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**NEW APPLICATIONS OF COPPER-CATALYZED REVERSIBLE-
DEACTIVATION RADICAL POLYMERIZATION**

Doctoral Thesis

Supervisor: Vladimír Raus, Ph.D.



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**NOVÉ APLIKACE MĚDÍ KATALYZOVANÉ RADIKÁLOVÉ
POLYMERIZACE S REVERZIBILNÍ DEAKTIVACÍ**

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The research work reported in this dissertation was conducted independently by the author under the supervision of Dr. Vladimír Raus at the Institute of Macromolecular Chemistry, Czech Academy of Sciences, Prague, Czech Republic, from October 2020 to June 2024.

Declaration

I hereby declare that I have worked on my dissertation by myself and that all the literature sources used are listed in the reference list. Neither this work, nor its significant part was used to obtain other academic title.

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*Dedicated to my parents and in the loving memory of my
grandparents*

List of abbreviations and symbols

- ATRA : Atom transfer radical addition
- ATRP : Atom transfer radical polymerization
- BA : *n*-Butyl acrylate
- BMA : *n*-Butyl methacrylate
- CPAs : Complex polymeric architectures
- CRP : Controlled radical polymerization
- Cu-RDRP : Copper-catalyzed reversible-deactivation radical polymerization
- Cu(0)-RDRP : Metallic copper-catalyzed reversible-deactivation radical polymerization

- DCT : Degenerative chain transfer
- DMAc : *N,N*-Dimethylacetamide
- DMF : *N,N*-Dimethylformamide
- DMSO : Dimethylsulfoxide
- dn/dc : Refractive index increment
- $\bar{D} (M_w/M_n)$: Dispersity
- EBPA : Ethyl 2-bromophenyl acetate
- ECPA : Ethyl 2-chlorophenyl acetate
- FRP : Free radical polymerization
- GMA : Glycidyl methacrylate
- GPC : Gel permeation chromatography
- HEA : 2-Hydroxyethyl acrylate
- HEMA : 2-Hydroxyethyl methacrylate
- IPA : Isopropyl alcohol
- IV : Intrinsic viscosity
- k_p : Propagation rate constant
- k_p^{app} : Apparent rate constant of propagation
- LS : Light scattering
- LALS : Low-angle light scattering
- MA : Methyl acrylate
- MBP : Methyl 2-bromopropionate
- M-H plot : Mark–Houwink plot
- MMA : Methyl methacrylate

- MW : Molecular weight
- NMP : Nitroxide-mediated polymerization
- NMR : Nuclear magnetic resonance
- PRE : Persistent radical effect
- RAFT : Reversible addition-fragmentation chain transfer polymerization
- RALS : Right-angle light scattering
- RDRP : Reversible-deactivation radical polymerization
- RI : Refractive index
- SARA ATRP : Supplemental activation by reducing agent atom transfer radical polymerization
- SEC : Size exclusion chromatography
- SET-LRP : Single-electron transfer living radical polymerization
- SI : Surface-initiated
- TAGs : Trichloroacetyl groups
- TAI : Trichloroacetyl isocyanate
- TD-SEC : Triple detection – Size exclusion chromatography
- V_h : Hydrodynamic volume

List of publications

Publications included in the thesis:

1. **Sachin Gupta**, Miroslav Janata, Eva Čadová, Vladimír Raus; Straightforward synthesis of complex polymeric architectures with ultra-high chain density. *Chemical Science*, 2024, in revision (minor revision).
2. **Sachin Gupta** and Vladimír Raus; Cu(0)-RDRP of 2-hydroxyethyl methacrylate in a non-polar solvent enables rapid synthesis of high-molecular weight homopolymers and direct access to amphiphilic copolymers. *Reactive and Functional Polymers*, 2023, 183, 105509.

Publications not included in the thesis:

1. Miroslav Janata, **Sachin Gupta**, Eva Čadová, Pavla Angelisová, Bankala Krishnarjuna, Ayyalusamy Ramamoorthy, Václav Hořejší, Vladimír Raus; Sulfonated polystyrenes: pH and Mg²⁺-insensitive amphiphilic copolymers for detergent-free membrane protein isolation. *European Polymer Journal*, 2023, 198, 112412.
2. Manisha Singh, Lenka Poláková, Andres de los Santos Pereira, Ognen Pop-Georgievski, Jan Svoboda, Tomáš Riedel, **Sachin Gupta**, Zdeňka Sedláková, Vladimír Raus and Rafał Poręba; Well-defined poly(2-isopropenyl-2-oxazoline) brushes provide fouling resistance and versatility in surface functionalization. *Polymer Chemistry*, 2024, in revision (minor revision).

Contributions at international conferences

- 1. Polymers for Sustainable Future, 85th Prague Meeting on Macromolecules (PMM) and 11th Green Chemistry and Nanotechnologies in Polymeric Materials (GCNPM), 2024, Prague, Czechia.** Poster title: Straightforward synthesis of complex polymeric architectures using natural substrates.
- 2. Polymer Meeting 15, 2023, Bratislava, Slovakia.** Lecture title: Rapid copolymerization of HEMA by Cu(0)-RDRP in a non-polar solvent.
- 3. EPF European Polymer Congress 2022, Prague, Czechia.** Poster title: Trichloroacetyl isocyanate adducts as a new class of initiators for Cu-RDRP.
- 4. International Conference POLY-CHAR [Halle | Siegen] 2022, Germany.** Lecture title: Trichloroacetyl isocyanate adducts as a new class of initiators for Cu-RDRP.
- 5. Czech-Slovak conference Polymers-2022, Třešť, Czechia.** Lecture title: Cu(0)-RDRP of HEMA in a non-polar solvent: Rapid synthesis of well-defined, high-molecular weight (co)polymers.

Abstract

Copper-catalyzed reversible-deactivation radical polymerization (Cu-RDRP) is one of the most important controlled radical polymerization (CRP) techniques. Cu-RDRP has been successfully employed for the preparation of both functional and non-functional polymers with well-defined composition and architecture. The aim of this dissertation was to identify new applications of Cu-RDRP, primarily focusing on the synthesis of complex polymeric architectures (CPAs) and optimizing polymerization conditions for important functional monomers.

CPAs with well-defined topology play a central role in today's polymer science. However, the synthesis of CPAs via Cu-RDRP suffers from the lack of a robust and efficient strategy for the attachment of initiation sites to CPA precursors, particularly macromolecular ones, and the attached initiation sites are mostly monofunctional, which significantly limits the design of new polymeric materials. In the first part of this work, trichloroacetyl isocyanate (TAI), an established NMR derivatization reagent, was readily repurposed for rapid and clean installation of trichloroacetyl groups (TAGs) as Cu-RDRP initiation sites into both small molecules and polymers. Conditions were developed under which TAGs initiate well-controlled Cu-RDRP of styrene and various (meth)acrylates. Through comprehensive NMR and triple-detection SEC studies on model compounds, it was shown that TAGs act as trifunctional initiation sites for Cu-RDRP. The TAG multifunctionality combined with the instant character of TAI reactions enables the application of unconventional synthetic procedures and preparation of novel CPA topologies. This was exemplified by the *de novo* one-pot synthesis of a peculiar "star-on-star" architecture, the preparation of β -cyclodextrin-based multi-arm star polymers, and facile grafting from otherwise problematic cellulose substrates both in solution, obtaining ultra-dense bottle-brush copolymers, and from surfaces, affording thick polymer layers with the possibility of spatial control.

As a side-product of this research, the most universal contemporary Cu-RDRP method for the (co)polymerization of an important functional monomer, 2-hydroxyethyl methacrylate (HEMA), was developed, utilizing a Cu(0) catalyst, a chlorinated initiator, and a non-polar reaction medium (1,4-dioxane). The developed method enables the preparation of well-defined poly(HEMA) of different molecular weights (MWs). The polymerization reaction rates obtained were significantly higher compared to the literature protocols. The use of a non-polar solvent enables, for the first time, a direct access to low-dispersity HEMA-rich copolymers with non-polar comonomers, including highly lipophilic ones. This is demonstrated on the successful copolymerization of HEMA with an equimolar amount of 2-ethylhexyl methacrylate and of lauryl methacrylate, yielding well-

defined amphiphilic copolymers at quantitative conversion. This work significantly expands the application scope of the HEMA monomer and demonstrates for the first time that Cu(0)-RDRP in a non-polar solvent is applicable also to comparatively polar monomers.

Abstrakt

Mědí katalyzovaná radikálová polymerizace s reverzibilní deaktivací (Cu-RDRP) představuje jednu z nejvýznamnějších metod řízené radikálové polymerizace (CRP). Cu-RDRP je úspěšně využívána pro přípravu polymerů s dobře definovaným složením a architekturou. Cílem této disertační práce bylo nalézt nové aplikace Cu-RDRP. Práce byla zaměřena zejména na syntézu komplexních polymerních architektur (KPA) a obecněji také na optimalizaci polymerizačních podmínek pro významné funkční monomery.

KPA s dobře definovanou topologií hrají ústřední úlohu v dnešní polymerní vědě. Jejich syntéza prostřednictvím Cu-RDRP nicméně trpí absencí robustní a efektivní strategie pro navázání iniciačních míst na KPA prekurzory, zejména ty makromolekulární, a také tím, že navázaná iniciační místa bývají zpravidla monofunkční, což představuje silně omezující faktor při designu nových polymerních materiálů. V první části této disertace byl trichloroacetyl isokyanát (TAI), jinak široce používaný v NMR jako derivatizační reagent, s výhodou využit pro rychlé a čisté navázání trichloroacetylových skupin (TAS), sloužících jako iniciační místa pro Cu-RDRP, na různé nízkomolekulární látky a polymery. Byly vyvinuty podmínky, za nichž TAS iniciují dobře řízenou Cu-RDRP styrenu a různých (meth)akrylátů. Prostřednictvím detailní NMR a SEC studie na modelových látkách bylo prokázáno, že TAS se při Cu-RDRP chovají jako trojfunkční iniciační místa. Tato polyfunkčnost TAS v kombinaci s extrémní reaktivitou TAI umožňuje návrh nekonvenčních syntetických postupů a přípravu KPA s novou topologií. To bylo ilustrováno na „de novo one-pot“ syntéze speciální „star-on-star“ polymerní architektury, přípravě mnohramenných hvězdicových polymerů založených na β -cyklodextrinovém jádře a jednoduchém roubováním z jinak problematických celulosových substrátů, a to jak v roztoku (poskytující ultrahusté „bottle-brush“ kopolymery), tak z povrchů (poskytující silné polymerní vrstvy s možností lokalizace místa roubování na povrchu).

Jako vedlejší produkt výše zmíněného výzkumu byla vyvinuta v současnosti nejuniverzálnější Cu-RDRP metoda pro (ko)polymerizaci významného funkčního monomeru, 2-hydroxyethyl methakrylátu (HEMA), založená na použití Cu(0) katalyzátoru, chlorovaného iniciátoru, a nepolárního reakčního média (1,4-dioxan). Tato metoda umožňuje přípravu dobře definovaných poly(HEMA) polymerů v širokém rozmezí molekulových hmotností. Pozorované polymerizační rychlosti byly navíc významně vyšší ve srovnání s dřívějšími protokoly popsány v literatuře. Použití nepolárního rozpouštědla poprvé umožnilo přímou syntézu kopolymerů HEMA s nepolárními komonomery, včetně lipofilních, které mají vysoký obsah HEMA a nízkou dispersitu.

Tato možnost byla demonstrována na úspěšné kopolymerizaci HEMA s ekvimolárním množstvím 2-hydroxyethyl methakrylátu či lauryl methakrylátu, poskytující dobře definované amfifilní kopolymer za kvantitativních konverzí. Tento výzkum značně rozšiřuje aplikační potenciál HEMA a poprvé ukazuje, že Cu(0)-RDRP prováděná v nepolárním rozpouštědle je aplikovatelná i na polární monomery.

Keywords

Copper-catalyzed reversible-deactivation radical polymerization (Cu-RDRP); atom transfer radical polymerization (ATRP); complex polymeric architectures (CPAs); triple-detection size exclusion chromatography (TD-SEC); trichloroacetyl isocyanate (TAI); 2-hydroxyethyl methacrylate (HEMA); amphiphilic copolymers; star polymers; cellulose.

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1. Introduction

Since their inception, reversible deactivation radical polymerization (RDRP) techniques have been at the forefront of the methods used for the controlled polymerization of vinyl monomers. The major advantage of RDRP is its ability to provide a high degree of control over both the macromolecular architecture and molecular weight (MW). One of the major RDRP methods is copper-catalyzed RDRP (Cu-RDRP). Cu-RDRP serves as an “umbrella” term for different protocols, the best known of which is atom transfer radical polymerization (ATRP). In this dissertation, the term ATRP is used for techniques directly employing copper salts (e.g. CuBr or CuCl) as catalysts while for polymerizations utilizing metallic copper the term Cu(0)-RDRP is used. This is done without any attempts at determining the actual mechanisms of particular polymerization processes described. Some mechanistic features are still under debate in literature, and these aspects are not the subject of this dissertation.

This dissertation focuses on different aspects of Cu-RDRP both from methodological and application points of view. The major part of this work is dedicated to the development of a new strategy for the straightforward synthesis of complex polymeric architectures (CPAs) with ultra-high chain density. This study was motivated by the general inefficiency of the contemporary protocols used for CPA synthesis via Cu-RDRP. Two bottlenecks of the current strategies are addressed: i) the inefficiency of the Cu-RDRP initiation site introduction, and ii) the low functionality of the currently employed initiation sites. Through the new strategy, an access to a whole new group of CPAs characterized by a severalfold higher number of polymeric chains (e.g., grafts in graft copolymers or arms in star polymers) is unlocked, new types of CPA topologies become accessible, and the synthetic procedures are greatly simplified.

The second part of this dissertation deals with a “side-product” of the research undertaken during the development of the new CPA synthetic strategy mentioned above. There, unconventional Cu-RDRP conditions were found to be applicable to an important functional monomer, 2-hydroxyethyl methacrylate (HEMA), exploiting metallic copper-catalyzed RDRP (Cu(0)-RDRP) in a non-polar solvent. Intrigued by the anticipated benefits of these conditions, in a separate study, the protocol was adapted to Cu-RDRP of HEMA initiated by commercially available initiators. The optimized conditions enabled, for the first time, the synthesis of well-defined HEMA homopolymers in a wide MW range, and also direct copolymerization of unprotected HEMA with lipophilic comonomers leading to amphiphilic copolymers with high HEMA content.

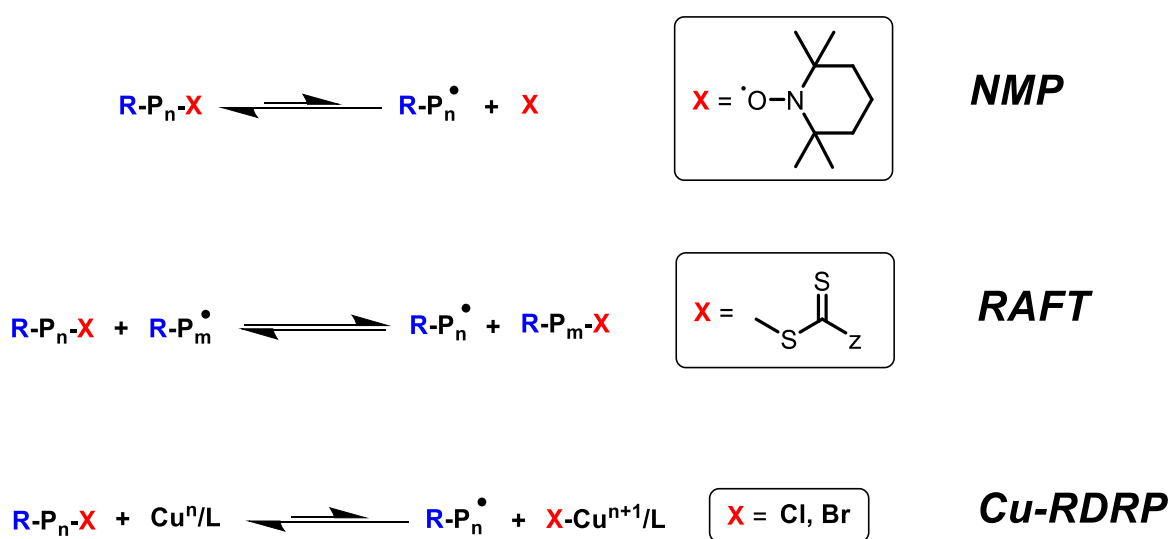
The dissertation is divided into several sections. The first section provides a *Literature review* covering different topics deemed relevant for research presented in the thesis, i.e., RDRP in

general with emphasis on Cu-RDRP and its different components; state-of-the-art of HEMA polymerization via Cu-RDRP; and strategies currently used for CPA synthesis via Cu-RDRP. Since extensive characterization of polymers via advanced size-exclusion chromatography (SEC) was conducted in the main dissertation part dealing with CPA synthesis, a small section of the literature review focuses on the polymer branching analysis via SEC and viscometry. Thereafter, *Experimental* section provides details of materials and synthetic procedures. Finally, the *Results and discussion* section elaborates on the two main dissertation topics detailed above.

2. Literature Review

2.1 Reversible-deactivation radical polymerization (RDRP)

Extensive development and expansion of RDRP techniques have been done in last 3-4 decades by different groups worldwide. Three major techniques are considered under RDRP: nitroxide-mediated polymerization (NMP), reversible addition-fragmentation chain transfer polymerization (RAFT) and Cu-RDRP. While the basic steps of radical polymerization (initiation, propagation and termination) still appear in the mechanisms of RDRP techniques, additional steps, such as controlled deactivation, differentiate them from classical free radical polymerization (FRP).^{1,2} RDRP techniques allow for the facile synthesis of various types of (co)polymers with control over the MW achieved and dispersity close to unity (<1.3). This is achieved by establishing a dynamic equilibrium between active ($R-P_n\cdot$) and dormant ($R-P_n-X$) species by the introduction of a mediating species (X) to reversibly “cap” the propagating radicals thus limiting their concentration and suppressing bimolecular radical termination reactions (**Scheme 1**).³ This leads to extended lifetime of the chain-end radical growth centre due to its reversible deactivation into the dormant form.

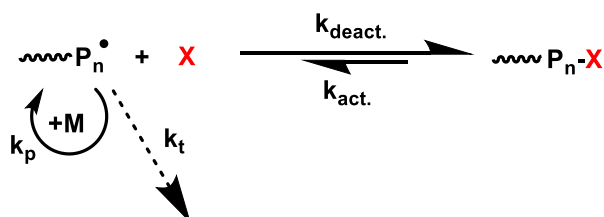


Scheme 1: Illustration of the dynamic equilibrium step for NMP, RAFT and Cu-RDRP.

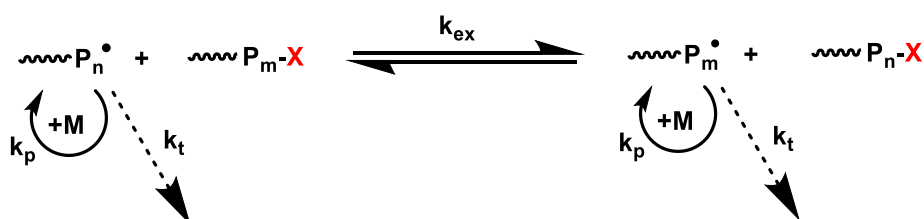
Two different mechanisms help in establishing the dynamic equilibrium a) persistent radical effect (PRE), b) degenerative chain transfer (DCT) (**Scheme 2**).⁴ NMP and Cu-RDRP are dependent on the PRE mechanism for establishing the equilibria; on the other hand, RAFT follows the DCT mechanism. PRE is a special kinetic feature which provides a self-regulating effect. Propagating radicals are trapped in the deactivation process (with a rate constant of deactivation, k_{deact}) by a mediating species. In NMP, the mediating species is a stable nitroxide radical. This nitroxide radical can either be directly added to the reaction mixture or obtained from the homolysis of the C-O bond in an

alkoxyamine NMP initiator.⁵ On the other hand, in Cu-RDRP, the mediating species is a catalyst which consists of a copper halide complexed with a ligand.⁶ The advantage of persistent radicals lies in their inability to terminate with each other and the ability to reversibly cross-couple with the growing species. In contrast to PRE, DCT mechanism follows usual FRP kinetics where steady state concentration of radicals is established via initiation and termination processes.⁴ In RAFT, a chain transfer agent (e.g., a dithioester compound) adds to the propagating radical thereby establishing the dynamic equilibrium since its concentration is larger than that of the used radical initiator.⁷ The rapid exchange between active and dormant species results in excellent control over the MW and dispersity. In addition, RDRP techniques provide control over (co)polymer architecture. Polymers obtained via RDRP techniques usually carry the dormant chain ends which can be used for chain extension (with the same monomer) or for the synthesis of block copolymers. Further, the attachment of the initiating/transfer sites to suitable substrates can be used for the synthesis of (macro)initiators affording different types of CPAs, such as graft or star (co)polymers.

Persistent radical effect



Degenerative chain transfer



Scheme 2: Dynamic equilibrium in RDRP established through PRE (top) and DCT (bottom).

2.2 Atom transfer radical polymerization (ATRP)

ATRP is one of the most versatile and powerful RDRP techniques, developed independently in 1995 by the groups of Sawamoto⁸ and Matyjaszewski⁹. A wide range of monomers could be (co)polymerized via ATRP, which made it one of the most prominent choices for the synthesis of

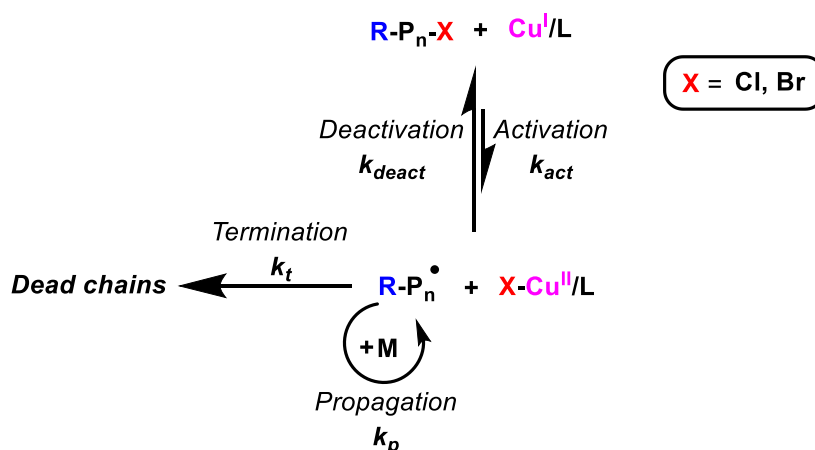
polymers with well-defined chain lengths. An important feature of ATRP arises from its tolerance towards functional groups present in different monomers. This allows for the preparation of different functional materials with numerous applications such as drug delivery, biomedical applications, electronics, catalysis, photonics, etc.⁶ Nowadays, copper-catalyzed ATRP (or, more generally, Cu-RDRP) is by far the most widespread approach. ATRP has several variations that are majorly related to the differences in the activation/initiation process.¹⁰ A list of different ATRP variants is provided in **Table 1**.

Table 1: List of different types of ATRP.¹⁰

Type of initiation in ATRP	Main difference
Normal	Cu(I)X is the main source of catalyst to generate the radical that initiates the ATRP process
Reverse	A Cu(II) salt is added as a deactivator while the initiation happens using a classical radical initiator
Photoinitiation	A source of light is used to reduce Cu(II) salts to Cu(I) and a halide radical which initiates the ATRP process
Electrochemical	Cu(II) salts are electrochemically reduced to Cu(I) species that activates the initiator and generate radical to initiate the ATRP process
Simultaneous Reverse and Normal initiation (SR&NI)	A radical initiator decomposes to generate radicals that rapidly reduce Cu(II) species to Cu(I) that activates an additional alkyl (pseudo)halide compound generating radical which initiates the ATRP process
Activator Generated by Electron Transfer (AGET)	A reducing agent reduces a Cu(II) species to Cu(I) that activates the initiator and generates a radical to initiate the ATRP process
Activator ReGenerated by Electron Transfer (ARGET)	A reducing agent reduces Cu(II) species throughout the course of polymerization to regenerate Cu(I) that activates the initiator and generates a radical to initiate the ATRP process
Initiators for Continuous Activator Regeneration (ICAR)	A radical initiator decomposes to generate a radical which slowly reduces Cu(II) species to Cu(I). An additional alkyl (pseudo)halide compound then initiates the ATRP. (Very low concentration of catalyst is used)
Supplemental Activation by Reducing Agent (SARA)	Cu(0) in the form of copper powder or copper wire is used to abstract the halide atom from an initiator, resulting in a Cu(I)X species and a radical which initiates ATRP

The seminal paper by Wang and Matyjaszewski reported the use of CuCl for the controlled polymerization of styrene at 130 °C in the presence of 1-phenylethyl chloride as an initiator and 2,2'-bipyridine as a complexing ligand.¹¹ The exact mechanism of the ATRP process follows the footsteps of atom transfer radical addition (ATRA), which is employed in organic synthesis for the

formation of carbon-carbon bonds with high yields. A reversible redox process is the key step in regulating the radical concentration. **Scheme 3** shows a general mechanism of conventional copper-catalyzed ATRP. The low-oxidation-state metal complex ($\text{Cu}^{\text{I}}/\text{L}$) serves as an activator that reversibly reacts with an alkyl halide (RX) initiator (in the initiation stage) or a halogen-capped dormant chain ($\text{R-P}_n\text{-X}$) (in the propagation stage). This reaction produces radicals along with the high-oxidation-state metal complex ($\text{X-Cu}^{\text{II}}/\text{L}$). The high-oxidation-state complex acts as a deactivator, reconvertng the radical to its dormant state. Consequently, ATRP proceeds through a series of activation and deactivation cycles, concluding either upon complete monomer consumption, through the deactivation of the catalytic complex, or through the complete termination of all the growing chains. The equilibrium in ATRP is strongly shifted towards the dormant species, resulting in a low concentration of growing macroradicals and minimizing termination reactions to less than 5% of polymer chains in an ideal scenario.¹



Scheme 3: General mechanism of ATRP showing different steps and the associated rate constants.

The overall rate of polymerization is dependent on the initiator concentration, monomer concentration, and propagation rate constant (k_p). Equations 1, 2 and 3 are relevant for the ATRP process.

$$R_p = -d[\text{M}]/dt = k_p[\text{M}][\text{R-P}_n^\bullet] \approx k_p^{\text{app}}[\text{M}] \quad (1)$$

$$K_{\text{Cu-RDRP}} = k_{\text{act}}/k_{\text{deact}} = [\text{R-P}_n^\bullet][\text{X-Cu}^{\text{II}}/\text{L}]/[\text{R-P}_n\text{-X}][\text{Cu}^{\text{I}}/\text{L}] \quad (2)$$

$$\ln ([\text{M}_0]/[\text{M}]) = k_p^{\text{app}}t \quad (3)$$

The controlled/“living” character of the ATRP process can be evaluated by plotting the semilogarithmic equation 3, which ideally gives a straight line with a slope directly representing the apparent propagation rate constant (k_p^{app}). With the knowledge of k_p for the particular system, the instantaneous concentration of radicals (**R-P•**) can theoretically be determined which should be constant throughout the course of polymerization under ideal conditions (i.e. no termination involved). To establish good control in ATRP, the rate of deactivation (k_{deact}) should be higher by several orders of magnitude compared to the rate of activation (k_{act}). This is sometimes achieved by increasing the concentration of the deactivator (**Cu^{II}** salt) by its external addition. Since Cu-RDRP involves several components, extensive research has been conducted to establish the effect of each component.

2.3 Metallic copper-catalyzed RDRP (Cu(0)-RDRP)

In 1997, Matyjaszewski and co-workers reported the use of Cu(0) as a source of copper to mediate an ATRP process.¹² Mechanistically, Cu(0) oxidizes to Cu(I) species by the abstraction of **X**. This Cu(I)X species is then expected to undergo a conventional ATRP activation process resulting in the formation of a deactivator, i.e. Cu(II)X. The resulting Cu(II) species not only act as a deactivator but also can undergo comproportionation with Cu(0) thus regenerating the Cu(I) species. The process was later named supplemental activation by reducing agent ATRP (SARA ATRP). However, in 2006, Percec and co-workers reported that Cu-RDRP mediated by Cu(0) follows the mechanism of single-electron transfer and named the process “single-electron transfer living radical polymerization (SET-LRP)”.¹³ According to this alternative SET mechanism, Cu(0) is the primary activator, and the Cu(I) species so formed undergo instantaneous disproportionation, producing Cu(II) species and “nascent” Cu(0) *in situ*. During the polymerization, deactivation occurs via Cu(II) species while the nascent Cu(0) (copper (nano)particles) are chiefly responsible for the activation process due to their high reactivity. There is an ongoing debate over the exact mechanism of Cu(0)-RDRP. Matyjaszewski and co-workers claim that SARA process prevails over SET-LRP whereas Percec and co-workers propose the contrary.^{14,15} Nevertheless, both the groups do not completely deny that the mechanism might involve both the processes although their extent can be significantly different.

Cu(0)-RDRP has been mostly used to polymerize simple acrylates,^{12,13} methacrylates,¹⁶ and less frequently, styrene¹⁷. Additionally, a few reports exist where other classes of monomers were polymerized using Cu(0)-RDRP. For example, Raus and co-workers have utilized Cu(0)-RDRP for the polymerization of functional monomers such as *N*-(2-hydroxypropyl) methacrylamide (HPMA),¹⁸ 2-isopropenyl-2-oxazoline (IPOx),¹⁹ and glycidyl methacrylate (GMA)²⁰ in polar solvents, and

POSSMA²¹ and HEMA²² in non-polar solvents. Most of the previous works report that the solvent plays a key role in determining the extent of contribution from disproportionation or comproportionation in Cu(0)-RDRP. While certain polar solvents such as DMSO and DMF promote disproportionation, other solvents, such as acetone, acetonitrile, or toluene, tend to favour comproportionation; however, the overall effects would depend also on the monomer's polarity.

2.4 Solvents

Solvents (or reaction media) have profound impact on the $K_{\text{Cu-RDRP}}$. Although, Cu-RDRP can be performed in bulk (i.e., in the absence of any solvent), solvents are used for various reasons. They generally help to offset the high polymerization mixture viscosity and are also introduced specifically for the synthesis of those polymers which are insoluble in their monomers (e.g., polyacrylonitrile).²³ The additional benefits of using solvents stem from their ability to dissipate the heat release during the radical polymerization, which on an industrial scale is an important parameter to be considered. Additionally, a solvent can also accelerate or decelerate the radical formation and stabilization during the polymerization. Early reports on Cu-RDRP utilized mostly non-polar solvents such as anisole, toluene, xylene, etc., for polymerization of non-polar monomers (styrene, MMA).¹¹ Soon polar solvents or mixed solvent systems were introduced, which facilitated controlled synthesis of polar polymers.²⁴ The effect of solvents is also related to their ability to dissolve not only the monomer and polymer but also the catalytic species. Examples of various solvents employed in Cu-RDRP were reported in several reviews.²⁵

2.5 Ligands

Ligands play a key role in establishing the dynamic equilibrium in all the Cu-RDRP processes. Multidentate nitrogen-containing ligands are often employed in Cu-RDRP. Ligands bind with the copper species in different oxidation states thereby stabilizing the catalyst and modifying its solubility in reaction media. The structure of the ligand affects the polymerization control to a large extent.²⁶ Multidentate ligands have been shown to work best for Cu-RDRP. Cyclic and/or bridged ligands yield more active catalysts than their linear counterparts. Examples of some ligands successfully used in Cu-RDRP are shown in **Figure 1**. It is noteworthy that the overall cost of a Cu-RDRP process includes a major contribution of the cost of ligand, which usually are expensive compounds. Thus, efforts are made to lower the cost of Cu-RDRP processes by using inexpensive ligands such as N,N,N',N',N''pentamethyldiethylenetriamine (PMDETA) as opposed to more costly

variants such as tris(2-dimethylamino)ethyl)amine (Me₆TREN). The stoichiometry of the ligand is also significant when developing a Cu-RDRP protocol for a particular monomer. In some cases, it is observed that a lower concentration of a ligand is most effective in regulating the $K_{Cu-RDRP}$ whereas high concentrations can lead to the loss of control.²⁷ Therefore, it is important to determine the most efficient ratio of copper catalyst and ligand to efficiently control the Cu-RDRP process. Nevertheless, frequently, one has to optimize also the other conditions, i.e., solvent, temperature, etc. In this dissertation, two different ligands, PMDETA and Me₆TREN, were predominantly used. PMDETA (tridentate) and Me₆TREN (tetradentate) ligands have also been a prominent choice for Cu(0)-RDRP of various functional monomers in polar and non-polar solvents.²⁵

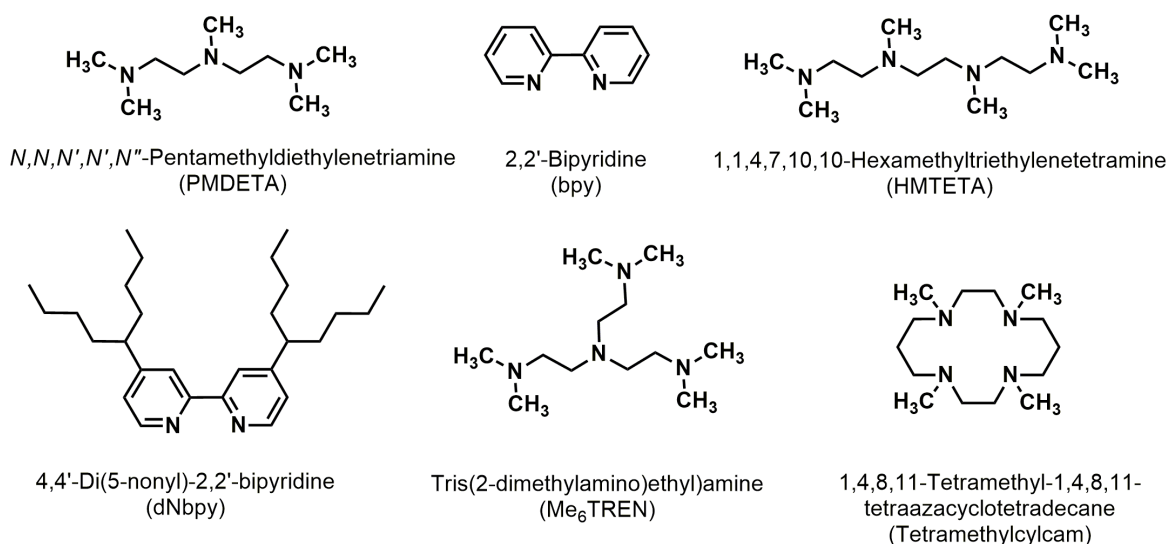


Figure 1: Examples of ligands used in Cu-RDRP.

2.6 Monomers

As mentioned above, the most important features of Cu-RDRP includes its applicability to different classes of monomers with diverse functionalities. When switching from one monomer to another, an extensive optimization study is often required to identify the exact conditions (solvent, initiator, Cu-source, ligand, temperature, time) for Cu-RDRP. **Figure 2** represents examples of monomers that have been polymerized using Cu-RDRP.

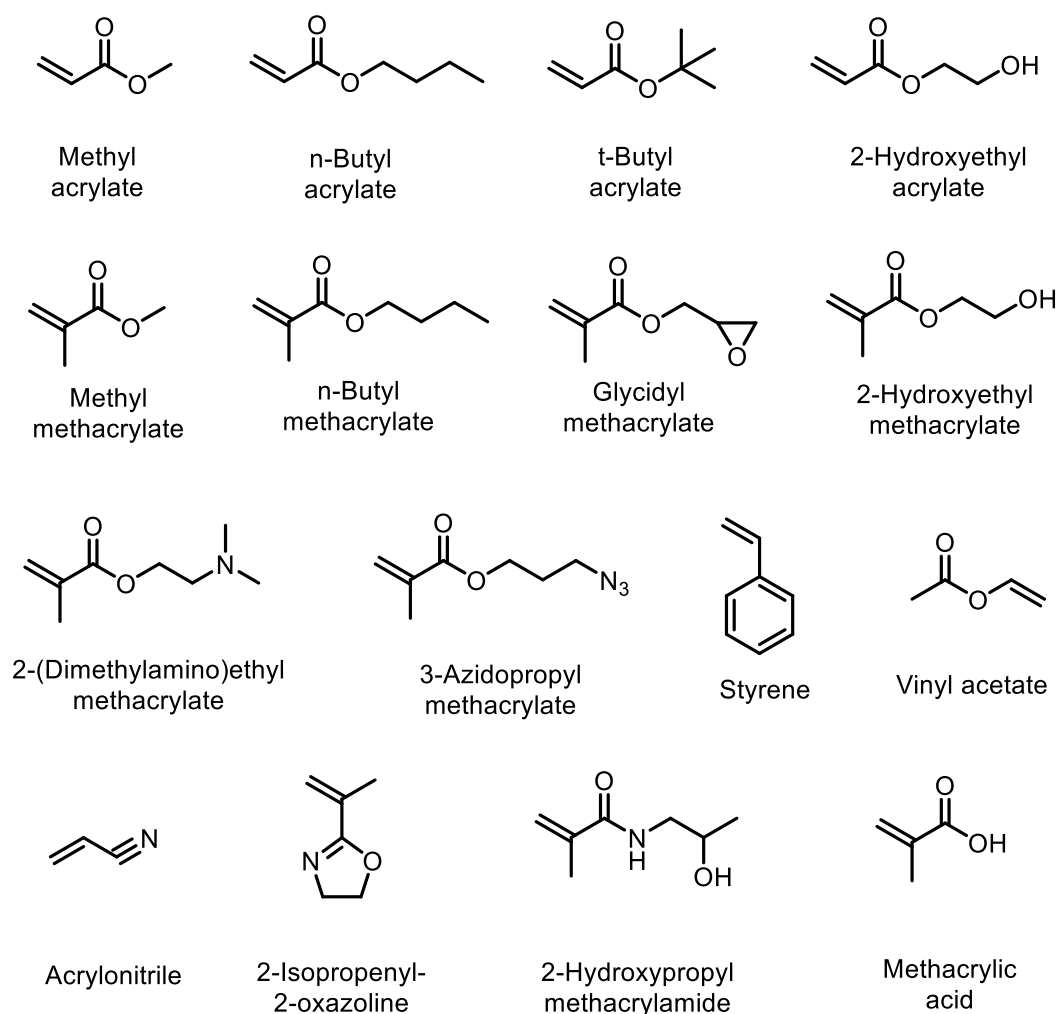


Figure 2: Examples of monomers polymerized via Cu-RDRP.

2.6.1 2-Hydroxyethyl methacrylate (HEMA)

As mentioned above, within the framework of this thesis, Cu-RDRP of an important functional monomer, HEMA, was studied extensively. Poly(HEMA) was introduced for the preparation of hydrogels for biological use by Lím and Wichterle in 1960.²⁸ Since then, poly(HEMA)-based materials have found numerous applications especially in the field of biomedical science,²⁹ including soft contact lenses,³⁰ wound dressings,³¹ tissue engineering scaffolds,³² surgical implants,³³ or drug delivery vehicles.³⁴ Synthesis of well-defined poly(HEMA)-based materials of diverse architectures has been enabled by the development of RDRP techniques.³⁵ In 1999, the first successful ATRP of HEMA was reported in a mixed solvent system comprised of methyl ethyl ketone (MEK) and 1-propanol.³⁶ The method worked well for low MWs but failed to produce high MWs polymer (limited conversion and high dispersity were observed). This issue was rectified by using HEMA monomer

with the hydroxyl group protected by trimethylsilyl. Later, synthesis of well-defined poly(HEMA) was reported by Armes and coworkers in methanol or methanol/water mixtures.³⁷⁻³⁹ Further, they also reported that isopropanol/water mixtures can be employed too.⁴⁰ Thereafter, several other groups reported the ATRP of poly(HEMA) in ethylene glycol⁴¹ and MEK/methanol mixture⁴². The latter medium was further employed by Oh and Matyjaszewski⁴³ for AGET-ATRP of HEMA whereas Baker and coworkers⁴⁴ used methanol for ARGET-ATRP of HEMA. Nonetheless, it was later found that the ATRP of HEMA conducted in alcoholic solvents suffered from monomer transesterification under standard ATRP conditions, leading to copolymers of HEMA and MMA when methanol was employed as a solvent.⁴⁵ Finally, DMSO was employed by Percec and coworkers for the synthesis of ultrahigh-MW poly(HEMA) via Cu(0)-RDRP.⁴⁶ However, the method suffered from long reaction times and high polymer dispersity for MWs higher than several tens of thousands. Interestingly, also all the other above-mentioned Cu-RDRP methods that employed polar media provided limited conversion^{36,41-43,46} and/or poor polymerization control^{36,41,42,44,46} when targeting high-MW polymers. As a result, the field lacked a reliable method for well-controlled polymerization of HEMA in a wide range of MWs.

Due to the polar character of HEMA, non-polar solvents were not generally considered for synthesis of homopolymers. However, copolymerization of HEMA with an excess of a non-polar comonomer could be conducted in a non-polar solvent.⁴⁷ If this was not possible, protected HEMA was used to obtain copolymers with well-defined chain lengths.^{48,49} The drawback of using protected HEMA is that it brings an additional deprotection step to obtain final polymer. Furthermore, Yuan et al. reported synthesis of an amphiphilic triblock copolymer with a poly(HEMA) block via Cu(0)-RDRP in toluene.⁴⁷

Considering these previous studies, it was realized that a well-controlled Cu-RDRP method for homopolymerization of unprotected HEMA and its copolymerization with lipophilic (non-polar) comonomers would be instrumental in the direct synthesis of amphiphilic polymers thereby increasing the application potential of HEMA.

2.7 Initiators

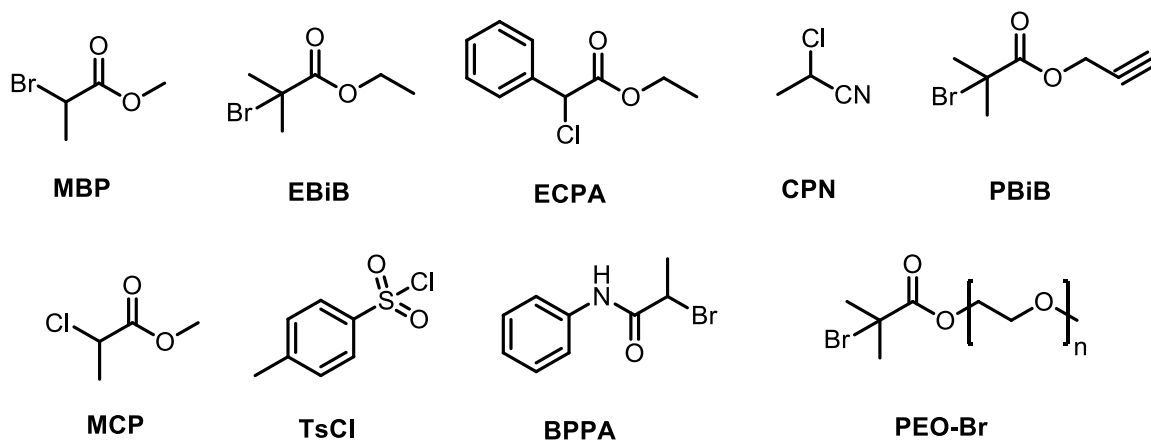
An initiator is the key to Cu-RDRP. Besides influencing if and when the polymerization control will be achieved, it determines the number of growing polymer chains and the type of the halogen atom that is installed at the end of the polymeric chain (the type of the used copper salt also plays a role in this respect). Various organic halides have been used as initiators, including alkyl halides, allyl and benzyl halides, α -haloesters, α -haloketones, α -halonitriles, and sulfonyl halides.²⁵ Brominated and chlorinated initiators are prominently employed in Cu-RDRP. Iodinated⁵⁰ and fluorinated⁵¹

initiators have been also used but compared to brominated/chlorinated variants the use was extremely limited because of unwanted side reactions (iodinated compounds) or very slow activation (fluorinated compounds). Fast and quantitative initiation is necessary to achieve narrow dispersity. An initiator that yields a high concentration of radicals that are not efficiently deactivated or do not easily initiate polymerization by the reaction with a monomer, may provide decreased initiation efficiency (IE) and, consequently, a mismatch between the theoretical and experimental polymer MWs. The activity of initiators arises from the bond dissociation energies of **R-X**. Brominated initiators (R-Br) are usually a primary choice due to their lower bond strength compared to the chlorinated initiators (R-Cl). However, the (in)stability of R-Br in different reaction media, especially aqueous ones, makes it vulnerable to hydrolysis, thereby making it less suitable in such instances.⁵² In such cases, chlorinated initiators are preferred as they are less readily hydrolyzed. Importantly, in this thesis, it is shown that also in non-polar solvents the use of chlorinated initiators can provide better control over polymerization compared to brominated initiators. However, the overall polarity of the reaction medium (monomer and solvent) can play a role.²² Better control over the propagation rate can be achieved by selecting the initiators with a structure similar to the monomer used. For example, methyl 2-bromopropionate (MBP) is used to polymerize methyl acrylate (MA) due to their structural similarity which allows for the generation of propagating radical with similar behavior as the initiating radical.⁵³ Generally, in a particular Cu-RDRP system, it is crucial to identify a suitable initiator that matches the activity of the monomer and thus results in an efficient and controlled polymerization.

Figure 3 shows several examples of initiators typically used in Cu-RDRP. While the depicted monohalogenated compounds act as monofunctional initiators, compounds bearing more than one halogen can theoretically act as multifunctional initiators. Note that the term multifunctional initiator is commonly used in different contexts. To clarify the differences between multifunctional initiators and multifunctional initiation sites, see **Figure 4**. It can be clearly seen that the number of halogen atoms present at the particular initiation site decides the number of polymeric chains that can be grown from that site. A compound bearing single monofunctional initiation site is usually termed as monofunctional initiator (e.g., ethyl 2-chlorophenylacetate (ECPA))⁵⁴ whereas both compounds bearing a single (or multiple) multifunctional initiation site(s) and compounds bearing multiple monofunctional initiation sites are termed as multifunctional initiators in the literature, with the latter variant being markedly more common. Clearly, differences in the functionality of the initiation sites present in multifunctional initiators will have a huge impact on the overall architecture of the polymer obtained.

Multifunctional initiators based on multifunctional initiation sites open avenues for the synthesis of specific CPAs, which will be discussed in the following section.

Monofunctional



Multifunctional

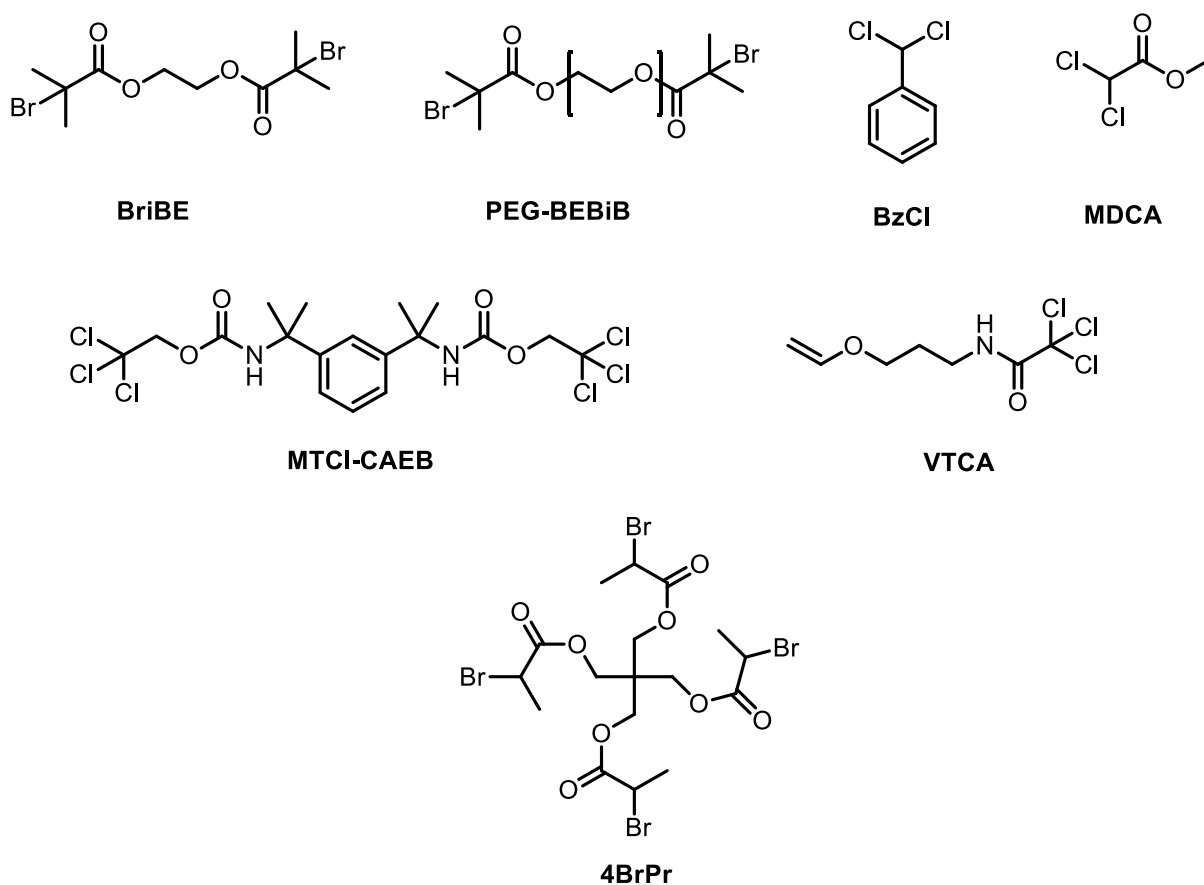


Figure 3: Examples of initiators employed in Cu-RDRP.

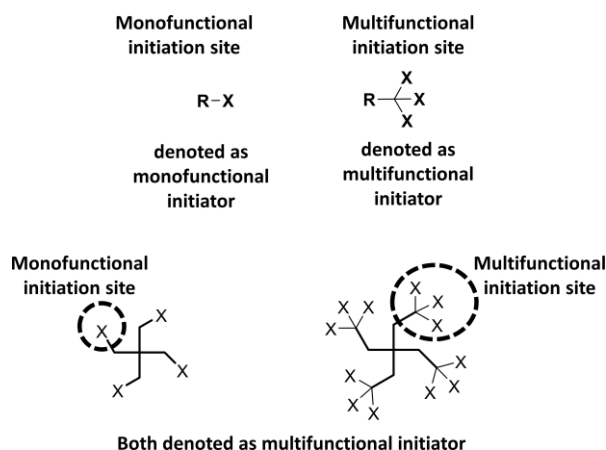


Figure 4: A comparison of initiators with different types of initiating sites.

2.8 Complex Polymeric Architectures (CPAs):

The development of some novel polymeric materials has been enabled by the availability of CPAs of well-defined composition, topology, and functionality. For example, CPAs can take the form of dendrimers,⁵⁵ bottle brushes,⁵⁶ stars,⁵⁷ or graft⁵⁸ and hyperbranched⁵⁹ (co)polymers (**Figure 5**). CPAs have found applications in diverse fields, including catalysis,⁶⁰ photonics,⁶¹ bioimaging,⁶² nanotemplating,⁶³⁻⁶⁵ or drug delivery.⁶⁶⁻⁶⁹

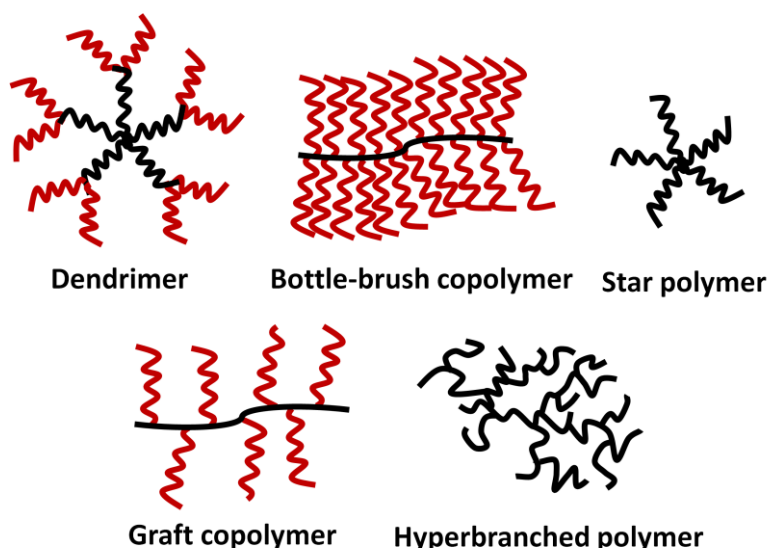


Figure 5: Examples of CPAs

Precise control over the composition, chain topology, and functionality of CPAs can be achieved using different RDRP methods. Synthesis of CPAs via RDRP techniques involves several layers of complexity. This includes finding a suitable substrate/CPA precursor based on the required

architecture, the attachment of initiation/transfer sites which can allow for polymer growth, the control over the chain length, the stability of linkers between the substrate/CPA precursors and polymeric chains, etc.

Among RDRP methods, RAFT⁷⁰ and Cu-RDRP^{71,72} have been extensively used for constructing different kinds of CPAs. The key step in the construction of CPAs is the attachment of initiation/transfer sites onto a CPA precursor, which allows for the subsequent polymer chain growth. For example, in RAFT, a CPA precursor needs to be decorated with transfer agents, whereas in Cu-RDRP, initiation sites that typically take the form of halogenated esters are installed onto a CPA precursor. These groups are usually attached via acylation reactions, e.g. with 2-bromoisobutyryl bromide (BriBBr).^{65,73-75} While this acylation strategy works relatively well for small molecules, its efficacy diminishes considerably when applied to macromolecular substrates, hampering the stoichiometric control over the number of introduced initiation sites and often limiting the maximum achievable site concentration.^{65,76,77} This represents a serious bottle-neck in certain applications. For instance, in graft copolymerization, the concentration of initiation sites is a key parameter influencing the grafting density and, in turn, determining the (co)polymer properties in bulk or when bound to a surface via surface-initiated (SI) grafting.⁵⁸ The substrate modification issues are particularly pronounced when targeting important natural substrates such as cellulose. The complex supramolecular structure of cellulose significantly decreases the functional group accessibility during the acylation step,^{65,75,76} necessitating the development of cumbersome multi-step protocols in order to prepare densely-grafted copolymers.⁶⁵ Additionally, acylation reactions produce byproducts that must be eliminated at different stages by either precipitation/extraction (for macromolecular substrates)⁷⁶ or recrystallization/chromatography (for small molecules)⁷⁸. Moreover, the acylation reactions used for the introduction of Cu-RDRP initiation sites usually require long reaction times, spanning from a few hours to a week.^{64,65,79,80} These aspects add to the general complexity of the synthetic protocols, making the preparation of CPAs via Cu-RDRP often tedious, multi-step processes. Improvements to the traditional protocol would therefore be highly desirable.

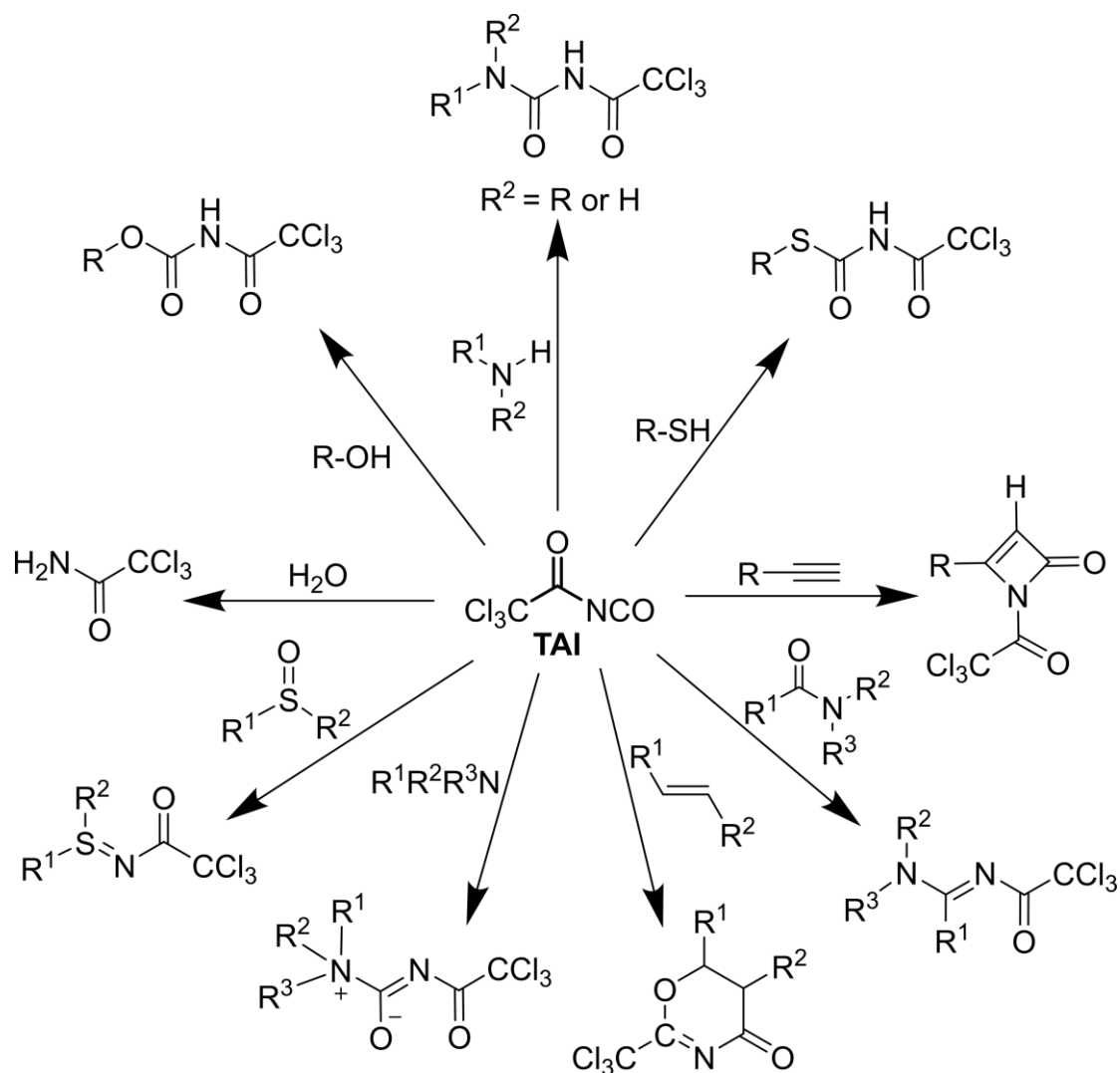
It is noteworthy that the Cu-RDRP approach to the CPA synthesis, as it is now typically implemented, uses nearly exclusively monofunctional initiation sites, permitting a maximum of one polymeric chain per site. Unfortunately, this restriction is sometimes made worse by the ineffectiveness of the reactions (e.g., acylation) employed to attach the initiation sites as well as the lower initiation efficiency (IE) that has been noted in certain Cu-RDRP systems.⁸¹ An effective solution to most of these problems lies in the use of Cu-RDRP initiators with multifunctional initiation sites. It is interesting to note that small-molecule multifunctional initiators (e.g., CCl₄ or di/trichloro esters)

have been studied since the inception of Cu-RDRP but have never found widespread use.⁸²⁻⁸⁴ As discussed above, in multifunctional Cu-RDRP initiation sites, a copper catalyst can activate more than one of the existing carbon-halogen bonds thereby allowing the growth of multiple polymeric chains from a single carbon atom. Bi- or trifunctional initiation sites can be used in the synthesis of CPAs to increase the functionality of the (macro)initiator derived from a CPA precursor. Our group at IMC has previously shown that bifunctional Cu-RDRP initiators can be used in CPA synthesis.^{85,86} In these pioneering works, cellulose esters were decorated with dichloroacetate initiation sites that resulted in higher grafting density when compared to monofunctional initiating sites. However, two serious limitations were observed with the use of the bifunctional dichloroacetate sites. Firstly, the universality of the initiator was not proven since it was used exclusively for methacrylates. More importantly, due to the inefficiency of the attachment of initiation sites, the overall grafting density was significantly reduced. In other words, the number of initiation sites introduced on the substrate did not correspond to the high stoichiometric excess of the acylation reagent used.^{65,76,77,85} Taken together, the macromolecular community has not yet been able to fully utilize the potential of multifunctional Cu-RDRP initiating sites in CPA synthesis because of the aforementioned limitations.

To effectively amplify the (macro)initiator functionality via multifunctional Cu-RDRP initiation sites, various criteria should be met. The first criterion lies in the universality of the multifunctional initiation sites, meaning that different monomer classes should ideally be polymerizable under diverse conditions. Next, the activation of all the carbon-halogen bonds present at the multifunctional initiation sites should be possible, which will directly impact the IE of both the particular multifunctional initiation site and the overall (macro)initiator. Lastly, the synthetic protocols for installing multifunctional initiation sites on CPA precursors should be significantly more effective when compared to contemporary acylation protocols. With all these criteria met, synthesis of CPAs with a higher number of polymeric chains, and thus higher chain density, will become possible.

In this work, it is proposed that adducts of TAI can become suitable candidates that meet all the above-mentioned criteria for multifunctional initiation sites. TAI holds several important features enabling it to be employed as a vehicle for the installation of trichloroacetyl groups (TAGs) on a variety of CPA precursors, both small molecules and macromolecules. TAI is a relatively inexpensive (~100 euros for 10 g) *in situ* derivatizing reagent that has for decades been employed for the structural assignment of organic compounds having amino,⁸⁷ thio,⁸⁸ and hydroxy^{87,89-91} functional groups via NMR spectroscopy. TAI reacts rapidly with these functional groups, affording quantitative and straightforward 1,2-addition reactions yielding urea, thiocarbamate, and carbamate derivatives as products, respectively. Using ¹H-NMR spectra, the identification of the

imidic hydrogens formed in these derivatives is easily possible due to their specific chemical shifts in downfield region (usually > 8 ppm) and their tendency to undergo H-D exchange upon D₂O addition. For this reason, the TAI method has found a widespread use in the determination of protic end-groups in synthetic polymers, including those prepared by RDRP.⁹²⁻⁹⁶ Besides simple 1,2-additions, TAI can also take part in several other types of reactions, such as 1,2- and 1,4-cycloadditions, which increases the diversity of substrates/CPA precursors it can potentially modify.^{89,97} Some of the TAI reactions relevant to polymer chemistry are depicted in **Scheme 4**.



Scheme 4: Selected reactions of TAI relevant to polymer chemistry.

As can be seen in **Scheme 4**, most TAI reactions lead to the installation of a TAG group *bearing three chlorine atoms* that may potentially initiate the growth of up to three polymeric chains per an initiation site. Importantly, several literature reports used TAG-bearing compounds as initiators for polymerization of different monomers via transition metal-catalyzed RDRP.^{82,83,98-101} Nevertheless, these reports provided only limited evidence supporting that TAGs can behave as bi- or trifunctional

initiation sites. It is also noteworthy that already in 1987, Bamford and coworkers designated TAI and other halo-isocyanates as “transformation reagents” usable for rapidly transforming polymeric substrates into macroinitiators for the synthesis of block and graft copolymers via free radical polymerization.¹⁰²

It can be envisaged that the combination of TAI modification and Cu-RDRP can become a powerful integrated strategy for CPA synthesis (further denoted as the TAI strategy herein). This would help overcome the hurdles associated with the inefficient initiator attachment and provide an access to a new group of CPAs with dramatically increased chain density that could be characterized by novel properties and applications. The highlights of the TAI strategy are as follows: (a) TAI reactions are expected to be cleaner, faster, and more efficient, both in homogeneous and heterogenous phase, as compared to traditional acylation protocols. (b) The instantaneous character of the TAI addition reactions opens avenues for *in situ* modifications and one-pot protocols avoiding the isolation and purification of (macro)initiators. (c) Depending on the modified functional group, the introduced trichloroacetyl initiation sites are bound to the substrate through linkers of different structure and reactivity, which could be potentially exploited in the programmed degradation of synthesized CPAs. (d) As mentioned above, TAG can theoretically behave as a trifunctional initiator, giving rise to three polymeric chains per one initiation site.^{82,101} This higher functionality could enable access to CPAs of novel topologies and properties (e.g., super-densely grafted bottle-brush copolymers and polymer brushes, hyperbranched polymers with unique branching patterns, etc.). (e) TAI can double function as both an analytical reagent and a RDRP initiator source; the easy identification of the initiation group concentration via NMR can help assume better control over the final CPA parameters.

Surprisingly, there is only single literature report on using a TAI-derived initiator in Cu-RDRP, which utilized a thiophene/TAI adduct to synthesize a thiophene-capped poly(methyl methacrylate) (MMA) macromonomers.¹⁰³ Therefore, the huge potential of the TAI strategy in CPA synthesis has remained untapped until today.

3. Determination of Molecular Weights

Gel permeation chromatography (GPC) or size exclusion chromatography (SEC) are two terms which are usually used to describe the same chromatographic process. SEC is the most common method used for the MW analysis of polymers. In this dissertation, both routine and advanced-detection SEC studies were conducted for the determination of MWs and structure of different polymers.

Different variants of SEC are employed in polymer characterization. Routinely, a single concentration detector (usually differential refractive index detector, dRI or simply RI) is employed in conjunction with SEC, using a conventional calibration to determine MWs (denoted as SEC-RI here). Through this technique, a relative MW of the polymer sample is determined using a calibration curve constructed using a series of low-dispersity standards of different MWs. However, the MW analysis via the conventional calibration suffers from various limitations. Firstly, to obtain an accurate MW of a polymer sample, the standards should be of the same chemical composition as the analyte. Additionally, for non-linear/branched polymers, conventional calibration provides incorrect MWs due to the large differences in the hydrodynamic volumes (V_h) of the polymers in solution. Therefore, more advanced analyses of branched polymers are conducted using more sophisticated detection systems. For this, light scattering (typically multi-angle light scattering (MALS) or the combination of low-angle light scattering (LALS) and right-angle light scattering (RALS)) and viscometry detectors are employed along with a concentration detector. The combination of these three detectors with SEC is often referred to as “triple detection SEC” (TD-SEC). There are several advantages to using TD-SEC over conventional SEC. For example, the calculation of MW using TD-SEC is independent of the calibration standards, thus “absolute” MWs are obtained. Additionally, several other polymer properties, such as intrinsic viscosity (IV), hydrodynamic radius (R_h), or radius of gyration (R_g), can be determined using TD-SEC. Since the major part of this dissertation deals with the synthesis of CPAs of different architectures, the TD-SEC technique was employed to verify the characteristics of the polymers (e.g., branching) using the viscometry detector as it provides key information about the differences in viscosity of polymers of different architectures. Thus, in the subsequent section, a brief discussion about the principle and application of the viscometry detector is provided.

3.1 Viscometry Detector

The viscometry detector measures the solution viscosity of the polymer sample as it elutes from the SEC column. The viscosity is measured relative to the solvent viscosity. This provides a specific viscosity (η_{sp}) of the polymer in the particular solvent that is then converted to IV using the

concentration measured by RI. It is generally observed that polymers with different MW have different IV. The overall effect of the MW on the IV is related to the V_h of the polymer in the particular solvent and is characterized by the equation 4.

$$V_h \propto MW \times IV \quad (4)$$

Using viscometry detector allows the assessment of the Mark-Houwink-Kuhn-Sakurada plot (also referred to as Mark-Houwink plot or M-H plot). M-H plot is the relationship between MW and IV for a given polymer sample in a particular solvent. It is generally described by the M-H equation (equation 5) or its logarithmic form (equation 6) where K and α are known as the M-H constants/parameters.

$$IV = KM^\alpha \quad (5)$$

$$\text{Log IV} = \text{log K} + \alpha \text{log M} \quad (6)$$

The plot of the equation 6 ideally provides a straight line with the intercept of log K and the slope of α . The values of K and α provide useful information about the properties of the polymer sample in solution. They are usually constant for a polymer and solvent pair. The parameter α is highly sensitive to the architecture of the polymer, and thus based on its value one can evaluate the compactness of the polymer coil in solution. For example, α between 0.5 to 0.8 is obtained for flexible polymers in a good solvent whereas lower values are obtained as the polymer structure gets denser and more compact (e.g. for star polymers, graft polymers, etc.).¹⁰⁴ With an increase in branching in the polymer structure, the compactness increases and thus α decreases. Therefore, the M-H plot is an excellent tool for studying CPA with diverse architectures, particularly when a direct comparison with a linear standard can be provided.

4. Experimental Section

4.1 Materials and Methods

Ethyl 2-chlorophenylacetate (ECPA; Sigma Aldrich, 97%), methyl 2-bromophenylacetate (MBPA; Aldrich, 97%), ethyl 2-bromophenylacetate (EBPA; Acros, 97%), CuBr₂ (Aldrich, 98%), CuCl₂ (Aldrich, 99%), CuCl (Sigma Aldrich, 98%), CuBr (Fluka, >98%), trichloroacetyl isocyanate (TAI; Acros Organics, NMR grade, >97%), hydrochloric acid (Lach-Ner, 35-38%) and phenothiazine (Sigma-Aldrich, 98%) were used as received. Cu-wire (Aldrich, diameter=0.64 mm) was activated before each polymerization by conc. HCl using procedure described below. N,N,N',N'',N''-Pentamethyldiethylenetriamine (PMDETA; Aldrich, 99%) was distilled under vacuum and Tris[2-(dimethylamino)ethyl]amine (Me₆TREN) was synthesized using a literature protocol.¹⁰⁵ Both the ligands were stored under argon at 4 °C. Solvents, i.e. N,N-dimethylacetamide (DMAc; Acros Organics, 99.5+%), dimethylsulfoxide (DMSO; Acros Organics, 99.7+%), toluene (Lach-Ner, p.a.), 1,4-dioxane (Lach-Ner, p.a.), isopropyl alcohol (IPA; Lach-Ner, p.a.), acetonitrile (Lach-Ner, p.a.), methanol (Lach-Ner, p.a.), tetrahydrofuran (THF; Lach-Ner, p.a.), dichloromethane (CH₂Cl₂, Lach-Ner, p.a.), and acetone (Lach-Ner, p.a.), diethyl ether (Et₂O; Lach-Ner, p.a.), were either used as received or dried using 3Å molecular sieves and purged with argon for 1 h (when used for polymerization) or dried over 3Å molecular sieves and stored under argon (when used for TAI modifications). Lithium chloride (LiCl; Fluka) was dried under vacuum at 190 °C for 8 h prior the use. Lithium bromide (LiBr; Sigma Aldrich, 99%) and DMAc (VWR-HPLC Grade, 99.5 %) were used for the preparation of mobile phase for TD-SEC. The prepared mobile phase was filtered through a 0.22 μm polyamide filter before use. THF used for SEC with relative calibration (Lach-Ner, p.a.) was distilled before use.

MA (Sigma-Aldrich, 99%), styrene (Fluka, 99.5%), MMA (Acros Organics, 99%), *n*-butyl methacrylate (BMA; Fluka, 99%), *n*-butyl acrylate (BA; Fluka, 99%), and glycidyl methacrylate (GMA; Fluka, 99.5%) were distilled under high vacuum to remove the inhibitor and stored under argon atmosphere at -20°C. 2-Hydroxyethyl acrylate (HEA; Sigma-Aldrich, 96%) was used as received. HEMA (Aldrich, 97%) was either vacuum distilled only to remove the stabilizer or purified using the protocol provided below in order to remove the EGDMA crosslinker. Lauryl methacrylate (LMA; Aldrich, 96%) and ethyl hexyl methacrylate (EHMA; Aldrich, 97%) was purified by passing through a column of neutral alumina and purged with argon for 1 h.

N,N-diisopropylamine (DIPA; Sigma-Aldrich, >99.5%), ethylene glycol (Fluka, >99.5%), pentaerythritol (Sigma-Aldrich, 98%), cellulose Avicel PH-101 (Fluka) and Sigmacell type 101

(Sigma), cotton thread Catania (Schachenmayr smc, 100% cotton), filter paper Whatman 1450-917, and β -cyclodextrin (β -CD, Sigma-Aldrich, $\geq 97\%$) were treated before the reaction with TAI as detailed in the experimental protocols.

Activation of Cu wire

The wire was immersed in approximately 5 mL of conc. HCl for 5 minutes. After removal, it was rinsed with water and then placed back into conc. HCl for an additional 10 minutes. Subsequently, the activated wire underwent successive washing with water and acetone. Finally, it was dried using a stream of argon and stored under argon atmosphere.

Purification of HEMA monomer

The method employed in this study was adapted from Wichterle and Chromeček¹⁰⁶ with slight adjustments. Initially, 50 mL of HEMA was mixed with 200 mL of Milli-Q water. The resulting mixture was subjected to hexane extraction (4 x 200 mL) to remove EGDMA. Next, NaCl was added to the aqueous layer to eliminate any methacrylic acid present, and the final mixture was extracted with Et₂O (3 x 200 mL). The etheric layer which contained the HEMA monomer, was subsequently dried with MgSO₄ and concentrated on a rotary evaporator. The resulting colorless liquid was purified further through high vacuum distillation in order to obtain purified HEMA that was stored under argon at -20 °C.

Methyl(trichloroacetyl)carbamate (MTAC)

Into a 50 mL reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet, dry methanol (20 mL) was added, and the flask was cooled in an ice bath. Upon dropwise addition of TAI (6.325 mL, 53.08 mmol), the flask was removed from the ice bath, and the mixture was left to stir at r.t. for 1 h. Thereafter, unreacted methanol was evaporated to afford a white solid (11.3 g, 97% yield) that was stored at 4 °C and used as a Cu-RDRP initiator without any further purification.

1,1-Diisopropyl-3-(2,2,2-trichloroacetyl)-urea (DTAU)

Into a 25 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and connected via a distillation bridge to another flask having an argon/vacuum inlet, dried CH₂Cl₂ (5 mL) and *N,N*-diisopropylamine (0.420 mL, 0.2965 mmol, pre-dried using 3Å molecular sieves) were added. The flask was placed in an ice bath, and TAI (0.442 mL, 0.3706 mmol) was added dropwise. Once the addition of TAI was complete, the flask was removed from the ice bath, and the mixture was left to stir at r. t. for 20 minutes during which the solution turned slight yellow. Thereafter, CH₂Cl₂ and the excess of TAI were distilled off under high vacuum, affording a slightly yellow solid

(0.834 g, 97% yield) that was further dried under vacuum and stored at 4 °C. The product was used as a Cu-RDRP initiator without any further purification.

Pentaerythritol tetrakis((2,2,2-trichloroacetyl)carbamate) (PTAC)

In a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and connected via a distillation bridge to another flask having an argon/vacuum inlet, pentaerythritol (0.25 g, 1.836 mmol, pre-dried under vacuum at 80 °C overnight) was mixed with dried dioxane (10 mL). Then, TAI (1.1 mL, 9.231 mmol) was added dropwise, which led to the dissolution of the solids. After 20 min, dioxane and the excess of TAI were distilled off under high vacuum, affording a white solid (1.513 g, 93% yield) that was further dried under vacuum and stored at 4 °C. The product was used as a Cu-RDRP initiator without any further purification.

Ethane-1,2-diyl bis((2,2,2-trichloroacetyl)carbamate) (ETAC)

Into a 25 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and connected via a distillation bridge to another flask having an argon/vacuum inlet, dried CH₂Cl₂ (5 mL) and ethylene glycol (0.112 mL, 0.2014 mmol, pre-dried using 3Å molecular sieves) were added. The flask was placed in an ice bath, and TAI (0.600 mL, 0.5035 mmol) was added dropwise. Once the addition of TAI was complete, the flask was removed from the ice bath, and the mixture was left to stir at r. t. for 20 min. Thereafter, CH₂Cl₂ and the excess of TAI were distilled off under the high vacuum, affording a white solid (0.865 g, 98% yield) that was further dried under vacuum and stored at 4 °C. The product was used as a Cu-RDRP initiator without any further purification.

Polymerization experiments for the project on CPAs and TAI strategy

During the optimization of polymerization conditions, Cu-RDRP experiments were conducted in a similar way regardless of the monomer used. Generally, the experimental scale was kept the same, i.e., 5 mL of a monomer and 5 mL of a solvent were used, with the amount of initiator adjusted based on the targeted M/I ratio. In the bulk polymerization of styrene, 10 mL of the monomer was used to keep a similar polymerization mixture volume. In Cu(0)-RDRP experiments, a fixed length of Cu wire (10 cm) was employed unless stated otherwise. Since the initiators used here are solids, in the polymerization protocols, generally first deoxygenation of the solid compounds (an initiator, Cu-salt(s), or Cu wire) was done followed by addition of a solvent and a monomer, and finally the polymerization was started by adding a ligand (and placing the flask into a heating bath if needed). Typically, the polymerization was stopped either when the viscosity of the polymerization mixture prevented efficient stirring or when 24 h elapsed. Monomer conversions were typically determined

by gravimetry (for styrene and MMA) or using $^1\text{H-NMR}$ (for other monomers). Below, sample procedures for Cu(0)-RDRP and ATRP experiments are provided.

Cu(0)-RDRP of MMA

MTAC (51.52 mg, 0.2337 mmol) and activated Cu wire (10 cm) were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, toluene (5 mL) was added, followed by the addition of MMA (5 mL, 46.74 mmol). Subsequently, the polymerization was started by the addition of PMDETA (49 μL , 0.2337 mmol), and the flask was placed into a stirred oil bath pre-heated to 85 °C. After 24 h, the experiment was ended, the flask was cooled down, the Cu-wire was removed, and the polymerization was quenched by adding a small amount of phenothiazine. Then, the mixture was diluted with THF and the product was precipitated in MeOH/water (4:1 v/v). The precipitate was collected on a glass frit, washed, and dried overnight under vacuum at 40 °C.

ATRP of styrene

CuBr (62.4 mg, 0.4349 mmol) and MTAC (96 mg, 0.4349 mmol) were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, styrene (10 mL, 86.98 mmol) was added. Subsequently, the polymerization was started by the addition of Me₆TREN (116 μL , 0.4349 mmol), and the flask was placed into a stirred oil bath pre-heated to 110 °C. After 6 h, the mixture was highly viscous, and so the experiment was ended, the flask was cooled down, and the polymerization was quenched by adding a small amount of phenothiazine. Then, the mixture was diluted with THF and the product was precipitated in MeOH. The precipitate was collected on a glass frit, washed, and dried overnight under vacuum at 40 °C.

Alkaline hydrolysis of star polymers and graft copolymers

In a 25 mL flask equipped with a magnetic stirring bar, a (co)polymer (100 mg), THF (8 mL), and 1 M solution of KOH in methanol (4 mL) were mixed, and the reaction mixture was stirred for 3 days at r. t. Then, the mixture was neutralized with 1 M HCl, solvents were evaporated, and the residuum was extracted with THF (3 mL). The product was then precipitated by the addition of the extract into MeOH/water (4:1 v/v) in case of poly(MMA) or neat MeOH in case of polystyrene. The precipitates were filtered, washed, and dried in vacuum at 40 °C.

Hydrolytic stability of the TAI-based carbamate linker

Poly(2-hydroxyethyl) acrylate (poly(HEA)): The preparation of the poly(HEA) starting polymer for the stability study was performed via Cu(0)-RDRP in DMSO at 60 °C using the standard procedure detailed above. Upon termination of the polymerization, the reaction mixture was dialyzed against deionized water, and the product was obtained by freeze-drying.

Attempted hydrolysis of the carbamate linker in poly(HEA) at different pH: In a 20 mL vial equipped with a magnetic stirring bar, 20 mg of the synthesized poly(HEA) was dissolved in the selected buffer (4 mL; pH = 1, 3, 5, 7, 9, or 11), and the solution was stirred at 37 °C for 24 h. Afterward, the solution was dialyzed against deionized water (MWCO = 1 000) and freeze-dried. The obtained polymer was analyzed by TD-SEC in DMAc/LiBr (dn/dc was calculated by the OMNISEC software considering 100% sample recovery).

De novo one-pot synthesis of poly(HEMA-co-MMA)-graft-poly(MMA) graft copolymer

Step 1: Activated Cu wire (4 cm) and MTAC (55.11 mg, 0.25 mmol) were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, dioxane (2.75 mL), HEMA (0.606 mL, 5.0 mmol), and MMA (2.14 mL, 20.0 mmol) were added. Subsequently, the polymerization was started by the addition of PMDETA (52.2 µL, 0.25 mmol), and the flask was placed into a stirred oil bath pre-heated to 85 °C. After 3 h, the flask was removed from the oil bath and cooled to r. t. A sample of the reaction mixture was withdrawn for SEC and NMR analysis.

Step 2: The polymerization mixture was diluted with dioxane (5 mL), which was followed by a dropwise addition of TAI (298 µL, 2.5 mmol, 0.5 eq. toward HEMA) under intensive stirring. The resulting mixture was further stirred at r. t. for 15 min. Then, 9 mL of the reaction mixture was removed from the flask: a sample was used for ¹H-NMR analysis, and the rest was isolated by precipitation in MeOH/water (4:1 v/v). The 1.5 mL of reaction mixture that remained in the reaction flask was used as a macroinitiator in the following step.

Step 3: The macroinitiator solution was diluted with dioxane (5 mL), and MMA (15 mL, 140 mmol, 400 eq. toward present TAGs) and PMDETA (75 µL, 0.357 mmol, 1.0 eq. toward the present TAGs) were added, and the flask was placed into a stirred oil bath pre-heated to 85 °C. After 2 h, the experiment was ended, the flask was cooled down, the Cu-wire was removed, and the polymerization was quenched by adding a small amount of phenothiazine. Then, the mixture was diluted with THF and the product was precipitated in MeOH. The precipitate was collected on a

glass frit, washed, and dried overnight under vacuum at 40 °C. A sample of the obtained product was further subjected to alkaline hydrolysis.

Synthesis of multi-arm poly(MMA) stars based on a β -cyclodextrin core

Modification of β -cyclodextrin with TAI: In a 5 mL round-bottomed flask equipped with a magnetic stirring bar and an argon/vacuum inlet, β -CD (0.030 g, 0.0264 mmol, pre-dried under vacuum at 80 °C) was dispersed in dried acetonitrile (800 μ L). Then, TAI (95 μ L, 0.793 mmol) was added, and the mixture was stirred at r.t. for 16 h. Into the obtained clear solution of the β -CD/TAI adduct, DMSO (~17 μ L) was added to quench the excess of TAI. Samples were withdrawn for $^1\text{H-NMR}$ and SEC analyses, and the remaining mixture was used as an initiator in the subsequent step.

ATRP of MMA initiated by the β -CD/TAI adduct: CuBr (57 mg, 0.397 mmol) was placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, dioxane (5.9 mL), MMA (5.9 mL, 55.15 mmol), and 400 μ L of the solution of β -CD/TAI adduct prepared in the previous step (0.397 mmol of TAGs) were added. Afterward, the polymerization was started by the addition of PMDETA (83 μ L, 0.397 mmol), and the flask was placed into a stirred oil bath pre-heated to 85°C. Samples of the polymerization mixture, withdrawn at 4 h and 7 h timepoints, were quenched with phenothiazine, diluted with THF, precipitated in MeOH, and used for SEC and NMR analyses. After 23 h, the experiment was ended, the flask was cooled down and opened to air, and the polymerization was quenched by adding a small amount of phenothiazine. The stabilized removed samples as well as the final mixture were analyzed by $^1\text{H-NMR}$ (conversion determination). Products were isolated as follows: the mixture was diluted with THF, the polymer was precipitated in MeOH, the precipitate was collected on a glass frit, washed, and dried overnight under vacuum at 40 °C. Isolated samples were analyzed by TD-SEC.

Modification of powder cellulose with TAI

Modification in DMAc/LiCl (homogeneous modification): Cellulose AVICEL PH-101 was activated by dioxane according to the literature protocol (the full activation protocol finished with freeze drying).¹⁰⁷ In a 25 mL reaction flask, activated cellulose (0.1 g, 0.617 mmol of monomeric units) was dissolved in 7.7% DMAc/LiCl (10 mL; prepared under anhydrous conditions). To the stirred solution, TAI (294 μ L, 2.467 mmol) was added dropwise. After 20 min, the excess of TAI was quenched with several drops of water, and the product was precipitated in IPA/water (1:1, v/v), collected on a glass frit, washed thoroughly with IPA, and dried in vacuum at 40 °C overnight. Product weight = 0.416 g (93% yield).

Modification in other solvents (heterogeneous modification): Modification of powder cellulose in other solvents was done in a similar way as described above, starting with the cellulose suspension in the respective solvent.

Synthesis of an ultra-dense bottle-brush graft copolymer by ATRP grafting of MMA from cellulose/TAI adduct

Preparation of the cellulose/TAI macroinitiator: Into a 10 mL round-bottomed flask, equipped with a magnetic stirring bar and an argon/vacuum inlet, containing the Avicel PH-101 (0.050 g, 0.3084 mmol, pre-dried in vacuum at 80 °C) suspension in dried acetonitrile (5 mL), TAI (0.221 mL, 1.8546 mmol) was added, and the mixture was left to stir at r. t. for 4 days. Then, MeOH (0.040 mL) was added into the homogeneous solution to quench any unreacted TAI. The prepared mixture was analyzed by SEC and used as a stock solution of the (macro)initiator in the subsequent polymerization step.

ATRP grafting of MMA from the cellulose/TAI adduct: CuBr (13.3 mg, 0.0927 mmol) was placed into a 50 mL reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, dioxane (7.9 mL), MMA (7.9 mL, 74.2 mmol), and the (macro)initiator solution from the previous step (250 μ L, 0.0927 mmol of TAGs) were added. Afterward, the polymerization was started by the addition of PMDETA (19.4 μ L, 0.0927 mmol), and the flask was placed into a stirred oil bath pre-heated to 85°C. At 5 h, a sample of the polymerization mixture was withdrawn for conversion determination by ¹H-NMR and for TD-SEC analysis (performed using the polymer isolated by precipitation into MeOH). At 24 h, the experiment was ended, the flask was cooled down and opened to air, and the polymerization was quenched by adding a small amount of phenothiazine. A sample was withdrawn for conversion determination via ¹H-NMR. Then, the mixture was diluted with THF and the product was precipitated in MeOH. The precipitate was collected on a glass frit, washed, and dried overnight in vacuum at 40 °C.

Surface-initiated grafting from TAI-modified filter paper

Modification of Whatman paper with TAI: Whatman paper (7 x 5.5 cm) was cut and soaked in dry DMSO for 3 days. Then, the paper was removed from DMSO, briefly dried with a paper towel, and placed on a customized mask (see picture below) with an “IMC” inscription. After closely tightening the paper inside the mask, TAI (100 μ L, 0.8392 mmol) was dripped evenly onto the exposed paper surface in argon flow. Subsequently, the mask was immersed into a beaker containing IPA in order to quench the excess of TAI. The paper was then removed from the mask and washed excessively with methanol in order to remove any unbound TAI adducts and dried in vacuum at r.t.

ATRP grafting of MMA from the TAI-modified paper: CuBr (120.4 mg, 0.8392 mmol) and the TAI-modified Whatman paper were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, dioxane (17.5 mL) and MMA (17.5 mL, 163.6 mmol) were added. Afterward, the polymerization was started by the addition of PMDETA (175 μ L, 0.8392 mmol), and the flask was placed into a stirred oil bath pre-heated to 85°C. After 30 min, the experiment was ended, the flask was cooled down, and the polymerization was quenched by adding a small amount of phenothiazine. The paper was removed, washed carefully first with THF to remove any free polymer and then with methanol to remove the catalytic complex residua, and finally dried in vacuum at r.t.

Surface-initiated grafting from TAI-modified cotton thread

Modification of cotton thread with TAI: 5 cm long cotton thread was placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After inertization, dry DMSO (10 mL) was added, and the thread was left to soak for 5 minutes after which TAI (400 μ L, 3.356 mmol) was added. After 15 minutes, the thread was removed from the flask, washed with an excess of methanol, and dried in vacuum at r.t.

ATRP grafting of MMA from the TAI-modified cotton thread: CuBr (34.4 mg, 0.2398 mmol) and TAI-modified cotton thread were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, dioxane (5 mL) and MMA (5 mL, 46.74 mmol) were added. Afterward, the polymerization was started by the addition of PMDETA (50 μ L, 0.2398 mmol), and the flask was placed into a stirred oil bath pre-heated to 85°C. After 1 h, the experiment was ended, the flask was cooled down, and the polymerization was quenched by adding a small amount of phenothiazine. The thread was removed, washed thoroughly with THF and methanol, and dried in vacuum at 40 °C.

Surface-initiated grafting from TAI-modified pine cone

Modification of a pine cone with TAI: A pine cone was left to soak in dry DMSO (80 mL) overnight. The original (discolored) DMSO was then replaced with a fresh one, and 3Å molecular sieves were added. After 7 days, the cone was quickly transferred into a 100 mL wide-neck reagent bottle equipped with a magnetic stirring bar and fitted with a rubber septum pierced with a needle connected to an argon/vacuum inlet. After inertization, dry DMSO (70 mL) was added, and the bottle was placed in an ice bath. TAI (2 mL, 16.78 mmol) was then added dropwise, and the mixture

was then stirred for 15 minutes. Thereafter, the cone was removed from the flask, washed thoroughly with methanol, and dried in vacuum at r.t.

ATRP grafting of MMA from the TAI-modified pine cone: CuBr (137.4 mg, 0.958 mmol) and the TAI-modified cone were placed into a 100 mL wide-neck reagent bottle equipped with a magnetic stirring bar and fitted with a rubber septum pierced with a needle connected to an argon/vacuum inlet. After thorough deoxygenation, dioxane (40 mL) and MMA (40 mL, 374 mmol) were added. Afterward, the polymerization was started by the addition of PMDETA (200 μ L, 0.958 mmol), and the flask was placed into a stirred oil bath pre-heated to 85°C. After 4 h, the experiment was ended, the flask was cooled down, and the polymerization was quenched by adding a small amount of phenothiazine. The cone was removed, washed thoroughly with THF and methanol, and dried in vacuum at 40 °C.

Polymerization experiments for the project on Cu(0)-RDRP of HEMA

Cu(0)-RDRP of HEMA

The protocol for a typical experiment conducted at M/I = 100:1 (Table 13; Entry 4) is provided as an example: Activated Cu wire (5 cm) and CuCl₂ (5.5 mg, 0.0412 mmol) were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, 1,4-dioxane (2.5 ml) was added, followed by the addition of HEMA (2.5 ml, 20.61 mmol) and ECPA (35.4 μ L, 0.2062 mmol). The polymerization was started by adding PMDETA (43 μ L, 0.2062 mmol), and the flask was placed into an oil bath preheated to 85 °C. After 60 min, the magnetic stirring of the mixture became impossible, and so the experiment was ended. The flask was cooled down, opened to air, the Cu-wire was removed, and samples of the reaction mixture were collected for NMR and SEC analyses followed by dilution with required solvents and addition of phenothiazine. Furthermore, note that stock solutions of ECPA and PMDETA in dioxane were used in the experiments with high M/I ratios in order to ensure accurate sampling of these components. Finally, it was also confirmed that adding ECPA as the last component (instead of PMDETA) led to a practically identical product.

Copolymerization of HEMA with non-polar comonomers via Cu(0)-RDRP in dioxane

Copolymerization with LMA is given as an example; the copolymerization with EHMA was conducted in the same way. Activated Cu wire (5 cm) and CuCl₂ (5.5 mg, 0.0412 mmol) were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough deoxygenation by several vacuum-argon cycles, 1,4-dioxane

(4.25 ml) was added, followed by the addition of HEMA (1.25 ml, 10.31 mmol), LMA (3 ml, 10.31 mmol), and ECPA (35.4 μ l, 0.2062 mmol). The polymerization was started by adding PMDETA (43 μ l, 0.2062 mmol), and the flask was placed into an oil bath preheated to 85 °C. After 3 hours, the experiment was ended, the flask was cooled, and samples of the highly viscous but homogeneous mixture were collected and processed in the same way as HEMA homopolymers.

Copolymerization of HEMA and LMA via Cu(0)-RDRP in DMSO

The method reported by Nguyen et al. was adapted.⁴⁶ Activated Cu-wire (5 cm) and CuBr₂ (2.3 mg, 0.0103 mmol) were placed into a reaction flask equipped with a magnetic stirring bar and a three-way stopcock connected to an argon/vacuum inlet. After thorough de-oxygenation by several vacuum-argon cycles, DMSO (4.25 ml), HEMA (1.25 ml, 10.31 mmol), LMA (3 ml, 10.31 mmol), and MBPA (32.5 μ l, 0.2062 mmol) were added. The polymerization was started by adding Me₆TREN (5.5 μ l, 0.0206 mmol), and the heterogeneous mixture was stirred at r.t. After 7 hours, the experiment was ended, and samples were collected and processed as indicated above.

4.2 Characterization

The number-average molecular weights (M_n), weight-average molecular weights (M_w), and dispersity (\mathcal{D}) of the (co)polymers were determined by SEC.

Most of the analyses during the optimization of polymerization conditions in the dissertation part focused on the TAI strategy were performed using an SEC system consisting of the SDS 150 pump (Watrex, Czech Republic), an RI detector (RI-101; Shodex, Japan), and two PLgel MIXED-C columns (300 \times 7.5 mm, SDV gel with particle size 5 μ m; Agilent, USA). Tetrahydrofuran was used as the mobile phase at 25 °C with a flow rate of 1 mL/min. The molecular weight (MW) values were calculated using the Clarity software (Dataapex, Czech Republic). Calibrations with polystyrene standards (PSS, Germany) in the molecular weight range of 580 and 1 820 000 and with poly(MMA) standards (PSS, Germany) in the MW range of 2 200 to 1 220 000 were used.

Advanced polymer characterization of different CPAs and of poly(HEMA) samples was done using the Malvern Panalytical OMNISEC TD-SEC system consisting of OMNISEC Resolve and OMNISEC Reveal units. Two PSS GRAM analytical linear columns with the dimensions of 8 x 300 mm and the particle size of 10 μ m were used. Triple detection with the following detectors was performed: differential refractive index (RI) detector, right-angle light scattering (RALS) + low-angle light scattering (LALS) measuring at an angle of 7° to the incident beam (laser wavelength of 640 nm), and a 4-capillary Wheatstone bridge viscometer. The columns and detectors were held at 55 °C.

Dimethylacetamide with 5g/L LiBr was used as an eluent at a flow rate of 1 mL/min. OMNISEC software from Malvern Panalytical was used for online monitoring and processing of the data. In some cases, universal calibration was used for the MW determination; in this case, the calibration was performed using the polystyrene standards (PSS, Germany) in the MW range of 1,930 to 990,500. All sample solutions were filtered through 0.2 µm PTFE filters prior to injection.

¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker Avance NEO 400 spectrometer operating at 400.13 MHz at 300 K or Bruker AVANCE-III operating at 600 MHz at 298 K.

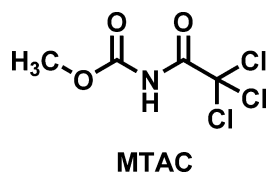
5. Results and Discussion

5.1 CPAs and TAI strategy

The first part of the results and discussion will deal with the results obtained within the framework of the CPA synthesis via the newly established TAI strategy.

5.1.1 Synthesis of the model TAI-based initiator methyl *N*-trichloroacetyl carbamate (MTAC)

In order to establish the TAI-strategy, a simple initiator (a methanol-TAI adduct) was prepared that could be employed for conducting Cu-RDRP experiments within the optimization of polymerization conditions for different monomer classes. To prepare MTAC (**Scheme 5**), TAI was directly added to dry methanol. The addition of TAI results in the instantaneous formation of the methanol-TAI adduct. The adduct was soluble in methanol and thus the final product was obtained as a white crystalline solid by evaporating the excess of methanol. The initiator was further subjected to ¹H-NMR and ¹³C-NMR analyses to confirm its structure (**Figure A1**). MTAC was used without further purification.

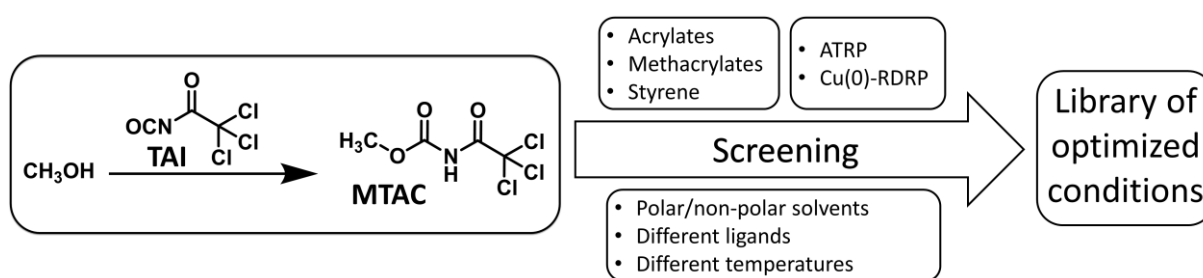


Scheme 5. The structure of the MTAC initiator used in the Cu-RDRP optimization studies.

5.1.2 Optimization of the polymerization conditions for Cu-RDRP initiated by MTAC

With the model initiator available, the next step was to optimize the polymerization conditions for different classes of monomers. Different parameters of the Cu-RDRP were tested in order to obtain conditions under which well-defined polymers can be prepared. The target was to achieve high monomer conversions, dispersity preferably less than 1.3, and MWs of products approaching the theoretical values. For Cu(0)-RDRP, activated copper wire was used as the catalyst source and for ATRP copper salts (CuBr, CuCl) were employed as catalysts. Two different ligands, i.e. Me₆TREN and PMDETA, were used at different ligand/initiator ratios. As mentioned above, the solvent plays an important role in Cu-RDRP in terms of polymerization rate and control; therefore, different solvents (both polar and non-polar) were tested to study their effect on the polymerization of different monomers. The choice of solvent will also be crucial from the perspective of solubility of different types of TAI adducts. Polar solvents such as DMSO, DMAc, and IPA, that are preferred in Cu(0)-RDRP,^{25,108,109} as well as non-polar solvents such as toluene and 1,4-dioxane, that are more typical

for ATRP,¹¹⁰ were used. Additionally, some experiments were also performed in bulk. Temperatures ranging from r.t. to 110 °C were utilized depending on the target monomer. Three different monomers, i.e. MA, MMA and styrene, were used as model monomers during the optimization studies. The monomer/initiator (M/I) ratios of 200:1 was majorly used for optimizing the conditions. For some of the developed conditions, which gave high monomer conversions and low dispersity, other M/I ratios were also verified, targeting thus different polymer MWs. Monomer conversions were determined using ¹H-NMR (for MA) or gravimetrically (for MMA and styrene). MW and dispersity were determined using SEC-RI in THF, calibrated against poly(MMA) (for MA and MMA) and polystyrene (for styrene) standards. A simple workflow diagram showcasing the strategy used for the optimization study is depicted in **Scheme 6** below.



Scheme 6. The workflow of the polymerization conditions screening.

5.1.3 Cu-RDRP of MA

Table 2 shows the results of polymerizations conducted with MA during the optimization study. SEC traces of products obtained under some of the successfully optimized conditions are provided along with the tables. Firstly, it can be seen that under host of different ATRP conditions, no polymerization was observed (entries 1 – 11 and 13 – 15). Switching from DMSO/DMAc to toluene/1,4-dioxane at r.t. did not result in any success. Toluene in combination with Me₆TREN at 60 °C afforded monomer conversion of 36% in an uncontrolled process characterized by high dispersity ($\mathcal{D} = 2.51$) of the product (entry 12). Switching to Cu(0)-RDRP in DMAc at r.t., polymerizations were plagued by low conversions when PMDETA was used at different ligand loadings, i.e. 0.2, 0.5, and 1.0 eq. (entries 16 – 18). Promising results were achieved at 60 °C with low ligand concentrations (0.2 eq.) for both PMDETA (entry 19) and Me₆TREN (entry 23), the latter giving slightly better conversions. On the other hand, at r.t., Me₆TREN use resulted in no polymerization with 0.2 eq. (entry 20) while with 0.5 and 1.0 eq. it resulted in polymers with lower dispersity (~ 1.24), the latter giving higher conversion (entries 21, 22).

Table 2. Results obtained during the optimization of polymerization conditions for MTAC-initiated Cu-RDRP of MA^a

Entry	Cat.	Solvent	Ligand (eq.)	M/I	T (°C)	Time (h)	Conv. (%) ^b	M_n (theor.) ^c	M_n (SEC) ^d	\mathcal{D}^d
1	CuBr	DMSO	PMDETA (1.0)	200	r.t.	24		<i>no polymerization</i>		
2	CuBr	DMSO	Me ₆ TREN (1.0)	200	r.t.	24		<i>no polymerization</i>		
3	CuBr	DMSO	PMDETA (1.0)	200	60	24		<i>no polymerization</i>		
4	CuBr	DMSO	Me ₆ TREN (1.0)	200	60	24		<i>no polymerization</i>		
5	CuBr	DMAC	PMDETA (1.0)	200	r.t.	24		<i>no polymerization</i>		
6	CuBr	DMAC	Me ₆ TREN (1.0)	200	r.t.	24		<i>no polymerization</i>		
7	CuBr	DMAC	PMDETA (1.0)	200	60	24		<i>no polymerization</i>		
8	CuBr	DMAC	Me ₆ TREN (1.0)	200	60	24		<i>no polymerization</i>		
9	CuBr	toluene	PMDETA (1.0)	200	r.t.	24		<i>no polymerization</i>		
10	CuBr	toluene	Me ₆ TREN (1.0)	200	r.t.	24		<i>no polymerization</i>		
11	CuBr	toluene	PMDETA (1.0)	200	60	24		<i>no polymerization</i>		
12	CuBr	toluene	Me ₆ TREN (1.0)	200	60	24	36	6 300	6 100	2.51
13	CuBr	dioxane	PMDETA (1.0)	200	60	24		<i>no polymerization</i>		
14	CuBr	dioxane	Me ₆ TREN (1.0)	200	60	24		<i>no polymerization</i>		
15	CuCl ^e	dioxane	Me ₆ TREN (1.5)	200	60	24		<i>no polymerization</i>		
16	Cu(0)	DMAC	PMDETA (0.2)	200	r.t.	24	32	5 700	8 200	1.74
17	Cu(0)	DMAC	PMDETA (0.5)	200	r.t.	24	18	3 300	6 000	1.55
18	Cu(0)	DMAC	PMDETA (1.0)	200	r.t.	24	22	4 000	12 400	1.34
19	Cu(0)	DMAC	PMDETA (0.2)	200	60	24	98	17 000	21 100	1.27
20	Cu(0)	DMAC	Me ₆ TREN (0.2)	200	r.t.	24		<i>no polymerization</i>		
21	Cu(0)	DMAC	Me ₆ TREN (0.5)	200	r.t.	24	29	5 100	5 300	1.23
22	Cu(0)	DMAC	Me ₆ TREN (1.0)	200	r.t.	24	71	12 300	18 700	1.24
23	Cu(0)	DMAC	Me ₆ TREN (0.2)	200	60	24	77	13 300	15 700	1.19
24	Cu(0)	DMSO	PMDETA (0.2)	200	r.t.	24	82	14 100	18 700	1.26
25	Cu(0)	DMSO	PMDETA (0.2)	200	60	4	96	16 500	22 200	1.19
26	Cu(0)	DMSO	PMDETA (0.5)	200	r.t.	24	97	16 700	26 100	1.22
27	Cu(0)	DMSO	PMDETA (0.5)	200	60	4	99	17 100	24 800	1.25
28	Cu(0)	DMSO	PMDETA (1.0)	200	r.t.	1	36	6 300	6 900	6.49
29	Cu(0)	DMSO	Me ₆ TREN (0.2)	200	r.t.	24		<i>no polymerization</i>		
30	Cu(0) ^f	DMSO	Me ₆ TREN (0.2)	200	r.t.	24	22	4 000	4 600	1.29
31	Cu(0)	DMSO	Me ₆ TREN (0.2)	200	60	5	88	15 200	18 400	1.21
32	Cu(0)	DMSO	Me ₆ TREN (0.5)	200	r.t.	24	95	16 400	20 400	1.12
33	Cu(0)	DMSO	Me ₆ TREN (0.5)	200	60	5	91	15 700	21 800	1.17
34	Cu(0)	DMSO	Me ₆ TREN (1.0)	200	r.t.	24	94	16 200	24 300	1.35
35	Cu(0) ^f	DMSO	Me ₆ TREN (1.0)	200	r.t.	24	94	16 200	25 500	1.25
36	Cu(0)	DMSO	Me ₆ TREN (0.5)	50	60	5	80	3 700	4 900	1.22
37	Cu(0)	DMSO	Me ₆ TREN (0.5)	100	60	5	89	7 800	10 500	1.18
38	Cu(0)	DMSO	Me ₆ TREN (0.5)	400	60	7	97	33 500	48 200	1.20
39	Cu(0)	toluene	Me ₆ TREN (0.5)	200	r.t.	24	3	730	3 000	1.44
40	Cu(0)	toluene	Me ₆ TREN (0.5)	200	60	24	89	15 300	18 600	1.19
41	Cu(0)	dioxane	Me ₆ TREN (0.5)	200	60	24	99	17 000	22 000	1.19
42	Cu(0)	toluene	PMDETA (0.5)	200	60	24	28	5 000	12 500	1.81
43	Cu(0)	dioxane	PMDETA (0.5)	200	60	24	18	3 300	10 000	1.82

^a Standard polymerization conditions: monomer/solvent = 1:1 (v/v), catalyst (Cat.): 10 cm of activated copper wire in Cu(0)-RDRP, 1 eq. of Cu(I) salt in ATRP.

^b Monomer conversion determined by ¹H-NMR (see **Figure A2** for sample NMR).

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% initiation efficiency.

^d Determined by SEC with poly(MMA) calibration.

^e CuCl₂ (0.5 eq.) was added as a deactivator.

^f CuCl₂ (0.05 eq.) was added as a deactivator.

In DMSO, the PMDETA (0.2 and 0.5 eq.) use resulted in polymers with low dispersity and high conversions both at r.t. (entries 24, 26) and 60 °C (entries 25, 27). A higher concentration of PMDETA (1.0 eq.) at r.t. led to uncontrolled polymerization as seen from the very high dispersity (entry 28). Switching to Me₆TREN afforded better results compared to PMDETA. It can be seen that at 0.2 eq. of Me₆TREN, efficient polymerization process was not established (entry 29,) but the addition of CuCl₂ as a deactivator enable the polymerization to run, albeit slowly (entry 30). However, at 60 °C, the polymerization was well controlled with 0.2 eq. Me₆TREN, providing well-defined poly(MA) (entry 31). Higher ligand concentration (i.e. 0.5 eq.) resulted in poly(MA) with dispersity less than 1.20 both at r.t. and 60 °C (entries 32, 33). Furthermore, the use of 1.0 eq. of Me₆TREN at r.t. showed slightly higher dispersity (~1.35) that was improved by the addition of CuCl₂ (cf. entries 34 and 35). Next, one of the optimized conditions was used to obtain poly(MA)s of different MWs. It can be seen that DMSO/Me₆TREN (0.5 eq.) at 60 °C was also successfully applicable to M/I = 50, 100 and 400 (entries 36 – 38) (see **Figure 6** for SEC traces). In toluene at r.t., Me₆TREN (0.5 eq.) provided negligible monomer conversion even in 24 h, and the dispersity was high (entry 39). In both toluene and 1,4-dioxane, Me₆TREN (0.5 eq.) use resulted in well-defined polymers (\bar{D} = 1.19) and provided almost quantitative conversions in 24 h at 60 °C while PMDETA (0.5 eq.) led to poor control over the polymerization as evidenced by higher dispersity (~1.8) and low monomer conversions (< 30%) under the same conditions (entries 40 – 43). A kinetic study conducted using one of the successful sets of conditions, i.e. DMSO/Me₆TREN (0.5 eq.) at 60 °C (entry 33), shows that excellent polymerization control was established (**Figure 7**).

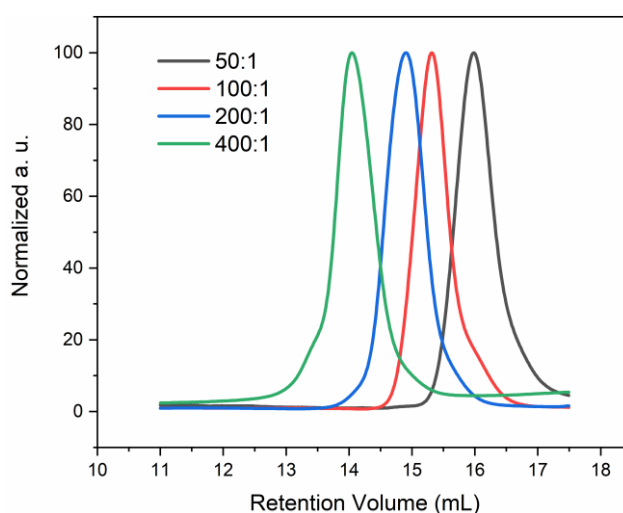


Figure 6. SEC elugrams of poly(MA) prepared at different M/I ratios via MTAC-initiated Cu(0)-RDRP of MA in DMSO at 60°C, 0.5 eq. of Me₆TREN. Product characteristics are provided in **Table 2**.

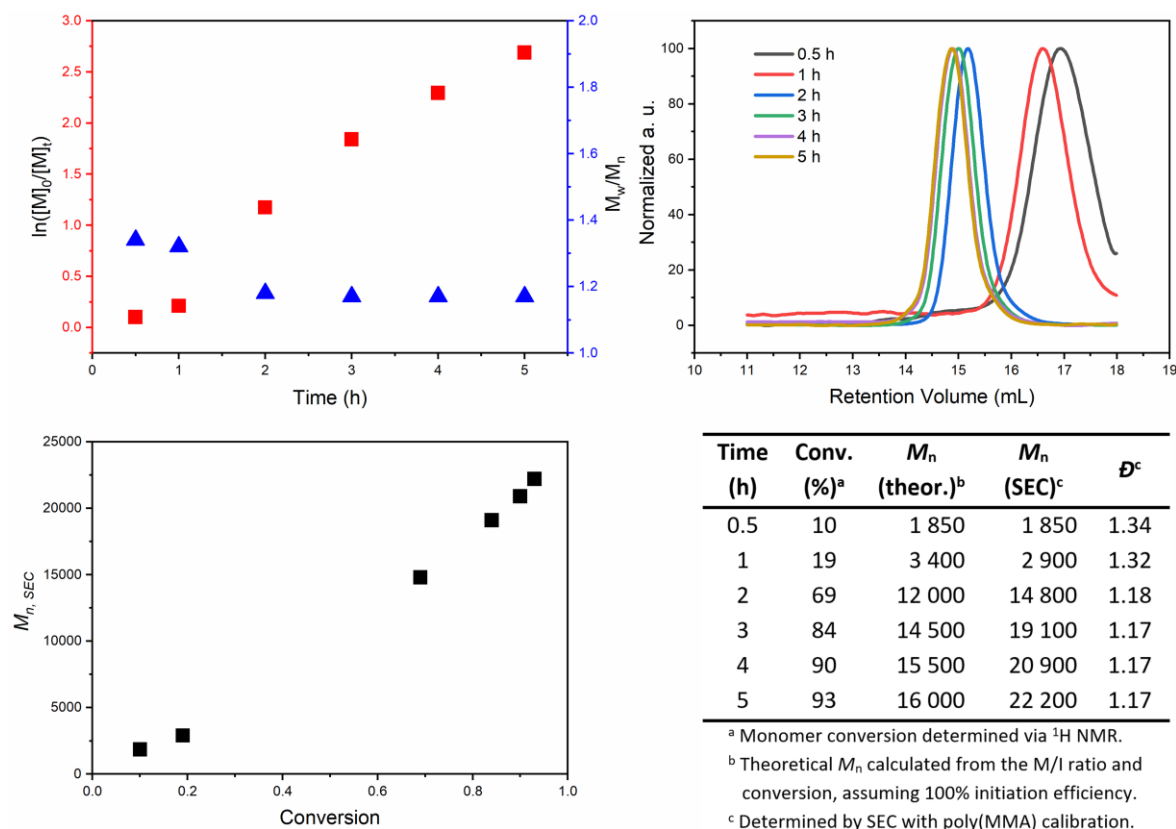


Figure 7. Kinetics of MTAC-initiated Cu(0)-RDRP of MA. Experimental conditions: MA/MTAC/Me₆TREN = 200:1:0.5; MA/DMSO = 1:1 (v/v), 60 °C, 10 cm of activated Cu wire.

Taken together, conditions were developed for Cu(0)-RDRP of MA in different solvents at r.t. or 60 °C using MTAC as an initiator. Conveniently, these conditions should be directly applicable to the synthesis of poly(MA) via Cu-RDRP initiated by TAI-adducts based on substrates of different solubility.

5.1.4 Cu-RDRP of MMA

Table 3 shows selected results obtained during the optimization of polymerization conditions for Cu-RDRP of MMA. The optimization study for MMA was conducted in a similar fashion as for MA above. Firstly, the Cu(0)-RDRP conditions were tested. It was found that in DMAc, polymerizations were well controlled albeit slightly lower monomer conversions were achieved when PMDETA was employed as a ligand at different concentrations at r.t. (entries 1 – 3). Raising the temperature to 85 °C for PMDETA (0.2 eq.) resulted in an increase in monomer conversion along with a slight decrease in dispersity (entry 4). On the other hand, Me₆TREN at r.t. and 0.2 eq. resulted in lower conversion (~40%) while still keeping the dispersity low (entry 5). Increasing the concentration of Me₆TREN to 0.5 eq. and 1.0 eq. led to higher conversions with a slight increase in dispersity (~1.3)

at r.t. (entries 6 and 7). Increasing the temperature to 85 °C while keeping Me₆TREN at 0.2 eq. led to almost quantitative conversion with low dispersity (entry 8). In DMSO, both PMDETA and Me₆TREN showed similar results. At r.t., different concentrations of ligands resulted in polymers with low dispersity and monomer conversions above 67% (entries 9 – 14). Surprisingly, 0.2 eq. of either ligand gave high monomer conversions (>90%) in 24 h (cf., entries 9 and 13). Upon increasing the temperature to 85 °C, the polymerization was faster using both PMDETA and Me₆TREN (cf., entries 10 and 14). To test the applicability of these conditions with different M/I ratios, DMSO/Me₆TREN (0.2 eq.) at 60 °C was used. M/I ratios of 50, 100 and 400 were tested, resulting in well-controlled polymerizations of poly(MMA) with quantitative conversions (entries 17 – 19, **Figure 8a**). Switching to non-polar solvents, the use of 1,4-dioxane with PMDETA (0.2 eq.) at 85 °C afforded no polymerization while increasing the ligand concentration to 1.0 eq. resulted in well-controlled polymerization at r.t. attaining 79% conversion in 23 h (entries 20 and 21, respectively). Upon increasing the temperature to 85 °C, the polymerization was faster (5 h) with excellent dispersity (1.16) (entry 22). On the other hand, Me₆TREN (0.2 eq.) led to well-controlled polymerization at 85 °C in 24 h with dispersity 1.14 (entry 23). Upon increasing the concentration of Me₆TREN to 1.0 eq. at r.t., the polymerization was plagued with higher dispersity (entry 24). This was improved by increasing the temperature to 85 °C (entry 25). Under otherwise similar conditions, Me₆TREN (1.0 eq.) in toluene resulted in slightly higher dispersity (1.36) when compared to 1,4-dioxane (cf., entries 25 and 26). PMDETA (1.0 eq.) in toluene gave better results leading to quantitative conversion and dispersity of 1.12 (entry 27). These conditions were further tested for different M/I ratios, affording well-defined poly(MMA) in all cases (entries 28 – 30, **Figure 8b**). Furthermore, when IPA was employed as a solvent with 0.2 eq. of PMDETA, it resulted in uncontrolled polymerizations and low monomer conversions (entry 31). Increasing the ligand concentration to 1.0 eq. resulted in higher monomer conversion with dispersity of 1.28 in 2 h (entry 32). On the other hand, with Me₆TREN, it was difficult to strike a balance between high conversion and low dispersity. With 0.2 eq. of Me₆TREN a product with low dispersity (1.14) was achieved at low conversion whereas with 1.0 eq. of Me₆TREN higher conversion was attained albeit with higher dispersity (1.46) (entries 33 and 34). Collectively, these results show that well defined poly(MMA) can be obtained via Cu(0)-RDRP of MMA with MTAC in all the solvents tested here under a range of different conditions. Switching to ATRP, virtually no polymerizations were obtained in both DMSO and DMAc with both the ligands tested (entries 35 - 38). Surprisingly, in IPA, well-defined poly(MMA)s were obtained albeit at low conversions (9 and 31% with PMDETA and Me₆TREN, respectively) (entries 39 and 40). Switching to non-polar solvents enabled the controlled polymerization of MMA, especially with PMDETA.

Table 3. Results obtained during the optimization of polymerization conditions for MTAC-initiated Cu-RDRP of MMA^a

Entry	Cat.	Solvent	Ligand (eq.)	M/I	T (°C)	Time (h)	Conv. (%) ^b	M_n (theor.) ^c	M_n (SEC) ^d	\bar{D}^d
1	Cu(0)	DMAc	PMDETA (0.2)	200	r.t.	24	69	14 000	20 500	1.27
2	Cu(0)	DMAc	PMDETA (0.5)	200	r.t.	24	70	14 200	24 500	1.25
3	Cu(0)	DMAc	PMDETA (1.0)	200	r.t.	5	77	15 700	28 300	1.32
4	Cu(0)	DMAc	PMDETA (0.2)	200	85	6	87	17 600	23 600	1.21
5	Cu(0)	DMAc	Me ₆ TREN (0.2)	200	r.t.	24	39	8 100	12 900	1.18
6	Cu(0)	DMAc	Me ₆ TREN (0.5)	200	r.t.	9.5	73	14 800	20 900	1.28
7	Cu(0)	DMAc	Me ₆ TREN (1.0)	200	r.t.	7.5	71	14 500	21 400	1.31
8	Cu(0)	DMAc	Me ₆ TREN (0.2)	200	85	24	92	18 600	22 100	1.24
9	Cu(0)	DMSO	PMDETA (0.2)	200	r.t.	24	94	19 000	27 100	1.26
10	Cu(0)	DMSO	PMDETA (0.2)	200	85	3	87	17 600	24 700	1.27
11	Cu(0)	DMSO	PMDETA (0.5)	200	r.t.	8.5	67	13 700	22 300	1.27
12	Cu(0)	DMSO	PMDETA (1.0)	200	r.t.	3.5	76	15 400	25 800	1.27
13	Cu(0)	DMSO	Me ₆ TREN (0.2)	200	r.t.	24	91	18 400	25 900	1.19
14	Cu(0)	DMSO	Me ₆ TREN (0.2)	200	85	4	85	17 200	23 000	1.20
15	Cu(0)	DMSO	Me ₆ TREN (0.5)	200	r.t.	7.5	69	14 000	23 100	1.23
16	Cu(0)	DMSO	Me ₆ TREN (1.0)	200	r.t.	3.5	78	15 900	29 200	1.31
17	Cu(0)	DMSO	Me ₆ TREN (0.2)	50	85	4	>99	5 200	5 900	1.27
18	Cu(0)	DMSO	Me ₆ TREN (0.2)	100	85	4	90	9 200	10 900	1.25
19	Cu(0)	DMSO	Me ₆ TREN (0.2)	400	85	7	93	37 400	43 700	1.20
20	Cu(0)	dioxane	PMDETA (0.2)	200	85	24		<i>no polymerization</i>		
21	Cu(0)	dioxane	PMDETA (1.0)	200	r.t.	23	79	16 100	20 800	1.21
22	Cu(0)	dioxane	PMDETA (1.0)	200	85	5	90	18 200	26 600	1.16
23	Cu(0)	dioxane	Me ₆ TREN (0.2)	200	85	24	87	17 600	23 000	1.14
24	Cu(0)	dioxane	Me ₆ TREN (1.0)	200	r.t.	24	69	13 900	28 100	1.62
25	Cu(0)	dioxane	Me ₆ TREN (1.0)	200	85	5	94	19 000	29 600	1.28
26	Cu(0)	toluene	Me ₆ TREN (1.0)	200	85	5	82	16 600	28 800	1.36
27	Cu(0)	toluene	PMDETA (1.0)	200	85	24	95	19 200	19 600	1.12
28	Cu(0)	toluene	PMDETA (1.0)	50	85	18	>99	5 200	5 100	1.26
29	Cu(0)	toluene	PMDETA (1.0)	100	85	18	96	9 800	10 800	1.22
30	Cu(0)	toluene	PMDETA (1.0)	400	85	45	92	37 000	33 000	1.12
31	Cu(0)	IPA	PMDETA (0.2)	200	85	24	25	5 200	12 000	1.39
32	Cu(0)	IPA	PMDETA (1.0)	200	85	2	89	18 000	34 000	1.28
33	Cu(0)	IPA	Me ₆ TREN (0.2)	200	85	24	15	3 200	9 700	1.14
34	Cu(0)	IPA	Me ₆ TREN (1.0)	200	85	2	72	14 600	27 000	1.46
35	CuBr	DMSO	PMDETA (1.0)	200	85	24		<i>no polymerization</i>		
36	CuBr	DMSO	Me ₆ TREN (1.0)	200	85	24		<i>no polymerization</i>		
37	CuBr	DMAc	PMDETA (1.0)	200	85	24		<i>no polymerization</i>		
38	CuBr	DMAc	Me ₆ TREN (1.0)	200	85	24	2	520	2 100	1.30
39	CuBr	IPA	PMDETA (1.0)	200	85	24	9	1 900	4 400	1.12
40	CuBr	IPA	Me ₆ TREN (1.0)	200	85	24	31	6 400	7 400	1.18
41	CuBr	toluene	PMDETA (1.0)	200	85	22	90	18 200	15 500	1.12
42	CuBr	toluene	Me ₆ TREN (1.0)	200	85	22	92	18 600	23 500	1.58
43	CuBr	dioxane	Me ₆ TREN (1.0)	200	85	22	86	17 400	20 700	1.69
44	CuBr	dioxane	PMDETA (1.0)	200	85	24	88	17 800	18 200	1.09
45	CuBr	dioxane	PMDETA (1.0)	50	85	18	>99	5 200	5 000	1.21
46	CuBr	dioxane	PMDETA (1.0)	100	85	18	85	8 700	9 500	1.13
47	CuBr	dioxane	PMDETA (1.0)	400	85	45	70	28 200	29 700	1.11
48	CuCl	dioxane	PMDETA (1.0)	200	85	23	83	16 800	17 700	1.16

^a Standard polymerization conditions: monomer/solvent = 1:1 (v/v), catalyst (Cat.): 10 cm of activated copper wire in Cu(0)-RDRP, 1 eq. of Cu(I) salt in ATRP.

^b Monomer conversion determined gravimetrically.

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% initiation efficiency.

^d Determined by SEC with poly(MMA) calibration.

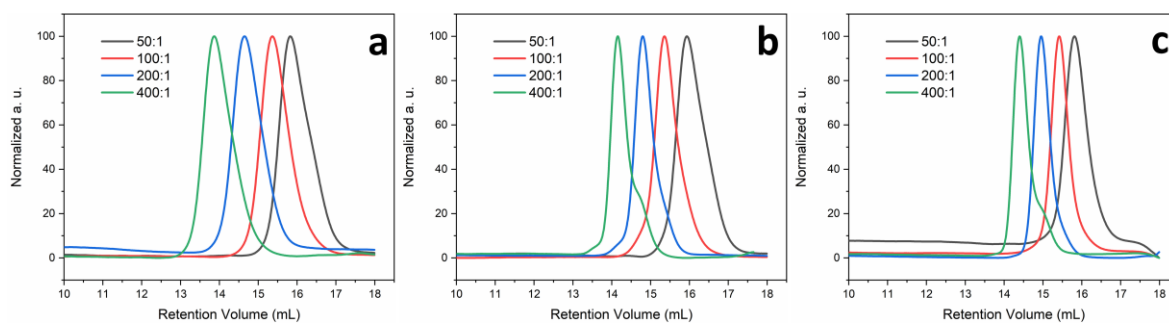


Figure 8. SEC elugrams of poly(MMA) prepared at different M/I ratios via MTAC-initiated a) Cu(0)-RDRP in DMSO at 85°C, 0.2 eq. of Me₆TREN; b) Cu(0)-RDRP in toluene at 85°C, 1.0 eq. of PMDETA; c) ATRP in 1,4-dioxane at 85°C, 1.0 eq. of PMDETA. Product characteristics are provided in **Table 3**.

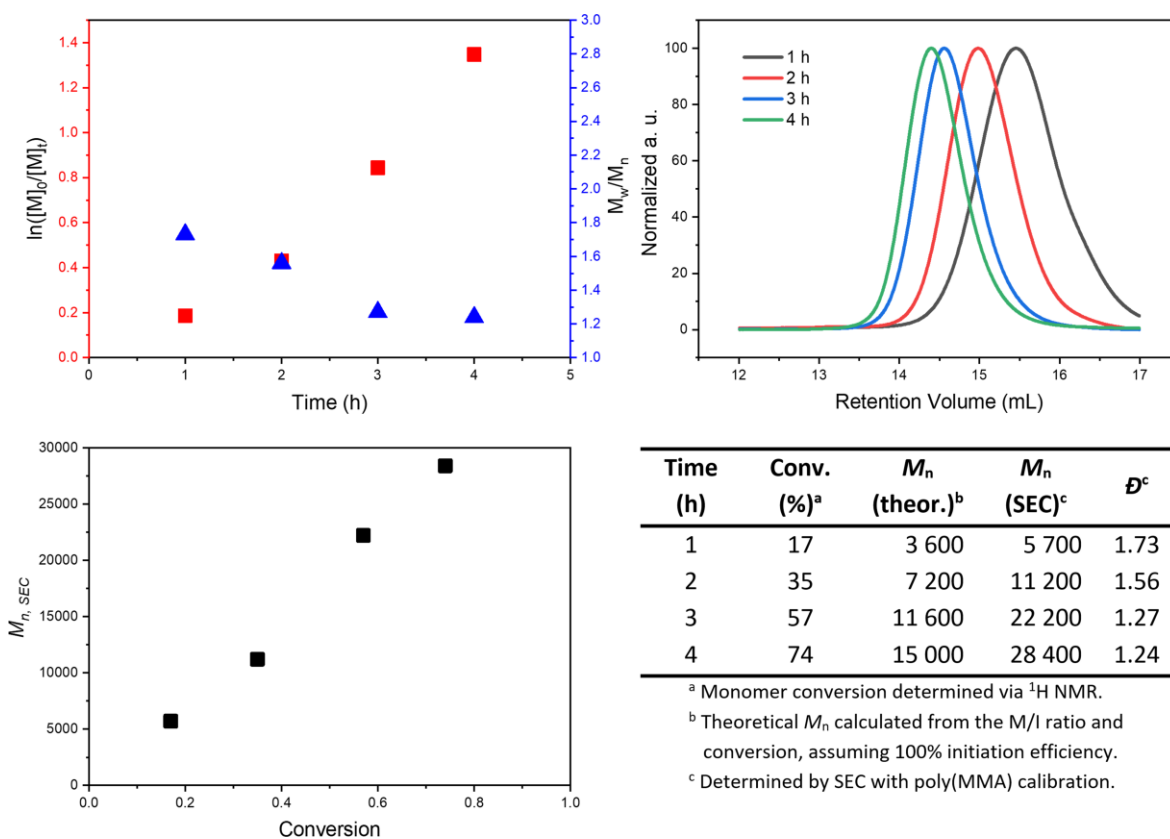


Figure 9. Kinetics of MTAC-initiated Cu(0)-RDRP of MMA. Experimental conditions: MMA/MTAC/Me₆TREN = 200:1:0.2; MMA/DMSO = 1:1 (v/v), 85 °C, 10 cm of activated Cu wire.

In toluene, a high conversion and low dispersity product was obtained with PMDETA whereas with Me₆TREN the polymerization was plagued with high dispersity of the products (cf., entries 41 and 42). Similarly, using 1,4-dioxane as a solvent also resulted in uncontrolled polymerization with

Me₆TREN but led to extremely well-defined poly(MMA) with PMDETA (\bar{D} = 1.09, 88% conv.) (entries 43 and 44). This result was remarkable as the lowest dispersity product was obtained compared to all other conditions. It was further tested for different M/I ratios. M/I ratios of 50 and 100 resulted in almost quantitative conversions in 18 h whereas the M/I ratio of 400 provided only 70% conversion in 45h (entries 45 – 47, **Figure 8c**). This slightly lower conversion is ascribed to the increase in viscosity of the reaction mixture during the polymerization. Notably, all the above experiments were performed with a mixed halogen system. Similar results were obtained in an additional experiment where CuCl was employed as a catalyst source with 1,4-dioxane/PMDETA (1.0 eq.) (entry 48). Kinetic studies were performed for three different successful sets of conditions as shown in **Figure 9**, **Figure 10** and **Figure 11**, confirming that the polymerization processes were well-controlled. Taken together, ATRP of MMA was mostly successful in non-polar solvents in contrast to ATRP of MA where no successful polymerizations were obtained. This supports the importance of the extensive optimization study undertaken and highlights that a slight change in one of the parameters of Cu-RDRP can lead to huge differences in the results obtained.

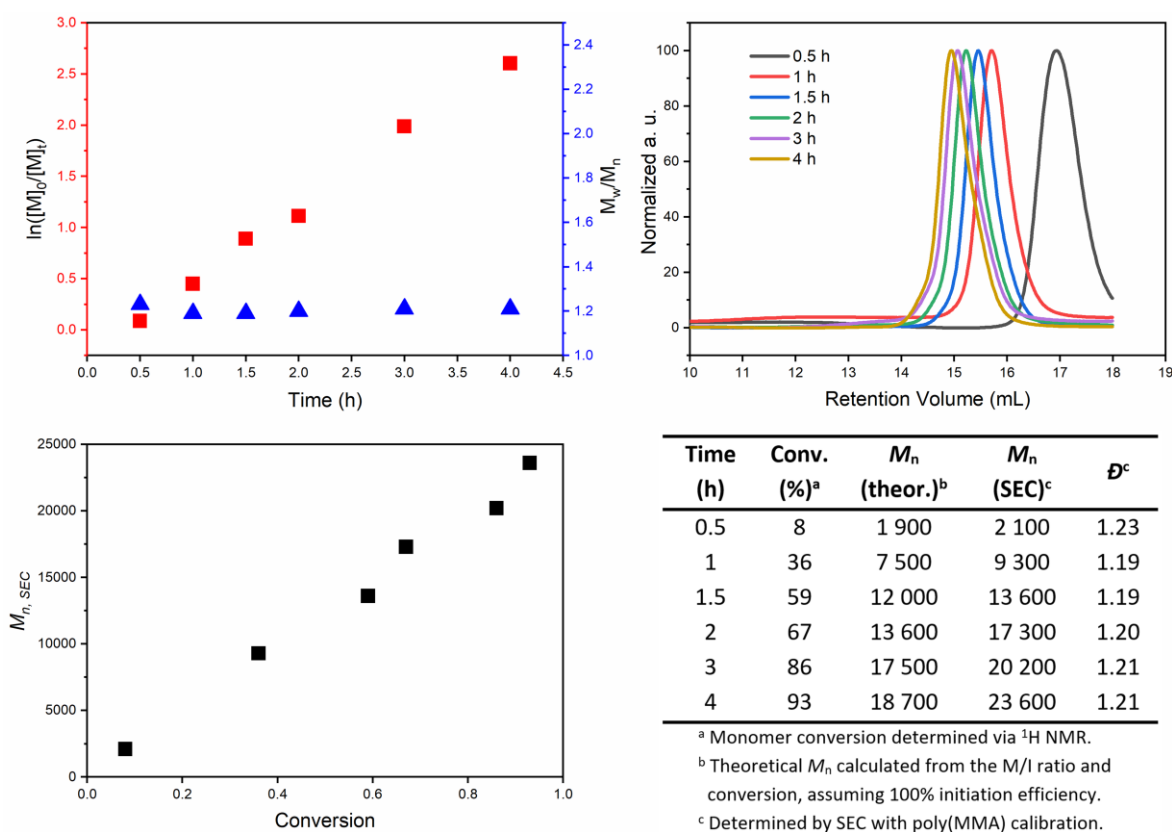


Figure 10. Kinetics of MTAC-initiated Cu(0)-RDRP of MMA. Experimental conditions: MMA/MTAC/PMDETA = 200:1:1; MMA/1,4-dioxane = 1:1 (v/v), 85 °C, 10 cm of activated Cu wire.

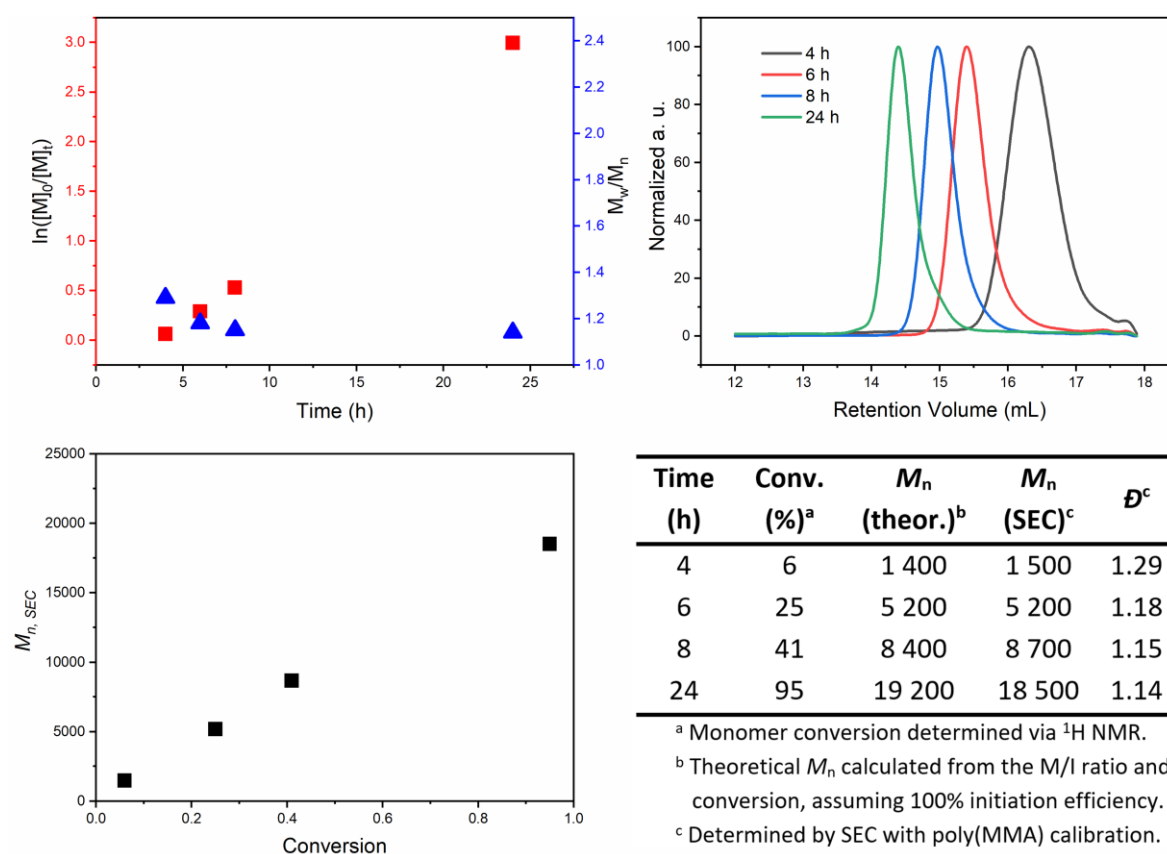


Figure 11. Kinetics of MTAC-initiated ATRP of MMA. Experimental conditions: MMA/MTAC/CuBr/PMDETA = 200:1:1:1; MMA/1,4-dioxane = 1:1 (v/v), 85 °C.

5.1.5 Chain extension study

Chain-extension experiments were performed to verify if the polymers prepared via TAG-initiated Cu-RDRP have high chain-end fidelity. For this purpose, a poly(MMA) sample with M_n of 9 500 and dispersity of 1.13 (Table 3, entry 46) was used as a macroinitiator and subjected to ATRP chain extension with MMA in 1,4-dioxane, and copolymerization with styrene in bulk. Table 4 summarizes the results obtained in this study, and the corresponding SEC traces are presented in Figure 12. It can be clearly seen that despite having the macroinitiator prepared at rather high conversion (85%), it was successfully chain extended to a higher-MW poly(MMA) and to a poly(MMA)-*b*-polystyrene block copolymer in a controlled fashion, with dispersity of 1.25 and 1.26 determined for the products, respectively.

Table 4. Results obtained during the chain-extension study of the poly(MMA) macroinitiator.

Entry ^a	Monomer	Solvent	Ligand (eq.)	M/I	T (°C)	Time (h)	Conv. (%) ^b	M_n (theor.) ^c	M_n (SEC)	\mathcal{D}
1	MMA	dioxane	PMDETA (1.0 eq.)	400	85	2	73	38 700	34 400 ^d	1.25 ^d
2	styrene	-	Me ₆ TREN (1.0 eq.)	800	110	1.5	26	31 000	30 000 ^e	1.26 ^e

^a Polymerization conditions: poly(MMA) macroinitiator ($M_n = 9\,500$, $\mathcal{D} = 1.13$; entry 46, Table 3), CuBr (1 eq.), solvent/monomer = 1:1 (v/v).

^b Monomer conversion determined by ¹H-NMR.

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% initiation efficiency; the macroinitiator M_n is included in the calculation.

^d Determined by SEC with poly(MMA) calibration.

^e Determined by SEC with polystyrene calibration.

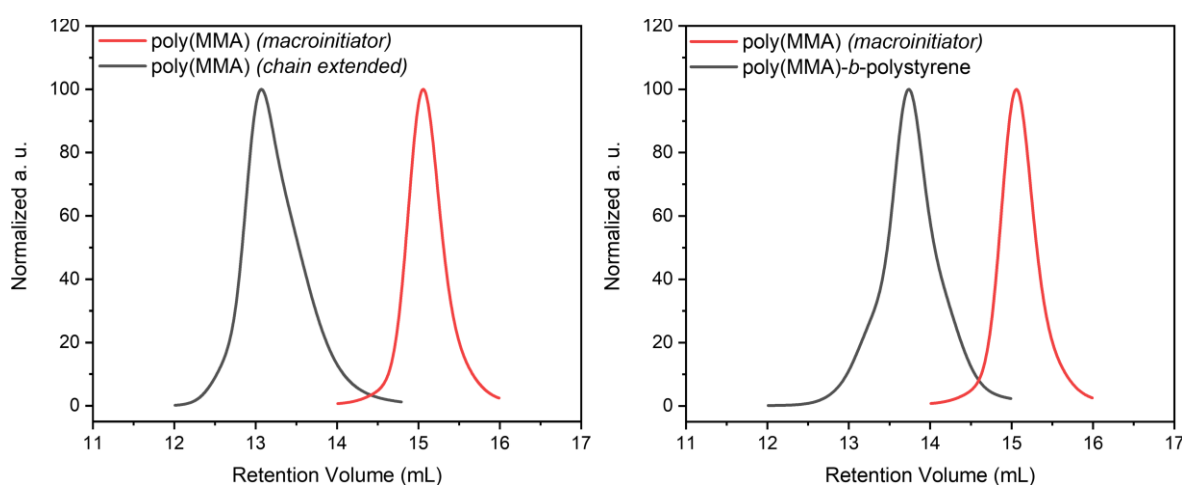


Figure 12. SEC elugrams for the chain-extension study of the poly(MMA) macroinitiator ($M_n = 9\,500$, $\mathcal{D} = 1.13$) and the chain-extended poly(MMA) (left) or the poly(MMA)-*b*-polystyrene block copolymer (right).

5.1.6 Cu-RDRP of styrene

Table 5 summarizes the results obtained during the optimization of styrene polymerization using the MTAC initiator. Starting with Cu(0)-RDRP in polar solvents, both DMSO and DMAc resulted into uncontrolled polymerization with PMDETA (0.5 eq.) at 90 °C in 24 h as evidenced by high dispersity (entries 1 and 2). With Me₆TREN (0.5 eq.), controlled polymerization was obtained in DMSO albeit with the conversion of 60% only which could be increased to 81% by using higher ligand loadings (cf., entries 3 and 4). Similarly, in DMAc, Me₆TREN (0.5 eq.) was able to drive the polymerization in a controlled fashion ($\mathcal{D} = 1.28$) but with higher ligand loadings the control was lost, giving dispersity 1.45 at similar conversions (entries 5 and 6). Notably, gel formation was observed on the copper wire when Me₆TREN was used as a ligand which makes these conditions less usable. Switching to

non-polar solvents, 1,4-dioxane led to poor control over polymerization with either of the ligands since high-dispersity polystyrenes were obtained at 90 °C in 24 h (entries 7 and 8). On the other hand, in toluene, no polymerization was obtained with PMDETA whereas Me₆TREN (0.2 eq.) led to good control over polymerization but with low conversion (45%) at 90 °C in 24 h which was only increased to 57% when the polymerization was prolonged to 48 h (entries 9 – 11). With higher ligand loadings of Me₆TREN (0.5 and 1.0 eq.), the control was lost as seen from the high dispersity of the polystyrenes obtained along with a significant gel formation on the copper wire (entries 12, 13). The polymerization conducted in bulk with the M/I ratio of 200:1 was uncontrolled when PMDETA was used (entry 14) but showed better control with Me₆TREN at different ligand loadings (entries 15 – 17). Unfortunately, all the experiments in bulk were plagued with the gel formation on copper wire. Surprisingly, styrene failed to polymerize under ATRP conditions at 90 °C and 24 h in DMSO, DMAc and IPA with either of the ligands and in 1,4-dioxane and toluene with PMDETA as a ligand (entries 18 – 25). Only with Me₆TREN (1.0 eq.) in 1,4-dioxane and toluene, some control over the polymerization was observed since low dispersity (1.29 and 1.23, respectively) polystyrenes were obtained, but the conversions were low ($\leq 42\%$) (cf., entries 26 and 27). ATRP conducted in bulk resulted in poor control when PMDETA was employed as a ligand (in 24 h) but showed decent control with Me₆TREN (in 22 h) at 90 °C as corroborated by dispersity of 1.20 achieved at 87% monomer conversion (entries 28 and 29). Despite having acceptable control, Me₆TREN resulted in poor initiation efficiency (IE), which did not improve by changing the catalyst to CuCl under otherwise identical conditions (entry 30). However, by increasing the temperature to 110 °C, excellent control over ATRP of styrene was achieved with Me₆TREN (1.0 eq.), resulting in a polymer with dispersity of 1.21 and conversion of 86% in just 6 h (entry 31). This result was promising and was tested for different M/I ratios. It was found that the ATRP conditions i.e., CuBr/Me₆TREN (1:1) at 110 °C in bulk were not suitable directly for the M/I ratio of 50 since high dispersity (1.61) polystyrene was obtained (entry 32). This is ascribed to the early termination reactions due to a high concentration of radicals produced with lower M/I ratios. However, upon an addition of an external deactivator i.e., CuBr₂ (0.2 eq.), the concentration of radicals was reduced, which resulted into controlled chain growth, affording polystyrene with dispersity 1.30 (entry 33). For other M/I ratios, i.e., 100, 400, and 800, CuBr/Me₆TREN (1:1) in bulk at 110 °C worked excellently, showcasing the applicability of these ATRP conditions to the synthesis of polystyrenes of different MWs (entries 34 – 36, see **Figure 13** for SEC traces). A kinetic study revealed that the polymerization control was established from the beginning as MWs grew linearly with monomer conversion (**Figure 14**). Taken together, Cu-RDRP of styrene using the MTAC initiator was comparatively more successful under ATRP conditions especially in bulk.

Table 5. Results obtained during the optimization of polymerization conditions for MTAC-initiated Cu-RDRP of styrene^a

Entry	Cat.	Solvent	Ligand (eq.)	M/I	T (°C)	Time (h)	Conv. (%) ^b	M_n (theor.) ^c	M_n (SEC) ^d	\bar{D}^d
1	Cu(0)	DMSO	PMDETA (0.5)	200	90	24	51	10 800	27 300	2.30
2	Cu(0)	DMAc	PMDETA (0.5)	200	90	24	36	7 800	12 500	1.65
3 ^e	Cu(0)	DMSO	Me ₆ TREN (0.5)	200	90	24	60	12 800	18 100	1.27
4 ^e	Cu(0)	DMSO	Me ₆ TREN (1.0)	200	90	24	81	17 100	25 800	1.31
5 ^e	Cu(0)	DMAc	Me ₆ TREN (0.5)	200	90	24	56	12 000	17 300	1.28
6 ^e	Cu(0)	DMAc	Me ₆ TREN (1.0)	200	90	24	54	11 400	20 500	1.45
7	Cu(0)	dioxane	PMDETA (1.0)	200	90	24	75	15 800	28 000	1.62
8	Cu(0)	dioxane	Me ₆ TREN (1.0)	200	90	24	71	15 000	61 600	5.29
9	Cu(0)	toluene	PMDETA (0.5)	200	90	24		<i>no polymerization</i>		
10	Cu(0)	toluene	Me ₆ TREN (0.2)	200	90	24	45	9 700	10 400	1.19
11	Cu(0)	toluene	Me ₆ TREN (0.2)	200	90	48	57	12 000	14 700	1.21
12 ^e	Cu(0)	toluene	Me ₆ TREN (0.5)	200	90	24	49	10 400	13 000	1.38
13 ^e	Cu(0)	toluene	Me ₆ TREN (1.0)	200	90	24	65	13 700	19 000	1.44
14 ^e	Cu(0)	-	PMDETA (0.5)	200	90	9	15	6 300	9 200	2.01
15 ^e	Cu(0)	-	Me ₆ TREN (0.2)	200	90	24	37	15 600	16 800	1.24
16 ^e	Cu(0)	-	Me ₆ TREN (0.5)	200	90	24	67	28 300	31 300	1.25
17 ^e	Cu(0)	-	Me ₆ TREN (1.0)	200	90	24	89	37 200	42 500	1.36
18	CuBr	DMSO	PMDETA (1.0)	200	90	24		<i>no polymerization</i>		
19	CuBr	DMSO	Me ₆ TREN (1.0)	200	90	24		<i>no polymerization</i>		
20	CuBr	DMAc	PMDETA (1.0)	200	90	24		<i>no polymerization</i>		
21	CuBr	DMAc	Me ₆ TREN (1.0)	200	90	24		<i>no polymerization</i>		
22	CuBr	IPA	PMDETA (1.0)	200	90	24		<i>no polymerization</i>		
23	CuBr	IPA	Me ₆ TREN (1.0)	200	90	24		<i>no polymerization</i>		
24	CuBr	dioxane	PMDETA (1.0)	200	90	24		<i>no polymerization</i>		
25	CuBr	toluene	PMDETA (1.0)	200	90	24		<i>no polymerization</i>		
26	CuBr	dioxane	Me ₆ TREN (1.0)	200	90	24	15	3 300	4 200	1.29
27	CuBr	toluene	Me ₆ TREN (1.0)	200	90	24	42	8 900	10 000	1.23
28	CuBr	-	PMDETA (1.0)	200	90	24	12	5 200	5 200	1.38
29	CuBr	-	Me ₆ TREN (1.0)	200	90	22	87	36 300	45 000	1.20
30	CuCl	-	Me ₆ TREN (1.0)	200	90	24	10	4 200	4 600	1.16
31	CuBr	-	Me ₆ TREN (1.0)	200	110	6	86	18 100	21 100	1.21
32	CuBr	-	Me ₆ TREN (1.0)	50	110	3	91	5 000	5 900	1.61
33 ^f	CuBr	-	Me ₆ TREN (1.2)	50	110	2	89	4 900	6 000	1.30
34	CuBr	-	Me ₆ TREN (1.0)	100	110	6	84	9 000	10 500	1.26
35	CuBr	-	Me ₆ TREN (1.0)	400	110	21	95	40 000	45 300	1.25
36	CuBr	-	Me ₆ TREN (1.0)	800	110	24	92	77 000	75 200	1.34

^a Standard polymerization conditions: monomer/solvent = 1:1 (v/v), catalyst (Cat.): 10 cm of activated copper wire in Cu(0)-RDRP, 1 eq. of Cu(I) salt in ATRP.

^b Monomer conversion determined gravimetrically.

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% initiation efficiency.

^d Determined by SEC with polystyrene calibration.

^e Gel formation on Cu wire was observed.

^f CuBr₂ (0.2 eq.) was added as a deactivator, and the concentration of ligand was increased to account for this addition.

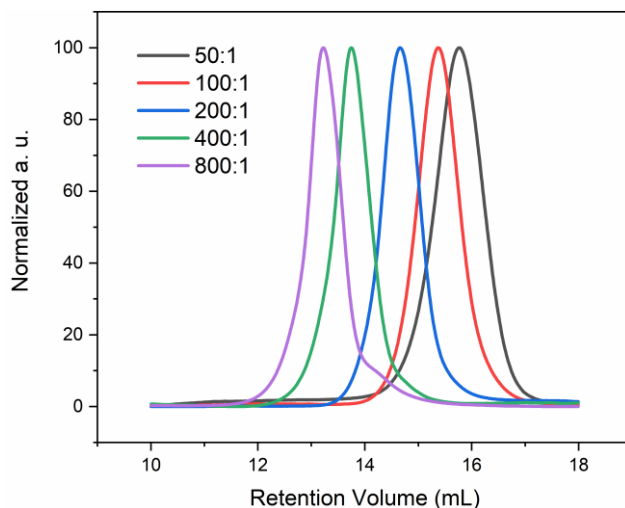


Figure 13. SEC elugrams of polystyrene prepared at different M/I ratios via MTAC-initiated ATRP of styrene in bulk at 110°C, 1.0 eq. of Me₆TREN. Product characteristics are provided in **Table 5**.

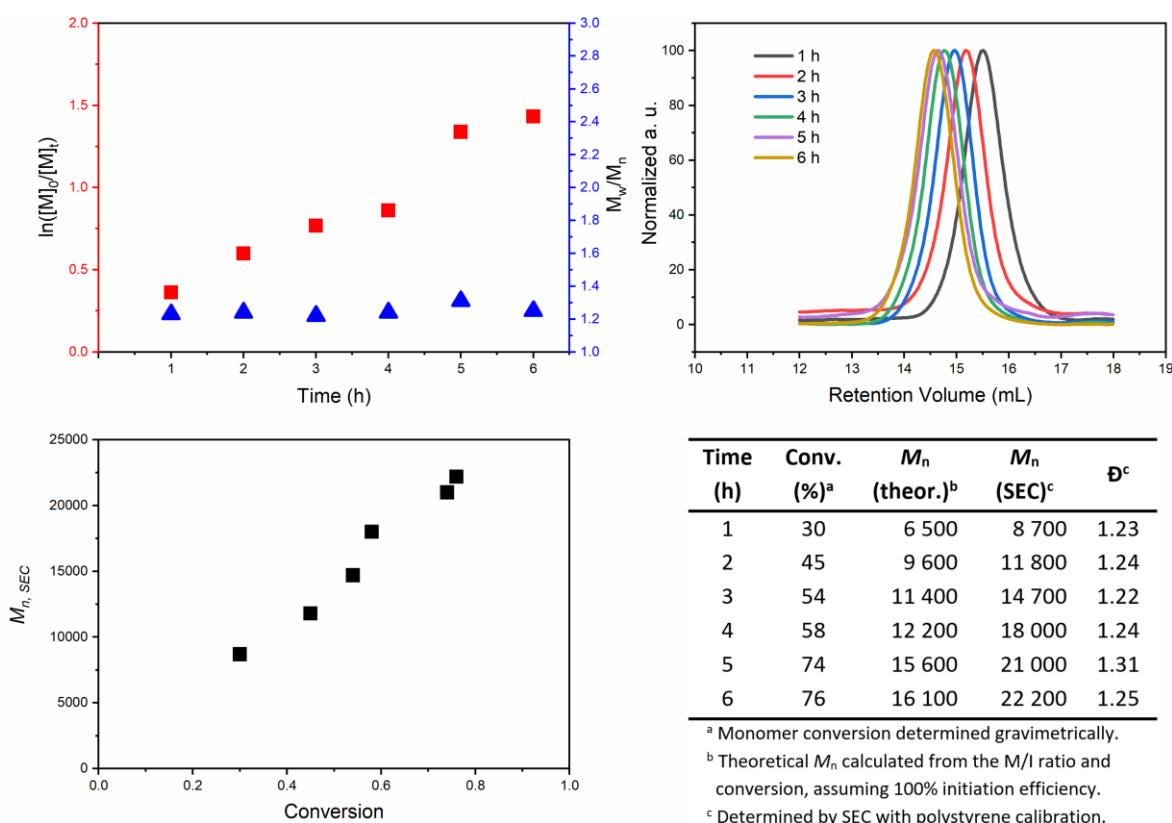
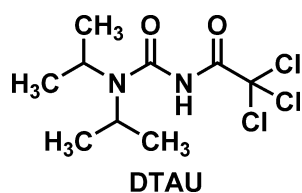


Figure 14. Kinetics of MTAC-initiated ATRP of styrene performed in bulk. Experimental conditions: styrene/MTAC/CuBr/ Me₆TREN = 200:1:1:1; 110 °C.

5.1.7 Verification of the TAI-borne linker influence on the outcome of Cu-RDRP initiated by TAI adducts.

To investigate the applicability of the Cu-RDRP conditions developed above using MTAC (which is a TAI adduct of an alcohol) to an initiator with a different substrate-TAG linker, an amine-based TAI adduct was synthesized. For this purpose, *N,N*-diisopropylamine was used as a substrate which was modified with TAI via a simple addition reaction in CH₂Cl₂, affording 1,1-diisopropyl-3-(2,2,2-trichloroacetyl)-urea (DTAU) (**Scheme 6**) which was used without further purification. ¹H-NMR spectrum of DTAU is shown in **Figure A3**. From the library of conditions established for MTAC-initiated Cu-RDRP of styrene, MMA and MA, conditions were selected under which analogous experiments were performed using DTAU as an initiator. **Table 6** summarizes the results obtained in this study. It can be seen that the DTAU-initiated Cu-RDRP of different monomers resulted into well-defined polymers with high monomer conversions, and the results were comparable to the polymers synthesized using MTAC as an initiator (**Figure 15**). These results suggest that regardless of the type of the substrate-TAG linker, similar polymers can be grown from the initiating sites. This finding confirms the wide applicability of the optimized Cu-RDRP conditions developed using MTAC.



Scheme 6. The structure of the DTAU initiator used in the Cu-RDRP verification studies.

Table 6. Results obtained for DTAU-initiated Cu-RDRP of styrene, MMA, and MA^a.

Entry ^a	Monomer	Cat.	Solvent	Ligand (eq.)	T (°C)	Time (h)	Conv. (%) ^b	<i>M_n</i> (theor.) ^c	<i>M_n</i> (SEC) ^d	<i>Đ</i> ^d
1	styrene	CuBr	-	Me ₆ TREN (1.0 eq.)	110	6	74	15 700	18 200	1.30
2	MMA	CuBr	dioxane	PMDETA (1.0 eq.)	85	24	75	15 300	18 900	1.10
3	MA	Cu(0)	DMSO	Me ₆ TREN (0.5 eq.)	60	5	96	16 600	21 800	1.30

^a Standard polymerization conditions: M/I = 200:1; catalyst (Cat.): 10 cm of activated copper wire in Cu(0)-RDRP, CuBr (1 eq.) in ATRP; monomer/solvent = 1:1 (v/v).

^b Monomer conversion determined gravimetrically (styrene, MMA) or by ¹H-NMR (MA).

^c Theoretical *M_n* calculated from the M/I ratio and conversion, assuming 100% initiation efficiency.

^d Determined by SEC with polystyrene (for polystyrene) or poly(MMA) calibration (for poly(MA) and poly(MMA)).

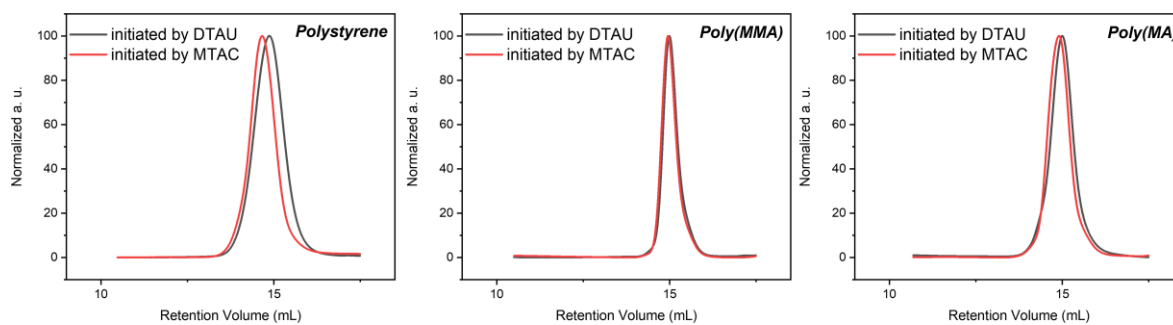


Figure 15. SEC elugrams of the polymers synthesized under identical conditions using MTAC and DTAU initiators.

5.1.8 Study on MTAC-initiated Cu-RDRP of other (meth)acrylates

With the polymerization conditions for well-controlled Cu-RDRP of styrene, MMA, and MA established, an obvious further step was to study if the developed conditions can be employed in Cu-RDRP of other monomers from the same class. For this purpose, different conditions were selected from the library of Cu-RDRP conditions developed using MTAC and applied to different (meth)acrylates, both functional and non-functional ones. **Table 7** summarizes the results obtained in this study, and the corresponding SEC traces are displayed in **Figure 16**. As anticipated, not all the conditions from the developed library were directly applicable to the (meth)acrylate analogues due to differences in the side groups. At this point, the great diversity in the developed Cu-RDRP conditions helped in identifying the specific conditions that can provide well-defined products. For instance, when Cu(0)-RDRP in toluene was applied to butyl acrylate (BA), the control over polymerization was poor and very low monomer conversion was obtained in 24 h (entry 1). However, upon switching to polar solvent, i.e., DMSO, well-defined poly(BA) was obtained at quantitative conversion in just 7 h in a biphasic system⁸⁰ (entry 2). Next, for 2-hydroxyethyl acrylate (HEA), a well-defined polymer was obtained when 0.2 eq. of Me₆TREN was used whereas under standard conditions, i.e., using 0.5 eq., the polymerization was plagued with high dispersity (cf. entries 3 and 4). On the other hand, for some monomers, the formerly developed conditions could be successfully applied directly without any changes: for butyl methacrylate (BMA), a low-dispersity product was obtained via Cu(0)-RDRP in toluene in 24 h, and for glycidyl methacrylate (GMA), this was achieved via Cu(0)-RDRP in DMSO, obtaining a high conversion in just 2 h (entries 5 and 6). Finally, Cu(0)-RDRP in DMSO was also employed for the polymerization of HEMA (entry 7). However, this resulted in a high-dispersity product although quantitative conversion was achieved. To rectify this problem, Cu(0)-RDRP in 1,4-dioxane with 1 eq. of PMDETA at 85 °C was performed, attaining well-defined poly(HEMA) in a rapid process (entry 8).

Table 7. MTAC-initiated Cu-RDRP of other (meth)acrylates^a

Entry	Monomer	Solvent	Ligand (eq.)	T (°C)	Time (h)	Conv. (%) ^b	M_n (theor.) ^c	M_n (SEC) ^d	\mathcal{D}^d
1	BA	toluene	Me ₆ TREN (0.5)	60	24	16	4 200	4 600	1.45
2 ^e	BA	DMSO	Me ₆ TREN (0.5)	60	7	97	25 100	35 100	1.25
3	HEA	DMSO	Me ₆ TREN (0.5)	60	8	50	11 800	46 500	1.37
4	HEA	DMSO	Me ₆ TREN (0.2)	60	24	42	10 000	15 000	1.18
5	BMA	toluene	PMDETA (1.0)	85	24	84	24 000	20 400	1.15
6	GMA	DMSO	Me ₆ TREN (0.2)	85	2	80	23 000	21 400	1.23
7 ^f	HEMA	DMSO	Me ₆ TREN (0.2)	85	24	99	13 100	20 000	1.85
8 ^f	HEMA	dioxane	PMDETA (1.0)	85	1	99	13 100	17 200	1.28

^a Standard polymerization conditions: MTAC initiator, M/I = 200:1, 10 cm of activated copper wire, monomer/solvent = 1:1 (v/v).

^b Monomer conversion determined by ¹H-NMR.

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% IE.

^d Determined by SEC with poly(MMA) calibration [directly (BA, BMA, GMA) or after acetylation⁴⁶ (HEMA)] or by TD-SEC (HEA).

^e Biphasic polymerization mixture.

^f M/I = 100:1 and 5 cm of activated copper wire were used.

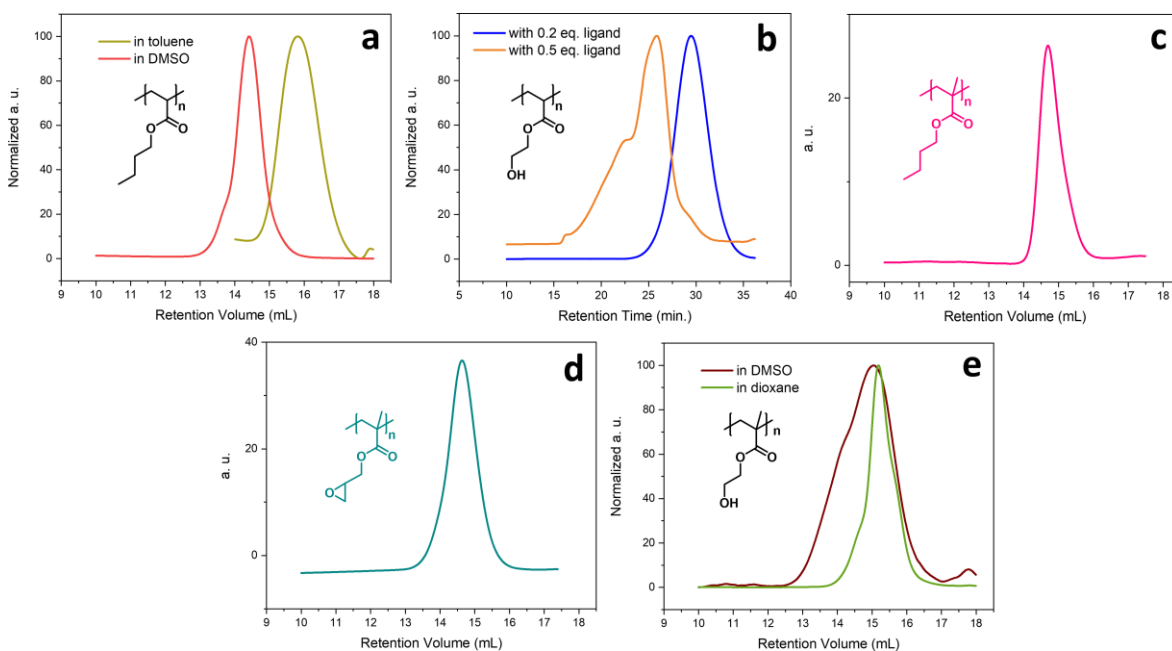


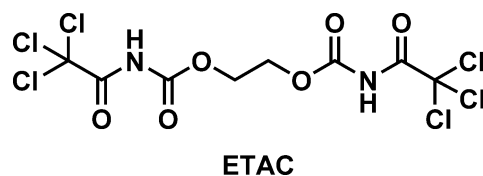
Figure 16. SEC elugrams of a) poly(BA), b) poly(HEA), c) poly(BMA), d) poly(GMA), and e) poly(HEMA) prepared using the previously optimized polymerization conditions (with or without modification). Experimental conditions and product characteristics are provided in **Table 7**.

It is important to note that the rapid and well-controlled polymerization of HEMA in 1,4-dioxane came out as a surprising result that encouraged us to explore these unconventional conditions

further using standard, monofunctional, commercially available initiators. This will be discussed in a subsequent section of this thesis. Altogether, the study with different (meth)acrylates showed that the library of successful conditions established with model monomers (**Tables 2, 3, 5**) can be used as an excellent starting point for the polymerization of other monomers using TAG-bearing compounds as initiators. This finding shows a remarkable versatility of these initiators which also demonstrates the wide scope of the TAI strategy.

5.1.9 Study on the hydrolytic stability of the in-chain TAI-derived carbamate linkers

Since MTAC has a carbamate unit linking the tri-chlorinated end to the original substrate's fragment, it was important to understand the hydrolytic stability of this linker when it gets incorporated into a polymer. For this reason, a water-soluble polymer, i.e., poly(HEA), was prepared via Cu(0)-RDRP of HEA using ethane-1,2-diyl bis((2,2,2-trichloroacetyl)carbamate) (ETAC) (**Scheme 7**) as an initiator and the HEA/ETAC/Me₆TREN ratio of 400:1:0.2 in DMSO at 60 °C. ETAC was prepared by the reaction of ethylene glycol with an excess of TAI in CH₂Cl₂, followed by the removal of unreacted TAI and CH₂Cl₂ through distillation. The prepared initiator was used without any further purification (see **Figure A4** for ¹H-NMR). The poly(HEA) synthesized using ETAC had $M_n = 24\ 300$ and $\bar{D} = 1.28$, and the expected architecture of a 6-arm star (if TAG is assumed to behave as a trifunctional initiator). The polymer was dissolved in buffers of six different pH values covering the range of 1 to 11, and maintained at 37 °C for 24 h. Using TD-SEC, we evaluated the MW of the polymer expecting that the degradation of the (potentially hydrolytically labile) carbamate linker will result in measurable changes in this parameter. As evidenced from the MW distributions (MWDs) shown in **Figure 17**, the carbamate linker in ETAC is tolerant to hydrolysis in the wide pH range used in this study. A small change in MWDs could be noticed at pH 9 and 11, but this shift was rather small and inconsistent with carbamate linker hydrolysis. This is particularly well-visible when considering the M_n and M_p (peak MW) values summarized in **Table 8**. The relatively small changes in MWs of poly(HEA) at pH 9 and 11 can be explained by partial hydrolysis of the ester side groups in poly(HEA) at alkaline pH. This notion is also supported by looking at the decrease in the dn/dc values determined for the poly(HEA) at pH 11 (0.060 mL/g) compared to the parent poly(HEA) (0.072 mL/g), which is a sign of a change in the polymer composition at alkaline pH. Taken together, these preliminary results indicate that the in-chain carbamate linkers obtained using the TAI strategy are considerably hydrolytically stable in a wide range of pH, which is not usually observed for low-MW carbamates.¹¹¹⁻¹¹⁴ Such a kind of stability of the TAI-derived carbamate linkers can be ascribed to the steric hinderance resulting from the crowding caused by the polymeric chains growing from these multifunctional initiation sites.



Scheme 7. The structure of the ETAC initiator used in the hydrolytic stability studies.

Table 8. Experimental results for the ETAC-initiated poly(HEA) before and after exposure to buffers of different pH^a.

Buffer pH	M_n^c	M_p^c	\bar{D}^c	dn/dc^d (mL/g)
- ^b	24 300	27 100	1.28	0.072
1	24 700	27 000	1.21	0.073
3	21 300	25 000	1.26	0.075
5	22 200	25 400	1.28	0.075
7	21 000	25 600	1.29	0.074
9	19 000	22 800	1.28	0.070
11	20 500	20 700	1.21	0.060

^a Experimental conditions: polymer concentration 5 mg/mL, 24 h at 37°C

^b Starting poly(HEA) before subjecting to different pH.

^c MWs of the isolated polymers were determined by TD-SEC in DMAc/LiBr.

^d The dn/dc values were determined by the OMNISEC software assuming 100% sample recovery.

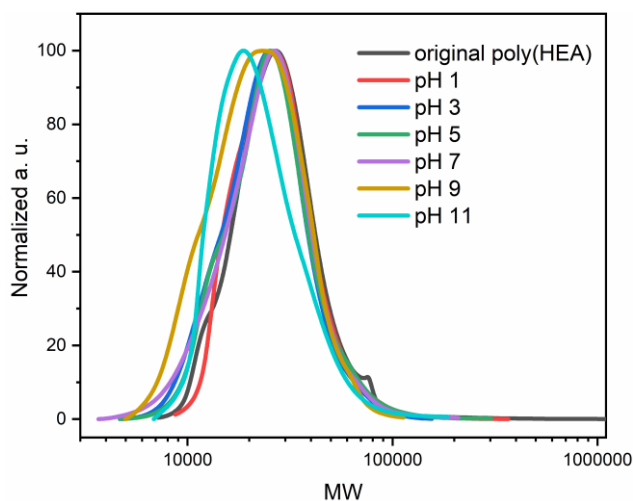


Figure 17. MWDs of the ETAC-initiated poly(HEA) before and after exposure to buffers of different pH for 24 h at 37 °C. The data were obtained for isolated samples by TD-SEC.

5.1.10 Functionality study of TAI-based initiation groups

One of the most important factors determining the final polymeric architecture obtained via the TAI strategy is the functionality of TAG(s) that are introduced into CPA precursors by their reaction with TAI. This sets the TAI strategy apart from earlier methods that relied on monofunctional initiation sites like BriB. Remarkably, there has been only handful of reports in the literature regarding the functionality of TAG-containing initiators for Cu-RDRP. Based on the NMR data, Destarac et al. reported in their seminal paper that the methyl trichloroacetate (MTCA) initiator under study behaves as—at least—a bifunctional initiator in the ATRP of styrene.⁸² Furthermore, trichloroacetic acid was used as a trifunctional initiator by Lorandi et al. to synthesize poly(acrylic acid) via ATRP.¹⁰¹ They pointed out that upon initiation, the residual chlorine(s) of the initial TAG unit become more susceptible to activation (and, consequently, initiation) as a result of the penultimate effect.¹¹⁵ In the light of these limited published results, it became imperative to investigate the overall functionality of the TAI-derived initiators under relevant Cu-RDRP conditions established in the library of conditions above.

5.1.10.1 Functionality study using ¹H-NMR for model low MW polymers

First, the initiator functionality (IF) was assessed using ¹H-NMR spectroscopy for low-MW model poly(MA), poly(MMA), and polystyrene synthesized by MTAC-initiated Cu-RDRP. In the corresponding NMR spectra, the distinctive signals of the terminal (chlorine-bearing) and in-chain monomeric units, as well as the initiator fragment (the –OCH₃ group), were identified. Then, IF was calculated using the relative intensities of all these signals in conjunction with the M_n values obtained by SEC for each polymer. Importantly, functionality values very close to 3 were obtained in all cases (see **Figures 18- 20** and the associated discussion).

It is noteworthy that the poly(MMA) sample employed for the functionality study was obtained at high conversion (entry 45, **Table 3**), which further signifies that the polymers synthesized using TAI-based initiators have high chain-end fidelity. Collectively, these results imply that MTAC-initiated polymers are characterized by a three-arm star structure and, because of the reduced V_h of branched polymers, the reported MWs obtained by SEC with relative calibration are somewhat underestimated. Furthermore, this result also implies that the poly(MMA)-*b*-polystyrene that was prepared in the chain-extension experiment above (**Figure 12, left**) is a 3-arm star with diblock arms.

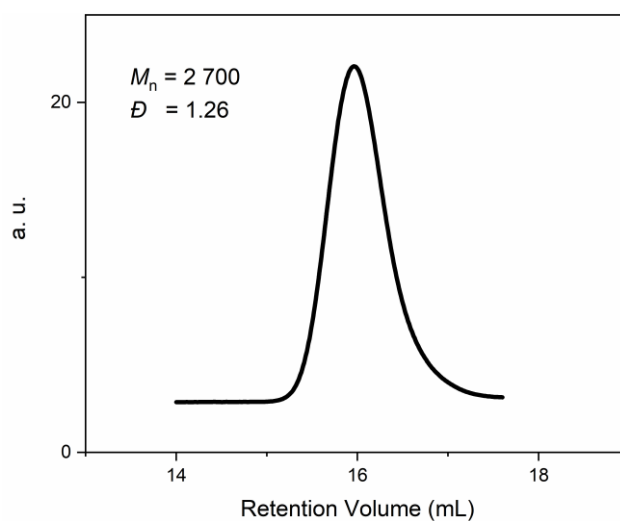
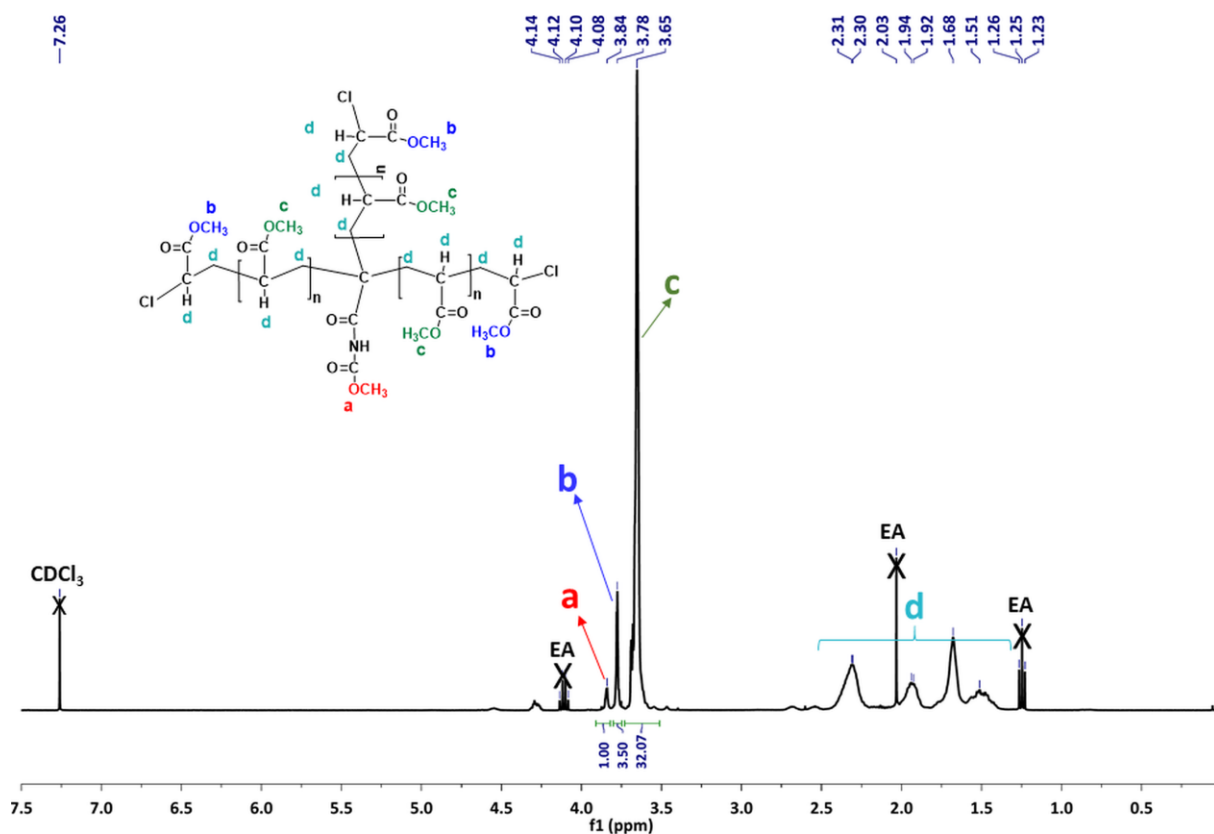


Figure 18. ¹H-NMR study of the MTAC initiator functionality in Cu-RDRP of MA. Top: ¹H-NMR (CDCl₃) of the isolated model poly(MA). Bottom: SEC elugram of the model poly(MA) (MW determined using poly(MMA) calibration). Polymerization conditions: Cu(0)-RDRP, DMSO, Me₆TREN 0.5 eq., 2.5 h, 60°C, 42 % conversion; polymer isolation: ethyl acetate-diluted polymerization mixture was extracted with water 3x, salted out with brine, dried with MgSO₄, and evaporated; the obtained solids were dried in vacuum.

Calculation of initiator functionality (IF) from NMR signal intensity (I):

1st approach: $IF = I_b/I_a = 3.5/1 = 3.5$

2nd approach: $M_{n(\text{single chain})} = [(I_c + I_b) / I_b] \times M_{MA} = [(32.07 + 3.50) / 3.50] \times 86.09 = 875$

$IF = M_{n(\text{SEC})} / M_{n(\text{single chain})} = 2700 / 875 = 3.1$

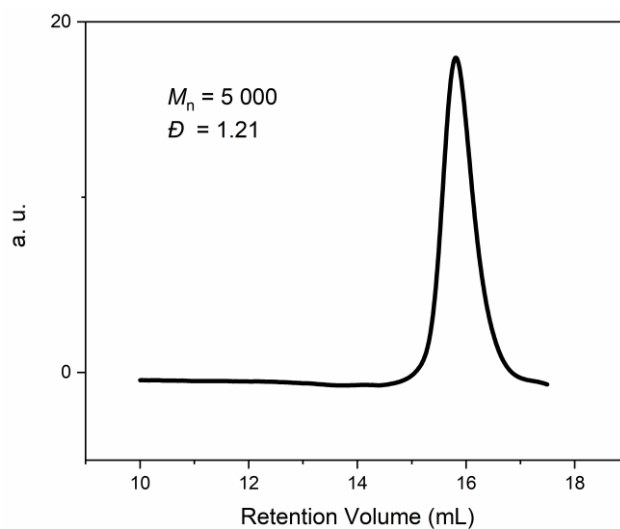
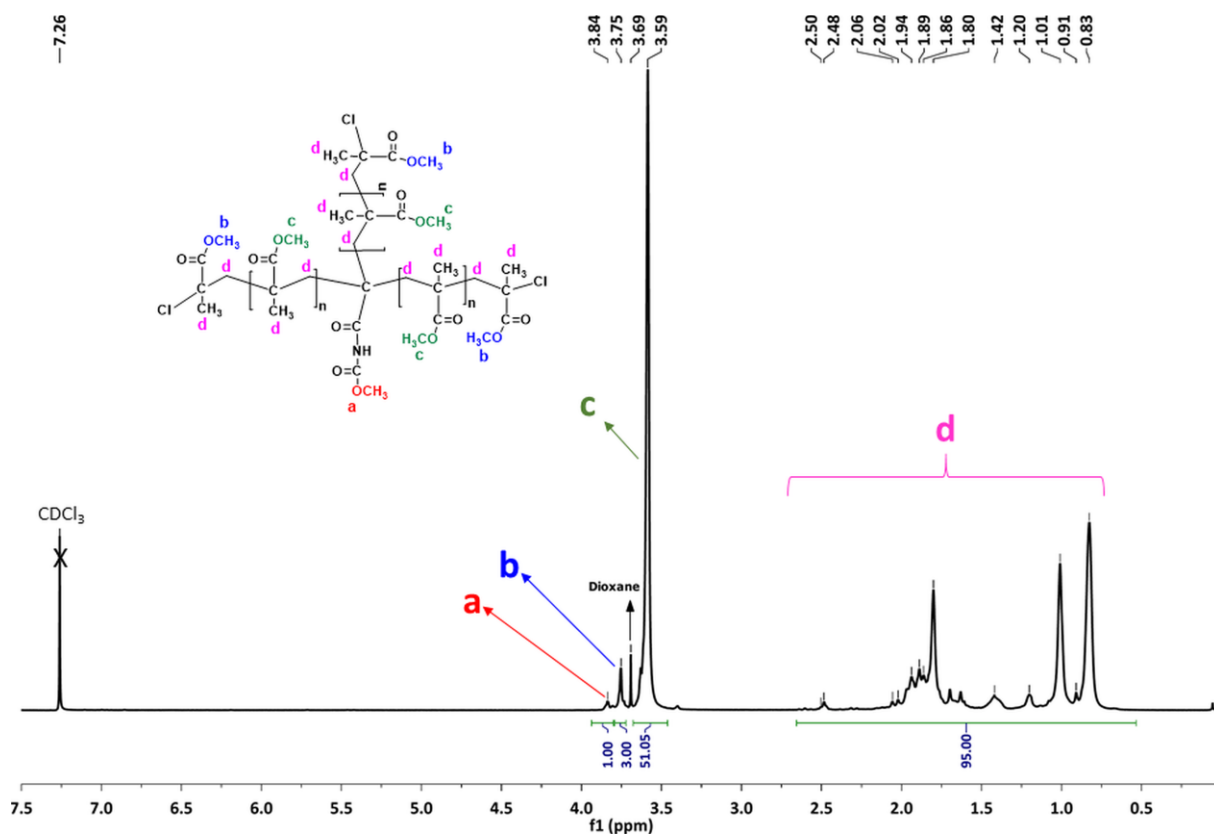


Figure 19. $^1\text{H-NMR}$ study of the MTAC initiator functionality in Cu-RDRP of MMA. Top: $^1\text{H-NMR}$ (CDCl_3) of the isolated model poly(MMA). Bottom: SEC elugram of the model poly(MMA) (MW determined using poly(MMA) calibration). Polymerization conditions are provided in entry 45, **Table 3**; the polymer was isolated via precipitation in MeOH/water (1:1 v/v) and dried in vacuum.

Calculation of IF from NMR signal intensity (I):

1^{st} approach: $\text{IF} = I_b/I_a = 3/1 = 3$

2^{nd} approach: $M_{n(\text{single chain})} = [(I_c + I_b)/I_b] \times M_{\text{MMA}} = [(51.05 + 3.00)/3.00] \times 100.12 = 1804$

$\text{IF} = M_{n(\text{SEC})}/M_{n(\text{single chain})} = 5000/1804 = 2.8$

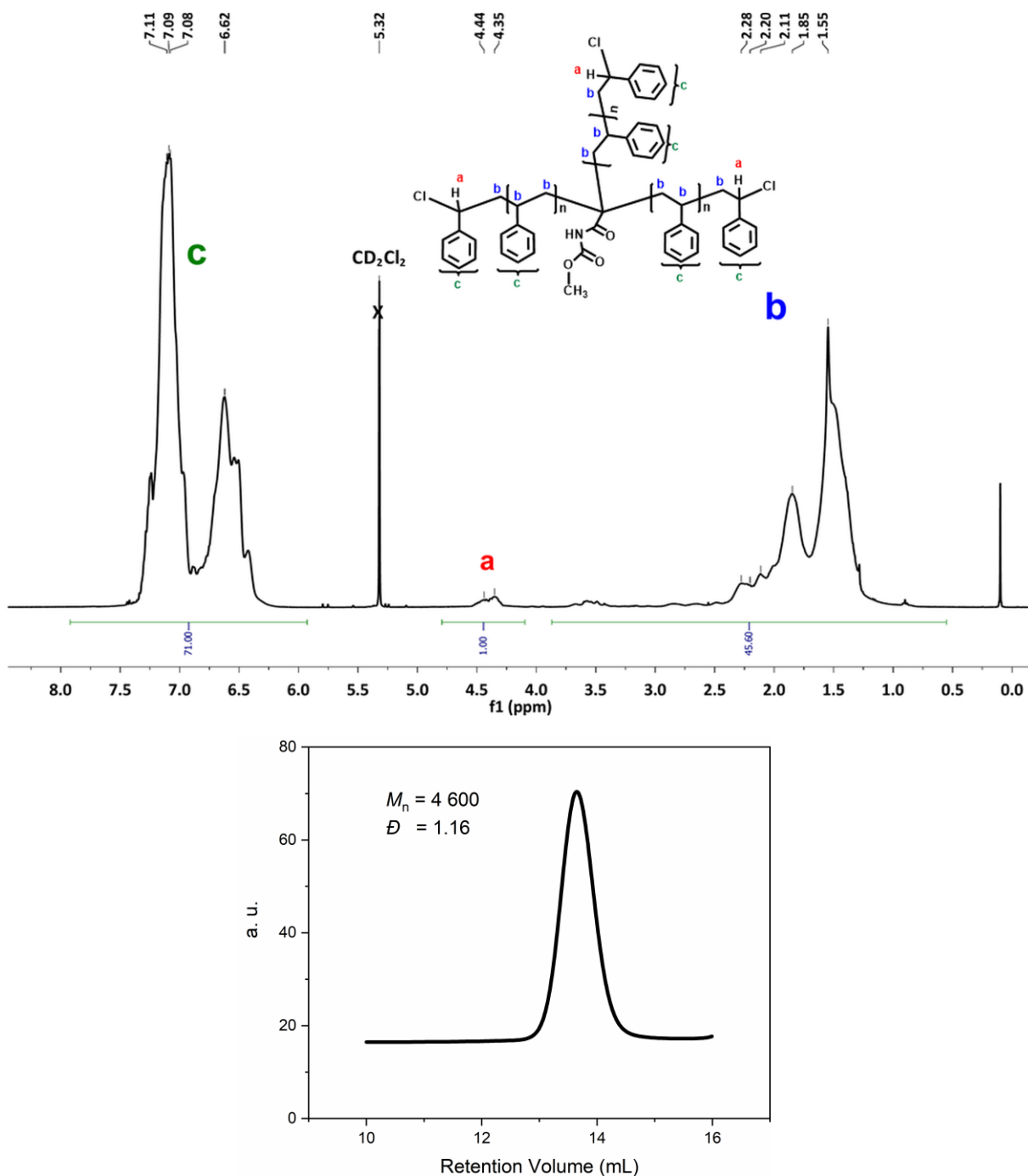


Figure 20. $^1\text{H-NMR}$ study of the MTAC initiator functionality in Cu-RDRP of styrene. Top: $^1\text{H-NMR}$ (CD_2Cl_2) of the isolated model polystyrene. Bottom: SEC elugram of the model polystyrene (MW determined using polystyrene calibration). Polymerization conditions are provided in entry 30, **Table 5**; the polymer was isolated via precipitation in MeOH and dried in vacuum.

Calculation of IF from NMR signal intensity (I):

$$M_{n(\text{single chain})} = [(I_c/5)/I_a] \times M_{\text{St}} = [(71.00/5)/1.00] \times 104.15 = 1479$$

$$\text{IF} = M_{n(\text{SEC})}/M_{n(\text{single chain})} = 4600/1479 = \mathbf{3.1}$$

(Note: This is the calculation by the 2nd approach; for all the studied polymers, the IF value calculated in this way is inherently slightly underestimated due to the underestimation of the M_n value determined by SEC with relative calibration that does not reflect the branching-related decrease in polymer hydrodynamic volume).

5.1.10.2 *Functionality study using TD-SEC for high MW model polymers*

As can be seen from the $^1\text{H-NMR}$ studies above, the TAG behaves as trifunctional for low-MW model polymers initiated by a simple TAI adduct. However, such an end group analysis-based approach is not feasible for real-world, high-MW TAI-based CPAs. Therefore, to verify if the trifunctionality of the initiating groups is achieved also for these polymers, a viscometric analysis using TD-SEC was employed. It was expected that the inherent branching characteristics of polymers prepared with TAI-based multifunctional initiators would be reflected in IV measured via a viscometry detector.¹¹⁶ For the purpose of this study, a multifunctional initiator was synthesized by the TAI modification of a tetrafunctional substrate, pentaerythritol. The reaction was conducted in 1,4-dioxane, using high-vacuum distillation to remove the excess of TAI and solvent to isolate pentaerythritol tetrakis((2,2,2-trichloroacetyl)carbamate) (PTAC). The prepared initiator was used without further purification (see **Figure A5** for $^1\text{H-NMR}$) in Cu-RDRP of poly(MMA) and polystyrene, utilizing the conditions from the library developed above. The obtained star-shaped polymers were subjected to alkaline hydrolysis⁷⁶ to cleave of the individual polymeric segments from all the four arms of PTAC. Thereafter, the original star polymers and the cleaved polymeric segments were analyzed using TD-SEC (**Figure 21**). The obtained results are summarized in **Table 9**. As can be seen, the original poly(MMA) star displayed low dispersity ($\mathcal{D} = 1.21$) with a very small high-MW shoulder (**Figure 21b**), which indicates that star-star coupling was negligible in this case even though monomer conversion was high (92%). On the other hand, for the original polystyrene star, the coupling products could be seen in the elugram along with some free arms/segments (**Figure 21c**), which inflated the dispersity to 1.69. Importantly, the hydrolytically released polymeric segments showed low dispersity for both poly(MMA) and polystyrene ($\mathcal{D} = 1.08$ and 1.14, respectively), which proved that the polymerization initiated from the TAGs on all the four sides of PTAC was very well controlled.

M-H plots for both the original star polymers and the hydrolytically released polymeric segments are shown in **Figure 21d,e**. Linear standards of poly(MMA) and polystyrene with broad MWD are shown for comparison. The corresponding α parameters from the M-H equation are reported alongside the M-H plots. The $\alpha \approx 0.6$ determined for the broad linear standards is in good agreement with the literature values.¹¹⁶ Further, the $\alpha \approx 0.4$ obtained for the hydrolytically released polymeric segments corroborates the non-linear characteristics of these polymers.¹¹⁶ This observation significantly supports the proposed trifunctionality of TAGs, as any mono- or bifunctional behavior would inevitably generate linear polymers, consequently yielding α values close to those found for linear standards. Furthermore, the α values of the original star polymers were even lower

(approximately 0.2), which is consistent with the presumed dense 12-arm star architecture of these polymers.¹¹⁶

Note that PTAC-initiated Cu(0)-RDRP of MA was also conducted, with detailed experimental conditions and results outlined in **Table 9**. However, the alkaline hydrolysis method used successfully for polystyrene and poly(MMA) stars above failed to provide clean star segment cleavage in the present case. Therefore, in **Figure A6**, solely the TD analysis of the original star polymer is presented along with comparative data for a broad linear poly(MA) which was synthesized using free-radical polymerization. The M-H analysis yielded a α value of ≈ 0.25 , i.e., comparable to the poly(MMA) star discussed above. This indicated a similar number of arms in the original star polymer and thus confirmed the trifunctionality of TAGs in this scenario as well.

Table 9. Synthesis of star polymers via PTAC-initiated Cu-RDRP of MMA, styrene, and MA^a

Monomer	Stage	Time (h)	Conv. (%) ^b	M_n (theor.) ^c	M_n (SEC) ^d	\bar{D} ^d
MMA	original star polymer	6	92	37 700	48 600	1.21
	hydrolyzed segments	-	-	9 400	14 900	1.08
styrene	original star polymer	6	50	84 200	74 700	1.69
	hydrolyzed segments	-	-	21 100	29 000	1.14
MA	original star polymer	4	92	32 000	32 600	1.48

^a Polymerization conditions: MMA polymerization - MMA/PTAC/CuBr/PMDETA = 400:1:1:1, MMA/dioxane = 1:1 (v/v), 85 °C; styrene polymerization - styrene/PTAC/CuBr/Me₆Tren = 1600:1:1:1, in bulk, 110 °C; MA polymerization - MA/PTAC/Me₆TREN = 400:1:0.5, MA/DMSO = 1:1 (v/v), copper wire 10 cm, 60 °C. Alkaline hydrolysis was conducted according to a literature procedure.⁷⁶

^b Monomer conversion was determined gravimetrically (MMA and styrene) or through a ¹H-NMR analysis (MA).

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% initiation efficiency.

^d Determined by TD-SEC.

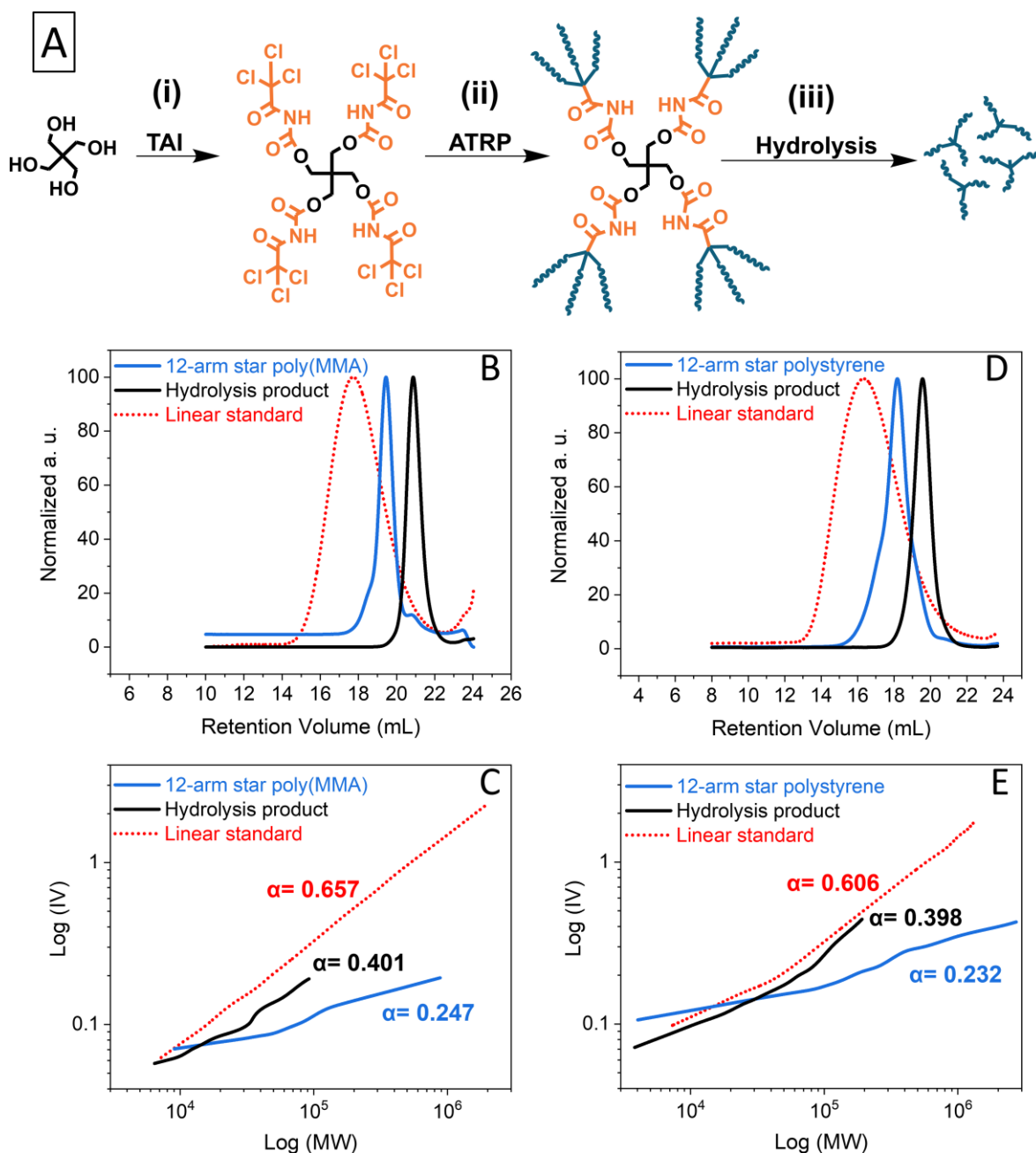


Figure 21. TAG functionality study: a general scheme of the synthesis of model multi-arm stars based on a pentaerythritol core (a); elugrams – RI traces (b, c) and M-H plots (d, e) from the TD-SEC analysis of the synthesized poly(MMA) (b, d) and polystyrene (c, e) multi-arm star polymers and of products of their alkaline hydrolysis. Data for broad linear poly(MMA) and polystyrene standards are shown for comparison.

5.1.11 Applications of TAI-based strategy

After demonstrating that TAI is a useful tool for installing universal multifunctional initiation sites onto various precursors, several advantages of this novel approach to CPA synthesis are exemplified in this section.

5.1.11.1 One-pot *de novo* synthesis of “star-on-star” architecture

As it is known that TAI can instantly modify certain types of functional groups in substrates, turning them into efficient Cu-RDRP initiating sites, it was envisaged that the TAI strategy can be utilized for the *de novo* synthesis of graft copolymers in a one-pot fashion. To demonstrate this application, a three-step procedure was implemented as shown in **Figure 22**. First, a copolymerization of HEMA and MMA (20/80 mol %) initiated by MTAC using Cu(0)-RDRP in dioxane was conducted. This process yielded a well-defined poly(HEMA-*co*-MMA) copolymer ($M_n = 23\,400$, $\mathcal{D} = 1.23$) with complete conversion, as depicted in **Figure A7 (top)**. Subsequently, TAI was introduced to modify some of the hydroxyl groups in the HEMA units *in situ* as shown in **Figure A7 (bottom)**. Finally, after adding another batch of MMA and solvent, the polymerization continued, providing the final graft copolymer as illustrated in **Figure A8**. Due to the inherent trifunctionality of the TAGs, it is anticipated that the copolymer will adopt a special architecture, “star-on-star”, formed by the grafting of three-arm stars from the parent three-arm star copolymer. The resulting graft copolymer potentially represents a new category of CPA, incorporating the features of both star and graft copolymers in its structure. **Table 10** summarizes the experimental details and results obtained within this application study. It is seen that the final “star-on-star” copolymer has rather high dispersity (1.95) due to the presence of a high-MW fraction seen as a shoulder in the SEC elugram (see **Figure 22 bottom left**), which is attributed to recombination reactions primarily occurring during the preparation stage of the macroinitiator where complete conversion was aimed for. Fine tuning of the conditions used for the synthesis of “star-on-star” copolymer could be pursued in future studies to obtain a better-defined product. Next, this copolymer was subjected to alkaline hydrolysis to cleave off the stars grafted from the TAI-modified hydroxyl groups. Upon TD-SEC analysis of the original three-arm star copolymer, star-on-star copolymer, and the hydrolyzed grafts, it was seen that excellent control was achieved during the grafting step. Well-defined poly(MMA) grafts with extremely low dispersity (1.05) were obtained. Importantly, from the M-H plots presented in **Figure 22 (bottom right)** it can be seen that the α values obtained for the original three-arm star copolymer and the hydrolyzed grafts are in good correlation with the expected values as seen above. Additionally, for the highly branched “star-on-star” architecture, the obtained α value was substantially low (~ 0.25) as expected. These results collectively underscore the

versatility of the TAI strategy in facilitating innovative approaches towards synthesizing graft and hyper-branched (co)polymers, opening avenues for customizing various CPA topologies.

Table 10. Experimental results of the *de novo* one-pot synthesis of the poly(HEMA-*co*-MMA)-*graft*-poly(MMA) “star-on-star” graft copolymer^a

Stage	Conv. (%) ^b	M_n (theor.)	M_n (SEC) ^e	\mathcal{D}^e
poly(HEMA- <i>co</i> -MMA)	99	10 800 ^c	23 400	1.23
poly(HEMA- <i>co</i> -MMA)- <i>graft</i> -poly(MMA)	30	288 300 ^d	328 000	1.95
removed poly(MMA) grafts	-	12 000 ^c	16 200	1.05

^a Polymerization conditions: MMA/HEMA copolymerization: MMA/HEMA/MTAC/PMDETA = 80/20/1/1, 4 cm of activated copper wire, monomers/solvent = 1:1 (v/v), 85 °C, 3 h; grafting: MMA/TAI/PMDETA = 400:1:1, copper wire from the previous step, monomer/solvent = 3:1 (v/v), 85 °C, 2 h.

^b Monomer conversion as determined by ¹H-NMR (Figure A7).

^c Theoretical M_n calculated from the M/I ratio and conversion, assuming 100% initiation efficiency.

^d Theoretical M_n calculated from the M_n (SEC) and the known composition of the macroinitiator, the average number of initiating sites per one macroinitiator chain, and the determined MW of the macroinitiator and grafts.

^e Determined by TD-SEC.

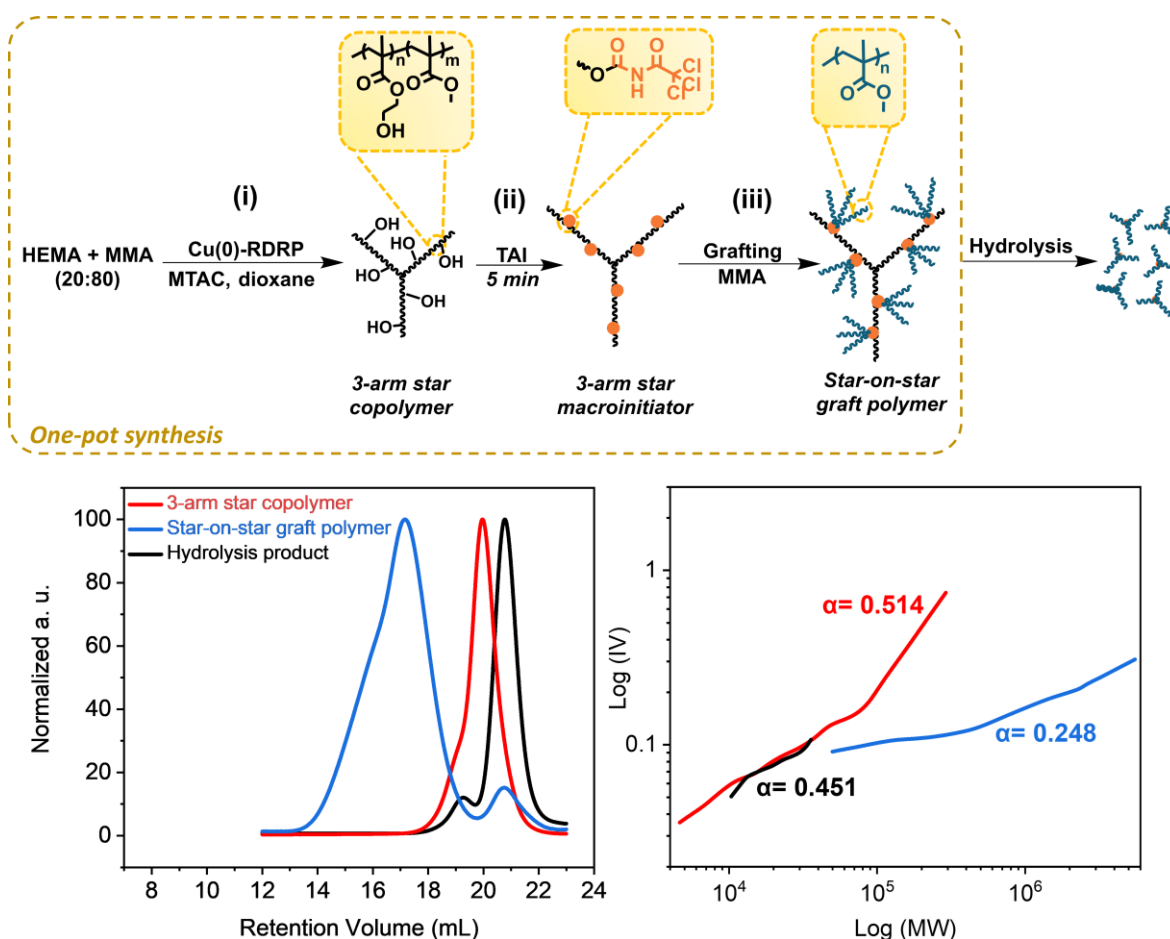


Figure 22. De novo one-pot synthesis of the poly(HEMA-*co*-MMA)-*graft*-poly(MMA) hybrid star/graft copolymer of “star-on-star” topology. Top: general reaction scheme; bottom: TD-SEC analysis of products at individual stages – elugrams (left) and M-H plots (right).

5.1.11.2 Synthesis of multi-arm star polymers using a β -cyclodextrin core

Another important application of the initiator functionality amplification via the TAI strategy is demonstrated by synthesizing previously inaccessible types of multi-arm star-shaped polymers. For this purpose, β -cyclodextrin (β -CD) was used as a precursor and modified with TAI in acetonitrile, followed by quenching of excess TAI with DMSO. Complete modification of β -CD was achieved as evidenced by the $^1\text{H-NMR}$ measurements (**Figure A9**), yielding the β -CD/TAI adduct along with some DMSO/TAI adduct and also trichloroacetamide that was derived from the reaction of TAI with residual water. The latter compounds were not removed and instead played a role of low-MW sacrificial initiators during the star polymer synthesis.^{71,76,117} The SEC elugrams presented in **Figure 23** reveal a distinct shift of the original β -CD peak towards higher MWs after TAI modification, with dispersity still found to be close to unity. In the next step, the β -CD/TAI adduct (macroinitiator) solution in acetonitrile was used to synthesize poly(MMA) via ATRP in 1,4-dioxane, resulting in a star polymer which was, in a subsequent step, subjected to alkaline hydrolysis to cleave off the arms for separate SEC analysis.

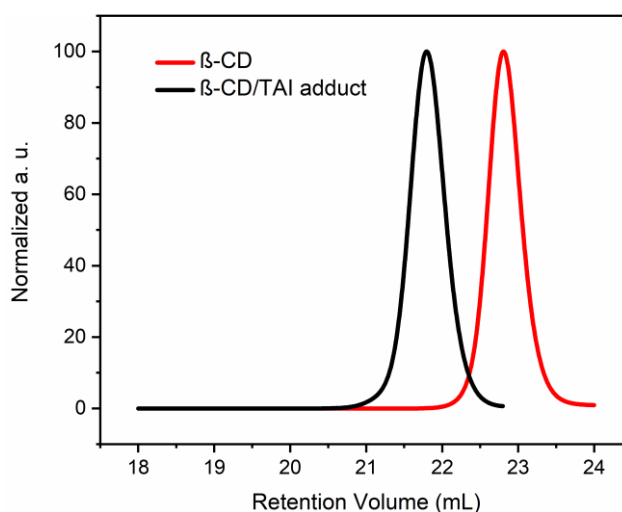


Figure 23. TD-SEC analysis (RI traces) of β -CD and β -CD/TAI adduct ($M_n(\text{theor.}) = 5\,100$, $M_n(\text{SEC}) = 5\,800$, $D = 1.02$)

Table 11 summarizes the results obtained within this study, and the corresponding SEC elugrams are presented in **Figures 24 and 25**. It is evident that the presence of sacrificial initiators largely suppresses the formation of intermolecular coupling products (visible in SEC elugrams as high-MW shoulders) even at the nearly complete monomer conversion achieved in this study. Exceptional control over the polymer chain growth was established during the polymerization course, generating well-defined star polymers and free-growing chains/broken away arms as seen by

narrow dispersity (1.15 and 1.05, respectively) even at almost quantitative conversion (96%). Moreover, the SEC analysis of the mixture of the star arms with the free-growing chains, obtained after alkaline hydrolysis of the product (**Figure 25**), shows that the M_n and \mathcal{D} values were in good agreement with those for the free-growing chains which grew in parallel to the star polymer in the polymerization mixture (the low-MW peaks in **Figure 24**). This observation supports the fact that the star arms were growing at similar rates as the free chains. At the same time, the measured M_n values exceeded significantly the theoretical values derived from the known monomer conversion and the MMA/TAI ratio. These findings collectively indicate that due to the presence of extreme steric crowding on the β -CD/TAI adduct some of the TAGs may have been unable to initiate the polymerization at all, whereas the remaining TAGs functioned as trifunctional initiators, likely due to the enhanced reactivity of the residual chlorine atoms on TAGs that participated in the initiation process.¹⁰¹ Nevertheless, based on the comparison of the M_n value of the final multi-arm star polymer and that of the released arms (3-arm stars on their own), it can be seen that one parent multi-arm star involves approximately 15 poly(MMA) 3-arm star segments. Therefore, the resulting multi-arm star polymer consists of roughly 45 (linear) arms, underscoring the superiority of the TAI-strategy over previous methods relying on monofunctional initiators that yielded a maximum of 21-arms from the β -CD core in a significantly more labor-intensive process.^{77,118}

Table 11. Synthesis of multi-arm poly(MMA) stars through ATRP initiated by the β -CD/TAI adduct^a

Time (h)	Conv. (%) ^b	Star polymer		Free-growing chains		Hydrolysis product		
		M_n (SEC) ^c	\mathcal{D} ^c	M_n (SEC) ^c	\mathcal{D} ^c	M_n (theor.) ^d	M_n (SEC) ^c	\mathcal{D} ^c
4	46	157 500	1.05	14 400	1.06	6 400	13 000	1.06
7	69	255 100	1.08	18 900	1.06	9 700	18 400	1.05
23	96	399 900	1.15	26 200	1.07	13 500	25 500	1.05

^a Polymerization conditions: MMA/TAI/CuBr/PMDETA = 140:1:1:1; MMA/dioxane = 1:1 (v/v), 85 °C.

^b Monomer conversion determined by ¹H-NMR.

^c Determined by TD-SEC.

^d Theoretical M_n calculated from the monomer/TAI ratio and conversion, assuming 100% initiation efficiency.

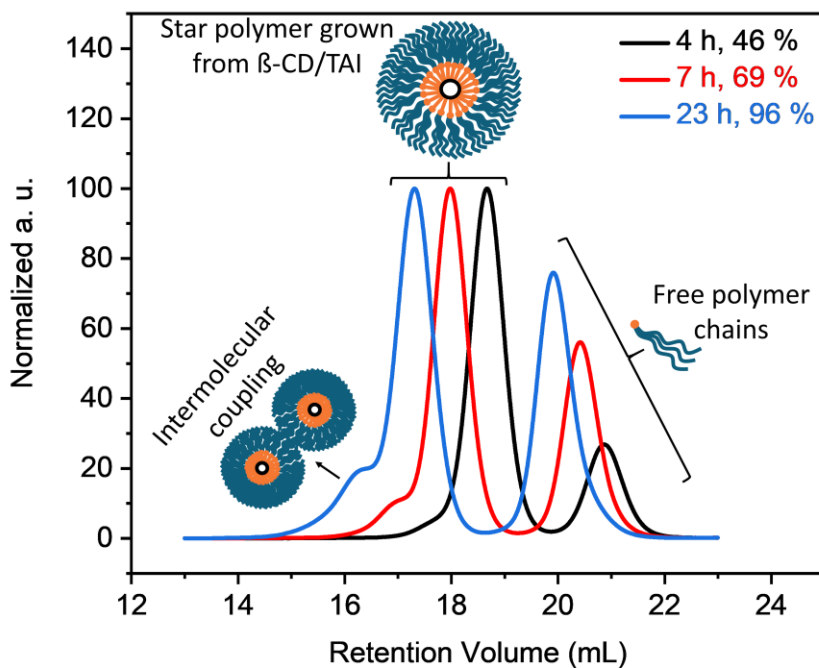
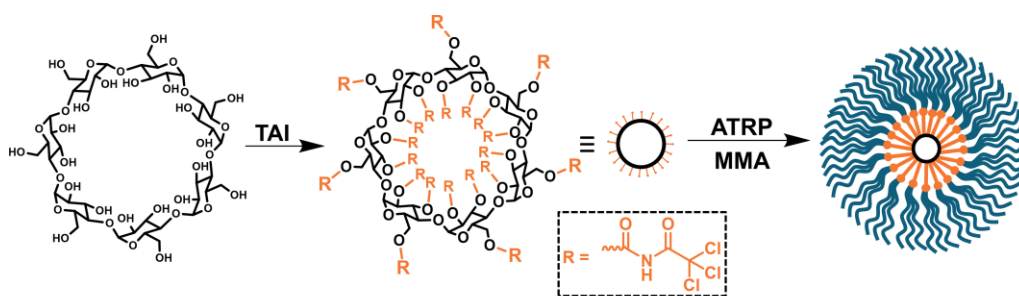


Figure 24. Synthesis of multi-arm poly(MMA) stars through ATRP initiated by the β -CD/TAI adduct. Top: general reaction scheme; bottom: TD-SEC analysis (elugrams – RI traces) of samples taken at different polymerization stages. Experimental details are provided in **Table 11**.

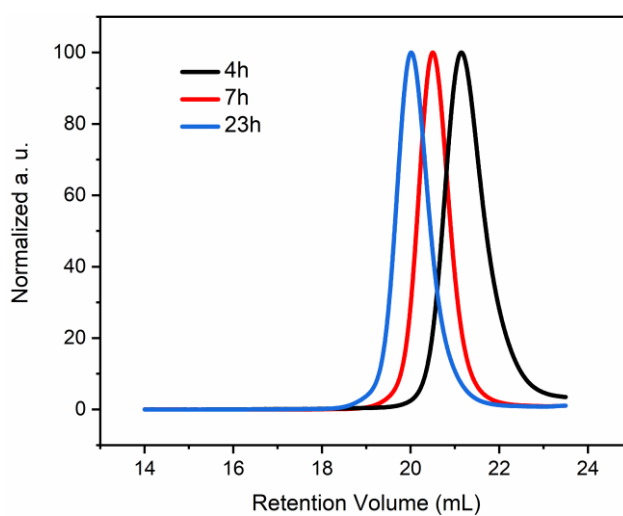


Figure 25. TD-SEC analysis (RI traces) of the polymers obtained after alkaline hydrolysis of isolated samples of poly(MMA) star polymers synthesized via ATRP initiated by the β -CD/TAI adduct.

5.1.11.3 *Synthesis of cellulose-based ultra-dense bottle brush copolymers*

Next, it was hypothesized that the high reactivity of TAI would render the new strategy especially advantageous for synthesizing CPAs from substrates that are normally challenging to modify. For this purpose, the most abundant natural organic substance, cellulose, was used which has been one of the important substrates modified previously via Cu-RDRP upon the incorporation of initiation sites through the standard acylation approach.^{65,76} However, these reports were unsuccessful with respect to the quantitative modification of cellulose due to its low reactivity in the acylation reactions, owing to its complex supramolecular structure. Since the incorporation of TAGs into the selected precursor represents the key step of the TAI strategy, the reactivity of cellulose towards TAI needed to be studied first. For this study, the microcrystalline cellulose AVICEL PH-101 was employed. It was found that, upon dissolution in the traditional DMAc/LiCl solvent system,¹⁰⁷ cellulose can be rapidly modified with a slight excess of TAI. The ¹H and ¹³C-NMR spectra of the isolated cellulose/TAI adduct show that complete modification of cellulose was achieved in this case (**Figure A10**). Furthermore, when dioxane-activated cellulose¹⁰⁷ was stirred overnight in 1,4-dioxane containing 4 eq. of TAI, the resulting product dissolved in 1,4-dioxane due to the complete modification of cellulose hydroxyls. When this experiment was conducted in THF with 6 eq. of TAI, a clear solution was obtained already after 2 h. Importantly, it was found that if a non-activated cellulose is pre-dried (under vacuum at 80 °C, overnight) and subjected to TAI (6 eq.) modification in acetonitrile, complete modification (clear reaction mixture) is achieved in 4 days. Remarkably, it was also found that cellulose shows extremely high reactivity towards TAI if the modification is performed in DMSO, which is an excellent solvent to swell cellulose, increasing its reactivity and accessibility of the hydroxyl groups.¹¹⁹ When a non-dried (or pre-dried and soaked overnight in DMSO) cellulose was subjected to TAI (5 eq.) modification in DMSO, less than a minute was needed to obtain a clear solution. This result is remarkable considering the fact that TAI reacts readily with DMSO. It confirms that the modification of substrates in TAI-reactive solvents (e.g., DMSO or DMAc), as proposed by Samek et al.,⁸⁹ is achievable also in heterogeneous reactions involving polymers. Although the primary focus of this dissertation did not entail testing the universality of this modification strategy across various types of cellulose, it is confirmed that a similarly rapid modification was achieved even for a significantly higher-MW cellulose, Sigmacell type 101, in DMSO. Consequently, it is anticipated that this protocol could have significant applications in the field of cellulose characterization, offering a viable alternative to the labor-intensive approach relying on the use of phenyl isocyanate to modify cellulose for MW determination via SEC.¹²⁰

The cellulose fully modified by TAI serves as a unique macroinitiator that can potentially generate up to 9 polymeric chains per backbone repeat unit. This enables the formation of ultra-dense bottle-brush copolymers through graft copolymerization. With the protocol for complete modification of cellulose in hand, a model cellulose/TAI adduct was synthesized and its potential was explored in the synthesis of a cellulose-graft-poly(MMA) copolymer using ATRP (**Figure 26**). Initially, a macroinitiator stock solution was prepared that contained the cellulose/TAI adduct and MTAC, a low-MW sacrificial initiator. This was achieved by subjecting cellulose (AVICEL) to TAI modification in acetonitrile as mentioned above, followed by quenching of excess TAI with methanol. TD-SEC analysis provided M_n (106 700) and dispersity (2.17) for the cellulose/TAI adduct, which aligned well with the previously determined characteristics of the cellulose precursor ($M_n = 18\ 000$, $\bar{D} = 1.94$) (**Figure 26 bottom-left**).¹⁰⁷ Next, the (macro)initiator solution was used to initiate ATRP of MMA in 1,4-dioxane. **Table 12** summarizes the results obtained within this study and shows that monomer conversion reached 27% in 5 h, corresponding to the theoretical M_n of 9 644 000, calculated using the number-average degree of polymerization (DP_n) of 147 for the cellulose/TAI adduct, assuming that every hydroxyl group is modified by TAI and all the initiation sites initiate polymerization. With prolongation of the polymerization to 24 h, monomer conversion reached 72%, giving theoretical M_n of 25 539 000. It was reported that the high-MW fractions of high-MW bottle-brushes could show non-SEC elution behavior during SEC analysis.^{121,122} Indeed this behavior was also observed in our study where a high-MW fraction of the sample eluted later than expected, overlapping with lower-MW fractions (**Figure A11**). This significantly distorted the LS signal traces, causing the peaks of the graft copolymer and free-growing chains to merge, a phenomenon particularly evident in the 24 h sample. As a result, the LS signal intensity for the graft copolymer decreased to an uncertain extent, while the intensity for the free-growing chains substantially increased. Consequently, calculating MWs based on LS data was highly unreliable or even infeasible due to software limitations. However, the viscometric detector's comparatively lower sensitivity to high-MW species allowed us to obtain relatively accurate MW values for the low-MW peak of the 5 h sample using the universal calibration approach (**Table 12**). For the 5 h sample, the chains that grew from the sacrificial initiator showed M_n of 28 300 as calculated using universal calibration instead of LS-based calculation. Thereafter, the bottle-brush polymers isolated after 5 h and 24 h were subjected to alkaline hydrolysis giving a mixture of hydrolyzed grafts along with the free-growing chains, which was further analyzed using TD-SEC. It was found that the M_n of the mixture from 5 h was in good agreement with that determined for the free-growing chains above. This confirmed that the initiation sites available on the cellulose backbone and the free sacrificial initiator (MTAC) enabled the polymer growth at a similar rate. The close match between the experimental M_n values and the $M_n(\text{theor.})$, calculated based on the monomer conversion and the MMA/TAG ratio (considering all

forms of TAI adducts), indicates that the much lower than theoretical M_n of the graft copolymer determined by TD-SEC (3 174 000) is severely underestimated due to the effects discussed above. **Figure 26 (bottom-right)** presents the M-H plots obtained within this study, with the α value estimated for the bottle-brush copolymer highlighting its high compactness. Further, although the TD-SEC analysis could not provide any MW for the sample at 24 h, it was possible to obtain the MW for the hydrolyzed product which matched well with the theoretical M_n . Notably, the narrow dispersity obtained in this case (data not shown) suggests that the M_n of the grafts on cellulose backbone was similar to that of the hydrolyzed product. Taken together, the data obtained in this study showcase the extremely high MW of the resulting cellulose-*g*-poly(MMA) copolymer even though a cellulose backbone with relatively low MW was employed. It is thus anticipated that using this approach with standard cellulose substrates with MWs in hundreds of thousands should enable the production of huge cellulose-based graft copolymers, reaching MWs in hundreds of millions.

Table 12. Synthesis of ultra-dense bottle-brush cellulose-*graft*-poly(MMA) copolymers via ATRP initiated by the cellulose/TAI adduct.^a

Time (h)	Conv. (%) ^b	Graft copolymer			Free-growing chains		Hydrolysis product		
		M_n (theor) ^c	M_n (SEC) ^d	\mathcal{D} ^d	M_n (SEC) ^d	\mathcal{D} ^d	M_n (theor) ^e	M_n (SEC) ^f	\mathcal{D} ^f
5	27	9 644 000	3 174 000	1.93	28 300	1.07	21 600	24 400	1.06
24	72	25 539 000	nd	nd	nd	nd	57 700	62 000	1.11

^a Polymerization conditions: MMA/TAI/CuBr/PMDETA = 800:1:1:1; MMA/dioxane = 1:1 (v/v), 85 °C; cellulose/TAI adduct macroinitiator: M_n = 106 700, \mathcal{D} = 2.17

^b Monomer conversion determined by ¹H-NMR.

^c Theoretical M_n calculated from the M/I ratio, monomer conversion, and the number-average degree of polymerization (DP_n) of 147 determined by the TD-SEC of the cellulose/TAI adduct (monomeric unit weight of 727.34), assuming that three TAI-modified hydroxyl groups per one monomeric unit initiate the polymerization.

^d Determined by TD-SEC using universal calibration.

^e Theoretical M_n calculated from the monomer/TAI ratio and monomer conversion.

^f Determined by TD-SEC using a light scattering detector.

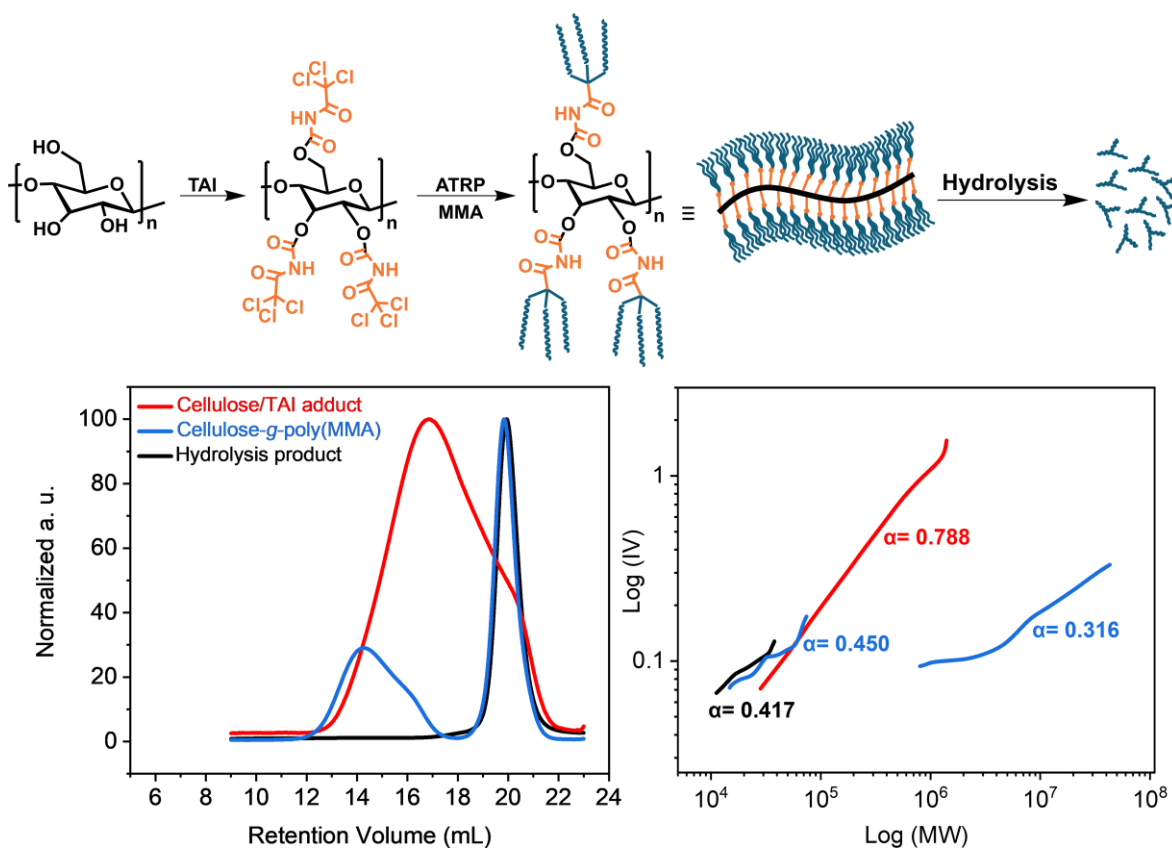


Figure 26. Synthesis of the ultra-dense bottle-brush cellulose-*g*-poly(MMA) graft copolymer via ATRP of MMA initiated by the cellulose/TAI adduct. Top: general reaction scheme; bottom: TD-SEC analysis (left – RI elugrams; right – M-H plots) of the cellulose/TAI macroinitiator, the copolymer obtained after 5 h, and poly(MMA) obtained after alkaline hydrolysis of the isolated product. Experimental details are provided in **Table 12**.

5.1.11.4 Grafting of poly(MMA) from cellulose based surfaces using the TAI-strategy

Finally, the potential of multifunctional initiation sites derived from TAI to significantly broaden the TAI strategy scope, particularly within the cellulose field, is underscored. This approach holds promise for the surface modification of different cellulose-based substrates. To illustrate this application, firstly a spatially controlled modification of cellulose Whatman filter paper by TAI was performed, which allowed for surface-initiated (SI) grafting from the flat cellulose surface. For this purpose, a DMSO-wetted Whatman paper was placed into a specially designed metallic mask and, upon dripping of TAI into the mask opening, the cellulose surface got instantly modified, which can be clearly seen in **Figure 27**. Thereafter, the TAI-modified Whatman filter paper was purified and used to initiate ATRP of MMA. Within 30 minutes, a macroscopic layer of poly(MMA) was grown from the TAI-modified regions on the surface of the Whatman paper, which upon purification led to a thick white polymeric layer on the surface of the paper. Importantly, when seen from the rear side, there was almost no polymer grown from the surface of the paper. This confirms that the TAI

reaction was extremely rapid thereby modifying only the regions that came into immediate contact with TAI in the dripping phase (i.e., TAI did not manage to diffuse through the paper).

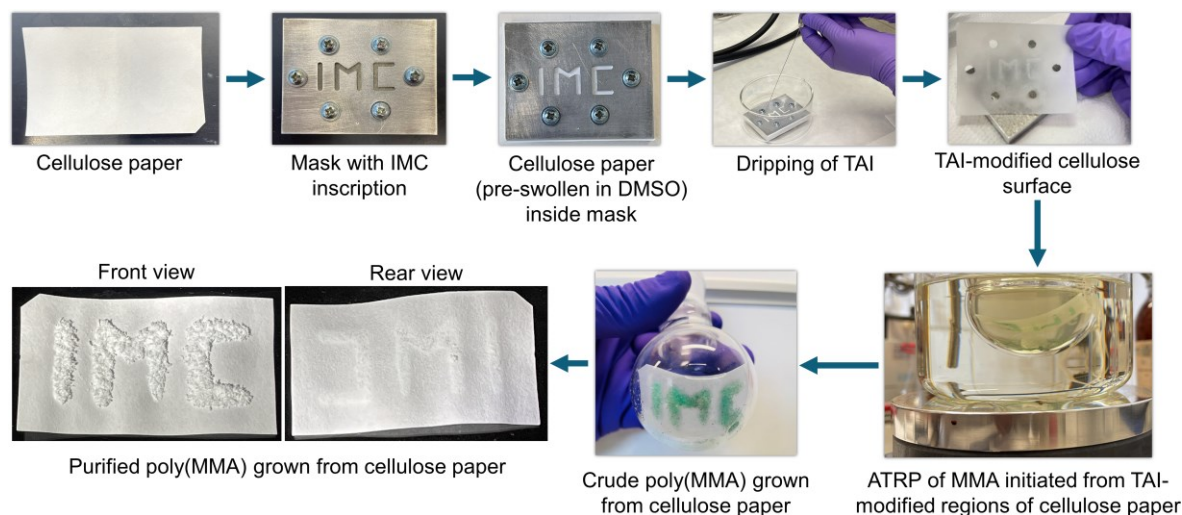


Figure 27. Spatial control in the modification of Whatman filter paper with TAI and subsequent ATRP SI grafting of MMA from the modified cellulose surface.

In another experiment, surface modification on a thick cotton thread (length of ca 5 cm) by TAI in DMSO was performed. The resulting TAI-modified thread surface was then used to initiate ATRP of MMA, leading to complete surface coverage with a thick poly(MMA) layer (**Figure 28 top, Figure A12 top**). In the close-up image, the separation of individual strands at the ends of the thread and the effective modification of even the smallest thread features are clearly visible.

Lastly, a much more complex natural substrate was employed to illustrate the advanced application of TAI strategy. To this end, a pine tree cone was modified with TAI in DMSO, followed by grafting of poly(MMA) layer from the TAI modified regions (**Figure 28 bottom, Figure A12 bottom**). While the white polymer layer is clearly visible, there were regions on the cone which did not modify at all due to the presence of seeds that blocked the penetration of TAI (the seeds were released during the course of polymerization). This further illustrates the precision that can be achieved with respect to the spatial control in the SI grafting using TAI strategy. Taken together, the preliminary results shown above display a huge potential that TAI strategy holds for grafting in both heterogenous and homogenous phase using natural polymeric materials as substrates, achieving unparalleled grafting density inaccessible by traditional protocols.^{75,123}

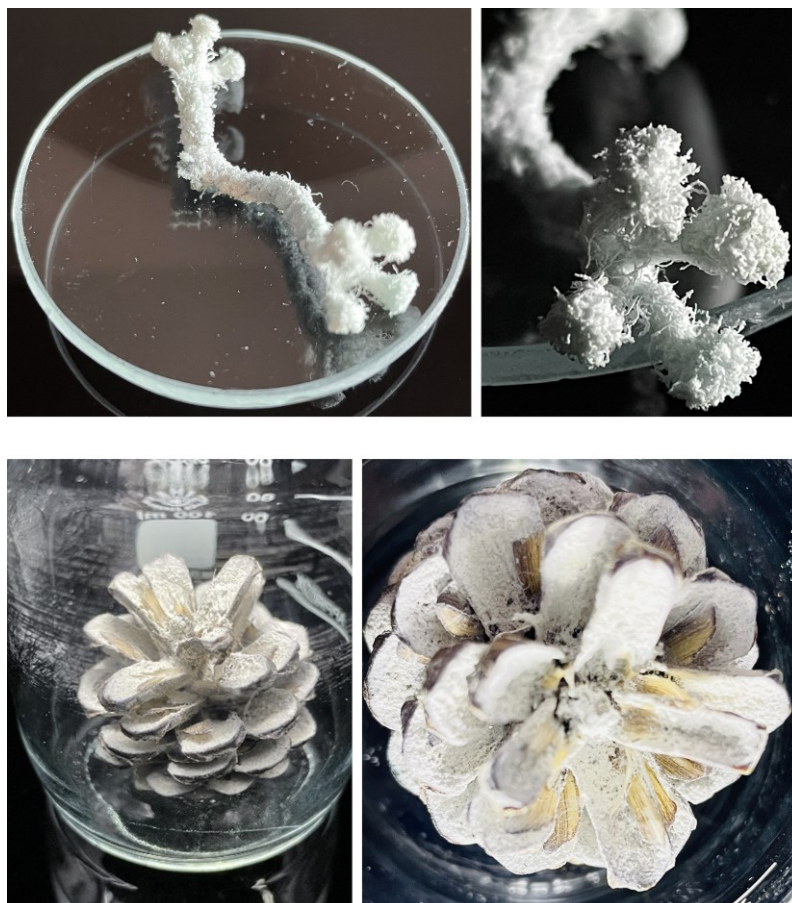


Figure 28. A cotton thread (top) and a pine tree cone (bottom) grafted with poly(MMA) *via* the two-step TAI-modification/ATRP-grafting strategy.

5.2 *Cu(0)-RDRP of HEMA*

As mentioned above, unconventional Cu(0)-RDRP conditions were obtained for polymerization of HEMA within the framework of the CPAs synthesis via the TAI strategy where MTAC was used as an initiator (entry 8, **Table 7**). In the following subsections, a more extensive optimization study of the obtained Cu(0)-RDRP condition with commercially available monofunctional initiators is presented. Furthermore, the application of the optimized conditions is shown in the synthesis of amphiphilic copolymers.

5.2.1 *Optimization of conditions for homopolymerization of HEMA*

In this study, 5 cm of activated copper wire was used as a copper source, and 1,4-dioxane, a relatively non-polar solvent, was employed as a reaction medium. 1,4-Dioxane is an excellent solvent that dissolves a wide range of compounds and is miscible with most of the common solvents (both polar and non-polar).^{124,125} Notably, it was found that even though poly(HEMA) exhibits only limited solubility in 1,4-dioxane (in the scenario when isolated polymer is added to the solvent), the polymer synthesized under the parameters of this investigation (monomer/solvent ratio of 1:1 (v/v)) remains in solution throughout the polymerization process, even at quantitative conversions. This mixture homogeneity was maintained even when aiming for high-MW polymers or conducting the experiments at r.t. PMDETA was the ligand of choice as it was successfully used in the MTAC-initiated Cu(0)-RDRP of HEMA in 1,4-dioxane above. Additionally, PMDETA was the preferred ligand also in previous reports where Cu(0)-RDRP was performed in non-polar solvents.^{16,17} The effectiveness of alkyl 2-halophenylacetates as highly efficient initiators¹²⁶ was previously examined, showing broad applicability when combined with different ligands across various Cu-RDRP methodologies.^{18,19,109,127,128} This includes their successful utilization in the Cu(0)-RDRP of HEMA in DMSO.⁴⁶ More precisely, comparative studies using EBPA and ECPA were performed to investigate the differences arising from using identical initiators bearing different halogens. The polymerizations were carried out at 85 °C to aid in the stirring of the polymer solutions that tend to be highly viscous especially at high conversions. Crude reaction mixtures were directly used for the determination of monomer conversions via ¹H-NMR (see **Figure A13** for a sample ¹H-NMR spectrum from this study), and MWs and dispersity by TD-SEC which was performed in DMAc/LiBr.

It is emphasized that employing a precise method for determining MWs is crucial as earlier studies on HEMA polymerization via Cu-RDRP extensively documented discrepancies between actual MWs and those obtained via SEC with relative calibration.^{36-38,43} In this study, the dn/dc value for poly(HEMA) was determined through on-line measurements based on the assumption of 100%

sample recovery from SEC columns. Given the analysis of crude polymerization mixtures used in this work, the specific concentrations of the polymer in each SEC sample was determined combining the knowledge of the initial mixture composition and the monomer conversion obtained from $^1\text{H-NMR}$. An average dn/dc value of $0.078 \pm 0.003 \text{ mL/g}$, obtained from multiple measurements, was subsequently utilized in the MW determination for all the poly(HEMA) samples analyzed by TD-SEC. Proper stabilization of the crude reaction mixtures was necessary for this determination. Phenothiazine, employed as an inhibitor, was difficult to disperse and dissolve in the highly viscous polymerization mixtures; therefore, immediate dilution with a suitable solvent became imperative for stabilization. Neglecting this step triggered additional polymerization of residual HEMA monomer during the sample storage. It is worth noting that residual HEMA monomer in inadequately stabilized polymerization mixtures underwent polymerization even when stored at $-20\text{ }^\circ\text{C}$, potentially due to the phase separation between HEMA-rich layer and the frozen 1,4-dioxane. This posed a significant problem in the determination of conversion, MWs, and MWDs. The greatest risk emerged in experiments with high yet incomplete conversions (approximately 70%), resulting in mixtures containing a substantial amount of unreacted monomer, where the elevated viscosity impedes successful dissolution of the stabilizer, unless the sample is diluted as mentioned above.

Furthermore, it should be mentioned that from an external determination of dn/dc performed using a differential refractometer from Brookhaven BI-DNDC (in DMAc/LiBr (5g/L) at $55\text{ }^\circ\text{C}$ in a batch mode) for a poly(HEMA) sample isolated by precipitation in ethyl acetate, significantly lower (0.051 mL/g) value was obtained, which is ascribed to the impurities in the isolated sample. When applying this dn/dc value for MW determination, the MWs obtained are highly inflated. It was thus hypothesized that the dn/dc value obtained through the former (online) method is significantly more precise due to the substantially reduced influence of impurities, such as water and solvents utilized for diluting the polymerization mixture and precipitating the polymer. This observation can be of general relevance for various polar monomers that frequently prove challenging to dry completely and that tend to exhibit high affinity to organic solvents.¹⁹ It is worth mentioning that the dn/dc value determined via the preferred on-line method closely aligns with that of poly(HEMA) measured in DMF as provided in the Polymer Handbook (0.076 mL/g).¹²⁹

Table 13 summarizes the results obtained from the preliminary study aiming at optimizing Cu(0)-RDRP of HEMA in 1,4-dioxane. In trial experiments, polymerizations initiated by EBPA and ECPA were compared under otherwise identical conditions, i.e., HEMA/initiator/PMDETA ratio of 100:1:1 (entries 1 and 2, **Figure A14**). The polymerizations were uncontrolled with both the initiators; however, ECPA gave substantially higher conversion even though the polymerization time was

shorter when compared to EBPA (94% in 1 h vs 75% in 2 h, respectively). It has been previously reported that conducting Cu(0)-RDRP in a non-polar solvent can become controlled upon the addition of an external Cu²⁺ deactivator which possibly helps in offsetting the insufficient deactivator concentration during the initial stages of polymerization.^{16,17,130} In our study, upon addition of Cu²⁺ salts, a negligible impact was observed when using a completely bromine-based system (entry 3, **Figure A14**) whereas with the completely chlorine-based system the polymerization control improved dramatically as seen by the reduced dispersity value (1.23) and the symmetrical and unimodal SEC trace (entry 4, **Figure 29**). Additionally, high conversion (95%) was obtained within 1 h at which point the experiment was ended due to the high viscosity of the polymerization mixture that obstructed magnetic stirring. For a comparison, an additional experiment was performed with the combination of EBPA and CuCl₂ (0.2 eq.); however, the product obtained had high dispersity (entry 5, **Figure A14**). These results clearly indicate that using the completely chlorine-based catalytic system, often preferred in aqueous media,^{18,19,52} can be a good choice also when polymerization conditions are optimized in non-polar solvents. In Cu(0)-RDRP protocols, the selection of the initiator halogen is especially critical. Unlike in conventional ATRP, in Cu(0)-RDRP, the initiator predominantly, or even exclusively, provides the halogen atoms essential for the key steps of the polymerization mechanism and the formation of polymer end groups. Furthermore, we performed an experiment with the complete chlorine-based system at r.t. and obtained practically identical results when compared to the polymerization run at 85 °C (cf., entries 4 and 6, **Figure 29**). Notably, the slight decrease in the conversion is ascribed to the extremely high viscosity of the polymerization mixture (almost solid at r.t.). Therefore, further polymerizations were conducted preferentially at higher temperature, especially when higher MWs were targeted, i.e., where mixtures tend to be more viscous.

Table 13. Optimization of polymerization conditions for Cu(0)-RDRP of HEMA^a

Entry	Initiator	Deactivator	Temp. (°C)	Time (min)	Conv. (%) ^b	<i>M_n</i> (theor.) ^c	<i>M_n</i> (SEC) ^d	Đ ^d
1	EBPA	-	85	120	75	9 800	15 100	2.36
2	ECPA	-	85	60	94	12 200	17 700	1.84
3	EBPA	CuBr ₂ (0.2 eq.)	85	120	81	10 500	16 000	2.26
4	ECPA	CuCl ₂ (0.2 eq.)	85	60	95	12 400	19 000	1.23
5	EBPA	CuCl ₂ (0.2 eq.)	85	120	94	12 200	22 000	1.76
6	ECPA	CuCl ₂ (0.2 eq.)	r.t.	60	90	11 700	20 500	1.25

^a Standard polymerization conditions: HEMA/initiator/PMDETA = 100:1:1, 5 cm of activated copper wire, dioxane/HEMA = 1:1 (v/v).

^b Monomer conversion as determined by a ¹H-NMR analysis.

^c Theoretical *M_n* calculated from the M/I ratio and conversion.

^d Determined by SEC with LS detection.

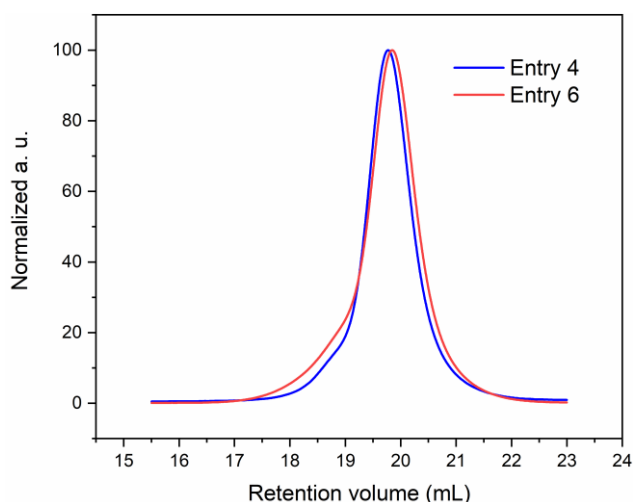


Figure 29. SEC elugrams (RI traces) from the SEC-LS analyses of poly(HEMA) obtained via Cu(0)-RDRP in dioxane under optimized conditions. Numbering of the traces corresponds to **Table 13**.

5.2.2 Synthesis of poly(HEMA) of different molecular weights

Next, to demonstrate the applicability of the optimized conditions to obtain poly(HEMA)s of different MWs, experiments with a range of different M/I ratios were performed. **Table 14** summarizes the results obtained within this study. The lowest MW polymer was synthesized using M/I = 50. The polymerization was remarkably well controlled and fast, leading to the monomer conversion of 92% in just 30 minutes (entry 1, **Figure 30**). To obtain high-MW polymers, experiments with M/I ratios of 400:1 and 1000:1 were performed. Both the polymers displayed a significant high-MW shoulder in the respective SEC elugrams, which was reflected in the overall increased dispersity of the polymers, especially for the M/I ratio of 1000:1 (entry 2 and 3). Initially, it was presumed that the high-MW fractions are the products of early termination reactions. However, the outcome could not be improved by increasing the concentration of the CuCl₂ deactivator to 0.5 eq. for the experiment with M/I ratio of 400:1 (entry 4, **Figure A15**). It is well established that commercial samples of HEMA are prone to contain ethylene glycol dimethylacrylate (EGDMA), a crosslinking agent, as an impurity. In different literature studies, HEMA monomers of varied purity has been employed; whereas some studies reported the use of HEMA purified using special protocols to remove EGDMA,^{36,42,46} other reports relied on using either only distilled or absolutely non-purified HEMA.^{37-40,43,44} Since the monomer used here for the initial experiments was purified solely through vacuum distillation, it was postulated that the presence of residual EGDMA might lead to limited crosslinking reactions, thus explaining the high-MW fraction observed at higher M/I ratios. This is particularly plausible for higher-MW polymers that are more likely to contain a statistically higher number of EGDMA-derived polymerizable double bonds in

their structure. To test this hypothesis, the monomer was purified using an established protocol,¹⁰⁶ reducing the EGDMA concentration from 0.1 wt.% to 0.01 wt.% as confirmed by GC analysis. Repeating the polymerizations at the M/I ratios of 400:1 and 1000:1 with the purified monomer resulted in SEC elugrams that no longer exhibited the previously observed high-MW shoulders (**Figure 30**; see also **Figure A15** and **Figure A16** for overlay comparisons). Importantly, still quite high conversion values were obtained within 60 min when the polymerizations had to be terminated due to inefficient stirring (entries 5 and 6). Additionally, the process remained well-controlled as indicated by low dispersity values in both the cases. For the M/I = 400:1 ratio, a kinetic experiment confirmed these results by displaying the standard features of a controlled process (**Figure 31**). Interestingly, the semilogarithmic plot provided the k_p^{app} value of 0.041 min^{-1} which is approximately ten-times higher than the value reported for Cu(0)-RDRP of HEMA in DMSO.⁴⁶ This finding highlights that the polymerization rate is very high in the non-polar solvent employed in this study, which is supported by the studies that observed similar behavior for different hydroxyl-bearing monomers.¹³¹

Finally, to assess the method's suitability for preparing ultrahigh-MW poly(HEMA), experiments using even higher M/I ratios of 2000:1 and 5000:1 were conducted (entries 7 and 8, **Table 14**, **Figure 30**). Pleasingly, the experiments maintained excellent polymerization control and rapid polymerization rates. In the latter experiment, poly(HEMA) with MW of approximately 500 000 were obtained within 150 minutes while maintaining dispersity of 1.25. This represents a significant advancement over the Cu-RDRP protocols for polymerization of HEMA established in literature. To the best of our knowledge, poly(HEMA) of $M_n > 100\ 000$ with $\mathcal{D} < 1.30$ has never been synthesized before via Cu-RDRP (and likely also other RDRP) methods. Note that the CuCl_2 content was increased to 0.5 eq. for M/I ratios of 1000:1 and 2000:1, and to 1.25 eq. for the 5000:1 ratio. This adjustment was made for practical reasons, as accurately weighing progressively smaller amounts of the deactivator while maintaining the same polymerization scale became challenging.

An obvious drawback of using the conditions developed in this study lies in the extremely high viscosity of the polymerization mixtures especially when targeting high-MW products, which restricts the achievable conversions before the mixtures solidify. High viscosity was also a limiting factor in the study by Nguyen et al., where ultrahigh-MW poly(HEMA) were prepared via Cu(0)-RDRP in DMSO.⁴⁶ Notably, in that study, polymerization control diminished as higher MWs were targeted, with the reported $\mathcal{D} \geq 1.39$ for MWs of approximately 150 000 and higher (based on SEC calibration against poly(MMA) standards). By contrast, the new approach established here maintains control even at high M/I ratios and, theoretically, even higher MWs than those described

here should be reachable. Notably, high IE values of 70–80% were typically obtained for the high-MW polymers (entry 5 - 8) in this study. These IE values were also observed in other literature reports where Cu(0)-RDRP of different methacrylates was performed using the methyl 2-chlorophenylacetate/PMDETA system.¹⁰⁹

Table 14. Cu(0)-RDRP of HEMA at different M/I ratios^a

Entry	M/I	CuCl ₂ (eq.)	Time (min)	Conv. (%) ^b	<i>M_n</i> (theor.) ^c	<i>M_n</i> (SEC) ^d	<i>Đ</i> ^d
1 ^e	50:1	0.2	30	92	6 000	10 600	1.15
2 ^e	400:1	0.2	60	87	45 300	68 000	1.28
3 ^e	1000:1	0.5	90	75	97 600	169 400	1.53
4 ^e	400:1	0.5	60	92	47 900	70 000	1.47
5 ^f	400:1	0.2	60	88	45 800	59 700	1.14
6 ^f	1000:1	0.5	60	77	100 200	138 200	1.22
7 ^f	2000:1	0.5	80	62	161 400	205 800	1.26
8 ^f	5000:1	1.25	150	58	377 400	469 000	1.25

^a Standard polymerization conditions: ECPA/PMDETA = 1:1, 5 cm of activated copper wire, dioxane/HEMA = 1:1 (v/v).

^b Monomer conversion as determined by a ¹H-NMR analysis.

^c Theoretical *M_n* calculated from the M/I ratio and conversion.

^d Determined by SEC with LS detection.

^e HEMA monomer purified only by distillation, containing 0.1 wt.% of residual EGDMA crosslinker, was used.

^f Purified HEMA with minimized EGDMA crosslinker content was used.

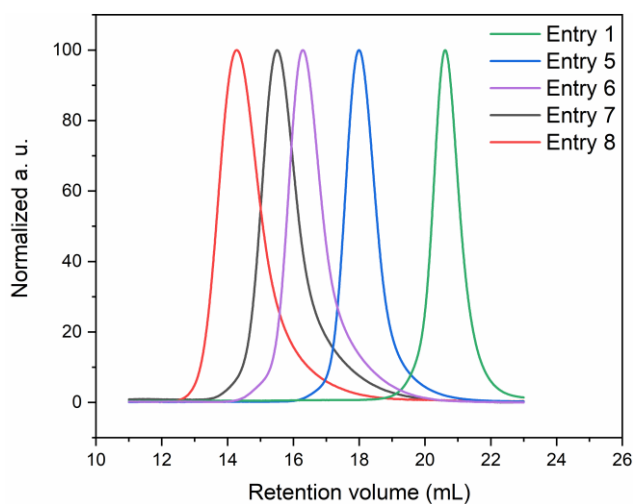


Figure 30. SEC elugrams (RI traces) from the SEC-LS analyses of poly(HEMA) obtained via Cu(0)-RDRP in dioxane at different M/I ratios. Numbering of the traces corresponds to **Table 14**.

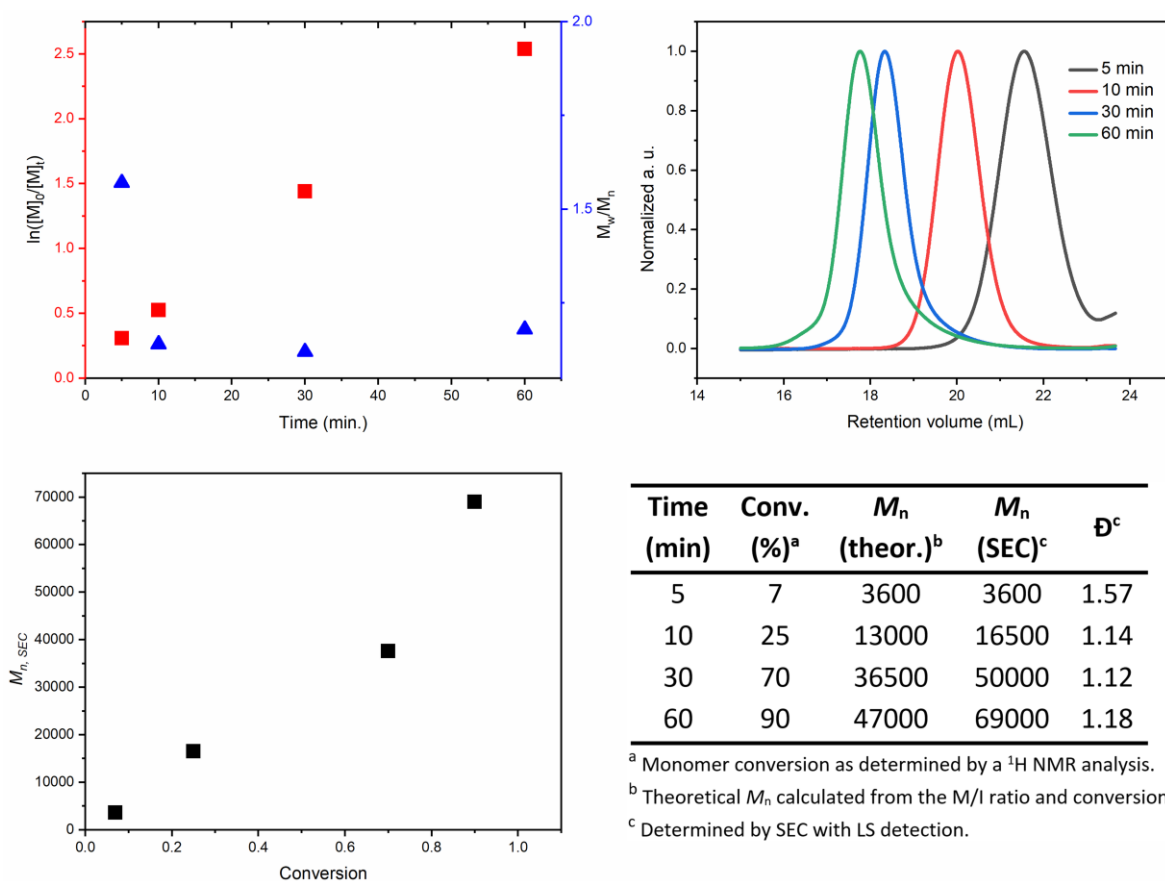


Figure 31. Kinetics of ECPA-initiated Cu(0)-RDRP of HEMA. Experimental conditions: HEMA/ECPA/PMDTA/CuCl₂ = 400:1:1:0.2, 5 cm of activated copper wire, dioxane/HEMA = 1:1 (v/v), 85 °C, purified monomer with minimized EGDMA content.

5.2.3 Direct copolymerization of HEMA with non-polar comonomers

To demonstrate the benefits of employing a non-polar medium for Cu(0)-RDRP of HEMA, the developed protocol was utilized for the synthesis of amphiphilic copolymers. To this end, copolymerization of HEMA was attempted with a non-polar comonomer 2-ethylhexyl methacrylate (EHMA) and a highly lipophilic comonomer lauryl methacrylate (LMA), keeping the HEMA/comonomer ratios equimolar, obtaining poly(HEMA-co-EHMA) and poly(HEMA-co-LMA) copolymers. The copolymerizations were conducted using the optimized conditions established above for HEMA (i.e., HEMA/comonomer/ECPA/PMDTA/CuCl₂ = 50:50:1:1:0.2, monomer/dioxane = 1:1 v/v, 5 cm of copper wire, and 85 °C).

Pleasingly, the polymerization mixtures remained homogeneous throughout the entire process, achieving nearly complete monomer conversion within 3 h. This was evidenced by the ¹H-NMR spectra of the crude mixtures that showed near-total disappearance of the monomeric vinylic

signals around 6 ppm (see **Figure A17**). Furthermore, TD-SEC analysis of both the copolymers revealed that the polymerizations were well controlled since narrow dispersity (1.13 and 1.09, respectively) for the poly(HEMA-co-EHMA) and poly(HEMA-co-LMA) products were obtained (**Figure 32**). Notably, the small bump in the SEC elugrams showed a presence of a high-MW fraction, noticeable much more clearly for the poly(HEMA-co-EHMA). This can be ascribed to the termination reactions. A comparative study was performed where HEMA was copolymerized with LMA using the conditions for homopolymerization of HEMA previously reported by Percec's group (i.e., Cu(0)-RDRP in DMSO; HEMA/LMA/MBPA/Me₆TREN/CuBr₂ = 50:50:1:0.1:0.05, monomers/DMSO = 1:1 v/v, 5 cm of copper wire and at r.t.).⁴⁶ The experiment also resulted in high monomer conversion despite the heterogeneity of the polymerization mixture. This heterogeneity was reflected in the characteristics of the obtained copolymer since the product did not dissolve in the mobile phase for SEC-LS (DMAc/LiBr). However, the product dissolved in THF allowing us to obtain relative MW values via SEC-RI analysis in THF calibrated against poly(MMA) standards. **Figure A18** provides the SEC elugram of the resulting polymer, showing a bimodal trace of a very high-MW ($M_n = 357\ 000$) product, with the main peak having dispersity of 2.35. In summary, these results suggest that the polymerization conditions established in this study are highly effective for synthesizing various amphiphilic HEMA-based copolymers. These conditions help avoid heterogeneous polymerization mixtures, which can adversely affect polymerization control.

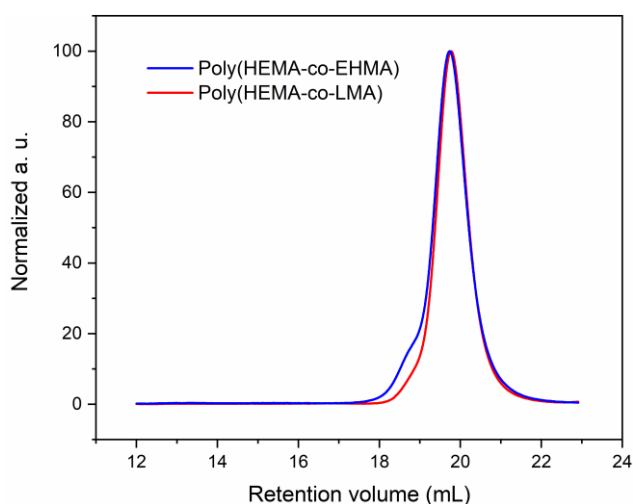


Figure 32. SEC elugrams (RI traces) from the SEC-LS analyses of poly(HEMA-co-EHMA) (blue) and poly(HEMA-co-LMA) (red) obtained via Cu(0)-RDRP in dioxane under optimized conditions (HEMA/comonomer/ECPA/PMDETA/CuCl₂ = 50:50:1:1:0.2, 5 cm of copper wire, monomers/dioxane = 1:1 v/v, 85°C, 3 h). Poly(HEMA-co-EHMA) characteristics: $M_n = 26\ 900$, $\mathcal{D} = 1.13$; poly(HEMA-co-LMA) characteristics: $M_n = 30\ 700$, $\mathcal{D} = 1.09$.

6. Conclusion

In conclusion, in this study, different applications of Cu-RDRP were studied.

In the first part, it was shown how Cu-RDRP in conjunction with the TAI strategy can be beneficial in the synthesis of different types of CPAs, combining the swiftness and cleanliness of TAI reactions with the well-controlled character of TAG-initiated Cu-RDRP. Based on an extensive optimization study, “out-of-the-box” Cu-RDRP conditions were provided that could be easily applied to the polymerization of a variety of monomers to different MWs in both polar and non-polar solvents. The TAG trifunctionality, clearly demonstrated through NMR and TD-SEC analyses, distinguishes the TAI strategy from earlier approaches based on monofunctional Cu-RDRP initiators. It was shown that the initiator multifunctionality enables access to CPAs of novel features, e.g. ultra-dense bottle brushes, multi-arm stars, or branched (co)polymers of novel topologies. Moreover, the high reactivity of TAI opens avenues for innovative synthetic methods (e.g., in situ modifications and one-pot protocols) and also greatly facilitates the modification of problematic substrates such as polysaccharides. This was exemplified by the successful homogeneous and surface-initiated grafting from various cellulose substrates. Additionally, in a preliminary study, considerable hydrolytic stability of the in-chain TAI-derived carbamate linker was observed for a water-soluble model polymer in a wide pH range.

In the second part, the novel Cu(0)-RDRP method of HEMA polymerization, discovered during the TAI strategy development, was tested with commercially available monofunctional initiators. Through the optimization study, conditions were obtained where a chlorine-based initiation/catalytic system (ECPA/CuCl₂/PMDETA, Cu-wire) was used in 1,4-dioxane. The developed protocol is superior to the previous Cu-RDRP protocols applied to the (co)polymerization of HEMA. With purified HEMA, the newly developed method provided a rapid access to well-defined poly(HEMA) in an unprecedentedly wide range of MWs without the risk of solvent transesterification side-reactions. Additionally, it was demonstrated that the developed conditions will be particularly useful for HEMA copolymerization with non-polar/lipophilic monomers where the current protocols (using highly polar solvents) may face compatibility problems. Well-defined HEMA-rich amphiphilic copolymers thus become readily accessible. This study also represents the first successful application of Cu(0)-RDRP performed in a non-polar solvent to a polar monomer.

7. Future directions

The research presented in this dissertation opens the door to numerous related studies that could be pursued in future. Potential future research directions include the following:

- The scope of the TAI strategy can be significantly extended from different perspectives. For example, the hydrolytic stability/pH sensitivity of other types of TAI-derived linkers should be investigated to assess the potential of the TAI strategy in the synthesis of CPAs with programmed degradation patterns. Further, thorough research should be conducted to find conditions for TAG-initiated Cu-RDRP of additional monomer classes (e.g. (meth)acrylamides), possibly applying alternative Cu-RDRP protocols such as aqueous Cu-RDRP or photo-Cu-RDRP. Furthermore, applicability of substrates featuring other TAI-reactive groups (e.g. amides, carboxylic acids) should be verified. Clearly, many other CPAs will be accessible via the TAI strategy. For instance, semi-telechelic polymers with a TAI modified end group could serve as precursors for miktoarm star copolymers, or step-wise introduction of TAGs into the polymeric backbone could afford graft copolymers with variable and programable graft length. In addition, the potentially superior grafting density accessible via the TAI strategy is expected to be of a high value in some SI grafting-based applications.
- The scope of the Cu(0)-RDRP in non-polar solvents for polymerization of functional/polar monomers might be broader than previously anticipated. In this direction, it is suggested to apply the developed conditions (or fine tune them) for (co)polymerization of other monomer classes (e.g. (meth)acrylamides, (meth)acrylic acid) which still lack a well-controlled Cu-RDRP method especially in organic solvents. This can facilitate the synthesis of amphiphilic copolymers of varied properties.

8. References

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Appendix

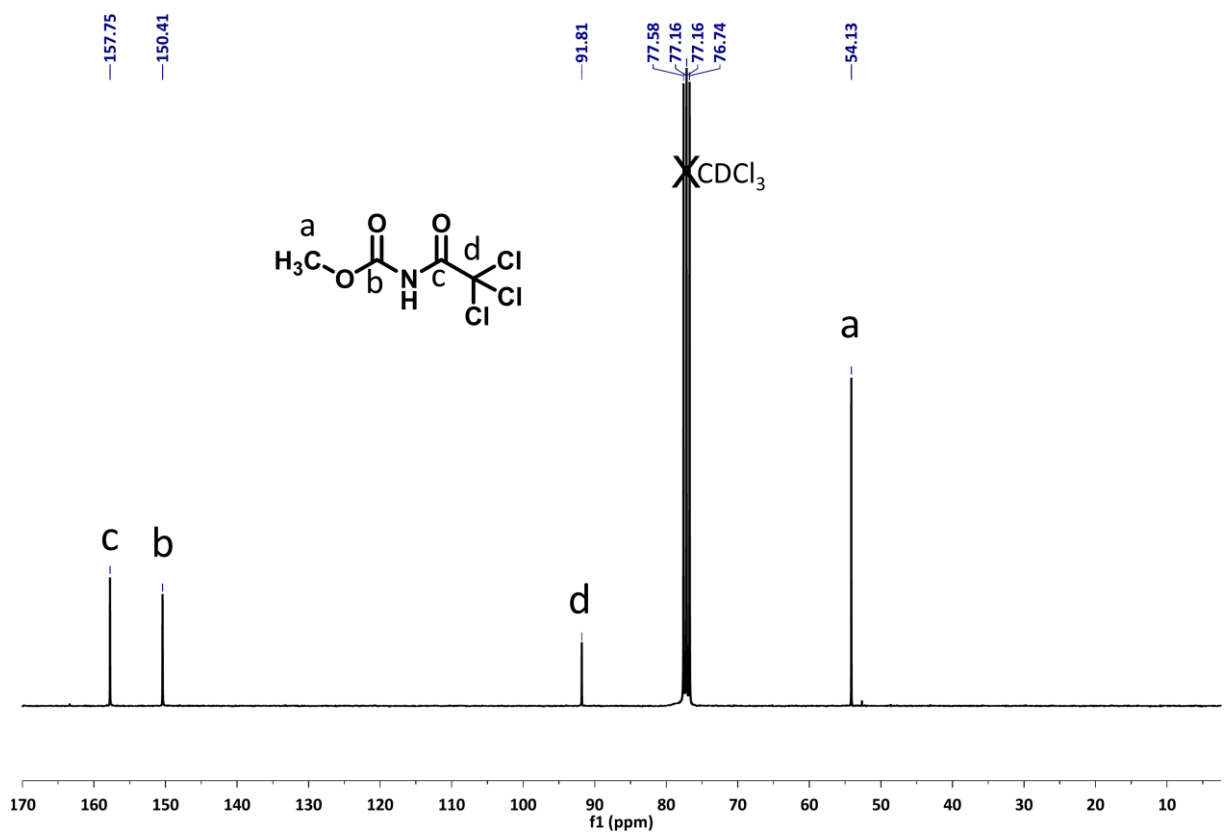
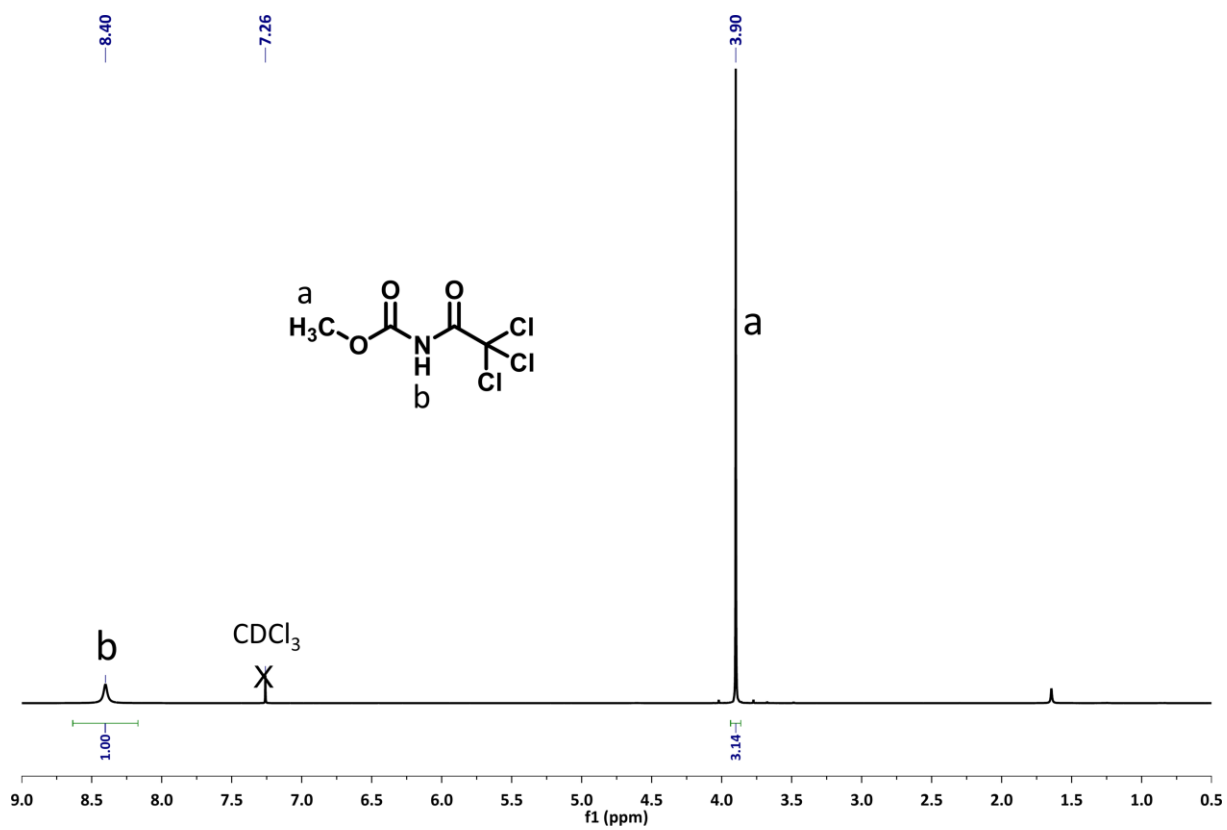


Figure A1. ¹H-NMR (top) and ¹³C-NMR (bottom) spectra of MTAC measured in CDCl₃.

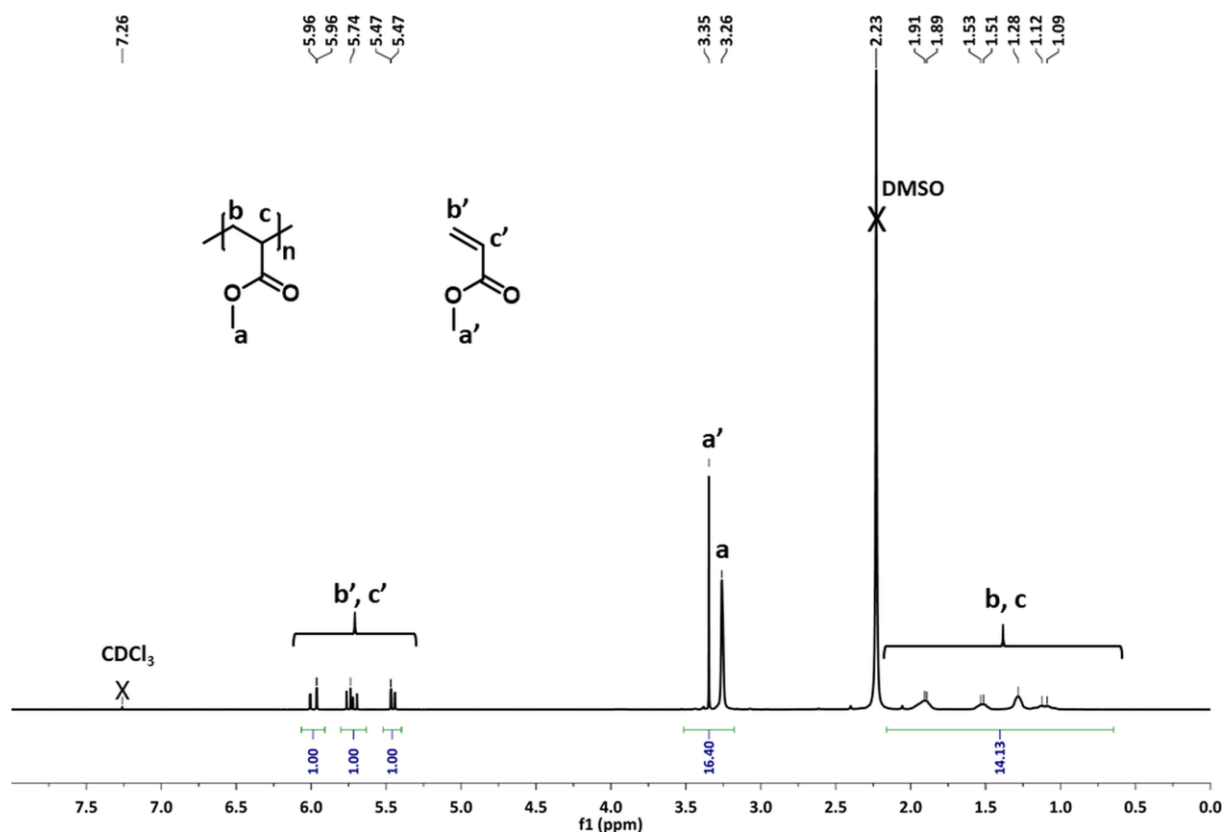


Figure A2. A representative $^1\text{H-NMR}$ spectrum (in CDCl_3) of a reaction mixture from Cu(0)-RDRP of MA (entry 24, Table 2). Monomer conversion was calculated by comparing the intensity of the signals of unreacted monomer (b', c') to that of the combined signals of the monomer and polymer (a, a'): $\text{conversion (\%)} = [1 - (I_{\text{b}', \text{c}'}/I_{\text{a}, \text{a}'})] \times 100$

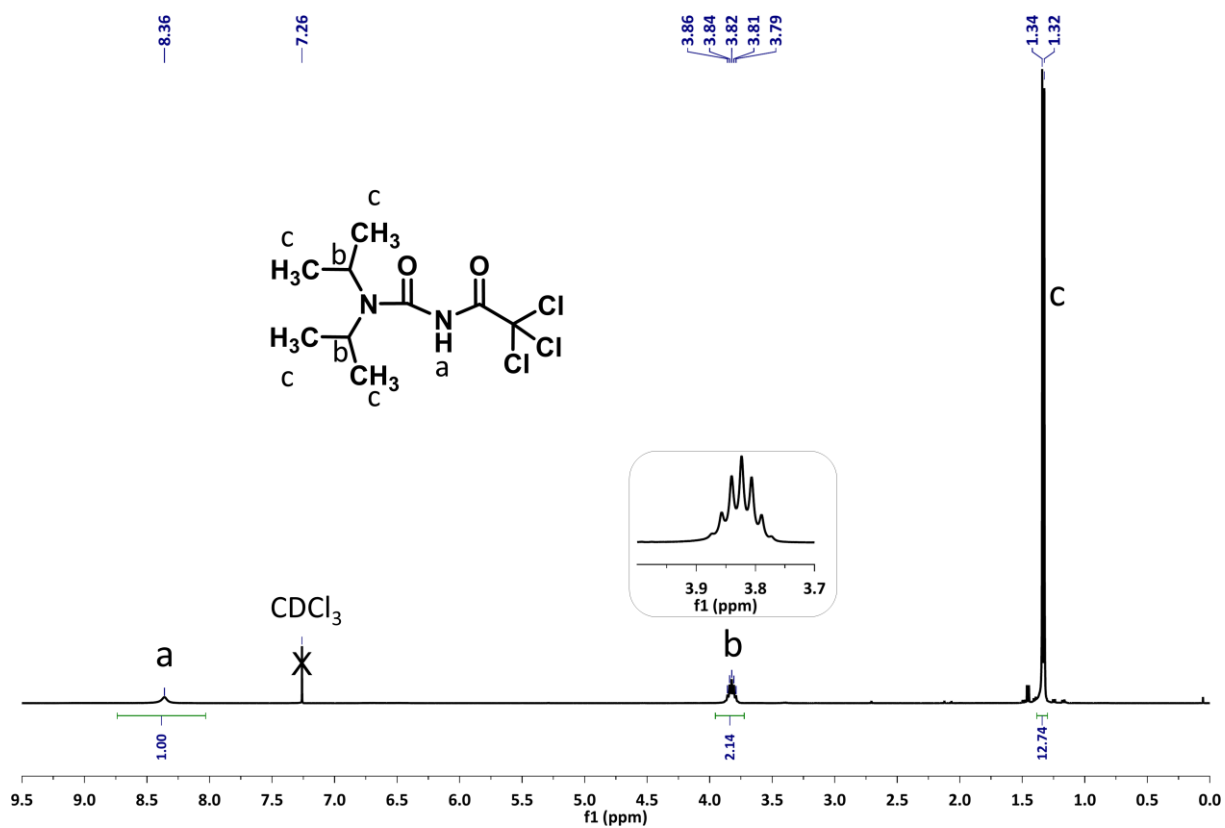


Figure A3. ¹H-NMR (CDCl₃) spectrum of the synthesized DTAU.

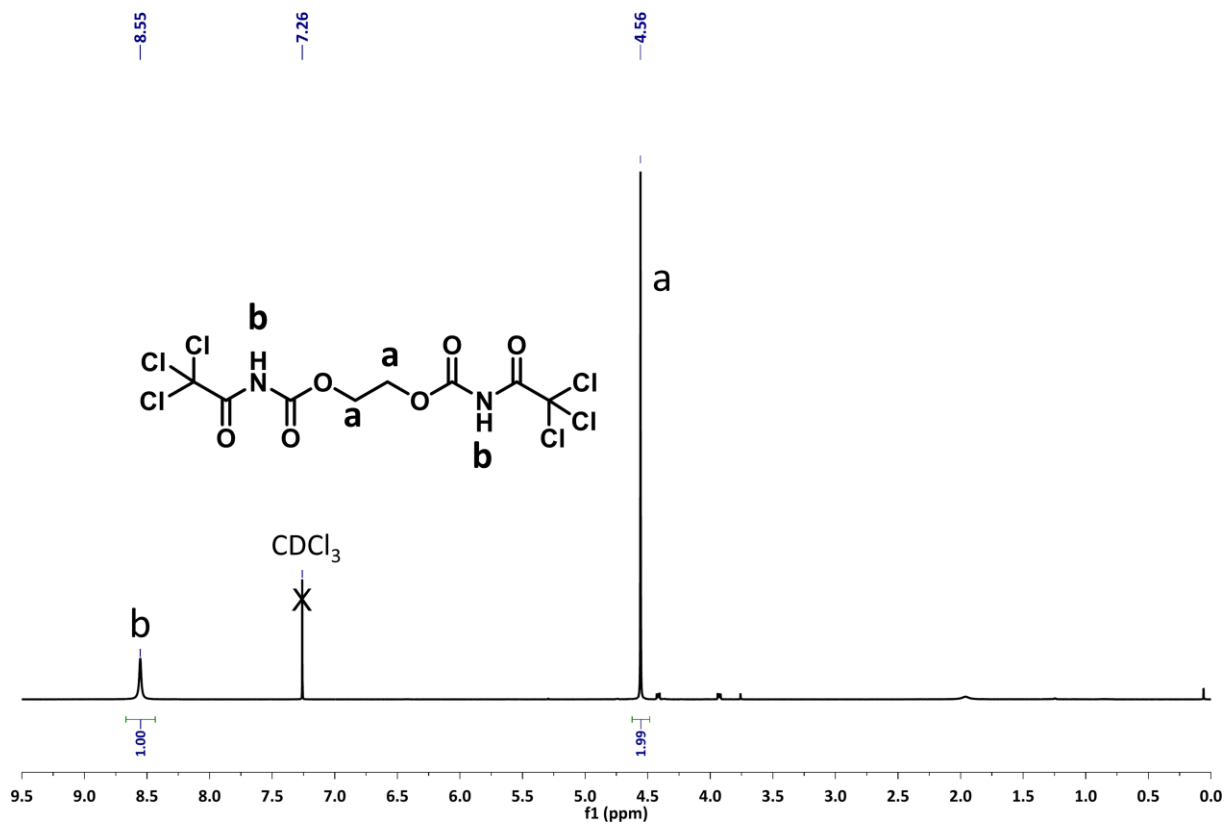
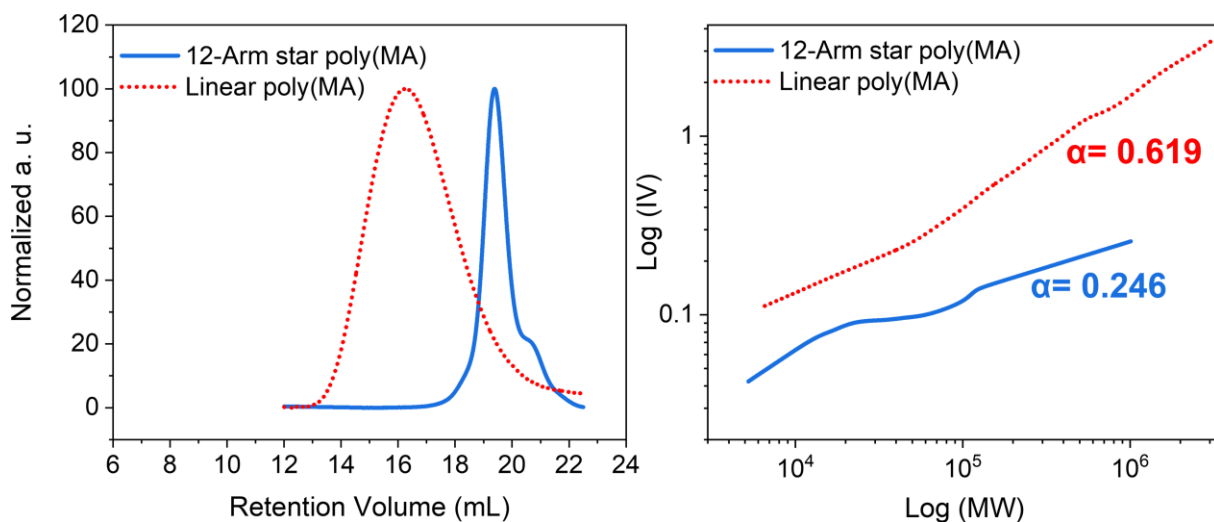
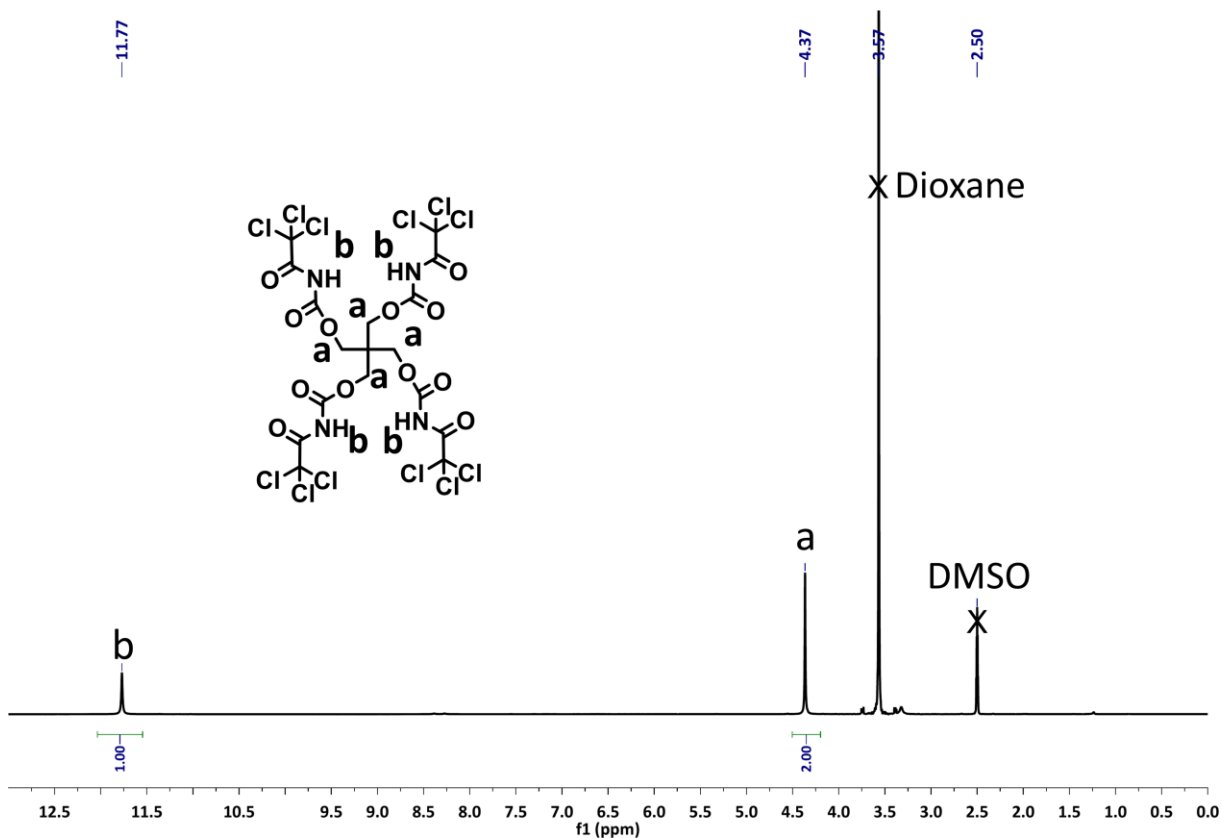


Figure A4. ¹H-NMR (CDCl₃) of ETAC.



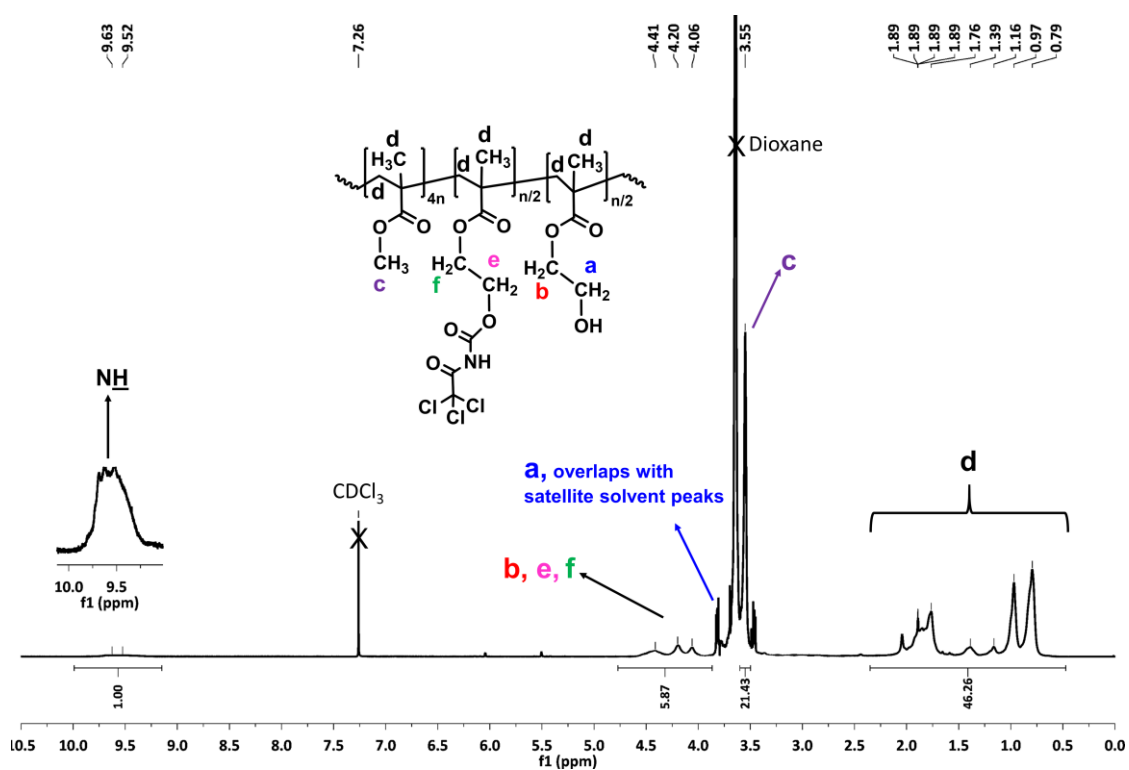
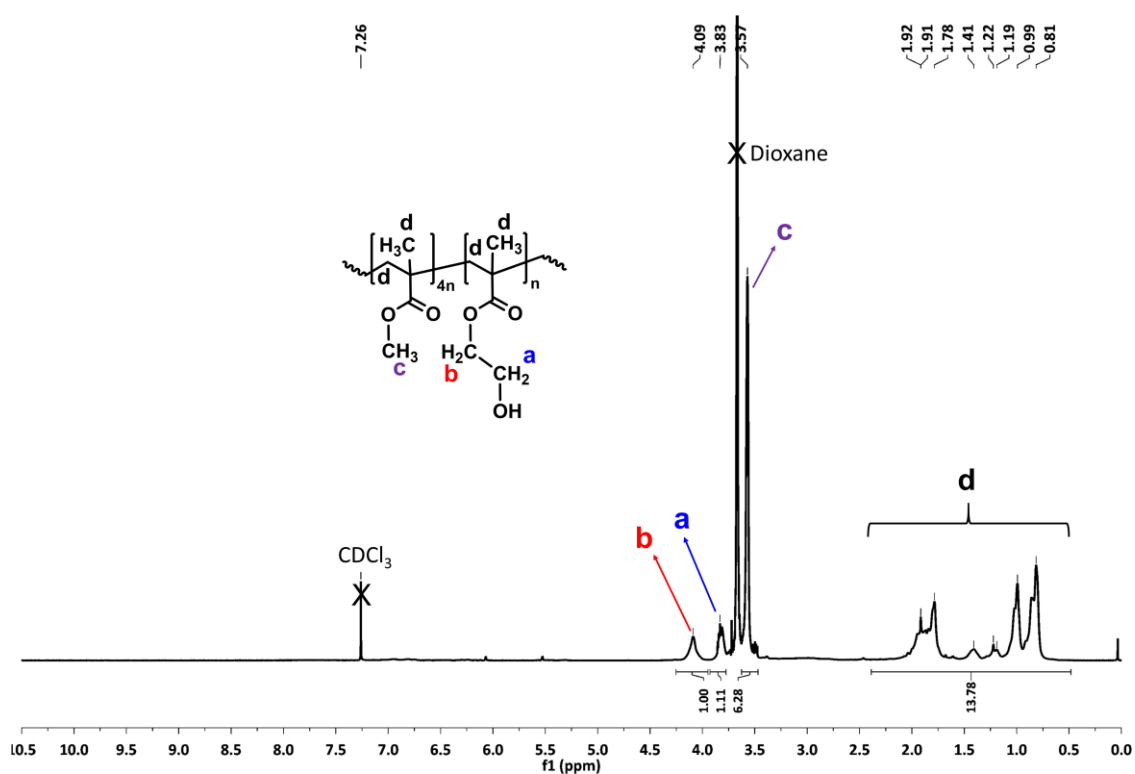


Figure A7. ¹H-NMR (reaction mixture; CDCl₃) of poly(MMA-co-HEMA) synthesized by MTAC-initiated Cu(0)-RDRP in dioxane before (top) and after (bottom) modification of a part of the hydroxyl groups by TAI (steps 1 and 2 in the *de novo* one-pot synthesis of a graft copolymer as per Figure 20).

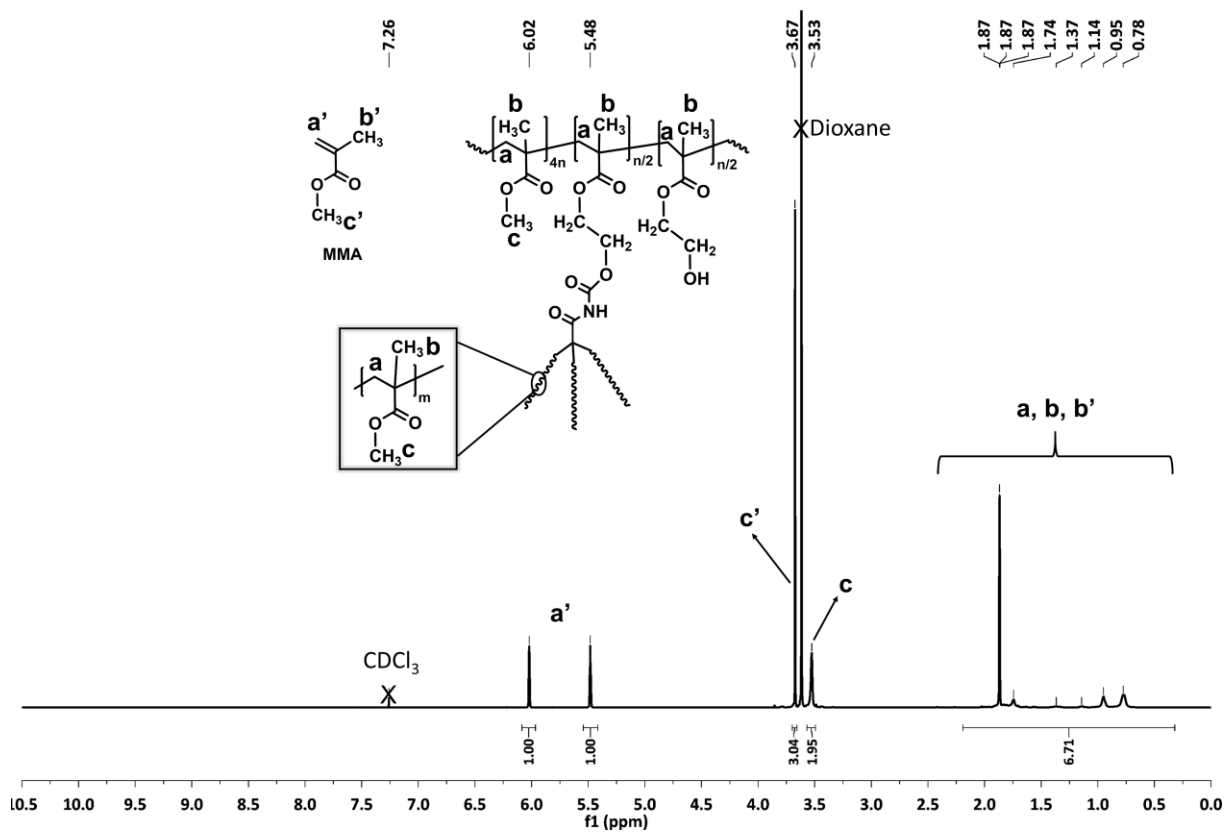


Figure A8. ¹H-NMR (reaction mixture; CDCl₃) of poly(MMA-co-HEMA)-graft-poly(MMA) synthesized via Cu(0)-RDRP of MMA initiated by the TAI-modified poly(MMA-co-HEMA) copolymer (step 3 in the *de novo* one-pot synthesis of a graft copolymer as per **Figure 20**).

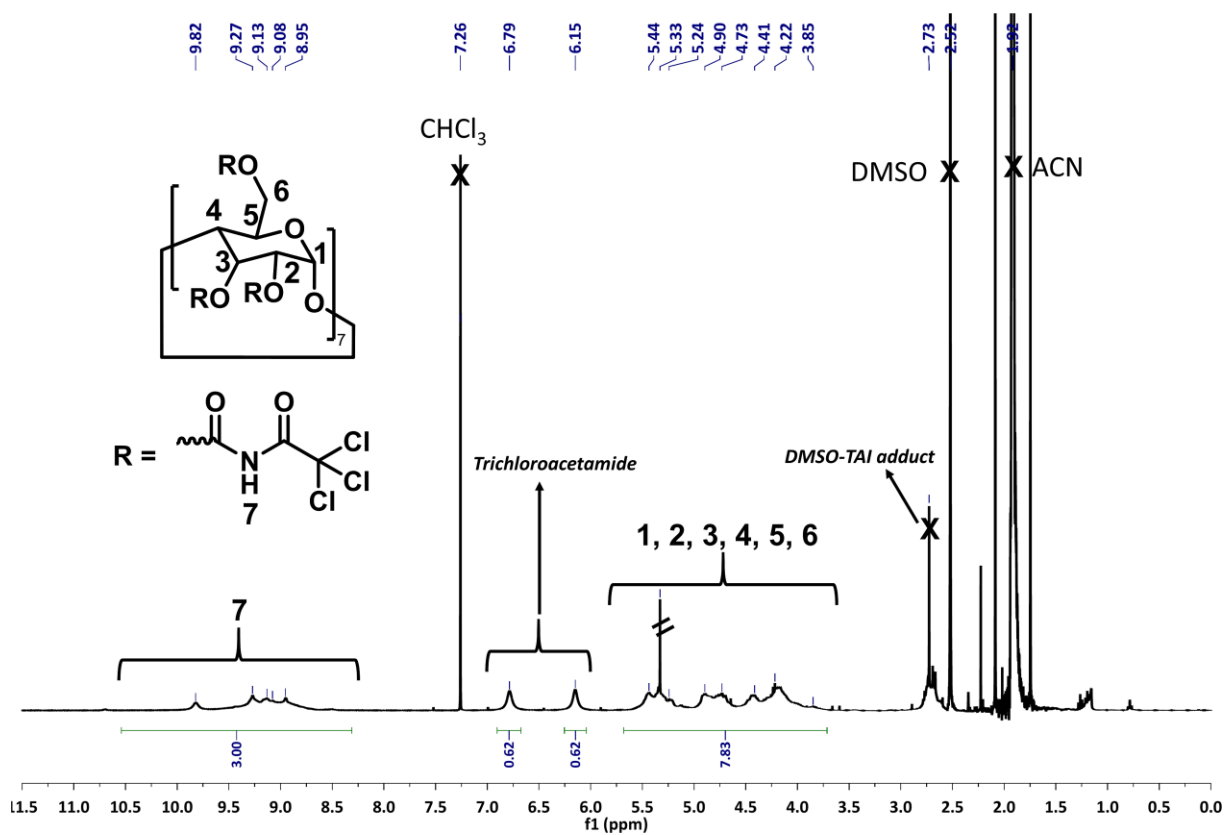


Figure A9. ¹H-NMR (reaction mixture; CDCl₃) of β-CD modified with TAI in acetonitrile.

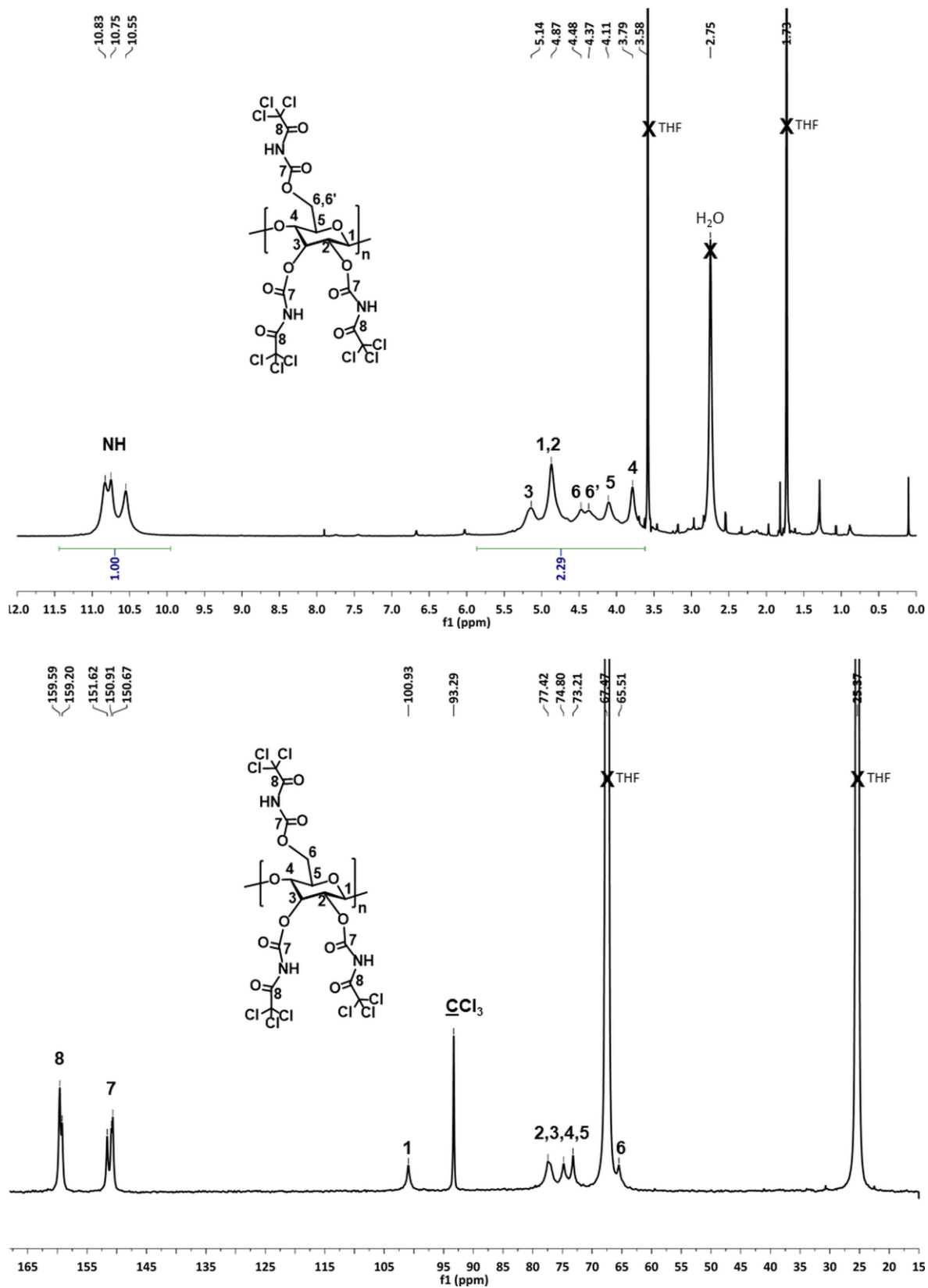


Figure A10. ¹H (top) and ¹³C-NMR (bottom) spectra (THF-d₈) of cellulose AVICEL PH-101 fully modified with TAI (modification performed in 7.7 wt.% DMAc/LiCl).

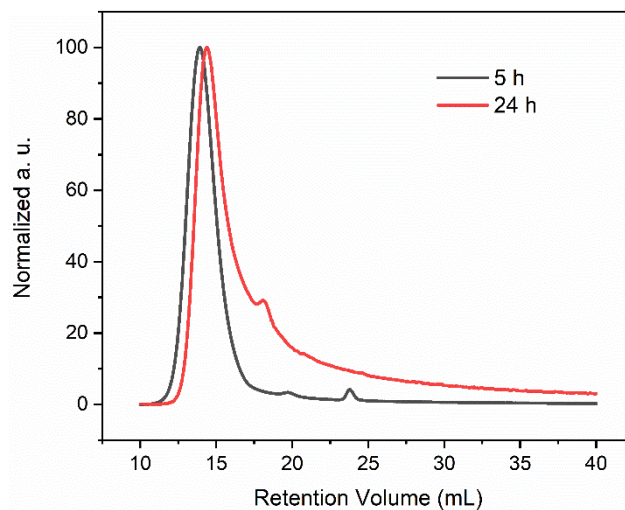


Figure A11. Light scattering signals from the TD-SEC analysis of samples of cellulose-*graft*-poly(MMA) bottle-brush graft copolymers taken at different polymerization time.



Figure A12. Surface-initiated ATRP grafting of poly(MMA) from a cotton thread modified with TAI (top) and the pine tree cone modified with TAI (bottom). The photographs were taken during the purification of the grafted thread during washing in methanol (top) and grafted cone (bottom left – washing in THF, bottom right -washing in methanol).

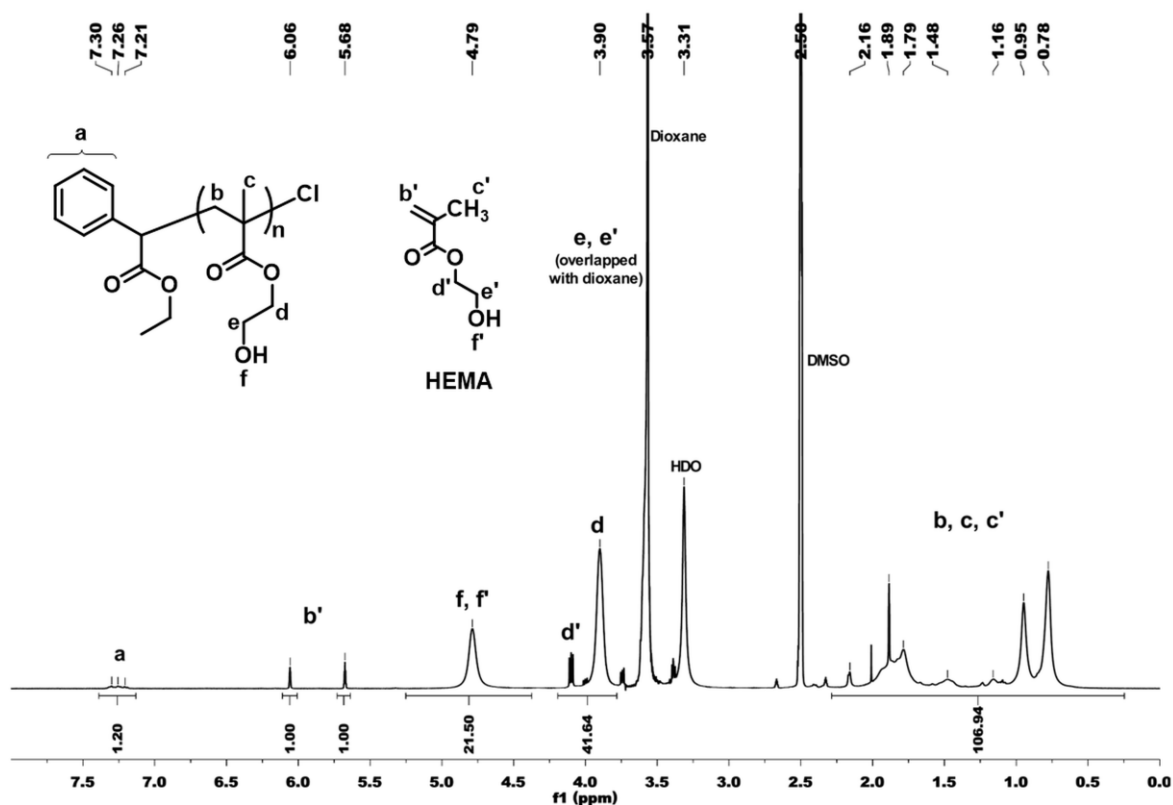


Figure A13. A typical ^1H -NMR spectrum of a crude polymerization mixture from Cu(0)-RDRP of HEMA in dioxane (the experiment from entry 4, **Table 1**). The analysis was performed in DMSO- d_6 . Monomer conversion was calculated based on the intensity of the signals corresponding to the unreacted monomer at 5.68 and 6.06 ppm and the monomer/polymer signals between 0.5 ppm to 2.2 ppm.

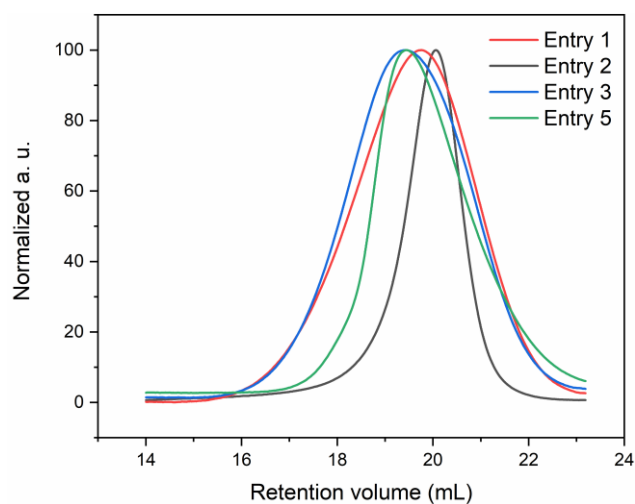


Figure A14. SEC elugrams (RI traces) of poly(HEMA) obtained via Cu(0)-RDRP in dioxane under different conditions. Numbering of the traces corresponds to **Table 13** where experimental details can be found.

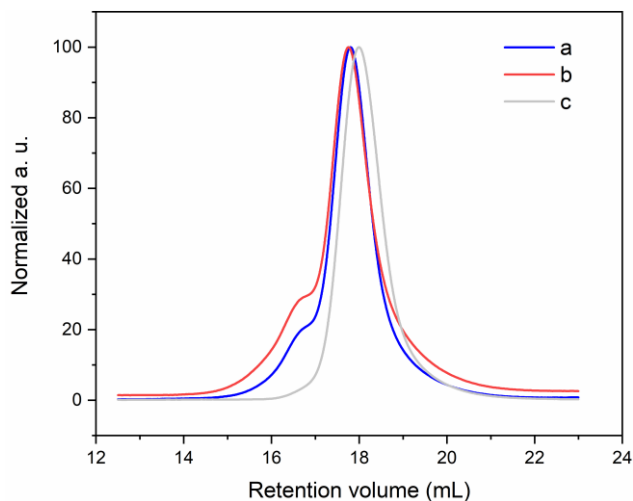


Figure A15. SEC elugrams (RI traces) of poly(HEMA) obtained at the M/I = 400:1 ratio via Cu(0)-RDRP of non-purified HEMA using (a) 0.2 eq. of CuCl₂ (entry 2, **Table 14**), and (b) 0.5 eq. CuCl₂ (entry 4, **Table 14**). Data for the experiment where purified HEMA with minimized EGDMA content, using 0.2 eq. of CuCl₂ (entry 5, **Table 14**) is displayed for a comparison (c).

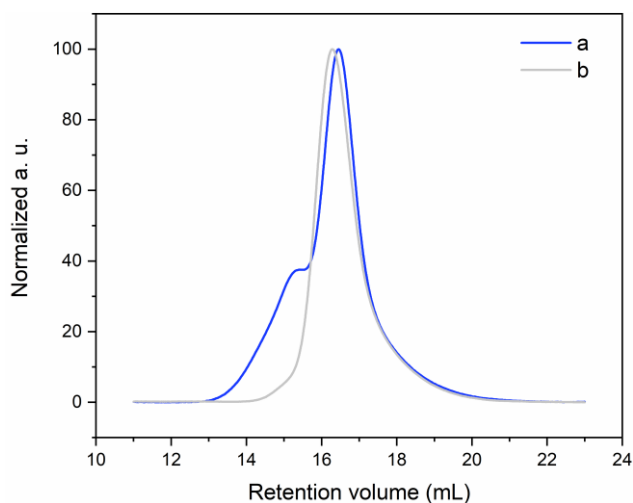


Figure A16. SEC elugrams (RI traces) of poly(HEMA) obtained at the M/I = 1000:1 ratio via Cu(0)-RDRP of non-purified HEMA (entry 3, **Table 14**) (a). Data for the experiment where purified HEMA with minimized EGDMA content was used (entry 6, **Table 14**) is displayed for a comparison (b).

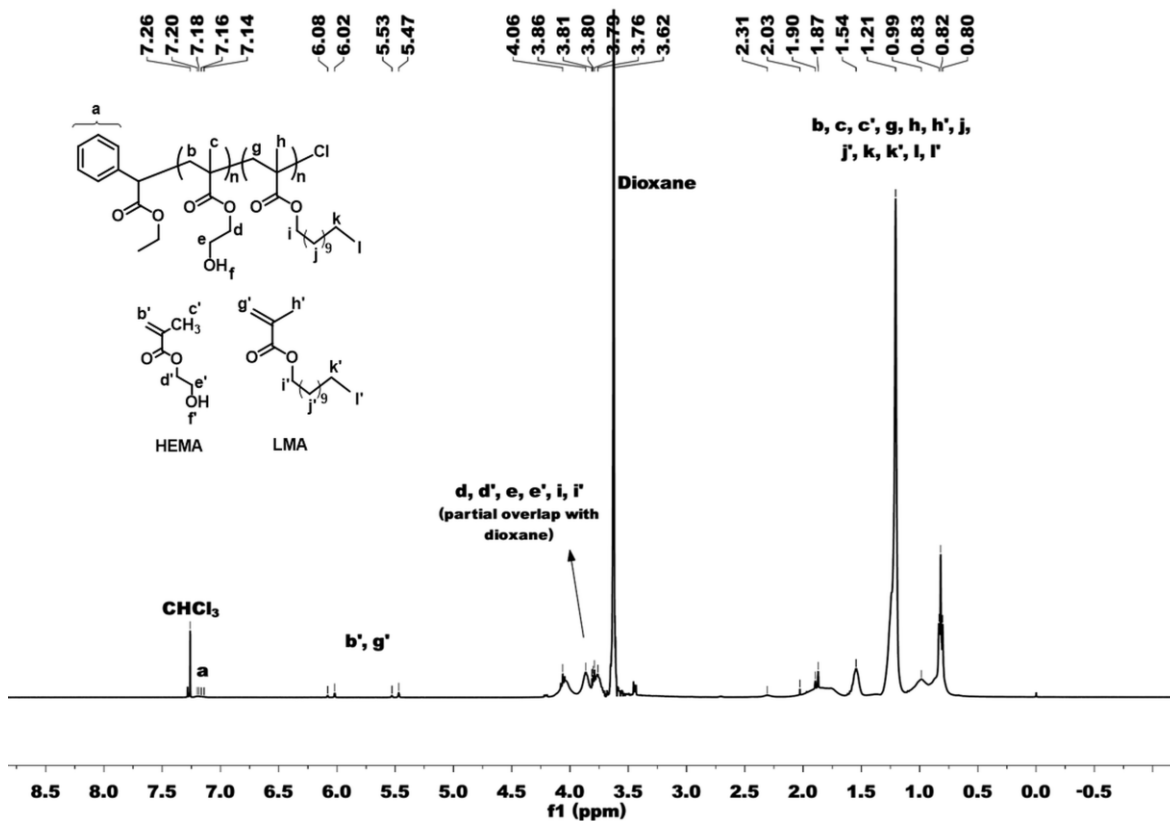
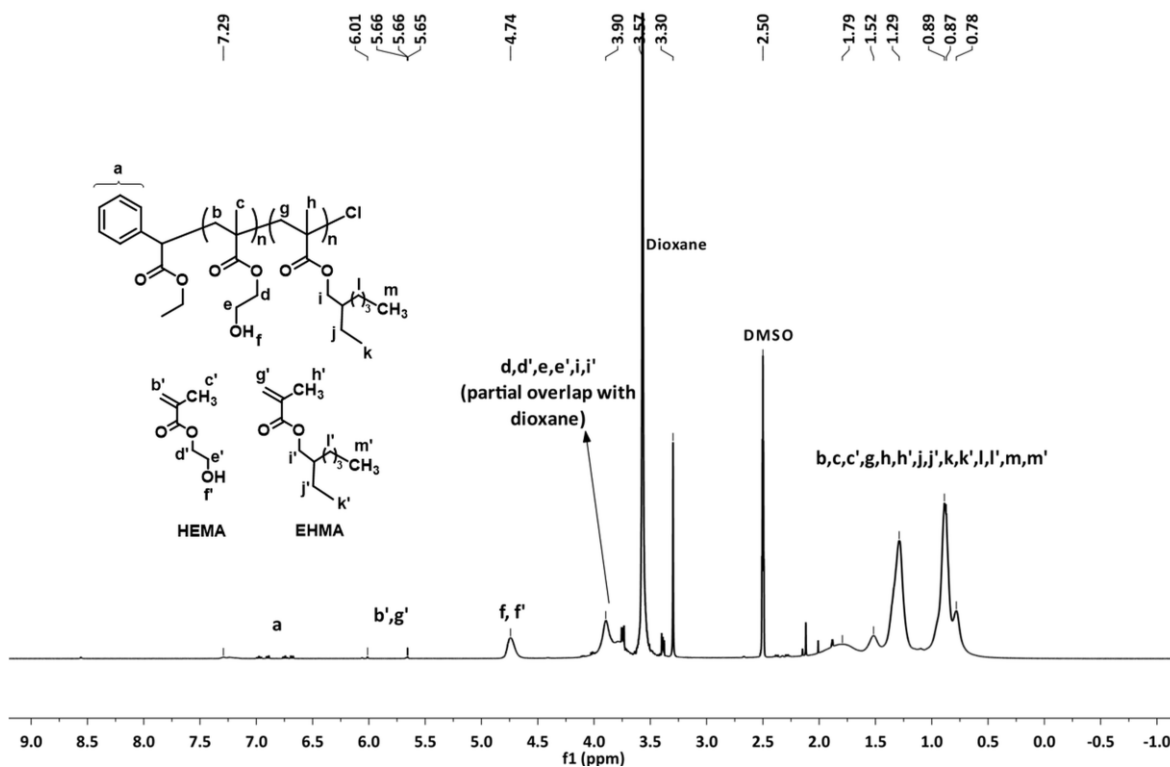


Figure A17. ^1H -NMR spectra of the crude polymerization mixtures from the copolymerization of a) top: HEMA and EHMA (measured in $\text{DMSO-}d_6$); b) bottom: HEMA and LMA (measured in CDCl_3); experimental conditions: Cu(0) -RDRP in dioxane (HEMA/comonomer/ECPA/PMDETA/ CuCl_2 = 50:50:1:1:0.2, monomers/dioxane = 1:1 v/v, 5 cm of copper wire and at 85°C).

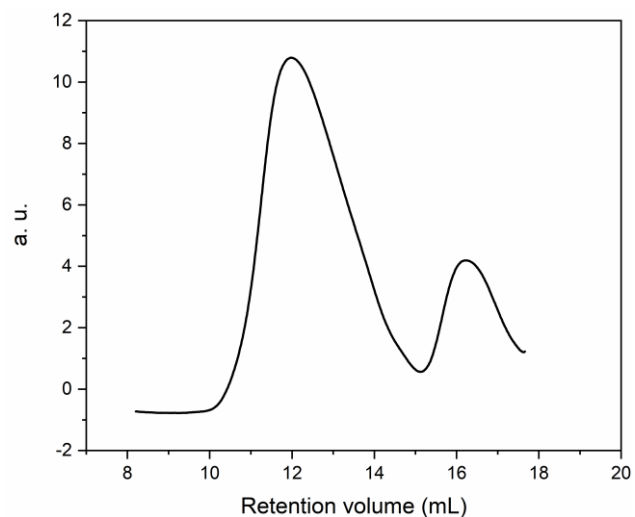


Figure A18. SEC elugram (RI trace) of poly(HEMA-*co*-LMA) obtained via Cu(0)-RDRP in DMSO according to a published procedure (HEMA/LMA/MBPA/Me₆TREN/CuBr₂ = 50:50:1:0.1:0.05, 5 cm of copper wire, monomers/DMSO = 1:1 v/v, r.t.).⁴⁶ The analysis was performed in THF with poly(MMA) calibration; the obtained values ($M_n = 357\,000$ and $\mathcal{D} = 2.35$ for the main peak) are thus relative.