# Formation of Polyesters by Thermally Induced Polymerization Reactions of Molecular Solids

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*Dedicated to Prof. Dr. R. D. Fischer on the occasion of his 65th birthday*

**Keywords:** Solid-state polymerization / Halogenocarboxylates / Polymers / Biomaterials / Materials chemistry

The development of solid-state polycondensation reactions, starting in 1857, is reviewed. In many cases, the elimination of metal halides from halogenated carboxylates leads to the formation of polyesters, among them polyglycolide, polylactides, polybutyrates, polymandelide, and poly(hydroxymethyl benzoates). In some cases, a reaction in the solid state is observed, whereas in other cases temporary liquefaction occurs. The resulting polymers usually have a lower degree of polymerization than the products from solution- or melt-polymerization. In some cases, polymers with a distinct micromorphology (high porosity with pores in the sub-µm range) are obtained and may be of interest for special applications, e.g. in medical technology.

## Introduction

Polymers constitute one of the major classes of materials. Owing to the tremendous progress made in polymer chemistry since the days of Hermann Staudinger, the properties of polymeric materials can now be fine-tuned within a wide range, so that they have replaced classical materials (metals, wood, ceramics) in many applications (the annual worldwide production of synthetic polymer fibers is approximately 20 Mio t/a). Usually, polymers are prepared in the melt or in solution.

An impressive number of solid-state polymerization reactions occurring in the solid state is known. They may be divided into radiation-induced reactions (photopolymerization reactions) and thermally induced reactions. However, although polymerization reactions in the solid state had been known since the last century,[1,2] they did not find an industrial application, probably due to the inherent difficulties involved in controlling a large-scale exothermic reaction in the solid state. In this article, we review one type of these reactions, i.e. thermally induced reactions that lead to polyesters, accompanied by salt elimination. In some special cases, the resulting materials may be useful for biomedical applications.

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**MICROREVIEWS:** This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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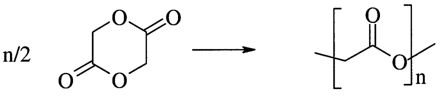
## Some Background Information on Polyesters

Polyesters, i.e. macromolecules with ester bonds between the repeating units, constitute an important group of materials with a high number of applications. Among the well-known polyesters are poly(ethyleneterephthalic acid) [polyethyleneterephthalate; PET], poly(butyleneterephthalic acid) [polybutyleneterephthalate; PBT], polyglycolide [poly(hydroxyacetic acid); PGA] and polylactide [poly(2-hydroxypropionic acid); PLA]. Note that if the ester groups are placed in side chains in a graft polymer, the polymer is not called a polyester.

Biodegradable polyesters constitute an important subset. The potentially hydrolyzable ester bond is used in a number of poly(hydroxycarboxylic acids) with polyglycolide, polylactide and P-3HB [poly(3-hydroxybutyric acid)] being the most prominent examples. As a contribution to a sustainable development, they may replace nonbiodegradable polymers made from fossil fuels in consumer chemicals.[3] For example, the Cargill−Dow Polymer Corporation has announced that in 2002 it intends to start the production of polylactide from corn starch with an annual capacity of 140,000 t, under the trade name NatureWorks$^{TM}$ PLA. Other examples of commercially available biopolymers are poly[(*R*)-3-hydroxybutyrate] and its copolymer poly[(*R*)-3-hydroxybutyrate-*co*-(*R*)-3-hydroxyvalerate], trade name BIOPOL$^{TM}$, both produced by biofermentation. In 1994, the production of BIOPOL was approximately 1,000 t (ICI−Zeneca).[4] Although these materials from renewable resources have good mechanical and chemical properties, the replacement of fossil fuel based polymers (such as polyethylene and polypropylene) appears to be constrained by the higher price of biodegradable polymers. Another aspect is the existence of operational production facilities and established distribution pathways for conventional polymers, so that a number of companies have again abandoned research on and production of biodegradable polymers.

A more specialized application of biodegradable polymers is in the field of medical technology. As many polyesters and their monomers are nontoxic, they can be used as implants within the body, for example, where a mechanical support of tissue is required. Typical applications are surgical sutures, wound covers (artificial skin), bone-fixation or bone-replacement devices, and carriers for controlled drug release.[5−9] The lifetime in the body depends mainly on the nature of the polymer: While polyglycolide is absorbed within months, polylactide is degraded over years, and the degradation times for poly(3-hydroxybutyrate) are even longer. Fine-tuning of the mechanical properties and of the degradation rate is possible by preparing copolymers, e.g. poly(glycolide-*co*-lactide), PGLA, or poly(3-hydroxybutyrate-*co*-3-valerate), PHBHV. Usually, poly(hydroxycarboxylic acids) are prepared by ring-opening polymerization[10] [Equation (1)] (e.g., polyglycolide, polylactide) or by biotechnological fermentation [(poly(3-hydroxybutyrate)].[4]



(1)

## Solid-State Polymerization Reactions

A considerable number of solid-state polymerization reactions has been reported in the literature. None of them are applied industrially, probably because exothermic solid-state reactions involving potentially flammable compounds (such as organic monomers and polymers) are difficult to scale up, and because of the more heterogeneous nature of the polymeric products. Reactions in the solid state depend on numerous parameters that are not significant in liquid-phase reactions (e.g., crystallinity, polymorphic phase, nucleation, defect structure, particle size). However, solid-state polymerization reactions may give:

- highly crystalline or oriented polymers[11−14]
- special product morphologies[15−18]
- high reaction extents[12,19]
- easily purified products without traces of monomers or catalyst.[11,20]

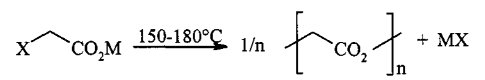
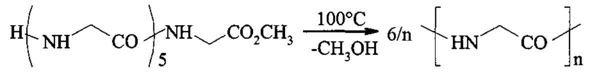
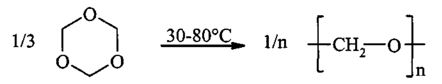
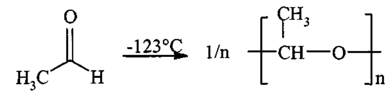
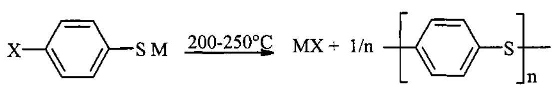
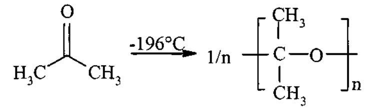
Table 1 contains a selection of unusual solid-state reactions that are initiated by thermal treatment. Some historical examples of solid-state polymerization reactions date back to the early days of chemistry, even before the concept of a polymer was developed.

The first example (to the best of our knowledge) is the thermally induced polycondensation that occurs in potassium chloroacetate, reported by Hoffmann in 1857.[21] The reaction leads to polyglycolide and potassium chloride as the only products (note that the product was originally postulated to be diglycolide, the cyclic dimer). In Figure 1, the original article from 1857 is shown.

It is interesting that the molecular formulae are different from those used today, because at the time the relative atomic weights of carbon and oxygen were thought to be 6 and 8, respectively. Therefore, potassium chloroacetate was represented as $C_4H_2ClKO_4$ instead of $C_2H_2ClKO_2$. One year later, Kekulé, Hoffmann's mentor, studied the reaction (Figure 2),[22] followed by Heintz in 1862,[23] and Norton and Tcherniak in 1878[24] who studied the reaction of sodium chloroacetate. In 1892, Anschütz studied polyglycolide obtained from such a solid-state reaction.[25,26] By cryoscopic measurements in molten phenol, he determined a molecular weight of approximately 5 to 6 glycolide units ($C_2H_2O_2$) without identifying it as a polymer. Systematic studies were then carried out by Bischoff and Walden in 1894 on sodium chloroacetate and sodium bromoacetate.[27,28] For the first time, a polymer was proposed instead of the dimer that had been suggested before.

In 1906, Emil Fischer observed the reaction of pentaglycylglycine methyl ester after prolonged heating at 100 °C to form an amorphous, water-insoluble, presumably polymeric product.[29,30] Fifty years later, this was corroborated by Sluyterman et al.[31] The product was never clearly identified, but it seems to have been polyglycine. The first oriented polymer from an organic solid-state reaction was prepared by Kohlschütter when he sublimed poly(oxymethylene) and obtained trioxane that contained some highly oriented polymer.[1] Six years later, two different groups independently discovered the solid-state polymerization of acet-

Table 1. A selection of "historical" solid-state polymerization reactions

| Reaction | Product | Source (Year) |
|---|---|---|
|  | Polyglycolide | Hoffmann (1857[21]), Kekulé (1858[22]), Heintz (1862[23]), Norton and Tcherniak (1878[24]), Anschütz (1892[25,26]), Bischoff and Walden (1893[27,28]) |
|  | Polyglycine (?) | Fischer (1906[29]) and Sluyterman (1952[31]) |
|  | Poly(oxymethylene) (para-formaldehyde) | Kohlschütter (1930[1]) |
|  | Poly(acetaldehyde) | Travers (1936[32]), Letort (1936[33]) |
| <br>M = Li, Na, K X = F, Cl, Br, I | Poly(p-phenylene Sulfide) | Lenz (1962[11]) |
|  | Poly(acetone) | Magat (1962[19]) |

aldehyde to poly(acetaldehyde), or poly(oxymethylmethylene).[32,33]

In some cases, high-quality polymers can only be obtained by solid-state reactions.[11] An example is the solid-state polymerization of alkali 4-halogenobenzothiolates. If the reaction is carried out in the solid state, a linear polymer results. The polymeric product is poly(4-phenylene sulfide). The eliminated alkali halides can be washed out easily with water. Until 1970, a linear polymer could only be prepared by this route, because the reaction in the melt was accompanied by cross-linking and chain-branching, leading to the formation of an insoluble product. Nowadays, linear poly(4-phenylene sulfide) can also be synthesized by melt polymerization of *p*-dichlorobenzene in the presence of sodium sulfide.[11] Acetone polymerizes only in the solid state due to the low thermal stability of the resulting polymer.[19] The solid-state polymerization of 4-amino-3,5-dihalobenzoyl chlorides to polybenzamides (with concomitant elimination of HCl) was recently shown by Sandor and Foxman. The preparation of this polymer in solution leads only to the formation of low-molecular weight polymers.[34]

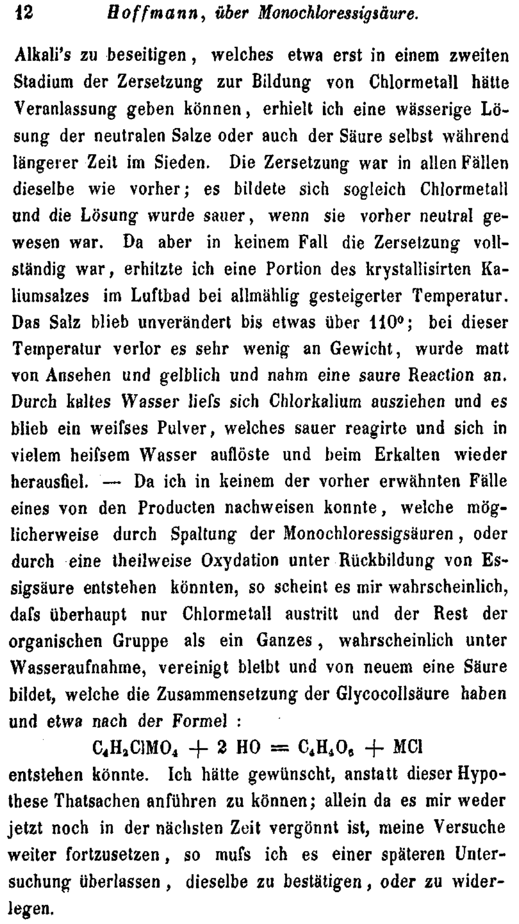
Starting in the 1950s and 1960s, attention was mainly focused on radiation-induced solid-state polymerization reactions of unsaturated or cyclic monomers. Prominent examples are diacetylenes, divinyl compounds and acrylic acid derivatives. Details of radiation-induced solid-state polymerization reactions can be found in a number of reviews.[17,19,35–41]

## Polyglycolide by Solid-State Reaction

As outlined above, the transformation of solid halogenoacetates to polyglycolide was discovered almost 150 years ago. Since the early studies in the 19th century, only few articles were published on this reaction. Nevertheless, the reaction received industrial interest. The parent compound for ring-opening polymerization, (di)glycolide, can be obtained by the pyrolysis of the (pre)polymer from the solid-state reaction in vacuo. The sublimed dimer is then subjected to ring-opening polymerization according to Equation (1). Little attention was paid to the raw product, and only few papers about this reaction were published until 1996.[42–46] In particular, no mechanistic studies were carried out, and the resulting polymer was not characterized. Essential details of our studies on this system are presented.

Formally, the elimination of metal halide MX from any halogenoacetate $MOOC-CH_2-X$ leads to the formation of polyglycolide (see Table 1). A systematic variation of most combinations of metal and halogen showed that almost all haloacetates undergo the desired reaction. The results are collected in Table 2.[20] Note that fluoroacetates were not included in the study as these compounds (as well as fluoroacetic acid) are highly toxic.

The three lithium salts, sodium iodoacetate and calcium chloroacetate are notable exceptions. The thermoanalytical data for all the compounds are collected in Table 3. It can be seen that the polymerization reaction is associated with a considerable exothermic heat of reaction. The underlying reason is probably the high lattice energy of the formed metal halide. There is a clear trend in the reaction temperatures, which are lowest for the combinations of large metal cations (like $Cs^+$) and small halogen anions (like $Cl^-$). Within the rectangle of alkali metals and halogens, the "corner of stability" is in the upper right, and the "corner of reactivity" is in the lower left of Table 3. The lack in



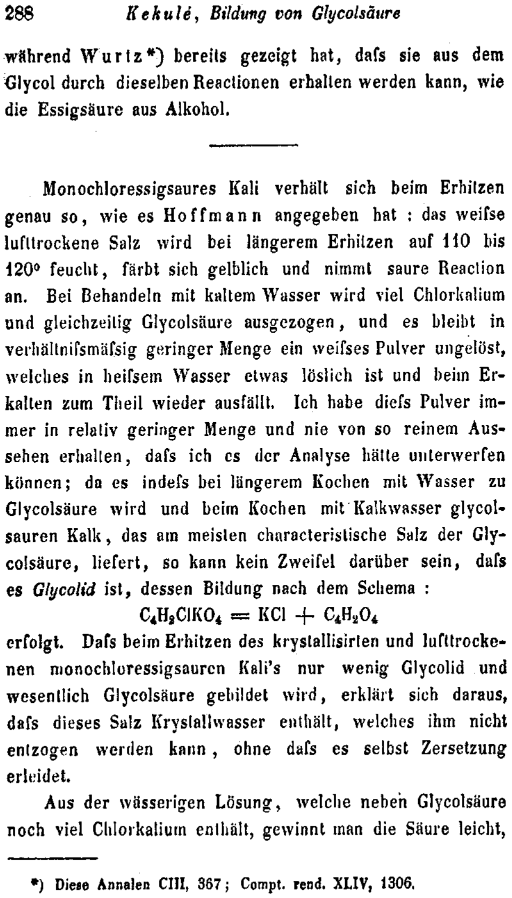
12 *Hoffmann, über Monochloressigsäure.*

Alkali's zu beseitigen, welches etwa erst in einem zweiten Stadium der Zersetzung zur Bildung von Chlormetall hätte Veranlassung geben können, erhielt ich eine wässerige Lösung der neutralen Salze oder auch der Säure selbst während längerer Zeit im Sieden. Die Zersetzung war in allen Fällen dieselbe wie vorher; es bildete sich sogleich Chlormetall und die Lösung wurde sauer, wenn sie vorher neutral gewesen war. Da aber in keinem Fall die Zersetzung vollständig war, erhitzte ich eine Portion des krystallisirten Kaliumsalzes im Luftbad bei allmählig gesteigerter Temperatur. Das Salz blieb unverändert bis etwas über 110°; bei dieser Temperatur verlor es sehr wenig an Gewicht, wurde matt von Ansehen und gelblich und nahm eine saure Reaction an. Durch kaltes Wasser lieſs sich Chlorkalium ausziehen und es blieb ein weiſses Pulver, welches sauer reagirte und sich in vielem heiſsem Wasser auflöste und beim Erkalten wieder herausfiel. — Da ich in keinem der vorher erwähnten Fälle eines von den Producten nachweisen konnte, welche möglicherweise durch Spaltung der Monochloressigsäuren, oder durch eine theilweise Oxydation unter Rückbildung von Essigsäure entstehen könnten, so scheint es mir wahrscheinlich, daſs überhaupt nur Chlormetall austritt und der Rest der organischen Gruppe als ein Ganzes, wahrscheinlich unter Wasseraufnahme, vereinigt bleibt und von neuem eine Säure bildet, welche die Zusammensetzung der Glycocollsäure haben und etwa nach der Formel:

$$C_4H_2ClMO_4 + 2\ HO = C_4H_4O_6 + MCl$$

entstehen könnte. Ich hätte gewünscht, anstatt dieser Hypothese Thatsachen anführen zu können; allein da es mir weder jetzt noch in der nächsten Zeit vergönnt ist, meine Versuche weiter fortzusetzen, so muſs ich es einer späteren Untersuchung überlassen, dieselbe zu bestätigen, oder zu widerlegen.

Figure 1. Facsimile of the original article by R. Hoffmann in *Justus Liebigs Annalen der Chemie*, "Ueber Monochloressigsäure" (On Monochloroacetic Acid) in 1857, the first known example of a solid-state polymerization reaction (see ref.[21])



288 *Kekulé, Bildung von Glycolsäure*

während Wurtz*) bereits gezeigt hat, daſs sie aus dem Glycol durch dieselben Reactionen erhalten werden kann, wie die Essigsäure aus Alkohol.

Monochloressigsaures Kali verhält sich beim Erhitzen genau so, wie es Hoffmann angegeben hat: das weiſse lufttrockene Salz wird bei längerem Erhitzen auf 110 bis 120° feucht, färbt sich gelblich und nimmt saure Reaction an. Bei Behandeln mit kaltem Wasser wird viel Chlorkalium und gleichzeitig Glycolsäure ausgezogen, und es bleibt in verhältniſsmäſsig geringer Menge ein weiſses Pulver ungelöst, welches in heiſsem Wasser etwas löslich ist und beim Erkalten zum Theil wieder ausfällt. Ich habe dieſs Pulver immer in relativ geringer Menge und nie von so reinem Aussehen erhalten, daſs ich es der Analyse hätte unterwerfen können; da es indeſs bei längerem Kochen mit Wasser zu Glycolsäure wird und beim Kochen mit Kalkwasser glycolsauren Kalk, das am meisten characteristische Salz der Glycolsäure, liefert, so kann kein Zweifel darüber sein, daſs es *Glycolid* ist, dessen Bildung nach dem Schema:

$$C_4H_2ClKO_4 = KCl + C_4H_2O_4$$

erfolgt. Daſs beim Erhitzen des krystallisirten und lufttrockenen monochloressigsauren Kali's nur wenig Glycolid und wesentlich Glycolsäure gebildet wird, erklärt sich daraus, daſs dieses Salz Krystallwasser enthält, welches ihm nicht entzogen werden kann, ohne daſs es selbst Zersetzung erleidet.

Aus der wässerigen Lösung, welche neben Glycolsäure noch viel Chlorkalium enthält, gewinnt man die Säure leicht,

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*) Diese Annalen CIII, 367; Compt. rend. XLIV, 1306.

Figure 2. Facsimile of the original article by A. Kekulé in *Justus Liebigs Annalen der Chemie* in 1858, "Bildung von Glycolsäure aus Essigsäure" (Formation of Glycolic Acid from Acetic Acid), in which he confirmed Hoffmann's observation (see ref.[22])

reactivity of the lithium salts and sodium iodoacetate corresponds well to this observation: These compounds appear to be have a high thermodynamical stability towards polymerization. After all, this depends on the difference between the free enthalpy of formation of the alkali halide and that of the alkali halogenoacetate, e.g. lithium chloroacetate vs. LiCl. Apparently, these compounds undergo decomposition before they can polymerize. No thermodynamic data are known, therefore this is merely speculation. We will discuss structural aspects below.

The calcium salt of chloroacetic acid does not show any tendency to form polyglycolide. Hoffmann (1857) also studied barium chloroacetate dihydrate and observed decomposition upon heating.[21] However, no details were given about the decomposition products. Possibly, polymerization did not occur because the divalent cations (Ca and Ba) do not support a topochemical reaction. Note that this cannot be generalized to all solid-state polymerization reactions, as radiation-induced polymerization reactions of salts of acrylic and methacrylic acids were observed for a variety of cations, including alkali metals, alkaline earth metals and zinc (however, this is a different type of reaction).[47−50]

Table 2. Ability of a combination of metal and halogen in different halogenoacetates $MOOC{-}CH_2{-}X$ to undergo polymerization; most compounds undergo a thermal elimination of a metal halide to form polyglycolide (see also Table 1); "+" = polymerization, "−" = no polymerization

| | Cl | Br | I |
|---|---|---|---|
| Li | − | − | − |
| Na | + | + | − |
| K | + | + | + |
| Rb | + | + | + |
| Ag | + | + | unstable |
| Cs | + | + | + |
| $NH_4$ | (+) | not studied | not studied |
| $Ca{\cdot}H_2O$ | − | not studied | not studied |

A molecular solid-state reaction relies on a suitable arrangement of the reactants in the crystal. The peculiarities of such reactions (low temperatures, bulky reactants, small diffusion coefficients) led to the formulation of the "topochemical principle" by Schmidt and co-workers in the 1960s: Solid-state reactions in molecular crystals take place with as little movement of the molecules as possible.[35,51,52] Consequently, knowledge of the crystal structures of all halogenoacetates is a prerequisite to understand the reactivity.

Table 3. Thermochemical data for halogenoacetates that in most cases react to form polyglycolide (values in italics: no polymerization); reaction temperatures are given as onsets and reaction enthalpies in kJ mol$^{-1}$ for the polymerization reaction by DSC with 5 K min$^{-1}$

| | Cl | Br | I |
|---|---|---|---|
| Li | *211 °C/+11.2*[a] | *210 °C/+16.6*[a] | *220 °C/−*[b] |
| Na | 198 °C/−25.2 | 186 °C/−23.4 | *204 °C/−72.0*[b] |
| K | 157 °C/−40.3 | 171 °C/−36.9 | 192 °C/−23.5 |
| Rb | 120 °C/−42.5 | 99 °C/−25.4[c] | 114 °C/−24.4 |
| Cs | <25 °C/−[d] | 35 °C/−26.9[e] | 86 °C/−35.7 |
| Ag | 134 °C/−64.2 | 78 °C/−63.9 | unstable |
| $NH_4$ | 107 °C/−21.8[e] | not studied | not studied |
| Ca | *95 °C/+48.3*[g]<br>*198 °C/+15.1*[h] | not studied | not studied |

[a] Endothermic melting of the salt followed by exothermic decomposition. − [b] No melting; exothermic decomposition. − [c] Two peaks at 99 °C and 142 °C. − [d] Polymerization below room temperature. − [e] Partial polymerization below room temperature. − [f] Oligomerization in the melt. − [g] Dehydration of the monohydrate. − [h] Melting of the anhydrous salt.

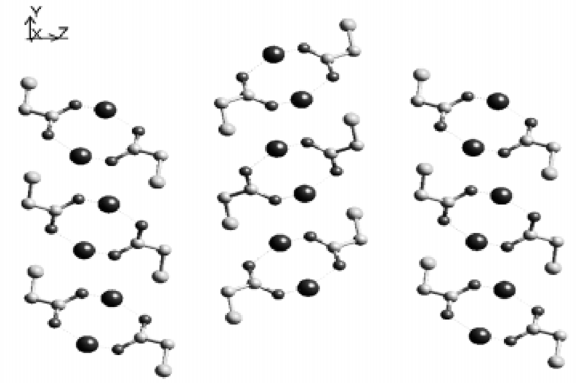
Unfortunately, the preparation of single crystals suitable for structural analysis is seldom possible for halogenoacetates because they tend to crystallize in the form of thin and disordered platelets or needles. In the literature, only the single-crystal structures of ammonium fluoroacetate[53] and of sodium fluoroacetate[54] are reported. It is unlikely that fluoroacetates undergo a polymerization reaction upon heating, owing to the fact that sodium fluoroacetate decomposes above 200 °C, with concomitant release of HF.

Only the structure of silver chloroacetate could be determined by single-crystal diffraction,[55] whereas the structures of lithium chloroacetate,[56] lithium bromoacetate,[56] lithium iodoacetate,[56] sodium chloroacetate,[57] and sodium bromoacetate[58] had to be solved from powder-diffraction data.

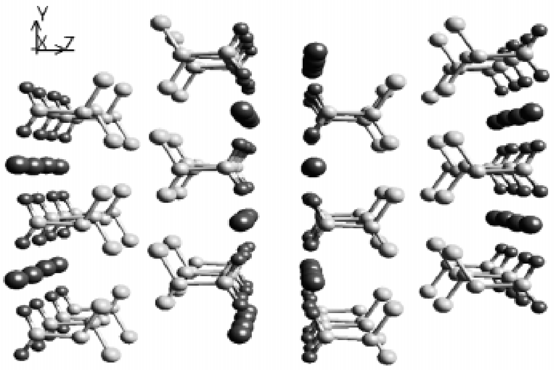
Analysis of the packing in the six known structures shows that the structure is determined by the metal ion rather than by the halide. The three lithium salts are isostructural, and the same is true for sodium chloro- and bromoacetate. Silver chloroacetate crystallizes with a completely different packing. The three structure types are shown in Figure 3.

Silver chloroacetate is discussed first. The structure consists of stacks of silver chloroacetate dimers. There is a short Ag−Cl distance of 2.90 Å that is only slightly longer than in silver chloride, the final reaction product (2.78 Å). We suspect that there is already some kind of interaction in silver chloroacetate. A side-view of the stacks shows that a nucleophilic attack of the carboxy group of a chloroacetate ion at an α-carbon atom is conceivable, a process that would finally lead to the formation of two antiparallel chains of polyglycolide from each stack of silver chloroacetate dimers (see ref.[55] for details). The crystal structure of polyglycolide actually consists of antiparallel chains of polyglycolide (Figure 4).[59] This crystalline phase of polyglycolide was unequivocally identified by X-ray powder diffraction studies.

(a) Silver chloroacetate



(b) Sodium chloro- and bromoacetate



(c) Lithium chloro-, bromo- and iodoacetate

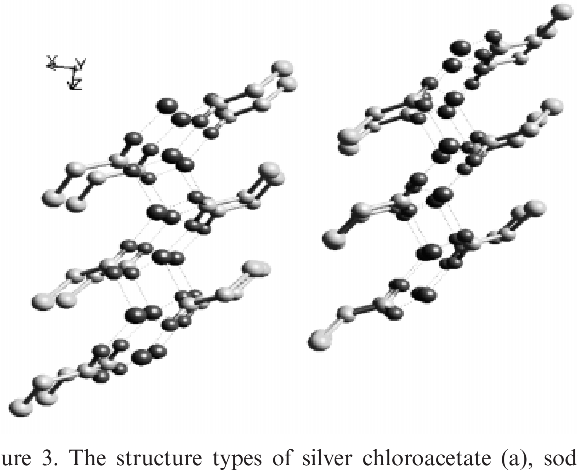


Figure 3. The structure types of silver chloroacetate (a), sodium chloro- and bromoacetate (b), and of lithium chloro-, bromo-, and iodoacetate (c); in cases (a) and (b), solid-state polymerization to form metal halide and polyglycolide is observed, whereas the lithium salts merely decompose

For the sodium salts, the mechanism is less obvious. There is no short distance between the metal and the halogen ions. Layers of metal ions alternate with layers of halogen atoms. However, a polymerization that occurs along

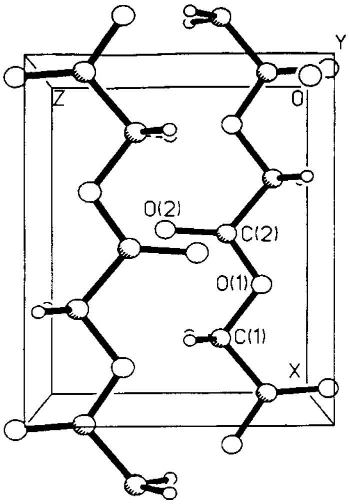


Figure 4. The crystal structure of polyglycolide shows antiparallel chains (see ref.[59])

the crystallographic *b* axis can be postulated (see ref.[57] for details).

The lithium salts do not polymerize. From the crystal structure this can be ascribed to the coordination of lithium by four oxygen atoms from four different carboxy groups. We speculate that the small, strongly polarizing lithium ion keeps the molecules from moving into a suitable orientation for polymerization (see ref.[56] for a detailed discussion).

Even when a topochemical mechanism can be postulated by inspection of the crystal structure, little is actually known about the way the molecules react:

- whether the reaction occurs in a single step,
- whether the crystal structure is preserved, and
- how two solid phases (salt and polyester) are formed from a single phase.

To acquire such information, it is necessary to follow the course of the reaction by suitable in-situ and ex-situ techniques that probe specific sample properties. The in-situ techniques are preferable as they yield more direct information.

The polycondensation reactions of halogenoacetates have been studied with a variety of techniques, each probing different structural features of the reaction. The results are summarized in Table 4. We now have a very detailed insight into this reaction and can therefore formulate a reaction mechanism as depicted in Figure 5.

This reaction can be considered as very well studied. Fortunately, the nature of the reaction makes it susceptible to techniques developed for inorganic solids, organic solids, and polymers and hence most available techniques to obtain structural information in situ have been applied. However, it is still clear that there is a line that we cannot cross, even with the most sophisticated techniques available today.

This is the question of how the actual processes occur on a molecular or on an atomic scale. All techniques probe *integral* sample properties. This does not give information about the changes going on in the actual reaction zone, i.e. the very thin layer between the parent compound and the product. The fraction of molecules that actually react is small at any given time, therefore we see mainly the parent compound and the reaction products, but not necessarily the small amount of transient molecules. We can only try to deduce this microscopic information from the integral parameters that we can measure. The same holds for deductions about the reaction pathway from the crystal structure.

For example, even if the structure of silver chloroacetate supports a topochemical polymerization mechanism, this is no proof but only a hint that the reaction actually follows this pathway. Also, the question as to how metal ions and halogen ions find themselves to form the salt lattice is still completely unresolved. In conclusion, it must be said that there are no experimental techniques available at the moment to answer these questions. Theoretical computations may be the only possible means to tackle such problems.

Finally, it should be mentioned that solvate crystals of halogenoacetates with halogenoacetic acid also undergo a solid-state polymerization. In these cases, an endothermic peak occurs in DSC, followed by an exothermic event. The endothermic event is associated with the release of halogenoacetic acid from the solvate crystal, and its sublimation or boiling. After this, the pure salt recrystallizes and begins to polymerize. This was demonstrated by in-situ EXAFS measurements of rubidium bromoacetate/bromoacetic acid[60] and by time- and temperature-resolved XRD measurements of potassium chloroacetate/chloroacetic acid. Table 5 shows the results collected from the literature.

## Poly(hydroxypropionates) by Solid-State Reaction

At least on paper, the polycondensation of haloacetates can be transposed to all salts of halogenocarboxylic acids. The question is whether the actual chemical pathway of such a system lives up to this expectation.

The next higher homologues of halogenoacetates are 2-halogenopropionic acids and 3-halogenopropionic acids. In the first case, we expect poly(2-hydroxypropionic acid), that is, polylactic acid (or polylactide), a polymer with a stereogenic carbon atom. In the second case, the product would be the achiral poly(3-hydroxypropionic acid).

Polylactide was first prepared in 1845 by Pelouze, who heated lactic acid.[61] The known examples of polycondensation reactions of halogenopropionates are collected in Table 6, together with data on similar polycondensation reactions.

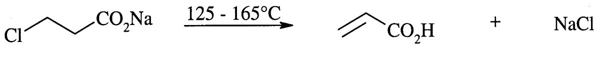
In 1894, Bischoff and Walden reported the formation of polyglycolide from sodium chloro- and bromoacetate. They extended their studies to sodium 2-bromopropionate, but obtained no polyester; the only product found was (di)lactide, which sublimed from the reaction mixture. This was probably due to the conditions of the experiments, as the salt was subjected to a temperature of more than 200 °C in vacuo. Under these conditions, pyrolysis of the formed polyester to lactide becomes dominant, and the intermediate product cannot be isolated from the reaction vessel. Furthermore, they did not analyze the solid residue.[62]

Table 4. Collection of facts about the solid-state polycondensation in halogenoacetates; note that side-products were not found with any technique; polyglycolide and the metal halide are the only products

| Technique | in-situ? | Property probed | Compound | Results |
|---|---|---|---|---|
| DSC | yes | enthalpy change | all halogenoacetates | exothermic polymerization reaction (see ref.[18,20,74]) |
| TG-DTA-MS | yes | volatile reaction products | all halogenoacetates | no mass loss during polymerization; at higher temperature, combustion of the formed polyglycolide (see ref.[20,74]) |
| X-ray diffraction (XRD) | yes | crystalline phases | sodium chloroacetate | no detectable crystalline intermediates (see ref.[20]) |
| EXAFS | no | short-range order (Cl) in all phases | sodium chloroacetate | no detectable intermediate containing chlorine (see ref.[74]) |
| EXAFS | yes | short-range order (Br, Rb in all phases | rubidium bromoacetate/ bromoacetic acid | desolvation is followed by polymerization (see ref.[60]) |
| EXAFS-XRD | yes | short-range order (Br) in all phases; crystalline phases | sodium bromoacetate | no detectable intermediates that either contain bromine or are crystalline;coalescence of small NaBr crystals to larger ones during annealing ("Ostwald ripening") (see ref.[79]) |
| EXAFS-DSC | yes | short-range order (Br) in all phases; enthalpy changes | sodium bromoacetate | no detectable intermediates that contain bromine; the reaction enthalpy is proportional to the reaction extent (see ref.[76]) |
| Small- and wide-angle X-ray scattering (SAXS-WAXS) | yes | structural order on different length scales | sodium chloroacetate | no detectable intermediates on all length scales; formation of short-range order in polyglycolide precedes formation of long-range order (long period of amorphous and crystalline domains) (see ref.[80]) |
| Solid-state NMR ($^{13}$C) | yes | chemical environment of carbon | sodium bromoacetate | no detectable intermediates containing carbon (see ref.[58]) |
| Solid-state NMR ($^{23}$Na) | yes | chemical environment of sodium | sodium chloroacetate; sodium bromoacetate | no detectable intermediates containing sodium (see ref.[58]) |
| IR | yes | chemical bonds in all phases | sodium chloroacetate | no detectable intermediates (see ref.[75]) |
| Scanning electron microscopy | no | morphologic changes | sodium chloroacetate | phase separation into a polymeric matrix containing microcrystals of NaCl (see ref.[74]) |
| Mercury porosimetry | no | morphologic changes in the formed polyglycolide/NaCl | sodium chloroacetate | the NaCl microcrystals increase in diameter with increasing reaction extent (see ref.[73]) |
| Viscosimetry | no | chain length of polyglycolide | sodium chloroacetate | the degree of polymerization increases with increasing reaction extent (polycondensation) (see ref.[73]) |
| Thermomicroscopy | yes | morphologic changes | sodium chloroacetate; silver chloroacetate | the reaction starts from defects in the crystal or from the surface; the single-crystalline order is not preserved (see ref.[73]) |

In an explorative study, we showed that sodium 2-chloropropionate indeed gives polylactide if the reaction temperature is 160 °C.[63] Two fractions with degrees of polymerization of 520 and 11, respectively, were detected by GPC. This corroborates the interpretation of the results of Bischoff and Walden that the polylactide formed previously was pyrolyzed during the reaction, leading to volatile lactide.

We found that the corresponding isomer, sodium 3-chloropropionate, gives a mixture of different products upon heating.[63] Oligomers of the desired polymer were formed (weight-average molecular weight of 420 g mol$^{-1}$), but the main competitive reaction is the intramolecular elimination of NaCl, resulting in the formation of acrylic acid [Equation (2)].



(2)

This unwanted reaction is probably favored at higher temperatures due to the higher gain in entropy relative to polymerization. It also precludes the preparation of the precursor salt by simple neutralization of the acid by NaOH or $Na_2CO_3$ at room temperature, because elimination occurs readily. Sodium 3-chloropropionate had to be prepared by neutralization at −50 °C, whereas sodium 2-chloropropionate can easily be prepared at room temperature.

## Poly(hydroxybutyrates) by Solid-State Reaction

Bischoff and Walden found the cyclic dimer and crotonic acid upon heating sodium 2-bromo-n-butyrate.[62] In contradiction to these results, Naruchi et al. obtained the corresponding polyester and oligomers from the alkaline and alkaline earth metal salts of 2-bromo-*n*-butyric acid.[64] The potassium and sodium salts gave polymeric products with number-average molecular weights between 1000 and 4000, and polydispersities close to 1.4. The alkaline earth and the lithium salts yielded only oligomers. The authors concluded that the crystallinity of the precursors played a decisive role because the salts of Na and K had a good crystallinity, whereas the Li, Mg, Ca, Sr, and Ba salts were of poor crystallinity, or even amorphous. We found oligomers with a degree of polymerization of 4 after heating sodium 2-chlorobutyrate at 160 °C for 30 min.[63]

Sodium 2-bromoisobutyrate starts to decompose at 30 °C, according to Bischoff and Walden. Sodium bromide was eliminated but the main product was methacrylic acid, which partially polymerized to form poly(methacrylic acid). Due to water incorporated in the crystal (they used the

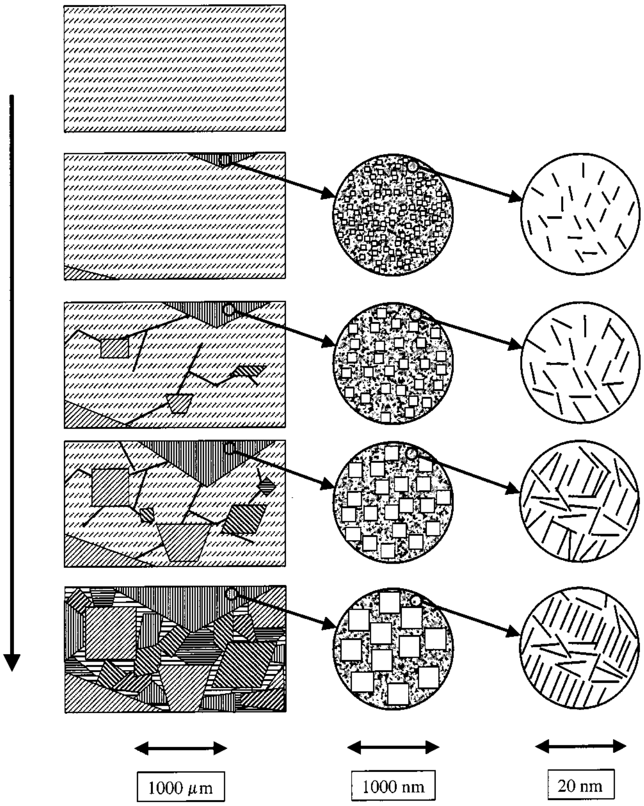


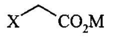
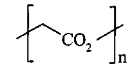
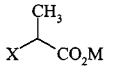
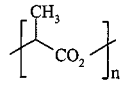
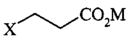
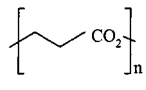
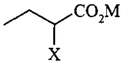
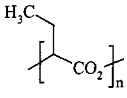
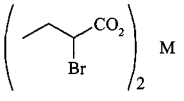
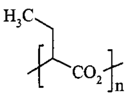
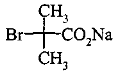
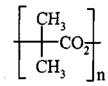
Figure 5. Schematic view of the solid-state polycondensation reaction of sodium chloroacetate to form polyglycolide and NaCl, viewed on different length scales; the following processes occur: 1. nuclei of reaction products form at the surface or at defects (left); 2. the new phase (polyglycolide and NaCl) grows within the halogenoacetate crystal; the local structure is damaged by a change in molar volume, thereby accelerating the reaction (left); 3. together with the phase separation, this leads to complete destruction of the single-crystalline order (left); 4. cubic NaCl crystals keep growing during the reaction within a matrix of polyglycolide (center); 5. after the reaction is complete, Ostwald ripening of the NaCl crystals occurs; larger crystals grow by consuming smaller ones (center); 6. the polyglycolide chains increase in length during the polycondensation reaction (right); 7. after larger amounts of polyglycolide have formed, ordering within the polymer phase into amorphous and crystalline domains occurs (right)

Table 5. Known solvate crystals of halogenoacetates of the type *n* halogenoacetate/*m* halogenoacetic acid; given are the molar ratios *n*:*m*/the temperature of the endothermic decomposition of the solvate/the temperature of the exothermic polymerization of the remaining halogenoacetate

| | Cl | Br |
|---|---|---|
| K | 1:1/142/150[a]<br>1:1/142/163[c] | 2:1/123/130[b] |
| Rb | 1:1/89,131/135[c][d]<br>1:2/98/135[c] | 1:1/119/125[e] |
| Cs | 1:1/108/135[c]<br>3:5/84/127[c] | |

[a] By DSC (5 K min$^{-1}$, onset temperature). – [b] By DSC (5 K min$^{-1}$, onset temperature, see also ref.[18] – [c] By DTA (3.2 K min$^{-1}$, peak maximum temperature, see also ref.[45]). – [d] Two endothermic signals are detected before the exothermic event. – [e] By DSC (5 K min$^{-1}$, onset temperature, see ref.[60]).

Table 6. Reactivity and resulting polyesters from simple aliphatic carboxylic acids; M = alkali, X = halogen

| **Precursor** | **Polymer ($T_{fus}$)** | **Remarks** |
|---|---|---|
| <br>Halogenoacetates | <br>Polyglycolide (220-233°C) | reacts quantitatively in the solid state[20] |
| <br>2-Halogenopropionates | <br>Polylactide (PLA; ~80°C) | dilactide (Na/Br; vacuum at 200°C)[62]; Polylactide (Na/Cl; 160°C)[63]; |
| <br>3-Halogenopropionates | <br>Poly(3-hydroxypropionate) (~90°C) | oligomers, acrylic acid, 3-hydroxypropionic acid (Na/Cl; 120°C)[63] |
| <br>M= alkali ions<br>2-Halogenobutyrates | <br>Poly(2-hydroxybutyric acid) | cyclic dimer, crotonic acid (Na/Br; 200-270°C)[62]; oligomers (Na/Cl; 160°)[63]; polymer (Na/Br and K/Br; 110-150°C)[64]; oligomers (Li/Br)[64] |
| <br>M= alkaline earth ions<br>2-Halogenobutyrates | <br>Poly(2-hydroxybutyric acid) | oligomers (Mg, Ca, Sr, Ba/Br; 110-150°C) [64] |
| <br>Sodium 2,2,2-bromodimethylacetate | <br>Poly(dimethyl glycolide) | Methacrylic acid, poly(methacrylic acid (Na/Br; 30-130°C)[62]; poly(dimethyl glycolide) (Na/Br; 90-180°C)[66] |

hemihydrate), 2-hydroxyisobutyric acid was also formed during the reaction.[62] However, Bezzi reported that he obtained poly(dimethyl glycolide) from sodium 2-bromoisobutyrate by heating the salt up to 90 °C,[65] 160 °C, or 180 °C.[66]

The most important poly(hydroxybutyrate) is P-3HB, as outlined above. Unfortunately, it is very difficult to prepare the corresponding precursor, sodium 3-chlorobutyrate, as elimination prevails even at low temperature. The same is true for sodium 4-chlorobutyrate. Therefore, there is no information available yet as to whether these polyesters can be obtained by solid-state polymerization.

## Poly(hydroxymethylbenzoates) by Solid-State Reaction

All previous listed reactions gave aliphatic polyesters. As mentioned in the introduction, linear polyesters with aromatic groups in their backbone are of special interest for industrial applications. The simplest halogenocarboxylic acids containing the benzene ring are halogenobenzoic acids. If the salts of halogenobenzoic acids were to undergo a polymerization reaction in which poly(hydroxybenzoic acid) were to be formed, a nucleophilic substitution on an aromatic ring system would be necessary (the chlorine atom acts as the leaving group). Therefore, strong nucleophiles or electron-withdrawing groups at the *ortho* or *para* position would be needed. The carboxylate group is an electron-donating substituent and its nucleophilicity is not very strong, thus substitution at the benzene ring appears to be unlikely. However, the polymerization of alkali *p*-halothiophenolates is possible,[11] but admittedly the thiophenoxide ion is a stronger nucleophile than the carboxylate anion. Anyway, the conditions may change in the solid state. For this reason, we prepared the alkali salts of 4-chlorobenzoic acid. No reaction was observed and decomposition took place at temperatures above 400 °C.

Introducing a benzene ring between the carbon−carbon bond in acetates leads to the formation of halogenomethylbenzoates (Table 7). Only the *meta*- and *para*-substituted compounds could be prepared, because the *ortho* compounds tend to form benzolactones by intramolecular substitution. The sodium, potassium and rubidium salts of 3- and 4-chloromethyl- and -bromomethylbenzoic acid undergo the desired polymerization to form poly(hydroxymethylbenzoic acid).[67] The lithium salts of the *para* compounds decompose at temperatures near 300 °C, without the formation of a polymeric product. This can be understood when analyzing the crystal structures of lithium 4-chloro- and 4-bromomethylbenzoate that were solved from powder-diffraction data.[68] They have a strong similarity to the corresponding acetates with the phenyl rings acting as "spacers". Lithium is tetrahedrally coordinated by four different oxygen atoms from four different carboxy groups, a fact that probably prevents polymerization. All attempts to solve the structures of the corresponding sodium or potassium compounds (that polymerize) failed, probably due to the presence of polymorphism, as suggested by solid-state NMR spectroscopy.[68]

For the *para*-halomethylbenzoates, the oxidation of the methylene group in the polyester as a side-reaction was found by IR spectroscopy. This reaction led to the formation of terephthalic acid as side product, via the carboxylic anhydride intermediate, even in the presence of small amounts of oxygen and water.

Table 7. Successful polymerization in other halocarboxylates; M = alkali, X = halogen

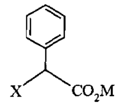
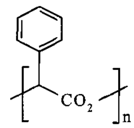
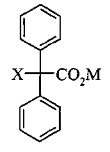
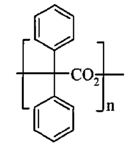
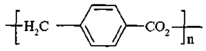
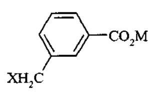
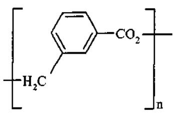
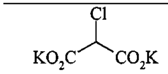
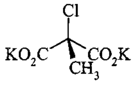
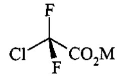
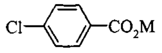
| Precursor | Polymer ($T_{fus}$) | Remarks |
|---|---|---|
|  *rac*-2,2-Halogeno-phenylacetates |  *rac*-Polymandelide (~80°C) | Unidentified solid product (Na/Cl; 117°C)[62]; polymandelide (Me$_3$Sb/Br; SnMe$_3$/Br; 170°C)[70] ; polymandelide (Na, K/Cl, Br; 70-170°C) (this work) |
|  2,2,2-Halogenodiphenylacetates |  Poly(diphenylglycolide) | (Na/Cl; 90-180°C)[66]; poly(diphenylglycolide) (SnMe$_3$/Br; 25°C)[70] |
|  4-Halogenomethylbenzoates |  Poly(4-hydroxymethyl-benzoic acid) (~250) | reacts in the solid state (Na,K,Rb/Cl,Br; 200-250°C)[68] |
|  3-Halogenomethylbenzoates |  Poly(3-hydroxymethyl-benzoic acid) (~150) | reacts in the solid state (Na,K/Cl,Br; 100-160°C)[68] |

Table 8. Unsuccessful attempts to induce polymerization in halogenocarboxylates; M = alkali, X = halogen

| Precursor | Reaction | Remarks |
|---|---|---|
|  Potassium chloromalonate | no polymerization | decarboxylation at 115°C[71] |
|  Potassium chloromethylmalonate | no polymerization | decarboxylation at 200°C[71] |
|  Chlorodifluoroacetates | no polymerization | decomposition above 160°C |
|  4-Chlorobenzoates | no polymerization | decomposition above 400°C |

## Other Polyesters by Solid-State Reaction

Besides these major classes of potential precursors to polyesters, other miscellaneous substances were investigated, sometimes with success, and sometimes without. The results can be found in Table 7 and Table 8.

When Bischoff and Walden tried to distill sodium 2,2-chlorophenyl acetate, they obtained a yellowish oil and a solid residue that melted at 117 °C. Further characterization was not carried out. The oil was not identified, and the residue was presumed to be stilbene.[69] Our recent studies on alkali 2,2-halogenophenylacetates showed that poly(mandelide) can be formed by thermal elimination of alkali halides. Similar to the halogenoacetates, the lithium salts do not polymerize, but decompose upon heating. We found a degree of polymerization (obtained by $^1$H NMR spectroscopic end-group analysis) ranging from 5 to very high numbers for sodium and potassium salts.

The first announcement of a polymeric product from 2,2-bromophenylacetates was in 1973. Okada and Okawara pyrolyzed the trimethyltin salt of the 2,2-bromophenylacetic acid and obtained poly(mandelide).[70] They also reported that the trimethyltin bromodiphenylacetate reacted in the same way. Bezzi reported the synthesis of poly(diphenylglycolide) from sodium chlorodiphenylacetate under the same conditions as for the poly(dimethylglycolide).[65]

Potassium chloromalonate and 2,2-chloromethylmalonate did not give any polymer or oligomer.[71] Instead of a polymeric product from the elimination, carbon dioxide was released in both cases at 115 °C and 200 °C. The mass loss during the reaction of potassium chloromalonate was in good agreement with the value calculated for the loss of one molecule of carbon dioxide per chloromalonate. Potassium chloride and an unidentified organic substance remained. Besides potassium chloride, the organic residue after the elimination reaction of the methylmalonate was identified as potassium acrylate.[71] The synthesis of the alkali salts of 4-bromo-2,2-diphenylbutyric acid was not successful at ambient temperature. It led to the conjugated lactone by intramolecular substitution of the bromo group by the carboxylate group.[72]

No polymerization is possible if further halogen atoms are inserted in the acetates as it is the case in di- and trichloroacetates, or in chlorodifluoroacetates. The additional halogen atoms apparently destabilize the carbon−carbon bond, resulting in bond cleavage if they are heated.

## Comparison of Polyesters from Solid-State Reaction and from Conventional Synthesis

If we summarize the preceding paragraphs, we can state that a considerable number of polyesters can be obtained from solid precursors. It remains to be discussed whether or not the obtained polymers are identical to those available from conventional synthesis.

With respect to structural or spectroscopic properties, the polyesters from solid-state reactions are often almost indistinguishable from those obtained in a classical way. The main difference is the degree of polymerization. It seems that polymers from solid-state reactions have a smaller degree of polymerization, i.e. a lower molecular weight. This property was not reported in all examples, but we can demonstrate it for polyglycolide, in which we extensively studied the properties of the polymer.[73]

Polylactide and polyglycolide from ring-opening polymerization with tin catalyst can reach molecular weights of more than 100,000 Da, representing more than 1000 monomeric units in the polymeric chain. As mentioned above, the degree of polymerization reported in the literature for solid-state chemically prepared polyglycolide is not very high. A number-average molecular weight of about 300 Da was determined by Anschütz.[26]

Detailed studies on the solid-state polycondensation reactions of sodium chloroacetate were carried out, with special attention being paid to the polymerization mechanism, and to the development of polymeric properties.[18,56−58,60,73−76] For polyglycolide, we showed that the average chain length (by viscosimetry) passes a maximum of approximately 40 monomeric units before the reaction extent reaches 1.[73] After the maximum, the chain length decreases again. This can be explained by a counterplay between the polycondensation reaction (increasing the chain length) and the thermal degradation of the formed polyglycolide. Degradation plays a minor role, as long as only few and short polymer chains are present. With increasing chain length and with a higher number of ester groups that can be cleaved, the degradation becomes dominant while the chain growth loses importance.

As in most other studies, the conditions were not optimized and in most cases a long reaction time and a high temperature were chosen to ensure that the reaction was complete. Consequently, the polyglycolide from solid-state reaction was obtained with a low molecular weight, due to thermal degradation. It may be inferred that the degree of polymerization for other polyesters from solid-state reactions could also be increased by careful choice of the reaction temperature.

If we take into account the fact that the reaction of haloacetates with polyglycolide occurs in the solid state in a topochemical way, the crystal perfection should have a strong influence on the chain length of the polymer. We speculate that in larger, perfect crystals, the chains could grow longer than in small, disordered crystals in which a defect (such as a dislocation) would lead to chain scission. This statement may be limited by the fact that the single-crystalline order is destroyed during the reaction, probably due to volume change, but nevertheless it remains an interesting assumption.[77] However, this has not been investigated so far for any solid-state polycondensation reaction.

A special feature of polyesters from solid-state reactions is their distinct micromorphology. Generally, a nonvolatile salt is eliminated, and thus the reaction must lead to an intimate mixture of polymer and salt. The geometry of both phases is determined by nucleation and diffusion. In the cases that we have studied (polyglycolide, polylactide, poly(hydroxymethylbenzoic acid)], we have always found micrometer-sized salt crystals within the polymeric matrix. These can be conveniently removed by washing the polymer with water, leaving behind a polymer with micrometer-sized pores.[18,67,78]

The dependence of the pore size on the precursor was studied for polyglycolide. Figure 6 summarizes scanning-electron micrographs of polyglycolide from various halogenoacetates. There are considerable differences in the product morphology. Their origin is not known, but it is clear that the size of the pores (identical to the size of the precipitated salt crystals) depends on the kind of salt that is eliminated. However, it must be noted that different polyglycolides were obtained at different reaction temperatures for each precursor. The highly porous structure of polyglycolide may be advantageous for biomedical applications. Less material has to be absorbed by the body, and a free flow of body fluids is possible through such a highly porous implant. We recently demonstrated the excellent biocompatibility of composite implants of both porous and compact polyglycolide with calcium phosphate.[9]

## Do These Reactions Really Occur in the Solid State?

All reactions that yield a polymer are initiated in the solid state, i.e. before the melting of the substance is observed. In

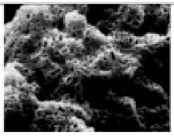
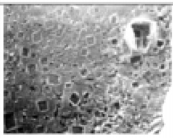
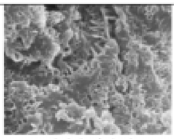
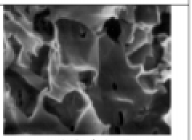
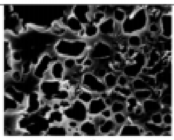
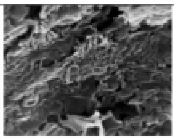
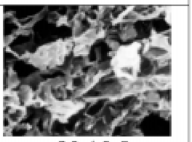
| | Cl | Br | I |
|---|---|---|---|
| Na | <br>260 / 0.3 | <br>460 / 0.3 | X |
| K | <br>280 / 0.3 | <br>855 / 0.3 | <br>14 / 1.5 |
| Rb | <br>30 / 1.1 | <br>260 / 0.4 | <br>90 / 0.8 |
| Cs | X | X | <br>65 / 0.9 |
| Ag | <br>240 / 0.4 | <br>17 / 0.9 | X |

Figure 6. Polyglycolide from the solid-state reaction of various precursors; the polymers were washed out with water (in the case of silver salts, with sodium thiosulfate solution), to obtain the porous polymer; the magnification is 4020× in all cases, and the printed section is approximately 12.5 × 9.5 µm$^2$; the table illustrates how the different pore-size distribution is dependent on the precursor; X means that the polymer could not obtained in a pure form by solid-state polymerization reaction; the two numbers for each polymer give the number of pores per 100 µm$^2$, and the average pore size in µm (computed by analysis of larger areas than shown here)

the case of a reaction temperature being higher than the melting point of the corresponding polyester (such as polylactide), the reaction mixture will liquefy with increasing conversion. On the other hand, if the reaction temperature is lower than the melting point of the polyester, a true solid-state reaction is possible (as is the case with polyglycolide). Both cases have been observed. In general, it is rather difficult to unequivocally prove that no liquid intermediates are present. It has been shown for polyglycolide formed from halogenoacetates (see above), but in most other cases there might be temporary liquefaction, followed by recrystallization.

Nevertheless, systems with high-melting polymers can also liquefy locally during the reaction owing to poor heat conduction in powders and subsequent self-heating of the mixture. Polyakov et al. showed that for sodium chloroacetate, a high-temperature gradient appeared inside the reaction vessel between the center of the reactor and the wall. The heat difference reached up to 100 K, depending on the reactor diameter and on the external temperature. This self-heating caused the sample to melt, and in extreme cases the polyester was pyrolyzed.[46] In order to prevent this, it is possible to choose other reactor types with better heat conductance, such as fluid-bed reactors, or to add inert materials such as copper turnings to obtain a better conduction.

## Conclusion

Many polyesters can be prepared without solvent. Unfortunately, the reaction pathway theoretically formulated beforehand is not always actually feasible. This is due to the peculiarities of solid-state reactions in which the crystal structure and intracrystalline interactions play a dominant role. This is a major difference from chemistry in solution, where the concept of functional groups is of decisive influence. In addition, thermodynamic data are usually not available and hence proposed reactions have to be tried out, and cannot be predicted.

Side-reactions that lead to different reaction pathways may occur. Possible side-reactions are:

- hydrolysis of the halogen group in the presence of moisture
- elimination of HX leading to the formation of unsaturated carboxylic acids
- decarboxylation
- cyclization to form lactones
- oxidation of the organic residue

However, the new properties of the resulting polymers (such as the porous micromorphology) may lead to applications in special cases. In any case, this is a fascinating field of research where expertise from solid-state chemistry, organic chemistry, physical chemistry and polymer chemistry can be combined to draw conclusions about the underlying processes.

## Acknowledgments

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous support during the preparation of this work. We also thank our collaborators who performed many of the reported experiments, their names are given in the citations.

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Received August 29, 2000
[I00329]