Polyhydroxyalkanoates: Recent Advances in Their Synthesis and Applications

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Polyhydroxyalkanoates (PHAs) are microbial biopolymers (polyesters) that have a wide range of functions and applications. They serve in nature mainly as carbon and energy storage materials for a variety of microorganisms. In past decades, their utilization has attracted much attention, from commodities and degradable plastics to specialty performance materials in medicine. PHA biosynthesis has been well understood, and it is now possible to design bacterial strands to produce PHAs with desired properties. The substrates for the fermentative production of PHAs are very manifold: some are derived from food-based carbon sources (e.g., fats and oils (triglycerids)), thus raising concerns with regard to the sustainability of their productions in terms of crop area and food. In addition, hemicellulose hydrolysates, crude glycerol, and methanol are very promising carbon sources for the sustainable production of PHAs. The integration of PHA production within a modern biorefinery is an important issue and can result in a simultaneous production of biofuels and bioplastics. Furthermore, many chemical-synthetic procedures by means of efficient catalysts can give access to a variety of PHAs. This article summarizes recent developments in these fields and emphasizes the importance of a sustainable PHA-based industry.

Practical Applications: Practical applications of the microbial polyesters PHAs are, for example, a variety of sustainably produced commodities as well as special applications in (bio)medicine, for example, tissue engineering.

1. Introduction

Sustainable polymers from renewable resources have attracted very much attention within the past decades.[1,2] Poly(hydroxyalkanoate)s (PHAs) are biopolymers that are produced by numerous bacteria in nature as an intercellular carbon

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and energy reserve. Poly(3-hydroxybutyrate) is the most important representative of this polymers. In 1925, the French microbiologist Maurice Lemoigne discovered and characterized PHB extracted from *Bacillus megaterium*. However, it is produced by a various number of microorganisms such as also *Cupriadavidus necator* or *Ralstonia eutroph*. In general, PHAs are thermoplastic and biodegradable polyesters with a structure as shown in **Figure 1**.[3–11]

Accumulation of PHAs occurs usually if a nutrient, for example, nitrogen or phosphorous, is limited while carbon is in excess.[12] These biocompatible polymers have meanwhile attracted very much attention up to the establishment of a PHA-based bio- and materials industry with regard to their use in commodities, medicine, pharmacy, and agriculture.[13–16] PHAs can also be produced in plants,[17] and they are also investigated via synthetic-chemical approaches, which are also briefly addressed in this article.

2. Properties of PHAs

Due to their fermentative synthesis, natural PHAs are strictly isotactic, featuring exclusively (R)-configuration at the chiral stereocenter in the main chain.[3–5] However, PHAs vary in their mechanical properties and can be grouped into two subcategories: PHA_{SCL}, which have short chain length and monomer unit consist of up to five carbon atoms, and PHA_{MCL}, which have medium chain length and where the monomer unit has more than five carbon atoms. PHA_{MCL} are amorphous macromolecules with decreasing glass transition temperature with increasing side chain length. Within the PHA_{SCL}, PHB is the most important representative. It has a high degree of crystallinity (55–80%) and form thin crystals with a melting point of ≈175 °C. With regard to Young modulus, tensile strength, impact strength and, UV resistance and oxygen permeability, PHB is similar to isotactic polypropylene (iPP), which shows his potential as, for example, packaging material. A main problem by replacing i-PP by PHB is brittleness after several days due to continual crystallization, and the strain elongation of PHB is much lower than that of i-PP (which can be improved by nucleating agents and post-treatment). However, the high melting temperature of PHB close to the decomposition temperature can lead to thermal degradation. For replacement of commodity
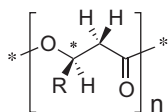
Figure 1. Structure of PHAs. R = alkyl; PHB: R = CH$_3$.
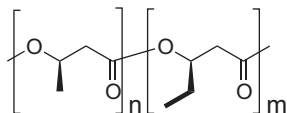
Figure 2. Structure of poly(3-HB-co-3-HV). For details see ref. [5].

plastics, melting temperature must be lowered, strain increased and crystallization has thus to be decreased.

When ICI introduced PHB into the market in 1982, they overcome these problems by using random copolymers consisting of 3-hydroxybutyrate (3-HB) and hydroxyvaleriate (HV), respectively, or 4-hydroxybutryate units (**Figure 2**). *Alcaligenes eutrophus,* a microorganism that can produce up to 80% of the dry cell weight of this copolymer upon application of a glucose/propionic acid mixture, was utilized for this, and many materials with different property profiles could be produced by ICI.[2,3] A more detailed discussion on the tacticity issue can be found in Section 6.

The barrier properties of these polymers are very important for their applications, for example, with regard to packaging (see also Section 7).

3. Degradation of PHB

There are several articles summarizing the degradation behavior of PHB stereoisomers in detail,[9,11] so this issue is only addressed here in brief. This polymer is mainly degraded under aerobic conditions. In general, degradation can mainly occur if phosphate, nitrogen sources temperature, salts and also moisture favor the growth of the involved microorganisms. These conditions are usually present in soil and compost, but not during normal applications and utilizations, which means that degradability does not trouble daily applications. Rate and state of degradation are dependent on tacticity or copolymer compositions. Under aerobic conditions, PHB degrades to carbon dioxide and water. In contrast, under anaerobic conditions methane is produced, and the corresponding intermediates are not harmful. Extracellular PHA depolymerases are very important for degradation. Furthermore, both aerobic and anaerobic microorganisms containing these enzymes are widespread in our environment.[3,9]

4. Biosynthesis and Biotechnological Accesses to PHAs

4.1. General Biosynthesis and Overview of PHA Substrates

There are several different systems that have been described for the biosynthesis of PHAs by PHA synthase enzymes,[5,6] and

their detailed elucidation would be beyond the scope of this article. In brief, one main biosynthesis route of PHAs starts from acetyl-CoA and proceeds in three consecutive enzymatic catalyzed steps. B-Ketothiolase (**PhbA**) catalyzes the reversible condensation of acetyl-CoA to acetoacetyl-CoA. After reduction by acetoacetyl-CoA reductase (**PhbB**) to D-(-)-3-hydroxybutyryl-CoA (consumption of NADPH), polymerization occurs promoted by P(3-HB) synthase (**PhbC**). After further steps, the cycle is closed by acetoacetyl-CoA synthetase (**AACS**) while acetoacetyl-CoA is regenerated and converted to acetyl-CoA, which can then also be converted in the citric acid cycle (**Figure 3**).[8,9]
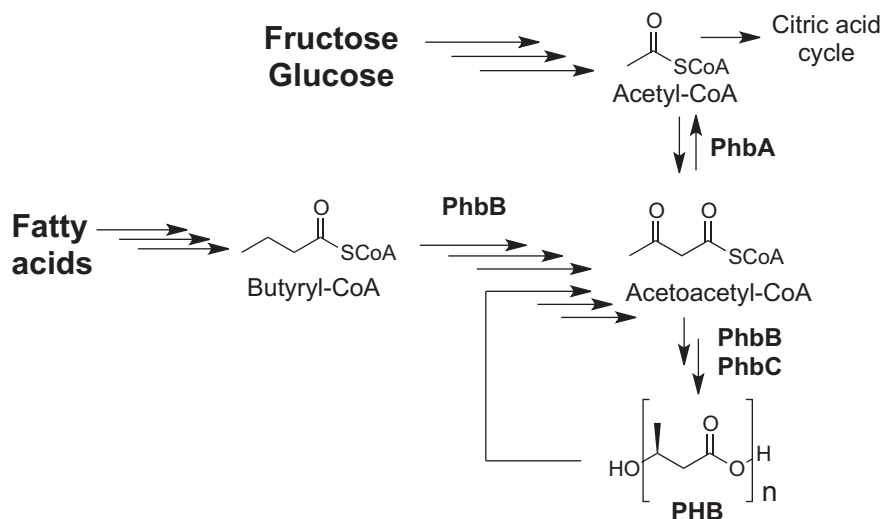
The development and engineering of two and three enzyme systems has been implemented to lower the costs of the one-enzyme system.[8,9] These pathways are utilized to convert many different compounds to PHB, and the industrial synthesis of PHAs has gained very high impact within the past decades. The expanding PHA industry has raised concerns since many PHAs are produced from food crops. Therefore, is has become essential to explore non-food-based carbon sources for a sustainable PHA production.

The main industrial scale PHA manufacturers (production capacities 10 000 t/a) are TianAn Biologic Materials Co. Ltd. (China), Tianjin GreenBio Materials Co. (China), and Bio-On Srl. (Bologna, Italy). Important players are also Biomer (Krailling, Germany) and the former Metabolix (Woburn, MA, USA) which is now Yield10 Bioscience (a crop research program).[11,12] PHAs are synthesized in bacterial cells through metabolic processes. It is possible to engineer bacterial strands in order to produce PHAs with defined properties. For this, many different substrates exist, which can be classified mainly into the three categories simple sugars (monosaccharides), hydrocarbons and triacylglyerols. The latter include accesses via direct fermentation, fatty acids and even glycerol. Most microorganisms that produce PHAs can utilize monosaccharides, while the utilization of triacylglycerols has only been reported for some microbes. A hydrocarbon metabolism is currently considered to be more limited, but can, for example, be used by the *Pseudonomas* species. Remarkably, different bacteria can produce different PHAs for the same substrate. For instance, glucose and other simple sugars are utilized by *Pseudonomas* spp. to produce medium chain-length PHAs, for example, poly(3-hydroxyhexanoate) (P3HHx), while, for example, *Ralstonia eutropha* synthesizes only poly(3-hydroxybutyrate) (P3HB) from glucose. The conversion of various substrates to PHAs is thus a result of selectivity and substrate specificity of the biocatalysts (enzymes), which has thus an analogy to chemical catalysis.
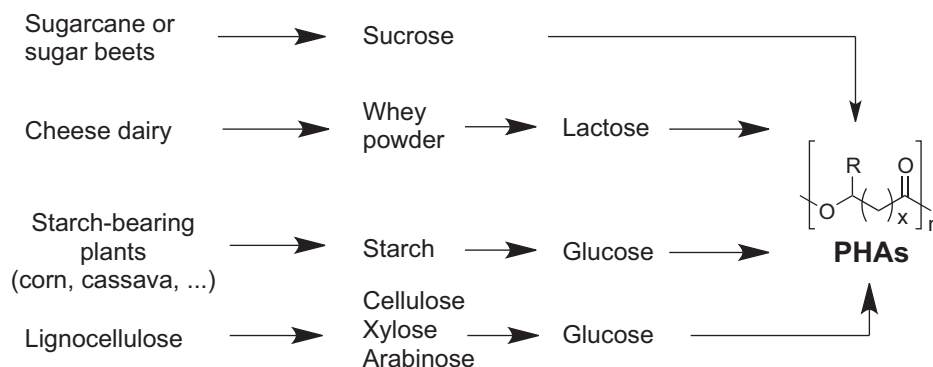
4.2. PHAs from Carbohydrates

Carbohydrates can be classified into monosaccharides, oligosaccharides and polysaccharides. Polysaccharides are polymeric carbohydrates, for example, starch, cellulose, and hemicellulose. Upon hydrolyzation of these polymers, different monosaccharides or disaccharides can be fermented to afford PHAs (**Figure 4**).[18–20]

Many bacterial strands as, for example, *Azeobacter vinelandii* and *Alcaligenes latus* can produce PHAs from sucrose, which is derived from sugar-bearing raw materials as, for example, sugar

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Figure 3. Biosynthesis and production pathways of PHB in *Escherichia coli* (simplified).[5,11]

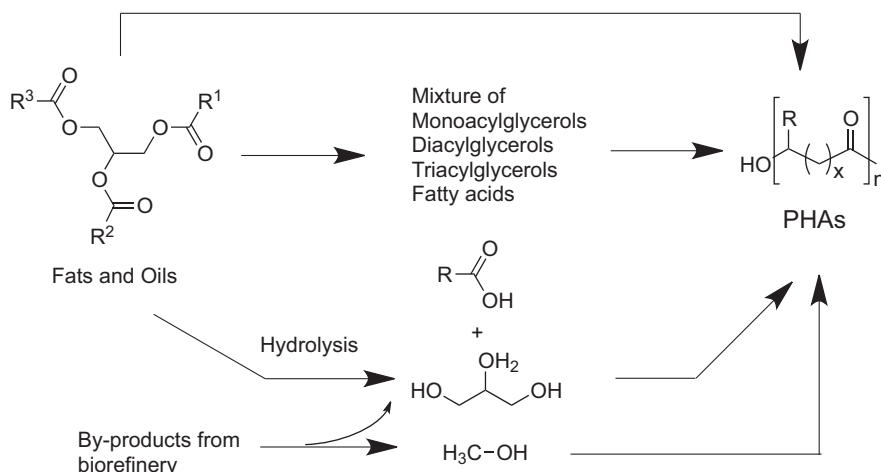**Figure 4.** Carbohydrate sources for the fermentative production of PHAs (schematic).[11]

beet or sugar cane.[21] Furthermore, lactose—a disaccharide consisting of galactose and glucose and obtained, for example, from whey—can be transformed by many microorganisms to PHAs, for example, by *Hydrogenophaga pseudoflava* DSM 1034 or by recombinant *Escherichia coli*.[22–24] A productivity of 2.57 g PHB L^{-1} h^{-1} could be achieved by using a recombinant strain of *E. coli* harboring *Alcaligenes latus* PHA biosynthesis genes. A two-step process from lactose via glucose and galactose by means of *Pseudomonas Hydrogenovora* (who cannot use lactose directly) was also employed.[19] With regard to starch, the earliest commercial PHA was produced by ICI using starch-derived glucose with *R. eutropha* (see also above), with an organic acid like propionic acid as the co-substrate for copolymer synthesis. Another example is Chemie Linz that uses *Alcaligenes latus* for the commercial production of P3HB from starch.[13]

Due to the fact that starch, sucrose, and lactose are important food sources, the derivation of glucose and other simple sugars from lignocellulose has gained great attention and is more justifiable for a large-scale production of PHAs for materials applications.[25] It contains cellulose, hemicellulose, and lignin. Cellulose consists of D-glucose, connected via β-1,4-glycosidic bonds, and hemicellulose consists of several pentoses such as

xylose (main component), mannose, galactose, arabinose, and rhamnose. Upon delignification (separation of cellulose and hemicellulose from lignin), hemicellulose hydrolysates (mainly composed of pentoses), cellulose, and lignin are obtained. These pentoses can be directly used for fermentable PHA production; *Pseudonomas cepacia* and *P. pseudoflava* were, for example, shown to have similar maximum specific growth rates on glucose and on xylose.[26,27] *E. coli* that contains PHA synthesis genes of *Ralstonia Eutropha* was demonstrated to accumulate PHB from xylose up to 74% of cell dry weight. The yield of 0.226 g PHB g^{-1} xylose is better here than for wild-types.[28,29] The use of liquefied wood as co-substrate with glucose is an interesting strategy to provide 3-hydroxyvalerate (3HV, which derived from levulinic acid and thus from cellulose) in the produced PHAs.[30]

4.3. PHAs from Triacylglycerols

Fermentation of the triacylglycerols, which are the main components of fats and oils and consist of three fatty acids esterificated with glycerol, requires triacylglycerol-utilizing bacteria and their lipases, which catalyze the acid release.[31] The fatty acids

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Figure 5. Triacylglycerols as starting materials for PHA production via fermentation.[11]

are then transported through the membranes into the cells and transformed via b-oxidation to PHA monomers and then to polymers (**Figure 5**).

With regard to plant oils, triacylglycerols were first transformed to PHAs via fermentation by means of the bacteria *Aeromonas caviae* in 1993, where complex copolymers were formed when the bacteria where grown on olive oil.[32] Furthermore, *Chromobactrerium* sp. was able to yield P3HB with a variety of plant oils—here the P3HB had a molecular weight range of 2×10^5–6×10^5.

R eutropha H16 could also produce P3HB homopolymers up to ≈80% (w/w) of the cell weight (dry) when used with various plant oils. Recombinant strains are commercially in use by Procter & Gamble Co., Ltd. That produce the copolymer P(3HB-*co*-3HHx). Through animal fats from food processing have not the same justification than plant oils for PHA production, some utilizations have been described, for example, for ester of fatty acids from tallow that can be transformed to PHAs by *P. citronellolis* with (mcl)PHA of 0.036–0.05 g L^{-1} h^{-1} and PHA contents of 20.1–26.6%.[33]

Bacterial strains grown on long-chain fatty acids can also produce PHAs.[34] Furthermore, fermentative production of PHAs from glycerol has been investigated.[35] With every 100 tons of biodiesel that is produced, about 10 t of glycerol is produced. For instance, a process that applies crude glycerol, which can contain impurities like, for example, glycerides or soap, for transformation into PHAs can be a valorization process.

Furthermore, methanol, which is used for the production of biodiesel by transesterification of oils and fats, can be applied for PHA production if the methanol-containing waste streams are utilized. Certain *Methylobacteria* can then perform the transformations.[36,37] Waste frying oils, which generally consist of 70% triacylglycerol and in addition of, for example, oligomeric or polymeric triacylglycerols, diacylglycerols, monoacyglycerols, free fatty acids, aldehydes, and ketones, can also be used for PHA production. Several improvements in the biosynthesis have been developed. Interestingly, in several investigations waste frying oil enhanced the production of PHAs because of other nutrients in it. For instance, in a 5-l batch fermentation

using *R. eutropha*, a productivity of 0.14 g PHB L^{-1} h^{-1} and a yield of 0.14 h PHB g^{-1} waste oil could be achieved.

4.4. PHAs from Hydrocarbons

It was discovered early that certain microorganisms can grow on, for example, octane and accumulate mcl-PHAs.[38] The production of PHAs form *n*-alkanoic acids by *P. oleoborans* was also investigated and showed that maximum isolated polymer yields of approximately 30% of the cell dry weight can be obtained. PHAs produced from hydrocarbons contain an alkyl group—from propyl to dodecyl groups—dependent on the substrates used. Furthermore, various aromatic hydrocarbons (e.g., terephtalic acid from PET) can be the substrates for PHA production by a number of *Pseudonomas* strains as well as other species (e.g., *Rhodococcus aetherivorans* IAR1).[39,40] The effective production of surfactants to solubilize and emulsify the hydrocarbons for an facilitated transport through cell walls is an important advantage of *Pseudonomas* strains. As currently the PHA productivity from hydrocarbons is rather low compared to other strategies, some improvements are required prior to the establishment of this approach for large-scale PHA production.

A very sustainable strategy is the PHA production from hydrocarbons derived from waste plastics, which has—though further improvements are needed—a very high impact due to the large quantities of suchlike starting materials, which can mainly be polyolefins, polystyrene, or polyethylene terephtalate.[41,42] The pyrolysis process is performed in a fluidized bed reactor, where shredded plastic particles are decomposed into small hydrocarbons and then to pyrolysis oils, which can then be utilized by hydrocabon-utilizing bacterial strands (*Pseudonomas* sp., *R. eutropha*, etc.) for PHA production. Another interesting hydrocarbon substrate is methane, which is readily available in oilfields and from the degradation of organic matter and which can be utilized by type II methylotrophs. A yield of 0.55 g PHB g^{-1} CH$_4$ and a productivity of 0.031 g PHB L^{-1} h^{-1} were, for example, reported for *Methylocystis* ssp., which matched the theoretically possible transversion of a suchlike procedure very well.[43]

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5. Raw Materials for PHAs: Additional Remarks

As currently a main carbon source for commercial PHAs are still food-based glucose and vegetable oils, there should (and will) be much more research on the alternative strategies (e.g., hydrocarbons) as described above. PHA production within a biorefinery (a facility that integrates biomass conversion processes and equipment to produce fuels, power, and chemicals from biomass)[44] is intensively developed, for example, together with bioethanol production from lignocellulose, plant oils, or fats and plant starch.[45] In the future, the second generation industrial biorefineries are supposed to refine lignocellulose, including different agricultural residues, agricultural wastes, forestry residues, and energy crops. Refining of the lignocellulose residues can afford a large amount of hemicellulose hydolysates in the pretreatment process. These contain sugars that can be transformed to the PHAs. Furthermore, optimizations of the fermentation conditions is required to improve the productivity.[3,11,46]

PHB is mainly produced by utilization of microorganisms from renewable feedstock as mentioned above. The recovery of PHAs from the bacterial cells is challenging, as they are tightly linked to biomass. This requires release from cells and prior to isolation and purification, which is an additional step that makes it different from many other biotechnological processes where the product the products are outside the cells because of secretion into the medium, or because synthesis in vitro in a cell-free enzyme reactor. This fact contributes remarkably to higher costs of production. In addition, the granules in which PHAs are stored are also of economic interest, as they may be suitable for nanobeads for drug delivery systems or protein purification. PHA recovery can be accomplished by, for example, solvent extraction, chemical disruption, enzymatic cell disruption, mechanical disruption, supercritical fluids extraction, genetically engineered cell fragility, air classification, dissolved-air flotation, or spontaneous release of PHA granules. For instance, disruption by surfactants such as, for example, sodium dodecyl sulfate (SDS) and others works via their disintegration of cells by incorporation of themselves into the lipid bilayer of the cytoplasmic membrane of the cell envelope. For *R. eutropha* ells, this release was, for example, described for PHB into the solution, where the polymers were surrounded by cellular debris as the surfactant can also solubilize other cellular materials. Addition of chelating agents can increase the amount of released PHAs.[1] Enzymatic cell disruption can be accomplished via different enzymes, for example, proteases, nucleases, lysozyme, and lipases that have hydrolytic effects on proteins and other polymers of the bacterial cells but only minor effects on PHAs. They can thus initiate cell lysis for PHA recovery. Several combinations of enzymes and chemicals were also investigated. Upon release of PHA granules and the primary purification step, often additional steps have to be done to obtain PHA products with sufficient purity. These can be treatment with hydrogen peroxide in combination with enzymatic disruption processes or the chelating agents, ozone treatment or blending with other polymers followed by additional solvent extraction (e.g., with chloroform).[47] With regard to costs, purity, and so on., all these methods have specific advantages and disadvantages that have been reviewed elsewhere in detail.[1]

In general, economically friendly and reliable raw materials are essential, and—due to competition with crop area and price
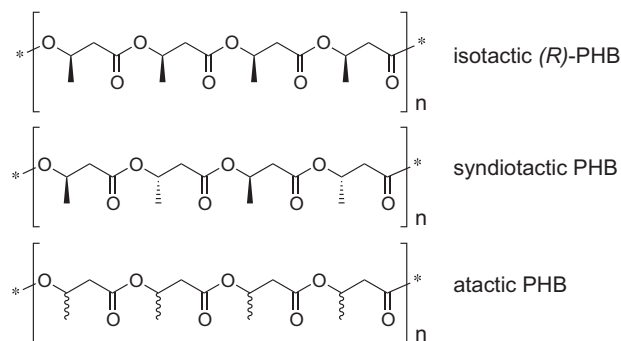
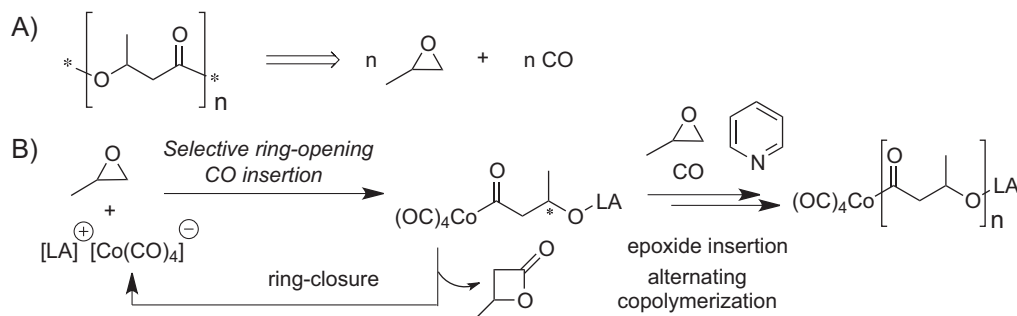**Figure 6.** Tacticity and stereoisomers of PHB.

volatility of sugar and starch—also crude oil is still an important source for materials production. Low costs and good availability are further important factors. The established value chains result in an expected low investment, which can lead to lower prices for the end consumers. Therefore, biodegradable polymers that are derived from fossil resources are still very interesting and partially growing in the markets. Difficulties of biochemical routes can be the lack of tacticity control and the time-consuming purification. Therefore—in addition to the biotechnological approaches—also new synthetic/catalytic routes come increasingly into the focus for PHA production, which are addressed in the next section.

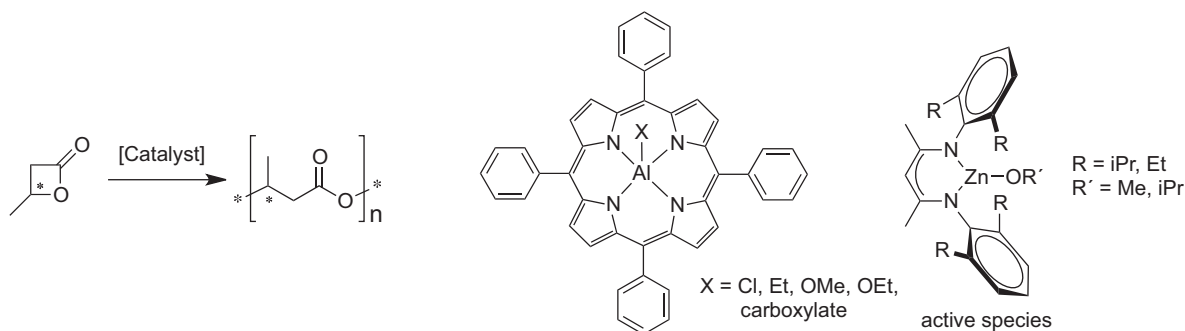## 6. Synthetic Routes Toward PHB from Fossil Fuel-Based Monomers

6.1. General Remarks on Tacticity

The tacticity of the homopolymers influences their properties: while atactic PHB is an oil, isotactic PHB has a high melting point. A lower melting point can be obtained by decreasing the isotacticity to 70–80%.[2–5] Syndiotactic PHB was later synthesized and showed also interesting properties: for instance, young modulus depends strongly on syndiotacticity, and while rising its degree, the melting transition increases linearly (183 °C for 94% syndiotacticity). Uniform crystalline ordering was proved by DSC that shows single and sharp transitions, which is different from variable isotactic PHBs, that show broad and thus superimposing melting transitions (120–150 °C). Stereocomplex formation between enantiomeric sections could be an explanation for this, as also known from other polymers, which offers to influence properties and thus new applications (**Figure 6**).[2–5]

Many different natural sources for PHAs have been found,[11] which are described in detail above. Determination of tacticity can be performed by means of NMR. 13C NMR spectra of natural PHB show four signals for each carbon atom of the repeating unit as long as end-group effects are disregarded. A change in stereoregularity results in a splitting of each signal because of diad and triad sequences.[5] Natural PHB is optically active. Therefore, if tacticity decreases, the torsion angle also changes, which enables a second and reliable methods for variable isotactic PHBs that is utilized in industry.[5,11]

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Figure 7. A) Retrosynthesis and B) epoxide/CO alternating copolymerization (simplified).[5]

Figure 8. ROP of β-BL and selected different catalysts for this reaction.[5] Active species can also dimerize.

6.2. Retrosynthesis of PHB and Direct Alternating Copolymerization of PO and CO

Propylene oxide and carbon monoxide are promising building blocks for the production of low cost PHB.[48] The industrial scale production of PO starts from propylene, which is mainly obtained from crude oil, and then oxidized with, for example, hydrogen peroxide. Furthermore, PO can also be obtained from renewable resources, for example, bioethanol. CO can be obtained from petroleum gas and also from biomass. The conversion of these feedstock is investigated by many researchers, and direct alternating copolymerization is a major issue here. This is, for example, accomplished by a Lewis acid by coordination to the oxygen atom, followed by CO insertion to yield the corresponding acyl compound. This intermediate can then further react, either by a backbiting reaction to produce the β-lactone under regeneration of the active species $[LA]^+[Co(CO)_4]^-$, or the alternating copolymerization of CO and PO, mediated by pyrimidine that plays an important role. Repeating steps yield polyhydroxybutyrate by multisite catalysis, which can be analyzed by means of in situ ATR-IR (**Figure 7**).[5]
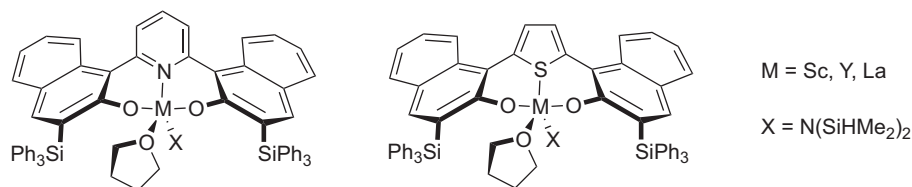
6.3. Ring-Opening Polymerization of β-BL

In general, a variety of good procedures have been described for the ROP of β-BL, which are more promising with regard to, for example, microstructure control.[49] In β-lactones, an alkyl cleavage 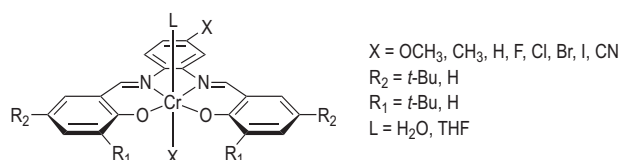and an acyl cleavage can occur (**Figure 8**). The first mechanism occurs with retention of the stereochemistry, whereas the nucleophilic attack on the b-carbon atom results in an inversion. It depends on different factors which mechanism is apparent, and both mechanism may also operate at the same time, which has an important impact on the polymer stereochemistry. While also cationic and enzymatic mechanism can be applied for this ROP, coordinative insertion mechanism are most promising due to the possibilities to control the stereoregularity and to introduce different pendant groups. Due to the fact that many catalysts comprise metals with different toxicity, removing of the metals after synthesis or low concentrations are important, which requires the usage of very active catalysts.[50]

A classification can be made into the continuous development from heterogeneous to discrete organometallic compounds, the utilization of rare-earth metal catalysts and dual site ROP. With regard to the first, it was early discovered that water and $AliBu_3$ or tetrabutylaluminoxane (TIBAO) catalyze the ROP of β-BL and resulted in mixtures of isotactic enriched and atactic polymers that can be separated. Though high molecular weights could be obtained ($\approx$300.000 g mol^{-1}), a relatively broad PD of 6 and rather low activity of the catalytic system (reactions up to 7 days) show the limits of this approach. This could be further improved by means of different strategies (almumoxane derivatives, addition of chiral cobalt salens, etc.).[51] Important examples are also aluminum-based porphyrins and salens, as well as Zn-based catalysts.[5,48]

Rare-earth metal catalysts described for the ROP of β-BL are manifold. For instance, certain yttrium catalysts as, for example, amino-alkoxy-bis(phenolate)yttrium were shown to combine high activity for the ROP of b-BL under mild condition, a living

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Figure 9. Catalysts based on yttrium, Sc, and La for the ROP of β-BL.[5,52] Also other residues as Ph are possible.

Figure 10. Active Cr^{III} (salphen) complexes for the ROP of β-BL.[5]

character of the polymerization and a high degree of stereoselectivity. Also Sc and La compounds with different ligand motifs were developed and showed similar good ROP catalysis. Interestingly, thiophene derivatives afford slightly syndiotactic-enriched polymers with $P_r < 0.70$, whereas pyridine-containing complexes also transform racemic b-BL to syndiotactic polymers with higher stereocontrol ($P_r = 0.87$). It was also shown that the living ROP is comparable to that of the yttrium-based complexes with similar trends, such as solvent dependency (**Figure 9**).[52]

A different type of ROP catalysts was reported by means of chromium salphen complexes, which convert racemic β-BL to isotactic enriched PHB with a molecular weight of up to 800 000 g mol^{-1} (PD up to 8.5). At moderate reaction condition, the catalysts combine high activity and high molecular weight of the products with a desired stereocontrol. This procedure could be further improved by similar complexes and also by dimer complexes with bridging units (**Figure 10**).[5]

The stereoselective synthesis of β-BL and subsequent ROP can also be performed, where a classification can be made into synthesis from chiral or prochiral lactone precursors and a lactone synthesis via ring expansion of epoxides. A closer look at these procedures would be beyond the scope of this article—these studies have been reviewed elsewhere in detail.[5]

The chemical synthesis of isotactic P3HB via the ROP of biosourced racemic cyclic diolide (DL; the dimer of butyrolactone) has also been described.[53] With stereoselective racemic catalysts, the obtained polymers feature high melting temperature (171 °C) and high molecular weight ($M_n = 1.54 \times 10^5$ g mol^{-1}). With enantiomeric catalysts, enantiopure (R,R)-DL and (S,S)-DL are yielded with <99% e.e. and the corresponding polymers with $T_m = 175$ °C.[53]

7. General Areas of Applications of PHAs

As is the case with all bioplastics, PHAs can be used for certain application when its environmental and property performance offers benefits.[2–9] The strictly isotactic microstructure of fermentative PHB has drawbacks for processing. It can be used for bottles and containers as well as trays, cups, and plates. These products can be conveniently composed due to their biodegradability under aerobic and anaerobic conditions. Furthermore, one of the most established applications for biodegradable polymers today is flexible films, which are used for, for example, compostable waste bags or carrier bags for organic waste. They can thus contribute to reduce landfill and to make the composting process more efficient. Biodegradable much films in agriculture offer the opportunity to reduce labor and disposal costs. Another application is packaging for (snack) foods, which makes use of the barrier properties of these polymers as an important trait. Furthermore, competition with polyethylene arises for applications in which biodegradability is not necessarily required.[5]

The wide field of medical applications of PHAs and their copolymers is addressed in the next section.

8. Biomedical Applications of PHAs

Due to their prosperous properties, PHAs find many applications in medicine.[54] A hydrophilication of these polymers can be performed with different methods, for example, addition of polar (functional) groups, block-copolymerization or graft-copolymerization. Attachment of hydrophilic polyethylene glycol (PEG), PEGylation, can be accomplished via synthetic and biological procedures.[55] For instance, supramolecular hydrogels have been prepared from PEG-PHB-PEG triblock copolymers from aqueous mixtures, which were then coupled to cyclodextrines (cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic cavity). Linear polymers can penetrate the inner cavity of these cyclodextrine to form inclusion complexes. The regioselective inclusion complexation of PEG and CD facilitated the formation of networks, which showed high potential for controlled long-term release applications with a fluorosceine isothiocyanate probe as a model compound (**Figure 11**).[56]

Further examples are active polymer surfaces for tissue engineering. Surface morphology, nanotopography, mechanical properties, and degradation products are known to influence cell behavior with regard to attachment, viability, or migration. In this context, attachment and proliferation of neural olfactory ensheathing cells (OECs) were investigated and could be remarkably increased on PHA/PEG systems by means of PEG100 (17.0% for PHB and 32.2% for P(HB-co-HV). Cell attachment was facilitated by increasing the surface hydrophilicity, water contact angles decreased and water uptake increased upon biopolymer and PEG loading, while cells maintained high viability. Promotion of biopolymer compatibility and degradability did not affect material properties, where the extension to break of the blends increased, while the crystallinity decreased.[57] Further examples for biomedical applications of PHAs are fluorescent bile
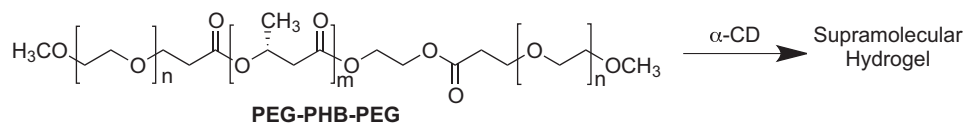
Figure 11. PEG-PHB-PEG copolymers for hydrogel formation together with α-CD for applications as effective drug delivery systems.[56]

acid PHB-PEG block copolymeric nanoparticles for drug delivery applications[58] or also the Bio-PEGylation of PHB that promotes nerve cell health and migration.[59] These and related examples have been reviewed elsewhere in detail.[54,55] In this context, also blend microspheres of poly(3-hydroxybutyrate) and cellulose acetate phthalate were applied for colon delivery of the anticancer drug 5-fluorouracil.[60,61] This is thus an interesting and valuable addition to other 5-fluoruracil targeting systems.[62]

9. Conclusions

PHAs are very important polymers that find a variety of applications in different fields, from commodities up to the biomedical area. Different biological and also various synthetic procedures enable accesses to a wide variety of suchlike polyesters and copolymers with different monomer compositions, chain lengths, and tacticities and thus properties that can vary over a range comparable to that of i-PP or PET. Different PHA composites and blends with other polymers are also very important for different applications. The biosynthesis pathways of PHAs have been elucidated an can be modified. Furthermore, a sustainable and comprehensive PHA-based industry has been established and is currently further developed. By integration of the PHA production into biorefinery frameworks, both biofuels and biopolymers can be produced efficiently, which is a very efficient strategy that is also similar to the petrochemical industry.

Conflict of Interest

The author declares no conflict of interest.

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