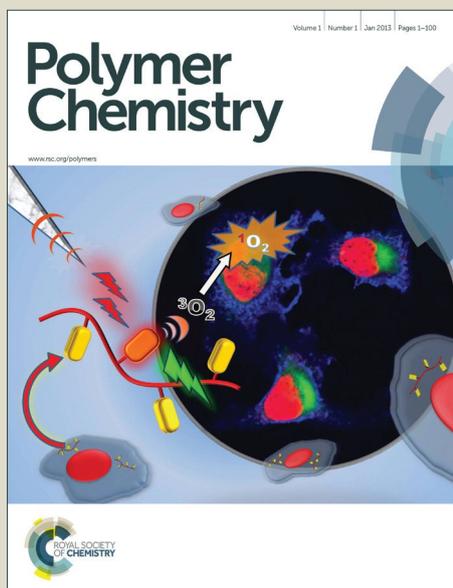


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ARTICLE

Ligand Switch in Photoinduced Copper-Mediated Polymerization: Synthesis of methacrylate-acrylate block copolymers

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The use of photo-induced copper-mediated radical polymerization (photoCMP) to synthesize mixed acrylate/methacrylate (methyl acrylate, MA and methyl methacrylate, MMA) block copolymers is investigated. Reactions in which only one type of ligand (Me₆TREN) is used leads to unsuccessful outcomes of the polymerization due to a mismatch in reactivity for the two monomers. A ligand exchange to PMDETA for the methacrylate is required to obtain good block structures. Due to insufficient re-initiation of polyacrylates, methyl methacrylate needs to be polymerized first, before the acrylate can be added for chain extension. A halogen exchange with CuCl is found to be beneficial to increase the re-initiation behaviour of the polyacrylate with respect to the acrylate chain propagation, but inherently compromises the livingness of the polymerization. Successful synthesis of block copolymers is only observed when the PMMA block is polymerized first and if all PMDETA ligand and residual monomer is removed prior to acrylate chain extension. The batch-type photoreactions were then transferred to a continuous flow tubular photoreactor, which leads to a significant acceleration of polymerizations, concomitant reduction in product dispersity and largely simplified block copolymer synthesis conditions.

Introduction

Without doubt, the invention of controlled radical polymerization (CRP) techniques has been one of the most paradigm-shifting developments in polymer science in the past 25 years. CRP allows generally for synthesizing polymers with well-defined architectures and molecular weights with narrow molar mass distributions.^{1,2} Generally, in CRP an equilibrium between an active and a dormant polymeric species is established, which is why these techniques are also referred to as reversible deactivation radical polymerizations (RDRP).³ Over time, many CRP methods have been introduced, with atom transfer radical polymerization (ATRP) being one of the most applied control methodologies from the whole choice of available techniques.³⁻⁵ Thereby, ATRP as a method is by no means static; synthesis procedures and mechanistic understanding are constantly refined. In all cases, however, ATRP uses a transition metal complex to mediate the

activation/deactivation equilibrium and is applicable to polymerize a wide range of vinyl monomers, such as acrylates, methacrylate or styrene.⁶

The early ATRP systems were initially intolerant to the presence of oxygen in a reaction and required a substantial amount of catalyst to maintain a good control over the polymerization while still allowing to reach reasonable reaction rates.⁷ Since then, the ATRP technique has been improved and today many sub-classes of ATRP are known. For example, activator generated by electron transfer (AGET) enables the use of the air-stable forms of catalyst complexes; activator regenerated by electron transfer (ARGET) or initiators for continuous activator regeneration (ICAR) reduces metal catalyst concentration to the parts per million scale and hence addresses a significant problem regarding metal contaminations of the final polymer products.⁸⁻¹⁰ Other developments also employ elemental copper, for example, single electron transfer

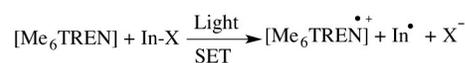
living radical polymerization (SET-LRP).^{11, 12} With SET, use of copper (0) as a major deactivator is postulated while copper (I) is believed to disproportionate to copper (0) and (II).^{11, 12} While the SET mechanism is somewhat in conflict with the definition of ATRP, another similar mechanism was proposed in which copper (0) would serve as a supplemental activator and as a reducing agent of copper (II), whereby copper (II) and (I) are de- and activator. This mechanism is known as supplemental activator and reducing agent (SARA) ATRP technique.^{13, 14} Which mechanism is indeed predominating is partially unclear, but from a practical point of view, both reactive systems are essentially identical. In any way, the distinct advantages of SET-LRP^{11, 12} and SARA-ATRP^{13, 14} include a high polymerization rate at room temperature and a high end-group fidelity at high monomer conversion.¹¹⁻¹⁴

The reduction in concentration of a transition metal can be achieved by redox processes,¹⁵ electrochemistry¹⁶ or photochemistry.¹⁷⁻²² Photochemistry has in this respect recently gained much interest because of its temporal-spatial control and simple application at room temperature. Yagci *et al.* have reported the effect of presence and absence of conventional photo-initiators on a UV-activated ATRP reaction.^{23, 24} Later, CuBr₂ in the presence of excess ligand, Me₆TREN, was reported to directly produce well-defined poly(acrylate)s under UV irradiation in a photoelectron transfer reaction.²⁵ In a similar reaction, photoinitiation was applied to synthesize poly(methyl methacrylate) poly(MMA). In this type of reaction, a CuBr₂ and N,N,N',N'',N'''-pentamethyl-diethylenetriamine (PMDETA) complex is used.^{26, 27} Continuous efforts have been devoted to explore the versatility of this photo-induced technique over acrylate monomers, including solketal acrylate, hydroxyethyl acrylate and glycidyl acrylate homopolymer, or even poly(methyl acrylate)-*b*-poly(solketal acrylate).²⁸ In our previous work, we have adopted photo-induced copper-mediated polymerization (photoCMP, note that CMP is used as term to avoid mechanistic discussion regarding the SET and SARA-ATRP process) and optimized the condition for synthesizing decablock copolymers, PMA-*Pt*BA-PMA-PDEGA-PMA-*Pt*BA-PMA-PDEGA-PnBA-PDEGA (where PMA is poly (methyl acrylate), *Pt*BA is poly(*tert*-butyl acrylate), PDEGA is poly(di(ethylene glycol) ethyl ether acrylate).^{29, 30} Followed by hydrolysis of *tert*-butyl group to hydroxyl group. The resulted decablock copolymer has shown complex thermo and pH-responsive self-assembled behavior. Similar sequence-controlled polymers were at the same time also introduced by the Haddleton group.^{31, 32} The highlights of using photoCMP for multiblock copolymer synthesis are the narrow molar mass distributions that can be achieved even for large numbers of blocks, short reaction times required to reach full conversion and the general ability to proceed reactions without further purification.^{29, 33, 34} Furthermore, we had also studied the use of flow reactor techniques in combination with photoCMP to polymerize methyl acrylate (MA).³³ The high surface to volume ratio of the (photo)flow reactor technology affords for a more homogenous and gradient free light

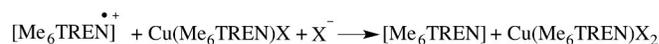
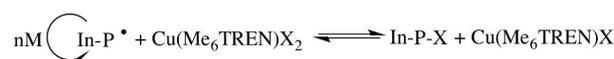
irradiation and improved heat dissipation, hence accelerating reactions significantly.^{33, 35, 36} PhotoCMP in flow reactors allowed methyl acrylate to polymerize in DMSO to over 90% conversion within 20 minutes while retaining pristine endgroup patterns.³³

Acrylate polymers are used in an extremely wide range of applications, *i.e.* drug delivery,^{37, 38} adhesives³⁹ and integrated circuits.^{40, 41} Many of these applications require polymers to self-assemble into specific conformations. The chemical nature of the monomer has thereby a direct influence on polymeric conformation. Much research has hence been devoted to employ CRP techniques to prepare diblock copolymers that consist of immiscible hydrophobic and hydrophilic blocks. The resulting polarity difference of a copolymer promotes self-assembly in a selective solvent, and thus allows for the formation of wide range of nanostructures, including micelles, lamella and vesicles. Not only polarity but also entropy between blocks can cause self-assembly in case a good solvent for both blocks is used.⁴² To vary the polymer composition and structures, a polymerization technique that is applicable to wide range of monomers in a controlled fashion is in any way essential.

Initiation:



Propagation:



Scheme 1. Proposed mechanism for Me₆TREN initiated photoelectron transfer initiation of photoCMP.

PhotoCMP is very effective to produce poly(acrylates), whereas polymerization of other monomers is hampered if not prohibited. For example, by using Me₆TREN/CuBr₂ complexes, practically no controlled polymerization of styrene can be achieved on a relevant time scale. Despite of the success with methacrylates with PMDETA, there are limited papers addressing the use of Me₆TREN-photoCMP to produce methyl methacrylate based polymers. This may seem to be a small difference; however, in order to copolymerize acrylates and methacrylates efficiently, the differences between PMDETA and Me₆TREN reactivities with respect to photoelectron transfer need to be addressed. Haddleton and coworkers²⁵ had proposed a preliminary mechanism for CuBr₂/Me₆TREN initiated photoCMP (see **Scheme 1**), in which the ligand is

firstly photoactivated, and creates concomitantly macroradicals, which is well in line with the observation that an excess of ligand is required for optimum reaction conditions.

Already the fact that in $\text{CuBr}_2/\text{PMDETA}$ initiated photoCMP of methacrylates, other ligand ratios are used compared to the Me_6TREN system indicates that the photoelectron transfer reaction is highly dependent on the choice of ligand, but also on the choice of type of monomer. In fact, even though methacrylates can be generally polymerized using the Me_6TREN system, reactions may follow a different pathway and may suffer from reduced efficiency.²⁷ To our best knowledge, a photoCMP process that allows for the synthesis of a block copolymer that consists of an acrylate and a methacrylate block, in bulk or in a flow reactor, has not yet been reported. In view of the importance to be able to combine these on first glance similar classes of monomers in block copolymers for self-assembly and multiblock copolymer synthesis studies, this gap needs to be closed. For classical ATRP or SET reactions limitations for reinitiation of a polyacrylate block for addition of methacrylates are well described. Yet, especially in the light of sequence-controlled polymerizations, it is of highest importance to test all possible variations systematically for such mixed acrylate/methacrylate block copolymerization, also since procedures (i.e. halogen exchange, see below) exist to overcome the typical hurdles. Additionally, due to the generally high efficiency of the photoCMP process, kinetic windows may be opened that allow for block extensions that in classical ATRP would not be accessible. Even if the chance for such window is relatively low, it is important to screen for its existence.

In this paper, we thus systematically describe in how far photoCMP can be used for this purpose, namely to create block copolymers containing poly(methyl acrylate) (PMA) and poly(methyl methacrylate) (PMMA) as model monomers. As noted, to efficiently polymerize usually two different ligands are employed in literature homopolymerization studies, thus we first focused on the individual ligand reactivity in the process, as this effect may be at least as significant as the inherent monomer reactivity differences. In addition, we also have examined the possibility of using a flow reactor to produce PMMA-*b*-PMA copolymers to see if flow chemistry may have a beneficial influence on such reactions in a similar way as it had on pure poly(acrylate) synthesis. As we will show, synthesis of the desired block copolymers is more complex than one would at first sight anticipate. As mentioned above, the aim of this paper is thus also to provide an overview over the challenges encountered when using photoCMP to synthesize acrylate/methacrylate block copolymers and to deliver input for future kinetic investigations on the to-date not fully resolved photoelectron transfer mechanism being operational.

Experimental

Materials

Methyl acrylate (MA) and methyl methacrylate (MMA) were purchased from Acros. All monomers were passed over basic aluminum-oxide prior to use. Ethyl 2-bromoisobutyrate (EBiB), Copper (II) bromide (CuBr_2), and N,N,N',N'',N'''-Pentamethyldiethylenetriamine (PMDETA) were used as received. Tris[2-(dimethylamino)-ethyl]amine (Me_6TREN) was synthesized according to previously reported literature procedures.⁴³

Analytical techniques

An OMNICURE Series 1000 lamp system was used as UV-light source. The system was equipped with a 100 W high-pressure mercury vapor short arc lamp (320–500 nm) at an iris setting of 100 %. In-Situ FTIR Spectroscopy (TM15, Mettler Toledo) was used to monitor monomer conversion by measuring the area of characteristic acrylate peaks. Analytical size exclusion chromatography (SEC) measurements were performed on a Tosoh EcoSEC HLC-8320GPC, comprising an autosampler, a PSS guard column SDV (50 x 7.5 mm), followed by three PSS SDV analytical linear XL (5 μm , 300 x 7.5 mm) columns thermostated at 40 °C (column molecular weight range: $1 \times 10^2 - 1 \times 10^6 \text{ g}\cdot\text{mol}^{-1}$), and a differential refractive index detector (Tosoh EcoSEC RI) using THF as the eluent with a flow rate of $1 \text{ mL}\cdot\text{min}^{-1}$ with toluene as flow marker. Calibration was performed using linear narrow polystyrene (PS) standards from PSS Laboratories in the range of $470\text{--}7.5 \times 10^6 \text{ g}\cdot\text{mol}^{-1}$. $^1\text{H-NMR}$ spectra were recorded on DPX-400 spectrometers using deuterated chloroform applying a pulse delay of 6 s and 64 scans. In this paper, the molecular weight of PMMA-Br derived from $^1\text{H-NMR}$ spectra is calculated by using the signal at 4.2 ppm, which assigned to CH_2 of EBiB, as the reference. Similarly, when calculating the molecular weight of MA block in a PMMA-*b*-PMA-Br, we use the CH_3 signal (*c.a.* 1.0-0.4 ppm) of PMMA-Br as the reference peak to integrate the peaks at *c.a.* 3.4-3.6 ppm that are assigned to the methyl groups (*i.e.*, the CH_3 that is adjacent to carbonyl group) of MA and MMA units. By eliminating the CH_3 signal from PMMA macroinitiator, we can calculate the molecular weight of MA.

Continuous tubular flow reactor setup

For the tubular flow reactor a 25 m fluorinated gastight PFA tubing (Advanced Polymer Tubing GmbH, 1/16" x 0.75 mm) was wrapped around a quartz glass tubing (outer diameter 4 cm). As light source a 15 Watt lamp tube (Vilber-Lourmat, peak emission 365 nm) was placed in the quartz glass tube. The reaction solution was pumped with a Knauer BlueShadow 20P HPLC-Pump from an amber laboratory bottle with a GL-45 screw cap and a nitrogen inlet into the PFA reactor tubing. A glass vial containing a hydroquinone/THF solution for quenching was used for sample collection.

General procedure of the synthesis of PMMA-Br in DMSO and chain extended with MA

The three-neck flask was connected to a UV source, an IR probe and sealed with a septum. Polymerization was conducted under UV and the monomer conversion was monitored by

online FT-IR spectroscopy. When the conversion reached 90%, the reaction was stopped and MA was added to the solution mixture. The reaction was then carried out under UV light.

General procedure for the synthesis of PMA-Br and PMA-*b*-PMMA-Br without intermediate purification

MA (10 DPn eq.), EBiB (1 eq.), CuBr₂ (0.021 eq.), Me₆TREN (0.13 eq.) and DMSO were added to a 10 mL vial and degassed by purging with Argon for 10 min. Polymerizations were conducted under UV. When the polymerization was close to 95% or above, the reaction was stopped by turning off the UV lamp. Then MMA monomer in solution (13 eq. to macro-initiator, PMA-Br), CuBr₂ (0.015 eq.), PMDETA (0.85 eq.) and DMF were added to the reaction vessel, and the mixture was purged for 10-15 minutes prior to UV exposure.

General procedure for the synthesis of PMA-Br and PMA-*b*-PMMA-Br with intermediate purification step

PMA-Br is prepared as the method presented in the previous section. When the polymerization was close to 90% or above, the reaction was stopped and the residual MA, Me₆TREN, DMSO were removed from the mixture in vacuo. Next, MMA (14 eq. to macro-initiator), PMA (1 eq.), CuBr₂ (0.30 eq.), PMDETA (2.2 eq.) and DMF/MeOH (80/20 v/v%) were added to the reaction vessel, and the mixture was purged for 10-15 minutes prior to further UV exposure.

General procedure for the synthesis of PMMA-Br and PMMA-*b*-PMA-Br without intermediate purification

MMA (20 eq.), EBiB (1 eq.), CuBr₂ (0.043 eq.), PMDETA (0.13 eq.) and DMF/MeOH (80/20 v/v%) were added to a 10 mL vial and degassed by purging with Argon for 10 min, followed by UV exposure. The monomer conversion was monitored by a gravimetric method.⁴⁴ When the polymerization reached *ca.* 75 % monomer conversion, MA (67 eq. to macro-initiator), CuBr₂ (0.11 eq.), Me₆TREN (0.55 eq.) and DMSO in solution were added to the reaction vessel, and the mixture was purged for 10-15 minutes prior to further UV exposure.

General procedure for the synthesis of PMMA-Br and PMMA-*b*-PMA-Br with intermediate purification step

PMMA-Br is prepared as the method presented in the previous section. When the polymerization was close to 50% or above, the reaction was stopped and the residual MA, Me₆TREN and solvent were removed from the mixture in vacuo. Next, MA (67 eq. to macro-initiator), PMMA (1 eq.), CuBr₂ (0.11 eq.), Me₆TREN (0.55 eq.) and DMF/DMSO (20/80 v/v%) in solution were added to the reaction vessel, and the mixture was purged for 10-15 minutes prior to further UV exposure.

General procedure for the synthesis of PMMA-Br using continuous tubular reactor setup

In a 100 mL amber volumetric flask 1.903 g (9.76 mmol, 1 eq) EBiB, 0.043 g (0.19 mmol, 0.02 eq) CuBr₂, 0.106 g (0.61 mmol, 0.06 eq) PMDETA and 18.912 g (188.89 mmol, 19 eq.) MMA were mixed and 25 mL methanol added. The volumetric

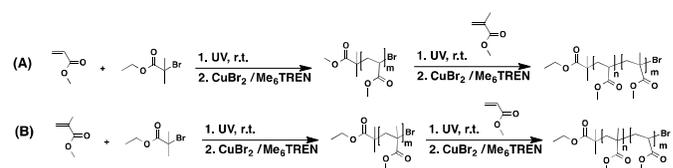
flask was filled with DMF next. Before purging with nitrogen for 30 minutes the mixture was transferred into a 100 mL amber laboratory bottle with a GL-45 screw cap. The flow reaction proceeded at 40 °C.

General procedure for the synthesis of PMMA-*b*-PMA-Br using continuous tubular reactor setup

0.336 g PMMA-Br macro-initiator (2600 g·mol⁻¹, 0.13 mmol, 1 eq.), 0.001 g CuBr₂ (0.01 mmol, 0.08 eq), 0.010 g Me₆TREN (0.04 mol, 0.31 eq), 1.343 g MA (15.60 mmol, 120 eq) and 5 mL DMF were mixed in a 25 mL volumetric flask and filled up with DMSO. The solution was purged for 15 min with nitrogen in an amber laboratory bottle before the reaction was started by pumping the solution into the reactor.

Results and discussion

Using CuBr₂ and Me₆TREN in DMSO to produce polyacrylates and their (multiple) chain extensions with other acrylates under photo-induced copper-mediated polymerization (photoCMP) are well reported.^{29, 33} It is documented that excess amount of Me₆TREN with respect to CuBr₂ in a reaction is required in order to produce polyacrylates, and the ratio of Me₆TREN and CuBr₂ at six to one affords well-controlled polymerization.²⁵ On the other hand, when using photoCMP to produce poly(methyl methacrylate) (PMMA), different types of ligands and other ligand to CuBr₂ ratio are employed.^{26, 27} Polymerization of MMA with ethyl α -bromoisobutyrate (EBiB) as an initiator was reported for a molar ratio of ligand (*e.g.* PMDETA) to CuBr₂ larger than one, for example, using three equivalent of PMDETA compared to CuBr₂.²⁶ Moreover, a ligand with lower activity had been reported to be more suitable for polymerizing MMA compared to a ligand with a higher activity. A recent report shows that in the presence of CuBr₂ and an initiator, MMA polymerization governed by Me₆TREN (*i.e.*, a higher activity ligand) yields similar molar mass but broader dispersity compared to that governed by PMDETA (*i.e.*, lower activity ligand).²⁷ This suggests progressive termination occurring due to a too high concentration of active macroradicals in the reaction.²⁷ In addition, PMDETA and Me₆TREN copper complexes feature different light absorption profiles and will not be equally efficient in the photoelectron transfer reaction. Regardless, it is important to use appropriate ligands in respect to the monomers in a photoCMP reaction.

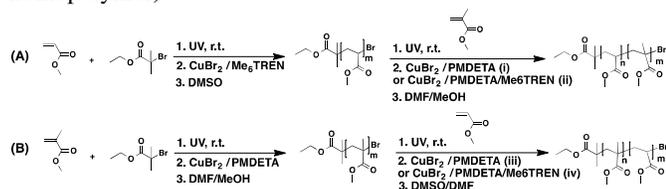


Scheme 2. PhotoCMP is used to produce PMA followed by chain extension with MMA using Me₆TREN (A); to produce PMMA and then chain extend with MA using Me₆TREN (B).

To produce a copolymer composed of MA and MMA thus the question arises if a single ligand is sufficient when conducting a chain extension in order to achieve a reasonable molar mass

distribution and molecular weight, or if a ligand switch must be carried out in order to achieve satisfactory polymerization results.

To begin with, we have thus approached block copolymerizations with only one type of ligand. MA is polymerized in presence of CuBr_2 , Me_6TREN and DMSO as reported in literature^{29, 31} (Scheme 2 (A)). The polymerization is followed by in-line FT-IR and once monomer conversions reached 90% or higher, MMA was introduced into the reaction vessel (Scheme 2 (A)). The corresponding FT-IR profiles are shown in a waterfall diagram in the SI (Fig. S1). Similar molecular weight distributions are in such case observed before and after targeted MMA chain extensions, suggesting that polymerizations have failed and that a direct monomer addition is not successful (See Fig. S2). It must be noted that this is within expectations as pMA-Br is known to be an ineffective macroinitiator for methacrylate chain addition. Yet, starting with the acrylate monomer features several advantages (fast reaction rates, ability to reach full conversion without significant loss of endgroups), hence it was tested. In the next step, the polymerization of MMA in presence of Me_6TREN and DMSO was conducted and monitored by IR (Scheme 2 (B)) to see how efficient these reactions potentially are. Such polymerization reaches 89% monomer conversion in *ca.* 4 hours (see Fig. S3) and hence demonstrate that MMA polymerization is slower compared to MA (as expected for a methacrylate), but nonetheless very feasible. Closer inspection reveals that the experimental number-average molecular weight M_n (2400 $\text{g}\cdot\text{mol}^{-1}$) is larger than the theoretically expected M_n (1500 $\text{g}\cdot\text{mol}^{-1}$), combined with a dispersity (D) of 1.39. Polymerization results are thus not ideal, but in line with previous observations. Nevertheless, we employed this PMMA-Br as macroinitiator along with CuBr_2 and Me_6TREN to chain extend MA (Scheme 2 (B)) to test if this order of monomer addition allows for better reaction outcomes. The IR spectra taken for such polymerization suggest that premature termination occurs when the monomer conversion reaches about 16% (see Fig. S3). Moreover, the polymers before and after chain extension have similar molecular weight distributions (see Fig. S4). This suggests that the observed loss of double bond signal during chain extension is most likely due to a homopolymerization (*i.e.* the growth of PMA homopolymer).



Scheme 3. PhotoCMP employing CuBr_2 and Me_6TREN to produce PMA-Br (A); and chain extension with MMA in the presence of PMDETA (B). (i-iv) denotes reactions with and without intermediate macroinitiator isolation.

The above two experiments suggest that using only Me_6TREN is largely unsuccessful to synthesize PMA-*b*-PMMA. Failure of the experiments is well reproducible and thus, we concentrated

in the following to use different ligands with respect to the two monomers. Clearly, MA is easier polymerized with Me_6TREN , while PMMA requires PMDETA and a change of ligand appears to be more promising. Such ligand switch method is illustrated in Scheme 3. As above, two possibilities exist to carry these reactions out. Either, one starts with MA polymerization followed by MMA chain extension, or vice versa. The first has the advantage, that acrylate polymerization can be easily preceded to full conversion, which takes significantly longer time in case of MMA. On the other hand, Me_6TREN binds much stronger to copper than PMDETA, and hence an exchange of the first by the latter may be problematic. Also the specific radical reactivity's do not favour a start with the acrylate block. Still, first MA was polymerized employing Me_6TREN to screen conditions systematically. Subsequently, MMA and PMDETA were added (Scheme 3 (A)). Thereby, reactions can be carried out with and without intermediate purification after PMA formation. Isolation allows to remove all ligand and hence results in the more "clean" chain extension (Scheme 3 (A-(i)) with macroinitiator isolation, or without the purification step, Scheme 3 (A-(ii)). In a similar fashion, also the polymerization of MMA supported by PMDETA can be followed by chain extension in a Me_6TREN system with and without purification. (Scheme 3 (B-(iii) and (iv)). Each of the four combinations is discussed in more detail in the following.

Ligand switch after synthesis of PMA-Br

In principle, block copolymerization without intermediate isolation is superior to reactions requiring isolation. Only if reactions can be carried out directly, sequence-controlled polymerizations as demonstrated before for pure poly(acrylates) can be achieved. Thus, it is of high importance to evaluate in detail if such approach can be successful or not. PMA-Br macroinitiator was synthesized as in the above experiments and the polymerization was stopped (by turning off the UV lamp) when a monomer conversion of 93% or above was reached (Scheme 3 (A)). Next, MMA (137 eq to PMA-Br) and PMDETA (8 eq. to Me_6TREN) are added into the reaction mixture and then exposed to UV. The large excess of PMDETA is required in order to push the majority of Me_6TREN out of the complex (note that the complex formation constants for both ligands are almost identical).⁴⁵ Nevertheless, the copolymerization appears to feature bimodal distributions (Fig. S7). This uncontrolled behaviour is also observed when different solvents (*e.g.* acetonitrile, DMF, methanol, or their combinations) and more concentrated PMDETA (up to 17 time excess of PMDETA compared to Me_6TREN) was tested, see Fig. S5). Furthermore, this bimodal molecular weight distributions features are also observed even when a purification step in prior to chain extension to remove all Me_6TREN from the mixture (Fig. S8). Hence, it can be safely assumed that the presence of Me_6TREN was not the decisive factor in the failure of the block extension. Rather, the bimodality can be assumed to occur due to very slow reinitiation of PMA-Br with MMA,^{46, 47} leading to uncontrollable behaviour. For thermal copper-promoted CRP, this reactivity mismatch was before overcome by halogen exchange

reactions.^{46, 47} Thus, we investigated if also the photoCMP process could benefit from the halogen exchange technique in photoCMP.

PMA-Br was hence mixed with copper chloride (CuCl) and PMDETA before copolymerizing MMA, under variation of the CuCl concentration to test if this had an influence on rate of re-initiation (note that in the polymer purification step volatiles were removed, but that CuBr₂ remained in the mixture as deactivator). The molecular weight distributions of copolymers in the presence of CuCl at different molar ratios with respect to MMA are depicted in Fig. 1. The reactions were tested under a fixed ratio of monomer to macroinitiator (PMA-Br) at 186:1, with ratios of macroinitiator to CuCl of 1:6 (B), 1:3 (C) and 1:1 (D). In all cases, mostly unimodal distributions were obtained. Still, significant tailing is observed, resulting in dispersities of $\bar{D} = 2.0 - 2.4$ (Fig. 3 and Table S1). The absence of bimodality suggests that the halogen exchange did mediate re-initiation successfully. Yet, no effective controlled polymerization is obtained, leading to the broad weight distributions. This hypothesis is also evidenced by failure of reactivating chlorine-terminated polymer chains in classical photoCMP (using CuBr₂) and by further experiments in which CuBr₂ was replaced by CuCl₂.

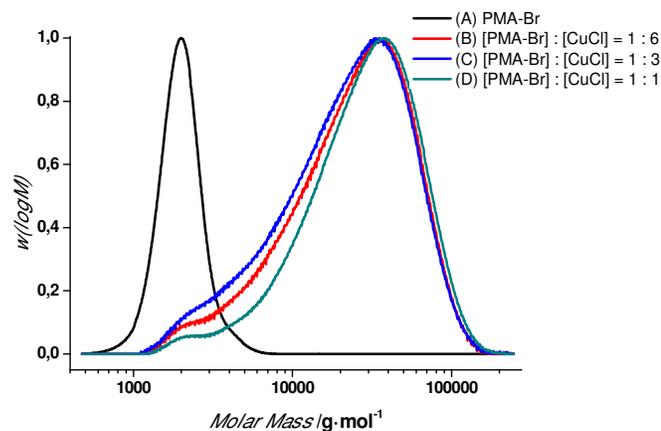


Fig. 1 Molecular weight distributions of PMA-Br obtained by photoCMP in the presence of CuBr₂ (A); followed by chain extension with MMA in the presence of PMA-Br and CuCl at different ratio, 1: 6 (B), 1: 3 (C), and 1: 1 (D).

Synthesis of block copolymers starting from PMMA-Br without intermediate macroinitiator purification

Since all approaches starting from PMA-Br were unsuccessful – and that insufficient re-initiation of the polyacrylate chain can be identified to be the reason of failure – further focus was put on the opposite approach, hence by starting from PMMA-Br. Therefore PMMA macroinitiator was obtained by conventional photoCMP with PMDETA (Scheme 3 (B)).

As mentioned above, it is difficult to reach high conversions in the photoCMP of MMA and hence polymerizations were stopped at less than 70-80% monomer conversions, which are in good agreements with maximum conversions found in literature.^{19, 27} In our first attempt of preparing PMMA-*b*-PMA-

Br, we synthesized PMMA-Br in the presence of PMDETA and CuBr₂ in DMSO. This reaction reaches 80% monomer conversion in two hours. Immediately, MA monomer and Me₆TREN were introduced into the reaction vessel, and the polymerization was monitored by IR probe. The IR spectra suggest the monomer was consumed completely, however, the SEC traces (Fig. S6) suggest otherwise, in which little change in molecular weight distribution is observed. The broad distribution of PMMA-Br suggests a not-well defined control over polymerization and potential loss of end group fidelity. This could promote the likelihood of MA to homopolymerize via self-initiation of the monomer, rather than to reinitiate from the macroinitiator. To gain a better control over PMMA-Br polymerization, a different solvent, DMF/MeOH, was used to carry on the reaction. In this case, 76% monomer conversion was achieved. The so-obtained PMMA-Br had an average molecular weight at 1500 g·mol⁻¹, close to the theoretical value (**Fig. 2** (A)). The dispersity of the macroinitiator is 1.4, which is also in line with literature reports.^{19, 26, 27} Without further purification, MA (138 eq. to PMMA-Br) and Me₆TREN (4 eq. to PMDETA) were injected into the reaction, followed by UV exposure (Scheme 3 (B)-(iv)). With an excess of Me₆TREN, almost full substitution of ligand in the copper complexes is expected. Aliquots were extracted from the chain extensions at 17, 39 and 55 minutes reaction time for molecular weight analysis (see **Fig. 2** (B-D)).

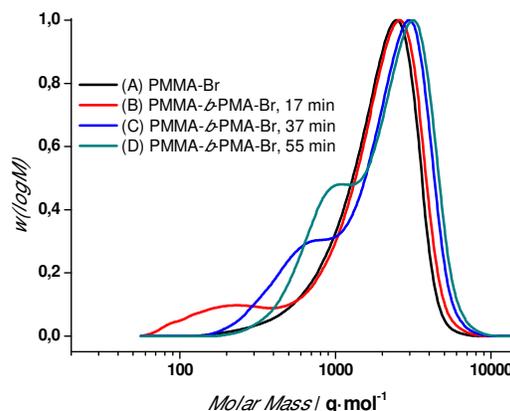


Fig. 2 Molecular weight distributions of PMMA-Br and chain extensions with MA after injection of Me₆TREN without intermediate macroinitiator isolation.

The MWDs show with increasing reaction time an increase in molar weight of the polymer, which is, however, accompanied by the rise of another polymer distribution on the low mass side of the distribution. Since both distributions grow in size with time, it can be assumed that the low molecular weight material is PMA homopolymer (potentially stemming from self-initiation of monomer under UV light), potentially stemming from transfer reactions or from direct initiation of Me₆TREN radicals formed during photoinitiation. Additionally, the choice of solvent has an influence on the degree of control over photo-induced reaction, and can improve the attachment of MA to

PMMA-Br. It is however rather difficult to confirm if block- or statistical copolymer are obtained due to the presence of unreacted MMA in the reaction of chain extension process. Hence, in order to produce neat block copolymers, it is important that a purification step is performed in the process.

Ligand switch including a purification step between synthesizing PMMA-Br and PMMA-*b*-PMA-Br

Even though the above described polymerizations showed some success, still no satisfactory result could be obtained. Thus, also here the system is compared to a reaction in which the macroinitiator was purified in order to cancel out side reactions. Therefore, again PMMA-Br was obtained from photoCMP, with subsequent removal of solvent and ligand. This procedure has the additional benefit that also residual MMA monomer could be removed at the same time, which seems to be required regardless if gradient block structures are to be avoided. Two different PMMA-Br polymers were obtained by variation of the reaction time (3 and 7 h, respectively). One macroinitiator had a M_n of 2900 $\text{g}\cdot\text{mol}^{-1}$ according to SEC, the other one of 1000 $\text{g}\cdot\text{mol}^{-1}$. Both experimental M_n are close to theoretical ones. Dispersities were between 1.2 and 1.4 (see sample 1 and 5, Table 1). Chain extension was then started employing pure Me_6TREN in the appropriate concentrations. Each polymerization was exposed to UV for 3 hours and the ratio of macroinitiator to MA was varied systematically (see entry 2, 3 and 4 in Table 1) Block copolymers with M_n of 6,000, 15,000 and 24,000 $\text{g}\cdot\text{mol}^{-1}$, respectively, were obtained, all featuring relatively narrow distributions ($\mathcal{D}\sim 1.25\text{--}1.28$). The molecular weight distribution of PMA-Br and the three copolymers, PMMA-*b*-PMA-Br, are depicted in Fig. 3. No bimodalities are observed, underpinning that re-initiation is effective. The overall narrowness of the distributions hints at effective chain-length control, yet this needs to be further tested. In any way, the superiority of introducing an isolation step between the block polymerizations is evident.

Polymerization of PMMA-Br and PMMA-*b*-PMA-Br in a continuous tubular flow reactor

Previously, it was shown that photoCMP generally benefits from the application of continuous flow techniques. In tubular photoreactors, much better light efficiencies can be obtained as the small diameters of the employed tubing allows for gradient-free irradiation profiles. This advantage increases reaction rates, and introduces a significant scalability to the polymerization, which is extremely difficult to reach in batch processes. Since all above experiments had shown that the only effective way to obtain mixed acrylate/methacrylate block copolymers is to first polymerize PMMA followed by product isolation, the same strategy was also followed for continuous flow.

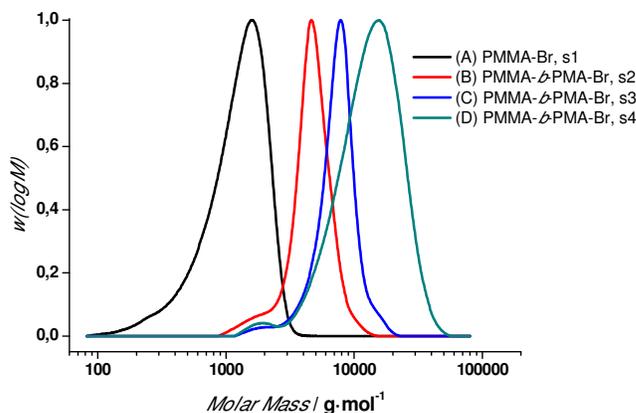


Fig. 3 Molecular weight distributions of PMMA-Br (A); and of chain extended block copolymers in different monomer and initiator concentrations (B-D). The samples are denoted as S1-S4, corresponding to Table 1.

Thus, in a first step, MMA is mixed with CuBr_2 , PMDETA and EBiB in DMF/Methanol (80/20 v/v%) and pumped into a tubular photoflow reactor for polymerization. Reactions were all well controlled. Fig. 6 shows the increase in number average molecular weight with increasing reaction times.

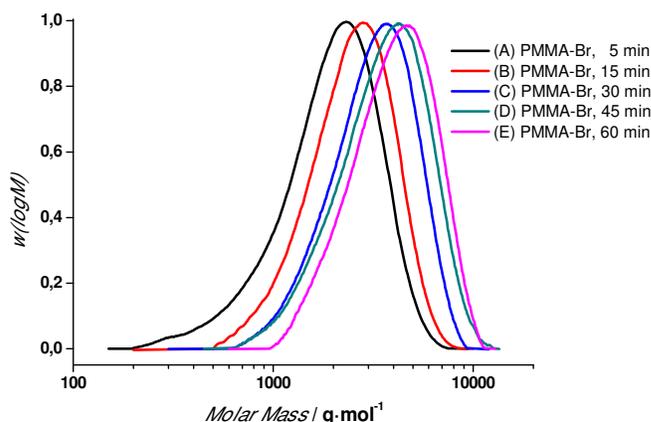


Fig. 4 Development of molecular weight distributions of PMMA with increasing reaction times, synthesized via photoCMP in a continuous tubular photoflow reactor.

The reaction reaches a monomer conversion of close to 50 % with a residence time of 60 minutes in the reactor. In comparison to similar batch reactions the photoflow process is hence up to 3 times faster (see Table 1). Similar rate increases have been observed for the acrylate polymerization as well. For small molecular masses (around 1000 $\text{g}\cdot\text{mol}^{-1}$) the dispersity of the photoflow PMMA-Br is lower than a comparable batch product ($\mathcal{D}\sim 1.15$ instead of 1.37). What needs to be noted is that the dispersity slightly increases for longer targeted polymer chains made in the continuous tubular reactor setup ($\mathcal{D}\sim 1.15\text{--}1.24$, see Table 1). Still, definition of the polymers is almost in

all cases higher, underpinning the advantage that is gained by flow processing compared to batch reactions. The photoflow reactor clearly improves the reaction efficiency of the MMA photoCMP reaction.

In the next step also the synthesis of PMMA-*b*-PMA-Br copolymer was carried out in the continuous tubular flow reactor after PMMA-Br isolation. For the second flow stage, the PMMA-Br macroinitiator ($2600 \text{ g}\cdot\text{mol}^{-1}$, $D \sim 1.30$) was dissolved with CuBr_2 , Me_6TREN and MA in a DMSO/DMF (80/20 v/v%) solution and pumped through the tubular photoflow reactor channel. The analysis of the PMMA-*b*-PMA-Br copolymer via SEC shows a clear shift in molecular weight to a higher mass for the chain extended polymer (Fig. 7, Table 1), even if some tailing to the low molecular weight side seems to occur. Also the addition of the PMA block to the PMMA-Br macroinitiator occurs faster in photoflow compared to the corresponding batch reaction. For the same conversion, similar molecular weight and dispersity is, however, obtained.

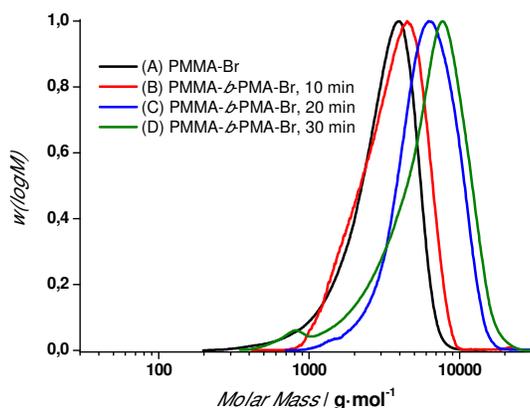


Fig. 5 Increase in molecular weight after chain extension of PMMA-Br (A) to PMMA-*b*-PMA-Br (B-D) in the continuous flow photoreactor.

Thus, for both the polymerization of PMMA-Br as well as the addition of a PMA block to the macroinitiator the usage of a continuous tubular photoflow reactor is beneficial as reaction rates are increased. It is additionally noteworthy, that also for the flow reaction, the different methods for block copolymerizations were tested, either starting from pMA-Br or by directly re-injecting the macroinitiator without ligand removal. In all cases, very comparable results to the above described batch reactions were obtained, confirming the conclusion that only block copolymers of the structure PMMA-*b*-PMA-Br can be obtained, and also only in clean state when the PMMA-Br macroinitiator is isolated and purified between the reactions.

Conclusions

The use of photoCMP to produce block copolymers composed of MA and MMA was investigated. It is demonstrated that using only one type of ligand, Me_6TREN , is unable to produce MA/MMA block copolymers due to a mismatch in reactivity for the two monomers. Besides all difficulties stemming from radical reactivity differences between chains with terminal acrylate of methacrylate units, a ligand exchange/switch is thus required to obtain good block structures. Starting first with the acrylate block fails due to insufficient re-initiation of the first block in presence of MMA. A halogen exchange could increase the ability to re-initiate, but then control over the photoCMP reaction is lost. Successful synthesis of block copolymers is only observed when the PMMA block is polymerized first and if all PMDETA ligand and residual monomer is removed prior to acrylate chain extension. Yet, when this protocol is followed, low dispersity block copolymers are obtained. The batch-type photoreactions were then transferred to a continuous flow tubular photoreactor. As described before for pure acrylate polymerizations, also here significant improvements of the polymerizations were observed for the flow reactions, with products being associated with lower dispersity and shorter reaction times. Next to performing block copolymerizations in flow, this is also the first report for continuous synthesis of polymethacrylates in photoflow reactors.

While the synthesis target could be reached, the above described experiments make clear that mixed acrylate/methacrylate copolymers are not easily obtained and require more tedious procedures than might be anticipated a priori. While the described isolation of the macroinitiator is by itself not too difficult to perform (in fact, most block copolymers are obtained with intermediate isolation steps), it has significant consequences for the synthesis of sequence-controlled polymers. The advantage of photoCMP (and other techniques) is that reactions can be carried out towards high conversions and that they can be performed iteratively without the necessity of product isolations. In other words, we have herein shown that even though mixed block copolymers are accessible from successive photoCMP, no longer multiblock copolymers can be obtained, unless product isolation occurs. Also, once the last block segment was switched to an acrylate, it appears almost impossible to return to a methacrylate, hence severely limiting the sequence order in such hypothetical multiblock copolymers. Such inability could in principle be anticipated based on experience from thermal CRP, yet also the classical work-arounds such as halogen exchange do not work, and as we have shown, also a ligand exchange is required in order to reach the desired aim in any block combination. Nevertheless, also (amphiphilic) diblock copolymers consisting of acrylates and methacrylates are of high importance in self-assembly studies. The presented methodology, especially when carried out in flow, has high potential to provide such materials. A switch from methyl esters to other functional (meth)acrylates can be expected to be unproblematic, since photoCMP has been

shown before to be extremely versatile with respect to the ester side chain functionalities.

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Notes and references

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TOC figure for “Ligand Switch in Photoinduced Copper-Mediated Polymerization: Synthesis of methacrylate-acrylate block copolymers”

