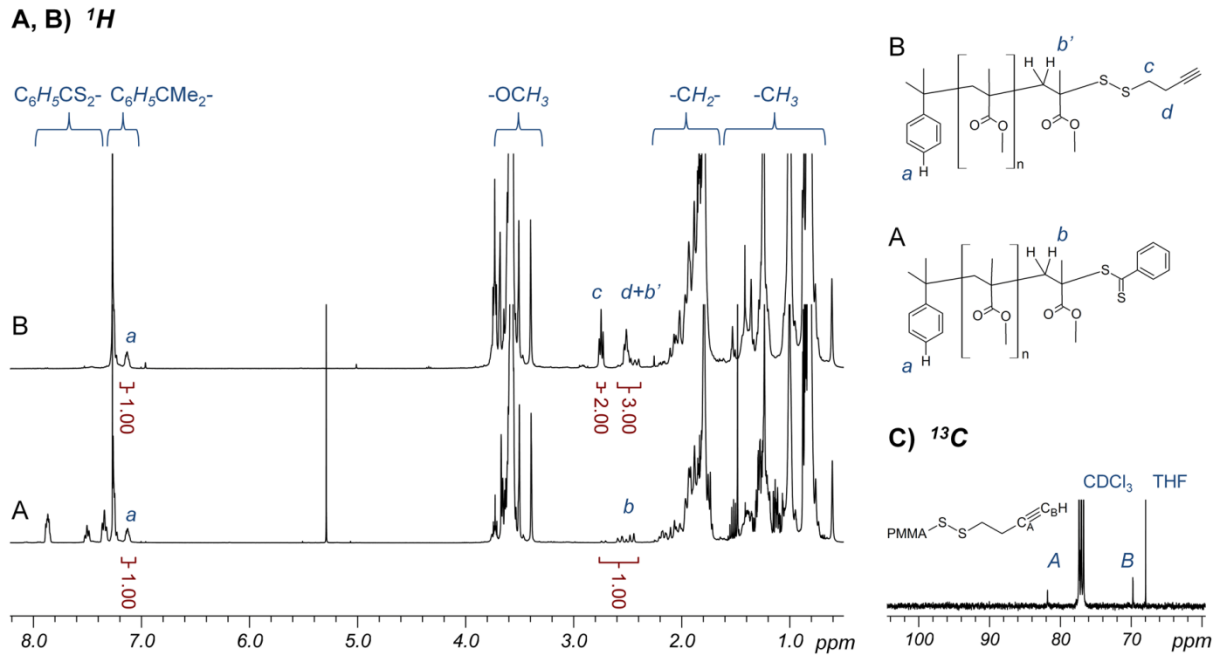


***Figure 3**. ^{1}H NMR spectra of PMMA **3a** with dithioester end group (A), PMMA **4a** with butynyl disulfide end group (B) and section of a ^{13}C NMR of PMMA **4a** showing the characteristic resonances of the acetylene moiety (C).*

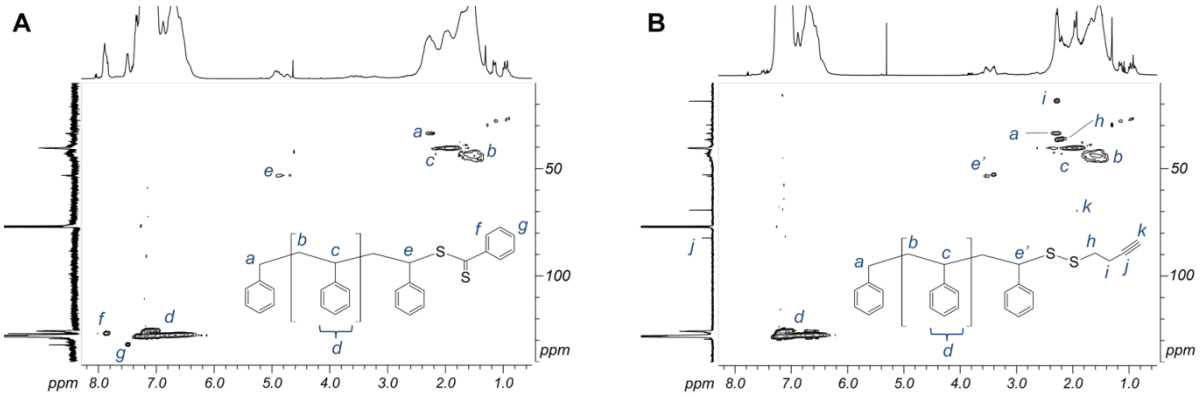
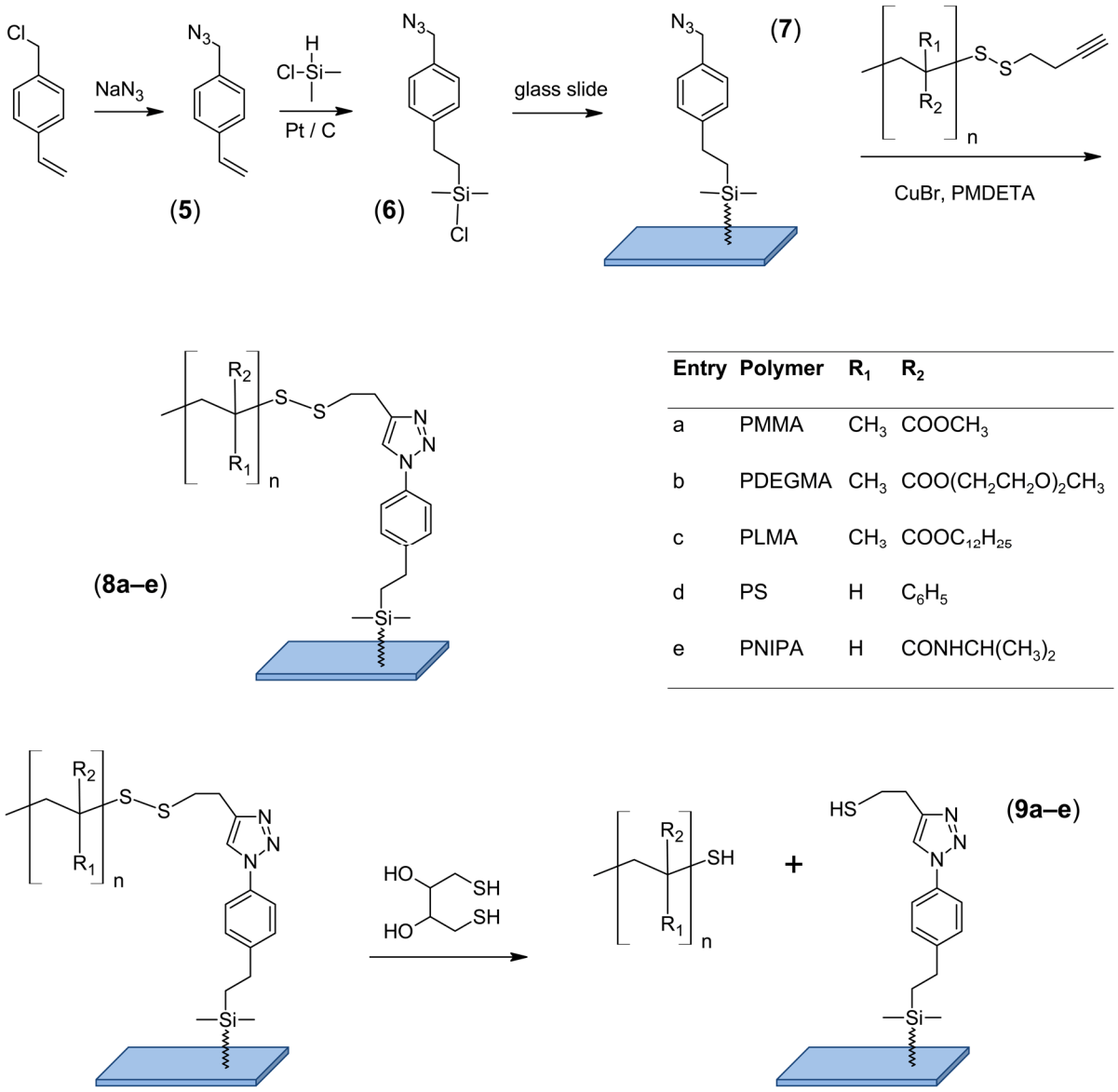


***Figure 4**. HSQC NMR spectra of PS **3d** (A) and of PS **4d** (B) showing the exchange of the dithioester end group with the butynyl residue.*

therefore exactly accounted for both the methylene *d* protons and proton *b'*. A section of the ^{13}C NMR spectrum of triple bond terminated PMMA **4a** is plotted in figure 3C, showing the signals of the acetylene carbons. As they were absent from a ^{13}C spectrum of the precursor PMMA **3a** (not shown), this data additionally confirms the presence of the butynyl end group.

Figures 4A and 4B show HSQC NMR spectra of polystyrenes **3d** and **4d**, respectively. As these polymers are very short (1.2K g/mol), the end groups can very well be observed. Of the three aromatic dithiobenzoate signals of the starting polystyrene **3d**, the ortho and para protons, labeled *f* and *g*, can be seen, whereas the meta proton lies underneath the aromatic backbone resonances *d*. Peaks *f* and *g* are completely absent from the spectrum of polystyrene **4d** (spectrum B). Instead, there arise signals from the two methylene groups of the butynyl disulfide end group located at 2.29 / 18.5 ppm and 2.21 / 36.5 ppm (^{1}H / ^{13}C), denoted *i* and *h*. Due to tacticity, the benzylic proton of the ultimate monomer unit gives rise to two broad absorbencies in the proton spectrum. With a terminal dithioester, these peaks are positioned at 4.87 and 4.69 ppm (spectrum A), whereas after the end group replacement the signals are completely shifted to 3.54 and 3.41 ppm (spectrum B). In the carbon spectrum of polystyrene **4d**, the acetylenic absorbencies located left and right of the internal $CDCl_3$ triplet at 82.3 ppm (*C*≡CH) and 69.3 ppm (C≡*C*H) are clearly visible. The resonance of the terminal acetylenic proton, labeled *k*, though visible, is very weak due to the high CH coupling constant, and only hardly distinguishable from the noise.

This data indicates that the end group functionalizations were successful. The dithioesters were completely removed, as seen from UV-vis measurements, whereas GPC showed that no double molecular weight material, such as a polymer-polymer disulfide was formed. For the polymers of low molecular weight, one- and two-dimensional NMR measurement could reveal the quantitative presence of the expected end groups. These experiments thus suggest that functional methanethiosulfonates can be employed for end group functionalizations of RAFT polymers. Such polymers may be derived from various common chain transfer agents and the method works equally well on polymethacrylates, polystyrenes and polyacrylamides.



Entry	Polymer	R_1	R_2
a	PMMA	CH_3	$COOCH_3$
b	PDEGMA	CH_3	$COO(CH_2CH_2O)_2CH_3$
c	PLMA	CH_3	$COOC_{12}H_{25}$
d	PS	H	C_6H_5
e	PNIPA	H	$CONHCH(CH_3)_2$

***Scheme 2**. Surface functionalization of glass slides: synthesis and self-assembly of a chlorosilane carrying an*

Surface Click Reactions. End group functionalized polymers have found broad application in the preparation of polymer brushes on surfaces via grafting-to methods[74], resulting in fine-tunable surface properties, i.e. surface wettability.[75] As the presence of the terminal triple bonds of polymers **4a-4e** had successfully been shown, we chose to click these polymers to azide functionalized glass surfaces **7**, producing polymer brushes on glass surfaces and allowing analysis through water contact angle measurements.[75] The success and high yield of polymer end group click reactions has already been demonstrated by several groups.[23,24,26,57,62,70] To obtain an azide functionalized surface, chlorosilane **6** was synthesized from 4-chloromethyl-styrene in two steps and was self-assembled onto glass slides from a 1 weight-% solution in THF (scheme 2). Before, the glass surface had a contact angle of 34° (see figure 5), typical of glass exhibiting silanols. After azide functionalization, the contact angle was 69°, suggesting the presence of more hydrophobic azidomethylphenyl groups on the surface. The copper(I) catalyst for click chemistry may be produced in situ by reducing a Cu(II) salt with e.g. citrate, but as our polymers contained a disulfide bond, no reducing agent could be applied. Instead, we used Cu(I)Br and pentamethyldiethylenetriamine (PMDETA) as ligand. This system is well known for ATRP and also works in the presence of disulfides, which are not reduced and do not coordinate

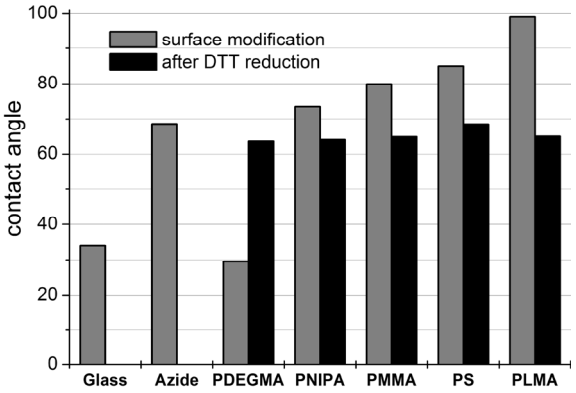


Figure 5. *Contact angles of the non-functionalized glass surface, after azide modification, after attaching acetylene terminated polymers via click chemistry (gray bars) and after selectively reducing the disulfide linkages with dithiothreitol (black bars). Contact angle values are given in table 1.*

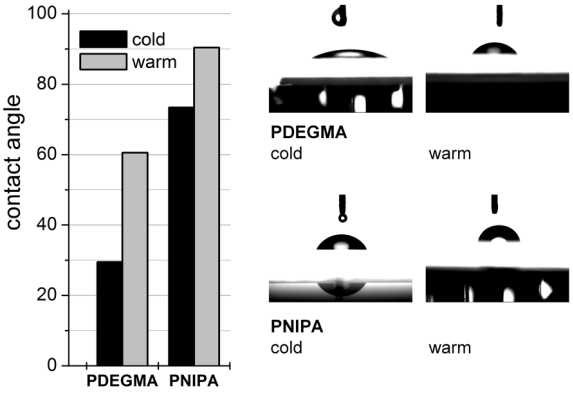


Figure 6. *Contact angles of stimulus responsive PDEGMA (**9b**) and PNIPA (**9e**) covered surfaces at room temperature (below LCST, black bars) and at around 40°C (above LCST, gray bars)*

to the copper.[76] The azide functionalized glass slide **7**, a solution of the acetylene terminated polymer **4a-4e** in THF and CuBr were first added into a flat flask with a ground neck; this mixture was degassed by four freeze-pump-cycles and then PMDETA was added. This ensured that no oxygen was present when the catalyst became soluble, therefore reducing the risk of an oxidative coupling forming diacetylenes. After the click reactions had proceeded overnight at room temperature, the glass slides **8a-8e** were thoroughly washed with THF to remove non-covalently bound polymer. Contact angles were measured after the slides had been dried in vacuum at 40°C for 24 hours. The contact angles are given in table 1 and are plotted in figure 5. The values ranged from 30° for the hydrophilic PDEGMA to 99° for the hydrophobic PLMA. All values were in agreement with measurements found in the literature, such as 70°[77] for PMMA compared to 80° found by us; 90°[77] for PS compared to 85° or 80°[78] for PNIPA compared to 73°. Contact angles do not only depend on the surface coverage with polymers, but also on the behavior of the upmost layer towards water. For both reasons, contact angles of polymeric substrates may vary.[79] A polyethylene glycol covered surface which is similar to PDGEMA had a contact angle of 33°,[78] which is comparable to 30° found by us for PDEGMA; and for a dodecyl acrylamide functionalized surface a contact angle of 102°[78] was reported, which is in good agreement with 99° found here for PLMA. The measurements thus indicate that polymers were indeed covalently bound to the surface in a way that thorough washing and rinsing could not remove them.

Two of the polymers employed, PDEGMA and PNIPA have a lower critical solution temperature (LCST) in water; PDEGMA of around 26°C,[80] PNIPA of about 32°C.[81] Below these values, the polymers are water soluble; above they become hydrophobic. Contact angles were thus also measured at elevated temperature. This was achieved by both using warm water and by warming the glass slide with a peltier element. The results are shown in figure 6. For both polymers, the contact angles increased significantly for temperatures above LCST. For PDEGMA a value of 61° (compared to 30° at room temperature) was reached, whereas the effect for PNIPA was not as pronounced (from 73° at room temperature to 90° above LCST), but in the same range as literature values where the contact angle increased from 80° to 103°.[78] Stimulus responsive surfaces are for great interest for applications in microfluidics.[82]

Reduction of the Disulfide Bonds. Five different acetylene terminated polymers could thus be clicked to a modified glass surface. They were connected via a disulfide bridge and in a next step, experiments were conducted to show that the polymers could easily be removed from the surfaces again by reducing the disulfide bonds (scheme 2). As reducing agent dithiothreitol (DTT) was chosen. It is well established in biochemistry as a quick and selective reducing agent for disulfides that is also well soluble in organic solvents. The polymer functionalized glass slides **8a-8e** were immersed into a DTT solution in chloroform for 48 hours and were then rinsed

with chloroform, thoroughly washed with THF and dried in vacuum at 40°C for 24 hours (same treatment as after click reactions). The contact angles measured after reduction are plotted as black bars in figure 5 and are also given in table 1. Independent of the polymer prior attached to the surface, all slides **9a-9e** showed contact angles between 63° and 65°, with only the former PS slide being a bit higher with 69°. All of these values being within a very small range suggest that the polymers were successfully removed and that largely, all surfaces were chemically identical, exhibiting free thiols.

Conclusion

In a previous report, we showed that for PMMA the formation of side products and product mixtures during the aminolysis of the terminal dithioester can be suppressed by the addition of methyl methane thiosulfonate. The thiol released at the polymer end group prefers the reaction with the methyl-MTS, which is itself very selective towards thiols, thus tolerating the excess of amines. Here, we showed that this reactivity can also be used to attach not only methyl disulfides but functional groups to various polymers, including polymethacrylates, poly[*N*-isopropylacrylamide] and polystyrene, originating from different common chain transfer agents. As an example, we used an acetylene end group. The corresponding reagent could easily be synthesized starting from the alkyl bromide. Compared to the common maleimide approach, the reaction proceeds in one step and is also applicable for poly[(meth)acrylates]. No inert atmosphere was needed because the reactivity of MTS towards thiols is high enough that oxygen oxidation is not a competing side reaction. Compared to the method of introducing a thiol reactive pyridyl disulfide into the CTA Z group,[49] the dithioester is not retained after end group functionalization and polymers derived from different common chain transfer agents could be employed for MTS end group conjugation. Availability of functional MTS reagents compared to functional thiols might limit this method, although many MTS reagents are commercially available. NMR measurements suggested quantitative conversions. The acetylene functionalized polymers were clicked onto an azide modified glass surface, resulting in surfaces exhibiting different contact angles. Also, the stimulus responsive behavior of PDEGMA and PNIPA functionalized surfaces could be monitored. As a consequence of the mechanism, disulfides are formed at the connection between polymer and end group. These could successfully be cleaved. The method offers the possibility of attaching a further functionality to a polymer end group by click chemistry and then removing it again using the complimentary reduction chemistry.

Supporting Information. UV-vis spectra of PMMA, PLMA, PNIPA and PDEGMA before reaction, after reaction and after purification. This data may be found in the online version of this article.

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Hetero–Telechelic Dye–Labeled Polymer for Nanoparticle Decoration

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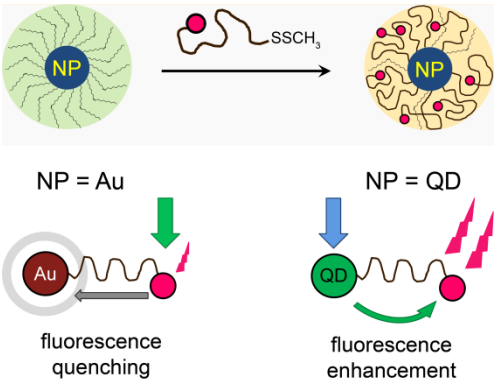


Abstract.

The synthesis of poly[methyl methacrylate] (PMMA) exhibiting one fluorescent dye (Texas Red) and one methyl disulfide end group is described. It is shown that the latter end group enabled the exchange of both oleic amine on gold nanoparticles (AuNP) and of oleic acid on CdSe / ZnS quantum dots (QD), allowing for a phase transfer of both types of nano particles (NP) from hexane into dimethylformamide due to the solubility provided by the PMMA chains. For AuNP, a fluorescence quenching of the dye was found due to fluorescence resonance energy transfer (FRET) from the dye to the AuNP, while QDs caused a fluorescence enhancement by FRET from the QD to the attached dyes. Due to the hetero-telechelic geometry of the polymer, the separation between NP and dye is governed by the end-to-end distance of the polymer.

Introduction

Polymers are promising materials for nanoparticle (NP) surface modifications, as hybrid materials combining the solubility, processability and functionality of the polymeric shells and the unique optical and electrical properties inherent to metal or semiconductor NP can be obtained.[1,2] Gold nanoparticles (AuNP) have an intense plasmon oscillation. Electronic excitation energy from a nearby molecule can be transferred to a AuNP, resulting for instance in the fluorescence quenching of chromophores.[3-5] Semiconductor NP (Quantum Dots, QD) are used as biolabels[2,6] and as energy donors in biological[7] and optoelectronic[8] research because of their high quantum yields, high photostability and their narrow fine-tunable emission spectra. For both types of NP, there is a strong dependency of the energy transfer efficiency on the distance between NP and chromophore.[4,9] Thus, there is a high scientific interest in fine-tuning this distance,[10-14] both to gain further insights into transfer mechanisms deviating from the r^{-6} distance dependence[5,15] and for applications such as (bio-) sensors[16] or optical memory.[17] Specific distances between dyes and a NP have especially been realized through DNA and protein spacers of a known size, requiring however an elaborate micro-scale multistep synthesis, as the biomolecules need to be tailored with a fluorescent dye and need to have an appropriate binding site for NP attachment.[6,7,11] Polymeric ligands have the advantages of functionalities such as anchor groups capable of coordinating to a NP surface, fluorescent dyes, or residues providing solubility being easily introduced along the backbone of a reactive polymer and of being available on a multi-gram scale.[18-19] However, the average NP–dye distance is ill-defined as both the dyes and the anchor groups are statistically distributed along each polymer chain. A straightforward polymer architecture giving rise to a well defined NP–dye distance would be a hetero-telechelic polymer with an anchor group at one end and a fluorescent dye at the other, with the polymer chain in between acting as a spacer with a known end-to-end distance.

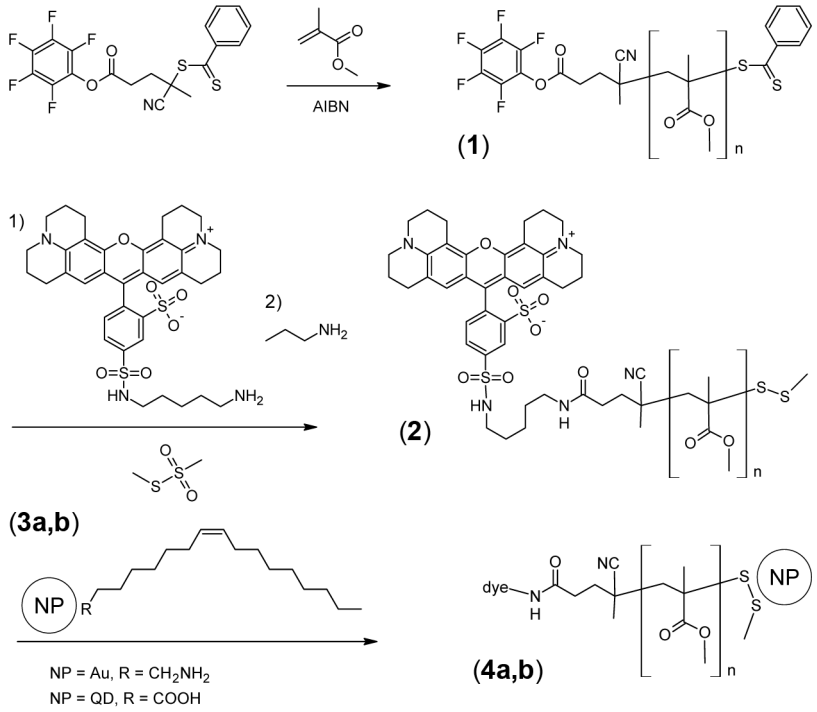
Herein, we present the synthesis of such a polymer by reversible addition fragmentation chain transfer (RAFT) polymerization combining two recent methods for end group functionalization. RAFT polymerization produces polymers with a dithioester or trithiocarbonate ω end group.[20] Aminolysis of this group may yield a terminal thiol, capable of coordinating to a gold surface, however, side reactions occur with poly[(meth)acrylates].[21] It was recently shown that addition of methyl methanethiosulfonate (MTS) to an aminolysis produces defined methyl disulfide end groups also on poly[(meth)acrylates]. The SS–CH_3 terminated polymers were well capable of attaching to a planar gold surface and could also stabilize AuNP.[22] For the present purpose, the use of MTS for ω end group modification was combined with an activated pentafluorophenyl (PFP) ester α end group,[23] to produce a poly[methyl methacrylate] carrying the fluorescent dye Texas Red and a SS–CH_3 moiety as end groups, in a one pot reaction. Apart from presenting a simple but effective route to hetero-telechelic polymers, we further exploit the use of terminal SS–CH_3 groups in tethering fluorescent dyes to both metal and semiconductor NP through ligand exchange and observing the effects of each type of NP onto the dye.

Experimental Part

Oleic Acid Stabilized CdSe / ZnS Quantum Dots (OA-QD, **3b**) with an emission maximum of 534 nm were courteously provided by the group of Prof. Char (SNU, Korea).[24]

α-Pentafluorophenyl, ω-Dithioester Poly[methyl methacrylate] (PFP-PMMA-DTE, 1) was synthesized as previously reported.[23] M_n (GPC) = 9800 g/mol, PDI (GPC) = 1.14.

α-Texas Red, ω-Methyl Disulfide Poly[methyl methacrylate] (TR-PMMA-SSMe, 2). 25.5 mg (2.6 μmol) of PFP-PMMA-DTE **1** was dissolved in 50 μL of dry chloroform and 300 μL of dry DMF. 4.92 μL (52 μmol) of methyl methanethiosulfonate were added, then 1.477 mg (2.1 μmol) of Texas Red Cadaverine and 1.32 μL (9.5 μmol) of triethylamine were added. The mixture was stirred at 35°C for 16 hours, then 2.14 μL (26 μmol) of n-propylamine were added. Stirring was continued at room temperature for 24 h. The polymer was precipitated into cold methanol three times and removed by centrifugation each time. After drying, 18.7 mg (73 %) of a dark violet solid were obtained. UV-vis: λ_{max} = 580



Scheme 1. *RAFT polymerization of methyl methacrylate using a pentafluorophenyl (PFP) activated ester functionalized chain transfer agent, synthesis of α-PFP, ω-methyl disulfide poly[methyl methacrylate] and its use in modifying OA-AuNP or OA-QD through ligand exchange.*

nm. M_n (GPC) = 12200 g/mol, PDI = 1.13. Amount of dye labeling: 74%.[25]

For synthesis of oleyl amine stabilized gold nanoparticles (**OA-Au, 3a**); modification of gold nanoparticles **3a** with polymer **2** (**Au-TR, 4a**) and modification of Quantum Dots **3b** with polymer **2** (**QD-TR, 4b**), please see supporting information.

Results and Discussion

The synthesis of the α, ω functionalized polymer **2** is outlined in scheme 1. RAFT polymerization employing a pentafluorophenyl (PFP) functionalized chain transfer agent afforded the α-PFP, ω-dithioester PMMA **1**. As the PFP ester reacts faster with amines than the dithioester, after the addition of an excess of MTS, 0.81 equiv. of Texas Red (TR) Cadaverine was added first. As several polymer chains would be attached to each NP, it was not necessary that every single chain be dye-functionalized, thus less than one equiv. of TR was used and a functionality of 74% was obtained. After 16 hours, an excess of n-propyl amine was added in order to aminolyze both the remaining PFP esters and to set free the terminal thiols on the other end group, which could then react with the MTS reagent. Gel permeation chromatography (GPC) using a UV-vis detector set to the absorbance maximum of the dye (580 nm) showed that the dye had been attached to the polymer and that repeated precipitation had successfully removed any lose dye (Figure 1a). The apparent molecular weight of polymer **2** was higher than expected from polymer **1**, because of a modified coil conformation in the presence of the two new end groups.[22] The polydispersity of polymer **2** did, however, not increase and no peak nor shoulder of double molecular weight appeared, indicating that no side reactions such as formation of polymer-polymer disulfides had occurred. The ability of the polymer to coordinate to a gold surface was confirmed by a surface plasmon resonance (SPR) measurement, indicating that the methyl disulfide had also successfully been introduced into the polymer (Figure 1b). The end-to-end distance of TR-PMMA-SSMe **2** was calculated to be 7.1 nm.[25]

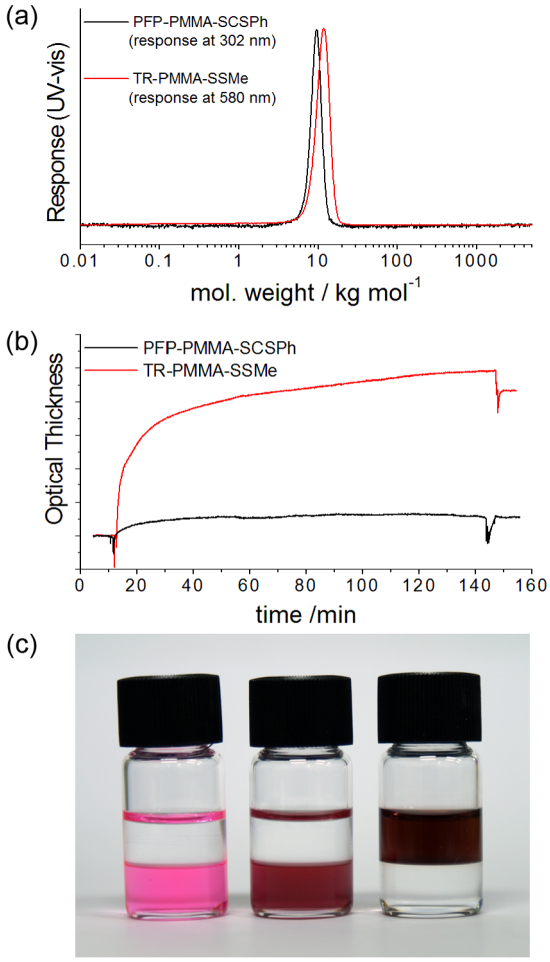


Figure 1.
(a) *Gel permeation chromatograms of the starting polymer **1** (black curve), recorded with a UV-vis detector set to 302 nm (maximum absorbance of dithioester end group) and of the product polymer **2** (red curve, UV-vis detector at 580 nm; absorbance maximum of dye end group). As the polymer itself has no absorbance at this wavelength this data suggests that the dye is attached to the polymer and that any (low molecular weight) lose dye was successfully removed.*

(b) *Surface plasmon resonance measurements of polymers **1** (black line) and **2** (red line). Whereas the dithioester terminated polymer showed only a light non-specific adsorption corresponding to a thickness of 0.47 nm, the methyl disulfide terminated polymer examined under the same conditions could build up a stable self-assembled monolayer of 3.68 nm thickness. Measurements were performed in ethyl acetate with a concentration of 0.4 mg / mL and a refractive index of 1.5 was assumed for both polymers.*

(c) *Photograph of two-phase mixtures of hexane (upper phase) and DMF (lower phase). The vials contain: TR-PMMA-SSMe **2** (left), hybrid Au-PMMA-TR **4a** with DMF soluble AuNP (middle) and OA-AuNP **3a** soluble in hexane (right).*

As phosphine oxides usually bind very strongly to the QD surface, we employed QD stabilized with oleic acid (OA-QD), (6.2 ± 1.0 nm diameter) which allowed for an easier ligand substitution with thiols or disulfides.[24] In order to also facilitate ligand exchange on AuNP, such stabilized with oleic amine (OA-Au) (3.9 ± 0.8 nm diameter) were chosen over thiol stabilized AuNP. The NP modification is outlined in scheme 1. Briefly, polymer **2** and either OA-Au **3a** or OA-QD **3b** were combined in a good solvent (toluene or chloroform), stirred overnight, and evaporated to dryness. For workup, a two-phase system consisting of hexane and DMF was employed for both types of NP. While both OA-Au and OA-QD are soluble in hexane, polymer **2** is not. It could transfer the NP into DMF as seen from the color of the DMF phases (see Figure 1c).[25] Also, TEM images showed the presence of non-aggregated, non-ripened NP in both DMF phases, accounting for a successful ligand exchange with the terminal methyl disulfide groups (Figure 2). Both NP dispersions could be passed through a 200 nm filter without product loss, indicating that no large agglomerates were present. In addition to the polymer functionalized NPs, which were transferred into the DMF phase, in both the case of AuNP and of QD, two side products were found. Trace amounts of NP remained in the hexane phases. Here, none or only an insufficient ligand exchange had taken place. Also, in both cases some material became insoluble in both phases and precipitated. Here, a partial ligand exchange could be assumed that provided solubility in neither phase. For AuNP, 32% of total Au was lost to these side reactions, while 10% of QD were not included in the hybrid material. As not all NP could be sufficiently functionalized with polymer, it could be assumed that the polymer was

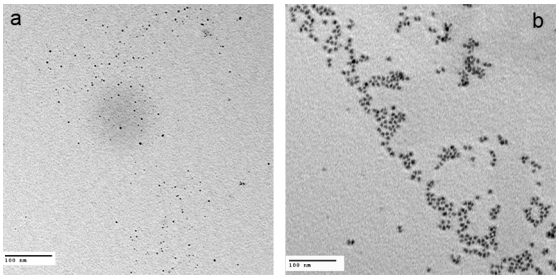


***Figure 2**. TEM images of **(a)** DMF soluble AuNP decorated with the dye labeled polymer **2** and **(b)** DMF soluble QD decorated with the dye labeled polymer **2**. Scale bars, 100 nm.*

the limiting reagent and that the amount of dye not connected to a NP in the products was low.

The hybrid materials were further characterized by UV-vis and fluorescence spectroscopy. Au-PMMA-TR **4a** showed an absorbance matching a calculated sum of 100% of the starting polymer **2** and 68% of OA-Au **3a** fed into the reaction, proposing the composition of **4a** (Figure 3b). In addition, a light band broadening of the dye caused by the near metal sphere occurred. The photoluminescence measurements shown in figure 3c were measured (a) directly after mixing polymer **2** and OA-Au **3a** together in toluene, and (b) from purified **4a** after re-dispersion into toluene. This last sample (b) contained the same amount of dye but only 68% of AuNP. The emission from Texas Red in **4a** was decreased by a factor of 1.75 compared to the emission before the reaction. When the lower AuNP absorbance, which allowed for a higher dye excitation, in sample **4a** was taken into account, an emission decrease by a factor of 2.22 could be estimated.[25] This suggested that FRET from the dye molecules to the AuNP was occurring, as was expected concerning the polymer dimensions (figure 3a). It also showed that the polymer was indeed attached to the AuNP, as otherwise there would have been no influence of the NP on the dye. For QD-TR **4b**, three samples of PMMA-TR **2**, OA-QD **3b**, and QD-TR **4b**, having the same dye and QD concentrations were prepared. The absorbencies are shown in figure 3e. Due to the influence of the NP core and the different local environment, the dye experienced a blue-shift. Exciting the three samples at 400 nm gave rise to the emission plots shown in figure 3f. The expected effects were found (figure 3d): The emission of the dye was increased by about factor of 2.5. On the other hand, QD emission in the hybrid material was decreased drastically, as energy was transferred non-radiatively. Again, the influence of the QD on the dye showed that the polymer was attached to the QD, tethering the chromophores to their surface. From the spectroscopic data, an average distance between QD and dyes could be estimated to be 6.4 nm, following the Förster formal-

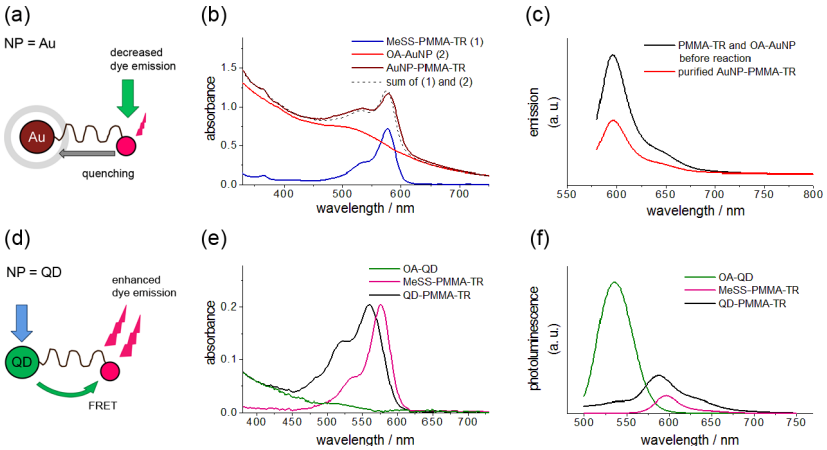


***Figure 3**. **(a)** Scheme illustrating the effect of the nearby Au core on the emission of the dye. **(b)** UV-vis absorbance of polymer **2**, OA-AuNP **3a**, Au-TR **4a** and the calculated sum of the former two curves. **(c)** Photoluminescence (excitation at 560 nm) of OA-AuNP **3a** mixed together with polymer **2** (before ligand exchange) and Au-TR **4a** after reaction, purification and re-dispersion into toluene. **(d)** Scheme illustrating the effect of the nearby QD on the emission of the dye. **(e)** UV-vis absorbance of samples of polymer **2**, OA-QD **3b** and QD-TR **4b** with the same dye and QD concentrations. **(f)** Photoluminescence (excitation at 400 nm) of the same samples as in figure d.*

ism.[25] This value is in good agreement with the end-to-end distance of the polymer as obtained by light scattering (7.1 nm) and suggested that the polymer coils were spacing the dyes from the NP surface. Dispersions of the composites were stable for several months without aggregation or precipitation occurring.

Conclusion

A simple one-pot synthesis of a hetero-telechelic polymer with fluorescent dye and methyl disulfide end groups was described. Each part of this product fulfilled a certain job; while the methyl disulfide end group enabled the attachment onto planar gold, gold NP, or semiconductor NP, the dye at the other end group could be used to probe local electronic effects caused by the NP. In addition, the polymer chain kept its end groups at a known distance and provided solubility of the encapsulated NP. Although the surface chemistry and the workup for both types of NP proceeded very similarly, the physical effects of the different cores on the dye molecules were quite contrary. While the dyes acted as energy donors for a nearby AuNP, the same core-shell configuration using QD gave the dyes the role of energy acceptor. The architectural setup allows creating hybrid materials with a tunable distance between NP and dyes, as it depends on the polymer end-to-end distance, which may easily be determined using conventional methods. Taking into account, that "smart" polymers may change their end-to-end distance on demand through external stimuli, more sophisticated setups become thinkable; experiments are in progress and will be published soon.

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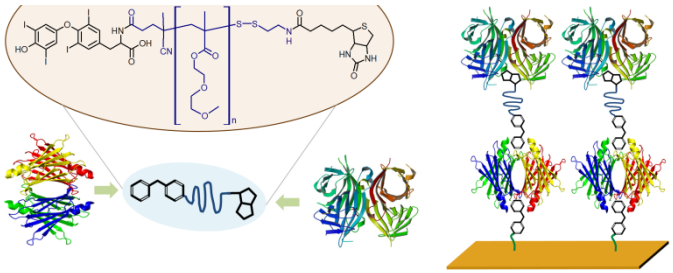
Synthesis of Hetero-Telechelic α, ω Bio-Functionalized Polymers

Roth, P. J.; Jochum, F. D.; Zentel, R.; Theato, P. *Biomacromolecules* **2009**, *in preparation*



Abstract.

Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization was used to synthesize poly[ethylene glycol monomethylether methacrylate] (PDEGMA) with a pentafluorophenyl (PFP) ester and a dithioester end group. The hormone thyroxin (T4) was quantitatively attached to the PFP activated α end group via its amino group. The ω-terminal dithioester was not harmed by this reaction and was subsequently aminolyzed in the presence of *N*-biotinylaminoethyl methanethiosulfonate, yielding a polymer with a thyroxin and a biotin end group with very high hetero-telechelic functionality. The polymer was characterized by ^{1}H NMR, ^{19}F NMR, UV-vis and IR spectroscopy, and gel permeation chromatography. The thyroxin transport protein prealbumin with two thyroxin binding sites and streptavidin, which has four biotin binding sites, were conjugated using the bio-target labeled polymer, resulting in the formation of a protein-polymer network, confirming the hetero-telechelic nature of the polymer. The polymer-protein micro gel formation was observed with dynamic light scattering. In order to realize a directed protein assembly, prealbumin was immobilized onto a surface, exposing one of its two thyroxin binding groups and thus allowing the conjugation with the thyroxin α end group of the hetero-telechelic polymer. The biotin ω-end group of the attached polymer layer enabled the subsequent immobilization of streptavidin, yielding multilayer system of two proteins connected with the synthetic polymer. Without the polymer, no streptavidin immobilization occurred. The layer depositions were monitored by surface plasmon resonance. The synthetic approach of combining PFP activated esters with functional MTS reagents presents a powerful method for obtaining well-defined hetero-telechelic (bio-) functionalized polymers.

Introduction

The use of synthetic polymers in medicine and biotechnology has found applications and research interests in many fields[1-5], such as improving the activity and stability of proteins[6,7] or for drug delivery purposes.[8-10] Besides the use of poly(ethylene glycol) (PEG) for stealth systems,[11] also "smart" polymers such as poly[*N*-isopropylacrylamide] or poly[ethylene glycol methacrylates] with PEG side chains are employed to create stimulus responsive polymer-protein conjugates.[12-17] Especially the end groups of a polymer are the focus for bio-functionalization, as they allow for a directed one-to-one attachment.[15,16,18] In addition to methods of covalently connecting synthetic materials and proteins, biology offers the possibility of strong non-covalent bonds based on the bio-affinity of certain proteins toward specific targets. This molecular recognition is especially exploited on surfaces for the development of biosensors and chip-based bioassays. In particular, due to the strong affinity between streptavidin and biotin,[19-21] streptavidin functionalized surfaces are used as a platform for the further immobilization and investigation of bio-molecules such as DNA or enzymes.[22-24] For such purposes, often multilayers of biological components are constructed, requiring building blocks with two specific binding sites.[25-28] It would be of considerable interest to include telechelic synthetic polymers in these constructions, exploiting the advantages of polymers, such as flexible functionalization or stimulus responsive behavior.

While numerous approaches for the bio-functionalization of one end group of a polymer have been published,[15,16,18] there is still a growing synthetic challenge to produce well defined narrowly distributed hetero-telechelic polymers carrying the same[29,30] or two different bio-functionalities[31,32]. Reversible addition fragmentation chain transfer (RAFT) polymerization[33] is a very promising method as it allows for an easy introduction of functional or reactive α end groups via functionalization of the leaving group (R) of the chain transfer agent (CTA).[15,18,29-35] A dithioester or trithiocarbonate is retained as ω end group and may also carry a functionality that was installed into the CTA.[31] The dithioester or trithiocarbonate link between an ω (bio-) functionality and the polymer chain is however very susceptible toward chemical decomposition.[36-40] The Maynard group has utilized a diazo-initiator carrying a protected maleimide to replace the trithiocarbonate end group with a bio-reactive functionality.[30,32] The deprotection step via retro Diels-Alder reaction however required harsh conditions that caused cleavages of ester bonds.[32] Poly[(meth) acrylates], such as poly[ethylene glycol methacrylates] are thus not eligible for this approach.

Herein, we report on the synthesis of poly[diethylene glycol monomethylether methacrylate][12] carrying to different terminal bio-targets, each capable of binding specifically to a certain protein. RAFT polymerization employing a CTA modified with a pentafluorophenyl (PFP) ester yielded a polymer having a PFP α end group and a dithioester ω end group.[41] Due to the high reactivity of the PFP ester toward amines present in many biomolecules, the α terminus could quantitatively be functionalized with the thyroid hormone thyroxin (T4) without harming the dithioester. We have recently shown that aminolysis of dithioesters in the presence of functional methane thiosulfonates introduces terminal functionalities with quantitative yields[42,43]. Here, this procedure was employed to introduce a biotin moiety at the ω end group. This combination of methods thus presents a novel, versatile pathway toward hetero-telechelic bio-functionalized polymers with very high end group conversions. As biotin binds very specifically to streptavidin,[19-21] and thyroxin is recognized and bound by its transport protein prealbumin (transthyretin),[44,45] we used the α, ω bio-target labeled polymer for hetero-dimeric protein conjugation both in solution and through directed surface immobilization.

Experimental Part

Materials and Methods. Biotin-MTS (*N*-biotinylaminoethyl methanethiosulfonate) was purchased from Toronto Research Chemicals. All other materials were obtained from Sigma-Aldrich or Acros and used as received. The PBS buffer contained 8.0 g/L of NaCl, 0.2 g/L of KCl, 1.44 g/L of Na_2HPO_4 and 0.24 g/L of KH_2PO_4 and was sterilized by boiling. Surface Plasmon Resonance (SPR) measurements were performed on 0.1 mg/mL

aqueous buffer solutions at 19°C in a self-built cell of 0.5 mL volume, using a Θ/2Θ setup, a 632 nm laser, and a photodiode. Glass slides were coated with 1.5 nm of chromium and 50 nm of gold by evaporation. SPR scans were fitted using WINSPALL, assuming a refractive index of all organic materials of 1.5. Dynamic light scattering was measured on a Malvern Zetasizer Nano in a low volume glass cuvette (45 µL) at 20°C.

α-Pentafluorophenyl Ester, ω-Dithioester Poly[diethyleneglycol monomethylether methacrylate] (PFP-PDEGMA-DTE, 1). The starting polymer was prepared according to a literature procedure.[41] M_n (GPC) = 8.0 kg /mol, M_n (NMR) = 10 kg/mol, PDI (GPC) = 1.18

α-Thyroxin, ω-Dithioester Poly[diethyleneglycol monomethylether methacrylate] (T4-PDEGMA-DTE, 2). To 5 mL of a 13.3 mM solution of PFP-PDEGMA-DTE (66.5 µmol), 51.7 mg (66.5 µmol) of thyroxin and 18.6 µL (133 µmol) of triethylamine were added. After 3 hours, the thyroxin had dissolved and the mixture was stirred overnight at room temperature. After removing the solvent in vacuum, the residue was dissolved in methanol and was purified by dialysis in methanol (12-14 k membrane) for 2 days with solvent changes thrice a day. Due to product loss through dialysis, the yield of T4-PDEGMA-DTE was 42 %. UV-Vis: λ_{max} = 302 nm. GPC: M_n = 8.8 kg/mol, PDI = 1.15.

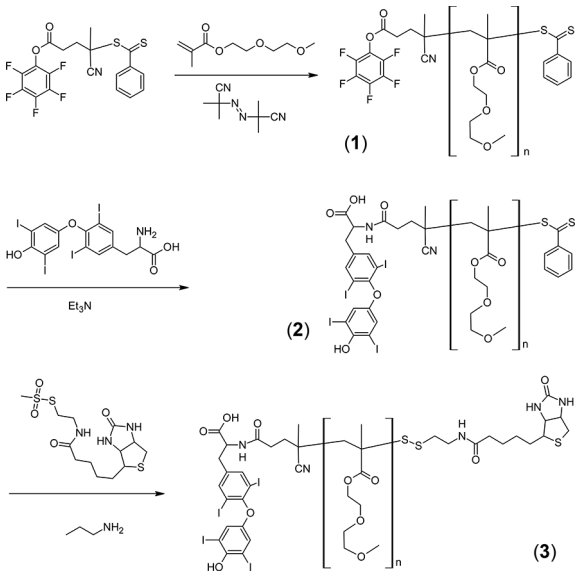
α-Thyroxin, ω-Biotin Poly[diethyleneglycol monomethylether methacrylate] (T4-PDEGMA-biotin, 3). To 850 µL of a 6.9 mM solution of T4-PDEGMA-DTE in dry DMSO (5.87 µmol), 30 mg (78.6 µmol) of *N*-biotinylaminoethyl methanethiosulfonate was added and after 1 minute, 30.2 µL (367 µmol) of n-propyl amine was added. The mixture was stirred overnight at room temperature. The product was purified by dialysis (12-14 k membrane) in methanol for 2 days with solvent changes thrice a day. T4-PDEGMA-biotin was obtained in 32 % yield; loss through dialysis. GPC: M_n = 10.2 kg/mol, PDI = 1.17.

Bis(5-carboxypentyl) disulfide bis thyroxin amide, **4**[46] and bis(6-hydroxyhexyl) disulfide, **5**[47] were prepared as previously described.

Results and Discussion

Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization was employed as method to produce a polymer carrying biotin and thyroxin (T4) end groups. These biomolecules were chosen as models because each of them specifically targets a protein. The strong specific binding of biotin to streptavidin has extensively been investigated and exploited.[19-21] Thyroxin binds to its three transport proteins thyroxin binding globulin (TBG), human serum albumin and prealbumin (transthyretin), which are responsible for distributing the hormone to target tissues.[44] Prealbumin recognizes phenols halogenated in both ortho positions and thus also binds to thyroxin if the amino group on the opposite side has been functionalized.[45,46]

A dithioester (DTE) chain transfer agent (CTA) carrying a pentafluorophenyl (PFP) activated ester was used for polymerization of diethyleneglycol monomethyl ether methacrylate (DEGMA) (scheme 1).[41] The resulting polymer **1** had a molecular weight of 8 kg / mol with a narrow molecular weight distribution (PDI = 1.18) as determined by gel permeation chromatography (GPC) measurement (figure 1). The PFP α end group was clearly visible in a



***Scheme 1**. Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization of diethylene glycol monomethylether methacrylate using a dithioester chain transfer agent carrying an activated pentafluorophenyl ester and successive functionalization of the end groups with the thyroid hormone thyroxin and biotin.*

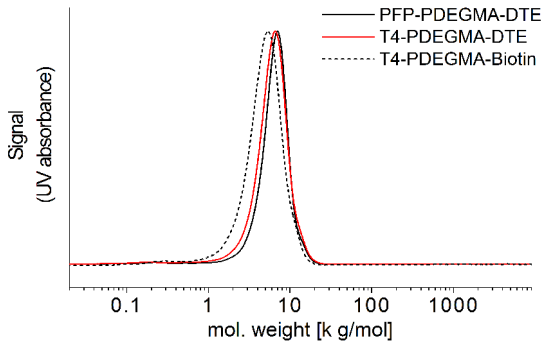


Figure 1. *Gel permeation chromatograms of PFP-PDEGMA-DTE **1** (black curve), T4-PDEGMA-DTE **2** (red curve) and T4-PDEGMA-biotin **3** (dotted curve).*

^{19}F NMR measurement and in IR spectroscopy through the characteristic carbonyl peak at 1778 cm^{-1} and the aromatic C=C valence band at 1520 cm^{-1} (see supporting information). The aromatic signals of the phenyl dithioester ω end group could be observed in ^{1}H NMR spectroscopy (figure 2) and the characteristic absorbance of the dithioester centered at 302 nm was recorded by a UV-vis measurement (figure 3).

The bio-functionalization of PFP-PDEGMA-DTE **1** proceeded in two steps. Both end groups were reactive toward amines. As however the PFP esters react quicker (see supporting information),[34,48] the PFP α end group could selectively be reacted with the amino group of one equiv. of thyroxin (scheme 1). The complete conversion of the PFP ester at the α end group was verified by the absence of fluorine signals in ^{19}F NMR measurement (see supporting information), while UV-vis showed that the ω-terminal DTE was still there (figure 3). GPC showed that the molecular weight and the PDI of T4-PDEGMA-DTE **2** had not significantly changed from the starting polymer. ^{1}H NMR spectroscopy showed the two distinct aromatic signals of the new thyroxin end group. Additionally, the aromatic signals of the DTE were still there, confirming that the ω end group had not been harmed. The conversion of T4 functionalization and extent of DTE retention were both estimated to be quantitative though integration of the signals. However, an error of 5 -10% should be allowed for this method. Higher precision evidence could be gained from a UV-vis absorbance measurement. The graph of T4-PDEGMA-DTE **2** consisted of two superimposed peaks of the ω-DTE and the α-T4 group (figure 3). Linear combination of the expected absorbencies matched the measured curve when a quantitative conversion at the α end group and retention of at least 91% of DTE at the ω end group were assumed (dotted line in figure 3). These conversions were consistent with the values from NMR integration and showed that modification of a PFP ester is possible in the presence of a dithioester. This ap-

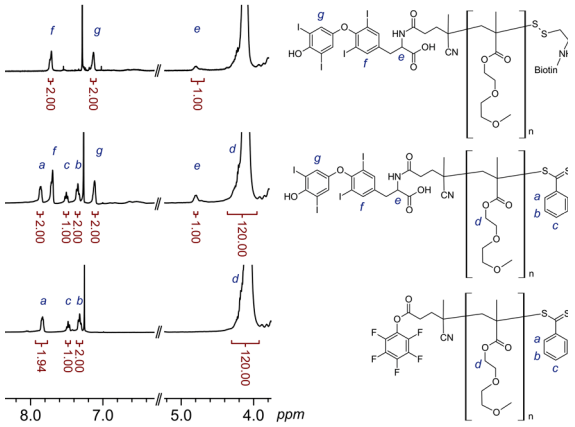


Figure 2. *Sections of NMR spectra of PFP-PDEGMA-DTE **1** (bottom), T4-PDEGMA-DTE **2** (middle) and T4-PDEGMA-biotin **3** (top) showing the retention of the ω-terminal dithioester upon introduction of the α-thyroxin group and the complete removal of the dithioester upon substitution with the biotin terminus*

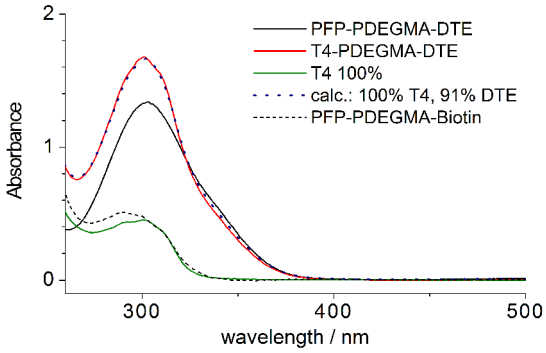


Figure 3. *UV-vis absorbance spectra of PFP-PDEGMA-DTE **1** showing the absorbance of its terminal dithioester, defined as 100% (black curve); of the exact amount (100%) of thyroxin expected to attach to the α end group (green curve); of T4-PDEGMA-DTE **2** giving rise to a spectrum superimposed of dithioester absorbance and thyroxin absorbance (red curve); of a calculated linear combination of 100% of thyroxin absorbance and 91% dithioester absorbance (blue dotted curve), nicely matching the measured spectrum of T4-PDEGMA-DTE **2**; and of the product T4-PDEGMA-biotin **3** (black dashed line).*

proach thus allowed the further modification of the ω DTE by means of aminolysis in the presence of a biotinylated methane thiosulfonate (MTS, see scheme 1). This method of employing functional MTS reagents has been shown to quantitatively introduce functional ω disulfides groups during aminolysis.[42,43] Disulfides are very stable in the absence of reducing agents or radicals and are often employed as linkers between polymers and biomolecules.[15,16,23,31,35,49] After reaction of T4-PDEGMA-DTE **2** with biotin-MTS (see scheme 1), the DTE absorbance peak had disappeared from the UV-vis absorbance spectrum, with only the absorbance of the T4 α end group remaining (figure 3). The aromatic signals of the phenyl dithioester group had also completely disappeared from the NMR spectrum (figure 2). These measurements indicated a complete decomposition of the DTE. The gel permeation chromatogram of T4-PDEGMA-biotin **3** showed a monomodal curve of the same width as the precursor polymers that had however shifted toward a lower molecular weight. We had observed this behavior in various other cases where a dithioester had been removed from a polymer and attribute it to a different coiling of the polymer around its new end group.[42,43,48] Evaluation of the GPC measurement was however performed using a light scattering detector capable of determining absolute molecular weights, which showed that the weight had not decreased (10.2 kg/mol) in spite of the denser coiling (figure 1). Noteworthy, no peak or shoulder of double molecular weight had appeared, indicating that no side reactions such as formation of polymer-polymer disulfides (which are favored in the absence of MTS reagents) had occurred and that the end group exchange had proceeded as intended. The presence of the terminal biotin moiety could be confirmed by IR spectroscopy. The spectra of the starting polymer PFP-PDEGMA-DTE **1** and of the product T4-PDEGMA-biotin **3** were compared. The characteristic peaks of the PFP end group at 1778 cm^{-1} and 1520 cm^{-1} were absent from the spectrum of polymer **3**. In contrary, the urea-carbonyl absorption of biotin around 1680 cm^{-1} and the C-N stretch absorption at 1259 cm^{-1} of biotin appeared in the spectrum of T4-PDEGMA-biotin (see supporting information). This data thus confirmed the successful α, ω bio-functionalization in a two-step procedure with very high yields.

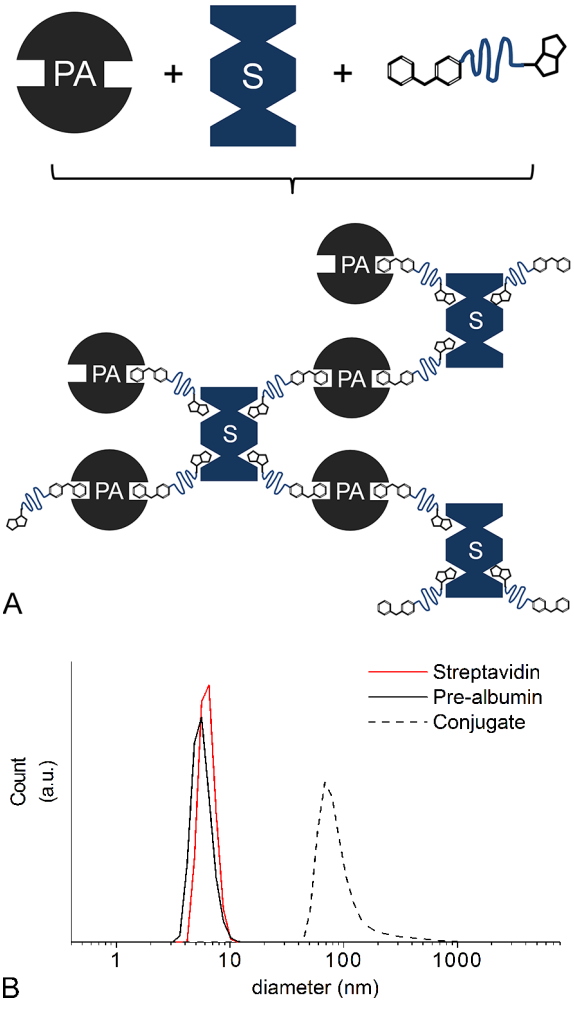


Figure 4. *(**a**) Schematics showing the formation of a 3-dimensional network of prealbumin (P) (with two binding sites for thyroxin), streptavidin (SA) (with four binding sites for biotin) and the hetero-telechelic polymer T4-PDEGMA-biotin **3**. (**b**) Results of dynamic light scattering on the individual proteins streptavidin (red curve) and prealbumin (back curve) and of the polyconjugate formed upon addition of polymer **3** (dashed line).*

The bio-conjugation of both end groups of polymer **3** was first investigated in solution. Diluted buffered solutions of prealbumin, streptavidin, and T4-PDEGMA-Biotin **3** were combined. As prealbumin has two thyroxin binding sites and streptavidin has four biotin binding sites, a molar ratio of 1 streptavidin: 2 prealbumin : 2 polymer **3** was chosen, to aim at a high conjugation resulting in a three dimensional super structure (figure 4a). Such an adduct can only be formed if polymeric connectors exhibiting both a biotin and a thyroxin end group are present. Dynamic light scattering was measured of each individual protein and of the conjugate with polymer **3** (figure 4b). As expected, both streptavi-

din and prealbumin gave rise to monomodal narrow peaks at 7 nm and 5.8 nm hydrodynamic diameter, respectively. After addition of polymer **3** to a mixture of both proteins, the signals corresponding to the individual proteins had vanished, to be replaced with a broad peak around 70 nm hydrodynamic diameter with a shoulder extending toward larger diameters. Theoretically, the stoichiometric addition these building blocks with two or four binding sites should create a gel converging to an infinite molecular weight. However, due to the low concentration of the reactants, the polyconjugation led to the formation of a micro gel. Still, this measurement confirmed the formation of a large 3-dimensional protein / polymer network, which consumed both individual protein building blocks, thus demonstrating the hetero-telechelic nature of polymer **3**. It also showed the successful protein identification of the polymer end groups. Such super-structures consisting of protein and polymer components are gaining an increasing importance in the development of biomaterials and in research field of tissue engineering.[50,51]

The polymer with its two different bio-target end groups was next used in a directed surface immobilization, which was monitored by surface plasmon resonance (SPR). Disulfide **4** carrying T4 groups was used for bio-labeling of a planar gold surface (figure 5a). In order to reduce any non-specific binding of proteins to a non-polar T4-surface however, a mixture of disulfide **4** and bis(6-hydroxyhexyl)disulfide **5** (molar ratio 1:12) was self-assembled onto the gold surface.[23,52] When prealbumin in PBS buffer was injected, a rapid binding of the protein to the surface was observed (figure 5b, part I). The average thickness of this first protein layer was fitted to be 14.4 Å, which was somewhat lower than 26.0 Å found for a dense prealbumin monolayer[46], and therefore in agreement with the T4 targets being "diluted" with hydroxyl groups on the surface.[52] After rinsing the prealbumin coated surface with PBS buffer, T4-PDEGMA-biotin **3** was injected into the cell. As each prealbumin has two binding sites for a T4 molecule, but does not interact with biotin or the polymer spacer, the observed thickness increase of 1.9 Å indicated the attachment of the T4 end groups of polymer **3** onto the prealbumin coated surface (figure 5b, part II). Next, streptavidin was injected, which bound rapidly to the surface already containing a prealbumin and a polymer layer, resulting in a thickness increase of 23.4 Å (figure 5b, part III). This showed that biotin groups had been available on the surface and ready for streptavidin conjugation. In dense monolayers, streptavidin produces layers with a thickness of around 52 Å.[46] The lower value found here thus proposed that only binding to the

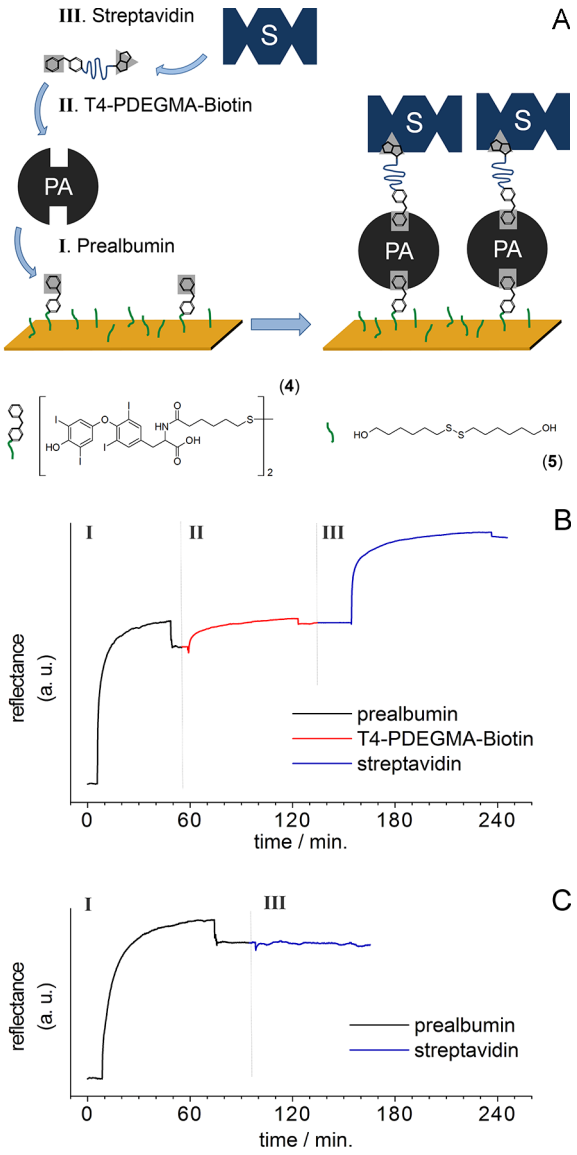


Figure 5. *(**a**) Schematics showing the successive immobilization of prealbumin, T4-PDEGMA-biotin **3** and streptavidin onto a self-assembled monolayer of T4-disulfide **4** and hydroxyl-disulfide **5** on a planar gold surface. (**b**) Surface plasmon resonance (SPR) measurement showing the increase of optical thickness upon immobilization of prealbumin (black curve), T4-PDEGMA-biotin **3** (red curve) and streptavidin (blue curve). (**c**) SPR measurement of the binding of prealbumin onto a self-assembled monolayer of disulfides **4** and **5** (black curve) and attempted immobilization of streptavidin (blue curve).*

biotin end groups had taken place and no non-specific binding had occurred.

From the ratios of layer thicknesses measured here to the thicknesses of dense monolayers of the proteins, an immobilization efficiency of 81% based on prealbumin was estimated, suggesting an accurate site-specific conjugation of streptavidin onto the biotin end groups. The same experiment was repeated, this time streptavidin was directly injected onto the prealbumin-coated surface, i.e. polymer **3** was omitted. In this case, no attachment of streptavidin to the surface and thus no increase in reflectance was found, showing that polymer **3** was essential for the recognition and conjugation of the two different proteins via its end groups (figure 5c).

Conclusion

The synthesis of a polymer carrying two different terminal bio-functionalities was described. The synthesis featured the use of a chain transfer agent carrying a pentafluorophenyl ester, which was retained as α end group of the polymer. Due to its high reactivity towards biological amines, α amidation was possible leaving the dithioester intact. This ω-end group could then be subjected to an aminolysis in the presence of a functional methane thiosulfonate (MTS) reagent, which had been shown to be a powerful method to introduce terminal functionalities with very high yields. The combination of α-PFP esters with functional MTS reagents thus presents a versatile pathway toward hetero-telechelic (bio-) functionalized polymers. As both steps of the synthesis can be performed at room temperature, there is no risk of decomposition of ester groups and thus, poly[(meth)acrylates] are eligible for this method. In the present case, α-thyroxin and ω-biotin end groups were introduced into a poly[diethylene glycol monomethylether methacrylate]. These end groups were specifically targeted by prealbumin and streptavidin, respectively, and a subsequent immobilization onto a surface was possible with the polymer connecting the two different proteins with its end groups. Combination of the building blocks in solution resulted in the formation of a 3-dimensional super structure that could be observed in dynamic light scattering.

The polymer presented here thus has the potential of acting as an "adapter" from a different protein (such as prealbumin) to streptavidin, which could then offer the broad range of analysis and conjugation possibilities available for streptavidin surfaces. Additionally, as a stimulus responsive polymer, poly[diethyleneglycol monomethylether methacrylate] invites to explore possibilities of reversible or stimulus-controlled conjugation.

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Supporting Information Available. IR spectra of polymers **1** and **3**; ^{19}F NMR spectra of polymers **1** and **2**. Data illustrating the reactivity difference of pentafluorophenyl esters versus dithioester toward amines. This material is available at http://pubs.acs.org.

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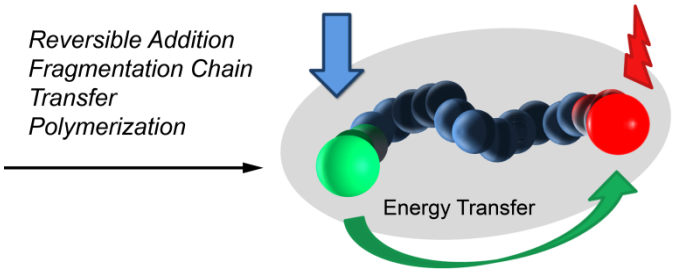
Synthesis of α, ω Dye Functionalized Polymer by the RAFT process and Energy Transfer between the End Groups

Roth, P. J.; Haase, M.; Fischer, K.; Basché, T.; Theato, P.; Zentel, R. *Macromolecules* **2009**, *in preparation*



Abstract.

The synthesis of a polymer with two different fluorescent dye end groups using reversible addition fragmentation chain transfer (RAFT) polymerization is described. Use of a pentafluorophenyl (PFP) activated ester chain transfer agent (CTA) provided a polymer with an α-end group reactive toward amines and a dithioester ω end group. The α PFP ester was amidated with Oregon Green Cadaverin. This did not harm the ω dithioester, which was subsequently aminolyzed with an excess of n-propyl amine in the presence of Texas Red-2-sulfonamidoethyl methanethiosulfonate resulting in a disulfide bond connecting the second dye to the polymer chain. Excess dyes and side products were removed by thin layer chromatography (TLC). Gel permeation chromatography (GPC) using a UV-vis detector could verify the presence of each dye on the polymer chain and the absence of free dyes. The synthesis of the polymer by a living radical technique and the mild complementary conjugation methods conducted after polymerization at each end group allowed the use of complex dye molecules possessing a very high brightness and photostability. Fluorescent dyes capable of acting as donor and acceptor for electronic excitation energy transfer were chosen. Time resolved fluorescence measurements were used to determine the time constant of energy transfer between the end groups of isolated polymer chains, which again confirmed the synthetic success. Assuming a Förster-type process, we calculated an average end-to end distance of 4.5 nm, which was in reasonable agreement with data obtained from light scattering.

Introduction

Of the many possibilities to synthesize and employ functional polymers, especially hetero-telechelic systems, i.e. polymer chains with two different functional end groups are receiving an increasing amount of attention. Generally, they allow the preparation of ABC-type structures, where A and C are arbitrary groups kept at a specific distance by the polymer B. The polymer may provide solubility or a stimulus dependent end group separation. One end group may as well be connected to a surface, with the polymer tethering the second end group to the surface but allowing it maximum distance and mobility. While end groups with high impact for biological research such as two different proteins have recently been reported,[1] polymers with functional end groups may also provide invaluable information for polymer physics. End to end distance, end group interactions and polymer conformation may be calculated from energy transfer measurements between two fluorescent dye end groups.[2-6]

Fluorescence (or Förster) resonance energy transfer (FRET) is a useful tool for the investigation of molecular arrangements and fluctuations thereof on a nanometer scale, as the FRET efficiency is strongly distance dependent.[7,8] Two dyes located at strategic points of the same[9-17] or two different[18] molecules may thus provide extensive information on the distance and the relative orientation of these two points. Winnik and coworkers have extensively studied the end-to-end cyclization of polymers terminated with pyrene and dimethylaniline or benzil moieties prepared by anionic polymerization[19-21] or cationic ring opening polymerization (CROP).[22] Only very few monomers are adequate for CROP, however. And as carbon anions are very reactive, the use of monomers and dye end groups in an anionic polymerization is greatly restricted to very inert molecules.[23-25] The dyes that have been employed in hetero-telechelic polymers were hydrocarbon based, pyrene being the most prominent example. Pyrene and similar dyes, however, generally have a low solubility in organic solvents, a low emission yield and easily undergo excimer and exciplex formation.

It would therefore be of considerable interest to have synthetic access to hetero-telechelic dye functionalized polymers without the harsh restrictions imposed by anionic polymerization or CROP. This would allow the use of more complex dye molecules with higher photostabilities, dyes suitable for single molecule spectroscopy[26,27] or functional groups which could for instance provide water solubility. Such systems would not only be of interest for the investigation of polymer behavior – for instance a chain collapse, but also for the optoelectronic branch of modern science, where FRET finds many applications in light harvesting arrays[28,29] or light emitting diodes.[30]

The past decade has seen the vast and rapid ascent of controlled radical polymerization (CRP). Most prominent are nitroxide mediated polymerization (NMP),[31] atom transfer radical polymerization (ATRP)[32,33] and reversible addition fragmentation chain transfer polymerization (RAFT).[34,35] As the propagating species are radicals, less restrictions apply to the polymerization conditions and a wide variety of monomers may easily be converted into polymers with excellent control over the molecular weight and very low polydispersity indices. As fairly new methods however, the work on functionalized end groups, especially hetero-telechelic polymers has only just begun in the past few years. Several functionalized initiators and chain transfer agents allowing the introduction of one fluorescent dye per chain or the same dye at both end groups have been described for NMP,[36] ATRP[37-40] and RAFT.[41-44] For polymers with two different functional end groups, generally two independent reactions for each end group modification have to be combined.[1,45-50] To the best of our knowledge, a polymer carrying two different fluorescent dyes at their end groups has, however, not been prepared by a CRP technique yet.

In this paper, the preparation of an α,ω dye-functionalized polymer by the RAFT process is described. The synthesis featured a functionalized chain transfer agent providing a polymer with a pentafluorophenyl (PFP) activated ester at the α end group and a phenyl dithioester (DTE) as ω end group. The PFP esters were reacted with an amine-functionalized dye. As dithioesters are chromophores and are known to interfere with dyes through exciplex formation and quenching, the ω terminal dithioesters were converted into functional disulfides carrying dye end groups by the use of a dye functionalized methane thiosulfonate (MTS) reagent during aminolysis.[51,52]. The dyes were chosen to be

capable of electronic excitation energy transfer and accordingly, the time constant of energy transfer between the end groups could be determined by recording the rise/decay time profile of the acceptor via time-correlated single photon counting (TCSPC).

Experimental Part

Materials. Oregon Green cadaverine was purchased from Molecular Probes. Texas Red methanethiosulfonate (Texas Red-2-sulfonamidoethyl methanethiosulfonate) was purchased from Toronto Research Chemicals. All other reagents and solvents were purchased from either Acros, Aldrich or Fluka. Thin layer chromatography (TLC) was performed on TLC aluminium sheets (20 x 20 cm, silica gel 60 F_{254}) purchased from Merck. Dialysis membranes (regenerated cellulose, 20 µm) were purchased from Roth and had a molecular weight cutoff (in water) of 12-14 k.

Methods. Static and dynamic light-scattering measurements were performed with an ALV-SP86 goniometer, a Uniphase HeNe laser (22 mW output power at 632.8 nm wavelength), an ALV/High QE APD avalanche diode fiber optic detection system, and an ALV-3000 correlator in linear mode. Prior to measurement, the solutions were filtered through 0.2 µm pore size Dimex filters (Millipore LG). The refractive index increment at λ=632.8nm was measured by a home-built Michelson interferometer.[53]

Steady state absorption and fluorescence measurements were performed with methanol solutions of the materials on an Omega 20 absorption spectrometer (Bruins Instruments, Germany) and a FluoroLog-3 (Instruments S.A., Jobin Yvon-Spex Division, New Jersey) spectrofluorometer, respectively. The fluorescence emission spectra (λ_{ex} = 470 nm) were corrected for the wavelength-dependence of the detector, and the fluorescence excitation spectrum of the dyad (λ_{ex} = 599 nm) was corrected for the intensity variations of the excitation light source. Time-resolved fluorescence measurements were performed on a FluoroLog-3 spectrofluorometer connected to a FluoroHub TCSPC (Time Correlated Single Photon Counting) unit containing a Time-to-Amplitude Converter (TAC) to construct the fluorescence decay histograms. In order to measure fast energy transfer times a pulsed laser diode LDH-P-C-470 (PicoQuant, Berlin) with pulse duration of τ_p = 70 ps was used for excitation (λ_{ex} = 470 nm, ν_{rep} = 10 MHz), and a fast single photon avalanche diode (SPAD, Micro-Photon-Devices) was coupled to the exit slit of the emission monochromator. The overall time resolution of the setup was quantified by the FWHM (Full Width at Half Maximum) of the Instrumental Response Function (IRF) to ≈ 180 ps at λ_{em} = 470 nm. The fluorescence rise/decay time profile of the acceptor TR was described by a convolution of a bi-exponential model function with the Instrumental Response Function (IRF).

$$I_A(t) = \left[A_1 \exp\left\{-\frac{t}{\tau_{\mathrm{fl}}}\right\} - A_2 \exp\left\{-\frac{t}{\tau_{\mathrm{EET}}}\right\} \right] \otimes \mathrm{IRF}(t) + B \quad (1)$$

The model function consists of two time constants; the fluorescence lifetime τ_{fl} contributes with the positive amplitude A_1 and the energy transfer time τ_{ETT} with the negative amplitude A_2 (rise time). The parameter B accounts for background fluorescence and stray light contributions. Data processing was performed with an integrated data manipulation/visualization package (Igor Pro 6.04, Wavemetrics, Lake Oswego, OR).

Synthesis of α-Pentafluorophenyl Ester, ω-Dithioester Poly[diethyleneglycol methacrylate] (PFP-PDEGMA-DTE, 1). The starting polymer was prepared according to a literature procedure.[54] As the dithioester has a characteristic absorbance band centered around 302 nm, the absence of free chain transfer could be confirmed by a gel permeation chromatography (GPC) with a UV-vis detector set to 302 nm. No low molecular weight absorbance could be detected, indicating that all dithioester was located on polymer chains. The molecular weight of the polymer was determined by both GPC in tetrahydrofuran using a light scattering detector (7500 g/mol) and by dynamic light scattering (DLS) in methanol (6900 g /mol). The polydispersity index was 1.10 (GPC).

Reaction of PFP-PDEGMA-DTE 1 with Oregon Green cadaverine (OG, 2). To 540 µL of a 18.65 mM solution of PFP-PDEGMA-DTE **1** in DMF (10.07 µmol), 5 mg (10.07 µmol) of Oregon Green cadaverine and 4.75 mg (22.15 µmol) of 1,8-bis(dimethylamino) naphthalene (proton sponge) were added. The mixture was stirred at room temperature overnight in the dark. Afterwards, the reaction mixture was dialyzed against methanol for 3

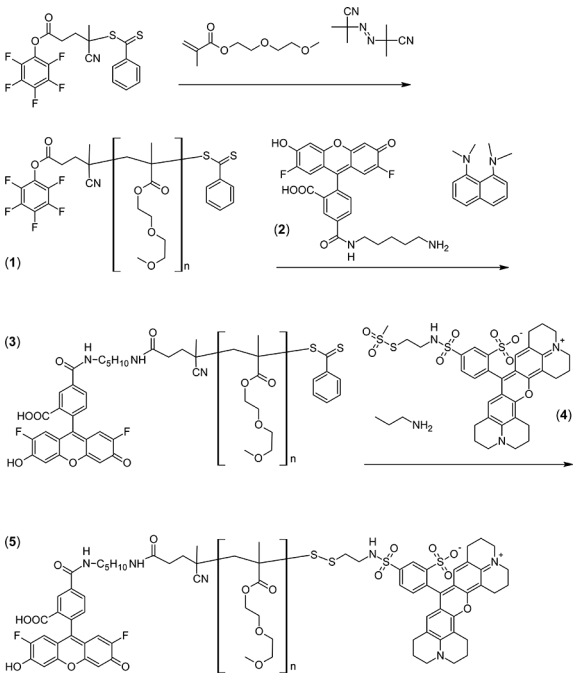
days using a 12-14 k membrane with solvent changes twice a day. The mixture was removed from the membrane and dried in vacuum. The residue was dissolved in chloroform and extracted several times with water. After drying the organic phase (magnesium sulfate) and removing the solvent, OGC-PDEGMA-DTE (**3**) could be obtained in a 46% yield. A considerable product loss probably occurred during dialysis, however, the product was devoid of free dye which could be seen from a GPC measurement with the UV-vis detector set to 502 nm and from thin layer chromatography (TLC) (see figure 3).

Reaction of OGC-PDEGMA-DTE 3 with Texas Red methanethiosulfonate (TR, 4). To 200 µL of a 3.36 mM solution of OGC-PDEGMA-DTE (**3**) in DMF (0.672 µmol) first 5 mg (6.72 µmol) of Texas Red-2-sulfonamidoethyl methanethiosulfonate were added and then 3.9 µL (47 µmol) of n-propyl amine were injected. The mixture was stirred at room temperature overnight in the dark. The complete reaction was dialyzed against methanol for 3 days using a 12-14 k membrane with solvent changes twice a day. After that time, a black precipitate had formed inside of the membrane probably composed of free dye or the corresponding dye-dye disulfide, which have a low solubility in methanol. The precipitate was removed by filtration. The solvent was removed in a light vacuum and water was added to the residue. Again, a black precipitate was removed by filtration. The water was removed in a light vacuum and the residue was dissolved in a minimum amount of dichloromethane. This raw product was further purified by TLC using methanol as solvent yielding the dye labeled polymer OGC-PDEGMA-TR (**5**) in 34% yield. R_f **5**: 0.75. R_f lose dye 0.59, R_f of a red side product, probably a dye-dye disulfide: 0.30.

Synthesis of PDEGMA-TR 6. α-n-propyl amide, ω-dithioester poly[diethyleneglycol methacrylate] was synthesized in analogy to the synthesis OGC-PDEGMA-TR **5** with the only difference being that PFP-PDEGMA-DTE **1** was used as starting material instead of polymer **3**. In this case, the excess of n-propyl amine performed both the aminolysis of the PFP ester and the dithioester. The n-propyl amide α-end group does not provide any fluorescence or influence the polymer's solulibity or size compared to the native PFP ester end group. For purification, dialysis was omitted; DMF was removed from the reaction and water was added. After filtration, the polymer was extracted from the aqueous phase with dichloromethane. The organic phase was dried with magnesium sulfate and concentrated on a rotovap. The raw product was purified by TLC with methanol as solvent. R_f values were the same as given above. Polymer **6** was obtained in 59% yield.

Results and Discussion

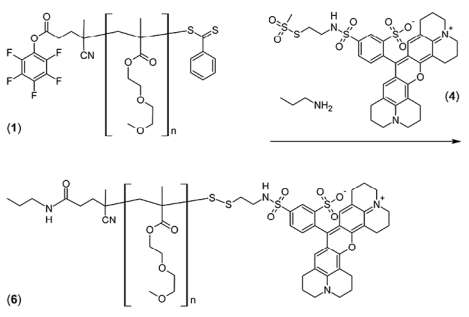
Method. Reversible addition fragmentation chain transfer (RAFT)[34,35] polymerization was chosen as method to prepare a polymer with orthogonally reactive end groups, which were then reacted with functional dye molecules to obtain a donor / acceptor end group modified polymer. Due to the polymerization mechanism, monomers are inserted between the leaving group R and the dithioester (DTE) (see upper part of scheme 1). Accordingly, the R group is retained as α end group, which is directly joined to the polymer chain, whereas the Z moiety in its subsequent role as ω end group is connected to the polymer chain via the dithioester. Incorporating functional[1,42,49,50, 55,56] or reactive[35,48,54,56-62] sites into the R



Scheme 1. *Synthesis of polymer with two functional end groups and successive attachment of fluorescent donor and acceptor dyes.*

group of the CTA or employing functional[44,50] or reactive[48,63-65] Z groups can therefore produce polymers with one or two[1,48-50] defined end groups. In addition to being susceptible toward chemical decomposition,[35,66-68] e.g. during storage in tetrahydrofuran,[69] dithioesters are chromophores and are known to interfere with dyes through exciplex formation and quenching.[70] For these reasons, it is not favorable to attach a fluorescent dye to the Z group, whether into the CTA before polymerization or onto an appropriately reactive Z group after polymerization. Alternatively, a dithioester may also be understood as a protected thiol. Aminolysis is a very common method to release the terminal thiols[41,71-76] which may regrettably undergo side reactions.[51,77,78] It was recently shown, that functional methane thiosulfonates (MTS) can be employed during aminolysis, quantitatively yielding functionalized disulfide end groups and thus avoiding side reactions of the thiols.[52]

In the present paper, we use an MTS reagent carrying the fluorescent dye Texas Red to introduce this dye at the ω end group. This method for ω functionalization was combined with a pentafluorophenyl (PFP) activated ester α end group which was installed into the polymer via a chain transfer agent carrying a PFP modified R group (see scheme 1).[54] Both literature results[56] and preliminary experiments conducted for this study[53] showed a sufficient difference of reactivity of activated esters versus dithioesters with primary amines and thus the possibility to quantitatively convert PFP esters with one equivalent of amine in the presence of the dithioester in ω position, which stayed intact. The fact that both end groups – α PFP and ω DTE – are reactive toward amines also invites progressing via a one-step reaction course where an excess of amine performs both reactions at the two end groups.



Scheme 2. *One-step synthesis of polymer with only acceptor dye.*

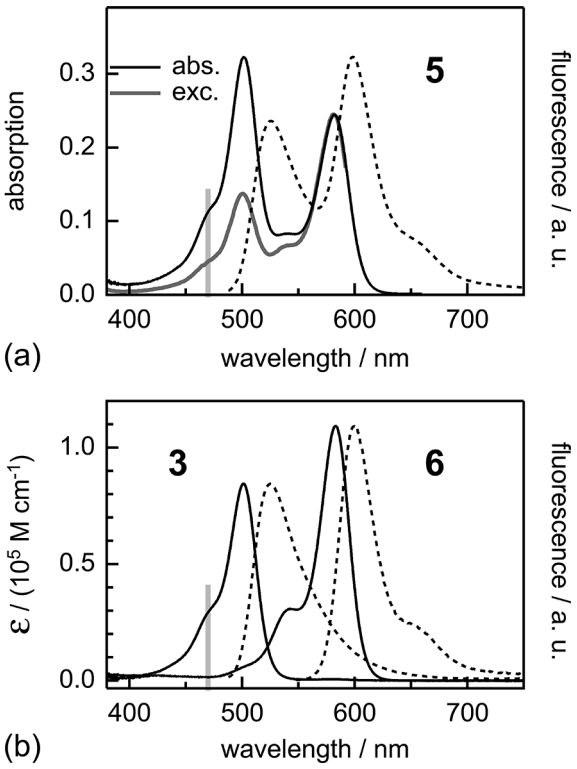


Figure 1. *Absorption (black lines) and fluorescence emission spectra (dashed lines) of (a) polymer **5** and (b) the one-dye-only-polymer compounds **3** and **6** in methanol solutions. Additionally, in (a) the fluorescence excitation spectrum of polymer **5** (λ_{em} = 599 nm) is displayed (gray line). The excitation wavelength of λ_{ex} = 470 nm is marked with a gray bar.*

However, as some complex functional amines such as e.g. the dye-functionalized amine (**2**) might have solubility issues, might be disadvantageous nucleophiles due to steric hindrance, and might simply be too expensive to be used in large excess, a two-step reaction might be favored. In this paper, we describe both the one-step and the two-step reaction pathways. The syntheses are outlined in schemes 1 and 2.

Dyes and Polymer. Texas Red (TR), introduced as MTS reagent (**4**) served as energy acceptor. As donor, Oregon Green (OG) cadaverine (**2**) was chosen, which was reacted with its primary amine. For this particular donor-acceptor couple the Förster radius (for details see below) was calculated to be R_0 = 6.1 nm. Since at this separation the energy transfer efficiency is 50%, we aimed for a polymer size (end-to-end distance) below this value to enable an efficient energy transfer between the end groups. In addition, the chosen donor-acceptor couple allowed for selective excitation of the donor and selective detection of the acceptor emission (see Fig. 1).

Poly[diethyleneglycol monomethylether methacrylate] (PDEGMA) was chosen as spacer between the dyes. As an energy transfer between the polymer end groups was intended, a narrowly distributed, low molecular weight polymer was synthesized. Molecular weights and size of the polymer determined by GPC and light scattering are given in table 1.

Synthesis of Hetero-Telechelic Polymer. The two-step synthesis of the donor / acceptor labeled polymer OG-PDEGMA-TR (**5**) is described in scheme 1. In order to avoid decomposition of the DTE during the modification of the PFP ester, only 1 equiv. of donor-amine (OG cadaverine, **2**) was employed. Additionally, 1,8-bis(dimethylamino)-naphthalene was used as non-nucleophilic scavenger for the acidic pentafluorophenol. The product **3** of this first step was purified by dialysis and extraction. It was intensely colored indicating a successful dye attachment and still showed the proton signals of the dithiobenzoyl group in ^{1}H and HSQC NMR, showing the presence of the desired DTE end group[53] and confirming the higher reactivity of PFP esters toward amines compared to DTE. In the second step, the DTE of the OG labeled polymer **3** was aminolyzed with a 70-fold excess of n-propyl amine in the presence of a 10-fold excess of Texas Red-MTS (**4**). The product was purified by dialysis and preparative thin layer chromatography (TLC) with methanol as solvent. This technique yielded a spot of orange color, as to be expected from a mixture of red and green emission, as well as two spots of red color. One of these spots corresponded to the reagent Texas Red-MTS, whereas the second one was assumed to originate from a dye-dye disulfide cause by hydrolysis and oxidative coupling of two MTS species. The orange spot yielded a material, which showed both red and green absorbance in UV-vis spectroscopy (solvent methanol) (see figure 1a). This product was characterized further by gel permeation chromatography (GPC, in DMF). Two measurements were performed, the only difference being the wavelength the UV-detector was set to. Setting it to 502 nm allowed the selective detection of the Oregon Green dye which has its absorbance maximum at that wavelength (in DMF), because the polymer itself has no absorbance in the visible range. The elution curve (figure 2, upper graph) showed a monomodal peak around 9K g/mol (polystyrene standard), indicating that the green dye now had the molecular weight of the polymer, because they had been covalently joined together, as was already known from the analysis of the intermediate product (**3**). No peak in the low molecular weight region was detected suggesting the complete removal of unbound dye. Moreover, the elution curve showed no signal of a double molecular weight material, confirming that no polymer-polymer disulfide of the structure OG-PDEGMA-S-S-PDEGMA-OG had been formed. In contrast, GPC analysis with the UV-vis detector set to 580 nm allowed the selective detection of the Texas Red dye, as neither polymer nor Oregon Green absorb at this wavelength (figure 2, lower graph). The monomodal peak at the molecular weight of the polymer gave evidence that the MTS reaction had successfully introduced a second dye onto the ω end group of the α-modified polymer. Again, the absence of strong signals of low molecular weight or double molecular weight suggested that the vast majority of red dye in the sample had been attached to the narrowly size distributed polymer. This data thus showed that the applied combination of PFP esters and MTS chemistry could successfully introduce two terminal fluorescent dyes onto a polymer chain.

Table 1. *Polymer Molecular Weight and Dimensions.*

entry	obtained from	value
M_w[a]	SLS[g]	6900 g/mol
M_n[b]	GPC[h]	7500 g/mol
M_w	GPC	8250 g /mol
PDI[c]	GPC	1.10
d_H[d]	DLS[i]	3.8 nm
r_{DA}[e]	TCSPC[j]	4.5 nm
R_0[f]		6.1 nm

[a] *weight average molecular weight;*
[b] *number average molecular weight;*
[c] *polydispersity index = M_w / M_n;*
[d] *hydrodynamic diameter (methanol);*
[e] *average dye-dye distance;*
[f] *Förster radius;*
[g] *static light scattering;*
[h] *gel permeation chromatography;*
[i] *dynamic light scattering;*
[j] *time-correlated single photon counting*

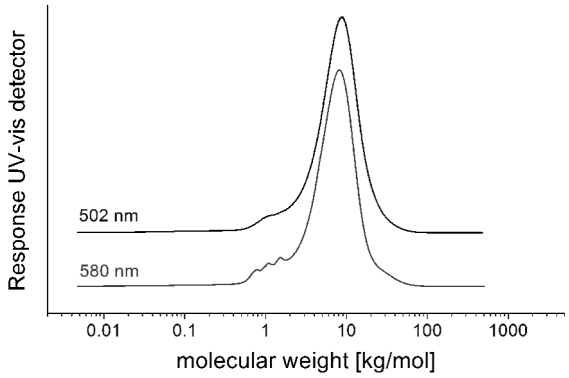


Figure 2. *Gel permeation chromatograms (DMF) of donor/acceptor labeled polymer* ***5*** *with the UV-vis detector set to 502 nm (upper curve, selective detection of donor), and 580 nm (lower curve, selective detection of acceptor). The position of the monomodal peaks and the absence of other signals showed the attachment of each dye to the polymer and the absence of excess free dyes.*

For energy transfer evaluations, measurements of systems with only the donor or only the acceptor are conducted and used for comparison. As green-only polymer, the intermediate **3** was employed. To have an appropriate red-only reference, a one-step reaction yielding a polymer PDEGMA-TR **6** was carried out. This way, the red-only material had the same solubility and diffusion properties as the donor/acceptor pair and was not prone to hydrolysis and subsequent oxidation, in contrast to a supposable Texas Red-MTS reagent reference. The synthesis is outlined in scheme 2. The starting α-PFP, ω-DTE PDEGMA **1** was subjected to an excess of n-propyl amine and Texas Red-MTS **4**. In this case, the amine formed the propyl amide at the α end group and released the terminal ω-thiol in one step. For purification, precipitation and preparative thin layer chromatography (TLC) were applied. TLC could also be employed to probe the successful attachment of dyes to the polymer as well as the absence of lose dyes. Both reactant dyes Oregon Green cadaverine **2**, Texas Red-MTS **4**, the three dye-labeled polymers (with both donor and acceptor **5**, only donor **3**, only acceptor **6)** and the starting polymer **1** were run on a TLC plate with chloroform / methanol / aqueous ammonia 3:2: 1 drop as eluent. Figure 3 shows a photograph of the TLC plate under UV light (365 nm) irradiation. In the solvent mixture, all polymers had an R_f value of 1, whereas the lose dyes were not transported all the way to the top. The orange color of the spot caused by the donor/acceptor labeled polymer (**5**, figure 3, spot 3) suggested the presence of both green and red dye within the polymer. The one-dye polymers **3** and **6** gave spots of distinct green and red color. No spots corresponding to lose dyes could be seen for polymer samples. The starting polymer (**1**, figure 3, spot 6) did not have any emission and could not be seen under this illumination. Using a wavelength of 254 nm however, a spot at $R_f = 1$ could be seen due to the fluorescent labeling of the TLC plate.

The end group conversions were calculated from the absorbance of solutions with defined concentrations, considering the molecular weight of the polymer and the molar extinction coefficient of each dye.[51] There was however an uncertainty about the exact molecular weight of the polymer. The conversion with Oregon Green cadaverine on polymers **3** and **5** was thus estimated to be at least 71%, still in the same range as conversions previously reported with a PFP α-end group.[54] The functionalization with Texas Red employing MTS chemistry was at least 47% in the case of polymer **5** prepared in two steps and at least 48% in case of polymer **6** synthesized in one step. These values are lower than expected from previous reports on quantitative conversions[51,52]. Noteworthy, both conversions of the MTS reactions are in the same range. It can therefore be ruled out that the α end group amidation in the two-step process had caused a significant loss of ω-DTE of polymer **3**, as even in the one-step reaction, where the complete presence of DTE of the starting polymer **1** can be assumed, no

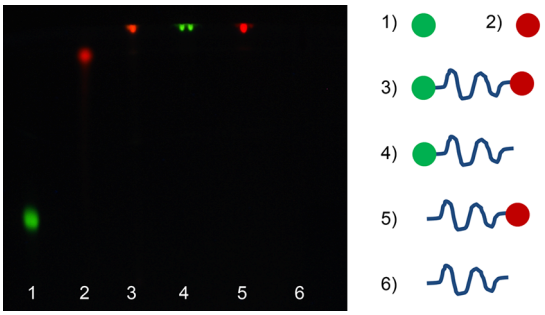


Figure 3. *Photograph of thin layer chromatography plate under UV irradiation (365 nm). Running direction was from bottom to top with chloroform/methanol/aqueous ammonia 3:2: 1 drop as eluent. (1) donor reagent Oregon Green cadaverine* ***2****; (2) acceptor reagent Texas Red-MTS* ***4****; (3) donor/acceptor labeled polymer* ***5****; (4) donor-only polymer* ***3****; (5) acceptor-only polymer* ***6****; starting polymer* ***1****.*

quantitative conversion was reached. A likely reason for the lower conversion is the rather poor solubility of the Texas-Red MTS reagent. Due to this, a lower absolute amount (10 compared to 20 equivalents[52]) of MTS reagent and also a significant lower polymer concentration (3.36 mM compared to 42 mM[52]) were employed. The lower end group conversions should thus be attributed to the intricacy of this MTS reagent. However, spectroscopic techniques discussed below are only sensitive to polymers carrying both dyes; thus, the presence of polymer bearing only one of the two chromophores was not an issue. The general method, however, of combining MTS conversions with PFP activated esters allows the orthogonal α/ω end group functionalization of RAFT polymers in one or two steps and thus introduces a synthetic route toward a broad range of possible end group modifications, including even challenging molecules such as complex fluorescent dyes. In the present project, the next step was the spectroscopic exploitation of polymer **5** with its strategically located dyes.

Spectroscopy. The absorption and fluorescence emission spectra of the donor-acceptor-labeled polymer **5** and the donor-only (acceptor-only) polymers **3** (**6**) in methanol solutions are shown in Figure 1. Within the experimental accuracy, no difference of the spectral positions and the shape of the spectra of free (data not shown) and polymer-coupled chromophores (**3**, **5**, **6**) could be observed. After selective excitation of the donor in **5** at 470 nm (gray bar in Fig. 1a), the emission spectrum showed donor as well as acceptor emission, suggesting the occurrence of excitation energy transfer. Compared to the single-dye systems (**3**, **6**) with the same dye concentrations, the emission spectrum showed a decreased donor emission and an increased acceptor emission (see supporting information). In addition to the absorption spectrum, also the excitation spectrum of **5** using a detection wavelength of 599 nm (selective acceptor emission) is shown in Figure 1a (gray curve). The obvious discrepancy between the absorption and excitation spectra was due to the presence of singly labeled polymer (or trace amounts of free donor) in the solution. Because of the low concentration of the components, however, diffusion-controlled energy transfer from donor-only labeled polymer only played a minor role, leading to a higher donor contribution in the absorption spectrum. Accordingly, by selective excitation of the donor and selective detection of the acceptor emission we could sort out to a high degree those polymer chains carrying both the donor and acceptor chromophore. As the concentration of the polymer solution could not be determined precisely, the molar extinction coefficients of the free dyes Oregon Green **2** and Texas Red-MTS **4** were used to scale the absorption spectra of **3** and **6** (Fig. 1b). Because of the low solubility of Texas Red-MTS **4** in methanol, the extinction coefficient was measured in DMF. For the following considerations, it was assumed that the coupling of the dyes to the polymer as well as the solvent change (in the case of Texas Red) had only minor influence on the molar extinction coefficients. According to Förster theory,[7] the time constant of energy transfer τ_{EET} and the transfer efficiency E_{EET} can be calculated by the following equations

$$\tau_{EET}^{-1}(r) = k_{EET}(r) = \frac{1}{\tau_D}\left(\frac{R_0}{r_{DA}}\right)^6 \quad \text{and}$$

$$E_{EET}(r) = 1/\left(1 + (r_{DA}/R_0)^6\right) \quad (2)$$

where τ_D is the donor fluorescence lifetime (in the absence of acceptor) and r_{DA} is the center-to-center distance of donor and acceptor. The characteristic Förster radius R_0 is given by the following expression:[18]

$$R_0 = 0.211\left[\kappa^2 n^{-4} Y_{fl}^D J(\lambda)\right]^{1/6} \quad (3)$$

For the donor-acceptor couple considered here, the value of the spectral overlap integral $J(\lambda) = 2.96 \times 10^{-22}$ m^6 mol^{-1} was obtained from a convolution of the absorption spectrum of **6** with the area-normalized emission spectrum of **3** (Fig. 1b). For the orientation factor we assumed a value of $\kappa^2 = 2/3$[18], corresponding to a random orientation of the transition dipoles of both chromophores due to rotational diffusion which in turn seems to be a reasonable approximation for the situation in **5**. The fluorescence lifetime of the isolated donor **3** was measured via time-correlated single photon counting (TCSPC) to be $\tau_D = 4.0$ ns (data not shown). With a fluorescence quantum yield $Y_{fl}^D = 0.92$ for Oregon Green **2**[79] and the refractive index $n = 1.33$ of methanol, a Förster radius R_0 of 6.1 nm was obtained.

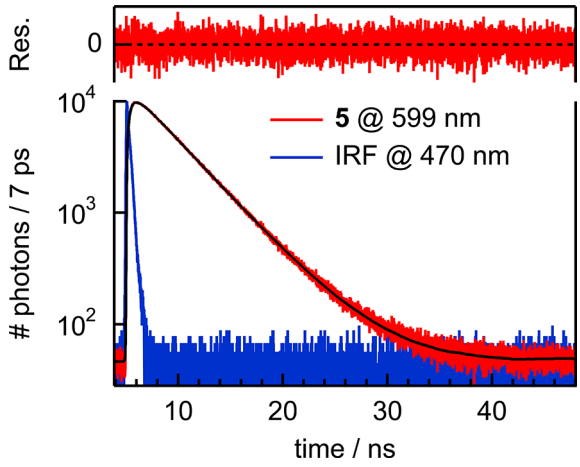


Figure 4. *Fluorescence rise/decay time profile for polymer* ***5*** *(red curve) at* λ_{em} = 599 nm *and the instrumental response function (IRF) recorded at* λ_{em} = 470 nm *(blue curve). An iterative re-convolution fit (solid line) according to equation 1 delivered a fluorescence lifetime* τ_{fl} = 4.4 ns *of the acceptor and an energy transfer time of* τ_{ETT} = 671 ps.

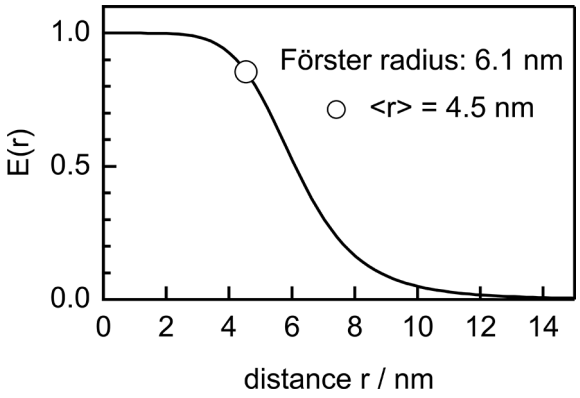


Figure 5. *Energy transfer efficiency* E_{EET} (r) *as a function of the donor-acceptor distance with the Förster Radius* R_0 = *6.1 nm of polymer* ***5****. The transfer efficiency determined by TCSPC (o) is shown.*

The energy transfer time could be directly measured with TCSPC by recording the rise/decay time profile of the acceptor after selective pulsed excitation of the donor.[80] The fluorescence rise/decay profile of polymer **5** recorded at an emission wavelength of 599 nm is shown in Figure 4 (red curve) together with the instrumental response function (IRF). The rise/decay profile could be described by equation (1) resulting in a fluorescence lifetime of the acceptor of τ_{fl} = 4.4 ns and an energy transfer time of τ_{EET} = 671 ps. The fluorescence lifetime of the acceptor-only polymer **6** was determined to be τ_A = 4.4 ns and was therefore not influenced by the polymer conjugation. Inserting the energy transfer time into equation (2), an average donor-acceptor distance of $\langle r_{DA} \rangle_{TCSPC}$ = 4.5 nm was obtained, corresponding to a transfer efficiency of $E_{EET}^{TCSPC}(r)$ = 0.85. From the DLS experiments the hydrodynamic radius of polymer **1** was found to be R_h = 1.9 nm. Based on this value, a mean donor-acceptor distance $\langle r_{DA} \rangle_{DLS}$ = 2 R_h = 3.8 nm was estimated. Taking into account that the two dye molecules attached to the end groups of polymer chain **5** effectively increased the average donor-acceptor-distance, we obtained a reasonable agreement between DLS and TCSPC data.

In Figure 5, the energy transfer efficiency E_{EET} (r) as a function of the donor acceptor distance r_{DA} for the donor-acceptor couple used in this study (Förster Radius R_0 = 6.1 nm) is shown. Notably, at a value corresponding to the Förster radius (R_0 = 6.1 nm) the transfer efficiency is 50 %. Also, given in the plot is the average donor-acceptor distance of polymer **5** as determined by TCSPC. In methanol solution, PDEGMA adopts an extended conformation. By inducing a coil collapse, the average donor-acceptor distance r_{DA} should decrease and the energy transfer efficiency increase. From figure 5, however, it can be estimated that even a reduction of the donor-acceptor-distance in the 1 nm range would lead to only a small change in the transfer efficiency for the given combination of D-A-couple and polymer, being difficult to detect within the error margins of the experiment. Therefore, it would be advantageous to use either a longer polymer chain or a different donor-acceptor couple (decreased spectral overlap) to shift the transfer efficiency of the non-collapsed state into the 50 % regime, where distance variations lead to strong changes in the transfer efficiency. With the successful synthesis of a hetero-telechelic dye-labeled polymer, we could envision to study a stimulus-induced chain collapse at the level of single polymer molecules.

Conclusion

Two previously independently reported methods to functionalize the end groups of RAFT polymers were combined to generate α, ω hetero-telechelic polymers carrying two different fluorescent dyes at their end groups. Pentafluorophenyl (PFP) activated ester α end groups were employed to be reacted with the amino group of Oregon Green cadaverine, which subsequently acted as energy donor. The success of the independent ω-functionalization relied on the polymers retaining their dithioester after the mild PFP ester conversion. Aminolysis in the presence of a methane thiosulfonate carrying the dye Texas Red introduced the energy acceptor onto the ω end groups via disulfide linkage. Through this method, the easy decomposable dithioester is not retained in between the polymer and the ω-functionality and the conversion at the ω end group (or also both end groups) may be carried out in a single step. Compared to anionic polymerization or cationic ring opening polymerization, fewer restrictions for monomer or dye end group choice applied, allowing the introduction of high-performance dyes. These end groups allowed for an easy detection of the successful attachment and the purification by TLC through GPC. Reference materials carrying only one of the two chromophores were synthesized.

An excitation spectrum showed that energy was transferred between the end groups of isolated polymer chains, which could be verified and quantified by time resolved fluorescence measurements. Following the Förster formalism, Förster radius and average dye-dye end group distance were calculated, the latter being in good agreement with data on the polymer size obtained from light scattering. The synthetic approach opens the possibility to investigate the stimulus induced chain collapse of polymers on single chains.

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Supporting Information Available. ^{19}F NMR and UV-vis absorbance data showing the selective conversion of an α-PFP ester in the presence of an ω-DTE; HSQC and UV-vis data showing the presence of α-dye and ω-DTE in polymer **3**; calculations of end group conversions; light scattering experiments and results, UV-vis and fluorescence spectra of polymers 3, 5, 6 with same dye concentrations. This material is available free of charge via the Internet at http://pubs.acs.org

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Proud am I that through this work alone
Of all the winding ways
Within the vast scientific maze
I have found my own

List of Publications

1. Roth, P. J.; Theato, P.; Versatile Synthesis of Functional Gold Nanoparticles: Grafting Polymers From and Onto, *Chem. Mater.*, **2008**, *20*, 1614–1621

2. Roth, P. J.; Wiss, K. T.; Zentel, R.; Theato, P.; Synthesis of reactive telechelic polymers based on pentafluorophenyl esters, *Macromolecules*, **2008**, *41*, 8513–8519

3. Roth, P. J.; Kessler, D.; Zentel, R.; Theato, P.; A Method for Obtaining Defined End Groups of Polymethacrylates Prepared by the RAFT Process during Aminolysis, *Macromolecules* **2008**, *41*, 8316-8319

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8. Roth, P. J.; Kim, K.-S.; Bae, S. H.; Sohn, B.-H.; Theato, P.; Zentel, R.; Hetero–Telechelic Dye–Labeled Polymer for Nanoparticle Decoration, *Macromol. Rapid. Commun*. **2009**, **DOI:** 10.1002/marc.200900254

9. Roth, P. J.; Theato, P.; Covalently Attaching Gold Nanoparticles to Polymers and Surfaces by UV Irradiation, **2009**, *in preparation*

10. Roth, P. J.; Jochum, F. D.; Zentel, R.; Theato, P.; Synthesis of Hetero-Telechelic α, ω Bio-Functionalized Polymers, *Biomacromolecules* **2009**, *in preparation*

11. Roth, P. J.; Haase, M.; Fischer, K.; Basché, T.; Theato, P.; Zentel, R.; Synthesis of α, ω Dye Functionalized Polymer by the RAFT Process and Energy Transfer between the End Groups, *Macromolecules* **2009**, *in preparation*

12. Jochum, F. D.; Roth, P. J.; Theato, P.; Thermo- and Lightresponsive Polymers Containing Photoswitchable Azobenzene End Groups, *Macromolecules* **2009**, *submitted*

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