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Synthesis and ring-opening polymerization of glycidyl ethylene phosphate with a formation of linear and branched polyphosphates

Ilya E. Nifant'ev,*[a,b] Andrey V. Shlyakhtin,[a] Vladimir V. Bagrov,[a] Pavel D. Komarov,[a] Maxim A. Kosarev,[a] Alexander N. Tavtorkin,[a,b] Mikhail E. Minyaev,[b] Vitaly A. Roznyatovsky[a] and Pavel V. Ivchenko[a,b]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 939 4098; e-mail: inif@org.chem.msu.ru*

[b] *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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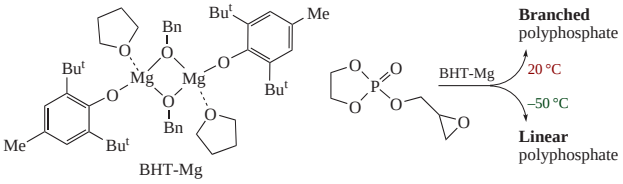
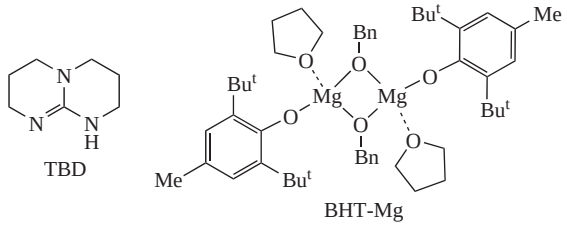
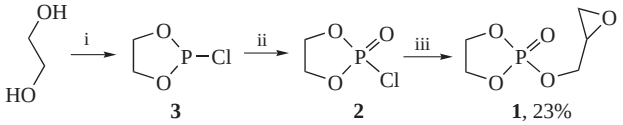
Newly obtained cyclic monomer, glycidyl ethylene phosphate, readily forms branched or linear polymers *via* ring-opening polymerization catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene or by [(BHT)Mg(OBn)(THF)]$_2$, respectively. The polymers obtained are promising for biomedical applications.



Poly(ethylene phosphates) (PEPs) are hydrophilic polymers that are structurally versatile, potentially biocompatible, and biodegradable.[1–8] These properties make it possible to develop tailored materials suitable for different uses, including biomedical applications.[9–17] Current synthetic approaches to PEPs employ ring-opening polymerization (ROP) of 1,3,2-dioxaphospholane 2-oxides catalyzed by organic bases such as 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)[18–21] or by complexes of 'biometals' such as Al[22,23] or Mg,[24] *e.g.*, BHT-Mg. Extremely high standards of the purity of cyclic phosphates as ROP substrates complicate their synthesis, separation and purification; to date, relatively few substituted 1,3,2-dioxaphospholanes were used in preparation of PEPs.[7,8] The chemical nature of 2-positioned fragment in a cyclic phosphate affects hydrophilicity and hydrolytic stability of the ROP products.[20,21,25,26] In recent years, much research attention has been paid to the post-modification of PEPs.[7–9,27,28]



We assumed that similar polymers derived from glycidyl ethylene phosphate **1** could be post-modified due to the high reactivity of the oxirane ring towards nucleophiles. The cyclic phosphate **1** was synthesized in moderate yield (23%) by the phosphorylation of glycidol with 2-chloro-1,3,2-dioxaphospholane 2-oxide **2** in the presence of NEt_3 at 0 °C (Scheme 1). The starting chlorophosphate **2** of the required purity cannot be obtained by the reaction of ethylene glycol with $POCl_3$ because of side product formation. For this reason, we prepared it by selective oxidation of ethylene chlorophosphite **3** with oxygen. The moderate yield of **1** was attributed to the presence of tiny quantities of Et_3NHCl (crystallization does not ensure its complete removal) that reduced the yield and the purity of the product during distillation.†

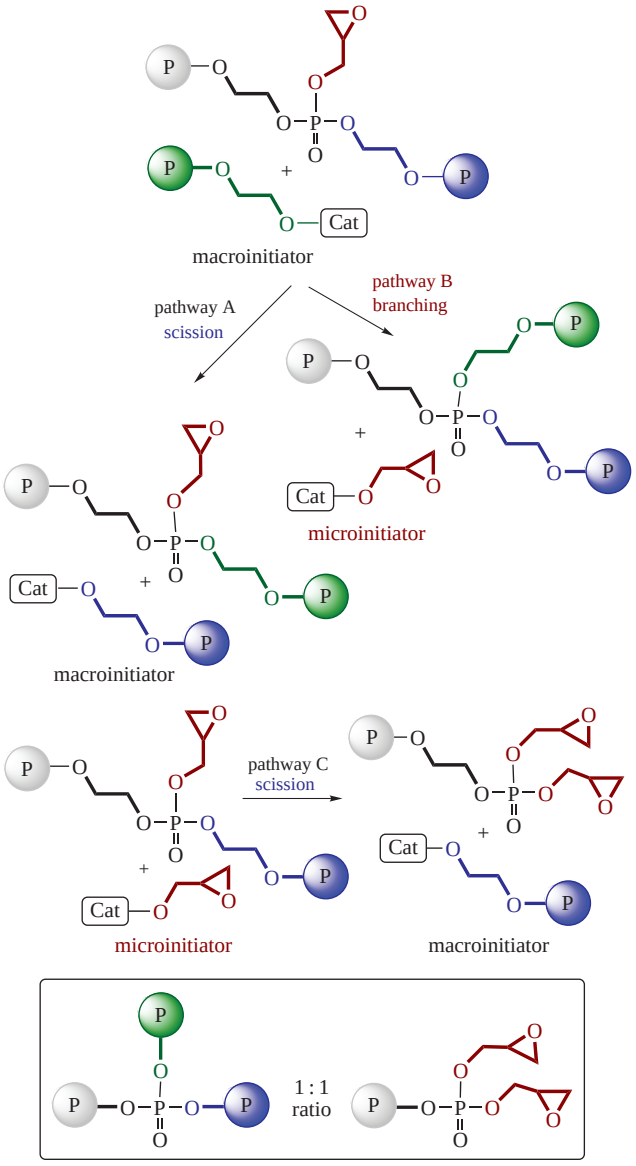


Scheme 1 *Reagents and conditions*: i, PCl_3; ii, O_2, benzene, 45 °C, 6 h; iii, glycidol, NEt_3, 0 °C, THF.

We supposed that polymerization of **1** could be complicated by nucleophilic reactions with oxirane fragment. Therefore, its ROP was studied with two different catalysts, TBD and highly active magnesium complex [(BHT)Mg(OBn)(THF)]$_2$[29] (BHT-Mg) (*cf.* refs. 30, 31). We found that polymerization of **1** at 20 °C catalyzed by both BHT-Mg and TBD occurred within 1 min with almost quantitative conversion (Table 1, runs 1 and 3). In the ^{31}P NMR spectra of the polymer prepared under catalysis with BHT-Mg (Table 1, run 1, see also Online Supplementary Materials) there are two relatively intensive groups of signals (–1.10/–1.14 and –1.44 ppm) in addition to the main signal (–1.29 ppm) that is typical of highly branched PEPs. The integral intensities of secondary signals were almost equal, which led us to supposition that the reaction mechanism comprised branched polymer formation (Scheme 2). According to this mechanism, branching occurs due to transesterification processes. Two types of catalytic alkoxy complexes may initiate transesterification of

† 2-Chloro-1,3,2-dioxaphospholane 2-oxide **2** (35.5 g, 0.25 mol) in dry THF (70 ml) was added dropwise at 0 °C to the mixture of glycidol (18.5 g, 0.25 mol), NEt_3 (35 ml, 0.25 mol) and THF (500 ml). After 20 h of stirring at room temperature, salt Et_3NHCl was filtered off, and the filtrate was concentrated *in vacuo*. The residue was extracted with toluene (10×50 ml), the combined extracts were evaporated under reduced pressure. The residue was divided into two portions, which were distilled separately. The total yield of **1** was 9.5 g (23%), bp 150–155 °C (0.5 Torr), colourless liquid. For NMR data and details, see Online Supplementary Materials.

polyphosphate chain. Both reactions of growing polymer chain (macroinitiator) with polymer phosphate fragment, chain transfer (Scheme 2, pathway A) and branching polymer with generation of microinitiator GlyO–Cat (pathway B) are possible. The microinitiator reacts with polymer phosphate fragment yielding the macroinitiator and polymer bearing $(GlyO)_2P(O)OCH_2CH_2$ end fragment (pathway C).



Scheme 2

The microstructure of the polymer was studied by NMR spectroscopy. The ^1H-^{31}P NMR correlation spectra of the same polymer (see Online Supplementary Materials) allows us to assign the signal at –1.44 ppm to nodal phosphates $[P(O)(OCH_2CH_2O)_3]$ and the signals at –1.10 and –1.14 ppm to terminal phosphates of two types (see Scheme 2). The $[P(O)(GlyO)(OCH_2CH_2O)_2]$/$[P(O)(OCH_2CH_2O)_3]$ ratio is 3.25. The polymer prepared using TBD (Table 1, run 3) was found to be even more branched (linear/branched phosphate ratio of 2.4, see Figure S16, Online Supplementary Materials). We tried to isolate this product by washing the polymer solution with dilute acid to remove the TBD, however this operation was accompanied by the reaction of TBD with the oxirane fragments of the polymer. Hence, the highly nucleophilic nitrogen-containing heterocycles are not optimal catalysts for the synthesis of polymers in question.

Table 1 Polymerization of compound **1** (reaction time 1 min, [**1**] = 1 mol dm^{-3}, [**1**]/[Catalyst] = 100:1).

Run	Catalyst	T/°C	Conversion (%)	M_n (SEC)	$Đ_M$	$M_{n,theor}$[a]
1	BHT-Mg	20	99	21100	1.73	17900
2	BHT-Mg	–50	99	15900	1.34	17900
3	TBD[b]	20	99	18300	1.80	17900

[a] $M_{n,theor} = MW_M[M]_0/[Cat]_0 \times$ conversion + MW_I, where MW_M is the molecular weight of **1**, MW_I is the molecular weight of the initiator BnOH, and $[M]_0/[Cat]_0$ is the monomer to catalyst initial concentration ratio. [b] 1 equiv. of BnOH was added for the initiation of TBD catalyst.

The polymerization of compound **1** at –50 °C catalyzed by BHT-Mg occurred with almost quantitative conversion (Table 1, run 2), and a substantially linear polymer was formed in this case. Treatment of the reaction mixture with a dilute acid with subsequent re-precipitation with Et_2O did not destroy the polymer chain or oxirane rings, and high-purity polyphosphate was isolated.

In summary, we synthesized new cyclic phosphate **1** containing highly reactive oxirane fragment and studied its polymerization initiated by organocatalyst TBD and coordination catalyst BHT-Mg. We found that in the presence of BHT-Mg under ambient conditions the polymerization is accompanied by transesterification with a formation of the branching polymer. The ratio of linear and branched fragments is temperature-dependent. We proposed the mechanism of transesterification and proved the structure of the branched polymer by the correlation NMR spectroscopy. Also, we have discovered that TBD ability to nucleophilic opening of the oxirane ring makes it of little use as a catalyst for the ROP of **1**. Due to the presence of labile epoxy fragments, polymer of **1** should be a material with extensive prospects of biomedical applications. The possible ways of post-modification of the polymer is an object of our further research.

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Online Supplementary Materials

Supplementary data associated with this article (experimental details, ^1H and ^{13}C NMR spectra of compounds) can be found in the online version at doi: 10.1016/j.mencom.2018.03.015.

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