Degradable Polymers

International Edition: DOI: 10.1002/anie.201500147
German Edition: DOI: 10.1002/ange.201500147

Poly(phosphoester)s: A New Platform for Degradable Polymers

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degradable polymers · phosphorus · polyesters · polymer synthesis · poly(phosphoester)s

***P**oly(phosphoester)s (PPEs) play an important role in nature. They structure and determine life in the form of deoxy- and ribonucleic acid (DNA and RNA), and, as pyrophosphates, they store up chemical energy in organisms. Polymer chemistry, however, is dominated by the nondegradable polyolefins and degradable poly(carboxylic ester)s (PCEs) that are produced on a large scale today. Recent studies have illustrated the potential of PPEs for future applications beyond flame retardancy, and provided a coherent vision to implement this classic biopolymer in modern applications that demand biocompatibility and degradability as well as the possibility to adjust the properties to individual needs.*

1. Introduction

"Why nature chose phosphates" is the title of a prominent article by Westheimer from 1987,[1] in which the peculiar properties of the phosphoester group are summarized and compared to other esters and amides. The relative stability of pyrophosphates in water makes them ideal for energy storage when compared to carboxylic acid anhydrides. The negative charge of the phosphate linking units in DNA and RNA bestows long-term stability, while other polyesters would hydrolyze rapidly. Furthermore, multiply charged phosphate and pyrophosphate residues are important leaving groups in substitution and elimination reactions within biochemical pathways. Interestingly, these benefits are not used in common organic chemistry because chemists often rely on highly reactive (and, therefore, often toxic) compounds to drive the reaction to the desired product in minimum time.

Living organisms, however, depend on phosphorus as one of the essential dietary minerals for the maintenance of life. No other element can be substituted for phosphorus, as the genetic information of all living organisms is stored on the poly(phosphate)s RNA and DNA. Nor is there a replacement for adenosine triphosphate, which provides the chemical energy that living cells use for their metabolism, cell signaling, transport, and DNA/RNA synthesis. Furthermore, phosphate and its corresponding acids are an essential part of biological buffer systems. Altogether, this diverse range of applications makes phosphorus and its compounds essential for all known forms of life.

Biopolymers have always inspired scientists to mimic their performance and properties with synthetic analogues (Figure 1). Natural rubber is a prominent example of such a transition process. The elastomer derived from rubber trees and its shortage during the world wars led to the development of synthetic alternatives and the founding of polyolefin chemistry. Polyesters, especially poly(hydroxyalkanoate)s (PHAs), are found in nature and have augmented synthetic polymers substantially. Polyamides (such as nylon) share polar amide bonds with the naturally occurring proteins and much effort is currently being undertaken to mimic the sequential control and the impressive mechanical properties offered by the polypeptide of spider silk.

In addition, synthetic main-chain poly(phosphoester)s (PPEs) are interesting candidates as biomimetic building blocks for biocompatible and biodegradable polymers, as their backbone is recognizable to enzymes and can be cleaved or built up under physiological conditions. The similarity to nucleic acids was the impetus for several pioneering studies by Penczek and co-workers in the 1970s.[2] Moreover, hydrolytic degradation of the polyphosphoester backbone with or without a specialized enzyme (e.g. alkaline phosphatase) also makes PPEs interesting for materials science.

The mechanical and chemical properties of PPEs can be manipulated in a straightforward manner from amorphous, water-soluble materials to crystalline, stiff plastics by alteration of the backbone or the side chains. As two ester bonds build up the polymer backbone, and every phosphate unit carries a pendant side chain, the pentavalence of the central phosphorus allows a modular synthesis with a high density of

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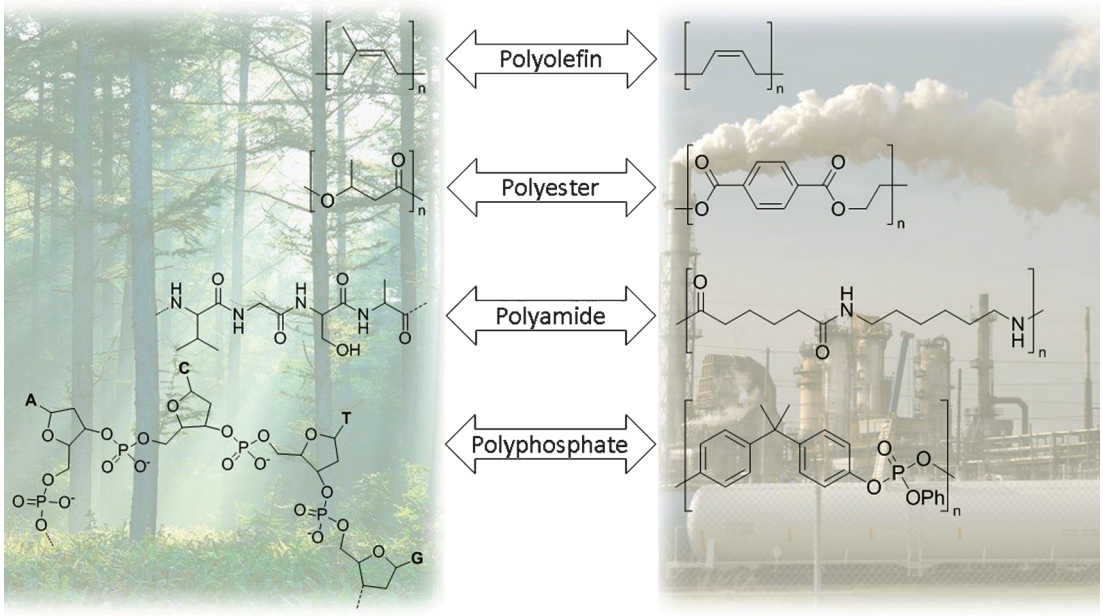

Figure 1. Comparison, with prominent examples, between the structural motifs of natural occurring polymers (left) and synthetic polymers produced industrially (right).

functional groups. Variation of the side chain opens further possibilities to generate not only polyphosphates, but also polyphosphonates or -phosphoamidates (Figure 2). This modularity is crucial for the development of new multifunctional polymers and makes PPEs complementary to already established materials.

Interest in phosphorus-containing polymers was initiated by the discovery of their flame-retarding properties in the 1950s. However, research efforts have declined since the 1960s because of the expensive starting materials which are usually derived from phosphate rock by an energy-intensive process. Furthermore, the molecular weights obtained were limited and the materials synthesized exhibited poor mechanical properties. On the other hand, PPEs show high thermal stability and strong adhesion properties to glass, metals, and cements. In particular, polyphosphates, which mimic the natural biopolymers DNA and RNA, are often found to be biodegradable and biocompatible as well as offering the possibility to adjust their water solubility and stimuli responsiveness, for example, towards changes in temperature, ion strength, or pH value. Adjusting these properties to a specific application makes PPEs one of the most promising polymers in the biomedical field.

In this Minireview, we survey the recent progress in PPE chemistry and the methods of synthesis that allow variation of the polymer main and side chain. The Minireview is divided into three sections: The first part compares the different synthetic approaches for PPEs, focusing on techniques developed in recent years. The second part discusses the degradation behavior and the potential toxicity of PPE homo- and copolymers and their degradation products, which need to be considered for any bio-application. The third part highlights advanced drug delivery systems based on PPEs, followed by a discussion about polymeric nanoparticles as drug carriers. Other systems based on PPE block copolymers and proteins will be discussed at the end.

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Frederik Wurm studied chemistry at the University of Mainz, Germany. After a PhD with Prof. Dr. Holger Frey on the design of branched macromolecular architectures, in 2009 he joined Prof. Dr. Harm-Anton Klok at the ETH Lausanne, Switzerland, as a Feodor-Lynen fellow to work on novel bioconjugation strategies. Since 2012, he has been a member of the Junior Faculty of the Max Planck Graduate Center and group leader at the MPI for Polymer Research in the department of Prof. Dr. Katharina Landfester. His research focuses on the development of nanotherapeutics, the design of biomimetic phosphorus-containing materials, metallocene polymers, and the development of anionic polymerization techniques.

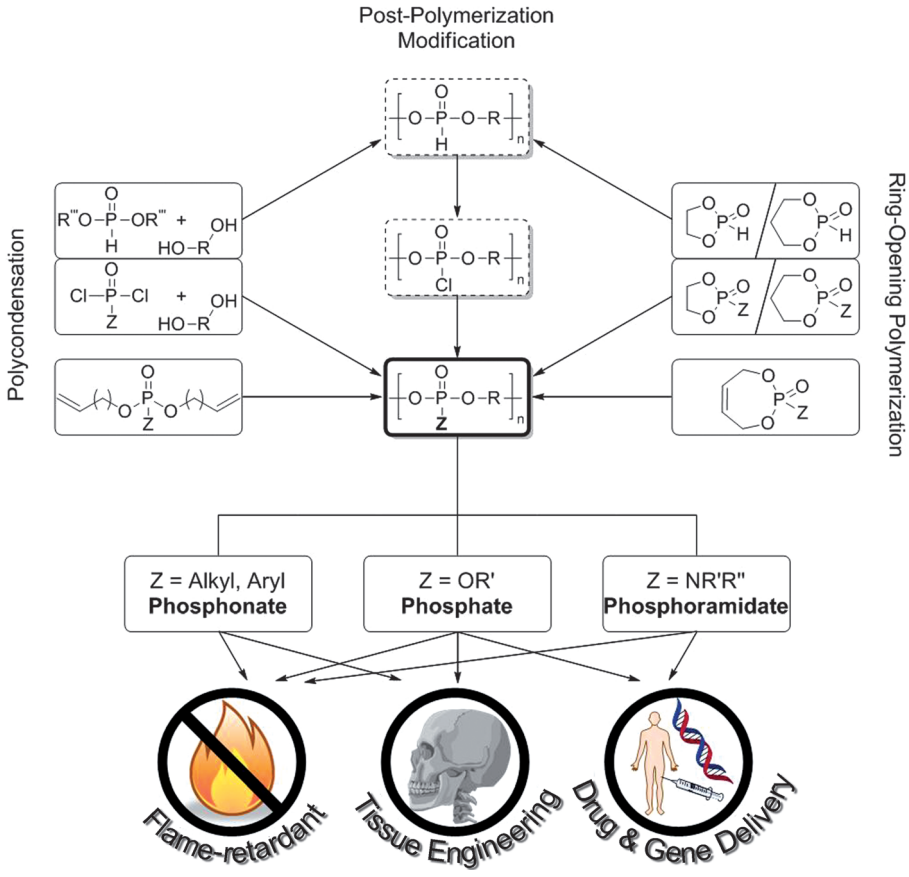

Figure 2. Synthetic pathways towards PPEs and major fields of application.

2. Synthetic Techniques for the PPE Platform

Efficient and controlled polymerization techniques are needed to adjust the characteristics of the polymer and to match a specific application that can range from inert and hydrophobic materials to bioactive and water-soluble polymers with architectures from linear to hyperbranched or cross-linked. These challenges facing polymer science are met by polycondensation, polyaddition, ionic, enzymatic, and metathesis polymerization, which were already employed in the preparation of PCEs, polyamides, polyethers, polyolefins and many other synthetic polymers.

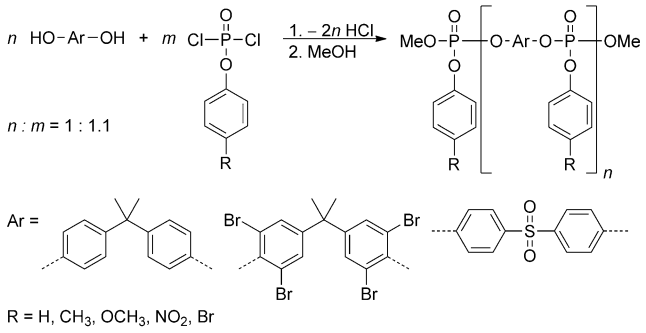

Figure 3. Synthesis of polyphosphates by polycondensation of bisphenols with aryl phosphodichlorides.[5]

Polycondensation. PPEs are mainly prepared by polycondensation reactions. Polycondensations are step-growth polymerization techniques that require the removal of a volatile side product (e.g. water, alcohol, or hydrogen chloride) by azeotropic distillation or reduced pressure to shift the reaction equilibrium to the product side. The first polyphosphate was prepared by Arvin in 1934 by treating phosphorus oxychloride with bisphenol A and phenol.[3] Following these experiments, Cass prepared a library of polyphosphates and observed the flame-retarding properties of this class of polymers for the first time (Figure 3).[4] However, the high cost and the low molecular weights obtained prevented PPEs from competing with halogenated carbon-based flame retardants until legislation gave preference to non-halogenated alternatives in recent years.

Polycondensation reactions are performed under various conditions, for example, in melt, under Lewis acid catalysis, by high-temperature solution polymerization, or aqueous interfacial polycondensation with a phase-transfer catalyst. The phase-transfer-catalyzed synthesis yields high-molecular-weight polymers (above 40000 g mol^{-1}) and makes elaborate structures accessible, for example, by the introduction of phenolphthalein or ferrocene units into the polymer backbone to increase the heat resistance and accelerate char formation (Figure 4).[6]

Harsh reaction conditions (temperatures up to 300 °C, vacuum, formation of acidic side products) are often necessary for polycondensation reactions to yield high-molecular-weight polymers and, therefore, limit the introduction of functional groups. However, other methods can still not compete with industrial polycondensation reactions economically because the starting materials are commercially available and allow modularity of the polymer backbone, as the introduction of (inert) aromatic or aliphatic diols is straightforward.

Polyaddition. Polyaddition reactions are also step-growth polymerizations but circumvent the removal of a side product as no reaction equilibrium has to be influenced. PPEs are prepared typically by the reaction of bis(expoxide)s with phosphorus dichlorides by utilizing a quaternary onium salt catalyst to yield polymers with molecular weights between 10 and 25000 g mol^{-1}. The polyaddition of bisoxetanes and phosphorus dichlorides was also studied in detail.[7]

Chain-growth polymerization. Chain-growth techniques were developed to produce well-defined polymers in regards to both molecular-weight distribution and microstructure. As

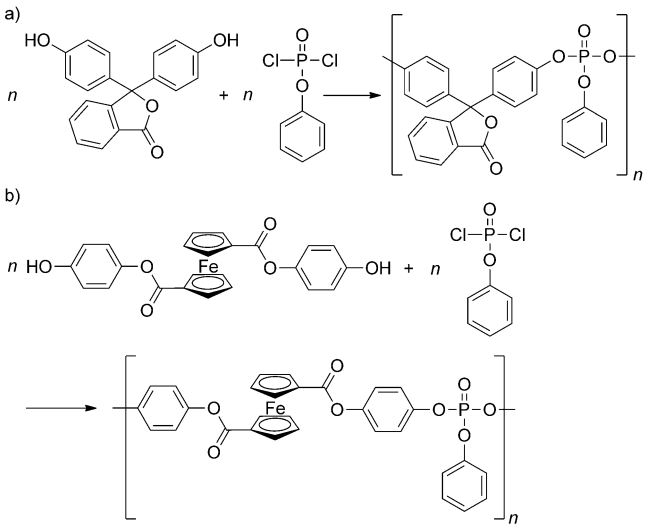

Figure 4. Synthesis of a) phenolphthalein-containing and b) ferrocene-containing, polyphosphate by polycondensation. Both polymers exhibit flame-retarding properties.[6b,c]

a consequence of the sophisticated and energy-intensive preparation of the monomers, the majority are of academic interest only. In particular, ring-opening polymerization (ROP) allows the defined introduction of functional groups in the α- or ω-position by using functional initiators or termination reagents. Moreover, high structural control can be achieved by a "living" (or controlled) polymerization mechanism, in which the monomer conversion is not limited by the reactants or side reactions which, in addition, makes high-molecular-weight ($M_w > 30000$) polymers accessible while maintaining low polydispersities (PDI < 1.2).

The development of ROP for PPE is closely connected to progress made for PCEs. A prominent example of a chain-growth technique is the ROP of lactones and dilactones, such as ε-caprolactone or lactide. Analogously, various five- and six-membered cyclic alkylene phosphates can be polymerized, as explored by Penczek and co-workers in the 1970s. The preparation of the cyclic monomers follows the synthesis of cyclic alkylene phosphites which was developed by Lucas et al. in 1950.[8] Oxidation with oxygen produces the corresponding cyclic phosphates, the so called phospholane oxides (Figure 5).[9]

The high ring strain (15–30 kJ mol^{-1}) makes these five-membered cyclic phosphates suitable monomers for ROP. Six-membered rings, however, were found to yield only low-molecular-weight polymers and oligomers because of a lower ring strain. The ROP of five- and six-membered cyclic monomers can be achieved by cationic, anionic, and insertion mechanisms. Cationic initiators (e.g. protic acids, Lewis acids, or alkylating agents) were used at the beginning of PPE chemistry, and yield mostly oligomers, and often side products.[2a,20] Similar observations were made for PCEs, thus making the cationic polymerization unattractive for the ROP of cyclic esters.[21] It was also discovered that anionic ring opening, for example, with sodium, lithium aluminum hydride, or ammonia as the nucleophiles, produced ill-defined PPEs. However, use of triisobutylaluminum, Grignard reagents, or butyllithium led to polymers with molecular weights up to 100000 g mol^{-1} for both PCEs and PPEs.[22] Other bases (e.g. triethylamine, potassium benzoate) initiate the polymerization at elevated temperatures as well, but are less used.[23]

Anionic and cationic polymerizations face several challenges. There is, for example, the need to protect functional groups within these monomers from the propensity to react with the ionic chain end. Furthermore, unwanted deprotonation of the monomer (with strong bases) can terminate the polymerization. In addition, the use of metal-containing initiators (e.g. aluminum alkylates) is often regarded as unsuitable, especially when the focus is on biocompatibility and bioresorbility.

Metal carboxylates have proven to be among the most efficient catalysts for ROP by an insertion mechanism. The most prominent catalyst is tin(II) 2-ethylhexanoate (Sn(Oct)$_2$), which is the only metal-containing catalyst for biopolymers approved by the FDA. The insertion mechanism was proven by Kowalski, Kricheldorf, and Penczek for the polymerization of lactide,[24] and a similar mechanism is assumed for the ROP of cyclic alkylene phosphates.[25] The obtained PPEs exhibit a narrow molecular-weight distribution and a controlled molecular weight up to 15000 g mol^{-1}.

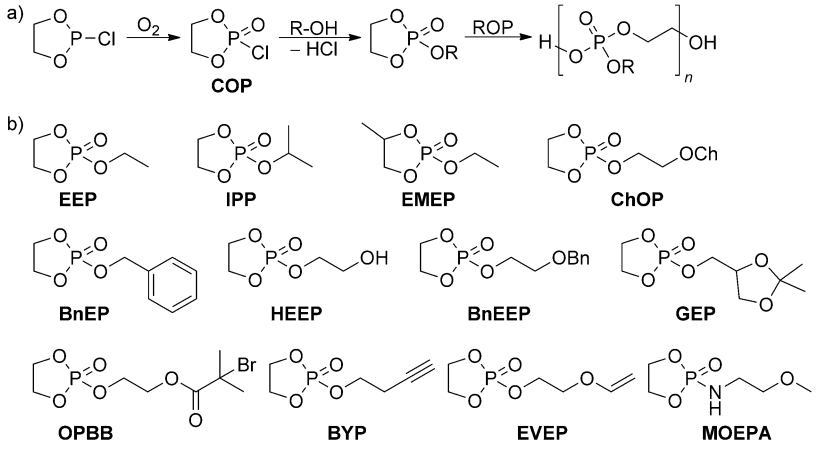

Figure 5. a) Synthetic route to dioxaphospholane oxide monomers prepared from COP (2-chloro-1,3,2-dioxaphospholane-2-oxide) and the representative ring-opening polymerization. b) Selection of monomers prepared from COP: EEP (ethyl ethylenephosphate), IPP (isopropoxy ethylenephosphate),[10] EMEP (2-ethoxy-4-methyl-2-oxo-1,3,2-dioxaphospholane),[11] ChOP (2-cholesteryl-2-oxo-1,3,2-dioxaphospholane),[12] BP (2-benzyloxy-2-oxo-1,3,2-dioxaphospholane),[13] HEEP (hydroxyethoxy ethylenephosphate),[14] BnEEP (benzyl-protected HEEP),[15] GEP (glycidyl ethylenephosphate),[16] OPBB (2-oxo-1,3,2-dioxaphosphoroyloxyethyl-2′-bromoisobutylate),[12] BYP (2-(but-3-yn-1-yloxy)-2-oxo-1,3,2-dioxaphospholane),[17] EVEP (2-ethylene glycol vinyl ether-1,3,2-dioxaphospholane-2-oxide),[18] and MOEPA (*N*-methoxyethyl phospholane amidate).[19]

Thus, $Sn(Oct)_2$ is frequently used for the polymerization of functional phosphates and sensitive initiators.[26]

A major challenge in polymer science, and also in polyester synthesis, is the use of less toxic catalysts, such as heavy metals. In this regard again, progress was first made for PCEs, and then adopted for their phosphorus counterparts. 4-Aminopyridines, such as DMAP (4-(dimethylamino)pyridine) and PPY (4-pyrrolidinopyridine), were reported to catalyze the polymerization of lactide.[27] The polymerization kinetics and stereoselectivity were initially improved by the use of thiourea-based bifunctional organocatalysts, and later by amidines (e.g. DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene) and guanidines (e.g. TBD, MTBD) as single catalysts.[28] These organobases, also known as "superbases", were first investigated by Iwasaki and Yamaguchi for PPEs.[29] Clément et al. found that polymerization with DBU can be improved (e.g. by means of less transesterification) by the addition of a thiourea co-catalyst, which was also beneficial for the polymerization of lactide.[30] PPEs with molecular weights of nearly 100000 g mol^{-1} (PDI < 1.10) are thereby accessible, and complex architectures become feasible, but the removal of the organocatalysts, however, must not be underestimated.[17,31]

Enzymatic polymerization. The enzymatic polymerization of useful polyesters and polycarbonates was established with different lipases, thereby circumventing the challenges involved with metal-containing catalysts and organobases. Lactones with ring sizes between 4 and 17 were polymerized by lipases to yield polyesters with molecular weights of up to 50000 g mol^{-1}.[32a] In analogy to PCEs, Wen and Zhuo reported the oligomerization of a cyclic phosphate using porcine pancreas lipase as a catalyst.[32b] However, the molecular weights did not exceed 1700 g mol^{-1} at elevated temperatures (100 °C). The polydispersity of the obtained oligomer was not determined, but is expected to be higher than for other ROP techniques as long reaction times (> 120 h) and elevated temperatures favor transesterification reactions. Other attempts to polymerize PPEs enzymatically have not been reported so far, as the attainable molecular weights seem to be limited.

Olefin metathesis polymerization. Functional PPEs with high molecular weights are accessible by olefin metathesis polymerization of readily available and easy to handle monomers. The combination of the high functional group tolerance of modern metathesis catalysts (**G1**: Grubbs first-generation catalyst;[33] **G2**: Grubbs second-generation catalyst;[34] **G3**: Grubbs third-generation catalyst;[35] **H-G 2**: Hoveyda–Grubbs second-generation catalyst)[36] with the advantages of either step-growth (fast access to monomers) or chain-growth techniques (functional end groups, block copolymers), allows the preparation of a range of polymers with tailored properties.

Acyclic diene metathesis (ADMET) is a polycondensation, while ring-opening metathesis polymerization (ROMP) is a chain-growth polymerization, both of which are initiated and promoted by metal carbenes. ADMET monomers contain two terminal double bonds that undergo metathesis in a step-growth fashion and release ethylene as a volatile side product, while ROMP monomers are strained, unsaturated ring systems. Both techniques have been employed to synthesize high-molecular-weight model compounds to study, for example, the effect of polar groups placed precisely within a polyethylene chain on crystallization. This is exemplified in the study undertaken by Ortmann and Mecking, who recently showed that the number of ester groups per 1000 methylene units of long-spaced aliphatic PCEs prepared by ADMET has a strong influence on the melting temperature since the ester functionalities disturb crystallization.[37] To approach and to mimic the thermal properties of polyethylene, the same research group also developed an elaborate route towards "ultralong"-chain PCEs by employing metathesis techniques.[38]

Analogously to the first report in 1991 by Wagener and coworkers on PCEs prepared by metathesis polymerization,[42] the synthesis of phosphorus-containing monomers is a straightforward esterification of a phosphoric or phosphonic acid with an ω-unsaturated alcohol. The polymerization is catalyzed by different Grubbs catalysts and carried out at moderate temperatures and at reduced pressure (Figure 6). In

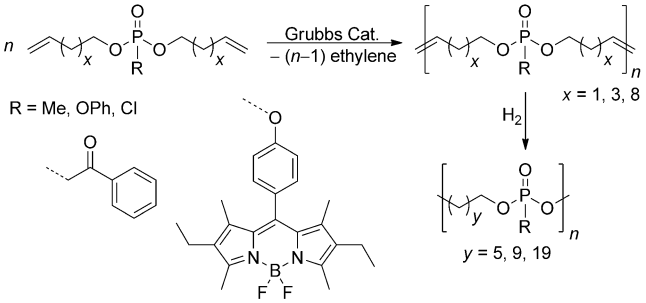

Figure 6. Linear, unsaturated PPEs prepared by ADMET polymerization to yield saturated PPEs after hydrogenation. BODIPY-labeled poly(phosphate)s,[39] reactive poly(chloro phosphate)s,[40] and poly(phosphonate)s for, for example, use in polymer-mediated HWE reactions,[41] are accessible from functional monomers.

this way poly(phosphate)s and poly(phosphonate)s were prepared by ADMET polycondensation. The modularity of the employed monomers allows the material's properties to be adjusted, for example, the hydrophobicity by copolymerization. A functional hydrophobic ADMET monomer was developed in our research group to perform polymer-mediated Horner–Wadsworth–Emmons (HWE) reactions: The use of linear, hydrophobic copolymers minimizes purification efforts because the polymer is converted into a poly(phosphate) during the HWE reaction. This product can be easily precipitated from the mixture by changing the polarity of the environment, thereby leaving the product in the organic supernatant.[41] In addition, nanoparticles generated by miniemulsion of hydrophobic PPEs exhibited a strong binding affinity towards a model bone tissue, thus making this system potentially useful for delivering drugs to bones.[43] Furthermore, the pathway of the nanoparticular drug carrier could be followed by fluorescence microscopy by employing a BODIPY-modified phosphate monomer.[39]

Acyclic triene metathesis (ATMET) polymerization requires monomers with three olefins and produces unsaturated

hyperbranched polyesters. Again, progress was first reported for PCEs using a triglyceride as a trifunctional monomer and methyl acrylate as a chain stopper to introduce functionality at the periphery (Figure 7).[44] The pentavalency of phosphorus offers the immediate introduction of three functionalities by esterification of $POCl_3$ with an ω-unsaturated alcohol. It was found that hyperbranched PPEs prepared from these phosphotriesters exhibit exceptional efficiency in the scavenging of singlet oxygen. This system was employed to protect the process of triplet–triplet annihilation photon upconversion against extinguishing by singlet oxygen under ambient conditions.[45] Furthermore, hyperbranched PPEs prepared by ATMET were also tested as flame-retardant additives and compared to traditional polyphosphate-based flame retardants (e.g. BDP).[46]

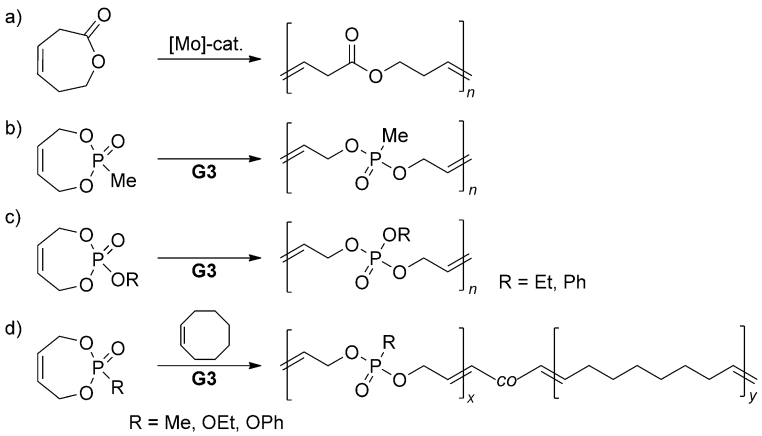

Figure 8. Ring-opening metathesis (co)polymerization (ROMP) of a) an unsaturated ε-caprolactone (6,7-dihydro-2(3*H*)-oxepinone) initated by a Schrock-type catalyst,[48] b) 2-methyl-4,7-dihydro-1,3,2-dioxaphosphepine-2-oxide, and c) 2-ethoxy- or 2-phenoxy-4,7-dihydro-1,3,2-dioxaphosphepine-2-oxides.[43b,51] d) Copolymerization with *cis*-cyclooctene afforded degradable, high-molecular-weight polymers.

In contrast to ADMET polymers, ROMP polymers are polyolefins prepared from unsaturated, cyclic monomers (e.g. norbornene or cyclooctene derivatives).[47] The preparation of PCEs from strained unsaturated ring systems, however, was found to be challenging, as the Grubbs catalyst does not initiate the polymerization of a strained unsaturated ε-caprolactone.[48] Considerable polymerization was only observed if a Schrock-type catalyst was employed. Surprisingly, macrocyclic olefin monomers with virtually negligible ring strain can undergo ROMP to yield polymers with high molecular weights.[49] This polymerization is not enthalpy-driven but entropy-driven, and referred to as ED-ROMP.[50]

In contrast to PCEs, PPEs can be prepared from strained ring systems which are accessible by esterification of a phosphoric or phosphonic acid with an unsaturated diol (e.g. *cis*-2-butene-1,4-diol). The ring strain of the 7-membered ROMP monomers is rather low, thereby giving rise to longer reaction times and lower molecular weights of the corresponding homopolymers compared to other systems.[43b,51] The 7-membered phosphorus-containing ROMP monomers (Figure 8) yield molecular weights of about 5000 g mol^{-1} after homopolymerization initiated by **G3**. The molecular weight, as well as the crystallinity, can be increased to 50000 g mol^{-1} by copolymerization with *cis*-cyclooctene. The thermal properties were adjusted by the monomer feed ratio, thus making ROMP of PPEs a versatile technique to prepare degradable hydrophilic as well as hydrophobic PPEs.

3. Degradability and Toxicity

Aliphatic PCEs have gained much interest in academia and industry because of their beneficial mechanical properties and their potential to be (bio-)degradable. Polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(ε-caprolactone) (PCL) have, therefore, found applications as compostable bags and cups as well as bioresorbable surgical suture and pins. However, the slow biodegradation or hydrolysis of these materials as a result of their high crystallinity and hydrophobicity are unfavorable for some applications. Furthermore, the introduction of functionality into PCEs can be challenging as postmodification of polyesters is difficult and functional monomers are not easily accessible. Copolymerization with phosphates was found to overcome these problems, as the new materials inherit the properties of the homopolymers, which allows adjustment of the final properties to the individual need. Leong and co-workers compared the degradation of PPE-PCE copolymers with the corresponding homo-PCE at neutral pH and found an accelerated degradation, which they attributed to the low crystallinity and increased hydrophilicity of the copolymers.[52]

Accelerated degradation is one important property facilitated by PPE copolymerization, because phosphoester linkages are cleaved

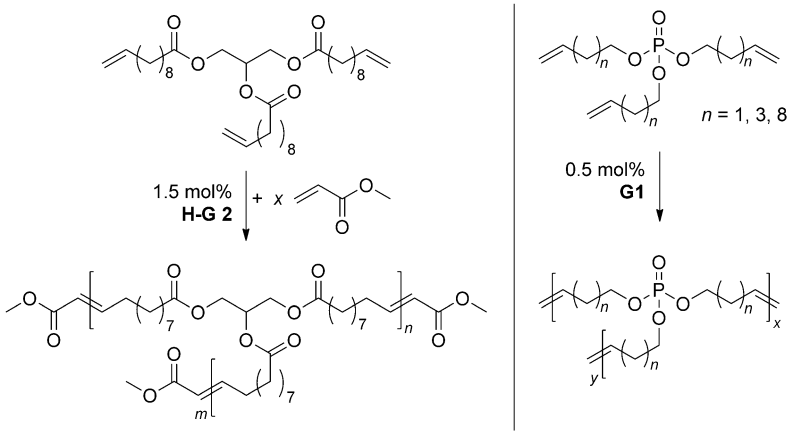

Figure 7. ATMET polymerization of trifunctional unsaturated monomers to prepare hyperbranched PCEs (left) and PPEs (right).[44,45]

either by spontaneous hydrolysis or by enzymatic degradation. Both processes are pH-dependent, as shown in detailed studies by the research groups of Penczek, Wang, Iwasaki, and Yan.[53] Baran and Penczek showed that the polymer side chain is attacked preferentially under acidic conditions, whereas the backbone and the side chain are hydrolyzed at similar rates in a basic environment. Furthermore, the degradation mechanism depends on the pH value, with the side chain more susceptible to a nucleophilic attack (e.g. by water) under acidic conditions, as the carbon atom is usually less sterically hindered compared to the carbon atoms of the main chain. Under basic conditions, however, hydrolysis is considered to proceed by nucleophilic attack at the phosphate center, which leads either to the release of the side chain or breaking of the polymer backbone. Nevertheless, degradation under basic conditions proceeds considerably faster than under acidic conditions.[53a]

The degradation rate itself can be adjusted by changing the chemical structure of the backbone and side chain. Wang, Mao, and Leong, for example, demonstrated an accelerated degradation of a polyphosphate with pendant amino groups that hydrolyzed rapidly.[54] Similar observations are reported by Wooley and co-workers, who studied the pH dependency of the hydrolysis of a polyphosphoamidate by ^{31}P NMR spectroscopy. The hydrolysis of these structures is accelerated at low pH values and can proceed within a few days, thereby enabling the design of an acid-cleavable phosphoamidate linkage to a therapeutic cargo, which is released in acidic tumor tissue or the endosome.[19]

The degradation products and their potential cyctotoxicity is a crucial parameter to consider for any material being applied in the biomedical field.[53b] PCEs, for example PLA and PGA, are considered to be biocompatible and biodegradable materials; however, their degradation products have exhibited toxic effects under high concentrations (which are barely reached in actual appplications).[55] Most water-soluble PPEs are prepared by AROP from the corresponding dioxaphospholane oxides to yield PPEs with ethylene glycol as the bridging units between the phosphate centers. The release of ethylene glycol during degradation of these structures was studied by Yan and co-workers by detailed NMR experiments.[56] In addition, cell lines treated with the degradation products at concentrations as high as 10 mg mL^{-1} did not show any toxic effects. However, the toxicity of elaborate structures has to be evaluated in detail before any application in higher lifeforms, as toxic effects often arise by interference with the complex metabolism in mammals which can not be simulated in single cell line experiments.

An in-depth study on the effect of PPE nanoparticles on cytotoxicity, immunotoxicity, and biofouling properties was published by Wooley and coworkers.[57] Alteration of the surface characteristics had a remarkable effect on the cytokines secreted from mouse macrophages. PPE-based micelles and cross-linked nanoparticles with different surface charges (non-ionic, anionic, cationic, and zwitterionic) were prepared and evaluated as potential vehicles for drugs and nucleic acids. The cytotoxic effect was significantly lower than for several commercially available systems (e.g. Lipofectamine, PEI) and was further decreased by cross-linking the micelles. The zwitterionic micelles and particles, in particular, showed negligible cytotoxicity and limited adsorption of cytokines, and thus have a low immunotoxic profile.

PPEs have been shown to be promising materials for biomedical applications due to their low toxicity and their potential biodegradability. Therefore, copolymers with established biocompatible polymers were prepared to study the self-assembly and degradation behavior of the novel phosphorus-containing materials. A thermoresponsive block copolymer of PEG and PPE was reported by Wang and coworkers which showed low in vitro toxicity and a presumed autocatalytic degradation behavior at neutral pH. These effects were attributed to the generation of an ionic phosphate polymer which is proposed to catalyze the degradation further.[53b] The accelerating effect was observed by SEC analysis, which showed a 7% drop in the molecular weight after two months and over 60% after 8 months. The degradability of these structures can be accelerated further by enzymatic catalysis. A completely biodegradable triblock copolymer (PPE-PCL-PPE) was prepared by Wang and coworkers that formed micelles composed of a hydrophilic PPE shell and a hydrophobic PCL core which could transport a hydrophobic drug.[53d] It was shown that the micellar structures are degraded under enzymatic catalysis with lipase and phosphodiesterase I, an enzyme present in the cytosome of mammalian cells, which could facilitate intracellular drug release. Therefore, PPEs are very promising materials for a variety of applications as these biodegradable and biocompatible polymers could be employed in tissue regeneration and in cell-responsive drug-delivery systems.

4. Selected PPE-Based Applications

Poly(phosphate)s and poly(phosphonate)s are well-known for their flame-retardant properties and are used as additives to lower the flammability of commodity plastics or coatings by acting as an intumescent flame retardant. In this way, PPEs can substitute toxic and potentially carcinogenic halogenated polycyclic aromatic compounds. The use of PPEs as flame retardants has already been reviewed in detail.[58]

PPEs have also been proposed for many applications beyond flame retardancy. High biocompatibility in vivo, controlled degradability, and low cyctotoxicity in vitro, were proven by several research groups for a wide range of PPEs.[59] Several elegant examples in the biomedical field, for example, the development of nanocarriers for drug and gene delivery in particular, have been reported and reviewed.[54,60] Some PPEs exhibit thermoresponsive behavior in aqueous solution (namely, they have a lower critical solution temperature, LCST), which can be advantageous for biomedical applications.[11,29,53b,61] Straightforward adjustment of the hydrophobicity and polyvalence by pendant ester groups or backbone variation in PPEs allows the encapsulation of different drugs (e.g. low-molecular-weight drugs, proteins, DNA, and plasmids). Paclimer, a copolymer of PLA and ethyl phosphate (Figure 9), is one of the most prominent PPE-based drug carrier systems. Microspheres with a diameter of about 50 μm were loaded with 10 wt% paclitaxel (PTX), a strong mitotic

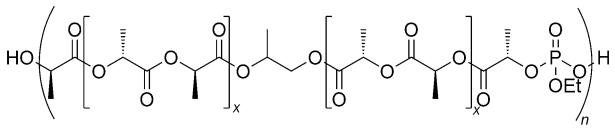

Figure 9. Molecular structure of the poly(ethylphosphate-*co*-lactide) copolymer used in Paclimer as a drug carrier system for paclitaxel.[60e]

inhibitor, to treat cancer in a phase I trial.[62] However, this system never entered the market because the manufacturer, Guilford Pharmaceuticals, deferred further clinical research.

In fact, a poly(phosphate) prodrug of estradiol was developed as early as 1953 by condensation of the female hormone with phosphorus oxychloride, and entered the market under the trade name Estradurin in 1958. This prodrug releases the steroid over several days, thereby keeping the serum level constant, but was superseded by novel forms of drug application.[63]

A novel drug delivery system was developed by employing hydrophobic poly(phosphate)s and poly(phosphonate)s that were synthesized by ADMET polycondensation.[43] Here, the targeting of model bone tissue was accomplished by increasing the hydrophobicity of the polyester, as the backbone can easily be adjusted using a suitable ADMET monomer (Figure 10). The nanoparticles were loaded with

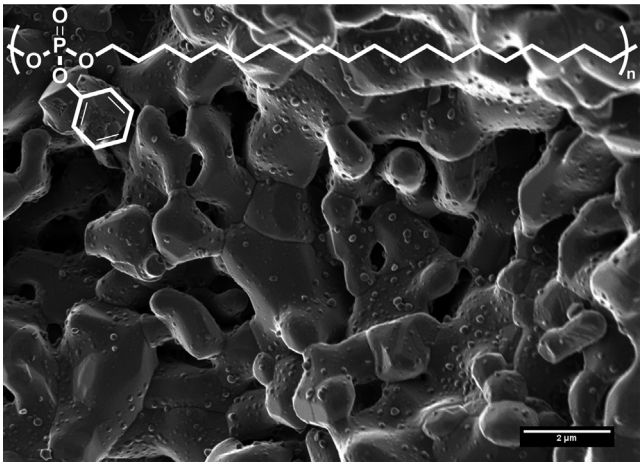

Figure 10. Scanning electron image (scale bar 2 µm) of an adhesion study on a model bone tissue with nanoparticles prepared from hydrophobic PPE with a saturated C20 backbone.[43a]

PTX and tested on different cancer cell lines to prove drug release. This system might find application in the local treatment of bone cancer. Ikeuchi and Iwasaki also developed a hydrophilic bone-targeting counterpart, by employing organocatalytic ROP. The copolymerization of EEP and BP monomers by ROP followed by hydrogenation yielded amphiphilic PPE ionomers with a strong affinity towards calcium minerals.[64]

Another PTX-loaded multifunctional nanoparticle was developed by Wooley and co-workers,[65] in which a block copolymer of poly(ethylene oxide)-*co*-poly(butynylethylene phosphate) was synthesized and a PTX-prodrug attached covalently to the PPE core of the micelles by a click reaction. This resulted in an impressive loading capacity of 65 wt% PTX, which was shown to be effective against several cancer cell lines.

PPE-PCE copolymers were also suggested for theranostical applications.[66] Among these, the micellar systems developed by Wooley and co-workers have received considerable interest, in particular.[31a] Four different micelles with different surface charges were prepared by post-modification of a block copolymer with non-ionic, anionic, cationic, and zwitterionic thiols by photoinitiated, radical-mediated thiol-yne chemistry (Figure 11). The block copolymer consisted of a hydrophobic poly(2-ethylbutylethylene phosphate) block and an alkyne-functionalized poly(butynylethylene phosphate) block synthesized from the corresponding phospholanes by an organocatalyzed, one-pot sequential ROP.

Different copolymers of PPEs with PCEs were also synthesized and investigated as potential drug delivery platforms by Wang and co-workers. Biodegradable vehicles were formed from PCL-*b*-PEEP by the thin-film hydration method and loaded with doxorubicin (DOX), another potent anticancer drug. This system has been proven to efficiently inhibit cell proliferation of human lung cancer cells.[67] Star-shaped P(CL-*co*-PE) DOX carriers assembled into micelles which released the internalized drug depending on the pH value of the aqueous environment, thereby allowing targeted release during the endocytic pathway.[68] Making use of the pH gradient between the inside and outside of tumor cells, Wang and co-workers have designed a dual pH-sensitive nanoparticle that can reverse its surface charge when exposed to tumor tissue (pH 6.8) to facilitate cell uptake. After internalization, the pH value of the endosome (pH 5.0) promotes the release of DOX that is been covalently bound to the PPE backbone.[69]

Cross-linked hydrogels were prepared from triblock copolymers, with PEEP making up the two outer blocks and a poly(propylene oxide) or poly(ethylene oxide) the middle block.[70] The thermoresponsive PEEP blocks facilitate aggregation and gelation. Subsequent cross-linking of a diacrylate of the triblock copolymer and loading with DOX then produces nanogels of adjustable size which release the drug in vitro and thereby inhibit cell proliferation more efficiently than the drug itself. Wang and co-workers also investigated triblock copolymers that allowed reversible redox cross-linking through labile disulfide bridges within the shell of a preformed micelle, which protects its cargo efficiently from external conditions.[71]

In addition to cancer treatments, PPEs have also been used as potential delivery platforms for a wide range of biological agents, for example, antibiotics. A triple-layered nanogel, consisting of a triblock copolymer (PEG-*b*-PCL-*b*-PPE), was used to preserve the antibiotic within the cross-linked PPE core and shielded by the PCL interlayer which degraded in the presence of bacteria, as PCL is lipase-sensitive. The PEG shell promoted the solubility of the nanogel in aqueous conditions.[72]

Proteins and other biomolecules were successfully delivered using poly(phosphate)s, for example, bovine serum albumin (BSA) which was loaded into a hydrogel prepared

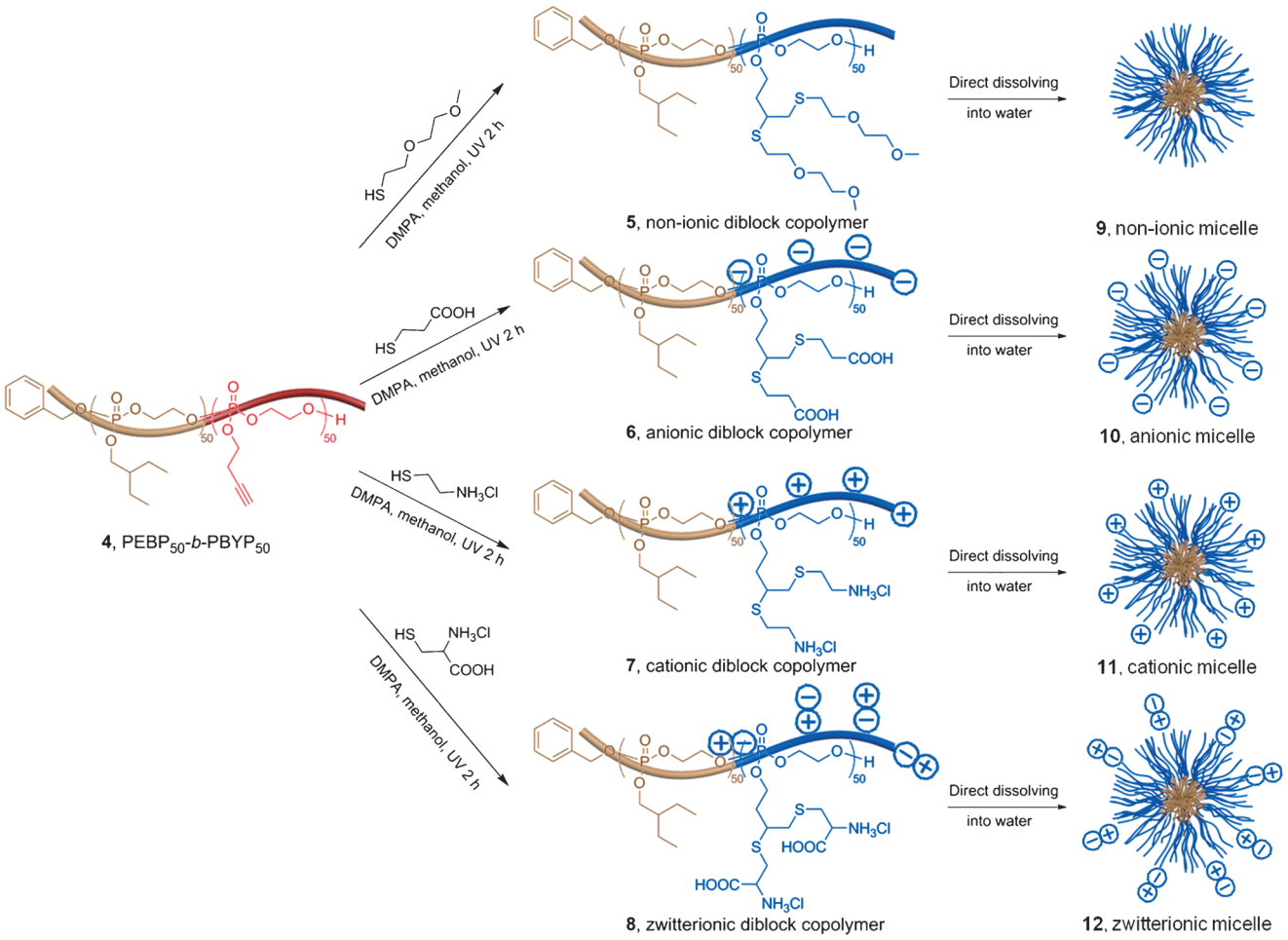

Figure 11. Functionalization of a phosphate block copolymer with four different thiols (charged and uncharged) to yield amphiphiles that self-assemble in water to the illustrated micelles.[31a]

from acrylic acid and α-methacryloyloxyethyl ω-acryloyl-modified PEEP by radical cross-linking polymerization. The degradation of the PEEP segments in aqueous media then released the protein cargo.[73]

PPEs were also developed for gene delivery systems. Delivering plasmid DNA or small interfering RNA (siRNA) to a target cell has proved to be an elegant and potent strategy to treat serious diseases while both allowing for modification of the cell's metabolism and minimizing side effects.[74] Cationic polymers complex negatively charged nucleic acids and protect the genetic cargo from degradation as well as facilitating cellular uptake through intelligent design of the nonviral vector. However, most cationic polymers are non-degradable (e.g. polyethylene imine, PEI) and very cytotoxic.[75]

Recent advances have demonstrated that the long-term release of DNA under physiological conditions using a cationic polyelectrolyte (poly(2-aminoethylethylene phosphate), PPEEA;[76] such as when siRNA was delivered to HEK293 cells by employing positively charged nanoparticles from a triblock copolymer ($mPEG_{45}$-*b*-PCL_{100}-*b*-$PPEEA_{12}$)) leads to successful gene silencing.[77] PPEs have been explored for gene delivery for the last two decades and early progress is reviewed elsewhere.[60c,e,g]

5. Conclusions and Outlook

The diverse family of PPEs is a rapidly growing class of materials whose potential and actual applications are expanding as novel synthetic techniques are explored and innovative materials with adjustable properties are synthesized. Motivated by the diversity of phosphorus chemistry, as well as the evolving multidisciplinary field of applications accessible by PPEs, the development of novel polymers and polymer architectures is attracting increasing attention. In contrast to other biocompatible (e.g. PEG) and biodegradable polymers (e.g. PLA), functionality can be accomplished using a set of diverse and modular synthetic pathways. Moreover, the precisely designed synthesis of multifunctional PPEs for sophisticated biomedical applications is feasible. Although PPEs may have not found considerable commercial application in materials science and the biomedical field to date, we believe that the developments and achievements that have been made in recent years will lead to considerable improvements in these fields.

The preparation of PPEs is feasible by a variety of different techniques, depending on the monomer and the properties of the desired polymer. Recent advances in controlled polymerization routes, for example, ROP by

organocatalysis and ruthenium-catalyzed metathesis polymerization, make PPEs readily available and accessible. It has been shown that efficient post-polymerization modifications, for example, click chemistry, can be applied to modify the biodegradable polymers for a wide range of applications in the biomedical field. Future in vivo studies, however, are necessary to evaluate if PPEs can keep up with the promising achievements of the in vitro experiments reported in many publications.

However, PPEs are currently not expected to substitute commodity plastics and will, therefore, not be encountered in customers daily lives, but will grow rapidly within its niche area, for example, as drug carrier systems. The large-scale production of PPEs is not only energy-intensive but also consumes a finite natural resource, namely phosphate rock. These limitations prevent PPEs from being considered as a sustainable alternative for future generations. Polymer chemistry has not overcome these challenges up to now and the development of novel controlled polymerization techniques has so far offered no solution. The first interesting approaches were made by employing enzyme catalysis, but with poor results. In our opinion, PPEs prepared analogously to DNA by polymerase enzymes straight from phosphate salts is the next step in PPE chemistry. In this way, polymer chemists can profit from the impressive progress made in synthetic biology and will help to merge the disciplines of natural science.

F.R.W. is grateful to the Max Planck Graduate Center (MPGC) for support. T.S. is a recipient of a fellowship provided by the Max Planck Graduate Center (MPGC). We thank Prof. Dr. Katharina Landfester (MPIP Mainz) for support.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 6098 – 6108
Angew. Chem. **2015**, *127*, 6196 – 6207

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Received: January 7, 2015

