Modular Diels-Alder Conjugation

An Efficient Tool for Polymer Architecture and Materials Design

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Classic. A book which people praise and don't read.

Mark Twain

Abstract

The development and application of modular Diels-Alder conjugations and their reversion by retro-Diels-Alder reactions for the design of advanced polymeric architectures and materials is reported.

The power of Diels-Alder cycloadditions for the construction of macromolecular architectures was demonstrated via the synthesis of high purity cyclic polymers employing α-maleimide-ω-cyclopentadienyl functionalized polymers. Combining a photo-triggered Diels-Alder reaction based on the formation of *o*-quinodimethanes with a thermally induced Diels-Alder or the widely used copper (I) catalyzed azide-alkyne *click* reaction enabled the ambient temperature formation of ABA and ABC triblock copolymers. The aforementioned studies demonstrated the great potential of cyclopentadienyl (Cp) capped polymers for modular polymer conjugations at ambient temperature. A limitation of these systems lies in the fact that the introduction of Cp end-group fidelities requires post-polymerization modifications because the high reactivity of Cp moieties has prevented the synthesis of Cp-functional initiators or chain-transfer agents. The one-pot synthesis of Cp capped polymers employing sodium cyclopentadienide as termination agent for the cationic ring-opening polymerization of 2-ethyl-2-oxazoline provided a new tool for the facile synthesis of novel precursors for ambient temperature conjugations. Hetero-Diels-Alder reactions of dithioester end-groups obtained via reversible addition fragmentation chain transfer polymerization (RAFT-HDA) represent an efficient method for the construction of macromolecular architectures. It was shown that utilizing water as solvent for RAFT-HDA reactions facilitates catalyst free ambient temperature polymer conjugations even when open-chain dienes were employed which require elevated temperatures and $ZnCl_2$ as catalysts in organic solvents. This study demonstrated for the first time that polymer-polymer conjugations can benefit from water as reaction medium. The reversibility of the RAFT-HDA cycloaddition at elevated temperatures was employed for the formation of nanoporous materials. For this purpose, poly(styrene)-*block*-poly(ethylene oxide) was synthesized by RAFT-HDA *click* chemistry. Nanoporous PS films were readily prepared by removal of the PEO block applying a simple heating and washing procedure. Spatially controlled surface patterning was achieved by Diels-Alder trapping of photo-generated thioaldehydes.

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1
Introduction

The philosophy of *click* chemistry[1] has undoubtedly changed the way in which researchers tackle problems in synthetic polymer chemistry.[2] The utilization of modular strategies is clearly predominant in the area of macromolecular architecture design in recent years. The separation of the polymerization process from the architectural buildup step enables the construction of otherwise inaccessible materials.[3-6] Diels-Alder reactions clearly represent a methodology standing at the forefront of *click* reactions in polymer science.[7-8] Although many publications addressing modular Diels-Alder conjugations for the construction of complex polymeric architectures have emerged in the last decade there are still significant findings to be made. The synthesis of cyclic polymers of high purity i.e. without contamination by linear chains is a challenging example. The construction of particular polymeric architectures demands for the combination of orthogonal *click* reactions. A powerful approach to gain a high orthogonality to other coupling methods is the use of photo-induced reactions. The fact that polymer coupling reactions should preferably be carried out at ambient conditions requires the incorporation of highly reactive functional groups into the polymer. Cyclopentadiene represents such a moiety for Diels-Alder reactions which is, however, difficult to handle due to its very high reactivity. The ultimate goal for polymer coupling reactions is to perform the conjugation not only at ambient conditions but also in benign solvents such as water. All the aforementioned challenges are targeted in the present thesis. The respective investigations comprise:

1. The utilization of Diels-Alder reactions as an efficient route to high purity cyclic polymers employing α-maleimide-ω-cyclopentadienyl functional linear precursors.

2. Combinations of orthogonal photochemical conjugations based on the light-triggered formation of *o*-quinodimethanes and thermally induced Diels-Alder as well as copper (I) catalyzed azide-alkyne *click* reactions.

3. The one-pot synthesis of cyclopentadienyl endcapped poly(2-ethyl-2-oxazoline) and subsequent ambient temperature Diels-Alder conjugations.

4. (Ultra)fast catalyst-free macromolecular conjugations in aqueous environment at ambient temperature employing dithioester end-groups obtained via RAFT polymerization as dienophile.

Although the mere synthesis of complex macromolecular architectures is still of interest for synthetic polymer chemists, applications of these structures and the employed *click* methodologies for the generation of functional soft materials come more and more into the focus of polymer and material scientists.[9-11] The reversibility of many Diels-Alder reactions is a useful feature for the design of stimuli-responsive materials.[12] Two sections of the present thesis address the design of functional polymeric materials:

1. The retro-Diels-Alder cleavage of block copolymers generated by RAFT-HDA *click* conjugation is utilized for the formation of nanoporous poly(styrene) films employing a simple heating and washing procedure.

2. Spatially controlled polymer surface patterning is achieved by Diels-Alder trapping of photo-generated thioaldehydes attached to a surface with a diene functionalized polymer.

Figure 1.1 provides an overview of all investigations presented herein.

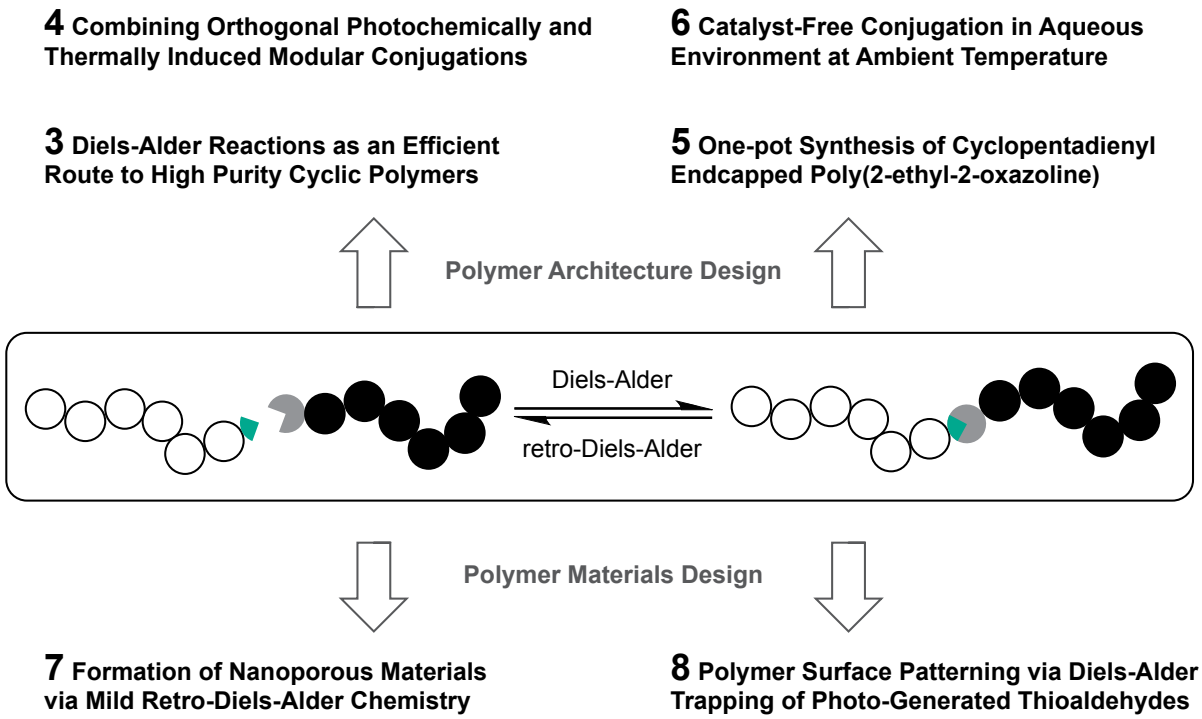

Figure 1.1 Overview of the individual investigations in the present thesis. The numbers refer to the numbering of the respective chapters.

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2

Diels-Alder Reactions in Polymer Architecture and Materials Design - A Literature Review

2.1 *Click* Chemistry in Polymer and Materials Science

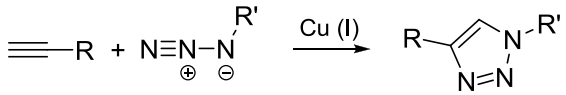
In a pioneering work published in 2001,[1] Sharpless and colleagues introduced the philosophy to employ highly efficient reactions between modular building "blocks" for the synthesis of novel molecules. The concept was termed *click* chemistry and the authors defined a set of stringent criteria a process must fulfill in this context. To be categorized as *click* process, a reaction must:

- be modular
- be wide in scope
- give very high yields
- generate only inoffensive byproducts
- be stereospecific.

In addition the process must have particular characteristics:

- simple reaction conditions
- readily available starting materials and reagents
- use of no solvent or a solvent that is benign or can easily be removed
- simple product isolation by nonchromatographic methods.

The *click* concept has attracted tremendously increasing interest after the groups of Meldal[2] and Sharpless[3] independently reported a drastic enhancement of the reaction rate and regioselectivity towards the 1,4-substituted ring by Cu(I) catalysis of the 1,3-dipolar cycloaddition between alkynes and azides (Scheme 2.1).



Scheme 2.1 The Cu-catalyzed azide-alkyne cycloaddition (CuAAC).

The CuAAC reaction rapidly evolved into the most popular reaction within the concept of *click* chemistry[4] and the term *click* is even often misleadingly used as synonym for the CuAAC. The first utilizations of the CuAAC in polymer and material science were reported in 2004.[5-7] The modular construction of block copolymers using CuAAC reactions was first demonstrated by Opsteen and van Hest.[8] It was then quickly realized that modular synthesis enables the construction of macromolecular architectures that are inaccessible by convergent pathways. A schematic comparison of the modular with the convergent approach is depicted in Figure 2.1.

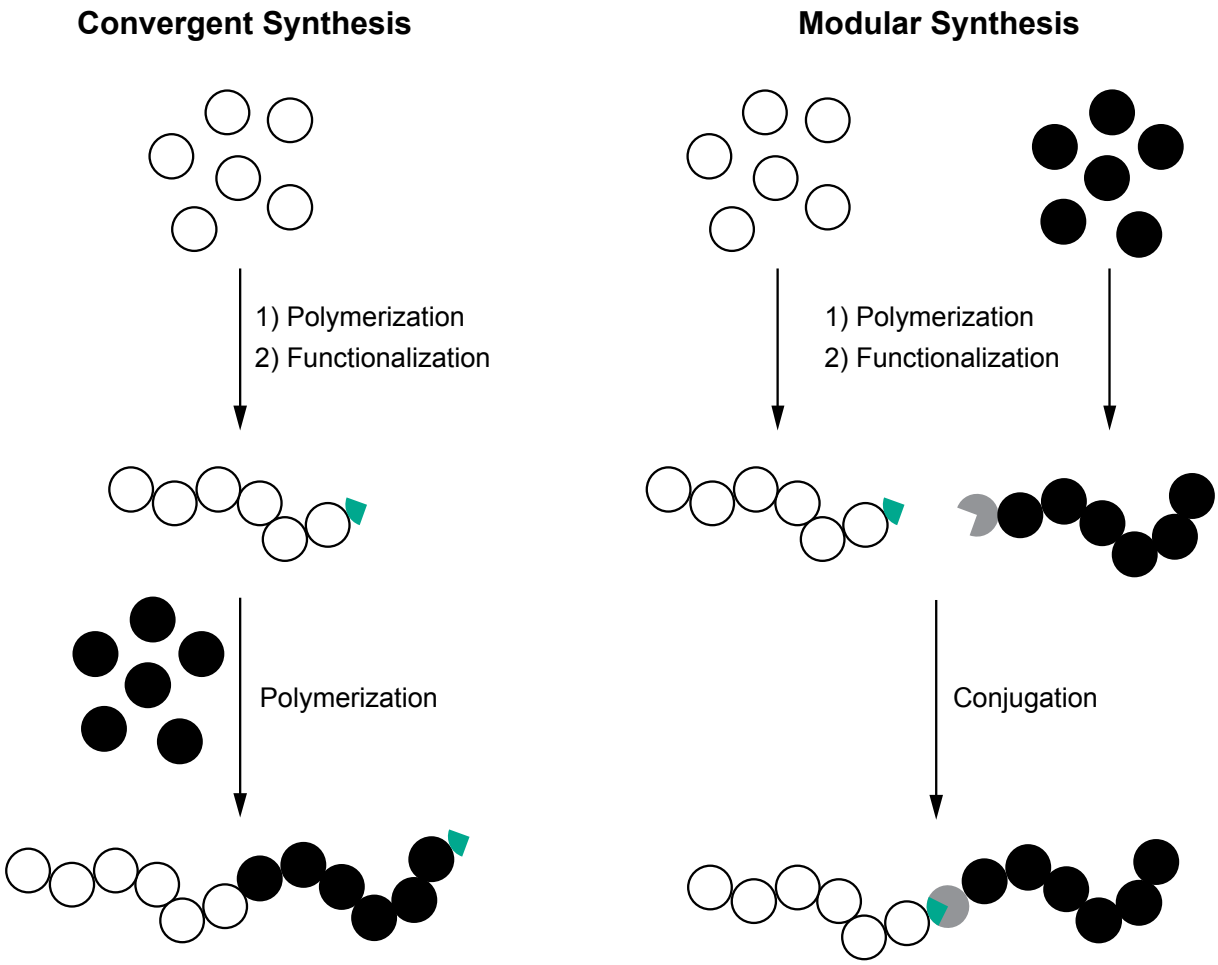


Figure 2.1 Convergent versus modular construction of macromolecular architectures.

The combination of different polymerization techniques with modular conjugations represents a powerful tool for the design of virtually any imaginable macromolecular

architecture within certain limits of purity and molecular weight[9-14] (see Figure 2.2 for typical examples) as well as functional soft materials.[15-16]

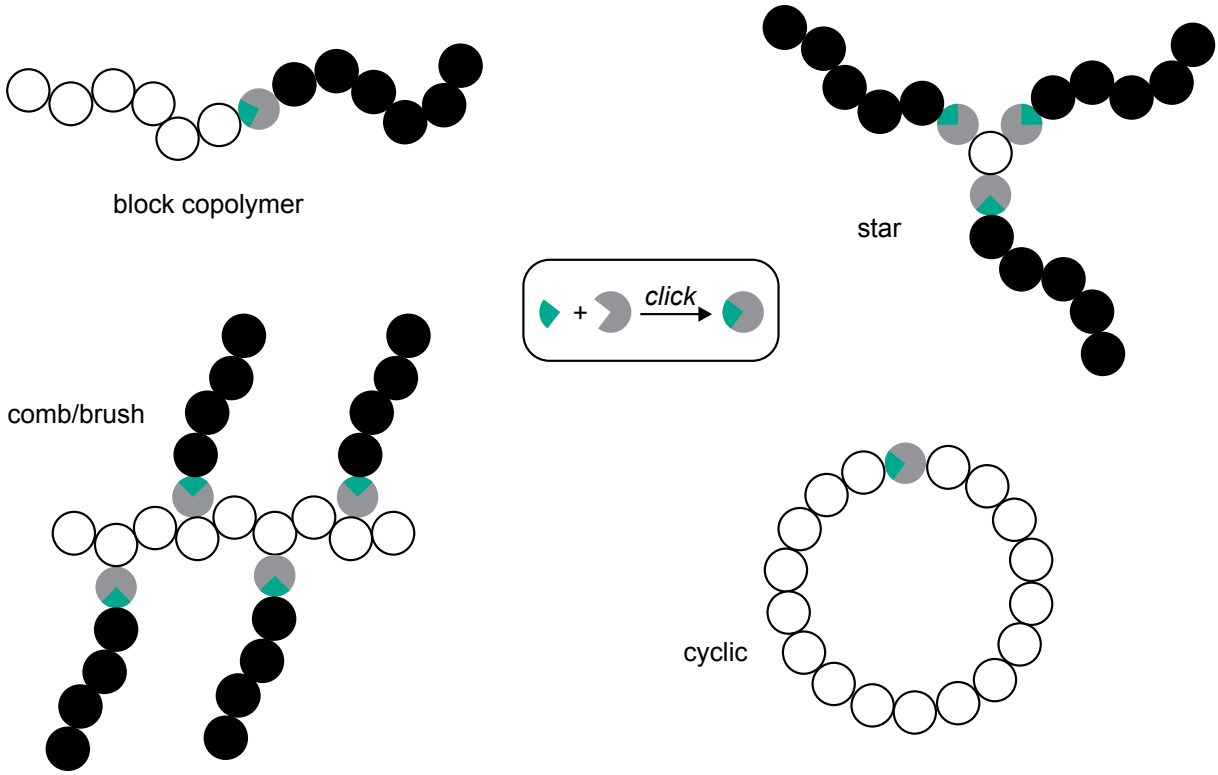
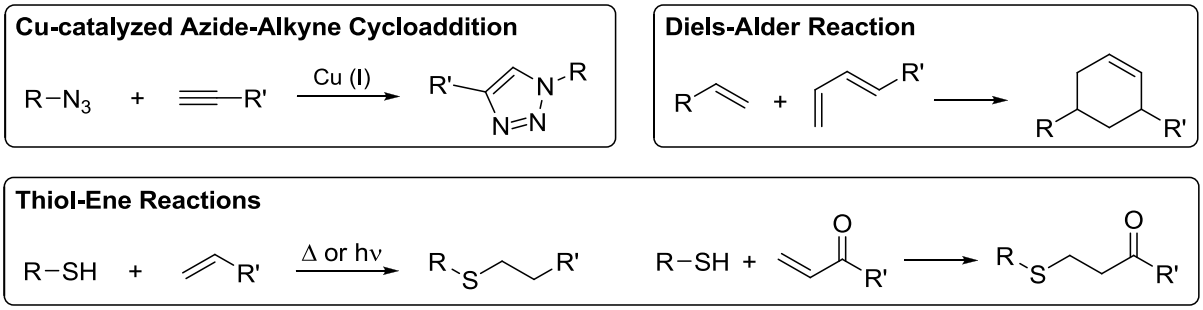


Figure 2.2 Schematic representations of polymeric architectures designed by modular conjugations.

The enormous impact of the *click* philosophy on polymer and materials design – which can be considered as "paradigm shift"[17] – led to the need to define specific criteria for *click* reactions in synthetic polymer chemistry.[18] While stereospecificity is often not required in polymer synthesis, the characteristics of polymeric materials demand for additional criteria for polymer *click* reactions. Facile purification methods for small organic molecules such as crystallization or distillation are generally not feasible for polymers so that the starting materials of polymer-polymer *click* reactions have to be used in equimolar amounts. The use of an excess of one building block is only acceptable when a simple large-scale purification process is applicable. The most extensively employed reactions in polymer science, CuAAC,[9, 19-21] thiol-ene[22-24] and Diels-Alder reactions[25-26] are shown in Scheme 2.2.

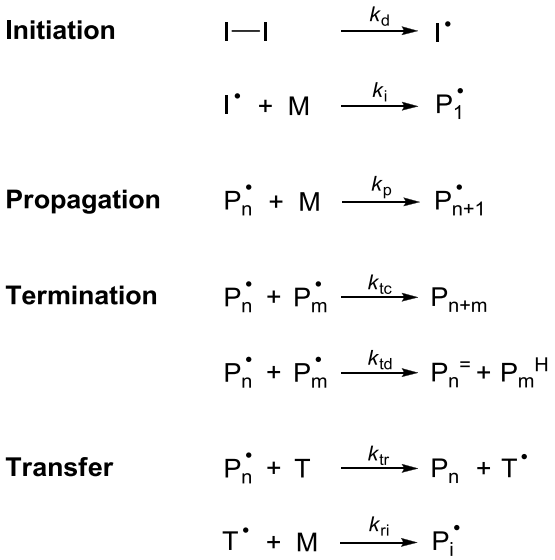


Scheme 2.2 The most widely employed *click* reactions in polymer chemistry.

2.2 *Click* Chemistry and Controlled Radical Polymerization

2.2.1 Free Radical Polymerization

Free radical polymerization (FRP) is a highly important method for industrial polymer synthesis. Currently approximately 50 % of all synthetic polymers are made via radical polymerization processes.[27] FRP is a chain reaction process comprising four elementary steps: initiation, propagation, termination and chain transfer (Scheme 2.3).



Scheme 2.3 The elementary steps of free radical polymerization.

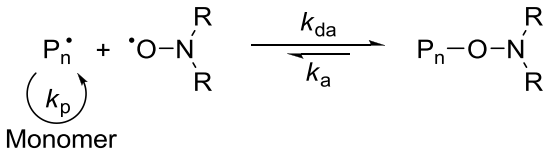
Initiation consists of two steps, the first of which is the generation of primary radicals. This is most commonly achieved through thermal or photochemical homolytic cleavage of an initiator molecule such as azo- or peroxy compounds. The second step is the addition of a primary radical to the C=C double bond of the monomer. Typical

rate coefficients for these processes are $k_d \approx 10^{-5}$ s^{-1} and $k_i > 10^4$ M^{-1} s^{-1}. Repetitive addition of the growing radicals to the double bond is called propagation with typical values of $k_p \approx 10^{3\pm1}$ M^{-1} s^{-1}. Termination of two growing radicals can occur by combination or disproportionation. Termination rate coefficients are chain length and conversion dependent and controlled by diffusion ($k_t \approx 10^{8\pm1}$ M^{-1} s^{-1}). An additional process that generates dead polymer chains is transfer to the monomer, polymer, solvent or a transfer agent. In case of transfer to the polymer it has to be distinguished between intramolecular transfer (backbiting) which produces short chain branches and intermolecular reactions resulting in the formation of long chain branches. Transfer reactions do not change the overall radical concentration and only influence the molecular weight distribution and not the kinetics if reinitiation is fast. Slow reinitiation, however, results in retardation/inhibition of the polymerization. FRP allows the polymerization of a wide range of monomers and represents a robust process tolerating water and protic impurities. However, FRP provides only limited control over polymer architecture and functionality. It is therefore not suitable for the construction of polymeric building blocks that are to be used in modular conjugation reactions.

Anionic polymerization provides an efficient control over polymer composition and end-group functionality. Szwarc[28] named anionic polymerization a *living* polymerization, defined as chain growth process without chain breaking reactions (termination and transfer). A radical chain growth process can never be *living* in the strict sense because it is impossible to completely suppress termination reactions. However, several methods have been developed which drastically reduce the proportion of terminated chains in radical polymerization providing efficient control over molecular weight and end-group functionality. Such controlled radical polymerizations (CRP)[29] can be achieved by reversible termination or degenerative chain transfer mechanisms. Although IUPAC recommends the term *controlled reversible-deactivation radical polymerization*[30] the still common term CRP will be used within the current thesis. The most widely employed CRP methods, nitroxide mediated polymerization (NMP),[31-32] atom transfer radical polymerization (ATRP)[33-35] and reversible addition-fragmentation chain transfer (RAFT) polymerization[36-37] will be briefly discussed in the following.

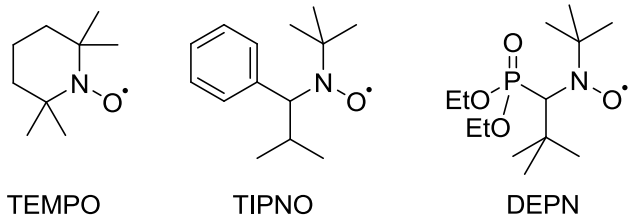
2.2.2 Nitroxide Mediated Polymerization

In NMP the concentration of propagating chains is drastically reduced by establishing an equilibrium between the propagating radical and a stable nitroxide radical on the one side and an alkoxyamine on the other side (Scheme 2.4).



Scheme 2.4 General mechanism of NMP.

NMP is an example of stable free radical polymerizations (SFRP) in which the homolytic cleavage of a relatively weak bond generates a growing and a persistent radical. The persistent radical should react reversibly only with growing radicals, while some of the propagating radicals will irreversibly terminate resulting in an excess of the persistent over the transient species in the reaction mixture. Consequently, the reversible cross-reaction channel is favored over irreversible terminations. This phenomenon is known as persistent radical effect.[38] A NMP can be conducted using a conventional radical initiator and a stable nitroxide such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or by employing an alkoxyamine which thermal decomposition generates a reactive radical and a stable nitroxide radical. TEMPO derivatives form relatively stable alkoxyamines ($K = k_a/k_{da} = 2.1 \times 10^{-11}$ M for TEMPO/styrene at 125 °C)[39] and therefore require high temperatures and are only suitable for styrenic monomers. Thus, other nitroxides (see Scheme 2.5 for examples) have been designed enabling the polymerization of a wide range of monomers such as acrylates, acrylamides and acrylonitrile at lower temperatures.

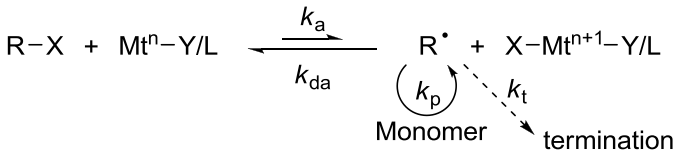


Scheme 2.5 Typical nitroxides employed in NMP.

The equilibrium constant for DEPN/styrene at 120 °C, $K = k_a/k_{da} = 6.0 \times 10^{-9}$ M is more than 100 times larger than that of the TEMPO system.[40]

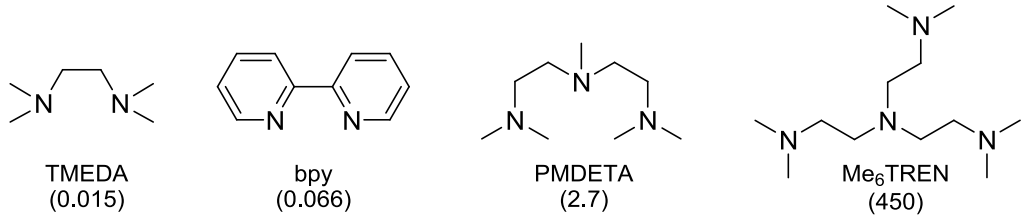
2.2.3 Atom Transfer Radical Polymerization

ATRP which was first reported by the groups of Matyjaszewski[41] and Sawamoto[42] 1995 is based on a reversible termination mechanism just as NMP. In ATRP, homolytic cleavage of an alkyl halide bond R-X by a transition metal complex Mt^n-Y/L generates reversibly the corresponding higher oxidation state metal halide complex X-Mt^{n+1}-Y/L and an alkyl radical $R^\bullet$ (Scheme 2.6). $R^\bullet$ can initiate polymerization, terminate or can be reversibly deactivated by X-Mt^{n+1}/L which takes on the role of the persistent radical (named deactivator in ATRP). Radical termination is decreased due to the previously described persistent radical effect so that the equilibrium is shifted towards the dormant species RX ($k_a << k_{da}$). The equilibrium constant $K_{ATRP} = k_a/k_{da}$ is typically within the range of 10^{-11} to 10^{-3} depending on the ligand, initiator, monomer and the reaction conditions (solvent, temperature and pressure).[43]



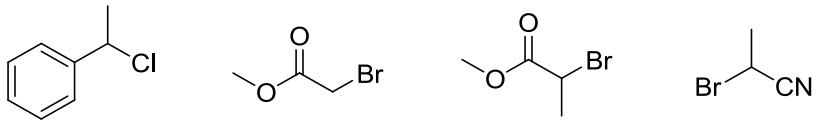
Scheme 2.6 General mechanism of ATRP. X = Halide, L = Ligand, Y = Ligand or counterion.

ATRP can be mediated by a variety of transition metals from which Cu is the most efficient and most widely employed. In Cu mediated ATRP polydentate nitrogen-containing ligands (Scheme 2.7) are most often used to form the catalyst complex.



Scheme 2.7 Typical ligands for Cu mediated ATRP. The numbers represent activation rate constants (k_a / M^{-1} s^{-1}) with 2-bromoisobutyrate in the presence of CuBr in MeCN at 35 °C.[35]

The wide variety of organo-halides that can be utilized as ATRP initiator represents a significant advantage of this CRP method. Essentially all compounds with halogen atoms activated by α-carbonyl, phenyl, vinyl, or cyano groups are efficient initiators (Scheme 2.8).



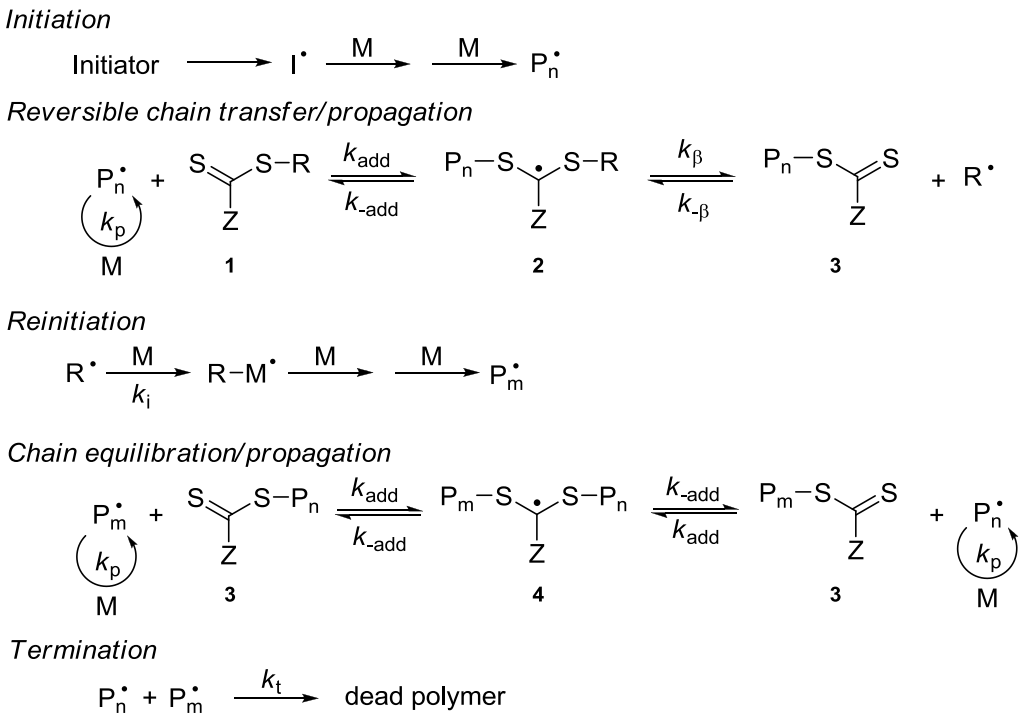
(0.01) (0.03) (0.33) (0.46)

Scheme 2.8 Representative examples of ATRP initiators. The numbers represent activation rate constants (k_a / M^{-1} s^{-1}) with CuX/PMDETA (X = Br or Cl) in MeCN at 35 °C.[35]

The retention of the halide functionality that can be utilized for post-polymerization modifications and the wide range of functional initiators[44] make ATRP an efficient tool for the construction of polymeric building blocks for modular architecture design. In this context it has to be kept in mind that the halide end-fidelity decreases with increasing conversion.[45] An enhanced functionality can be obtained via activator regenerated by electron transfer (ARGET) ATRP[46] in which the catalyst is continuously regenerated by a reducing agent allowing the use of ppm amounts of the copper catalyst. However, there is still a limit of functionality that can be obtained even with the ARGET process and the removal of copper is nevertheless a crucial point.

2.2.4 Reversible Addition-Fragmentation Chain Transfer Polymerization

1998 a group from the Commonwealth Scientific and Industrial Research Organization (CSIRO) reported the controlled radical polymerization of various monomers employing dithioesters as transfer agents.[47] The process was called reversible addition-fragmentation chain transfer (RAFT) polymerization. A procedure based on the same mechanism utilizing xanthates as transfer agents was reported independently and termed macromolecular design by interchange of xanthates (MADIX) by a team of French researchers.[48] The underlying mechanism of RAFT polymerization is based on degenerative chain transfers and thus fundamentally different from NMP and ATRP. The accepted mechanism of the RAFT process consisting of a sequence of addition-fragmentation equilibria is shown in Scheme 2.9.



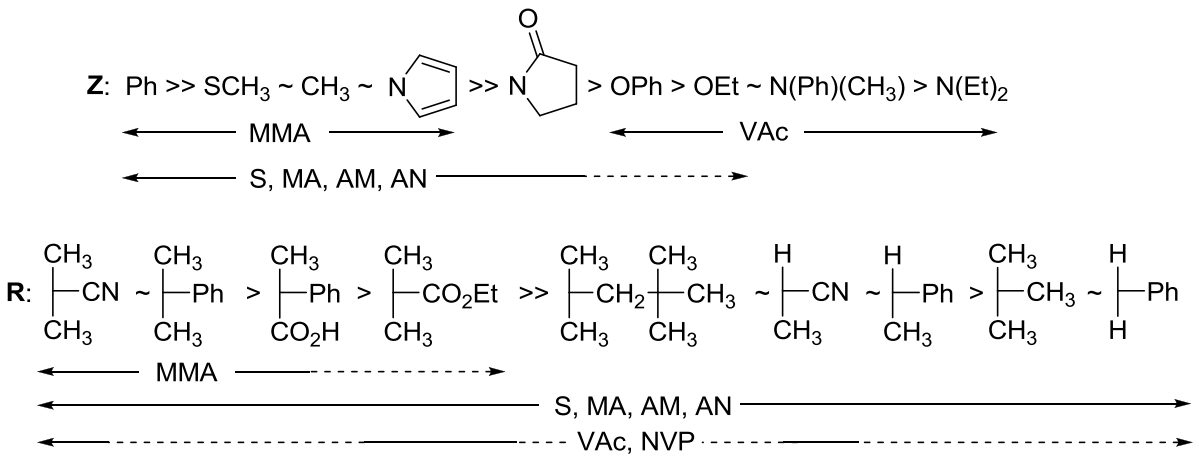
Scheme 2.9 Mechanism of RAFT polymerization.

Initiation is achieved by decomposition of an initiator and subsequent propagation as in FRP. In the early stages of the polymerization, addition of a propagating radical to the thiocarbonylthio compound **1** is followed by fragmentation of the intermediate radical **2** into a polymeric thiocarbonylthio compound **3** and a new radical ($R^{\bullet}$). Addition of $R^{\bullet}$ to the monomer forms a new propagating radical ($P_m^{\bullet}$). A rapid equilibrium between the propagating radicals ($P_n^{\bullet}$ and $P_m^{\bullet}$) and the dormant species **3** results in an equal probability for all chains to grow and enables the production of narrow dispersity polymers. In contrast to processes based on the persistent radical effect the radical concentration is not reduced in RAFT polymerization. Consequently there is no inherent retardation of the propagation rate although retardation is often observed in practice. The rate-retardation phenomenon can be explained by cross-termination reactions of the intermediate radical **4** or by slow fragmentation of the intermediate radicals.[49] The choice of a suitable RAFT agent is required to control the polymerization of a specific monomer. For an efficient RAFT polymerization:[36]

- The initial RAFT agent **1** and the polymer RAFT agent **3** should have a reactive C=S double bond (high k_{add}).
- The intermediate radicals **2** and **4** should fragment rapidly (high k_{β}, weak S-R bond in the intermediate) and give no side reactions.

- The intermediate **2** should partition in favor of products ($k_\beta \geq k_{-add}$).
- The expelled radicals ($R^\bullet$) must efficiently re-initiate the polymerization ($k_i > k_p$).

A summary of appropriate RAFT agents for particular monomers is shown in Scheme 2.10.



Scheme 2.10 Guidelines for selection of RAFT agents. For Z, addition rates decrease and fragmentation rates increase from left to right. For R, fragmentation rates decrease from left to right. Dashed line indicates partial control (i.e. control of molecular weight but poor polydispersity or substantial retardation in the case of VAc or NVP).[50]

Combining RAFT polymerization and *click* chemistry represents a powerful tool for the construction of macromolecular architectures and materials.[51-52] It should be noted that the thiocarbonylthio end-groups of RAFT polymers are not only useful synthetic handles[53] but also cause color and their decomposition can generate odor which may be a limitation especially for commercial applications.

2.3 Construction of Macromolecular Architectures via (Hetero-) Diels-Alder Reactions

The discovery of the [4+2] cycloaddition between a diene and an ene (the dienophile) by Otto Diels and Kurt Alder[54] was a pioneering result that was honored with the Nobel prize in 1950. (Hetero-)Diels-Alder [(H)DA] reactions belong to the most widely used reactions in organic synthesis.[55-57] The DA reaction is a concerted pericyclic reaction and its characteristics can be explained with the frontier molecular orbital (FMO) theory.[58] Indications for a diradical or di-ion mechanism can only be found

in certain cases.[59-60] Efficient DA reactions require the combination of electron-poor dienophiles and electron-rich dienes, (normal electron demand) or electron-rich dienophiles and electron-poor dienes (inverse electron demand) to realize a small HOMO-LUMO gap as depicted in Figure 2.3.

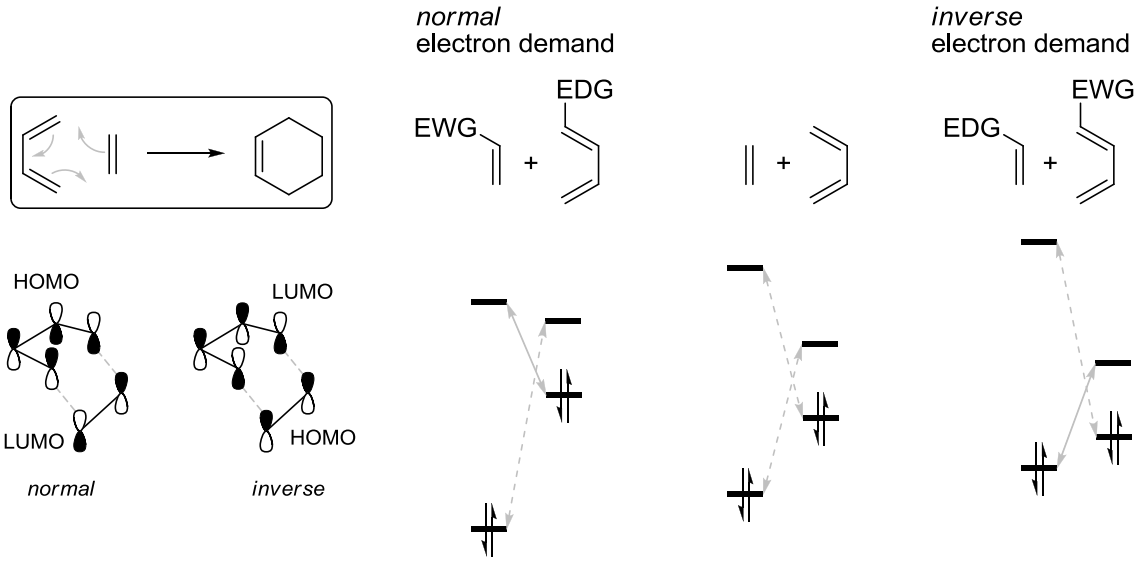
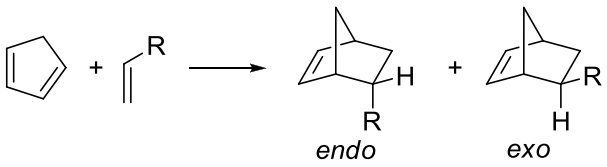


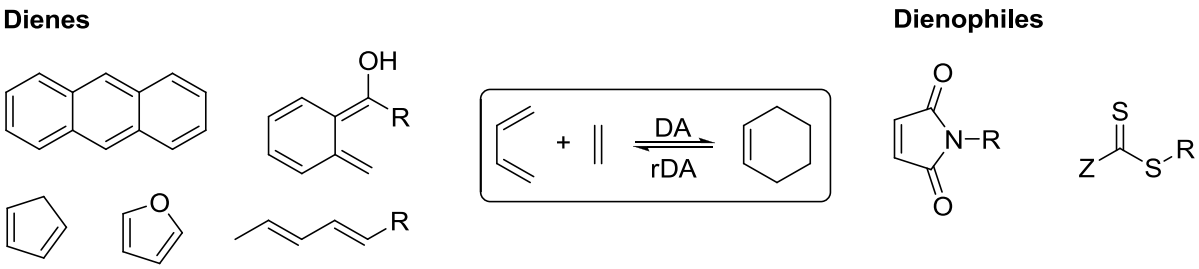
Figure 2.3 Frontier orbital interactions in DA reactions with different electron demand. EWG = electron withdrawing group, EDG = electron donating group.

Due to the concerted mechanism DA reactions are highly stereospecific, i.e. the stereochemical information (*E* or *Z*) of the diene and the dienophile is transferred into the product. In addition DA reactions show a high regioselectivity towards the *ortho* and *para* substituted product over the *meta* product. The regiochemical preferences of DA reactions can be determined by analyzing the FMO coefficients of the atoms forming the σ-bonds.[61] In DA reactions which generate two diastereomers such as the reaction in Scheme 2.11 the *endo* adduct is often, but not always, predominant. The stereoselectivity is often explained with secondary orbital interactions but can also be explained with solvent effects, steric interactions, hydrogen bonds, electrostatic forces, and other effects.[62]



Scheme 2.11 A DA reaction that generates two diastereomers.

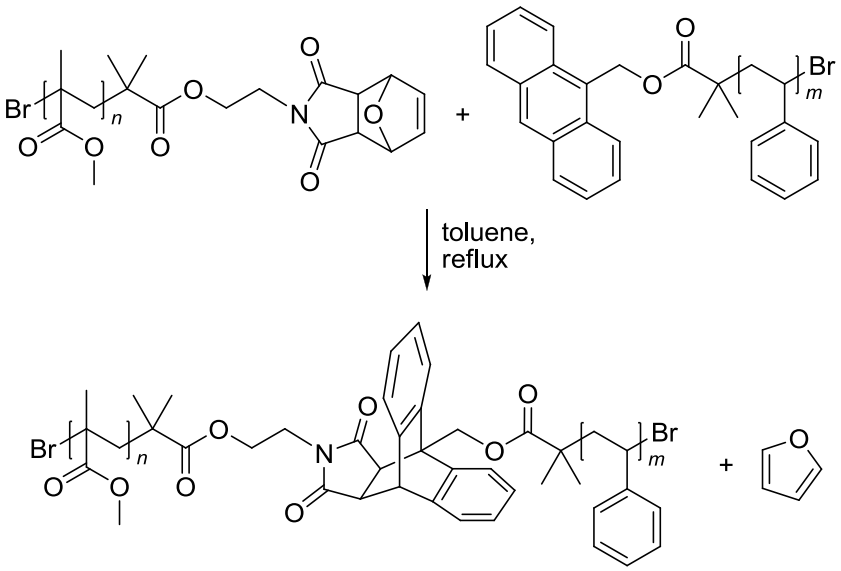
The utilization of chiral catalysts or auxiliaries enables enantioselective (H)DA reactions.[63-65] A drastic rate enhancement is observed for many (H)DA reactions employing water or salt solutions as reaction medium.[66-67] Interestingly, this phenomenon has not been utilized for polymer-polymer coupling reactions to date. (H)DA reactions were already identified as potential *click* reaction in the initial publication by Sharpless and colleagues.[1] Although the CuAAC reaction is an extremely powerful tool for the modular construction of polymeric architectures, the potential toxicity of metal catalysts has created increasing interest in developing metal-free *click* reactions.[68] The utilization of (H)DA cycloadditions represents an exceptionally versatile strategy for polymer architecture and materials design as will be outlined in the following.[25-26] The utilization of the reversibility of certain (H)DA reactions for the construction of functional materials will be highlighted in the last section of the present chapter.



Scheme 2.12 General representation of the Diels-Alder/retro-Diels-Alder reaction and dienes and dienophiles which have been employed for the modular construction of polymeric architectures.

2.3.1 Anthracene-Maleimide Diels-Alder Reactions

In normal DA reactions[58] an electron-rich diene is reacted with an electron-poor dienophile. Maleimides represent an attractive moiety for this reaction type because of their highly reactive electron-poor C=C double bond and the possibility to attach various substituents on the nitrogen atom which makes them easy to incorporate in polymers. Anthracene moieties react in a quantitative fashion with maleimide groups at temperatures around 110 °C forming a stable cycloadduct. The high stability of anthracenes allows the facile synthesis of anthracene functionalized polymers by various polymerization methods including (controlled) radical processes. The maleimide functionality is often generated in situ by deprotection of a furan protected precursor via a retro-DA reaction. Tunca and Hizal demonstrated the potential of the maleimide-anthracene system for modular constructions of macromolecular architectures by synthesizing block copolymers as depicted in Scheme 2.13.[69]



Scheme 2.13 Modular block copolymer synthesis by DA conjugation of maleimide- and anthracene-capped polymers.

DA reactions between maleimide and anthracene functionalities were further employed for polymer end-group[70] and backbone functionalization[71-72] as well as for the construction of complex macromolecular architectures such as brush copolymers,[73-74] stars,[75-77] cyclic,[78] dendronized[79] and H-shaped[80] polymers. The orthogonality of the anthracene-maleimide DA reaction to several other *click* reactions could be employed for the synthesis of a wide variety of complex macromolecular architectures as summarized in Table 2.1.

Table 2.1 Complex polymer architectures synthesized via combination of anthracene-maleimide DA reactions with other modular conjugations.

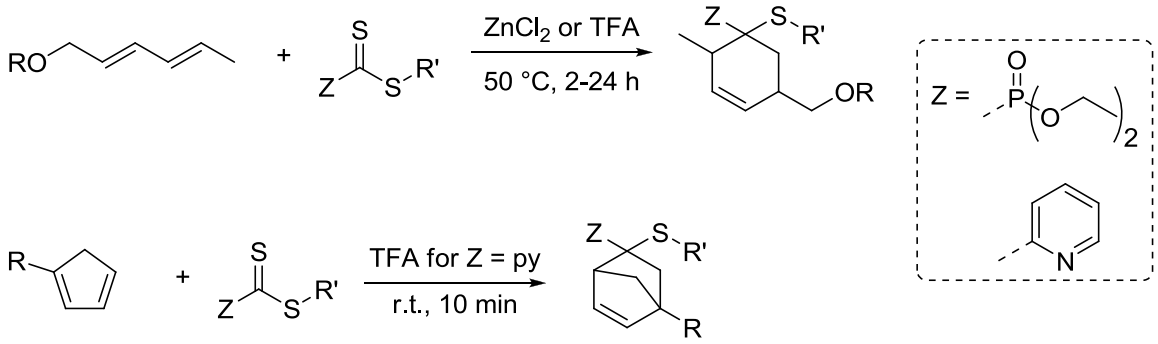
Combined reactions[a]	Topology	Ref.
DA and CuAAC	Linear ABC block copolymer	[81]
DA and CuAAC	Hetero-graft copolymer	[82]
DA and CuAAC	Multiblock-graft copolymer	[83]
DA and CuAAC	Dendritic star polymers	[84]
DA and CuAAC	Mikto-arm star	[85]
DA and CuAAC	Multi-arm star triblock terpolymers	[86]
DA and CuAAC	Dendritic multi-arm star polymers	[87]
DA and CuAAC	Multi-miktoarm star block copolymers	[88]
DA, CuAAC and NRC	Linear tetrablock quaterpolymers	[89]
DA, CuAAC and NRC	Tadpole shaped polymers	[90]
DA, TE, CuAAC and NRC	Functionalized multiblock polymers	[91]
DA, TE and SPAAC	Functionalized graft copolymer	[92]

[a]NRC: nitroxide radical coupling; TE: thiol-ene; SPAAC: strain-promoted azide-alkyne cycloaddition.

2.3.2 RAFT-HDA Chemistry

RAFT polymerization is a facile strategy for the synthesis of polymers bearing a dithioester end-group without post-polymerization modification as described in Chapter 2.2.4. Thiocarbonyl compounds are generally more reactive hetero-dienophiles as their carbonyl analogues.[93] To achieve efficient HDA reactions at mild conditions dithioesters need to be activated by an electron-withdrawing group (EWG). However, it has to be considered that many dithioesters bearing an EWG are not able to mediate a RAFT polymerization. The groups of Barner-Kowollik and Stenzel pioneered the utilization of dithioester capped polymers synthesized via RAFT polymerization as dienophiles in HDA cycloadditions. Different dithioesters bearing an EWG were identified which can act as controlling agents in RAFT polymerization and react quantitatively with hexadienoyl based dienes at 50 °C in the presence of an appropriate catalyst (Scheme 2.14).[94] The potential of the RAFT-HDA concept was demonstrated by construction of various macromolecular architectures including block copolymers,[94-95] (multi-arm) star polymers,[96-97] and combs.[98]

The orthogonality of the RAFT-HDA approach to the CuAAC was demonstrated by constructing star polymers via consecutive HDA and CuAAC conjugations.[99]

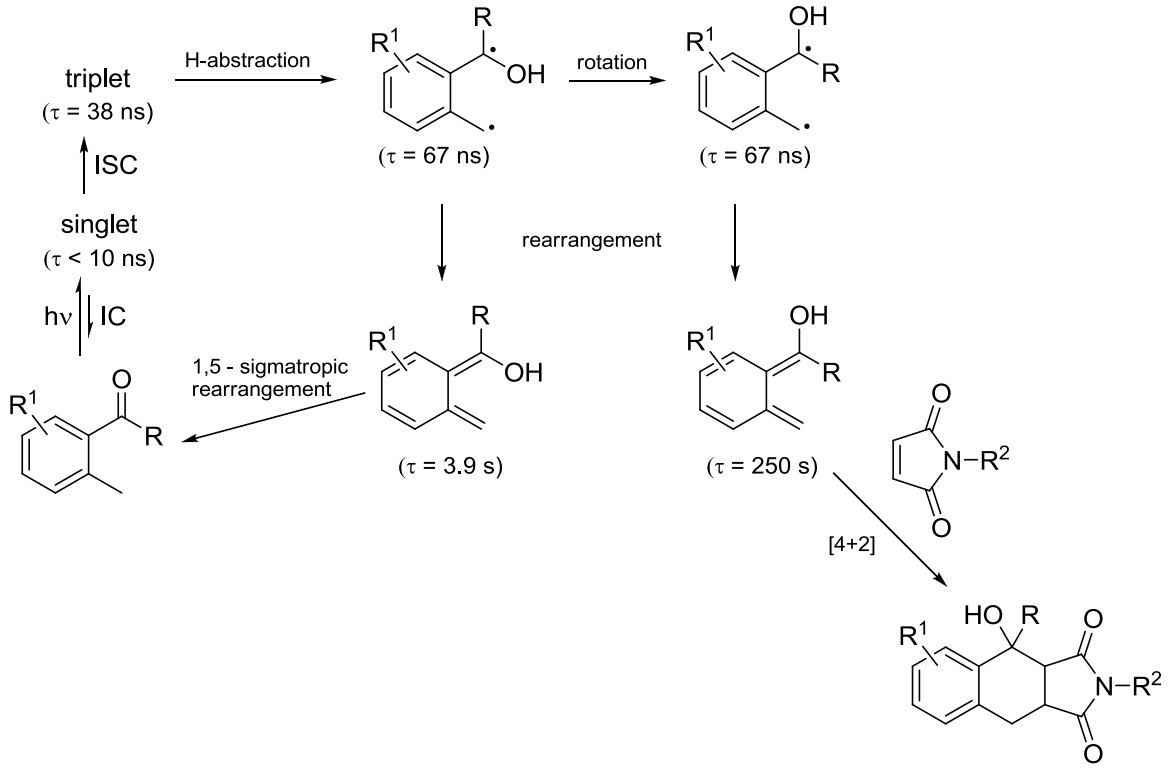


Scheme 2.14 RAFT-HDA cycloadditions of electron-deficient dithioesters.

Employing cyclopentadienyl (Cp) capped polymers as diene, block copolymer formation can be achieved at ambient temperature within 10 min reaction time.[100] Cp-functional polymers can be synthesized by substitution of an appropriate leaving group with NaCp or milder and with much broader applicability by a recently reported strategy using $NiCp_2$ as the Cp source.[101] Modifications of microspheres[102] and biosurfaces[103] further confirm the great potential of the RAFT-HDA strategy. α-sulfonyl dithioesters are extremely reactive hetero-dienophiles, yet their use in the RAFT-HDA concept is limited as they react with monomers such as styrene and *n*-butyl acrylate.[104] However, isobornyl acrylate could be polymerized in a controlled fashion, without occurrence of side-reactions. The reversibility of RAFT-HDA reactions at elevated temperatures can represent a limitation of the concept as well as a tool for the construction of functional materials as will be discussed later.

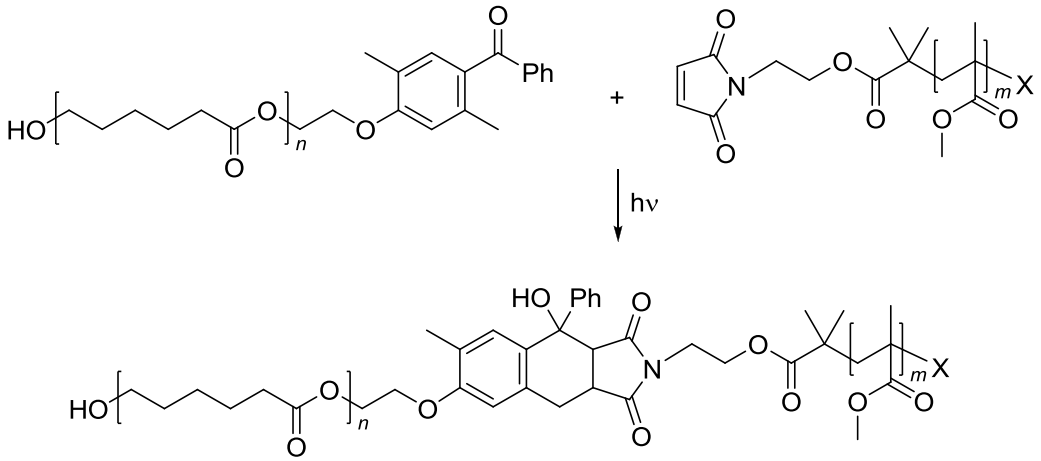
2.3.3 Photo-induced Diels-Alder Reactions via *o*-Quinodimethanes

Employing light as trigger for a chemical reaction offers the possibility to gain spatial and temporal resolution. When *o*-methylphenyl ketones and -aldehydes are irradiated with UV light intramolecular hydrogen abstraction followed by bond reorganization generates an *o*-quinodimethane (photoenol) intermediate. Scheme 2.15 shows the detailed mechanism of this process which was proposed by Tchir and Porter based on flash photolysis experiments.[105] Photoenols are highly reactive dienophiles which react rapidly with electron-deficient alkenes such as maleimides (Scheme 2.15).



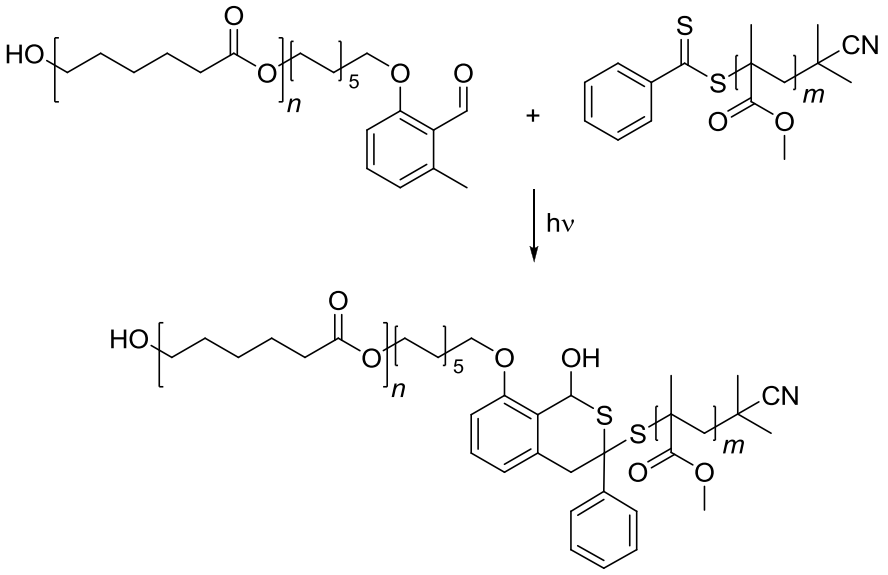
Scheme 2.15 General mechanism of the photo-induced formation of *o*-quinodimethanes and in situ DA reaction with maleimides. The lifetimes refer to species derived from 2,4-dimethylbenzophenone measured in degassed cyclohexane.[106]

It was shown that the conjugation of 2,5-dimethyl benzophenone and maleimide terminated polymers enables block copolymer formation at ambient temperature within 100 min irradiation time employing a 36 W compact fluorerscent lamp (λ_{max} = 320 nm) as displayed in Scheme 2.16.[107]



Scheme 2.16 Modular block copolymer synthesis via photo-induced formation of an *o*-quinodimethane and in situ DA reaction with a maleimide capped polymer.

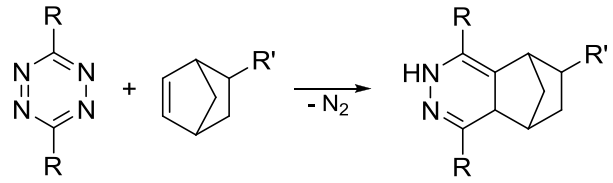
Photoenol functionalized silicon wafers enabled the spatially controlled surface-patterning employing various maleimide containing (bio)molecules.[108] A study conducted simultaneously with the present investigation revealed that photoenols derived from 2-methoxy-6-methylbenzaldehyde undergo a DA reaction with dithiobenzoate functional polymers.[109] Consequently, block copolymers could be constructed employing polymers synthesized by RAFT polymerization with a conventional, non-electron-deficient transfer agent such as 2-cyanopropyl dithiobenzoate as dienophile (Scheme 2.17).



Scheme 2.17 Modular block copolymer synthesis via photoenol-RAFT-HDA chemistry.

2.3.4 Inverse Electron-Demand Diels-Alder Reactions

All the aforementioned DA reactions involve an electron-poor dienophile and an electron-rich diene. This type of DA reaction is referred to as Diels-Alder reaction with normal electron demand.[58] Even though the vast majority of DA reactions belong to this type, inverse electron-demand DA reactions (DA_{inv}) are promising candidates for polymer coupling reactions. The DA_{inv} reaction between tetrazines and strained alkenes or acetylenes has been successfully employed for bioconjugation reactions.[110-113] O'Reilly, Du Prez and co-workers recently reported the utilization of the tetrazine-norbornene DA_{inv} reaction depicted in Scheme 2.18 for the post-functionalization of synthetic polymers.[114] The high efficiency of the catalyst free reaction at ambient conditions was demonstrated by block copolymer formation.



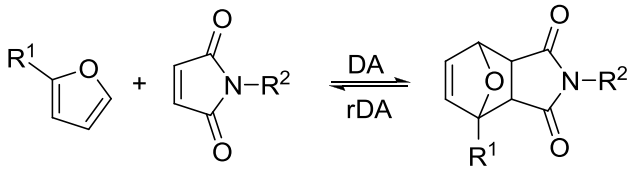
Scheme 2.18 The tetrazine-norbornene DA_{inv} reaction.

2.4 (Hetero-)Diels-Alder Cycloadditions-Cycloreversions for Functional Materials Design

The (H)DA reaction is not only a highly efficient method for the coupling of two molecules but also implies the interesting characteristic that (H)DA cycloadducts can undergo a cycloreversion at elevated temperatures, named retro-DA (rDA) reaction.[115-116] The ability to build and break linkages on demand turns the DA/rDA reaction into a "powerful combo in materials design."[117] The thermally reversible cross-linking of polymers offers great potential for the design of self-healing materials which do not require the addition of an extra chemical.[118-120]

2.4.1 The Furan-Maleimide System

The cycloaddition-cycloreversion equilibrium between maleimides and furans (Scheme 2.19) is strongly temperature dependent. As rule of thumb it can be stated that up to around 60 °C the cycloadduct is mostly stable whereas above about 110 °C the rDA reaction becomes predominant. Due to this convenient conditions and the fact that usually no side-reactions are observed the furan-maleimide system represents a powerful tool for the construction of thermoreversible macromolecular architectures.[121]



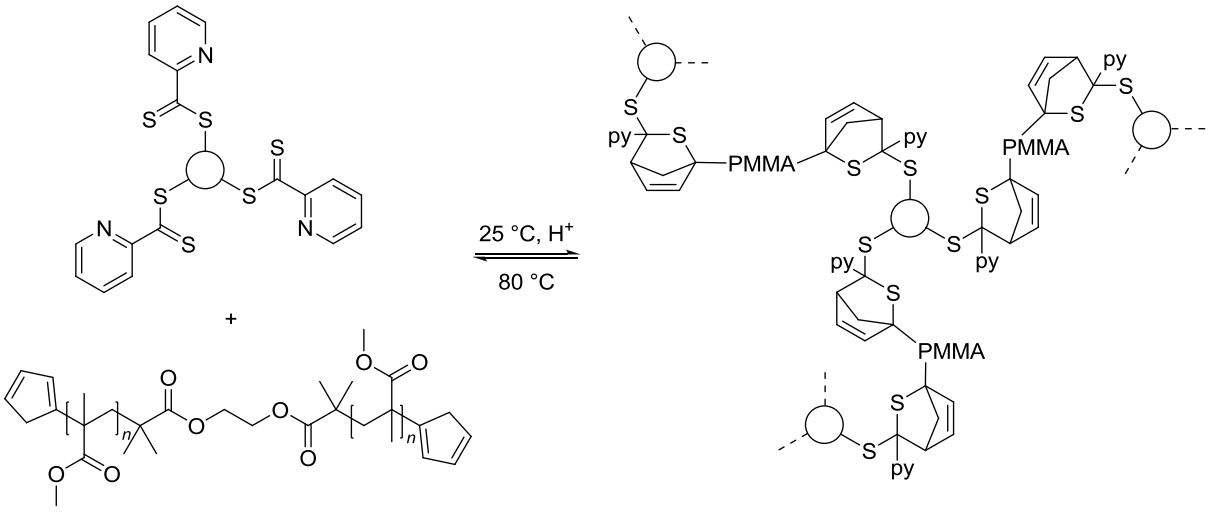
Scheme 2.19 The DA/rDA equilibrium between furans and maleimides.

The first DA polycondensation employing a bisfuran and a bismaleimide monomer combination was reported 1986[122] paving the way for numerous successive publications dealing with linear thermoreversible DA polymerizations.[123-129] Polymer networks containing furan-maleimide DA linkages are the first example of thermally

mendable cross-linked materials. Combinations of tetrafuran and trismaleimide monomers were utilized in the pioneering work of Wudl and co-workers for the thermally reversible preparation of highly cross-linked polymer networks.[130] Heating of cracked samples to temperatures above 120 °C for 2 h and subsequent cooling to ambient temperature enabled the reformation of DA cycloadducts with a healing efficiency of 57 %. An improvement of the healing efficiency up to 87 % could be achieved by incorporation of bismaleimides.[131] Polymer networks can be prepared using different strategies: (i) DA polymerization of multifunctional monomers, (ii) cross-linking of polymers bearing furan or maleimide side-chain functionalities, (iii) utilization of a cross-linker or initiator with a DA linkage. The synthesis of self-healing materials using any of these strategies has received enormous interest in recent years as can be seen from the huge number of emerging publications.[132-139]

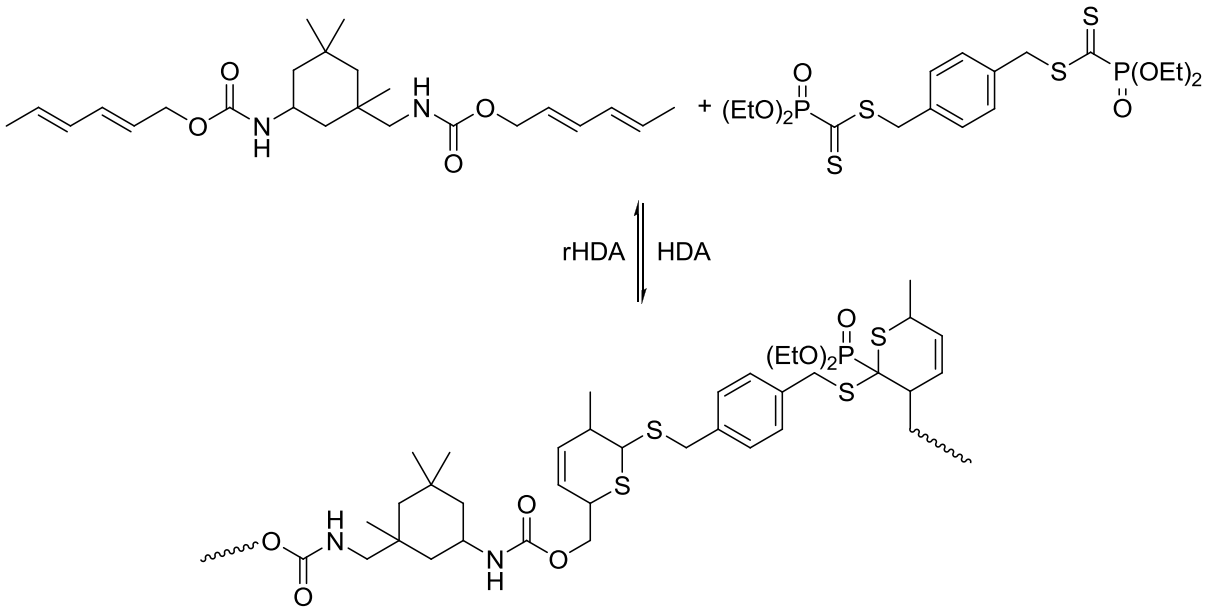
2.4.2 Reversible RAFT-HDA Reactions

A study into the stability of 3,6-Dihydro-2*H*-thiopyran rings formed by HDA cycloadditions between hexadienoyl based dienes and diethoxy phosphoryl- or pyridinyl-dithioesters (Scheme 2.14) revealed that the RAFT-HDA linkage undergoes a rDA reaction at elevated temperatures.[140] Complete disappearance of the HDA adduct in mass spectrometric analysis was observed above 160 and 180 °C for the phosphoryl- and the pyridinyl-RAFT agent respectively. When cyclopentadiene is employed as diene quantitative reversion of the HDA reaction can be achieved at 100 °C.[141] It was further shown that the rDA reaction produces the starting materials without any observable side reactions enabling the regeneration of the HDA adduct upon cooling to ambient temperature. Thermally reversible network formation was achieved employing a trifunctional dithioester to cross-link biscyclopentadienyl poly(methyl methacrylate) (Scheme 2.20) at ambient temperature.[142] The resulting material possesses a high bonding/debonding efficiency when switching the temperature between 25 and 80 °C.



Scheme 2.20 Thermally reversible cross-linking via HDA/rHDA reactions.

A step-growth polymerization employing a hexadienoyl bis-diene and a bis-RAFT agent with diethoxy phosphoryl Z-groups is depicted in Scheme 2.21.[143]

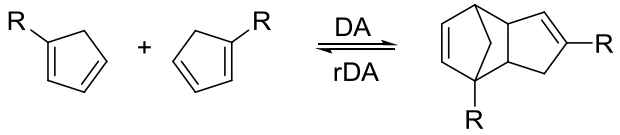


Scheme 2.21 Thermally reversible RAFT-HDA step-growth polymerization.

Under optimized conditions (1.8 M of each monomer in acetonitrile with 1.1 equivalents of zinc chloride at 50 °C for 4 h) a polymer with a peak molecular weight of 9600 g mol^{-1} relative to poly(styrene) standards was obtained. A maximum of 59% debonding was achieved at 219 °C after 30 min. It was shown that *ab initio* quantum chemical calculations of the debonding process are in excellent agreement with the data obtained experimentally.

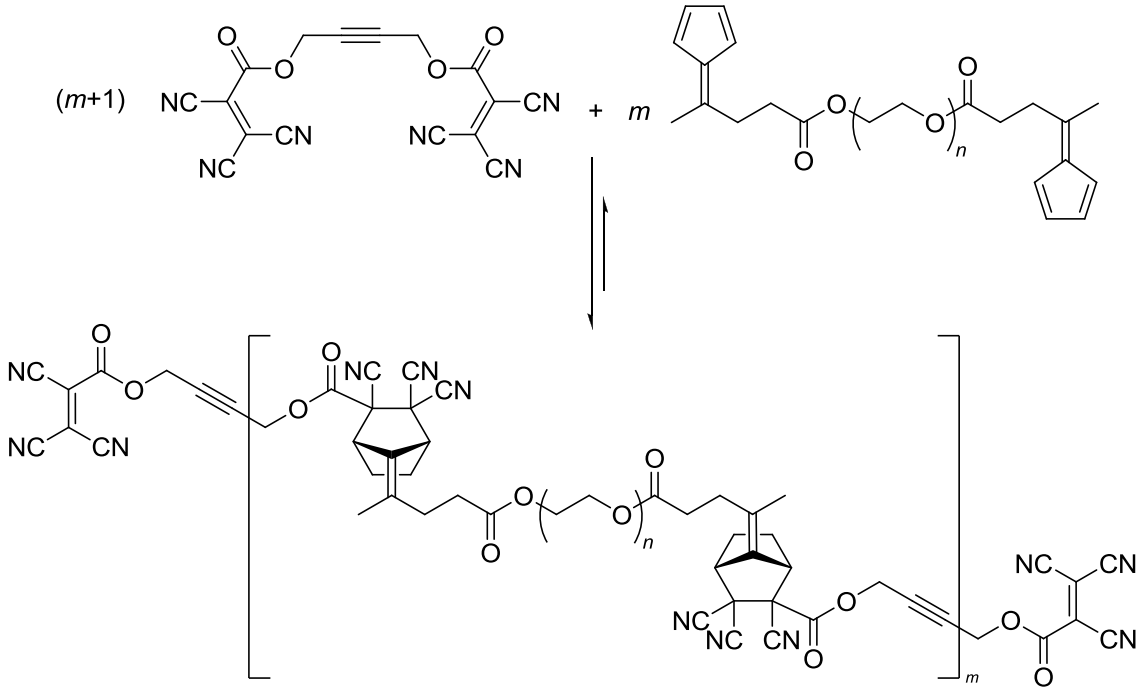
2.4.3 Other Reversible Diels-Alder Systems

Cyclopentadiene can react with itself at ambient temperature acting as both the diene and the dienophile in the DA reaction (Scheme 2.22). The reversibility of the self-dimerization at elevated temperatures has been used for the construction of thermally reversible cross-linked polymer networks.[144-147]



Scheme 2.22 Self-dimerization of cyclopentadienes.

The DA reaction between maleimides and anthracenes which has been widely used for the synthesis of polymer architectures is also reversible. However, only a few publications[136, 148] employing the system are known to date which is due to the fact that temperatures above 200 °C are required for the cycloreversion. A polymer film healable at ambient temperature was reported by Lehn and co-workers[149] employing a cyanfumarate di-linker cross-linked with a fulvene functionalized polymer (Scheme 2.23).



Scheme 2.23 DA/rDA equilibrium between a cyanfumarate and a fulvene di-linker.

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3

Diels-Alder Reactions as an Efficient Route to High Purity Cyclic Polymers

3.1 Introduction

Cyclic polymers are of strong interest for polymer and material science as their closed topology creates unique physical properties compared to linear analogues.[1-2] Although various synthetic methods have been developed in the last decades[3-4] to access these interesting architectures, finding a straightforward and efficient cyclization strategy is an ongoing challenge within polymer chemistry. Previously, cyclic polymers were mainly prepared through bimolecular coupling, utilizing living anionic polymerization with difunctional initiators followed by reaction with difunctional coupling agents[5-7] as depicted in Figure 3.1. In most cases, however, as well as producing the cyclic target, a substantial amount of linear starting material/by-products also remain. Access to high cyclic purity polymers free of linear chains is particularly important for the assessment of the cyclic polymers' physical properties. For this reason cyclic polymers produced via the bimolecular coupling method generally must undergo fractionation, chromatography or other purification techniques.

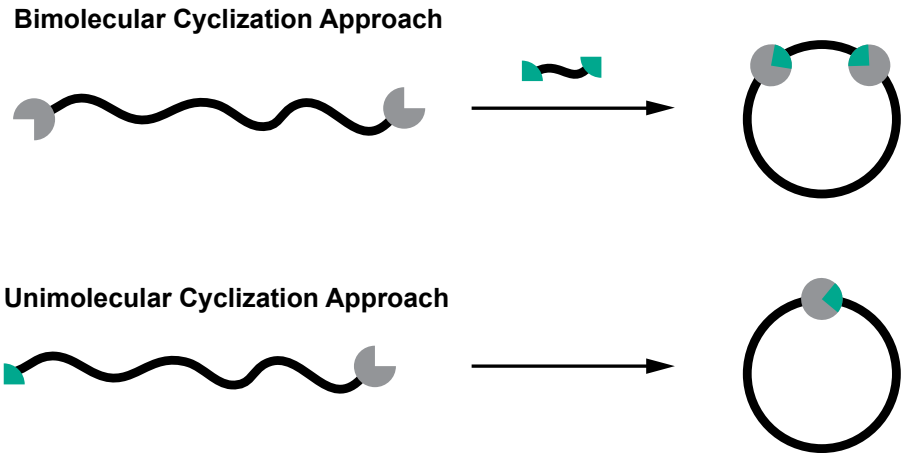


Figure 3.1 Schematic representations of the bimolecular and the unimolecular cyclization approach.

Instead of a bimolecular system, application of a unimolecular coupling technique (Figure 3.1 bottom) allows for the isolation of products with increased cyclic purity. This occurs by allowing the suppression of the competing oligomerization reaction through dilution while not compromising coupling speed as the reactive groups are covalently tethered. The development of controlled/living radical polymerization techniques such as nitroxide-mediated polymerization (NMP),[8-9] reversible addition fragmentation chain transfer (RAFT) polymerization[10-11] and atom transfer radical polymerization (ATRP)[12-13] has provided a powerful aid in the construction of macromolecular architectures due to the fine control these techniques give over both end-group fidelities. The group of Hemery[14] was the first to report the utilization of NMP in the synthesis of such systems by polymerizing styrene using 4,4'-azobis(4-cyanovaleric acid) as an initiator and 4-hydroxy-TEMPO as the terminator, taking the formed α-hydroxy-ω-carboxy-PS chain and subsequently cyclizing it via esterification. Monteiro and colleagues[15] pioneered the use of RAFT polymerization in this field by first producing a PS chain capped at both ends by a RAFT agent, employing aminolysis to yield an α,ω-thiol-PS which could then be (reversibly) cyclized using redox processes. Today, the most common method for the preparation of cyclic polymers is the extremely fast Cu(I) catalyzed azide-alkyne *click* reaction (CuAAC), first employed by Grayson and coworkers[16] for the synthesis of *c*-PS. Since then various cyclic homo- and block copolymers have been synthesized by combinations of ATRP,[17-21] RAFT[22-23] and NMP[24] with the CuAAC *click* reaction. Efficient cyclization reactions of symmetrically functionalized polymers have also recently been realized employing atom transfer radical coupling (ATRC),[25-27] ring-closing metathesis (RCM)[28-29] and Glaser coupling.[30-31] These symmetrically functionalized polymers can generally be prepared more easily, however all of the aforementioned cyclization strategies require a transition metal catalyst. An efficient and catalyst free method for the construction of various macromolecular architectures is the coupling of functional polymers through (hetero) Diels-Alder reactions as described in detail in Chapter 2. The intramolecular Diels-Alder reaction between a maleimide and a pentadienyl end-group has previously been employed, in the context of cyclic polymer synthesis by Mizawa et al., to prepare cyclic poly(methyl methacrylate) (*c*-pMMA).[32] Durmaz et al. also recently reported the synthesis of cyclic homo- and block copolymers via Diels-Alder cyclization of anthracene with maleimide end-groups.[33] The relatively unreactive dienes employed in these reactions, required - however - long reaction times at high temperatures and the linear precursors must be prepared using complex, multi-step synthesis. In both the aforementioned cases, SEC analysis of the

products showed that the cyclization was not completely efficient with a tail on the higher molecular weight side of the elugram consistent with remaining uncyclized starting material and/or the formation of linear multiblock chains.

3.2 Experimental Section

2-Bromo-2- methyl-propionic acid 2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.02,6]-dec-8-en-4-yl)-ethyl ester (**1**) was synthesized according to the literature.[34]

Synthesis of Furan Protected Maleimide Functionalized pMMA (*l*-Mal-pMMA-Br)

Methyl methacrylate (MMA), initiator (**1**), copper(I) bromide (CuBr), copper(II) bromide ($CuBr_2$), and 2,2′-bipyridine (bpy) were added to a round-bottom flask in the ratio 100/1/0.105/0.01250/0.25. Acetone was subsequently added such that the resulting mixture contained 50 vol.% acetone. Nitrogen was bubbled through the mixture for 30 min to remove residual oxygen. The mixture was subsequently sealed under nitrogen and placed in a thermostated oil bath set to 50 °C. After 2.5 h, the polymerization was stopped by cooling the mixture in an ice bath and exposure to oxygen. The mixture was then passed through a short column of neutral alumina to remove the copper catalyst. *l*-Mal-pMMA-Br was isolated by 2-fold precipitation in cold *n*-hexane and dried under high vacuum.

SEC (THF): M_n = 2600 g·mol^{-1}, *PDI* = 1.20. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.54 (s, vinylic), 5.26 (s, bridge-head protons), 4.20–4.07 (m, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, $NCH_2CH_2OC{=}O$), 3.66–3.50 (m, OCH_3 of pMMA), 2.85 (s, bridge protons), 2.05–0.73 (m, pMMA backbone).

Synthesis of Furan Protected α-Maleimide-ω-Cyclopentadienyl Functionalized pMMA (*l*-Mal-pMMA-Cp)

A solution of *l*-Mal-pMMA-Br (0.18 mmol), triphenylphosphine (0.36 mmol, 2 eq.) and sodium iodide (1.08 mmol, 6 eq.) in anhydrous THF (2.0 mL) was prepared under a nitrogen atmosphere. Separately, a stock solution of $NiCp_2$ in anhydrous THF (0.18 mol·L^{-1}) was prepared under a nitrogen atmosphere. The $NiCp_2$ solution (2.0 mL, 4 eq.) was then added to the polymer solution and allowed to stir overnight at ambient temperature. At the end of the reaction, the mixture was passed through a short column of basic alumina to remove the precipitated nickel (II) bromide and

l-Mal-pMMA-Cp was recovered by 2-fold precipitation in cold *n*-hexane and dried under high vacuum.

SEC (THF): M_n = 2600 g·mol^{-1}, *PDI* = 1.20. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.54 (s, 2H, vinylic), 6.44–6.04 (m, Cp, vinylic), 5.26 (s, 2H, bridge-head protons), 4.20–4.07 (m, 2H, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, 2H, $NCH_2CH_2OC{=}O$), 3.66–3.50 (m, OCH_3 of pMMA), 2.95–2.84 (m, bridge protons and Cp), 2.05–0.73 (m, pMMA backbone).

Cyclization of *l*-Mal-pMMA-Cp

A solution of *l*-Mal-pMMA-Cp (55 mg, 0.021 mmol) in toluene (300 mL) was refluxed for 6 h. Subsequently, the solution was allowed to cool to ambient temperature and concentrated in vacuo. The polymer was precipitated in cold *n*-hexane and dried under high vacuum.

SEC (THF): M_n = 2100 g·mol^{-1}, *PDI* = 1.22 relative to linear pMMA. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.33–5.83 (m, vinylic), 4.20–4.07 (m, 2H, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, 2H, $NCH_2CH_2OC{=}O$), 3.66–3.50 (m, OCH_3 of pMMA), 3.45–3.19 (m, cycloadduct), 2.05–0.73 (m, pMMA backbone and bridge protons of cycloadduct).

Synthesis of Furan Protected Maleimide Functionalized p*t*BA (*l*-Mal-p*t*BA-Br)

tert-Butylacrylate (*t*BA), initiator (**1**), copper(I) bromide (CuBr) and PMDETA were added to a round-bottom flask in the ratio 100/1/1/1 . Nitrogen was then passed through the mixture for 30 min to remove residual oxygen. The mixture was subsequently sealed under nitrogen and placed in a thermostated oil bath set to 40 °C. After 8 h, the polymerization was stopped by cooling the mixture in an ice bath and exposure to oxygen. The mixture was then diluted with THF and passed through a short column of neutral alumina to remove the copper catalyst. The solvent and residual monomer were removed under reduced pressure and the polymer was dried under high vacuum.

SEC (THF): M_n = 3500 g·mol^{-1}, *PDI* = 1.15 relative to linear polystyrene standards. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.54 (s, vinylic), 5.26 (s, bridge-head protons), 4.20–4.07 (m, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, $NCH_2CH_2OC{=}O$), 2.85 (s, bridge protons), 2.25–1.00 (m, p*t*BA).

Synthesis of Furan Protected α-Maleimide-ω-Cyclopentadienyl Functionalized p*t*BA (*l*-Mal-p*t*BA-Cp)

A solution of *l*-Mal-p*t*BA-Br (0.18 mmol), triphenylphosphine (0.36 mmol, 2 eq.) and sodium iodide (1.08 mmol, 6 eq.) in anhydrous THF (2.0 mL) was prepared under a nitrogen atmosphere. Separately, a stock solution of $NiCp_2$ in anhydrous THF (0.18 mol·L^{-1}) was prepared under a nitrogen atmosphere. The $NiCp_2$ solution (2.0 mL, 4 eq.) was then added to the polymer solution and allowed to stir overnight at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residual *l*-Mal-p*t*BA-Cp was dried under high vacuum.

SEC (THF): M_n = 3500 g·mol^{-1}, *PDI* = 1.15 relative to linear polystyrene standards. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.54 (s, 2H, vinylic), 6.44–6.04 (m, Cp, vinylic), 5.26 (s, 2H, bridge-head protons), 4.20–4.07 (m, 2H, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, 2H, $NCH_2CH_2OC{=}O$), 2.95–2.84 (m, bridge protons and Cp), 2.25–1.00 (m, p*t*BA).

Cyclization of *l*-Mal-p*t*BA-Cp

A solution of *l*-Mal-p*t*BA-Cp (74 mg, 0.021 mmol) in toluene (300 mL) was refluxed for 6 h. Subsequently, the solution was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. The polymer was dried under high vacuum.

SEC (THF): M_n = 2900 g·mol^{-1}, *PDI* = 1.15 relative to linear polystyrene standards. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.33–5.83 (m, vinylic), 4.20–4.07 (m, 2H, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, 2H, $NCH_2CH_2OC{=}O$), 3.45–3.19 (m, cycloadduct), 2.25–1.00 (m, p*t*BA and bridge protons of cycloadduct).

Test Reaction with Excess Maleimide

A 10-fold excess maleimide was added to a solution of the cyclization product in $CHCl_3$ (0.05 mol·L^{-1}) and stirred overnight at ambient temperature. The polymer was isolated by precipitation in cold *n*-hexane and analyzed by SEC/ESI-MS.

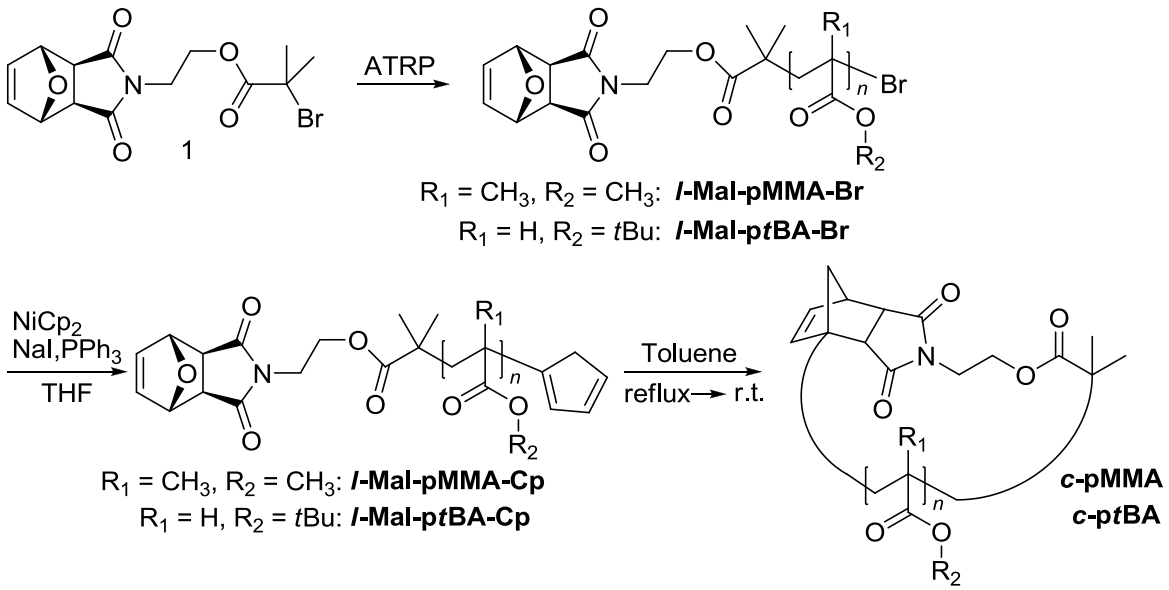
Blind Sample: Deprotection of *l*-Mal-pMMA-Br

The deprotection was carried out under the same conditions as for the Cp-functional polymer (see above).

3.3 Results and Discussion

An efficient synthetic route to cyclic poly(meth)acrylates via an intramolecular Diels-Alder reaction between maleimide and highly reactive cyclopentadienyl (Cp) end-groups is presented in the present chapter. Characterization of the final product using NMR, SEC and SEC/ESI-MS demonstrate the exceptional purity of the material with close to quantitative conversion (> 95 %) of the linear precursor and no indication of the formation of linear multiblock chains.

The unimolecular starting system proposed for this study is based on the Diels-Alder coupling of cyclopentadiene and maleimide which has been shown in various small molecule syntheses to undergo fast reaction under mild conditions.[35-36] Low molecular weight poly(methyl methacrylate) (2600 g·mol^{-1}) and poly(t*ert*-butyl acrylate) (3500 g·mol^{-1}) precursors were employed in the present study because an efficient cyclization is less probable for higher molecular weight precursors according to the Jacobson-Stockmayer theory.[21]



Scheme 3.1 Synthetic route for the preparation of *c*-pMMA and *c*-p*t*BA via the Diels-Alder cyclization of linear α-maleimide-ω-cyclopentadienyl functionalized precursors.

The synthetic pathway for the formation of cyclic poly(methyl methacrylate) (*c*-pMMA) and poly(*tert*-butyl acrylate) (c-p*t*BA) is depicted in Scheme 3.1. A protected maleimide unit was initially coupled to bromoisobutyryl bromide to give **1**, which was subsequently used as an ATRP initiator yielding a polymer with a terminal bromine. Conversion of the bromine end-group into a Cp moiety was then per-

formed using the previously reported nickelocene methodology.[37] The cyclization reaction was achieved by simply refluxing the linear precursors in toluene at a concentration of 7×10^{-5} mol·L^{-1} for 6 h to deprotect the maleimide functionality and subsequent cooling to ambient temperature to enable the intramolecular Diels-Alder cycloaddition. All transformations were monitored by size exclusion chromatography-electrospray ionization-mass spectrometry (SEC/ESI-MS) as displayed in Figure 3.2

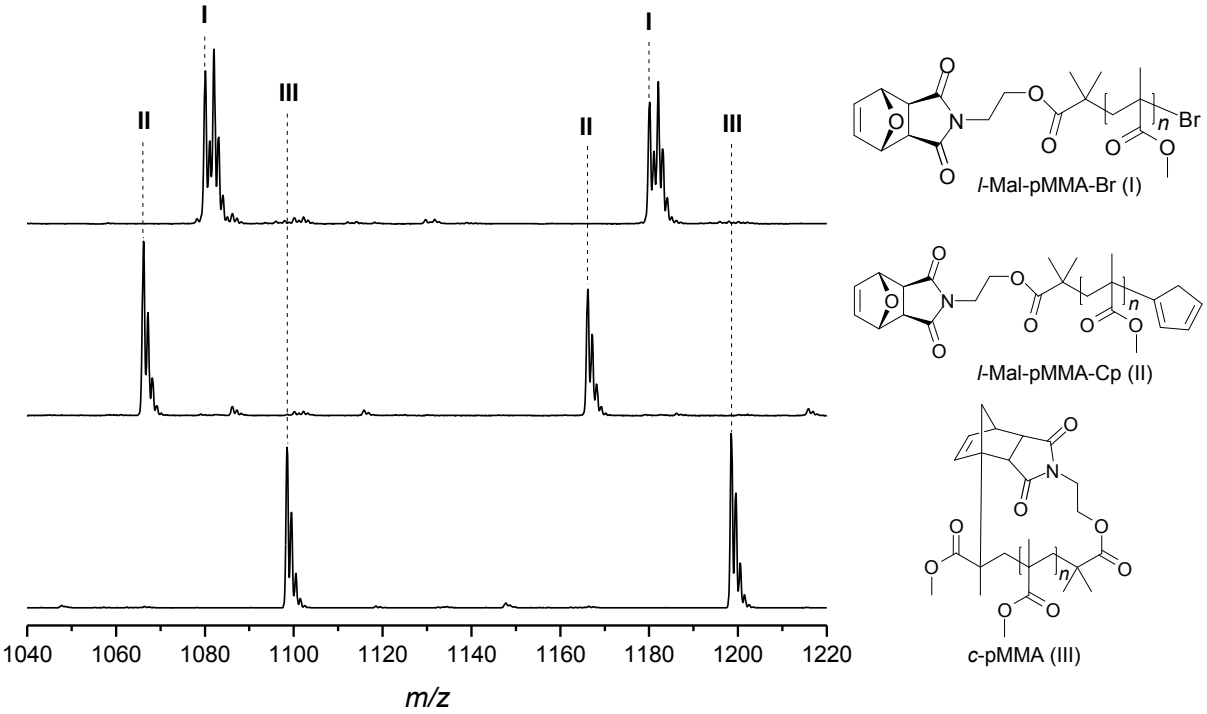


Figure 3.2 SEC/ESI-MS monitoring of the transformation of *l*-Mal-pMMA-Br (I) into *l*-Mal-pMMA-Cp (II) and the subsequent deprotection/Diels-Alder cyclization.

Inspection of Figure 3.2 indicates that the highly functional *l*-Mal-pMMA-Br (I) obtained by ATRP is quantitatively transformed into *l*-Mal-pMMA-Cp (II). After 6 h reflux in toluene *l*-Mal-pMMA-Cp completely disappears and the main peak shifts to 68 amu lower mass-to-charge ratio, which corresponds to the loss of furan. The transformations and cyclization worked in an equally efficient manner for p*t*BA as can be seen from Figure 3.3, yet a small amount (< 5 %) of the protected precursor remains in this case (see Figure 3.4 for an enlarged image of the product ESI-MS).

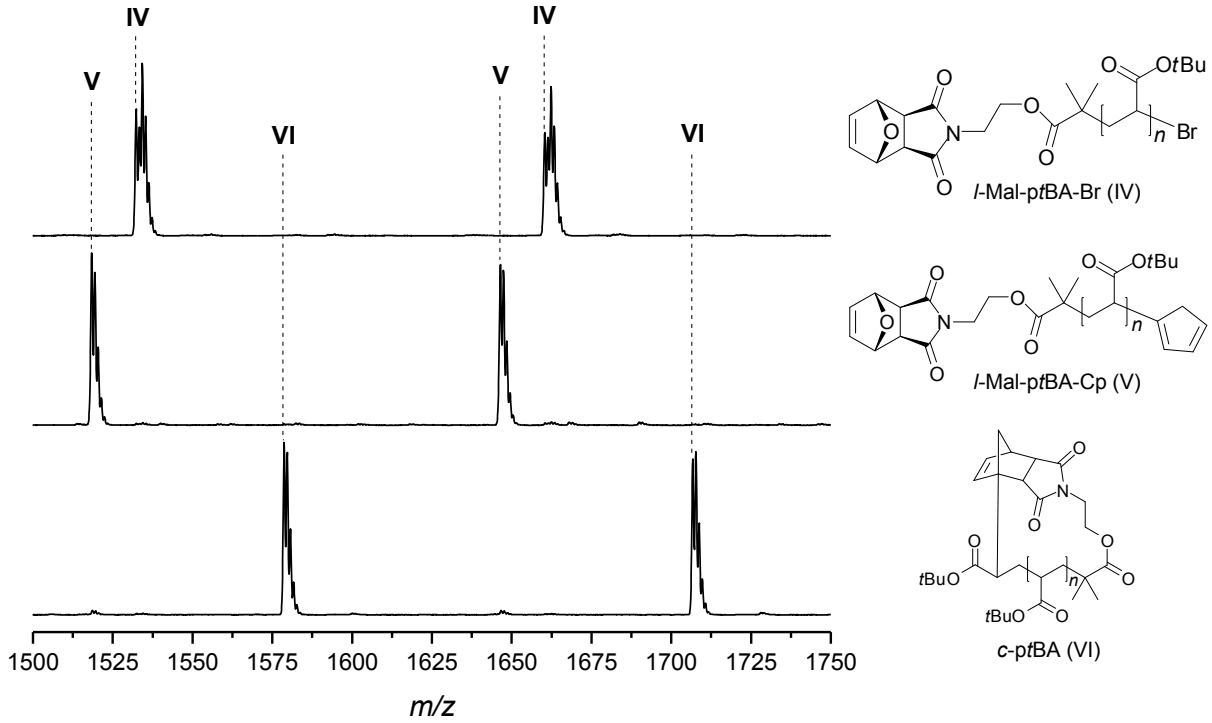


Figure 3.3 SEC/ESI-MS monitoring of the transformation of *l*-Mal-p*t*BA-Br (IV) into *l*-Mal-p*t*BA-Cp (V) and the subsequent deprotection/Diels-Alder cyclization.

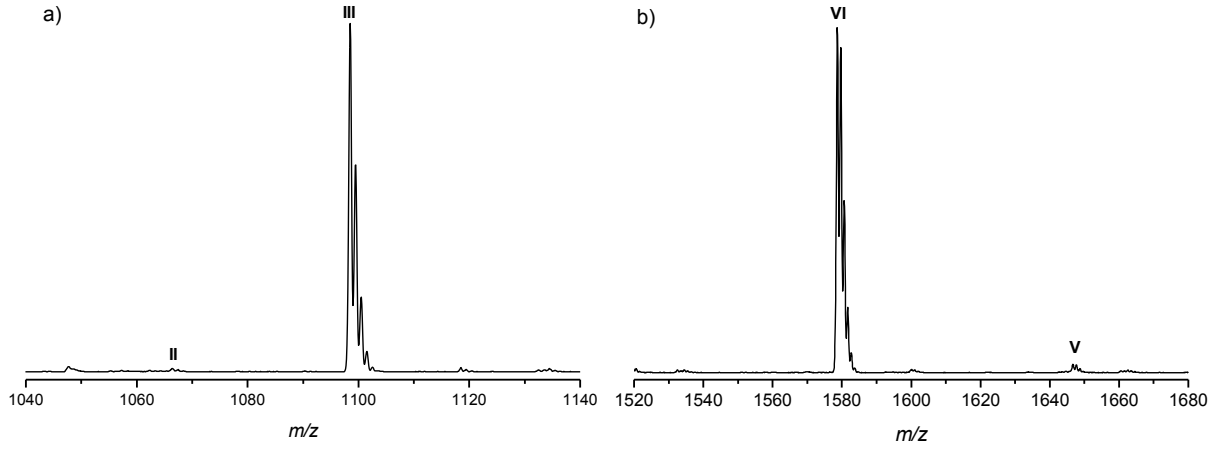


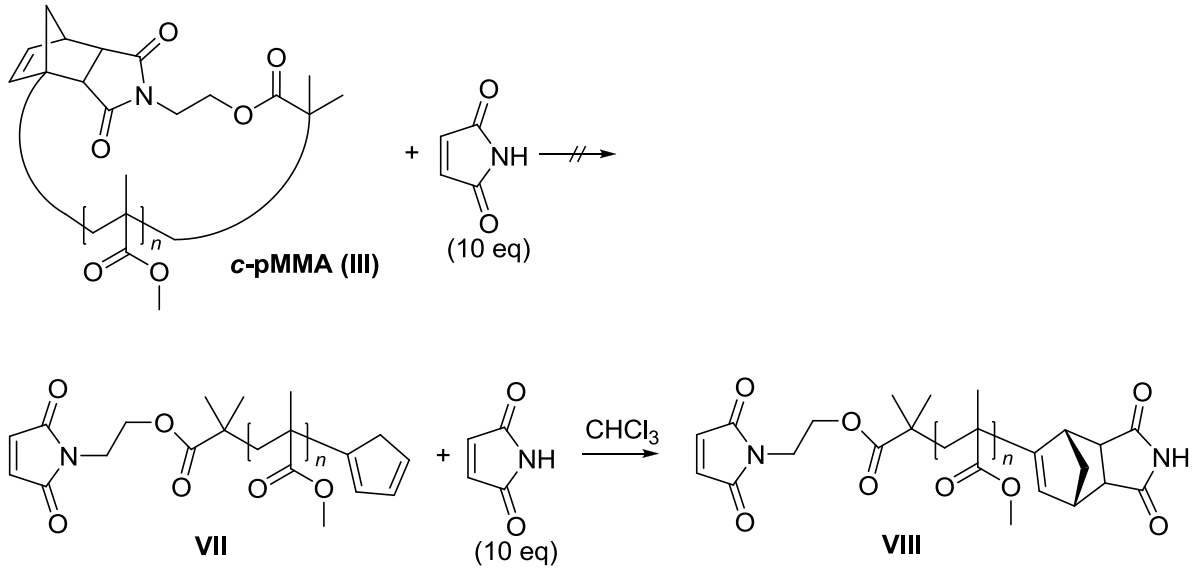
Figure 3.4 Enlarged SEC/ESI-MS spectra of the cyclization products of (a) *l*-Mal-pMMA-Cp and (b) *l*-Mal-p*t*BA-Cp.

The theoretical and measured *m*/*z*-ratios of the involved species collated in Table 3.1 are in excellent agreement within experimental error.

Table 3.1 Theoretical and measured m/z ratios ($[M+Na]^+$) of the main species involved in the synthesis of *c*-pMMA and *c*-p*t*BA. The values refer to the first peak of the isotopic pattern.

Structure	Formula	m/z^{theo}	m/z^{meas}	$\Delta\, m/z$
l-Mal-pMMA-Br (I)	$[C_{54}H_{80}BrNO_{21}Na]^+$	1180.43	1180.17	0.26
l-Mal-pMMA-Cp (II)	$[C_{59}H_{85}NO_{21}Na]^+$	1166.55	1166.17	0.38
c-pMMA (III)	$[C_{55}H_{81}NO_{20}Na]^+$	1098.52	1098.50	0.02
l-Mal-p*t*BA-Br (IV)	$[C_{77}H_{124}BrNO_{23}Na]^+$	1532.76	1532.33	0.43
l-Mal-p*t*BA-Cp (V)	$[C_{82}H_{129}NO_{23}Na]^+$	1518.89	1518.42	0.47
c-p*t*BA (VI)	$[C_{85}H_{137}NO_{24}Na]^+$	1578.94	1578.67	0.18

Based on these spectra alone, one cannot unequivocally verify the success of the cyclization reaction because both the Diels-Alder adduct and the linear deprotected precursor have the same sum formula. In order to evidence that no linear precursor remained, *c*-pMMA was subsequently stirred with an excess of maleimide, precipitated and reevaluated using SEC/ESI-MS. If linear polymer had remained, the unreacted cyclopentadiene moiety would have undergone a rapid reaction with the maleimide (refer to Scheme 3.2) and a peak shift would have been observed in the MS. However, no shift occurs in the SEC/ESI-MS spectra shown in Figure 3.5 indicating that the linear precursor has undergone complete Diels-Alder cyclization.



Scheme 3.2 Expected reactions of *c*-pMMA (III) and VII with an excess maleimide.

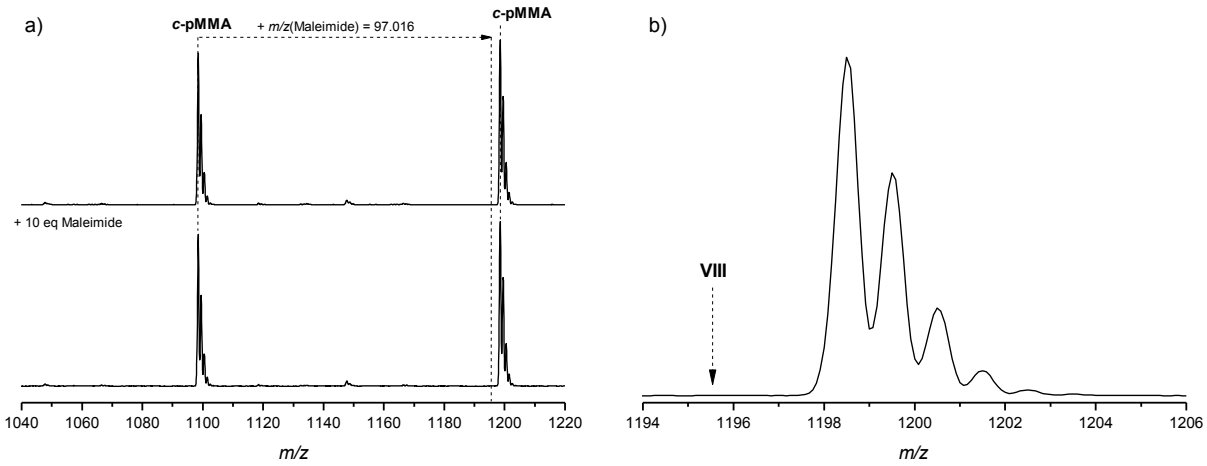


Figure 3.5 a) SEC/ESI-MS spectra of the cyclization product of *l*-Mal-pMMA-Cp and the product after reaction with 10 equivalents maleimide. b) Zoom into the m/z-range in which VIII (m/z^{theo} =1195.54) would occur.

Evidence of cyclization can also be provided by analysis with size exclusion chromatography (SEC). In general, cyclization leads to a more compact topology resulting in a smaller hydrodynamic volume and thus a longer retention time in SEC. This is exactly what is observed in both systems, as shown in Figure 3.6. When *l*-Mal-pMMA-Br was deprotected under the same conditions (Scheme 3.3) no shift of the SEC elugram could be observed while ESI-MS confirms deprotection of the maleimide functionality (see Figure 3.7). It should also be noted, unlike other recent examples, that with the clear shift to a higher retention time there is an absence of any tail on the higher molecular weight side due to an intermolecular Diels-Alder reaction forming linear multiblock polymer chains. This is further substantial support for an efficient cyclization leading to high purity material.

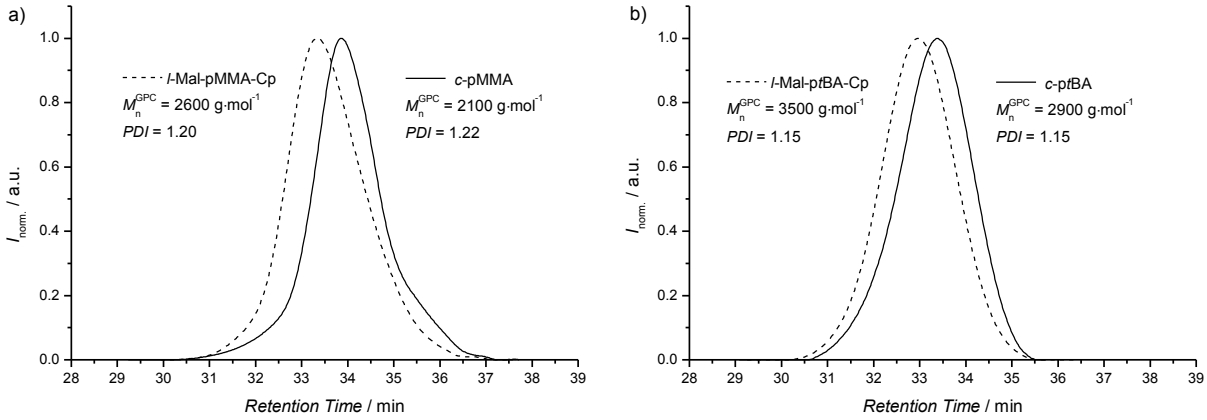
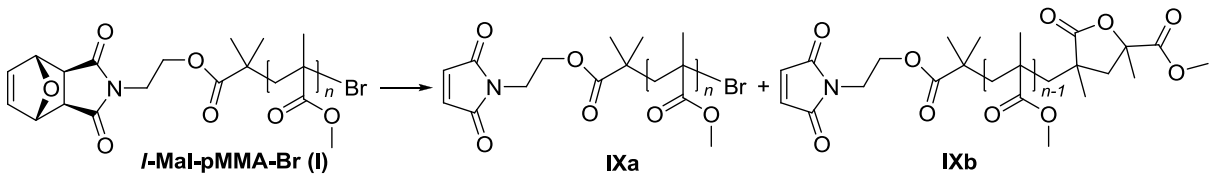


Figure 3.6 Overlay of SEC traces for a) Linear precursor, *l*-Mal-pMMA-Cp, and the cyclic polymer, *c*-pMMA; b) Linear precursor, *l*-Mal-p*t*BA-Cp, and the cyclic polymer, *c*-p*t*BA. Molecular weights are based on calibration with linear pMMA or PS standards, respectively.



Scheme 3.3 Blind Sample: Deprotection of *l*-Mal-pMMA-Br.

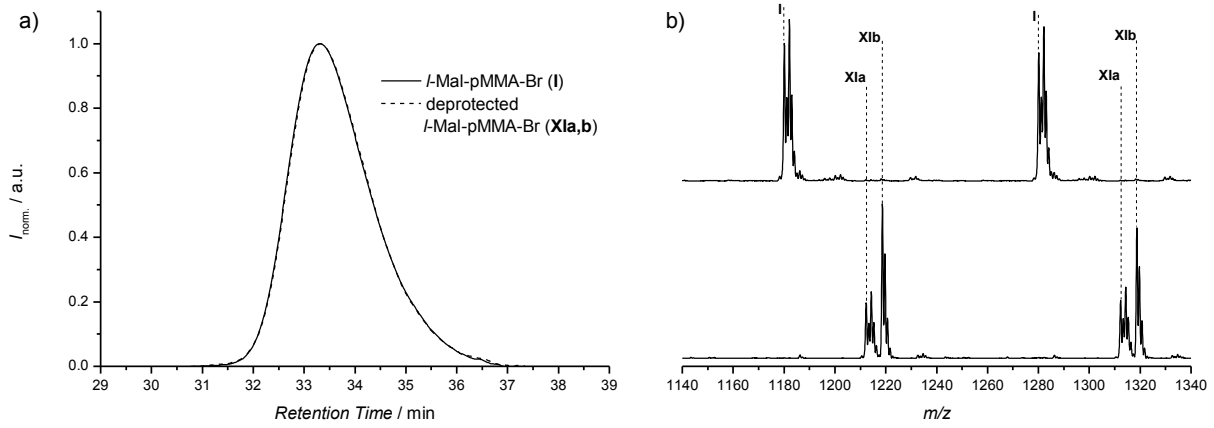


Figure 3.7 a) Overlay of SEC traces for the furan protected linear precursor, *l*-Mal-pMMA-Cp (I) and the linear deprotected pMMA (IXa,b). b) SEC/ESI-MS monitoring of the deprotection of *l*-Mal-pMMA-Br (I). The formation of the lactone terminated pMMA (IXb) is due to thermal loss of MeBr during deprotection (see ref. [38] for details).

The successful cyclization is further confirmed by disappearance of the Cp end-group signals in the range of 6.4–6.0 ppm and by appearance of the cycloadduct signals between 6.3–5.8 ppm in the ^{1}H-NMR spectra as depicted in Figure 3.8.

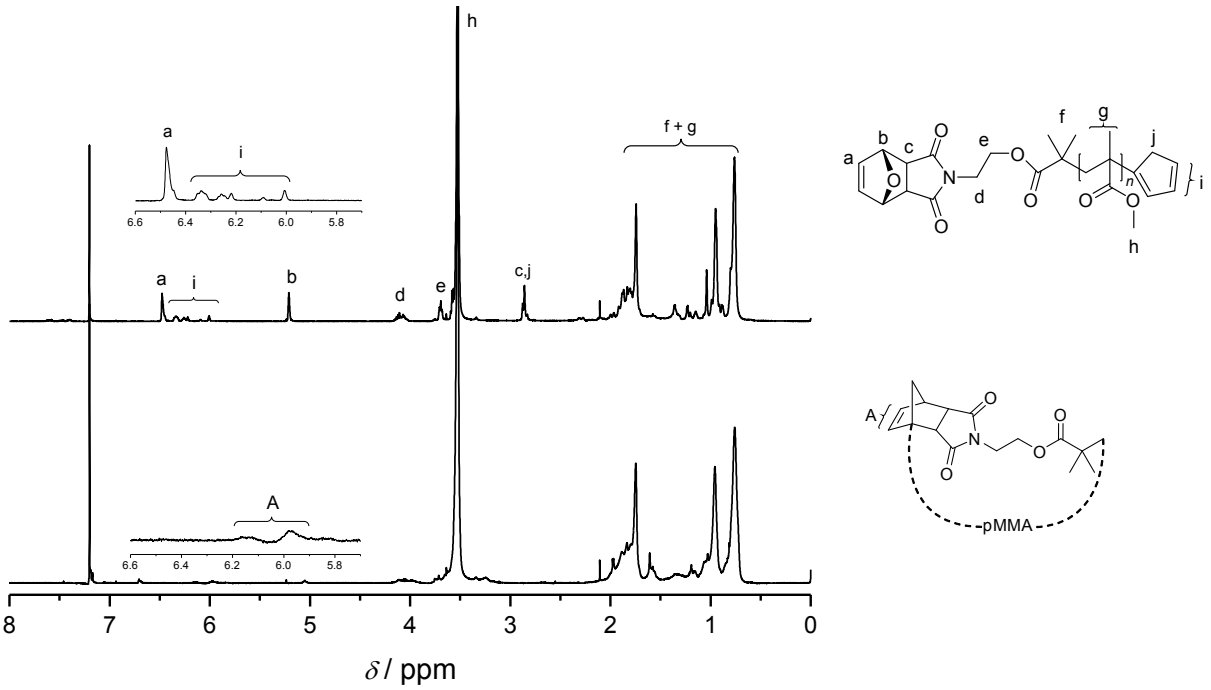


Figure 3.8 ^{1}H-NMR spectra of *l*-Mal-pMMA-Cp (top) and the cyclization product *c*-pMMA (bottom) in $CDCl_3$. Note that the vinylic protons (A) of the cycloadduct give a broad multiplet due to the formation of various regio-/stereoisomers.

3.4 Conclusions

In summary, linear α-maleimide-ω-cyclopentadienyl functionalized polymers were prepared by ATRP of MMA or *t*BA using a maleimide functional initiator and subsequent conversion of the bromine end-group into cyclopentadiene. Highly efficient cyclization reactions without formation of linear multiblock polymers were achieved by deprotection in refluxing toluene for 6 h under high dilution followed by intramolecular Diels-Alder reaction. The formation of well-defined and extremely high purity cyclic polymers was confirmed by NMR, SEC and SEC/ESI-MS. The approach presented here provides a simple and efficient strategy for the synthesis of high purity, cyclic polymers that is readily applicable to other polymeric systems.

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4

Combining Orthogonal Photochemically and Thermally Induced Modular Conjugations

4.1 Introduction

Block copolymers consisting of two or more thermodynamically incompatible segments have attracted increasing interest due to their ability to form various nanostructures in bulk and solution.[1-4] The classical approach for the synthesis of block copolymers is controlled/living polymerization – including powerful anionic process – with sequential addition of monomers. In recent years an enormous progress in this field was achieved by the utilization of controlled/living radical polymerization techniques such as nitroxide-mediated polymerization (NMP),[5] reversible addition fragmentation chain transfer (RAFT) polymerization[6-7] and atom transfer radical polymerization (ATRP).[8-9] The extension of the concept of *click* chemistry introduced by Sharpless and colleagues in 2001[10] to polymer synthesis[11] provided a powerful novel approach for the construction of macromolecular architectures from polymer building blocks, by effectively separating the polymerization process from the architectural buildup step as pointed out in Chapter 2. Polymer architectures that are inaccessible by only one *click* reaction can be synthesized by smart combinations of different orthogonal *click* reactions.[12] Tunca and coworkers utilized in situ CuAAC and Diels-Alder reactions for the one-pot synthesis of ABC triblock copolymers.[13] The construction of linear tetrablock polymers via CuAAC, Diels-Alder and nitroxide radical coupling was recently reported by the same group.[14] An alternative approach to gain high orthogonality to other coupling methods is the use of photo-induced reactions. However, only a few *click*-protocols have been developed so far that may be regarded as photo-induced. Thiol-ene[15] and thiol-yne[16] reactions employing radical photoinitiators are the most frequently used photo-controlled systems. However, the lack of spatial resolution is the major drawback of these three component systems. Bowman and coworkers recently reported an azide-alkyne cycloaddition by photoinitiated reduction of Cu(II).[17] The photo-induced in situ formation of nitrile imines from tetrazoles and subsequent 1,3-dipolar

cycloaddition with alkenes was employed for protein-modification by Lin and colleagues.[18-19] Our group recently reported a rapid polymer-polymer conjugation at ambient temperature via a UV-light triggered Diels-Alder reaction.[20] The reaction proceeds via photo-induced in situ formation of a highly reactive diene from a 2,5-dimethylbenzophenone precursor and subsequent cycloaddition to a maleimide functional polymer (see Chapter 2.3.3).

In the present chapter, the one-pot synthesis of ABA triblock copolymers via the combination of the aforementioned photo-induced conjugation with an orthogonal thermally induced Diels-Alder reaction at ambient temperature will be presented. α-2,5-dimethylbenzophenone-ω-cyclopentadienyl functional polystyrene and poly(methyl methacrylate) and maleimide capped poly(*tert*-butyl acrylate) as well as poly(ethylene glycol) are employed as building blocks within this context. The synthesis of ABC triblock copolymers through sequential photo-triggered and thermally induced Diels-Alder reactions as well as CuAAC *click* chemistry further demonstrates the orthogonality of the photo-induced Diels-Alder conjugation protocol.

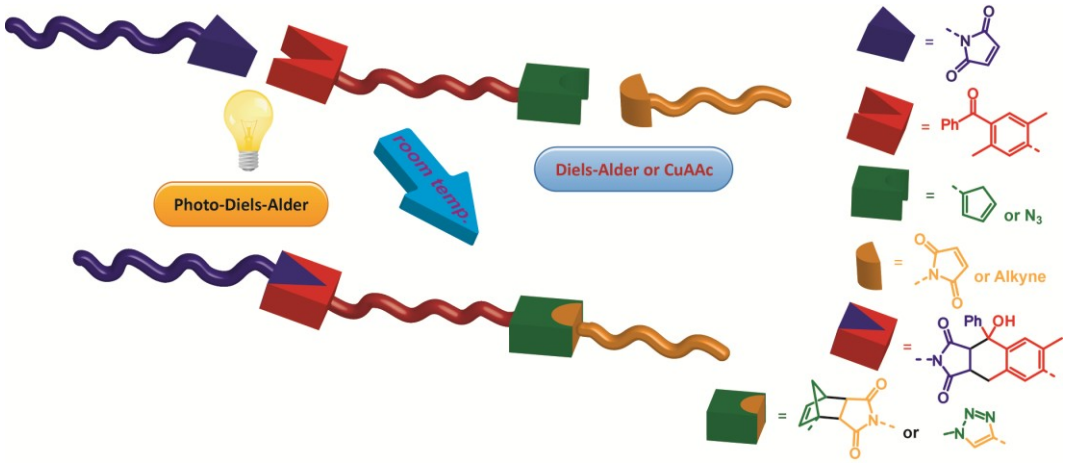


Figure 4.1 Schematic representation of the formation of triblock copolymers via orthogonal photochemically and thermally induced modular conjugation.

4.2 Experimental Section

2-Bromo-2-methyl-propionic acid 2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.02,6]-dec-8-en-4-yl)-ethyl ester (**1**)[21], 4-(2-{[(3-Acetyl-7-oxabicyclo[2.2.1]-hept-5-en-2-yl) carbonyl]-amino}ethoxy)-4-oxobutanoic acid (**2**)[22] and (4-(2-hydroxyethoxy)-2,5-dimethylphenyl)phenylmethanone (**3**)[20] were synthesized according to the literature.

Synthesis of maleimide functionalized poly(*tert*-butyl acrylate) (P*t*BA-Mal)

tert-Butylacrylate (*t*BA), initiator **1**, copper(I) bromide (CuBr) and PMDETA were added to a round-bottom flask in the ratio 100/1/1/1 . Nitrogen was bubbled through the mixture for 30 min to remove residual oxygen. The mixture was subsequently sealed under nitrogen and placed in a thermostated oil bath set to 40 °C. After 6 h, the polymerization was stopped by cooling the mixture in an ice bath and exposure to oxygen. The mixture was then diluted with THF and passed through a short column of neutral alumina to remove the copper catalyst. Subsequently, the solvent and residual monomer were removed under reduced pressure. The polymer was redissolved in toluene and refluxed for 6 h. The toluene was removed under reduced pressure and the polymer was dried under high vacuum.

SEC (THF): M_n = 1800 g·mol^{-1}, *PDI* = 1.23. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.71 (s, vinylic), 4.20–4.07 (m, $NCH_2CH_2OC{=}O$), 3.78–3.70 (m, $NCH_2CH_2OC{=}O$), 2.25–1.00 (m, P*t*BA).

Synthesis of maleimide functionalized poly(ethylene glycol) (PEG-Mal)

A solution of DCC (562 mg, 2.72 mmol) in 3 mL CH_2Cl_2 was added to a solution of MeO-PEG-OH (M_n = 550 g·mol^{-1}) (1.00 g, 1.81 mmol), DMAP (221 mg, 1.81 mmol) and **2** (842 mg, 2.72 mmol) in 5 mL CH_2Cl_2. The reaction mixture was stirred overnight at ambient temperature. The mixture was filtered, washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was dissolved in toluene, filtered and refluxed for 6 h. The toluene was removed under reduced pressure and the polymer was dried under high vacuum.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.71 (s, vinylic), 4.24–4.20 (m, $NCH_2CH_2OC{=}O$), 3.78–3.51 (m, PEG backbone), 3.36 (s, PEG-OCH_3), 2.61–2.56 ($C{=}OCH_2CH_2C{=}O$).

Synthesis of alkyne functionalized poly(ethylene glycol) (PEG-Alkyne)

MeO-PEG-OH (M_n = 2000 g·mol^{-1}) (2.00 g, 1.00 mmol), 4-pentynoic acid (294 mg, 3.00 mmol) and DMAP (24.4 mg, 0.20 mmol) were dissolved in 15 mL CH_2Cl_2. The resulting mixture was cooled to 0 °C and a solution of DCC (619 mg, 3.00 mmol) 5 mL CH_2Cl_2 was added dropwise. After the addition, the stirred mixture was allowed to warm to ambient temperature and allowed to continue stirring for 20 h. The

formed precipitate was removed by filtration and the polymer was recovered from the filtrate by two-fold precipitation in cold diethyl ether.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 4.25–4.23 (m, $CH_2OC{=}O$), 3.78–3.51 (m, PEG backbone), 3.36 (s, PEG-OCH_3), 2.59–2.55 (OC=OCH_2), 2.51–2.46 ($CH_2C{\equiv}CH$), 2.59–2.55 (OC=OCH_2), 1.97 (t, ^4J = 2.6 Hz, C≡CH).

Synthesis of 2-(4-benzoyl-2,5-dimethylphenoxy)ethyl 2-bromo-2-methylpropanoate (4)

Compound **3** (0.800 mmol, 216 mg) and triethylamine (0.880 mmol, 89.0 mg) were dissolved in dry THF (5 mL), and cooled to 0 °C. 2-Bromo-2-methylpropionyl bromide (0.832 mmol, 191 mg), dissolved in THF (3 mL), was added slowly dropwise to the solution under stirring. The suspension was stirred at 0 °C for 3 h and then allowed to reach ambient temperature over night. The formed salt was removed by filtration and the solvent removed under reduced pressure. The residue was dissolved in DCM (5 mL), washed three times with 10% KOH (10 mL) solution and subsequently filtered by passing through a column filled to 5 cm with silica (hexane : ethyl acetate, 2 : 1). The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure to give the pure product as a pale yellow solid (98% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 1.66 (bs, 1H, OH), 2.13 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (t, J = 4.14Hz, 2H, CH_2), 4.10 (t, J = 4.20Hz, 2H, CH_2), 6.66 (s, 1H, ArH), 7.10 (s, 1H, ArH), 7.35–7.41 (m, 2H, ArH), 7.46–7.53 (m, 1H, ArH), 7.68–7.72 (m, 2H, ArH).

Synthesis of 2,5-dimethylbenzophenone functionalized polystyrene (DMBP-PS-Br)

In a 25 mL Schlenk tube a mixture of styrene, initiator **4**, copper(I) bromide (CuBr), copper(II) bromide ($CuBr_2$), and PMDETA in the ration 200/1/1.02/0.21/1.22 was deoxygenated by three consecutive freeze-pump-thaw cycles and left under nitrogen. The Schlenk tube was placed in a thermostated oil bath held at 80 °C. After a predetermined time the polymerization was stopped by cooling the mixture in an ice-bath and exposure to oxygen. After dilution with THF, the mixture was passed through a short column of neutral alumina to remove the copper catalyst. Poly(styrene) was isolated by two-fold precipitation in cold methanol.

DMBP-PS(A)-Br: Polymerization time 2.5 h: M_n (THF-SEC) = 2400 g·mol^{-1}, *PDI* = 1.06.
DMBP-PS(B)-Br: Polymerization time 3 h: M_n (THF-SEC) = 3200 g·mol^{-1}, *PDI* = 1.06.

Synthesis of 2,5-dimethylbenzophenone functionalized poly(methyl methacrylate) (DMBP-PMMA-Br).

Methyl methacrylate (MMA), initiator **4**, copper(I) bromide (CuBr), copper(II) bromide ($CuBr_2$) and 2,2'-bipyridine (bpy) were added to a round-bottom flask in the ratio 100/1/0.105/0.01250/0.25. Acetone was subsequently added such that the resulting mixture contained 50 vol.% acetone. Nitrogen was subsequently bubbled through the mixture for 30 min to remove residual oxygen. The mixture was subsequently sealed under nitrogen and placed in a thermostated oil bath set to 50 °C. After 2.5 h, the polymerization was stopped by cooling the mixture in an ice bath and exposure to oxygen. The mixture was then passed through a short column of neutral alumina to remove the copper catalyst. PMMA was isolated by two-fold precipitation in cold *n*-hexane and dried under high vacuum.

SEC (THF): M_n = 3200 g·mol^{-1}, *PDI* = 1.14.

Synthesis of α-2,5-dimethylbenzophenone-ω-cyclopentadienyl functional polymers (DMBP-PS-Cp and DMBP-PMMA-Cp)

A solution of bromine terminated polymer (DMBP-Ps-Br or DMBP-PMMA-Br) (0.18 mmol), triphenylphosphine (0.36 mmol, 2 eq.) and sodium iodide (1.08 mmol, 6 eq.) in anhydrous THF (2.0 mL) was prepared under a nitrogen atmosphere. Separately, a stock solution of $NiCp_2$ in anhydrous THF (0.18 mol·L^{-1}) was prepared under a nitrogen atmosphere. The $NiCp_2$ solution (2.0 mL, 4 eq.) was then added to the polymer solution and allowed to stir overnight at ambient temperature. At the end of the reaction, the mixture was passed through a short column of alumina to remove the precipitated nickel (II) bromide and the polymer was recovered by two-fold precipitation in cold methanol (for PS) or *n*-hexane (for PMMA) and dried under high vacuum.

Synthesis of α-2,5-dimethylbenzophenone-ω-azide functional polystyrene (DMBP-PS-N_3)

DMBP-PS(B)-Br (0.06 mmol, 200 mg) and NaN_3 (0.56 mmol, 36 mg) were dissolved in DMF (10 mL) and stirred overnight at ambient temperature. DMBP-PS-N_3 was isolated by two-fold precipitation in methanol.

One-pot synthesis of ABA triblock copolymers (P*t*BA-*b*-PS-P*t*BA and P*t*BA-*b*-PMMA-P*t*BA)

α-DMBP-ω-Cp functionalized polymer (10 µmol) and P*t*BA-Mal (20 µmol) were weighted in a vial (Pyrex, dia. 20 mm), crimped air tight and flushed with nitrogen. Degassed CH_2Cl_2 (2 mL) was injected and the reaction mixture stirred for 12 h. The solution was subsequently irradiated for 2 h by revolving around a 36 W compact low-pressure UV-A fluorescent lamp (Arimed B6, Cosmedico GmbH, Stuttgart, Germany, see Appendix for a schematic drawing) emitting at 320 nm (±30 nm) at a distance of 40-50 mm in a custom built photo reactor. The triblock copolymers were precipitated in methanol (PS middle block) or *n*-hexane (PMMA middle block) respectively.

Synthesis of PEG-*b*-PS-P*t*BA via consecutive thermal and photo-induced Diels-Alder reactions

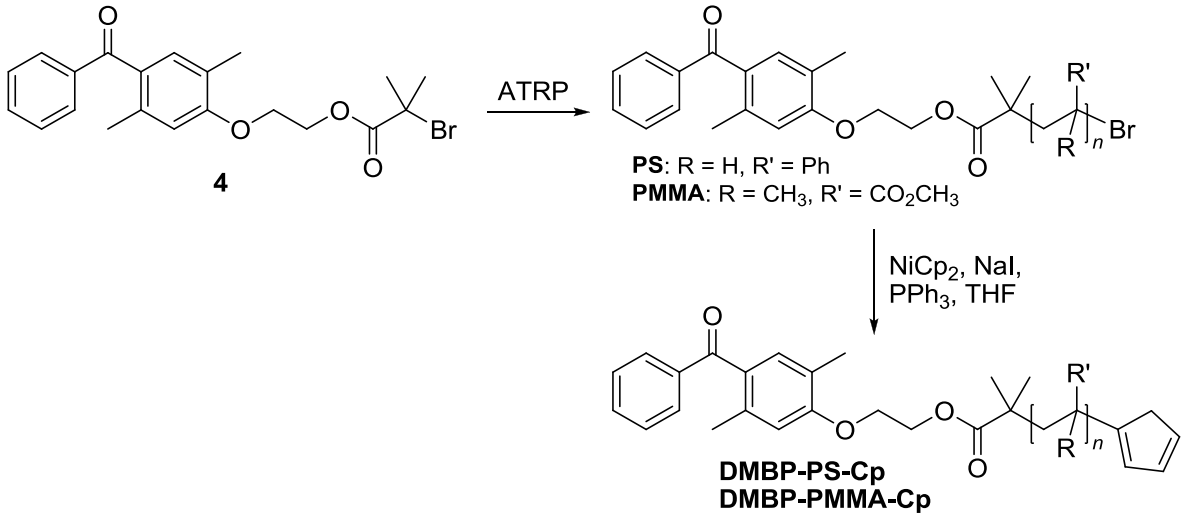
A solution of DMBP-PS-Cp (10 µmol) and PEG-Mal (11 µmol) in CH_2Cl_2 (2 mL) was stirred in the dark overnight and the resulting block copolymer was precipitated in methanol. The photo-induced formation of PEG-*b*-PS-P*t*BA was performed in the same way described for the ABA triblock copolymers using 1 eq. P*t*BA-Mal.

Synthesis of PEG-*b*-PS-P*t*BA via consecutive CuAAC and photo-induced Diels-Alder reactions

DMBP-PS-N_3 (10 µmol), PEG-Alkyne (10 µmol) and CuBr (11 µmol) were added to a Schlenk tube which was then sealed with a septum, evacuated and back-filled with nitrogen. In another Schlenk tube a mixture of DMF (3 mL) and PMDETA (11 µmol) was deoxygenated by three freeze-pump-thaw cycles and subsequently transferred to the Schlenk tube containing the polymers and CuBr via cannula. The reaction mixture was stirred overnight at ambient temperature. The solution was passed through a short column of neutral alumina to remove the copper catalyst and the DMF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and precipitated in *n*-hexane. The resulting PEG-*b*-PS was reacted with 1 equivalent P*t*BA in the photoreactor as described above.

4.3 Results and Discussion

To enable the synthesis of various 2,5-dimethylbenzophenone functional polymers the hydroxyl functional precursor **3**, which was used as ROP initiator in a previous study,[50] was reacted with 2-bromo-2-methylpropionyl bromide to give the ATRP initiator **4**. Highly functional α-2,5-dimethylbenzophenone-ω-bromine PS (DMBP-PS-Br) and PMMA (DMBP-PMMA-Br) was synthesized via ATRP utilizing **4** as initiator as depicted in Scheme 4.1.



Scheme 4.1 Synthesis of α-2,5-dimethylbenzophenone-ω-cyclopentadienyl functional polystyrene and poly(methyl methacrylate).

The bromine end-group was subsequently converted to a cyclopentadienyl (Cp) functionality employing the previously reported nickelocene method[23] yielding α-2,5-dimethylbenzophenone-ω-cyclopentadienyl telechelic polymers. Monitoring of the transformation by size exclusion chromatography-electrospray ionization-mass spectrometry (SEC/ESI-MS) (Figure 4.2) shows that DMBP-PMMA-Cp is attained with high functionality and only small amounts of impurities which can be assigned to inescapable side products of the ATRP process.[24]

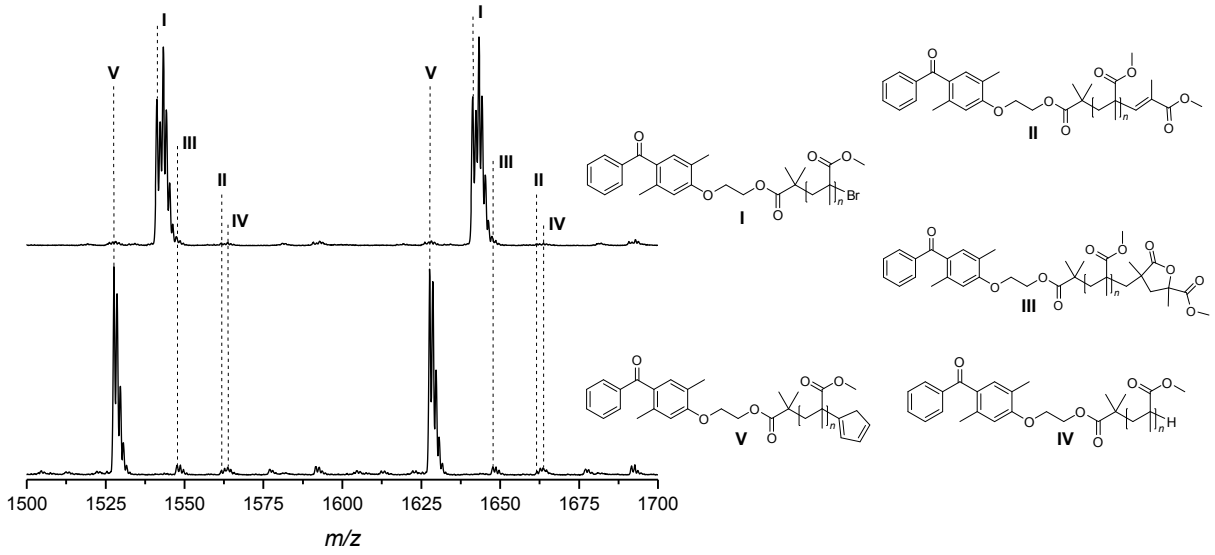


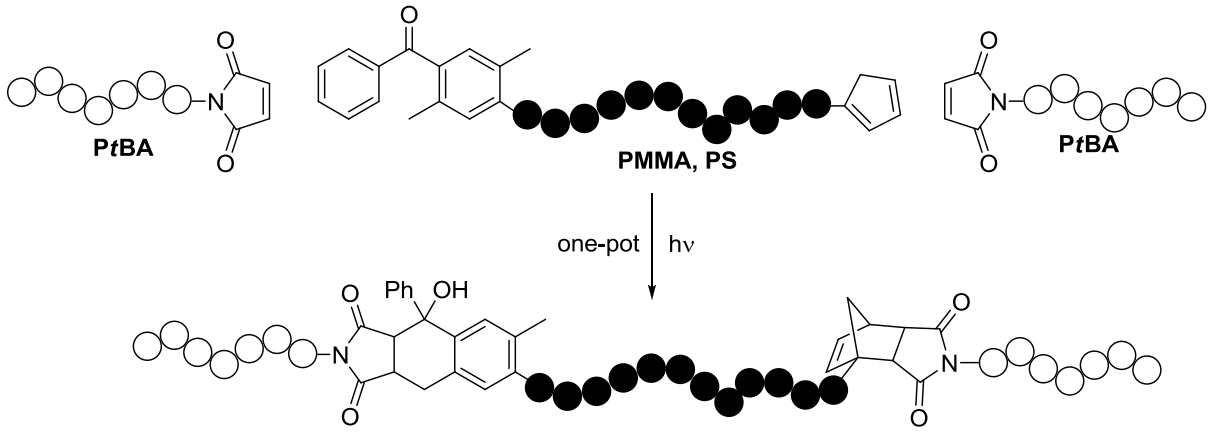
Figure 4.2 Expanded region of a typical repeat unit in the SEC/ESI-MS spectra of DMBP-PMMA-Br Precursor (top) and the resulting DMBP-PMMA-Cp (bottom).

The theoretical and measured mass-to-charge ratios of the involved species collated in Table 4.1 are in excellent agreement within experimental error.

Table 4.1 Theoretical and measured m/z ratios ($[M+Na]^+$) of the main species involved in the synthesis of DMBP-PMMA-Cp. The values refer to ther first peak of the isotopic pattern.

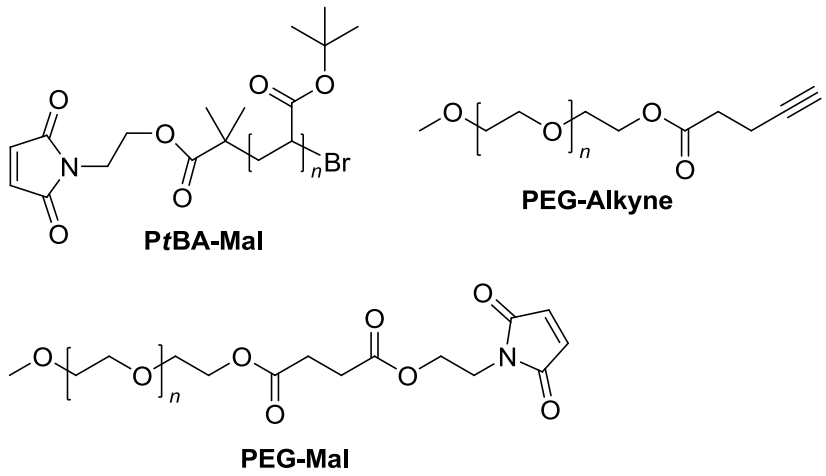
Structure	Formula	m/z^{theo}	m/z^{meas}	$\Delta\, m/z$
I	$[C_{76}H_{111}BrO_{26}Na]^+$	1541.64	1541.33	0.31
II	$[C_{81}H_{118}O_{28}Na]^+$	1561.77	1561.17	0.02
III	$[C_{80}H_{116}O_{28}Na]^+$	1547.76	1547.50	0.09
IV	$[C_{81}H_{120}O_{28}Na]^+$	1563.79	1563.33	0.12
V	$[C_{81}H_{116}O_{26}Na]^+$	1527.77	1527.42	0.10

In the case of PS the success of the reaction sequence is confirmed by ^{1}H-NMR spectroscopy (see Figure 4.8 in the Appendix). It was shown in a previous study[20] that 2,5-dimethylbenzophenone functional polymers undergo a rapid Diels-Alder reaction with maleimide functional polymers via the UV-light induced in situ formation of *o*-quinodimethanes. These species act as highly reactive dienes in the [4+2] cycloaddition. It is known that maleimides undergo a fast Diels-Alder reaction with cyclopentadiene at ambient temperature.[25] Thus, the combination of photo-induced and thermal Diels-Alder reactions permits an efficient one-pot synthesis of ABA triblock copolymers at ambient temperature as displayed in Scheme 4.2.



Scheme 4.2 One-pot synthesis of ABA triblock copolymers via photo-induced and thermal Diels-Alder reactions.

Maleimide capped P*t*BA (P*t*BA-Mal) was synthesized by ATRP employing a furan protected maleimide functional initiator (**1**) and subsequent deprotection in refluxing toluene. Maleimide functional PEG (PEG-Mal) was obtained from commercially available MeO-PEG-OH via esterification with the carboxylic acid functional protected maleimide derivative (**2**), followed by deprotection as described for P*t*BA (see Scheme 4.3 for exact structures). ^{1}H-NMR and ESI-MS spectra of the individual building blocks are provided in the Appendix.



Scheme 4.3 Maleimide and alkyne functional polymers used in the present chapter.

The one-pot synthesis of P*t*BA-*b*-PS-*b*-P*t*BA and P*t*BA-*b*-PMMA-*b*-P*t*BA was performed by stirring a deoxygenated solution of α-DMBP-ω-Cp functional polymer and 2 equivalents P*t*BA-Mal in CH_2Cl_2 for 12 h at ambient temperature. After this time, a sample for SEC analysis was taken and subsequent irradiation for 2 h with a

36 W compact fluorescent lamp (λ_{max} = 320 nm) was performed, followed by precipitation of the resulting triblock copolymer in methanol (for PS middle block) or *n*-hexane (for PMMA middle block). Figure 4.3 shows the SEC traces of the macromolecular building blocks, the resulting triblock copolymers and the samples taken before irradiation.

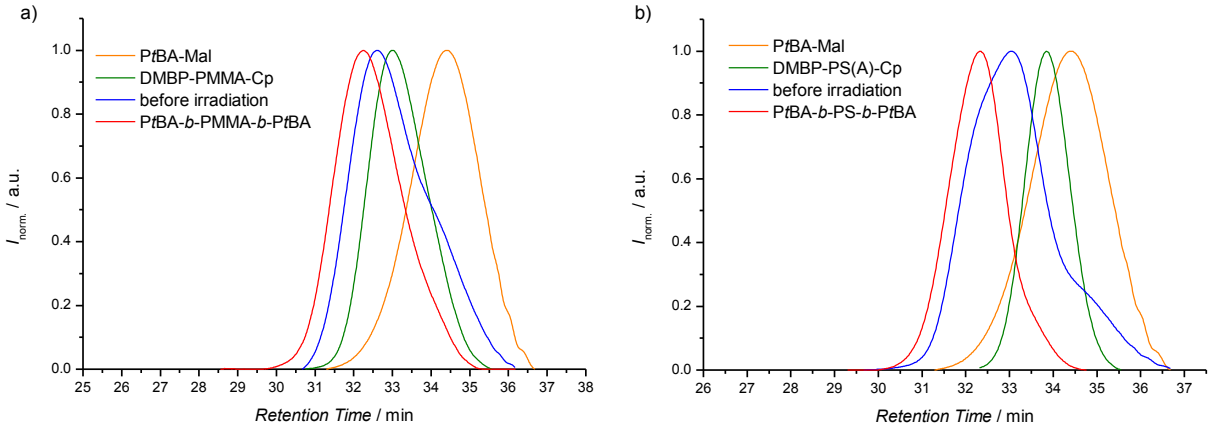


Figure 4.3 Overlay of SEC traces showing the one-pot formation of triblock copolymers. a) P*t*BA-*b*-PMMA-*b*-P*t*BA from P*t*BA-maleimide and DMBP-PMMA-Cp. b) P*t*BA-*b*-PS-*b*-P*t*BA from P*t*BA-maleimide and DMBP-PS-Cp. Efficient block formation was achieved after 2 h irradiation time.

Inspection of Figure 4.3a shows a clear shift to lower retention times after reaction at ambient temperature and a further shift to lower retention times after irradiation with UV-light, indicating the formation of ABA triblock copolymer (thus the SEC traces are showing the expected double shift). The shoulder at higher retention times in the SEC trace before irradiation is due to the remaining second equivalent of P*t*BA. The same observations can be made when PS is acting as middle block (see Figure 4.3b). Close inspection of the sample taken before irradiation in the case of PS reveals a shoulder at lower retention times that can be explained by ambient-light induced formation of P*t*BA-*b*-PS-*b*-P*t*BA. The observation that the Diels-Alder reaction between 2,5-dimethylbenzophenone precursors and maleimides can be triggered by ambient-light was already described in a previous publication.[20] Number average molecular weights and polydispersities of the macromolecular building blocks and the final ABA triblock copolymers are collated in Table 4.2. The number average molecular weights of the triblock copolymers should, however, be treated with care as they are based on a linear PMMA and PS calibration, respectively and are thus only apparent values.

Table 4.2 SEC characterization of the macromolecular building blocks and the final ABA triblock copolymers prepared in a one-pot reaction.

	$M_{n,SEC}$ / g·mol^{-1}	*PDI*
DMBP-PMMA-Cp[a]	3200	1.14
DMBP-PS(A)-Cp[b]	2400	1.06
P*t*BA-Mal[c]	1800	1.23
P*t*BA-*b*-PMMA-*b*-P*t*BA[a]	4300	1.21
P*t*BA-*b*-PS-*b*-P*t*BA[b]	4800	1.09

[a]relative to linear PMMA standards; [b]relative to linear PS standards. [c]Values for P*t*BA-Mal have been corrected by applying the Mark-Houwink parameters provided in Chapter 9.2.

To further confirm the structure of the ABA triblock copolymers P*t*BA-*b*-PS-*b*-P*t*BA and their individual building blocks, they were analyzed via ^{1}H-NMR spectroscopy. For DMBP-PS(A)-Cp the number average molecular weight was calculated by integration of the backbone signals relative to the signals according to the DMBP end-group (see Figure 4.8 in the Appendix) resulting in a $M_{n,NMR}$ (DMBP-PS(A)-Cp) of 3100 g·mol^{-1}. Comparison of the vinylic maleimide signals with the P*t*BA backbone gives an $M_{n,NMR}$ (P*t*BA-Mal) = 1500 g·mol^{-1}. Thus, the theoretical ratio of PS repeat units, n(PS) to P*t*BA repeat units, n(P*t*BA) is n(PS)/n(P*t*BA) = 1.30 for the ABA triblock copolymer. The experimental result n(PS)/n(P*t*BA) = 1.39 obtained from the ^{1}H-NMR spectrum depicted in Figure 4.4 is very close to the theoretical value for the ABA triblock copolymer thus underpinning the formation of P*t*BA-*b*-PS-*b*-P*t*BA.

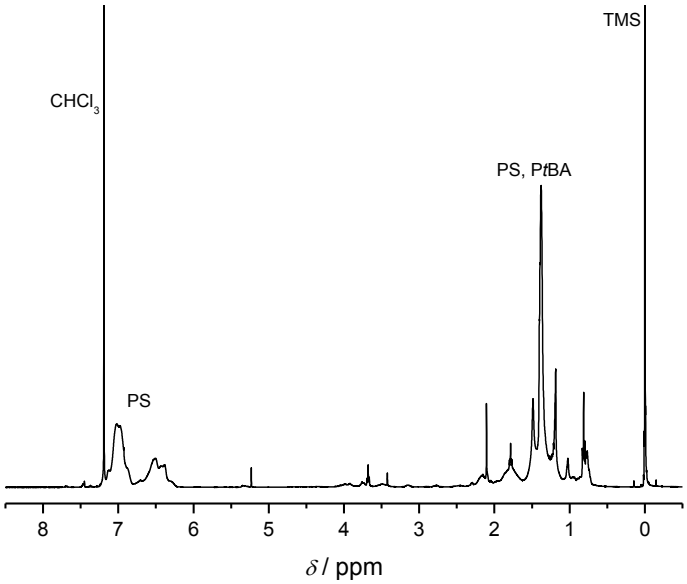
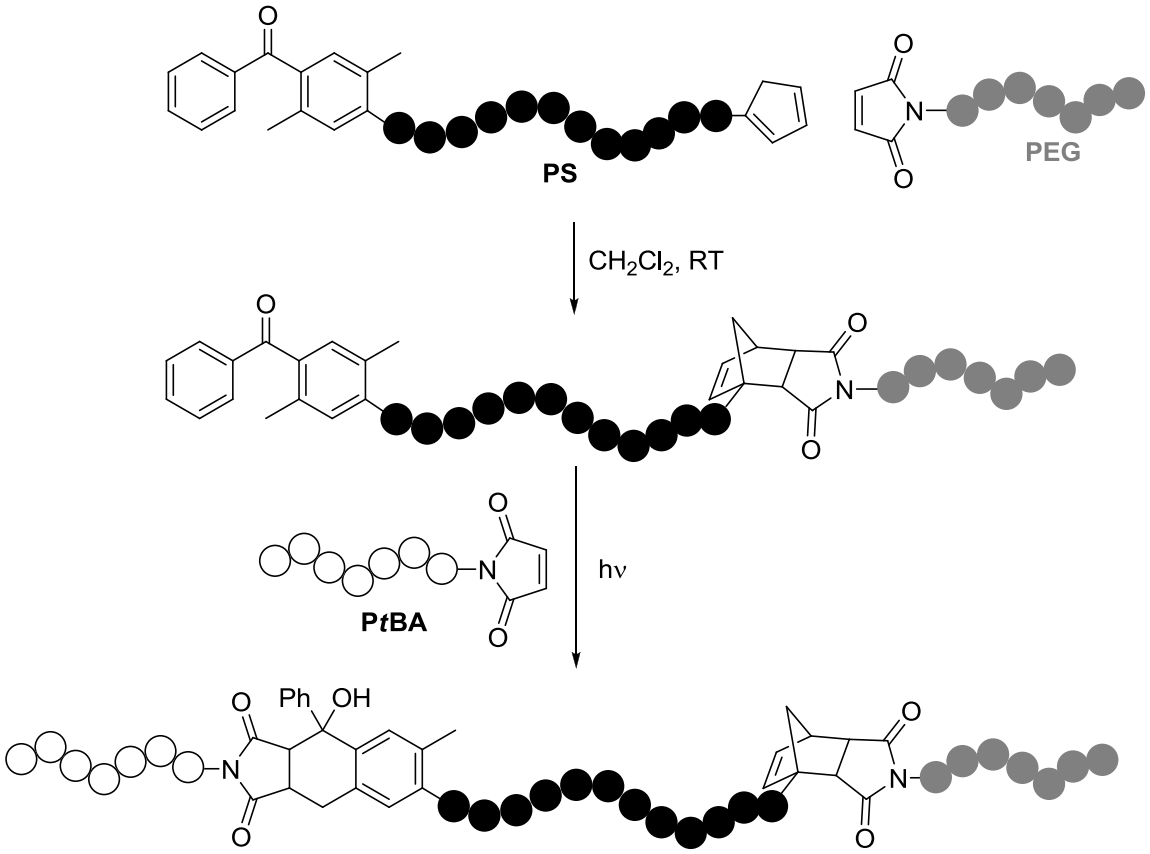


Figure 4.4 ^{1}H-NMR spectrum of P*t*BA-*b*-PS-*b*-P*t*BA in $CDCl_3$.

The fact that Diels-Alder reactions of the DMBP moiety are fully suppressed when the compounds are handled in the dark can be utilized for the modular construction of ABC triblock copolymers via consecutive thermal and photo-induced Diels-Alder reactions as illustrated in Scheme 4.4.



Scheme 4.4 Synthetic strategy for the modular construction of ABC triblock copolymer (PEG-*b*-PS-*b*-P*t*BA) via consecutive thermal and photo-induced Diels-Alder reactions.

To investigate the combination of photochemically and thermally induced Diels-Alder reactions a solution of DMBP-PS(B)-Cp and PEG-Mal in CH_2Cl_2 was initially stirred overnight in the dark and the resulting PEG-*b*-PS was subsequently irradiated with UV-light for 2 h in the presence of an equimolar amount of P*t*BA-Mal yielding the triblock copolymer PEG-*b*-PS-*b*-P*t*BA. SEC traces of the starting materials, the diblock copolymer PEG-*b*-PS as well as the triblock copolymer PEG-*b*-PS-*b*-P*t*BA are depicted in Figure 4.5.

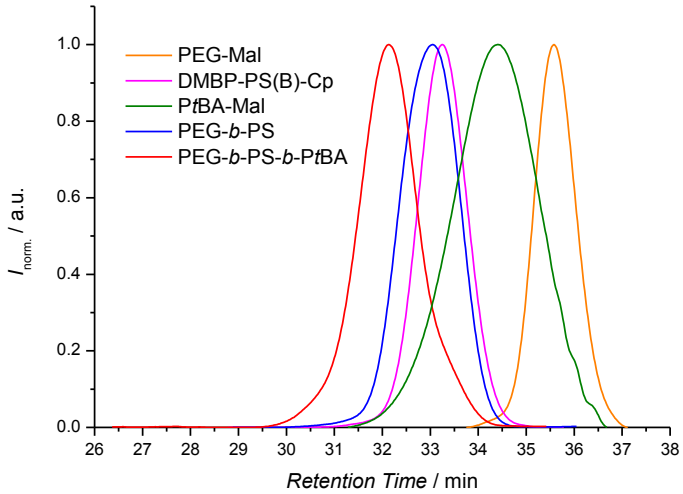


Figure 4.5 Overlay of SEC traces showing the modular formation of PEG-*b*-PS and PEG-*b*-PS-*b*-P*t*BA from PEG-Mal, DMBP-PS(B)-Cp and P*t*BA-Mal. Efficient triblock formation was achieved after 2 h irradiation time at ambient temperature.

The SEC chromatogram after reaction in the dark is shifted to lower retention times indicating the formation of PEG-*b*-PS. The efficient formation of PEG-*b*-PS-*b*-P*t*BA triblock copolymer is indicated by an additional shift to lower retention times after the UV-light triggered reaction with P*t*BA-Mal. A unimodal and narrow molecular weight distribution results, devoid of any tail assignable to the starting materials. Estimated M_n values and *PDI*s for the building blocks and the copolymers are given in Table 4.3.

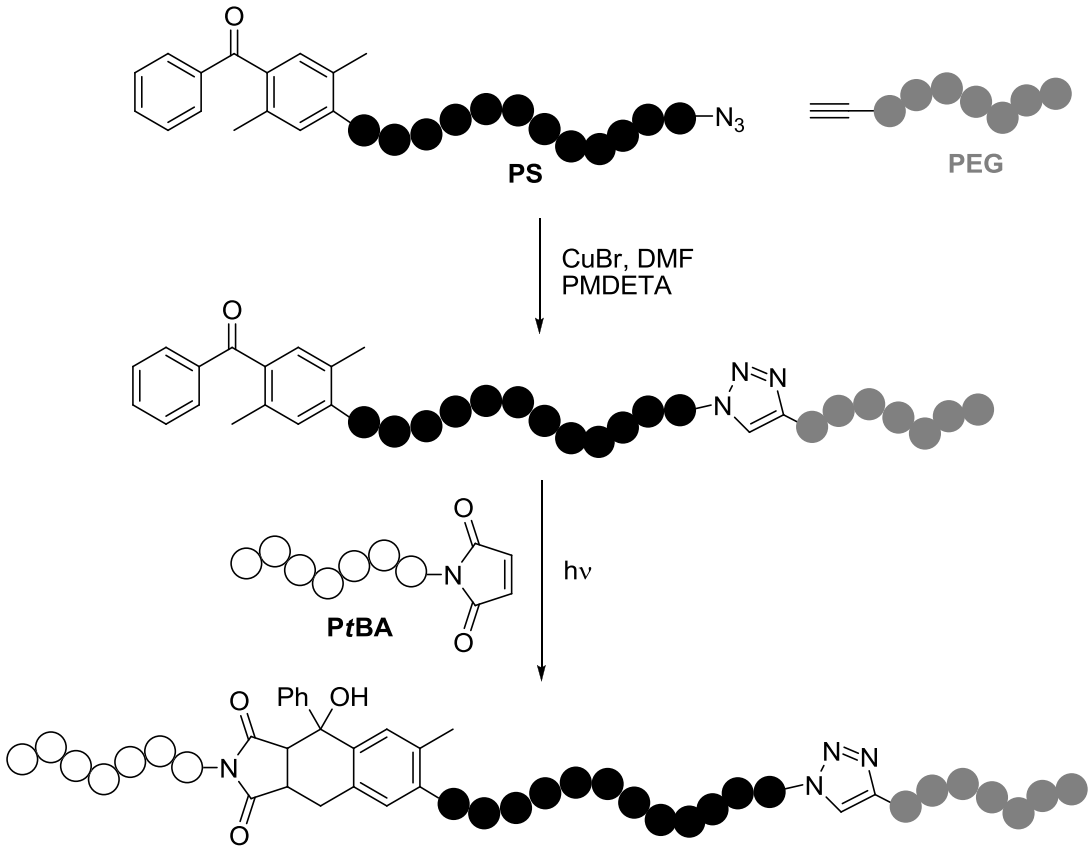
Table 4.3 SEC derived molecular weight data of the macromolecular building blocks and the block copolymers resulting from the modular formation of PEG-*b*-PS and PEG-*b*-PS-*b*-P*t*BA from PEG-Mal, DMBP-PS(B)-Cp and P*t*BA-Mal.

	$M_{n,SEC}$[a] / g·mol^{-1}	*PDI*
PEG-Mal	800	1.09
DMBP-PS(B)-Cp	3200	1.06
P*t*BA-Mal	1800	1.23
PEG-*b*-PS	3700	1.07
PEG-*b*-PS-*b*-P*t*BA	5200	1.10

[a]relative to linear PS standards. Values for P*t*BA-Mal have been corrected by applying the Mark-Houwink parameters provided in Chapter 9.2.

The formation of the triblock copolymer PEG-*b*-PS-*b*-P*t*BA is further confirmed by the calculated number average molecular weight (M_n = 5200 g·mol^{-1}) which is close to the sum of the individual building blocks (5800 g·mol^{-1}) estimated via SEC.

Utilizing CuAAC *click* chemistry as first conjugation method renders it unnecessary to perform the construction of the AB block copolymer in the dark. α-2,5-dimethylbenzophenone-ω-azide functionalized PS (DMBP-PS-N_3) was thus synthesized by nucleophilic substitution of the bromine end-group with sodium azide (see Figure 4.10 in the Appendix for a ^{1}H-NMR spectrum) and employed for the modular construction of PEG-*b*-PS-*b*-P*t*BA triblock copolymer via consecutive CuAAC and photo-induced Diels-Alder reactions as shown in Scheme 4.5.



Scheme 4.5 Synthetic strategy for the modular construction of ABC triblock copolymer (PEG-*b*-PS-*b*-P*t*BA) via consecutive CuAAC and photo-induced Diels-Alder reactions.

Figure 4.6 depicts the SEC elugrams of the macromolecular building blocks and the resulting di- and triblock copolymers.

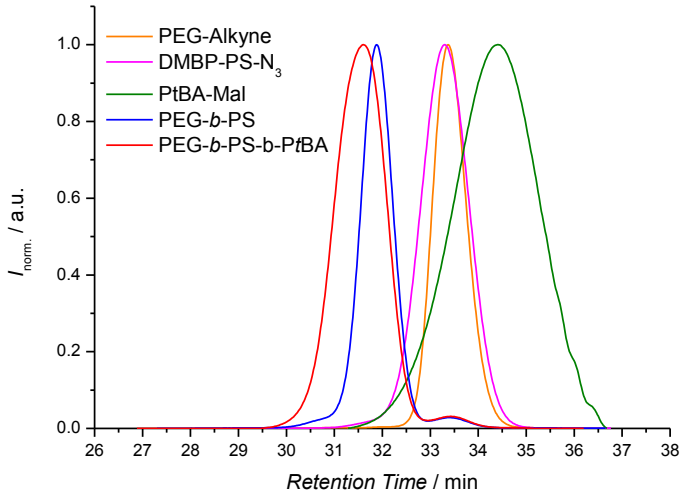


Figure 4.6 Overlay of SEC traces showing the modular formation of PEG-*b*-PS and PEG-*b*-PS-*b*-P*t*BA from PEG-Alkyne, DMBP-PS-N_3 and P*t*BA-Mal. Efficient triblock formation was achieved after 2 h irradiation time.

Inspection of Figure 4.6 shows a clear shift to lower retention times for the CuAAC product and a further shift after the UV light-triggered reaction with P*t*BA-Mal indicating the formation of PEG-*b*-PS-*b*-P*t*BA. The SEC elugram of the di- and triblock copolymers indicates only a very small shoulder that can be assigned to PEG as remaining PS would have undergone photo-induced conjugation to p*t*BA forming PS-*b*-P*t*BA which is not observed in the SEC elugram of the final product. The estimated molecular weights collated in Table 4.4 are in good agreement with the sum of the individual building blocks keeping in mind that the M_n values of the block polymers are decreased by a small shoulder due to remaining PEG.

Table 4.4 SEC and ^{1}H-NMR characterization of the macromolecular building blocks and the resulting block copolymers of the modular formation of PEG-*b*-PS and PEG-*b*-PS-*b*-P*t*BA from PEG-Alkyne, DMBP-PS-N_3 and P*t*BA-Mal.

	$M_{n,SEC}$[a] / g·mol^{-1}	$M_{n,NMR}$ / g·mol^{-1}	*PDI*
PEG-Alkyne	3000	2200	1.03
DMBP-PS-N_3	3200	3100	1.06
P*t*BA-Mal	1800	1500	1.23
PEG-*b*-PS	5800	-	1.05
PEG-*b*-PS-*b*-P*t*BA	6700	6300	1.07

[a]relative to linear PS standards. Values for P*t*BA have been corrected by applying the Mark-Houwink parameters provided in Chapter 9.2.

To independently confirm the molecular weight of the polymers and thus the synthetic success, PEG-*b*-PS-*b*-PtBA was analyzed via ^{1}H-NMR spectroscopy (see Figure 4.7)

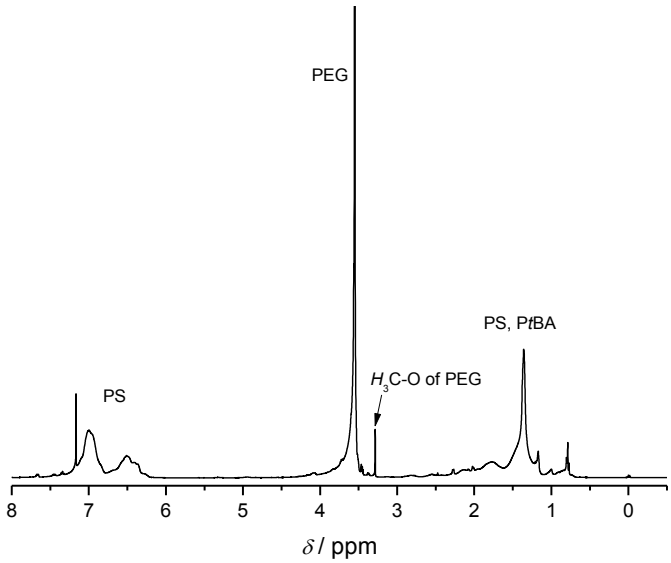


Figure 4.7 ^{1}H-NMR spectrum of PEG-*b*-PS-*b*-P*t*BA in $CDCl_3$.

The number-average molecular weight of the triblock copolymer was calculated from the ratio of the integrated signal at 3.36 ppm (OCH_3 end-group of PEG) to the PEG, PS and P*t*BA backbone signals. $M_{n,NMR}$(PEG-*b*-PS-*b*-P*t*BA) = 6300 g·mol^{-1} is in excellent agreement with the sum of values of the individual segments (6800 g·mol^{-1}) within experimental error.

4.4 Conclusions

Photo-induced Diels-Alder reactions were combined with thermal Diels-Alder reactions and azide-alkyne *click* chemistry for the modular ambient temperature synthesis of ABA and ABC triblock copolymers. Highly functional precursors were synthesized via ATRP. The present approach demonstrates for the first time the orthogonality of the novel photo-triggered conjugation method to other well-established *click* methodologies. The high photo-reactivity of the employed *o*-quinodimethane functionalized macromolecules allows efficient block formation in stoichiometric systems,[11] within 2 h reaction time at ambient temperature for the currently investigated polymers. The use of low intensity and soft UV-B irradiation from a low-cost light-source or even ambient light to induce conjugation makes this protocol easy to implement in the organic laboratory.

Appendix

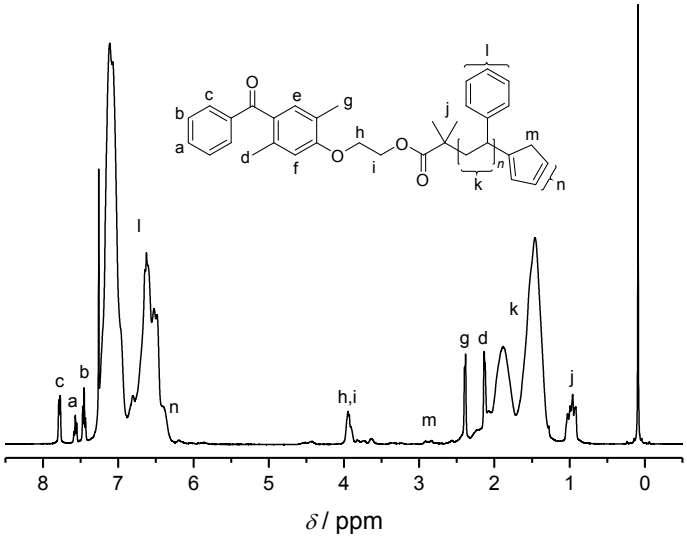


Figure 4.8 ^{1}H-NMR spectrum of DMBP-PS-Cp in $CDCl_3$.

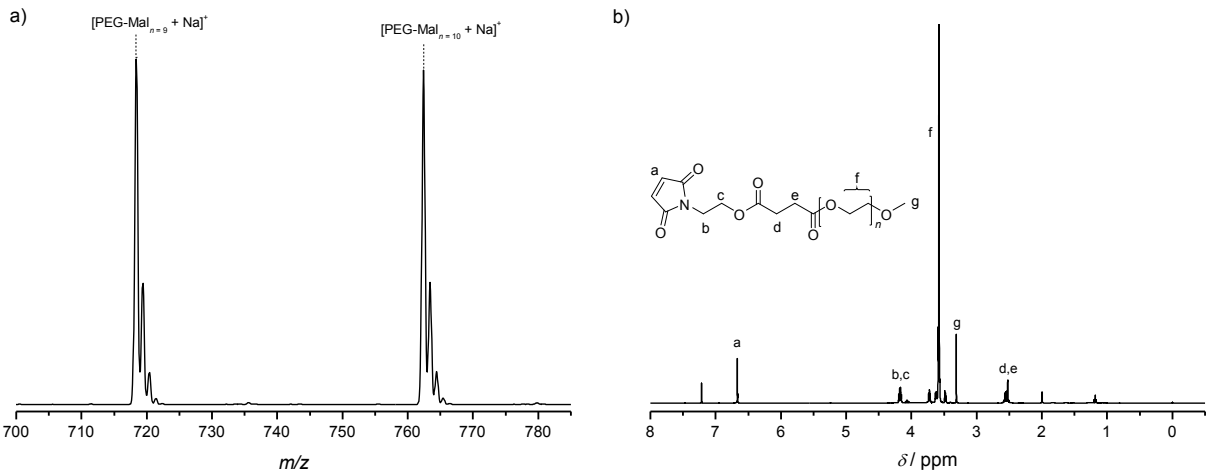


Figure 4.9 a) SEC/ESI-MS spectrum and b) ^{1}H-NMR spectrum of PEG-Mal in $CDCl_3$.

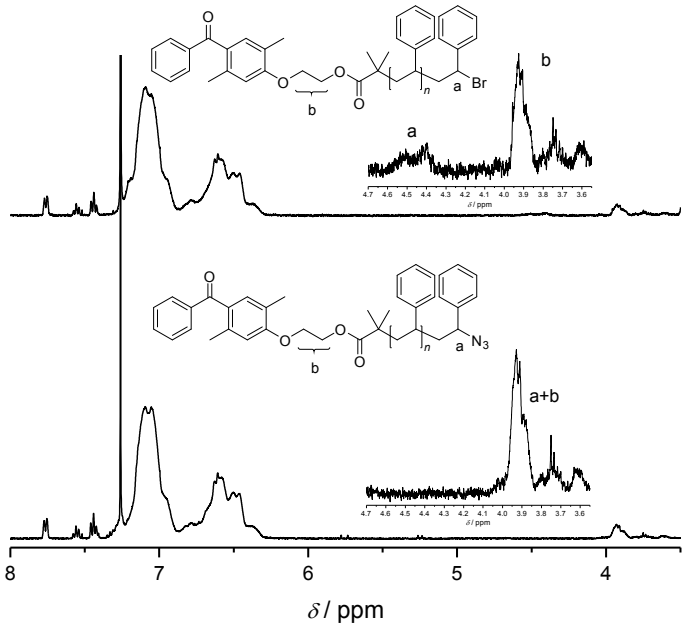


Figure 4.10 ^{1}H-NMR spectra of DMBP-PS-Br (top) and DMBP-PS-N_3 (bottom) in $CDCl_3$.

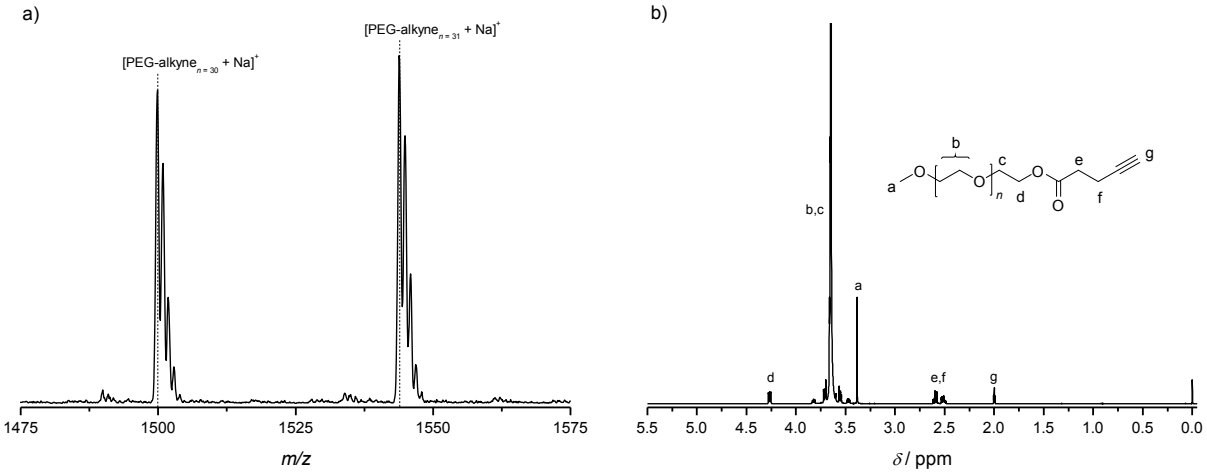


Figure 4.11 a) SEC/ESI-MS spectrum and b) ^{1}H-NMR spectrum of PEG-Alkyne in $CDCl_3$.

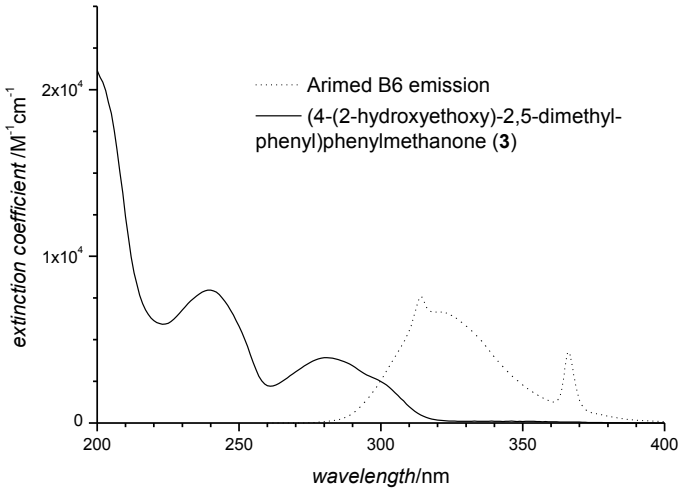


Figure 4.12 Absorption spectrum of (4-(2-hydroxyethoxy)-2,5-dimethyl-phenyl) phenyl methanone (**3**) together with the emission spectrum of the employed compact low-pressure fluorescent lamp (Arimed B6).

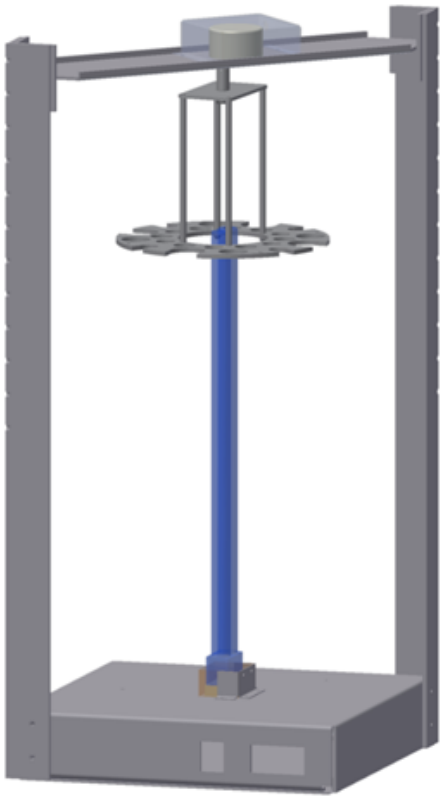


Figure 4.13 Drawing of the custom-built photoreactor employed in the current study.

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5

One-pot Synthesis of Cyclopentadienyl Endcapped Poly(2-ethyl-2-oxazoline)*

5.1 Introduction

The preparation of end-functionalized macromolecules represents a major area of study in modern synthetic polymer chemistry.[1] Polymers possessing a high end-group fidelity are of particular interest within the context of efficient polymer conjugation reactions including those obtained via *click* chemistry concepts.[2-3] The *click*-approach permits the construction of various macromolecular architectures from variable polymerization methodologies.[4] The most widely employed *click* protocol for polymer-polymer conjugation is the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAc).[5] An efficient strategy that avoids transition metal catalysis is the utilization of Diels-Alder reactions as highlighted in Chapter 2. Commonly employed systems include furan-maleimide[6] and anthracene-maleimide[7] as diene-dienophile pairs. However, a restriction of these systems is the fact that they require elevated temperatures. This can be overcome via the use of cyclopentadienyl (Cp) endcapped polymers as more reactive diene component. The combination of Cp-functionalized polymers and polymers carrying an electron-deficient dithioester end-group prepared via reversible addition-fragmentation chain transfer (RAFT) polymerization facilitates ultrafast polymer-polymer conjugations at ambient temperature.[8] The reaction between Cp and maleimide end-groups was employed for the construction of cyclic polymers and linear multi-block copolymers in Chapter 3 and 4, respectively. The Cp-capped polymers employed in the aforementioned publications and the previous chapters were prepared by post-polymerization nucleophilic substitution of a tosyl or bromine end-group with sodium cyclopentadienide or nickelocene.[9] To date, the direct incorporation of Cp-functionalities could not be accomplished. The fact that Cp-moieties are highly reactive functional groups has prevented the synthesis of Cp-functional initiators or chain-transfer agents. An emerging class of poly-

* This work was carried out in collaboration with K. Kempe, Prof. U. Schubert (Friedrich-Schiller-University Jena) and Prof. R. Hoogenboom (Ghent University).

mers providing a promising platform for the synthesis of highly functional materials are the poly(2-oxazoline)s (POx).[10-12] The living cationic ring-opening polymerization (CROP) allows the incorporation of various functionalities into POx using functional initiators,[13-14] termination agents[15-16] as well as monomers[17-19] enabling efficient post-polymerization modifications.

5.2 Experimental Section

4-(2-{[(3-Acetyl-7-oxabicyclo[2.2.1]-hept-5-en-2-yl)carbonyl]aminoethoxy)-4-oxobutanoic acid (**1**)[20] and *N*-(2-hydroxyethyl)maleimide[21] were synthesized according to a literature procedure. The synthesis of maleimide functionalized poly(ethylene glycol) (PEG-Mal) is described in Chapter 4.2.

Synthesis of Cylopentadienyl Functionalized Poly(2-ethyl-2-oxazoline) (PEtOx-Cp)

A polymerization solution containing methyl tosylate (0.08 g, 0.43 mmol), 2-ethyl-2-oxazoline (0.88 g, 8.9 mmol) and acetonitrile (3.9 g, 95 mmol) was prepared under an argon atmosphere and polymerized under microwave irradiation (140 °C, 9 min). The polymer solution was cooled to 0 °C and 3 equivalents of a sodium cyclopentadienide solution (2.0 M THF) (0.54 mL, 1.1 mmol) were added dropwise under vigorous stirring. After 30 min the solution was allowed to warm to room temperature and stirring was continued overnight. The resulting mixture was then poured into a saturated NH_4Cl solution and extracted with dichloromethane. The organic phase was washed twice with cold distilled water, dried over $MgSO_4$ and concentrated in vacuum. Precipitation in ice-cold diethyl ether yielded a light brown solid (550 mg, 70%). $M_{n,SEC}$ = 1900 g mol^{-1}, *PDI* = 1.06. ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 6.70–6.17 (m, Cp vinylic), 3.43 (s, N-CH_2-CH_2-N), 3.01 (s, H_3C-N), 2.94 (s, Cp bridge head), 2.53–1.95 (m, CH_2CO), 1.18–1.00 (m, CH_3-CH$_2$CO).

Diels-Alder reactions with small molecule *N*-substituted maleimides

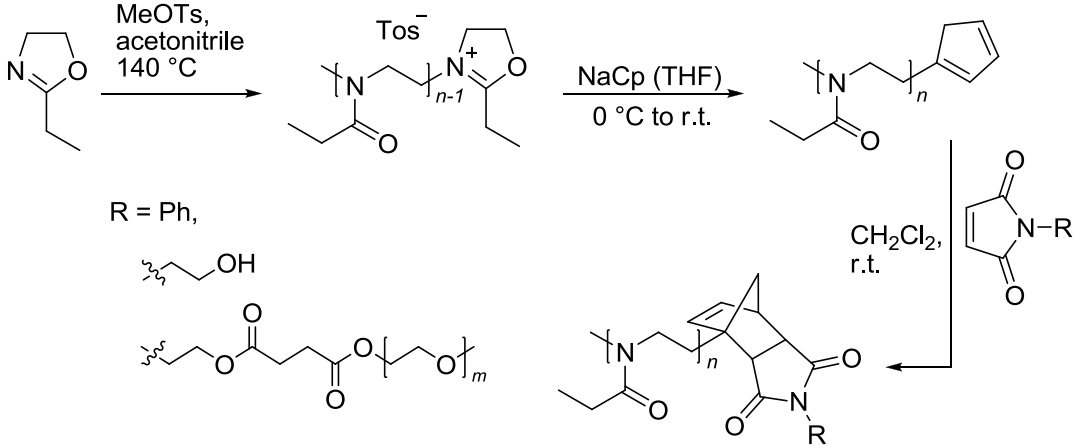
A solution of PEtOx-Cp (2 μmol) and *N*-substituted maleimide (10 μmol) in 0.5 mL CH_2Cl_2 was stirred 24 h at ambient temperature. The solvent was removed under a stream of nitrogen. The residue was re-dissolved in THF and analyzed by SEC/ESI-MS.

Synthesis of PEG-*b*-PEtOx

A solution of PEtOx-Cp (0.5 mmol) and PEG-Mal (0.6 mmol) in 5 mL CH_2Cl_2 was stirred 48 h at ambient temperature. PEG-*b*-PEtOx was isolated by two-fold precipitation in diethyl ether and dried under vacuum. $M_{n,SEC}$ = 3000 g mol^{-1}, *PDI* = 1.07. ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 6.17–5.89 (m, cycloadduct vinylic), 4.24–4.20 (m, N-CH_2CH_2-OCO), 3.62 (s, O-CH_2-CH_2-O), 3.43 (s, N-CH_2-CH_2-N), 3.36 (s, PEG-OCH_3), 3.01 (s, H_3C-N), 2.53–1.95 (m, CH_2CO and CO-CH_2CH_2-CO), 1.18–1.00 (m, CH_3-CH$_2$CO).

5.3 Results and Discussion

The direct endcapping of a living POx chain with sodium cyclopentadienide (NaCp) is presented in the present chapter. The successful synthesis of PEtOx-Cp is proven by means of ^{1}H-NMR spectroscopy, MALDI-TOF MS as well as SEC/ESI-MS. Furthermore, Diels-Alder reactions at ambient temperature with various maleimides were performed in order to demonstrate the potential of this reactive polymer endgroup. PEtOx homopolymers were prepared with methyl tosylate as initiator in acetonitrile at 140 °C under microwave irradiation. In order to guarantee sufficient mixing of the polymer solution with NaCp the polymerization concentration was set to 1.5 M. After complete monomer consumption,[22] the living polymer chains were terminated by the addition of a NaCp solution at 0 °C (Scheme 5.1). After 30 min, stirring was continued at ambient temperature overnight.



Scheme 5.1 Synthesis of cyclopentadienyl-capped poly(2-ethyl-2-oxazoline) (PEtOx-Cp) and subsequent Diels-Alder conjugations with *N*-substituted maleimides. Note that only the 1-isomer of PEtOx-Cp is presented throughout for reasons of brevity, although a mixture of the 1- and 2-isomer is produced.

^{1}H-NMR spectroscopy of the purified product showed near-quantitative attachment of Cp to the PEtOx (Figure 5.1). Furthermore, MALDI-TOF MS analysis revealed the formation of the desired product accompanied by a negligible amount of proton-initiated PEtOx-Cp (see Figure 5.2). SEC confirmed the formation of a well-defined polymer with a narrow molar mass distribution (*PDI* = 1.06).

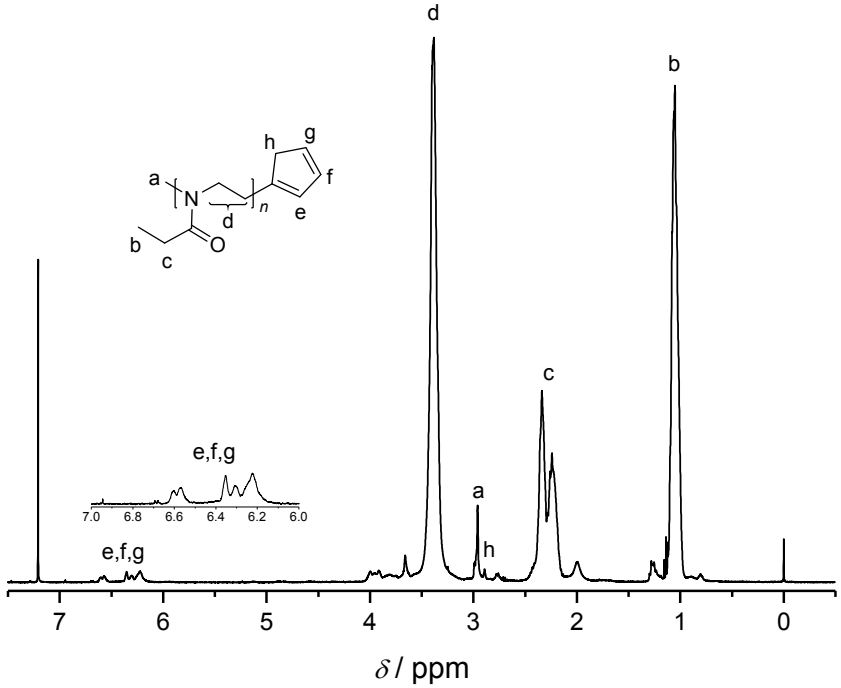


Figure 5.1 ^{1}H-NMR spectrum of PEtOx-Cp in $CDCl_3$. The inset shows the expanded region of the Cp signals.

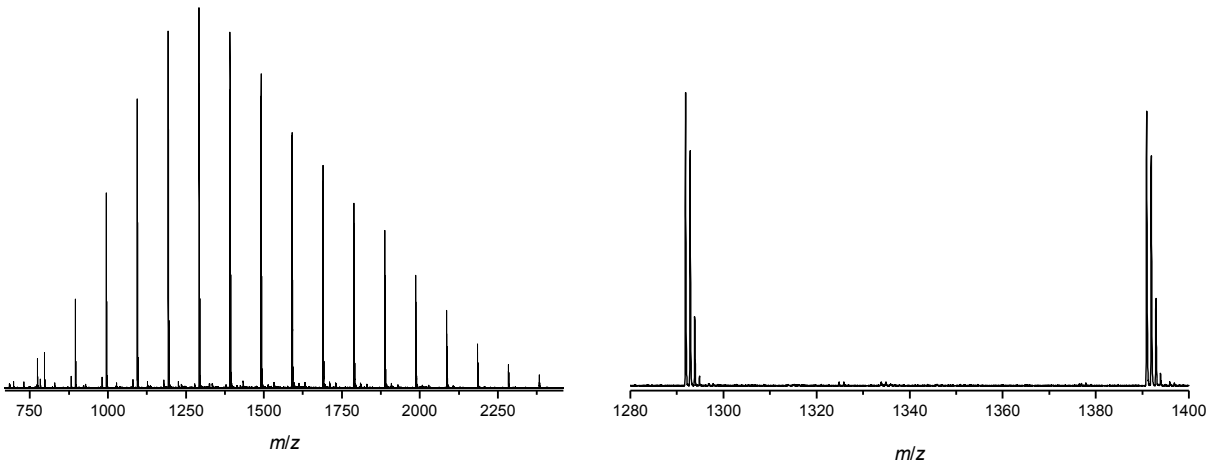


Figure 5.2 MALDI-TOF MS spectrum of PEtOx-Cp (left) and a zoom into one repeat unit (right).

To investigate the ability of PEtOx-Cp to undergo Diels-Alder cycloadditions it was reacted with an excess (5 eq.) of various *N*-substituted maleimides in CH_2Cl_2 at ambient temperature for 24 h. The transformations were monitored by size exclusion chromatography/electrospray ionization-mass spectrometry (SEC/ESI-MS) as depicted in Figure 5.3 for *N*-phenylmaleimide as dienophile.

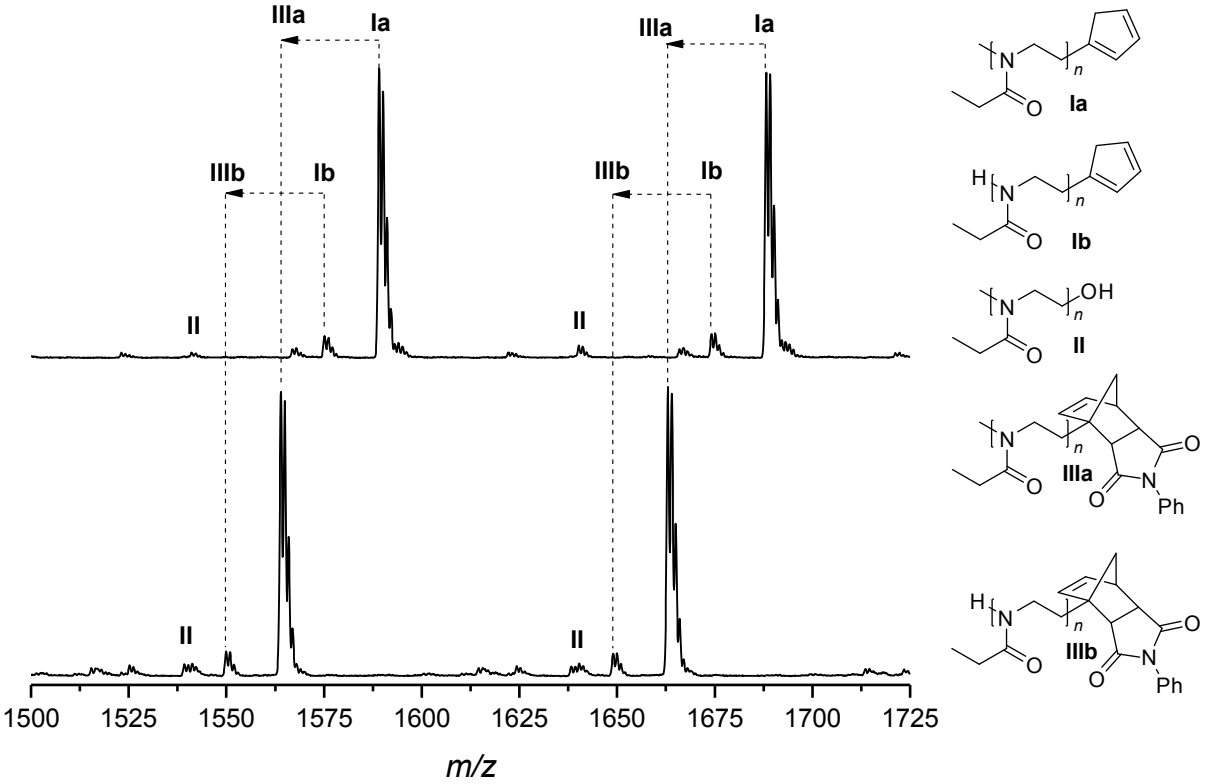


Figure 5.3 Expanded region of a typical repeat unit in the SEC/ESI-MS spectra of PEtOx-Cp (top) and the Diels-Alder cycloadduct with *N*-phenylmaleimide (bottom). Within the presented *m/z* range, it should be noted that the number of monomer repeat units of Ia, Ib and II differs from that of IIIa and IIIb.

Inspection of Figure 5.3 indicates that the Cp-functionalized species (Ia, Ib) are quantitatively transformed into the corresponding cycloadducts (IIIa, IIIb). The theoretical and measured *m/z* ratios of the involved species collated in Table 5.1 are in excellent agreement. The SEC/ESI-MS also revealed a minor fraction of hydroxy-terminated PEtOx resulting from water endcapping. The overall Cp-functionality calculated via integration of the mass spectral abundances[23] is 94 %. The transformation worked in an equally efficient manner with *N*-(2-hydroxyethyl)maleimide as dienophile (see Figure 5.4).

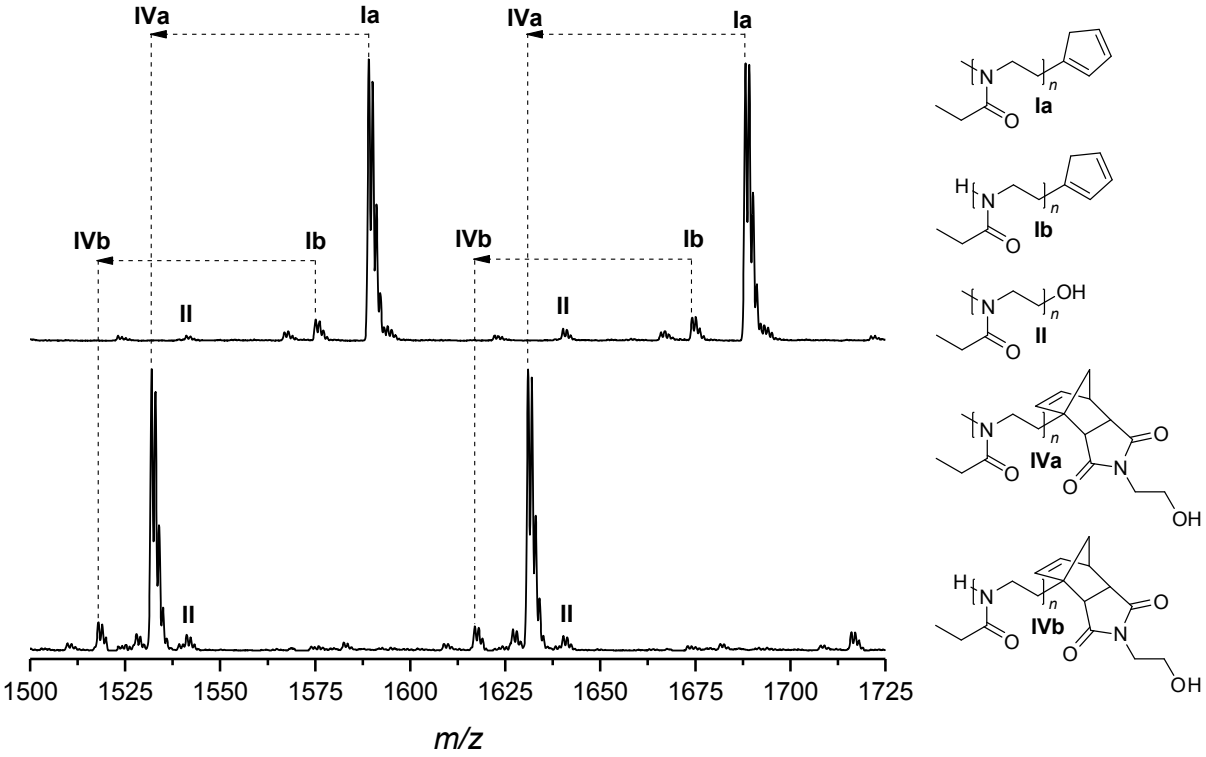


Figure 5.4 Expanded region of a typical repeat unit in the SEC/ESI-MS spectra of PEtOx-Cp (top) and the Diels-Alder cycloadduct with *N*-(2-hydroxyethyl)maleimide. Within the presented m/z range, it should be noted that the number of monomer repeat units of Ia, Ib and II differs from that of IVa and IVb.

Table 5.1 Theoretical and measured m/z ratios ($[M+Na]^+$) of the species involved in the synthesis of PEtOx-Cp and the Diels-Alder reactions with *N*-phenylmaleimide and *N*-(2-hydroxyethyl)maleimide.

Structure	Formula	m/z^{theo}	m/z^{meas}	$\Delta\, m/z$
I	$[C_{81}H_{143}N_{15}O_{15}Na]^+$	1589.08	1589.08	0.00
Ib	$[C_{80}H_{141}N_{15}O_{15}Na]^+$	1575.06	1575.08	0.02
II	$[C_{76}H_{139}N_{15}O_{16}Na]^+$	1541.04	1541.08	0.04
IIIa	$[C_{81}H_{132}N_{14}O_{15}Na]^+$	1563.99	1564.00	0.01
IIIb	$[C_{80}H_{130}N_{14}O_{15}Na]^+$	1549.97	1549.92	0.05
IVa	$[C_{77}H_{132}N_{14}O_{16}Na]^+$	1531.98	1531.92	0.06
IVb	$[C_{76}H_{130}N_{14}O_{16}Na]^+$	1517.97	1518.00	0.03

To confirm the utility of PEtOx-Cp for the modular construction of macromolecular architectures, a block copolymer was prepared employing maleimide terminated poly(ethylene glycol) (PEG-Mal, see Chapter 4) as dienophile. For this purpose a solution of PEtOx-Cp and PEG-Mal (1.2 eq) in CH_2Cl_2 was stirred for 48 h at ambient

temperature and the resulting block copolymer was precipitated in diethyl ether. Figure 5.5 shows the SEC traces of the polymeric building blocks and the coupling product. A clear shift to lower retention times indicates the successful formation of PEG-*b*-PEtOx. Number average molecular weights, M_n, and polydispersities, *PDI*, of PEG-*b*-PEtOx and the individual building blocks are collated in Table 5.2.

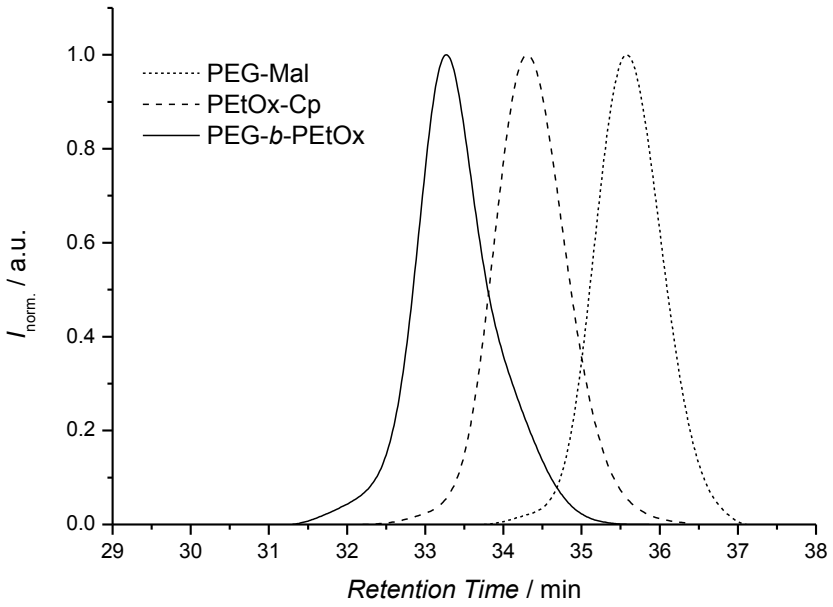


Figure 5.5 Overlay of SEC traces showing the formation of PEG-*b*-PEtOx from PEtOx-Cp and PEG-Mal.

Table 5.2 SEC and ^{1}H-NMR Characterization data of PEG-*b*-PEtOx and the polymeric building blocks PEG-Mal and PEtOx-Cp.

	$M_{n,SEC}$[a] / g·mol^{-1}	$M_{n,NMR}$ / g·mol^{-1}	*PDI*
PEG-Mal	800	900	1.09
PEtOx-Cp	1900	1700	1.06
PEG-*b*-PEtOx	3000	2700	1.07

[a]relative to linear PS standards

Signals according to each of the individual segments are clearly visible in the ^{1}H-NMR spectrum of PEG-*b*-PEtOx depicted in Figure 5.6. The absence of the Cp signals and the occurrence of the multiplet at 6.17–5.89 ppm that can be assigned to the vinylic protons of the cycloadduct further confirm the success of the Diels-Alder coupling reaction. The number-average molecular weight calculated from the integration ratio of the last mentioned peak and the methyl protons of PEtOx is in good

agreement with the sum of the two homopolymers and the data obtained via SEC (Table 5.2).

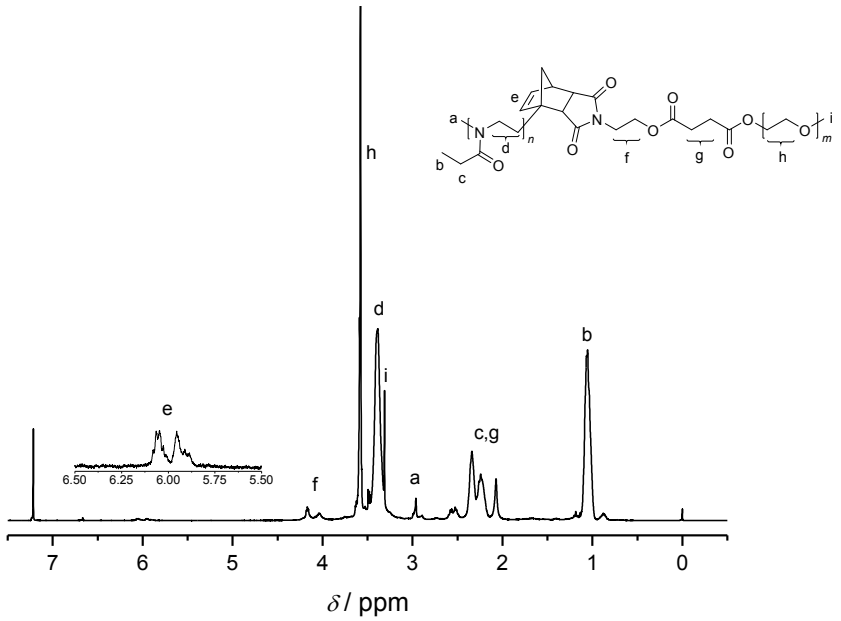


Figure 5.6 ^{1}H-NMR spectrum of PEG-*b*-PEtOx in $CDCl_3$. The inset shows the expanded signals of the vinylic protons of the cycloadduct.

Additional verification of block copolymer formation is provided by SEC/ESI-MS analysis of the reaction product as shown in Figure 5.7. All peaks occurring in the spectrum can be assigned to PEG-*b*-PEtOx. Theoretical and measured *m*/*z*-ratios of the individual peaks are in good agreement and are listed in Table 5.3.

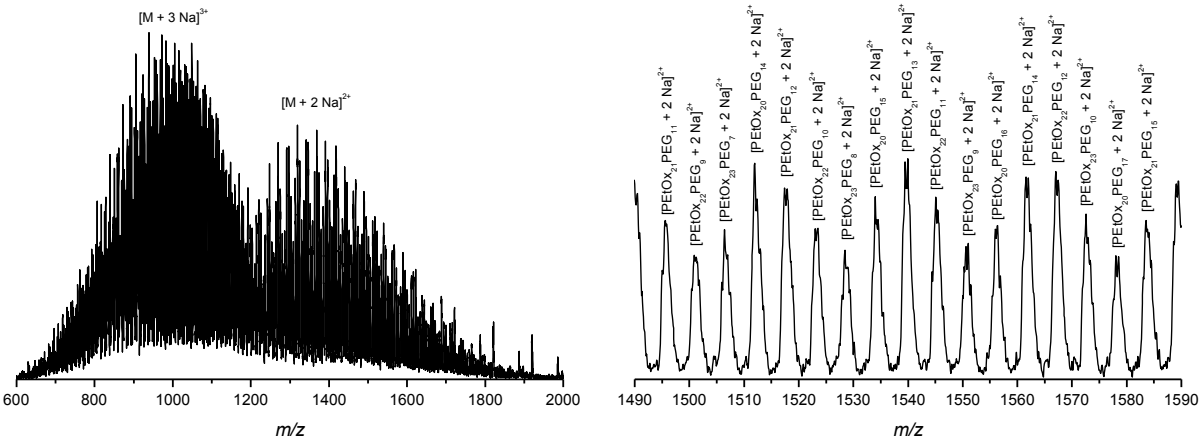


Figure 5.7 SEC/ESI-MS spectrum of PEG-*b*-PEtOx (left) and expanded region of the charge state z = 2 (right).

Table 5.3 Theoretical and measured m/z-ratios ($[M+2Na]^{2+}$) of possible copolymer compositions. The values refer to the peak-maxima of the isotopic patterns.

n(EtOx)	m(EG)	Formula	m/z^{theo}	m/z^{meas}	$\Delta\, m/z$
20	14	$[C_{147}H_{261}N_{21}O_{41}Na_2]^{2+}$	1511.94	1512.00	0.06
20	15	$[C_{149}H_{265}N_{21}O_{42}Na_2]^{2+}$	1533.95	1534.00	0.05
20	16	$[C_{151}H_{269}N_{21}O_{43}Na_2]^{2+}$	1555.97	1556.00	0.03
20	17	$[C_{153}H_{273}N_{21}O_{44}Na_2]^{2+}$	1577.98	1578.00	0.02
21	11	$[C_{146}H_{258}N_{22}O_{39}Na_2]^{2+}$	1495.44	1495.58	0.14
21	12	$[C_{148}H_{262}N_{22}O_{40}Na_2]^{2+}$	1517.45	1517.42	0.03
21	13	$[C_{150}H_{266}N_{22}O_{41}Na_2]^{2+}$	1539.46	1539.42	0.04
21	14	$[C_{152}H_{270}N_{22}O_{42}Na_2]^{2+}$	1561.47	1561.58	0.11
21	15	$[C_{156}H_{274}N_{22}O_{43}Na_2]^{2+}$	1583.49	1583.58	0.09
22	9	$[C_{147}H_{259}N_{23}O_{38}Na_2]^{2+}$	1500.94	1500.92	0.02
22	10	$[C_{149}H_{263}N_{23}O_{39}Na_2]^{2+}$	1522.95	1523.00	0.05
22	11	$[C_{151}H_{267}N_{23}O_{40}Na_2]^{2+}$	1544.97	1545.08	0.11
22	12	$[C_{153}H_{271}N_{23}O_{41}Na_2]^{2+}$	1566.98	1567.00	0.02

5.4 Conclusions

In summary, an efficient strategy for the one-pot synthesis of PEtOx bearing a highly reactive Cp end-group via CROP employing NaCp as termination agent has been presented. This strategy allows for the first time the synthesis of Cp functionalized polymers without a post-polymerization modification. It was further demonstrated that PEtOx-Cp undergoes quantitative Diels-Alder reactions with various *N*-substituted maleimides. This strategy was successfully employed for the modular construction of PEG-*b*-PEtOx. One can envisage that the herein introduced method can be extended to CROPs of different monomers, thus providing a new tool for the facile synthesis of novel precursors for ambient temperature conjugations.

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6

Catalyst-Free Conjugation in Aqueous Environment at Ambient Temperature

6.1 Introduction

Combining controlled/living polymerizations[1] with modular orthogonal conjugation[2] has led to a paradigm shift with regard to macromolecular design within polymer science as discussed in Chapter 2.[3-5] This effective combination resulted in a multitude of novel materials with a wide array[6-10] of functionality and architecture for applications in fields as varied as biology[11-13] through to high-end semiconductor manufacturing.[14-15] At the forefront of the free radical polymerization/*click* conjugation field, reversible addition-fragmentation chain transfer polymerization with subsequent hetero-Diels-Alder cycloaddition (RAFT-HDA) has proven to be one of the premier synthetic tools.[16-18] This is due to the ultra-fast kinetics of the reaction, the mild conditions required, the occasional absence of catalyst, the compatibility with a number of substrates, and the potential reversibility of the linkage.[17, 19-22] However, to date, no RAFT-HDA conjugations in benign solvents such as water have been reported. Water presents non negligible advantages for organic reactions. Its abundance and low impact on the environment makes it a cheap and green solvent. Some direct effects were also observed on specific reactions. Water can increase the rate of some reactions, e.g., Diels-Alder cycloadditions[23-24] or even enhance selectivity.[25] The ability to carry out macromolecular conjugations in aqueous environments has numerous advantages, especially when considering biological applications. For instance, polymer-protein[26-29] *click* conjugations have been achieved previously in aqueous media using the copper-catalyzed azide alkyne 1,3-dipolar cycloaddition (CuAAC). However, from a biological point of view, the need for a metal catalyst in CuAAC can be problematic.[30-32] There have been catalyst-free examples of this reaction employing strained cyclooctynes,[33-34] yet the latter require multiple steps for their synthesis and incorporation. The difficulty in the synthesis of the starting materials represents the major limitation of the recently reported tetrazine norbornene *click* reaction as well.[35] The ultimate goal is to develop a methodology where one

can first synthesize a polymer with common reagents and subsequently employ this polymer with no further functionalization and efficiently carry out further conjugation without catalyst in biologically relevant media. Such an achievement would represent a major step forward in the field of polymer (bio)conjugation.

6.2 Experimental Section

The hexadiene-1-ol derivative (**7**)[36], 3-O-acryloyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside (AIpGlc)[37], benzylpyridin-2-yl dithioformate (BPDF)[38] and 2-cyanoprop-2-yl diethoxyphosphoryldithioformate[39] were synthesized according to the literature.

Synthesis of tosylated poly(ethylene glycol) monomethyl ether (PEG-OTs)

NaOH (1.4 g) was dissolved in 7.5 mL of H_2O. A solution of poly(ethylene glycol) monomethyl ether (4.00 g, 2.00 mmol) in 10 mL THF was subsequently added. The resulting mixture was cooled in an ice bath. A solution of *p*-toluenesulfonyl chloride (3.82 g, 20.0 mmol) in 6 mL THF was added. The mixture was stirred overnight at ambient temperature. The mixture was extracted with CH_2Cl_2 and the organic phases were combined and washed three times with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Precipitation in cold diethyl ether yielded a white solid.

Synthesis of cyclopentadienyl functionalized poly(ethylene glycol) monomethyl ether (PEG-Cp)

PEG-OTs (800 mg, 0.37 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C. To this solution 3 equivalents sodium cyclopentadienide solution (2.0 M in THF) (0.56 mL, 1.11 mmol) were slowly added. The mixture was then stirred at 0 °C for 30 min and subsequently overnight at ambient temperature. The resulting mixture was then poured into a saturated NH_4Cl solution and extracted with dichloromethane. The organic phase was washed once with water, dried over $MgSO_4$ and concentrated to a volume of 10 mL. Precipitation in cold diethyl ether yielded a brown solid.

Synthesis of open chain diene functionalized poly(ethylene glycol) monomethyl ether

Poly(ethylene glycol) monomethyl ether (2.00 g, 1.00 mmol), 4-dimethylaminopyridine (7.0 mg, 0.6 mmol) and **7** (595 mg, 3.00 mmol) were dissolved in 10 mL dry CH_2Cl_2. A solution of DCC (619 mg, 3.00 mmol) in 2 mL dry CH_2Cl_2 was added and the reaction mixture stirred overnight at ambient temperature. The solution was filtered and the polymer was precipitated in cold diethyl ether to give a white solid.

RAFT polymerization of 2-hydroxyethyl acrylate

A solution of 2-cyanoprop-2-yl diethoxyphosphoryldithioformate (329 mg, 1.17 mmol), AIBN (95 mg, 0.58 mmol) and 2-hydroxyethyl acrylate (20 mL, 174 mmol) in ethanol (20 mL) was deoxygenated by purging with nitrogen for 30 min. The polymerization reactions were performed at 60 °C for 4.5 h (**1a**) and 6 h (**1b**), respectively. The reactions were stopped by chilling in an ice bath and exposure to oxygen. The resulting poly(2-hydroxyethyl acrylate)s were isolated by repeated precipitations in cold diethyl ether. **1a**: $M_{n,SEC}$ = 2700 g·mol^{-1}, *PDI* = 1.13; **1b**: $M_{n,SEC}$ = 3500 g·mol^{-1}, *PDI* = 1.13.

RAFT polymerization of AIpGlc and deprotection to PAGlc

A solution of AIBN (12.4 mg, 0.075 mmol), BPDF (62.4 mg, 0.25 mmol) and the protected glycomonomer AIpGlc (4.00 g, 12.73 mmol) in toluene (1 mol·L^{-1} according to the glycomonomer) was deoxygenated by three consecutive freeze-pump-thaw cycles. The flask was placed into a preheated oil-bath at 75 °C for 4 h. The reaction was stopped by cooling in an ice-bath and exposing the reaction mixture to oxygen. The solvent was removed in vacuo and the solid residue employed without further purification.

The raw glycopolymer (poly(3-O-acryloyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside) (PAIpGlc) (1.16 g) was dissolved in 80% formic acid (70 mL) and stirred at room temperature for 48 hours. After the addition of water (15 mL) the reaction was stirred for additional 3 hours. Approximately half of the solvent was removed in vacuo and the remaining solution dialyzed against distilled water employing a SpectraPor3 membrane (MWCO = 1000 Da). After lyophilization poly(3-O-acryloyl-α,β-D-glucopyranoside) (PAGlc) (151 mg) was isolated as a slightly pink solid.

Cycloaddition reactions of PHEA and Cyclopentadiene or *trans,trans*-2,4-hexadien-1-ol

Cyclopentadiene (50 µmol) or *trans,trans*-2,4-hexadien-1-ol (50 µmol) was added to a solution of PHEA (**1a**) (10 µmol) in 0.2 mL distilled water and the mixture was stirred for 60 min at ambient temperature. The solvent was subsequently removed under vacuum at ambient temperature. The residue was dissolved in THF and analyzed by SEC/ESI-MS. For NMR analysis the aqueous mixture was extracted four times with diethyl ether to remove unreacted diene.

Cycloaddition reaction of PHEA and PEG-Cp

A solution of PHEA (10 µmol) and PEG-Cp (10 µmol) in 0.2 mL distilled water was stirred for 15 minutes. The solvent was subsequently removed under vacuum at ambient temperature and the residue analyzed by SEC in THF. For NMR analysis the reaction was carried out in D_2O without removal of the solvent.

Cycloaddition reaction of PHEA and PEG-OCD

A solution of PHEA (10 µmol) and PEG-OCD (10 µmol) in 0.2 mL distilled water was stirred for 4 h. The solvent was subsequently removed under vacuum at ambient temperature and the residue analyzed by SEC in THF. For NMR analysis the reaction was carried out in D_2O without removal of the solvent.

Cycloaddition reaction of PAGlc and PEG-Cp

A solution of PAGlc (10 µmol) and PEG-Cp (10 µmol) in 0.2 mL 0.01 M aqueous HCl was stirred for 15 min. The solvent was subsequently removed under vacuum at ambient temperature and the residue analyzed by SEC in DMAc containing 0.3 wt% LiBr.

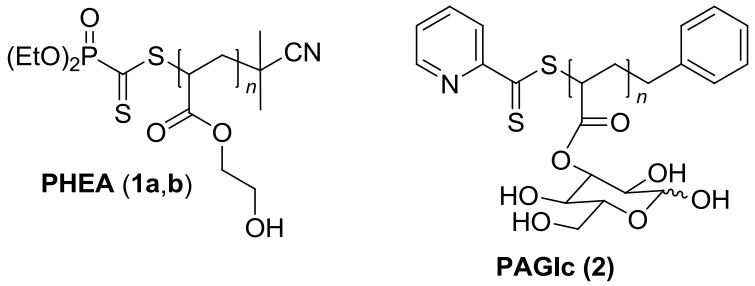
Kinetic monitoring by UV/Vis spectroscopy

A solution of PEG-Cp or PEG-OCD in distilled water was added to a stirred solution of PHEA (**1b**) in distilled water such that the overall concentration of each polymer was 0.01 $mol \cdot L^{-1}$ and the measurement started immediately. The temperature was maintained at 293 K over the reaction time. The raw data were normalized to give a relative absorbance of 1 at the reaction start and 0 after the reaction had ended.

6.3 Results and Discussion

Herein, the aqueous modular ligation of poly(hydroxyethyl acrylate) and poly(glucopyranosyl acrylate) synthesized with classical RAFT-HDA agents without the need for a post-functionalization method is presented. The ability of these agents to control the polymerization is demonstrated. The potential of these as-formed polymers for subsequent efficient conjugations in aqueous environments with no catalyst is demonstrated through their (ultra-)fast and stoichiometric reactions with diene-functionalized poly(ethylene glycol)s (PEGs).

To demonstrate the possibility of RAFT-HDA cycloadditions in aqueous solution, water soluble poly(2-hydroxyethyl acrylate), PHEA (**1a,b**) was prepared employing 2-cyanoprop-2-yl diethoxyphosphoryldithioformate as chain transfer agent (Scheme 6.1).



Scheme 6.1 Polymers prepared by RAFT polymerization serving as dienophiles in the RAFT-HDA reaction. **1a** and **1b** represent poly(2-hydroxyethyl acrylate)s of different molecular weights.

Addition of an excess cyclopentadiene to an aqueous solution of **1a** resulted in an instantaneous discoloration indicating the consumption of the dithioester end-group. Figure 6.1 depicts the monitoring of the reaction by size exclusion chromatography/electrospray-ionization-mass spectrometry (SEC/ESI-MS). A shift of the main distribution of 66 amu reveals the cycloaddition of cyclopentadiene (M = 66.05 Da). A series of signals of lower intensity shows an equal shift to higher m/z-values. These signals correspond to the incorporation of one repeat unit of ethylene glycol diacrylate (EGDA) which is formed from HEA by transesterification (see Figure 6.2 for structures and a zoom into one repeat unit). Signals corresponding to **1a** in the product spectrum do not necessarily indicate incomplete conversion. Previous MS-MS investigations[16] and the fact that the cycloadition reaction can be quantitatively reversed at 90 °C[20] suggest that their occurrence can be explained by a retro-HDA reaction under ESI-MS conditions (capillary temperature 315 °C, see Chapter 9.2).

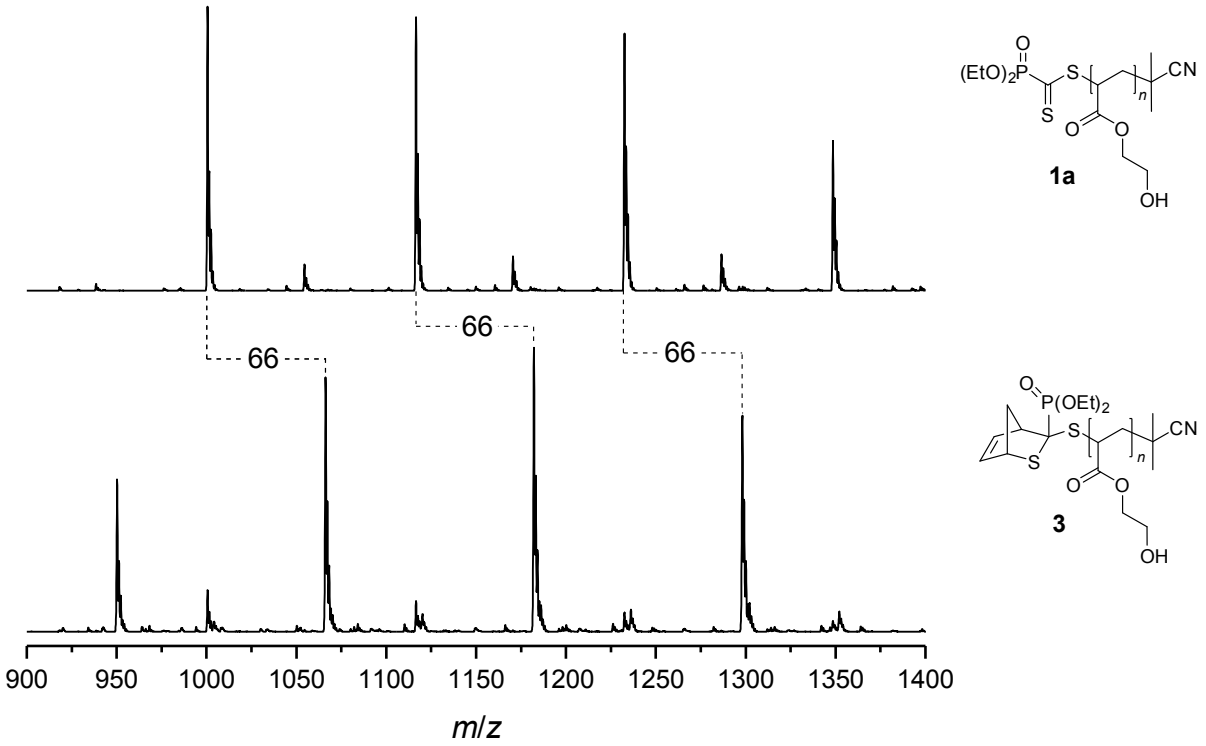


Figure 6.1 SEC/ESI-MS spectra of PHEA (**1a**) prior to (top) and after (bottom) reaction with cyclopentadiene.

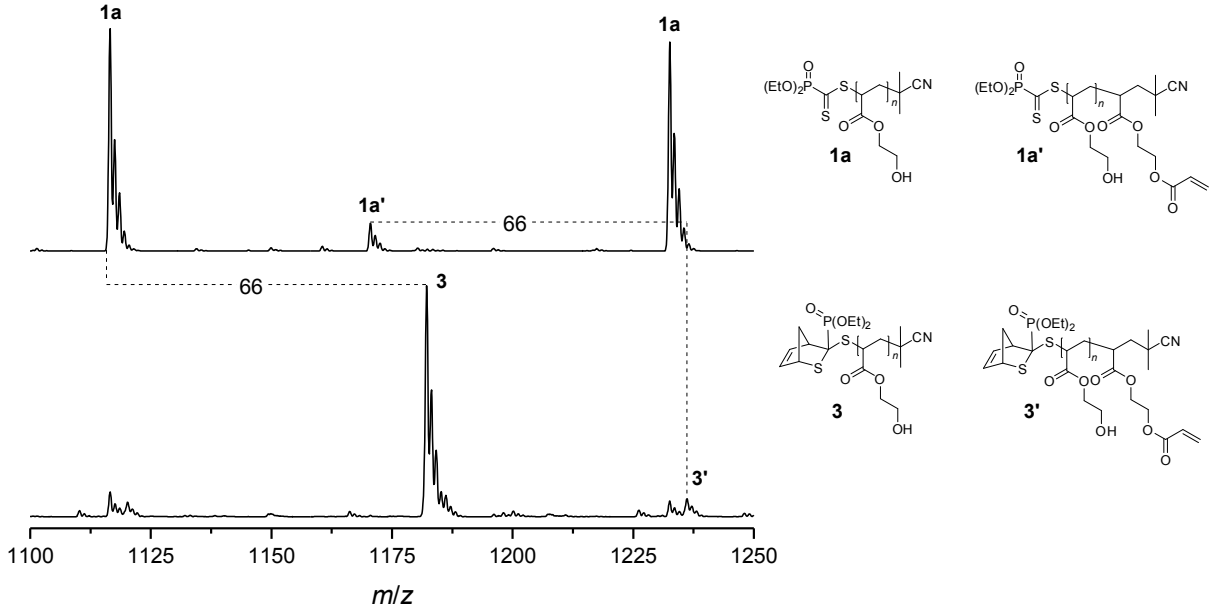


Figure 6.2 Zoom into the SEC/ESI-MS spectra of PHEA (**1a**) prior to (top) and after (bottom) reaction with cyclopentadiene.

It was demonstrated in previous publications that diethoxyphosphoryl dithioester functionalized polymers react with *trans,trans*-2,4-hexadien-1-ol based open-chain

dienes in a quantitative fashion at elevated temperatures (50 °C) in the presence of $ZnCl_2$ in chloroform solution.[16] The drastic acceleration of many (hetero-)Diels-Alder reactions in aqueous media compared to organic solvents[24] encouraged us to investigate the ability of **1a** to react with *trans,trans*-2,4-hexadien-1-ol in water at ambient temperature. The SEC/ESI-MS spectra in Figure 6.3 and Figure 6.4 prove that quantitative conversion was achieved without a catalyst employing water as reaction medium. The achievement of RAFT-HDA conjugations at ambient temperature employing open-chain dienes represents a major advancement of the concept. Functionalization of molecules with a hexadienoyl moiety is straightforward in contrast to the incorporation of a cyclopentadienyl group which can undergo self-dimerization.

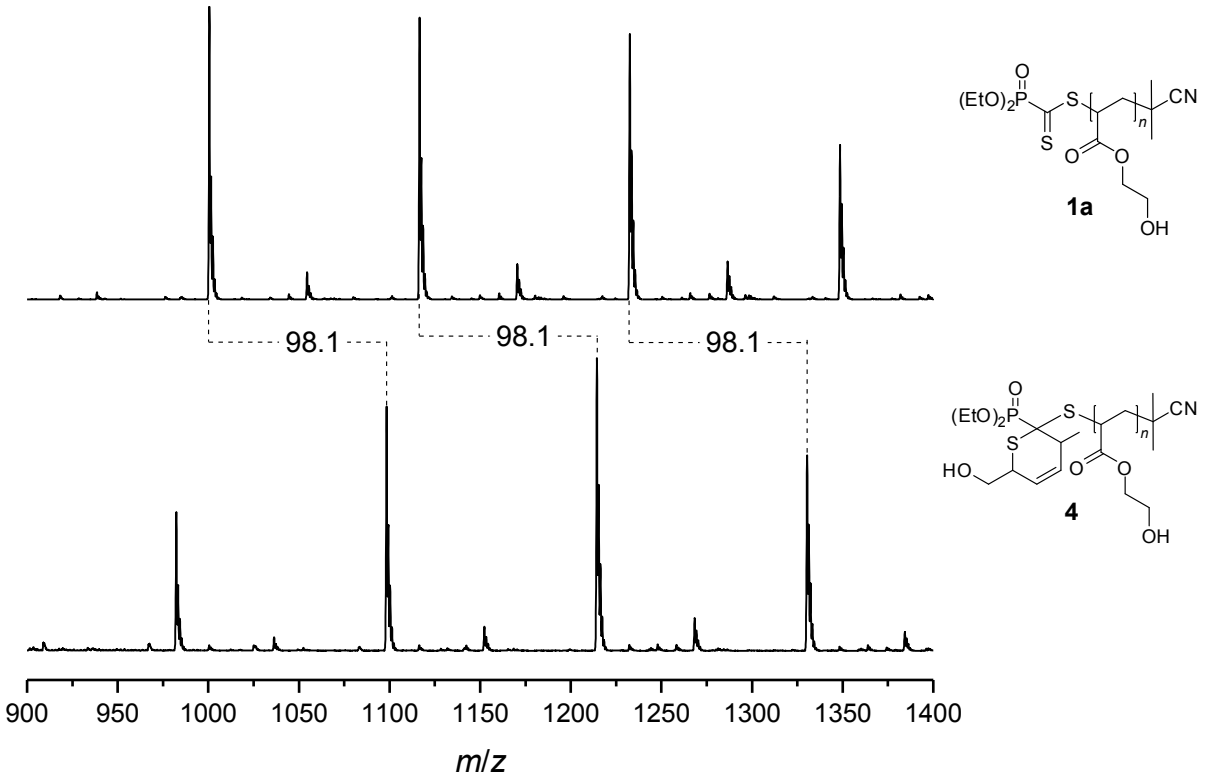


Figure 6.3 SEC/ESI-MS spectra of PHEA (**1a**) prior to (top) and after (bottom) reaction with *trans,trans*-2,4-hexadien-1-ol in water at ambient temperature.

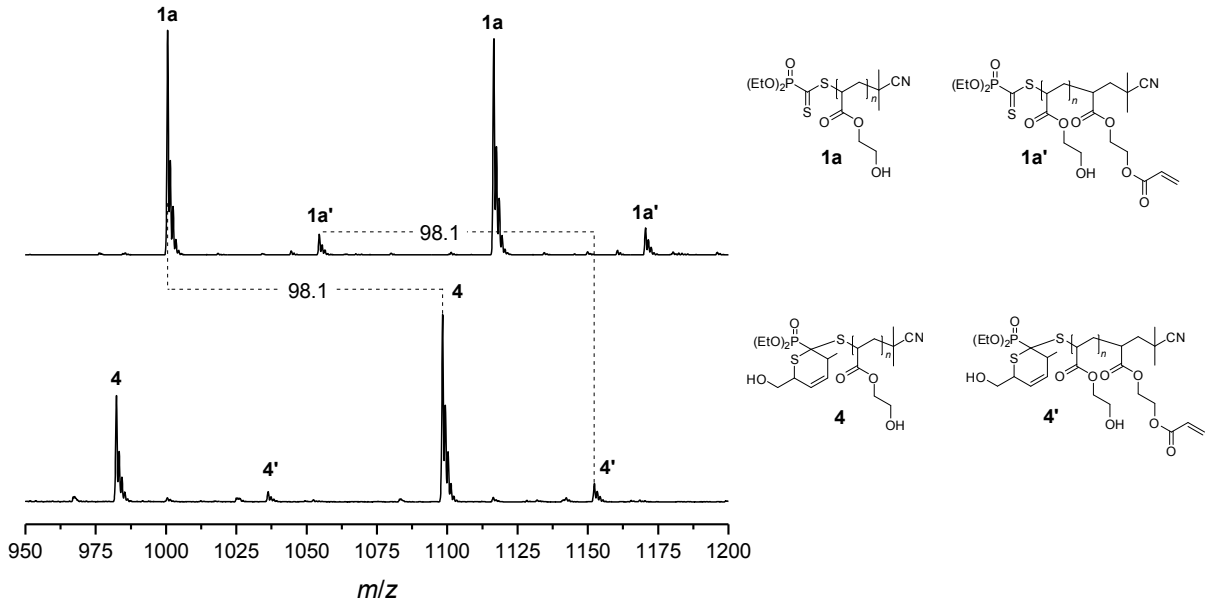


Figure 6.4 Zoom into the SEC/ESI-MS spectra of PHEA (**1a**) prior to (top) and after (bottom) reaction with *trans,trans*-2,4-hexadien-1-ol in water at ambient temperature.

Theoretical and measured m/z-ratios of the individual peaks are in good agreement and are listed in Table 6.1.

Table 6.1 Theoretical and measured m/z ratios oft the species involved in the transformations of Figure 6.2 and Figure 6.4.

Structure	Formula	m/z^{theo}	m/z^{meas}	$\Delta\, m/z$
1a	$[C_{44}H_{72}NO_{24}PS_2Na]^+$	1116.35	1116.42	0.07
1a′	$[C_{47}H_{74}NO_{25}PS_2Na]^+$	1170.36	1170.42	0.06
3	$[C_{49}H_{78}NO_{24}PS_2Na]^+$	1182.40	1182.33	0.07
3′	$[C_{52}H_{80}NO_{25}PS_2Na]^+$	1236.41	1236.33	0.08
4	$[C_{45}H_{74}NO_{22}PS_2Na]^+$	1098.38	1098.42	0.04
4′	$[C_{45}H_{74}NO_{22}PS_2Na]^+$	1152.39	1152.33	0.06

Further confirmation for the assigned structures is provided by ^{1}H-NMR spectroscopy (Figure 6.5). In the case of cyclopentadiene employed as the diene two new signals (e+d) between 6.0–6.1 ppm and 6.4–6.6 ppm can be assigned to the protons of the olefinic double bond of the cycloadduct **3**.[40]

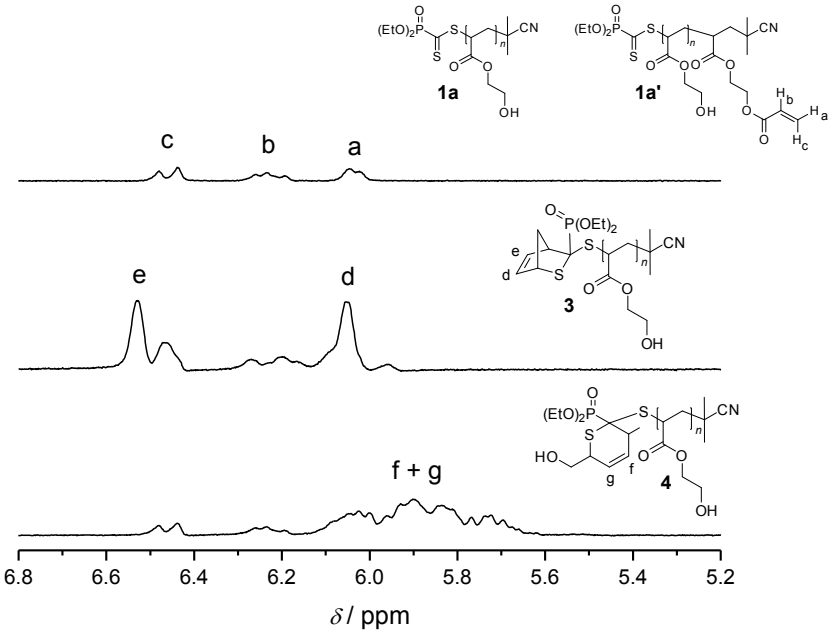
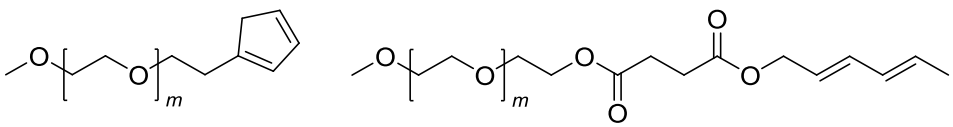


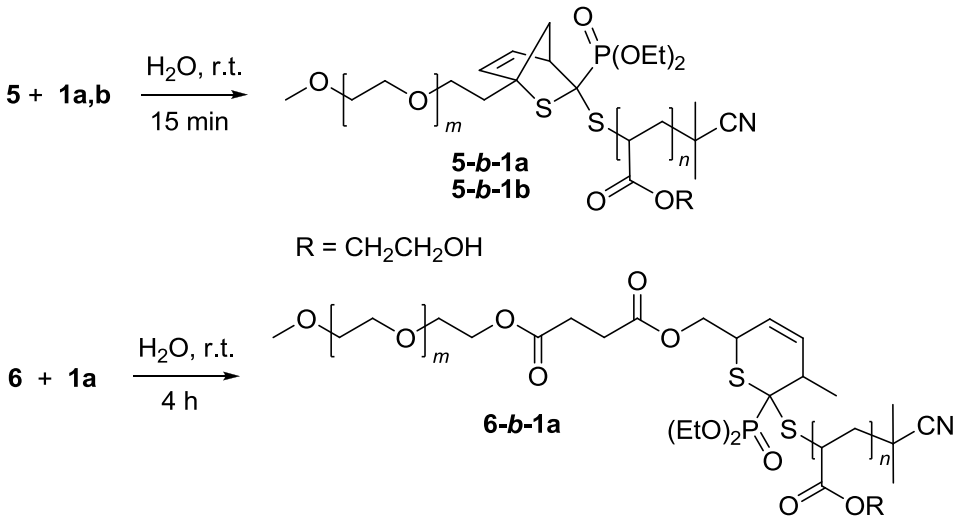
Figure 6.5 Partial ^{1}H-NMR spectra of PHEA prior to (top) and after reaction with cyclopentadiene (middle) and *trans,trans*-2,4-hexadien-1-ol (bottom) in water at ambient temperature. See Figure 6.16 in the Appendix for full spectra.

The formation of a 3,6-dihydro-2*H*-thiopyran ring using *trans,trans*-2,4-hexadien-1-ol as diene, is indicated by the occurrence of a multiplet between 5.6–6.1 ppm arising from the olefinic protons (f+g) of different stereo/regioisomers of the cycloadduct **4**.[16] It should be noted that the product signals partially overlap with three signals (a+b+c) originating from the acrylic double bond of the PHEA species **1a'** with a EGDA repeat unit.

To explore the possibility of polymer-polymer conjugations in water, two poly(ethylene glycol)s bearing appropriate end-groups (Scheme 6.2) were employed as dienes in the HDA reactions displayed in Scheme 6.3. Importantly, no purification step was performed after the coupling reactions.



Scheme 6.2 Cylopentadienyl (**5**) and hexadienoyl (**6**) functionalized poly(ethylene glycol)s. ^{1}H-NMR and SEC/ESI-MS spectra can be found in the Appendix (Figure 6.14 and Figure 6.15).



Scheme 6.3 Formation of block copolymers by HDA cycloaddition in water at ambient temperature.

The progress of the coupling reaction can be monitored by UV/Vis spectroscopy utilizing the strong absorbance at 327 nm caused by an allowed $\pi \rightarrow \pi^*$ transition of the terminal dithioester (See Figure 6.6a for a UV/Vis spectrum of PHEA **1b**).

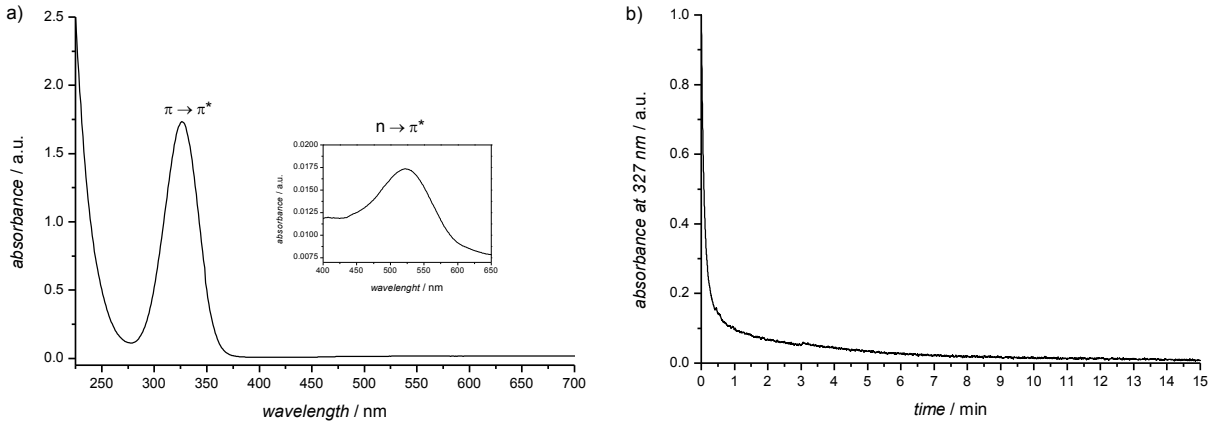


Figure 6.6 a) UV/Vis spectrum of PHEA (**1b**) in water (0.01 mol·l^{-1}). The inset shows a zoom into the region of the $n \rightarrow \pi^*$ transition of a sample at higher concentration (0.03 mol·l^{-1}). b) UV/Vis monitoring of the HDA coupling of PHEA (**1b**) and PEG-Cp (**5**) in equimolar ratios in water at ambient temperature. The decrease of the absorbance at 327 nm is associated with the polymer-polymer conjugation.

UV/Vis monitoring of the HDA coupling confirms that utilizing PEG-Cp (**5**) as diene enables quantitative polymer conjugation within 15 min (Figure 6.6b). Thus, the reaction proceeds in an equally fast manner as in chloroform solution.[18] Although inspection of Figure 6.7 indicates that the cycloaddition is significantly slower with PEG-OCD (**6**) as the diene, block copolymer formation is achieved in a remarkably

short reaction time of 4 h and thus even faster as in organic media at 50 °C in the presence of $ZnCl_2$ as catalyst.[16]

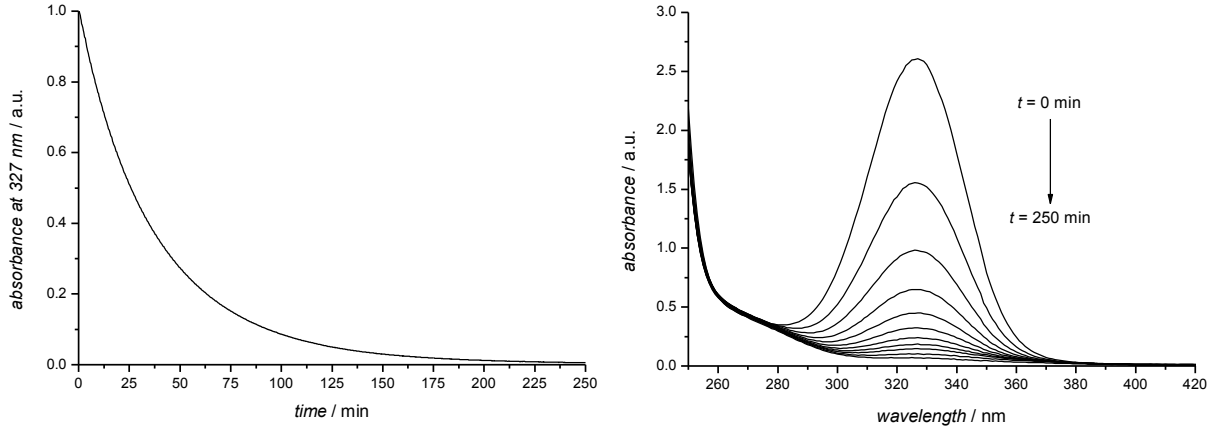


Figure 6.7 UV/Vis monitoring of the HDA coupling of PHEA (**1b**) and PEG-OCD (**6**) in equimolar ratios in water at ambient temperature. The decrease of the absorbance at 327 nm is associated with the polymer-polymer conjugation. The evolution of the UV/Vis spectra with reaction time is shown on the right.

To further investigate the coupling efficiency, an equimolar solution of PHEA (**1a**) and PEG-OCD (**6**) in water was stirred for 4 h at ambient temperature. The solvent was removed in vacuo and the residue analyzed by SEC as depicted in Figure 6.8.

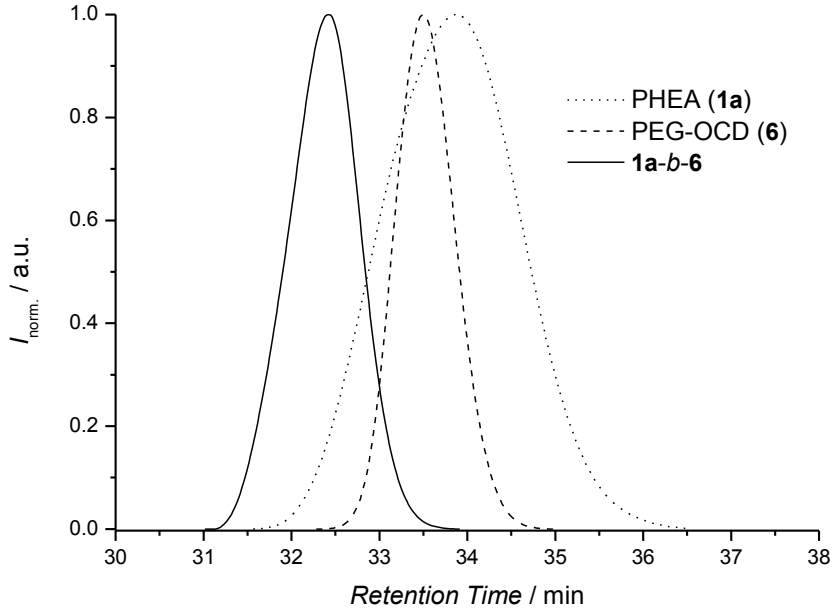


Figure 6.8 Overlay of SEC traces (THF) showing the formation of **1a**-*b*-**6** from PHEA (**1a**) and PEG-OCD (**6**) in water at ambient temperature. Refer to Table 6.2 for the molecular weight averages associated with the depicted distributions.

A clear shift to lower retention times indicates the successful block copolymer formation. The *click* product displays a unimodal distribution without any tail or shoulder associated with the starting materials. When PEG-Cp is employed as diene block copolymer formation is achieved within 15 min as can be seen from the SEC traces in Figure 6.9.

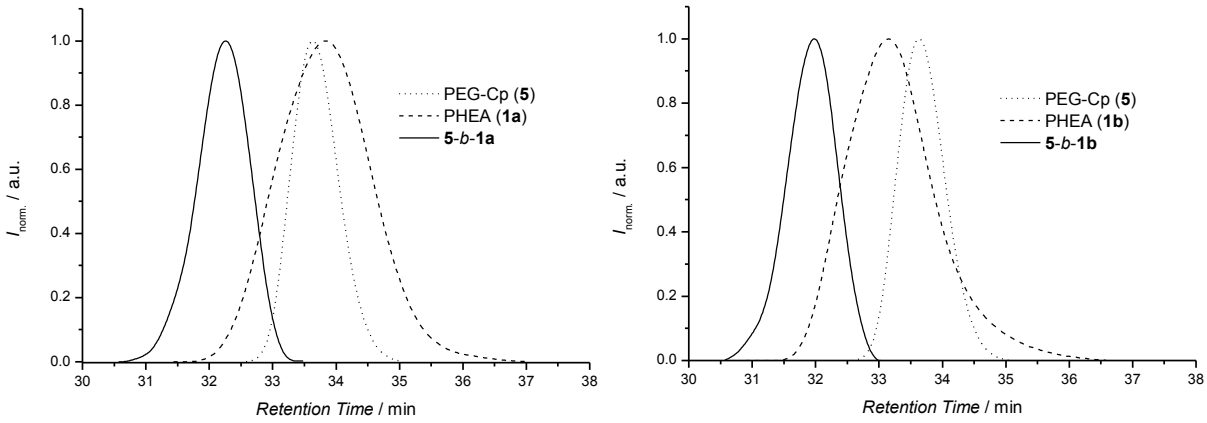


Figure 6.9 Overlay of SEC traces showing the formation of **5**-*b*-**1a** and **5**-*b*-**1b** from PEG-Cp (**5**) and PHEA (**1a,b**). Refer to Table 6.2 for the molecular weight averages associated with the depicted distributions.

Table 6.2 SEC characterization data of all polymers.

Polymer	$M_{n,SEC}$ / g·mol^{-1}	*PDI*
1a	2700[a]	1.13
1b	3500[a]	1.13
2	6400[b]	1.14
5	3000[a]/5000[b]	1.04
6	3200[a]	1.04
5-*b*-**1a**	5900[a]	1.05
5-*b*-**1b**	6700[a]	1.05
6-*b*-**1a**	5500[a]	1.05
5-*b*-**2**	13600[b]	1.11

[a]THF, [b]DMAc + 0.3 wt% LiBr; relative to linear PS standards

In addition, ^{1}H-NMR analysis provides unambiguous evidence for the generation of a new C=C double bond associated with the formation of the HDA cycloadduct (Figure 6.10 signals d+c and Figure 6.11 signals e+f).

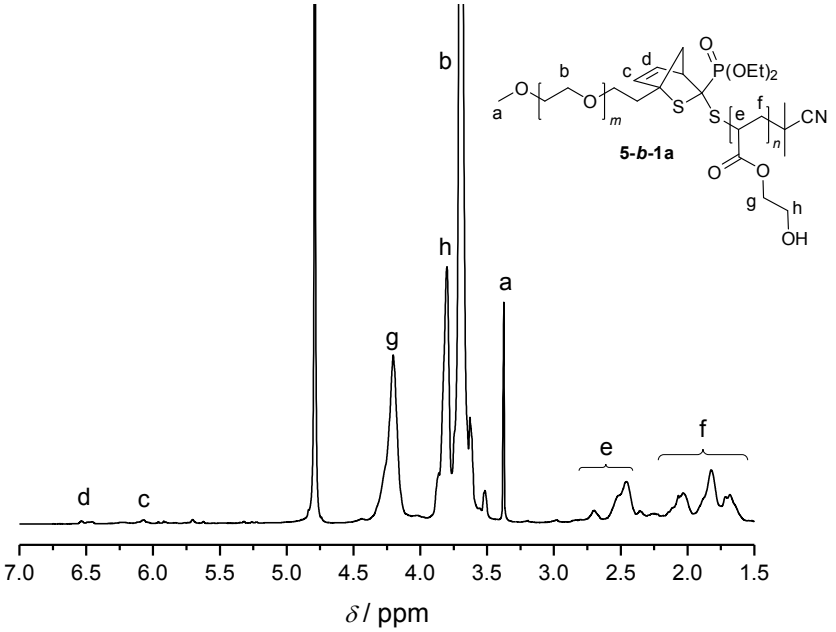


Figure 6.10 ^{1}H-NMR spectrum of **5**-*b*-**1a** in D_2O.

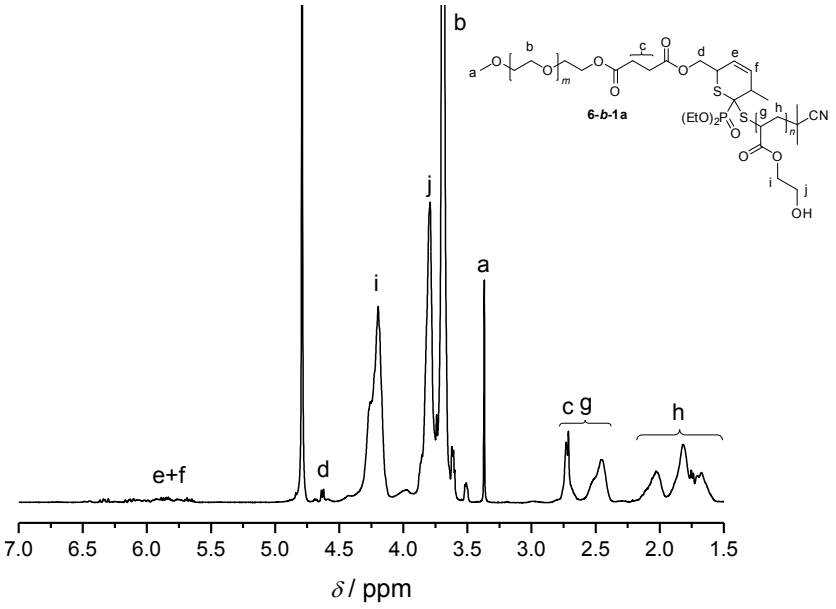
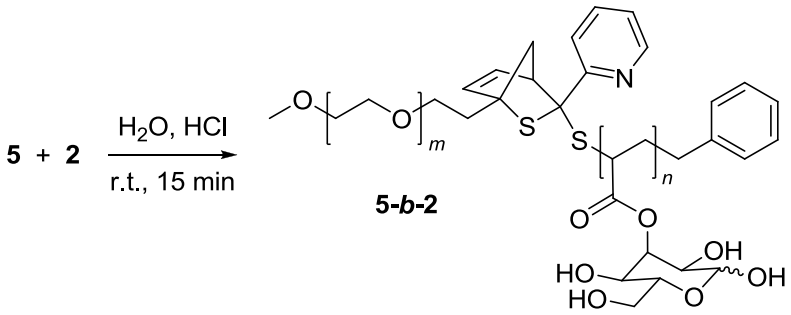


Figure 6.11 ^{1}H-NMR spectrum of **6**-*b*-**1a** in D_2O.

To further expand the scope of RAFT-HDA conjugation in aqueous solution we investigated the utilization of the glycopolymer poly(3-*O*-acryloyl-α,β-D-glucopyranoside) (PAGlc, **2**) (Scheme 6.1) as dienophile. Glycopolymers represent a valuable class of water-soluble polymers due to their biocompatibility and the ability to form specific binding interactions with biomolecules.[41] The HDA ligation with PEG-Cp (Scheme 6.4) was carried out in a 0.01 M aqueous HCl solution as the pyridinyl dithioester end-group must be activated by protonation.



Scheme 6.4 Formation of PEG-*b*-PAGlc by HDA cycloaddition in aqueous HCl at ambient temperature.

The SEC trace of the coupling product after 15 min reaction time shows a clear shift to lower retention times compared to the individual building blocks (Figure 6.12) indicating the quantitative formation of the desired block copolymer.

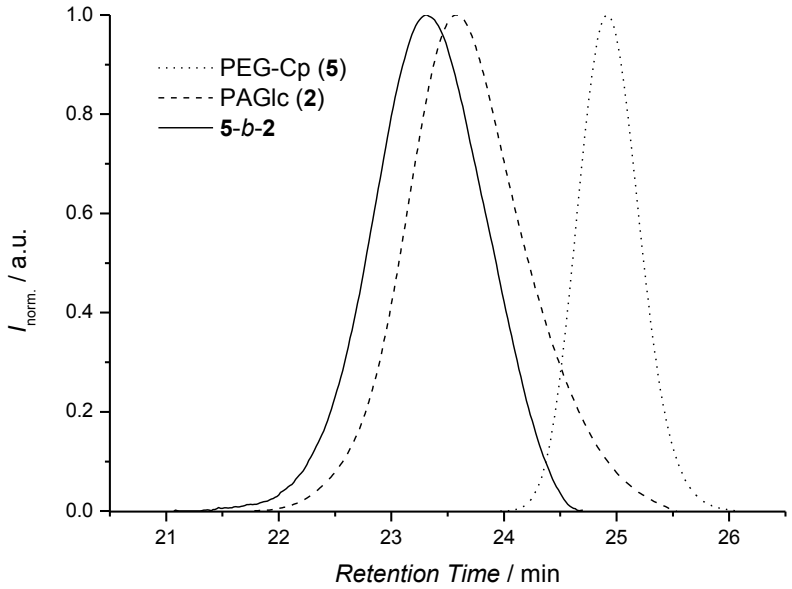


Figure 6.12 Overlay of SEC traces (DMAc) showing the formation of **5**-*b*-**2** from PEG-Cp (**5**) and PAGcl (**2**) in 0.01 M aqueous HCl at ambient temperature. Refer to Table 6.2 for the molecular weight averages associated with the SEC data.

6.4 Conclusions

In summary, it was demonstrated that the HDA cycloaddition of RAFT polymers permits an efficient and rapid conjugation in aqueous solution at ambient temperature without the need of a catalyst. The effect of water as solvent enables for the first time the use of open-chain dienes at ambient temperature within the RAFT-HDA concept. These findings pave the way for the application of RAFT-HDA as a tool for protein functionalization.

Appendix

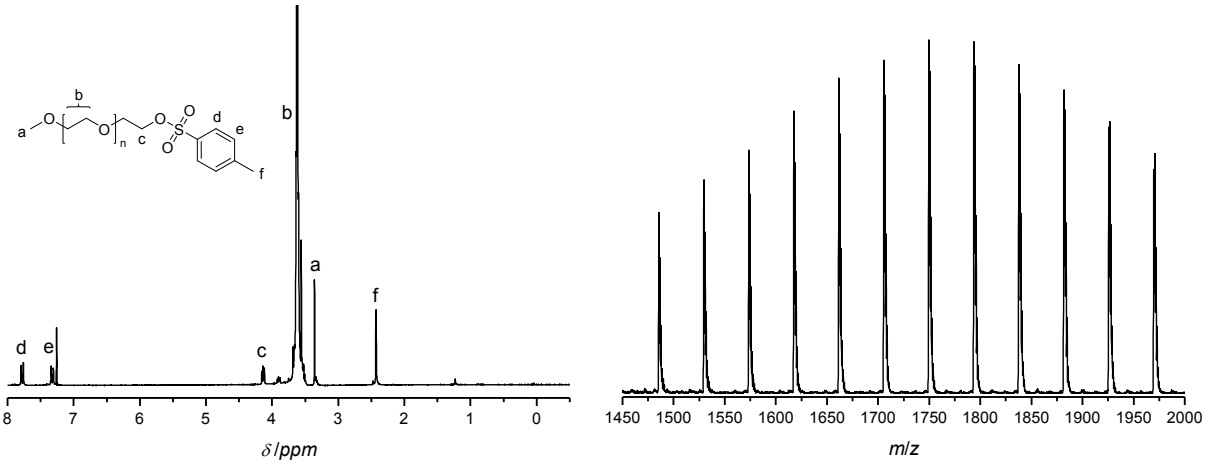


Figure 6.13 ^{1}H-NMR (left) and SEC/ESI-MS spectrum (right) of PEG-OTs.

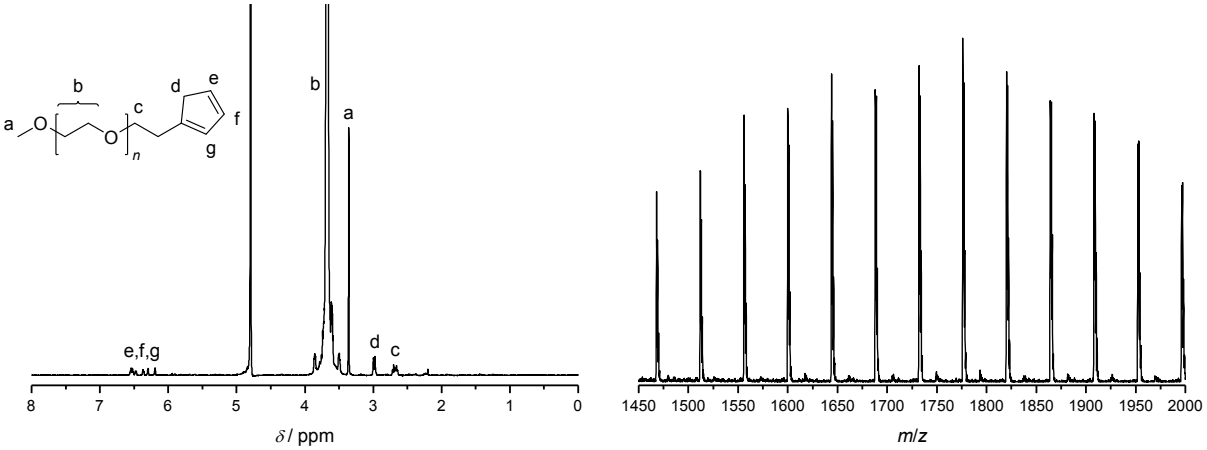


Figure 6.14 ^{1}H-NMR (left) and SEC/ESI-MS spectrum (right) of PEG-Cp.

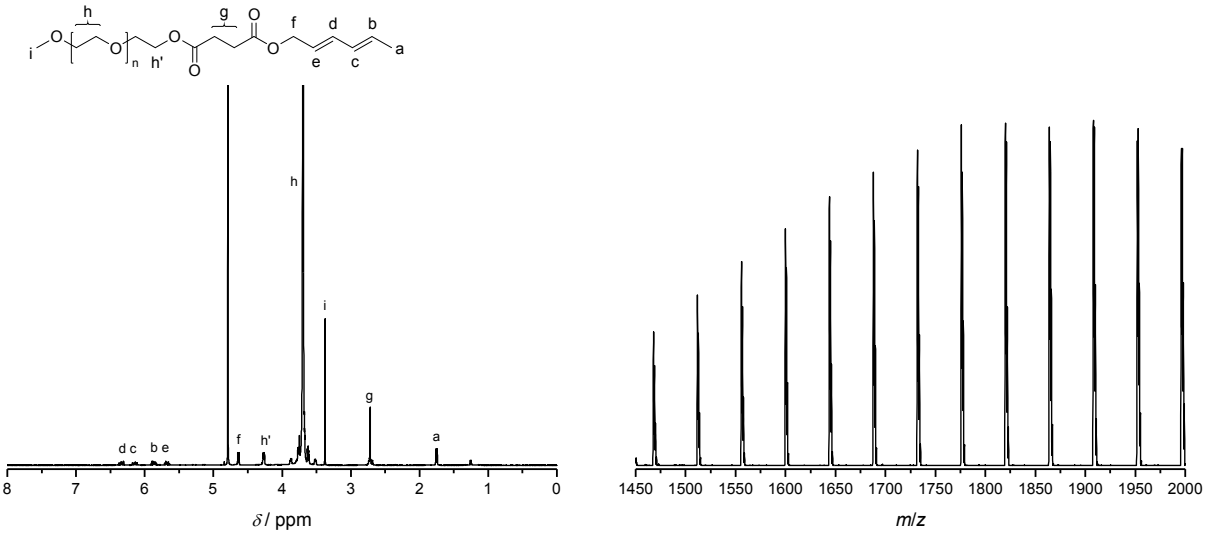


Figure 6.15 ^{1}H-NMR (left) and SEC/ESI-MS spectrum (right) of PEG-OCD.

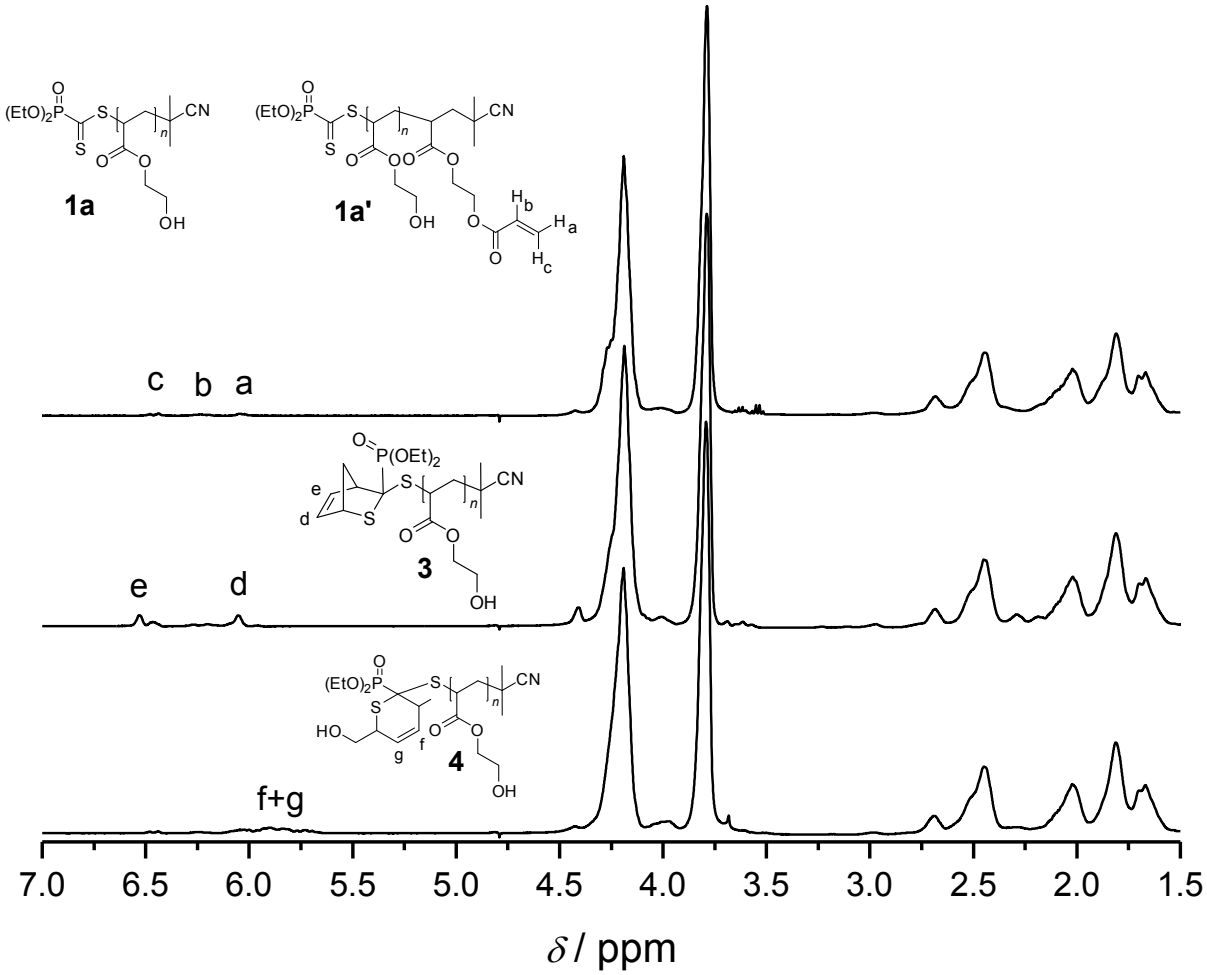


Figure 6.16 Full overview spectra oft the ^{1}H-NMR spectra of Figure 6.5.

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7

Formation of Nanoporous Materials via Mild Retro-Diels-Alder Chemistry

7.1 Introduction

Materials which contain nanoporous architectures have received remarkable attention because of their attractive applications as membranes, sensors and in catalysis.[1-3] One technique for the generation of nanoporous materials is to commence with an amphiphilic block copolymer which undergoes phase separation and to subsequently remove one block preferentially.

Currently, the most common methodology employed for this removal is the destruction of one block via ozonolysis,[4-5] UV degradation,[6-8] reactive ion etching[9] or chemical etching.[10-15] However, these techniques are limited to a few systems as several polymers undergo side chain hydrolysis or degradation under such harsh conditions. A strategy that avoids possible degradation problems is the introduction of a labile linker between two blocks with differing solubilities that can be cleaved under mild reaction conditions. Such an approach allows one block to be removed by a simple washing process once cleavage has taken place. Additionally, a judicious choice of juncture and cleavage conditions can produce pore walls that bear reactive functional groups which provide access to further chemical transformations.[11, 16-17] Penelle *et al*. prepared poly(styrene)-*block*-poly(methyl methacrylate) copolymers with a [4+4] anthracene photodimer at the junction that could be cleaved either photolytically or thermally.[18] Poly(styrene)-*block*-poly(ethylene oxide) (PS-*b*-PEO) linked with a thermally-labile alkoxyamine between the PS and PEO segments was also prepared via free radical polymerization of styrene utilizing a TEMPO functionalized PEO block.[19] PS-*b*-PEO is the most frequently used block copolymer for the preparation of nanoporous thin films, because simple solvent-annealing leads to highly ordered arrays of PEO cylinders oriented normal to the surface.[20] PS-*b*-PEO block copolymers with various linkers have been employed for the construction of nanoporous thin films including an acid-sensitive trityl ether,[21] a photo-cleavable

ortho-nitrobenzyl moiety,[17, 22] an imine linkage that can be cleaved with an acid[23] and a disulfide bond that undergoes scission upon exposure to a redox stimuli.[24]

A simple approach for the synthesis of various block copolymers is the conjugation of end-group functionalized macromolecular blocks via efficient coupling reactions as discussed in Chapter 2. One reaction that has been used for such coupling is the hetero Diels-Alder (HDA) reaction between a diene end-functionalized polymer and the electron deficient dithioester end-group of a polymer synthesized by reversible addition fragmentation chain transfer (RAFT) polymerization.[25-27] Copolymers formed via the RAFT-HDA methodology have the added advantage that the thiopyran linkage has been shown to be reversible, undergoing a retro-Diels-Alder (rDA) reaction upon thermal treatment in solution.[26, 28] However, the open-chain diene employed in ref. [28] required temperatures above 120 °C at which point the released dithioesters were unstable and underwent rapid degradation. Recently, it was shown that the use of more reactive cyclopentadienyl functional polymers also resulted in a reduction in the required temperature (ca. 80-90 °C) for the rDA reaction to take place.[29]

7.2 Experimental Section

Synthesis of α-Methoxy-ω-toluenesulfonyl-PEO

NaOH (1.4 g, 35 mmol) was dissolved in 7.5 mL of H_2O. A solution of poly(ethylene oxide) monomethyl ether (10.0 g, 2.0 mmol) in 12 mL THF was subsequently added. The resulting mixture was cooled in an ice bath. To this a solution of *p*-toluenesulfonyl chloride (4.3 g, 23 mmol) in 6 mL THF was added. The mixture was stirred overnight at ambient temperature. The mixture was extracted with CH_2Cl_2 and the organic phases were combined and washed three times with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Precipitation in cold diethyl ether yielded a white solid (9.41 g, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 2.45 (s, CH_3-C_6H_5), 3.38 (s, CH_3-O), 4.15 (t, CH_2-CH_2-OTs), 7.36 (m, arom), 7.81 (m, arom).

Synthesis of α-methoxy-ω-cyclopentadienyl-PEO (1)

A solution of α-methoxy-ω-toluenesulfonyl-PEO (1.8 mmol), triphenylphosphine (3.6 mmol, 2 eq.) and sodium iodide (10.8 mmol, 6 eq.) in anhydrous THF (20 mL)

was prepared under a nitrogen atmosphere. Separately, a stock solution of $NiCp_2$ in anhydrous THF (0.36 mol·L^{-1}) was prepared under a nitrogen atmosphere. The $NiCp_2$ solution (10 mL, 4 eq.) was subsequently added to the polymer solution and allowed to stir 70 h at 40 °C. The mixture was extracted with CH_2Cl_2 and the CH_2Cl_2 phase was washed three times with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated. PEO (**1**) was isolated by repeated precipitations in cold diethyl ether (yield 76 %). ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 2.71 (m, CH_2-C_5H_5), 2.95 (m, bridge head), 3.38 (s, H_3C-O-), 6.47–6.08 (m, C_5H_5, vinylic).

Synthesis of Poly(styrene) (2a,b)

A solution of BPDF (14.6 mmol·L^{-1}) and AIBN (2.4 mmol·L^{-1}) in styrene (30 mL) was deoxygenated by purging with nitrogen for 30 min. The polymerization reactions were performed at 60 °C for 10 h (**2a**) and 20 h (**2b**), respectively. The reactions were stopped by chilling in an ice bath and exposure to oxygen. The resulting poly(styrene)s were isolated by two-fold precipitation in cold methanol. **2a**: $M_{n,SEC}$ = 10600 g·mol^{-1}, PDI_{SEC} = 1.14; **2b**: $M_{n,SEC}$ = 18500 g·mol^{-1}, PDI_{SEC} = 1.12

Synthesis of PS-*b*-PEO (3a,b)

Cyclopentadienyl terminated PEO (**1**) (50 μmol) and dithioester capped PS (**2a,b**) (50 μmol) were dissolved in 10 mL $CHCl_3$. After the addition of 1.5 equivalents TFA, the mixture was stirred for 2 h at ambient temperature. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent removed in vacuo. The solid residue was extracted with diethyl ether to remove any residual homo-PS, redissolved in $CHCl_3$ and precipitated in cold methanol to give PS-*b*-PEO (**3a,b**) as light brown solid. **3a**: $M_{n,SEC}$ = 16900 g·mol^{-1}, PDI_{SEC} = 1.6; M_n (PS)/M_n (PEO) = 1.9 calculated by ^{1}H-NMR integration. **3b**: $M_{n,SEC}$ = 24100 g·mol^{-1}, PDI_{SEC} = 1.11, M_n (PS)/M_n (PEO) = 3.2 calculated by ^{1}H-NMR integration.

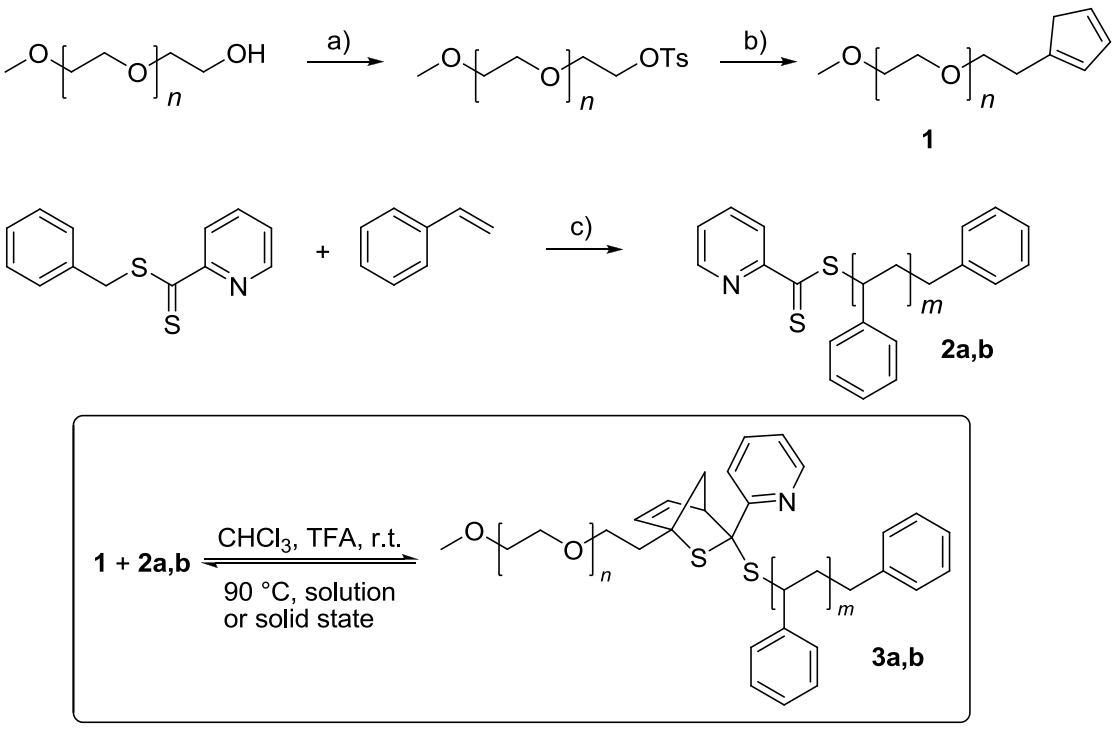
Film Casting

PS-*b*-PEO films were drop-cast onto silicon wafers from a 2 wt.% solution in chloroform. After drying under vacuum, the films were heated at 90 °C for 15 h, washed with water to remove the PEO and dried again under vacuum. The cross-section was prepared by fracturing the sample immediately after submerging in liquid nitrogen.

7.3 Results and Discussion

Herein, the synthesis of PS-*b*-PEO copolymers via the RAFT-HDA approach which can subsequently undergo a quantitative cleavage into the constituent blocks in the solid state under mild heating conditions is described. It is further demonstrated that nanoporous polystyrene films can be prepared from these copolymers after the rDA reaction, as the PEO segments can easily be removed by washing the films with water.

The synthetic pathway for both blocks and the HDA conjugation is depicted in Scheme 7.1. Cyclopentadienyl (Cp) functionalized PEO **1** was synthesized by tosylation of monomethylated PEO followed by conversion into the Cp functionalized polymer using the recently reported nickelocene method.[30] Benzylpyridin-2-yldithioformate was used as controlling agent to prepare poly(styrene) **2a,b** by RAFT polymerization. The RAFT-HDA cycloaddition of PEO **1** and PS **2a,b** was performed in chloroform in the presence of trifluoroacetic acid (TFA).



Scheme 7.1 Synthetic strategy for producing cleavable PS-*b*-PEO via the RAFT-HDA *click* reaction. The reaction conditions are as follows: a) TsCl, NaOH, THF/H_2O; b) $NiCp_2$, NaI, PPh_3, THF, 40 °C; c) RAFT polymerization, AIBN, 60 °C.

Figure 7.1 shows an overlay of SEC traces of the individual building blocks PEO **1** and PS **2a,b** as well as the coupling product **3a,b**. A clear shift of the distributions to

lower retention times indicates the successful formation of PS-*b*-PEO which is consistent with the estimated number average molecular weights, M_n collated in Table 7.1.

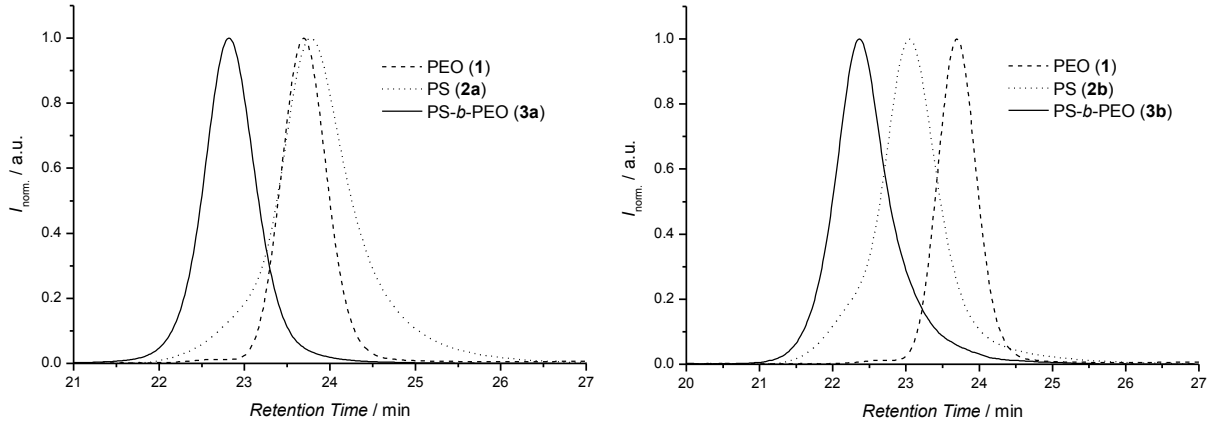


Figure 7.1 Overlay of SEC traces showing the formation of PS-*b*-PEO **3a** (left) and **3b** (right). The BCPs were purified by extraction of residual homo-PS with diethyl ether and precipitation in methanol.

Table 7.1 SEC characterization data of the individual building blocks and the resulting block copolymers.

Polymer	$M_{n,SEC}$[a] / g·mol^{-1}	*PDI*
PEO **1**	5000	1.05
PS **2a**	10600	1.14
PS **2b**	18500	1.12
PS-*b*-PEO **3a**	16900	1.06
PS-*b*-PEO **3a**	24100	1.11

[a]relative to linear PS standards in DMAc containing 0.3 wt% LiBr

To investigate the thermal cleavage of the block copolymer in the solid state, PS-*b*-PEO (**3b**) was suspended in water and heated to 90 °C. The insoluble residue was collected by filtration at predetermined time intervals (4 - 30 h) and analyzed via SEC, as shown in Figure 7.2. Inspection of Figure 7.2 indicates that after just 4 h of heating the majority of the BCP has undergone a rDA with the disappearance of the SEC elugram of **3b** and the reappearance of the elugram corresponding to the homopolymer block **2b**. The SEC elugram of **1** is not observed as once the rDA has occurred it dissolves in the water and is removed during filtration. Under these conditions the rDA reaction was essentially quantitative after 20 h.

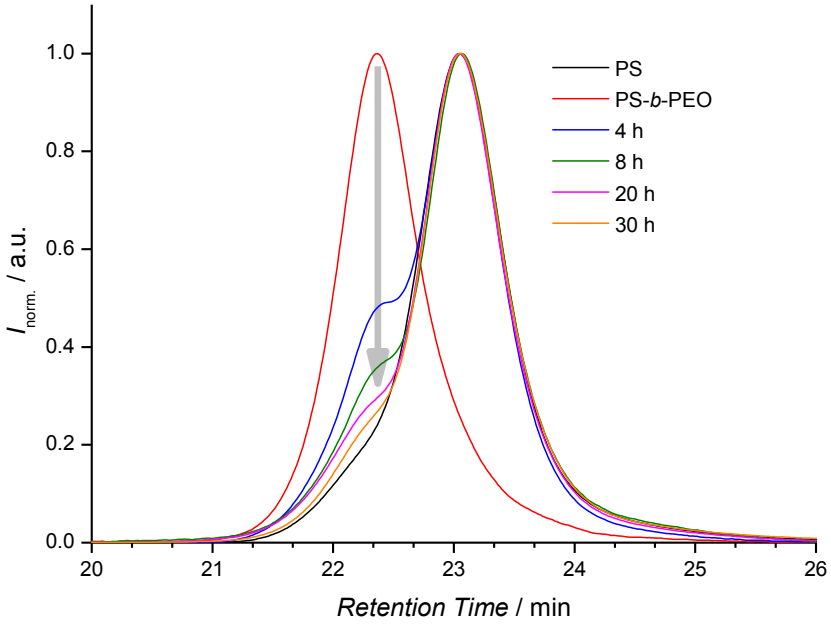


Figure 7.2 SEC monitoring of the rDA cleavage of PS-*b*-PEO (**3b**, 18.5-*b*-5.0 kg·mol^{-1}) in the solid state in water at 90 °C.

^{1}H-NMR analysis of the recovered solid, after precipitation in methanol, also demonstrated that the majority of the PEO was removed, as can be seen from the decrease of the PEO backbone signal at 3.62 ppm (Figure 7.3). A comparison of the integral ratios shows that only 10 % of **3b** is remaining.

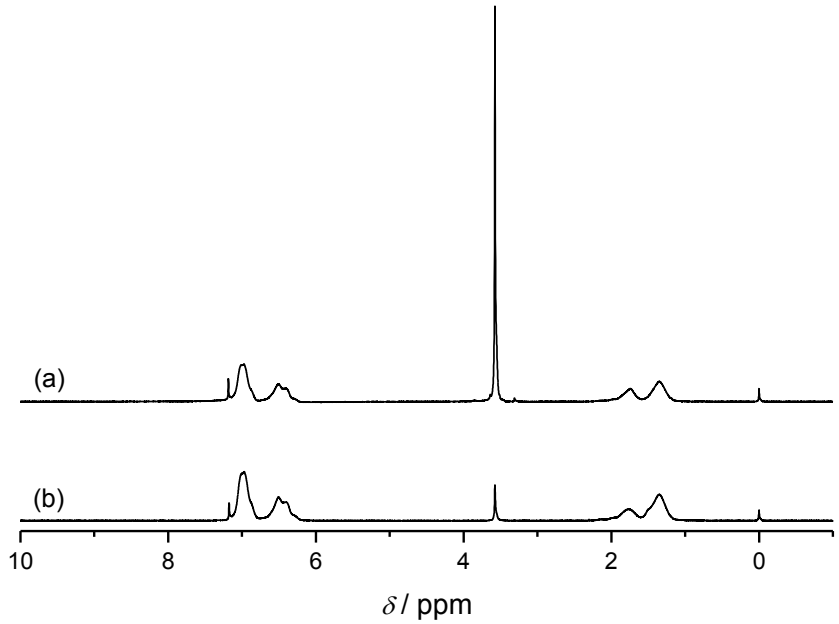


Figure 7.3 ^{1}H-NMR spectra in $CDCl_3$ of PS-*b*-PEO (a) and of the precipitate in MeOH after 20 h at 90 °C (b).

The data from Figure 7.2 and Figure 7.3 and the fact that the HDA reaction between a Cp-functionalized polymer and the pure RAFT agent is fully reversible[29] allow for the conclusion that block copolymers with a shorter PS block like **3a** can undergo a complete rDA reaction as well.

The fact that dithioesters are colored due to a n→π* transition of the C=S double bond can be used for a direct monitoring of the rDA reaction by UV-Vis spectroscopy because the absorbance is proportional to the concentration of the dithioester capped PS. Figure 7.4a shows the UV-Vis spectrum of the dithioester capped PS **2b**.

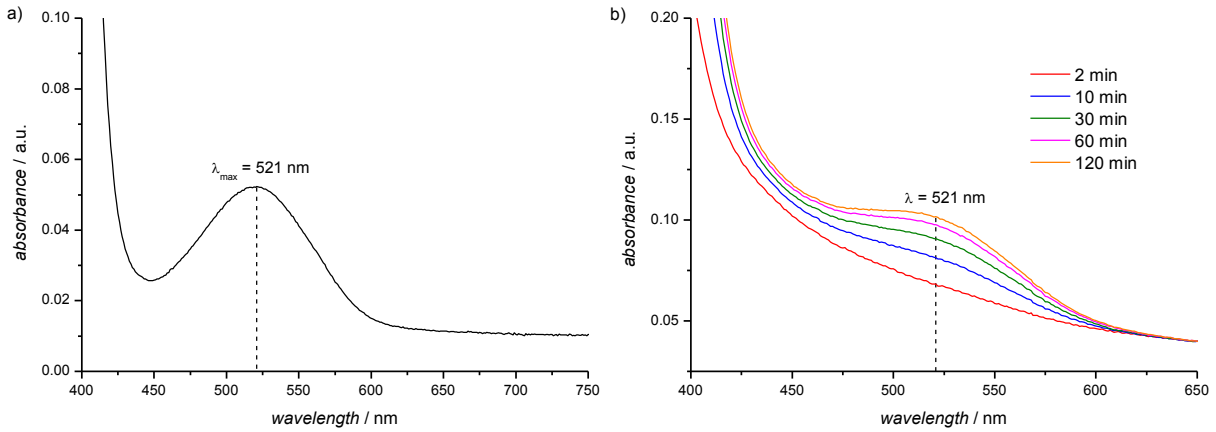


Figure 7.4 a) UV-Vis spectrum of the pure dithioester capped PS (**2b**). The absorbance reaches its maximum at 521 nm. b) UV-Vis spectra of PS-*b*-PEO (**3b**) in toluene at 90 °C. Due to the rDA reaction the concentration of the dithioester capped PS (**2b**) increases.

UV-Vis absorbance spectra of PS-*b*-PEO (**3b**) in toluene (0.7 mmol·L^{-1}) at 90 °C are depicted in Figure 7.4b. One can observe an increase in the absorbance with time due to an increasing concentration of the dithioester functionalized PS (**2b**). The maximum absorbance occurs at the same wavelength (521 nm) as for the pure RAFT polymer (see Figure 7.4a). After 120 min, no further increase of the absorbance was observed which indicates a faster reaction in solution compared to the solid state.

Once optimum cleavage conditions were established for PS-*b*-PEO, an investigation into the removal of the PEO block from a thin film by washing with water after the rDA reaction was undertaken. PS-*b*-PEO films were drop-cast on silicon wafers from a 2 wt.% solution in chloroform. After drying under vacuum, the films were heated at 90 °C for 15 h, washed with water to remove the PEO and dried again under vacuum. Scanning electron microscopy (SEM) images of PS-*b*-PEO films after heating and washing with water are displayed in Figure 7.5.

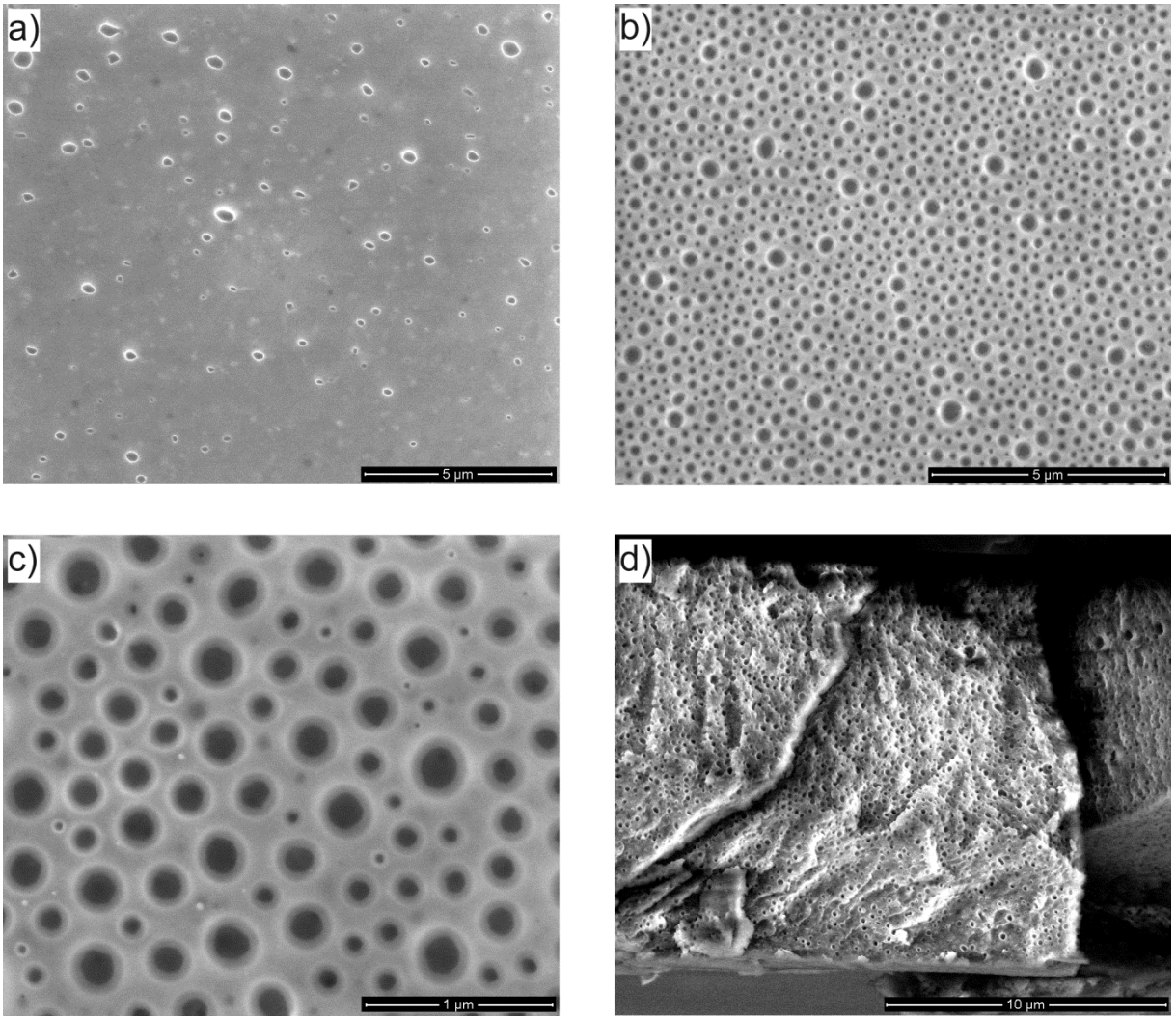


Figure 7.5 SEM images of a) PS-*b*-PEO **3b** (18.5-*b*-5.0 kg·mol^{-1}) after heating to 90 °C and washing with water; b) PS-*b*-PEO **3a** (10.6-*b*-5.0 kg·mol^{-1}) after heating to 90 °C and washing with water; c) PS-*b*-PEO **3a** (10.6-*b*-5.0 kg·mol^{-1}) after heating to 90 °C and washing with water; d) freeze-fracture cross-section of PS-*b*-PEO **3a** (10.6-*b*-5.0 kg·mol^{-1}) after heating to 90 °C and washing with water.

The formation of random nanopores can be clearly seen in Figure 7.5a which proves that the PEO block could be removed by the simple heating and washing procedure. SEM images of various blind samples (PS-*b*-PEO **3a,b** before heating, PS **2b** after heating/washing and PS-*b*-PEO **3b** after washing with water) showing no pore formation are displayed in Figure 7.6. While a porous structure is formed, employing PS-*b*-PEO **3b** (18.5-*b*-5.0 kg·mol^{-1}) only yielded a film with a limited number of pores. When considering the size of the blocks used to form **3b**, PEO only accounts for close to 20 wt.% of the total polymer system. It is thus not surprising that only few pores are formed. Increasing the fraction of PEO within the block copolymer should lead to an increase in the number of pores formed in the material. To achieve a pore count

increase, a shorter PS block was employed in the initial RAFT-HDA reaction forming PS-*b*-PEO **3a** (10.6-*b*-5.0 kg·mol^{-1}) in which the overall percentage of PEO within the BCP was close to 50 wt.%. When **3a** undergoes the same rDA treatment and washing as **3b**, a marked increase in porosity of the film can be observed (see Figure 7.5b). As depicted in Figure 7.5b (and more clearly in the enlargement, Figure 7.5c) the pore diameters range from 40 nm to 200 nm, which is in the same size range as the pores observed in Figure 7.5a yet, there is an over six-fold increase in the number of observed pores.

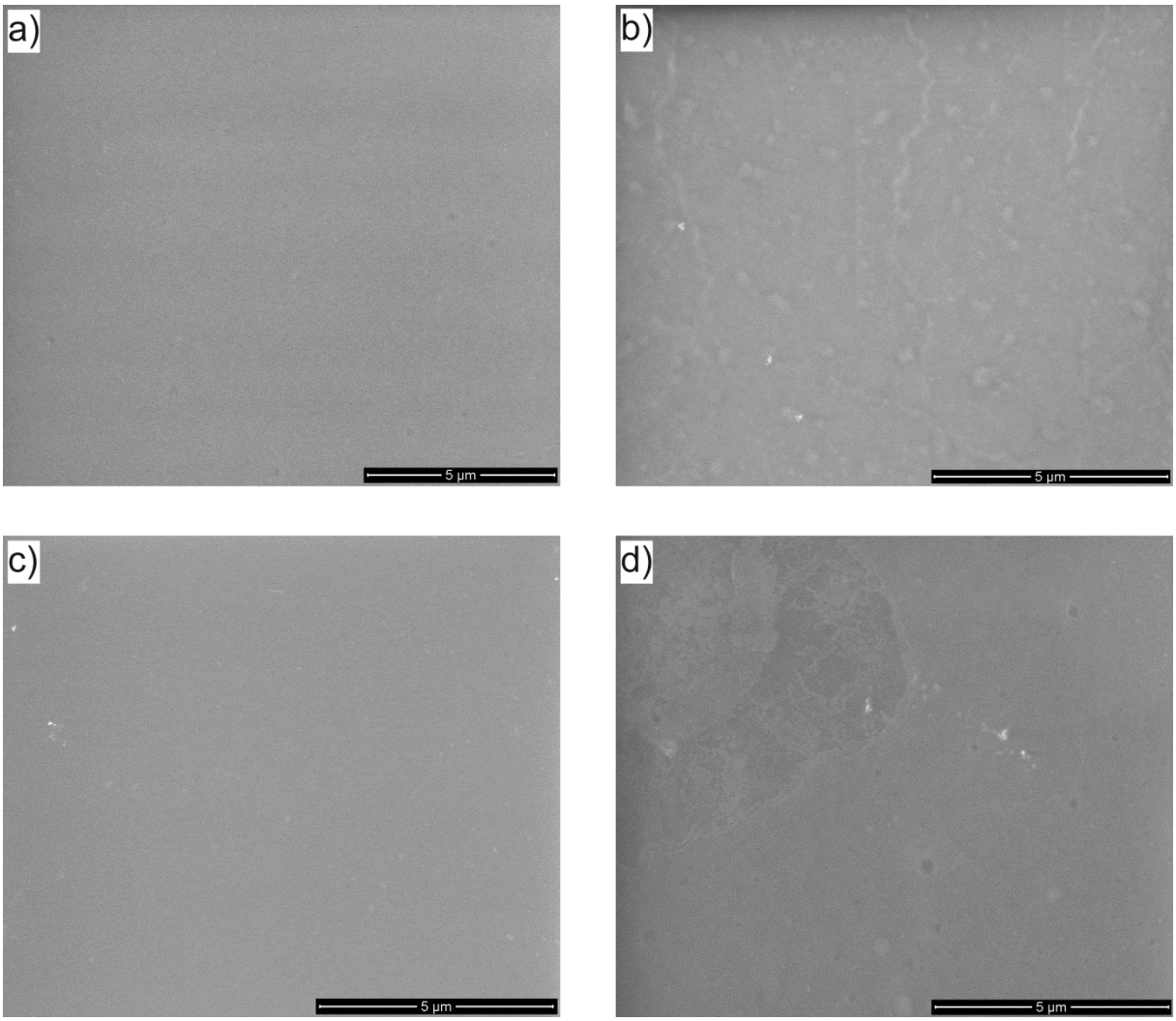


Figure 7.6 SEM images of blind film samples. a) PS-*b*-PEO **3b** before heating and washing; b) PS-*b*-PEO **3a** before heating and washing; c) PS **2b** after heating and washing; d) PS-*b*-PEO **3b** after washing with water (without heating).

Importantly, the cross-section SEM image of a freeze-fractured sample in Figure 7.5d confirms that the pore formation is not limited to the film's surface but occurs throughout the entire bulk of the film. As the PEO block is synthesized independently to the PS block, interchanging different PS blocks can be achieved with ease. Such an approach should allow the described technique to be extended further, enabling the tuning of film porosity by substituting PS blocks of differing lengths.

7.4 Conclusions

In summary, it was possible to synthesize thermally cleavable PS-*b*-PEO block copolymers by RAFT-HDA *click* chemistry. The cleavage of PS-*b*-PEO can be carried out by heating to 90 °C in the solid state or in solution. UV-Vis analysis confirmed that the dithioester end-group of the RAFT polymer is returned to the reformed homopolymer and that it is stable under these conditions. Nanoporous PS films were readily prepared by removal of the PEO block by applying a simple heating and washing procedure. The method described here enables a facile preparation of nanoporous films bearing a reactive thiocarbonyl thio group which provides access to further transformations from block copolymer precursors which are accessible in various molecular weight compositions via the combination of RAFT polymerization and HDA cycloaddition.

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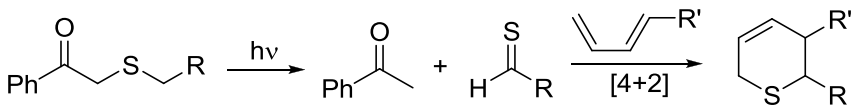
8

Polymer Surface Patterning via Diels-Alder Trapping of Photo-Generated Thioaldehydes

8.1 Introduction

Spatially controlled functionalization of surfaces can be realized by employing photo-induced reactions. The immobilization of biomolecules such as carbohydrates,[1] proteins[2-3] and peptides[4] is of special interest within this context. Photoinitiated thiol-ene[5-6] and thiol-yne[7-8] reactions are common strategies for light-induced surface modifications. Spatial control of the popular copper catalyzed azide-alkyne *click* reaction was realized by photoreduction of Cu(II) to Cu(I).[9] In recent years, several methods for the light-induced formation of reactive groups on surfaces have been developed which avoid the loss of spatial resultion through diffusion of the photoactive component. Functional groups such as cyclooctynes,[10] nitrile imines,[11] oximes[12] and *o*-naphthoquinone methides[13] can be utilized for the highly efficient ligation of an appropriate reaction partner. A novel UV light-triggered *click* methodology via Diels-Alder conjugation of *o*-quinodimethanes (photoenols)[14-15] was recently introduced as discussed in Chapter 2.3.3. It was demonstrated in a recent publication that the photoenol strategy represents an efficient tool for spatially controlled surface (bio)functionalization.[4] Our group has also established hetero-Diels-Alder (HDA) reactions of thiocarbonyl compounds at ambient temperature as efficient conjugation tool (refer to Chapter 2.3.2).[16-17] Photofragmentation of phenacyl sulfides is a mild and efficient method for the preparation of highly reactive thioaldehydes which can be trapped in situ by various dienes to give the Diels-Alder adducts (Scheme 8.1).[18-19]



Scheme 8.1 Photolytic cleavage of phenacyl sulfides yielding acetophenone and thioaldehydes that can be trapped with a diene to give the Diels-Alder adduct.

8.2 Experimental Section

(Phenacylthio)acetic acid was synthesized according to the literature[20] and recrystallized from $CHCl_3$.

Synthesis of phenacyl sulfide functionalized poly(ethylene glycol) monomethyl ether (1)

Poly(ethylene glycol) monomethyl ether (2.00 g, 1.00 mmol), 4-dimethylaminopyridine (7.0 mg, 0.6 mmol) and (phenacylthio)acetic acid (631 mg, 3.00 mmol) were dissolved in 10 mL dry CH_2Cl_2. A solution of DCC (619 mg, 3.00 mmol) in 2 mL dry CH_2Cl_2 was added and the reaction mixture stirred overnight at ambient temperature. The solution was filtered and the polymer precipitated in cold diethyl ether to give a white solid.

Photo-reactions with small molecule dienes

Phenacyl sulfide functionalized PEG **1** (10 mg, 5 μmol) and the diene (7.5 μmol) were dissolved in 1 mL dry CH_2Cl_2 in a headspace vial (Pyrex, dia. 20 mm) which was crimped airtight using styrene/butadiene rubber seals with PTFE inner liner. The solution was deoxygenated by purging with nitrogen for 5 min. The vial was irradiated by revolving around a 36 W compact low-pressure fluorescent lamp (Philips CLEO Compact PL-L, λ_{max} = 355 nm) at a distance of 40-50 mm in a custom built photo reactor (see Figure 4.13 for a drawing). After a preset time interval irradiation was stopped and the solvent was removed under a stream of nitrogen. The residue was redissolved in THF and analyzed by SEC/ESI-MS.

Synthesis of phenacyl sulfide functionalized silane (7)

1.00 g (4.76 mmol) (phenacylthio)acetic acid was dissolved in 20 mL dry THF. 730 μL of triethylamine were subsequently added. The solution was purged with nitrogen for 5 min, 619 mg (5.71 mmol) ethyl chloroformate were added at 0 °C and stirred at 0 °C for 4 h. 1.05 g (4.76 mmol) 3-(triethoxysilyl)propan-1-amine were added dropwise at 0 °C and the reaction mixture was stirred over night at ambient temperature. The solution was filtered and the solvent was removed under reduced pressure. Ethyl acetate was added and the organic layer was washed with water, saturated $NaHCO_3$ solution and brine. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexane 1:1). 451 mg (1.09 mmol,

23%) of silane **7** were obtained as a slightly yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.93–7.86 (m, 2H), 7.57–7.52 (m, 1H), 7.45–7.40 (m, 2H), 3.90 (s, 2H), 3.74 (q, ^{3}J = 7.0 Hz, 6H), 3.23–3.15 (m, 2H), 3.17 (s, 2H), 1.62–1.52 (m, 2H), 1.15 (t, ^{3}J = 7.0 Hz, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 194.28 (C), 135.18 (C), 133.96 (CH), 128.98 (CH), 128.80 (CH), 58.58 (CH_2), 42.42 (CH_2), 38.30(CH_2), 36.08 (CH_2), 23.04 (CH_2), 18.43 (CH_3), 7.89 (CH_2). ESI-MS: m/z = 436.25 ([M+Na]$^{+}$, m/z^{theo} = 436.16).

Cleaning and preactivation of silicon wafers

All Si wafers were cleaned three times by ultrasonification for 15 min in chloroform, acetone, and ethanol. Preactivation of the surfaces was achieved by placing them in glass vials containing acidic piranha solution (sulfuric acid 95 % aqueous hydrogen peroxide 35 % 3:1 v/v) for 60 min at 100 °C. The wafers were subsequently rinsed with deinoized water and dried under a stream of nitrogen. Caution: piranha solution is an extremely strong oxidant and should be handled with care!

Silanization of Si wafers with phenacyl sulfide functionalized silane 7

Preactivated substrates were placed separately in small glass vials containing a solution of phenacyl sulfide functionalized silane **7** (10 mg, 22.1 μmol) dissolved in anhydrous toluene (2 mL). They were subsequently heated to 50 °C for 2 h without stirring. The solution was brought to ambient temperature and the wafers were left immersed for another 12 h. The wafers were subsequently ultrasonicated in dry toluene (10 mL, 10 min), acetone (10 mL, 5 min), and finally CH_2Cl_2 (10 mL, 5 min) to remove any physisorbed silane and subsequently dried under a stream of nitrogen.

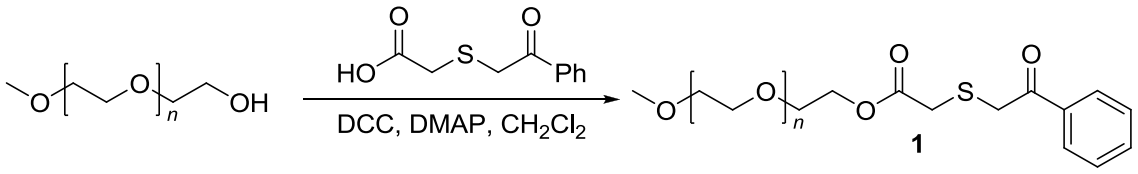
Polymer surface patterning with PEG-Cp

In a headspace vial (Pyrex, diameter 20 mm), PEG-Cp (20 mg, 10 μmol) was dissolved in CH_2Cl_2 (3 mL). A mask (see Figure 8.5) was placed onto a phenacyl sulfide functionalized Si wafer. The latter was placed into the headspace vial, which was crimped air-tight using SBR seals with PTFE inner liner. The solution was deoxygenated by purging with nitrogen for 10 min. The flasks were subsequently irradiated for 2 h in the photoreactor. After irradiation, the mask was removed. The wafer was subsequently rinsed with CH_2Cl_2 and sonicated 3 times for 5 min in CH_2Cl_2 to remove any physisorbed material. The wafer was finally dried under a stream of nitrogen. The sample for XPS analysis was irradiated without a mask.

8.3 Results and Discussion

An efficient and rapid ambient temperature method for spatially controlled polymer surface patterning via Diels-Alder trapping of photo-generated thioaldehydes is presented. Model reactions in solution demonstrate that thioaldehyde end-groups generated by photolysis of phenacyl sulfides can be quantitatively trapped with various dienes. Cyclopentadienyl-capped poly(ethylene glycol) is immobilized on a phenacyl sulphide functionalized surface in a spatially controlled fashion via irradiation through a shadow mask.

To perform model reactions in solution, phenacyl sulfide functionalized poly(ethylene glycol) (**1**) was synthesized by esterification with (phenacylthio)acetic acid (Scheme 8.2).



Scheme 8.2 Synthesis of phenacyl sulfide functionalized PEG **1**.

The success of the transformation was confirmed by ^{1}H-NMR spectroscopy as depicted in Figure 8.1a.

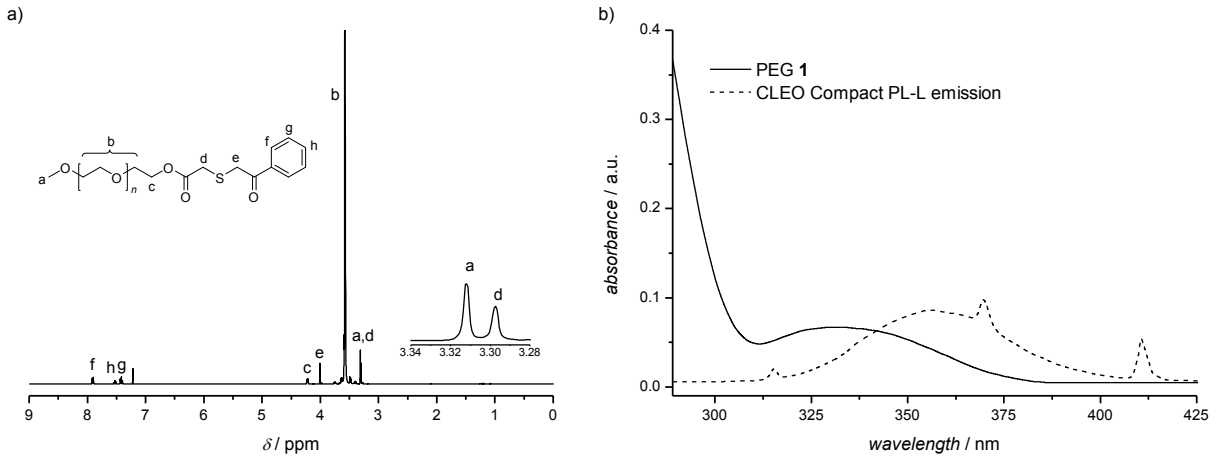


Figure 8.1 a) ^{1}H-NMR spectrum of phenacyl sulfide functionalized PEG **1**. b) UV-Vis spectrum of phenacyl sulfide functionalized PEG **1** together with the emission spectrum of the employed compact low-pressure fluorescent lamp (Philips CLEO Compact PL-L).

A 36 W compact fluorescent lamp with an absorbance maximum of 355 nm was employed as light source. The absorption spectrum of **1** and the emission spectrum of

the employed lamp show a sufficient overlap as can be seen from Figure 8.1b. Degassed solutions of **1** and 1.5 equivalents of various dienes (2,3-dimethyl-1,3-butadien, *trans,trans*-2,4-hexadien-1-ol, cyclohexadiene, cyclopentadiene and *trans,trans*-2,4-hexadienoic acid) in dichloromethane were irradiated at ambient temperature and the progress of the reactions was monitored by electrospray ionization mass spectrometry (ESI-MS) as depicted in Figure 8.2.

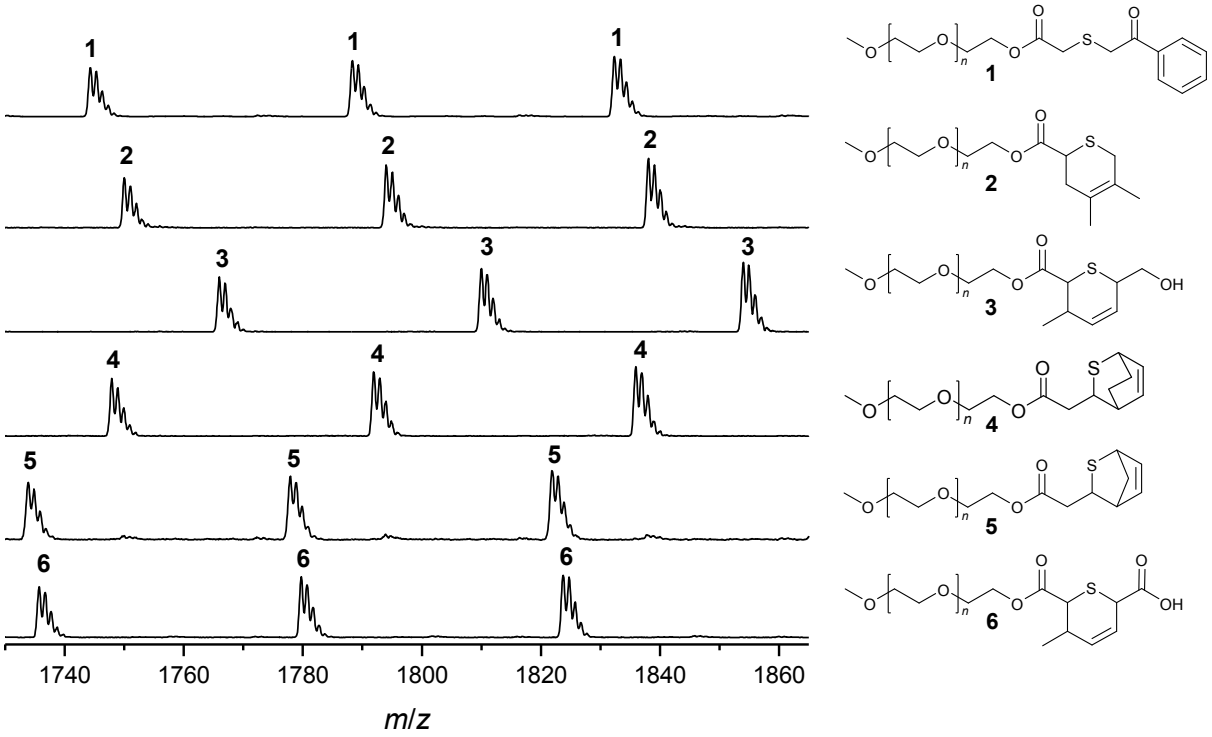


Figure 8.2 ESI-MS spectra of phenacyl sulfide capped PEG (**1**) before and after 30 min irradiation with 2,3-dimethyl-1,3-butadien (**2**) *trans,trans*-2,4-hexadien-1-ol (**3**), cyclohexa-diene (**4**), cyclopentadiene (**5**) and *trans,trans*-2,4-hexadienoic acid (**6**).

Inspection of Figure 8.2 clearly indicates that close to quantitative formation of the thioaldehyde Diels-Alder adduct can be observed in all cases. It is noteworthy that not only donor-substituted dienes but even dienes bearing an electron-withdrawing group which decreases the Diels-Alder reactivity such as *trans,trans*-2,4-hexadienoic acid react in a quantitative fashion without any observable side products. When cyclopentadiene is employed as diene a small amount of a side product (~ 10% peak intensity) occurs at 16 amu higher m/z ratios which may be assigned to oxidation of the thioether **5** to the corresponding sulfoxide. The theoretical and measured *m/z* ratios of the involved species collated in Table 8.1 are in excellent agreement.

Table 8.1 Theoretical and measured m/z ratios ($[M+Na]^+$) of phenacyl sulfide functionalized PEG **1** and the Diels-Alder adducts with different dienes (Figure 8.2). The values refer to the first peak of the isotopic pattern.

Structure	Formula	m/z^{theo}	m/z^{meas}	$\Delta\, m/z$
1	$[C_{81}H_{152}O_{38}SNa]^+$	1787.96	1788.17	0.21
2	$[C_{81}H_{158}O_{38}SNa]^+$	1794.01	1794.08	0.07
3	$[C_{81}H_{158}O_{39}SNa]^+$	1810.00	1810.00	0.00
4	$[C_{81}H_{156}O_{38}SNa]^+$	1791.99	1791.92	0.07
5	$[C_{80}H_{155}O_{38}SNa]^+$	1777.97	1777.92	0.05
6	$[C_{79}H_{152}O_{39}SNa]^+$	1779.95	1779.75	0.20

Figure 8.3 displays a kinetic investigation of the reaction with *trans,trans*-2,4-hexadien-1-ol.

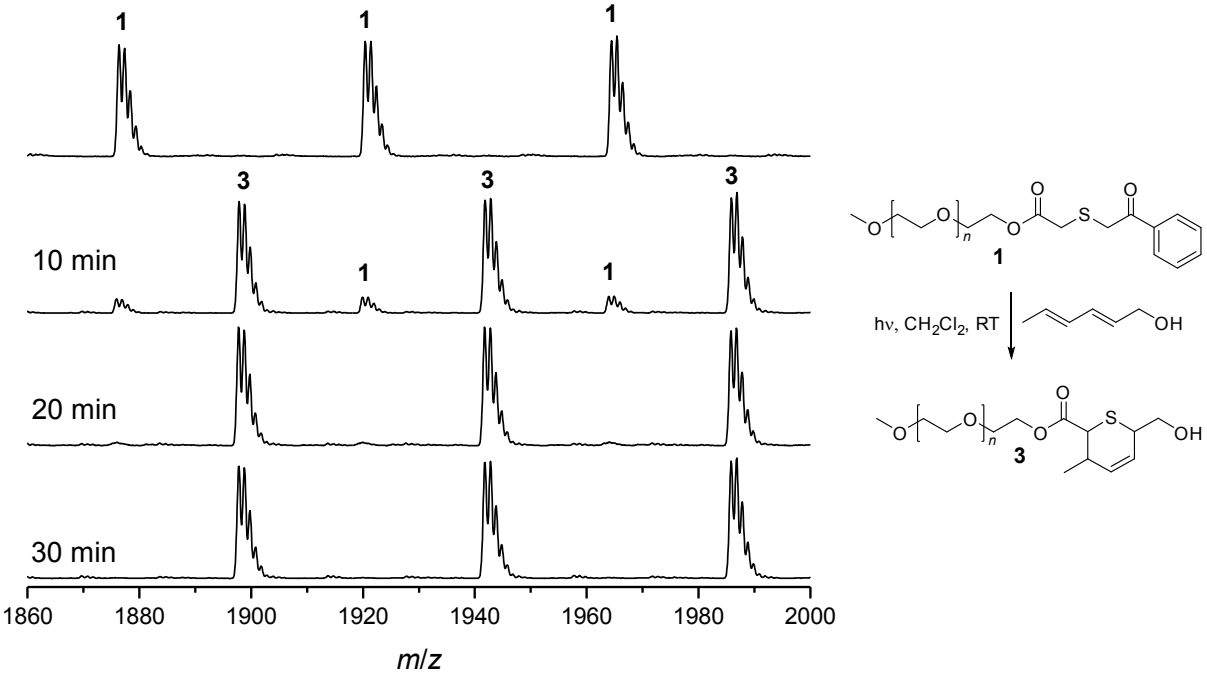
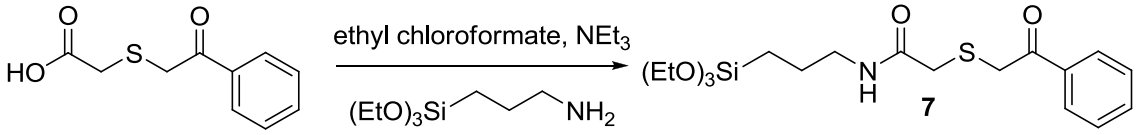


Figure 8.3 ESI-MS spectra of phenacyl sulfide capped PEG (**1**) before and after irradiation with *trans,trans*-2,4-hexadien-1-ol for different time intervals.

Inspection of the ESI-MS spectra taken after different time intervals reveals that after just 10 min irradiation ca. 85 % of PEG **1** are already transformed in the Diels-Alder adduct **3**. Full conversion was achieved after 30 min irradiation.

To demonstrate the potential of the photo-HDA reaction for spatially controlled surface patterning, the phenacyl sulfide containing silane **7** was synthesized from (phenacylthio)acetic acid and commercially available (3-aminopropyl)triethoxysilane as shown in Scheme 8.3 (see Appendix for NMR and ESI-MS spectra) and reacted with activated silicon wafers.



Scheme 8.3 Synthesis of phenacyl sulfide functionalized silane **7**.

Successful silanization was confirmed by X-ray photoelectron spectroscopy (XPS). Figure 8.4a shows the C1s spectrum of a Si-wafer after silanization with **7**.

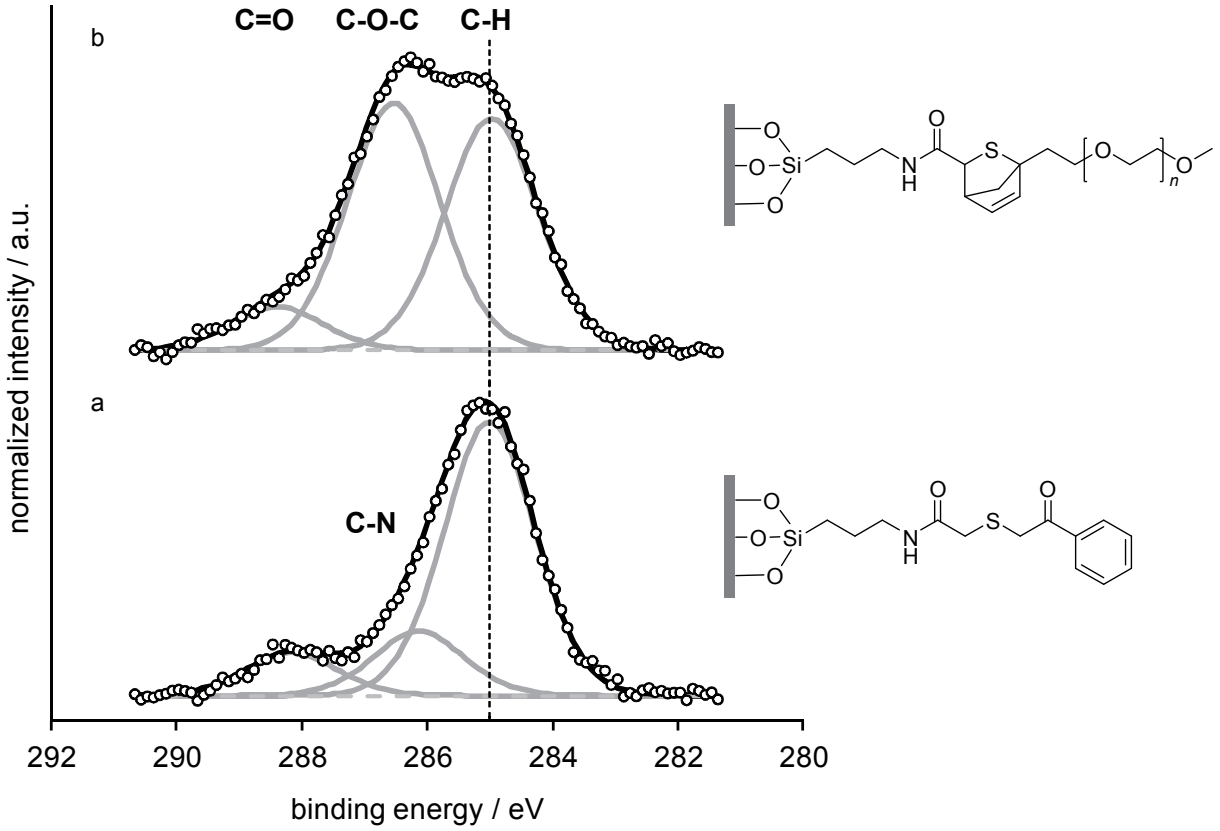
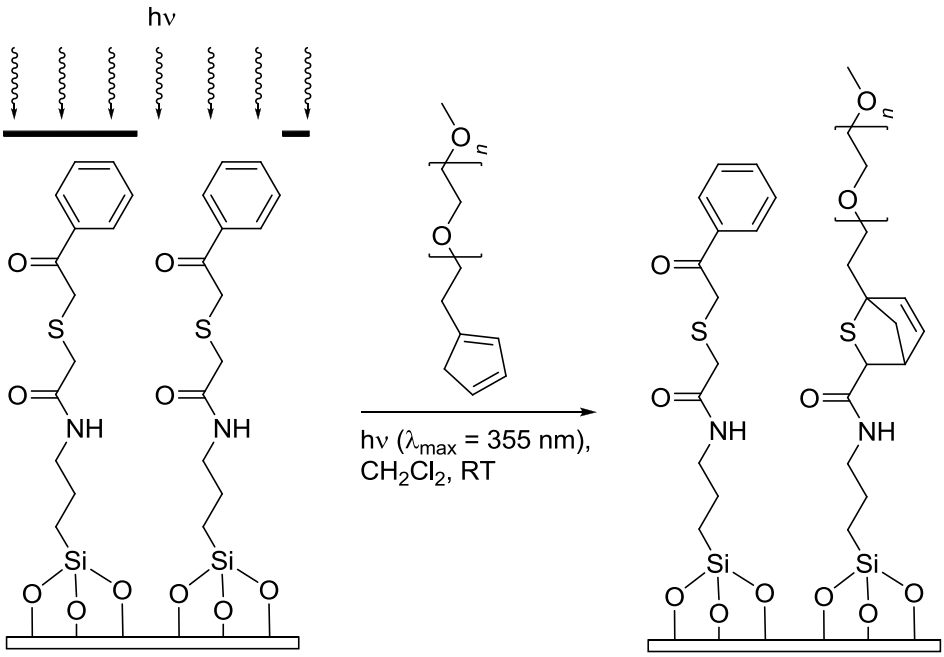


Figure 8.4 Comparison of the C1s XPS spectra of Si wafers after silanization with **7** (a) and after subsequent photo-reaction with PEG-Cp (b). The spectra are normalized to maximum intensity.

The main peak in the C1s spectrum at 285.0 eV is assigned to hydrocarbon atoms (C-C, C-H), the component at 286.1 eV is attributed to C-N[21], and the component at

288.2 eV can be assigned to the C=O groups[21], both confirming successful silanization. The silicon wafers were subsequently immersed in a CH_2Cl_2 solution of cyclopentadienyl capped poly(ethylene glycol) (PEG-Cp) and irradiated 60 min as depicted in Scheme 8.4. After the photo-reaction with PEG-Cp a new main peak at 286.6 eV reflecting the C-O binding energy[21-22] is present in the C1s spectrum (Figure 8.4 b). This finding indicates the coupling of PEG to the surface. It has to be noted that due to the high C-O intensity the weak C-N component is no longer distinguishable.



Scheme 8.4 Surface patterning via HDA trapping of photo-generated thioaldehydes with PEG-Cp.

To create a polymer surface patterning, the silicon wafers were covered with a micropatterned shadow mask (Figure 8.5 right) before irradiation. Analysis of the photo-patterning was conducted by time-of-flight secondary ion mass spectrometry (ToF-SIMS), which enables spatially resolved analysis of molecular patterns on solid substrates.[23] Inspection of Figure 8.5 clearly reveals that characteristic mass fragments of PEG ($C_2H_5O^+$, $C_2H_3O^+$, CH_3O^+, $C_3H_7O^+$) can only be found in the irradiated area thus confirming the site-specific immobilization of PEG-Cp.

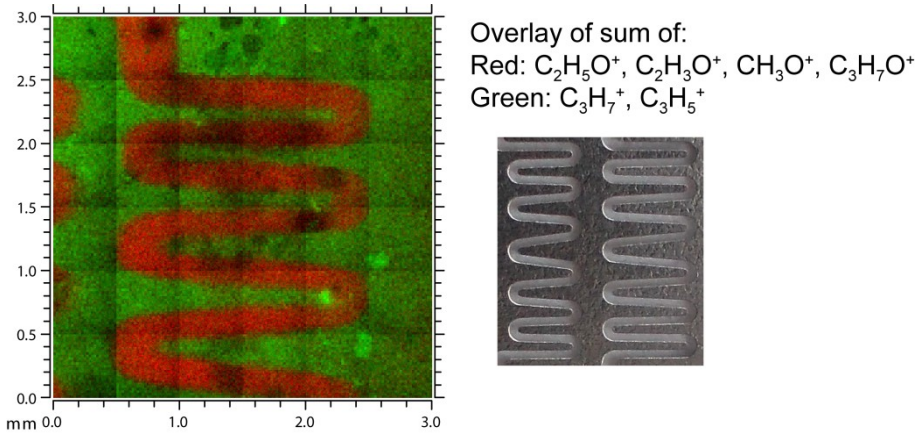


Figure 8.5 ToF SIMS image of a silicon wafer patterned with poly(ethylene glycol) employing the shadow mask shown on the right. An overlay of positive secondary ions is depicted. Red: PEG fragments ($C_2H_5O^+$, $C_2H_3O^+$, CH_3O^+, and $C_3H_7O^+$), green: alkyl fragments ($C_3H_7^+$, $C_3H_5^+$).

8.4 Conclusions

In summary, it was shown that thioaldehyde polymer end-groups generated by photolysis of phenacyl sulfides can be quantitatively trapped in a Diels-Alder reaction employing different dienes. It was further demonstrated that the trapping of photogenerated thioaldehydes attached to a surface with a diene functionalized polymer enables a spatially controlled surface patterning. The extremely fast and efficient reaction and the straightforward synthesis of (phenacylthio)acetic acid make this method a convenient strategy for applications demanding a light-triggered reaction.

Appendix

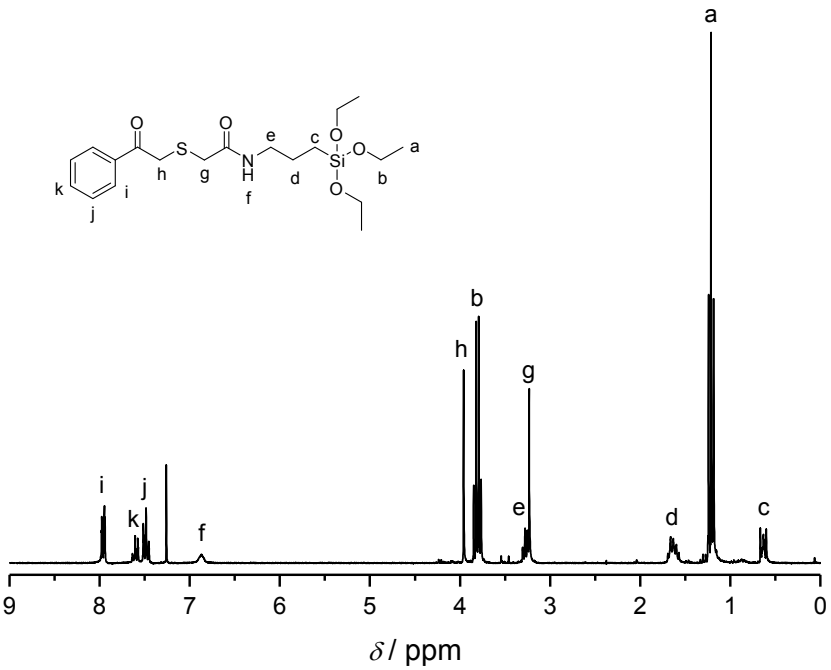


Figure 8.6 ^{1}H-NMR spectrum of phenacyl sulfide functional silane **7** in $CDCl_3$.

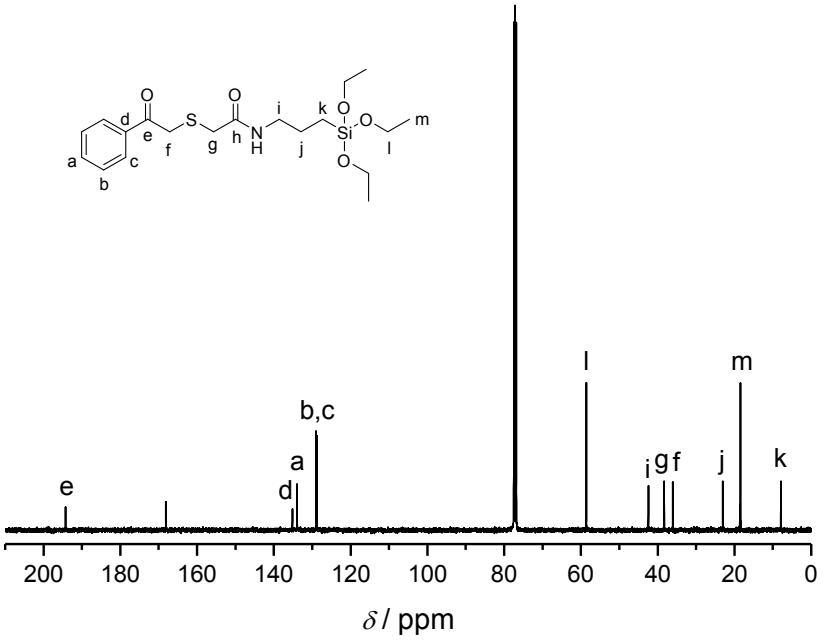


Figure 8.7 ^{13}C-NMR spectrum of phenacyl sulfide functional silane **7** in $CDCl_3$.

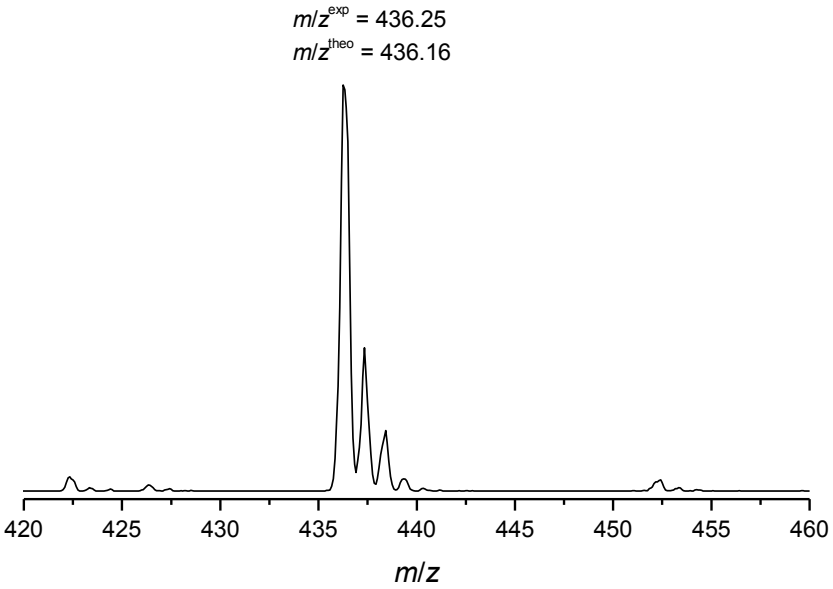


Figure 8.8 ESI-MS spectrum of phenacyl sulfide functional silane **7**.

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9
Materials and Characterization

9.1 Materials

Methyl methacrylate (Acros), *tert*-butyl acrylate (Aldrich), and styrene (Merck) were passed through a short column of basic alumina to remove inhibitor. 2-hydroxyethyl acrylate (Merck) was purified according to a literature procedure.[1] 2,2'-Azobis(isobutyronitrile) (AIBN, Sigma-Aldrich) was recrystallized twice from methanol and stored at - 18 °C prior to use. Copper (I) bromide (Fluka) was purified by sequential washing with sulphurous acid, acetic acid, and ethanol, followed by drying under reduced pressure prior to use. 2-Ethyl-2-oxazoline (EtOx, Acros), methyl tosylate (MeOTs, Acros) and acetonitrile (Aldrich) were distilled to dryness over barium oxide (BaO) and stored under argon. Cyclopentadiene was prepared by thermal cracking and distillation of dicyclopentadiene (Sigma-Aldrich). Dichloromethane, tetrahydrofuran and toluene were dried and stored over 4 Å molecular sieves where the use of dry solvents is stated. All other chemicals were purchased at their highest available purity and used as received.

9.2 Characterization

^{1}H-NMR and ^{13}C-NMR Spectroscopy

NMR spectra were recorded using a Bruker AM 400 spectrometer at 400 MHz for hydrogen nuclei and 101 MHz for carbon nuclei. All samples were dissolved in $CDCl_3$ or D_2O. The δ-scale is referenced to the chemical shift of the residual solvent resonances ($CDCl_3$: δ = 7.26 ppm (^{1}H), δ = 77.16 ppm (^{13}C) and D_2O: 4.79 ppm(^{1}H)).

Size Exclusion Chromatography (SEC)

THF-System: For the determination of molecular weight distributions (MWD), a SEC system (Polymer Laboratories PL-GPC 50 Plus) comprising an auto injector, a guard column (PLgel Mixed C, 50 × 7.5 mm) followed by three linear columns (PLgel Mixed

C, 300 × 7.5 mm, 5 µm bead-size) and a differential refractive index detector was employed. THF was used as the eluent at 40 °C with a flow rate of 1 mL·min^{-1}. The SEC system was calibrated using linear polystyrene standards ranging from 160 to 6·10^6 g mol^{-1} and linear poly(methyl methacrylate) standards ranging from 700 to 2·10^6 g mol^{-1}. The resulting molecular weight distributions were determined by universal calibration using Mark-Houwink parameters for PS (K = 14.1 10^{-5} dL g^{-1}, α = 0.70)[2], PMMA (K = 12.8 10^{-5} dL g^{-1}, α = 0.69)[3] and P*t*BA (K = 19.7 10^{-5} dL g^{-1}, α = 0.66).[4] PS-equivalent molecular weights are stated for PEG, PHEA and PEtOx.

DMAc-System: SEC measurements were performed on a Polymer Laboratories PL-GPC 50 Plus Integrated System, comprising an autosampler, a PLgel 5 µm bead-size guard column (50 × 7.5 mm) followed by three PLgel 5 µm MixedC columns (300 × 7.5 mm) and a differential refractive index detector using *N,N*-dimethylacetamide (DMAc) containing 0.3 wt% LiBr at 50 °C as the eluent with a flow rate of 1 mL·min^{-1}. The SEC system was calibrated using linear polystyrene standards ranging from 160 to 6·10^6 g·mol^{-1}.

Size Exclusion Chromatography- Electrospray Ionization Mass Spectrometry (SEC-ESI-MS)

Spectra were recorded on an LXQ mass spectrometer (ThermoFisher Scientific, San Jose, CA) equipped with an atmospheric pressure ionization source operating in the nebulizer assisted electrospray mode. The instrument was calibrated in the *m/z* range 195 - 1822 using a standard containing caffeine, Met-Arg-Phe-Ala acetate (MRFA) and a mixture of fluorinated phosphazenes (Ultramark 1621) (all from Aldrich). A constant spray voltage of 6 kV was used and nitrogen at a dimensionless sweep gas flow-rate of 2 (approximately 3 L·min^{-1}) and a dimensionless sheath gas flow-rate of 5 (approximately 0.5 L·min^{-1}) were applied. The capillary voltage, the tube lens offset voltage and the capillary temperature were set to 10 V, 70 V and 315 °C respectively. The LXQ was coupled to a Series 1200 HPLC-system (Agilent, Santa Clara, CA, USA) consisting of a solvent degasser (G1322A), a binary pump (G1312A), a high-performance autosampler (G1367B), followed by a thermostated column compartment (G1316A). Separation was performed on two mixed bed size exclusion chromatography columns (Polymer Laboratories, Mesopore 250 × 4.6 mm, particle diameter 3 µm) with precolumn (Mesopore 50 × 4.6 mm) operating at 30 °C. THF at a flow rate of 0.30 mL·min^{-1} was used as eluent. The mass spectrometer was coupled to the column in parallel to an RI-detector (G1362A with SS420x A/D) in a setup de-

scribed earlier.[5] 0.27 mL·min^{-1} of the eluent were directed through the RI-detector and 30 µL·min^{-1} infused into the electrospray source after postcolumn addition of a 100 µM solution of sodium iodide in methanol at 20 µL·min^{-1} by a micro-flow HPLC syringe pump (Teledyne ISCO, Model 100DM). A 20 µL aliquot of a polymer solution with a concentration of 3 mg·mL^{-1} was injected onto the HPLC system.

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-ToF MS)

For the MALDI measurements which were carried out at the Friedrich-Schiller-University Jena an Ultraflex III TOF/TOF apparatus (Bruker Daltonics, Bremen, Germany) equipped with a Nd:YAG laser and a collision cell was used. All spectra were measured in the positive reflector or linear mode. The instrument was calibrated prior to each measurement with an external PMMA standard from PSS Polymer Standards Services GmbH (Mainz, Germany).

UV/Vis Spectroscopy

UV/Vis spectra were recorded on a Varian Cary 300 Bio spectrophotometer equipped with a thermostatted sample cell holder and a magnetic stirrer.

Scanning Electron Microscopy (SEM)

SEM was performed on a FEIQuanta 650 FEG ESEM operating at 5.0 kV accelerating voltage.

X-Ray Photoelectron Spectroscopy (XPS)

XPS measurements were performed using a K-Alpha XPS instrument (ThermoFisher Scientific, East Grinstead, UK). Data acquisition and processing using the Thermo Avantage software is described elsewhere.[6] All samples were analyzed using a microfocused, monochromated Al Kα X-ray source (30-400 µm spot size). The K-Alpha charge compensation system was employed during analysis, using electrons of 8 eV energy and low-energy argon ions to prevent any localized charge build-up. The spectra were fitted with one or more Voigt profiles (BE uncertainty: +/- 0.2eV). The analyzer transmission function, Scofield sensitivity factors,[7] and effective attenuation lengths (EALs) for photoelectrons were applied for quantification. EALs were calculated using the standard TPP-2M formalism.[8] All spectra were referenced to

the C1s peak of hydrocarbon at 285.0 eV binding energy controlled by means of the well-known photoelectron peaks of metallic Cu, Ag, and Au.

Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS)

Time-of-flight secondary ion mass spectrometry was performed on a TOF.SIMS 5 instrument from ION.TOF GmbH, Münster, Germany. This instrument is equipped with a Bi cluster liquid metal ion source and a reflectron type time-of-flight analyzer and is operated at $< 5 \cdot 10^{-9}$ mbar. For spectrometry and imaging short primary ion pulses (< 1 ns) of Bi^+ at an energy of 25 keV were applied providing high mass resolution secondary ion spectra with a spot size of about 2 μm (bunched mode). The primary ion beam was rastered over 500 × 500 μm. To obtain larger scan sizes also the sample holder was shifted and images stitched automatically. Images were recorded at 100 pixel/mm. Spectra were calibrated on the omnipresent C^+, $CH^+$and CH_2^+ peaks. Deviations from the theoretical mass were usually < 10 ppm.

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10
Concluding Remarks and Outlook

10.1 Concluding Remarks

Diels-Alder reactions are certainly among the most efficient tools for the precision design of polymeric materials. The present thesis has demonstrated the versatility and efficiency of modular Diels-Alder conjugations by a range of examples. Diels-Alder reactions between cyclopentadienyl and maleimide end-groups were employed in Chapter 3 for the synthesis of cyclic polymers with exceptional purity. The combination of orthogonal conjugation reactions enables the synthesis of macromolecular architectures that are inaccessible by use of a single ligation technique. It was demonstrated in Chapter 4 that the combination of a photochemical conjugation based on the light-triggered formation of *o*-quinodimethanes with thermally induced Diels-Alder as well as copper (I) catalyzed azide-alkyne *click* reactions is an efficient tool for the synthesis of ABA and ABC triblock copolymers. The modular construction of polymeric architectures necessitates the synthesis of polymers bearing specific functional groups. The one-pot synthesis of cyclopentadienyl endcapped poly(2-ethyl-2-oxazoline) presented in Chapter 5 represents a facile tool for the synthesis of novel precursors for ambient temperature Diels-Alder conjugations as demonstrated by the formation of block copolymers. It is highly desirable to perform polymer coupling reactions in cheap and benign solvents such as water, to avoid environmental impacts and facilitate conjugations of synthetic polymers with sensitive biomolecules. (Ultra)fast catalyst-free macromolecular conjugations in aqueous environment at ambient temperature were realized in Chapter 6 employing dithioester end-groups obtained via RAFT polymerization as dienophile. It was demonstrated that the use of water as reaction medium does not only permit efficient conjugations, but enables polymer-polymer coupling reactions at ambient temperature utilizing open-chain diene end-groups that require elevated temperatures and a transition metal catalyst when used in organic solvents. The applications of (reversible) modular Diels-Alder conjugations presented in Chapter 7 and 8 demonstrate that the potential of such strategies goes far beyond the mere construction of polymeric architectures. The retro-Diels-Alder cleavage of block copolymers generated by RAFT-HDA *click* conjuga-

tion is utilized in Chapter 7 for the formation of nanoporous poly(styrene) films employing a simple heating and washing procedure. It is finally demonstrated in Chapter 8 that the Diels-Alder trapping of photo-generated thioaldehydes attached to a surface with a diene functionalized polymer enables spatially controlled polymer surface patterning.

10.2 Outlook

The author of the current thesis hopes that the present body of work makes a contribution to broaden the field in which modular Diels-Alder conjugations and retro-Diels-Alder cleavages will be employed in the future. The strategies established herein, the methodologies they are based on as well as manifold procedures developed simultaneously with the present investigation load the toolbox for modular (macromolecular) conjugations from which researchers can choose. It can be envisaged that a range of sophisticated functional materials will be designed in the future employing modular strategies addressing diverse challenges in materials science as well as bio- and nanotechnology. The ambient temperature HDA reaction of RAFT polymers in aqueous solution (Chapter 6) is a promising strategy for the synthesis of biohybrid materials. One can imagine the conjugation of synthetic RAFT polymers to diene functionalized peptides, proteins, carbohydrates, lipids or other biomolecules by simply mixing the two compounds in an aqueous solvent. The thermally reversible formation of block copolymers demonstrated in Chapter 7 may be combined with the ability of amphiphilic block copolymers to self-assemble into various morphologies to a nanolitographic technique for the construction of nanoscale polymer patterns. The Diels-Alder reaction of photo-generated thioaldehydes which was utilized for the first time for polymer functionalizations and surface patternings in Chapter 8 is a powerful strategy for other applications demanding a light-triggered reaction. Readers are encouraged to let their minds go creative to develop new fascinating synthetic materials employing the herein presented technologies.

List of Abbreviations

λ	wavelength
AIBN	2,2′-azobis(2-methylpropionitrile)
AIpGlc	3-O-acryloyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside
AM	acrylamide
AN	acrylonitrile
ARGET	activators regenerated by electron transfer
ATRP	atom transfer radical polymerization
BPDF	benzyl pyridin-2-yldithioformate
bpy	2,2′-bipyridine
Cp	cyclopentadienyl
c-PMMA	cyclic poly(methyl methacrylate)
c-P*t*BA	cyclic poly(*tert*-butyl acrylate)
CROP	cationic ring-opening polymerization
CRP	controlled radical polymerization
CSIRO	Commonwealth Scientific and Industrial Research Organization
CuAAC	copper (I) catalyzed azide alkine cycloaddition
DA	Diels-Alder
DA_{inv}	inverse electron-demand Diels-Alder
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEPN	4-(diethoxyphosphinyl)-2,2,5,5-tetramethyl-3-azahexane-*N*-oxyl
DMAc	dimethylacetamide
DMAc	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMBP	2,5-dimethylbenzophenone
EDG	electron donating group
EGDA	ethylene glycol diacrylate
eq.	equivalents
ESI-MS	electrospray ionization mass spectrometry
EWG	electron withdrawing group
FMO	frontier molecular orbital
FRP	free radical polymerization
HDA	hetero Diels-Alder

HOMO	highest occupied molecular orbital
HPLC	high performace liquid chromatography
IUPAC	international union of pure and applied chemistry
k_a	rate coefficient of activation
k_{add}	rate coefficient of addition
k_d	rate coefficient of dissociation
k_{da}	rate coefficient of deactivation
k_i	rate coefficient of initiation
k_p	rate coefficient of propagation
k_{ri}	rate coefficient of re-initiation
k_t	rate coefficient of termination
k_{tc}	rate coefficient of termination by combination
k_{td}	rate coefficient of termination by disproportionation
k_β	rate coefficient of fragmentation
L	ligand
LUMO	lowest unoccupied molecular orbital
MA	methyl acrylate
MADIX	macromolecular design by interchange of xanthates
Mal	maleimide
MALDI	matrix-assisted laser desorption/ionization
Me_6TREN	tris[2-(dimethylamino)ethyl]amine
meas	measured
M_n	number-average molecular weight
MS	mass spectrometry
MS-MS	tandem mass spectrometry
Mt	metal
MWCO	molecular weight cut-off
NaCp	sodium cyclopentadienide
$NiCp_2$	nickelocene
NMP	nitroxide mediated polymerization
NMR	nuclear magnetic resonance
NRC	nitroxide radical coupling
NVP	*N*-vinylpyrrolidone
OCD	open-chain diene

PAGlc	poly(3-O-acryloyl-α,β-D-glucopyranoside)
PAIpGlc	poly(3-O-acryloyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside)
PDI	polydispersity index
PEG	poly(ethylene glycol)
PEO	poly(ethylene oxide)
PEtox	poly(2-ethyl-2-oxazoline)
PHEA	poly(2-hydroxyethyl acrylate)
PMDETA	*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine
PMMA	poly(methyl methacrylate)
Pox	poly(oxazoline)
PPh_3	triphenyl phosphine
ppm	parts per million
PS	poly(styrene)
P*t*BA	poly(*tert*-butyl acrylate)
PTFE	poly(tetrafluoroethylene)
py	pyridinyl
RAFT	reversible addition fragmentation chain transfer
rDA	retro-Diels-Alder
RI	refractive index
ROP	ring-opening polymerization
S	styrene
SEC	size exclusion chromatography
SEM	scanning electron microscopy
SFRP	stable free radical polymerization
SIMS	secondary ion mass spectrometry
SPAAC	strain-promoted azide-alkyne cycloaddition
*t*BA	*tert*-butyl acrylate
TE	thiol-ene
TEMPO	2,2,6,6-tetramethylpiperidine-N-oxyl
TFA	trifluoroacetic acid
theo	theoretical
THF	tetrahydrofuran
TIPNO	2,2,5-trimethyl-4-phenyl-3-azahexane-*N*-oxyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine

TOF	time-of-flight
Ts	tosyl
UV-Vis	ultra-violet-visible
VAc	vinyl acetate
XPS	X-ray photoelectron spectroscopy
YAG	Yttrium aluminium garnet

Curriculum Vitae

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03/2012 – 06/2012	**Karlsruhe House of Young Scientists** Research Travel Scholarship

List of Publications and Conference Contributions

Refereed Journal Publications

[10] *Polymer Surface Patterning via Diels-Alder Trapping of Photo-Generated Thioaldehydes*
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[01] *Facile Conversion of RAFT Polymers into Hydroxyl Functional Polymers: A Detailed Investigation of Variable Monomer and RAFT Agent Combinations*
Dietrich, M.; Glassner, M.; Gruendling, T.; Schmid, C.; Falkenhagen, J.; Barner-Kowollik, C. *Polym. Chem*. **2010**, *1*, 634-644.

Conference Contributions

[04] *Hetero-Diels-Alder Reactions of Thiocarbonyl Compounds for Polymer Architecture and Materials Design*
Glassner M.; Delaittre G., Kaupp M.; Blinco J.; Oehlenschlaeger K. K.; Welle A.; Bruns M.; Barner-Kowollik C.; **Belgian-German (Macro)Molecular Meeting**, Houffalize, Belgium, December 3-4, 2012 (Poster Presentation).

[03] *Hetero-Diels-Alder Chemistry for Nano-Structured Materials Design*
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[02] *With Modular Strategies and Controlled Radical Polymerization to Functional Materials: Surface Design and Bonding on Demand Systems.*
Barner-Kowollik, C.; Altintas, O.;Barner, L.; Blinco, J.; Bruns, M.; Glassner, M.; Goldmann, A.S.; Hubner, C.; Inglis, A. J.; Nebhani, L.; Schmiedl, D.; Schmidt, F. G.; Tischer, T.; Zydziak, N. **American Chemical Society 242th National Meeting and Exposition**, August 2011, San Francisco, USA
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[01] *Facile Conversion of RAFT Polymers into Hydroxyl Functional Polymers: A Detailed Investigation of Variable Monomer and RAFT Agent Combinations*
Dietrich, M.; Glassner, M.; Gruendling, T.; Schmid, C.; Falkenhagen, J.; Barner-Kowollik, C. **CRP meeting 2009**, Houffalize, Belgium, September 17-18, 2009 (Poster Presentation).

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Ich erkläre hiermit, dass ich die vorliegende Arbeit im Rahmen der Betreuung durch Prof. Dr. Christopher Barner-Kowollik, selbständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe.

Karlsruhe, den 07.11.2012