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Photoinduced sequence-control via one pot living radical polymerization of acrylates

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The ability to regulate the activation and deactivation steps via an external stimulus has always been a challenge in polymer chemistry. In an ideal photo-mediated system, whereby high monomer conversion and excellent end group fidelity can be maintained, precise control over the polymer composition and microstructure would be a significant breakthrough. Herein, we report, a versatile, simple and inexpensive method that allows for the synthesis of sequence-controlled multiblock copolymers in a one pot polymerization reaction at ambient temperature. In the absence of a conventional photoredox catalyst and dye-sensitisers, low concentrations of $CuBr_2$ in synergy with Me_6-Tren mediate acrylic block copolymerization under UV irradiation ($\lambda_{max} \approx 360$ nm). Four different acrylate monomers were alternated in various combinations within the polymer composition illustrating the potential of the technique. Narrow disperse undecablock copolymers were obtained ($Đ < 1.2$) with quantitative conversion achieved between the iterative monomer additions. The effect of the chain length was investigated allowing for higher molecular weight multiblock copolymers to be obtained. This approach offers a versatile and inexpensive platform for the preparation of high-order multiblock functional materials with additional applications arising from the precise spatiotemporal "on/off" control and resolution when desired.

Introduction

A challenge in polymer science is the effective control over the molecular weight, dispersity and end group functionality, towards the synthesis of materials with ever increasing precise control over macromolecular compositions and architectures. More recently this improved level of control has been extended to discreet sequences or blocks within polymer macromolecules. The evolution of controlled living radical polymerization (CLRP) methods including reversible addition fragmentation polymerization (RAFT),[1] nitroxide mediated radical polymerization (NMP),[2] as well as atom transfer living radical polymerization (ATRP)[3-5] and single electron living radical polymerization (SET-LRP)[6-8] has significantly contributed to this field.

Recently, there has been continued effort to expand the scope of traditional living radical polymerization protocols through the development of sophisticated methods that allow for the control of the activation and deactivation equilibrium through external stimuli,[9] including photochemical,[10-13] pressure,[14, 15] and electrochemistry.[16] With respect to photochemical control, photoinitiators are employed to provide access to rapid initiation leading to fast polymerization but often with relatively poor control over molecular weight and dispersity furnishing polymers with relatively broad molecular weight distributions.[17] Independently, Hawker,[18] Yagci,[19-23] and Matyjaszewski[24] have contributed significantly to this field demonstrating elegant, novel and sophisticated systems to maintain good control over the molecular weight distributions while achieving parallel spatiotemporal control upon demand.[25, 26]

An ambitious target is to develop synthetic procedures capable of replicating, or approaching, the precision over monomer sequence exhibited by natural polymers such as nucleic acids, carbohydrates, peptides and proteins. These remarkable and complicated structures which are capable of storing an abundance of information are efficiently constructed by cellular organelles such as the nucleus and ribosome. The ability to mimic these precise structures in synthetic polymers would be beneficial in many applications including nanomedicine and nanotechnology whereby a high level of monomer sequence control confers the potential for molecular targeting, recognition and biocatalysis, as well as molecular information storage. However, as synthetic chemists we are

currently far away from complementing the sophistication and complexity of the cell with the macromolecular 'tool kit' and as such comparable synthetic analogues have not yet been realized. Nevertheless, over the last 30-40 years notable progress has been made to harness the potential of step-growth and chain-growth polymerization methods in order to gain synthetic control over the polymer primary sequence.[27-32] Chain-growth polymerization has seen a number of approaches explored including single monomer addition,[33] tandem monomer addition and modification,[34, 35] kinetic control,[36-39] solution[40-46] and segregated templating.[47]

The implementation of single monomer addition via radical chain-growth polymerization techniques is challenging given the reactive nature of the radical and potential for radical-radical bimolecular reactions. This has stimulated the development of synthetic methods focusing on controlling the sequence of multiple discreet regions within the overall macromolecular structure. Whilst this sacrifices ability to obtain the control attained by nature it allows for functional domains which are often sufficient for specific applications. Whittaker and co-workers exploited the degree of control and end-group retention available from Cu(0)-mediated living radical polymerization to report the first example of a one-pot synthesis of multiblock copolymers via iterative monomer addition.[48-50] Multiblock (up to decablock) copolymers containing discreet block lengths (2-10) in linear and star architectures were reported. However, a limitation of this exemplary work was recognized during the synthesis of linear decablock copolymers, whereby molecular weight distributions were found to gradually increase, indicative of the accumulation of terminated chains. The same technique was employed to synthesize a number of multiblock glycopolymers with a good degree of monomer sequence control in various compositions containing mannose, glucose, and fucose moieties in the presence and absence of spacer comonomers.[51, 52] Higher molecular weight multiblocks with narrower dispersities have also been attained but the yield of the intermediates blocks was often < 95%, compromising the integrity of the multiblock structures.[53]

More recently, Perrier and co-workers reported the synthesis of multi-block copolymers comprising acrylamide monomers using an optimized RAFT approach, achieving up to an icosa-block (20 block) copolymer in both organic (dioxane) and aqueous media.[54-56] However, the high temperature (65-70 °C) required for the polymerization reaction potentially limits the possibility of simultaneous biological modifications. This has been addressed by the use of the *fac*-[Ir(ppy)$_3$] photoredox catalyst, previously employed by Hawker *et al.* to induced photo-mediated ATRP of methacrylates.[18] Boyer *et al.* have reported RAFT polymerization of activated and unactivated vinyl monomers at ambient temperature, highlighting the utility of the photoredox catalysis via recycling in iterative chain extension experiments.[57]

Herein, we report the Cu-mediated photopolymerization of acrylates to prepare multi-block copolymers, up to a dodecablock (12 blocks), containing repeat units comprised of four alternating monomer sequences whilst maintaining narrow dispersities ($Đ$ < 1.2). In the absence of a photoredox catalyst and dye-sensitisers, careful optimization of the polymerization conditions provides access to a variety of single-block chain lengths (DP_n = 3, 10, 25 and 100) all of which present narrow dispersities at high conversions (> 99%) upon iterative monomer addition without the need for rigorous degassing procedures. The monomer sequence can also be manipulated,

showing little ill effects in either the polymerization rate or the final dispersity. Importantly, under UV irradiation (λ_{max} = 360 nm) in a jacketed cell, with a steady flow of cold water to maintain a constant, sub-ambient internal temperature, the polymerization can proceed with equal efficiency, enabling a natural transition to biological applications. Finally, this photo-mediated approach confers the potential of spatiotemporal control when desired, simply by switching "on" and "off" the system upon demand.

Results and discussion

Block copolymer synthesis; initial attempts. Recently, we demonstrated that excellent end group fidelity could be attained during the photo-mediated living radical polymerization of acrylates in the presence of low concentrations of CuBr$_2$ and aliphatic tertiary amines (Me$_6$-Tren).[58, 59] The remarkable degree of control obtained during both homo and block copolymerizations motivated further investigation into the scope of the system in pursuit of acrylic multiblock copolymers, with good sequential control over discreet block compositions, synthesised via a photo-mediated approach at ambient temperature in a one-pot process without intermediate purification steps and in the absence of potentially costly additives such as photo-redox catalysts, initiators and dye sensitisers (Figure S1).
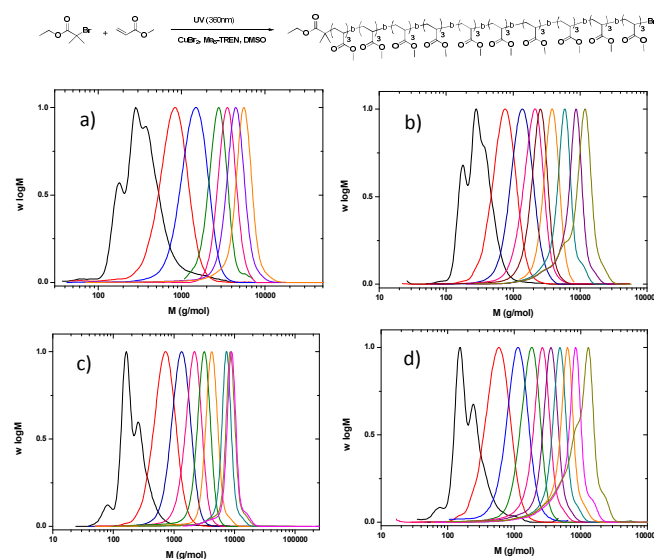

Figure 1: Molecular weight distributions for successive additions during the synthesis of multiblock homopolymers (DP_n = 3 per block) in DMSO at ambient temperature with a) MA and DMSO (2 : 1 v/v); b) neat MA upon every 2nd iteration; c) as (a) with CuBr$_2$/Me$_6$-Tren ([0.02] : [0.12] w.r.t. [I]$_0$) every 4th iteration; d) as (a) with CuBr$_2$/Me$_6$-Tren ([0.02] : [0.12] w.r.t. [I]$_0$) every 2nd iteration.

Initially, the synthesis of a model decablock homopolymer poly(MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA-*b*-MA) was attempted via sequential addition of individual aliquots of MA employing an initial feed ratio of [I]$_0$: [CuBr$_2$]$_0$: [Me$_6$-Tren]$_0$ = [1] : [0.02] : [0.12] in DMSO 50% (v/v). Each block was designed to have DP_n = 3 in order to facilitate electrospray mass-spectrometry (ESI-MS) analysis and demonstrate the versatility as well as the high efficiency of this technique. Under the aforementioned conditions, the first PMA

block was obtained at full conversion within 10 hrs with a dispersity = 1.25 (Figure 1a, Table 1 entry 1). This relatively broad dispersity was attributed to the low molecular weight of the polymer. The absence of chain termination events during homopolymerization should maximize the end group fidelity of the final polymer and facilitate efficient *in situ* chain extension. Indeed, upon addition of the second aliquot of MA in DMSO (2 : 1 v/v), high conversion was attained within 12 hrs (>99% conversion, Table S1), revealing a symmetrical SEC chromatogram without any visible trace of low or high molecular weight shoulders which would indicate potential termination events. This process was repeated several times with SEC analysis of the molecular weight distributions confirming the successful chain extensions as manifested by clear shifts to higher molecular weights after each addition (Figure 1a). However, the time required to achieve quantitative conversion increased upon each monomer addition with the 7th block achieving 96% yield (Figure S2) only after a total time of 48 hrs. Although narrow dispersities ($Đ$ < 1.18) were maintained following addition of an eighth aliquot of MA, little if any, monomer consumption was observed over the course of 48 hrs indicating the rate of polymerization had approached zero.

Optimization studies; effect of varying the [MA], [CuBr$_2$] and [Me$_6$-Tren]. In an attempt to optimize the reaction conditions (Table 1), it was speculated that an increase in the polymerization rate could circumvent the accumulated termination enabling synthesis of higher order multiblock copolymers.

Table 1: Summary of the investigation towards optimizing the polymerization

Entry	Blocks #	Conv.^{a}	$M_{n.th}$ (g.mol^{-1})	$M_{n.SEC}^{b}$ (g.mol^{-1})	$Đ$
1^c	7	96%	2000	4700	1.18
2^d	9	95%	2500	8000	1.35
3^e	8	96%	2500	8400	1.09
4^f	10	90%	2800	6200	1.59
5^g	11	99%	3300	7000	1.19

^{a} Final conversion by ^{1}H NMR; ^{b} CHCl$_3$; the following was added upon each iteration ^{c} MA and DMSO (2 : 1 v/v); ^{d} neat MA upon every 2nd iteration; ^{e} as (c) with CuBr$_2$/Me$_6$-Tren ([0.02] : [0.12] w.r.t. [I]$_0$) every 4th iteration; ^{f} as (c) with CuBr$_2$/Me$_6$-Tren ([0.02] : [0.12] w.r.t. [I]$_0$) every 2nd iteration; ^{g} as (c) with CuBr$_2$/Me$_6$-Tren ([0.02] : [0.12] w.r.t. [I]$_0$) every 3rd iteration.

Accordingly, the polymerization concentration was increased by injecting monomer in the absence of additional solvent upon every 2nd iterative addition (Table 1 entry 2). Initially, a faster reaction rate was observed, accompanied by an observable viscosity increase . Following addition of the 8th aliquot of MA agitation ceased as stirring was completely retarded as a result of the increase in the solution viscosity. This was translated to a loss of control, as indicated by the broader molecular weight distributions ($Đ$ > 1.3, Figure 1b) as observed by SEC. Nevertheless, very high conversions were achieved in every cycle and the preceding heptablock copolymer presented a narrow final dispersity ($Đ$ = 1.15) (Figure S3, Table S2).

In an attempt to further increase the reaction speed, a fresh solution of CuBr$_2$/Me$_6$-Tren in DMSO ([0.02] : [0.12] with respect to [I]$_0$) was fed into the polymerization mixture,

together with additional monomer once every 4 monomer additions. This allowed for an octablock copolymer to be obtained with narrow molecular weight distributions ($Đ$ < 1.10, Figure 1c) at very high conversions (Figure S4). Further chain extension was found to be significantly slower and the polymerization eventually stopped with no recognizable increase in molecular weight observed according to SEC. Encouraged by these findings, we subsequently decided to feed the polymerization with additional CuBr$_2$ and Me$_6$-Tren once every 3 monomer additions (Figure 2). High monomer conversions were attained at each iteration as confirmed by ^{1}H NMR (Figure 2b) and a well-defined pseudo-undecablock homopolymer was obtained with low dispersity ($Đ$ ≤ 1.20, Figure 2a). High resolution electrospray ionization mass spectroscopy (HR-ESI-MS) analysis was employed to verify the end group fidelity of the intermediate block homopolymers. As expected by the successful chain extensions, a gradual increase the molecular weight was observed from block 1 to block 5 with the spectrum presenting two main polymer peak distributions (Figure 2c). The first polymer peak distribution corresponds to PMA initiated by initiator (EBiB) and terminated by a bromine atom. The second main peak distribution also reveals initiation from the EBiB fragment, however, in this experiment chlorine is at the terminus of the polymer chains as indicated by the characteristic isotopic pattern (Figure S5c). This is attributed to halogen exchange[60] due to the dilution of the samples with deuterated chloroform (^{1}H NMR analysis) or from the chloroform eluent (SEC analysis) prior to performance of HR-ESI-MS analysis.
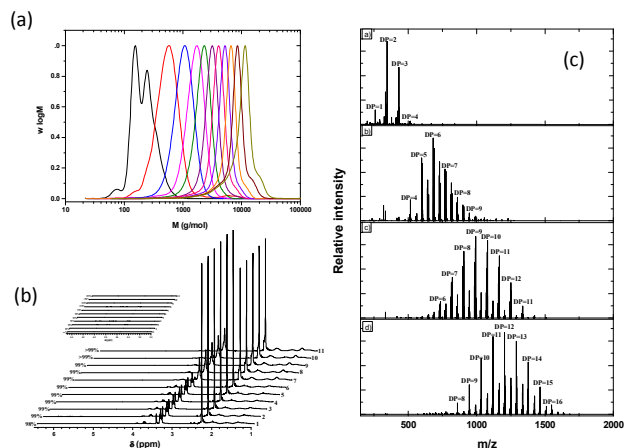

Figure 2: a) Molecular weight distributions by CHCl$_3$ SEC, b) ^{1}H NMR in CDCl$_3$ c) HR-ESI-MS for successive cycles during the synthesis of multiblock homopolymers (DP$_n$ = 3 per block) in DMSO at ambient temperature.

Further chain extensions resulted in broader molecular weight distributions. Nevertheless, a dodecablock homopolymer could be achieved with an impressive final dispersity ($Đ$ = 1.30, Table S4) at full monomer conversion (Figure S5a,b). Increasing the frequency of catalyst feed to every other monomer addition resulted in significant loss of control for the final decapolymer ($Đ$ ~ 1.6, Figure S6, Table S5), characterized by significant low molecular weight tailing in SEC (Figure 1d). This is in agreement with previously reported results that indicated that even small changes in the
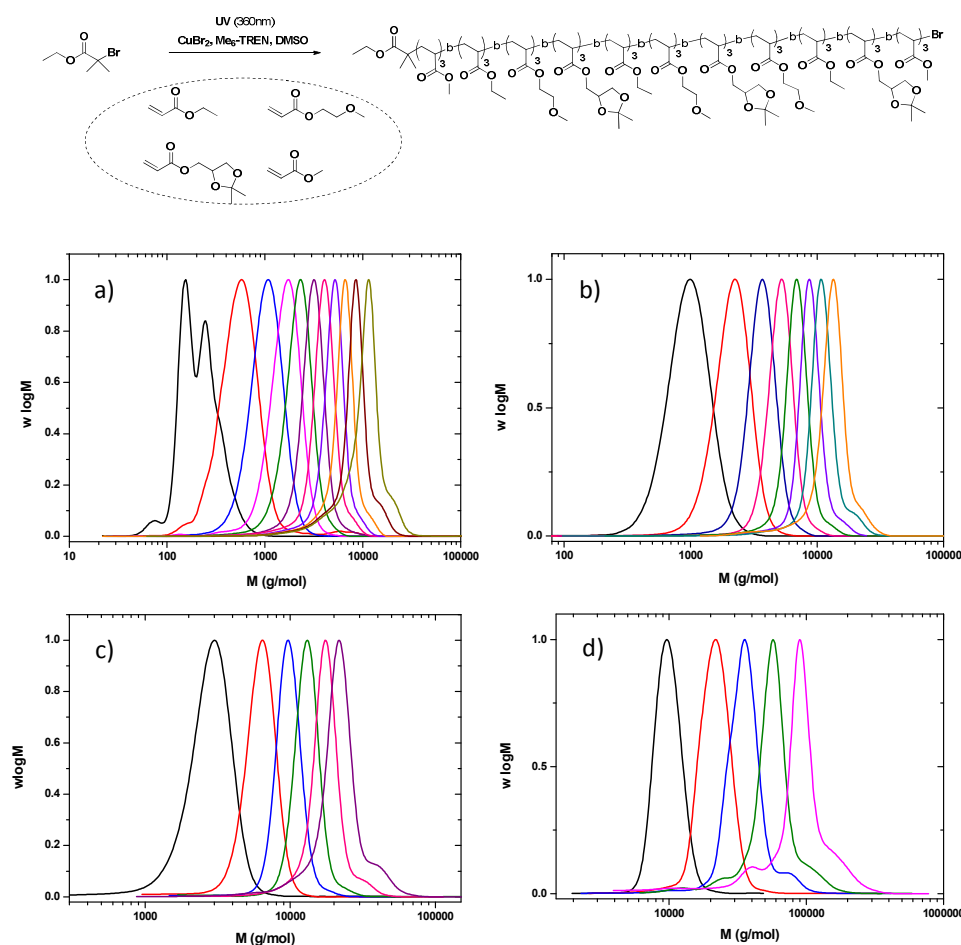
Figure 3: Molecular weight distributions for successive cycles during the synthesis of a) an undecablock copolymer (DP$_n$ = 3 per block); b) an octablock copolymer (DP$_n$ = 10 per block); c) a hexablock block copolymer (DP$_n$ = 25 per block); d) a pentablock copolymer (DP$_n$ = 100 per block) in DMSO at ambient temperature. Monomers A,B,C,D were alternated during the synthesis as illustrated and summarized in the ESI.
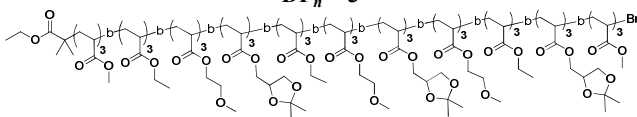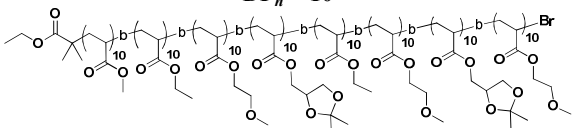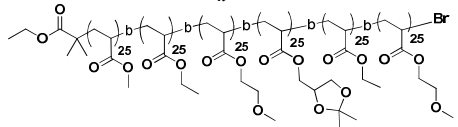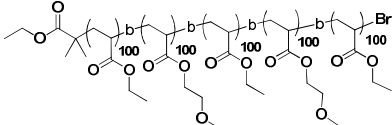
ligand concentration can dramatically affect the end group fidelity of the polymer chains due to chain transfer to the ligand and via quarternization reactions.[61] Control experiments, in which CuBr$_2$ (Figure S7) or Me$_6$-Tren (Figure S8) were added were also conducted, resulting in slow polymerization rates and significant termination events respectively. Thus, the addition of both CuBr$_2$ and Me$_6$-Tren is required in order to maintain high end group fidelity and pushing the polymerization further. In our original publication introducing photo-mediated polymerization in the presence of CuBr$_2$ and Me$_6$-Tren we proposed that the presence of free ligand was required for initiation and subsequent reactivation of dormant chains by the photochemical process. This new data implies that the excess ligand, present in the initial feed ratio, is gradually consumed during the polymerization process and an excess relative to copper(II) must be present to maintain activity and acceptable reaction rates.

An increase in the polymerization rate could alternatively be achieved by reducing the concentration of Cu(Me$_6$-Tren)Br$_2$ in the initial feed ratio ([Cu(Me$_6$-Tren)Br$_2$] = [CuBr$_2$] = [0.02]). Thus, the initial feed ratio was modified to [I] : [CuBr$_2$] : [Me$_6$-Tren] = [1] : [0.01] : [0.12] and considering the best results obtained thus far were achieved by feeding additional CuBr$_2$ and Me$_6$-Tren upon every three iterations of monomer addition, an identical approach was adopted. Although faster polymerization kinetics were observed, the dispersities of the polymers obtained were noticeable higher as compared with those when higher amounts of copper were employed, indicating that a higher ratio of deactivator is essential for achieving optimum control over the molecular weight distributions (Figure S9).

Sequence-controlled multiblock copolymers. Having optimized the reaction conditions using methyl acrylate (MA) we were interested in applying them to construct more complex multiblock compositions. Thus, a family of four monomers was employed including alkyl acrylates; MA and ethyl acrylate (EA), a short PEG containing acrylate; ethylene glycol methyl ether acrylate (EGA) and a protected functional monomer; solketal acrylate (SA). An initial feed ratio of [M]$_0$: [I]$_0$: [CuBr$_2$]$_0$: [Me$_6$-Tren]$_0$ = [3] : [1] : [0.02] : [0.12] was

employed with iterative additions ($DP_n = 3$) consisting of [M]/[DMSO] = 2 : 1 v/v with an additional feed of [CuBr] :

Table 2: Summary of the multiblock copolymers synthesized in this study.

Multiblock copolymer	Conversion (%)*	$M_{n,th}$ (g.mol^{-1})	$M_{n,SEC}$ (g.mol^{-1})	Đ
$DP_n = 3$	99	4500	7000	1.19
$DP_n = 10$	99	11200	12400	1.10
$DP_n = 25$	99	18200	19900	1.15
$DP_n = 100$	98	56200	80000	1.21

* ^{1}H NMR, CDCl$_3$. Overall monomer conversion for all additions. Conversions for each iteration are tabulated in the ESI.

[Me$_6$-Tren] = [0.02] : [0.12], with respect to [I]$_0$, every three iterations. Despite the inclusion of different monomers, the final dispersity of the multiblock copolymer was not compromised, presenting narrow molecular weight distributions for an undecablock copolymer (Đ < 1.20, Figure 3a), combined with near quantitative conversions (Figure S10b) during each iterative monomer addition. Sequence control was installed by alternating the order of monomer addition during the polymerization reaction. Pleasingly, each of the acrylates was found to support propagation, enabling the desired manipulation of the monomer sequence to yield a well-defined multiblock copolymer poly(MA$_3$-b-EA$_3$-b-EGA$_3$-b-SA$_3$-b-MA$_3$-b-EGA$_3$-b-EA$_3$-b-SA$_3$-b-EA$_3$-b-MA$_3$-b-SA$_3$). Attempts to extend the sequence beyond the undecablock resulted in an increase in dispersity (Đ = 1.39, Figure S10a, Table S9). Nevertheless, this represents an excellent example of sequence design within a multiblock copolymer composition, illustrating the robustness of the system and hinting at the potential for mass information storage in the guise of functional monomer side chains.

Increasing block chain length; higher molecular weight multiblock copolymers. We were interested to investigate if this photo-mediated process could support the multiblock copolymerization of higher molecular weight block lengths (Scheme S3). Thus, a multiblock copolymer comprised of 10 repeat units per block was attempted. Under the previously optimized polymerization conditions ([I]$_0$: [CuBr$_2$]$_0$: [Me$_6$-Tren]$_0$ = [1] : [0.02] : [0.12]), including an additional

CuBr$_2$/Me$_6$-Tren feed every three iterations, a well-defined heptablock copolymer with a target block length of $DP_n = 10$ was attained with a narrow final dispersity (Đ ~ 1.15, Figure S11) while further chain extension resulted in loss of control (Đ ~ 1.35, Table S10). Increasing the frequency of the CuBr$_2$/Me$_6$-Tren feed to every two monomer additions, resulted in an improvement in the control leading to the octablock copolymer (Đ = 1.10, Figure 3b, Figure S12). Further attempts to reduce the dispersities or extend the 'livingness' of the system beyond an octablock were unsuccessful. Increasing the catalyst feed frequency to every addition (Figure S13) and reducing the [CuBr$_2$] feed concentration (Figure S14) resulted in significantly higher dispersities (Đ > 1.3) in the latter stages of the polymerizations.

Higher molecular weight multiblock copolymers are of interest due to the potential applications that arise from the combination of monomers with different physicochemical properties, confined within block sequences. These systems can undergo self-assembly and phase separation on the micro- and nanometer scale forming higher ordered structures.[62-64] Thus we were inspired to investigate the potential for higher molecular weight multiblock copolymer synthesis under photo-mediated conditions. When each block was comprised of 25 repeat units ($DP_n = 25$), an initial feed ratio of [M]$_0$: [I]$_0$: [CuBr$_2$]$_0$: [Me$_6$-Tren]$_0$ = [25] : [1] : [0.02] : [012] with additional CuBr$_2$ and Me$_6$-Tren fed into the polymerization every other iteration furnished a hexablock copolymer with low dispersity (Đ = 1.15) and high conversions (>97%) maintained throughout (Figure 3c, Figure S15).

Identical conditions were subsequently applied for a multiblock copolymerization with block chain lengths of $DP_n = 100$ ($[M]_0 : [I]_0 : [CuBr_2]_0 : [Me_6\text{-}Tren]_0 = [100] : [1] : [0.02] : [012]$). Initial homopolymerization of MA presented a low dispersity and high conversion (97 %, $Đ = 1.05$). Four subsequent additions of monomer again resulted in high conversions (> 97%), presenting a relatively low final dispersity ($Đ = 1.21$, Figure 3d) of the corresponding pentablock. However, upon addition of a 6th and final aliquot of monomer, conversion was limited 84% conversion and an increase in dispersity was observed ($Đ = 1.33$, Figure S16). Nevertheless, a well-controlled hexablock copolymer was attained with a relatively narrow final dispersity and molecular weight of ≈ 100 kDa.

Considering propagation occurs via homolytic bond cleavage, termination, either due to radical coupling events or adventitious chain transfer reactions, occurs at each iteration and has a deleterious effect on the end group fidelity of polymer chains. This is best illustrated by plotting the evolution of molecular weight with each addition of monomer (Figure S17-S20). Ideally the M_n should increase linearly with little deviation from $M_{n,th}$ which is indeed the case with $DP_n = 10/25$ sequential monomer feeds (Figure S18-S19). The high degree of end group retention is confirmed by close agreement between $M_{n,th}$ and $M_{n,SEC}$ for the final polymers (Table 2). The deviation in final molecular weight data observed at higher and lower DP_n monomer feeds can be better understood with examination of the related evolution of molecular weight. At lower DP_n ($DP_n = 3$, Figure S17), good agreement between $M_{n,th}$ and $M_{n,SEC}$ is maintained up to a heptablock copolymer, comparable to the data obtained for $DP_n = 10/25$. Deviations in the molecular weight data are shown to occur after this point, probably as a consequence of increased reaction times, resulting in increased termination and adventitious side reactions. Conversely, when targeting $DP_n = 100$, deviations from linearity are evident after only 2 chain extension events (Figure S20). Loss of end group fidelity in this case has a much more drastic effect on M_n considering that there are fewer chains from the outset, and a relatively high concentration of monomer is added with each iteration. The sensitivity of the higher molecular weight system is accentuated in blocks 4, 5 and 6 (Figure S20) and translates to a significant deviation in $M_{n,th}$ and $M_{n,SEC}$ of the final polymer (Table 2). Nevertheless, such high molecular weight multiblock copolymers have not yet been reported in the literature and we believe that our approach paves the way for the design and synthesis of a new class of functional polymeric materials.

Conclusions

In summary, we report the synthesis of high-order acrylic multiblock copolymers comprising of four different repeat units which have been alternated in various combinations in order to illustrate the versatility and the robustness of the technique. High conversions (>97%) were obtained throughout the polymerizations while the possibility to perform the reactions at ambient temperature expands the scope of the multiblock copolymers to biological applications where milder reaction conditions are frequently required. Narrow dispersity multiblock copolymers were obtained (typically $Đ < 1.20$) while the effect of the chain length was also investigated. Under carefully optimized conditions higher molecular weight copolymers could also be obtained ($M_{n,SEC} \approx 100$ kDa). Importantly, this approach utilizes an inexpensive catalyst ($CuBr_2$) in low concentration in conjunction with tertiary amines and can be carried out under very low intensity/power light. The amines are consumed by a photo reduction in the polymerisation requiring replenishing through a feed process to maintain the polymerisation rates. The end group fidelity and very low rates of termination are quite remarkable and allow for multi block polymers where the DP of each block can be quite low or quite high resulting in a very versatile polymerisation process.

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Notes and references

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