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Well-defined amine-reactive polymethacrylates through organocatalyzed controlled radical polymerization†

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A novel alkyl iodide bearing an azlactone group was synthesized and used as a reversible complex-mediated polymerization (RCMP) initiator for the organocatalyzed RCMP of methyl methacrylate (MMA) and poly(ethylene glycol) methyl ether methacrylate (mPEGMA). The efficiency of the new initiator was studied under different processes including thermal and photochemical activation. Well-defined α -azlactone-functionalized polymethacrylates ($D < 1.30$) with an absence of "free" toxic transition metals were obtained for the first-time. The amine-scavenging ability of these functional polymers was demonstrated by using benzylamine.

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Introduction

Over the past decade, the azlactone functionality has become one of the most useful functional groups for organic chemistry and (bio)material synthesis.^{1–4} Due to its high reactivity towards amines, azlactone reacts readily with amine containing molecules without the need for a catalyst. Furthermore, the absence of side-product formation is a considerable advantage of the "azlactone-amine" reaction.⁵ Thanks to its high reactivity towards amines the azlactone group has been incorporated into polymer chains to obtain azlactone-based materials. These azlactone functionalized polymers were further used to immobilize amine-containing (bio)molecules such as peptide and protein for affinity chromatography,⁶ drug delivery⁷ and enzyme immobilization.⁸ Moreover, azlactone-containing polymers have also been used for preparing core-shell nanoparticles⁹ and nanostructured thin-films.¹⁰ Azlactone-functionalized polymers can be obtained either by introducing azlactone groups along the polymer backbone or by functionalization of the polymer chain-end. While polymers bearing multi-azlactone groups have been widely reported, there are few studies on the synthesis of azlactone-terminated polymers. In an early study, Fontaine and coworkers described post-polymerization modification (PPM) as a powerful method

to obtain ω -azlactone-functionalized polymers using "click" reactions of thiol or alkyne-terminated polymers with azlactone molecules bearing vinyl or azido ($-N_3$) groups, respectively.^{11,12} In these studies, the ω -azlactone-terminated polymers were successfully coupled to lysozyme to obtain the lysozyme-polymer conjugated product. However, the multi-step synthesis is a major drawback of chain-end PPM approach. Alternatively, the combination of reversible-deactivation radical polymerization¹³ (RDRP) with an azlactone-functionalized molecule as initiator or transfer agent has been shown to be a suitable method to access azlactone-terminated polymers.¹ This approach is not only a directly synthetic route to obtain α -azlactone functionalized polymers with a well-defined structure, but also allows a quantitative azlactone functionalization unlike PPM. For example, Lewandowski *et al.*¹⁴ have reported the atom transfer radical polymerization (ATRP) of methyl methacrylate (MMA) using a bromo-azlactone molecule as an initiator and copper(i) chloride/bipyridine as a catalytic system to afford an α -azlactone functionalized poly(methyl methacrylate) (PMMA). However, the residual copper catalyst raises the question of the toxicity of ATRP-based polymers for biomedical applications.¹⁵ Similarly, different α -azlactone-terminated (co)polymers have also been obtained using an azlactone-functionalized alkoxyamine as a nitroxide-mediated polymerization (NMP) initiator, whereas the synthesis of α -azlactone-terminated polymethacrylates by NMP has not been reported.¹⁶ Additionally, the NMP approach suffers from the tedious synthesis of the starting nitroxide radical as well as potential residual traces of the copper used as a catalyst during the synthesis of the alkoxyamine initiator. To avoid the use of a copper catalyst, Ho *et al.*¹⁷ reported the synthesis of a series of α -azlactone-functionalized polystyrenes, poly(ethyl

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acrylate)s and poly(*N*-isopropyl acrylamide)s by reversible addition-fragmentation chain transfer (RAFT) polymerization using an azlactone-trithiocarbonate as a transfer agent. Nevertheless, the ability of azlactone-trithiocarbonate to control the RAFT polymerization of methacrylates remains challenging. Therefore, the copper-free synthesis of azlactone-terminated polymethacrylates has become a major challenge.

In this context, the development of metal-free RDRP techniques offered new opportunities to synthesize well-defined polymers. Among them, the reversible complexation-mediated polymerization (RCMP) has emerged as a powerful organocatalyzed technique for synthesizing polymethacrylates with a well-defined structure.^{18–21} RCMP is known as a simple and versatile process that can be performed under thermal or photo-irradiation without the addition of a radical initiator. In this context, this contribution focuses on the use of RCMP to synthesize well-defined α -azlactone-terminated polymethacrylates. In this study, we describe the synthesis of a new azlactone-functionalized iodide RCMP initiator to prepare well-defined α -azlactone terminated polymethacrylates. The efficiency of this new initiator in polymerizing methacrylates by RCMP was investigated for the first time, and then the reactivity of the resulting azlactone-terminated polymers towards amines was then demonstrated by a coupling reaction with benzylamine.

Experimental

Materials and characterization

See ESI.†

Synthesis of 2-(1-iodoethyl)-4,4-dimethyloxazol-5(4H)-one (iodo-azlactone, I-Azl). In a round bottom flask equipped with a magnetic stirrer and a dropping funnel, sodium iodide (NaI, 3.00 g, 20.0×10^{-3} mol) and acetone (15.0 mL) were added and stirred at room temperature under argon. Then, a solution of 2-(1-bromoethyl)-4,4-dimethyloxazol-5(4H)-one¹⁷ (bromo-azlactone, 2.00 g, 9.09×10^{-3} mol) in acetone (5.0 mL) was added dropwise into the reaction mixture at room temperature, with a white solid forming during the addition. The reaction mixture was then stirred continuously at room temperature for 10 min and then at 40 °C for 2 h. The reaction mixture was filtered to remove the white salt and the filtrate was subsequently concentrated under reduced pressure at room temperature. The crude product was dissolved in diethyl ether, filtered and concentrated under vacuum to yield the final product as an orange oil. Yield: 75% (1.83 g). The product was stored under argon at –20 °C avoiding any contact with light and water. HR-MS analysis ($C_7H_{10}NO_2I$): detected ion $[M + H]^+$, calculated value m/z_{calc} = 267.9829 Da and experimental value m/z_{exp} = 267.9828 Da. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 4.73 (q, J = 7.1 Hz, I-CH(CH₃)-), 2.08 (d, J = 7.1 Hz, I-CH(CH₃)-), 1.41 and 1.40 (s, –C(CH₃)₂) (Fig. 1A). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 180.23 (C=O)azlactone, 164.10 (C=N)azlactone, 66.18 (C(CH₃)₂), 23.89 and 23.70 (C(CH₃)₂), 23.18 (ICH(CH₃)-), 8.17 (ICH(CH₃)-) (see ESI Fig. S1†). FT-IR (cm^{–1}): 1824 ($\nu_{(C=O)}$ azlactone), 1657 ($\nu_{(C=N)}$ azlactone) (see ESI Fig. S2†).

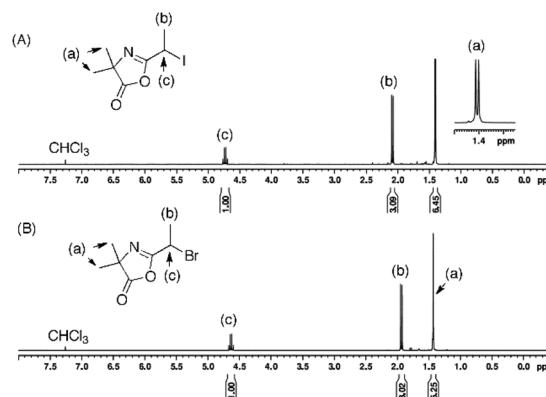


Fig. 1 ^1H NMR (300 MHz) spectra of (A) I-Azl and (B) bromo-azlactone in CDCl_3 .

Typical thermal procedure for the reversible-mediated complex polymerization (RCMP)

RCMP of methyl methacrylate (MMA). MMA (3.70 g, 0.037 mol), I-Azl (0.10 g, 3.75×10^{-4} mol), and tetrabutylammonium iodide (TBAI, 0.070 g, 1.90×10^{-4} mol) were sequentially added into a headspace vial equipped with a magnetic stir bar. The vial was then sealed using a headspace cap. The resulting mixture was deoxygenated by bubbling argon for 30 min under cooling in an iced bath. The mixture was then continuously stirred under argon for 10 min to reach room temperature. The vial was immersed in an oil bath thermostated at 80 °C to allow the polymerization to occur (initial reaction time, $t = 0$). Samples were removed periodically using a deoxygenated syringe to perform size exclusion chromatography (SEC) analysis and to monitor monomer conversion by ^1H NMR spectroscopy. After 120 min, the polymerization was quenched by rapid cooling and exposure of the polymerization solution to air. The reaction mixture was afterwards dissolved in dichloromethane (DCM) and precipitated in methanol. The final polymer was filtered out and dried under vacuum at room temperature to obtain a white solid with $D_{\text{NMR}} = 81$, $M_{\text{n,SEC}} = 9460 \text{ g mol}^{-1}$, $D = 1.19$. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 3.77 (–C(CH₃)₂)COOCH₃, 3.58 (–COOCH₃), 2.06–1.65 (–CH₂–C(CH₃)₂–), 1.33–0.72 (–CH₂–C(CH₃)₂– and –CH₃azlactone) (Fig. 3). FT-IR (cm^{–1}): 1820 ($\nu_{(C=O)}$ azlactone), 1725 ($\nu_{(C=O)}$ ester) (see ESI Fig. S3†).

RCMP of mPEGMA. Polymerization of mPEGMA was conducted according to the similar previous protocol for MMA at 80 °C using I-Azl (0.020 g, 7.49×10^{-5} mol), mPEGMA ($M_{\text{n}} = 475 \text{ g mol}^{-1}$, 3.55 g, 7.47×10^{-3} mol) and TBAI (33.4 mg, 9.05×10^{-5} mol). After 180 min, the mPEGMA conversion was at 7% with $M_{\text{n,SEC}} = 7440 \text{ g mol}^{-1}$ and $D = 1.09$.

Typical procedure for the photo-polymerization of mPEGMA by using I-Azl initiator with UV lamp operating at 365 nm

Using tri(*n*-butylamine) as a catalyst. I-Azl (0.020 g, 7.49×10^{-5} mol), mPEGMA ($M_{\text{n}} = 475 \text{ g mol}^{-1}$, 1.42 g, 2.99×10^{-3} mol) and tri(*n*-butyl)amine (13.14 mg, 7.10×10^{-5} mol) were



sequentially added into a headspace vial equipped with a magnetic stir bar. The vial was then sealed using a headspace cap. The mixture was then deoxygenated by bubbling argon for 30 min at room temperature. The deoxygenated vial was then irradiated inside the operating UV nail box ($\lambda = 365$ nm, 36 W) to allow the polymerization to occur (initial reaction time, $t = 0$). During polymerization, the temperature of the nail box was kept below 40 °C using computer fans. Samples were removed periodically using a deoxygenated syringe to perform SEC analysis and to monitor monomer conversion by ^1H NMR spectroscopy. After 240 min, the polymerization was quenched by rapid cooling and exposure of the reaction mixture to air. The α -azlactone-functionalized poly(poly(ethylene glycol) methyl ether methacrylate) (poly(mPEGMA)) was precipitated in diethyl ether and dried under vacuum at room temperature to obtain a yellow gummy paste with $M_{n,\text{SEC}} = 18\,410\text{ g mol}^{-1}$, $D = 1.18$ (see ESI Table S1,† run 8). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.07 ($-\text{COOCH}_2\text{CH}_2\text{O}-$), 3.76–3.57 ($-\text{CH}_2\text{CH}_2\text{O}-$ of PEG unit), 3.37 ($-\text{OCH}_3$), 2.05–1.47 ($-\text{CH}_2\text{C}(\text{CH}_3)-$), 1.44–0.74 ($-\text{CH}_2\text{C}(\text{CH}_3)-$ and $-\text{CH}_3$ azlactone) (Fig. 6A). FT-IR (cm^{-1}): 1820 ($\nu_{\text{C=O}}$ azlactone), 1725 ($\nu_{\text{C=O}}$ ester) (see ESI Fig. S4A†).

Using TBAI as a catalyst. Photo-polymerization was carried out according to the previous procedure using I-Azl (0.020 g, 7.49×10^{-5} mol), mPEGMA ($M_n = 475\text{ g mol}^{-1}$, 1.2 g, 2.53×10^{-3} mol) and TBAI (11.3 mg, 3.06×10^{-5} mol) (see ESI Table S2 and Fig. S4B†).

Coupling reaction of benzylamine with α -azlactone-functionalized polymethacrylates

α -Azlactone-functionalized PMMA ($M_{n,\text{SEC}} = 9180\text{ g mol}^{-1}$, $D = 1.22$, 0.3 g, 3.27×10^{-5} mol) or poly(mPEGMA) ($M_{n,\text{SEC}} = 20\,770\text{ g mol}^{-1}$, $D = 1.20$, 0.3 g, 1.44×10^{-5} mol) (see ESI Table S3†) and tetrahydrofuran (THF, 2.00 mL) were charged into a glass scintillation flask equipped with a magnetic stir bar. Then, a solution of benzylamine (0.0243 g, 2.27×10^{-4} mol and 0.010 g, 9.35×10^{-5} mol for α -azlactone-functionalized PMMA and poly(mPEGMA), respectively) in THF (1.0 mL) was added into the reaction mixture and the resulting solution was stirred at 40 °C for 24 h under argon. The solution was then concentrated under rotary evaporator and precipitated in diethyl ether. The final polymer was filtered out and dried under vacuum at room temperature. SEC analysis: after coupling reaction of benzylamine with (1) α -azlactone-functionalized PMMA: $M_{n,\text{SEC}} = 11\,000\text{ g mol}^{-1}$, $D = 1.13$ and (2) α -azlactone-functionalized poly(mPEGMA): $M_{n,\text{SEC}} = 20\,500\text{ g mol}^{-1}$, $D = 1.18$.

Results and discussion

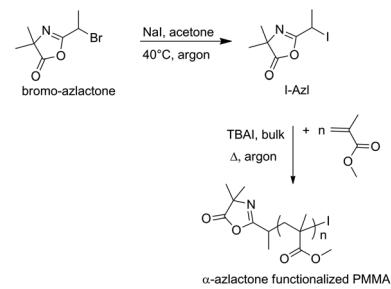
Organocatalyzed RCMP synthesis of well-defined α -azlactone-functionalized PMMA

The use of azlactone derivatives as an initiator or transfer agent in RDRP process has been rarely reported in the literature. We are only aware of three studies using azlactone derivatives as an ATRP initiator,¹⁴ NMP alkoxymine¹⁶ or RAFT

agent.¹⁷ Therefore, in this study a new azlactone-functionalized iodide was proposed and used as an initiator for the reversible complex-mediated polymerization (RCMP) of two methacrylate monomers. The 2-(1-iodoethyl)-4,4-dimethyloxazol-5(4H)-one (I-Azl) initiator was synthesized by the reaction between 2-(1-bromoethyl)-4,4-dimethyloxazol-5(4H)-one (bromo-azlactone) and sodium iodide (NaI) in acetone at 40 °C (Scheme 1).

The successful bromine-iodine nucleophilic displacement reaction was confirmed by proton (^1H) nuclear magnetic resonance (NMR) spectroscopy, with the signal $-\text{CH}(\text{CH}_3)\text{X}$ (labeled (c) in Fig. 1) shifting from 4.63 ppm to 4.73 ppm when bromine (X = Br) is replaced by a iodine (X = I) (Fig. 1A). I-Azl is expected to be a useful RCMP initiator for the synthesis of α -azlactone-functionalized polymers due to its secondary alkyl iodide structure adjacent to the strongly electron-withdrawing azlactone cycle acting as a stabilizing group.

Organic catalysts play an important role in the control and kinetic of RCMP as well as in the synthesis of high molar mass polymers.^{18–20} Due to its high reactivity, tetrabutylammonium iodide (TBAI) is widely chosen as catalyst for RCMP of methyl methacrylate (MMA).^{19,20} Typically, the polymerization temperature is strongly influenced by the initiator structure. For instance, previous studies showed that the RCMP initiators I-CH(CH₃)– adjacent to an ester group (R: ethyl, phenyl) could only be initiated at 110 °C.^{22,23} To highlight the efficiency of the I-Azl where the I-CH(CH₃)– part is adjacent to the azlactone group, the polymerization was carried out at 70 °C and 80 °C in bulk with the presence of 0.51 equiv. TBAI relative to I-Azl under argon (Scheme 1). Kinetic studies (Fig. 2A) showed linearity of pseudo-first order plots with a constant propagating radical concentration during polymerization at both temperatures. Fig. 2A also indicated an induction period. Such behavior could be due to the time required for complexation between the TBAI catalyst and the I-Azl initiator to trigger polymerization and/or to solubilize the TBAI in MMA. Furthermore, faster polymerization at 80 °C compared to 70 °C can be explained by an increase in the solubility of TBAI. Moreover, the low dispersities ($D < 1.30$) together with a linear evolution of the number-average molar masses determined by SEC analysis ($M_{n,\text{SEC}}$) against monomer conversion were observed, indicating that simultaneous polymer chain growth



Scheme 1 Synthesis of 2-(1-iodoethyl)-4,4-dimethyloxazol-5(4H)-one (I-Azl) and its mediated RCMP of MMA by using TBAI as a catalyst.



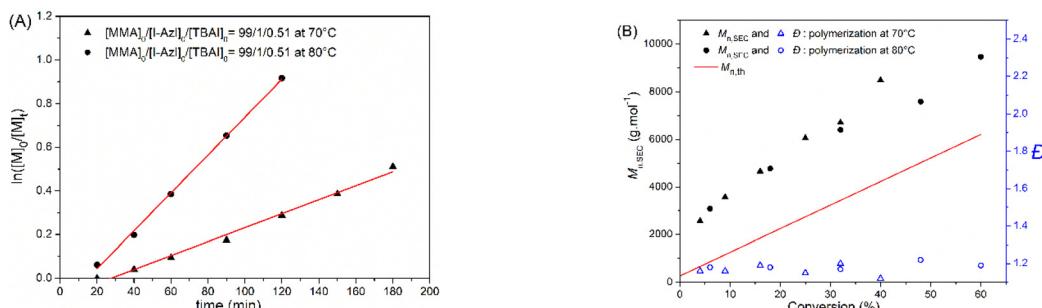


Fig. 2 Polymerizations of MMA at 70 °C and 80 °C using I-Azl as the initiator and TBAI as the catalyst with: (A) kinetic plot versus time polymerization; (B) evolution of number-average molar mass and dispersities with conversion.

and no significant transfer reaction occurred during both polymerizations (Fig. 2B). The difference value between $M_{n,SEC}$ and the theoretical number-average molar masses ($M_{n,th}$) could be attributed to the insufficient amount of deactivator (iodine/catalyst complex) accumulated in the early stage of polymerization. Indeed, the generated alkyl radicals from I-Azl or oligomers can combine quickly to terminate the polymerization reducing the initiator efficiency.

After precipitation, the presence of the azlactone group in the α -azlactone-terminated PMMA was confirmed by Fourier-Transform Infra-Red (FT-IR) spectroscopy with a characteristic band at 1820 cm^{-1} due to the carbonyl group of the azlactone ring ($\nu_{(\text{C}=\text{O})\text{azlactone}}$) and a strong band at 1725 cm^{-1} due to the carbonyl ester ($\nu_{(\text{C}=\text{O})\text{ester}}$) of the PMMA chain (ESI Fig. S3†).

In addition, the chemical structure of ω -iodide-terminated PMMA chain was confirmed by ^1H NMR analysis with the presence of a small signal at 3.77 ppm assigned to the methyl ester group adjacent to the ω -iodide end chain¹⁹ ($-\text{C}(\text{CH}_3)\text{I}-\text{COOCH}_3$, labeled (g) in Fig. 3); the large signal at 3.58 ppm being attributed to the $-\text{COOCH}_3$ groups of the main chain (labeled (f) in Fig. 3). Finally, the number-average degree of polymerization ($DP_{n,NMR}$) was determined by ^1H NMR from the ratio of the integrations of these two signals and was estimated to be $DP_{n,NMR} = 81$. This $DP_{n,NMR}$ value corresponds to a polymer chain having $M_{n,NMR} = 8370\text{ g mol}^{-1}$ that correlates well with the $M_{n,SEC} = 9460\text{ g mol}^{-1}$. These results show that

the I-Azl is an efficient RCMP initiator to mediate the controlled RCMP of MMA to prepare a well-defined α -azlactone-functionalized PMMA.

Impact of oxygen, catalyst amount and monomer structure on the efficiency of I-Azl

Due to the oxygen reaction with propagating radicals, the deoxygenation of a reaction mixture is a crucial step in radical polymerization. Therefore, the development of oxygen tolerant polymerization processes is still highly desired in polymer synthesis.²⁴ Recently, Wang *et al.*²⁵ have reported that the RCMP of MMA could be carried out without deoxygenation by using the iodine (I_2) and *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA) as a catalyst. However, aside from this report, most RCMP experiments have been performed under inert atmosphere. Accordingly, we evaluated the oxygen tolerance of RCMP using TBAI catalyst and investigated the efficiency of the I-Azl initiator in performing a polymerization process under air. The I-Azl-mediated polymerization of MMA has been carried out with $[\text{MMA}]_0/[\text{I-Azl}]_0/[\text{TBAI}]_0 = 99/1/0.51$ at 80 °C without the deoxygenation step. Fig. 4 confirmed the good control of the polymerization of MMA as indicated by the linear first-order kinetic plot of the polymerization and the low D values of the resulting polymers. This result clearly demonstrates the oxygen tolerance of RCMP technique as well as the efficiency of I-Azl in controlling polymerization of MMA even under air and without addition of I_2 . A longer inhibition period is observed for the polymerization performed under air (Fig. 4A and Table 1), oxygen being known to be a radical inhibitor, preventing the growth of macromolecular chains. Subsequently, deoxygenation was considered as a crucial step for further experiments to improve the efficiency of I-Azl. The influence of the $[\text{TBAI}]_0/[\text{I-Azl}]_0$ ratio was also studied during RCMP of MMA. Increasing $[\text{TBAI}]_0/[\text{I-Azl}]_0$ ratios from 0.51 to 1.21 resulted in a faster polymerization rate with higher monomer conversion after 90 min (entry 1 vs. entry 3, Table 1 and Fig. 4).

Among the methacrylic monomers, due to the biocompatible and ionic conductive properties of poly(ethylene oxide), mPEGMA has emerged as one of the leading monomers for the preparation of the biorelevant materials as well as solid

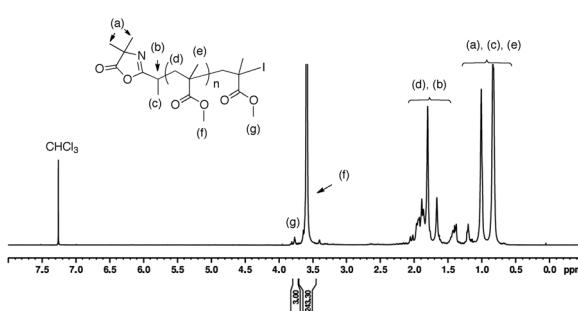


Fig. 3 ^1H NMR spectrum (400 MHz) of a well-defined α -azlactone-functionalized PMMA ($DP_{n,NMR} = 81$, $M_{n,SEC} = 9460\text{ g mol}^{-1}$, $D = 1.19$) in CDCl_3 .



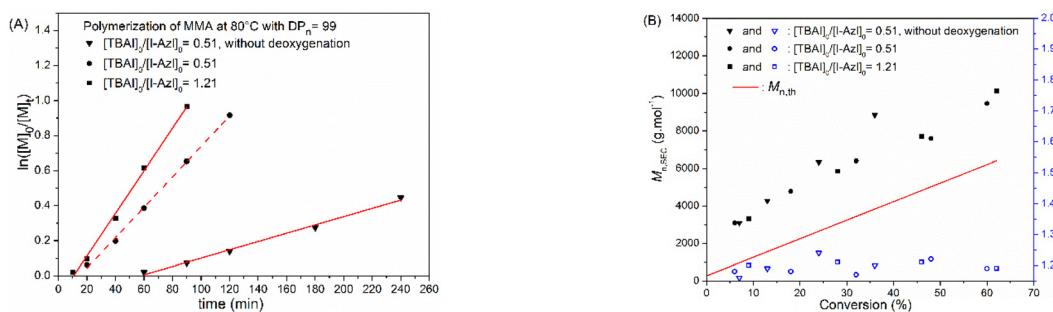


Fig. 4 Polymerization of MMA at 80 °C using I-AzI as the initiator and TBAI as the catalyst with: (A) kinetic plot *versus* time polymerization; (B) evolution of number-average molar mass and dispersity values with monomer conversion.

Table 1 Summary of I-AzI mediated RCMP of MMA at 80 °C under different conditions

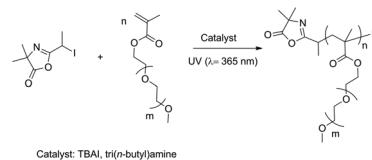
Entry	$[MMA]_0 : [I-AzI]_0 : [TBAI]_0$	Time (min)	Conv. ^a (%)	$M_{n,th}^b$ (g mol ⁻¹)	$M_{n,SEC}^c$ (g mol ⁻¹)	D^c
1	99 : 1 : 0.51	90	48	5020	7590	1.22
2	99 : 1 : 0.51 ^d	90	7	960	3090	1.16
3	99 : 1 : 1.21	90	62	6400	10 140	1.19

^a Determined by ¹H NMR spectroscopy. ^b $M_{n,th} = M_{I-AzI} + (99 \times \text{Conv.} \times M_{MMA}/100)$ with $M_{MMA} = 100$ g mol⁻¹. ^c Determined by size exclusion chromatography with THF as an eluent and PMMA standards used for the calibration curve. ^d Without deoxygenation step.

polyelectrolyte for battery applications.^{26,27} To expand our research, the I-AzI initiator was used for the polymerization of mPEGMA with a $[m\text{PEGMA}]_0/[I\text{-AzI}]_0/[TBAI]_0$ ratio of 100/1/1.21 at 80 °C under argon. After 180 min of polymerization, the monomer conversion was only 7% giving a polymer with $M_{n,SEC} = 7440$ g mol⁻¹ and $D = 1.09$. According to the literature, RCMP in polar media at high temperatures higher than 55 °C can lead to the elimination of hydrogen iodide (HI) from the polymer chain-end.²⁸ Therefore, the low conversion of mPEGMA can be attributed to the deactivation of the propagating radical by elimination of ω -iodide due to the hydrophilicity character of the mPEGMA monomer as a polar medium at 80 °C. To avoid the ω -iodide elimination, the RCMP process of mPEGMA could be improved by either using a thermal radical initiator and iodine (I_2) at 60 °C or by photopolymerization.^{19,21,29} Nevertheless, the addition of co-initiators/ I_2 can lead to uncontrollable polymer chains and high polymer dispersity values. Therefore, the photopolymerization of mPEGMA using I-AzI as an initiator was considered in this study to synthesize well-defined α -azlactone-functionalized poly(mPEGMA).

I-AzI mediated RCMP of poly(ethylene glycol) methyl ether methacrylate under UV irradiation

The C-I bond of an alkyl iodide can be easily broken under exposure to visible or Ultra-violet (UV) radiation. So, the photo-irradiation has widely used to as alternative effective approach to initiate the RCMP process.^{29,30} Photo-triggered RCMP (photo-RCMP) was then carried out in bulk with tri(*n*-butyl)amine or TBAI as the catalyst (Scheme 2). In photo-RCMP, the best control of polymerization of mPEGMA was achieved with a $[\text{catalyst}]_0/[\text{initiator}]_0$ ratio equal to 0.95 when using tri(*n*-butyl)



Scheme 2 Photo-polymerization of mPEGMA at $\lambda = 365$ nm with I-AzI initiator and tri(*n*-butyl)amine or TBAI catalyst.

amine as a catalyst. This $[\text{catalyst}]_0/[\text{initiator}]_0$ ratio was adjusted to 0.41 when TBAI was used as a catalyst, in order to maintain a homogeneous solution due to the low solubility of TBAI in mPEGMA.

Fig. 5A and B show a pseudo-first order of kinetic plot and a linear evolution of $M_{n,SEC}$ with monomer conversion together with low dispersity values ($D < 1.2$) for both catalysts. In addition, the unimodal SEC traces along with the progressive shift to shorter retention times illustrate the observed increase in molar mass throughout the polymerization, which is clearly indicative of a controlled radical polymerization (Fig. 5C and D). The structure of the obtained polymers was also verified by ¹H NMR analysis showing the characteristic signals of the repeating poly(ethylene oxide) side chains at 3.76–3.57 (labeled (g) in Fig. 6) and 3.37 (labeled (h) in Fig. 6). Because of the low resolution of the signals of the two extremities in comparison with the other part of the polymer chain, it is difficult to determine the number-average degree of polymerization *via* NMR analysis. The presence of the azlactone group at the chain-end of poly(mPEGMA) was confirmed by FT-IR spectroscopy with the appearance of the distinguishable band $\nu_{(\text{C}=\text{O})\text{azlactone}}$ at 1820 cm⁻¹ (see ESI Fig. S4†). All these results indicate that



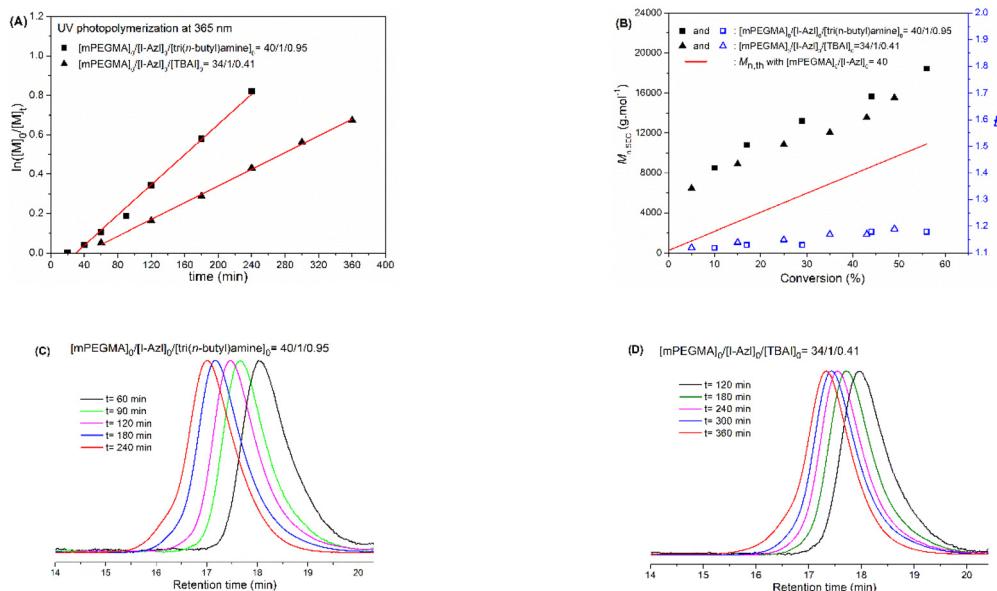


Fig. 5 Photo-polymerization of mPEGMA at $\lambda = 365$ nm using tri(*n*-butyl)amine or TBAI as the catalyst: (A) kinetic plot *versus* time polymerization; (B) evolution of number-average molar mass and dispersity values with monomer conversion; (C) and (D) overlaid SEC traces of resulting polymer.

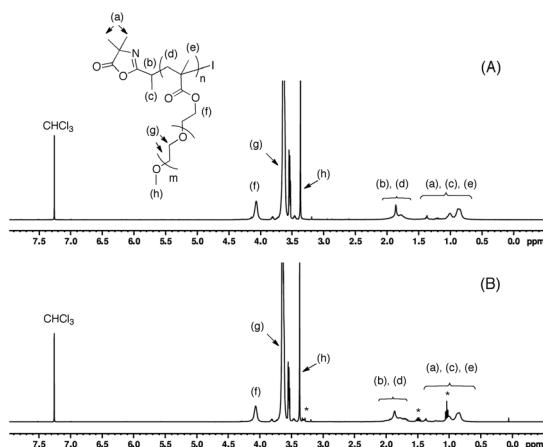
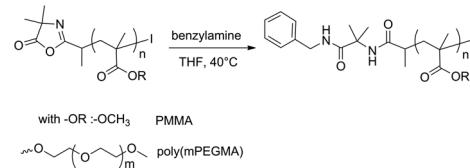


Fig. 6 ^1H NMR spectra (400 MHz) of azlactone-functionalized poly(mPEGMA) obtained using (A) tri(*n*-butyl)amine and (B) TBAI catalyst in CDCl_3 (* denoted the signal of residual TBAI catalyst).

I-AzI is an efficient initiator to synthesize well-defined α -azlactone-functionalized poly(mPEGMA)s using a photo-RCMP process.

Reactivity of azlactone-terminated polymers towards an amine

The azlactone ring has become an increasingly useful functionality for the rapid and modular design of functional materials thanks to its reactivity towards primary amines. To demonstrate the amine scavenging ability of the azlactone-group installed at the polymer chain-end, α -azlactone-functionalized PMMA and α -azlactone-functionalized poly(mPEGMA) (ESI Table S3†) were reacted with an excess of benzylamine (6.9–6.5 equiv.) as a model amine (Scheme 3).



Scheme 3 Coupling reaction between benzylamine and α -azlactone-functionalized PMMA and α -azlactone-functionalized poly(mPEGMA).

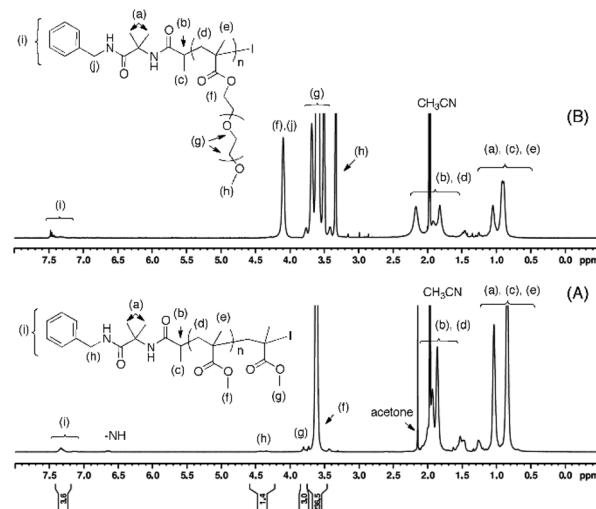


Fig. 7 ^1H NMR spectra (400 MHz) of (A) benzylamine-functionalized PMMA ($M_{n,\text{SEC}} = 11\,000 \text{ g mol}^{-1}$, $D = 1.13$) and (B) benzylamine-functionalized poly(mPEGMA), $M_{n,\text{SEC}} = 20\,500 \text{ g mol}^{-1}$, $D = 1.18$) in CD_3CN .



FT-IR analysis showed the disappearance of the characteristic carbonyl band of the azlactone group at 1820 cm^{-1} which confirmed the reaction between benzylamine and the azlactone chain-end (ESI Fig. S5 and 6 \dagger). The successful post-polymerization reaction of α -azlactone-terminated polymethacrylates was also confirmed by ^1H NMR with the appearance of the aromatic signals of the benzyl group at 7.21–7.41 ppm (C_6H_5- , labeled (i) in Fig. 7) along with the characteristic signal of the polymer main chains. The benzylamide chain-end functionality of PMMA was calculated to be 72% by comparing the signal intensity of the phenyl group (C_6H_5- , labeled (i) in Fig. 7A) and the methyl ester of the MMA unit adjacent to the iodide end group ($-\text{COOCH}_3$, labeled (g) in Fig. 7A).

Conclusion

In conclusion, a novel azlactone-functionalized alkyl iodide (I-Azl) was successfully synthesized and used as an efficient initiator for the controlled polymerization of MMA under different experimental conditions to afford well-defined α -azlactone-functionalized PMMA by a metal-free process. The RCMP process with I-Azl as the initiator has proven to be tolerant to oxygen. Furthermore, I-Azl was demonstrated to be an excellent initiator for the photo-RCMP synthesis of α -azlactone-terminated poly(mPEGMA). The reactivity of the resulting α -azlactone-terminated polymers towards primary amines was demonstrated by their reaction with benzylamine as a model amine. These azlactone-terminated polymers based on a metal-free I-Azl mediated RCMP and having a highly amine-reactive terminal groups could be useful as a platform for new polymer materials and for bioconjugation applications.

Conflicts of interest

There are no conflicts to declare.

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References

- 1 H. T. Ho, M. E. Levere, D. Fournier, V. Montembault, S. Pascual and L. Fontaine, *Aust. J. Chem.*, 2012, **65**, 970–977.
- 2 P. P. de Castro, A. G. Carpanez and G. W. Amarante, *Chem. – Eur. J.*, 2016, **22**, 10294–10318.
- 3 S. M. Heilmann, J. K. Rasmussen and L. R. Krebski, *J. Polym. Sci., Part A: Polym. Chem.*, 2001, **39**, 3655–3677.
- 4 H. T. Ho, V. Montembault, M. Rollet, S. Aboudou, K. Mabrouk, S. Pascual, L. Fontaine, D. Gigmes and T. N. T. Phan, *Polym. Chem.*, 2020, **11**, 4013–4021.
- 5 M. E. Buck and D. M. Lynn, *Polym. Chem.*, 2012, **3**, 66–80.
- 6 P. L. Coleman, M. M. Walker, D. S. Milbrath, D. M. Stauffer, J. K. Rasmussen, L. R. Krebski and S. M. Heilmann, *J. Chromatogr. A*, 1990, **512**, 345–363.
- 7 J. S. Kim, A. R. Sirois, A. J. Vazquez Cegla, E. Jumai'an, N. Murata, M. E. Buck and S. J. Moore, *Bioconjugate Chem.*, 2019, **30**, 1220–1231.
- 8 S. P. Cullen, I. C. Mandel and P. Gopalan, *Langmuir*, 2008, **24**, 13701–13709.
- 9 M. E. Levere, H. T. Ho, S. Pascual and L. Fontaine, *Polym. Chem.*, 2011, **2**, 2878–2887.
- 10 J. W. Choi, M. C. D. Carter, W. Wei, C. Kanimozhi, F. W. Speetjens, M. K. Mahanthappa, D. M. Lynn and P. Gopalan, *Macromolecules*, 2016, **49**, 8177–8186.
- 11 H. T. Ho, M. E. Levere, S. Pascual, V. Montembault, N. Casse, A. Caruso and L. Fontaine, *Polym. Chem.*, 2013, **4**, 675–685.
- 12 H. T. Ho, A. Bénard, G. Forcher, M. Le Bohec, V. Montembault, S. Pascual and L. Fontaine, *Org. Biomol. Chem.*, 2018, **16**, 7124–7128.
- 13 A. D. Jenkins, R. G. Jones and G. Moad, *Pure Appl. Chem.*, 2010, **82**, 483–491.
- 14 K. M. Lewandowski, D. D. Fansler, B. N. Gaddam, S. M. Heilmann, L. R. Krebski, S. B. Roscoe and M. S. Wendland, US6894133B2, 2005.
- 15 K. Matyjaszewski, *Macromolecules*, 2012, **45**, 4015–4039.
- 16 V. Delplace, S. Harrisson, H. T. Ho, A. Tardy, Y. Guillaneuf, S. Pascual, L. Fontaine and J. Nicolas, *Macromolecules*, 2015, **48**, 2087–2097.
- 17 H. T. Ho, F. Leroux, S. Pascual, V. Montembault and L. Fontaine, *Macromol. Rapid Commun.*, 2012, **33**, 1753–1758.
- 18 A. Goto, T. Suzuki, H. Ohfuji, M. Tanishima, T. Fukuda, Y. Tsujii and H. Kaji, *Macromolecules*, 2011, **44**, 8709–8715.
- 19 A. Goto, A. Ohtsuki, H. Ohfuji, M. Tanishima and H. Kaji, *J. Am. Chem. Soc.*, 2013, **135**, 11131–11139.
- 20 C.-G. Wang, A. M. L. Chong, H. M. Pan, J. Sarkar, X. T. Tay and A. Goto, *Polym. Chem.*, 2020, **11**, 5559–5571.
- 21 Z.-H. Chen, X.-Y. Wang and Y. Tang, *Polym. Chem.*, 2022, **13**, 2402–2419.
- 22 L. Lei, M. Tanishima, A. Goto, H. Kaji, Y. Yamaguchi, H. Komatsu, T. Jitsukawa and M. Miyamoto, *Macromolecules*, 2014, **47**, 6610–6618.
- 23 J. Zheng, C.-G. Wang, Y. Yamaguchi, M. Miyamoto and A. Goto, *Angew. Chem., Int. Ed.*, 2018, **57**, 1552–1556.
- 24 J. Yeow, R. Chapman, A. J. Gormley and C. Boyer, *Chem. Soc. Rev.*, 2018, **47**, 4357–4387.
- 25 W. Wang, L. Bai, H. Chen, H. Xu, Y. Niu, Q. Tao and Z. Cheng, *RSC Adv.*, 2016, **6**, 97455–97462.
- 26 J.-F. Lutz, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 3459–3470.



27 T. N. T. Phan, S. Issa and D. Gigmes, *Polym. Int.*, 2019, **68**, 7–13.

28 C.-G. Wang, F. Hanindita and A. Goto, *ACS Macro Lett.*, 2018, **7**, 263–268.

29 A. Ohtsuki, A. Goto and H. Kaji, *Macromolecules*, 2013, **46**, 96–102.

30 Y. Ni, L. Zhang, Z. Cheng and X. Zhu, *Polym. Chem.*, 2019, **10**, 2504–2515.

