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The synthesis of a homochiral methacrylate macromonomer by polymerisation of (R)- or (S)-methyl *β*-hydroxyisobutyrate

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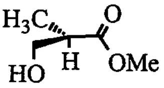
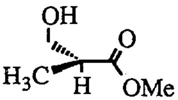
Summary

Polymerisations of either enantiomer of commercially available methyl β-hydroxyisobutyrates **1a** and **1b** were carried out. $Ti(OBu^n)_4$ catalysed transesterification of the neat monomer generated either polymer **3** at lower temperatures (~100°C) or homochiral macromonomer **2** at higher temperatures. Under optimal conditions for the preparation of the macromonomer **2**, a soluble material (Mn 3600, Mw 7000) was produced which displayed high crystallinity as judged by X-ray powder diffraction analysis.

Introduction



(R)-1a



(S)-1b

Main chain homochiral polyesters such as poly(R-β-hydroxybutyrate) and poly(L-lactide) have been widely explored as biodegradable materials[1-3], in the former case for its environmental compatibility and in the latter for its biocompatibility in drug release and surgical suture applications. Main chain chiral materials are now being designed for their inherent catalytic properties[4] rather than their biodegradability. In general a fundamental understanding of main chain chirality and how chirality effects function and properties in polymer science, is very much in its infancy.[5,6]

In this paper we report our investigations into the polymerisation of the enantiomers of methyl β-hydroxyisobutyrate **1a** and **1b**. It was anticipated that high molecular weight materials would be difficult to achieve as the β-hydroxyl functionality is susceptible to elimination. However, termination by elimination, during the polymerisation of **1a** and **1b**, should generate the homochiral macromonomer **2**. Access to such a macromonomer would allow us to dope methacrylate polymerisations and investigate effects on both the physical properties and performance characteristics of the resultant films. This study extends an

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ongoing programme in our laboratory on the nature and influence of chirality in methacrylate systems.[7]

Experimental

The monomers methyl (R)-(-) and (S)-(+) - 3-hydroxy-2-methylpropionate (99% ee) (**1a** and **1b**) and titanium tetrabutoxide[8], were purchased from the Aldrich Chemical Co. Thermogravimetric analyses were carried out using a Stanton Redcroft TG 760 Thermobalance. Differential scanning calorimetry was performed on a Perkin-Elmer DSC-7. ^{1}H and ^{13}C n.m.r. spectra were recorded on a Varian 200 MHz, Varian 400 MHz or Bruker 250 MHz spectrometers and were referenced to TMS. Gel permeation chromatography was carried out in chloroform using three in series 5 µm columns of PL gel with pore size 100 Å, 10^3 Å and 10^5 Å. X-ray powder diffraction was carried out on a Siemens Diffractometer D5000. The polycondensation reactions were carried out using the apparatus shown diagrammatically in Figure 1.

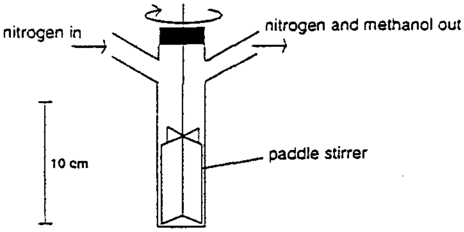


Figure 1 **Graphic illustration of the reaction vessel used for the polymerisations**

Typical polymerisation procedure

The reaction vessel was lowered into a Woods metal bath, preheated to 100°C, whilst stirring the monomer, (S)-(+)-3-hydroxy-2-methylpropionate **1b** (4g, 33.8 mmol) with titanium tetrabutoxide (50 µl) under a flow of nitrogen. The bath temperature was increased at a rate of 10°C/min to 150°C with continued stirring, where it was held for 5 hours. At this stage, the flow of nitrogen was stopped and the pressure in the reaction vessel reduced (1 mmHg). Heating was continued for a further hour at 150°C to remove residual methanol and drive the reaction to higher conversion. On completion of the reaction, the nitrogen flow was restored and the reaction mixture cooled to room temperature. The resultant oil solidified to give a brittle pale yellow polymeric material which was soluble in chloroform. Addition of a chloroform solution of the polymer to a large excess of diethyl ether resulted in the precipitation of the polymer which was collected by filtration and dried under vacuum to yield a white solid (2.75 g), m.pt. 124°C.

δ_H: 1.18-1.20 (d, 3H, $C\underline{H}_3$); 1.92 (s, 3H, $C\underline{H}_3$); 2.76-2.84 (m, 1H, $C\underline{H}CH_3$); 3.71 (s, 3H, OCH_3); 4.21-4.23 (br d, 2H, $OC\underline{H}_2$), 5.56 (s, 1H, $C\underline{H}_2$=), 6.08 (s, 1H, $C\underline{H}_2$=).
δ_C: 13.70 ($\underline{C}H_3$); 38.92 ($\underline{C}HCH_3$); 51.92 ($O\underline{C}H_3$); 65.59 ($O\underline{C}H_2$); 173.19 ($\underline{C}$=O);.
$[\alpha]^{20}$ +31.5° (c = 3.8, $CHCl_3$).

Results and Discussion

Either (R) or (S) methyl β-hydroxyisobutyrate (**1a** or **1b**) was treated with $Ti(OBu^n)_4$ (0.04-0.05 mol %), a well described[8,9] catalyst for transesterification reactions. The reaction vessel is shown in Figure 1 and to facilitate efficient mixing there was a clearance of 1 mm between the walls and a revolving paddle driven by an overhead mechanical stirrer. Care was taken to exclude moisture, by flame drying the apparatus prior to use, and the transesterification reaction was conducted under a positive pressure of flowing nitrogen which removed methanol generated during the reaction.

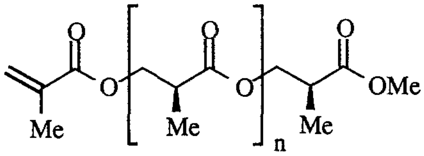
We were conscious that the poly(β-hydroxyisobutyrate) is susceptible to elimination and therefore a series of experiments was carried out at different temperatures to assess optimum conditions. The data are shown in Table 1.

Entry	Substrate[a] enantiomer	Temp.°C	Time, h	Catalyst[b]	M_n[c]	M_w[c]	M_w/M_n PDI
1	**(S)-(+)**	**150**	**6**	**$Ti(OBu^n)_4$**	**3621**	**7000**	**1.92**
2	(S)-(+)	175	6	$Ti(OBu^n)_4$	2073	5875	2.83
3	(S)-(+)	100	6	$Ti(OBu^n)_4$	1327	1955	1.47
4	(S)-(+)	220	4	$Ti(OBu^n)_4$	2074	2707	1.31
5	(S)-(+)	200	2	$Ti(OBu^n)_4$	1400	1715	1.23
6	(S)-(+)	200	4	$Ti(OBu^n)_4$	1533	2800	1.81
7	(R)-(-)	200	5	$Ti(OBu^n)_4$	2580	3617	1.40
8	(S)-(+)	200	6	$Ti(OBu^n)_4$	2907	4100	1.41

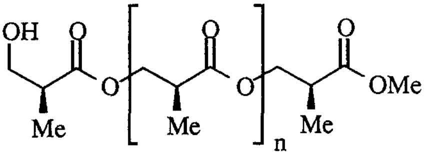
[a] All polymerisations were conducted on 4-5 g of monomer.
[b] 0.04-0.05 mol. %.
[c] As determined by GPC in chloroform.

Table 1 Polymerisation conditions and molecular weight data

Molecular weight was dependant both on the temperature and the duration of the reaction. The highest molecular weight (entry 1) was achieved at 150°C after 6 hours. Increasing the temperature to 175°C (entry 2) and 200°C (entry 8) had a progressively detrimental effect on the molecular weight. Also lowering the temperature to 100°C (entry 3) resulted in a much lower molecular weight material. A series of reactions carried out at 200°C (entries 5-8) demonstrates a progressive increase in molecular weight with time (2-6 h) however reactions beyond 6 hours did not significantly increase the molecular weight of the resultant materials. $Sb_2O_3/Mn(OAc)_2$ was also studied (data not shown) as this combination is a good transesterification catalyst in other systems[10,11] however these conditions proved less satisfactory giving consistently lower molecular weights under comparative conditions.



2
macromonomer
shown for (S)-1b



3
polymer shown
for (S)-1b

^{1}H-NMR analysis of all of the reprecipitated materials, except that prepared at 100°C (entry 3), showed two olefinic (5.56 and 6.08 ppm) and a vinyl methyl (1.92 ppm) resonance. The intensity of these peaks was consistent with an end group as the vinyl methyl integrated at a 1:1 ratio with the methyl ester resonance (3.7 ppm) at the other end of the molecule. Thus, in these cases, the macromonomer **2** with a methacrylate end group is the product of the polymerisation reactions above 150°C. At the lower temperature of 100°C the ^{1}H-NMR end group analysis is entirely consistent with the generation of polymer **3**, showing no evidence of any elimination. These observations are consistent with polyester chain termination by elimination at higher temperature to generate macromonomer **2**.

Differential scanning calorimetry (DSC) analysis of the macromonomers **2** consistently showed a melting point endotherm at 124°C demonstrating that the material was not amorphous. The thermograph for the material prepared in entry 1 is shown in Figure 2. A high level of crystallinity (>50%) was unambiguously established by X-ray powder diffraction analysis of this latter material. The X-ray diffraction trace is shown in Figure 3. Thermal gravimetric analysis (TGA) shows that the polymer is stable up to 350°C (10% weight loss).

This is the first report on the attempted polymerisation of the homochiral β-hydroxyisobutyrates **1a** and **1b**, which are isomeric to the naturally occurring poly(β-hydroxybutyrates) developed by ICI as BIOPOL[1]. Despite the anticipated susceptibility of this system to elimination we have developed a straight forward preparation of homochiral

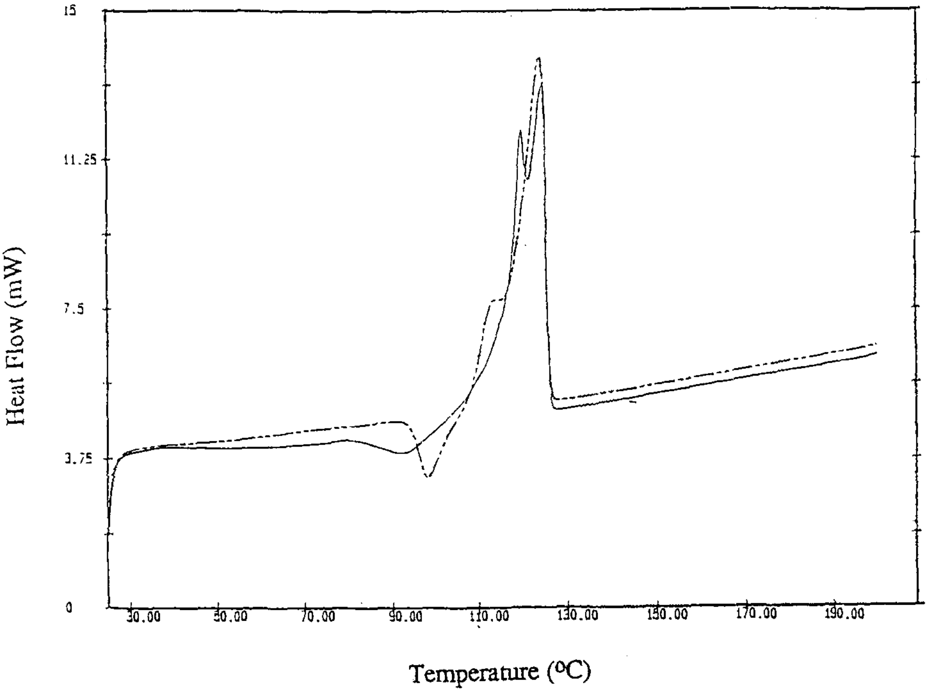


Figure 2 DSC thermograph of 2 (entry 1 of Table 1). Bold line; reprecipitated polymer heated at 10°C/min^{-1}. Dotted line; cooled polymer reheated at 10°C/min^{-1}.

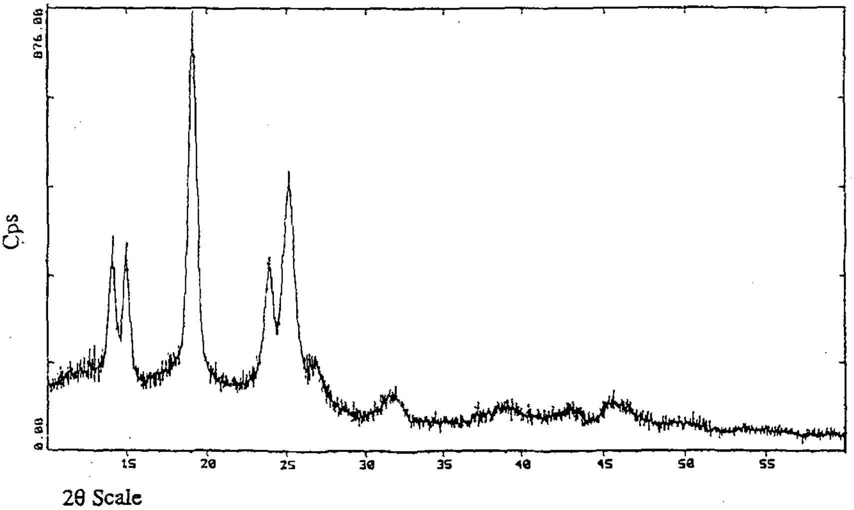


Figure 3 X-ray powder diffraction analysis of 2 (entry 1 of Table 1)

macromonomers which result as a consequence of this susceptibility. We are currently investigating the properties of methacrylates doped with macromonomer **2**.

Acknowledgement

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