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Sylilation of poly(alkylene H-phosphonate)s – Rapid and efficient method for obtaining poly(alkylene trisilylmethylphosphite)s

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ABSTRACT

Well-defined poly(alkylene trimethylsilylphosphite)s (P + 3) were obtained for the first time via silylation of poly(oxyethylene H-phosphonate)s (P + 5) with N,O-bis(trimethylsilyl)acetamide or trimethylsilyl chloride. The reaction with both silylating agents proceeds at room temperature in quantitative conversion. It has been followed by ^{1}H and ^{31}P NMR spectroscopy. Poly(alkylene trimethylsilylphosphite)s represent important precursors for the preparation of polymeric aminophosphonic acids, α-hydroxyphosphonates, as well as in a Staudinger-polyphosphite reaction with azides yielding polyphosphoramides.

1. Introduction

The most important feature of the polyphosphoesters of the trivalent phosphorus atom is their high reactivity, predetermined by the oxidation state of the phosphorus atom (+3). Synthesis of poly(alkylene phosphite)s from diamides of the corresponding trivalent phosphorus acid [1], or triphenyl phosphite [2] and glycols has been accompanied by side reactions and resulted in the formation of branched and rubber-like low molecular products. Using these methods it is hard well-defined poly(alkylene phosphite)s to be synthesized. Since 1963 there has been no any data in the literature reporting the synthesis of poly(alkylene phosphite)s [3]. In the recent years the tervalent silyl phosphites have gained a certain interest. The silyl group can be easily transferred thus affecting the nature of the obtained products and the reaction conditions [4]. Dialkyltrimethylsilyl phosphites are important precursors for the preparation of biologically active α-aminophosphonates and related derivatives [5–9], and α-hydroxyalkylphosphonates, and α-hydroxyphosphonamides [10]. Hackenberger's group has used the Staudinger-phosphite reaction [11] between azides and phosphites to deliver phosphoramidate-linked glycoconjugates [12]. Phosphonamidate peptides are especially interesting because of their ability to bond to proteases and therefore applicable for targeted drug delivery. From this point poly(alkylene trimethylsilylphosphite)s will represent important precursors for the preparation of polymeric α-aminophosphonic acids, α-hydroxyphosphonates or in a Staudinger-polyphosphite reaction yielding polyphosphoramides.

We suggest an alternative approach for the preparation of linear and well defined poly(alkylene trimethylsilylphosphite)s starting from the corresponding poly(alkylene H-phosphonate)s. Poly(alkylene H-phosphonate)s are attractive functional polymers due to the following advantages [3]: (i) they are highly reactive; (ii) possibility for control of the

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Abbreviations: BSA, N,O-bis(trimethylsilyl)acetamide; TMCS, Trimethylsilyl chloride; THF, Tetrahydrofuran; TEA, Triethylamine.

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hydrophilic/hydrophobic balance; (iii) they can be regarded as degradable and biocompatible synthetic polymers; (iv) they can be designed to be water-soluble and to have non-toxic building blocks, e.g. poly(oxyalkylene H-phosphonate)s (POEHP) are low toxic (IC50 1000 mg/kg); (v) easy to prepare in an industrial scale. Poly(alkylene H-phosphonate)s, which have been developed in our and other laboratories [3,13–15], offer a unique opportunity for introducing various modifications at the phosphorus center by different reaction schemes.

In the current study we report an efficient and rapid method for the preparation of poly[alkylene trimethylsilyl-phosphite(III)]s from poly(alkylene H-phosphonate)s and N,O-bis(trimethylsilyl)acetamide (BSA) or trimethylsilyl chloride (TMSC). The reaction product has been applied as a precursor in a Staudinger-phosphite reaction for conjugation of an azide derivative and yielding a polymer with phosphoramide structural units.

2. Experimental

2.1. Materials

All reagents, starting materials and solvents were purchased from commercial suppliers. Bis(trimethylsilyl)acetamide (BSA), trimethylsilyl chloride (TMSC) and anhydrous tetrahydrofuran (THF) were purchased from Sigma. Dimethyl H-phosphonate and triethylamine (TEA) (Fluka products) were distilled prior to use. Poly(ethylene glycol) with molecular weight 600 was obtained from Sigma and dried by azeotropic distillation with toluene. Fmoc-*p*-azido-L-phenylalanine was obtained from (Aldrich). Acetonitrile (Sigma) was dried over calcium hydride and distilled prior to use.

2.2. Measurements

All ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance II+600 and 250 MHz instruments in $CDCl_3$. The molecular weight characteristics of the polymers were investigated by size-exclusion chromatography (SEC) in tetrahydrofuran at 40 °C using three 5-lm Waters Styragel HR columns (100 Å, 500 Å, and mixed bed) and 16 monodisperse poly(ethylene glycol) calibration standards.

2.3. Synthesis of poly(oxyethylene H-phosphonate)

Poly(oxyethylene H-phosphonate) (degree of polymerization $n = 14$, $M_n = 9782$, Mw/Mn = 1.38) based on PEG 600 was synthesized via the conventional two-stage polycondensation technique [16] (see Scheme S1).

2.4. Silylation of dimethyl H-phosphonate – a model reaction

Dimethyl H-phosphonate (1.67 mL, 0.018 mol) was set into a three-necked round bottom flask, equipped with a magnetic stirrer, a condenser and an input for inert gas – argon. Acetonitrile (2.5 mL) was added at room temperature under Ar-atmosphere. The next step was the addition of the silylating reagent BSA (17.97 mL, 0.073 mol). The solution was stirred at room temperature under Ar-atmosphere. The silylation was controlled by $^{31}P\{H\}$ NMR spectroscopy. Samples were analyzed at predetermined time intervals. The silylation was also performed at a molar ratio of 1:1 between the dimethyl H-phosphonate and BSA.

^{1}H NMR ($CDCl_3$), δ (ppm): 6.51 (d, $^{1}J(P,H) = 696.15$ Hz, $(CH_3O)_2P(O)\mathit{H}$); 3.52 (d, $^{3}J(P,H) = 12.00$ Hz, $(C\mathit{H}_3O)_2P(O)H$); 3.19 (d, $^{3}J(P,H) = 6.00$ Hz, $(C\mathit{H}_3O)_2P[OSi(CH_3)_3]$); 0.00 (s, $(CH_3O)_2P[OSi(C\mathit{H}_3)_3]$).

^{31}P NMR ($CDCl_3$), δ (ppm): 127.27 (septet, $^{3}J(P,H) = 9.72$ Hz, $CH_3O\mathit{P}OCH_3[OSi(CH_3)_3]$; 116.54 (q, $^{3}J(P,H) = 9.72$ Hz, $CH_3O\mathit{P}OH[OSi(CH_3)_3]$; 10.30 (dseptets, $^{1}J(P,H) = 696.87$ Hz; $^{3}J(P,H) = 12.14$ Hz $(C\mathit{H}_3O)_2P(O)H$); –1.69, multiplet.

2.5. Silylation of poly(oxyethylene H-phosphonate) with N,O-bis(trimethylsilyl)acetamide

The silylation was performed at molar ratios 1:1; 1:2 and 1:4 between poly(oxyethylene H-phosphonate) and BSA. A representative example is given for the last ratio. Poly(oxyethylene H-phosphonate) (1.0 g, 1.55×10^{-3} mol repeating units) was set into a three-necked round bottom flask, equipped with a magnetic stirrer, a condenser and an input for inert gas – argon. Acetonitrile (2.5 mL) was added and the mixture was stirred at room temperature under Ar-atmosphere until the polymer was completely dissolved and a clear homogenous solution was obtained. The next step was the addition of the silylating reagent BSA (1.53 mL, 6.19×10^{-3} mol). Stirring at room temperature and under Ar-atmosphere continued. The silylation was followed by $^{31}P\{H\}$ NMR spectroscopy. Samples were analyzed at selected time intervals. Conversion – 100% (based on the ^{31}P NMR data).

^{31}P NMR ($CDCl_3$), δ (ppm): 127.75 (sextet, $^{3}J(P,H) = 9.71$ Hz, $CH_3O\text{-}\mathit{P}[OSi(CH_3)_3]OCH_2\text{-}$ end group); 127.38 (quintet, $^{3}J(P,H) = 7.28$ Hz, $—CH_2O—\mathit{P}[OSi(CH_3)_3]\text{-}OCH_2—$ repeating unit); 117.07 ppm (t, $^{3}J(P,H) = 7.28$ Hz, $—CH_2O\text{-}\mathit{P}[OSi(CH_3)_3]OH$ end group); –9.02 (quintet, $^{3}J(P,H) = 7.28$ Hz,; –17.26 ppm (t, $^{3}J(P,H) = 7.28$ Hz).

^{13}C {H} NMR ($CDCl_3$), δ (ppm): 2.18 [d, $^{3}J(P,C) = 3.01$ Hz, $—CH_2O\ —P(OSi(\mathit{C}H_3)_3—OH]$; 2.73 [d, $^{3}J(P,C) = 4.51$ Hz, $—CH_2O—P[OSi(\mathit{C}H_3)_3]—OCH_2—$; 60.75 (d, $^{2}J(P,C) = 6.00$ Hz, $—P—O\mathit{C}H_2CH_2—$); 71.37 (s, $O\mathit{C}H_2\mathit{C}H_2O—$ repeating unit of PEG); 71.89 [d, $^{3}J(P,C) = 6.00$ Hz, $—POCH_2\mathit{C}H_2—$]; 117.24 (s, $CH_3\mathit{C}N$); 176.28 (s, $CH_3\mathit{C}{=}O$).

2.6. Silylation of poly(oxyethylene H-phosphonate) with trimethylsilyl chloride

Poly(oxyethylene H-phosphonate) (1.0 g, 1.55×10^{-3} mol repeating units) and THF (15 mL) were stirred under Ar-atmosphere with a magnetic stirrer in a round-bottom flask, equipped with a condenser, and once the polymer is completely dissolved trimethylsilyl chloride (TMSC) (0.79 mL, 6.19×10^{-3} mol) was added. The mixture was stirred further for 0.5 h at room temperature. Then TEA (0.86 mL, 6.19×10^{-3} mol) was added dropwise to the reaction solution and immediately a white precipitate was formed. The mixture was stirred further under the same conditions for 24 h. The silylation was followed by $^{31}P\{H\}$ NMR spectroscopy. Samples were analyzed at