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Ultrafast hydrolytic degradation of 2,3-dihydroxypropyl functionalized poly(ethylene phosphates)

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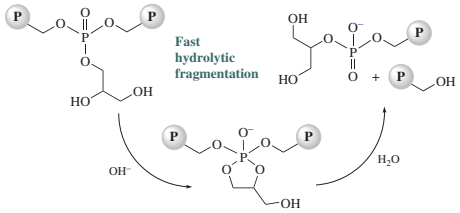
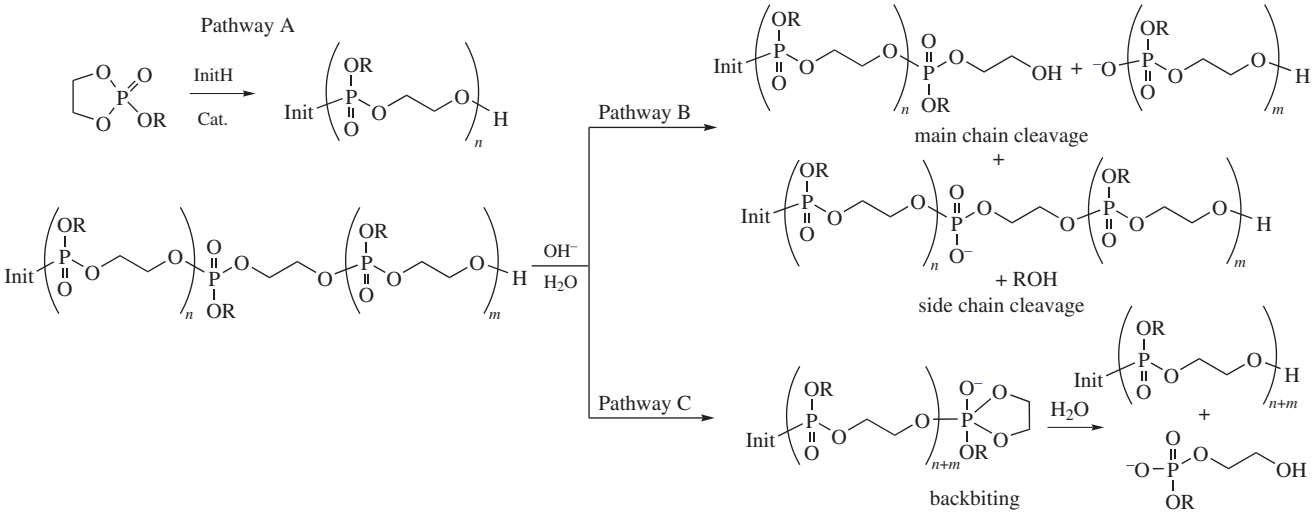
2,3-Dihydroxypropyl functionalized polyphosphates obtained *via* controlled acid-catalyzed hydrolysis of 2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]- or 2-(oxiran-2-ylmethoxy)-1,3,2-dioxaphospholane 2-oxide homopolymers are highly sensitive to basic hydrolysis along the polyphosphate chain.



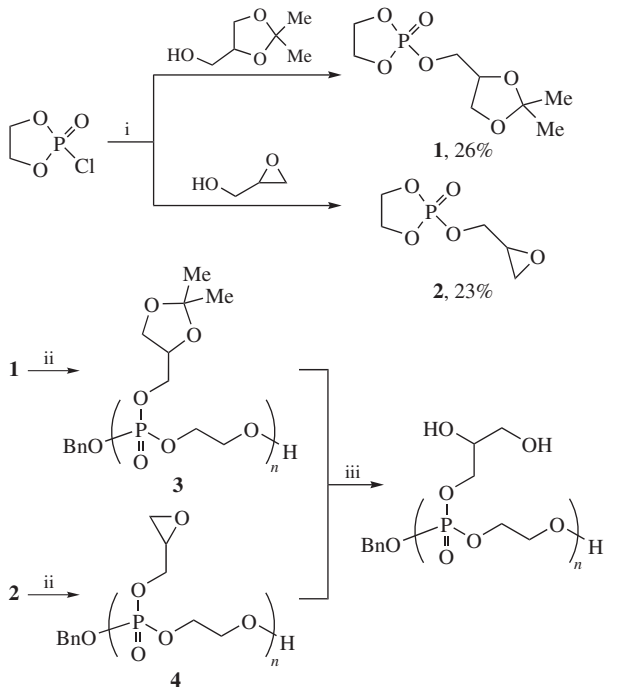
Ring-opening polymerization (ROP) of functionalized 1,3,2-dioxaphospholanes (ethylene phosphate monomers, EPMs; Scheme 1, pathway A) allows one to obtain poly(ethylene phosphates) (PEPs) with given molecular weight (MW) and narrow MW distribution.[1–5] PEPs represent prospective compounds for biomedical applications due to their structural versatility, potential biocompatibility, and adjustable degradation kinetics.[6–23] Acidic hydrolysis of PEPs proceeds slowly *via* protonation followed by nucleophilic attack of H_2O on the α-carbon atom.[24] Two mechanistic concepts are developed for basic hydrolysis. Penczek *et. al*[24] proposed a nucleophilic attack of hydroxide anion on the P atom followed by statistical cleavage of main or side chains (Scheme 1, pathway B). Note that the product of side-chain cleavage is hydrolytically stable due to polyanionic nature. The second concept of basic hydrolysis mechanism comprising backbiting process was proved by Wurm *et al.*,[26] when intramolecular attack of the chain-end 2-oxyalkoxy fragment on phosphorus atom (Scheme 1, pathway C)[26] caused piecemeal depolymerization.

We proposed that PEPs containing 2-hydroxyalkoxy side fragments could be affected by fast basic hydrolysis *via* cyclic intermediates along the polymer chain. Although such polymers were synthesized earlier,[27] their hydrolytic stability was not studied. To confirm this assumption, we prepared PEPs equipped with 2,3-dihydroxypropyl substituents from two cyclic ethylene phosphates, namely 2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-1,3,2-dioxaphospholane 2-oxide (DdmOEP, **1**) that was obtained earlier by Wang *et al.*,[28] and 2-(oxiran-2-ylmethoxy)-1,3,2-dioxaphospholane 2-oxide (glycidyl ethylene phosphate, GlyOEP, **2**) that was synthesized by our group recently.[29] Both monomers are accessible by the reaction of 2-chloro-1,3,2-dioxaphospholane 2-oxide[30] with the corresponding alcohols (Scheme 2, stage i).

We prepared poly(DdmOEP) **3** and poly(GlyOEP) **4** samples by ROP of monomers **1**,**2** in the presence of single-component catalyst $[(BHT)Mg(\mu\text{-}OBn)(THF)]_2$[31,32] (see Scheme 2, conditions ii). At 20 °C in CH_2Cl_2, branched polymers were obtained (Table 1, runs 1 and 4). To reduce the branching of poly(DdmOEP)



Scheme 1



Scheme 2 *Reagents and conditions*: i, NEt_3, THF, 0 °C, 2 h; ii, cat. $[(BHT)Mg(\mu\text{-}OBn)(THF)]_2$, CH_2Cl_2, see Table 1 for details; iii, acid hydrolysis.

3, we conducted polymerization of monomer **1** in the presence of trimethyl phosphate[33] at 20 and 0 °C (runs 2 and 3), highly linear polymer having been obtained at 0 °C. Cyclic phosphate **2** was more active in ROP in comparison with compound **1**, and linear poly(GlyOEP) **4** was prepared at –50 °C (run 5).

We applied acid-catalyzed hydrolysis of polymers **3**,**4** obtained to prepare 2,3-dihydroxypropyl-substituted poly(ethylene polyphosphates) (see Scheme 2, stage iii). For poly(DdmOEP) **3**, the hydrolysis in diluted HCl has been completed after 1 h (Figure S24, part A, see Online Supplementary Materials). For poly(GlyOEP) **4**, the acidic hydrolysis was complicated by noticeable destruction of polyphosphate chains and cross-linking due to lability of oxirane fragment toward nucleophiles.

Thus, poly(DdmOEP) **3** was a better starting material for the synthesis of 2,3-dihydroxypropyl-substituted PEP. Hydrolytic stability of these polymer samples was studied in aqueous $NaHCO_3$ and Na_2CO_3 solutions at initial pH 8.5 and 11, respectively. We found that, in contrast with poly(alkyl ethylene phosphates) that undergo a very slow (40 h) hydrolysis at pH ~11,[26] 2,3-dihydroxypropyl-substituted PEPs readily decompose with a formation of low-MW products even under much milder conditions.

NMR monitoring of the hydrolysis at pH 8.5 showed that at the initial stages of the reaction (after 7 min) the polyphosphate chain was fragmented keeping the chemical environment of the phosphorus atom (see Figure S24, part B); after 6 h we did not observe the signals of the starting high-MW polyphosphate (see part C). In the ^{31}P NMR spectra, we detected a number of signals in the region from 1 to –2 ppm, and characteristic signal at 18.6 ppm that corresponds to five-membered cyclic orthophosphate. The similar signal of the end-group cyclic fragment (δ_P = 19 ppm) that confirmed chain-end backbiting mechanism was detected by Wurm.[26] Note that ^{31}P NMR spectra of the reaction mixtures (see Figure S24) did not contain characteristic signals of six-membered cyclic phosphates of type **A** (Figure 1) at 6–8 ppm.[16,34]

Five-membered phosphate **B** results from hydrolysis of five-membered cyclic intermediate (see Figure 1). The hydrolysis of such intermediates may also occur *via* the reaction pathways comprising formation of salts **C1** and **C2** being primary or secondary ring-opening products, respectively. To compare these pathways, we optimized the molecular structures of model cyclic anion **D** (as a complex with water molecules), intermediates **E1** and **E2** that readily transform to the reaction products (see Figure 1), and corresponding transition states. The calculated value of $\Delta G^{\neq}$ for

Table 1 Polymerization of EPMs **1** and **2**.[a]

Run	EPM	[EPM]/[cat.] ratio	*T*/°C	Reaction time/min	Conversion (%)	M_n[b]×10^3	M_n×10^3 (SEC)	$Đ_M$ (SEC)	Linear/branched ratio[c]
1	**1**	50	20	60	96	14.3	10.0	1.61	8
2	**1**[d]	50	20	60	93	13.4	6.9	1.51	15
3	**1**[d]	50	0	60	95	12.9	6.2	1.55	>20
4	**2**	100	20	60	>99	18.5	21.1	1.73	4
5	**2**	100	–50	3	>99	18.3	15.9	1.34	>90

[a] Reaction time 10 min, [EPM] = 1 mol dm^{-3} in CH_2Cl_2. [b] From ^1H NMR data, calculated by formula $M_n = 108.14 + P_n M_{EPM}$, where 108.14 is MW of BnOH, P_n is degree of polymerization determined as a ratio of integrals in the spectra of the signals of polymer OCH_2CH_2O fragments and $PhCH_2O$ end groups. [c] From ^{31}P NMR spectra by integration of the signals of branched and unbranched phosphorus atoms. [d] In the presence of trimethyl phosphate.

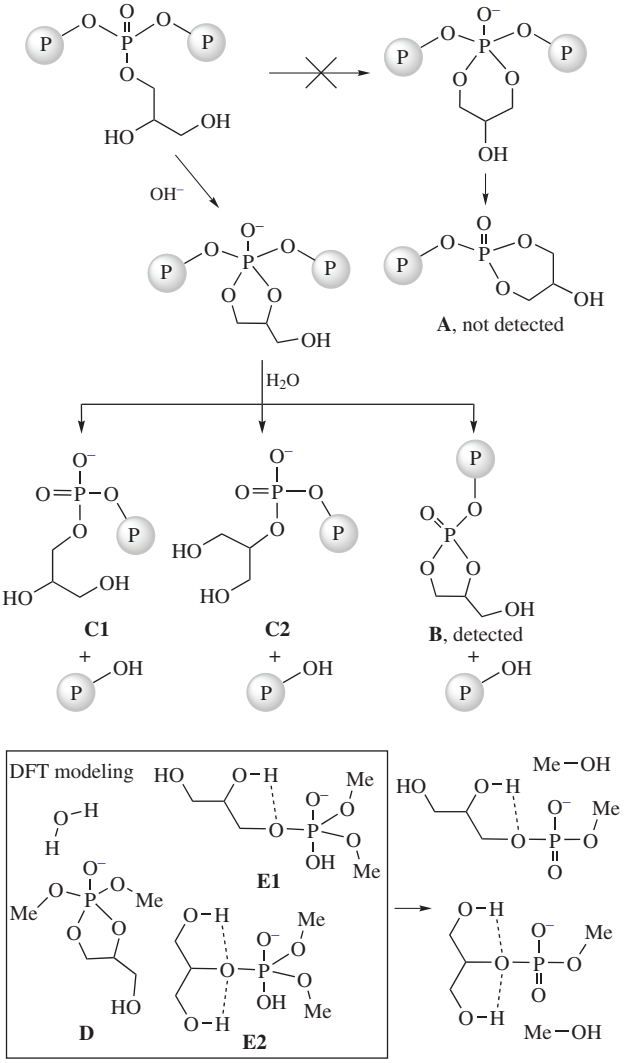


Figure 1 Hydrolysis of 2,3-dihydroxypropyl-substituted PEP.

† DFT modeling was performed using Gaussian-09 program at B3PW91/DGDZVP level of theory for gas phase and for water media (IEFPCM model). Free energies and free enthalpies are provided in Table S1, energy characteristics and Cartesians of stationary points and transition states are also given in Online Supplementary Materials.

C2 was ~10 kcal mol^{-1}, thus, this pathway is not unfeasible under the ambient conditions.†

In conclusion, we have demonstated that poly(ethylene phosphates) containing 2,3-dihydroxypropyl fragments as side chain substituents are orders of magnitude more labile against basic hydrolysis in comparison with non-hydroxylated poly(alkyl ethylene phosphates), and they degrade with a fast destruction of the polyphosphate backbone and formation of the low-MW products. These polymers can be obtained by acid-catalyzed hydrolysis of PEPs that are readily accessible *via* ROP of cyclic phosphate **1**. The results of our study allow one to adjust degradation of polyphosphate fragments in prospective copolymers tailored for biomedical applications.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.010.

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