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Dihydrolevoglucosenone (CyreneTM) as a bio-renewable solvent for Cu(0)wire-mediated reversible deactivation radical polymerization (RDRP) without external deoxygenation[†]

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Biorenewable dihydrolevoglucosenone (CyreneTM) is used as an effective dipolar aprotic solvent for Cu(0) wire-mediated RDRP of various monomers without external deoxygenation being applied. The solvent is used to give products with a broad range of molar masses ($M_n \sim 700$ –28 000), *in situ* chain extension and as low as 7.8×10^{-4} eq. of $[\text{Cu}(\text{II})\text{Br}_2]$ relative to initiator.

Controlled radical polymerization (CRP) has enabled the synthesis of a large number of well-defined materials,^{1–6} with well-defined shape, different functionalities and molecular architectures.^{7,8} Amongst them, Cu-mediated reversible deactivation radical polymerization (Cu-RDRP) has evolved into an efficient technique for the polymerization of many functional vinyl monomers, including hydrophilic and hydrophobic (meth)acrylates, styrenics and (meth)acrylamides using many different dipolar solvents (e.g. water, DMSO, DMF, NMP), verifying the versatility of this technique.^{10–12} However, many of these solvents have been added to the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) restricted substances list due to their negative environmental effects and are becoming undesirable reagents in many applications. In this context, several solvent selection guides have been published in order to replace many commonly used volatile organic solvents or compounds that could form toxic gases upon incineration (CO_x , NO_x , SO_x), with solvents derived from natural or/and renewable resources.^{13–15}

Dihydrolevoglucosenone (CyreneTM) is a bio-based and fully biodegradable (99%, 14d) aprotic dipolar solvent that can be synthesized in a two-step process from biomass, mainly from cellulose.^{9,16} Cyrene is not mutagenic, has a median lethal

dose (LD_{50}) $> 2000 \text{ mg kg}^{-1}$ (above the value of high toxicity solvents, 50 mg kg^{-1}) and it is hardly ecotoxic.¹⁷ Therefore, it has potential as a greener and safer alternative to widely used dipolar aprotic solvents, such as DMF, NMP, DMAc and DMSO.^{17–19} Furthermore, Cyrene has similar solvating behavior with the abovementioned solvents, demonstrating similar Hansen solubility parameters.²⁰ A further characteristic of Cyrene is that it is completely miscible with water, since it is in equilibrium with its hydrate (a geminal diol), in contrast to most conventional ketones in water.²¹ CyreneTM is currently manufactured on a relatively small scale by Circa Group in Tasmania leading to relatively high prices when compared to DMSO. However, as of 2020 new 1000 and 5000 tonne plants are planned for construction in Europe which should reduce the costs to become within 1.5–2 of DMSO at current pricing.²²

Recently, Cyrene has attracted significant interest as a biodegradable solvent in the synthesis of metal–organic frameworks,¹⁷ synthetic transformations,²⁰ metal catalyzed processes,²³ in the synthesis of ureas²⁴ and amides.^{25,26} Moreover, upon further hydrogenation, Cyrene could lead to more renewable chemicals that can be used as precursors for drugs, flavors and polymers.²⁷ In the field of polymer synthesis, the use of Cyrene as solvent has been underexplored, with few examples of its use being as a co-solvent in low toxicity solvent systems for polyamideimide and polyamide amic acid resin manufacture,²⁸ in sustainable membrane preparation²⁹ and in membrane performance tests of interpenetrating polymer networks.³⁰ Conversely, in some cases Cyrene has been used as a monomer precursor. In a recent work, Ray *et al.* reported the development of bio-acrylic polymers from a methacrylic monomer synthesized from Cyrene.³¹ This monomer was polymerized under different free radical polymerization conditions (bulk, solution and emulsion) and it was found that polymers

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obtained from emulsion polymerization had higher yields and molecular weights, in contrast with solution polymerization.

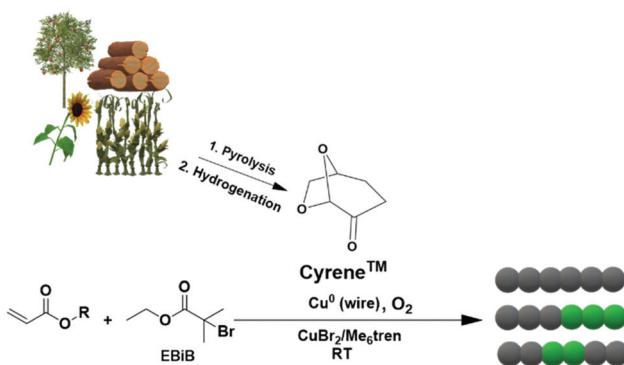
In this current work, we report the use of Cyrene as a bio-alternative solvent for the polymerization of various monomers using Cu(0) wire-mediated RDRP without applying any external deoxygenation or addition of external additives (Scheme 1). Well-defined polymers with high conversions, narrow molecular weight distributions and high end-group fidelity were obtained, enabling the synthesis of diblock and triblock copolymers. Moreover, a wide range of molar masses from 700 to 28 000 g mol⁻¹ (targeted DP_n = 5–800) of poly(methyl acrylate) (pMA) were obtained in the absence of deoxygenation and with Cyrene as solvent. The use of a low catalyst concentration was investigated for the Cu(0) wire-RDRP of MA (targeted DP_n = 50), to test the limits of this system. Finally, the oxygen tolerance profile of the polymerization was elucidated by employing an oxygen probe.

The choice of solvent is important for a successful Cu-RDRP process due to the effect on the rate of the polymerization,^{32,33} the solubility of the Cu complexes, monomers and polymers,^{34–36} as well as potential of solvent coordination to the copper.³⁷ Initially, in order to investigate Cyrene as a solvent for Cu(0) wire-mediated RDRP, polymerizations were conducted under an inert nitrogen atmosphere. For this purpose, MA was used as monomer (targeted DP_n = 50), ethyl α -bromo isobutyrate (EBiB) as initiator, 5 cm of Cu(0) wire and Cu(II)Br₂ as copper source and the aliphatic multidentate ligand tris(2-(dimethylamino)ethyl)-amine (Me₆Tren) as ligand with Cyrene as solvent (Table S1, entry 1, Fig. S1 & S4a†). Polymerization was carried out at ambient temperature with [EBiB]:[Me₆Tren]:[Cu(II)Br₂] = 1:0.18:0.05 (as previously reported when DMSO was used as solvent³⁸), leading to pMA₅₀ with high monomer conversion (>95% after 18 h), M_n, NMR = 4400 g mol⁻¹ and D_{SEC} = 1.09. It is noted that, although it has previously been reported that under basic conditions and in the presence of amines, Cyrene can exhibit sensitivity, we observed no evidence of side reactions in this study (Fig. S2†).²³ We think this is as the reactions were conducted at ambient temperature with low concentrations of Me₆Tren (18.7 mM for pMA₅₀). Apart from EBiB, we explored the possi-

bility to use the more hydrophobic dodecyl 2-bromo isobutyrate as an initiator for the polymerization of MA (targeted DP_n = 50), resulting in pMA₃₃ (74% conversion after 24 h) with M_n, SEC = 4000 g mol⁻¹ and D = 1.08 (Table S1, entry 2, Fig. S4b†). Apart from MA, the efficiency of Cyrene as solvent for the synthesis of polymethacrylates was explored. In this context, the polymerization of methyl methacrylate (MMA) was conducted under similar conditions with methyl α -bromophenylacetate as initiator, yielding pMMA₅₀ (95% after 18 h) with M_n, SEC = 6000 g mol⁻¹ and D = 1.12 (Table S1, entry 3, Fig. S3 & S4c†). Therefore, based on these initial experiments it was anticipated that Cyrene could be efficiently employed as an alternative, biodegradable solvent for the Cu(0) wire-RDRP of both MA (acrylates) and MMA (methacrylates).

Some of our previous work has focused on the Cu-RDRP of various monomers without any type of deoxygenation.^{39–42} Thus, we explored the possibility to polymerize a variety of hydrophobic monomers including MA, MMA, *tert*-butyl acrylate (*t*BA), benzyl acrylate (BzA), trifluoroethyl acrylate (TFEA) and styrene (St), *via* Cu(0)-RDRP *by omitting deoxygenation*, thus rendering this approach more user-friendly. Cu(0)-RDRP of MA over 3 h resulted in 90% monomer conversion with M_n, SEC = 4800 g mol⁻¹ and D = 1.08, the time needed for the other monomers varied from 20 to 45 h all leading to high conversions, good control over the M_n and relatively low dispersities (Table S2, Fig. S5–S11†). These results are similar to the M_n, SEC, dispersity and conversion observed for the non-deoxygenated Cu(0) wire-RDRP of MA in commonly used organic solvents, as described by Liarou *et al.*³⁹ It is noteworthy that following the polymerization of *t*BA the formation of a biphasic system was observed, with a top polymer-rich phase and a bottom solvent-rich layer containing the majority of the catalyst and residual monomer (3%).

Subsequently, we were interested in investigating the ability to achieve a range of molecular weights in Cyrene as solvent and in the presence of air/oxygen. By targeting DP_n values from 5 to 800, polymers with molecular weights from 700 to 28 000 g mol⁻¹ with narrow dispersities were obtained (Table 1, Fig. 1). When low DPs were targeted (higher [EBiB]) (Table 1, entries 1–4) high conversion of MA and very good



Scheme 1 Cu(0) wire-mediated RDRP in Cyrene, a bio-alternative solvent derived from biomass (cellulose) in a two-step process.⁹

Table 1 ¹H NMR and SEC analysis for the Cu(0) wire-mediated RDRP of various DPs of pMA in Cyrene, without deoxygenation

Entry ^a	DP _n	Time (h)	Mon. Conv. ^b (%)	M _n , theor. (g mol ⁻¹)	M _n , SEC ^c	D
1	5	3	99	630	700	1.12
2	10	3	>99	1100	1000	1.11
3	20	3	>99	1900	2000	1.12
4	50	3	90	4100	4800	1.08
5	100	24	86	7600	11 600	1.09
6	200	44	88	15 000	19 100	1.08
7	800	96	43	29 800	27 800	1.10

^a In all polymerizations the volume ratio of monomer to solvent was maintained at 1:1. ^b Conversion was calculated *via* ¹H NMR in CDCl₃.

^c Determined by CHCl₃ SEC analysis and expressed as molecular weight relative to pMMA narrow molecular weight standards.



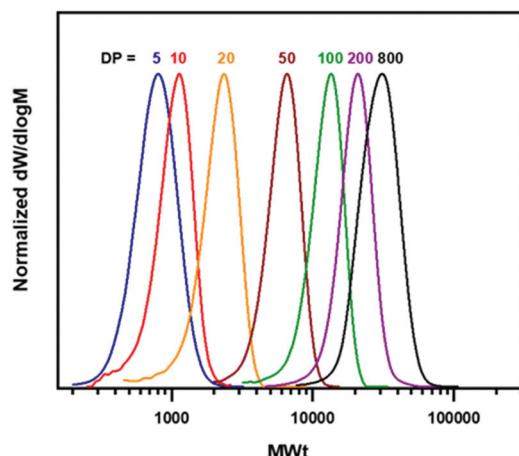


Fig. 1 CHCl_3 -SEC derived molecular weight distributions showing the evolution of MWts for various DP_n values (5, 10, 20, 50, 100, 200, 800) of pMA synthesized by $\text{Cu}(0)$ wire-mediated RDRP in Cyrene without deoxygenation. Conditions: $[\text{EBiB}]:[\text{Cu}(\text{II})\text{Br}_2]:[\text{Me}_6\text{Tren}] = 1:0.05:0.18$, $V_{\text{Cyrene}} = 50\% \text{ v/v}$ with respect to monomer.

agreement between theoretical and experimental M_n values was observed. However, moving to higher DP_n values with lower $[\text{EBiB}]$, and thus lower concentration of propagating chains led to an increase of the polymerization times, while lower yields and loss of initiator efficiency (I_{eff}) was also seen (Table 1, entries 5–7, Table S4, Fig. S12–S18†). The higher molar masses required prolonged reaction times leading the polymerization to be more susceptible to side reactions. It has also been reported that the initiator participates in the O_2 -consumption mechanism,³⁹ therefore low $[\text{EBiB}]$ could affect the rate of O_2 -consumption and subsequently result in loss of I_{eff} and chain termination.

To verify the ω -Br functionality of the obtained polymers, matrix assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-ToF-MS) was employed for pMA₂₀.^{43,44} A single peak distribution corresponding to bromine-capped polymer chains was found, indicating the retention of the ω -end (Fig. 2a & b) with a calculated mass for bromine terminated polymer with $\text{DP}_n = 25$ of 2369.9 Da and an observed mass = 2370.2 Da with the associated isotopic pattern expected for incorporation of bromine, confirming the structure as shown in Fig. 2a. This led us to proceed to the synthesis of AB and ABA block copolymers consisting of methyl and ethyl acrylate (A = MA, B = EA) (Table S3,† Fig. 2c) *via* sequential monomer addition, thus verifying that the end-group fidelity could be attained not only in the case of the pMA₁₀ macro-initiator, but also for the pMA₁₀-*b*-pEA₁₀ diblock, leading to a well-defined triblock copolymer synthesized in the presence of oxygen.

Apart from the facile removal of $\text{Cu}(0)$ *via* simply removing the stirrer bar with the wrapped copper wire, we were also interested in exploring the limits of this chemistry by lowering the $[\text{Cu}(\text{II})\text{Br}_2]$. Consequently, polymerization of MA (targeted $\text{DP}_n = 50$) was conducted by varying the amount of $[\text{Cu}(\text{II})\text{Br}_2]$. Starting from 0.05 equivalents of $[\text{Cu}(\text{II})\text{Br}_2]$ and reducing its

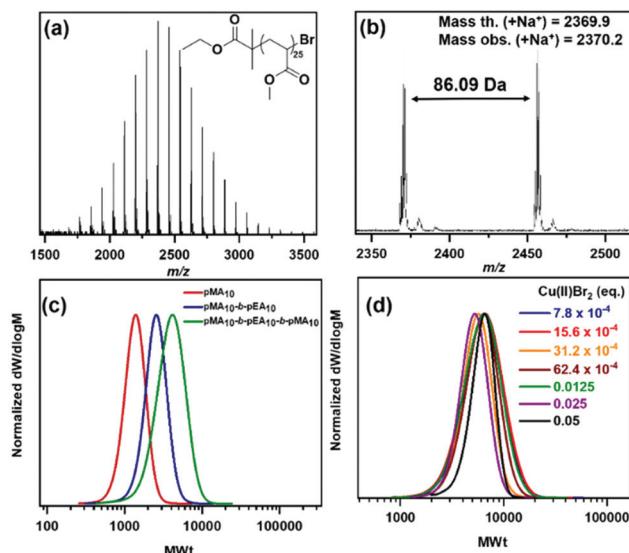


Fig. 2 (a) and (b) MALDI-ToF-MS spectra for the $-\text{Br}$ terminated pMA₂₅. CHCl_3 -SEC derived molecular weight distributions showing the evolution of MWts of (c) pMA₁₀ (red), pMA₁₀-*b*-pEA₁₀ (blue) and pMA₁₀-*b*-pEA₁₀-*b*-pMA₁₀ (green) and (d) pMA₅₀ synthesized by $\text{Cu}(0)$ wire-mediated RDRP in Cyrene without any type of deoxygenation with various $[\text{Cu}(\text{II})\text{Br}_2]$.

amount by half, we were able to limit the catalyst content to 7.8×10^{-4} eq., which is 64-fold lower than the 0.05 eq. of $[\text{Cu}(\text{II})\text{Br}_2]$ previously used. All polymerizations were carried out at ambient temperature for 3 h, achieving monomer conversions from 92 to 97% (Table 2). By comparing the SEC results from these polymerizations (Table 2, Fig. 2d), slightly higher molecular weights and dispersities were observed with decreasing $[\text{Cu}(\text{II})\text{Br}_2]$. It might have been expected that by changing the $[\text{Me}_6\text{Tren}]:[\text{Cu}(\text{II})\text{Br}_2]$ ratio, the equilibrium between dormant and active species is affected and this is depicted in the molecular characteristics *i.e.* M_n and D .

Finally, the oxygen consumption profile for polymerization to pMA in Cyrene was monitored by use of an oxygen concentration probe. As shown in Fig. S19,† in the absence of head-

Table 2 ¹H NMR and SEC analysis for pMA₅₀ synthesized by $\text{Cu}(0)$ wire mediated-RDRP in Cyrene without any type of deoxygenation using various $[\text{Cu}(\text{II})\text{Br}_2]$

$\text{Cu}(\text{II})\text{Br}_2^a$ (eq.)	Time (h)	Mon. Conv. ^b (%)	M_n , theor. (g mol ⁻¹)	M_n , NMR ^b	M_n , SEC ^c	D
0.00078	3	97	4400	4900	5600	1.20
0.00156	3	94	4200	5500	5600	1.20
0.00312	3	92	4200	4800	5500	1.20
0.00625	3	94	4200	4800	5600	1.15
0.0125	3	92	4200	4500	5100	1.12
0.025	3	92	4200	4600	4800	1.10
0.05	3	97	4400	4800	4800	1.08

^a In all polymerizations, the volume ratio of monomer to solvent was maintained at 1:1. ^b Conversion was calculated *via* ¹H NMR in CDCl_3 .

^c Determined by CHCl_3 SEC analysis and expressed as molecular weight relative to pMMA narrow molecular weight standards.

space, full oxygen consumption takes place within the first 5 minutes of the reaction (2 mL total reaction volume), while even when 0.5 mL of headspace is present, the oxygen consumption lasts for 24 minutes. This observation comes in agreement with previous work by Liarou *et al.*, and verifies the importance of headspace, which is highlighted in smaller scale reactions (2 mL total reaction volume). As has previously been reported,³⁹ all the reagents of the polymerization (Cu(0)-wire, initiator, Cu(II)Br₂/Me₆Tren) contribute to oxygen consumption, and synergistically lead to full consumption of dissolved oxygen, which occurs within the first minutes of the reaction (in the absence of headspace) (Fig. S19†). It is noted that the [O₂] at *t* = 0 in the reaction mixture containing Cyrene was < 6 mg L⁻¹, while in the case of DMSO it was >8 mg L⁻¹. However, the effect of solvent on the evolution of oxygen consumption will be further discussed in a forthcoming publication.

In summary, we report the use of Cyrene, which derives from renewable resources, as an alternative dipolar aprotic solvent for the Cu(0) wire-mediated RDRP of various hydrophobic monomers. Polymerization proceeded successfully under both deoxygenated and non-deoxygenated conditions, allowing production of polymers with high end-group fidelity at high conversions, allowing for sequential monomer addition for the synthesis of di- and tri- block copolymers. Even with very low [Cu(II)Br₂] (as low as 7.8 × 10⁻⁴ eq.) the obtained pMAs exhibited controlled macromolecular characteristic. Cyrene offers a valuable biorenewable alternative to harsh aprotic polar solvents which are increasingly seen as unattractive.

Conflicts of interest

There are no conflicts to declare.

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