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Poly(phosphonate)s via Olefin Metathesis: Adjusting Hydrophobicity and Morphology

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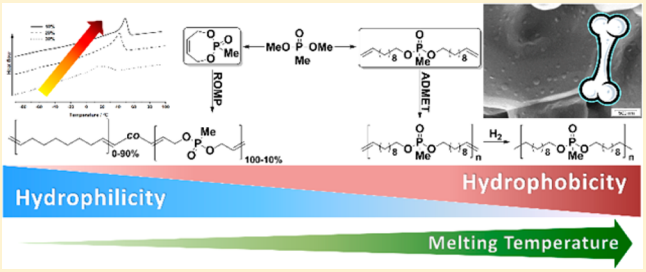
Supporting Information

ABSTRACT: Olefin metathesis step-growth (acyclic diene metathesis (ADMET)) and chain-growth (ring-opening metathesis) polymerization was used to prepare linear poly(phosphonate)s with variable hydrophilicity. The first phosphonate monomer, i.e., di(undec-10-en-1-yl) methylphosphonate, for ADMET polymerization was developed, and potentially degradable and biocompatible, unsaturated poly(phosphonate)s were prepared with molecular weights up to 23 000 g mol^{-1} with molecular weight dispersities $Đ < 2$. These polymers were studied with respect to their interaction with a calcium phosphate bone substitute material from an aqueous nanoparticle dispersion that was prepared by a solvent evaporation miniemulsion protocol. Ring-opening metathesis polymerization (ROMP) was employed to synthesize more hydrophilic amorphous polyphosphonates from a novel seven-membered cyclic phosphonate monomer, i.e., 2-methyl-4,7-dihydro-1,3,2-dioxaphosphepine 2-oxide, as well as hydrophobic crystalline copolymers with *cis*-cyclooctene. ROMP yielded polymers with molecular weights up to 6000 g mol^{-1} (homopolymer) and 47 000 g mol^{-1} (copolymers). Poly(phosphonate)s are potentially hydrolytically degradable materials and therefore promising materials for biomedical applications.



INTRODUCTION

Living nature is dominated by phosphate esters and anhydrides, which link the nucleotides in DNA or RNA and are used for chemical energy storage in adenosine triphosphate (ATP). Because of the high stability of the poly(phosphate) anion, nature has "chosen" phosphate esters to store biological information efficiently over an entire lifetime.[1] The structural motif of the phosphate unit can also be employed in synthetic polymer chemistry to generate poly(phosphoester)s (PPEs) that exhibit high biocompatibility and adjustable degradability.[2−4]

One major advantage of phosphorus-based materials is the versatility that the pentavalent phosphorus offers in designing a wide range of polymers altering the main and/or the side chains. PPEs are usually subdivided into four main classes, depending on the side chain: poly(phosphate)s, poly(phosphonate)s, poly(phosphite)s, and poly(phosphoamidate)s.

Recently, several elegant strategies have been studied for the synthesis of PPEs with precise control over the polymerization kinetics. Especially the anionic ring-opening of cyclic phosphates has found increasing attention via the polymerization of phospholanes via ultrafast organic catalytic systems.[5−10] Poly(phosphate)s have also been synthesized by olefin metathesis via acyclic diene metathesis (ADMET) polymerization and ring-opening metathesis polymerization (ROMP).[11−13] Only two recent reports deal with the polymerization of the respective cyclic phosphoamidates and phosphonates.[10,14]

Research interest in poly(phosphonate)s has faded since the 1960s, despite the unique and interesting properties of this PPE subclass. The backbone of poly(phosphonate)s is a main-chain polyester, whereas the alkyl or aryl side chain is directly linked to the phosphorus forming a stable phosphonate bond. These structures are reported to be more stable than the corresponding poly(phosphate)s due to the lack of a hydrolyzable side chain.[15] Poly(phosphonate)s are usually synthesized by classical polycondensation routes to date, limiting the introduction of functional groups and yielding products with broad molecular weight distributions and low molecular weights. Therefore, we developed the first chain-growth protocol toward water-soluble poly(ethylene methyl phosphonate)s via living anionic ROP.[10] Never before have poly(phosphonate)s been synthesized with such a high control over molecular weight and polydispersity.

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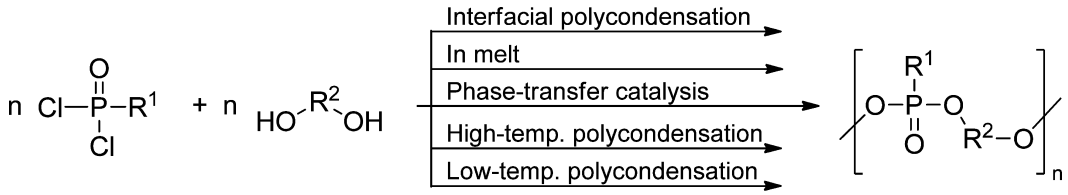
Scheme 1. Overview over Classical Polycondensation Routes toward Poly(phosphonate)s (R^1,R^2= Alkyl or Aryl Groups)



In contrast to the anionic ring-opening polymerization, classical polycondensation of alkyl (or aryl) phosphonic acid dichorides is conducted with diols or dihydroxy aromatics. Different reaction conditions have been studied and can be summarized as follows: (1) interfacial polycondensation,[16−20] (2) polycondensation in the melt,[21,22] (3) low-[23,24] and high-temperature solution polymerization, and (4) (inverse)[25] phase-transfer-catalyzed polycondensation[26−30] (Scheme 1).

Poly(phosphonate)s are considered to be "high-performance" plastics, especially with regards to their flame-retardant properties since phosphorus-containing polymers tend to char and not to burn.[31−33] Incorporation of phosphorus into the polymer chain as a straightforward way to decrease the flammability of the resulting material and was studied in detail by Howell and co-workers.[34,35] Especially the poly(arylene aryl phosphonate)s are used as a fire-retardant additive.[36] Other applications include plasticizers, coatings, and lubricating oil additives.[37] The outstanding benefit of its flame-retardant properties has also led to a considerable commercial interest with companies (FRX Polymers) specializing on phosphonate-based polymer additives in flammable plastics to meet government regulations.[38−40] Poly(phosphonate)s therefore help to reduce the usage of halogenated additives, such as brominated aromatics. In contrast to phosphonate additives, halogenated additives may form highly toxic and potentially carcinogenic brominated furans and dioxins during combustion. These concerns have led the European Community and the United States government to review the toxicity of the currently used flame-retardants.[33] Furthermore, halogenated additives are usually nondegradable, causing environmental problems when disposed and burned.

In order to enlarge possible applications for poly(phosphonate)s, properties of the desired material need to be adjustable to the individual need. Two of the most important properties of a material with potential biomedical applications are hydrophilicity and crystallinity. Poly(phosphonate)s derived from arylphosphonic acid with a rigid backbone are often highly hydrophobic and crystalline materials. A high degree of crystallinity has a strong effect on the degradation of polyesters. Amorphous plastics degrade typically faster as the loose packaging of the polymer chains allows enzymes or microorganisms to degrade the material faster. Moreover, amorphous materials are known to be more impact resistant. Therefore, the synthesis of entirely amorphous poly(phosphonate)s promises to close the gap between oligo(phosphonate)s as additives and rigid poly(phosphonate)s which are used as high performance plastics.

To establish poly(phosphonate)s for future applications, our aim was to overcome the limitations of classical polycondensation reactions and expand modern synthetic pathways to poly(phosphonate)s. Facing new challenges in materials science and biomedical polymers, a single polymerization chemistry will not be enough. Herein, we report the development of two efficient and general synthetic platforms for the synthesis of poly(phosphonate)s with tunable properties: acyclic diene metathesis (ADMET) polycondensation and ring-opening metathesis polymerization (ROMP), the latter being the second report on a chain-growth polymerization of poly(phosphonate)s. Olefin metathesis polymerization of acylic and cyclic unsaturated esters of methylphosphonic acid was employed to generate mainly hydrophobic polymers. Both techniques are robust protocols for the synthesis of these polymers. For the first time, high molecular weight poly(phosphonate)s are accessible with tailorable structure, allowing the investigation of this unusual polymer class in a variety of applications. Olefin metathesis allows convenient and controlled polymerization methods, yielding potentially degradable polymers with promising applications in the biomedical field and materials science. Both techniques allow the adjustment of hydrophobicity and morphology depending on the concentration of phosphonate groups within the polymer backbone. ADMET polymerization was used to prepare an unsaturated, hydrophobic poly(phosphonate) which was subsequently hydrogenated to yield a saturated semicrystalline polymer. Since phosphonates and phosphates are known for their strong affinity toward tooth and bone tissue, these saturated poly(phosphonate)s were used in a miniemulsion evaporation technique to prepare nanoparticles for which the adhesion to a model bone substrate was studied. Furthermore, unsaturated poly(phosphonate)s were synthesized via ring-opening metathesis polymerization to yield amorphous and hydrophilic polymers. The morphology and hydrophilicity was altered by copolymerization with *cis*-cyclooctene to obtain a potentially biodegradable material with adjustable phosphorus content. The advances in poly(phosphonate) chemistry as well as the unique chemical and physical properties of the materials generated are presented here.

EXPERIMENTAL SECTION

Materials. Solvents were purchased from Acros Organics, Sigma-Aldrich, or Fluka and used as received, unless otherwise stated.

Dimethylmethylphosphonate (DMMP), thionyl chloride, *N,N*-dimethylformamide (DMF), dichloromethane (DCM), chloroform (TCM), sodium dodecyl sulfate (SDS), pyridine over molecular sieves, triethylamine (TEA), and *cis*-butene-1,4-diol were used as received from Sigma-Aldrich (Germany). Tetrahydrofuran (THF) was purchased from Sigma-Aldrich and distilled from sodium prior to use. Undec-10-en-1-ol was purchased from Apollo Scientific (UK), distilled from CaH_2 prior to use, and stored over molecular sieve (4 Å). *cis*-Cyclooctene was purchased from Sigma-Aldrich and distilled prior to use. Grubbs catalyst first generation and Grubbs catalyst third generation were purchased from Sigma-Aldrich and stored under argon at −28 °C. Deuterated solvents were purchased from Deutero GmbH (Kastellaun, Germany) and used as received. A micro−macro porous biphasic calcium phosphate cement (MBCP+), composed of 60% hydroxyapatite and 40% β-tricalcium phosphate, was donated from Biomatlante (Vigneux de Bretagne, France).

Instrumentation and Characterization Techniques. Size exclusion chromatography (SEC) in chloroform or tetrahydrofuran

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was performed using an instrument consisting of a Waters 717 plus autosampler, a TSP Spectra Series P 100 pump, and a set of three PSS SDV columns (10^4/500/50 Å). Signal detection was achieved using a UV (TSP Spectra System UV 2000, 254 nm) and a refractive index (Agilent 1260) detector. Calibration was carried out using poly(styrene) standards provided by Polymer Standards Service.

^{1}H, ^{13}C, and ^{31}P{H} NMR spectra were acquired using a 400 MHz Bruker AMX system. The temperature was kept at 298.3 K and calibrated with a standard ^{1}H methanol NMR sample using Topspin 3.0 (Bruker). ^{13}C NMR spectra were referenced internally to solvent signals. ^{31}P{H} NMR spectra were referenced externally to phosphoric acid. The ^{13}C NMR (101 MHz) and ^{31}P{H} NMR (168 MHz) measurements were obtained with an ^{1}H power gate decoupling method using 30° degree flip angle. 2D (^{1}H, ^{31}P HMBC) were measured using a Bruker 400 AMX NMR spectrometer The spectra were referenced to the residual proton signals of the deuterated solvent ($CDCl_3$ (^{1}H) = 7.26 ppm; DMSO (^{1}H) = 2.50 ppm). All 1D and 2D spectra were processed with MestReNova 6.1.1-6384. Differential scanning calorimetry (DSC) measurements were performed using a PerkinElmer DSC 8500 equipped with a PerkinElmer CLN2 in the temperature range from −100 to 80 °C under nitrogen with a heating rate of 10 K min^{-1}.

Nanoparticle Characterization. The average particle size and particle size distribution were determined by dynamic light scattering (DLS) in a submicron particle sizer NICOMP 380 equipped with a detector to measure the scattered light at 90°. The zeta-potential of the solutions were obtained using a Zetasizer NanoZ using as dispersive phase an aqueous 1×10^{-3} M KCl solution. The particle morphology was studied by scanning electron microscopy (SEM) using a microscopy Zeiss LEO Gemini 1530. Prior to the measurement, a thin carbon coating layer was deposited using a vacuum coating system Leica EM MED020.

Calcium Phosphate Attachment Studies. The calcium phosphate granules (MBCP+, 80−200 μm, Biomatlante) were dispersed in ultrapure water (10 mg mL^{-1}, Millipore) and washed for 30 min under horizontal agitation (200 rpm) before use. The poly(phosphonate) nanoparticle dispersion in deionized water at an initial concentration of 1−3 wt % was diluted to application concentrations of 0.01% with deionized water in 1.5 mL Eppendorf centrifuge vials (1 mL nanoparticle solution volume). The calcium phosphate granules were mixed with the nanoparticle dispersion and placed on a shaker for 30 min. Then, the mixture was centrifuged at 1000 rpm for 5 min, the majority of the liquid was pipetted from the tube and removed, and the tube was refilled with deionized water and vortexed to remove the not bound nanoparticles from the mixture. This process of centrifuging, removing, and replacing the supernatant with fresh deionized water, and vortexing was repeated two additional times. After the three rinses were complete, the samples were centrifuged again, and stored in water before observation in the scanning electron microscope (SEM, Zeiss LEO Gemini 1530). Prior to the measurement, a thin carbon coating layer was deposited using a vacuum coating system Balzer Union (BAE250).

Synthetic Procedures. *Synthesis of Methylphosphonic Dichloride (1).* The dichloride was synthesized as previously reported.[42] Briefly, a mixture of 62.0 g of dimethyl methylphosphonate (0.5 mol) and DMF (0.5 mL) was added dropwise to refluxing thionyl chloride (90 mL). Strong gas evolution of methyl chloride and sulfur dioxide indicated the progress of the reaction. After 12 h the gas evolution declined. To complete the reaction, the bath temperature was increased to 120 °C. Fractional distillation of the raw product yielded the desired dichloride as colorless crystals (49.82 g, yield: 75%, bp 71−73 °C/65 mbar). ^{1}H NMR ($SOCl_2$, ppm): δ 2.54 (d, $^2J_{PCH}$ = 15 Hz). ^{31}P{H} NMR ($SOCl_2$, ppm): δ 44.9.

Synthesis of Di(undec-10-en-1-yl) Methylphosphonate (2). Methylphosphonic dichloride (13.29 g, 100 mmol) was dissolved in dry THF (200 mL) and cooled to 0 °C. A solution of 3-undec-10-en-1-ol (34.06 g, 200 mmol) and pyridine (15.82 g, 200 mmol) in THF (50 mL) was added dropwise. After completion of the addition, the solution was stirred for 2 h and stored overnight at −28 °C to facilitate the precipitation of the pyridinium hydrochloride. The precipitate was removed by filtration, and the solvent was removed at reduced pressure. Column chromatography (ethyl acetate:petroleum 1:2, R_f = 0.35) yielded the desired product (23.96 g, yield: 60%). ^{1}H NMR ($CDCl_3$, ppm): δ 5.81 (ddt, J = 16.9, 10.2, 6.7 Hz, 2H, H_2C═C$\underline{H}$−), 5.12−4.81 (m, 4H, $\underline{H_2}C$═CH−), 4.13−3.86 (m, 4H, P−O−C$\underline{H_2}$), 2.17−1.92 (m, 4H, H_2C═CH−C$\underline{H_2}$), 1.74−1.57 (m, 4H, O−CH_2−C$\underline{H_2}$−), 1.46 (d, $^2J_{PCH}$ = 17.4 Hz, 3H, P−C$\underline{H_3}$), 1.28 (br s, 24H). ^{13}C NMR ($CDCl_3$, ppm): δ 139.32 (H_2C═C$\underline{H}$−), 114.28 ($H_2\underline{C}$═CH−), 65.70 (d, J = 6.0, P−O−C$\underline{H_2}$), 33.94 (═CH−C$\underline{H_2}$), 30.68 (d, J = 6.0, O−CH_2−C$\underline{H_2}$), 29.58, 29.31, 29.24, 29.06, 25.68 (O−CH_2−CH_2−C$\underline{H_2}$), 10.14 (d, $^1J_{CP}$ = 144 Hz, P−C$\underline{H_3}$). ^{31}P{H} NMR ($CDCl_3$, ppm): δ 30.7. ESI MS: 823 ($2MNa^+$).

Synthesis of 2-Methyl-4,7-dihydro-1,3,2-dioxaphosphepine 2-Oxide (5). Methylphosphonic dichloride (7.30 g, 55 mmol) was dissolved in dry THF (500 mL), 8 equiv of triethylamine was added, and the solution was cooled to 0 °C. A solution of *cis*-buten-1,4-diol (5.47 g, 62 mmol) in THF (40 mL) was added slowly (4 h) to the solution via a syringe pump. After complete addition the solution was stirred for 2 h and stored overnight at −28 °C to facilitate the precipitation of the hydrochloride salt. The precipitate was removed by filtration, and the solvent was removed from the filtrate at reduced pressure. Column chromatography (acetone, R_f = 0.65) yielded the desired product (4.496 g, yield: 55%) .^{1}H NMR ($CDCl_3$, ppm): δ 5.75 (t, J = 1.8 Hz, 2H, C$\underline{H}$═C$\underline{H}$), 4.91−4.66 (m, 2H, CH−C$\underline{H_2}$−O), 4.63−4.42 (m, 2H, CH−C$\underline{H_2}$−O), 1.59 (d, $^2J_{PCH}$ = 17.5 Hz, 3H, P−C$\underline{H_3}$). ^{13}C NMR (DMSO-d_6, ppm): δ 127.66 (C$\underline{H}$═C$\underline{H}$), 63.53 (d, J = 7.0, CH−C$\underline{H_2}$−O), 9.07 (d, $^1J_{PC}$ = 142.4 Hz, P−C$\underline{H_3}$). ^{31}P{H} NMR ($CDCl_3$, ppm): δ 36.11. ESI MS: 255 (MAg^+).

Representative Procedure for the Acyclic Diene Metathesis Polymerization of 2. Monomer **2** (220 mg, 1.08 mmol) was placed in an oven-dried Schlenk tube, and Grubbs' first generation catalyst (7.1 mg, 8.6 μmol, 0.8 mol %) was added under an argon atmosphere with stirring. The catalyst dissolved rapidly in the monomer, yielding a purple liquid. Reduced pressure (2×10^{-2} mbar) was applied to remove the evolving ethylene. The reaction mixture was stirred for 24 h at 60 °C and for another 48 h at 80 °C. The reaction mixture was allowed to cool to room temperature, and the resulting viscous oil was dissolved in 1 mL of dichloromethane. Ethyl vinyl ether (100 μL) was added to cap the active chain end. After treatment with activated charcoal the solution was filtered through Celite, and the polymer (**3e**) was precipitated from dichloromethane into methanol and finally dried at reduced pressure (136 mg, yield: 62%).^{1}H NMR ($CDCl_3$, ppm): δ 5.47−5.25 (m, C$\underline{H}$═C$\underline{H}$), 4.12−3.87 (m, C$\underline{H_2}$−O−P), 2.19−1.78 (m, C$\underline{H_2}$−CH), 1.74−1.54 (m, C$\underline{H_2}$−CH_2−O), 1.45 (d, J = 17.4 Hz, P−CH_3), 1.26 (s, backbone). ^{13}C NMR ($CDCl_3$, ppm): δ 130.43 (C$\underline{H}$═C$\underline{H}$), 129.97 (C$\underline{H}$═C$\underline{H}$), 65.7 (d, J = 6.1 Hz, C$\underline{H_2}$−O−P), 32.74, 30.69, 30.63, 29.89, 29.78, 29.75, 29.67, 29.63, 29.56, 29.52, 29.42, 29.32, 29.30, 29.23, 27.34, 25.67, 11.14 (d, $^1J_{PC}$ = 145.4 Hz, P−C$\underline{H_3}$). ^{31}P{H} NMR ($CDCl_3$, ppm): δ 30.6.

Hydrogenation of 3f. A 300 mg sample of the polymer **3f**, 10 mL of THF, and 100 mg of 20 wt % $Pd(OH)_2$/C catalyst were charged into a 250 mL ROTH autoclave. Hydrogenation was performed with vigorous stirring under a hydrogen pressure of 50 bar at room temperature for 48 h. The solution was then filtered through Celite to remove the catalyst. The product was isolated after precipitation into methanol and dried at reduced pressure to give a solid polymer (**4**, 252 mg). ^{1}H NMR ($CDCl_3$, ppm): δ 4.15−3.87 (m, C$\underline{H_2}$−O−P), 1.73−1.55 (m, C$\underline{H_2}$−CH_2−O), 1.46 (d, J = 17.4 Hz, P−CH_3), 1.24 (br m, backbone). ^{13}C NMR ($CDCl_3$, ppm): δ 65.73 (d, J = 6.1 Hz, C$\underline{H_2}$−O−P), 30.70, 30.65, 29.86, 29.81, 29.74, 29.69, 29.35, 25.69, 11.17 (d, $^1J_{PC}$ = 144.4 Hz, P−C$\underline{H_3}$). ^{31}P{H} NMR ($CDCl_3$, ppm): δ 30.6.

Representative Procedure for the Ring-Opening Metathesis Polymerization of 5. The monomer **5** (or a mixture of **5** and freshly distilled *cis*-cyclooctene) (114.5 mg, 773 μmol) was dissolved in 2 mL of dry chlorobenzene under an argon atmosphere. A stock-solution of third generation Grubbs' catalyst was prepared in dry chlorobenzene and added via syringe (0.3 mL, 0.4 mol %) to the stirring monomer solution. The mixture was stirred at room temperature for 12 h (homopolymer) or for 2 h (copolymers) before 100 μL of ethyl vinyl ether was added to terminate the active chain end. After treatment

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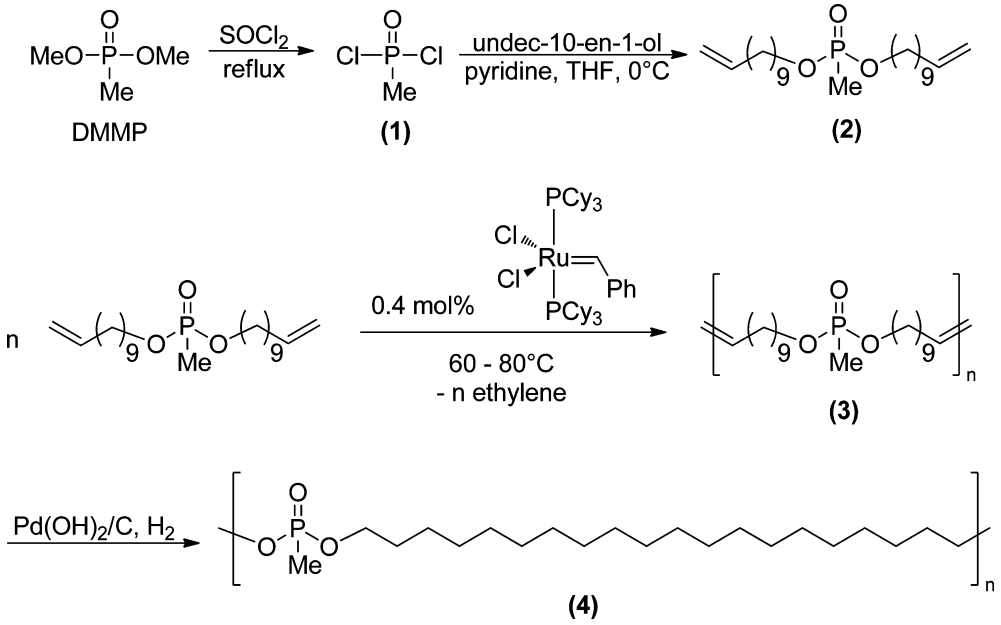
Scheme 2. Polyphosphonates via ADMET polymerization: (top) Condensation of Methylphosphonic Dichloride (1) with Undec-10-en-1-ol Yields the ADMET Monomer (2); (bottom) Polymerization of 2 with Grubbs' First Generation Catalyst in Bulk Produces Unsaturated Polyphosphonate (3); and after Hydrogenation a Saturated Polyphosphonate (4) Is Obtained



with activated charcoal and filtration through Celite, the dichloromethane solution was poured into excess cold diethyl ether (homopolymer) or methanol (copolymers) to precipitate the polymer which was dried at reduced pressure (**6a**, 48.1 mg, yield: 42%). ^{1}H NMR ($CDCl_3$, homopolymer, ppm): δ 5.89 (t, J = 2.8 Hz, C<u>H</u>=C<u>H</u>), 4.82–4.41 (m, C<u>H</u>$_2$–O–P), 1.51 (d, $^{2}J_{PCH}$ = 17.6 Hz, P–C<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$, homopolymer, ppm): δ 128.91, 128.85, 128.48, 128.42, 64.70 (d, J = 6.1, CH–<u>C</u>H$_2$–O), 11.59 (d, $^{1}J_{PC}$ = 144.4 Hz, P–<u>C</u>H$_3$). ^{31}P{H} NMR ($CDCl_3$, homopolymer, ppm): δ 31.7.

Nanoparticle Preparation. Poly(phosphonate) nanoparticles were synthesized using an adapted combination of the miniemulsion technique and the solvent-evaporation strategy.[41] Polymer **4** (30 mg) was dissolved in 1.25 g of chloroform. Milli-Q water (5 g) containing 10 mg of SDS was added to the chloroform solution, and the mixture was stirred over a period of 60 min for the formation of a pre-emulsion which was submitted to a pulsed ultrasonication process under ice cooling over a period of 120 s (30 s sonicated and 10 s paused) at 70% amplitude in a 1/4 in. tip Brason 450 W sonifier. The obtained miniemulsion was kept at 30 °C in an oil bath over a period of 8 h to completely evaporate the organic solvent. The obtained nanoparticle dispersion was further purified by exhaustive dialysis against water before being used for further studies.

RESULTS AND DISCUSSION

The synthesis of poly(phosphonate)s has been limited to classical polycondensation methods which often results in broad molecular weight distributions and often low molecular weights. Furthermore, the introduction of functional groups is very limited since polycondensations are typically performed under harsh conditions, i.e., high temperatures and reduced pressure, and often involve the use of highly electrophilic phosphonic acid dichlorides.

We recently developed the first chain growth strategy to synthesize highly water-soluble poly(phosphonate)s by living anionic polymerization of cyclic five-membered phosphonates.[10] However, tailoring of the materials properties and especially altering the backbone are challenging via ring-opening strategies and would not allow the preparation of a whole range of poly(phosphonate)s with precisely adjusted properties. Olefin metathesis allows fast access to a variety of (functional) monomers, and ruthenium-catalyzed polymerizations are performed at mild temperatures or even at room temperature. As shown by others, sensitive functionalities can be introduced since olefin metathesis tolerates many reactive groups.[43]

Acyclic Diene Metathesis Polymerization (ADMET). Phosphorus chemistry allows fast and straightforward access to various phosphonate esters. Starting from methyl phosphonic dichloride (**1**), the successful preparation of di(undec-10-en-1-yl) methylphosphonate (**2**) suitable for acyclic diene metathesis polymerization is presented (Scheme 2).

The monomer investigated in this study was prepared from methylphosphonic dichloride (**1**), which is readily available from dimethyl methylphosphonate (DMMP) by treatment with thionyl chloride under reflux in reasonable yield (75%) and high purity after distillation. Methylphosphonic dichloride (**1**) was esterified with undec-10-en-1-ol in the presence of pyridine, yielding the phosphonate monomer in high yield (60%) and purity (Figures S1–S3 show the respective ^{1}H, ^{13}C, and ^{31}P{H} NMR spectra of **2**). The monomer is a colorless liquid at room temperature and can be stored under ambient conditions without the danger of decomposition or unwanted polymerization. This makes the ADMET procedure superior to all other techniques for the preparation of PPEs.

Grubbs first generation catalyst was chosen to promote the ADMET polymerization of di(undec-10-en-1-yl) methylphosphonate (**2**). All polymerizations were carried out in bulk with stirring at different temperatures: The polymerization temperature was kept at 60 °C for 48 h and then increased to 80 °C for another 24 h to shift the reaction equilibrium to high molecular weight species and to remove evolving ethylene from the viscous reaction mixture.

The ruthenium-catalyzed ADMET polycondensation is an important and versatile alternative to the well-established polycondensation methods presented in the Introduction and

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can easily be conducted on large scale at moderate temperatures.

Table 1 summarizes the molecular weights and thermal properties of the resulting polymers. Increasing the amount of

Table 1. Molecular Weights and Thermal Properties of Linear Poly(icos-10-en-1,20-dioxy methylphosphonate)s Prepared by ADMET in This Study

code	catalyst (mol %)	M_n[a] (g mol^{-1})	M_w[a] (g mol^{-1})	M_w/M_n[a]	T_g (°C)	T_m (°C)
3a	0.1					
3b	0.25	6200	9600	1.54	n.d.	n.d.
3c	0.5	12600	19700	1.56	−46	+15
3d	0.6	17700	23900	1.35	−37	+19
3e	0.8	23600	35400	1.50	−40	+21
3f	1.0	22200	32000	1.45	−38	+19
4		19400	24000	1.23	−15	+64

[a]Number-average of the molecular weight and molecular weight dispersity (M_w/M_n) determined via SEC in THF vs PS standards.

catalyst led to an increase in molecular weight, which reached a maximum at about 23 000 g mol^{-1} for 0.8 mol % of Grubbs catalyst added to the system (Figure S28). No polymerization was observed if less than 0.25 mol % of catalyst was added. The unsaturated nature of these polyesters is verified by ^{1}H NMR spectroscopy (Figure 1): A strong resonance from 5.50 to 5.25

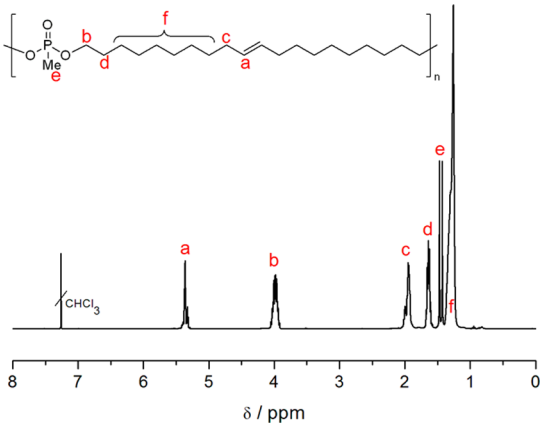

Figure 1. ^{1}H NMR (400 MHz) spectrum of polymer **3f** in $CDCl_3$.

ppm (signal a) indicates the presence of internal double bonds. The ratio between *cis*- and *trans*-double bonds can be calculated from this spectrum (approximately 20% *cis*-content). Typically, the methylene groups next to the phosphonate unit exhibit a chemical shift of ca. 4.0 ppm (multiplet b in Figure 1). The pendant methyl group gives rise to a doublet at 1.45 ppm with the characteristic ^2J coupling of about 17 Hz.

It is important to note that all poly(phosphonate)s prepared via the ADMET of **2** are partly crystalline polymers (with melting points of ca. 15−20 °C) due to the long oligomethylene spacer between the phosphonate groups. Crystallinity is disturbed by the statistical distribution of *cis*- and *trans*-double bonds in the polymer backbone which is typical for polymers prepared via Ru catalysis.[44] To further increase the melting points, these "defects" can be removed by hydrogenation. Thus, sample **3f** was hydrogenated in the presence of $Pd(OH)_2/C$ to produce a fully saturated polymer with a T_m of 64 °C (Figure S30). Successful hydrogenation was also verified by NMR spectroscopy (Figures S6−S8): The ^{1}H NMR spectrum indicates complete transformation of all unsaturated bonds as well as the ^{13}C NMR spectrum, whereas ^{31}P{H} NMR spectroscopy does not show any shift of the single resonance, indicating stability of the phosphonate moiety under these conditions as expected.

Polymer **4** was treated with 1 vol % trifluoroacetic acid (TFA) in chloroform for 24 h at room temperature to show the degradability of the hydrophobic saturated poly(phosphonate) as a proof of principle. The SEC trace of the resulting degradation product is shown in Figure S29.

Low molecular weight phosphonates, especially the broad family of bisphosphonates, are known for their outstanding bone-targeting properties.[45] In order to examine the bone adhesion properties of the herein prepared polymers, potentially biodegradable nanoparticles were prepared from **4** using a solvent evaporation miniemulsion procedure.[41,46] A model bone tissue was treated with the nanoparticle dispersion to study the adhesion of the poly(phosphonate) nanoparticles. These particles could be useful for the encapsulation of hydrophobic drugs, for example in bone tissue engineering.[47] The polymer was dissolved in chloroform and dispersed in water containing sodium dodecyl sulfate (SDS) as surfactant to generate a stable miniemulsion via ultrasound. After evaporation of the organic solvent the polymer precipitated as nanoparticle dispersion which was stable over a period of several months (Figure 2). The hydrodynamic diameter of the

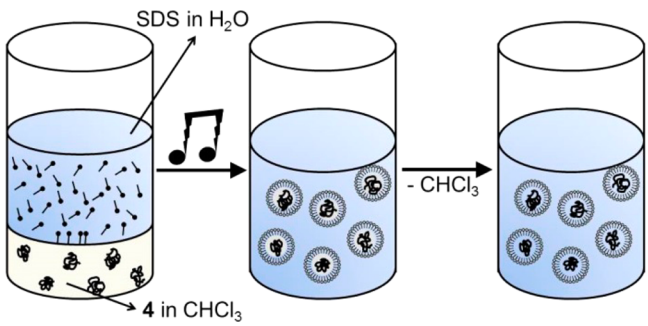

Figure 2. Solvent evaporation miniemulsion protocol for the preparation of poly(phosphonate) nanoparticles: A heterophase system of **4** dissolved in chloroform and an aqueous SDS solution was emulsified via ultrasonication. Nanoparticles of **4** were obtained after evaporation of the organic solvent.

particles in aqueous dispersion after dialysis was found to be 114 ± 35 nm by dynamic light scattering. Zeta-potential values of −51.7 ± 7.7 mV for the particles underline the colloidal stability of the dispersion (Figures S33 and S34). Figure 3a shows a representative SEM image of the spherical poly(phosphonate) nanoparticles (NPs) with sizes measured by SEM corresponding to the values obtained from dynamic light scattering.

The model bone tissue (MBCP+ granules by Biomatlante) is currently used in clinical applications as a bone substitute and has shown bioactivity and osteoconduction properties as this material (a biphasic micro- and macroporous ceramic composed of 40% of β-tricalcium phosphate and 60% of hydroxyapatite) resembles bone tissue very well.[48−51] The presence of adhered nanoparticles on the surface of MBCP+ was demonstrated by scanning electron microscopy (Figure 3). The nanoparticles (**4-NP**) can be observed on the top of the cement (Figure 3c,d) even after several extensive washing steps

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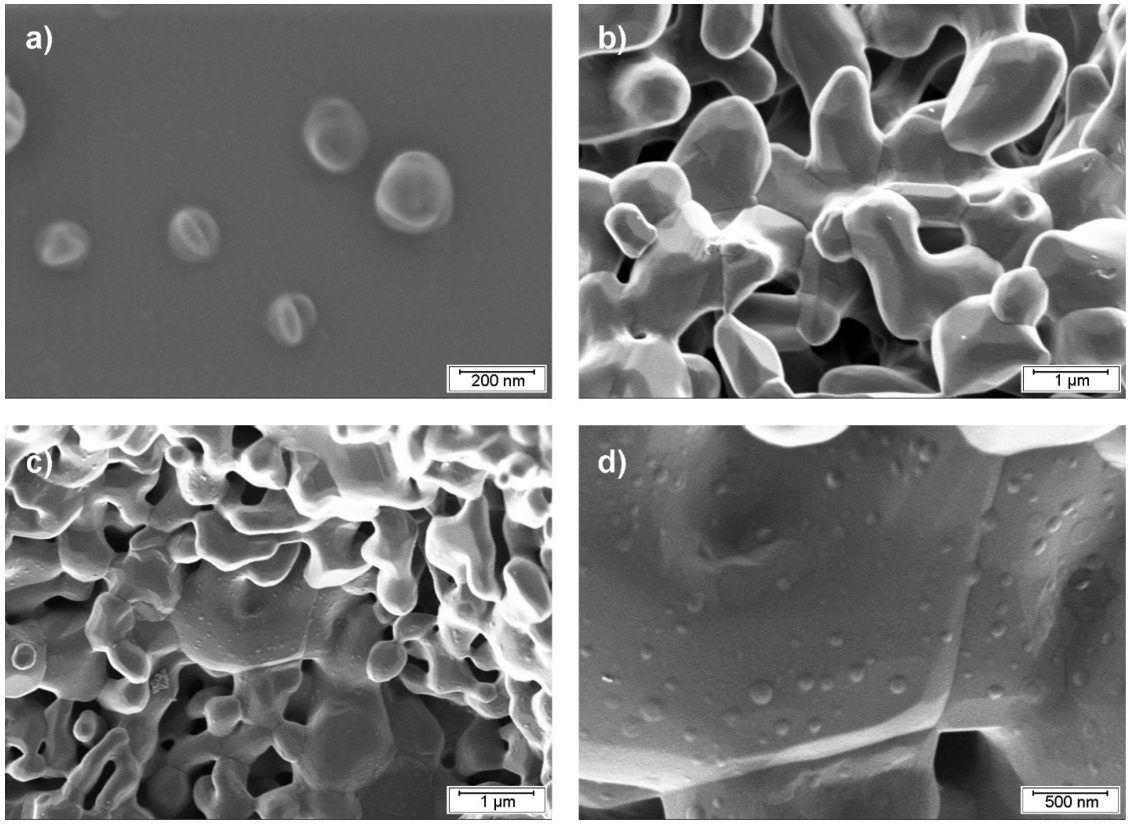
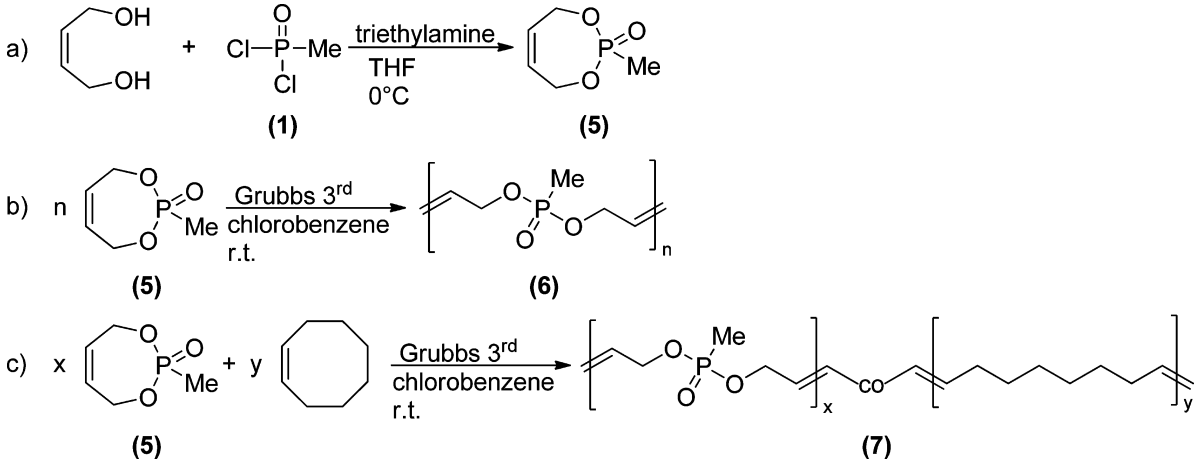


Figure 3. Representative scanning electron micrographs of (a) nanoparticles obtained from **4**, (b) of untreated calcium phosphate granules (MBCP+), and (c) of calcium phosphate granules treated with **4-NP** (MBCP+/4-NP). (d) Magnification of (c) to aid clarity and to show the adherence of the nanoparticles.

Scheme 3. (a) Synthesis of 2-Methyl-4,7-dihydro-1,3,2-dioxaphosphepine 2-Oxide 5; (b) Polymerization of 5 Using Grubbs Third Generation Catalyst; (c) Copolymerization of 5 with *cis*-Cyclooctene



with ultrapure water, indicating a high interaction with calcium phosphate surfaces. Recently, it has been shown by our group that other hydrophobic nanoparticles with different functional groups, compositions, and detergents, e.g., NPs prepared from poly(lactide) or poly(butyl cyanoacrylate), do not adhere on calcium phosphate surfaces.[47] However, hydrophobic nanoparticles derived from the phenoxyphosphate analogues of **4** (viz. poly(icos-10-en-1,20-dioxy phenoxyphosphate)) also showed adhesion to MBCP+. As both poly(phosphate)s and poly(phosphonate)s adhere to calcium phosphate surfaces, the adhesion mechanism is an inherent property of poly(phosphoester)s, regardless of the presence of a hydrolyzable side chain, making this class of materials even more interesting for further investigations. The level of interaction of the different poly(phosphoester)s with calcium phosphate minerals is currently under investigation.

Ring-Opening Metathesis Polymerization (ROMP). Poly(phosphonate)s are mainly obtained from polycondensation reactions, as outlined in the Introduction. In order to widen the synthetic horizon for poly(phosphonate)s and to prepare hydrophilic and amorphous polymers, we moved from the typical step-growth polymerization methods to chain-

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Table 2. Molecular Weights and Thermal Properties of Homopolymers of 5 and Copolymers of 5 and CO Prepared by ROMP in This Study

code	ratio CO:$\mathbf{5}_{theo}$ [a]	ratio CO:$\mathbf{5}_{NMR}$ [b]	catalyst (mol %)	M_n [c] (g mol^{-1})	M_w [c] (g mol^{-1})	M_w/M_n [d]	T_g [d] (°C)	T_m [d] (°C)
6a	0	0	0.4	5900	10900	1.84	−43	−*
6b	0	0	0.8	4200	7400	1.75	−44	−*
6c	0	0	1.0	1200	2700	2.24	−56	−*
7a	9:1	10:1	0.5	47000	108000	2.30	−71	+42
7b	5:1	6:1	0.5	40800	120000	2.94	−66	+31
7c	7:3	7:3	0.5	24700	61500	2.49	−64	+2

[a]Monomer molar ratio between CO and **5**. [b]Molar ratio between CO and **5** determined from ^{1}H NMR. [c]Number-average of the molecular weight and polydispersity index determined via SEC in chloroform vs PS standards. [d]Glass transition temperature (T_g) and melting points (T_m) determined via differential scanning calorimentry (* = no melting point observed).

growth techniques. Exceptionally hydrophilic poly(phosphonate)s were synthesized by our group recently, employing sophisticated anionic polymerization techniques at low temperatures.[10] Herein, ROMP was chosen to prepare poly(phosphonate)s at room temperature under less strict conditions. In order to maximize the hydrophilicity of this polyester, the distance between two ester groups needs to be minimized by introducing short alkyl spacers as a linkage. Our group has previously shown that polyphosphates are accessible by ROMP, closing the gap of a hypothetical ADMET polymerization of a diallyl phosphate monomer, which does not undergo ADMET polymerization due to the "negative neighboring group effect" of the phosphate ester.[13] In the case of the unsaturated seven-membered phosphates (2-phenoxy- and 2-ethoxy-4,7-dihydro-1,3,2-dioxaphosphepine 2-oxide), polymerization was promoted by the ring-strain in the presence of Grubbs third generation catalyst at ambient temperatures under an argon atmosphere. A similar procedure for a corresponding phosphonate monomer was expected to give poly(phosphonate)s with similar or higher hydrophilicity since the hydrophobic carbon content of the backbone is reduced to a minimum compared to the poly(phosphonate)s prepared via ADMET. Degradation of poly(phosphate)s prepared by AROP,[10] ROMP,[13] and ADMET (*vide supra*) was already shown as a typical behavior of polyesters toward hydrolysis. A similar degradation behavior can be expected from the poly(phosphonate) structures synthesized in this study as the backbone of the polyester is not altered compared to our previous study and is currently under investigation with respect to bone tissue engineering.

To generate a phosphonate suitable for ROMP, the precursor methylphosphonic dichloride was allowed to react with *cis*-1,4-butenediol. The ring closure was performed in a dilute THF solution (ca. 10 g L^{-1}) with slow addition of the diol via a syringe pump to avoid unwanted oligomerization (Scheme 3a). The ROMP monomer (**5**, 2-methyl-4,7-dihydro-1,3,2-dioxaphosphepine 2-oxide) was obtained in reasonable yield (55%) and high purity (Figures S9−S11 show the respective NMR spectra). In the ^{1}H NMR, it is noteworthy that the resonances for the protons of the methylene groups next to the phosphonate split up into two distinct signals as they are diastereotopic. This indicates that the phosphonate ring is conformationally locked (Figure S9).

5 was polymerized in a chlorobenzene solution with Grubbs third generation catalyst (Scheme 3b and Table 2) over a period of 12 h to achieve maximum monomer conversion. Low amounts of residual monomer (<5%) are left after the polymerization, as indicated by NMR (Figures S12−S14). In analogy to our previously reported ROMP of seven-membered ring phosphate monomers, monomer **5** polymerizes more efficiently using Grubbs third generation catalyst, giving higher yields and higher molecular weights under the same conditions. After polymerization, ^{1}H NMR analysis showed broad polymer resonances, and the two resonances from the diastereotopic methylene groups (multiplets at 4.79 and 4.54 ppm) merge to a broad multiplet at 4.82−4.41 ppm. Furthermore, the methyl group is shifted from 1.59 to 1.51 ppm during polymerization (Figure 4a). ^{31}P{H} NMR analysis revealed a shift to higher field (from 36.1 to 31.7 ppm) for the phosphonate group after ring strain was released. A similar shift to higher field was found after polymerization of 2-methyl-1,3,2-dioxaphospholane 2-oxide (MeEP).[10] As expected for a chain growth polymerization (and in contrast to ADMET), the molecular weight increases with decreasing amount of catalyst (compare Table 2). This observation also suggests that monomer **5** does not terminate a living ROMP as analogue cyclic phosphoamidates do, as reported recently.[52]

The thermal properties of poly(**5**) were investigated by DSC. It was found that the completely amorphous polymers (**6a**, **6b**) exhibit a very similar glass transition temperature of about −44 °C, similar to the materials prepared by ADMET, whereas very low molecular weight polymers (**6c**) show an expected shift to a lower T_g (Table 2 and Figure S31).

Unlike poly(phosphonate)s prepared by ADMET, poly(**5**) showed good solubility in polar solvents such as DMSO, methanol, and aqueos methanol (20 vol %) underlining the transition from strictly hydrophobic crystalline materials to more hydrophilic amorphous polymers.

In additional experiments, the copolymerization of **5** with *cis*-cyclooctene (CO) as a comonomer was studied (Scheme 3c). Linear polyolefins have already been synthesized via ROMP of CO and its derivatives.[53] The polymerization of CO is driven by the substantial ring strain of the eight-membered ring (29 kJ mol^{-1}).[54] Therefore, the copolymerization of **5** with CO was feasible. Different comonomer ratios were investigated, and the thermal properties of the obtained copolymers were studied (Table 2). In contrast to the poly(phosphonate)s prepared by ADMET (**3a**−**d**), the materials based on **5** and synthesized by ROMP are amorphous due to a very short unsaturated spacer group between the phosphonate moieties; however, crystallinity can be introduced by copolymerization with CO (Table 2).

Up to 30% phosphonate monomer was incorporated into the PCO backbone, yielding a molecular weight of about 25 000 g mol^{-1}. For lower phosphonate content the molecular weight increased up to 50 000 g mol^{-1}, and the molecular weight distribution was found to be rather broad for all copolymers with PDIs between 2.3 and 2.9 at full monomer conversion (Figure 5), which is in good agreement with observations for

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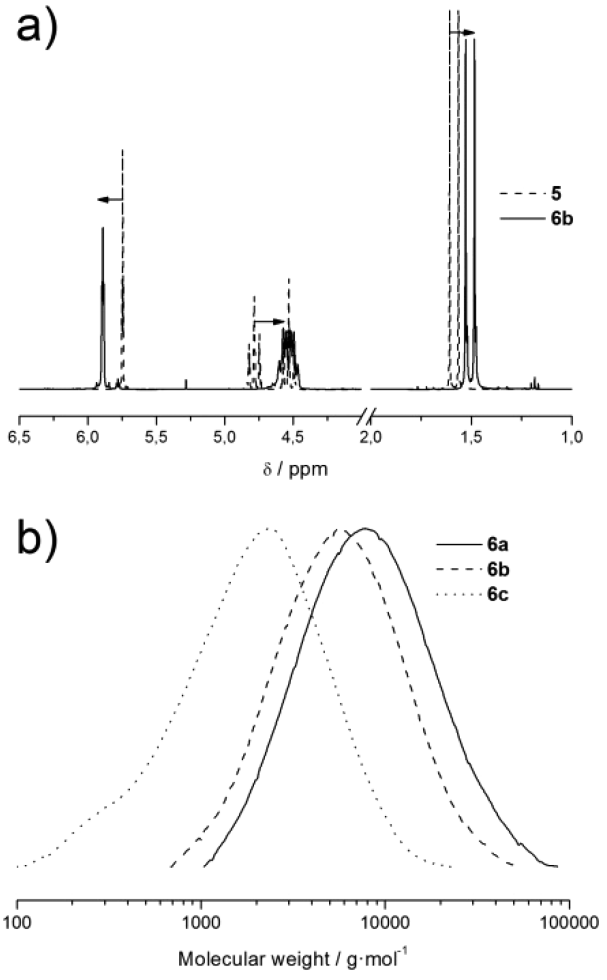

Figure 4. (a) ^{1}H NMR spectra of monomer **5** and polymer **6b**; the resonance of the methylene group and the methyl side chain shifts to higher field whereas the double bond protons of the backbone shift to lower field after ring opening. (b) SEC elugram of poly(phosphonate) homopolymers prepared by ROMP with different amounts of Grubbs third generation catalyst. The molecular weight decreases with increasing amount of catalyst (SEC measured in chloroform vs polystyrene standards).

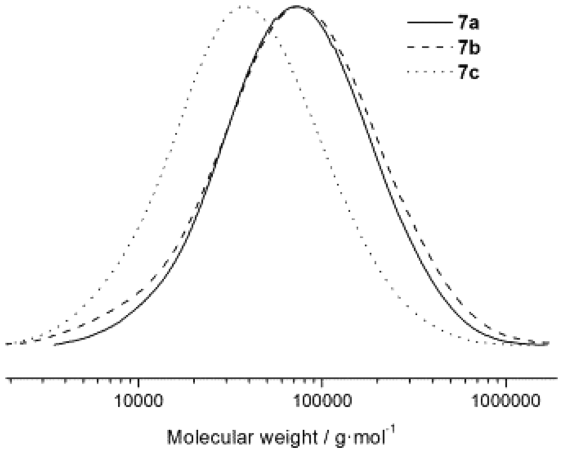

Figure 5. SEC elugram of poly(**5**-*co*-cyclooctene) copolymers prepared by ROMP (SEC measured in chloroform vs polystyrene standards).

other CO copolymers. The thermal properties of all copolymers were investigated by DSC. With increasing degree of incorporation of the amorphous phosphonate monomer, the melting temperature of the copolymers is decreased from ca. 42 °C (9% phosphonate content) to 2 °C when 30% of **5** is copolymerized with CO (Figure S32). Since the incorporation of the phosphonate monomer along the polymer backbone can be regarded as defects hindering the crystallization, the melting point is expected to decrease with increasing phosphonate content.

Successful incorporation of **5** was verified by ^{1}H NMR spectroscopy (Figure S15, S20, and S23) and additional ^{1}H,^{1}H−COSY and ^{1}H,^{1}H-TOSCY experiments (Figures S18, S19, S26, and S27). With increasing phosphonate content the intensity of the resonance of the P−O−CH_2 protons at 4.65 to 4.35 ppm rises as expected and is in close proximity to the feed ratio when compared to the PCO signals (Figure 6). As the two

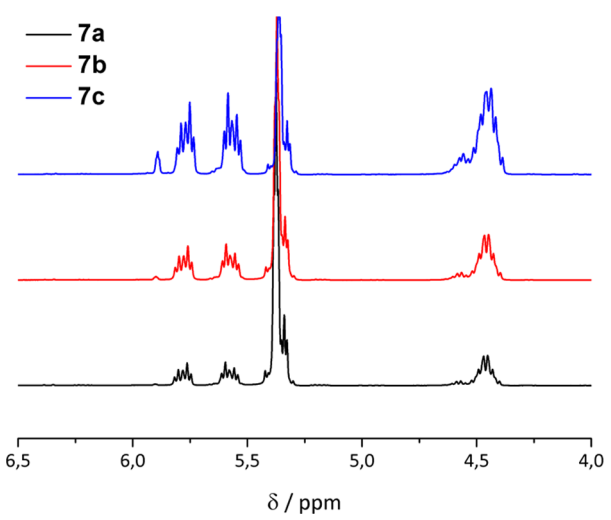

Figure 6. Comparison of the ^{1}H NMR spectra of poly(**5**-*co*-cyclooctene) copolymers. The region from 6.5 to 4.0 ppm is magnified to aid clarity. Increasing signal intensity of the multiplett from 4.65 to 4.35 ppm indicates increasing phosphonate content (for further details please refer to the main text).

monomers are incorporated into the polymer backbone, several signals between 5.0 and 6.0 ppm are detected for the double bonds. Similar patterns were previously reported for the copolymerization of CO and carborane-containing oxanorbornenes.[55] The observed pattern was studied in detail to elucidate the origin of this unusual pattern. Three different dyad structures were found, underlining the random copolymerization of the two monomers. ^{1}H,^{1}H−COSY and ^{1}H,^{1}H-TOSCY NMR allowed the assignment of *cis* (5.32 ppm) and *trans* (5.36 ppm) double bonds of the olefin backbone consisting of CO units exclusively as no cross-relaxation to the methylene groups of the phosphonate ester at 4.46 ppm was observed. As expected for ROMP, 20−25% *trans* double bonds were found. For a **5**−CO dyad two broad resonances at 5.6 and 5.8 ppm were detected at lower field, indicating the close proximity of the phosphonate ester group which is also expressed in the cross-relaxation to these protons at 4.46 ppm. Only for very high contents of **5**, a third resonance at 5.9 ppm can be detected corresponding to the double bond of a **5**−**5** dyad, as revealed by ^{1}H,^{1}H−COSY and ^{1}H,^{1}H-TOSCY NMR analysis. This signal showed cross-relaxation with a broad multiplet at

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4.56 ppm, which can be assigned to the methylene protons between two phosphonate units in a **5**−**5** dyad (Figure S26). This chemical environment also explains the slight shift to lower field. Furthermore, the absence of cross-relaxation to signals of CO units verified that these protons are isolated and spacially separated from the CO backbone (Figure S27). These observations, made from NMR spectroscopy as well as those from the thermal analysis by DSC, indicate the successful and random copolymerization of both monomers reflecting the feed ratio in all cases.

SUMMARY

Several robust protocols have been developed to synthesize novel poly(phosphonate)s with variable microstructure. Both step-growth and chain-growth polymerizations were used to generate high molecular weight polymers. Acyclic diene metathesis polymerization resembles a polycondensation route that allows the introduction of many functional groups due to mild reaction conditions and the tailoring of the polymer structure at several positions including the phosphonate side chain utilizing the versatility that phosphorus chemistry offers. Reported here, ADMET has been applied for the first time to produce strictly linear hydrophobic high molecular weight (unsaturated) poly(phosphonate)s by bulk polymerization employing Grubbs first generation catalyst. Furthermore, it has been demonstrated that the saturated poly(phosphonate) can be used in a solvent evaporation miniemulsion technique to prepare potential degradable nanoparticles that adhere to bone substituent cement. The materials are currently under investigation for bone tissue engineering applications.

In addition, ROMP was chosen as a chain growth polymerization to generate unsaturated poly(phosphonate)s. Amorphous poly(phosphonate) homopolymers with variable molecular weight depending on the catalyst:monomer ratio were prepared, and partly crystalline copolymers with *cis*-cyclooctene were synthesized.

In conclusion, we believe that both strategies presented in this report are superior to the established polycondensation methods that were used earlier to prepare poly(phosphonate)s. By combination of the phosphonate chemistry with olefin metathesis, a great variety of structurally diverse poly(phosphonate)s are accessible for the first time and are currently being investigated in various applications. The ADMET approach allows the variation of the phosphonate side chain more than any other technique, whereas ROMP combines the versatility of a metathesis polymerization with the benefits of a chain-growth mechanism. Both techniques are expected to facilitate the preparation of a wide range of polyphosphonates with various architectures and properties.

ASSOCIATED CONTENT

Supporting Information

NMR spectra, SEC chromatograms, DSC thermograms, and DLS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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