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Porous poly(D,L-lactide) and poly(D,L-lactide-*co*-glycolide) produced by thermal salt elimination from halogenocarboxylates†

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Poly(D,L-lactide) has been obtained by thermal elimination of alkali chloride from alkali 2-chloropropionates. Preparative studies and differential scanning calorimetry (DSC) have shown that while the sodium and potassium compounds undergo a clean polymerisation, the lithium analogues decompose on heating without polymerisation. The energetics of the polymerisation reaction have also been investigated by determining the enthalpies of formation of sodium and lithium (*S*)-2-chloropropionates (from reaction-solution calorimetry), and the enthalpies of formation of poly(L-lactide) and poly(D,L-lactide) (from micro combustion calorimetry). The results suggest that the polymerisation process is thermodynamically favourable for the sodium compounds but not for the lithium compounds, in good agreement with the experimental observations. Copolyesters of glycolic acid (polyglycolide) and lactic acid (polylactide) have been prepared by thermal reaction of crystal mixtures of sodium or potassium chloroacetates and sodium or potassium 2-chloropropionates, which were obtained by co-precipitation of the precursor compounds from methanol solutions. The crystal mixtures and reaction products have been characterised by a number of techniques, including solid state NMR spectroscopy and X-ray powder diffraction. For high contents of glycolide, the reaction occurred entirely in the solid state, whereas for cases with more than 10 mol% lactide, a melt is formed which solidifies on cooling to room temperature. The products are lactide-terminated block copolymers with typical chain lengths of 40 monomer units. Due to the solvent-free nature of the synthesis, all polymers can be obtained with microporous morphology.

Introduction

Biodegradable polyesters, such as polyglycolide (polyglycolic acid; PGA) or polylactide (polylactic acid; PLA), are of great importance in medicine and pharmaceutical technology, and can be employed, for example as absorbable surgical suture,[1] for internal bone fracture fixation (osteosynthesis),[2] as scaffold for extracorporal tissue cultures ("tissue engineering"),[3,4] and as controlled drug-delivery systems.[5,6] The properties of these biomaterials can be fine-tuned, with a view to selected applications, by chemically blending two types of monomeric units to give copolymers. In general, the main goal is to improve the mechanical properties, and the degradation behaviour *in vitro* and *in vivo*, both of which are related, *inter alia*, to the composition of the polymer, its morphology, its crystallinity, its hydrophilicity, and its degree of polymerisation.

Conventionally, these homopolymers and copolymers are produced by ring-opening polymerisation of the corresponding cyclic diesters (dilactones).[7] We have instead developed an alternative route to polyglycolide starting from alkali metal halogenoacetates that eliminate alkali halides upon heating according to eqn. (1) (M = alkali metal; X = halogen):

$$XCH_2COOM\ (s) \longrightarrow MX\ (s) + 1/n\ [–CH_2–COO–]_n\ (s) \quad (1)$$

The reaction occurs entirely in the solid state,[8–10] and leads to an intimate mixture of polymer and alkali halide, out of which the alkali halide can be extracted by washing with water. We have also reported attempts to transfer this reaction scheme to higher homologues (halogenopropionates and halogenobutyrates), for which oligomers are obtained.[11]

Here we present results of detailed structural and thermochemical studies concerning the polymerisation of racemic and enantiomerically pure 2-chloropropionates. We also report the preparation of copolyesters of polyglycolide and polylactide by heating co-precipitated mixtures of crystals of chloroacetates and 2-chloropropionates. To our knowledge, this is the first report of the preparation of copolyesters by solvent-free reaction.

Results and discussion

Polylactide from alkali 2-chloropropionates

On paper, the reaction of halogenoacetates (eqn. (1)) can be readily transposed to 2-halogenopropionates (eqn. (2)), leading

$$ClC^*H(CH_3)COOM\ (s) \longrightarrow MCl\ (s) + 1/n\ [–C^*H(CH_3)–COO–]_n\ (l) \quad (2)$$

to polylactide rather than polyglycolide as the reaction product. There are, however, some expected differences of reactivity between the halogenoacetate and 2-halogenopropionate

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† Electronic supplementary information (ESI) available: detailed results of the combustion calorimetric experiments. See http://www.rsc.org/suppdata/dt/b1/b104979h/

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Table 1 Reaction temperatures and reaction enthalpies obtained by DSC for the polymerisation of alkali 2-chloropropionates (reaction (2))

Precursor	T_r/ °C	$\Delta_r H_m(2)$/kJ mol^{-1}	Product
Lithium (*S*)-2-chloropropionate	177	—	Decomposition
Sodium (*S*)-2-chloropropionate	165	−33.0	Poly(D,L-lactide)
Potassium (*S*)-2-chloropropionate	146	−35.9	Poly(D,L-lactide)
Sodium (*R*)-2-chloropropionate	165	−31.8	Poly(D,L-lactide)
Potassium (*R*)-2-chloropropionate	144	−35.3	Poly(D,L-lactide)
Lithium (*RS*)-2-chloropropionate	189	—	Decomposition
Sodium (*RS*)-2-chloropropionate	169	−26.7	Poly(D,L-lactide)
Potassium (*RS*)-2-chloropropionate	142	−32.4	Poly(D,L-lactide)

systems. Oligomers of lactic acid have a lower melting point (*ca.* 130 °C)[12] than oligomers of glycolic acid (130–190 °C),[13] and it is therefore unlikely that the polymerisation of 2-chloropropionates will occur strictly in the solid state, since a melt may be formed at the reaction temperature (140 to 170 °C).

Furthermore, the α-carbon of the 2-chloropropionates is a stereogenic centre, and we may carry out the reaction for enantiomerically pure or racemic 2-chloropropionates, and the products may be expected to be isotactic poly(L-lactide) (PLLA) or atactic (racemic) poly(D,L-lactide) (PDLLA), respectively.

Lithium, sodium, and potassium salts of (*R*)- and (*S*)-2-chloropropionic acid and of racemic 2-chloropropionic acid were prepared, and their thermal reactivity was studied first by differential scanning calorimetry (DSC; Table 1). We found that both the sodium and potassium compounds undergo polymerisation according to reaction (2) as indicated by the observation of an exothermic DSC signal around 165 °C for M = Na and around 145 °C for M = K (interestingly, there are no significant differences in reaction temperatures between 2-chloropropionates with the same cation but different stereochemistry). NMR analysis of the products of these reactions, when carried out on a preparative scale, confirmed that polylactide is indeed formed (see Experimental section). The lithium compounds, on the other hand, first melt and then undergo an ill-defined decomposition. This differing behaviour in the case of lithium is in accordance with earlier observations for halogenoacetates and halogenomethylbenzoates, for which the lithium compounds were also not reactive. In these cases, the different reactivities can be explained on the basis of crystal structures (determined from powder diffraction data): lithium is coordinated to four oxygen atoms from four different carboxylate groups, a fact that inhibits the solid-state polymerisation reaction.[14,15]

Table 1 summarises the DSC results for the polymerisation of 2-chloropropionates. The temperature of the onset of the reaction is denoted T_r, and the corresponding reaction enthalpy is denoted $\Delta_r H_m$. The results indicate that for the potassium compounds the polymerisation is slightly more exothermic and T_r is *ca.* 20 K lower than for the sodium compounds. It is also found that the reaction is more exothermic for the enantiomerically pure precursors than for the corresponding racemic mixtures.

An unexpected feature, however, is the fact that fully racemic poly(D,L-lactide) is always obtained, regardless of whether the precursor is enantiomerically pure or racemic (see below for proof). This observation indicates that racemisation occurs while the reaction mixture is liquid, most likely by multiple substitution at the α-carbon atom. If the number of substitution steps were small, we would not expect complete loss of stereochemistry; racemisation is the result of a hitherto unknown process. In principle, elimination could also be a reason for racemisation.

Thermodynamics of the polymerisation reactions in (*S*)-2-chloropropionates

The energetics of reaction (3) (to solid polylactide) were also investigated for M = Li and Na by using the enthalpies of formation of sodium and lithium (*S*)-2-chloropropionates (obtained by reaction-solution calorimetry) and the enthalpies of formation of poly(L-lactide) and poly(D,L-lactide) (obtained by micro combustion calorimetry).

$$\mathrm{ClC^*H(CH_3)COOM\ (s)} \longrightarrow \mathrm{MCl\ (s)} + 1/n\,[\mathrm{-C^*H(CH_3)-COO-}]_n\ \mathrm{(s)} \quad (3)$$

Detailed results of the combustion calorimetric experiments are given as Supporting Information. These experiments led to the standard molar enthalpies of combustion ($\Delta_c H^\circ_m$) of poly(L-lactide) and poly(D,L-lactide) at 25 °C indicated in Table 2. The uncertainties quoted represent twice the overall standard deviation of the mean of six determinations, in each case, and include the contributions from the calibration with benzoic acid and from the energy of combustion of the auxiliary oil.[16–18] The $\Delta_c H^\circ_m$ values obtained refer to the reaction:

$$1/n\ (\mathrm{C_3H_4O_2})_n\ \mathrm{(s)} + 3\ \mathrm{O_2\ (g)} \longrightarrow 3\ \mathrm{CO_2\ (g)} + 2\ \mathrm{H_2O\ (l)} \quad (4)$$

and in conjunction with $\Delta_f H^\circ_m(\mathrm{CO_2}, \mathrm{g}) = -(393.51 \pm 0.13)$ kJ mol^{-1} [18] and $\Delta_f H^\circ_m(\mathrm{H_2O}, \mathrm{l}) = -(285.830 \pm 0.040)$ kJ mol^{-1} [19] lead to the standard molar enthalpies of formation of poly(L-lactide) and poly(D,L-lactide) in the solid state indicated in Table 2. As described in the Experimental section, these results were obtained using commercial samples of amorphous poly(D,L-lactide) and considerably crystalline poly(L-lactide), with average chain lengths of *ca.* 1500 and 1700 monomers, respectively (see Experimental section).

As expected, the less negative enthalpy of formation corresponds to the amorphous sample. This value is likely to best represent the poly(D,L-lactide) polymers synthesised in this work (reaction (3)), which have significantly smaller chain lengths (*ca.* 30 to 50 monomers) but are also fully amorphous (see below).

The enthalpies of formation of sodium and lithium (*S*)-2-chloropropionates were obtained from reaction-solution calorimetric studies of reaction (5) and of the dissolution processes (6) and (7):

$$\mathrm{ClCH(CH_3)COOM\ (s)} + 4.666(\mathrm{HCl{\cdot}553.41H_2O})\ \mathrm{(aq)} \longrightarrow [\mathrm{MCl{\cdot}ClCH(CH_3)COOH{\cdot}3.666HCl{\cdot}2582.21H_2O}]\ \mathrm{(aq)} \quad (5)$$

$$\mathrm{ClCH(CH_3)COOH\ (l)} + 3.666(\mathrm{HCl{\cdot}704.37H_2O})\ \mathrm{(aq)} \longrightarrow [\mathrm{ClCH(CH_3)COOH{\cdot}3.666HCl{\cdot}2582.21H_2O}]\ \mathrm{(aq)} \quad (6)$$

$$\mathrm{MCl\ (cr)} + [\mathrm{ClCH(CH_3)COOH{\cdot}3.666HCl{\cdot}2582.21H_2O}]\ \mathrm{(aq)} \longrightarrow [\mathrm{MCl{\cdot}ClCH(CH_3)COOH{\cdot}3.666HCl{\cdot}2582.21H_2O}]\ \mathrm{(aq)} \quad (7)$$

The corresponding results are shown in Table 3, in which the uncertainties quoted represent twice the standard deviation of the mean of at least five independent determinations. These values were taken together with the enthalpy ($\Delta_{dil} H^\circ_m(8) = -0.22$ kJ mol^{-1} [19]) of the dilution process:

$$3.666(\mathrm{HCl{\cdot}553.41H_2O})\ \mathrm{(aq)} + 553{\cdot}41\mathrm{H_2O\ (l)} \longrightarrow 3.666(\mathrm{HCl{\cdot}704.37H_2O})\ \mathrm{(aq)} \quad (8)$$

Table 2 Results of the combustion calorimetric experiments of poly(L-lactide) and poly(D,L-lactide) at 25 °C

	$\Delta_c H^\circ_m$/kJ mol^{-1}	$\Delta_f H^\circ_m$(s)/kJ mol^{-1}
Poly(L-lactide)	-1352.4 ± 2.2	-399.8 ± 2.2
Poly(D,L-lactide)	-1363.4 ± 3.4	-388.4 ± 3.4

Table 3 Results of the reaction-solution calorimetric studies on lithium and sodium (*S*)-2-chloropropionate at 25 °C

	ClC*H(CH$_3$)COOLi	ClC*H(CH$_3$)COONa
$\Delta_r H^\circ_m(5)$/kJ mol^{-1}	-12.97 ± 0.20	-5.21 ± 0.15
$\Delta_{sln} H^\circ_m(6)$/kJ mol^{-1}	-2.05 ± 0.13	-2.05 ± 0.13
$\Delta_{sln} H^\circ_m(7)$/kJ mol^{-1}	-35.01 ± 0.29	4.15 ± 0.24
$\Delta_r H^\circ_m(9)$/kJ mol^{-1}	24.31 ± 0.38	-7.09 ± 0.31
$\Delta_f H^\circ_m$(s)/kJ mol^{-1}	-800.8 ± 1.6	-772.2 ± 1.2

Table 4 Computed enthalpies of reaction (3) from lithium and sodium (*S*)-2-chloropropionate to produce solid polylactide (to 25 °C)

M	Product [–C*H(CH$_3$)–COO–]$_n$	$\Delta_r H^\circ_m(3)$/kJ mol^{-1}
Li	Poly(L-lactide)	-7.3 ± 3.0
	Poly(D,L-lactide)	4.1 ± 3.9
Na	Poly(L-lactide)	-38.7 ± 2.5
	Poly(D,L-lactide)	-27.3 ± 3.6

in order to derive the enthalpy of the standard state reaction (9) (M = Li, Na):

$$\mathrm{ClCH(CH_3)COOM\ (s) + (HCl{\cdot}553.41H_2O)\ (aq) \longrightarrow MCl\ (cr) + ClCH(CH_3)COOH\ (l) + 553.41H_2O\ (l)\ (aq)} \quad (9)$$

as:

$$\Delta_r H^\circ_m(9) = \Delta_r H^\circ_m(5) - \Delta_{sol} H^\circ_m(6) - \Delta_{sol} H^\circ_m(7) - \Delta_{dil} H^\circ_m(8) \quad (10)$$

The enthalpies of formation of the sodium and lithium (*S*)-2-chloropropionates were finally derived from:

$$\Delta_f H^\circ_m[\mathrm{ClCH(CH_3)COOM, cr}] = -\Delta_r H^\circ_m(9) + \Delta_f H^\circ_m[\mathrm{MCl, cr}] + \Delta_f H^\circ_m[\mathrm{ClCH(CH_3)COOH, l}] - \Delta_f H^\circ_m[\mathrm{HCl{\cdot}553.41H_2O, aq}] \quad (11)$$

by using $\Delta_f H^\circ_m$[LiCl, cr] = -408.266 ± 1.142 kJ mol^{-1},[19] $\Delta_f H^\circ_m$[NaCl, cr] = -411.120 ± 0.340 kJ mol^{-1},[19] $\Delta_f H^\circ_m$[ClCH(CH$_3$)COOH, l] = -534.8 ± 1.1 kJ mol^{-1},[20] $\Delta_f H^\circ_m$[HCl·553.41H$_2$O, aq] = -166.598 kJ mol^{-1}.[19] The values obtained are given in Table 3.

(*S*)-2-Chloropropionates: lithium salts are thermodynamically prevented from polymerisation

The results in Tables 2 and 3, together with the enthalpies of formation of NaCl and LiCl quoted above, lead to the enthalpies of reaction (3) at 25 °C shown in Table 4. As seen in Table 4, the reaction is always significantly exothermic for M = Na, regardless of the polymer (L or D,L) assumed to be present in the final state. Note also that the value $\Delta_r H^\circ_m(3) = -27.3 \pm 3.6$ kJ mol^{-1} at 25 °C (Table 4), which refers to the formation of amorphous poly(D,L-lactide), is very similar to the results of the DSC experiments for the polymerisation of *S*, *R*, and *RS* sodium 2-chloropropionates, namely $\Delta_r H^\circ_m(2) = -33.0$ kJ mol^{-1} at 165 °C, $\Delta_r H^\circ_m(2) = -31.8$ kJ mol^{-1} at 165 °C, and $\Delta_r H^\circ_m(2) = -26.7$ kJ mol^{-1} at 169 °C, respectively (Table 1).

These values are not expected to change significantly by correction to 25 °C. Using $C^\circ_{p,m}$(NaC$_3$H$_4$O$_2$Cl, s) = 140.6 J K^{-1} mol^{-1}, $C^\circ_{p,m}$(C$_3$H$_4$O$_2$, s) = 89.8 J K^{-1} mol^{-1}, and $C^\circ_{p,m}$(C$_3$H$_4$O$_2$, l) = 108.0 J K^{-1} mol^{-1}, estimated by Kopp's rule,[21] and $C^\circ_{p,m}$(NaCl, s) = 50.509 J K^{-1} mol^{-1},[22] it is concluded that $\Delta_r C^\circ_{p,m}(2) \approx 18$ J K^{-1} mol^{-1} and $\Delta_r C^\circ_{p,m}(3) \approx 0$ J K^{-1} mol^{-1} at 25 °C. According to these estimates, $\Delta_r H^\circ_m(3)$ will be approximately independent of temperature, and decreasing the temperature of the reaction (2) from the temperature of the DSC experiments (*ca.* 165 °C, Table 1) to 25 °C will change $\Delta_r H^\circ_m(2)$ by only -2.6 kJ mol^{-1}.

The results in Table 4 also indicate that for M = Li, reaction (3) is slightly exothermic [$\Delta_r H^\circ_m(3) = -7.3 \pm 3.0$ kJ mol^{-1}] if poly(L-lactide) is formed and slightly endothermic [$\Delta_r H^\circ_m(3) = 4.1 \pm 3.9$ kJ mol^{-1}] if poly(D,L-lactide) is produced. This latter value is expected to be a better estimate of the enthalpy of polymerisation of lithium (*S*)-2-chloropropionate under the experimental conditions used in the DSC experiments since it refers to an amorphous polymer as found for M = Na and K. Note that in these cases, liquefaction of the polymer occurs during the thermally-induced polymerisation above 140 °C. Solidification is observed after cooling to room temperature. Because the poly(D,L-lactide) formed in the reaction is amorphous, no enthalpy of melting needs to be considered when comparing the enthalpies of reaction (2) (to liquid PDLLA) and reaction (3) (to solid PDLLA). This fact is supported by DSC experiments on pure PDLLA (see Fig. 5), for which only a glass transition is detectable. By using the heat capacities of C$_3$H$_4$O$_2$ quoted above together with $C^\circ_{p,m}$(LiCl, s) = 48.028 J K^{-1} mol^{-1},[22] and $C^\circ_{p,m}$(LiC$_3$H$_4$O$_2$Cl, s) = 137.7 J K^{-1} mol^{-1}[21] it is concluded that $\Delta_r C^\circ_{p,m}(2) \approx 19$ J K^{-1} mol^{-1} and $\Delta_r C^\circ_{p,m}(3) \approx 0$ J K^{-1} mol^{-1}, at 25 °C. Thus for M = Li, the enthalpies of reactions (2) and (3) are again not expected to be affected significantly by the temperature.

The results in Table 4 therefore suggest that the difference in reactivity of the lithium and sodium 2-chloropropionates towards polymerisation is of thermodynamic origin. In other words, the lithium 2-chloropropionates are too stable to undergo elimination of LiCl, a fact that may be related to the highly polarising nature of the small lithium cation, contributing to the energetic stability of the crystal structure.

Unfortunately, all our attempts to solve the crystal structures of the 2-chloropropionates have so far failed, as single crystals appropriate for single crystal diffraction could not be obtained, and powder diffraction patterns (including high-resolution synchrotron X-ray powder diffraction data) could not be indexed, rendering structure solution from powder diffraction data impossible. We strongly suspect that the inability to index the powder diffraction patterns is due to the presence of two or more polymorphic phases. We note that the crystal structures of lithium halogenoacetates[14] and lithium 4-halogenomethylbenzoates,[15] as well as sodium chloroacetate[23] and sodium bromoacetate[24] have been determined from powder diffraction data.

The chemical and structural properties of the pure 2-chloropropionates are discussed further below in the context of studies of mixtures of crystals of 2-chloropropionates with chloroacetates.

Mixtures of crystals of chloroacetates and 2-chloropropionates: structural details

As the polycondensation of chloroacetates to polyglycolide and the polycondensation of 2-chloropropionates to polylactide have both been shown to occur, we have attempted to prepare copolyesters from mixtures of crystals of chloroacetates and 2-chloropropionates. For this purpose, we used sodium chloroacetate and sodium (*RS*)-2-chloropropionate, and the corresponding potassium compounds.

For clarity, the various crystal mixtures synthesised are identified below by the acronym L$_x$G$_y$, where *x* and *y* refer to the molar percentages of racemic 2-chloropropionate and

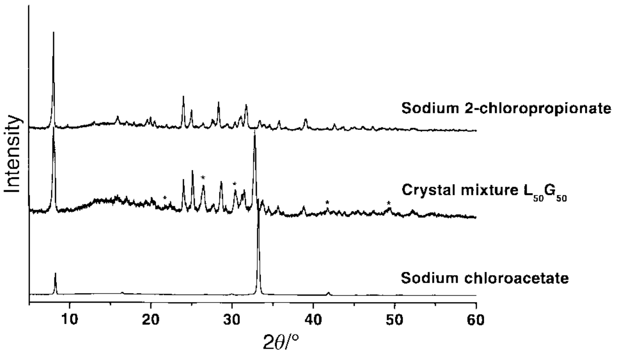

Fig. 1 X-Ray powder diffraction patterns of sodium 2-chloropropionate (top), the co-precipitated crystal mixture $L_{50}G_{50}$ (centre), and sodium chloroacetate (bottom). Reflections assigned to the mixed crystal phase are marked (*).

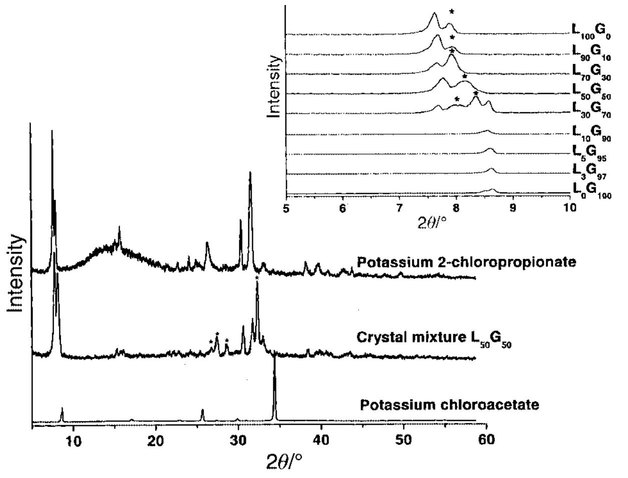

Fig. 2 X-Ray powder diffraction patterns of potassium 2-chloropropionate (top), the co-precipitated crystal mixture $L_{50}G_{50}$ (centre) and potassium chloroacetate (bottom). The insert shows an enlargement of the 2*θ* region between 6 and 10° for all mixtures prepared, demonstrating both the gradual change in composition as well as the intermediate presence of a new phase ascribed to mixed crystals of potassium 2-chloropropionate and potassium chloroacetate. Reflections assigned to the mixed crystal phase are marked (*).

chloroacetate, respectively. During the polymerisation reaction, NaCl or KCl are eliminated, and a "composite" of polymer and alkali halide is formed.

A series of co-precipitated chloroacetate and 2-chloropropionate materials was prepared by precipitation from methanol, characterised, and studied in terms of the ability of each member of the series to form mixed crystals (X-ray powder diffraction, solid-state NMR) and to undergo thermal polymerisation (DSC). X-Ray powder diffraction patterns of the 50 : 50 crystal mixture and of the pure compounds are shown in Fig. 1 for the sodium compounds and in Fig. 2 for the potassium compounds. The following observations can be made. (1) The crystal mixtures and the 2-chloropropionates appear to be significantly less crystalline than the chloroacetates. (2) The structure of the 2-chloropropionate dominates the diffraction pattern for the crystal mixtures, both in the case of sodium and potassium (*i.e.* the powder diffraction patterns of the crystal mixtures closely resemble that of the corresponding 2-chloropropionate). (3) Some peaks in the powder diffractograms of the crystal mixtures can be ascribed to neither the chloroacetate phase nor the 2-chloropropionate phase. (4) The powder diffractograms of the mixtures represent mostly a superposition of those of the pure phases, indicating that we have essentially a mixture of crystals (*i.e.* a physical mixture of the two pure phases) instead of mixed crystals (*i.e.* a solid solution consisting of both precursors).

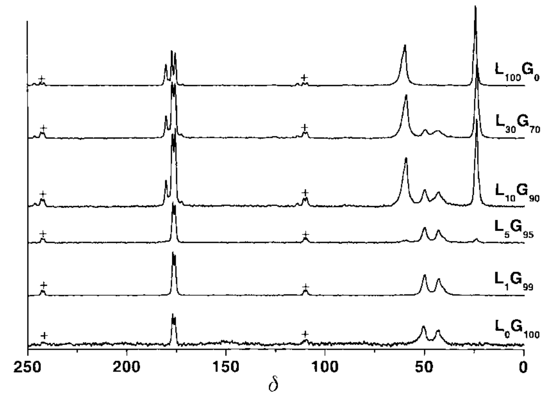

Fig. 3 High-resolution solid-state ^{13}C NMR spectra of sodium (*RS*)-2-chloropropionate (top), the crystal mixtures (centre), and sodium chloroacetate (bottom). The numbers refer to the molar ratio of chloroacetate to 2-chloropropionate. The symbols (+) indicate spinning side bands.

All these effects occur gradually within the series of L_xG_y compounds studied. However, the presence of some "new" reflections (point 3 above; marked with a "*" in Fig. 1 and 2) indicates that a third phase is present. This new phase may be assigned to a mixed crystal system of chloroacetate and 2-chloropropionate. Unfortunately, this phase represents a small fraction of the sample in both cases, and it could neither be indexed nor structurally characterised. The small insert in Fig. 2 illustrates the gradual change of the powder diffraction patterns and the appearance of the mixed crystal phase along an L_xG_y series.

High-resolution solid-state ^{13}C NMR spectroscopy experiments (recorded under conditions of CP/MAS and highspower ^{1}H decoupling) were carried out to gain further insight into the structure of the crystal mixtures. The results obtained for some of the sodium compounds are shown in Fig. 3. These spectra show only the expected signals for a mixture of the two precursors with three regions corresponding to the methyl (23.9 ppm), methine (broad peak with shoulder at 59.3 ppm), and carboxylate (three peaks in the range 170–182 ppm) carbons of sodium 2-chloropropionate ($L_{100}G_0$), and two split signals associated with the methylene (46.4 ppm) and the carboxylate (176.2 ppm) carbons of sodium chloroacetate (L_0G_{100}). In the case of pure sodium chloroacetate, these splittings arise from the dipolar coupling between the ^{13}C nuclei and the $^{35,37}Cl$ isotopes that is well described in the literature.[25] The same effect may also contribute to the observed spectrum of the pure sodium 2-chloropropionate, although the multiple peaks observed for the carboxylate carbon and the broad peak (with shoulder) observed for the methine carbon may also originate from the presence of more than one polymorph, as alluded to earlier. The solid-state ^{13}C NMR results give no indication of the presence of the mixed crystal phase shown in the X-ray powder diffraction patterns, probably because the chemical environment of the molecules in the mixed crystal closely resembles that in the pure phases.

Formation of copolyesters upon heating mixtures of crystals

The polymerisation of a series of crystal mixtures of the sodium compounds was studied by differential scanning calorimetry and combined thermogravimetry–differential thermal analysis–mass spectrometry (TG-DTA-MS). The DSC results are shown in Fig. 4 and in Table 5. All materials show an exothermic signal due to the polymerisation reaction (Fig. 4). For the pure compounds, this signal corresponds to the sharp peaks at 202 °C (sodium chloroacetate, L_0G_{100}) and 169 °C (sodium 2-chloropropionate, $L_{100}G_0$). Upon addition of chloroacetate to 2-chloropropionate, the onset temperature of polymerisation decreases. However, when the fraction of

Table 5 Reaction temperatures and reaction enthalpies for the crystal mixtures of sodium (*RS*)-2-chloropropionate and sodium chloroacetate

	First peak		Second peak	
Compound	$T_r{}^a$/°C	$\Delta_r H_m{}^b$/kJ mol^{-1}	$T_r{}^a$/°C	$\Delta_r H_m{}^b$/kJ mol^{-1}
Sodium 2-chloropropionate $L_{100}G_0$	169	−26.7	—	—
$L_{90}G_{10}$	157	−28.6	—	—
$L_{70}G_{30}$	158	−26.8	—	—
$L_{50}G_{50}$	160	−27.7	—	—
$L_{30}G_{70}$	158	−26.8	—	—
$L_{10}G_{90}$	155	−2.3	165	−25.4
L_5G_{95}	157	−0.9	178	−26.5
L_3G_{97}	150	−0.6	185	−25.5
L_1G_{99}	—	—	190	−24.4
Sodium chloroacetate L_0G_{100}	—	—	202	−24.9

[a] The temperature of the reaction onset. [b] The corresponding reaction enthalpy.

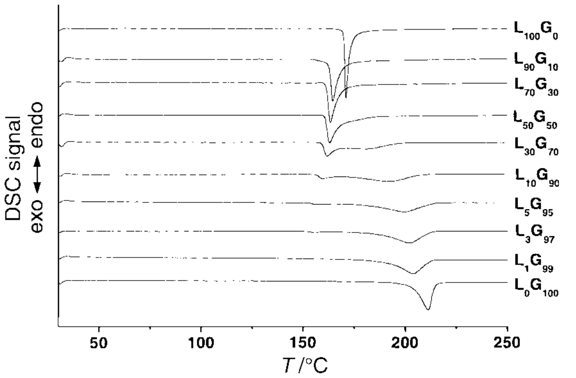

Fig. 4 DSC thermograms of the crystal mixtures of sodium (*RS*)-2-chloropropionate and sodium chloroacetate. The polymerisation reaction occurs in one or two exothermic peaks.

chloroacetate becomes larger than 50%, the development of a second peak becomes apparent in Fig. 4. The peak at lower temperature is attributed to the polymerisation of the mixtures and that at higher temperature is attributed to the polymerisation of excess sodium chloroacetate. It is important to note that the cumulated enthalpies of reaction are almost the same for all reaction mixtures, suggesting that there are no drastic differences in the reaction mechanism.

The polymerisation of mixtures of sodium or potassium compounds covering a complete range of L_xG_y compositions was also carried out on a preparative scale (*i.e.* with a total mass of mixture of about 40 g per batch, stirred and heated in a round bottom flask; see Experimental section for details). For $x > 10\%$ we observed liquefaction of the reaction mixture. In the other cases, a solid-state reaction is likely to occur, as in the pure halogenoacetate system. Upon cooling to room temperature, all reaction mixtures that were previously liquid solidified to a brownish solid. As it will be demonstrated in the following, all reaction products consist of mixtures of alkali halide salts and poly(D,L-lactide-*co*-glycolide).

The DSC analyses of the copolymers prepared by heating crystal mixtures of sodium (*RS*)-2-chloropropionate and sodium chloroacetate are shown in Fig. 5 and Table 6. For high contents of glycolide ($y > 90$) the polymers are crystalline, as indicated by the observation of a strong endothermic peak due to fusion. The temperature and the enthalpy of fusion both decrease with increasing lactide content as a result of the increasing structural disorder introduced by this "additive" to the polyglycolide. For higher contents of lactide ($x > 10$), the polymers are amorphous, as evidenced by the exclusive observation of a glass transition in the corresponding DSC curves. The same is also true for the poly(D,L-lactide) ($L_{100}G_0$) obtained from pure sodium 2-chloropropionate (top of Fig. 5), in good agreement with literature data.[1]

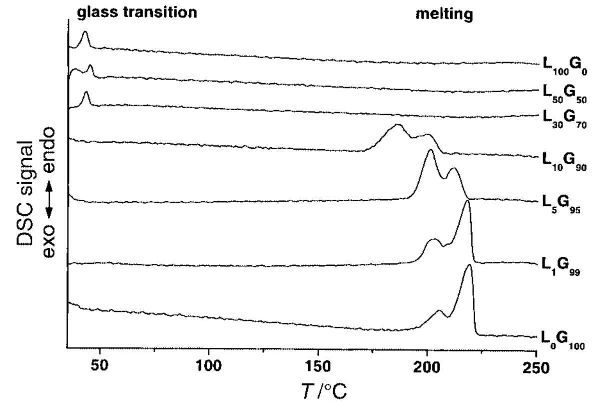

Fig. 5 DSC thermograms of the polymer/alkali halide mixtures obtained from reacted crystal mixtures of sodium 2-chloropropionate and sodium chloroacetate. The numbers refer to the molar ratio of chloroacetate to 2-chloropropionate. For up to 10 mol% lactide, the polymer is crystalline as indicated by the endothermic melting peak observed between 170 and 220 °C. All other mixtures are fully amorphous and show only a glass transition around 40 °C.

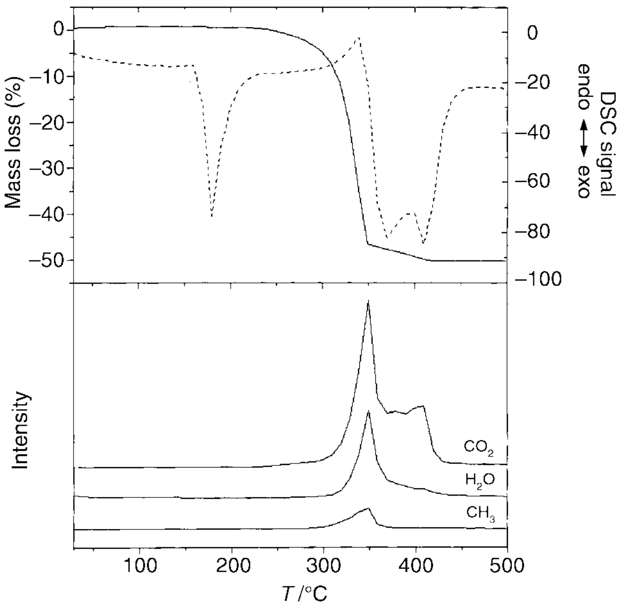

Fig. 6 TG-DTA-MS scan of the sodium crystal mixture $L_{30}G_{70}$.

Fig. 6 shows the results of a TG-DTA-MS experiment on the $L_{30}G_{70}$ sodium crystal mixture. The exothermic polymerisation reaction (around 160 °C) and the subsequent exothermic combustion of the polymer formed (above 250 °C) are well separated, demonstrating that the polymerisation reaction takes place without loss of volatile products. The only gaseous reaction products identified were *m*/*z* = 15 (methyl), *m*/*z* = 18

Table 6 Thermochemical data for poly(D,L-lactide-*co*-glycolide) prepared by heating crystal mixtures of sodium (*RS*)-2-chloropropionate and sodium chloroacetate[a]

Precursor compound	T_{fus}/°C	$\Delta_{fus}H_m$/kJ mol^{-1}	T_{gt}/°C
Sodium 2-chloropropionate $L_{100}G_0$	—	—	38
$L_{50}G_{50}$	—	—	35
$L_{30}G_{70}$	—	—	38
$L_{10}G_{90}$	173	4.7	—
L_5G_{95}	192	5.7	—
L_1G_{99}	194	6.0	—
Sodium chloroacetate L_0G_{100}	194	6.2	—

[a] T_{fus}, $\Delta_{fus}H_m$, and T_{gt} represent the melting temperature, the molar enthalpy of fusion, and the glass transition temperature, respectively. Note that the enthalpies of fusion refer to one monomer unit of the polymer. For the glass transition, the onset temperature is given.

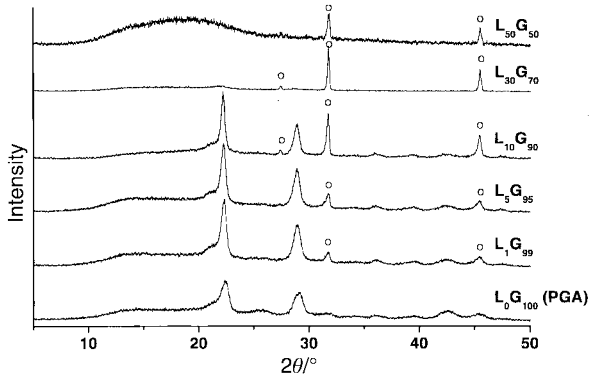

Fig. 7 X-Ray powder diffraction patterns of poly(D,L-lactide-*co*-glycolide) copolymers obtained from reactions in sodium halogenocarboxylates after treatment with water for five hours. Reflections attributed to remaining sodium chloride are marked with circles. Note that all materials produced from precursors with more than 50 mol% lactide are fully amorphous and give powder diffractograms similar to that of the $L_{50}G_{50}$ mixture.

(water), and m/z = 44 (carbon dioxide), all resulting from high temperature pyrolysis and combustion of the polymer. The observed mass loss of 49.7 wt% up to 420 °C agrees well with the expected mass loss of 51.6 wt% for only NaCl remaining.

Structural studies of the copolyesters with X-ray diffraction and solid-state NMR spectroscopy

X-Ray powder diffraction patterns of the reaction products (polymer + salt mixtures) do not contain any reflections due to the precursor compounds, and only contain reflections due to NaCl or KCl, suggesting that the reaction may be quantitative (data not shown). The polymers were analysed subsequently by X-ray powder diffraction after removal of the NaCl or KCl present by washing with water. The results for poly(D,L-lactide-*co*-glycolide) obtained from different crystal mixtures of sodium (*RS*)-2-chloropropionate and sodium chloroacetate are shown in Fig. 7. It is clear that in most cases some alkali halide remains in the polymer following the washing procedure, with the amount increasing as the lactide character of the polymer is increased.

It can also be concluded from Fig. 7 that with more than 10 mol% lactide present, the polymers are fully amorphous, underlining the results from DSC. In the other cases, the powder diffraction pattern of the copolymer strongly resembles that of pure polyglycolide.[26]

Increasing the content of lactide leads to a more hydrophobic polymer and is also responsible for the increasing time required to extract the alkali halide with water. Another factor is the liquefaction of the lactide-rich phases during polymerisation, which may lead to isolated alkali halide crystals within the polymer that cannot be easily washed out.

The polymer–alkali halide mixtures (before washing with water) were also characterised by solid-state ^{13}C NMR spectroscopy. The spectra show the two expected peaks for polyglycolide [methylene carbon (62.5 ppm) and carbonyl carbon (167.9 ppm)] and three broader signals for poly(D,L-lactide) [methyl carbon (16.8 ppm), methine carbon (69.5 ppm) and carbonyl carbon (169.8 ppm)] (Fig. 8). We observe a gradual superposition of the spectra corresponding to the two homopolymers as the molar percentages of glycolide and lactide in the copolymer change. Such copolyesters have been studied previously by Kister *et al.*[27] using this technique, and it was observed that in amorphous copolymers the methine carbon resonances give rise to large symmetric signals. In polymers with a higher content of L-lactic acid (>85 mol%), crystalline domains are detected by an increased asymmetry of the observed resonances, probably due to the tendency of the PLLA domains to form a 10_3 helical conformation.[27,28]

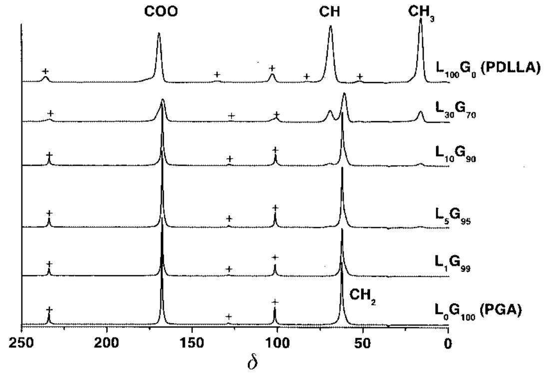

Fig. 8 High-resolution solid-state ^{13}C NMR spectra of the polymer/NaCl mixtures obtained by heating the crystal mixtures of sodium 2-chloropropionate and sodium chloroacetate. The symbols (+) indicate spinning side bands.

To clarify the stereochemistry of the polylactides, additional experiments were carried out with commercial samples of poly(L-lactide) and poly(D,L-lactide), and with the polylactides obtained from the reactions of sodium (*S*)-2-chloropropionate and sodium (*RS*)-2-chloropropionate (Fig. 9). The results prove unequivocally that poly(D,L-lactide) is obtained from both precursors, as indicated by the unresolved peaks in comparison with those observed for the well-crystalline poly(L-lactide).

The porous morphology of the formed polyesters

To investigate the morphology of the different products (homopolymer and copolymer), we have used scanning electron microscopy (SEM). Fig. 10 shows that in all cases a polymer/salt composite containing alkali halide inclusions (in approximately cubic morphology) in the μm range is formed. Upon washing the mixture with water, the alkali halide is extracted and a highly porous polymer remains. This behaviour is identical to that observed for polyglycolide produced from halogenoacetates and poly(hydroxymethylbenzoic acid) produced from halogenomethylbenzoates.[10,29]

Polymer-chemical analysis of the copolyesters

The polymers were finally characterised by viscosity measurements and solution state ^{1}H and ^{13}C NMR spectroscopy. Viscosity measurements give the average chain length, and ^{1}H NMR allows identification of the polymer endgroups and the links between glycolide and lactide units. ^{13}C NMR was used to identify the reaction products and to confirm the absence of by-products. The results show that block copolymers with chain lengths of about 40 monomer units and lactide termination are formed (see Table 7 and Experimental section). Note that different values of the average chain length are obtained from the NMR and viscosity measurements, reflecting the well-known limitations of both methods (particularly of viscosity measurements).

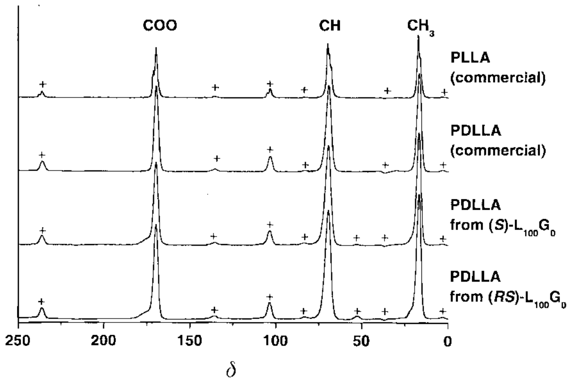

Fig. 9 High-resolution solid-state ^{13}C NMR spectra of (from top to bottom) commercial poly(L-lactide), commercial poly(D,L-lactide) (both from Sigma), poly(D,L-lactide) produced from sodium (*S*)-2-chloropropionate, and poly(D,L-lactide) produced from sodium (*RS*)-2-chloropropionate. The symbols (+) indicate spinning side bands.

Conclusions

We have shown that poly(D,L-lactide) can be prepared by heating sodium or potassium 2-chloropropionate, and poly(D,L-lactide-*co*-glycolide) can be prepared by heating crystal mixtures of sodium or potassium 2-chloropropionate and sodium or potassium chloroacetate. Accurate thermochemical data suggest that the failure of lithium 2-chloropropionate compounds to undergo this polymerisation reaction is of thermodynamic origin.

The reaction occurs in the solid state for samples containing a high glycolide content, whereas liquefaction is observed for samples containing more than about 10 mol% lactide. The products are lactide-terminated block-copolymers with chain lengths of about 40, *i.e.* molecular weights of 2000 to 2500 g mol^{-1}. No side products are observed in any of the reactions described. As in the case of other halogenocarboxylates, the reaction product is an intimate mixture of a polyester matrix with micron-sized alkali halide crystals dispersed therein. Washing this material with water leads to a highly porous polymer that can possibly be of interest for biomedical or pharmaceutical application.

Experimental

Synthesis

(*S*)-2-Chloropropionic acid was synthesised by the method of Fu *et al.*[30] and characterised by elemental analysis, polarimetry, and NMR spectroscopy. Elemental analysis made on a Heraeus XHN-O-Rapid Analyser led to the following results: Found: C, 32.92; H, 4.83. Calc. for C_3H_5OCl: C, 33.20; H, 4.64%. Optical rotation measurements, carried out on a Perkin-Elmer 341 polarimeter, gave $\alpha_D^{25} = -17.48°$ (l = 10 cm, pure) (lit.[30] $\alpha_D^{25} = -18.2°$). ^{1}H and ^{13}C NMR spectra were obtained at ambient

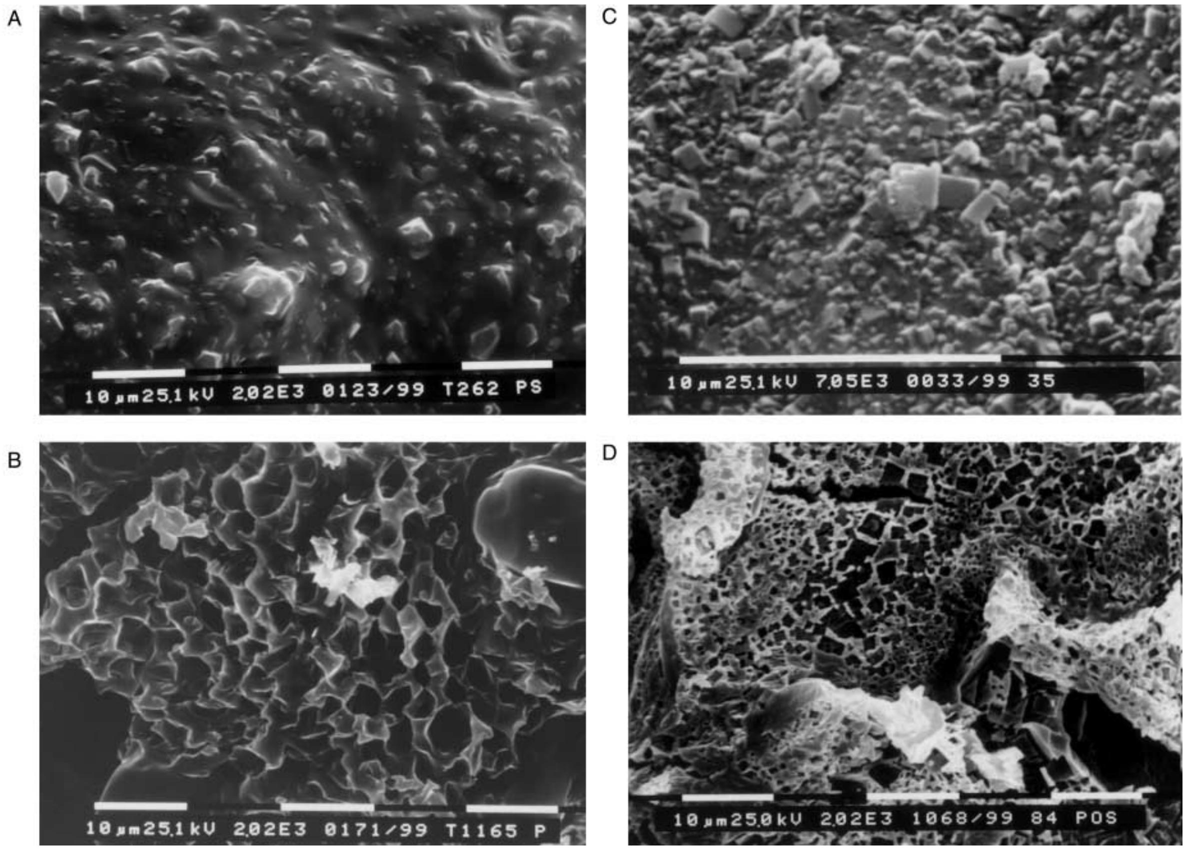

Fig. 10 Scanning electron micrographs of (A) the polymer/KCl mixture produced from potassium (*S*)-2-chloropropionate (2020×), (B) the same polymer with the KCl washed out (2020×), (C) the polymer/NaCl mixture produced from sodium 2-chloropropionate/sodium chloroacetate ($L_{50}G_{50}$) (7050×), and (D) a poly(D,L-lactide-*co*-glycolide) produced from sodium 2-chloropropionate/sodium chloroacetate/($L_{30}G_{70}$) with NaCl washed out (2020×).

Table 7 Polymer-chemical characterisation, by viscosity measurements and by ^{1}H NMR spectroscopy, of the homopolyesters and copolyesters prepared

Polymer	Average chain length from viscosity measurements	Average chain length from ^{1}H NMR endgroup analysis
Poly(D,L-lactide) from sodium (*R*)-2-chloropropionate	45	46
Poly(D,L-lactide) from sodium (*S*)-2-chloropropionate	49	51
Poly(D,L-lactide) from sodium (*RS*)-2-chloropropionate	39	27
Poly(D,L-lactide(50)-*co*-glycolide(50)) from $L_{50}G_{50}$	14	23
Poly(D,L-lactide(30)-*co*-glycolide(70)) from $L_{30}G_{70}$	13	24
Poly(D,L-lactide(10)-*co*-glycolide(90)) from $L_{10}G_{90}$	25	18
Poly(D,L-lactide(5)-*co*-glycolide(95)) from L_5G_{95}	23	32
Poly(D,L-lactide(1)-*co*-glycolide(99)) from L_1G_{99}	33	25
Polyglycolide from sodium chloroacetate	30	—

temperature on a Bruker AMX instrument (400 MHz). δ_H(400 MHz; solvent $CDCl_3$; standard $SiMe_4$) 1.73 (3 H, d, *J* = 7.12 Hz, CH_3), 4.46 (1 H, q, *J* = 7.12 Hz, CH); δ_C(100.69 MHz; solvent $CDCl_3$; standard $SiMe_4$) 21.40 (s, CH_3), 52.41 (s, CH), 176.36 (s, COO). All carboxylates were prepared by neutralising the corresponding halogenocarboxylic acids with LiOH, NaOH, and KOH, respectively, in methanol solution at 0 °C. The compounds obtained were characterised by elemental analysis (C, H), ^{1}H and ^{13}C NMR spectroscopy (D_2O), infrared spectroscopy, X-ray powder diffraction, differential scanning calorimetry (DSC) and thermogravimetry (TG). The enantiomeric purity of all carboxylates was confirmed by polarimetry (as above).

The crystal mixtures of 2-chloropropionates and chloroacetates were prepared by fast precipitation from methanol solution in a rotary evaporator at 40 °C, followed by drying at 0.1 mbar. They were all characterised by solution state ^{1}H and ^{13}C NMR spectroscopy (D_2O), infrared spectroscopy, X-ray powder diffraction, differential scanning calorimetry (DSC), and thermogravimetry (TG).

Polymerisation on a preparative scale was carried out by heating about 40 g of carboxylate(s) under air in a round bottom glass flask immersed in an oil bath. The reaction temperatures were approximately the onset-temperatures determined previously by DSC (Table 1). The reaction mixture was occasionally stirred with a spatula until the reaction was completed, typically after 2–3 h. The reaction extent was checked from time to time on aliquots by infrared spectroscopy. The alkali halide formed was extracted for 5 h in excess water at room temperature under stirring.

Characterisation

Viscosity measurements were carried out with an Ubbelohde capillary viscometer (DIN 51562), in $CHCl_3$, for pure polylactides, and in 1,1,1,3,3,3-hexafluoroisopropanol, HFIP, (99+%), for polyglycolide and all copolyesters. Only reduced viscosities at concentrations of 10–20 mg ml^{-1} were determined. For conversion into molecular weights, we used Mark–Houwink relationships with the parameters K_η and *a* (reduced viscosities in ml g^{-1}). We applied an averaged Mark–Houwink relationship for all polylactide-*co*-glycolide copolyesters (in HFIP, 20 °C) with $K_\eta = 4.8 \times 10^{-2}$ and $a = 0.73$.[31] In the case of poly(D,L-lactide) (in $CHCl_3$, 20 °C), the values of $K_\eta = 7.4 \times 10^{-3}$ and $a = 0.87$ were used.[32]

X-Ray powder diffractometry (XRD) was carried out using a Philips PW10503/25 diffractometer with a proportional detector (Cu-K$_\alpha$-radiation, λ = 154.178 pm, Ni-filter) in Bragg–Brentano geometry.

Differential scanning calorimetry analysis was performed under static air atmosphere with a Mettler TA 4000 instrument in aluminium crucibles sealed in air. The heating rate was 5 K min^{-1} and the average sample mass was 5–8 mg. Combined thermogravimetry–differential thermal analysis–mass spectrometry (TG-DTA-MS) was carried out with a Netzsch STA 409/Balzers QMS 421 system, employing a dynamic air atmosphere (50 ml min^{-1}) and a heating rate of 5 K min^{-1}. Open alumina crucibles were used as sample holders. Scanning electron microscopy was carried out on gold-sputtered samples using a Philips SEM 515 instrument operated at 25 kV.

Solution state NMR spectroscopy: polylactide: δ_H(400.13 MHz; solvent $CDCl_3$; standard $SiMe_4$) 1.4–1.6 (3 H, m, CH_3), 1.7–1.8 (m, CH_3 at lactide end group), 3.2 (OH, lactide alcohol end group), 5.1–5.3 (m, CH); δ_C(100.69 MHz; solvent $CDCl_3$; standard $SiMe_4$) 16.65 (CH_3), 69.32 (CH), 169.27 (COO ester group). Poly(D,L-lactide-*co*-glycolide): δ_H(400.13 MHz; solvent trifluoroacetic acid-d^1; standard $SiMe_4$) 1.6–1.7 (s, CH_3, lactide with lactide neighbour), 1.7–1.8 (s, CH_3, lactide with glycolide neighbour), 4.0 (s, CH_2 glycolide alcohol end group), 4.6 (m, CH lactide alcohol end group), 4.9–5.0 (s, CH_2 glycolide chain group), 5.3–5.4 (s, CH, lactide chain group); δ_C(100.69 MHz; solvent DMSO-d$_6$; standard $SiMe_4$) 16.91 (CH_3, lactide chain), 61.20 (CH_2, glycolide chain), 69.17 (CH, lactide chain), 79.66 (weak, not assigned), 167.01 (COO ester group, glycolide), 169.27 (COO ester group, lactide). The composition ratio of the copolymers was determined by ^{1}H NMR spectroscopy as described by Aydin *et al.*[33] The block nature of the copolymers was inferred from the observed 13 : 1 ratio of lactide–lactide connections to lactide–glycolide connections, using the intensity of the lactide methyl groups (1.6/1.7 *vs.* 1.7/1.8 ppm). This ratio can be compared with the expected ratio for a random copolymer (*e.g.* 1 : 1 for $L_{50}G_{50}$). The lactide termination was deduced from the much higher number of lactide alcohol end groups compared to glycolide alcohol end groups (ratio about 6 : 1).

High-resolution solid state ^{13}C NMR spectra were recorded at 75.49 MHz (B_o = 7.05 T) on a Chemagnetics CMX Infinity 300 spectrometer, using a Chemagnetics 7.5 mm magic angle spinning (MAS) probe. All spectra were recorded at 25 °C for powder samples under conditions of magic angle spinning (typical MAS frequency 5000 ± 3 Hz), $^{13}C \leftarrow {}^1H$ cross-polarisation (CP) (typical contact time 8 ms) and high-power ^{1}H decoupling (using the TPPM decoupling sequence with typical ^{1}H decoupling field strength of *ca.* 62.5 kHz). The recycle delay was typically *ca.* 7 s. Isotropic ^{13}C chemical shifts are given relative to tetramethylsilane, using adamantane (methine carbon signal at δ 29.47) as an external standard.

Combustion calorimetry of polylactides

The poly(D,L-lactide) (PDLLA) and poly(L-lactide) (PLLA) samples used in the combustion calorimetric studies were from Sigma and had molar masses in the ranges of 90000–120000 and 85000–160000, respectively. Both polymers were analysed by differential scanning calorimetry using a Setaram DSC 121 apparatus. The masses used were 23.71 mg for PDLLA and 21.27 mg for PLLA. In these experiments the samples were sealed in aluminium crucibles under air, and studied at a scan rate of 5 K min^{-1}, using a dynamic argon atmosphere. The DSC curve obtained for PDLLA shows a single peak corresponding to a glass transition, with an onset at 49.8 °C and a maximum at 52.7 °C. The curve for the PLLA sample shows a small signal probably corresponding to a glass transition, with an onset at 54.5 °C and a maximum at 60.6 °C, and a second larger peak corresponding to fusion, with an onset at 168.3 °C and a maximum at 177.8 °C. Both samples undergo a series of ill-defined decomposition reactions above *ca.* 200 °C. The *n*-hexadecane used as auxiliary in the combustion calorimetric studies was from B.D.H. and has a specific heat of combustion of $\Delta_c u° = -(47150.10 \pm 1.33\ \mathrm{J\ g^{-1}})$.[34]

Details of the micro combustion calorimetric apparatus and the general experimental procedure have been reported elsewhere.[34,35] In a typical experiment, a pellet of the compound was placed in a platinum crucible containing *n*-hexadecane, and burned under 3.04 MPa of oxygen with 50 µL of distilled and deionised water inside a stainless steel bomb of 17.95 $\mathrm{cm^3}$ internal volume. The sample and the auxiliary were weighed to 0.1 µg on a Sartorius 4504 Mp8-1 ultra-micro balance. In the case of PDLLA, the mass of sample (m_s), and the mass of auxiliary (m_{aux}) varied in the ranges 14–20 mg and 3–4 mg, respectively. For PLLA m_s = 30–45 mg and m_{aux} = 3–5 mg. The HNO_3 formed from traces of atmospheric N_2 inside the bomb was determined as NO_3^-, using a Dionex 4000i ion chromatography apparatus.

Reaction-solution calorimetry of 2-chloropropionates

The lithium and sodium (*S*)-2-chloropropionate samples used in the reaction-solution calorimetric studies were prepared and characterised as indicated above. An aqueous $HCl \cdot 553.41H_2O$ solution (0.1 M, Riedel de Haën, Fixanal®) was used as the calorimetric liquid. NaCl (José Manuel Gomes dos Santos, 99.8%) and LiCl (Aldrich, 99.99+%) were dried in an oven at 100 °C and kept in a desiccator over P_2O_5 prior to use.

The apparatus and method used in the reaction-solution calorimetry experiments were essentially identical to those described previously.[36–38] The calorimeter consisted of a transparent Dewar vessel closed by a lid which supported a stirrer, a quartz crystal thermometer probe, a resistor for electrical calibration, and an ampoule breaking system. The assembled vessel was immersed in a thermostatic water bath, the temperature of which was controlled at 25.000 ± 0.001 °C by a Tronac PTC-40 unit. In a typical experiment, a thin-walled glass ampoule was loaded with the sample, weighed to $\pm 10^{-5}$ g on a Mettler AT201 balance, and placed in the ampoule breaking system inside the calorimetric vessel. The reaction or solution process under study was started by breaking the glass ampoule containing the sample in 125 ml of calorimetric solution. This was preceded by an electrical calibration in which a potential difference of *ca.* 2.6 V was applied to a 48 Ω resistance during *ca.* 200 s.

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