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Preparation of Stereoregular Isotactic Poly(mandelic acid) through Organocatalytic Ring-Opening Polymerization of a Cyclic *O*-Carboxyanhydride**

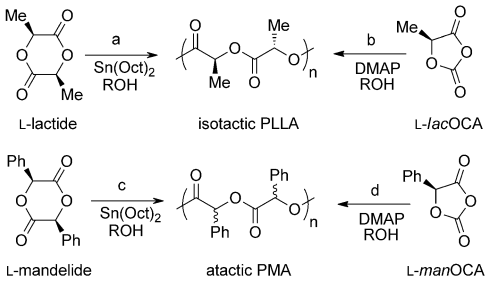
Antoine Buchard, David R. Carbery, Matthew G. Davidson,* Petya K. Ivanova, Ben J. Jeffery, Gabriele I. Kociok-Köhn, and John P. Lowe*

In memory of Ken Wade

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

Degradable polymers based on renewable resources are desirable alternatives to common commodity polymers. The environmental persistence and dependence on fossil-based resources of the latter polymers are increasingly viewed as unsustainable.[1] Polylactide (PLA) is a thermoplastic aliphatic polyester derived from lactic acid and is perhaps the most widely studied degradable and renewable polymer.[2,3] PLA is commercially available for packaging and fiber applications and prepared through 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 led to a 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 to be addressed. For example, the glass-transition temperature (T_g) of PLA remains low (typically 30–60 °C) as a result of 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) through a 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), but is available from renewable resources and degradable as PLA. However, the synthesis of mandelide requires extended reaction times and high-boiling solvents and results in poorly soluble monomers in poor to moderate yields. Furthermore, relative to lactide, the decreased reactivity of mandelide, coupled with its increased C–H acidity makes the racemization of the monomer during the polymerization unavoidable, meaning that only atactic material is available through this route (Scheme 1).



Scheme 1. Metal- and organocatalyzed ring-opening polymerization leading to isotactic poly-L-(lactic acid) (PLLA) and atactic poly(mandelic acid) (PMA) from: a) L-lactide (commercial process), b) L-*lac*OCA (Ref. [14]), c) L-mandelide (Ref. [13]), and d) L-*man*OCA (this work).

Building on these intriguing results, and the elegant demonstration of the controlled synthesis of PLA from the *O*-carboxyanhydride (OCA) activated monomer (L-*lac*OCA) by Bourrisou and others,[14,15] we reasoned that an organocatalytic approach to the ROP of an activated mandelic acid monomer (*man*OCA) might promote controlled polymerization under sufficiently mild conditions to prevent racemization and give stereoregular isotactic PMA. Herein, we report the successful application of this strategy to the synthesis and unambiguous characterization of high-molecular-weight isotactic PMA using an organocatalytic adduct.

[*] Dr. A. Buchard, Dr. D. R. Carbery, Prof. M. G. Davidson, Dr. P. K. Ivanova, Dr. B. J. Jeffery, Dr. G. I. Kociok-Köhn, Dr. J. P. Lowe
Department of Chemistry and Centre for Sustainable Chemical Technologies, University of Bath, Bath, BA2 7AY (UK)
E-mail: d.carbery@bath.ac.uk
m.g.davidson@bath.ac.uk

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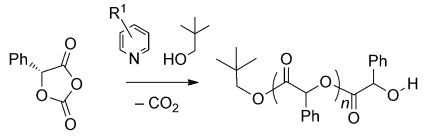
The enantiomerically pure, activated monomer *man*OCA was prepared in good yield by modification of a reported procedure (see the Supporting Information).[16] Initial investigations of the polymerization of *man*OCA focused on pyridine-based catalysts and initiators that proved effective for well-controlled organocatalytic ROPs of *lac*OCA and related monomers.[14] A series of pyridines was chosen to provide 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,[14b] trends in activity did not correlate well with the basicity of the pyridines. These observations are consistent with a polymerization mechanism that was more complex than a simple base-catalyzed ROP. Furthermore, the methine region of the ^{1}H NMR spectra displayed 10 signals for DMAP (Figure S1), typical of a random stereosequence distribution at the pentad level indicative of base-catalyzed racemization of the monomer leading to atactic PMA (Scheme 1). Development of a dominant singlet signal for the methine moiety in the polymer, attributable to isotactic enrichment of the polymer, was observed as the basicity of the pyridine decreased, which is consistent with a partial suppression of the racemization (Figure S2–S4). It is noteworthy that Tighe et al. previously reported the reaction of *man*OCA with pyridine (using water as an initiator) to give low-molecular-weight polymers, and these exhibited broad phenyl and methine resonances in the NMR spectra, indicative of atactic PMA.[17]

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). Noting variable levels of free mandelic acid present in the monomer samples (presumably because of 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 by preparing a crystalline 1:1 adduct of mandelic acid and pyridine (Py·MA), which we unambiguously characterized by single-crystal X-ray diffraction (Figure 1 and the Supporting Information).

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]	t [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 ($CDCl_3$, 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 the conversion (in [%]).

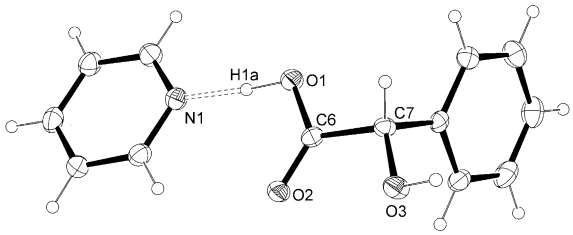
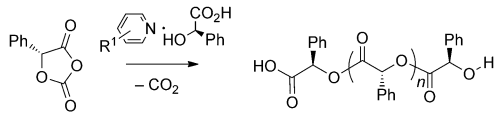


Figure 1. Crystal structure of pyridine/mandelic acid adduct Py·MA. Displacement ellipsoids at the 50% probability level (Supporting Information).[18]

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), the molecular weights of the polymers were close to calculated values, with polymers exhibiting low molecular-weight distributions, which is indicative of a well-controlled ROP. Most importantly, high levels of isotactic enrichment were observed, as evidenced by NMR spectroscopy (Figures 2 and S5–S8). Essentially, the observation of a single resonance in the methine region supports 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) versus $T_g = 91.0$ °C, (10.4 kDa atactic PMA synthesized under the same reaction conditions from racemic monomer, Figure S16 and Table 2, entry 8). This enhance-

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



D-*man*OCA isotactic PMA

Entry	R^1	[M]/[C]/[I]	Conv [%][b]	t [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-NMe_2	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 ($CDCl_3$, 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 ^{1}H NMR spectrum. [c] GPC measured in THF (1 mL min^{-1}, 35 °C) referenced against polystyrene standards. [d] Calculated based on the conversion (in [%]).

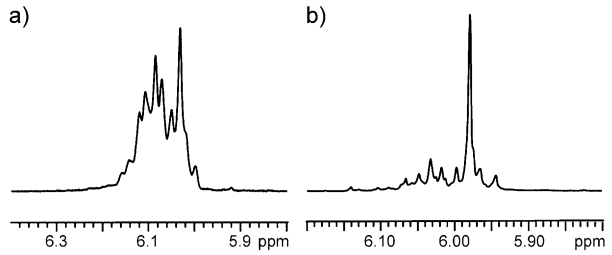


Figure 2. ^{1}H NMR spectra of the methine region of poly(mandelic acid) prepared with a) pyridine catalyst (Table 1, entry 3), showing partial racemization resulting in an atactic polymer, and with b) Py·MA initiator (Table 2, entry 6), showing significantly improved stereoretention and an isotactic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

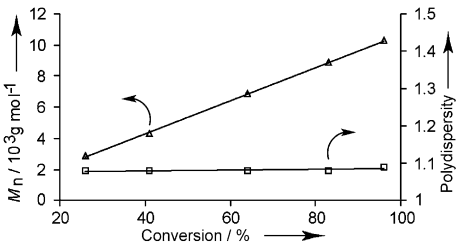


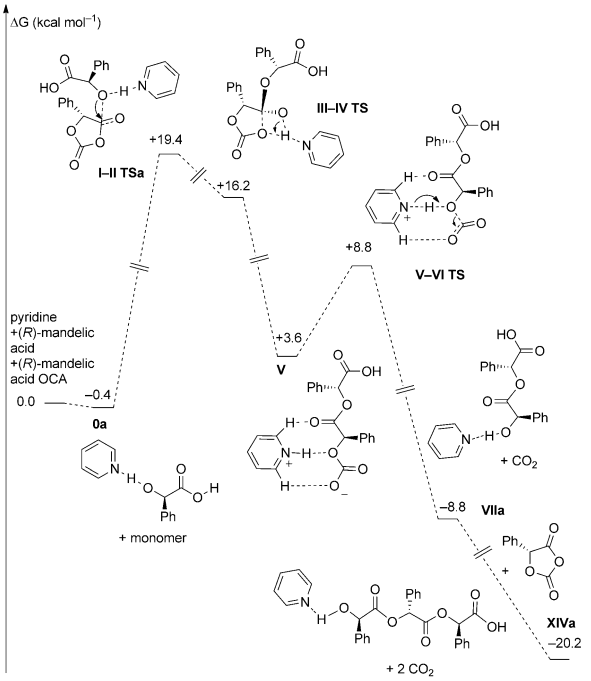
Figure 3. Plot of number average molecular weight M_n (△) and polydispersity index (□) of poly(mandelic acid) versus conversion, highlighting the well-controlled nature of the polymerization (conditions as for Table 2, entry 6).

ment in the T_g is also apparent with regard 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 made by ^{1}H NMR spectroscopy of high levels of polymer enantiopurity. Even greater control can be achieved, but at a lower polymerization rate, using a 3-Br-pyridine·MA initiator (Table 2, entry 11). This initiator gave a polymer with an optical rotation of −116, which correlates to the ^{1}H and ^{13}C NMR spectra (Figure S7 and S8), showing close to 100% stereoretention. Importantly, the observation of such high levels of isotacticity over prolonged reaction times suggests that isotactic PMA is resistant to epimerization under our polymerization conditions.

With the Py·MA initiator, polymers of 48 kDa could be obtained while a polydispersity level as low as 1.17 was maintained (Table 2, entry 10). MALDI-TOF mass spectrometry of low-molecular-weight species confirmed the expected PhCH(CO_2H)O and OH end groups and the absence of cyclic oligomers (Figure S10). Modification of the catalyst adduct to Py·*R*-4-methyl-MA further revealed that PMA chains are end-capped with the initiating α-hydroxy acid group (Figure S11 and S14). Reaction monitoring further confirmed the well-controlled 'living' nature of the polymerizations (Figure 3 and S18).

The reaction between Py·MA and up to two molecules of *man*OCA (to account for both initiation and propagation steps) was examined using DFT calculations.[20] Scheme 2 illustrates the initiation step of the most favorable reaction path toward the ROP of *man*OCA (see the Supporting Information for the full mechanism and alternative reaction paths). In accordance with previous calculations, to open the monomer, a basic activation of the OH moiety of the initiator by hydrogen bonding is energetically favored relative to the direct nucleophilic attack by the pyridine.[15] The ring opening and evolution of CO_2 are then discrete processes rather than 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 the initiation and the propagation steps, respectively, are low enough for the reaction to occur at room temperature. The overall ΔG for the initiation was calculated to be $-8.8\,kcal\,mol^{-1}$ and that of the propagation $-20.2\,kcal\,mol^{-1}$ at 298 K. No evidence could be found for initiation of ROP through the activation of the CO_2H moiety of mandelic acid by pyridine (resulting in the formation of a carbonate species). Similarly, the initial attack of the OH group at the carbonyl moiety, again forming a carbonate species, is disfavored. For Py·MA, initiation and propagation of the polymerization occur through hydrogen-bond activation of the hydroxy group of MA. This offers a potential explanation for the observed low reactivity of DMAP, which is more basic and therefore will deactivate this pathway through the formation of a pyridinium salt.

In conclusion, we have achieved the synthesis of isotactic poly(mandelic acid) through a well-controlled ROP of cyclic *O*-carboxyanhydrides using organocatalytic pyridine/man-



Scheme 2. DFT modelling of the polymerization mechanism (selected steps from the initiation step, full details of the polymerization mechanism calculations can be found in the Supporting Information).

delic acid adducts. We demonstrated that thus prepared highly stereoregular poly(mandelic acid) 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 highlighted 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 investigating the potential for stereocomplexation[21] of isotactic PMA to further enhance physical and mechanical properties.

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[18] Crystal data for Py·MA: $C_8H_8O_3{\cdot}C_5H_5N$, $M_w = 231.24\ g\,mol^{-1}$, $a = 5.66060(10)$, $b = 7.9224(2)$, $c = 26.3426(7)$ Å, $V = 1181.35(5)$ Å^3, $T = 150(2)$ 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 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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