Ring opening copolymerisation of lactide and mandelide for the development of environmentally degradable polyesters with controllable glass transition temperatures

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**Abstract**

Environmentally degradable polyesters offer an interesting perspective for a vast number of applications. However, current front-runners like poly(lactide), poly(glycolide) and poly(ε-caprolactone) are either semi-crystalline excluding applications for which optical transparency is desired, or exhibit low glass transition temperatures (Tg) resulting in poor dimensional stability at temperatures exceeding the Tg. In the present work, copolymers of lactide and mandelide are explored as a method to obtain amorphous, environmentally degradable polyesters with a glass transition temperature exceeding 50°C. Mandelide and lactide can be successfully copolymerised and the resulting copolymers revealed rising Tg values upon increasing the mandelide content. The obtained molecular weights were superior to the molecular weights previously obtained via polycondensation, but were limited by the epimerisation of the mandelide monomer, which passes through an enolic intermediate that is able to initiate the polymerisation.

Keywords:

Polyester, Ring Opening Polymerisation, mandelide, lactide, glass transition temperature

# Introduction

Environmentally degradable polymers are receiving increasing interest to allow novel applications of polymers in mostly (bio)medical and agricultural applications such as bioresorbable sutures [1,2], drug delivery applications [3–6], (implantable) tissue engineering scaffolds [7–9] and degradable mulch films [10–12]. In addition, these materials can be applied as bulk material for disposable devices, which are currently associated with the image of landfills and microplastics contaminating the oceans [13].

All of the above-mentioned applications directly benefit from materials that are engineered to degrade over a specific amount of time or after fulfilling their intended use, which has in turn led to an increase in the industrial interest for these materials. Moreover, degradable materials are becoming more and more competitive with traditional bulk plastics as a result of governmentally imposed regulations and levies. Currently, biodegradable and bio-based polymers make up about 300,000 metric tons of the total plastics market, which only accounts for 1% of the global market of synthetic plastics [14,15]. However, the market for degradable and sustainable polymers grows about 20-30% each year, which is considerably higher than the total market growth. Although produced synthetically, polyesters make up a large fraction of the biodegradable plastics market and are often preferred over natural degradable polymers, as their properties can be tailored by simply selecting the appropriate monomers and polymerisation conditions. Moreover, the resulting materials have more predictable batch-to-batch uniformity than their natural counterparts [16].

Aliphatic polyesters like poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and poly(ε-caprolactone) (PCL) are among the front-runners in the field of degradable materials [17–19], but are opaque due to the presence of crystalline domains or show low softening temperatures (e.g. approx. 40-50 °C) when amorphous grades are considered. Mandelic acid with its bulky phenyl side-group has already been proposed as an interesting monomer to yield polyesters with an increased glass transition temperature in polycondensations [20]. This effect can be attributed to a reduction of the chain mobility as a result of the incorporation of the rigid aromatic side groups along the polymer backbone. However, the mandelic acid content of these polymers was limited (approx. 10%). Moreover, the molecular weights attainable via direct polycondensation of lactic acid and mandelic acid, were limited to approx. 5 kg/mol. In 2007, Liu *et al.* introduced a lactide-analogue derived from mandelic acid (i.e. mandelide) to allow the synthesis of poly(mandelic acid) via ring-opening polymerisation [21]. The current contribution continues on this earlier work and describes the first copolymerisation of lactide and mandelide via ring-opening polymerisations with the aim to obtain amorphous polyesters with Tg exceeding 50 °C and molecular weights exceeding 10 kg/mol.

# Materials and methods

## Materials

All chemicals were used as received unless stated otherwise. Chloroform (HPLC grade), neohexanol, p-toluenesulfonic acid, Sn(2-ethylhexanoate)2, toluene and mixed xylenes were purchased from Sigma Aldrich (Diegem, Belgium). Calcium hydride, rac-mandelic acid, sodium bicarbonate and sodium chloride were obtained from Acros Organics (Geel, Belgium). Ethyl acetate and methanol were obtained from Chem-Lab Analytical (Zedelgem, Belgium). Dichloromethane was purchased from TCI Europe (Zwijndrecht, Belgium). All NMR spectra were recorded in deuterated solvents obtained from Euriso-top (Saint-Aubin, France). Toluene was refluxed over Na/benzophenone until a deep blue colour persisted, distilled and subsequently stored over molecular sieves (4 Å). Neohexanol was distilled over calcium hydride and stored over molecular sieves (4 Å). R,S-lactide was recrystallised from hot ethyl acetate (approx. 77 °C) and dried *in vacuo*.

## Synthesis procedures

### Synthesis of mandelide

Mandelide was prepared following a slightly adapted procedure from literature.[21] In brief, 20 g (132 mmol) DL-mandelic acid and 0.68 g p-toluenesulfonic acid (3.96 mmol) were dissolved in 2 L toluene or mixed xylenes. Contrary to [21], the solution was degassed by passing a nitrogen stream through the solution for at least half an hour while stirring by means of a magnetic stirring bar. A Dean-Stark trap and condenser were mounted on the flask and the set-up was subsequently purged with nitrogen. The solution was refluxed for 3 days under nitrogen atmosphere. Next, the reaction was allowed to cool to room temperature during which precipitation occurred. The precipitated racemic mandelide (5.63 g, yield = 32%) was removed by filtration and dried *in vacuo*.

1H-NMR (CDCl3, ppm): 7.28 (5H, m), 6.15 (1H, s); 13C-NMR (CDCl3, ppm): 166.77, 132.43, 129.64, 128.94, 126.45 and 77.62; FT-IR (ATR, cm-1): 3065 (ν(aromatic C-H)), 1754 (ν(C=O)), 1499 (ν(C=C)), 1071 (νas(C-O)), 743 (δ aromatic C-H); MS (EI, m/z): 268

The filtrate was washed with a saturated sodium bicarbonate solution (3 x 100 mL) and brine (3 x 100 mL) and dried over anhydrous magnesium sulphate. After filtration, the solvent was removed by rotary evaporation and the formed meso-mandelide (4.46 g, yield = 25%) recrystallised from hot ethyl acetate (approx. 77 °C) and finally dried *in vacuo*.

1H-NMR (CDCl3, ppm): 7.47 (5H, m), 5.87 (1H, s) ; 13C-NMR (CDCl3, ppm): 164.96, 131.38, 130.21, 129.52, 126.73 and 78.11 ; FT-IR (ATR, cm-1): 3066 (ν(aromatic C-H)), 1731 (ν(C=O)), 1498 (ν(C=C)), 1039 (νas(C-O)), 739 (δ aromatic C-H); MS (EI, m/z): 268

### Reaction of mandelide with trichloroacetyl isocyanate

Meso-mandelide (10 mg, 40 µmol) was added to an NMR-tube and dissolved in 800 µL deuterated DMSO. After recording a 1H-NMR spectrum, 14 µL trichloroacetyl isocyanate (TAIC, 120 µmol.) was added to the NMR-tube and another 1H-NMR spectrum was subsequently recorded.

1H-NMR (DMSO-*d6*, ppm): 8.41 (1 H, d) (10 H, m), 6.62 (0.7 H, s) 6.41 (0.3 H, s);

### Copolymerisation of lactide and mandelide

Copolymers of lactide and mandelide (target DP 100) were prepared by adding the appropriate amounts of all reagents (table 1) in flame-dried Schlenk vials. Given the low required amounts of initiator and catalyst, 1 M stock solutions were prepared in toluene. All manipulations of these reagents were performed in an argon-filled glovebox to prevent the enclosure of moisture. The filled vials were closed by means of rubber septa and removed from the glovebox. The Schlenk vials’ contents were frozen by means of liquid nitrogen after which the vials were connected to the Schlenk line and subjected to three freeze-pump-thaw-cycles (FPT) to remove traces of moisture and oxygen. After the final FPT-cycle, the vials were brought under Ar-atmosphere and placed in an oil bath at 100 °C. The solutions were stirred overnight (16 h), followed by the removal of the solvent *in vacuo*. The obtained product was redissolved in a minimal amount of dichloromethane and precipitated in cold methanol. The polymer was finally removed via filtration and dried *in vacuo*.

### Comparison of polymerisation kinetics of lactide and meso-mandelide

To compare the polymerisation kinetics of lactide and mandelide, both monomers were polymerised with a target degree of polymerisation (DP) of 50. After the addition of 5 mmol of each monomer and 5 mL toluene to two separate Schlenk vials, these vials were sealed with a rubber septum. Both monomer solutions as well as the catalyst and initiator solutions were removed from the glovebox and immediately frozen in liquid nitrogen to allow three subsequent FPT-cycles. The appropriate amounts of initiator (100 µmol) and catalyst (50 µmol) were added to the Schlenk vials, which were then placed in an oil bath (100 °C) to initiate the polymerisation. At regular intervals, a drop of reaction medium (approx. 50 µL) was collected via dry and Ar-purged syringes and subsequently analysed via 1H-NMR spectroscopy and size exclusion chromatography (SEC).

## Methods

1H-NMR spectra were recorded on a Bruker (Brussels, Belgium) AVANCE Ultrashield spectrometer (300 MHz). 13C-NMR spectra were recorded on a Bruker AVANCE II Ultrashield spectrometer (400 MHz). Free induction decays were converted to NMR-spectra by means of the Topspin software package.

Attenuated total reflectance infrared (ATR-IR) spectroscopy was performed on a PerkinElmer (Zaventem, Belgium) BioRad FTS 575C combined with a specac (Orpington, United Kingdom) MKII Golden Gate setup equipped with a diamond crystal. These results were analysed with the Bio-Rad Win-IR Pro software.

Mass spectroscopy was performed on a Hewlett Packard 5890 gas chromatograph, coupled to a Hewlett Packard G1800B GCD MS-single quadrupole detector (electron impact ionisation) with a mass range of 10-450 Da.

UV-VIS spectra were recorded on a UVIKON XL spectrometer (Bio-Tek Instruments) equipped with thermostated cuvette holders. Mandelide was dissolved in various solvents at a concentration of 1 mg/mL in quartz cuvettes and the absorbance of the resulting solutions was determined in a wavelength range of 180-900 nm.

Size exclusion chromatography (SEC) was performed on a Waters (Zellik, Belgium) Alliance 2596 set-up coupled to an Agilent (Diegem, Belgium) guard column (PLGel 5 µm) and a mixed D 5 µm column from Polymer Laboratories (Middelburg, The Netherlands). The column was eluted with HPLC grade chloroform at a flow rate of 1 mL/min. Detection was based on a Waters refractive index detector 2414. The molecular weights were determined from the obtained retention times via an external calibration curve using polystyrene standards (1.2 - 177 kg/mol). Samples were prepared by dissolving 10 mg polymer in 2 mL HPLC grade chloroform. The resulting solutions were passed through a 0.45 µm syringe filter, transferred to a mass vial and subsequently analysed.

Thermogravimetric analyses (TGA) were performed on a TA Instruments (Zellik, Belgium) Q50 TGA device. Samples (5-20 mg) were placed in a Pt sample pan and automatically loaded into the furnace. All experiments were performed under inert atmosphere (N2). When the sample had been placed in the furnace, the temperature was set to equilibrate at 45 °C after which the temperature was ramped to 800 °C at a heating rate of 10 °C/min. Data analysis was performed using TA Instruments' Universal Analysis software and provided the degradation onset temperature and the amount of residue present at 750 °C.

Differential scanning calorimetry (DSC) was performed on a TA Instruments (Zellik, Belgium) Q2000 DSC device. Samples (5-10 mg) were placed in hermetic T0 aluminium sample pans and subsequently sealed using an aluminium hermetic lid. Samples were then introduced into the device furnace, equilibrated at 45 °C and ramped at 10 °C/min to the temperature at which 1% mass loss was observed in the preceding TGA analysis. The sample was kept isothermal for 5 minutes and was cooled at 10 °C/min to -90 °C followed by another isothermal period of 5 minutes. Finally, the sample was reheated to the previous maximum temperature at 10 °C/min. Data analysis was performed using TA Instruments' Universal Analysis software and provided the glass transition temperature for the studied materials.

# Results and Discussion

Since commonly applied (bio)degradable polyesters such as PGA, PLA and PCL are either semi-crystalline or are characterised by relatively low deformation temperatures (i.e. a low glass transition temperatures ≤ 50 °C), we aimed to synthesise materials of which the Tg values can be engineered towards higher values than the ones reported earlier for amorphous PLA by varying the monomer feed composition [22]. At the same time, the degradation rate of the obtained copolymers through hydrolysis is expected to be faster than for the poly(mandelide) homopolymer which is characterised by rather slow degradation kinetics (10% mass loss detected after incubation at 50 °C for 3 months in phosphate buffer at pH 7.8) [21]. Amorphous PLA on the other hand can be completely degraded within this timeframe under similar conditions (> 90% mass loss after 1 month) [23]. A straightforward way to achieve this goal can be found in the copolymerisation of lactide with monomers that carry a bulky substituent thereby restricting rotational freedom of the polymer chains. Mandelide, a lactide analogue synthesised from mandelic acid, has been proposed as an interesting monomer for the synthesis of degradable polyesters characterised by a Tg around 100 °C. Herein, we report for the first time the applicability of mandelide in copolymerisations with lactide to obtain amorphous copolymers of which the Tg values can be controlled in the range determined by the Tg values of both homopolymers (i.e. 30-100 °C) by selecting the appropriate monomer feed composition, while ROP allows high molecular weights to be targeted in a straightforward way.

## Mandelide synthesis

The synthesis of mandelide was performed following a slightly modified procedure found in literature [21]. Rigorous degassing of the mandelic acid solution prior to refluxing the solution under Dean-Stark conditions was found to be necessary to further increase the reaction yield. Refluxing the mandelic acid solution in mixed xylenes in a Dean-Stark set-up during three days resulted in the highest yield (yield 25-35% for meso-mandelide) which is a further improvement compared to a previous report by Liu *et al.* (24%)[21]*.* Statistically speaking, the dimerization of mandelic acid would yield a reaction product composed of 50% rac-mandelide (25% R,R-mandelide and 25% S,S mandelide) and 50% meso-mandelide (R,S-mandelide). As discussed in the materials and methods section, both diastereomers can be separated from each other in a straightforward way based on the difference in solubility of both diastereomers in mixed xylenes or toluene. Since rac-mandelide is the thermodynamically most stable form, the reaction yields an excess of rac-mandelide and a deviation from the above-mentioned 50-50 ratio is observed (figure 1A). In addition, mandelic acid oligomers can be formed under the experimental conditions, leading to lower overall yields as these compounds are removed from the crude reaction product during the extraction step. This is also the reason why lower yields for both diastereomers are observed for reaction times > 3 days, as the formation of mandelic acid oligomers is favoured at higher conversion (cfr. polycondensation reactions) [24]. Since meso-mandelide is characterised by a lower melting temperature (137 °C) and a higher solubility in organic solvents (1.5 M in acetonitrile at 50 °C) than its diastereomer rac-mandelide, meso-mandelide is the preferred monomer for the synthesis of environmentally degradable polyesters.

To study the influence of the applied solvent on the relative amount of meso-mandelide being produced during the above-mentioned dimerisation reaction, another series of monomer syntheses were performed in toluene following the above-mentioned protocol. Since previous reports on the racemisation of lactide showed that an increased temperature and the presence of bases facilitated the racemisation of lactide [25], it was hypothesised that performing the synthesis in toluene with its lower boiling point might result in higher relative amounts of meso-mandelide as the epimerisation of meso-mandelide to the more stable rac-mandelide could be suppressed.

Unfortunately, the overall reaction yield (sum of both diastereomers) in toluene (figure 1B) was lower than in mixed xylenes (i.e. 43±4% at the optimum reaction duration of 6 days in toluene versus 73±9% at the optimum reaction duration of 3 days in mixed xylenes). Moreover, the obtained amount of the desired meso-mandelide diastereomer was generally lower than in mixed xylenes. Both effects can be attributed to the lower reaction temperature in toluene and the higher water content of the xylene-water azeotrope (mole fraction water = 0.7667) as compared to the toluene-water azeotrope (mole fraction water = 0.5230), which makes xylenes more efficient in removing the water formed as condensation product [26]. Mixed xylenes thus remains the solvent of choice to perform the dimerisation of mandelic acid.

## Racemisation of meso-mandelide in polar solvents

Following the isolation of both diastereomers, the structure of both fractions needed to be confirmed by comparing the recorded 1H-NMR spectra with the chemical shifts reported in literature [21]. However, when the 1H-NMR spectra were recorded using DMSO-*d6* as solvent as proposed by Liu *et al.*, three distinct proton signals were observed between 6 and 6.8 ppm. The initial assumption that the separation of both diastereomers was incomplete based on the chemical shift of the two main signals (6.6 ppm ~ rac-mandelide and 6.4 ppm ~ meso-mandelide) was quickly disproven as multiple recrystallisations from hot ethyl acetate did not alter the ratio between the signals corresponding to each diastereomer, despite the significant difference in solubility between both diastereomers [21]. Moreover, the additional peak at 6.2 ppm remained present. The 1H-NMR spectra of both diastereomers were therefore recorded in a number of deuterated solvents, which led to the conclusion that mandelide readily racemises in highly polar solvents (i.e. DMSO and DMF), while spectra recorded upon applying less polar solvents (e.g. CDCl3 or toluene-*d8*) indicated that this process was less prevalent as indicated by a high diastereomeric excess (approx. 90%) observed for both rac-mandelide as well as meso-mandelide (table 2).

To definitely rule out the presence of rac-mandelide in the meso-mandelide crystals, X-ray diffraction (XRD) experiments were performed on the meso-mandelide crystals. Since none of the studied crystals revealed the presence of rac-mandelide, the possibility of rac-mandelide contamination of the meso-mandelide fraction can be excluded. The combination of both the 1H-NMR-spectra (table 2 and figure S1, supporting information) and the XRD analyses (figures S2-S4, supporting information) thus indicate that meso-mandelide is being converted to rac-mandelide when dissolved in e.g. DMSO.

Since the dissolution of meso-mandelide in DMSO coincided with a yellowing of the solution (figure 2A), UV-VIS spectroscopy revealed an additional absorbance around 379 nm (figure 2B) for meso-mandelide dissolved in DMSO and, to a lesser extent, in DMF, while other solvents did not give rise to this absorbance (see supporting information figure S5). As previously mentioned, an additional proton signal could be observed at 6.2 ppm in the 1H-NMR spectra recorded for meso-mandelide using DMSO-*d6* as solvent. The combination of both observations led to the hypothesis that racemisation of meso-mandelide occurs via an enolic intermediate (scheme 1) which is sufficiently stabilised by DMSO and DMF thereby becoming apparent in the 1H-NMR spectra, while the formed enol would be conjugated to the aromatic ring and may thus account for the observed colour change.

This hypothesis was verified by adding trichloroacetyl isocyanate to the NMR samples of both rac-mandelide as well as meso-mandelide in DMSO-*d6* (scheme 1). This reagent is known to react quantitatively with alcohol moieties and has been previously used for structure elucidation of various alcohols, amines and phenols via 1H-NMR spectroscopy [28–30]. The 1H-NMR spectra (figure 3) reveal an inversion of the ratio between both diastereomers starting from meso-mandelide dissolved in DMSO-*d6* (figure 3A), which may be explained by the fact that rac-mandelide is thermodynamically more stable and is not readily converted to the enolic intermediate [21]. Meso-mandelide on the other hand is converted to the TAIC-adduct thereby depleting the meso-pool and resulting in the inversion of the ratio between both diastereomers. This is consistent with the epimerisation reported in table 2, in which the conversion of meso-mandelide to racemic mandelide was demonstrated. This hypothesis is consistent with the fact that solutions of rac-mandelide in DMSO-*d6* (figure 3B) do not change in composition when TAIC is added.

## Comparison of the polymerisation kinetics of lactide and mandelide

Since NMR spectra recorded in e.g. toluene indicated that both mandelide diastereomers are in fact pure and only small amounts (≤ 7%) of the other diastereomer are present, meso-mandelide and DL-lactide were applied as monomers for (co)polymerisations.

Although both lactide as well as mandelide polymerise via the same ring-opening polymerisation mechanism, limited information is available on the polymerisation of mandelide using the experimental conditions commonly applied for lactide polymerisations. Indeed, Liu *et al.* mentioned the limited solubility of mandelide in toluene and therefore selected acetonitrile (solubility 1.5 M at 50 °C) as a solvent to perform the polymerisation of mandelide. However, when considering the Sn(II)octoate catalyst system, polymerisations of lactide are generally performed at temperatures exceeding 100 °C in bulk or in high-boiling solvents such as toluene [18]. At this temperature, the solubility of meso-mandelide in toluene is not an issue. Moreover, the results in table 2 indicated that racemisation of meso-mandelide is less likely to occur in toluene than in acetonitrile. Therefore, the polymerisation rate constants for both monomers were first determined in toluene at 100 °C for the neohexanol/Sn(2-ethylhexanoate)2 initiator/catalyst system. This catalyst was selected based on its preferred status in industrial applications owing to its lower sensitivity to moisture and oxygen [31]. The obtained results are visualised in figure 4. As shown in figure 4A, the evolution of the poly(lactide) molecular weight closely matches the values expected based on the monomer conversion determined via 1H-NMR spectroscopy.

Poly(mandelide) follows a similar curve although a plateau is reached at longer polymerisation times which can be attributed to the higher degree of steric hindrance around the diester ring. However, a pronounced deviation from the expected molecular weight was observed. This discrepancy between the targeted and the actual molecular weight has been previously reported for poly(mandelide) and was attributed to side reactions occurring for the mandelide monomer [32]. However, the authors did not further specify the nature of these side reactions. Given the high reaction temperatures, the above-mentioned epimerisation of meso-mandelide may contribute to the lower than expected molecular weights (i.e. 4-5 kg/mol instead of 13 kg/mol). Indeed, the formed enolic intermediate may act as an additional initiator. This would explain why the experimental molecular weight is considerably lower compared to the theoretical one, while dispersities remain relatively low (< 1.5). Repeating the 1H-NMR spectra of meso-mandelide in toluene-*d8* at 100 °C however did not reveal a substantial increase in racemisation (data not shown) making it impossible to link the lower molecular weights to the occurrence of monomer racemisation. However, Liu *et al.* reported on the rapid racemisation of the mandelide monomer during the polymerisation in acetonitrile (ACN) [21], which indicates that the above-mentioned process may be facilitated by the added stannous octoate catalyst. Stukenbroeker *et al.* investigated the polymerisation of lactide in the presence of superbases and demonstrated the possibility of initating by an *in situ* formed enolate species [33]. However, masses observed in preliminary MALDI-TOF analyses on poly(mandelide) did not correspond to an enolate end group (figure S8, supporting information). Instead, the observed peaks correspond the most to HO-terminated chains. This observation prevents the low molecular weights to be directly attributed to the racemisation of the monomer, as was observed in polar solvents (section 3.2). However, given the confirmed dryness of the reagents via Karl-Fisher titration and the good control over the molecular weight for the polymerisation of lactide, it remains unclear how these end groups were introduced.

The polymerisations of both monomers show first order kinetics at low to moderate conversion (< 60%) as indicated in figure 4B. Mandelide’s polymerisation rate constant was found to be 4 times lower than the polymerisation rate constant of R,S-lactide (i.e. 1 x 10-4 s-1 versus 4 x 10-4 s-1). The latter is also attributed to the increased steric hindrance in mandelide. However, the polymerisation rate constant at 100 °C in toluene was higher than the value reported by Liu *et al.* (0.25 x 10-4 s-1) when performing the polymerisation of mandelide in acetonitrile at 70 °C [21].

## Copolymerisation of lactide and mandelide

Given our interest in materials with increased Tg values, copolymers with a target DP of 100 were synthesised. When copolymerising both monomers at 100 °C using the same initiator/catalyst system as applied for the homopolymerisations, the FT-IR and 1H-NMR spectra of the obtained materials showed both monomers being present in the polymer backbone of the copolymers and that the ratios determined based on the integration of the methine protons follow the initial monomer feed (table 3, full spectra included in supporting information, figures S6-7

Next, table 3 shows the obtained molecular weight for the polymerisation of lactide using toluene as a solvent and Sn(2-ethylhexanoate)2 and neohexanol as respectively catalyst and initiator, which is close to the target molecular weight. However, when mandelide is added to the monomer feed, similar deviations from the target molecular weight can be observed as discussed earlier for the homopolymerisation kinetics of mandelide, although the obtained dispersities (ĐM) remain low (< 1.1) which is consistent with the values reported for poly(mandelide) [21]. Despite this discrepancy, both the obtained molecular weights as well as the polymer yield (> 80%) were considerably higher compared to a prior report covering copolymers of lactic and mandelic acid obtained via a polycondensation (Mn < 5 kg/mol, yield ≤ 10%) considering polymers with a similar ratio between lactic acid and mandelic acid [20].

## Thermal characterisation of the obtained copolymers

In a last part of our work, we evaluated the synthesised materials’ thermal properties. First, the materials were subjected to thermogravimetric analyses (TGA) to assess their thermal stability. The latter is an important parameter to determine the upper processing temperature that can be applied for these materials. The results are shown in table 4 (full thermograms can be found in supplementary information, figure S9). PLA exhibited a degradation onset of 239 °C, while this value increased to values ranging from 269 °C to 291 °C for the various mandelide containing copolymers. The residue at 750 °C remained below 1% for PLA indicating near complete degradation [34]. When mandelide was introduced to the monomer feed (table 3), the amount of residue increased as the mandelic acid aromatic moieties facilitate char formation [20].

Following the assessment of the copolymers’ thermal stability, the studied materials were subjected to differential scanning calorimetry (DSC) to determine their glass transition temperature (Tg), which is related to the state a polymer is in at a given temperature. If the ambient temperature exceeds the Tg, the material will be in rubbery state, while at temperatures below the Tg, the polymer will be in the glassy state. This has its implication on the appropriateness of a material for a given application, as the transition between both states is associated with a.o. changes in brittleness and heat capacity. The normalised heat flows shown in figure 5A indicate that the obtained materials are 100% amorphous since no melting or crystallisation transitions could be observed. Moreover, the results revealed that the proposed strategy to synthesise polyesters with higher Tg-values (> 50 °C) by copolymerising lactide with mandelide was successful (table 4 and figure 5A). As the mandelide content of the monomer feed rises, the Tg increases according to the Fox equation linking the observed Tg to the copolymer composition and the Tg of the corresponding homopolymers (figure 5B). Despite the lower than expected molecular weights, it can be observed that already for a 50/50 ratio of lactide and mandelide the Tg rises above 50 °C, which is the upper limit for amorphous PLA. The deviation from the linear trend proposed by the Fox equation observed for the PLAMA 25-75 sample can be rationalised by the relatively large difference in molecular weight between the latter and the other mandelide containing copolymers (30% discrepancy, table 3). The influence of the molecular weight on the observed Tg is particularly important for low molecular weight polymers [35].

# Conclusion

In the present study, mandelide was applied as co-monomer for lactide with the aim to develop copolymers that reveal higher glass transition temperatures compared to amorphous poly(lactide) and thus exhibit a higher dimensional stability at elevated temperatures.

Meso-mandelide was first synthesised via a slightly modified protocol derived from literature which allowed to enhance the yield (approx. + 40%) of the monomer synthesis by supressing oxidative side-reactions. When characterising the obtained mandelide diastereomers, a rapid epimerisation was observed when dissolved in highly polar solvents. Our experiments point towards an enolic intermediate being formed in this process.

Next, the first ring-opening copolymerisation of lactide and mandelide was discussed. The low dispersities and the correlation between monomer feed and polymer composition indicate a successful copolymerisation. The attainable molecular weights for the mandelide containing polymers remained lower than expected based on the monomer to initiator ratio (17-35% of the targeted molecular weight), which negatively affects the reported Tg compared to the expectations based on previous reports covering the corresponding high molecular weight homopolymers [35]. The discrepancy between the theoretically expected and the experimental molecular weights may be the result of the racemisation of the meso-mandelide monomer via an enolic intermediate, although this hypothesis so far has not been confirmed. However, despite this discrepancy, the molecular weights presented herein are considerably higher than the ones previously reported for copolymers of lactic acid and mandelic acid obtained via direct polycondensation reactions (approx. 12 kg/mol compared to 5 kg/mol).

It was demonstrated that the glass transition could be increased in a straightforward way according to Fox’ law by increasing the mandelide content in the monomer feed. At a 50-50 ratio, the observed Tg already surpassed the 50 °C threshold, which serves as the upper limit for amorphous PLA. The materials were amorphous as was derived from the absence of melting or crystallisation transitions in the DSC thermograms. Experiments are currently underway to synthesise structurally similar polymers via mandelic acid derived monomers that do not suffer from the effect associated with epimerisation and are therefore expected to yield higher and more reproducible molecular weights.

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**Supporting Information**

The online supporting information can be obtained from the publisher’s website.

In addition, CCDC-1550625 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44-1223-336033; or deposit@ccdc.cam.uk).

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# Figure captions

Figure 1: Obtained mandelide yields (white: rac-mandelide; grey: meso-mandelide) for reactions in mixed xylenes (graph A, left) and toluene (graph B, right).

Figure 2: Illustration of the yellowing of meso-mandelide solutions in DMSO. (A) Colour difference observed when meso-mandelide is dissolved in chloroform (left vial) or DMSO (right vial). The colour can be attributed to an additional absorbance peak (379 nm) as determined via UV-VIS spectroscopy (B). For reasons of clarity, the graphs are spaced in the vertical axis by an increment of 0.5 A.U.

Scheme 1: Scheme indicating the principle of the use of trichloro-acetyl isocyanate (TAIC). If the racemization in DMSO indeed passes through an enol-adduct, the formed enol functions would react quantitatively with TAIC resulting in a urethane bond, thereby locking the enolic structure.

Figure 3: NMR spectra recorded in DMSO-*d6* indicating the effect of TAIC on meso- (A) and rac-mandelide (B). The different curves represent the spectra prior to TAIC addition (black), 15 minutes after TAIC addition (red) and 24h after TAIC addition (blue).

Figure 4: Kinetics of the solution polymerisation of lactide (black ■) and mandelide (red ●) [Monomer]:[Sn(2-ethylhexanoate)2]:[neohexanol] = 100:1:2; [monomer] = 1 mol/L. **A** shows the evolution of the molecular weight as a function of polymerisation time and compares the experimental results with the expected values based on monomer conversion (lactide: black, solid line; mandelide: red, dashed line). Dispersities remain well below 1.5 for both lactide (black □) as well as mandelide (red ○) **B** shows the reaction kinetics under the same conditions and indicates first order kinetics at low to moderate conversion.

Figure 5: DSC thermograms obtained for the developed copolymers (A) and the fitting of the observed Tg values according to the Fox equation (B).