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5  **Synthesis of Methacrylate-Terminated Block Copolymers with Reduced**
6  **Transesterification by Controlled Ring-Opening Polymerization**
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25 **Abstract**

26 This work presents a robust method to achieve the synthesis of low molecular weight polyesters

27 via ring-opening polymerization (ROP) initiated by 2-hydroxyethyl-methacrylate (HEMA)

28 when using triazabicyclodecene (TBD) as catalyst. The effect that the HEMA:TBD ratio has

29 upon the final reaction rate and final polymer molecular architecture is discussed. The optimum

30 HEMA:TBD ratio and reaction conditions required to minimize competing transesterification

31 reactions were determined, in order to synthesize successfully the target ROP macromonomer

32 species containing only a single 2-methacryloyloxyethyl end-group. Additionally, to confirm

33 the terminal end-group fidelity of the product macromonomers and confirm TBD utility for

34 block copolymer manufacture, a small series of di-block polyesters were synthesized using

35 TBD and shown to exhibit good control over the final polymer structure whilst negating the

36 side transesterification reactions, irrespective of the monomers used.

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42     ## 1. Introduction

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44     Synthetic aliphatic polyesters, such as poly(lactic acid) (PLA), polycaprolactone (PCL), or

45     polycarbonates such as poly(trimethylene carbonate) (PTMC) and their copolymers are widely

46     used for pharmaceutical and environmental applications due to their controllable

47     biodegradability and low cost of production.[1,2] To extend their use into more demanding

48     applications, aliphatic polyesters with a wider variety of terminal or side-chain functionality are

49     required.[3,4] For example, the introduction of a reactive double-bond, as either a side chain or

50     an end-terminus on the main polymeric backbone, has paved the way for the production of

51     highly functional copolymers where the functionality can be used as platform for post-

52     functionalization or further polymerization.[5] In particular, the free hydroxyl group of 2-

53     hydroxyethylmethacrylate (HEMA) has been exploited as a ring-opening polymerization

54     (ROP) initiator for the production of polyesters bearing a methacrylate terminus.[6] These

55     HEMA-terminated-polyester macromonomers have been used in copolymerization with other

56     (metha)acrylic monomers,[7] to produce graft-copolymers *via* controlled radical polymerization

57     techniques such as ATRP and RAFT.[8, 9] However, the majority of the HEMA-based polyesters

58     and polycarbonates, including the examples reported above, have been prepared using Sn based

59     catalysts.[10-14] Unfortunately, Sn-residues can be difficult to remove during polymer

60     purification, which may compromise the quality of the final product and the potential

61     applicability.[15] An alternative route to polyesters utilizes enzymes as the catalyst system.[16]

62     However, enzyme catalyzed ROP (eROP) generally results in slow reactions with limited

63     control over the final polymer architecture.[17] In HEMA-initiated Lipase catalyzed eROP, even

64     at low monomer conversion, numerous unwanted by-products are routinely obtained. This has

65     been attributed to the low reaction selectivity of the enzyme, which allows competition between

66     ROP and other transesterification processes.[16,17] The use of triazabicyclodecene (TBD) as a

67     catalyst for ROP has been demonstrated with a variety of cyclic monomers, resulting in the

68 synthesis of polymers with controlled molecular weight and polydispersity.[18] The enhanced

69 catalytic activity of TBD when compared with other organo-catalysts such as 1,8-

70 Diazabicyclo[5.4.0]undec-7-ene (DBU) and 4-Dimethylaminopyridine (DMAP) results from

71 its ability to activate both monomer and initiator simultaneously.[19]

72 Building on these previous reports, the present study focuses on the development of a synthetic

73 strategy which ensures good selectivity towards polymerization when using an α,ω-functional

74 initiator such as HEMA, without compromising the end-group functionality. The reported

75 method shows that TBD can be used as a catalyst to obtain HEMA-terminated-polyesters from

76 three classes of monomer while demonstrating good control over the final polymer structure.

77 These monomers, D,L-lactide (LA), ε-caprolactone (CL) and trimethylene carbonate (TMC),

78 were chosen to exemplify a wide range of polymers commonly produced by ROP. Previous

79 reports of TBD catalyzed ROP have suggested that implementing the correct initial

80 initiator:catalyst ratio (HEMA:TBD in this case) is of vital importance for maintaining

81 polymerization control, due to the dual nature of the catalyst activating both monomer and

82 initiator.[18] Applying incorrect ratios and/or conditions can generate unwanted pre-

83 polymerization and concomitant acyl transfer side reactions. Therefore, we conducted a

84 systematic study of the extent of HEMA transesterification by varying the initial HEMA:TBD

85 ratio, to determine the optimum initiator:catalyst feed that would minimize undesired side

86 transesterification reactions in the synthesis of a target set of low molecular weight polymers.

87 To achieve the desired low molecular weight materials (i.e. DP's in the region 8 − 45), these

88 experiments require relatively high HEMA concentrations and so are susceptible to the onset

89 of side reactions. The present work has identified the reaction conditions which allowed the

90 successful production of mono(methyl)acrylated polymers with well-defined structures and

91 molecular weights, irrespective of the monomers used. More specifically, high conversion of

92 monomer into polymers as well as controlled molecular weight with respect to the initial [M]:[I]

93 feed-ratio, and polydispersitiy below 1.3 were simultaneously achieved. By identifying the

94     correct ratios of monomer, initiator and catalyst, the reported synthetic methodology has

95     overcome the previously described unsuccessful attempts to use TBD as catalyst in HEMA-

96     initiated ROP due to the formation of uncontrollable by-products.[20] Finally, to validate the

97     overall robustness and versatility of the proposed synthetic strategy, the chain-extension of a

98     HEMAPCL polyester from the hydroxyl-end group, to generate mixed block copolymers, was

99     successfully demonstrated.

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101     **2. Experimental Section**

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103     **2.1 Materials and Methods**

104     D,L-lactide 99% (LA) was purchased from Alfa Aesar (by Thermo Fisher Scientific).

105     Trimethylene carbonate (TMC) was purchased from Polyscience. ε-caprolactone (CL), extra

106     dry dichloromethane (DCM), deuterated chloroform (CDCl$_3$) and triazabicyclodecene (TBD)

107     were acquired from Sigma Aldrich. Hexane, diethyl ether and methanol were obtained from

108     Fisher. In all cases the vials were dried in an oven at 100 °C overnight prior to use, and the

109     HEMA and DCM were stored over molecular sieves and under an inert atmosphere.

110     **2.2 Synthesis**

111     **HEMA Transesterification Kinetics in Presence of TBD.** In a typical procedure, pre-

112     calculated amounts of HEMA and TBD were mixed in 3 mL of DCM at room temperature to

113     commence the chemical transformations. As the reactions proceeded, aliquots of the solution

114     were taken at predetermined time points (0, 5, 15 and 60 min) and were analyzed by ^{1}H NMR

115     spectroscopy. The quantities of HEMA and TBD were selected in order to mimic the reaction

116     conditions in which 1000 mg of εCL (8.77 mmol) would be present as the initial monomer

117     loading. Namely, HEMA was used at two distinct feed levels which mimicked a hypothetical

118     final targeted molecular weight of 2000 Da and 10,000 Da respectively. They were defined as

119     the "high" and "low" levels of HEMA (High: 0.46 mmol, 60 mg and Low: 0.10 mmol, 13 mg).

120   TBD was also systematically introduced and two levels to reproduce the limiting reaction

121   conditions of 1 and 2.5 % mol:mol ratios when compared to the monomer, i.e. these are the

122   "low" (12 mg) and "high" (30 mg) TBD definitions. Four different boundary transesterification

123   scenarios were then applied and analyzed with respect to the result of the ROP reaction. An

124   unpaired t-test ($p < 0.05$ indicating significant difference) analysis was performed at each time-

125   point for each selected ratio.

126   **HEMA Initiated ROP of the Cyclic Monomers.** ROP experiments were performed adopting

127   'standard laboratory' conditions, i.e. ambient temperature and atmosphere.[21] The desired

128   amount of cyclic monomer (500-1000 mg) and HEMA-initiator ([M]:[I] or $DP_0$ ratios targeted

129   to produce final molar masses of either 2500 or 5000 Da) were weighed into a vial, which had

130   been dried in an oven at 100 °C overnight and capped with a rubber septum. DCM (10 ml), was

131   then added via syringe and the mixture was allowed to dissolve at room temperature (RT) for

132   5-10 minutes. Varying amounts of catalyst (from 1-2.5 % mol/mol of TBD with respect to

133   monomer) were then added to trigger the ring-opening process. Reactions were observed to

134   occur     in     time-frames     ranging     from     1-240     minutes,     according     to     the

135   monomer:initiator :solvent :catalyst  adopted ratios. The reaction was terminated by catalyst

136   deactivation upon adding an acidic solution and the polymer purified by means of  multiple

137   precipitation steps and dried in a vacuum oven.

138   **HEMAPCL (Entries 7 and 8, Table 1) Initiated ROP.** The required amount of cyclic

139   monomer (500-1000 mg) and PCLHEMA-initiator to give the [M]:[I] ratios needed to achieve

140   a targeted extension of 10 units for TMC and 35 units for LA, were weighed into a vial which

141   had been dried in an oven at 100 °C overnight and capped using a rubber septum. DCM (10

142   ml), which had been dried over molecular sieves and kept under inert gas environment, was

143   then added via syringe and the mixture was allowed to dissolve at RT for 5-10 minutes. A

144   certain amount of TBD equal to 1% mol:mol compared to the amount of monomer was then

145    added to trigger the ring-opening process. The TBD was quenched by adding an acid solution

146    after 3 minutes to terminate the reaction.

147    **2.3 Polymer Characterization**

148    **HEMA-PDLLA.** Characterization data was obtained after three precipitation cycles in hexane

149    and diethyl ether. *$^1$H NMR (400 MHz, CDCl$_3$):* δ 6.14 (s, 1H), 5.61 (s, 1H), 5.19 (m,

150    2H*[M]:[I]), 4.36 (m, 5H), 1.95 (m, 3H), 1.59 (m, 6H*[M]:[I]), presence of residual catalyst

151    and solvents (from synthesis and purification) can be spotted. *Conversion*: monomer to final

152    polymer conversion determined by NMR was 90-95% with a recorded gravimetric yield of 70-

153    75% (700-750 mg when aiming at theoretical 1000 mg of polymer). Further characterization

154    shown in Table 1. *Molecular Weight:* As all polymers exhibited transesterification levels below

155    10%, $M_n$ values were evaluated by $^1$H NMR.[6,8]

156    **HEMA-PTMC.** Characterization data was obtained after three precipitation cycles in hexane

157    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

158    (m, 4H*[M]:[I]), 3.74 (m, 2H), 2.04 (m, 2H *[M]:[I]), 1.96 (m, 3H), presence of residual

159    catalyst and solvents (from synthesis and purification) can be spotted. *Conversion:* monomer

160    to final polymer conversion determined by NMR was 90-95% with a recorded gravimetric yield

161    of 50-60% (500-600 mg when aiming at theoretical 1000 mg of polymer). Further

162    characterization shown in Table 1. *Molecular Weight:* As all polymers exhibited

163    transesterification levels below 10% $M_n$ values were evaluated by $^1$H NMR.[6]

164    **HEMA-PCL.** Characterization data was obtained after purification *via* three cycles of

165    precipitation in cold MeOH. *$^1$H NMR:* (400 MHz, CDCl$_3$): δ 6.14 (s, 1H), 5.61 (s, 1H), 4.40-

166    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,

167    4H*[M]:[I]), 1.41 (m, 2H*[M]:[I]), presence of residual catalyst and solvents (from synthesis

168    and purification) can be spotted. *Conversion:* monomer to final polymer conversion determined

169    by NMR was 75% with a recorded gravimetric yield of 70% (700 mg when aiming at theoretical

170     1000 mg of polymer). Further characterization is shown in Table 1. *Molecular Weight:* When

171     the degree of transesterification was below 10%, $M_n$ values were evaluated by $^1$H NMR.[6]

172     **HEMAPCL-PTMC.** Characterization data was obtained after purification *via* three cycles of

173     precipitation in cold hexane-diethyl ether: *$^1$H NMR (400 MHz, CDCl₃):* δ 6.14 (s, 1H), 5.61 (s,

174     1H), 4.40-4.20 (m, from HEMA and TMC), 4.08 (t, 2H*35), 3.80 (m, 2H), 2.33 (t, 2H*35),

175     1.97 (m, 3H), 2.04 (m, 2H *[M]:[I]), 1.67 (m, 4H*35), 1.41 (m, 2H*35), presence of residual

176     catalyst and solvents (from synthesis and purification) can be spotted. *Conversion*: TMC

177     monomer to final block copolymer monomer conversion determined by NMR was 80% with a

178     recorded gravimetric yield of 70%. Further characterization shown in Table 1. *Molecular*

179     *Weight:* As all polymers exhibited transesterification levels below 10% $M_n$ values were

180     evaluated by $^1$H NMR.[6]

181     **HEMAPCL-PDLLA.** Characterization data was obtained after purification *via* three cycles of

182     precipitation in cold hexane-diethyl ether: *$^1$H NMR (400 MHz, CDCl₃):* $^1$H NMR (400 MHz,

183     CDCl₃): δ 6.14 (s, 1H), 5.61 (s, 1H), 5.19 (m, 2H*28), 4.40-4.20 (m, 5H from LA end group

184     and HEMA), 4.08 (t, 2H*35), 3.68 (m, 2H), 2.33 (t, 2H*35), 1.97 (m, 3H), 1.67 (m,

185     4H*35), 1.59 (m, 6H*28) 1.41 (m, 2H*35), presence of residual catalyst and solvents (from

186     synthesis and purification) can be spotted. *Conversion*: LA monomer to final block copolymer

187     monomer conversion determined was 80% with a recorded gravimetric yield of 75%. Further

188     characterization shown in Table 1. *Molecular Weight:* As all polymers exhibited

189     transesterification levels below 10% $M_n$ values were evaluated by $^1$H NMR.[6]

190     **2.4 Characterization Methodologies**

191     **NMR Spectroscopy:** $^1$H NMR spectra were recorded on a Bruker AV3400 400.1 MHz

192     spectrometer using CDCl₃ as the solvent reference (7.26 ppm). Chemical shifts are expressed

193     in parts per million (d) downfield from internal standard tetramethylsilane.

194     **2D-NMR Spectroscopy:** $^1$H - $^{13}$C heteronuclear single quantum correlation (HSQC) and $^1$H -

195     $^{13}$C heteronuclear multiple-bond correlation (HMBC) (one-bond suppression) spectra were

196    recorded on a Bruker AV 3500 (500.1 MHz for $^1$H, 125.8 MHz for $^{13}$C) spectrometer using

197    CDCl$_3$ as the solvent reference (7.26 ppm for $^1$H, 77.16 ppm for $^{13}$C). The final HSQC spectrum

198    depicts a peak for each unique pair of directly coupled nuclei ($^1$H - $^{13}$C). The final HMBC

199    spectrum depicts correlations between coupled nuclei pairs ($^1$H - $^{13}$C) that are separated by two

200    – four bonds, with direct one-bond correlations suppressed.

201    **GPC Analysis:** Gel Permeation Chromatography (GPC) was performed by using a PL50+

202    Polymer Laboratories system. An RI constructed calibration curve from PMMA (Mn range

203    350000-620 Da) was adopted to analyze polymer molar masses. 2 PL mixed-D columns at

204    50 °C were employed, using 0.1 % LiBr DMF as the mobile phase with a flow rate of 1 ml/min.

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211    **3. Results and Discussion**

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213    A number of prior reports have shown that TBD is an efficient acyl-transfer and

214    transesterification catalyst. Its high activity is linked to its ability to interact with both initiator

215    and monomer (**Scheme 1**),[22] and it has been proposed to follow a pseudo bifunctional

216    nucleophilic catalytic mechanism.[23] This feature allows TBD to catalyze the ROP reaction of

217    ε-CL, commonly known as refractive monomer in ROP process, without the need to adopt a

218    co-catalyst (for example a thiourea) that is required for alternative organocatalyst such as

219    DBU.[22]It the same way tin octoate, which is currently the most widely used catalyst for ROP,

220    exploits a coordination-insertion process allowing interactions with both initiator (nucleophile)

221    and monomer without the need of a co-catalyst.[20] However, the main drawbacks related with

222    tin octoate are the intrinsic toxicity and the high temperature required to activate any ROP

223     reactions enabling intermolecular and intramolecular esterification to occur and thus

224     broadening the final polymer molecular polydispersity.[22] .

225     On the basis of this, in the present work, it was speculated that TBD can also trigger a self-acyl

226     transfer of the methacrylic group of HEMA, producing ethylene bis-methacrylate and ethylene

227     glycol (**Scheme 2**).

228     This was supported by both species being detected in the ^{1}H NMR of the reaction mixture

229     (**Figure S1**). This HEMA self-transesterification can compete, as side reaction, with the ROP

230     process by altering the concentration and/or identity of the active initiator. Consequently, by

231     affecting the [M]:[I] ratio, the presence of this competitive acyl transfer process can severely

232     affect the quality of the final polymer in terms of molecular weight and architecture.

233     In order to evaluate the magnitude of the effect of the acyl transfer reaction, a kinetic study was

234     conducted by systematically varying the "high" and "low" [HEMA]:[TBD] ratios to mimic the

235     concentration ranges applied in an ideal ROP reaction to synthesize a 2000 Da and 10,000 Da

236     product. The results of these experiments are compared in **Figure 1** and the supporting NMR

237     data are shown in **Figure S1**.

238     These data show that transesterification is more pronounced when both the concentrations of

239     HEMA and TBD are at the "high" values, reaching almost 25 % of transesterification within 5

240     minutes. However, when the amount of HEMA was kept "high", while the amount of TBD was

241     reduced to "low", a reduction in transesterification was observed during the same time-frame,

242     namely, only 8-10 % of unwanted reaction was detected. Furthermore, when HEMA was

243     reduced ("low"), as expected, the kinetics of the reaction considerably reduced and,

244     independently of the TBD concentration, only 5-6 % of transesterification occurred after 5 min.

245     An unpaired t-test ($p < 0.05$ indicating significant difference) analysis was performed at each

246     time-point and confirmed that significant differences were observed at each time point between

247     the two selected initiator:catalyst ratios. Therefore, this set of experiments demonstrated that

248     keeping the HEMA concentration at the "low" level is important to reduce side-reactions.

249  We subsequently explored the ability of TBD to selectively catalyze ROP of lactide (LA), ε-

250  caprolactone (CL) and trimethylene carbonate (TMC) monomers, [18,22,23] while controlling

251  methacrylate transfer side reactions. LA polymerizations (**Figure 2**) were performed with

252  [LA]:[HEMA] ratios targeting final molecular weights of 5000 Da and 6500 Da (i.e. $DP_0$ of 35

253  and 45) respectively.

254  PDLLA polymers were produced within seconds of introducing the catalyst at room

255  temperature. The reactions exhibited good control of the molecular weight (Đ ranging from

256  1.18-1.21, **Table 1**), which was in agreement with prior literature reports.[18,23]

257  The experimental DP of the PDLLA products (Entries 1 and 2, **Table 1**) were observed to match

258  the theoretical DP and subsequent analysis by ^{1}H-NMR (**Figure 2**) confirming the presence of

259  only a single set of methacrylic proton peaks indicating a good control of the polymer and no

260  evidence of transesterification.

261  Furthermore, 2D-NMR experiments indicated that the ROP mechanism was predominant, with

262  the HSQC spectrum (**Figure 3**) showing a single acrylic (vinylic) carbon peak directly

263  correlated to the two methacrylic protons (see inset **Figure 3A**). This confirms the presence of

264  only a single HEMA-terminated group per polymeric chain. The HMBC spectrum further

265  confirms a single correlation between the two methacrylic protons and both a single carbonyl

266  and methyl group species (**Figure 3B**), with no additional peaks related to the methacrylic

267  protons observed.

268  Good control over the final polymer features was also observed for the PTMC mono-

269  methacrylic polymer (**Figure 4**). Despite a change in the molecular structure of the cyclic

270  monomer, fast kinetics similar to that exhibited by the PDLLA were observed. The final

271  molecular weight was in agreement with the target of approximately 5000 Da as confirmed by

272  ^{1}H-NMR and GPC (Entry 3, **Table 1**). This confirmed the ability of TBD to selectively catalyze

273  the ROP of cyclic monomers of different molecular structures which exhibit fast polymerization

274  kinetics.

275  To exemplify further the importance of the TBD-catalyzed ring-opening kinetics to the

276  production of defined polymer structures, the polymerization of ε-CL was then explored, due

277  to its lower ROP reactivity when compared to monomers such as LA. [18] In agreement with the

278  literature, a slower rate of polymerization was observed for CL when compared to LA and TMC

279  and as a consequence the overall reaction was noted to be less controlled (Entry 4-6, **Table 1**

280  and **Figure S3**). Analysis of the final products showed that this was due to both the tendency

281  of the PCL terminal chain group to transesterify[18,24] and an increased level of HEMA:TBD

282  interaction prior to polymerization which generated a diol initiator over time. When the 1%

283  mol:mol of TBD:Monomer ratio was used as for TMC and LA, no CL polymerization was

284  observed. This was attributed to the slow ROP kinetics and consequent dominance of the self-

285  transesterification kinetics of HEMA. Thus, a TBD:monomer ratio of 2.5 % mol:mol was then

286  adopted. Polymerization was observed, and the reaction was complete within 120-240 min (see

287  Entry 4, **Table 1** and **Figure S2**). The formation of sub-products was evident in the NMR

288  analysis (**Figures S3** and **Figure 5** see methacrylate peaks inset). Thus, it was not possible to

289  evaluate the final molecular weight by ^{1}H NMR, due to a splitting of the HEMA peaks and the

290  contribution to the polymeric CL peaks arising from polymer formed from other initiating

291  species such as the diol. As a consequence, a broader value of Đ (1.55) was observed in the

292  GPC data. The ^{1}H-NMR spectra showed that the transesterification occurred over time as the

293  splitting of the vinyl peaks in the 6.20 to 5.50 ppm region increased as the reaction proceeded

294  (see **Figure S2-S3**). This splitting was in accordance with the initial screening reported in

295  **Figure S1**.

296  A series of 2D-NMR experiments were performed, to clarify the presence of both HEMA and

297  methacrylic end-capped terminal groups and to link unambiguously the vinyl peak splitting to

298  a transesterification process. The HSQC spectrum (**Figure S3)** showed the presence of two

299  different types of carbons correlating to the two sub-families of methacrylic proton peaks. This

300  indicates the presence of two unique end-capping methacrylic groups, and thus an undesired

301 end-terminal methacrylic group in addition to the HEMA-initiation end-terminus. This was

302 further exemplified in the HMBC spectra, where two sets of multiple-bond correlations between

303 the two types of methacrylic protons and both of the two kinds of carbonyl and methyl group

304 species were observed (**Figure S4**).

305 By reducing the TBD loading to 1.5 % mol:mol, HEMAPCL could be synthesized with a

306 significant reduction of the side acyl transfer reactions (see ^{1}H-NMR, **Figure 5, Figure S5** and

307 Entry 6**, Table 1** ).

308 Using these conditions and restricting the reaction time to 120 min, an average conversion of

309 monomer to polymer of *circa* 60-70 % could be reached before the reaction was quenched. This

310 confirmed that by reducing the amount of TBD, and thus tuning the initial HEMA:TBD ratio,

311 there was a drop in the undesired transesterification reaction at the 1.5 %mol:mol when

312 compared with the PCL synthesized using 2.5 % mol:mol of catalyst (see inset within **Figure**

313 **5**). At this TBD concentration only 2 to 5 % of bis-methacrylic chains were observed in a series

314 of experiments with targeted molecular weights of approximately 2500 and 5000 Da (Entries 5

315 and 6, **Table 1**) compared to the ~ 50% observed in prior literature by using Lipase catalysts.[16]

316 Finally, in order to assess the level of retention of the hydroxyl group at the end of each

317 polymeric chain and thus confirming good end group fidelity, HEMA initiated PCL with a

318 targeted $DP_0$ of 35 (see Entry 6, **Table 1**) was then employed as a macroinitiator for the

319 synthesis of block copolymers with TMC or LA as the chain extending monomers. The targeted

320 $DP_0$ for the second TMC block was 10 units whilst for LA was 35 units (i.e. $35 + DP_o10$ of

321 TMC or $35 + DP_o 35$ of LA). After the polymerization of TMC and post-purification steps an

322 experimental $DP_e$ of 8 was observed (Entry 7, **Table 1** and **Figure 6**). For the LA extension, a

323 conversion of 80 % in the second block of PDLLA was achieved to reach a $DP_e$ of 28 (Entry 8

324 **Table 1**), which is what would be expected from the conversion corrected target. In both cases,

325 the characteristic NMR peaks attributed to the main chains TMC and LA were present in spectra

326 of the final copolymer as were the characteristic end groups for the second added monomer

327 (**Figure 6 Left**). Increases in the molecular weight of the polymers compared to that of the

328 HEMA initiated PCL-macroinitiator (**Figure 6 Right**) were evident in the GPC chromatograms,

329 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

330 respectively. This confirmed the formation of block copolymers. The existence of only a single

331 peak for the sequential block copolymers proved the successful control over the addition of the

332 second monomer onto the initial HEMAPCL macroinitiator.

333 The success of the regrowth from the macro-initiator in this proof-of-concept experiment

334 confirmed both the control of the reaction conditions for the production of block copolymers,

335 as well as the end group (hydroxyl group in this case) fidelity that can be achieved in the

336 production of the macro-initiator. The increase in molecular weight shown in the GPC traces

337 (Entries 7 and 8, **Table 1**) to produce single monodispersed peaks confirmed both the

338 availability of the hydroxyl PCL terminal group to initiate the polymerization of the second

339 sequential block and the level of control exercized over the extension step on the initial

340 HEMAPCL macro-initiator.

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345 **4. Conclusions**

346 The synthetic strategy reported here is the first example of successful HEMA-initiated ROP

347 catalyzed by TBD. To highlight the novelty and the broad applicability of the synthetic

348 methodology developed in the present work, it is important to note that in recent work it has

349 been reported that when TBD was adopted, as catalyst of ROP reactions, with HEMA as

350 nucleophilic initiator,  no controlled polymerization events were observed due to a series of

351 uncontrollable side reactions.[20]Consequently, tin octoate was needed to prepare the targeted

352 (metha)acrylated-macromolecules. On the contrary, the present study has demonstrated that

353 TBD indeed can be employed as an active and selective catalyst for HEMA-initiated ROP of

354     LA, TMC, and CL, to synthesize polymers and block copolymers with controlled molecular

355     weight, low polydispersity and a mono-methacrylate final architecture (see **Table 1**).

356     Success in achieving the target ROP while minimizing polyester transesterification reactions

357     was demonstrated to be minimal when fast polymerization kinetics were obtained from the

358     monomer of choice. In the cases where monomer types presenting slower kinetics were

359     employed, both significant levels of "by-products" (> 50%) and subsequent loss of control over

360     the molecular structure of the polymer was observed. This study has shown that these unwanted

361     side reactions could be minimized (i.e. reduced to < 5%) by controlling the relative

362     HEMA:TBD ratio and the reaction time.

363     This study has also concluded that TBD is a more efficient ROP catalyst when compared to

364     lipases. In fact, it has been well documented that lipases cannot discriminate ROP from the

365     transesterification sub-processes in the presence of cleavable ester initiators such as HEMA,

366     even at low monomer conversion.[16,17] This leads to the production of di-methacrylated

367     macromolecular chains and an inability to produce well-defined polymers. By comparison, this

368     study has demonstrated that, by using TBD as a catalyst in small scale reactions and adopting

369     the simple precautions of controlling the catalyst concentration and reaction times, mono-

370     methacrylated chains with no (for HEMA initiated PDLLA and HEMA initiated PTMC) or

371     limited (<5 % for HEMA initiated PCL) di-methacrylated chains can be produced. Additionally,

372     this ROP reaction can be achieved with reagents that are readily available and under mild

373     reaction conditions, i.e. room temperature and atmosphere, in comparison to tin octoate that

374     requires high temperature and longer reaction time. All the aforementioned properties of TBD

375     will facilitate the production of biodegradable polymers bearing an active (metha)acrylic group

376     with the view to produce novel biodegradable architectures not achievable with one synthetic

377     approach alone.[27] In particular, HEMA-terminated-polyester macromonomers have been used

378     in copolymerization with a plethora of methacrylic-acrylic monomers,[27] to produce graft-

379     copolymers *via* controlled radical polymerization techniques such as ATRP[27] and RAFT.[27]

380 By rendering more accessible and easier the ROP step it would quickly broaden the number of

381 possible novel "smart materials" that can be explored and developed.

382 Furthermore, it has also been shown that it is possible to produce block copolymers via

383 sequential ROP reaction from a preformed macroinitiator using the same processing strategies

384 with TBD. This confirms TBD as an accessible catalyst for solution-phase ROP of cyclic esters

385 initiated by cleavable esters and, as the macro-initiators chosen were synthesized from

386 caprolactone, it also confirms the high level of hydroxyl termination when the correct synthetic

387 strategies were applied. Thus, TBD has been shown to be a practical alternative to metal-based

388 catalysts that exhibits higher selectivity than Lipases in the reactions tested.

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401 **Keywords:** Ring-Opening Polymerization, triazabicyclodecene (TBD) catalyst, hydroxyethyl-
402 methacrylate (HEMA) initiated, monofunctional -methacrylate polyesters
403

404 **Data access statement**

405 All raw data created during this research are openly available from the corresponding author

406 (vincenzo.taresco@nottingham.ac.uk) and at the University of Nottingham Research Data

407    Management Repository (https://rdmc.nottingham.ac.uk/) and all analyzed data supporting this

408    study are provided as supplementary information accompanying this paper.

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411    **References**

412    [1]    C. Jérôme, P. Lecomte, *Adv. Drug Deliv. Rev.* **2008**, *60*, 1056.

413    [2]    J. Feng, R. X. Zhuo, X. Z. Zhang, *Prog. Polym. Sci.* **2012**, *37*, 211.

414    [3]    R. Tong, *Ind. Eng. Chem. Res.* **2017**, *56*, 4207.

415    [4]    H. Seyednejad, A. H. Ghassemi, C. F. Van Nostrum, T. Vermonden, W. E. Hennink, *J.*

416    *Control. Release* **2011**, *152*, 168.

417    [5]    Y. Zhang, D. Chu, M. Zheng, T. Kissel, S. Agarwal, *Polym. Chem.* **2012**, *3*, 2752.

418    [6]    Y. Zhao, G. He, W. Guo, L. Bao, M. Yi, Y. Gong, S. Zhang, *Polym. Chem.* **2016**, *7*,

419    5698.

420    [7]    Y. You, C. Hong, W. Wang, W. Lu, C. Pan, *Macromolecules* **2004**, *37*, 9761.

421    [8]    H. Shinoda, K. Matyjaszewski, *Macromolecules* **2001**, *34*, 6243.

422    [9]    M. Le Hellaye, C. Lefay, T. P. Davis, M. H. Stenzel, C. Barner-Kowollik, *J. Polym.*

423    *Sci. Part A Polym. Chem.* **2008**, *46*, 3058.

424    [10]    R. Ferrari, C. Colombo, M. Dossi, D. Moscatelli, *Macromol. Mater. Eng.* **2013**, *298*,

425    730.

426    [11]    R. Ferrari, Y. Yu, M. Morbidelli, R. A. Hutchinson, D. Moscatelli, *Macromolecules*

427    **2011**, *44*, 9205.

428    [12]    J. A. Wallach, S. J. Huang, *Biomacromolecules* **2000**, *1*, 174.

429    [13]    J. Kiehl, C. Delaite, S. Bistac, A. S. Schuller, H. Farge, *Polymer (Guildf).* **2012**, *53*,

430    694.

431    [14]    F. F. Wolf, N. Friedemann, H. Frey, *Macromolecules* **2009**, *42*, 5622.

432    [15]    J. Xu, J. Song, S. Pispas, G. Zhang, *Polym. Chem.* **2014**, *5*, 4726.

433    [16]    M. Takwa, Y. Xiao, N. Simpson, E. Malmstrom, K. Hult, C. E. Koning, A. Heise, M.

434            Martinelle, *Biomacromolecules* **2008**, *9*, 704.

435    [17]    Y. Xiao, M. Takwa, K. Hult, C. E. Koning, A. Heise, M. Martinelle, *Macromol. Biosci.*

436            **2009**, *9*, 713.

437    [18]    B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F.

438            Nederberg, J. Choi, C. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**,

439            *39*, 8574.

440    [19]    N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L.

441            Hedrick, *Chem. Rev.* **2007**, *107*, 5813.

442    [20]    U. Capasso Palmiero, M. Sponchioni, N. Manfredini, M. Maraldi, D. Moscatelli,

443            *Polym. Chem.* **2018**, *9*, 4084.

444    [21]    H. Qian, A. R. Wohl, J. T. Crow, C. W. MacOsko, T. R. Hoye, *Macromolecules* **2011**,

445            *44*, 7132.

446    [22]    M. Labet, W. Thielemans, *Chem. Soc. Rev.* **2009**, *38*, 3484.

447    [23]    R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, R. M. Waymouth, J. L. Hedrick, *J. Am.*

448            *Chem. Soc.* **2006**, *128*, 4556.

449    [24]    S. A. Pendergraph, G. Klein, M. K. G. Johansson, A. Carlmark, *RSC Adv.* **2014**, *4*,

450            20737.

451    [25]    P. K. Kuroishi, M. J. Bennison, A. P. Dove, *Polym. Chem.* **2016**, *7*, 7108.

452    [26]    O. Persenaire, M. Alexandre, P. Dege'e, P. Dubois, *Biomacromolecules* **2001**, *2*, 288.

453    [27]    X. Guo, B. Choi, A. Feng, S. H. Thang, X. F. Guo, B. Choi, A. C. Feng, S. H. Thang,

454            *Macromol. Rapid Commun.* **2018**, 1800479.

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459  **TOC**

460  **Methacrylated block co-polyesters were synthesized via TBD catalyzed ROP.** TBD has

461  been successfully employed as an active and selective catalyst for HEMA- initiated ROP of LA,

462  TMC, and CL in order to synthesize, under mild and standard laboratory conditions,

463  homopolymers and block copolymers with controlled molecular weight, low polydispersity and

464  a mono-methacrylate final architecture.

465
466  Laura A. Ruiz-Cantu, Amanda K. Pearce, Laurence Burroughs, Thomas M. Bennett, Catherine
467  E. Vasey, Ricky Wildman, Derek J. Irvine*, Cameron Alexander*, and Vincenzo Taresco*
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471  **Synthesis of Methacrylate-Terminated Block Copolymers with Reduced**
472  **Transesterification by Controlled Ring-Opening Polymerization**
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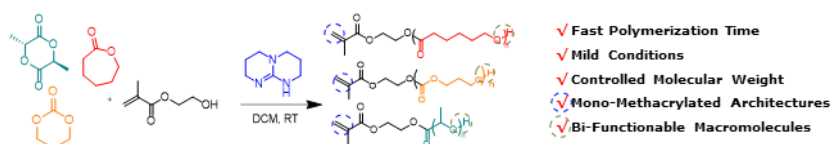


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489    **Captions to Figures, Schemes and Tables**

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

491    TBD.

492    **Scheme 2.** Schematic of TBD triggered self-acyl transfer of the methacrylic group of HEMA

493    producing ethylene bis-methacrylate and ethylene glycol from 2 equivalent of HEMA.

494    **Figure 1**. Comparison of the kinetic profiles showing the level of transesterification achieve
495    when varying the relative quantities of HEMA and TBD. An unpaired t-test ($p < 0.05$ indicating
496    significant difference) analysis was performed at each time-point and confirmed that significant
497    differences were observed at each time point between the two selected initiator:catalyst ratios.
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499    **Figure 2.** (Top) LA reaction scheme, polymer stoichiometry takes into account the corrected

500    conversion. (bottom) Full ^{1}H-NMR spectrum of purified HEMAPDLLA 5000, in the 7.5 to 1.0

501    ppm spectral range.  Note: residual catalyst and diethyl ether in the spectral range of 4.0 to 3.2

502    ppm.


503    **Figure 3. A)** HSQC NMR spectra of PDLLA, showing the presence of a single methacrylic

504    species (inlay) in the final polymer and confirming the presence of a single HEMA end group

505    for each polymeric chain. Peaks assigned a1 and b1 represent the two vinyl protons and c1

506    represents the vinylic carbon. **B)** HMBC ^{1}H-^{13}C NMR spectra of HEMA initiated PDLLA,

507    demonstrating the presence and multiple bond correlations confirming (inlay top) a single

508    methyl (methacrylate) species and (inlay bottom) a single carbonyl (methacrylate) species in

509    the final polymer.


510    **Figure 4**. (Top) HEMA initiated TMC reaction scheme, polymer stoichiometry takes into

511    account the corrected conversion and (Bottom) ^{1}HNMR spectrum. Inset, the vinyl region which

512    exhibits only two peaks as expected, demonstrating a satisfactory controlled ROP without side-

513    transesterification.


514    **Figure 5.** (Top) HEMAPCL reaction scheme, polymer stoichiometry takes into account the

515    corrected conversion. (Bottom) ^{1}H-NMR spectrum of HEMAPCL (synthesized employing 1.5

516 % mol:mol TBD) (red traces) showing a reduction of the vinyl peaks related to the

517 transesterification sub-products in the range of 6.2-5.5 ppm. (Inset) Difference in magnitude of

518 transesterification between the polymer synthesized with 2.5% (blue trace) and 1.5% (red trace)

519 catalyst.

520 **Figure 6. LEFT.** Stacking ^{1}H-NMR spectra, in the region between 6.5 to 3.5 ppm, of

521 HEMAPCL macroinitiator (red trace), HEMAPCL-PTMC (green trace) and HEMAPCL-

522 PDLLA (black trace) block copolymers showing that they characteristic peaks for PTMC and

523 PLA end groups, there PCL, PTMC and PDLLA end group functionalities are shown as *, Δ

524 and + respectively. **RIGHT.** GPC traces of HEMAPCL, HEMAPCL-PTMC and the

525 HEMAPCL-PDLLA block copolymers.

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**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) | $DP_o$:$DP_c$:$DP_e$ | $M_n^a$ (GPC) (g mol$^{-1}$) | $M_n^b$ (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%

559 **Figure 1**
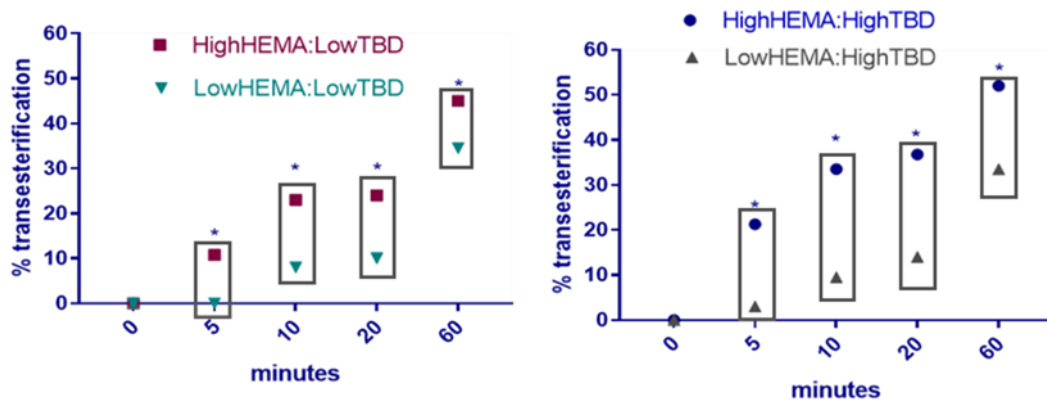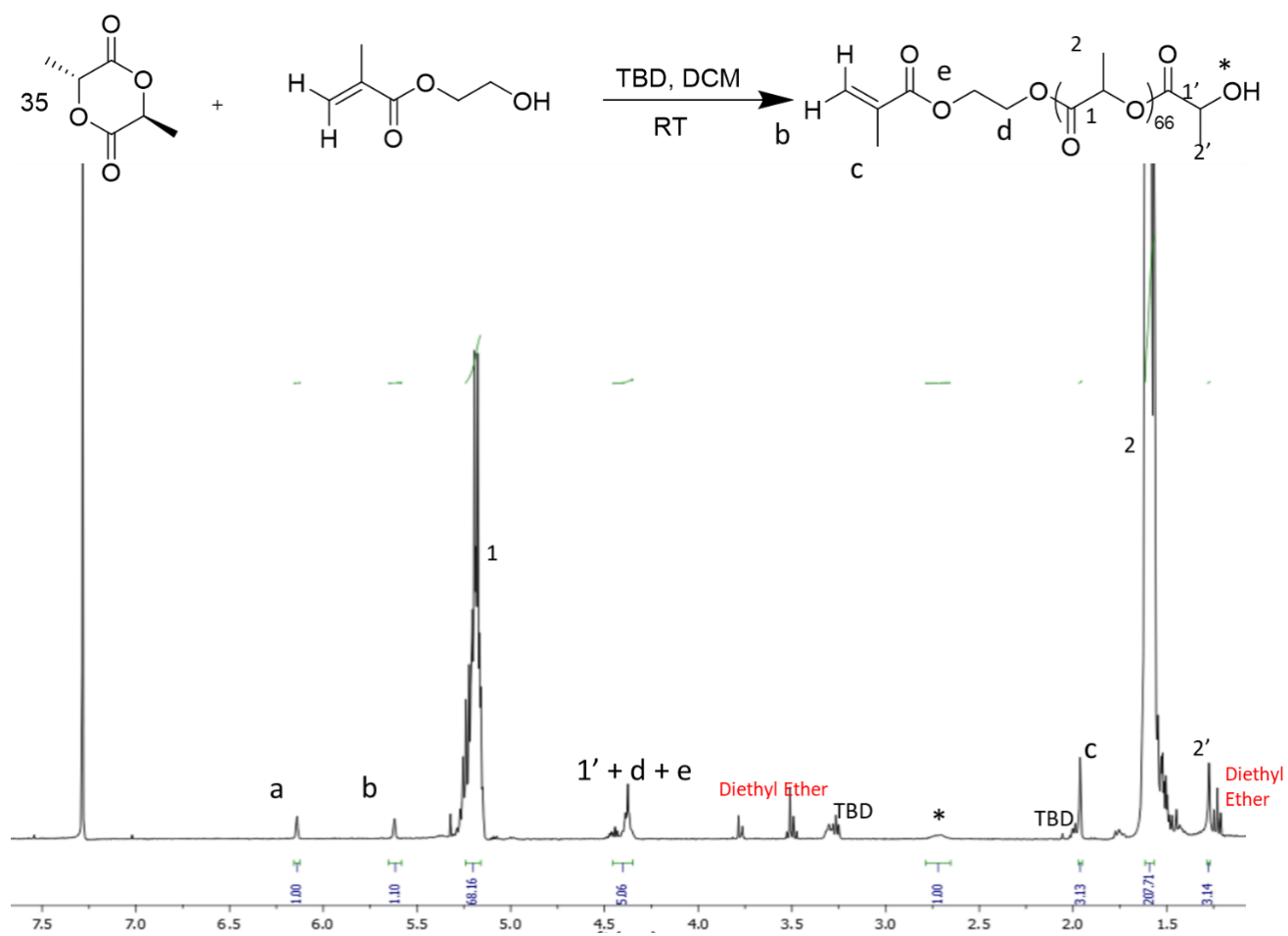
579 **Figure 2**

603    **Figure 3**

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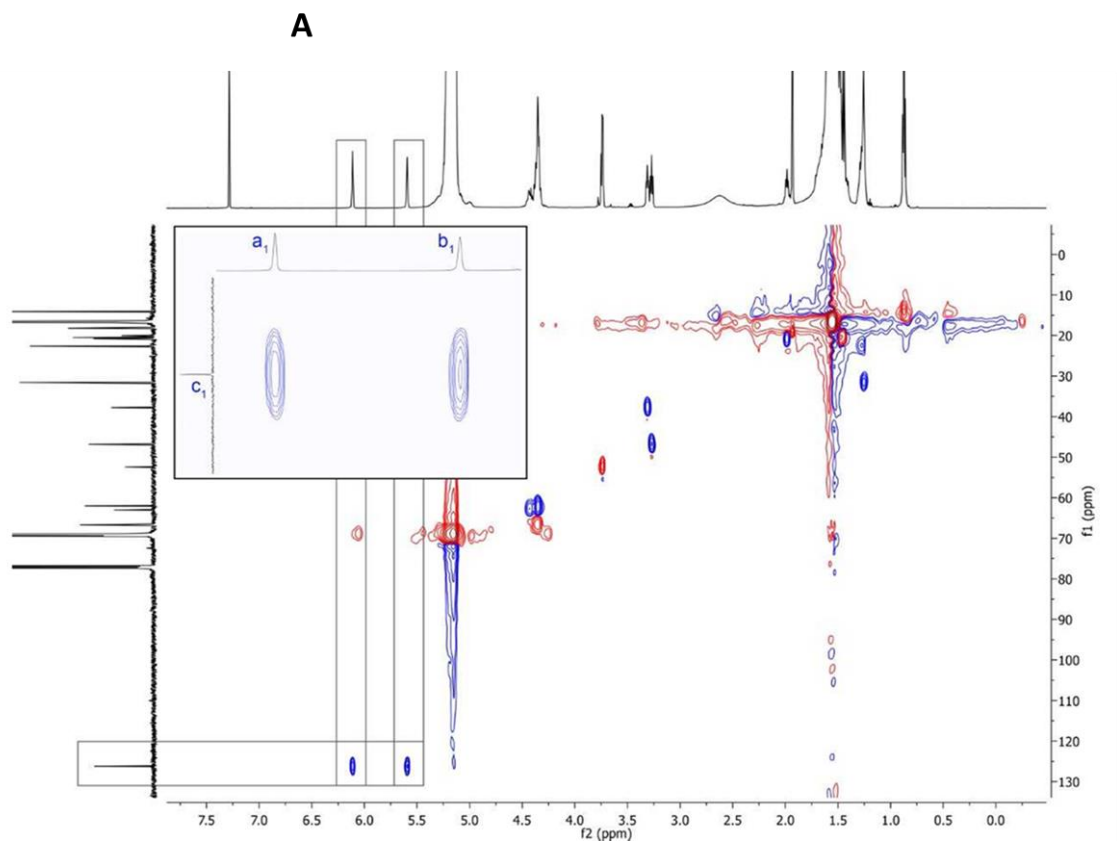


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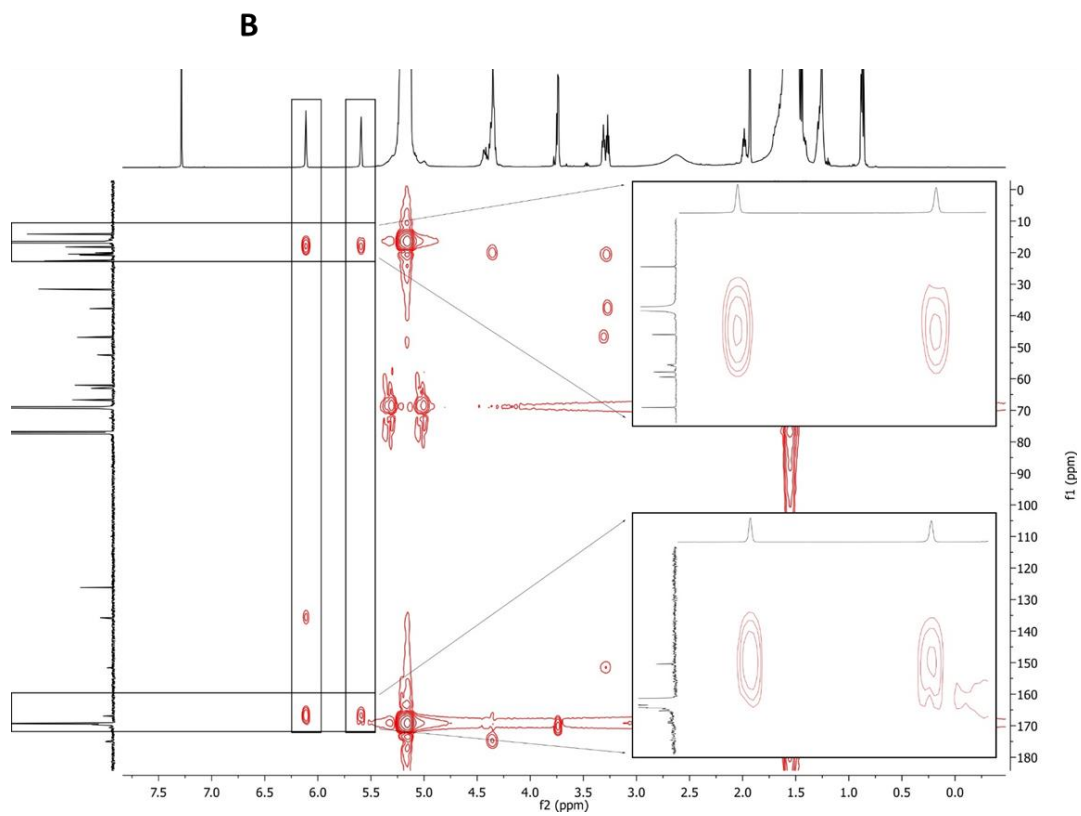


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609 **Figure 4**

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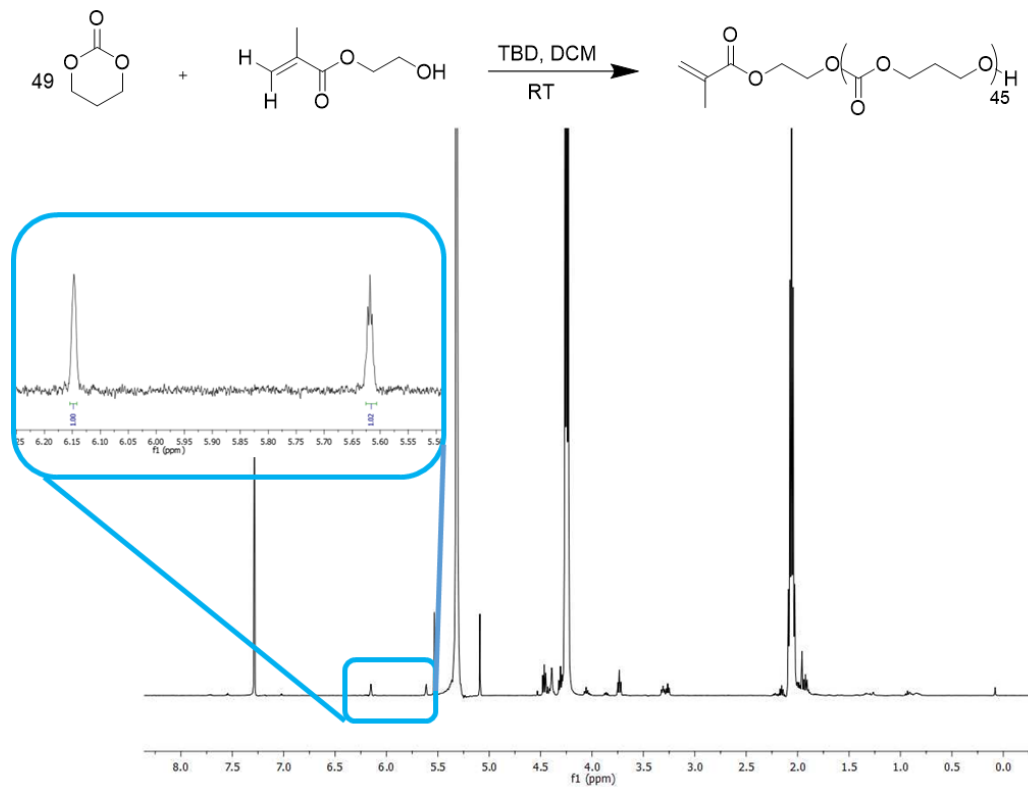


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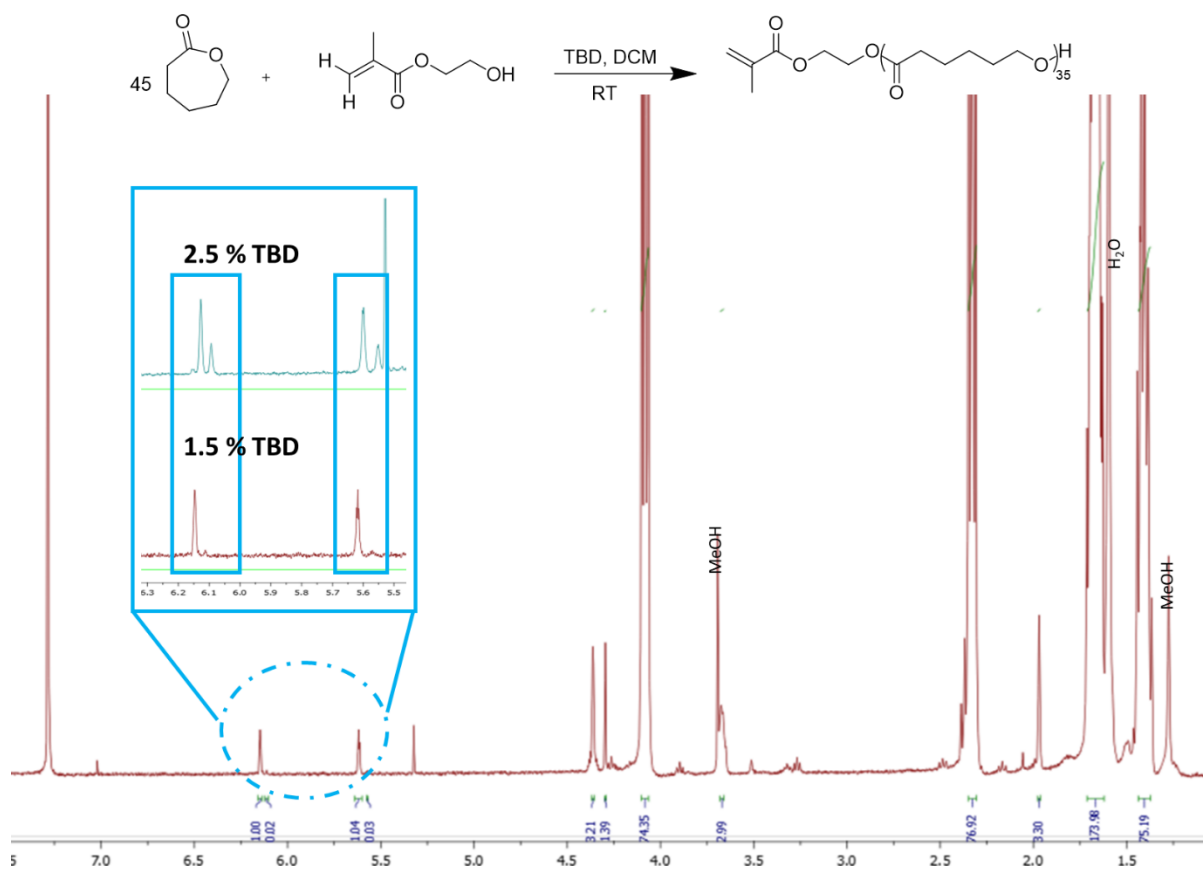
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636    **Figure 5**

**Figure 6**
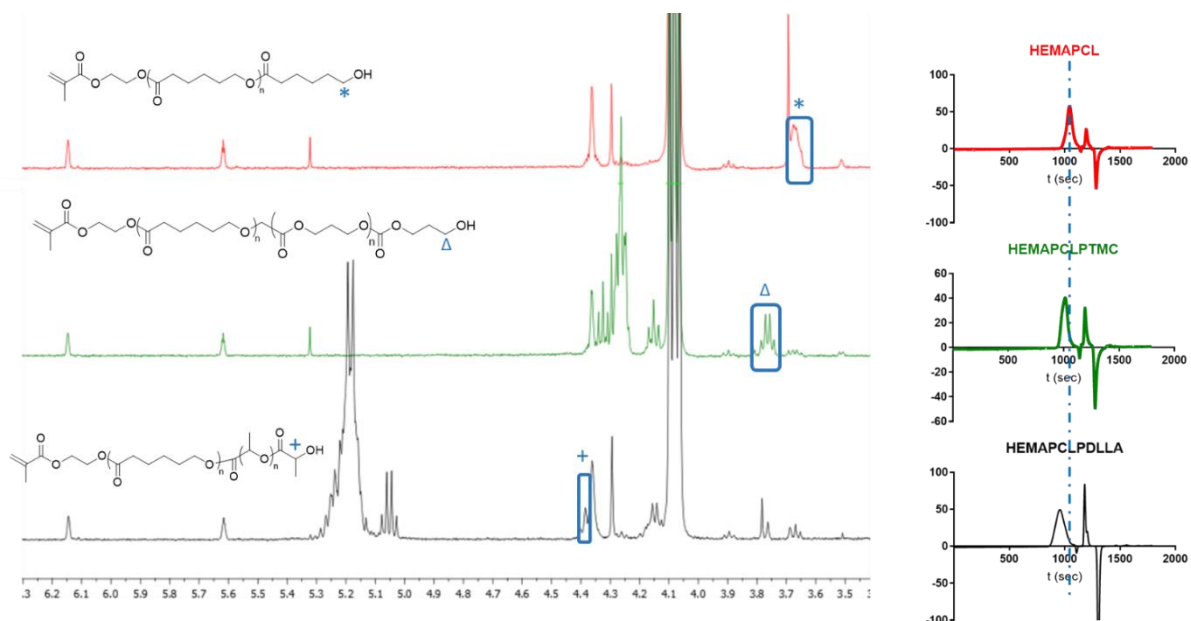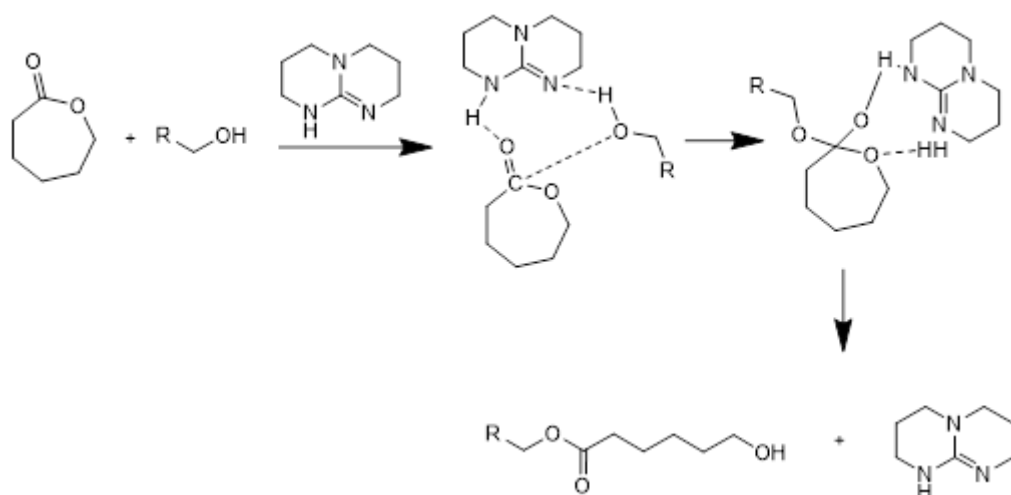


**Scheme 1**

686 **Scheme 2**

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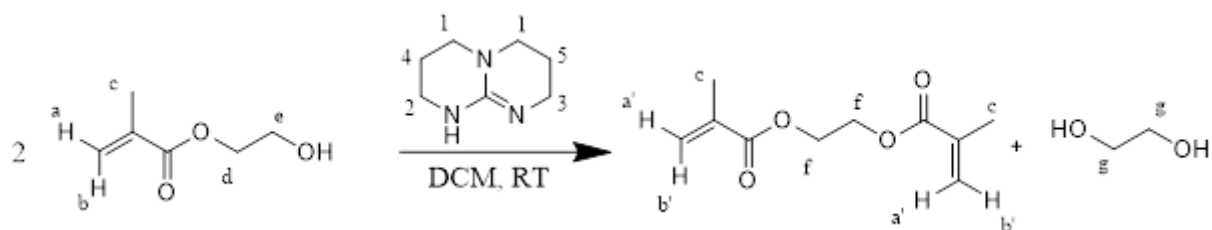


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# Supporting Information

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

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School of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD, UK.


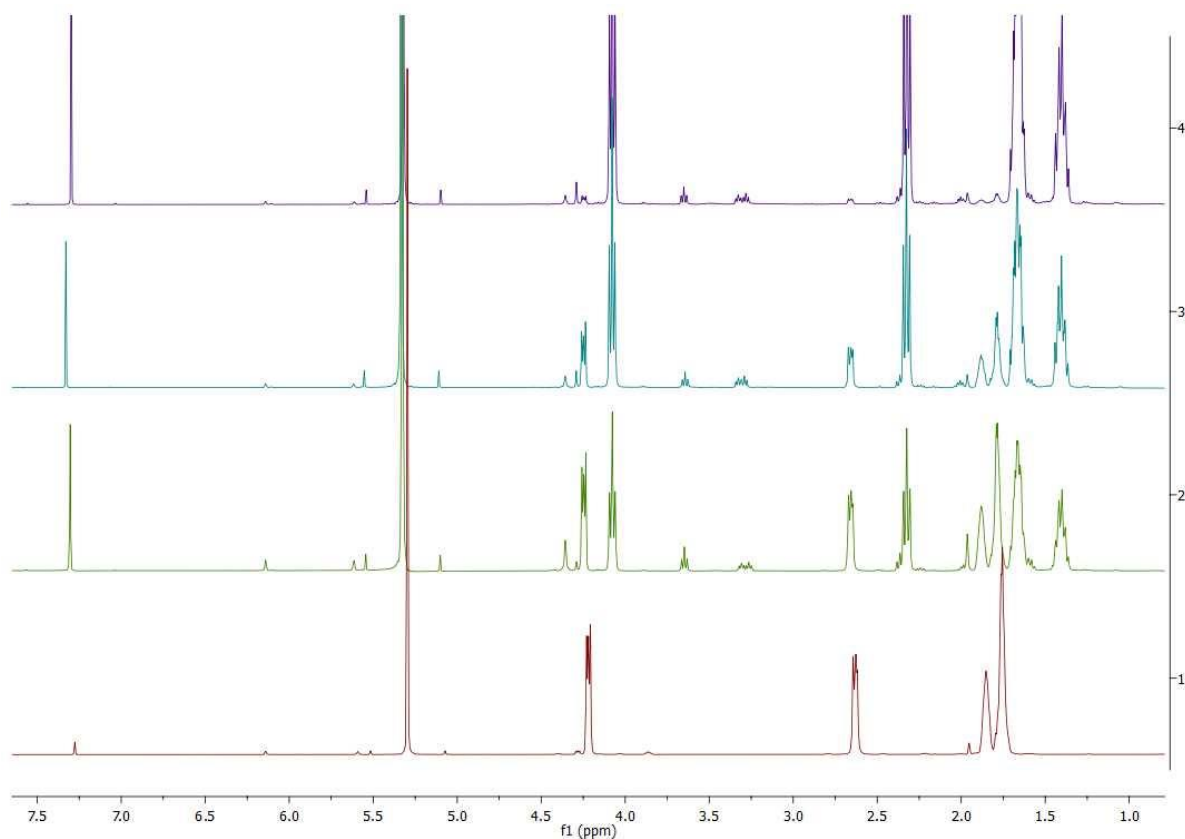E-mail: derek.irvine@nottingham.ac.uk, cameron.alexander@nottingham.ac.uk vincenzo.taresco@nottingham.ac.uk.

**Figure S1.** NMR spectra confirming feed ratio (HEMA:TBD) dependent presence of both ethylene bis-methacrylate and ethylene glycol as secondary species.
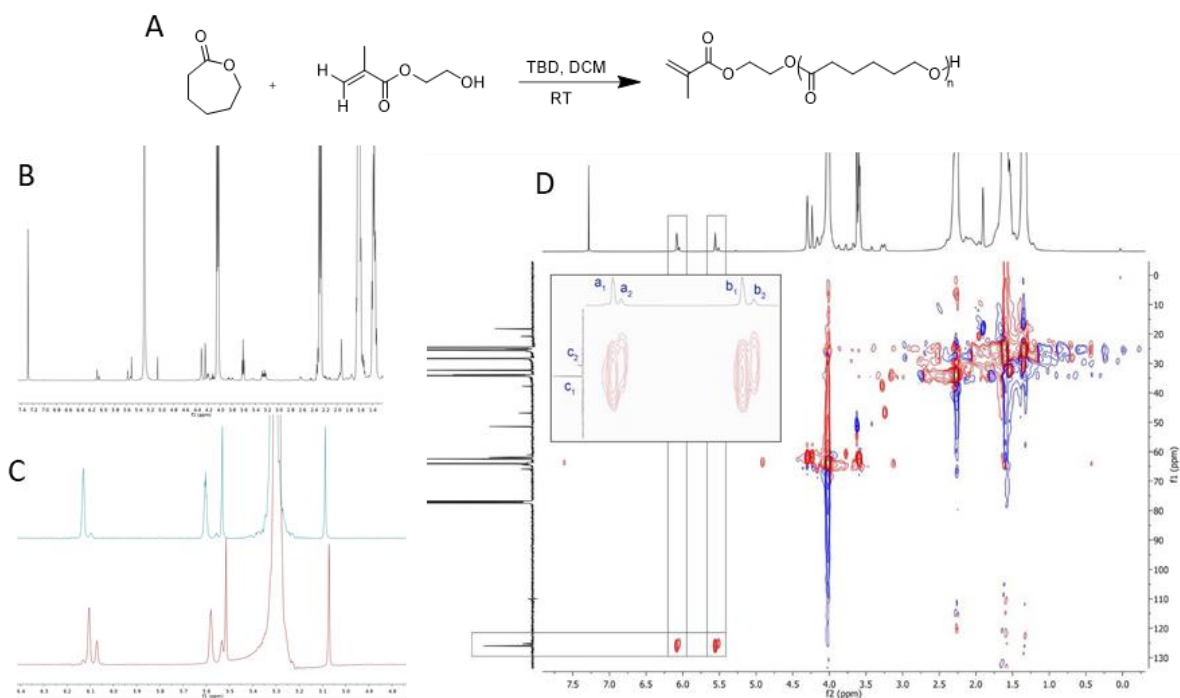
**Figure S2:** Kinetic profile of HEMAPCL ROP at 0, 20, 60, and 240 minutes (from bottom to top). Note: 240 min is shown to justify the full conversion of monomer to polymer.

**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.
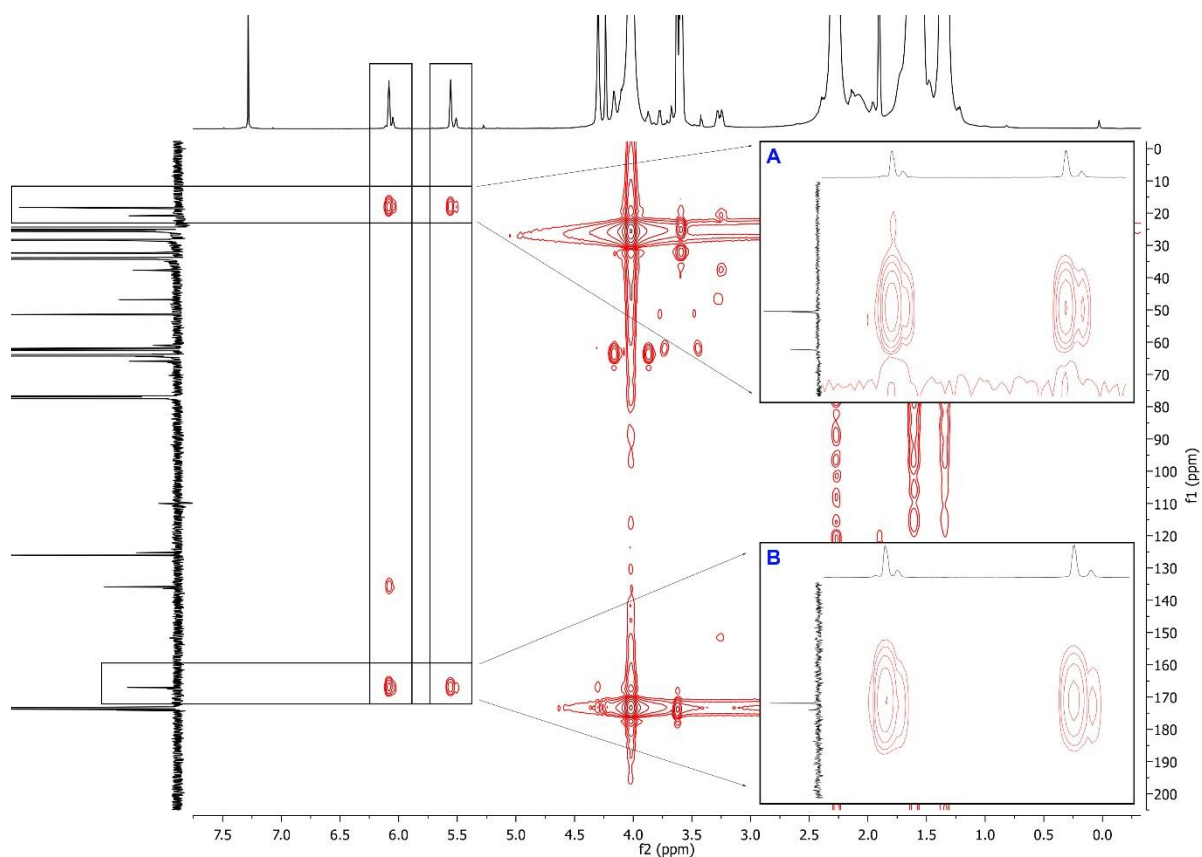
**Figure S4**. HMBC $^1$H-$^{13}$C NMR spectra of HEMAPCL, demonstrating the presence and multiple bond correlations confirming (inlay a) two different methyl (methacrylate) species and (inlay b) two different carbonyl (methacrylate) species in the final polymer. This effect is easily observed when a high amount of TBD was used leading to an uncontrolled polymer functionalization.
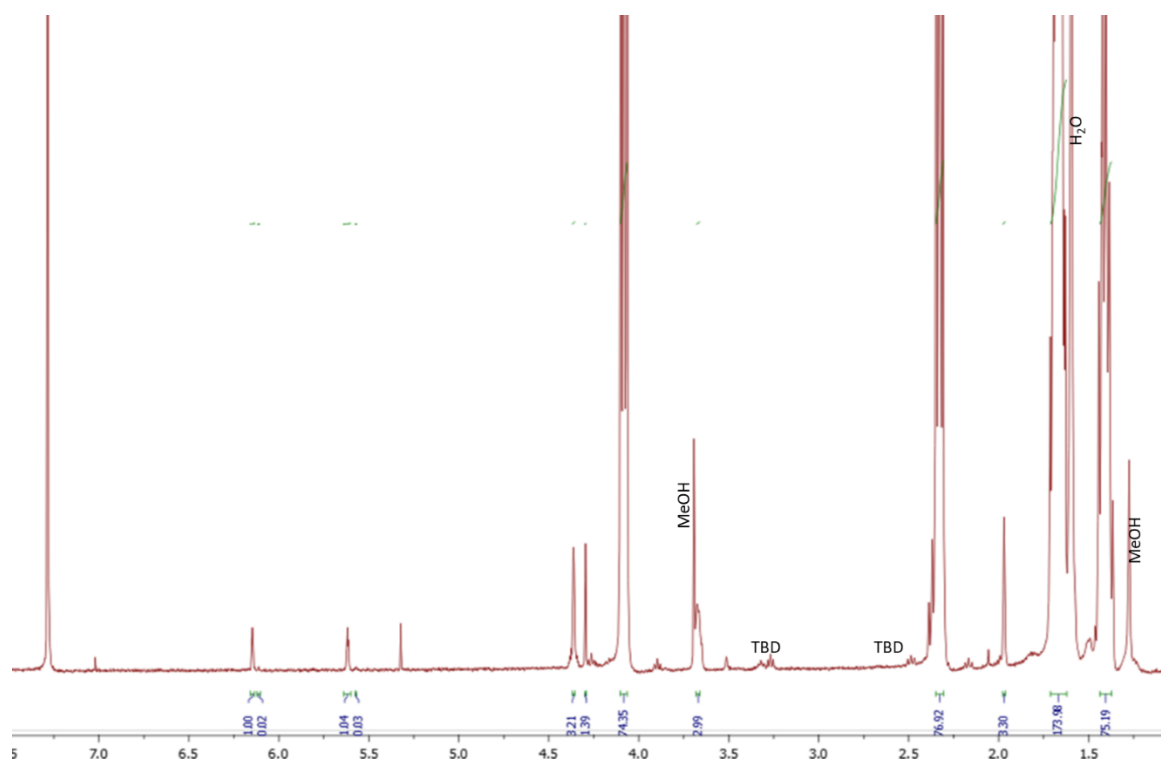
**Figure S5**. ^{1}H-NMR of HEMAPCL polymers showing full integration, vinyl peaks splitting ratios and PCLHEMA functionality proportions.