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Stereoregular Isotactic Poly(mandelic acid) via Organocatalytic Ring-Opening Polymerization of a Cyclic *O*-carboxyanhydride**

Antoine Buchard, David R. Carbery,* Matthew G. Davidson,* Petya K. Ivanova, Ben J. Jeffery, Gabriele I. Kociok-Köhn, John P. Lowe

Dedicated to the memory of Ken Wade: a friend, a mentor and a brilliant chemist

Abstract: Poly(mandelic acid), PMA, is an aryl analogue of poly(lactic acid), PLA, and a biodegradable analogue of polystyrene. Preparation of stereoregular PMA is reported for the first time in this work using a pyridine-mandelic acid adduct (Py·MA) as an organocatalyst for the ring-opening polymerisation (ROP) of the cyclic *O*-carboxyanhydride, *man*OCA. Polymers with narrow polydispersity index and excellent molecular weight control were prepared at ambient temperature. These highly isotactic chiral polymers exhibit glass transition temperature (T_g) enhancement of 15 ˚C compared to the racemic polymer, suggesting potential future application as high performance commodity and biomedical materials.

Degradable polymers based on biorenewable resources are desirable alternatives to common commodity polymers. The environmental persistence and dependence on fossil-based resources of the latter are increasingly viewed as unsustainable.[1] Polylactide (PLA) is a thermoplastic aliphatic polyester derived from lactic acid that is perhaps the most widely studied degradable and renewable polymer.[2],[3] PLA is commercially available for packaging and fibre applications via solvent-free ring-opening polymerization (ROP) of lactide, (Scheme 1).[4]-[6] In recent years, the drive to achieve enhanced physical and mechanical properties such as impact and heat resistance for such applications of PLA has led to detailed mechanistic understanding and prompted the development of a wide range of single-site metal alkoxides and organocatalytic bases for the well-controlled and stereoselective ROP of lactide.[3],[7]-[11].

Despite these impressive advances, major challenges remain. For example, the glass transition temperature (T_g) of PLA remains low (typically 30-60 ˚C) due to the inherently flexible polymer backbone. This low heat resistance limits the range of applications for which PLA-based materials are applicable.[12] Recently, in an intriguing report, Baker *et al.* demonstrated the first synthesis of high molecular weight poly(mandelic acid), PMA, via the tin-catalyzed ROP of mandelide, the cyclic dimer of mandelic acid (an aryl analogue of lactide) (Scheme 1).[13] They demonstrated that polymandelide shares many physical and mechanical properties with polystyrene, including a high T_g (95-100 ˚C) while, in common with PLA, it is available from renewable resources and is degradable. However, the synthesis of mandelide requires extended reaction times, high-boiling solvents and results in poor to moderate yields of poorly soluble monomers. Furthermore, relative to lactide, decreased reactivity of mandelide, coupled with its increased C-H acidity makes racemization of the monomer during polymerization unavoidable, meaning that only atactic material is available via this route (Scheme 1).
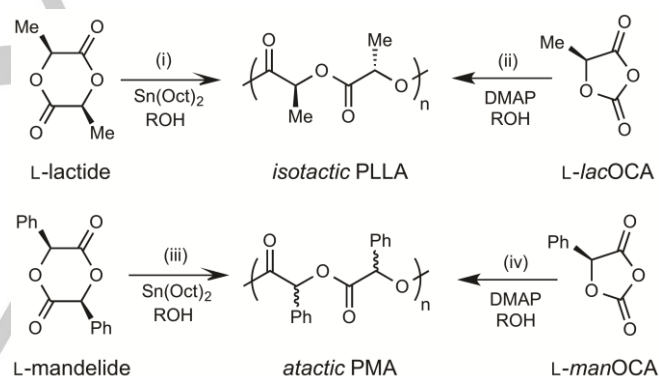
Scheme 1. Metal- and organo-catalysed ring-opening polymerization to isotactic poly-L-(lactic acid) (PLLA) and atactic poly(mandelic acid) (PMA) from: (i) L-lactide (commercial process); (ii) L-*lac*OCA (ref 14); (iii) , L-mandelide (ref 13); and (iv) L-*man*OCA (this work).

Building on these intriguing results, and the elegant demonstration of controlled synthesis of PLA via the *O*-carboxyanhydride (OCA) activated monomer, L-*lac*OCA by Bourrisou and others,[14],[15] we reasoned that an organocatalytic approach to ROP of an activated mandelic acid monomer, *man*OCA might promote controlled polymerization under sufficiently mild conditions to prevent racemization and yield stereoregular isotactic PMA (Scheme 1). Herein, we report the successful application of this strategy to achieve, for the first time, the synthesis and unambiguous characterization of high molecular weight isotactic PMA via a new organocatalytic adduct. The enantiomerically pure activated monomer *man*OCA was prepared in good yield by modification of a literature procedure (Supporting Information, SI).[16] Initial investigations of polymerization of *man*OCA focused on pyridine-based catalysts and initiators which have proved effective for well-controlled organocatalytic ROP of *lac*OCA and related monomers.[14] A
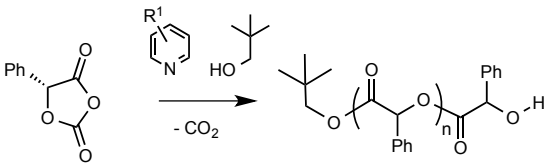
[*]   Antoine Buchard, David R. Carbery,* Matthew G. Davidson,* Petya K. Ivanova⁺, Ben J. Jeffery⁺, Gabriele I. Kociok-Köhn and John P. Lowe
        Department of Chemistry and Centre for Sustainable Chemical Technologies
        University of Bath
        Bath, BA2 7AY, United Kingdom
        Fax: (+)44 01225 386231
        E-mail: m.g.davidson@bath.ac.uk, d.carbery@bath.ac.uk

series of pyridines were chosen to provide catalysts with a range of basicity (Table 1). With a neopentyl alcohol initiator, good conversion to PMA was achieved, although molecular weights were not as predicted and, in contrast to related polymerizations,[14(b)] trends in activity do not correlate well with pyridine basicity. These observations are consistent with a polymerization mechanism more complex than simple base-catalyzed ROP. Furthermore, the methine region of ^{1}H NMR spectra displayed 10 peaks for DMAP (Fig S1), typical of a random stereosequence distribution at the pentad level indicative of base-catalysed racemization of the monomer leading to atactic PMA (Scheme 1). Development of a dominant singlet peak for the polymer methine signal, attributable to isotactic enrichment of the polymer, is observed as the basicity of the pyridine decreases which is consistent with partial suppression of racemization (Fig S2 - S4). It is noteworthy that Tighe *et al.* previously reported the reaction of *man*OCA with pyridine (using water as an initiator) to yield low molecular weight polymers and these exhibited broad phenyl and methine resonances in the NMR, indicative of atactic PMA.[17]

Table 1. Polymerization reactions using pyridine base as a catalyst and neopentyl alcohol as an initiator.[a]

D-*man*OCA   PMA

Entry	R[1]	Conv. [%][b]	Time [h]	M_n [kDa][c]	Calc. M_n [kDa][d]	M_w/M_n[c]
1	4-NMe[2]	95	47	2.2	13.0	1.47
2	4-OMe	99	6	11.5	13.0	1.24
3	4-H	98	23	22.8	13.0	1.33
4	3-Br	83	430	31.6	11.0	1.29

[a] Reactions conducted in a sealed NMR tube (CDCl₃, 298 K) with D-*man*OCA [M]₀ = 0.56 M, [M]/[C]/[I] = 100:1:1; [b] Determined by relative integration of the aromatic region of the ^{1}H NMR spectrum; [c] GPC measured in THF (1 mL min⁻¹, 35 °C) referenced against polystyrene standards; [d] Calculated based on % conversion.

Our initial studies were also hampered by a lack of reproducibility, with the observation of occasional high levels of isotactic enrichment of the isolated poly(mandelic acid). In noting variable levels of free mandelic acid present in monomer samples (presumably due to adventitious water) we reasoned that the origin of high stereoselectivity might be due to the presence of mandelic acid. To test this reasoning, we investigated the controlled and stoichimetric introduction of mandelic acid via the preparation of a crystalline 1:1 adduct of mandelic acid and pyridine (Py·MA) which was unambiguously characterized by single-crystal X-ray diffraction (Figure 1 and SI).
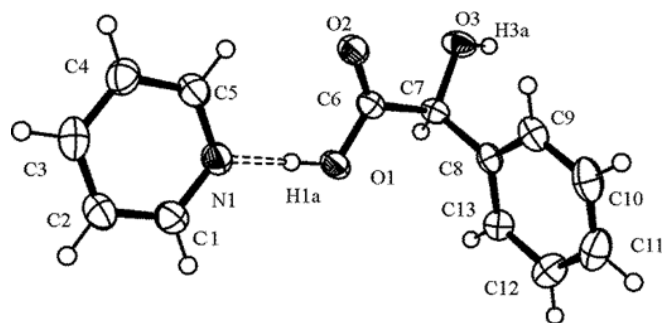

Figure 1. Crystal structure of pyridine-mandelic acid adduct Py·MA. Displacement ellipsoids at the 50% probability level (SI).[18]
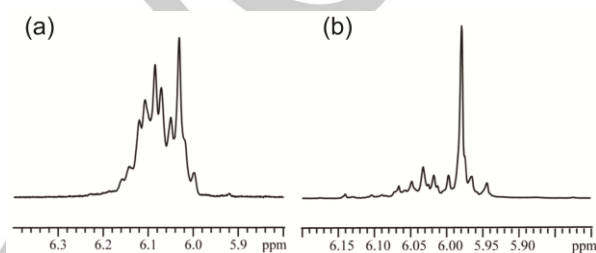

Figure 2. ^{1}H NMR spectra of the methine region of poly(mandelic acid): (a) pyridine catalyst (Table 1, entry 3) showing partial racemization resulting in an atactic polymer; and (b) Py·MA initiator (Table 2, entry 6), showing significantly improved stereoretention and an isotactic polymer.

Polymerization experiments were performed using Py·MA as a single initiator system for ROP of *man*OCA.[19] Over a range of catalyst concentrations (Table 2) molecular weights were close to calculated values with polymers exhibiting low molecular weight distributions, indicative of well-controlled ROP. Most importantly, high levels of isotactic enrichment were observed, as evidenced by NMR spectroscopy (Figures 2 and S5-S8). Essentially a single resonance in the methine region is observed supporting the assertion that PMA is formed from *man*OCA with stereoretention. Isotactic polymers synthesized in this way exhibited enhanced heat resistance: T_g = 105.5 °C, (12.9 kDa, Figure S15 and Table 2, entry 6) verses T_g = 91.0 °C, (10.4 kDa atactic PMA synthesized under the same reaction conditions from racemic monomer, Figure S16 and Table 2, entry 8). This enhancement in the T_g is also apparent relative to the previously reported high molecular weight atactic PMA (T_g = 100 °C, when 68 kDa)[13] and offers a potential pathway for the development of new high performance sustainable materials. Optical rotations recorded for polymers prepared from enantiopure *L-man*OCA and *D-man*OCA, display opposite rotations of comparable magnitudes (-82 and +92, for 12.9 and 11.6 kDa polymers, Table 2, entry 6 and 7, respectively) supporting the observation by ^{1}H NMR of high levels of polymer enantiopurity. Even greater control can be achieved, albeit at a lower polymerization rate, using a 3-Br-pyridine·MA initiator (Table 2, entry 11). This initiator yields a polymer with optical rotation of -116, which correlates to ^{1}H and ^{13}C NMR spectra (Figures S7 and S8) showing close to 100% stereoretention. Observation of such high levels of isotacticity over prolonged
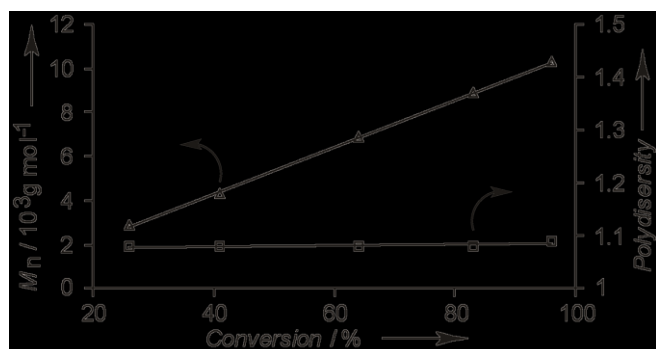
Figure 3. Plot of poly(mandelic acid) M_n (Δ) and molecular weight distribution (□) versus conversion highlighting the well-controlled nature of polymerization (conditions as for table 2, entry 6).

Table 2. Polymerization reactions using pyridine-mandelic acid adducts as catalysts.[a]

D-*man*OCA → *isotactic* PMA

Entry	R¹	[M]/[C]/[I]	Conv [%][b]	Time [h]	M_n[c] [kDa]	Calc.M_n [kDa][d]	M_w/M_n[c]
5	4-H	50:1:1	99	4	6.9	6.9	1.08
6	4-H	100:1:1	99	25	12.9	13.0	1.08
7[a]	4-H	100:1:1	99	14	11.6	13.0	1.07
8[a]	4-H	100:1:1	99	14	10.4	13.0	1.08
9	4-H	200:1:1	99	25	25.0	27.0	1.09
10	4-H	500:1:1	97	89	48.0	65.1	1.17
11	3-Br	100:1:1	95	312	12.9	13.0	1.08
12	4-NMe₂	100:1:1	97	71	3.9	13.0	1.32
13	4-OMe	100:1:1	99	2	10.9	13.0	1.10

[a] Reactions conducted in a sealed NMR tube (CDCl₃, 298 K) with *R*-mandelic acid OCA, except for entry 7 (*S*-mandelic acid OCA), and entry 8 (*rac*-mandelic acid OCA), [M]₀ = 0.56 M; [b] Determined by relative integration of the aromatic region of the ¹H NMR spectrum; [c] GPC measured in THF (1 mL min⁻¹, 35 °C) referenced against polystyrene standards; [d] Calculated based on % conversion.

With the Py·MA initiator, polymers of 48 kDa could be achieved while maintaining the polydispersity level as low as

1.17 (Table 2, entry 10). MALDI-ToF mass spectrometry of low molecular weight species confirms the expected mandelate and hydroxyl end groups and the absence of cyclic oligomers (Figure S10). Modification of the catalyst adduct to Py·*R*-4-methyl-MA further reveal that PMA chains are end-capped with the initiating α-hydroxy acid group (Figures S11 and S14). Reactions were investigated through reaction monitoring, which further confirms the well-controlled 'living' nature of polymerizations (Figure 3 and S18).
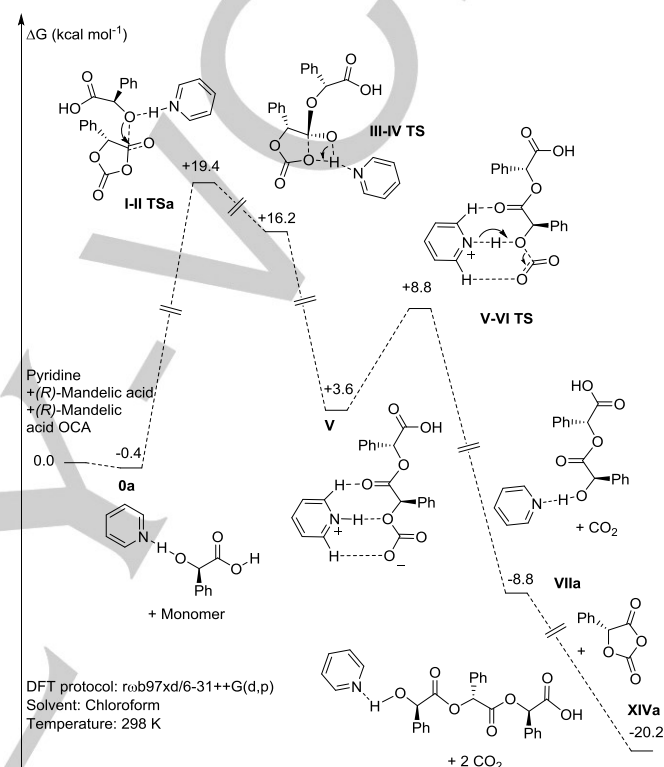
Scheme 2. DFT modelling of the polymerization mechanism (selected steps from the initiation step, full details of the polymerisation mechanism calculations can be found in the SI).

The mechanism of the products of the reaction between Py·MA, and up to two molecules of *man*OCA (to account for both initiation and propagation steps) were examined using DFT calculations.[20] Scheme 2 illustrates the initiation step of the most favourable reaction path towards the ROP of *man*OCA (see SI for full mechanism and alternative reaction paths). In accordance with previous calculations, to open the monomer, basic activation of the initiator OH moiety by hydrogen bonding is energetically favoured relative to direct nucleophilic attack by the pyridine.[15] The ring opening and evolution of CO_2 are then discrete processes rather than being concerted, with the pyridine mediating the proton transfer stepwise through tetrahedral intermediates. Limiting energy barriers of $\Delta\Delta G$= +20.6 and +16.7 kcal mol⁻¹ for respectively the initiation and the propagation steps are low enough for the reaction to happen at room temperature. The overall ΔG for the initiation is calculated to be -8.8 kcal mol⁻¹ and the propagation -20.2 kcal mol⁻¹ at 298 K.

ROP initiated via the activation of the CO_2H moiety of mandelic acid by pyridine, resulting in the formation of a carbonate species, could not be found. Similarly, initial attack of the OH at the carbonate carbonyl, again forming a carbonate species, is disfavoured. For Py·MA, initiation and propagation of polymerization is via hydrogen-bond activation of the hydroxyl group of MA. This offers a potential explanation for the observed low reactivity of DMAP, which is more basic and therefore will be deactivated for this pathway via formation of a pyridinium salt.

In conclusion, we have demonstrated for the first time the synthesis of isotactic poly(mandelic acid). This has been achieved through well-controlled ROP of cyclic *O*-carboxyanhydrides using organocatalytic pyridine-mandelic acid adducts. We demonstrate that highly stereoregular poly(mandelic acid) thus prepared has enhanced heat resistance over atactic polymers and an enhanced glass transition temperature very similar to that of polystyrene, suggesting possible future application of such materials in commodity and biomedical applications. DFT calculations highlight the key roles played by both the pyridine and the mandelic acid as part of a single initiator system in achieving this degree of control. Further work is ongoing with a view to understanding and optimizing these polymerizations and to investigate the potential for stereocomplexation[21] of isotactic PMA to provide materials with further enhanced physical and mechanical properties.

Keywords: poly(mandelic acid) • organocatalysis• stereoregular polymer • sustainable chemistry • ring-opening polymerization

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[18] Crystal data for (Py·MA): $C_8H_8O_3$•C_5H_5N, M_w = 231.24 g mol⁻¹, a = 5.66060(10) Å, b = 7.9224(2) Å, c = 26.3426(7) Å, V = 1181.35(5) Å³, T = 150(2) K, space group $P2_12_12_1$, Z = 4, μ(MoKα) = 0.093 mm⁻¹, 12963 reflections measured, 2678 independent reflections (R_{int} = 0.0372). The final R_1 values were 0.0357 ($I > 2\sigma(I)$). The final wR(F^2) values were 0.0733 ($I > 2\sigma(I)$). The final R_1 values were 0.0544 (all data). The final wR(F^2) values were 0.0799 (all data). The goodness of fit on F^2 was 1.057. Flack parameter = -0.9(6). CCDC-972538.

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[20] DFT calculations were carried out using the following protocol: ωB97XD/6-31++G(d,p)/SCRF=(cpcm,solvent=chloroform) at a temperature of 298 K. The protocol includes an attractive dispersion term shown to reproduce reaction barriers effectively.[22],[23]

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Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Highly isotactic chiral poly(mandelic acid), PMA, was prepared for the first time. Pyridine alone as an organocatalyst yielded only atactic PMA. In contrast, utilizing a well-defined pyridine-mandelic acid adduct resulted in excellent control over the ring-opening polymerization and provided highly isotactic polymers. The enhanced heat resistance of isotactic PMA (increase in T_g of 15 ºC) suggests it as a promising renewable alternative to poly(styrene).
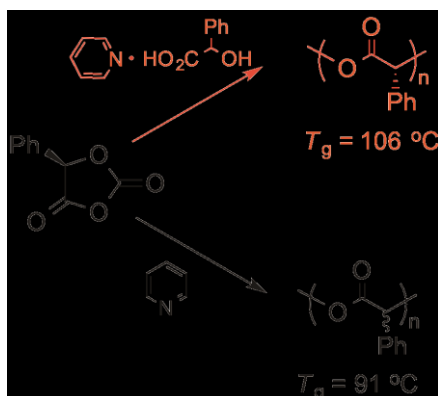
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