WILEY-VCH

3
4
5   **Synthesis of Methacrylate-Terminated Block Copolymers with Reduced**
6   **Transesterification by Controlled Ring-Opening Polymerization**
7

8   *Laura A. Ruiz-Cantu[a], Amanda K. Pearce[b], Laurence Burroughs[b], Thomas M. Bennett[c],*
9   *Catherine E. Vasey[b], Ricky Wildman[a], Derek J. Irvine[a]*, Cameron Alexander[b]* and Vincenzo*
10   *Taresco[b]**
11
12   Dr. L. A. Ruiz-Cantu, Dr., Prof. R. Wildman, Prof. D.J. Irvine,
13   Faculty of Engineering, University of Nottingham, University Park, Nottingham, NG7 2RD,
14   UK.
15   Dr. T. M. Bennett
16   School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK.
17   Dr. A. K. Pearce, Dr. L. Burroughs, C. E. Vasey, Prof. C. Alexander and Dr. V. Taresco.
18   School of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD, UK.
19
20
21   E-mail: derek.irvine@nottingham.ac.uk,   cameron.alexander@nottingham.ac.uk
22   vincenzo.taresco@nottingham.ac.uk.
23
24

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.
37
38
39
40
41

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

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.

100

101 **2. Experimental Section**

102

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.

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.

205

206

207

208

209

210

211   **3. Results and Discussion**

212

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.

341
342
343
344
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.

389

390

391

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.

409

410

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.

455

456

457

458

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*
468
469
470
471 **Synthesis of Methacrylate-Terminated Block Copolymers with Reduced**
472 **Transesterification by Controlled Ring-Opening Polymerization**
473
474
475

476
477

478

479

480

481

482

483

484

485

486

487

488

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.
498

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.

526
527
528
529
530
531
532
533
534
535

536

537

538

539

540

541

542

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**

560

561

562

563

564

565

566

567

568

569

570

571

572

573

574

575

576

577

578

579 **Figure 2**

603   **Figure 3**

604

A

605
606

B

607

24

608

609 **Figure 4**

610
611

612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635

25

636 **Figure 5**

Figure 6

Scheme 1

27

686 **Scheme 2**
687

688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729

Supporting Information

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

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

Dr. L. A. Ruiz-Cantu, Dr., Prof. R. Wildman, Prof. D.J. Irvine,
Faculty of Engineering, University of Nottingham, University Park, Nottingham, NG7 2RD, UK.
Dr. T. M. Bennett
School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK.
Dr. A. K. Pearce, Dr. L. Burroughs, C. E. Vasey, Prof. C. Alexander and Dr. V. Taresco.
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.
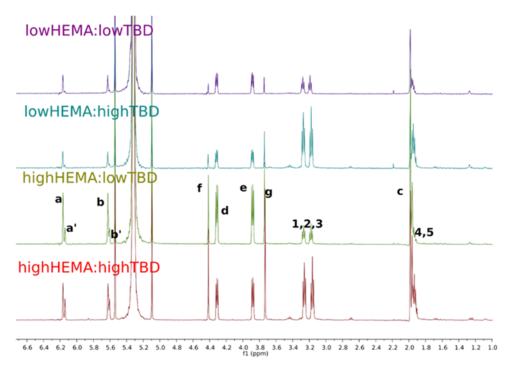
Figure S1. NMR spectra confirming feed ratio (HEMA:TBD) dependent presence of both ethylene bis-methacrylate and ethylene glycol as secondary species.
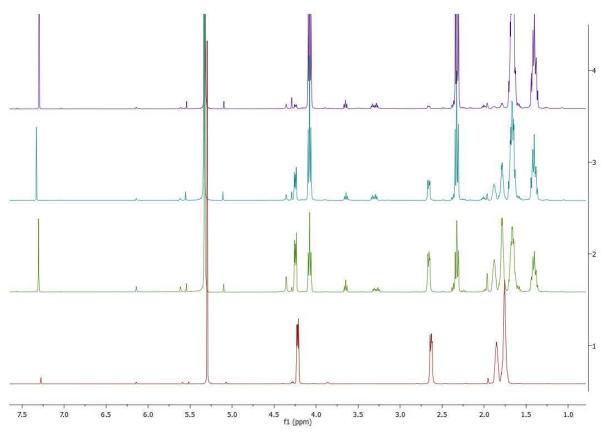
Figure S2: Kinetic profile of HEMAPCL ROP at 0, 20, 60, and 240 minutes (from bottom to top). Note: 240 min is shown to justify the full conversion of monomer to polymer.
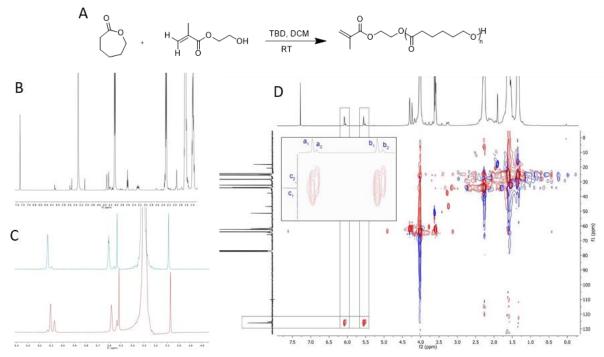
Figure S3. A) CL scheme of reaction. **B)** Full ^{1}H-NMR spectrum HEMAPCL. **C)** Stacked ^{1}H-NMR methacrylic protons region; peaks splitting in two limiting acyl transfer conditions (6.1-5.5 ppm). **D)** HSQC NMR spectra of HEMAPCL, confirming the presence of a two different methacrylic species (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.
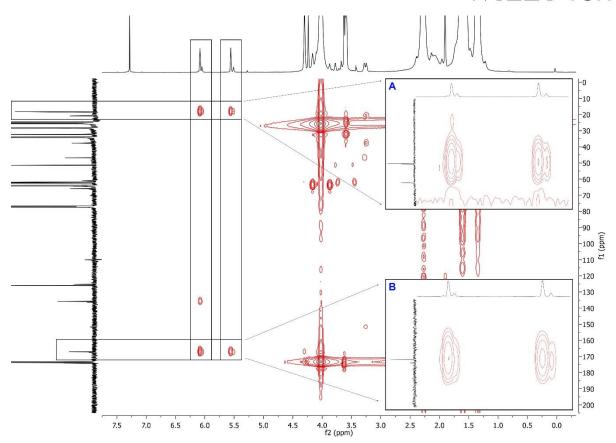
Figure S4. HMBC ^{1}H-^{13}C NMR spectra of HEMAPCL, demonstrating the presence and multiple bond correlations confirming (inlay a) two different methyl (methacrylate) species and (inlay b) two different carbonyl (methacrylate) species in the final polymer. This effect is easily observed when a high amount of TBD was used leading to an uncontrolled polymer functionalization.
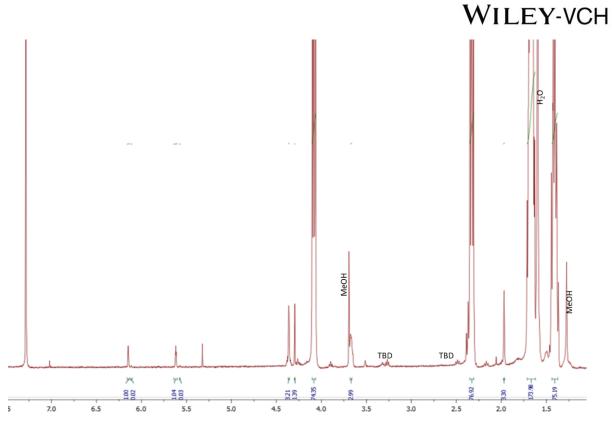
Figure S5. ^{1}H-NMR of HEMAPCL polymers showing full integration, vinyl peaks splitting ratios and PCLHEMA functionality proportions.