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Polyester Stereocomplexes Beyond PLA: Could Synthetic Opportunities Revolutionize Established Material Blending?

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This review summarizes the current literature regarding stereocomplexation of different polyesters based on α- as well as β-hydroxy acids beyond the well-known poly(lactic acid). Representing the initial step toward stereocomplexation, synthetic approaches needed to obtain and analyze isotactic polyesters are summarized. The basic technologies for the preparation and characterization of the respective stereocomplexes (SCs) are described, and published material properties are related to the structure of the respective polyesters. The variety of available SC materials is very limited despite the multiple options provided by state-of-the-art stereoselective monomer synthesis and polymerization methods. A combination of knowledge from the three scientific areas (i.e., organic chemistry, synthetic macromolecular chemistry, and materials science) thus has enormous potential to create novel materials with additional features enabled by the introduction of functional moieties to such materials besides the adjustment of thermal as well as mechanical properties.

1. Introduction

Ever since polymers were invented, they have been an interdisciplinary field between synthetic macromolecular chemistry, physical chemistry, physics, and materials science, in particular due to the manifold applications that were quickly found.

Polyesters as one example, are applied as packaging materials, for prosthesis, tissue engineering,[1] and drug delivery.[2–4] Representing a sustainable polymer class, they could solve current major problems such as environmental pollution due to microplastic contamination. This is mainly due to two facts: a) Many polyesters can be obtained from natural resources, and b) polyesters are biodegradable.[5] Although initially obtained by polycondensation by Carothers in 1932,[6] it was not until the 1950s that polyesters attracted considerable attention.[7] Poly(lactic acid) (PLA), probably representing the most well-known polyester, is produced nowadays from starch by fermentation yielding lactic acid, oligomerization and subsequent ring-opening polymerization (ROP) of lactide.[8] Obtained via green chemistry, the ROP even enables to tailor molar masses and end groups. However, PLA represents a brittle material with a low processing window of 12 °C[9] because the melting temperature is close to its degradation temperature.[10] Its brittleness necessitates the use of plasticizers, that is, substances whose extensive use is debated because of leakage from the material and resulting effects on human health.

On the other hand, a simple statistical copolymerization with another monomer can easily alter a homopolymer's property, a fact that is well-known among the polymer community.[11] The development of poly(lactic-*co*-glycolic acid) (PLGA), that is, the copolymer of lactide and glycolide, represents an excellent example.[12,13] The degradability as well as the thermal properties can be easily tuned, which has led to their commercialization under the trade name RESOMER.

In fact, there is a wealth of other monomers that can be applied for polyester synthesis, some even representing naturally occurring lactones. Already homopolymers offer a wide range of properties, and the parameter space offered by copolymerizations is far from being exploited, even by academia.[14] However, industry has limited itself to more traditional polyesters including PLA, PLGA, or polycaprolactone (PCL). Although poly(3-hydroxy butyric acid) (P3HB)[15] is simply produced by several microorganisms as a form of energy storage via fermentation with high molar mass, it has not found broad applications in commercial products so far. Why is that? Besides approval issues, in particular for bio-medical applications, economical reasons drive forward innovations in small steps. In view of that, blending represents an option to alter properties in a straightforward fashion minimizing the need to replace well-established materials.

Stereocomplexation represents a very specific type of blending that can occur when stereo-defined polymers with different tacticities or configurations are mixed. If stereoselective association prevails over the interactions between the parent polymers, new macromolecular arrangements are formed.[16]

Nature has been structuring via chirality ever since. Proteins and DNA double helix represent well-known examples. In fact, the first report about stereocomplexation was published by Pauling and Corey regarding the formation of "racemate species" based on polypeptides in 1953,[17] describing what is known today as stereocomplexes. Apart from other polyamides,[18–20] polyethers,[21,22] polythioethers,[23] polyketones,[24]

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vinyl-based polymers,[25] in particular, the polyester PLA is capable of undergoing stereocomplexation.[26,27]

Resulting in altered material properties[28] such as, slower hydrolysis kinetics,[29] increased temperature stability, higher degree of crystallinity and, therefore, altered mechanical properties,[26,30] these macroscopic properties are caused by structural features at the molecular level. Structural requirements for PLA stereocomplexation are based on crystallite formation,[31] conformation of the individual macromolecules in a 10_3 α- or 3_1 helix,[32] and ultimately tacticity. Playing with the latter, that is, with the configuration at the varying repeating units, actually offers another opportunity to alter polymer properties without even introducing structural isomers as building units.[12] This can easily lead to different macroscopic properties such as melting temperature T_m, degree of crystallinity or degradation rate. Stereocomplexation of such materials can further be used to widen the application range, offering more opportunities, again simply by blending.

Modern polymer materials must not only be able to meet the requirement of one specific problem but include additional benefit to provide added value. Following nature's example, as in proteins, the introduction of functional moieties to established materials represents a reasonable approach. But how can this be realized for biodegradable polyesters,[33] a material class that has not had thousands or millions of years of optimization time by the evolution? A small portion of functional monomers incorporated to a well-known matrix could serve the purpose. The combination with stereocomplexation would further expand the window of accessible properties compared to the isolated materials.

We provide an overview of synthetic approaches toward (functional) monomers suitable to produce polyesters, keeping in mind stereoselectivity as an ultimate requirement to produce novel materials suitable for stereocomplexation. Narrowing down the structural variety known for monomers, we briefly introduce opportunities to produce polyesters to finally further concentrate on the materials that have actually been utilized for this purpose. To encourage the scientific community to dive further into the interdisciplinary topic, we complement our review with a short introduction about the methods to produce stereocomplexes and to confirm their existence.

2. Strategies to Synthesize Stereo-Defined Polyesters

Polyesters that have been used for the preparation of stereocomplexes include poly(α-hydroxy acid)s (PαHA) and poly(β-hydroxy acid)s (PβHA). PαHA are based on poly(glycolic acid) (PGA), a non-chiral polyester featuring low solubility in common organic solvents. Substitution at PGA's methylene groups results in stereocenters and, hence, in PαHA that could be suited for stereocomplexation (**Figure 1**). PLA represents the most well-known PαHA capable of stereocomplexation, but several other isotactic PαHA such as, for example, poly(2-hydroxybutyric acid) (P2HB),[34] poly(2-hydroxy-3-methylbutyric acid) (P2H3MB),[35] poly(phenyllactic acid) (PPhLA)[36] or poly(mandelic acid) (PMA)[37,38] have been synthetically accessed. PβHA with stereoinformation represent substituted poly(3-hydroxypropanoic acid)s, several of which are known to undergo stereocomplexation (Figure 1).

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PαHA as well as PβHA can be obtained via polycondensation or ROP. For both strategies, the corresponding α- or β-hydroxy acids represent the key starting materials introducing chirality. Hydroxy acids are a large family of compounds often found as biological products.[39] Besides lactic acid, which can be obtained via bacterial fermentation in both enantiomeric

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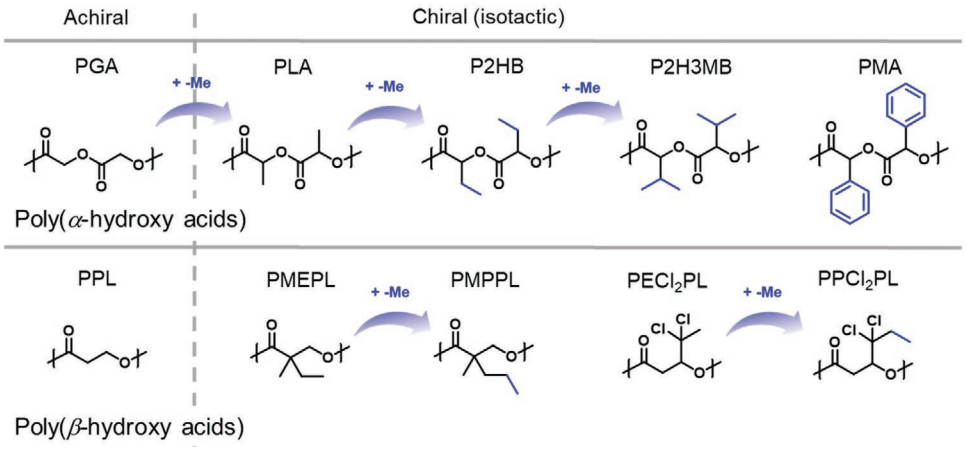

Figure 1. Schematic representation of the poly(α-hydroxy acids) and poly(β-hydroxy acids) potentially suited for stereocomplexation: poly(glycolic acid) (PGA), poly(2-hydroxybutanoic acid) (P2HB), poly(2-hydroxy-3-methylbutanoic acid) (P2H3MB), poly(propiolactone) (PPL), poly(α-methyl-α-ethyl-β-propiolactone) (PMEPL), poly(α-methyl-α-*n*-propyl-β-propiolactone) (PMPPL), poly(α-(1,1-bischloro)ethyl-β-propiolactone) ($PECl_2PL$), and poly(α-*n*-(1,1-bischloro)propyl-β-propiolactone) ($PPCl_2PL$).

forms, that is, L- or D-lactic acid,[40] other α-hydroxy acids such as 2-hydroxybutanoic acid (2HB) or 2-hydroxy 3-methylbutanoic acid (2H3MB) can be synthesized in a similar fashion. In particular, these three monomers are frequently employed for the preparation of polyesters used in stereocomplexation. However, many other α-hydroxy acids are commercially available with high enantiopurity. Examples include 2-hydroxy-3-methylpentanoic acid, 2-hydroxy-3,3-dimethylbutyric acid, mandelic acid, 2-hydroxy-2-phenylpropionic acid, 3-phenyl lactic acid, and 2-hydroxy-2-methyl-3-phenylpropionic acid.

2.1. Polycondensation of α- and β-Hydroxy Acids

Already these simple hydroxy acids represent AB monomers to obtain the corresponding polyesters via polycondensation,[41] a method that has been known since the first polycondensation of lactic acid was reported by Carothers in 1932.[6] The approach has since been developed further to increase the molar mass of the PLA accessible by direct polycondensation (**Figure 2**).[42,43] Post synthesis modifications through chain coupling or melt treatment represent two routes that can be applied on a large scale. On the other hand, azeotropic and enzymatic polycondensation[44] enable the preparation of high molar mass PLA from its α-hydroxy acid monomer.

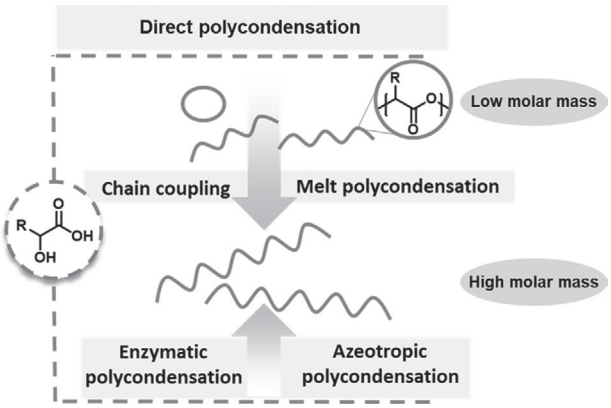

Figure 2. Schematic representation of polycondensation approaches of α-hydroxy acids.

Whereas polycondensation is used for polymerization of α-hydroxy acids such as lactic acid, 2HB, and 2H3MB, the polycondensation of β-hydroxy acids is less common. It has, to the best of our knowledge, only successfully been reported for a derivative of malic acid, albeit with comparably low molar mass and high dispersity.[45]

A major benefit of polycondensation is the stereocontrol during polymerization as the configuration at the chiral center of the hydroxy acid is often retained.[46,47] However, long reaction times, high temperatures and an efficient water removal are required, resulting in a moderate control of molar mass and dispersity.[46,48]

2.2. ROP of α- and β-Hydroxy Acid Based Monomers

Enabling the tuning of molar masses and low polydispersity values, the ROP of glycolides and β-lactones has become a common procedure to prepare PαHA as well as PβHA, respectively. Stereocontrol is usually granted for ROP of enantiopure monomers,[49,50] making their preparation a central issue. A large variety of catalysts can be employed to tune the polymerization of such monomers; however, the optimum reaction conditions have to be carefully evaluated based on the reaction mechanism as well as the properties of the monomers.[14,51–53]

Being less exploited, the ROP of *O*-carboxyanhydrides (OCAs) represents an alternative route to yield PαHA, whereas the ROP of dioxolanones (DOXs) enables the synthesis of poly(ester ketals) as well as PαHA.

2.2.1. Monomer Synthesis and Polymerization to Yield PαHA via ROP

The stereo-controlled synthesis of cyclic esters from α-hydroxy acids represents a key step for the synthesis of the

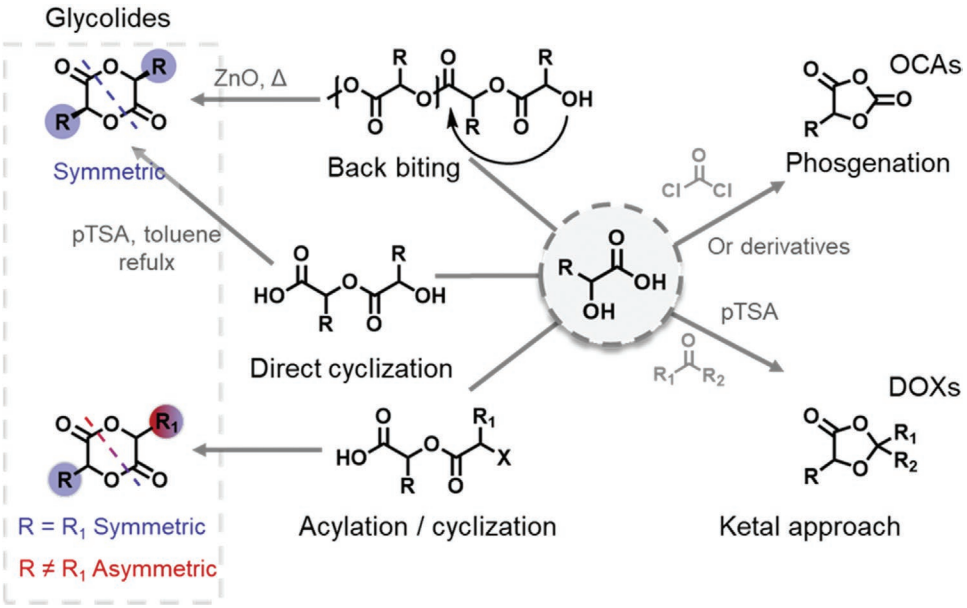

Figure 3. Schematic representation of synthetic strategies to obtain monomers for ROP to obtain PαHAs. pTSA, *p*-toluensulfonic acid; OCAs, *O*-carboxyanhydrides; DOX, dioxolanones.

corresponding polyesters to be used for stereocomplexation. Initial reports on the formation of cyclic diesters of αHA such as lactic or glycolic acid date back to the 19th century.[54–56] Nowadays, glycolide (the cyclic diester of glycolic acid) and lactide (the cyclic diester of lactic acid) represent common monomers for the ROP to produce PαHA and are commercially available. All three stereoisomers of lactide, that is, D-lactide, L-lactide, *meso*-lactide as well as the racemate can be purchased. Prepolymer backbiting and the biotechnological synthesis (**Figure 3**) are the most common ways to produce lactide industrially.[8,57] (3S,6S)-3,6-Diisopropyl-1,4-dioxane-2,5-dione (**2** in **Figure 4**) represents the only other substituted glycolide on the market, to the best of our knowledge. Monomer synthesis hence represents a polymer chemist's first task if new polyester stereocomplexes are targeted.

Taking glycolide as basic structure, a substitution at both or only one methylene moiety leads to symmetric or asymmetric monomers, respectively (Figure 3). Direct cyclization and backbiting of oligomers exclusively yield symmetrically substituted glycolides, whereas asymmetric glycolides can only be produced via the acylation/cyclization pathway. In particular, the latter is suitable to introduce functional moieties, as recently reviewed by Yu et al.[58] as well as by Becker and Wurm.[59] The synthesis of OCAs has been adopted from the more well-known NCAs,[60–62] whereas the ketal approach yielding DOX represents a rather new field of research. As central issue with respect to stereocomplexation, we hence focus on enantiopurity of the cyclic esters reported here. It should be noted that, despite the vast series of monomers accessible via different reaction pathways, only few have been utilized for the synthesis of stereo defined polymers and the preparation of stereocomplexes.

Synthesis of Symmetrically Substituted Glycolides: The direct cyclization of α-hydroxy acids is a straightforward technique used for the preparation of symmetrically substituted glycolides with alkyl,[63–66] alkynyl,[67] PEGylated,[68] and aromatic[69–71] substituents (Figure 4).

To minimize the formation of oligomers, the cyclization is performed in a diluted solution of the target α-hydroxy acid in toluene or xylenes at reflux conditions employing *p*-toluensulfonic acid (*p*TSA) as a catalyst. The equilibrium reaction is driven toward the formation of the glycolide derivatives by removal of the condensation byproduct water using a Barrett trap. Typical reaction conditions involve several days of reaction time, as summarized in **Table 1**. Subsequent to simple purification by means of distillation or recrystallization, the products were obtained in low to moderate yields (15–71%).

Stereochemistry represents a central aspect to be taken into account. In glycolides obtained from chiral α-hydroxy acids, the carbon atoms adjacent to the ester moieties (positions 3 and 6) represent stereocenters (Figure 4). In principle, the two enantiomers with *R,R* and *S,S* configuration, respectively, as well as the *meso* form can result from cyclization.

In the majority of reports the cyclization is performed employing racemic α-hydroxy acids, resulting in a mixture of the two enantiomers and the *meso* form. Representing a diastereomer, the latter can be separated from the mixture of the two enantiomers in *R,R* and *S,S* configuration.[66] However, when enantiopure α-hydroxy acids are converted, the stereochemistry is retained, as reported by Noga et al.[71] for the dibenzyloxy functionalized glycolide **9**, where epimerization was avoided.

Synthesis of Asymmetrically Substituted Glycolides: To enable access to asymmetrically substituted glycolides, a slightly more laborious route is required. The introduction of asymmetry takes advantage from the difference in reactivity of carboxylic acid derivatives. In a two or three-step synthetic approach, a hydroxy acid is first esterified using a halogen-substituted acyl bromide such as, for example, 2-bromoacetyl bromide, to

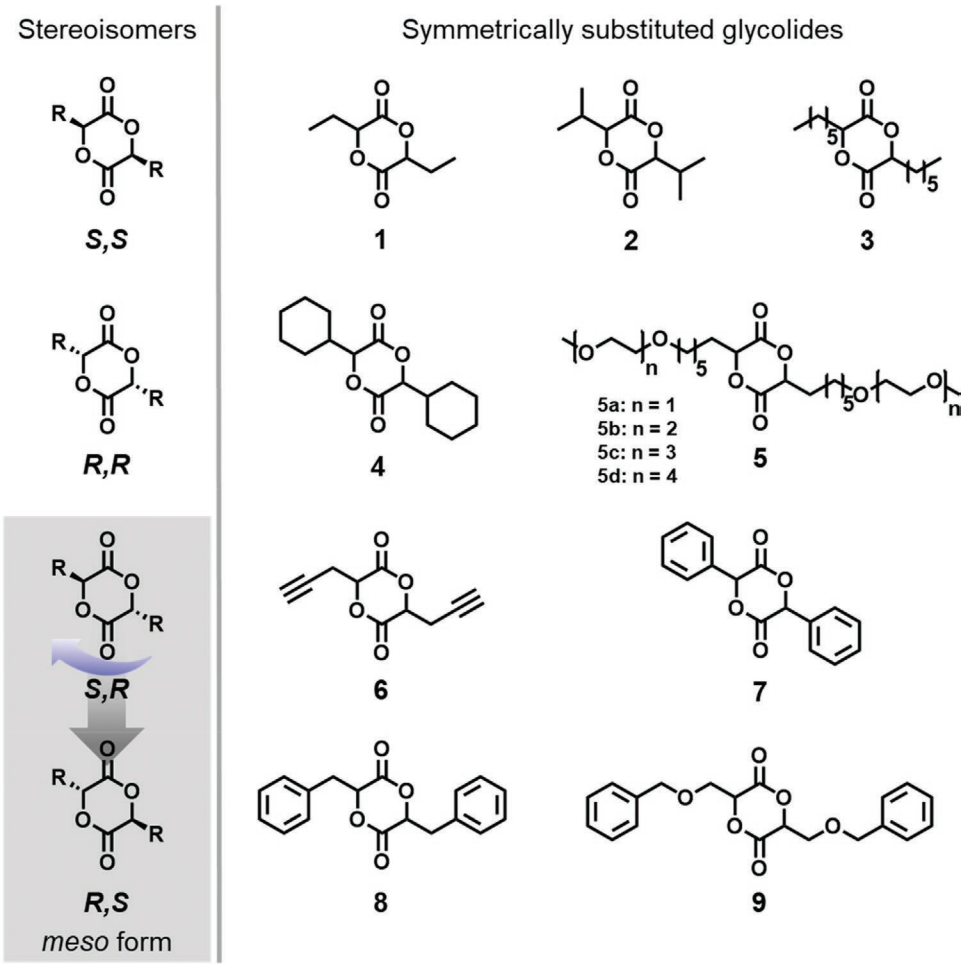

Figure 4. Schematic representation of symmetrically substituted glycolides obtained via the direct cyclization of α-hydroxy acids. Note that the stereoisomers with *R,S* configuration and *S,R* configuration represent identical *meso*-forms for all symmetric glycolides.

Table 1. Experimental overview of the symmetric glycolides obtained from direct cyclization. Structures are depicted in Figure 4.

Entry	Reaction conditions[a]			Stereoisomer ratio RR or SS/*meso*	Yield [%]	Ref.
	[αHA][mol L^{-1}]	Catalyst loading [mol%]	Time[d]			
1	0.14	1	4	1/1	63	[63]
2	0.1	30	6	1/0[b]	16	[66]
3	0.1	30	4	1/1	65	[63]
	0.06	10	1	mixture	65	[65]
4	0.1	30	6	1/0[b]	21	[66]
5a	0.06	5	3	n.d.	41	[68]
5b	0.06	5	3	n.d.	28	[68]
5c	0.06	5	3	n.d.	21	[68]
5d	0.06	5	3	n.d.	15	[68]
6	0.09	5	3	mixture	34	[67]
7[c]	0.07	3	3	1/1	53	[69]
8	0.02	0.8	3	n.d.	42	[70]
9	0.03	2	20	1/0	21	[71]

[a]Catalyst: *p*-toluensulfonic acid. Reaction performed in reflux conditions. If not indicated otherwise, toluene was used as solvent; [b]The ratio of the RR and SS forms was 1:1; [c]Xylene was used as solvent.

produce a bromo-substituted carboxylic acid as linear precursor, which is converted to the desired product via an intramolecular nucleophilic substitution under basic conditions. The acylation reaction is either performed in bulk at 75–80 °C, or in solution at 0 or 25 °C in the presence of triethylamine as scavenger for the formed hydrobromic acid (**Table 2**). Subsequent to purification of the linear precursor, the cyclization step is performed in acetone or acetonitrile under reflux conditions at low concentrations, again employing a base as acid scavenger (e.g., triethylamine, sodium bicarbonate). The acylation as well as the cyclization step have been modified to account for the availability of the two main educts (**22**, **23**, **25**), including a replacement of the acyl bromide by a *N,N′*-dicyclohexylcarbodiimide (DCC) activated carboxylic acid, as well as an additional Finkelstein reaction prior to the cyclization to increase the leaving group quality during the nucleophilic substitution.[72]

Based on the acyl bromide used in the linear precursor synthesis, the substituted dilactones are based on glycolide, lactide, or can carry ethyl or other substituents (**Figure 5**). Singly substituted glycolides feature one asymmetric carbon atom. Hence racemates of the two enantiomers in *R* or *S* configuration are produced from racemic starting materials. For synthetic procedures, starting from other acyl bromides, two stereocenters are usually introduced, resulting in the four stereoisomers depicted in Figure 5.

The acylation/cyclization approach has been applied for the synthesis of a wide range of substituents, including alkyl,[63,64,73] alkenyl, alkynyl,[74] halogenated,[75] PEGylated,[76] azide-functional,[74] and aromatic[72,73,76,77] moieties (Figure 5). Alkenyl, alkynyl, and azide functionalities can serve as moieties for further modification, either at the monomer or in a post polymerization modification via click chemistry.[59] Moreover, the synthetic route has been adopted for the preparation of substituted morpholine 2,5-diones from α-amino acids,[78,79] as well as for the synthesis of cyclic diesters with larger ring size, such as salicidelactide (**40** in Figure 5).[77]

A comparison of the direct cyclization (vide supra) with the acylation/cyclization pathway was reported by Yin and Baker[63] for the symmetrically substituted diethylglycolide (**1** in Figure 4) from racemic reactants. The direct cyclization resulted in a higher yield of 63% comprising an equimolar ratio of diastereomers, whereas the two-step reaction yielded 41% of **1** and a decreased fraction of the *meso* form (4:1 mixture of the *R,R*/*S,S* and *R,S* diastereomers).

It should be noted that, despite the variety of reported asymmetrically substituted glycolides, in particular most compounds including a quarternary carbon atom have not been used as monomers for a ROP but rather served as intermediates for the synthesis of other classes of compounds, as performed by Schöllkopf et al. for **27**–**37**.[73]

ROP of Glycolides: The ROP of glycolides represents a well-established polymerization approach.[49,80–82] Used for the industrial production of PLA and PLGA from lactide and glycolide, tin octanoate ($Sn(Oct)_2$) is one of the most frequently employed catalysts.[83–85] The polymerization mechanism proceeds via coordination insertion, based on the interaction of the tin center with one of the ester groups of the substituted glycolide and with a suitable initiator (e.g., alcohols). The latter interactions are developed at temperatures higher than 60 °C and allow good stereocontrol during the polymerization as the configuration of the monomer is retained after the ROP.[85,86] Besides $Sn(Oct)_2$, a plethora of metal catalysts based on transition metals[81,83,87,88] as well as alkaline earth metal complexes[87,89] are able to promote the polymerization of lactide under mild conditions assuring the control of stereo-information, molar mass and dispersity during the polymerization. Delicate ligand design enables to tune the activity of the catalyst with respect to the stereochemistry of the monomer and, therefore, for example, to produce isotactic, syndiotactic or heterotactic polyesters.[49,87,90,91]

More recently, metal free approaches led to the development of catalysts mostly based on organic bases,[92–94] fluorinated alcohols,[95] phosphazenes, organic acids and *N*-heterocyclic carbenes.[96–98] These organic catalysts have been used for the ROP of lactide and lactones, assuring the tailoring of molar masses and dispersity of the final polyester. However, in comparison with the reaction mechanism of $Sn(Oct)_2$, multiple activation pathways have been reported for organic base catalysts for the ROP of lactide and lactones.[99–103] Several reports describe the tacticity of various PLA obtained from thiourea,[104] phosphazene,[105,106] *N*-heterocyclic carbene,[107] or mTBD[108] catalysis. Stereocomplexes from PLA obtained via thiourea catalysis have been successfully formed, showing the high potential of organocatalysts in the field, in particular as many are simply commercially available.[109]

Synthesis and ROP of OCAs: The polymerization of OCAs represents an alternative route to access PαHAs. Providing a brief introduction into the topic, the reader is kindly referred to the excellent reviews by Vaca and Bourissou[60] as well as by Zhong and Tong[61] for a more detailed overview.

The synthesis of OCAs was firstly reported by Davies in 1951 from glycolic, lactic as well as mandelic acid with phosgene.[110] More recently, phosgene has been replaced by diphosgene and triphosgene with similar reactivity,[111,112] enabling access to a range of OCAs from various α-hydroxy acids (**Figure 6**). It should be noted that several enantiopure α-hydroxy acids can be obtained from the respective amino acids, as summarized by Basu et al.[113] as well as Yin et al.[114] Retaining the configuration of the α-hydroxy acid, the synthetic approach provides the respective OCA in typical yields between 40% and 85%.[37,110–112,114–118]

Similar to the ROP of glycolides, the ROP of OCAs can be catalyzed by organobases such as DMAP[111] or other pyridine derivatives,[37] using alcohols as initiators. Whereas the ROP of a symmetrically substituted glycolide derivative yields the PαHA comprising two repeating units with the proper catalyst,[108,119,120] the loss of carbon dioxide during the ROP provides the PαHA with a single hydroxy acid as repeating unit (Figure 6).[111] The release of CO_2 represents also the major driving force for the ROP of OCAs, influencing not only the thermodynamics of the polymerization[121] but also increasing the polymerization rate in comparison to a ROP of a glycolide under the same experimental conditions,[111] as reported for the ROP of **42**.

Many other catalyst types known from the ROP of glycolides such as *N*-heterocyclic carbenes or various metal-based catalysts are also suited to polymerize OCAs.[61] In particular for the latter, ligand design enables stereocontrol during the ROP to

Table 2. Experimental overview of the asymmetrically substituted glycolides obtained from the acylation cyclization pathway. Structures are depicted in Figure 5.

Entry	Reaction conditions		Stereoisomer ratio RR:SS/SR:RS	Overall yield [%]	Ref.
	Acylation	Cyclization			
10	2-Bromopropionyl bromide, glycolic acid, 1,4-dioxane, 15 °C, 2 h	DMF, Na_2CO_3, 90 °C, 2.5 h	Racemate	43	[203]
11	2-Bromoacetyl bromide, 2-hydroxy- butyric acid, NEt_3, Et_2O, 0 °C, 6 h	Acetone, $NaHCO_3$, reflux, overnight	Racemate	27	[108]
12	1. 2-Bromoacetyl bromide, CH_2Cl_2, DMAP, 0 °C 2. Allyl-glycolic acid, NEt_3, RT, 16 h	DMF, Na_2CO_3, RT, 16 h	n.d.	40	[204]
13	2-Bromopropionyl bromide, hydroxy acid,[a] bulk, 75–80 °C, 12 h	Acetone, NEt_3, reflux, 3 h	n.d.	35	[64]
14			n.d.	40	
15			n.d.	45	
16	2-Bromopropionyl bromide, 2-hydroxy-4-pentynoic acid, DMAP CH_2Cl_2, NEt_3, 0–25 °C, 18 h	DMF, Na_2CO_3, RT, 46 h	n.d.	41	[205]
17	2-Bromopropionyl chloride, hydroxy acid,[a] NEt_3, CH_3CN, 0–25 °C, 0.5 h	CH_3CN, NEt_3, 70 °C, 3 h	n.d.	43	[74]
18			n.d.	46	
19	2-Bromopropionyl bromide, (S)-mandelic acid, NEt_3, CH_3CN, 0–25 °C, 1 h	Acetone, $NaHCO_3$, reflux, overnight	n.d.	n.d.	[77]
20	2-Bromopropionyl bromide, 2-cyclohexyl-2-hydroxyacetic acid, NEt_3, THF, 0–25 °C, overnight	Acetone, $NaHCO_3$, reflux, 2 days	n.d.	59	[66]
21	2-Bromopropionyl bromide, D,L-3-phenyllactic acid, bulk, 90 °C, 12 h	Acetone, NEt_3, reflux, 3 h	n.d.	35	[64]
22	2-Bromo-propionic acid, hydroxy acid,[a] bulk, 75 °C, 6 h	1. Acetone, KI, reflux, 12 h 2. Acetone, DIEA, reflux, 9 h	n. d.	40	[72]
23	1. *(S)*-2-Bromo-propionic acid, HOBt, CH_2Cl_2, DCC 0–25 °C, 1 h 2. Hydroxy acid,[a] CH_2Cl_2, 25 °C, 12 h	1. Acetone, KI, reflux, 12 h 2. Acetone, DIEA, reflux, 9 h	n. d.	66	[72]
24	2-Bromopropionyl chloride, hydroxy acid,[a] NEt_3, CH_3CN, 0–25 °C, 0.5 h	CH_3CN, NEt_3, 70 °C, 3 h	Mixture	46	[74]
25	1. *(S)*-2-Bromo-propionic acid, HOBt, CH_2Cl_2, DCC 0–25 °C, 1 h 2. Hydroxy acid,[a] CH_2Cl_2, 25 °C, 12 h	1. Acetone, KI, reflux, 12 h 2. Acetone, DIEA, reflux, 9 h	n.d.	70	[72]
26	2-Bromopropionyl bromide, trifluorolactic acid, NEt_3, CH_3CN, 0–25 °C, 3 h	CH_3CN, NaH, 0–25 °C, 3.5 h	1/8	27	[75]
27	2-Bromopropionyl bromide, α-hydroxyisobutyric acid, bulk, 75 °C, 12 h	Acetone, NEt_3, reflux, 3 h	n.d.	46	[64]
28	2-Bromopropionyl chloride, hydroxy acid,[a] bulk, 80 °C, 2 h	Acetone, NEt_3, 60 °C, 1 h	n.d.	62	[73]
29			n.d.	72	
30			n.d.	75	
31			n.d.	66	
32			n.d.	73	
33			n.d.	85	
34			n.d.	67	
35			n.d.	70	
36			n.d.	85	
37			n.d.	80	
38	2-Bromooctadecanoyl chloride, hydroxy acid,[a] NEt_3, Et_2O, 0 °C, 5 h	Acetone,	n.d.	12	[76]
39		NEt_3, reflux, 16 h	n.d.	10	
40	2-Bromopropionyl bromide, salicylic acid, NEt_3, CH_3CN, 0–25 °C, 1 h	Acetone, $NaHCO_3$, reflux, overnight	n.d.	n.d.	[77]

[a]Please see Figure 5 for the corresponding α-hydroxy acid. HOBt, 1-hydroxybenzo-triazole; DIEA, *N,N*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DCC, *N,N´*-dicyclohexylcarbodiimide.

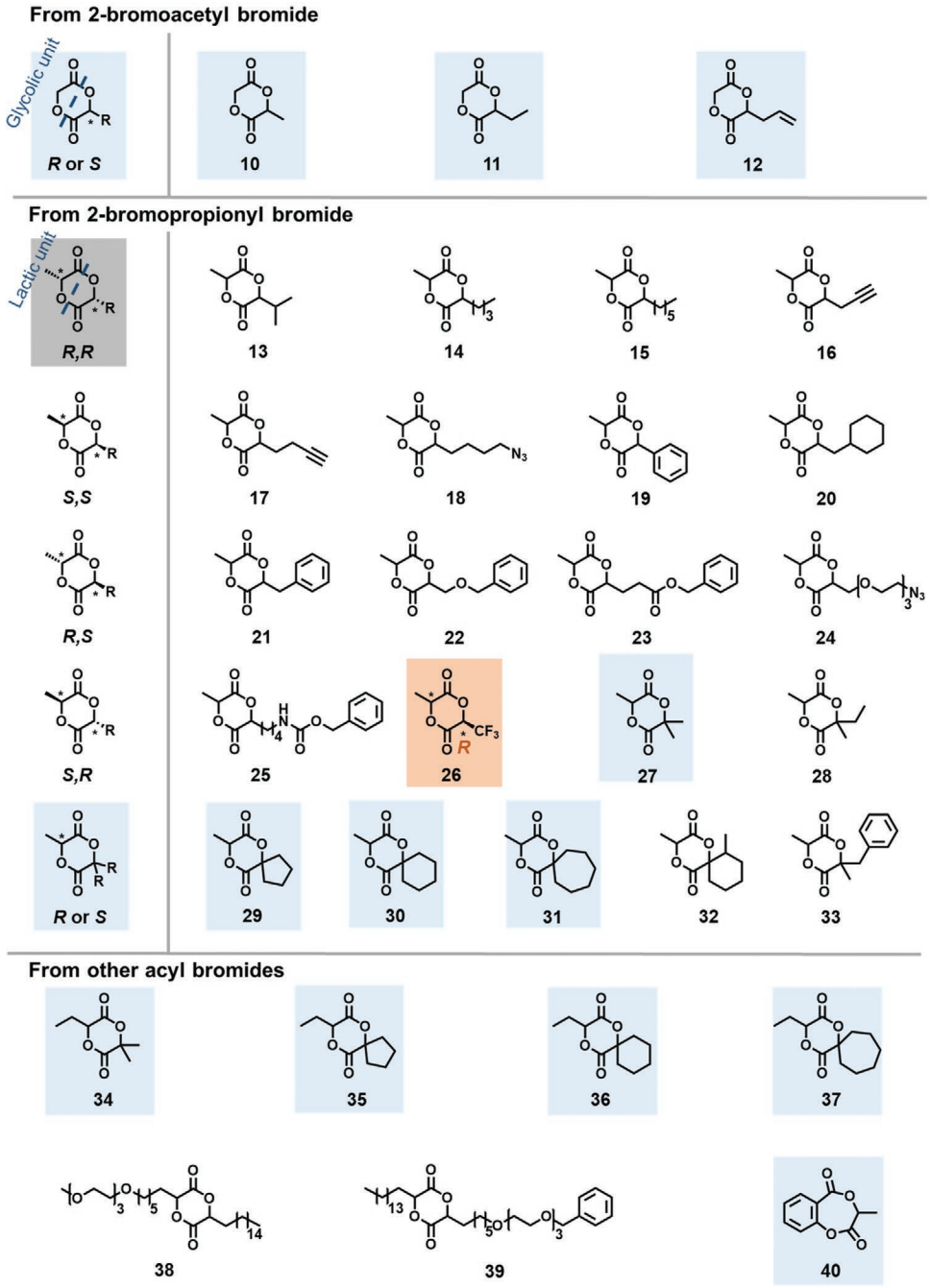

Figure 5. Schematic representation of asymmetrically substituted glycolides obtained via the acylation cyclization of α-hydroxy acids and the related salicidelactide (entry **40**). Compounds marked in blue include two possible stereoisomers, whereas the presence of two or more stereocenters results in at least four different stereoisomers for all other compounds. For the compound marked in orange (entry **26**) the stereochemistry of the asymmetric carbon is reversed due to the higher priority of the trifluoromethyl substituent.

obtain isotactic polyesters. It should be noted that the experimental conditions and the catalysts have to be carefully evaluated to minimize epimerization for organobase catalysts.[37] Additional activation by hydrogen bonding through thiourea moieties has been recently reported to give stereoregular poly(**43**) with both *R* as well as *S* configuration.[115] Initial differential scanning calorimetry (DSC) experiments even hinted toward the formation of stereocomplexes, although more detailed analyses have not yet been reported.

Synthesis and ROP of 1,3-Dioxolan-4-ones: Recently the polymerization of 1,3-dioxolan-4-ones (DOXs) yielding PαHA has been reported by Cairns et al. (**Figure 7**).[38] This route represents a valid alternative to OCAs and is based on non-toxic and inexpensive resources. Since the work of Cairns et al., only

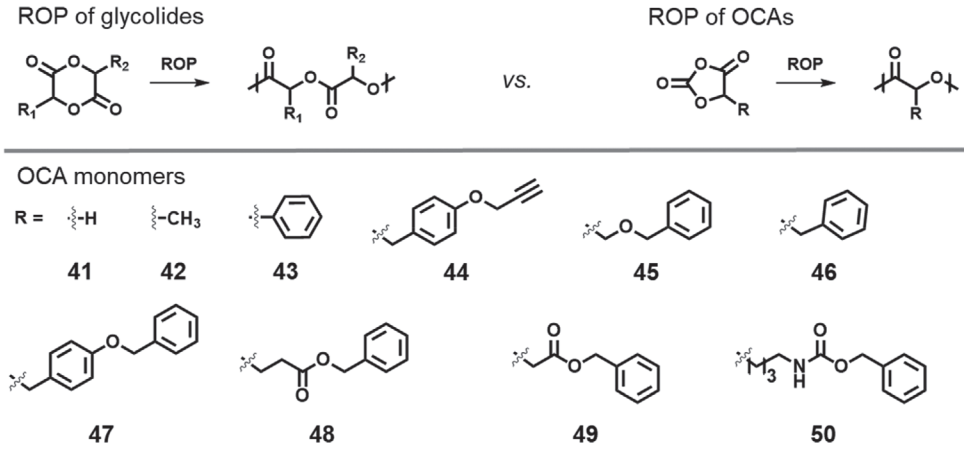

Figure 6. Schematic representation of the ring-opening polymerization (ROP) of *O*-carboxyanhydrides (OCAs) in direct comparison to the ROP of glycolides (top) and schematic representation of OCA monomers (bottom).

a few articles have been published regarding the polymerization of DOXs. However, the according monomers, that is, heterocycles that can be regarded as lactones as well as cyclic ketals, have long been known in the field of organic chemistry.

The synthesis of such compounds can be accomplished via an acid catalyzed reaction of α-hydroxy acids with aldehydes or ketones, respectively (Figure 3). The approach has provided aliphatic, aromatic and fluorinated DOX in yields between 20% and 95% (Figure 7).[122–124] Interests in the regiochemistry of the conversion of citric or tartaric acid with formaldehyde or acetone from the 1970s[123,125,126] have further triggered organic chemists to investigate the stereochemistry of the reaction. The configuration of the α-hydroxy acid is retained in 5-position of the DOX, and diastereomers are resulting from a *cis* or *trans* configuration of the substituent in 2-position, which is introduced via the carbonyl compound.[122]

Modified synthetic routes include the use of, for example, 2,2-dimethoxypropane[127] or alkynes[128] as substitutes for acetone or aldehydes, respectively, as well as sophisticated methods to introduce more complex or two different substituents in 5-position of the 1,3-dioxolane ring.[127,129,130]

The elimination of hydrochloric acid from the halide-substituted DOX **59**, **64**, or **74** yielded the alkylene functional heterocycles **60**, **65**, or **75**, respectively.[131,132] Miyagawa et al. confirmed the excellent stability of the DOX **65** in the absence of radical initiators.[132]

As first reported by Hillmyer for the respective 1,3-dioxanones yielding PβHA,[133] a ROP initiated by an alcohol and catalyzed by $Zn(Et)_2$ can proceed also for DOX to produce PαHA (Figure 7, top).[38] It should be noted that low amounts of the catalyst gave rise to poly(ester ketal)s, but at [catalyst ratios] / [initiator] ≥ 1, exclusively polyesters were obtained.[38,133] The latter is due to the loss of the carbonyl compound during the ROP via a Tishchenko reaction taking place at the catalytic metal center. The ROP including the elimination of the carbonyl compound proceeded in a more controlled fashion when aluminium-salen complexes were applied as catalysts.[38,134] The catalysts were also successfully applied for **51–55**, **57–58**, **62**, and **71**. Careful adjustment of the salen ligand as well as the polymerization conditions enabled the preparation of isotactic PMA.[38] Organic bases were scarcely investigated for the copolymerization of lactide and **51**,[38] whereas the standard catalyst $Sn(Oct)_2$ performed poorly for homopolymerizations of **51**, **52**, and **58** but yielded poly(ester ketal)s in a copolymerization with lactide.[135] Also cationic homopolymerization of **52** and **67** failed but the ketal moieties could be introduced into a number of copolymers.[136]

To summarize, the relatively new route to PαHAs has high potential, in particular as the range of monomers has not yet been fully exploited. For example, monomers such as the bis-dioxolanone **63**[137] could serve as branching moieties to enable access to more sophisticated polymer architectures based on the ROP of DOX. However, a suitable polymerization approach yielding the sole polyester or polyesteracetal species represent challenges to be met if the application of such materials is intended.

2.3. Monomer Synthesis from β-Hydroxy Acids and Their ROP

The synthesis of poly(β-hydroxy acid)s via ROP can be achieved using β-lactones as monomers. Several β-lactones such as β-propiolactone, α- and β-methyl- β-propiolactone are commercially available. A variety of other substituted β-lactones can be obtained via many different reaction pathways that have been comprehensively reviewed.[45,138] Besides the metal catalyzed insertion of carbon monoxide into epoxides,[139–141] the recent discovery of β-lactone synthetase, an enzyme that is capable of catalyzing β-lactone synthesis from β-hydroxy acids,[142,143] should be noted. However, the cyclization of β-bromo functionalized carboxylic acids under alkaline conditions in a nucleophilic substitution reaction represents the most direct route toward β-lactones (**Figure 8**).[144] Variations include the usage of other leaving groups or activated carboxylic acid derivatives and hydroxyl groups.[138]

The stereoselctive [2 + 2] cycloaddition of a ketene and an aldehyde or a ketone, respectively, represents an alternative route that was reported by Wynberg and Staring in 1982.[145] The initial catalyst quinidine[145,146] has since been modified, resulting in a variety of substituted β-lactones that could

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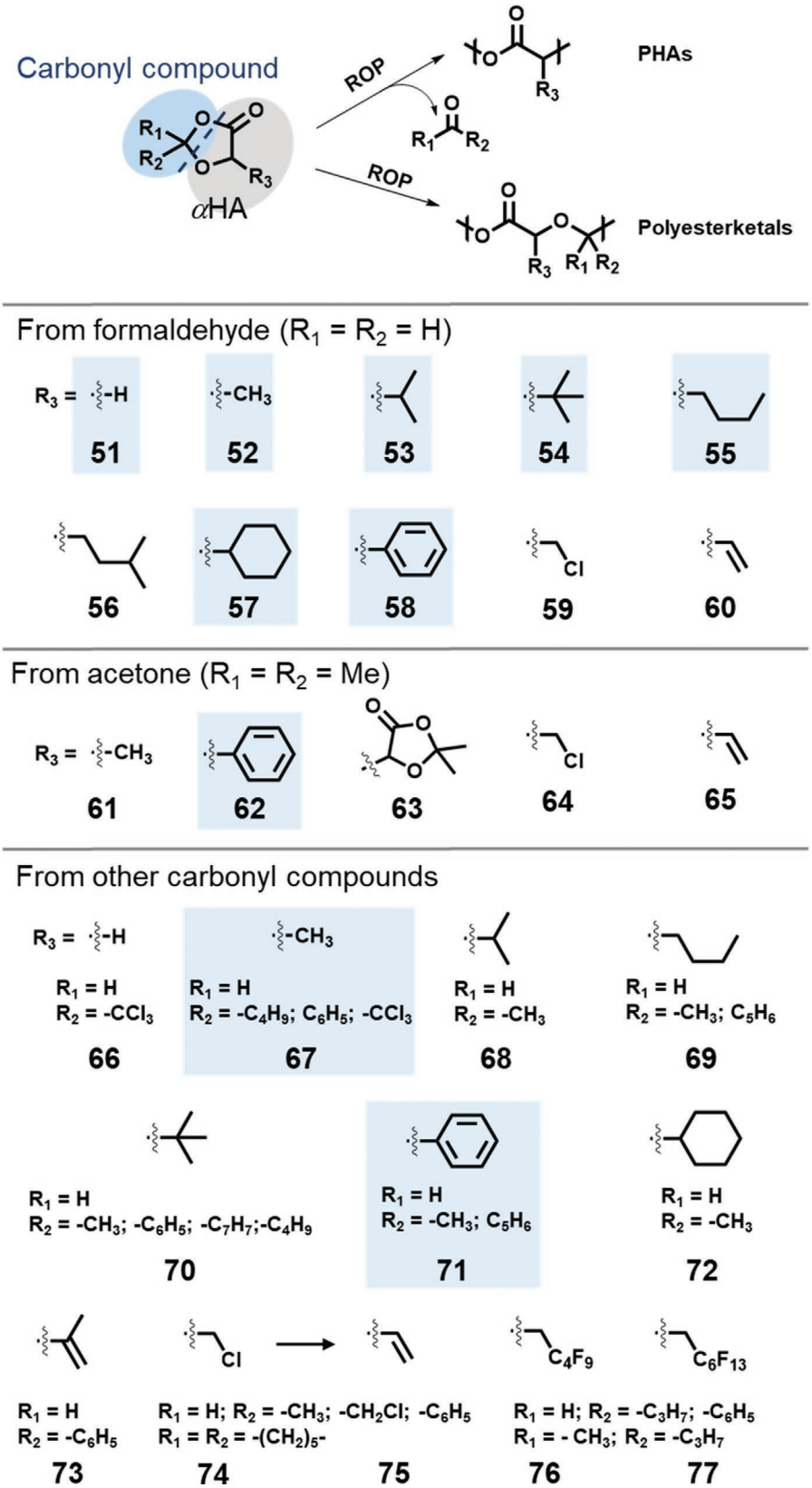

Figure 7. Schematic representation of the ROP of 1,3-dioxolan-4-ones (DOX) yielding PαHA or poly(ester ketal)s and DOX obtained from various α-hydroxy acids via the ketal approach.

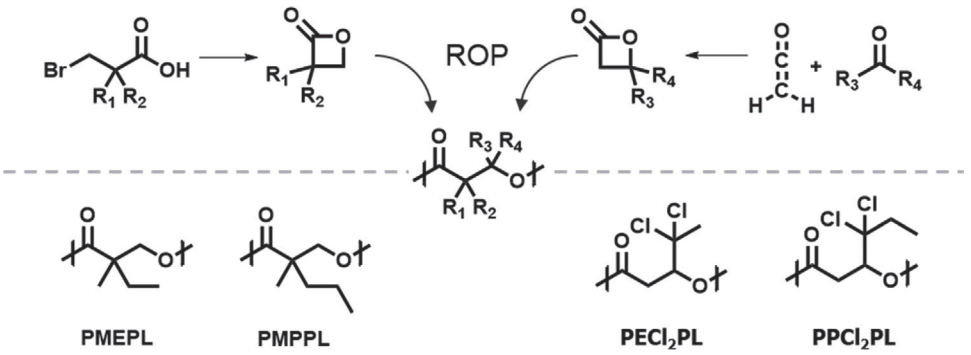

Figure 8. Schematic representation of common strategies to synthesize β-lactones and subsequent ring-opening polymerization to yield PβHA.

be obtained with enantiomeric excesses between 65% and 97%.[147,148] Catalysts such as BF_3 etherate yielded racemic products.[149]

Similar as the ROP yielding PαHA, the ROP of β-lactones can be performed via anionic, coordination insertion, carbocationic, carbene-based and enzymatic processes.[51,150,151] Among those mechanisms, the anionic ROP has been applied to obtain PβHA used for stereocomplexation because of its excellent control of molar mass and stereochemistry.[45] The polymerization of 1,3-dioxan-4-ones as alternative route toward PβHA is described in Section 2.2.1.[133]

3. Methods to Investigate Tacticity

The various synthetic routes yielding PαHA as well as PβHA enable control of molar masses and dispersity. However, a certain stereoregulatity of the obtained polyesters is of utmost importance for the formation of stereocomplexes from these materials. One could expect that the use of enantiopure monomers for the polymerization would result in polyesters with retained configuration. However, epimerization has been reported,[49] making the evaluation of tacticity a crucial point before stereocomplexation is attempted.

PαHA feature an asymmetrically substituted sp³ hybridized carbon atom in α position of each ester moiety. The absolute configuration of two adjacent stereocenters in relation to each other, that is, a diad, can be defined on the basis of the Bovey formalism introduced for polyolefins (**Figure 9**).[152] If the configuration is the same, that is, *-SS-* or *-RR-*, an *iso*-diad (*i*) is present, whereas an altered configuration, that is, *-RS-* or *-SR-*, produces a so-called syndio-diad (*s*). Triads and tetrads represent two or three successive diads and are defined in an analogous fashion involving three or four stereocenters, respectively. Transferred to the entire PαHA macromolecule, three major types of tacticities are resulting: In isotactic PαHA, each stereocenter features the same configuration, polyesters revealing alternating *S* and *R* configurations are defined as syndiotactic, whereas a random stereocenter configuration is observed in atactic polymers.

Nuclear magnetic resonance (NMR) spectroscopy represents the analytical technique of choice to determine the tacticity. The PLA methine protons appear as a quartett signal in a ^{1}H NMR spectrum. For isotactic PLA,[153] only one quartett

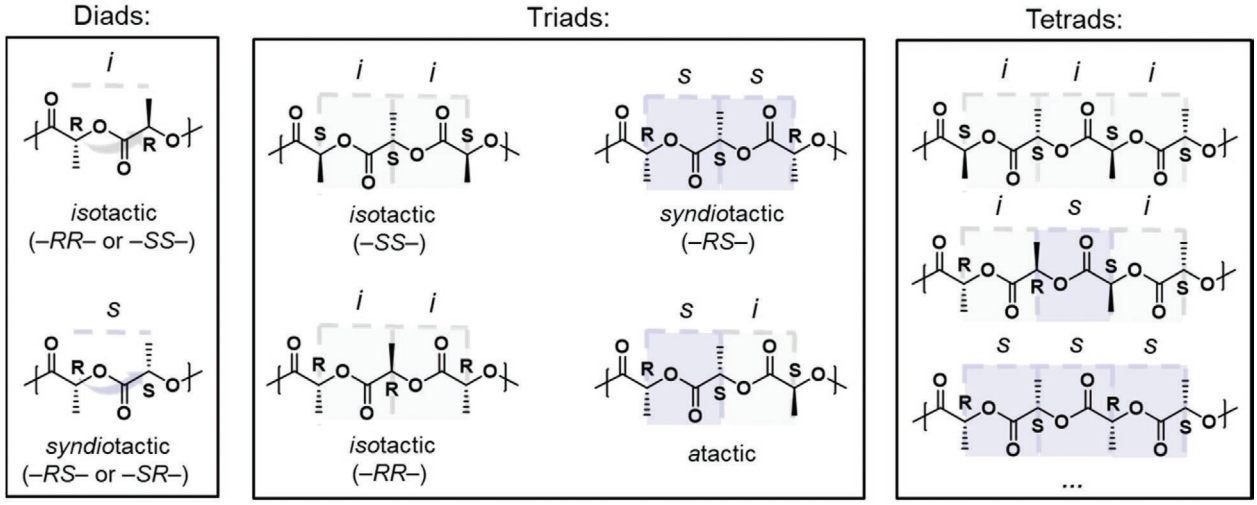

Figure 9. Schematic representation of diads, triads, and tetrads arising from the stereochemistry of PLA.

is observed. When the stereoregularity is disturbed, slightly shifted superimposed signals[153] are obtained (**Figure 10**), which makes an individual integration or peak fitting very difficult. Through homonuclear decoupling by irradiation of an additional radiofrequency, the spin transitions become saturated and the splitting of all coupling partners with this certain nucleus collapses.[154] The resulting singuletts can be integrated in a much more straightforward fashion, enabling the determination of the stereosequence probability, if the, for example, tetrads, were previously assigned (see below). Although ^{13}C NMR spectroscopy provides a better signal resolution, signals assigned to different tetrads may still overlap and cannot be unambiguously assigned.[155,156] However, if assignments are known, also ^{13}C NMR spectroscopy can be used to determine the stereosequence probability.[157]

2D NMR spectroscopy is required for assignment of the signals in the ^{1}H and ^{13}C NMR spectra and has, to the best of our knowledge, only been unambiguously performed for PLA to date (Figure 10, right).[158,159] However, the presence of isotactic PαHA can be verified based on ^{1}H NMR spectroscopy. It should be noted that homonuclear proton decoupling experiments can be helpful, in particular for PLA, but other PαHA such as, for example, PMA, already feature singulett methine signals.[115]

Because the stereoregularity of polymers influences several properties such as the rotation of polarized light or the thermal properties, methods such as polarimetry or DSC can hint toward the presence of isotactic polyesters. However, as other parameters can exhibit additional influence, these methods should not be utilized as sole proof of tacticity.

4. Methods to Induce Stereocomplexation

Various methods to induce stereocomplexation have been developed during the last two decades,[160] most of which represent classical procedures reported for PLA and can also be applied for the less common polyesters PαHAs and PβHAs. In

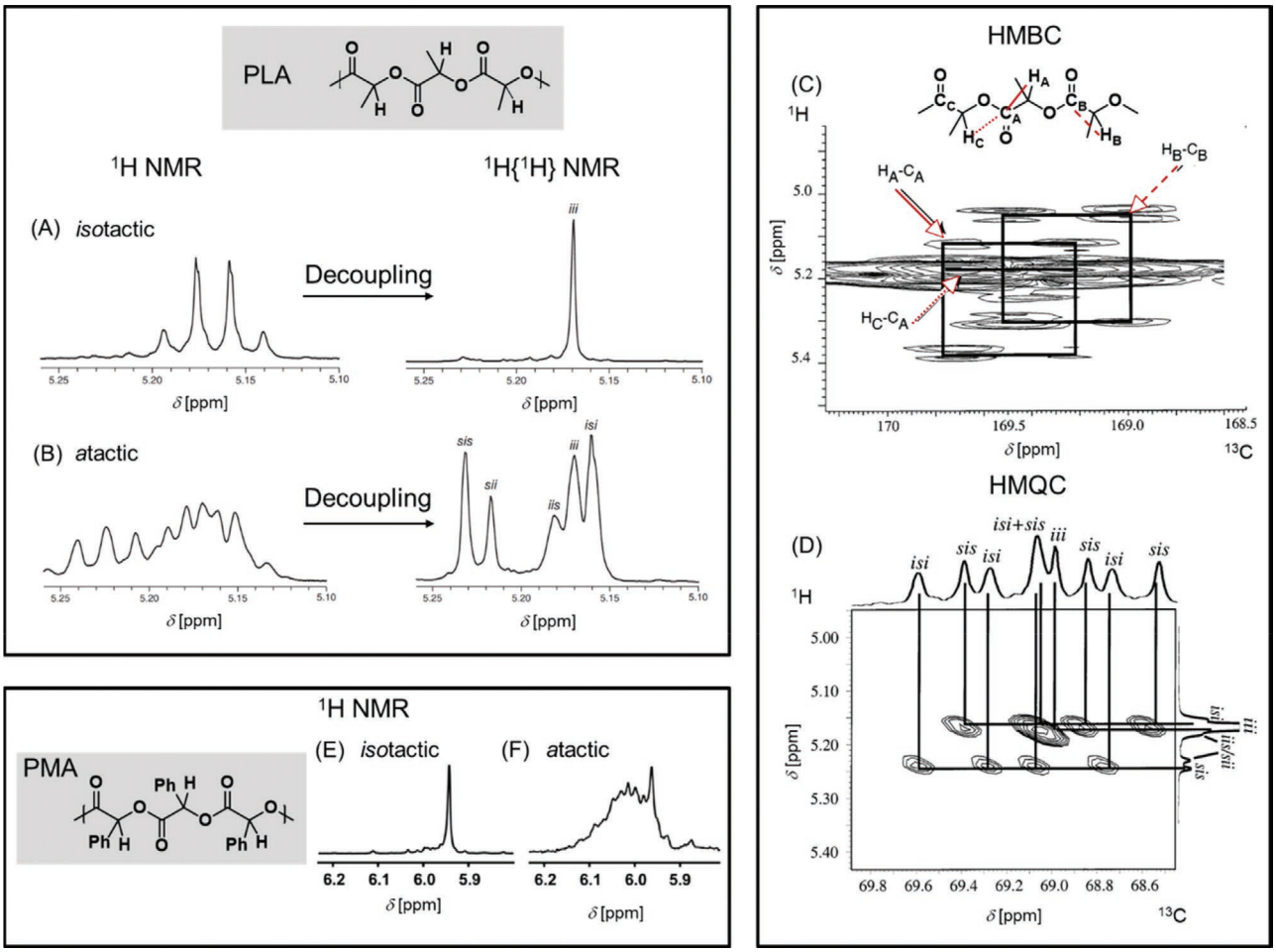

Figure 10. Left (top): Selective homonuclear decoupled ^{1}H NMR spectrum of A) isotactic and B) atactic PLA producing a singlet from initially quartet signals of the methine protons. Reproduced with permission.[153] Copyright 2008, American Chemical Society. Right: Experimental NMR data for the evaluation of PLA synthesized using 5% ^{13}C labeled L-lactide and 95% D-lactide.[159] C) Zoomed-in HMBC spectrum in the region of the carbonyl coupling with the methine proton and schematic representation of the couplings. D) HMQC spectrum and full evaluation of tacticity at the tetrad level (see Figure 9). Reproduced with permission.[159] Copyright 2002, American Chemical Society. Left (bottom): Zoom into the methine proton region of the ^{1}H NMR spectra of E) isotactic and F) atactic poly(mandelic acid). Reproduced with permission.[115] Copyright 2019, American Chemical Society.

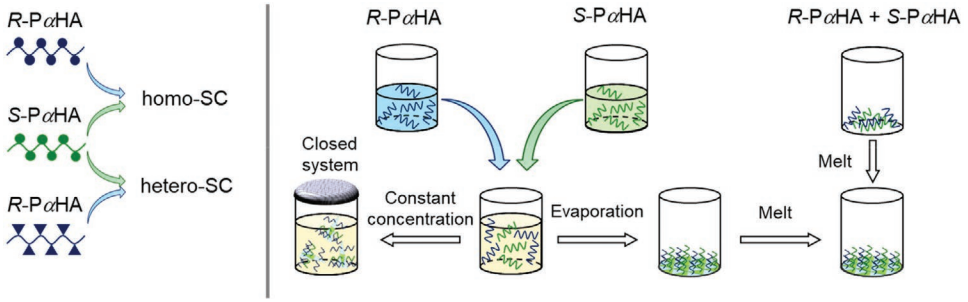

Figure 11. Schematic representation of solvent and melt procedures applied for stereocomplexation.

principle, stereocomplexation can occur whenever two isotactic polyesters of different configuration are present in a system allowing diffusion. Solution[161] and melting[162] approaches can be distinguished (**Figure 11**).[163]

If both polyesters represent the same polymer type, for example, PLLA is mixed with PDLA, so-called homo-stereocomplexes (homo-SCs) are obtained. The same process can be applied for the blending of two different polymer types, for example, PL2HB and PDLA. The resulting material is called a hetero-SC. The extent of SC in the final material can be varied by the blending ratio of the two components, and the blending of three or more components results in ternary or quaternary stereocomplexes, respectively.[16]

The solution methods imply the preparation and subsequent mixing of two different solutions containing D- and L-chains, respectively. The basic principle relies on the fact that every substance stays dissolved until a critical concentration is reached. The lower critical concentration of the stereocomplex compared to that of the D- and L-chains represents the driving force for the process. Due to the stronger interactions between stereocomplexes compared to the homopolymers, the good solvent for the homocrystallites becomes a poor or non-solvent for the stereocomplex. Chloroform,[164] dichloromethane,[165] THF at room temperature,[166] or acetonitrile at ≈80 °C represent solvents suitable for this purpose.[167] While PLA stereocomplexes from chloroform produced rather films,[168] the precipitates from THF can be nanoparticles.[166] At sufficient crystal thickness, stereocomplexes remain insoluble at elevated temperatures.[26]

It should be noted that the concentration of the mixture can be kept constant, or the solvent is allowed to evaporate slowly, thereby increasing the concentration of the polymer mixture (solution casting). In general, solution casting is faster than the "constant concentration" method. The increase of the concentration in the solvent evaporation method is an additional driving force for SC formation.[26]

Crystallization from the melt is probably the most frequently applied method. Either the solution casting sample is used for crystallization, or another bulk mixture is heated and quickly cooled to a certain crystallization temperature (T_c). Typically, T_c values are chosen between the T_m of the homocrystallites and the T_m of the stereocomplex crystallites.[169,170] Other methods are quenching of the melt and subsequent crystallization by raising the temperature to a fixed T_c.[171] However, the most straightforward way is simply crystallization during cooling from the melt.[171]

5. Methods to Investigate Stereocomplexation

When isotactic polyesters with different configurations are mixed, the associative interactions between the chains of different configurations can prevail over the interactions of the parent polyesters entailing stereocomplexation. Due to the new stereoselective interactions, a different macromolecular packing is obtained, leading to a variation of the thermal as well as the mechanical properties of the final material. These properties can be used to verify the SC formation on an analytical basis.

In fact, DSC as a method to determine thermal properties of bulk materials is important not only for estimating suitable conditions for processing of materials from the melt, but it represents the usual and easily accessible way to investigate the success of an attempted stereocomplexation process. As depicted in **Figure 12** (left) for P2HB, the T_m of the two isotactic polymers in *R* or *S* configuration, respectively, is significantly lower compared to the T_m of the stereocomplex,[172] a fact that is generally observed for polyester homo-SCs. In addition, the enthalpy of fusion ΔH_m of the homo-SCs is increased compared to that of the single components (See section 6).

Wide-angle X-ray scattering (WAXS) represents a complementary method to monitor stereocomplexation because the SC crystallites vary in lattice distances compared to crystallites of the pure isotactic polymer crystallites (Figure 12, right). As a consequence, WAXS represents a more sensitive method that is capable of following SC formation even if DSC results remained inconclusive.[35] The combination of DSC and WAXS is hence a common and suitable approach to investigate novel SC materials.

In particular, to monitor the formation, the growth and morphology of SC crystallites over time, imaging methods such as polarized light microscopy (PLM) and atomic force microscopy (AFM) are very valuable.[173,174] As depicted in **Figure 13** for the crystallization of P2HB,[175] the radial growth rate of spherulites can be determined via PLM, whereas the laminar growth rate is accessible from AFM. The evaluation of radial growth rates revealed that SC crystallization occurred at higher temperatures but with significantly increased rate compared to homocrystallization. This shows that conditions for SC formation represent a major factor to be considered when tailoring the blend material properties. It should be noted that also data related to mechanical properties can be extracted from AFM, which can provide a

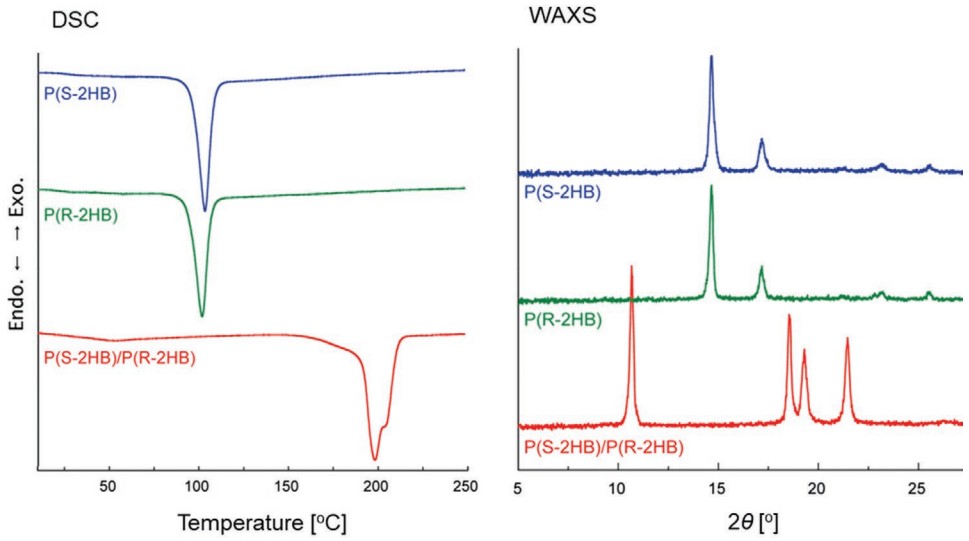

Figure 12. Thermal and WAXS analysis on the sole P2HB and the stereocomplex. A) DSC thermograms; B) WAXS analysis. Reproduced with permission.[172] Copyright 2009, American Chemical Society.

first indication with respect to application fields of these materials at an early stage of research.[176]

Spectroscopic methods such as solid state NMR, Infrared or Raman spectroscopy are capable of tracking conformational changes, which occur during stereocomplexation.[177–179] Although it was difficult to distinguish the SCs of Poly(α-methyl-α-ethyl-β-propiolactone) (PMEPL) from atactic species by solid state NMR spectroscopy in 1992,[180] the instrumental possibilities have since significantly improved, enabling detailed insights into the structure of crystalline as well as amorphous regions for PLA SCs.[181,182]

6. Homo-SCs

Homo-SCs represent the simplest type of SC as they are formed by blending the same polymer type in L and D configurations, respectively. As only two components are used for SC formation, homo-SCs represent binary SC. Access to the two isotactic polymers with opposite configuration is a clear prerequisite. There are hence only few polyester homo-SCs reported. These include the SCs from the PαHA (PLA,[183] P2HB,[34,172] P2H3MB[35]), and the SCs from the PβHA (PMEPL,[183,196–198] poly(α-(1,1-bischloro)ethyl-β-propiolactone)

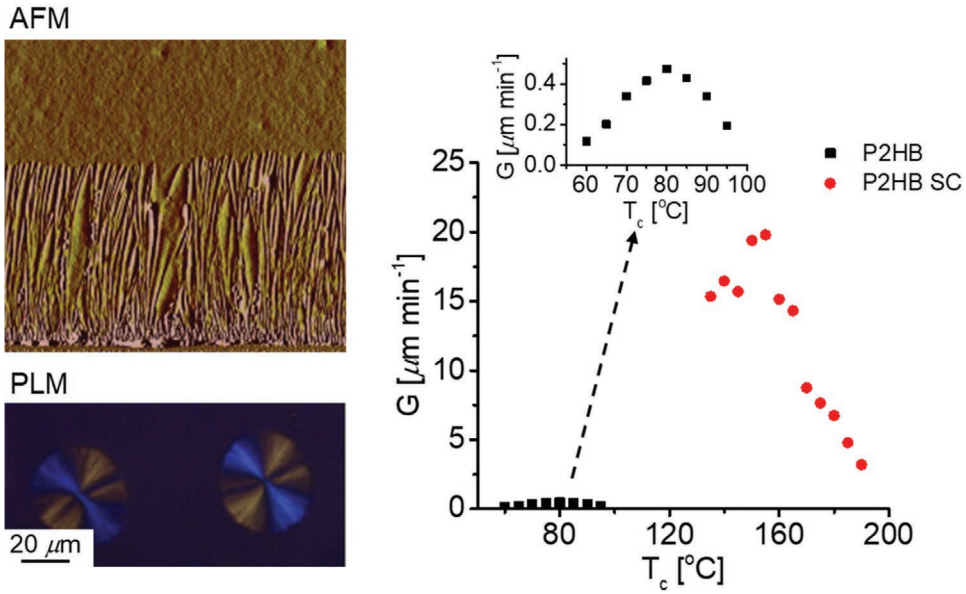

Figure 13. Investigation of SC crystallization of P2HB by means of AFM and PLM. PLM was used to determine the radial growth rates G that are plotted versus the crystallization temperature T_c. Adapted with permission.[175] Copyright 2017, Elsevier.

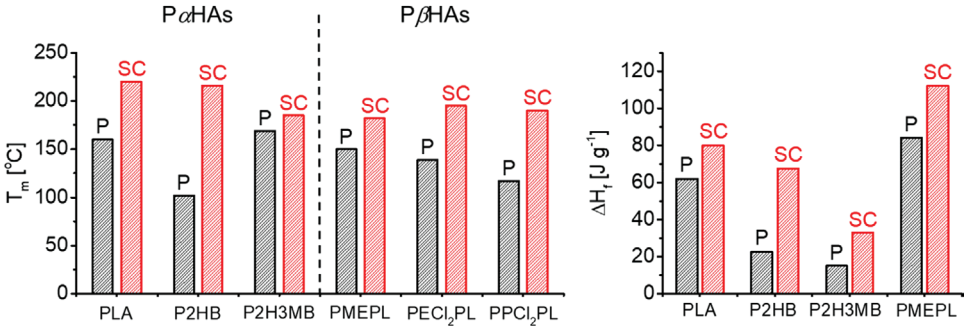

Figure 14. Melting temperatures T_m and enthalpies of fusion ΔH_f of crystallites of polyester homo-SC in direct comparison with the respective values of the isotactic polyesters. The ratio of the PLHA and PDHA was kept as 50:50 (wt%) during SC formation. Data were taken from literature publication (PLA,[183] P2HB,[188] P2H3MB,[35] PMEPL,[187] PECl$_2$PL,[184] PPCl$_2$PL[184]).

[PECl$_2$PL],[184] poly(α-*n*-(1,1-bischloro)propyl-β-propiolactone) [PPCl$_2$PL][184]). The fourth homo-SC from the PαHA PMA has only very recently been suggested based on preliminary DSC investigations.[115]

In general, DSC measurements indicated elevated T_m of SC crystallites compared to those of the pure isotactic PαHAs and PβHA (**Figure 14**). Although not reported for all SCs, the same trend can be observed considering the enthalpies of fusion ΔH_f.

Considering the substituents in α-position, the PαHA capable of SC formation feature substituents with increased steric demand (a methyl substituent for PLA, an ethyl substituent for P2HB, and an isopropyl substituent for P2H3MB). Although no clear trend is visible with respect to T_m, the ΔH_f of the crystallites systematically decreases with increasing bulkiness of the substituent for both, the crystallites of the isotactic polymers and the homo-SC crystallites. It should be noted that a complete resolution of the helical structures in the SC crystallites of PαHAs has, to the best of our knowledge, only been achieved for PLA so far.[32] However, the higher spacing values obtained from WAXS analysis indicated that the higher steric hindrance of the substituents also increased the unit cell size for P2HB[172] as well as P2H3MB.[35]

Only the homo-SCs from the PβHA PMEPL and the PαHA P2HB were investigated in more detail. Research on PMEPL SCs has been conducted by Prud'homme and co-workers since 1984.[185] Based on isotactic enantiopure PLMEPL and PDMEPL, the SC was formed. Additional blending with atactic polyester or excess of one enantiopure PMEPL isomer revealed that the crystallization of the SC controlled the morphology of the sample. The binary homo-SCs were further investigated by X-ray diffraction[186] and solid state NMR[180] studies to examine the SC structure in more detail. Crystallization from the melt resulted in crystallites of isotactic PMEPL in a zigzag conformation, whereas SC formation yielded a 2_1 helical structure and an increased unit cell. In an investigation regarding the effect of molar mass on the SC formation,[187] PDMEPL (molar mass [M_n] ≈ 2 kg mol^{-1}) was blended via a solution approach with PLMEPL of M_n between 3 and 33 kg mol^{-1} in a 1:1 ratio. The SC formation was favored when blending polymers of opposite configuration with similar molar masses. Variation of the feed ratio during stereocomplexation revealed that the SC crystallites acted as a nucleation agents inducing the crystallization of the isotactic polymer used in excess.

The SC formation of the PαHA P2HB has been investigated in the Tsuji lab within the last decade.[172] Initially, solution and melting approaches were compared for oligomeric species (M_n ≈ 3 kg mol^{-1}, $Đ$ ≥ 3.7), showing that melt crystallization resulted in more well-defined homo-SCs. Interested in a further comparison of properties of the SC material with the isotactic P2HB, the thermal and hydrolytic degradation was studied for higher molar mass P2HB (M_n ≈ 16 kg mol^{-1}).[188] Whereas stereocomplexation did not affect thermal degradation, the hydrolytic degradation of the SC was significantly delayed due to a faster hydrolysis of amorphous domains, which were present to a lesser extent in the SC material. The effect of the molar mass of P2HB on the stereocomplexation process was investigated by combining six pairs of the isotactic PαHA of different configuration at similar M_n from 0.75 to 26 kg mol^{-1}.[34] Whereas solution casting resulted in the formation of the sole stereocomplex, melt crystallization at 70 °C yielded a mixture of homo and SC crystallites. Elevated crystallization temperatures were needed to increase the fraction of SC crystallites.

7. Hetero-SCs

Hetereo-SCs are formed when two different polymer types of *R* and *S* configuration are blended. The mixing of more than two components is also possible (**Figure 15**). The increasing level of complexity from homo-SCs, over binary hetero-SCs to ternary or even quarternary SCs makes the analysis by means of DSC and WAXS a challenging task. In this respect, a detailed comparison with analytical data of blends of the same configuration (where sterecomplexation can be excluded) can certainly be helpful. However, it should be clearly stated that even for binary blends, the structure of crystallites in a blend might be altered by other effects such as epitaxy. Hence, a stereocomplex is not necessarily formed, as reported by Prud'homme for the binary system PMEPL/PMPPL (poly(α-methyl-α-n-propyl-β-propiolactone).[189,190] In addition, partial SC formation has been observed while crystallites of the initial compounds remained visible, as reported for the binary hetero-SC formation of PLA and P2HB.[191] On the other hand, the hetero stereocomplexation of PL2HB and PD2H3MB proceeded smoothly via solution casting as well as melt blending.[192]

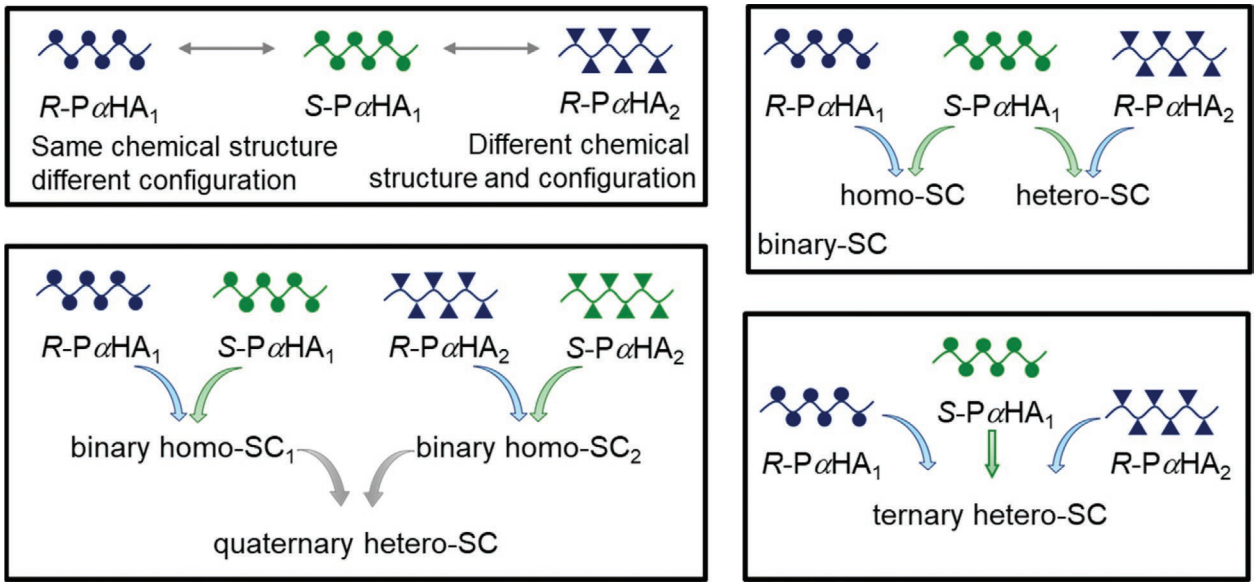

Figure 15. Schematic representation of the stereocomplexation of PαHAs yielding binary, ternary, and quaternary SCs.

7.1. Binary Hetero-SCs Composed of PLA and P2HB

The hetero-stereocomplexation of P2HB and PLA was investigated comprehensively in the Tsuji lab. Initially, PL2HB synthesized by polycondensation and linear PDLA obtained by ROP of D-lactide were blended in equal mass fractions.[191] DSC and WAXS analysis indicated that SC formation via melt crystallization was unsuccessful but solution casting yielded partial crystallization in form of a hetero-SC. The melt crystallization conditions were further optimized by varying crystallization temperatures in feed ratios of 25, 50, and 75 mass% of the homopolymers in the binary blends (**Figure 16**, left).[193] In fact, hetero-SCs could only be obtained by crystallization at around 160 °C, whereas amorphous blends were obtained at higher temperatures. Partially homocrystallites were formed upon crystallization at lower temperatures. PLM data suggested that the formation of stereocomplexes occurred at the interface between the PLA and P2HB domains in these mixtures.

Additional variation of the polyester architecture by utilization of four-arm star-shaped polyesters synthesized by polycondensation using pentaerythritol further complicated the system, perturbing the formation of hetero-SC crystallites (Figure 16, right).[194] Maintaining an equimolar ratio of PLLA and P(D2HB) in a P(D2HB)-*b*-PLLA block copolymer enhanced the SC formation of the two blocks of opposite configuration during melt crystallization, enabling the exclusive formation of SC crystallites in a wide crystallization temperature range from 70 to 160 °C.[195]

7.2. Ternary and Quarternary Blends

SC formation and analysis are not straightforward already for binary hetero-SCs. The effects of the addition of a third

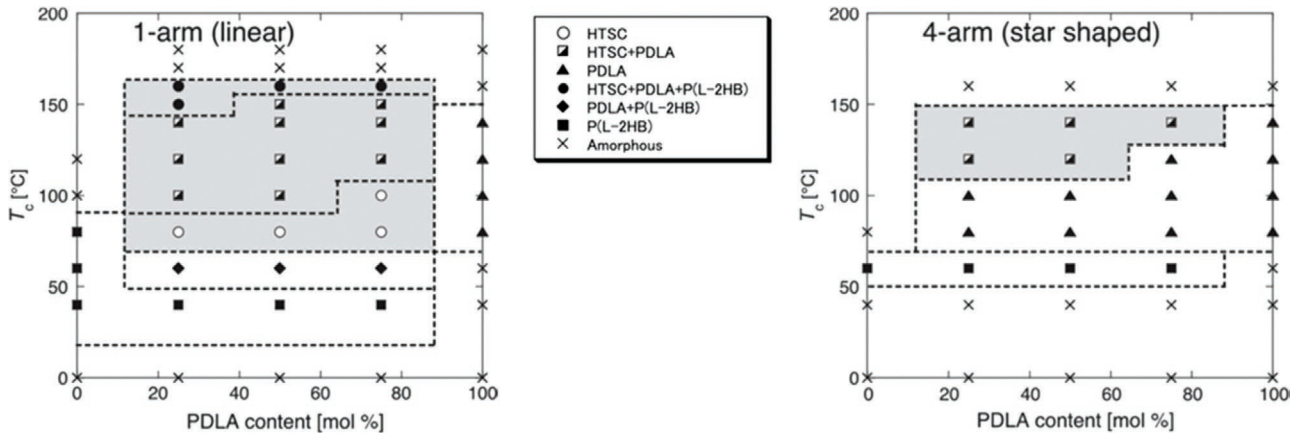

Figure 16. Formation of homo- and hetero-SC crystallites from PDLA and PL2HB by melt crystallization at varying temperatures T_c. Left: Linear PDLA and PL2HB. Right: 4 Arm star-shaped PDLA and PL2HB (HTSC, hetero stereocomplex). Adapted with permission.[194] Copyright 2014, Wiley-VCH.

component were investigated by Tsuji and co-workers for ternary blends of PLA, P2HB and P2HB. PLM as additional characterization tool was of utmost importance, as sole analysis by means of DSC and WAXS was not sufficient to unravel the multiple crystallite types that were formed in such a complex blend. The addition of 10% of SCs resulted in an increased crystallization rate of the PLLA matrix.[196] More specifically, P2HB homo-SC crystallites as well as PD2HB/PLLA hetero-SC crystallites acted as nucleation agents during non-isothermal crystallization from the melt as well as during isothermal crystallization by heating. Variation of the PDLA, PL2HB, and PD2HB ternary blend composition resulted in the formation of ternary SC crystallites with higher T_m as well as degree of crystallinity compared to those of the respective binary SCs at certain crystallization conditions, suggesting a random incorporation of PDLA and PD2HB chains in the SC crystallites formed with PL2HB chains.[197] Similar findings were reported using the even more complex quarternary blend of PL2HB/PD2HB and PL2H3MB/PD2H3MB, showing that quarternary SCs could be realized.[198]

8. Conclusion and Future Perspectives

The PαHA PLA represents a well-investigated polymer with respect to SC formation.[26] On the other hand, other polyesters have been scarcely investigated in this respect, although enantioselective monomer as well as polymer syntheses enable access to a multitude of new materials that could potentially be suitable for this purpose because isotactic polyesters have been or could theoretically be produced (**Figure 17**). Despite the current lack of comprehensive data, first structure property relationships can be deduced, showing that the steric hindrance induced by substituents plays a major role during tuning of T_m and crystallinity of the SC materials. One should, however, consider that SC formation might not always be successful, as reported for PPhLA[36] as well as for the blend of P3HB with PLA.[199]

It should be noted that potential novel materials of that type require access to the, sometimes also novel, isotactic polyester of both configurations. With respect to avoiding this challenge, the statistical copolymerization of two monomers has to be stressed, as the variation of many properties is straightforward. One comonomer would serve the purpose of inducing stereocomplexation, whereas another comonomer would add additional functional features to the material if SC formation remains unperturbed, as in the case of PLGA.[165] A multitude of interesting candidates (potentially) suitable for ROP copolymerization are described in Section 2 of this review.

It has been pointed out that, aside from PLA, the majority of PαHA used for SC formation have been obtained via polycondensation approaches. However, the use of mixed dimers for polymerization as reported for poly(lactic-*alt*-glycolic acid),[200] or the combination with cross-metathesis polymerization as reported for poly(lactic-*alt*-caprolactic acid)[201] represent recent approaches to further expand the range of accessible polyesters capable of SC formation. The regioselective copolymerization of cyclic anhydrides and epoxides is another unusual but very promising route to obtain alternating copolyesters,[202] hinting toward the fact that isotactic alternating copolymers can undergo stereocomplexation in a similar fashion as isotactic homopolymers.

Substituted PCL analogs offer a vast parameter space for creating novel polyesters with defined tacticity. However, the corresponding lactone monomers for ROP are mainly available as racemates, a fact that could encourage organic chemists to make enantiopure starting materials more easily available

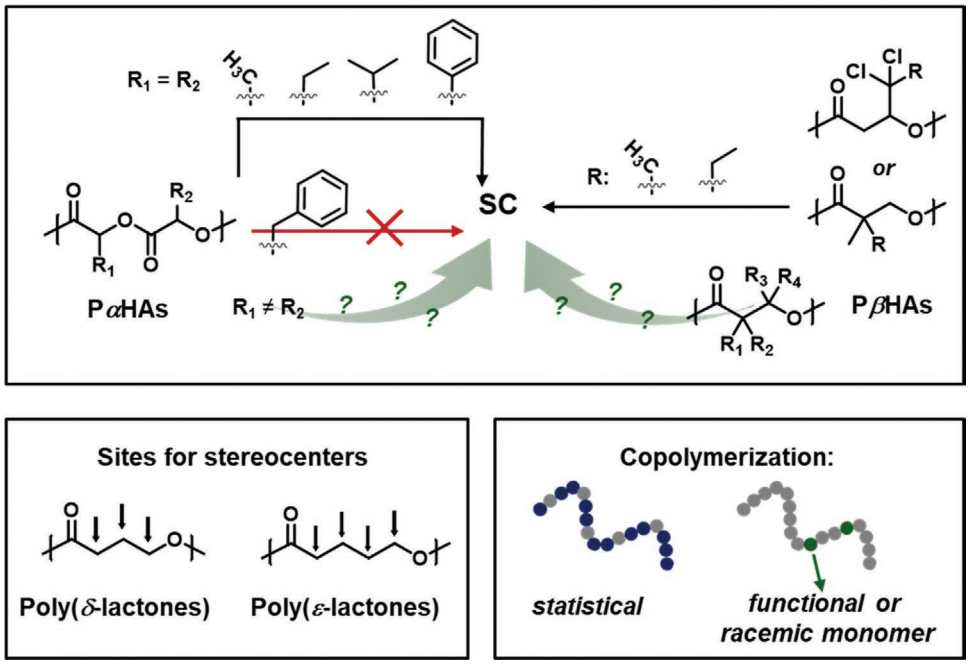

Figure 17. Schematic representation of PαHA and PβHA employed for stereocomplexation and opportunities to create novel SC materials by using alternative monomers and polyesters.

in order to investigate the resulting polyesters with respect to potential SC formation.

Synthetic polymer chemists are always eager to increase the level of complexity of available polymer architectures, including block, star-shaped, or graft copolymers. Whereas this could certainly be done for many isotactic PαHA and PβHA in a similar fashion as it has been achieved for PLA,[26] the resulting materials would probably not be available in sufficient amounts to strive for large-scale industrial applications. On the other hand, a vast series of parameters based on the blending method can be adjusted in order to access new materials, which represents the material scientist's way to tailor the properties of materials. In addition, only small variations of an established macromolecule can have tremendous effects on the material properties, for example, by including additional features through copolymerization. Hence, the current request for sustainable new materials applicable in the biomedical field as well as for commodity polymers can only be met by maintaining the living cooperation between these two major fields of polymer research.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

poly(α-hydroxyacid)s, poly(β-hydroxyacid)s, polyesters, ring-opening polymerization, stereocomplexes

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