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Synthesis of Methacrylate-Terminated Block Copolymers with Reduced Transesterification by Controlled Ring-Opening Polymerization

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Abstract

This work presents a robust method to achieve the synthesis of low molecular weight polyesters via ring-opening polymerization (ROP) initiated by 2-hydroxyethyl-methacrylate (HEMA) when using triazabicyclodecene (TBD) as catalyst. The effect that the HEMA:TBD ratio has upon the final reaction rate and final polymer molecular architecture is discussed. The optimum HEMA:TBD ratio and reaction conditions required to minimize competing transesterification reactions were determined, in order to synthesize successfully the target ROP macromonomer species containing only a single 2-methacryloyloxyethyl end-group. Additionally, to confirm the terminal end-group fidelity of the product macromonomers and confirm TBD utility for block copolymer manufacture, a small series of di-block polyesters were synthesized using TBD and shown to exhibit good control over the final polymer structure whilst negating the side transesterification reactions, irrespective of the monomers used.

1. Introduction

Synthetic aliphatic polyesters, such as poly(lactic acid) (PLA), polycaprolactone (PCL), or polycarbonates such as poly(trimethylene carbonate) (PTMC) and their copolymers are widely used for pharmaceutical and environmental applications due to their controllable biodegradability and low cost of production.[1,2] To extend their use into more demanding applications, aliphatic polyesters with a wider variety of terminal or side-chain functionality are required.[3,4] For example, the introduction of a reactive double-bond, as either a side chain or an end-terminus on the main polymeric backbone, has paved the way for the production of highly functional copolymers where the functionality can be used as platform for post-functionalization or further polymerization.[5] In particular, the free hydroxyl group of 2-hydroxyethylmethacrylate (HEMA) has been exploited as a ring-opening polymerization (ROP) initiator for the production of polyesters bearing a methacrylate terminus.[6] These HEMA-terminated-polyester macromonomers have been used in copolymerization with other (metha)acrylic monomers,[7] to produce graft-copolymers *via* controlled radical polymerization techniques such as ATRP and RAFT.[8, 9] However, the majority of the HEMA-based polyesters and polycarbonates, including the examples reported above, have been prepared using Sn based catalysts.[10-14] Unfortunately, Sn-residues can be difficult to remove during polymer purification, which may compromise the quality of the final product and the potential applicability.[15] An alternative route to polyesters utilizes enzymes as the catalyst system.[16] However, enzyme catalyzed ROP (eROP) generally results in slow reactions with limited control over the final polymer architecture.[17] In HEMA-initiated Lipase catalyzed eROP, even at low monomer conversion, numerous unwanted by-products are routinely obtained. This has been attributed to the low reaction selectivity of the enzyme, which allows competition between ROP and other transesterification processes.[16,17] The use of triazabicyclodecene (TBD) as a catalyst for ROP has been demonstrated with a variety of cyclic monomers, resulting in the

synthesis of polymers with controlled molecular weight and polydispersity.[18] The enhanced catalytic activity of TBD when compared with other organo-catalysts such as 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 4-Dimethylaminopyridine (DMAP) results from its ability to activate both monomer and initiator simultaneously.[19]

Building on these previous reports, the present study focuses on the development of a synthetic strategy which ensures good selectivity towards polymerization when using an α,ω-functional initiator such as HEMA, without compromising the end-group functionality. The reported method shows that TBD can be used as a catalyst to obtain HEMA-terminated-polyesters from three classes of monomer while demonstrating good control over the final polymer structure. These monomers, D,L-lactide (LA), ε-caprolactone (CL) and trimethylene carbonate (TMC), were chosen to exemplify a wide range of polymers commonly produced by ROP. Previous reports of TBD catalyzed ROP have suggested that implementing the correct initial initiator:catalyst ratio (HEMA:TBD in this case) is of vital importance for maintaining polymerization control, due to the dual nature of the catalyst activating both monomer and initiator.[18] Applying incorrect ratios and/or conditions can generate unwanted pre-polymerization and concomitant acyl transfer side reactions. Therefore, we conducted a systematic study of the extent of HEMA transesterification by varying the initial HEMA:TBD ratio, to determine the optimum initiator:catalyst feed that would minimize undesired side transesterification reactions in the synthesis of a target set of low molecular weight polymers. To achieve the desired low molecular weight materials (i.e. DP's in the region 8 – 45), these experiments require relatively high HEMA concentrations and so are susceptible to the onset of side reactions. The present work has identified the reaction conditions which allowed the successful production of mono(methyl)acrylated polymers with well-defined structures and molecular weights, irrespective of the monomers used. More specifically, high conversion of monomer into polymers as well as controlled molecular weight with respect to the initial [M]:[I] feed-ratio, and polydispersitiy below 1.3 were simultaneously achieved. By identifying the

correct ratios of monomer, initiator and catalyst, the reported synthetic methodology has overcome the previously described unsuccessful attempts to use TBD as catalyst in HEMA-initiated ROP due to the formation of uncontrollable by-products.[20] Finally, to validate the overall robustness and versatility of the proposed synthetic strategy, the chain-extension of a HEMAPCL polyester from the hydroxyl-end group, to generate mixed block copolymers, was successfully demonstrated.

2. Experimental Section

2.1 Materials and Methods

D,L-lactide 99% (LA) was purchased from Alfa Aesar (by Thermo Fisher Scientific). Trimethylene carbonate (TMC) was purchased from Polyscience. ε-caprolactone (CL), extra dry dichloromethane (DCM), deuterated chloroform ($CDCl_3$) and triazabicyclodecene (TBD) were acquired from Sigma Aldrich. Hexane, diethyl ether and methanol were obtained from Fisher. In all cases the vials were dried in an oven at 100 °C overnight prior to use, and the HEMA and DCM were stored over molecular sieves and under an inert atmosphere.

2.2 Synthesis

HEMA Transesterification Kinetics in Presence of TBD. In a typical procedure, pre-calculated amounts of HEMA and TBD were mixed in 3 mL of DCM at room temperature to commence the chemical transformations. As the reactions proceeded, aliquots of the solution were taken at predetermined time points (0, 5, 15 and 60 min) and were analyzed by ^{1}H NMR spectroscopy. The quantities of HEMA and TBD were selected in order to mimic the reaction conditions in which 1000 mg of εCL (8.77 mmol) would be present as the initial monomer loading. Namely, HEMA was used at two distinct feed levels which mimicked a hypothetical final targeted molecular weight of 2000 Da and 10,000 Da respectively. They were defined as the “high” and “low” levels of HEMA (High: 0.46 mmol, 60 mg and Low: 0.10 mmol, 13 mg).

TBD was also systematically introduced and two levels to reproduce the limiting reaction conditions of 1 and 2.5 % mol:mol ratios when compared to the monomer, i.e. these are the "low" (12 mg) and "high" (30 mg) TBD definitions. Four different boundary transesterification scenarios were then applied and analyzed with respect to the result of the ROP reaction. An unpaired t-test ($p<0.05$ indicating significant difference) analysis was performed at each time-point for each selected ratio.

HEMA Initiated ROP of the Cyclic Monomers. ROP experiments were performed adopting 'standard laboratory' conditions, i.e. ambient temperature and atmosphere.[21] The desired amount of cyclic monomer (500-1000 mg) and HEMA-initiator ([M]:[I] or DP_0 ratios targeted to produce final molar masses of either 2500 or 5000 Da) were weighed into a vial, which had been dried in an oven at 100 °C overnight and capped with a rubber septum. DCM (10 ml), was then added via syringe and the mixture was allowed to dissolve at room temperature (RT) for 5-10 minutes. Varying amounts of catalyst (from 1-2.5 % mol/mol of TBD with respect to monomer) were then added to trigger the ring-opening process. Reactions were observed to occur in time-frames ranging from 1-240 minutes, according to the monomer:initiator :solvent :catalyst adopted ratios. The reaction was terminated by catalyst deactivation upon adding an acidic solution and the polymer purified by means of multiple precipitation steps and dried in a vacuum oven.

HEMAPCL (Entries 7 and 8, Table 1) Initiated ROP. The required amount of cyclic monomer (500-1000 mg) and PCLHEMA-initiator to give the [M]:[I] ratios needed to achieve a targeted extension of 10 units for TMC and 35 units for LA, were weighed into a vial which had been dried in an oven at 100 °C overnight and capped using a rubber septum. DCM (10 ml), which had been dried over molecular sieves and kept under inert gas environment, was then added via syringe and the mixture was allowed to dissolve at RT for 5-10 minutes. A certain amount of TBD equal to 1% mol:mol compared to the amount of monomer was then

added to trigger the ring-opening process. The TBD was quenched by adding an acid solution after 3 minutes to terminate the reaction.

2.3 Polymer Characterization

HEMA-PDLLA. Characterization data was obtained after three precipitation cycles in hexane and diethyl ether. *^{1}H NMR (400 MHz, $CDCl_3$):* δ 6.14 (s, 1H), 5.61 (s, 1H), 5.19 (m, 2H*[M]:[I]), 4.36 (m, 5H), 1.95 (m, 3H), 1.59 (m, 6H*[M]:[I]), presence of residual catalyst and solvents (from synthesis and purification) can be spotted. *Conversion*: monomer to final polymer conversion determined by NMR was 90-95% with a recorded gravimetric yield of 70-75% (700-750 mg when aiming at theoretical 1000 mg of polymer). Further characterization shown in Table 1. *Molecular Weight:* As all polymers exhibited transesterification levels below 10%, M_n values were evaluated by ^{1}H NMR.[6,8]

HEMA-PTMC. Characterization data was obtained after three precipitation cycles in hexane and diethyl ether. *^{1}H NMR (400 MHz, $CDCl_3$):* δ 6.14 (s, 1H), 5.61 (s, 1H), 4.39 (m, 4H), 4.25 (m, 4H*[M]:[I]), 3.74 (m, 2H), 2.04 (m, 2H *[M]:[I]), 1.96 (m, 3H), presence of residual catalyst and solvents (from synthesis and purification) can be spotted. *Conversion:* monomer to final polymer conversion determined by NMR was 90-95% with a recorded gravimetric yield of 50-60% (500-600 mg when aiming at theoretical 1000 mg of polymer). Further characterization shown in Table 1. *Molecular Weight:* As all polymers exhibited transesterification levels below 10% M_n values were evaluated by ^{1}H NMR.[6]

HEMA-PCL. Characterization data was obtained after purification *via* three cycles of precipitation in cold MeOH. *^{1}H NMR:* (400 MHz, $CDCl_3$): δ 6.14 (s, 1H), 5.61 (s, 1H), 4.40-4.30 (m, 4H), 4.08 (t, 2H*[M]:[I]), 3.68 (m, 2H), 2.33 (t, 2H*[M]:[I]), 1.97 (m, 3H), 1.67 (m, 4H*[M]:[I]), 1.41 (m, 2H*[M]:[I]), presence of residual catalyst and solvents (from synthesis and purification) can be spotted. *Conversion:* monomer to final polymer conversion determined by NMR was 75% with a recorded gravimetric yield of 70% (700 mg when aiming at theoretical

1000 mg of polymer). Further characterization is shown in Table 1. *Molecular Weight:* When the degree of transesterification was below 10%, M_n values were evaluated by ^{1}H NMR.[6]

HEMAPCL-PTMC. Characterization data was obtained after purification *via* three cycles of precipitation in cold hexane-diethyl ether: *^{1}H NMR (400 MHz, $CDCl_3$):* δ 6.14 (s, 1H), 5.61 (s, 1H), 4.40-4.20 (m, from HEMA and TMC), 4.08 (t, 2H*35), 3.80 (m, 2H), 2.33 (t, 2H*35), 1.97 (m, 3H), 2.04 (m, 2H *[M]:[I]), 1.67 (m, 4H*35), 1.41 (m, 2H*35), presence of residual catalyst and solvents (from synthesis and purification) can be spotted. *Conversion*: TMC monomer to final block copolymer monomer conversion determined by NMR was 80% with a recorded gravimetric yield of 70%. Further characterization shown in Table 1. *Molecular Weight:* As all polymers exhibited transesterification levels below 10% M_n values were evaluated by ^{1}H NMR.[6]

HEMAPCL-PDLLA. Characterization data was obtained after purification *via* three cycles of precipitation in cold hexane-diethyl ether: *^{1}H NMR (400 MHz, $CDCl_3$):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 1H), 5.61 (s, 1H), 5.19 (m, 2H*28), 4.40-4.20 (m, 5H from LA end group and HEMA), 4.08 (t, 2H*35), 3.68 (m, 2H), 2.33 (t, 2H*35), 1.97 (m, 3H), 1.67 (m, 4H*35), 1.59 (m, 6H*28) 1.41 (m, 2H*35), presence of residual catalyst and solvents (from synthesis and purification) can be spotted. *Conversion*: LA monomer to final block copolymer monomer conversion determined was 80% with a recorded gravimetric yield of 75%. Further characterization shown in Table 1. *Molecular Weight:* As all polymers exhibited transesterification levels below 10% M_n values were evaluated by ^{1}H NMR.[6]

2.4 Characterization Methodologies

NMR Spectroscopy: ^{1}H NMR spectra were recorded on a Bruker AV3400 400.1 MHz spectrometer using $CDCl_3$ as the solvent reference (7.26 ppm). Chemical shifts are expressed in parts per million (d) downfield from internal standard tetramethylsilane.

2D-NMR Spectroscopy: ^{1}H - ^{13}C heteronuclear single quantum correlation (HSQC) and ^{1}H - ^{13}C heteronuclear multiple-bond correlation (HMBC) (one-bond suppression) spectra were

recorded on a Bruker AV 3500 (500.1 MHz for ^{1}H, 125.8 MHz for ^{13}C) spectrometer using $CDCl_3$ as the solvent reference (7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C). The final HSQC spectrum depicts a peak for each unique pair of directly coupled nuclei (^{1}H - ^{13}C). The final HMBC spectrum depicts correlations between coupled nuclei pairs (^{1}H - ^{13}C) that are separated by two – four bonds, with direct one-bond correlations suppressed.

GPC Analysis: Gel Permeation Chromatography (GPC) was performed by using a PL50+ Polymer Laboratories system. An RI constructed calibration curve from PMMA (Mn range 350000-620 Da) was adopted to analyze polymer molar masses. 2 PL mixed-D columns at 50 °C were employed, using 0.1 % LiBr DMF as the mobile phase with a flow rate of 1 ml/min.

3. Results and Discussion

A number of prior reports have shown that TBD is an efficient acyl-transfer and transesterification catalyst. Its high activity is linked to its ability to interact with both initiator and monomer (**Scheme 1**),[22] and it has been proposed to follow a pseudo bifunctional nucleophilic catalytic mechanism.[23] This feature allows TBD to catalyze the ROP reaction of ε-CL, commonly known as refractive monomer in ROP process, without the need to adopt a co-catalyst (for example a thiourea) that is required for alternative organocatalyst such as DBU.[22]It the same way tin octoate, which is currently the most widely used catalyst for ROP, exploits a coordination-insertion process allowing interactions with both initiator (nucleophile) and monomer without the need of a co-catalyst.[20] However, the main drawbacks related with tin octoate are the intrinsic toxicity and the high temperature required to activate any ROP

reactions enabling intermolecular and intramolecular esterification to occur and thus broadening the final polymer molecular polydispersity.[22] .

On the basis of this, in the present work, it was speculated that TBD can also trigger a self-acyl transfer of the methacrylic group of HEMA, producing ethylene bis-methacrylate and ethylene glycol (**Scheme 2)**.

This was supported by both species being detected in the ^{1}H NMR of the reaction mixture (**Figure S1**). This HEMA self-transesterification can compete, as side reaction, with the ROP process by altering the concentration and/or identity of the active initiator. Consequently, by affecting the [M]:[I] ratio, the presence of this competitive acyl transfer process can severely affect the quality of the final polymer in terms of molecular weight and architecture.

In order to evaluate the magnitude of the effect of the acyl transfer reaction, a kinetic study was conducted by systematically varying the "high" and "low" [HEMA]:[TBD] ratios to mimic the concentration ranges applied in an ideal ROP reaction to synthesize a 2000 Da and 10,000 Da product. The results of these experiments are compared in **Figure 1** and the supporting NMR data are shown in **Figure S1**.

These data show that transesterification is more pronounced when both the concentrations of HEMA and TBD are at the "high" values, reaching almost 25 % of transesterification within 5 minutes. However, when the amount of HEMA was kept "high", while the amount of TBD was reduced to "low", a reduction in transesterification was observed during the same time-frame, namely, only 8-10 % of unwanted reaction was detected. Furthermore, when HEMA was reduced ("low"), as expected, the kinetics of the reaction considerably reduced and, independently of the TBD concentration, only 5-6 % of transesterification occurred after 5 min. An unpaired t-test ($p<0.05$ indicating significant difference) analysis was performed at each time-point and confirmed that significant differences were observed at each time point between the two selected initiator:catalyst ratios. Therefore, this set of experiments demonstrated that keeping the HEMA concentration at the "low" level is important to reduce side-reactions.

We subsequently explored the ability of TBD to selectively catalyze ROP of lactide (LA), ε-caprolactone (CL) and trimethylene carbonate (TMC) monomers, [18,22,23] while controlling methacrylate transfer side reactions. LA polymerizations (**Figure 2**) were performed with [LA]:[HEMA] ratios targeting final molecular weights of 5000 Da and 6500 Da (i.e. DP_0 of 35 and 45) respectively.

PDLLA polymers were produced within seconds of introducing the catalyst at room temperature. The reactions exhibited good control of the molecular weight (Đ ranging from 1.18-1.21, **Table 1**), which was in agreement with prior literature reports.[18,23]

The experimental DP of the PDLLA products (Entries 1 and 2, **Table 1**) were observed to match the theoretical DP and subsequent analysis by ^{1}H-NMR (**Figure 2**) confirming the presence of only a single set of methacrylic proton peaks indicating a good control of the polymer and no evidence of transesterification.

Furthermore, 2D-NMR experiments indicated that the ROP mechanism was predominant, with the HSQC spectrum (**Figure 3**) showing a single acrylic (vinylic) carbon peak directly correlated to the two methacrylic protons (see inset **Figure 3A**). This confirms the presence of only a single HEMA-terminated group per polymeric chain. The HMBC spectrum further confirms a single correlation between the two methacrylic protons and both a single carbonyl and methyl group species (**Figure 3B**), with no additional peaks related to the methacrylic protons observed.

Good control over the final polymer features was also observed for the PTMC mono-methacrylic polymer (**Figure 4**). Despite a change in the molecular structure of the cyclic monomer, fast kinetics similar to that exhibited by the PDLLA were observed. The final molecular weight was in agreement with the target of approximately 5000 Da as confirmed by ^{1}H-NMR and GPC (Entry 3, **Table 1**). This confirmed the ability of TBD to selectively catalyze the ROP of cyclic monomers of different molecular structures which exhibit fast polymerization kinetics.

To exemplify further the importance of the TBD-catalyzed ring-opening kinetics to the production of defined polymer structures, the polymerization of ε-CL was then explored, due to its lower ROP reactivity when compared to monomers such as LA. [18] In agreement with the literature, a slower rate of polymerization was observed for CL when compared to LA and TMC and as a consequence the overall reaction was noted to be less controlled (Entry 4-6, **Table 1** and **Figure S3**). Analysis of the final products showed that this was due to both the tendency of the PCL terminal chain group to transesterify[18,24] and an increased level of HEMA:TBD interaction prior to polymerization which generated a diol initiator over time. When the 1% mol:mol of TBD:Monomer ratio was used as for TMC and LA, no CL polymerization was observed. This was attributed to the slow ROP kinetics and consequent dominance of the self-transesterification kinetics of HEMA. Thus, a TBD:monomer ratio of 2.5 % mol:mol was then adopted. Polymerization was observed, and the reaction was complete within 120-240 min (see Entry 4, **Table 1** and **Figure S2**). The formation of sub-products was evident in the NMR analysis (**Figures S3** and **Figure 5** see methacrylate peaks inset). Thus, it was not possible to evaluate the final molecular weight by ^{1}H NMR, due to a splitting of the HEMA peaks and the contribution to the polymeric CL peaks arising from polymer formed from other initiating species such as the diol. As a consequence, a broader value of Đ (1.55) was observed in the GPC data. The ^{1}H-NMR spectra showed that the transesterification occurred over time as the splitting of the vinyl peaks in the 6.20 to 5.50 ppm region increased as the reaction proceeded (see **Figure S2-S3**). This splitting was in accordance with the initial screening reported in **Figure S1**.

A series of 2D-NMR experiments were performed, to clarify the presence of both HEMA and methacrylic end-capped terminal groups and to link unambiguously the vinyl peak splitting to a transesterification process. The HSQC spectrum (**Figure S3)** showed the presence of two different types of carbons correlating to the two sub-families of methacrylic proton peaks. This indicates the presence of two unique end-capping methacrylic groups, and thus an undesired

end-terminal methacrylic group in addition to the HEMA-initiation end-terminus. This was further exemplified in the HMBC spectra, where two sets of multiple-bond correlations between the two types of methacrylic protons and both of the two kinds of carbonyl and methyl group species were observed (**Figure S4**).

By reducing the TBD loading to 1.5 % mol:mol, HEMAPCL could be synthesized with a significant reduction of the side acyl transfer reactions (see ^{1}H-NMR, **Figure 5, Figure S5** and Entry 6**, Table 1**).

Using these conditions and restricting the reaction time to 120 min, an average conversion of monomer to polymer of *circa* 60-70 % could be reached before the reaction was quenched. This confirmed that by reducing the amount of TBD, and thus tuning the initial HEMA:TBD ratio, there was a drop in the undesired transesterification reaction at the 1.5 %mol:mol when compared with the PCL synthesized using 2.5 % mol:mol of catalyst (see inset within **Figure 5**). At this TBD concentration only 2 to 5 % of bis-methacrylic chains were observed in a series of experiments with targeted molecular weights of approximately 2500 and 5000 Da (Entries 5 and 6, **Table 1**) compared to the ~ 50% observed in prior literature by using Lipase catalysts.[16] Finally, in order to assess the level of retention of the hydroxyl group at the end of each polymeric chain and thus confirming good end group fidelity, HEMA initiated PCL with a targeted DP_0 of 35 (see Entry 6, **Table 1**) was then employed as a macroinitiator for the synthesis of block copolymers with TMC or LA as the chain extending monomers. The targeted DP_0 for the second TMC block was 10 units whilst for LA was 35 units (i.e. 35 + DP_o10 of TMC or 35 + DP_o 35 of LA). After the polymerization of TMC and post-purification steps an experimental DP_e of 8 was observed (Entry 7, **Table 1** and **Figure 6**). For the LA extension, a conversion of 80 % in the second block of PDLLA was achieved to reach a DP_e of 28 (Entry 8 **Table 1**), which is what would be expected from the conversion corrected target. In both cases, the characteristic NMR peaks attributed to the main chains TMC and LA were present in spectra of the final copolymer as were the characteristic end groups for the second added monomer

(**Figure 6 Left**). Increases in the molecular weight of the polymers compared to that of the HEMA initiated PCL-macroinitiator (**Figure 6 Right**) were evident in the GPC chromatograms, i.e. 4307 Da (Đ of 1.13) to 6295 Da (Đ of 1.09) and 8125 Da (Đ of 1.15) for TMC and LA respectively. This confirmed the formation of block copolymers. The existence of only a single peak for the sequential block copolymers proved the successful control over the addition of the second monomer onto the initial HEMAPCL macroinitiator.

The success of the regrowth from the macro-initiator in this proof-of-concept experiment confirmed both the control of the reaction conditions for the production of block copolymers, as well as the end group (hydroxyl group in this case) fidelity that can be achieved in the production of the macro-initiator. The increase in molecular weight shown in the GPC traces (Entries 7 and 8, **Table 1**) to produce single monodispersed peaks confirmed both the availability of the hydroxyl PCL terminal group to initiate the polymerization of the second sequential block and the level of control exercized over the extension step on the initial HEMAPCL macro-initiator.

4. Conclusions

The synthetic strategy reported here is the first example of successful HEMA-initiated ROP catalyzed by TBD. To highlight the novelty and the broad applicability of the synthetic methodology developed in the present work, it is important to note that in recent work it has been reported that when TBD was adopted, as catalyst of ROP reactions, with HEMA as nucleophilic initiator, no controlled polymerization events were observed due to a series of uncontrollable side reactions.[20]Consequently, tin octoate was needed to prepare the targeted (metha)acrylated-macromolecules. On the contrary, the present study has demonstrated that TBD indeed can be employed as an active and selective catalyst for HEMA-initiated ROP of

LA, TMC, and CL, to synthesize polymers and block copolymers with controlled molecular weight, low polydispersity and a mono-methacrylate final architecture (see **Table 1**).

Success in achieving the target ROP while minimizing polyester transesterification reactions was demonstrated to be minimal when fast polymerization kinetics were obtained from the monomer of choice. In the cases where monomer types presenting slower kinetics were employed, both significant levels of "by-products" (> 50%) and subsequent loss of control over the molecular structure of the polymer was observed. This study has shown that these unwanted side reactions could be minimized (i.e. reduced to < 5%) by controlling the relative HEMA:TBD ratio and the reaction time.

This study has also concluded that TBD is a more efficient ROP catalyst when compared to lipases. In fact, it has been well documented that lipases cannot discriminate ROP from the transesterification sub-processes in the presence of cleavable ester initiators such as HEMA, even at low monomer conversion.[16,17] This leads to the production of di-methacrylated macromolecular chains and an inability to produce well-defined polymers. By comparison, this study has demonstrated that, by using TBD as a catalyst in small scale reactions and adopting the simple precautions of controlling the catalyst concentration and reaction times, mono-methacrylated chains with no (for HEMA initiated PDLLA and HEMA initiated PTMC) or limited (<5 % for HEMA initiated PCL) di-methacrylated chains can be produced. Additionally, this ROP reaction can be achieved with reagents that are readily available and under mild reaction conditions, i.e. room temperature and atmosphere, in comparison to tin octoate that requires high temperature and longer reaction time. All the aforementioned properties of TBD will facilitate the production of biodegradable polymers bearing an active (metha)acrylic group with the view to produce novel biodegradable architectures not achievable with one synthetic approach alone.[27] In particular, HEMA-terminated-polyester macromonomers have been used in copolymerization with a plethora of methacrylic-acrylic monomers,[27] to produce graft-copolymers *via* controlled radical polymerization techniques such as ATRP[27] and RAFT.[27]

By rendering more accessible and easier the ROP step it would quickly broaden the number of possible novel "smart materials" that can be explored and developed.

Furthermore, it has also been shown that it is possible to produce block copolymers via sequential ROP reaction from a preformed macroinitiator using the same processing strategies with TBD. This confirms TBD as an accessible catalyst for solution-phase ROP of cyclic esters initiated by cleavable esters and, as the macro-initiators chosen were synthesized from caprolactone, it also confirms the high level of hydroxyl termination when the correct synthetic strategies were applied. Thus, TBD has been shown to be a practical alternative to metal-based catalysts that exhibits higher selectivity than Lipases in the reactions tested.

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Keywords: Ring-Opening Polymerization, triazabicyclodecene (TBD) catalyst, hydroxyethyl-methacrylate (HEMA) initiated, monofunctional -methacrylate polyesters

Data access statement

All raw data created during this research are openly available from the corresponding author (vincenzo.taresco@nottingham.ac.uk) and at the University of Nottingham Research Data

Management Repository (https://rdmc.nottingham.ac.uk/) and all analyzed data supporting this study are provided as supplementary information accompanying this paper.

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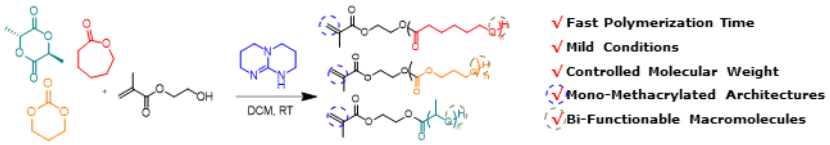
TOC

Methacrylated block co-polyesters were synthesized via TBD catalyzed ROP. TBD has been successfully employed as an active and selective catalyst for HEMA- initiated ROP of LA, TMC, and CL in order to synthesize, under mild and standard laboratory conditions, homopolymers and block copolymers with controlled molecular weight, low polydispersity and a mono-methacrylate final architecture.

Laura A. Ruiz-Cantu, Amanda K. Pearce, Laurence Burroughs, Thomas M. Bennett, Catherine E. Vasey, Ricky Wildman, Derek J. Irvine*, Cameron Alexander*, and Vincenzo Taresco*

Synthesis of Methacrylate-Terminated Block Copolymers with Reduced Transesterification by Controlled Ring-Opening Polymerization



Captions to Figures, Schemes and Tables

Scheme 1. ε-CL ROP dual activation mechanism in presence of a generic alcohol catalyzed by TBD.

Scheme 2. Schematic of TBD triggered self-acyl transfer of the methacrylic group of HEMA producing ethylene bis-methacrylate and ethylene glycol from 2 equivalent of HEMA.

Figure 1. Comparison of the kinetic profiles showing the level of transesterification achieve when varying the relative quantities of HEMA and TBD. An unpaired t-test ($p<0.05$ indicating significant difference) analysis was performed at each time-point and confirmed that significant differences were observed at each time point between the two selected initiator:catalyst ratios.

Figure 2. (Top) LA reaction scheme, polymer stoichiometry takes into account the corrected conversion. (bottom) Full ^{1}H-NMR spectrum of purified HEMAPDLLA 5000, in the 7.5 to 1.0 ppm spectral range. Note: residual catalyst and diethyl ether in the spectral range of 4.0 to 3.2 ppm.

Figure 3. A) HSQC NMR spectra of PDLLA, showing the presence of a single methacrylic species (inlay) in the final polymer and confirming the presence of a single HEMA end group for each polymeric chain. Peaks assigned a1 and b1 represent the two vinyl protons and c1 represents the vinylic carbon. **B)** HMBC ^{1}H-^{13}C NMR spectra of HEMA initiated PDLLA, demonstrating the presence and multiple bond correlations confirming (inlay top) a single methyl (methacrylate) species and (inlay bottom) a single carbonyl (methacrylate) species in the final polymer.

Figure 4. (Top) HEMA initiated TMC reaction scheme, polymer stoichiometry takes into account the corrected conversion and (Bottom) ^{1}HNMR spectrum. Inset, the vinyl region which exhibits only two peaks as expected, demonstrating a satisfactory controlled ROP without side-transesterification.

Figure 5. (Top) HEMAPCL reaction scheme, polymer stoichiometry takes into account the corrected conversion. (Bottom) ^{1}H-NMR spectrum of HEMAPCL (synthesized employing 1.5

% mol:mol TBD) (red traces) showing a reduction of the vinyl peaks related to the transesterification sub-products in the range of 6.2-5.5 ppm. (Inset) Difference in magnitude of transesterification between the polymer synthesized with 2.5% (blue trace) and 1.5% (red trace) catalyst.

Figure 6. LEFT. Stacking ^{1}H-NMR spectra, in the region between 6.5 to 3.5 ppm, of HEMAPCL macroinitiator (red trace), HEMAPCL-PTMC (green trace) and HEMAPCL-PDLLA (black trace) block copolymers showing that they characteristic peaks for PTMC and PLA end groups, there PCL, PTMC and PDLLA end group functionalities are shown as *, Δ and + respectively. **RIGHT.** GPC traces of HEMAPCL, HEMAPCL-PTMC and the HEMAPCL-PDLLA block copolymers.

Table 1. Characterization data for ROP polymers synthesized using HEMA, TBD. DP_0 = Theoretical M_n, DP_e = Experimentally observed M_n (NMR) post-purification and DP_c is the conversion corrected M_n.

	Polymer (TBD Mole % wrt Monomer)	**Time** (Min)	**DP_0:DP_c:DP_e**	**Mn[a]** (GPC) (g mol^{-1})	**Mn[b]** (NMR) (g mol^{-1})	**Đ**	**Yield[c]** (%)	**Trans** (%)
1	HEMAPDLLA (1.0)	< 3	35:33:35	4930	5090	1.18	95	--
2	HEMAPDLLA (1.0)	< 3	45:43:43	7860	6120	1.21	95	--
3	HEMAPTMC (1.0)	< 3	49:45:50	3600	5175	1.25	90	--
4	HEMAPCL (2.5)	120	45:--:--	3860	---	1.51	75	> 30
5	HEMAPCL (1.5)	120	22:17:24	3155	2780	1.14	75	< 3
6	HEMAPCL (1.5)	120	45:34:35	4310	4170	1.13	75	< 5
7	HEMAPCL-PTMC (1.0)	< 3	35+10:35+8: 35+10	6295	5190	1.09	80	< 3
8	HEMAPCL-PDLLA (1.0)	< 3	35+35:35+23 :35+28	8125	8200	1.15	80	< 3

a) Referenced to PMMA standards, [b)] calculated by ^{1}H-NMR, [c)] Quoted to nearest 5%

Figure 1

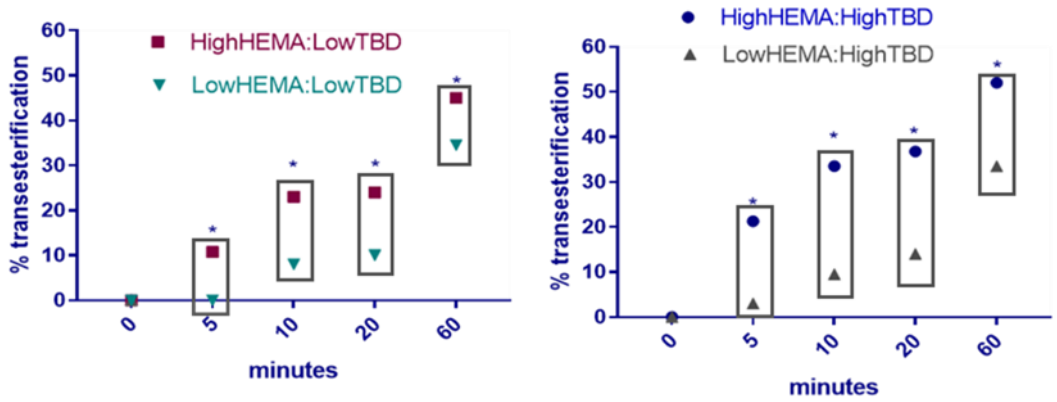
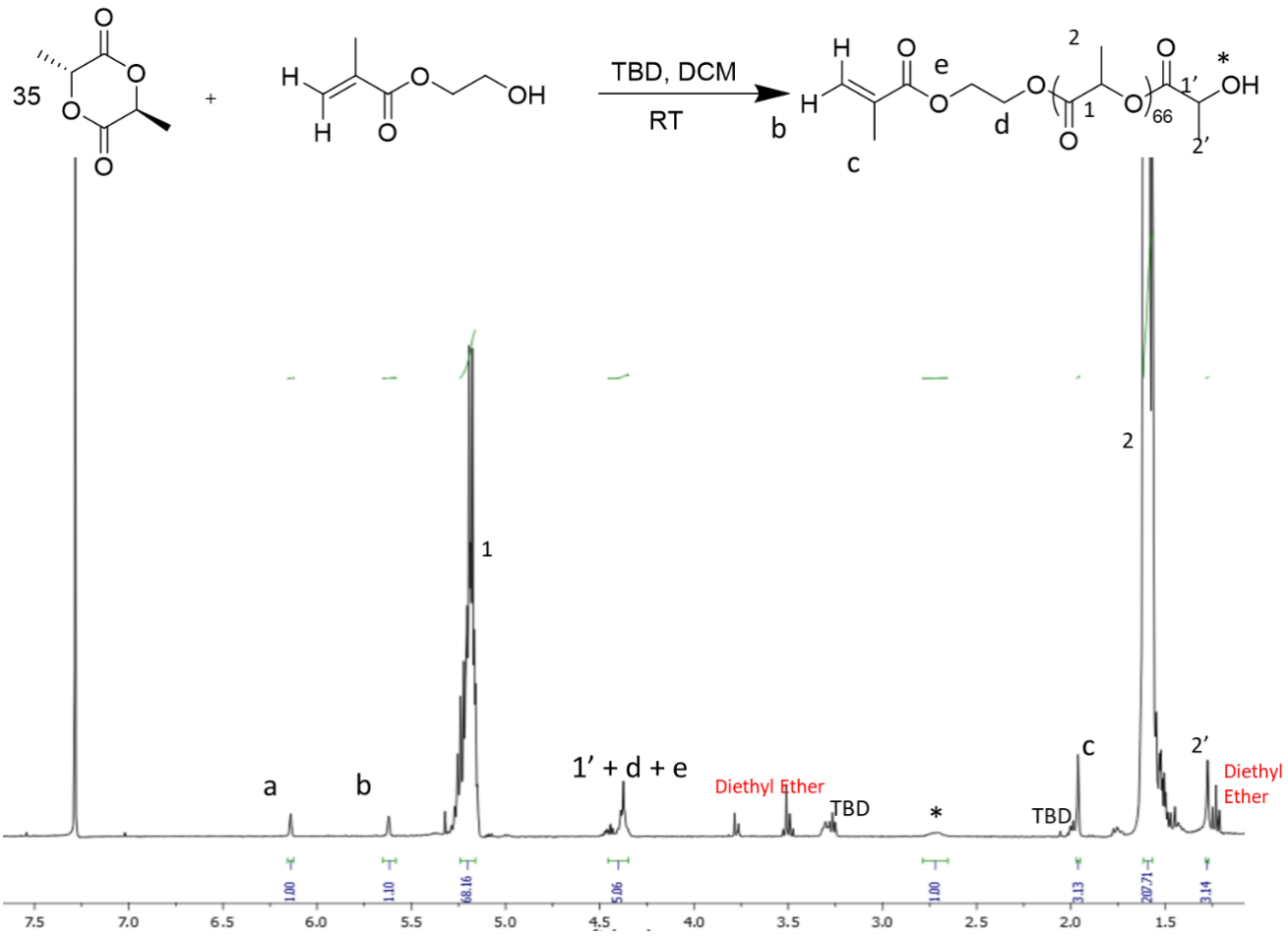

HighHEMA:LowTBD
LowHEMA:LowTBD
% transesterification
minutes
0
5
10
20
60
HighHEMA:HighTBD
LowHEMA:HighTBD
% transesterification
minutes

Figure 2


35
TBD, DCM
RT
a
b
c
d
e
1
2
1′
2′
66
OH
1′ + d + e
Diethyl Ether
TBD
Diethyl Ether
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
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2.0
1.5

603 **Figure 3**

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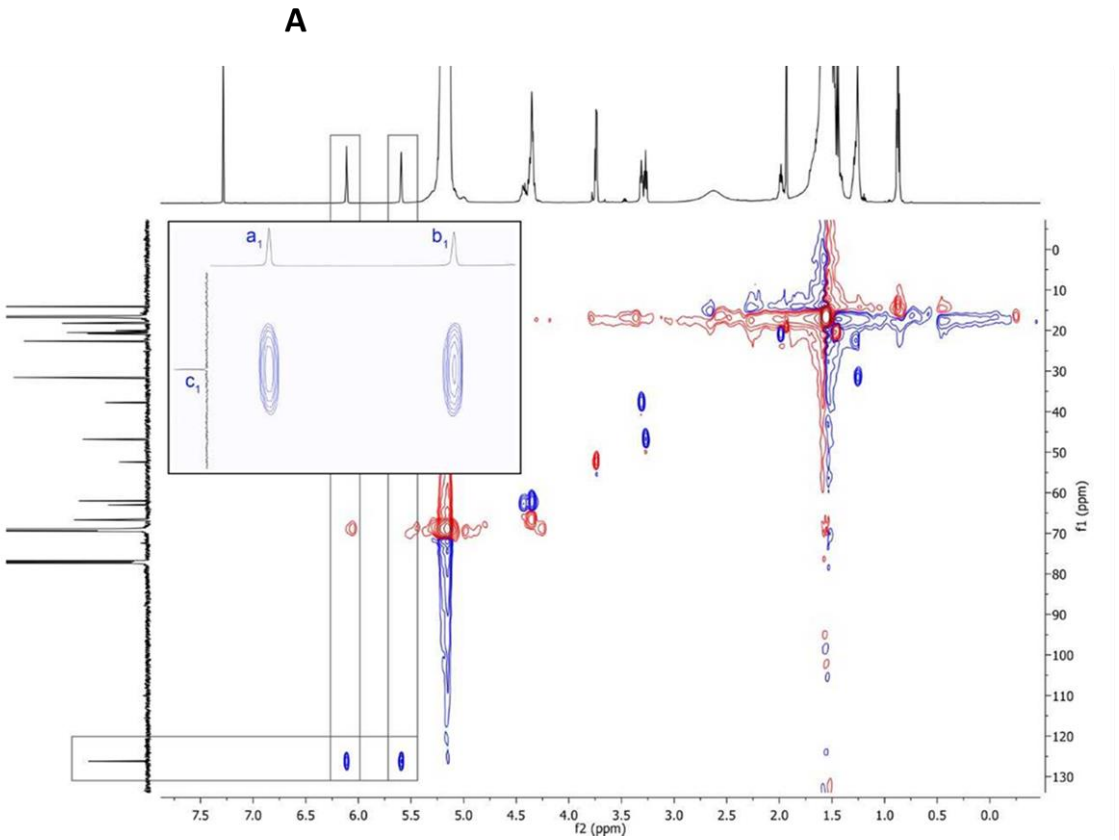

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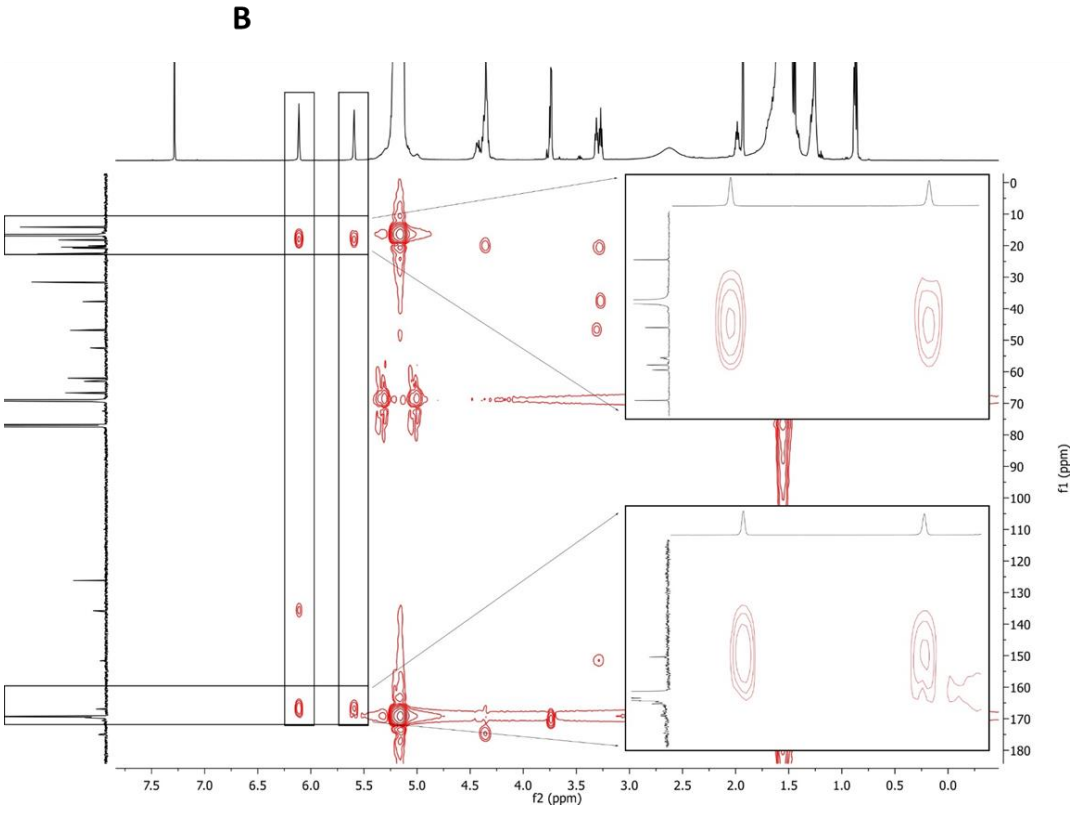

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Figure 4

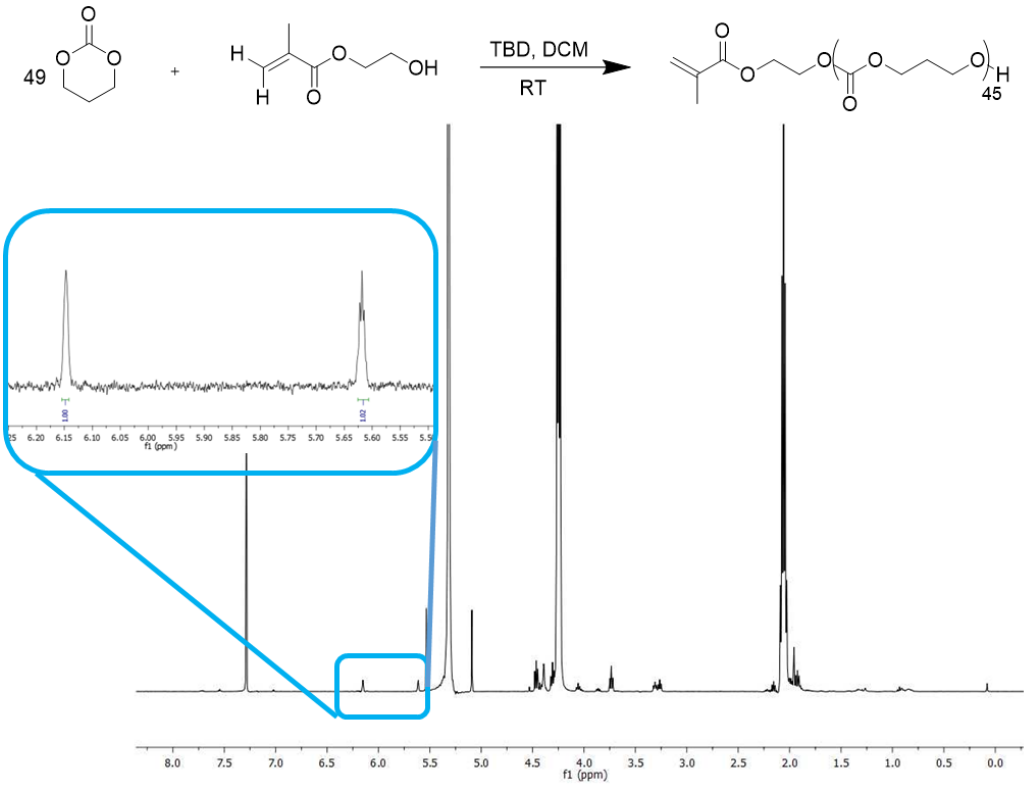


Figure 5

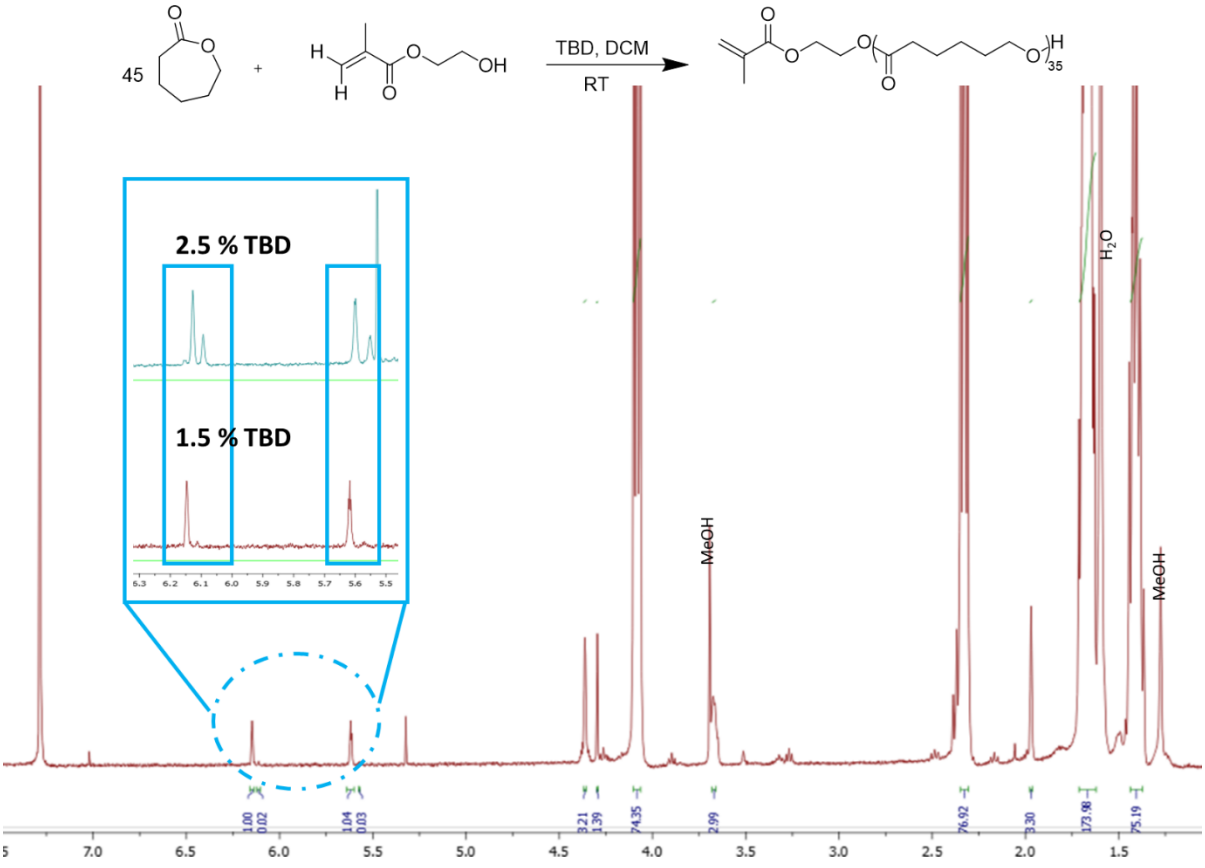
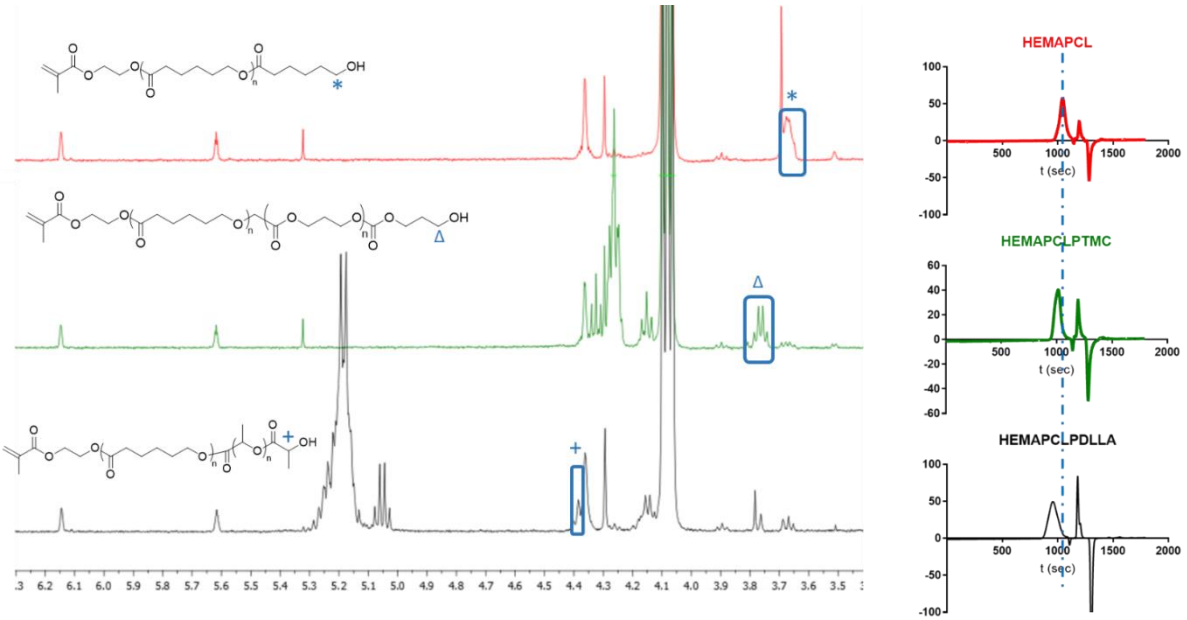
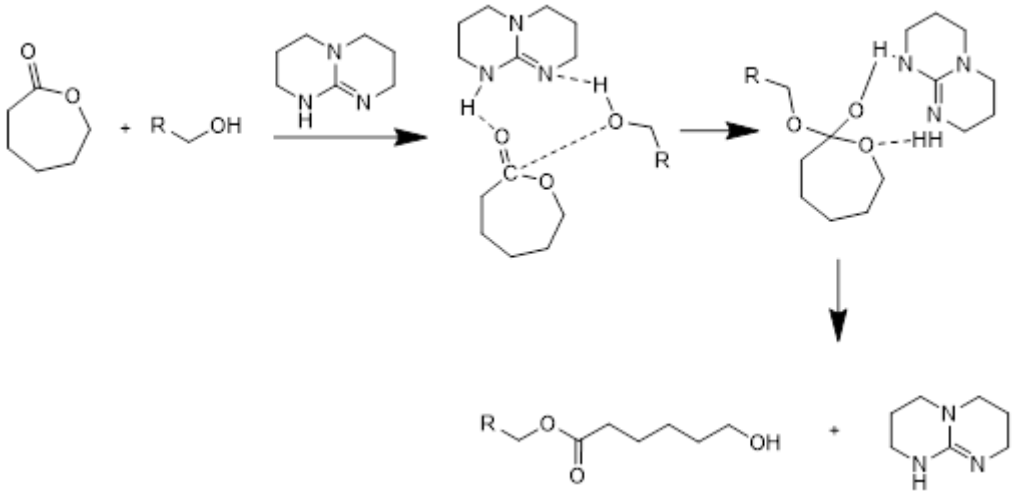


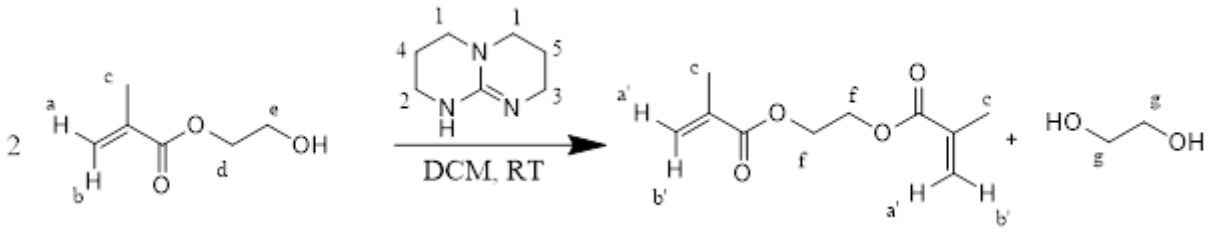
Figure 6



Scheme 1



Scheme 2



Supporting Information

Synthesis of Methacrylate-Terminated Block Copolymers with Reduced Transesterification by Controlled Ring-Opening Polymerization

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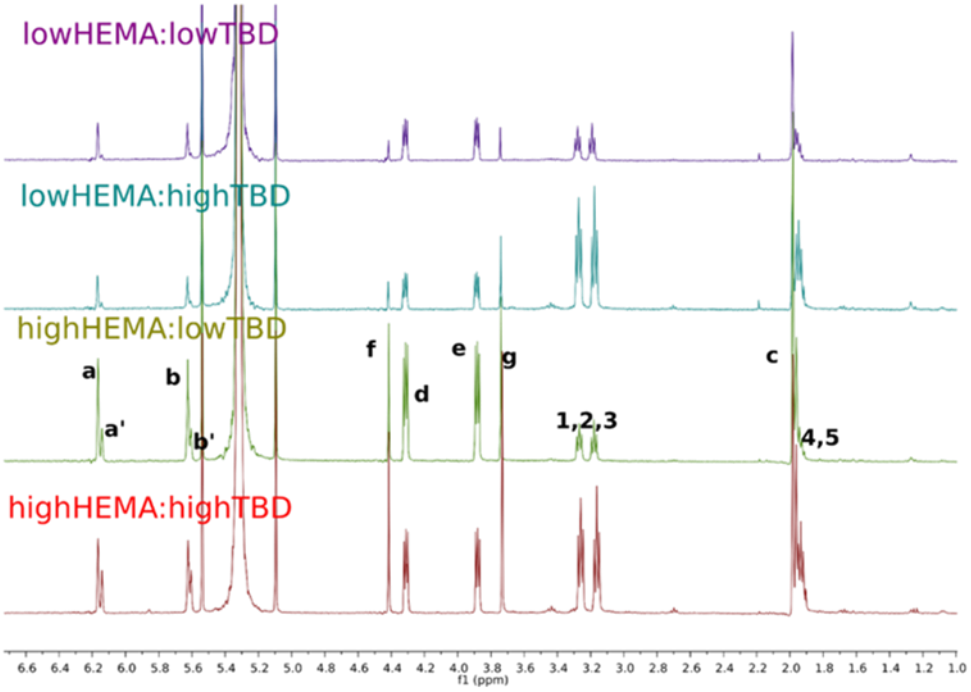

Figure S1. NMR spectra confirming feed ratio (HEMA:TBD) dependent presence of both ethylene bis-methacrylate and ethylene glycol as secondary species.

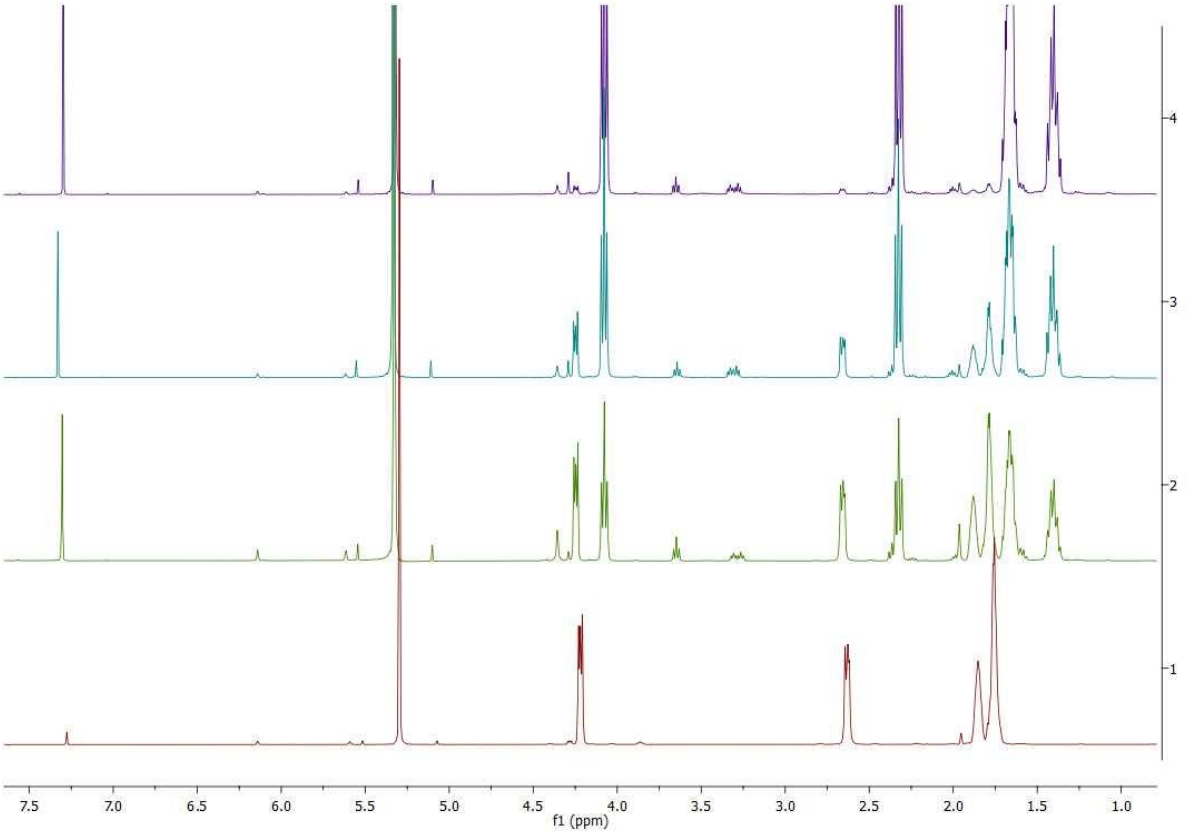

Figure S2: Kinetic profile of HEMAPCL ROP at 0, 20, 60, and 240 minutes (from bottom to top). Note: 240 min is shown to justify the full conversion of monomer to polymer.

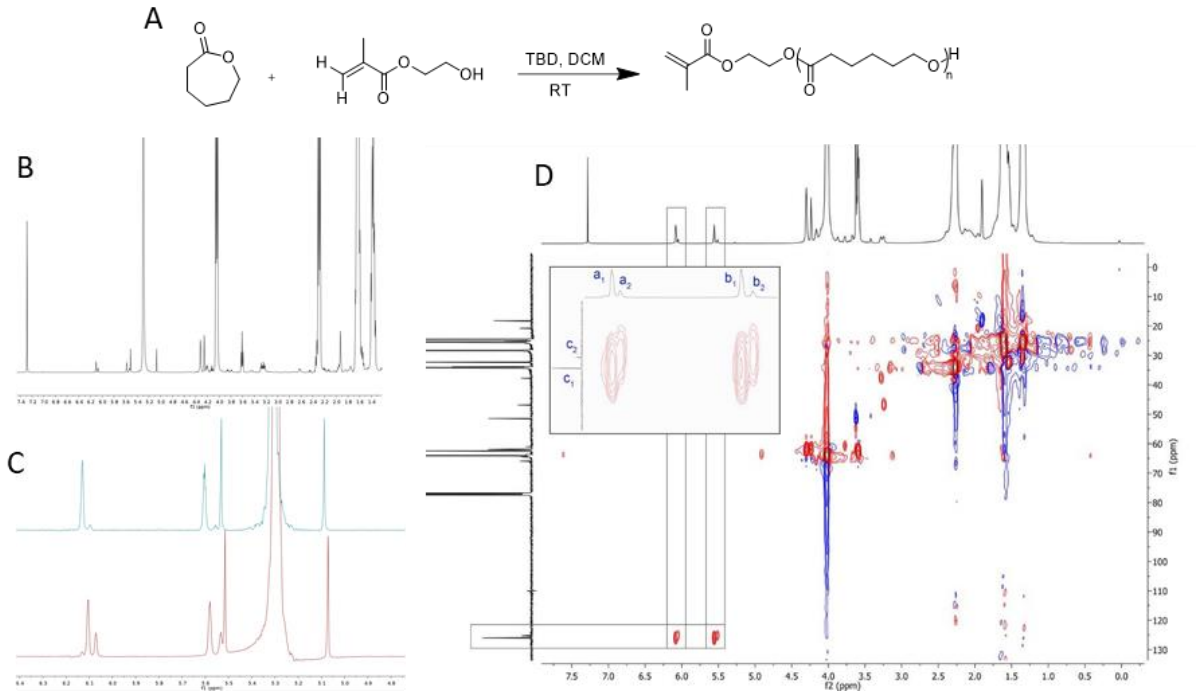

Figure S3. A) CL scheme of reaction. **B)** Full ^{1}H-NMR spectrum HEMAPCL. **C)** Stacked ^{1}H-NMR methacrylic protons region; peaks splitting in two limiting acyl transfer conditions (6.1-5.5 ppm). **D)** HSQC NMR spectra of HEMAPCL, confirming the presence of a two different methacrylic species (inlay) in the final polymer. Peaks assigned a1, a2, b1 and b2 represent the 4 vinyl proton species, and c1 and c2 represent the 2 vinylic carbon species in the final polymer. This effect is easily observed when a high amount of TBD was used leading to an uncontrolled polymer functionalization.

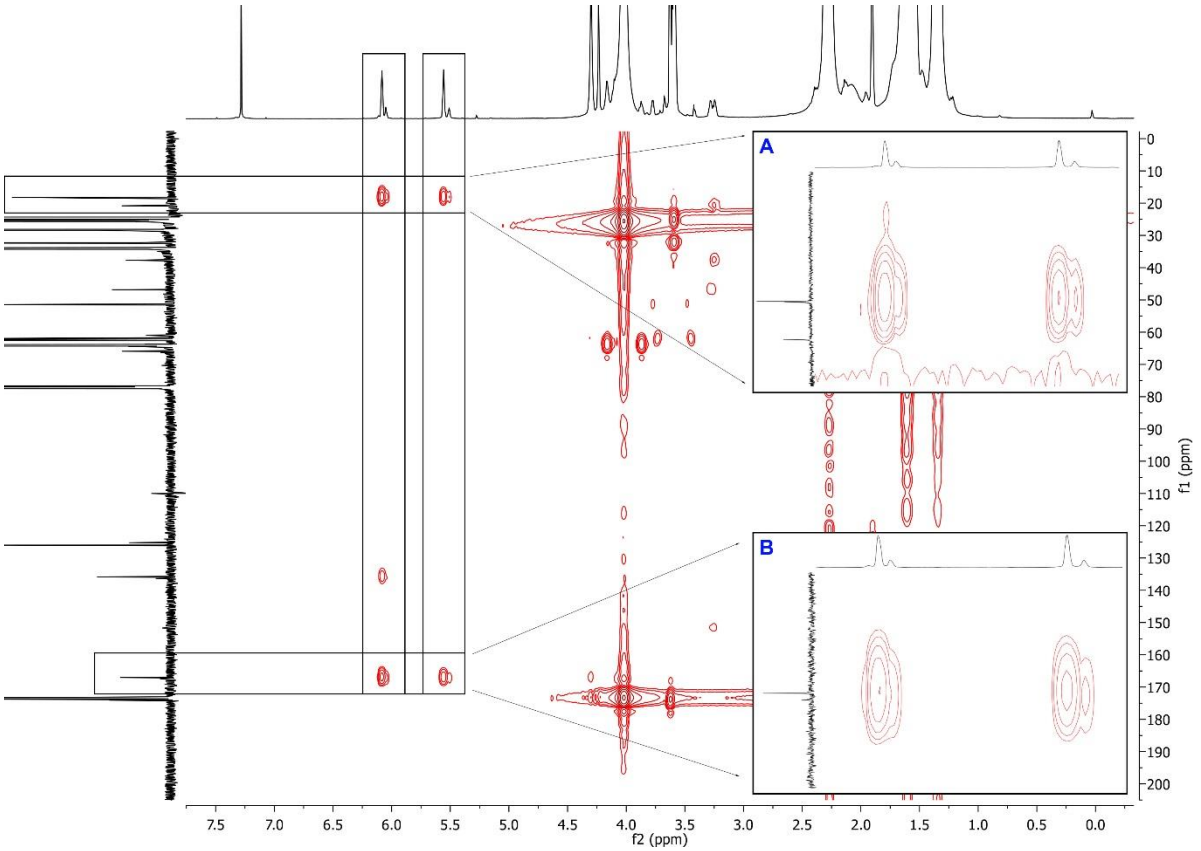

Figure S4. HMBC ^{1}H-^{13}C NMR spectra of HEMAPCL, demonstrating the presence and multiple bond correlations confirming (inlay a) two different methyl (methacrylate) species and (inlay b) two different carbonyl (methacrylate) species in the final polymer. This effect is easily observed when a high amount of TBD was used leading to an uncontrolled polymer functionalization.

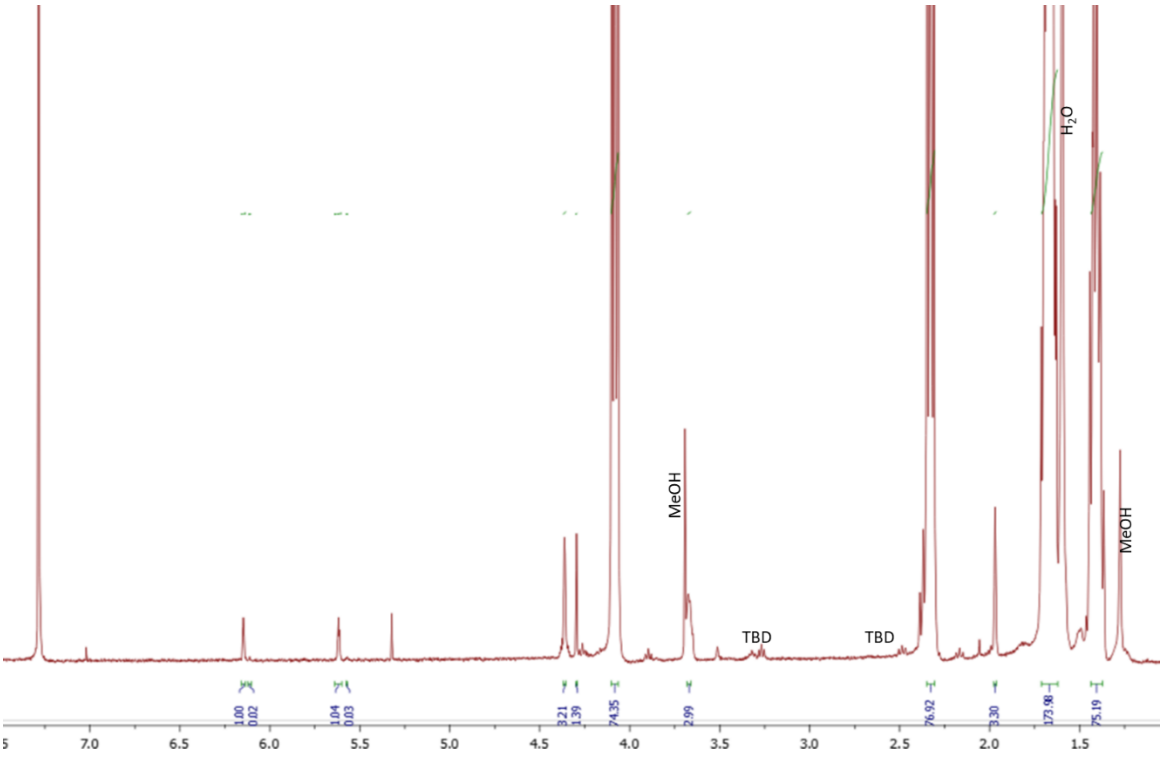

Figure S5. ^{1}H-NMR of HEMAPCL polymers showing full integration, vinyl peaks splitting ratios and PCLHEMA functionality proportions.