Syntheses of Biodegradable and Biocompatible Polymers by Means of Bismuth Catalysts

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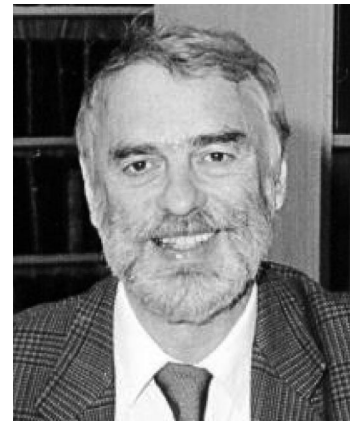

Hans Rytger Kricheldorf was born and educated in Germany. He obtained his diploma and Ph.D. in Chemistry from the University of Freiburg i.Br. He continued his academic career in Freiburg i.Br. with tenure (Habilitation) in 1975 and was appointed associate professor in 1980. In 1982 he took over a full professor position for polymer science at the University of Hamburg. His research activities concern two life-long working fields, namely ring-opening polymerization and polycondensation. His preparative work mainly concerned biodegradable polymers, thermostable engineering plastics, and liquid-crystalline polymers. More recently his research interests also focus on syntheses of cyclic and multicyclic polymers.

1. Introduction

Since polymer chemistry became a widely accepted branch of science after WWI, academic research and technical production of polymers has mainly concentrated on materials with the highest possible chemical and thermal stability. Yet, over the past two decades, the interest in biodegradable polymers has rapidly increased and thousands of publications and patents dealing with their preparation and characterization have meanwhile appeared. The most important group of biodegradable polymers are polyesters, which allow for a broad variation of their structure and properties, and thus, enable optimization for a broad variety of applications. Resorbable medical sutures, drug-delivery systems, resorbable and transparent films for wound dressing, or films designed for agricultural applications should be mentioned as representative examples.

Aliphatic or semialiphatic polyesters (i.e., polyesters derived from aliphatic diols and aromatic dicarboxylic acids) possess a handful of useful properties. For instance, polyesters based on aliphatic hydroxy acids or dicarboxylic acids are biodegradable in such a sense that they hydrolyze either in the human body or upon composition at temperatures $\leq$ 50 °C. The rate of hydrolysis depends, of course, on their structure, on their surface, and on the presence and size of the crystallites. Semialiphatic polyesters may be at least biocompatible, which means implants may have good blood and tissue compatibility, and if slow degradation takes place, the degradation products are nontoxic. Both groups of polyesters are not immunogenic, in contrast to the case of biodegradable polymers resembling or derived from biopolymers. Furthermore, physical and mechanical properties can be varied over a broad range by variation of crystallinity, glass-transition temperature (T_g), and melting temperature (T_m).

The technical production of both aliphatic and semialiphatic polyesters follows two synthetic strategies: either ring-opening polymerization (ROP) of cyclic esters (including cyclic carbonates and cyclic oligoesters) or polycondensation of α,ω-dihydroxyalkanes with dicarboxylic acids or their di(m)ethyl esters. Both strategies require a catalyst or initiators. In the case of nonbiodegradable polymers, the only criterion for the quality of a catalyst or initiator is its performance. A high performance may be defined by the following points:

(A) high productivity, which means rapid polymerizations and large quantities of polymers per molecule of catalyst;
(B) high molar masses should be accessible;
(C) initiator or catalyst allows for tailor-making the molar masses;

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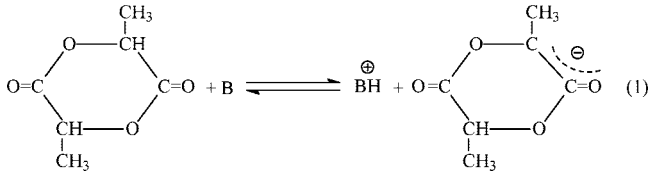
Scheme 1. Mechanism of the Base-Catalyzed Racemization of L-Lactide



(1)

(D) narrow molar mass distributions are desirable for syntheses of block copolymers;
(E) various architectures should be accessible (e.g., random copolymers, block-copolymers, star-shaped polymers, etc.);
(F) side reactions should be suppressed.

In the case of biodegradable polymers designed for pharmaceutical or medical applications, a new criterion comes into play, namely the toxicity. The most widely used group of initiators and catalysts for ROP of lactones and other cyclic esters is tin compounds. Three factors are responsible for this fact. First, the excellent performance of many tin compounds as initiators or catalysts. Second, the easy synthesis (and good thermostability) of a broad variety of tin compounds, which allows one to vary their reactivity over a broad range and to optimize their reactivity for selected reaction conditions. Third, tin(II)-2-ethylhexanoate ($SnOct_2$) has been admitted by the American Food and Drug Administration (FDA) as a food stabilizer. This application is based on the fact that $SnOct_2$, like most tin compounds, possesses a rather high cytotoxicity. This means tin compounds are toxic for the metabolism of almost any kind of cells and, thus, for almost any kind of living organism. Therefore, tin compounds have broad applications as antifouling agents, for instance in paints for ships and other marine objects. This situation has prompted several research groups to look for a less toxic group of catalysts and initiators with a performance similar to that of the tin compounds. In this context, sodium, potassium, magnesium, calcium, iron, manganese, and zinc salts, and complexes were examined for their usefulness as catalyst or initiators, because they play a role in the human metabolism. Although a full review of all the studies published in this field cannot be given here, a few important aspects should be mentioned. Sodium, potassium, magnesium, and calcium exist in relatively large quantity in the human organism and possess certainly the lowest toxicity of metals under consideration.

However, those Na- and K-salts which are catalytically active (e.g., oxides, carbonates, acetates, etc.) rapidly racemize L-lactide above 120 °C[1] in the melt, and the alkoxides cause racemization even at room temperature.[2] The racemization is based on the α-deprotonation of the monomer (Scheme 1) and has the additional disadvantage that the resulting anion can initiate a new chain. Such a frequent reinitiation has, in turn, the consequence that only low molar mass polylactides can be obtained. The problem of deprotonation and reinitiation (chain transfer) also exists for homo- and copolymerizations of glycolide. This problem is aggravated by the fact that technical production of homo- and copolymers of lactide or glycolide is conducted in the melt at temperatures ≥ 150 °C. Therefore, salts and complexes of magnesium and calcium are also useless for technical syntheses,[1,3] and for the highly reactive dibutyl magnesium it was found that it racemizes L-lactide even at 20 °C in solution.[4]

The risk of deprotonation of lactide and glycolide is rather low for iron[3,5−7] and manganese salts[8] or complexes, but their performances as initiators or catalysts are also low. Furthermore, the toxicity of manganese salts in any kind of internal applications is rather high.[9] Fe-alkoxides are far more reactive than Fe-salts and allow efficient polymerizations of lactides and lactones below 100 °C,[10−12] but they are not thermostable enough for technical polymerizations of lactide (or glycolide) in the melt. Zinc salts and complexes seemingly represent the best compromise, but their performance is definitely lower than that of $SnOct_2$ and other tin-based initiators and their toxicity may be higher than that of bismuth, as discussed below. Numerous papers dealing with aluminum alkoxides as initiators for ROPs were published and a complete citation is beyond the scope of this introduction. The performance of Al-based initiators may be high,[23−25] but when used for polymerization of L-lactide or glycolide in the melt, the risk of racemization and other side reactions resulting from deprotonation is also high and Al^{3+} ions are suspected to favor several diseases (e.g., Alzheimer). Quite recently, a handful of papers has appeared describing ROPs initiated by zirconium, alkoxides, and complexes.[26−30] It seems that Zr-salts possess a lower toxicity than tin salts, but no comparison with Zn- or Bi-salts has been reported and neither a pharmaceutical nor a medical application is known. Furthermore, the problem of deprotonation and racemization above 120 °C has not been studied yet. As shown below, Bi-salts have a long tradition as external and internal drugs and possess a particularly low toxicity, although Bi-ions do not play any role in the human body. Therefore, it seemed to be worthwhile to explore the usefulness of Bi-compounds as initiators or catalysts for the preparation of biodegradable and biocompatible polymers.

2. Medical Application, Toxicity, and Reactivity of Bismuth Compounds

Cosmetic and pharmaceutical applications of bismuth compounds have a 250-year-old history which has more or less explicitly been discussed in several review articles.[31−37] Prior to any discussion of details, it seems to be advisible for a review article in the field of polymer chemistry to define the term toxicity. The classical definition goes back to Paracelsus von Hohenheim (1493−1541): "Dosis sola facit venemem", freely translated: "the quantity alone is decisive for the toxic effect". This definition is decisive for a proper understanding of the risk connected to the amount of initiator or catalyst present in a biodegradable polymer designed for pharmaceutical or medical applications. In their recent review article,[37] Briand and Burford summarized almost all patents and publications dealing with the physicochemical characterization of bismuth compounds and their biological or medicinal relevance. That review article comprises more than 1000 references, which makes clear that this section of the present review cannot serve the purpose to mention and discuss all these data again. Therefore, it is the intention of the author to present only a selection of facts and papers which highlight typical properties of bismuth compounds.

The most widely used and intensively studied bismuth compounds are bismuth subnitrate (BSN), bismuth subsalicylate (BSS), colloidal bismuth subcitrate (CBS), and tripotassium dicitrato bismuthate (TDB). It is characteristic for numerous O-containing bismuth salts and complexes that they form μ-oxo-bridged cage structures and clusters which are poorly soluble in inert solvents and, thus, not easy to characterize. In the case of BSN, which in a pure form corresponds to the formula $[Bi_6O_4(OH_2)_4](NO_3)_6 \cdot 4H_2O$, the

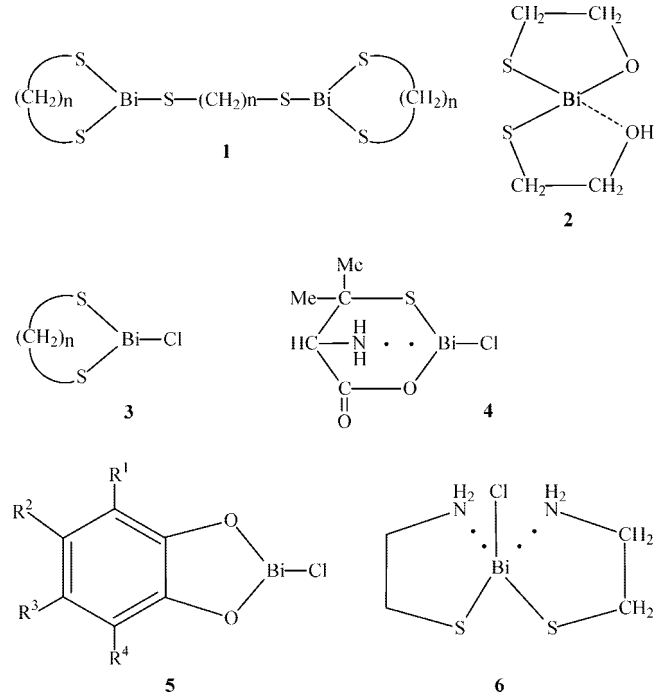
crystal structure has been determined.[38] This bismuth salt has been utilized for cosmetic application since the beginning of the 17th century under the "trademark" "magisterium bismuti". Even in the 20th century, basic bismuth salts such as the oxide and the subcarbonate served for external application as major ingredients of ointments designed for skin care and treatment of infected skin and burn wounds. European trademarks of such ointments are Xeroderm, Noviform, and Dermatol.

The most common applications of bismuth compounds concern gastrointestinal disorders.[39−62] For instance, BSS has a tradition of almost 100 years as an over-the-counter drug (under the U.S. trademark Pepto-Bismol) against travelers' diarrhea,[39−43] against nonulcer dyspepsia,[44,45] and against other gastrointestinal complaints.[33] All three, BSS, CBS, and TDB, were widely used and studied during the past decades in therapies against duodenal and stomach ulcers.[31,33,35,39,41,44,45,47−58] More recently, their interaction with the bacterium Heliobacter pylori, which is involved in the pathogenesis of gastroduodenal ulcers, has attracted much interest.[40,41,56,59−62] Further studies and potential applications concern treatment of syphilis,[63−67] tumors,[68,69] radiotherapy,[70,71] and the reduction of the renal toxicity of "cisplatin".[72]

In this context, two toxicity studies which are particularly informative should be mentioned. Rodilla et al.[73] compared the toxic influence of $CdCl_2$, $HgCl_2$, $ZnCl_2$, and $Bi(NO_3)_3$ on cultured human kidney tubular cells. The results showed that bismuth ions were not toxic even at the highest dose (0.1 mmol), while the other three metal ions exhibited various degrees of toxicity, decreasing in the following order: Hg > Cd > Zn. It is remarkable that bismuth proved less toxic than zinc, although small amounts of zinc are needed in the human metabolism. In the second toxicity study,[74] one of the few patients which were (worldwide) found to suffer from intoxication by bismuth compounds was examined in a hospital in various directions. This patient, a 54 year old man, had consumed 8 ounces of BSS every day over a period of several months. With such a high dose of Cd-, Pb-, or Hg-salts, he had hardly survived one week. The toxic effects of BSS concerned beginning delirium, psychosis, ataxia, myoclonus, and seizures. Surprisingly, this patient recovered almost completely from this intoxication within three months after the intake of BSS was stopped. The standard, nontoxic dose of Pepto-Bismol is 1−3 g per day.[75] These amounts should be compared to the single dose of 1−10 mmol of Bi-salts, which a patient will "take in" from an implantation of biodegradable polyesters. For instance, 0.5 g of drug-delivery system based on a polylactide prepared with a monomer/initiator (M/I) ratio of 500:1 corresponds to 1.4 mg of Bi^{3+}. A plate and screws made from 15 g of polylactide polymerized with a M/I ratio of 1000/1 corresponds to 21 mg of Bi^{3+}. Therefore, it may be concluded that the amounts of bismuth needed as initiator or catalyst for the preparation of biodegradable materials do not involve any risk of intoxication.

Since bismuth(V) salts are strong oxidizing agents, all stable Bi-salts considered for medical application or as polymerization catalysts and initiators are Bi(III) salts and compounds. $Bi(NO_3)_3$ is the only commercial bismuth salt with good solubility (and sufficient stability) in water. $BiCl_3$ has moderate solubility in several polar organic solvents, but it is sensitive to irreversible hydrolysis, yielding insoluble, ill-defined bismuth hydroxides/oxides. The poor solubility of most Bi-salts and compounds can be overcome in the case

Scheme 2. Cyclic Compounds and Complexes of Bi Reported in the Literature



of acidic complexes (such as the monomeric Bi-citrate), which turn soluble in water by addition of various amines. For instance, the adduct of Bi, citrate and Ramitidin, a histamine antagonist, has recently been commercialized as a new water-soluble drug.[76,77]

Like tin, bismuth has a high affinity to sulfur, forming thermodynamically stable sulfide bonds which are insensitive to hydrolysis at moderate temperatures and over a wide pH range. For instance, the trissulfide derived from Bi^{3+} and three cystein molecules is stable between pH 2 and 10.[78] Bi^{3+} can replace Zn^{2+} in the cystein-rich protein metallothionein,[20] and it forms stable complexes with glutathion.[79,80] Therefore, it is obvious that the interaction of bismuth with the SH group of proteins plays a major role for its usefulness as a drug and for toxic effects. This stability of the Bi−S bond is responsible for its low reactivity, with the consequence that Bi-compounds exclusively built on Bi−S bonds are useless as catalysts or initiators for polymerizations of lactones or for other transesterification reactions at low or moderate temperatures (e.g., <150 °C). Therefore, all bismuth salts or complexes successfully used so far as initiator or catalysts for syntheses of polymers contain Bi−O bonds or Bi−Cl, Bi−Br, and Bi−J groups. From tin compounds, which resemble in many aspects analogous Bi-compounds, it is known that the reactivity in any kind of transesterification reactions decreases in the order Sn-SR < SnO_2C-R < Sn-OAryl < Sn-OAlkyl.

Qualitatively, the same order seems to be valid for Bi-compounds. In other words, the highest reactivity is expected for initiators and catalysts possessing Bi-alkoxide groups. Unfortunately, simple Bi-alkoxides such as $Bi(OR)_3$ are rather difficult to synthesize,[81,82] and their thermostability is particularly low (in contrast to Sn-alkoxides). Particularly interesting as reactive "single-site initiators" for ROPs of lactones and cyclic diesters are Bi-compounds containing one alkoxide group. A first example for the usefulness, which will be discussed below, is complex **2** (Scheme 2).[83] Diphenyl bismuth methoxide or ethoxide are known[84] and stable up

to approximately 100 °C. The first results illustrating the usefulness of Ph_2BiOEt as initiator for the ring-opening polymerization of ε-caprolactone (εCL) or trimethylene carbonate (TMC) will be presented below. Furthermore, numerous complexes containing one Bi−Cl group are known (e.g., formulas **3**−**6**).[85−97] If it is feasible to transform the Bi−Cl bond into a Bi alkoxide group, such complexes may be promising initiators, but until the end of the year 2008, no information on this aspect was available yet. This short comment has the purpose to demonstrate that the field of Bi-based initiators is still in its infancy and considerable progress may be expected in the future.

3. Ring-Opening Polymerizations

3.1. Homopolymerizations of Cyclic Esters Catalyzed by Bi(III) Salts

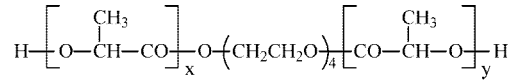
To the best of our knowledge, the first report on a polymerization of a cyclic ester catalyzed by a Bi-compound was published in 1985[1] and dealt with the homopolymerization of L-lactide at higher temperatures (120−180 °C) in the bulk. The purpose of that study was to find out which metal salts allow for a racemization free polymerization of L-lactide under conditions required for the technical production of homo- and copolylactides. From anionic polymerizations of L-lactide in solution, it was learned[2] that L-lactide is highly sensitive to base-catalyzed racemization, because the α-proton is rather acidic ($pK_a \approx 16 \pm 2$). The resulting carbanion (Scheme 1) is delocalized and trigonal planar, so that reversible protonation/deprotonation automatically involves racemization. Twenty-three metal salts were compared in that study,[1] including Bi(III) 2-ethylhexanoate ($BiOct_3$). When compared under rather harsh conditions (i.e., 48 h at 180 °C), $BiOct_3$ caused less racemization than any other metal salts, including $SnOct_2$.[1,3]

More recently, polymerizations of L-lactide with a Bi(III) acetate/alcohol combination were studied in detail.[98] These polymerizations were performed in concentrated chlorobenzene solutions at 120 °C. Tetra(ethylene glycol), TEG, 1,1,1-trimethylol propane, or pentaerythritol served as initiators, so that telechelic or star-shaped poly(L-lactide)s of structures **7**−**9** were obtained (Scheme 3). The full incorporation of the initiators via ester bonds was confirmed by ^{1}H NMR spectroscopy and MALDI-TOF mass spectrometry. A comparison of $BiAc_3$/TEG with $SnOct_2$/TEG under identical conditions revealed that $SnOct_2$ is the more reactive catalyst. Nonetheless, even $BiAc_3$ causes transesterification in the form of "backbiting" degradation at 120 °C, as evidenced by the presence of cyclic oligolactides in all mass spectra. In this regard, the Bi-salts are not significantly different from other conventional initiators/catalysts, when compared at the same temperature (i.e., ≥100 °C). However, the mass spectra and SEC measurements agree in that the weight fraction of the cyclic oligomers is of the order of 1 wt % or less.

Regardless which alcohol was used as initiator, the monomer−initiator ratio (M/I) was varied from 20 to 160. Since the ^{1}H NMR spectra indicated almost 98% conversion, they allowed the calculation of the average number molecular weights (M_n's) from end group signals. These M_n's were in good agreement with the M/I ratios, and M_n's up to 23 000−24 000 Da were obtained.

Analogous polymerizations were conducted with ε-caprolactone (εCL), so that the di-, tri-, and tetrafunctional polylactones **10**, **11**, and **12** were isolated (Scheme 4).[99] The

Scheme 3. Telechelic and Star-Shaped Polylactides Prepared by $BiAc_3$-Catalyzed ROPs of L-Lactide



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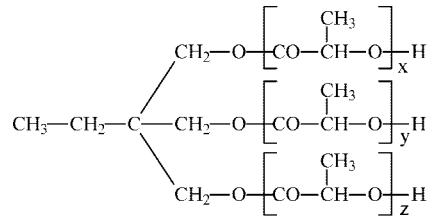

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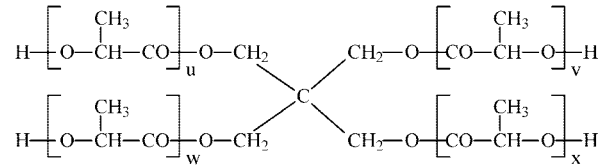

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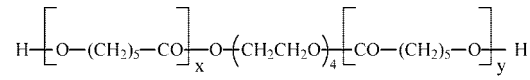
Scheme 4. Telechelic and Star-Shaped Polyesters Prepared by $BiAc_3$-Catalyzed ROPs of ε-Caprolactone



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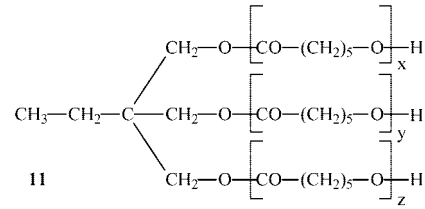

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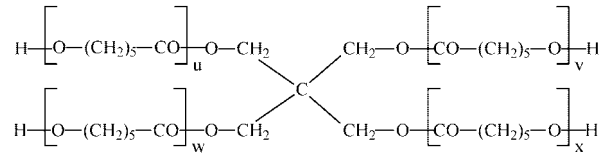

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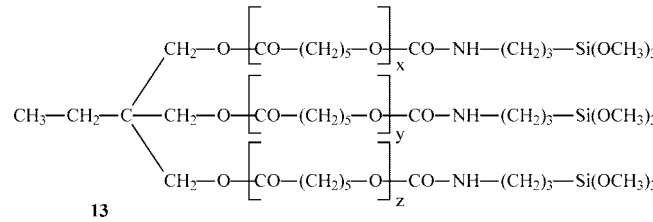

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mass spectrum presented in Figure 1 proves that even coinitiation with pentaerythritol at 150 °C was rather a clean process. Again, the M_n's paralleled the feed ratios, and the M_n's determined by ^{1}H NMR spectroscopic end group analyses were in satisfactory agreement with SEC measurements. Yet, at this point, it should be emphasized that the conventional calibration of SEC curves with polystyrene standards overestimates the real molecular weights of poly(εCL) and other aliphatic polyesters by more than 50%. This relationship was proven by several research groups[100−107] using a variety of analytical methods. Therefore, the M_n (and M_w) data obtained by direct calibration with polystyrene need to be multiplied with a correction factor of 0.54−0.60 for

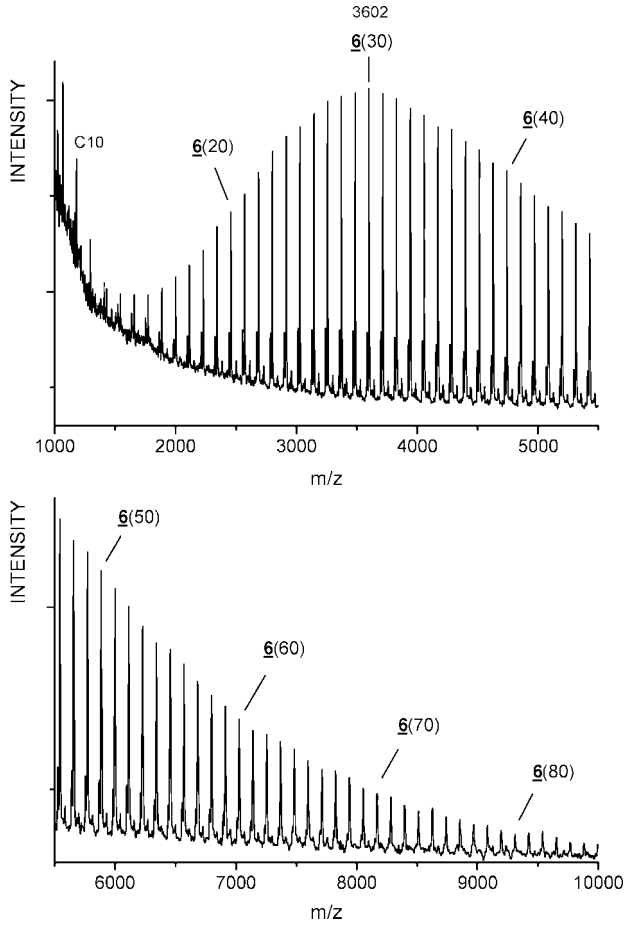
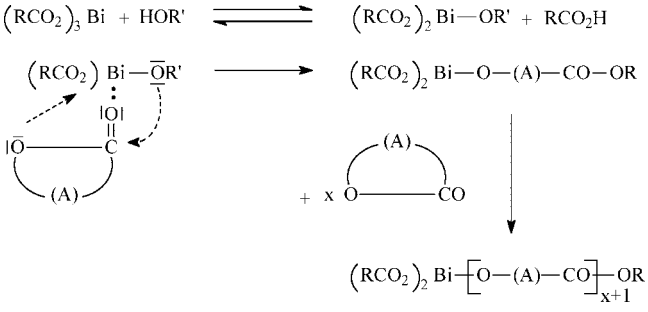


Figure 1. MALDI-TOF mass spectrum of a star-shaped poly(εCL) initiated with pentaerythritol and $BiAc_3$ in bulk at 150 °C (the numbers in parentheses indicate the degree of polymerization). Reprinted with permission from ref 99. Copyright 2004 American Chemical Society.

Scheme 5. Simplified Presentation of the Coordination−Insertion Mechanism Initiated by the Combination of a Bi(III) Salt and an Alcohol



low M_n's or 0.67 for high M_n's. Alternatively, the Mark−Houwink eqs 2[84] can be used for calibration of poly(ε-caprolactone). Finally, it should be mentioned that the SEC measurements gave polydispersities in the range of 1.4−1.5.[99]

The results obtained with homopolymerizations of L-lactide and εCL suggest that the polymerization mechanism largely follows the mechanism which was previously elaborated by two research groups for polymerizations initiated by $ScOct_2$ (Sn(II)2-ethylhexanoate)[104,108,109] in combination with alcohols. As outlined in Scheme 5, this mechanism begins with the reversible exchange of one (or more) carboxylate groups against an alcohol, whereby a highly reactive Bi-alkoxide group is formed which is the true initiator of the polymerization process. The propagation steps obey the definition of a coordination−insertion mechanism, as it was found for various metal alkoxide-initiated polymerizations.[110] As discussed below, this mechanism is supported by the results of Ph_2Bi-OEt-initiated polymerizations.

In a separate study,[111] syntheses of telechelic or star-shaped poly(εCL) and poly(L-lactide) were repeated using Bi(III) *n*-hexanoate ($BiHex_3$) as catalyst. The resulting OH-terminated polyesters were in situ reacted with 3-isocyanatopropyl trimethoxysilane or triethoxysilane. It was found that $BiHex_3$ also catalyzed the addition of the OH-end groups onto the isocyanate without causing side reactions with the trimethoxysilyl group. In that study, several trimethoxysilyl-terminated polylactones and polylactides were prepared, as exemplarily illustrated by formula **13** (Scheme 4). The trimethoxysilyl group is far more sensitive to hydrolysis than the polyester chains and the liberated Si−OH groups easily react with each other or with OH-groups on surfaces of paper, wood, ceramics, or oxidized metals. Therefore, functionalized polylactones such as **13** may be applied as biodegradable adhesives or as precursors for the preparation of hybride networks.

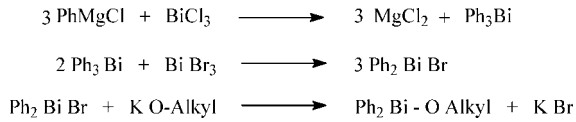
Quite recently, the usefulness of BiF_3, $BiCl_3$, $BiBr_3$, and BiJ_3 as catalysts for the polymerization of εCL was studied.[112] All polymerizations were conducted in bulk at 100 or 120 or 140 °C. BiF_3 was found to be unreactive, presumably to a particularly stable crystal lattice combined with an extremely low solubility in εCL. Kinetic measurements indicated that the reactivity of the other Bi-halides increased in the order $BiCl_3 < BiBr_3 < BiI_3$.

Furthermore, the highest molecular weights were obtained with BiI_3. ^1H NMR end group analyses revealed that two types of chains were formed (in addition to small amounts of cyclic oligomers): chains having one CH_2OH plus one CO_2H end group and chains having one CH_2X plus one CO_2H group. The CH_2OH/CH_2X ratio increased in the order $BiCl_3 < BiBr_3 < BiJ_3$ and suggested that the BiX_3 initiated/catalyzed polymerization proceeded by a coordination−insertion mechanism involving Bi-OCH_2 end groups. These active end groups yield CH_2OH end groups in contact with moisture or methanol. The highest molecular weights resulting from BiJ_3-catalyzed polymerizations approached M_n values around 120 000 Da (uncorrected SEC data). In other words, only BiJ_3 proved to be superior to Bi-carboxylate catalysts with regard to high M_n's.

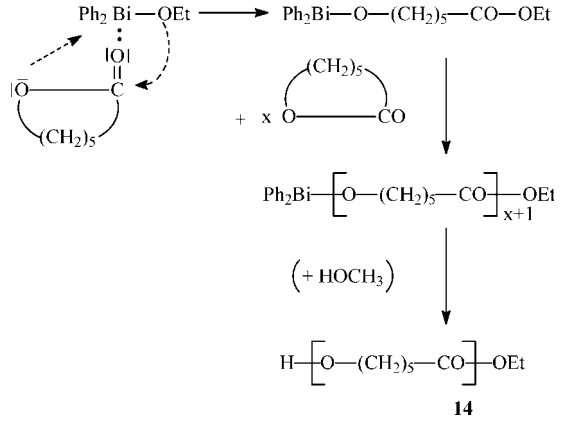
3.2. Homopolymerizations Initiated by Phe_2Bi Compounds and Bi-Complexes

Bismuth salts such as $BiAc_3$, Bi(*n*-hexanoate)$_3$, Bi-subsalicylate, BiO_3, or $BiCl_3$ have the advantages to be commercial, inexpensive, stable on storage, and nontoxic in the quantities needed as initiators. However, they are less reactive than $SnOct_2$, and they are not suited to prepare high molar mass polylactones, which means number average molecular weights above 50 000 Da.[113] Furthermore, the control of the molecular weight requires addition of an alcohol as coinitiator. Therefore, a reactive single site initiator, meaning a Bi-compound having one Bi-alkoxide group, was expected to overcome these shortcomings. The only Bi-compounds described in the literature which obey the definition of a reactive single site initiator were diphenyl bismuth alkoxides.[84] There synthesis is outlined in Scheme 6.[84,114,115] This reaction pathway has the advantage that a broad variety of diphenyl bismuth alkoxides can be prepared as soon as Ph_2BiBr is available. Yet, the only Bicompound of this kind used as initiator so far was Ph_2BiOEt.

Scheme 6. Syntheses of Diphenyl Bismuth Alkoxides



Scheme 7. Mechanism of Ph_2BiOEt-Initiated Polymerization of εCL



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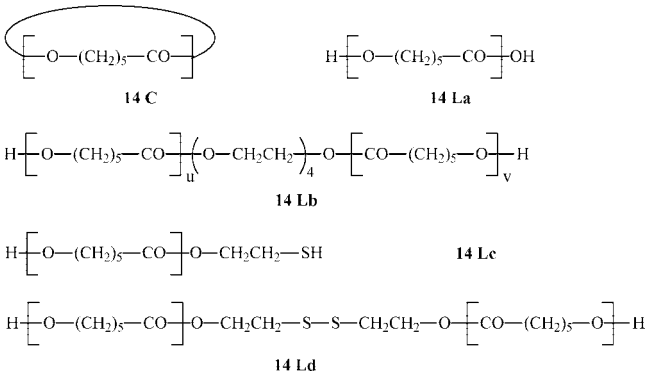
MALDI-TOF (MT) mass spectra of poly(εCL) prepared in bulk by initiation with Ph_2BiOEt indicated that the polymerizations followed the coordination−insertion mechanism outlined in Scheme 7.[113] All linear chains had the structure **14**, and small amounts cyclic oligolactones were the only byproducts. Also in line with the mechanism of Scheme 7 is the finding that the M_n's could be controlled via the M/I ratio. Up to a M/I of 1000 corresponding to a M_n of 115 000 Da, a satisfactory parallel was observed. Yet, regardless of the M/I, relatively high polydispersities (in the range of 1.7−2.3) were found. Time−conversion curves revealed a sigmoidal shape, in contrast to time−conversion curves of $SnOct_2$ (plus alcohol) or in contrast to Bi(*n*-hexanoate)$_3$, $BiHex_3$, plus alcohol-initiated polymerizations. The sigmoidal shape indicates an activation process in the earliest stage of the polymerization, and this activation may result by solvation and dissociation of an originally associated Ph_2BiOEt species. This interpretation is supported by two findings. First, tetrahydrofuran also caused an activation, when compared to nondonating reaction media such as dichloromethane or toluene. Second, the crystal structure analysis of Ph_2BiOEt demonstrated that the O-atoms form a bridge between two Bi-atoms, and thus, the donor−acceptor interactions between O-electrons and free Bi-orbitals are most likely responsible for the association in solution. Another interesting finding concerned the temperature dependence of the reactivity. In agreement with the polymerization mechanism outlined in Schemes 1 and 3, Ph_2BiOEt proved to be more reactive than $BiHex_3$ plus alcohol at any temperature (compared between 90 and 120 °C). When compared to $SnOct_2$ plus alcohol, Ph_2BiOEt was slightly less reactive at 120 °C but showed an almost equal reactivity at 90 °C and a considerably higher reactivity at 60 °C. Ph_2BiOEt allowed for a slow polymerization of εCL even at 20 °C.[111]

These positive results had the consequence that the reactivity of Ph_2BiBr, the precursor of diphenyl bismuth alkoxides, was also studied.[116] It indeed initiated or catalyzed polymerizations of εCL in bulk at temperatures ≥ 40 °C. It turned out to be somewhat less reactive than Ph_2BiOEt and, thus, significantly less reactive than $SnOct_2$ (+ alcohol). However, this is only valid for temperatures > 40 °C, whereas at 40 °C Ph_2BiBr proved to be slightly more reactive than $SnOct_2$ in combination with alcohol. Furthermore, Ph_2BiBr was found to be significantly more reactive as initiator than $BiBr_3$. Since $BiBr_3$ is the stronger Lewis acid, this comparison suggests that Ph_2BiBr does not catalyze a cationic polymerization but rather a coordination−insertion mechanism in combination with traces of water or a purposely added alcohol as (co)initiator. From the preparative point of view, it was particularly interesting to see that Ph_2BiBr yielded poly(εCL) with corrected M_n's up to 500 000 Da (760 000 Da by direct comparison with polystyrene). Furthermore, polycarbonate having M_n up to 300 000 Da was obtained from Ph_2BiBr-initiated polymerizations of trimethylene carbonate (TMC) in bulk at 120 °C.[117] Yet, regardless if εCL or TMC was polymerized, a proper control of M_n via the M/I ratio was not feasible. This disadvantage may be overcome by addition of an alcohol. Using tetra(ethylene glycol), TEG, as coinitiator, telechelic poly(εCL) was prepared with full incorporation of TEG, and the M_n paralleled the εCL/TEG ratio. Concerning Ph_2BiBr-initiated polymerizations of TMC, it is also worth noting that this Bi-compound proved to be more reactive as initiator than $SnOct_2$ + alcohol at all temperatures between 40 and 120 °C.

For the sake of curiosity, Ph_3Bi, the precursor of Ph_2BiBr, was also studied with regard to its potential as initiator.[118] Considering the polymerization mechanism of Schemes 5 and 7, Ph_2Bi should be an inert Bi-compound. However, experiments with εCL performed at 120 °C revealed that Ph_3Bi initiates or catalyzes polymerizations of εCL in bulk, when a sufficiently long reaction time is allotted. High molar mass poly(εCL) was obtained (corrected M_n's up to 300 000 Da were obtained), but attempts to control M_n via the M/I ratio failed. Yet, a control of M_n was achieved by addition of TEG as co-initiator. The M_n's paralleled the εCL/TEG ratio. These findings lead to the question, if Phe_3Bi reacts with lactones via a pentacovalent transition state (hypothesis I) or if side reactions produce an active Ph_2BiOR species which initiates the normal coordination−insertion mechanism (hypothesis II). A first clue toward hypothesis II was provided by the time conversion curves, which showed a sigmoidal shape with an unusually long induction period. This induction period suggests that a side reaction occurs, generating a Ph_2BiOR species, which, in turn, plays the role of the initiator. Several model reactions conducted with controlled addition of O_2 water, or TEG, or conducted by heating of neat Ph_3Bi in various solvents revealed that Ph_3Bi is unstable at temperatures ≥ 100 °C and slowly yields insoluble products which seemingly consist of polymeric PBiO. All these results together clearly favor hypothesis II. Side reactions yielding Bi−O bonds are required to activate Ph_3Bi. From the preparative point of view, Ph_3Bi proved to be less attractive than Ph_2BiOEt or Ph_2BiBr, because of the long and impredictable induction period.

Finally, polymerization of εCL initiated with the mercaptoethanol complex **2** should be discussed.[119] This complex has one important structural aspect in common with Ph_2BiOEt; namely, it possesses one Bi-alkoxide bond. Therefore, it was expected that its reactivity is higher than that of $BiHex_3$ (or other Bi(III) salts), and this expectation was confirmed by measurements of time−conversion curves.[119] Furthermore, it was found that its reactivity was comparable with that of $SnOct_2$ (at 140 °C) regardless if TEG was added or not. However, the shapes of the time−conversion curves were quite different, because a sigmoidal curve was

Scheme 8. Reaction Products of 2-Initiated Polymerizations of εCL as Revealed by MT Mass Spectrometry



found for $SnOct_2$ but not for the complex **2**. The reaction products of the TEG-coinitiated polymerizations were rather complex, because, in addition to cyclic oligoesters, linear chains of structure **La**, **Lb**, and **Lc** were found (see Scheme 8 and Figure 2). In the absence of TEG, a clean product was obtained having the unexpected telechelic structure **Ld**. If the formation of the disulfide group was an automatic consequence of the reaction mechanism including a redox reaction of Bi^{3+} or it was caused by oxidation during the workup of the reaction mixture was not clarified. Nonetheless, polymerizations initiated by complex **2** are of theoretical interest, because they represent the first example of a ring-expansion polymerization initiated by Bi-compounds (Scheme 9). Since both O-atoms in complex **2** are, in principle, equivalent because the O-proton can rapidly move from one O-atom to the next, it is most likely that both mercaptoethanol units act as initiators, so that the reaction products will most likely possess structure **16** and not **15**. In this context, it should be mentioned that ring-expansion polymerizations are known from numerous cyclic tin or germanium alkoxides.[120−122]

3.3. Stereocopolymerizations

In this work, stereocopolymerizations are defined as copolymerizations of L- and D- (or *S*- and *R*-) monomers. Copolymerizations may, in principle, yield three different types of sequences, namely random sequences, alternating sequences, and two-block copolymers. It is well-known from ring-opening polymerizations initiated by other metal compounds that, in real experiments, perfectly alternating or perfectly blocky sequences are difficult to obtain. The nature of stereosequence has important consequences for the physical properties and potential applications of the stereocopolymers. Stereocopolymers having a random stereosequence are usually amorphous and suited as soft segments in block copolymers or for the production of transparent films, if the glass transition is higher than 30 °C. Stereocopolymers with an alternating sequence or stereoblock copolymers are usually crystalline, turbid, and relatively hard materials.

At least, two racemic cyclic esters are commercial, β-D,L-butyrolactone and D,D,L,L-lactide. Detailed studies of their stereocopolymerizations initiated by Bi-salts or complexes have not been described yet, but a few preliminary experiments were reported. For instance, polymerizations of racemic D,L-lactide were conducted in bulk or as concentrated solution in xylene at 120 °C.[123] Commercial (relatively impure) Bi(III) 2-ethylhexanoate was used as initiator. Amorphous, transparent poly(D,L-lactide)s were obtained, and

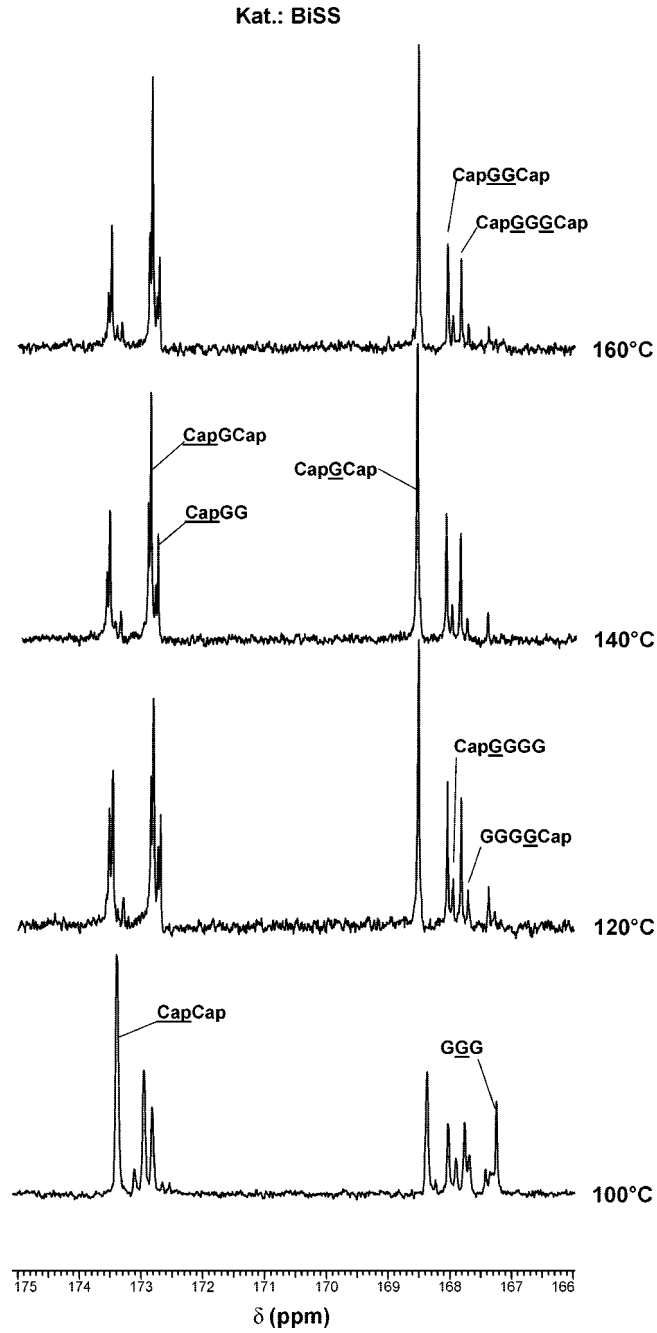


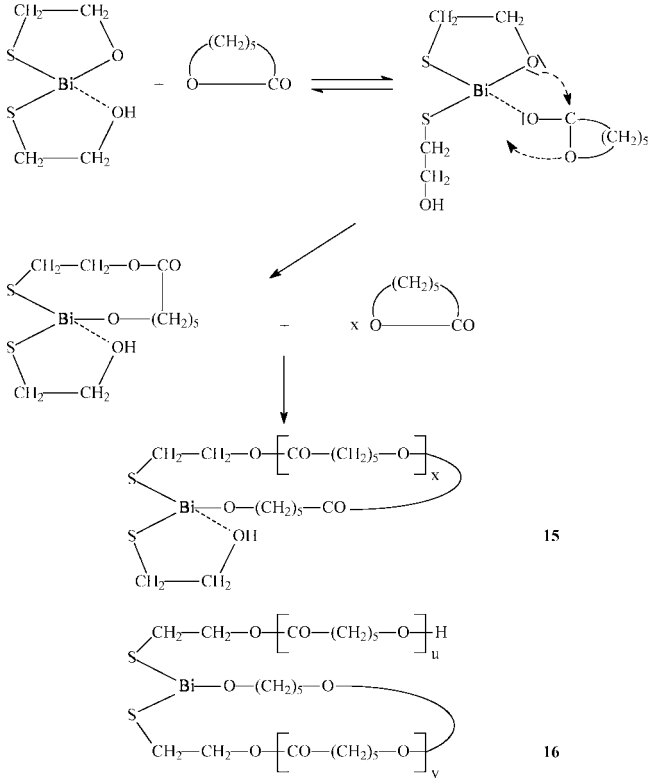
Figure 2. 100.4 MHz ^{13}C NMR spectra of εCL/glycolide copolyesters prepared in bulk with variation of temperature using Bi-subsalicylat as catalyst. Reprinted with permission from ref 125. Copyright 2005 American Chemical Society.

the ^{13}C NMR spectra proved a low level of blockiness close to perfect randomness. Under the same conditions, zinc stearate and antimony 2-ethylhexanoate yielded higher degrees of blockiness.[123] Further studies have to elucidate if Bi-based catalysts indeed possess a high potential to produce random poly(D,L-lactide)s. Random stereosequences have the advantage of homogeneous hydrolytic degradation in pharmaceutical or medical applications.

3.4. Copolymerizations of Different Cyclic Esters

Copolymerization of two or three different monomers is a standard strategy to vary the properties of polymeric materials over a wide range. Variation of molar composition and sequence allows for optimization of the properties for

Scheme 9. Ring-Expansion Polymerization of εCL by the Bi 2-Mercaptoethanol Complex 2



certain applications. In the field of biodegradable polyesters, two types of copolymers are particularly interesting:

(I) Random copolymers with exactly or nearly equimolar compositions. Such copolymers are usually amorphous and form transparent films or glues. Depending on the monomer combination, such copolymers allow for optimization of glass-transition temperature (T_g) and/or rate of degradation.

(II) Random sequences combined with molar compositions >5/1. The predominant monomer will automatically form blocks the average lengths of which depend on the molar fraction of the minor comonomer. This type of copolymerization allows for fine-tuning of the crystallinity, of the T_g, and of the rate of degradation.

Copolymers of εCL and glycolide (GG) are interesting, because glycolide ester groups are particularly sensitive to hydrolytic degradation, whereas poly(εCL) is a slowly degrading polyester. If the sequence is close to randomness, these copolyesters are amorphous and may possess a low T_g (< −30 °C). If TEG is used as coinitiator, the copolyesters possess two OH end groups and may serve as soft segments in A-B-A triblock or multiblock copolymers (see below). Copolymerization of εCL and GG with a feed ratio of 2:1 (taking into account the dimeric nature of glycolide, the εCL/G ratio was 1:1) was studied using $BiHex_3$ as initiator (in combination with TEG).[124] TEG was completely incorporated, so that telechelic copolyesters were obtained. Due to nearly complete conversions of both monomers, the chain lengths corresponded to the εCL + G/TEG ratios, and the molar composition (εCL/G) corresponded to the feed ratio. The temperature was varied from 100 to 160 °C, and its influence on the monomer sequences was studied. ^{1}H and ^{13}C NMR spectroscopy were used to analyze the sequences, which were characterized in terms of alternating dyads and average block lengths. For a perfectly random sequence, the content of alternating dyads is 50% and the average block lengths of εCL and G units are 2.0. At 100 °C, the average block lengths were slightly above 2.0 (i.e., around 2.0 ± 0.1) and the percentage of alternating dyads was below 50%. Yet, surprisingly higher temperatures had the consequence that the average block lengths decreased to values between 1.25 and 1.30 and the alternating dyads reached values up to 78%. This means that $BiHex_3$ quite unexpectedly favored the formation of alternating triads εCL-G-εCL.

This surprising finding is interesting for three reasons. First, these copolyesters are completely amorphous regardless of the polymerization temperature, and due to their telechelic structure and T_g's around −40 °C, they are well suited as soft segments in triblock and multiblock polymers (see next section). Second, under the same reaction conditions, $SnOct_2$ yielded copolyesters with a considerably lower content of εCL-G-εCL triads and higher blockiness. This means that the polymerization mechanisms of Sn- and Bi-salts involve characteristic differences in the coordination and activation of different monomers, even when both metals initiate a coordination−insertion mechanism. This difference cannot be explained by a higher transesterification activity of Bi-salts, because the percentage is higher than expected for a random sequence and because Bi-salts are poorer transesterification catalysts than analogous Sn-salts, as revealed by time−conversion measurements. Third, the preferential formation of εCL-G-εCL triads means that Bi-salts catalyze a special transesterification mechanism which favors the cleavage of G-G dyads by εCL units. A speculative mechanism explaining this point was published.[124,125] Yet, as discussed below, more recent results indicate that this mechanism cannot be correct. Regardless of mechanistic details, the experimental results obtained from $BiHex_3$-initiated copolymerizations were confirmed by analogous copolymerizations conducted with bismuth subsalicylate (BiSS).[125] The content of alternating triads was again higher than that calculated for a random sequence (50%) and higher than that resulting from $SnOct_2$-initiated copolymerization (see Table 1). The ^{13}C NMR spectra in Figure 2 exemplarily demonstrate this tendency and also demonstrate that higher temperatures surprisingly favor the alternating triads (Cap-G-Cap).

Quite recently, copolymerizations of εCL and GG were also initiated by Ph_2BiOEt.[126] In most experiments, TEG was used as coinitiator and the reaction conditions were selected to match those used for $SnOct_2$, $BiHex_3$, and BiSS-initiated polymerizations. Interestingly, alternating sequences were again favored, quite analogous to $BiHex_3$ and BiSS. When neat Ph_3BiOEt was used, this tendency was less pronounced. Anyway, the sequences resulting from Ph_2BiOET-initiated polymerizations were different from those produced by $SnOct_2$ and underline that the Sn- and Bi-initiated polymerization mechanisms involve characteristic differences. These results also mean that the hypothetical reaction mechanism previously presented to explain the prevalent formation of εCL-G-εCL triads is not correct. A simultaneous growth of two or three chains from one Bi-atom is clearly not necessary for the cleavage of G-G dyads by εCL. A reaction mechanism providing a satisfactory explanation for the predominant formation of alternating triads does not exist at this time.

Bi-initiated copolymerizations of εCL- and L-lactide (LLA)[127] were also conducted in bulk, and the temperature was varied from 100 to 140 °C. TEG served again as co-

Table 1. Copolymerizations of ε-Caprolactone and Glycolide in Bulk, Initiated by $SnOct_2$[a] or BiSS[a], in Combination with Tetra(ethylene glycol), TEG, at Various Temperatures

copolymer. no.	initiator	temp (°C)	time (h)	εCL/GL/TEG[b] (^{1}H NMR)	L_{CL}[c] ^{1}H	L_{CL}[c] ^{13}C	altern. dyads (%) GL−εCL	L_{GL}[d] ^{1}H	L_{GL}[d] ^{13}C	altern. dyads (%) εCL-GL
1	$SnOct_2$	100	24	27/13/1	3.70	3.10	27	3.20	2.90	31
2	$SnOct_2$	120	8	26/12/1	2.00	1.90	48	2.20	1.95	45
3	$SnOct_2$	140	2	27/13/1	1.60	1.50	62	1.60	1.50	61
4	$SnOct_2$	160	0.5	26/12/1	1.55	1.50	63	1.55	1.45	63
5	BiSS	100	48	25/13/1	2.25	2.05	44	2.30	2.10	44
6	BiSS	120	24	26/12/1	1.60	1.65	63	1.55	1.50	65
7	BiSS	140	5	27/13/1	1.50	1.50	67	1.50	1.40	70
8	BiSS	160	2	25/12/1	1.47	1.45	69	1.45	1.40	72

[a] Monomer initiator ratio (M/I = 1000/1). [b] Molar feed ratio: 26/13/1. [c] Average lengths of the homogeneous blocks calculated from the O−CH_2 ^{1}H NMR signals and from the CO-signals, respectively. [d] Average lengths of the homogeneous blocks calculated from the O−CH_2 ^{1}H NMR signals and from the CO-signals, respectively.

Table 2. Copolymerizations of εCL and LLA in Bulk (Feed Ratio 1:1) Coinitiated with Tetra(ethylene glycol), TEG, (M/C = 200/1) and Initiated with $SnOct_2$ or $BiHex_3$ (M/I = 500/1)

copolymer no.	initiator	temp (°C)	time (h)	yield (%)	η_{inh}[a] (dL/g)	(εCL)/(lactyl)[b]	$\bar{L}_{CL}$[c] (^{1}H NMR)	$\bar{L}_{CL}$[d] (^{13}C NMR)	$\bar{L}_{LA}$[e] (^{13}C NMR)	altern.[f] dyads (%)	morphology
1	$Sn(Oct)_2$	100	21	81	0.52	0.50	5.2	5.4	12.2	19	crystalline
2	$BiHex_3$	100	48	68	0.44	0.50	1.5	1.5	2.3	65	amorphous
3	$Sn(Oct)_2$	120	14	71	0.50	0.52	2.8	2.9	5.2	36	crystalline
4	$BiHex_3$	120	24	48	0.42	0.51	1.5	1.5	2.7	68	amorphous
5	$Sn(Oct)_2$	140	2	70	0.51	0.49	2.6	2.6	5.3	38	crystalline
6	$BiHex_3$	140	6	36	0.42	0.49	1.4	1.5	2.4	68	amorphous

[a] Measured at 20 °C with c = 2 g/L in CH_2Cl_2. [b] Molar composition determined by ^{1}H NMR spectroscopy for O−CHMe−CO (lactyl) units. [c] Average block lengths of εCL calculated from the ^{1}H NMR CH_2CO signal. [d] Average block lengths of εCL calculated from ^{13}C NMR signals. [e] Average block lengths calculated from ^{13}C NMR signals of lactyl units. [f] Calculated from ^{1}H NMR (−CH_2CO−) signals of εCL units.

initiator, with the consequence that telechelic copolymers were obtained. As illustrated by the data in Table 2, the incorporation of both monomers followed the 1:1 feed ratio and the monomer/TEG ratio in the isolated copolyesters agreed with the feed ratio. The most important result concerned again the sequences which showed a conspicuous predominance of alternating εCL-LLA-εCL triads quite analogous to the εCL/G copolymerizations. Once again, $SnOct_2$ favored blocky sequences under the same conditions and these differences were reflected in the physical properties of the copolyesters. Whereas all copolyesters prepared by means of $BiHex_3$ were amorphous and transparent, those obtained from $SnOct_2$-initiated copolymerizations were semicrystalline. These different physical properties have, in turn, consequences for the rates of hydrolytic degradation and, thus, for potential applications. Time−conversion proved again that $BiHex_3$ is less reactive as a transesterification catalyst than $SnOct_2$, so that the formation of alternating triads cannot be explained by more rapid equilibration of all ester bonds, and a special mechanism favoring the cleavage of LLA-LLA bonds must exist. This mechanism has to do with the different basicities and reactivities of εCL, on the one hand, and εCL or LLA, on the other.

This conclusion is supported by $BiHex_3$-initiated copolymerizations of GG and LLA.[128] For this monomer, combination time−conversion measurements indicated that $BiHex_3$ and $SnOct_2$ possesses nearly identical reactivities. Furthermore, the sequences of these copolyesters were similar, with a slightly higher tendency toward random sequences, when $BiHex_3$ was used as initiator. In other words, $BiHex_3$ did not have a significant advantage or disadvantage over $SnOct_2$ in terms of reactivity or properties of the copolyesters, but it still has the important advantage of a much lower toxicity.

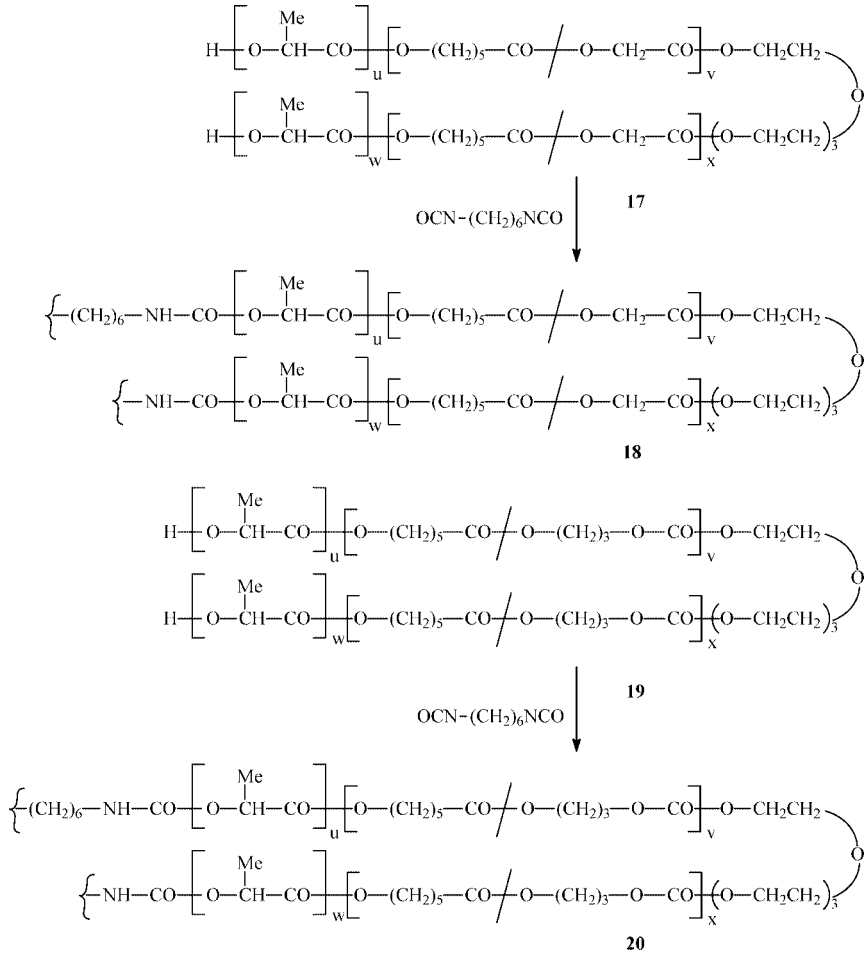
Finally, copolymerizations of εCL and trimethylenecarbonate, TMC, were studied using $BiHex_3$ combined with TEG as initiator system.[129] The ^{13}C NMR spectra indicated equal frequencies of all four dyads, as expected for a random sequence, and in agreement with this interpretation, these copoly(ester carbonate)s were amorphous and transparent. Their application as soft segments in block copolymers is discussed below.

3.5. A-B-A Triblock and Multiblock Copolymers

Syntheses of block copolymers are an important and, in most cases, successful approach to combine positive properties of different homopolymers. Usually, one sort of blocks is crystalline (so-called hard segment) and has the purpose to impart mechanical stability (e.g., high heat deflection temperature), whereas another sort of blocks is typically amorphous, having a T_g below 0 °C. This so-called soft segment has the purpose to improve the flexibility, to impart elasticity, or to absorb shock energy. An important and widely used group of such block copolymers are the thermoplastic elastomers (TPEs).[130] The combination of shaping by extrusion or injection molding from the melt with high elasticity at service temperature is a particularly attractive and useful property, and thus, the preparation of biodegradable of TPEs was and is highly desirable.

A first class of biodegradable A-B-A triblock copolymers and multiblock copolymers derived from them was prepared in the following way.[105] By means of the $BiHex_3$/TEG combination, telechelic, amorphous εCL/G copolymers were prepared, and after almost complete conversion, chain extension with L-lactide was performed in situ. Under optimized reaction conditions, this chain extension was feasible without detectable transesterification. The triblock copolymers **17** (Scheme 10) were isolated and characterized, but in parallel experiments an additional chain extension with 1,6-hexamethylene diisocyanate was conducted and the multiblock copolymers **18** were obtained. Unfortunately, the

Scheme 10. Syntheses of Multiblock Copolyesters by Chain Extension with Diisocyanates



mechanical properties were poor, because the elongation at break determined by stress−strain measurements remained low.

A similar class of triblock and multiblock copolymers was prepared analogously, but the soft segments consisted of a random εCL/TMC copolymer (structures **19** and **20** in Scheme 10).[131] Once again, $BiHex_3$ proved to allow for the preparation of the multiblock copolymer in a one pot procedure without significant side reactions. The stress−strain measurements of these multiblock copolymers were displayed in Figure 3. Initial stress and elongation at break varied with the lengths of the soft and hard segments, as expected, and highly elastic TPEs were obtained (curves A, B, and C). In summary, $BiHex_3$ proved to be a useful catalyst for the in situ preparation of triblock and multiblock copolyesters.

3.6. Ring-Opening Polymerizations of Various Monomers

Cyclic esters are not the only group of monomers that can be polymerized by bismuth-catalysts or initiators. Lewis acids such as the Bi-halides or the more acidic Bi-triflate ($Bi(OTf)_3$) should be capable of polymerizing monomers prone to cationic polymerizations. A first example illustrating this view is the polymerization of 2-alkyl oxazolines catalyzed by $BiCl_3$, $BiBr_3$, BiJ_3, and ($Bi(OTf)_3$).[132] BiF_3 was not active, possibly due to its extremely low solubility in organic monomers and solvents. Other Bi-salts such as Bi-oxide, Bi-acetate, and Bi-subsalicylate were inactive because of the low acidity. The order of activity was found to reflect the Lewis acidity of the Bi-salts.

$$(Bi(OTf)_3) > BiCl_3 > BiBr_3 \sim BiJ_3$$

The molecular weights proved to be almost independent of the monomer−catalyst ratio, apparently due to side reactions resulting from deprotonation of the alkyl substitutent in the α-position. The MT mass spectra almost exclusively dis-

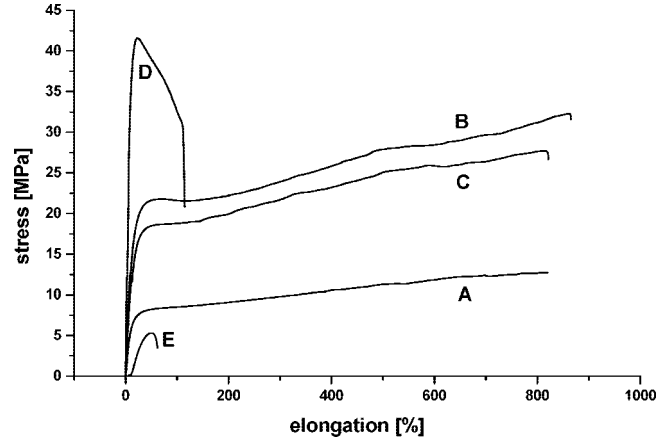
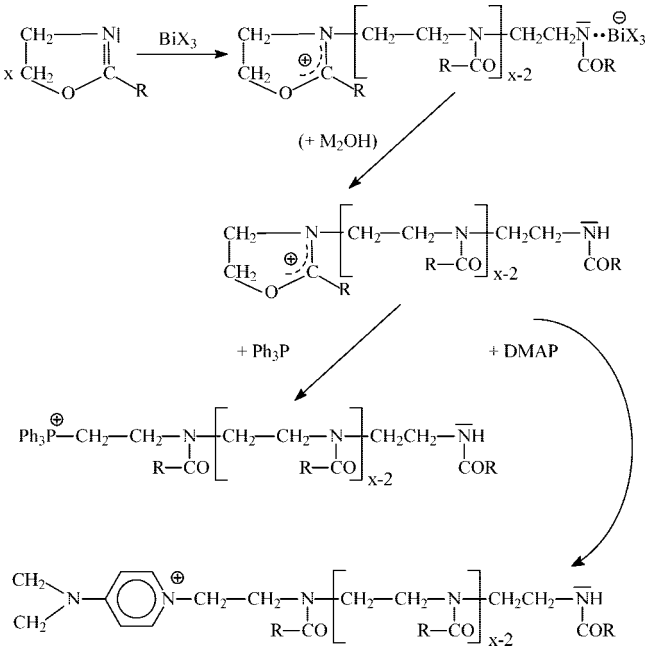


Figure 3. Stress−strain measurements of multiblock copolyesters based on crystalline L-lactide and amorphous εCL/TMC random copolymer segments. The weight ratio crystalline/amorphous blocks increases in the order A−D. Reprinted with permission from ref 131. Copyright 2005 American Chemical Society.

Scheme 11. Cationic Polymerization of 2-Alkyloxaozolines Catalyzed by Bi-halides and Reaction Products Obtained from Triphenylphosphine or *N*,*N*-Dimethyl-4-aminopyridine (DMAP)



played peaks of linear chains having a cationic end group suggesting the mechanism outlined in Scheme 11. This interpretation was confirmed by reactions with triphenyl phosphin or *N*,*N*-dimethyl 4-aminopyridine (Scheme 11).

Furthermore, $BiCl_3$ and ($Bi(OTf)_3$) reacted with hexamethylcyclotrisiloxane at temperatures ≥ 60 °C. The ^1H NMR spectra indicated complete conversions when ($Bi(OTf)_3$) was used at 100 °C, whereas the conversions achieved with $BiCl_3$ at 100 °C did not exceed 80%. The MT mass spectra revealed the formation of cyclic oligomers and polymers in the mass range up to 4000 Da. However, SEC measurements demonstrated that, in addition to a large fraction of oligomers in the mass range up to 5000 Da, polysiloxanes with masses around 200−400 kDa were formed.[133]

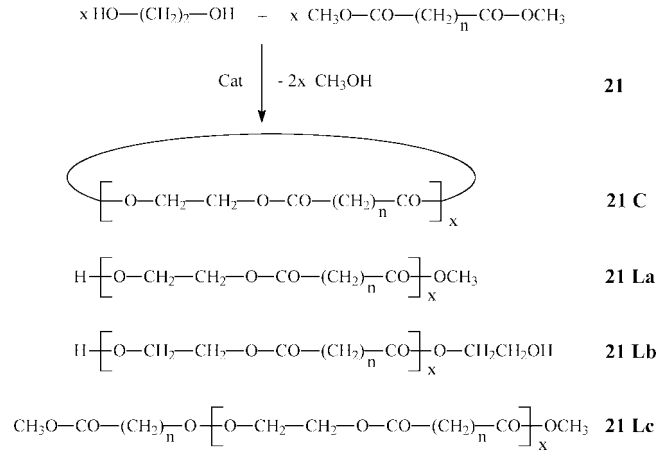
Unpublished experiments of the author proved that ($Bi(OTf)_3$) catalyzes the polymerizations of 1,3-dioxolane at temperatures > 20 °C and polymerizations of epoxides at ≥60 °C. Therefore, Bi-salt catalyzed polymerizations of heterocycles are a wide area which is still open for intensive and interesting studies.

4. Step-Growth Polymerizations

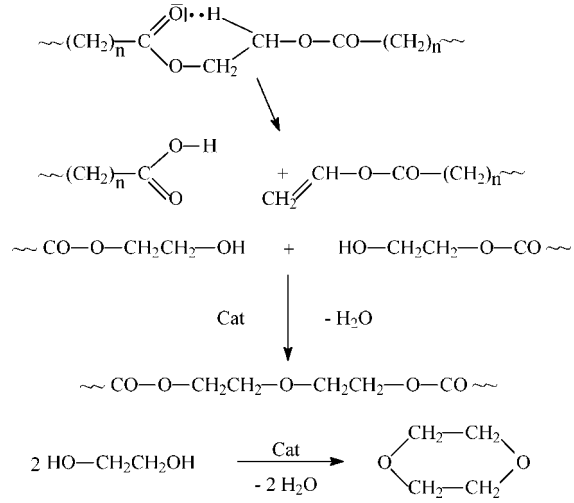
4.1. Polycondensations of Aliphatic Diols by Transesterification

Ring-opening polymerization of lactones or cyclic diesters is not the only approach to a convenient preparation of biodegradable aliphatic polyesters. Polycondensations of α,ω-dihydroxyalkanes (alkane diols) with aliphatic dicarboxylic acids or with their dimethyl esters are alternatives. The transesterification process outlined in Scheme 12 involves few side reactions (illustrated for ethanediol in Scheme 13), may be conducted in bulk, and may give high molecular weights. Polyesters such as poly(ethylene succinate) or poly(ethylene adipate) prepared via this transesterification process have recently been commercialized. A clean

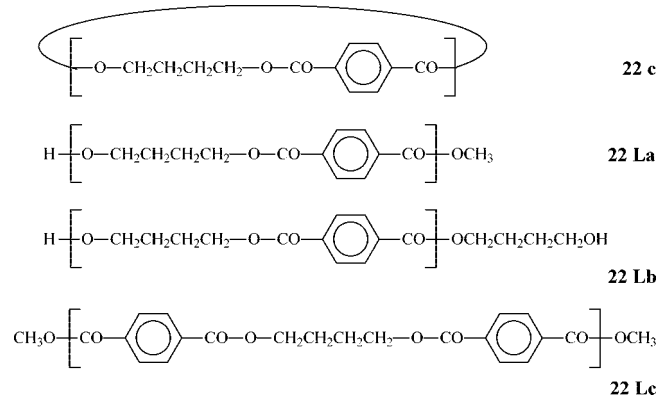
Scheme 12. Reaction Products Resulting from Clean Polycondensations of Ethanediol with Dimethyl Esters of Aliphatic Dicarboxylic Acids



Scheme 13. Side Reaction Which May Occur at High Temperatures (e.g. >220 °C) in Polycondensations of Ethanediol



Scheme 14. Reaction Products of a Clean Polycondensation of 1,4-Butanediol with Dimethyl Terephthalate



polycondensation process of this kind may yield the four reaction products outlined in Schemes 12 and 14 for certain polycondensations discussed below in more detail. Increasing conversion favors the formation of cyclic oligoesters and polyesters, and at 100% conversion, all reaction products are cycles.[134,135] Yet, when a relatively low boiling diol is used as monomer, it is usually applied in a large excess and partially removed by distillation (together with the liberated

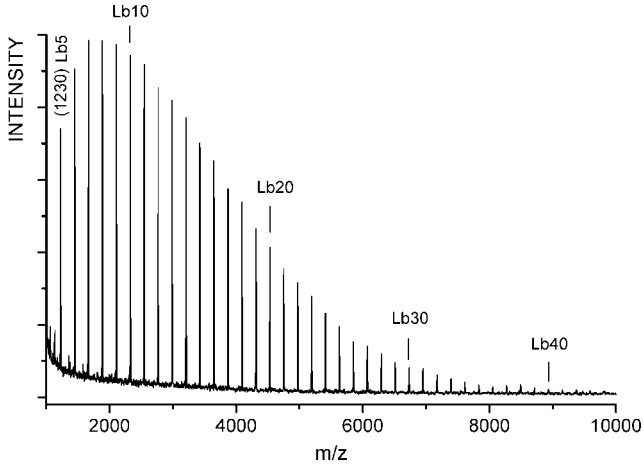


Figure 4. MALDI-TOF mass spectrum of poly(butylenes terephthalate) prepared in bulk at 240 °C with Bi_2O_3 as catalyst. The **Lb** mass peaks represent linear chains having two butanediol end groups. Reprinted with permission from ref 138. Copyright 2005 American Chemical Society.

methanol) during the polycondensation. The excess of ethane diol has the consequence that linear chains having two OH end groups (**21Lb**, in Scheme 12) are the predominant reaction products up to high conversions. Such polyesters are of particular interest, because their telechelic character allows for various modifications of the end groups, for chain extension with electrophilic coupling agents (e.g., diisocyanates), and for syntheses of A-B-A triblock copolymers.

In a recent publication, polycondensations of ethanediol with dimethyl adipate or dimethyl sebacate were reported.[136] These polycondensations were conducted in bulk at 240 or 260 °C with titanium tetrabutoxide, tin(II) 2-ethylhexanoate, or $BiHex_3$ as transesterification catalysts. The cleanest polycondensations were obtained with the Bi-catalyst. Only mass peaks of chains having structure **21Lb** (see Scheme 12) were detectable, when the maximum temperature was limited to 240 °C. Cyclic polyesters (**21C**) and ether groups (Scheme 13) were detected in the mass spectra, when $Ti(OBu)_4$ was used as catalyst. With a maximum temperature of 260 °C, cyclic polyesters and ether groups were also formed in small amounts by $BiHex_3$. This finding agrees with a study of other authors[137] which proved that aliphatic polyesters undergo thermal degradation and side reactions above 240 °C.

Furthermore, the preparation of poly(butylenes terephthalate), PBT, was studied. PBT is not biodegradable, but like poly(ethylene terephthalate) (already used as implant), is a biocompatible material. Polycondensations of 1,4-butanediol with dimethyl terephthalate were conducted in bulk at temperatures up to 280 °C.[138] Various catalysts such as Sn, Zn, Y, Ti, and Bi-salts were compared. With 1,4-butanediol as monomer, thermal cis-β-elimination reactions are less likely than in the case of ethanediol (see the first equation in Scheme 10), but the tendency to form a cyclic ether (i.e., tetrahydrofuran instead of 1,4-dioxane) is much higher. This comparison revealed that basic Bi-catalysts such as Bi_2O_3, Bi-subcarbonate, or Bi-subsalicylate caused fewer side reactions than all other catalysts and rather clean telechelic polyesters having structure **22Lb** (Scheme 14) were obtained. The mass spectrum of Figure 4 is an exemplary demonstration of these results. Interestingly, $BiCl_3$ also yielded telechelic polyesters, but their structure corresponds to formula **22Lc**. This unexpected result was explained on the basis of model reactions which demonstrated that $BiCl_3$ is an excellent catalyst for the cyclization of butanediol. This cyclization begins above 110 °C, so that the reaction mixture loses most butanediol in the form of tetrahydrofuran before the final condensation temperature is reached. The resulting stoichiometric imbalance favors the formation of **22Lc** chains. In summary, Bi-catalysts allowed for the preparation of two different kinds of telechelic PBTs.

However, it should also be mentioned that Bi-salts did not sufficiently catalyze polycondensations of 1,4-butenediol with dimethyl sebacate. Even at temperatures up to 220 °C and reaction times of several hours, the conversions were far from compatible. Yet, more reactive catalysts such as $Ti(OBu)_4$ also failed to give high conversions.

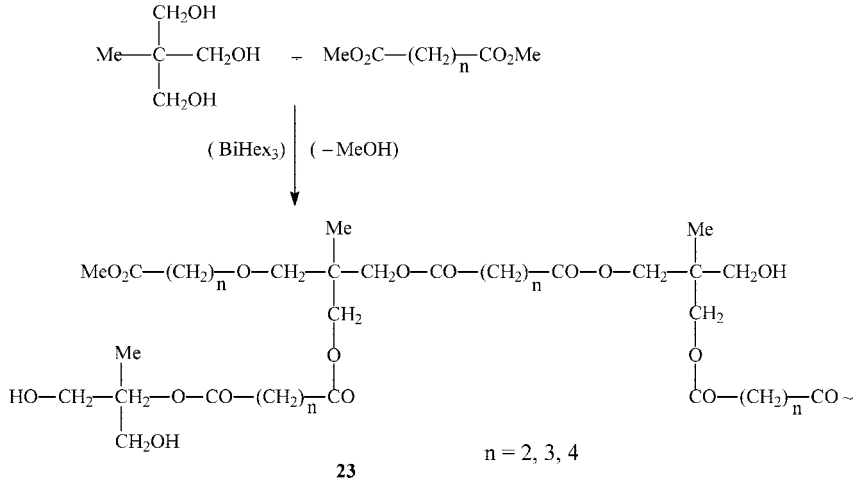
Further studies concerned syntheses of OH-functional hyperbranched polyesters from 1,1,1-tris(hydroxymethyl)-ethane (THME, **23**) (Scheme 15)[139] or from pentaerythritol (PENT).[140] THME was polycondensed in bulk with the dimethyl esters of sebacic, adipic, glutaric, and succinic acid, whereby $BiHex_3$ served as transesterification catalyst (Scheme 15). The reactivity increased in the given order of acids, and this reactivity played a key role for the maximum conversion that was achieved. With a maximum reaction temperature limited to 240 °C a conversion of only 7% was achieved with dimethyl sebacate. With dimethyl glutamate and dimethyl succinate, conversions up to 91% were reached and completely soluble hyperbranched polyesters of low molecular weight were obtained. The extent of branching was detectable from the splitting of signals in the ^1H NMR spectra in these reaction products. All attempts to achieve conversions above 91% of the ester groups ended with gelation. These hyperbranched polyesters **23** cross-linked with diisocyanates at room temperature even in the absence of catalyst. Furthermore, quantitative acylation with methacrylic anhydride was feasible. Such multifunctional methacrylates may serve as biodegradable cross-linkers in radical polymerizations of vinyl monomers.

Since the melting temperature of PENT is considerably higher than that of THME and its solubility in organic liquids lower, it was difficult to obtain a homogeneous reaction mixture with dimethyl sebacate. Initial temperatures up to 280 °C were needed for 0.5 h. Therefore, the lower boiling dimethyl esters of other dicarboxylic acids were not useful as reaction partners. Broad variation of the reaction conditions finally suggested that $BiHex_3$ is a useful catalyst for the homogenization process at high temperatures, but lowering of the temperature and addition of the more reactive $Ti(OBu)_4$ catalyst was needed as a second step to achieve high conversions. Yet, quite analogous to the polycondensations of TMP, conversion $\geq$92% resulted in gelation and soluble hyperbranched polyesters were only obtained at lower conversions. The resulting polyesters reacted easily with diisocyanates and carboxylic acid anhydrides. The structure of a methacrylated hyperbranched polyester (**24**) is presented in Scheme 16 as an example.

4.2. Polycondensations of Aliphatic Diols by Esterification

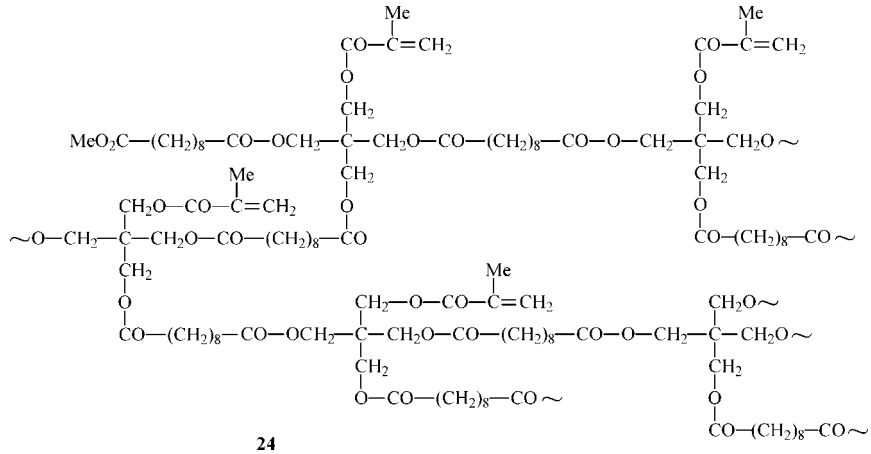
As reported by a Japanese research group,[141,142] scandium triflate catalyzes polycondensations of methylsuccinic acid with various alkanediols under mild conditions (e.g., temperature down to 45 °C). However, the M_n's of the twice or three times reprecipitated polyesters were rather low (<13 000 Da, uncorrected SEC measurements). The triflates of yttrium,

Scheme 15. BiHex$_3$-Catalyzed Polycondensations of 1,1,1-Tris(hydroxymethyl) Ethane and Dimethyl Esters of Aliphatic Dicarboxylic Acids



23

Scheme 16. Methacrylated Hyperbranched Polyester Prepared from Pentaerythritol and Dimethyl Sebacate

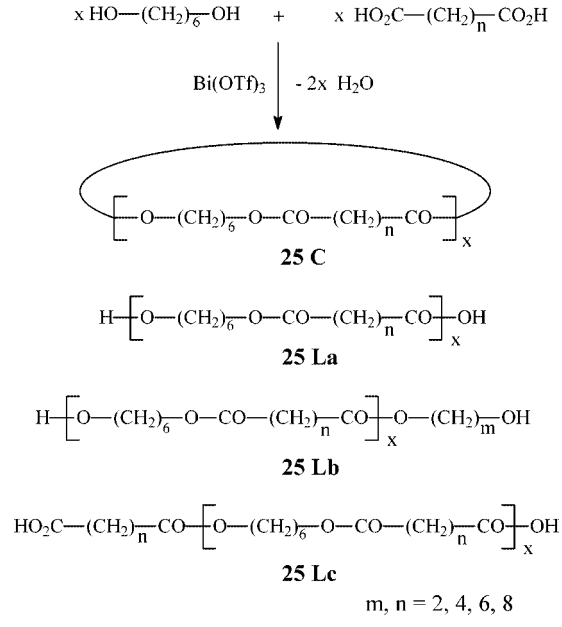


24

ytterbium, and samarium were found to be almost ineffective under these conditions. More recently, the usefulness of Bi-triflate as catalyst for polyesterifications of alkanediols and aliphatic dicarboxylic acids (ADAs) was studied in more detail.[143,144] For polycondensations of 1,6-hexanediol and sebacic acid (Scheme 17), it was found that a reaction temperature of 80 °C and a reaction time of 48 h in vacuo were optimum.[143] This polycondensation method also proved successful, when other α,ω-alkanediols or ADAs were used. However, 1,4-butenediol and 1,4-butynediol gave black tars, but this negative result was also obtained with protic acids as catalysts. M_n values up to 30 000 Da (uncorrected SEC measurements) were obtained from alkanediols. The MALDI-TOF mass spectra revealed that all species which may be expected from such a polycondensation (Scheme 13) were present in the reaction product. The fraction of cycles significantly increased with higher molecular weight and higher conversion, in agreement with the theory of the author.[140,146] Furthermore, it was found by ^{1}H NMR spectroscopy that rapid equilibration reactions (e.g., hydrolysis and formation of ester groups) occur, so that this approach may be useful for the preparation of random copolyesters from mixtures of diols and mixtures of ADAs.

The catalytic effect of Bi-triflate was compared to those of 20 other metal triflates, including all lanthanides with the exception of promethium.[144] For polycondensations of 1,6-hexanediol and sebacic acid, only Sm-triflate yielded slightly higher M_n's than Bi-triflate. This result was in sharp contrast

Scheme 17. Reaction Products of Bi-Triflate-Catalyzed Polycondensation of 1,6-Hexanediol with Dicarboxylic Acids



25 C

25 La

25 Lb

25 Lc

to the poor results reported[142] for Sm-triflate-catalyzed polycondensations of methyl succinic acid. Furthermore, it was observed[143,144] that the acidity of the catalyst (measured in water at a concentration matching that in the melt) does

not play a significant role for its effectivity. These results suggest that the reaction mechanism involves complexation of the carboxylic acid groups with the metal ion.

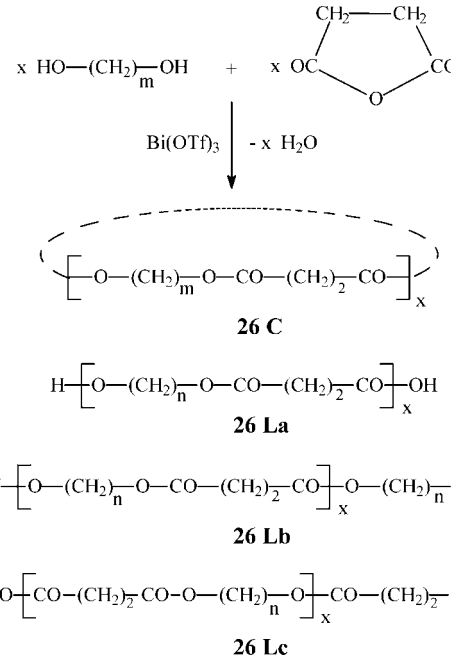
Since succinic acid is a biogenic monomer and polyesters of succinic acid are more prone to a rather rapid hydrolytic (bio)degradation than polyesters of other ADAs, convenient syntheses of polysuccinates are of particular interest. It was found that in the presence of Bi-triflate, succinic anhydride reacts rapidly and quantitatively with alkanediols at 80 °C. After application of vacuum for two days, M_n's up to 35 000 Da (uncorrected SEC data) were obtained.[145] When the catalytic effectivities of various metal triflates were compared, Bi- and Al-triflate gave the best results. However, the preparation of poly(1,4-butylene succinate) proved problematic, because the melting temperature of these polyesters amounts to 120−122 °C. This is the highest T_m of unsubstituted polyesters based on alkanediols and has the advantage of a relatively high heat distortion temperature. The obvious disadvantage is the requirement of reaction temperature ≥ 120 °C for its preparation in bulk, because, in the presence of acidic catalysts, 1,4-butanediol rapidly forms THT at temperatures above 110 °C. The resulting stoichiometry imbalance prevents high conversions with high molecular weights. However, in combination with a special procedure[146] using a high boiling nonsolvent for the azeotropic removal of water and byproduct $BiCl_3$ and Bi-triflate yielded PBuS with M_n's around 30 000 to 35 000 Da. In summary, Bi-salts proved to be efficient catalysts for the preparation of aliphatic polyester by polycondensations of alkanediols either via transesterification or via acidic esterification. Since unsaturated monomers such as maleic anhydride or aromatic dicarboxylic acids have not been studied, there is ample space for further studies of Bi-catalyzed polycondensations.

4.3. Polyurethanes

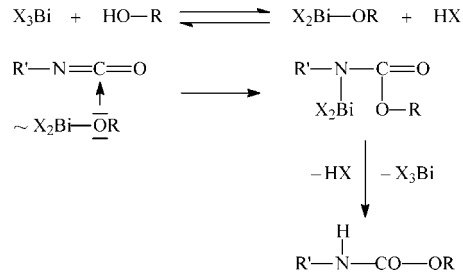
The modification of telechelic poly(ε-caprolactone) with 3-isocyanatopropyl trialkoxysilanes (Scheme 4, formula 13) and the chain extension with 1,6-hexamethylene diisocyanate (Scheme 10) have already demonstrated that Bi-salts are good catalysts for the addition of alcohols onto isocyanates. Only two short review articles[147,148] dealing with nontoxic catalysts as alternatives of dibutyltin laurate, the standard catalyst in polyurethane production, were found in the open literature. It was assumed that bismuth activates the isocyanate group.[147] However, the author prefers a mechanism that is analogous to the coordination−insertion (transesterification) mechanism of cyclic esters in that bismuth-alkoxides play the key role as outlined in Scheme 18. Such a mechanism fits in with the observation that functional polar groups in the β-position of a CH_2OH group strongly influence the reaction rate of the urethane formation, when Bi-salts are used as catalysts.[147] In this regard, Bi-based catalysts differ from dibutyl tin laurate, but as an overriding trend, Bi-salts were found to be less reactive than this standard tin catalyst. This overriding trend is not necessarily negative, and when a high reaction rate is needed, a larger quantity of the Bicatalyst may be added.

Anyway, the author has learned from members of several chemical companies that the tin catalysts were systemically substituted by Bi-salts due to environmental concerns. This tendency is reflected in a larger number of patents. References 149−158 were selected as examples of relatively new patents concentrating on Bi-based catalysts. However, Bi-salts are mentioned in many more patents in addition to other

Scheme 18. Bi-Triflate-Catalyzed Synthesis of Polyesters from α,ω-Alkanediols and Succinic Anhydride



Scheme 19. Bi-Salt-Catalyzed Addition of Alcohols onto Isocyanates



catalysts. At the end of 2008, the Internet provided 173 references concerning the topic "polyurethanes/bismuth-catalysts". These figures demonstrated that the interest of chemical companies in substituting Sn-catalysts by environmentally benign Bi-catalysts was and is high.

5. Conclusion

Bismuth salts and covalent organobismuth compounds were found to catalyze ring-opening polymerizations of various cyclic esters, so that high molecular weights and a proper control of the molecular weights can be achieved. Various structures and architectures were accessible, such as homopolyesters, random copolyesters, triblock- and multiblock copolyesters, and telechelic and star-shaped polyesters. In addition to catalyzing coordination−insertion mechanisms (including ring-expansion polymerizations), certain Bi-salts also catalyze cationic polymerizations, such as those of 2-alkyloxazolines. Furthermore, simple commercial Bi-salts catalyze polycondensations of aliphatic monomers either by transesterification or by acidic esterification. Moreover, Bi-salts catalyze the formation of urethane groups and syntheses of polyurethanes. Considering this versatility and the unusually low toxicity of most Bi-salts, Bi is an extraordinarily useful and interesting element as catalyst in polymer syntheses. Two comparisons should exemplarily highlight this statement. First, tin salts and compounds are certainly as versatile as Bi-salts and compounds, but they are several

orders of magnitude more toxic. Magnesium or calcium salts or complexes are somewhat less toxic than bismuth salts and catalyze ROPs and polycondensations based on transesterification, but they do not catalyze cationic polymerizations or esterifications. The polymer syntheses presented above are a first step into the wide field of Bi-catalyzed reactions in polymer chemistry, and many more reactions need to be studied in the future.

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