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On the formation of poly(3-hydroxybutyrate) by thermolysis of metal 3-halogenobutyrates in the absence of a solvent

Thomas Annen, Matthias Epple*

Inorganic Chemistry and Centre for Nanointegration Duisburg-Essen (CeNIDE), University of Duisburg-Essen, Universitaetsstrasse 5-7, D-45117 Essen, Germany

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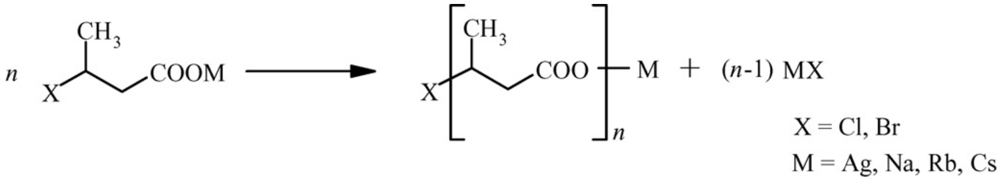
ABSTRACT

The thermochemical behaviour of metal salts (M = Na, Rb, Cs, Ag) of 3-chloro- and 3-bromobutyric acid was studied with respect to the elimination of a metal halide and the formation of poly(3-hydroxybutyrate), P-3HB, a biodegradable polyester. Two possible reaction pathways for this elimination reaction were found. The polycondensation to P-3HB was favoured at lower temperature whereas the formation of volatile crotonic acid and isocrotonic acid was favoured at higher temperature. In the case of silver 3-chlorobutyrate where AgCl was eliminated and P-3HB was the major product. All other combinations of metals and halogen gave only small amounts of polymer.

1. Introduction

Metal halogenocarboxylates can undergo a thermal elimination of metal halides which can be accompanied by the formation of the corresponding polyester (see Ref. [1] for a review on such reactions). This was shown in the case of halogenoacetates [2], 2-halogenopropionates [3], and 4-halogenomethylbenzoates [4], and it could be demonstrated that the crystal structure has a considerable influence on this reaction pathway, i.e. the orientation of the monomers must be favourable if the reaction is to occur in the solid state [4–8]. This is in line with many studies on organic solid-state chemistry where crystal structures and chemical reactivity are together controlling the reaction pathway [9–13]. Solid-state polymerization reactions can be induced thermally and also by irradiation and have been studied since about 50 years [14–30].

The extension to 3-halogenobutyrates would permit the synthesis of poly(3-hydroxybutyrate), a biodegradable polyester of considerable practical interest [31–33].



(1)

We have prepared a number of 3-chloro- and 3-bromobutyrates with single-valent metals and subjected them to thermal treatment. In principle, each of those should eliminate the corresponding metal halide (whose lattice energy is the driving force for this reaction type [34]) and form the desired polyester according to Eq. (1). However, as neither crystal structures nor thermodynamic properties of the 3-halogenobutyrates are known, this had to be experimentally explored.

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* Corresponding author. Tel.: +49 201 183 2413; fax: +49 201 183 2621.
E-mail address: matthias.epple@uni-due.de (M. Epple).

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2. Materials and methods

2.1. Preparation of 3-chlorobutyric acid

The synthesis was carried out according to Sato [35] by the addition of HCl to crotonic acid. 5.03 g crotonic acid were dissolved in 60 mL dry diethylether under inert gas atmosphere and cooled to 0 °C. Gaseous HCl was introduced through a frit with about 50 mL min^{-1} for 5 h. The product was isolated by removal of the solvent by distillation. The yield was 97%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 1.56 (d, CH_3), 2.78 (m, CH_2), 4.38 (m, CH), 11.91 (s, COOH).

2.2. Preparation of 3-bromobutyric acid

The synthesis was carried out with a modified procedure according to Tanaka et al. [36] by the addition of HBr to crotonic acid. 5.01 g crotonic acid were dissolved in 75 mL aqueous HBr (62 wt%) and stirred at room temperature for 6 days. The product was extracted with 50 mL CH_2Cl_2 (six times). The extracted solution was dried over Na_2SO_4, filtered, and the solvent was removed by distillation. The yield was 90%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 1.75 (d, CH_3), 2.91 (m, CH_2), 4.41 (m, CH), 11.65 (s, COOH).

2.3. Preparation of the sodium salts

The acids were neutralized with NaOH in dry methanol. A small amount of solid Na_2SO_4 was added to bind the reaction water. Two grams of the corresponding acid was dissolved in 5 mL methanol and an equimolar amount of NaOH, dissolved in 20–50 mL methanol was added dropwise at 0 °C (Cl) or −8 °C (Br) under stirring. Na_2SO_4 was filtered off and extracted with dry methanol. The methanol was removed in vacuum. The resulting solid was washed with diethylether (Cl) or ethanol (Br) and dried in vacuum. The yield was 93% (Cl) and 100% (Br).

- *Sodium 3-chlorobutyrate*: ^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 1.38 (d, CH_3), 2.47 (m, CH_2), 4.27 (m, CH). Elemental analysis C 32.88 (calc. 33.24), H 4.33 (calc. 4.19), Na 14.6 (calc. 15.9), Cl 25.84 (calc. 24.53). IR (cm^{-1}) 2986/2931 (C–H), 1569 (COO^-), 1401/1385 (COO^-), 646 (C–Cl).
- *Sodium 3-bromobutyrate*: ^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 1.55 (d, CH_3), 2.58 (m, CH_2), 4.33 (m, CH). Elemental analysis C 25.53 (calc. 25.42), H 3.32 (calc. 3.20), Na 12.2 (calc. 12.2), Br 42.03 (calc. 42.28). IR (cm^{-1}) 2983/2930 (C–H), 1574 (COO^-), 1398/1339 (COO^-), 590/520 (C–Br).

2.4. Preparation of the rubidium and cesium salts

The acids were neutralized with the corresponding hydroxides. The acids were dissolved in ethanol (20 wt%) and a stoichiometric amount of the corresponding hydroxides, dissolved in water/ethanol (about 1:4, v/v; about 1 M) was added dropwise at −21 °C. The solvent was immediately removed without warming the solution in vacuum. The solid residue was washed with ethanol and dried in vacuum at room temperature. The salts were stored at −25 °C to prevent reaction/degradation. The yield was 100% in all cases on a typical scale of 1–2 g product.

- *Rubidium 3-chlorobutyrate*: ^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 1.42 (d, CH_3), 2.50 (m, CH_2), 4.31 (m, CH). Elemental analysis C 22.80 (calc. 23.21), H 3.04 (calc. 2.92), Cl 17.02 (calc. 17.13). IR (cm^{-1}) 2984 (C–H), 1581 (COO^-), 1401/1385 (COO^-), 642 (C–Cl).
- *Rubidium 3-bromobutyrate*: ^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 1.56 (d, CH_3), 2.59 (m, CH_2), 4.33 (m, CH). Elemental analysis C 18.85 (calc. 19.11), H 3.24 (calc. 2.40), Br 30.77 (calc. 31.78). IR (cm^{-1}) 2983/2930 (C–H), 1577 (COO^-), 1399/1339 (COO^-), 592/520 (C–Br).
- *Cesium 3-chlorobutyrate*: ^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 1.41 (d, CH_3), 2.50 (m, CH_2), 4.31 (m, CH). Elemental analysis C 18.39 (calc. 18.88), H 2.53 (calc. 2.38), Cl 14.13 (calc. 13.93). IR (cm^{-1}) 2983 (C–H), 1568 (COO^-), 1399/1384 (COO^-), 643 (C–Cl).
- *Cesium 3-bromobutyrate*: ^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 1.57 (d, CH_3), 2.59 (m, CH_2), 4.33 (m, CH). Elemental analysis C 15.32 (calc. 16.02), H 2.42 (calc. 2.02), Br 26.98 (calc. 26.73). IR (cm^{-1}) 2983/2930 (C–H), 1575 (COO^-), 1399/1339 (COO^-), 591/520 (C–Br).

2.5. Preparation of the silver salt

3-Chlorobutyric acid was dissolved in water/ethanol (about 5:2, v/v) and a stoichiometric amount of calcium carbonate was added dropwise under stirring at 0 °C. When the release of carbon dioxide was finished, a small amount of remaining calcium carbonate was filtered off, and a stoichiometric amount of aqueous silver nitrate (1 M) was added. All further steps were carried out under exclusion of light to prevent photolytic decomposition. The silver salt was filtered off and washed with a small amount of water/ethanol (5:2). Subsequent washing with diethyl ether gave a material which could be easily dried in vacuum at room temperature. The salt was stored at −25 °C in the dark. The yield was 76% on a typical scale of 1–2 g product.

Silver 3-chlorobutyrate: ^{1}H NMR (NaCN/D_2O, 300 MHz): δ (ppm) = 1.42 (d, CH_3), 2.51 (m, CH_2), 4.33 (m, CH). Elemental analysis C 20.23 (calc. 20.94), H 2.49 (calc. 2.64), Ag 45.36 (calc. 47.02) Cl 13.16 (calc. 15.45). IR (cm^{-1}) 2983/2931 (C–H), 1573 (COO^-), 1398/1339 (COO^-), 797/590 (C–Cl).

2.6. Thermal treatment of the salts towards solvent-free polymerization

One to two grams of the corresponding salt was put into a round bottom flask and slowly heated in a rotary evaporator under constant rotation to the onset temperature of the main exothermal effect as determined by DSC (see Table 1). The extent of reaction was monitored by taking small aliquots and measuring their IR spectra. Typically, the annealing time was of the order of 30 min. After the reaction was completed, the product was freely cooled to room temperature. The conversion can be easily followed by monitoring the carbonyl band around 1570 cm^{-1} (3-halogenobutyrate) which is shifted to around 1710 cm^{-1} in the reaction products (ester bond).

2.7. Analytical techniques

Combined thermogravimetry-differential thermal analysis-infrared spectroscopy (TG-DTA-IR) was carried out with a Netzsch STA 209 TG-DTA/DSC instrument connected to a Bruker Vertex 70 infrared system for *in situ* gas analysis. Samples were heated at a rate of 1 K min^{-1} under dynamic N_2 or O_2 atmosphere (50 mL min^{-1}). DSC was carried out with a Netzsch DSC 204 instrument at a heating rate of 2 K min^{-1} in aluminium crucibles whose lid was pierced with a small needle. IR spectroscopy was carried out with a Bruker Vertex 70 spectrometer with KBr pellets. ^{1}H NMR spectroscopy was performed with a Bruker DPX-300 spectrometer. Scanning electron microscopy was carried out with an ESEM Quanta 400 instrument (FEI) on Au/Pd-sputtered samples. X-ray powder diffraction (XRD) was carried out with a Siemens D500 diffractometer operating with Cu Kα radiation (λ = 1.5406 Å) at 40 kV and 20 mA in Bragg–Brentano mode. Atomic absorption

Table 1
Summary of results for all metal 3-halogenobutyrates

Compound		Onset temperature T_o of the exothermal reaction event in DSC (°C)	Corresponding enthalpy of reaction by DSC (kJ mol^{-1})	Temperature range of mass loss in TG, T_{min}–T_{max} (°C)	Mass loss in TG up to T_{max} (wt%)	Mass loss in TG (calculated for a residue of MX) (wt%)	Ratio of crotonic acid:oligomers in the solid residue by ^{1}H NMR (n:n)
Metal	Anion						
Na	3-Chlorobutyrate	135.9	−24	105–190	59.3	59.6	2:1
Rb	3-Chlorobutyrate	111.5	−28	95–180	37.0	41.6	2:1
Cs	3-Chlorobutyrate	102.5	−29	85–180	32.3	33.8	3:1
Ag	3-Chlorobutyrate	93.1	−26	75–200	35.4	37.5	1:5
Na	3-Bromobutyrate	104.8/117.2	−2	85–180	44.7	45.6	1:1
Rb	3-Bromobutyrate	66.9	−14	50–180	31.9	34.2	5:1
Cs	3-Bromobutyrate	53.6	−15	50–170	25.9	28.8	4:1

Any endothermal event occurring just before the exothermal reaction was included into the DSC integral. The heating leads to a complete vaporization of the organic part of the compound so that only the metal halide remains. In the rightmost column, the molar ratio of crotonic acid to oligomer after the synthesis at the onset temperature T_o is shown.

spectroscopy (AAS) was performed with a Thermo Electron Corporation instrument (M series) to determine the metal contents. The contents of carbon and hydrogen were determined by standard combustion analysis with an EA 1110 (CE Instruments) instrument. Halogens were determined by potentiometric titration with a Metrohm 716 DMS Titrino.

3. Result and discussion

All metal salts (Na, Rb, Cs, and Ag) showed a strong exothermal effect in DSC upon heating, typically preceded by a small endothermal peak (Fig. 1). This indicates a melting process before the salt elimination [37]. The onset temperature strongly depended on the metal and the anion, with a clear tendency towards a lower temperature with heavier metals. In general, the bromobutyrates showed this thermal effect at a lower temperature than the corresponding chlorobutyrates. The exothermal reaction enthalpy was comparable with that found for halogenoacetates and 2-halogenopropionates [1,3,34]. Note that the measured enthalpy of reaction consists of a number of individual processes that comprise, e.g., the melting of the butyrate, the reaction itself, the solidification of the polymer and the crystallization of the metal halide [34]. The corresponding enthalpies of reaction can only be roughly estimated. Furthermore, as shown below, the reaction does not lead to a single product. Therefore, not too much attention should be paid to the absolute numbers of these exothermal reaction events, and they should not be compared among themselves.

The mass loss in thermogravimetry started shortly before the exothermal reaction and was finished around 180–200 °C (Fig. 2). Only small differences in the thermogravimetric curves were observed in this temperature range between a thermolysis under nitrogen and under oxygen. In any case, the temperature is too low to lead to oxidative combustion. We conclude that this mass loss is associated with the evaporation of volatile reaction products.

This is supported by simultaneously recorded IR spectra of the evolved gases (Fig. 3). Crotonic acid (E-2-butenoic acid) and isocrotonic acid (Z-2-butenoic acid) are likely side-products (see Eq. (2)). In addition, volatile low-molecular condensation products (esters) were detected. HCl or HBr were not observed in the released gas. However, their bands (split up into rotational transitions, around 2990 cm^{-1} (HCl) and 2650 cm^{-1} (HBr), respectively) may be hidden in the spectral background if only small amounts are present. The final sample mass was close to that expected for a residue of pure metal halide, MX, in all cases. We conclude that the whole organic part of the molecule is released in gaseous form. The remaining metal halides were identified by X-ray powder diffraction. All thermochemical results are summarized in Table 1.

The thermogravimetric data indicate that it is impossible to carry out the polymerization reaction at a temperature that is too high because only volatile products are formed in this case. This is different from halogenoacetates and halogenopropionates which can be converted into a composite of polyester and metal halide by simply heating above the exothermic elimination event [2,3,38]. Therefore, the reaction temperature had to be lowered. The metal halogenobutyrates were carefully heated in preparative scale just below the onset temperature as determined by DSC (Table 1) and

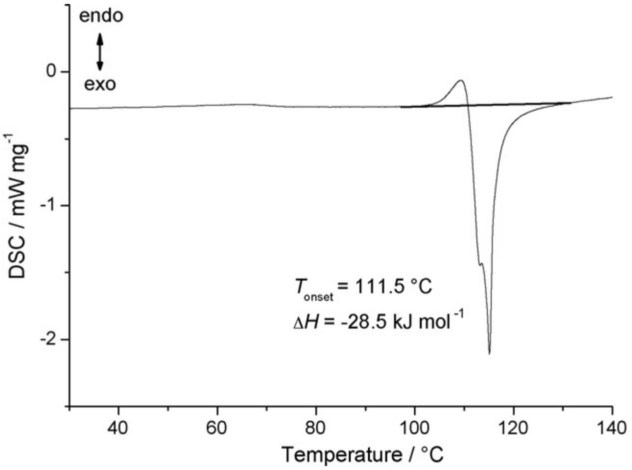


Fig. 1. A representative DSC experiment with rubidium 3-chlorobutyrate, showing the exothermal effect, preceded by a small endothermal effect which probably indicates melting process the salt elimination.

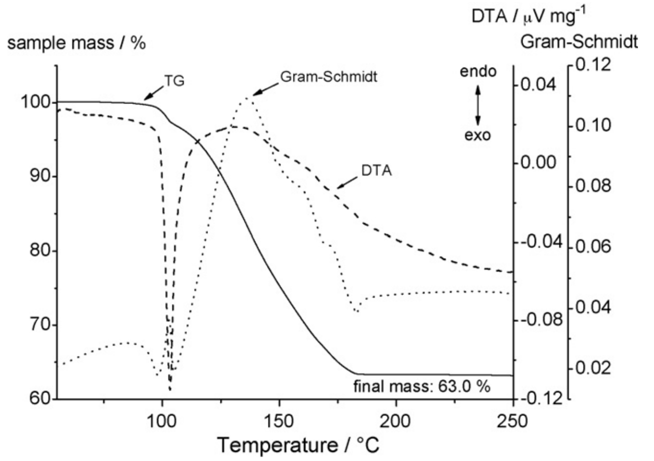


Fig. 2. A representative thermogravimetric experiment with rubidium 3-chlorobutyrate under N_2. The exothermal event is accompanied by a continuous mass loss up to 180 °C. The total intensity of the infrared spectra in the evolved gases, as represented by the Gram-Schmidt number, confirms the release of gaseous products during the mass loss.

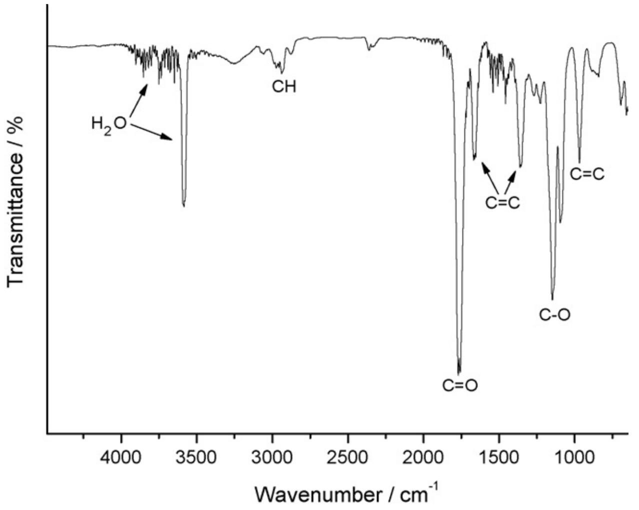


Fig. 3. Representative gas-phase IR spectrum, recorded during the thermolysis of sodium 2-chlorobutyrate at 150 °C. Crotonic/isocrotonic acid are detectable by the C═C-bands, esters are detectable by the C═O-band and the C—O-band. Gaseous HCl was not clearly detected.

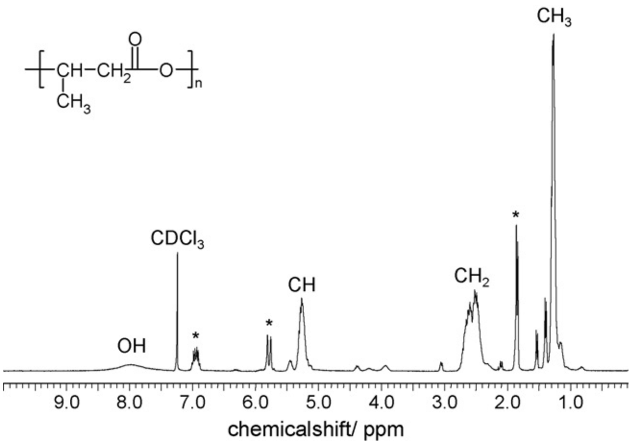


Fig. 4. ^{1}H NMR of the solid residue of silver 3-chlorobutyrate, showing poly(3-hydroxybutyrate) and crotonic/isocrotonic acid (as indicated by *).

then isothermally converted into the reaction products. The extent of reaction was monitored by IR spectroscopy to avoid decomposition and incomplete reaction. After the experiment, the products were analyzed by NMR spectroscopy in D_2O. All reaction products were easily soluble in D_2O (indicating the absence of polyester with higher molecular weight). Only for the reaction product from silver 3-chlorobutyrate, an insoluble residue remained (polymer and AgCl). Therefore, the polymeric part of reaction product was dissolved in $CDCl_3$, and only the white residue of AgCl remained.

^{1}H and ^{13}C NMR spectroscopy confirmed that the halogenobutyrates underwent decomposition to crotonic acid and other low-molecular weight products. The side-products crotonic acid (mp 72 °C; bp 185 °C) and isocrotonic acid (mp 15 °C; bp 169 °C) show almost the same ^{1}H NMR spectrum and cannot be distinguished by this method. However, in the reaction product from silver-3-chlorobutyrate we could clearly see both isomers in the

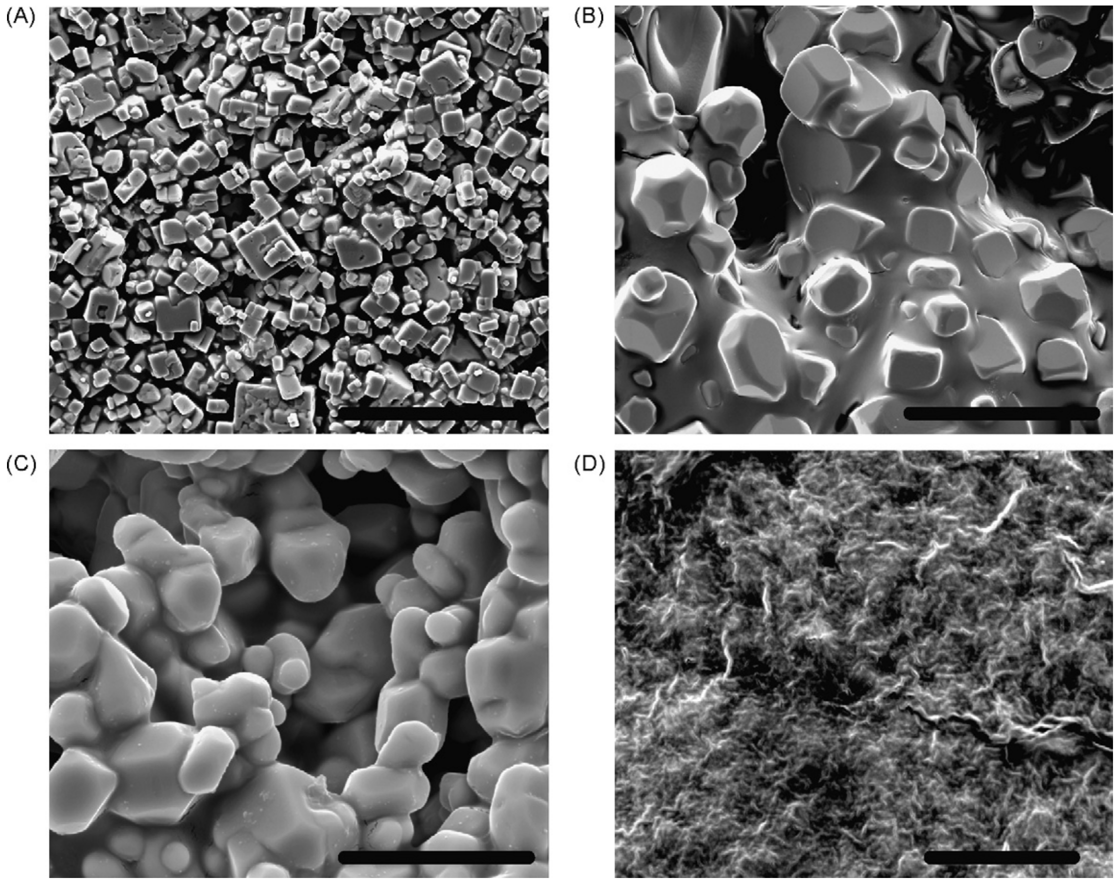
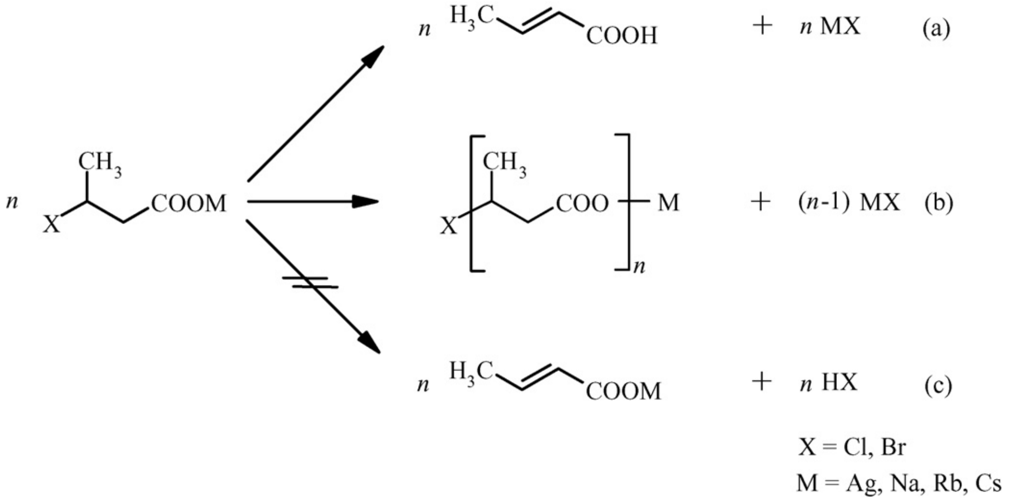


Fig. 5. Representative scanning electron micrographs of the reaction product of 3-halogenobutyrates after isothermal reaction (at T_o from DSC), consisting of the metal halide and the organic residue as given in Table 1. (A) CsBr from cesium 3-bromobutyrate; scale bar 20 μm; (B) NaCl from sodium 3-chlorobutyrate; scale bar 20 μm; (C) RbBr from rubidium 3-bromobutyrate; scale bar 5 μm; (D) AgCl/polymer from silver 3-chlorobutyrate; scale bar 5 μm.



(2)

^{13}C NMR spectrum (crotonic acid: 17, 122, 145, and 164 ppm; isocrotonic acid: 15, 122, 147, and 170 ppm). By ^{1}H NMR spectroscopy and ^{13}C NMR spectroscopy, it was also possible to identify condensation products, i.e. short-chain oligomers of poly(3-hydroxybutyrate) in all cases (^{13}C NMR peaks at 20, 40, 67, and 169 ppm). The only compound which gave a considerable amount of water-insoluble poly(3-hydroxybutyrate) with a higher molecular mass was silver-3-chlorobutyrate. In this case, the desired product was clearly identified by ^{1}H NMR (Fig. 4).

By scanning electron microscopy, the solid reaction products showed cubic metal halide crystals. These have a diameter of a few micrometres (Fig. 5). Their identity was confirmed by X-ray powder diffraction. In the case of the reaction product of silver 3-chlorobutyrate (which should ideally consist of AgCl and poly(3-hydroxybutyrate), the AgCl crystals were much smaller ($\ll$1 μm) and the polymeric product occurred as fibres. The infrared spectrum of the reaction product showed the expected bands for poly(3-hydroxybutyrate) (Fig. 6).

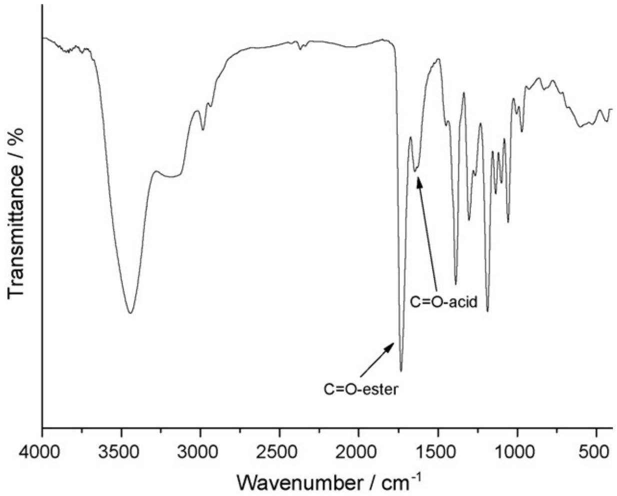


Fig. 6. Infrared spectrum of the p-3HB/AgCl composite obtained by thermal elimination of AgCl from silver 3-chlorobutyrate.

4. Conclusions

Upon heating, metal 3-halogenobutyrates undergo a thermal elimination of metal halide. In principle, three reaction pathways are possible.

From the thermogravimetric experiments we can derive that at a higher temperature the formation of (*iso*-)crotonic acid (pathway a) is favoured over the polycondensation to poly(3-hydroxybutyrate) (pathway b). At a lower temperature, the polycondensation is possible. The polycondensation is entropically disadvantageous, and the evaporation of (*iso*-)crotonic at higher temperature is shifting the equilibrium towards pathway a). The elimination of HX (pathway c) is unlikely because HX was not detected in the gas-phase IR spectra of the reaction products. In addition, we did not find an indication for crystalline sodium (*iso*-)crotonate in the solid reaction product and the mass loss in thermogravimetry was very close to that expected for residual MX. In case of a halogen loss by HX elimination, the residual mass would have been smaller than calculated for MX. Notably, it was only possible to prepare the desired polyester from silver 3-chlorobutyrate under elimination of AgCl. Therefore, the thermal elimination reaction that works very well for halogenoacetates and 2-halogenopropionates is not applicable to 3-halogenobutyrates as a facile synthetic method.

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