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Macromolecules
COMMUNICATION TO THE EDITOR

Synthesis of Hyperbranched Polyphosphates by Self-Condensing Ring-Opening Polymerization of HEEP without Catalyst

Jinyao Liu, Wei Huang,* Yongfeng Zhou, and Deyue Yan*

School of Chemistry and Chemical Engineering, State Key Laboratory of Metal Matrix Composites, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai, 200240, P. R. China

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Introduction. As a class of biodegradable polymers, polyphosphates (PPE) have aroused a great deal of interest and have been investigated as a biomaterial for almost 3 decades.[1,2] They can be degraded naturally through hydrolysis or enzymatic digestion of phosphate linkages under physiological conditions. For example, biodegradable polyphosphates are promising in delivery of chemotherapeutics and other pharmaceutical agents[3−6] as well as in fabrication of tissue engineering scaffold.[7−9] Recently some amphiphilic polyphosphates have been synthesized as well and applied to drug and gene delivery.[10,11] Furthermore, some new biocompatible and biodegradable hydrogels on the basis of polyphosphates have been produced for cell encapsulations.[12−15]

The synthesis of polyphosphates was pioneered by Penczek and co-workers at the end of the 1970s as analogues of nucleic and teichoic acids or biomembranes toward polymer−inorganic hybrids or mimicking biomineralization.[16,17] To date, a number of different synthetic routes for polyphosphates have been reported,[18] including anionic and cationic ring-opening polymerizations,[19−21] polyaddition,[22] polycondensation,[23] transesterfication,[24,25] and enzyme-catalyzed polymerization.[26] However, all the polyphosphates prepared from aforementioned approaches possess linear architecture.

It is well-known that Flory first presented the concept of highly branched polymers in 1952, but no attention had been paid to this type of polymer until Kim and Webster[27−29] reported hyperbranched polyphenylene in 1988. Since then, a large number of hyperbranched polymers have been synthesized via various polymerization strategies.[30−34] It is worthy of mention that Fréchet and Hedrick have presented an elegant approach, i.e., self-condensing ring-opening polymerization (SCROP), to prepare hyperbranched polyester from cyclic esters.[35,36] In recent years, a variety of linear polyphosphates or copolyphosphates has been prepared from some cyclic phosphate monomers by ring-opening polymerization.[37−48] Furthermore, some phosphorus-containing hyperbranched structures have also been reported.[49,50] To the best of our knowledge, the synthesis of hyperbranched polyphosphates from cyclic phosphate inimers by SCROP has not been reported yet.

In this Communication, a novel hydroxyl-functionalized cyclic phosphate inimer, i.e. 2-(2-hydroxyethoxy)ethoxy-2-oxo-1,3,2-dioxaphospholane (HEEP), was designed and synthesized successfully. Then the SCROP of HEEP in bulk results in a hyperbranched polyphosphate. Because of the facile polymerization without a catalyst, the resulting product is very pure and would be a perfect material for biomedical applications. Furthermore, a great number of terminal hydroxyl groups in this biocompatible and biodegradable hyperbranched polyphosphates provide a unique opportunity for further modification and functionalization. The further investigation in detail will be reported in our follow-up work.

Results and Discussions. *a. Monomer Synthesis.* By molecular design, we synthesized a novel AB* inimer HEEP with a five-membered cyclic phosphate and a primary alcoholic hydroxyl. The synthetic route of HEEP is shown in Scheme 1. Due to the high reactivity of chlorine atom in 2-chloro-2-oxo-1,3,2- dioxaphospholane (COP), it was easy to react with the alcoholic hydroxyl in diethylene glycol (DEG). In order to ensure only one alcoholic hydroxyl in DEG molecule reacted with a COP to produce an inimer HEEP, COP in THF was dropped into DEG in THF at −20 °C and triethylamine (TEA) was used as a deacid reagent. The ^{1}H, ^{13}C and ^{31}P NMR spectra of the resulting HEEP are exhibited in the Supporting Information, Figure S1, and the signals were attributed to the

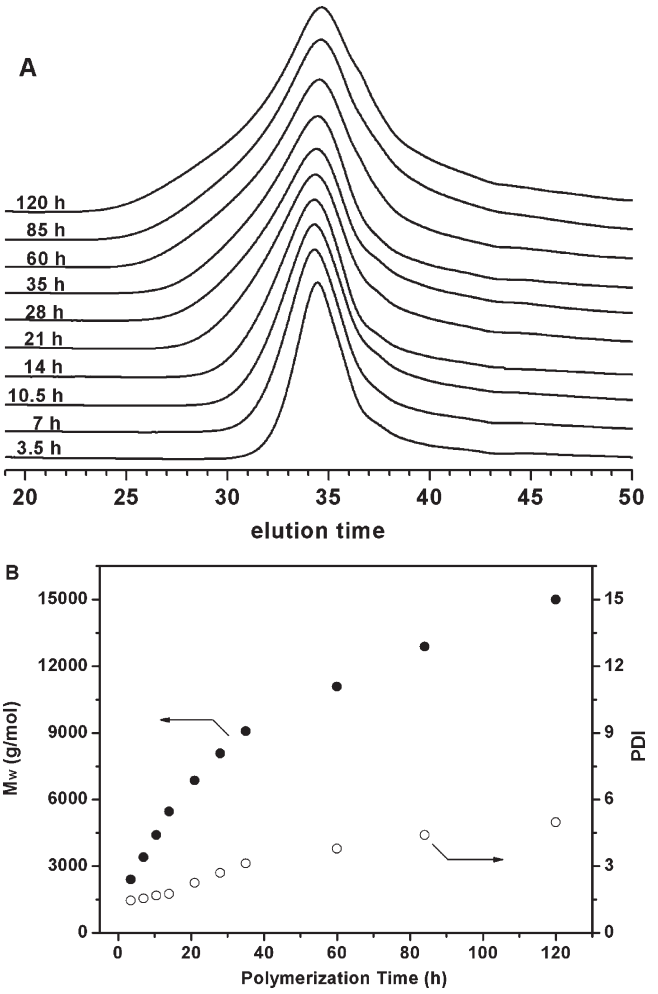

Figure 1. GPC analysis of HPHEEP at different polymerization times at 60 °C.

*Corresponding authors. E-mail address: (W.H.) hw66@sjtu.edu.cn; (D.Y.) dyyan@sjtu.edu.cn.

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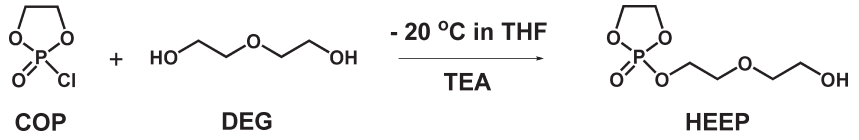
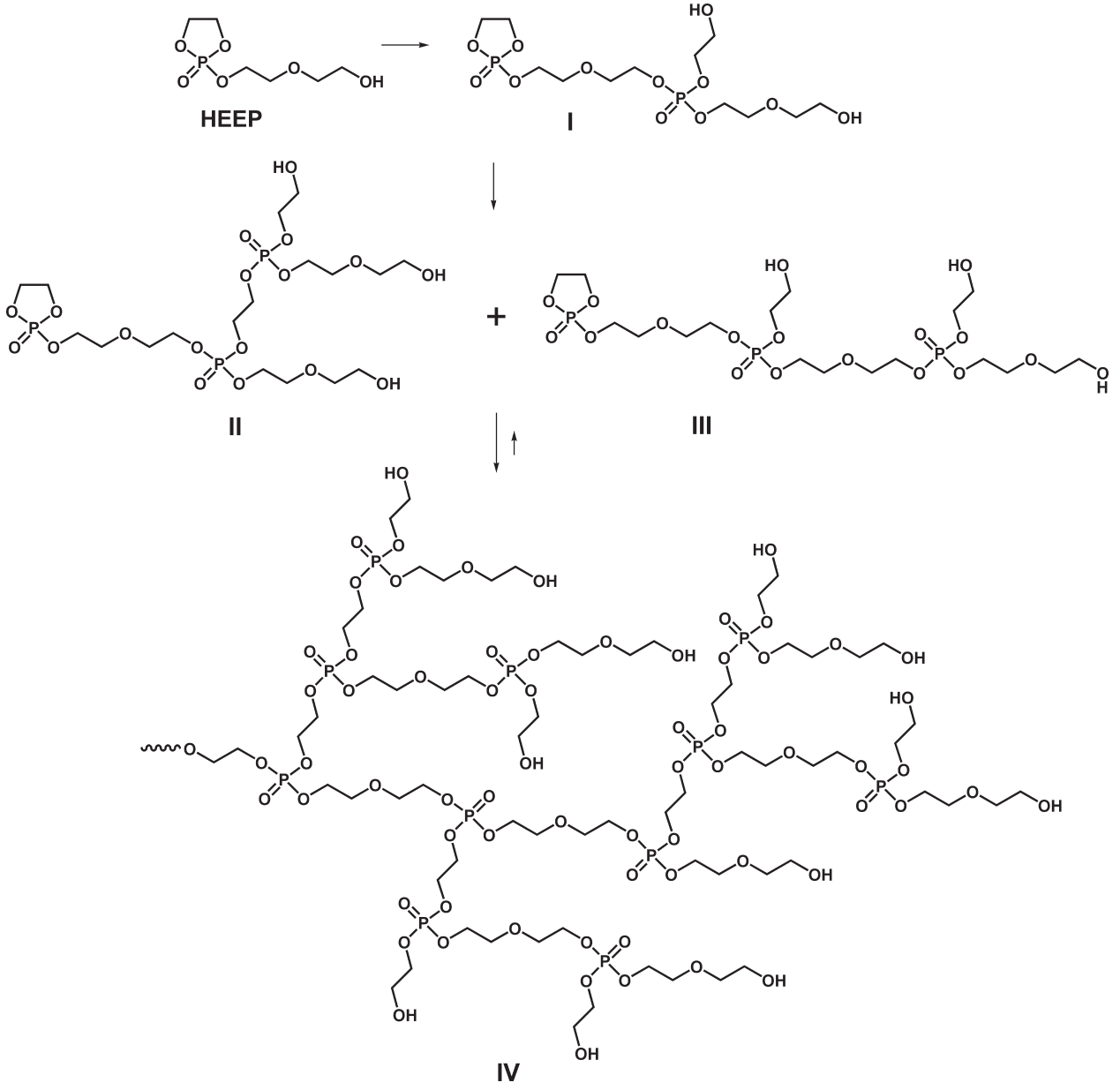
Scheme 1. Synthetic Route of Inimer HEEP



Scheme 2. SCROP of HEEP



corresponding protons, carbons and phosphorus. The results of the NMR measurements confirmed the chemical structure of HEEP.

b. Polymerization. The SCROP process of HEEP in bulk is shown in Scheme 2. It is well-known that primary alcoholic hydroxyls can initiate the ring-opening polymerization of five-membered cyclic phosphates. Evidently, HEEP is a typical AB* inimer with a reactive five-membered cyclic phosphate and a primary alcoholic hydroxyl as the initiating moiety. In the polymerization, the alcoholic hydroxyl in one HEEP molecule initiates the ring-opening reaction of the five-membered cyclic phosphate in another HEEP molecule to afford a dimer **I** with one five-membered cyclic phosphate and two primary alcoholic hydroxyls. That is to say, two AB* inimers transformed into an AB^*_2 species. Further the ring-opening reactions of HEEP and dimer **I** may result in two kinds of trimers **II** or **III**. Finally, high molecular weight hyperbranched polyphosphate **IV** are produced by subsequent addition reaction and condensation of the formed various species.

All the samples of hyperbranched polyphosphates (HPHEEP) were synthesized by the bulk polymerization of HEEP at the different temperature without a catalyst. The polymerization process was monitored by GPC

measurements. As a typical example, the overlaid GPC profiles of HPHEEP samples obtained at different polymerization time and 60 °C are shown in Figure 1A. It was found that the molecular weight of the products as well as the width of the molecular weight distribution increased with the polymerization time. In detail, the weight-average molecular weight ($\overline{M}_w$) and the polydispersity index (PDI) of HPHEEP **IV** were 2400 and 1.46, respectively, when the polymerization proceeded for 3.5 h. The $\overline{M}_w$ reached 5200 and the PDI increased to 1.75 after the polymerization was performed for 14 h. If the polymerization time was prolonged to 120 h, a slightly high molecular weight shoulder and a clearly low molecular weight tail were observed in the GPC chromatogram of the HPHEEP. Surprisingly, its PDI increased to 4.98

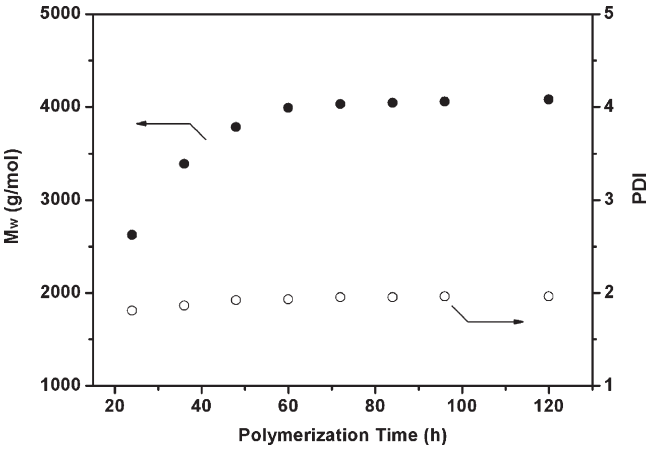


Figure 2. GPC analysis of HPHEEP at different polymerization times at 20 °C.

while the $\overline{M}_w$ approached 15000. The dependence of $\overline{M}_w$ and PDI on the polymerization time was shown in Figure 1B, which reveals that the PDI became broader and broader with increasing $\overline{M}_w$ during the polymerization. These unusual data indicate that the reversible transesterification and depolymerization in HPHEEP macromolecules occurred and reached the dynamic balance during the polymerization due to the pentavalent nature of phosphorus.[41,51] The resulting HPHEEP **IV**, which was obtained after polymerization for 120 h at 60 °C, was soluble in water, methanol, and ethanol, and partly soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF) due to its large number of phosphate and terminal hydroxyl groups, but insoluble in THF, dichloromethane and chloroform etc. However, when the polymerization was performed at 90 °C, the resulting HPHEEP **IV** became insoluble in water and alcohol solvents after polymerization for 10.5 h. Furthermore, it became insoluble only after 3 h when the polymerization was conducted at 130 °C. We speculate that this may be attributed to some side reactions occurred at the higher reaction temperature that led to the gelation of the reaction system.[52] Interestingly we found that the viscosity of HEEP increased gradually when it was stored at 20 °C. In other words, the SCROP of HEEP can proceed slowly at 20 °C without catalysts. The results of GPC measurement were shown in Figure 2. It exhibited that the molecular weight of the resulting HPHEEP increased step by step with the polymerization time prolonged and reached a maximum at about 60 h. Then it was almost kept constant and no insoluble material was formed even the polymerization time was further prolonged. We consider that the side reactions such as transesterification and depolymerization were absent at such a low temperature.

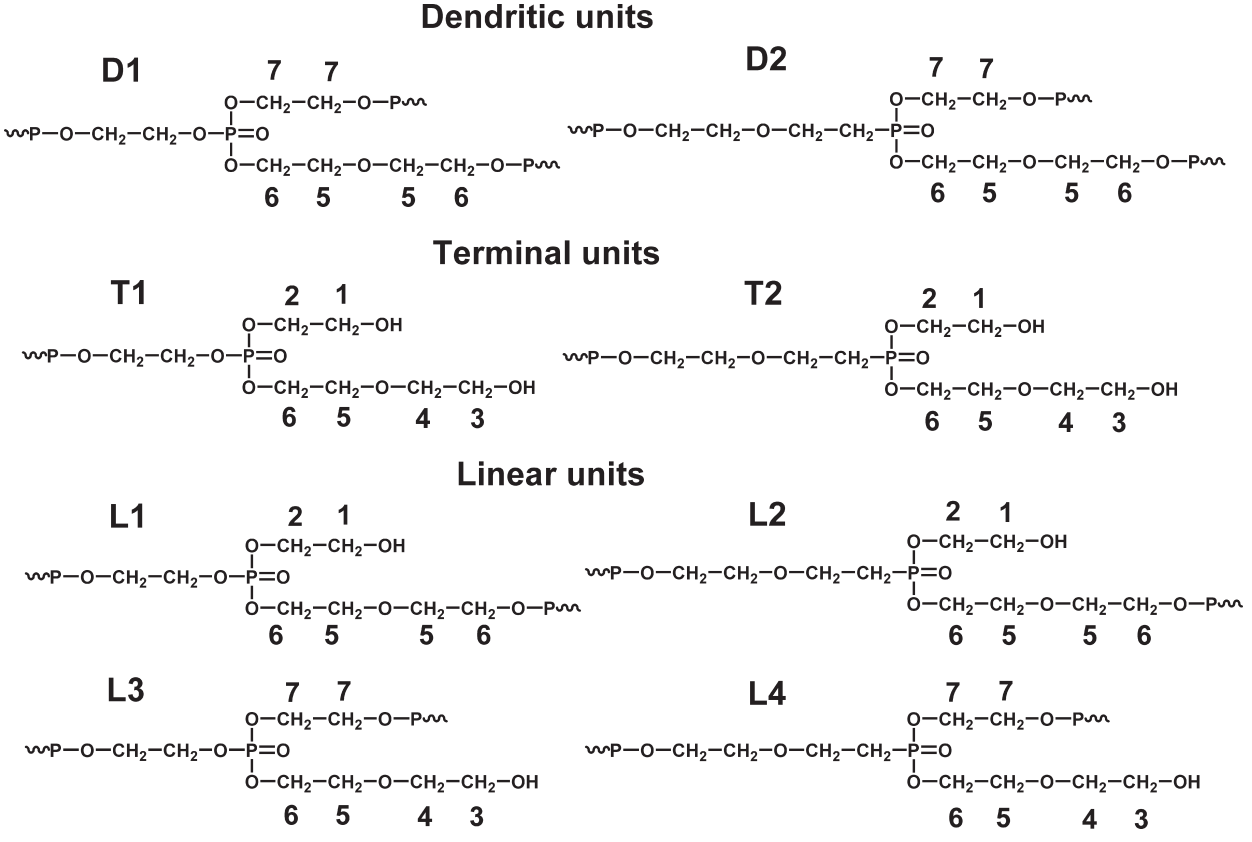


Figure 3. The various structural units of HPHEEP **IV**.

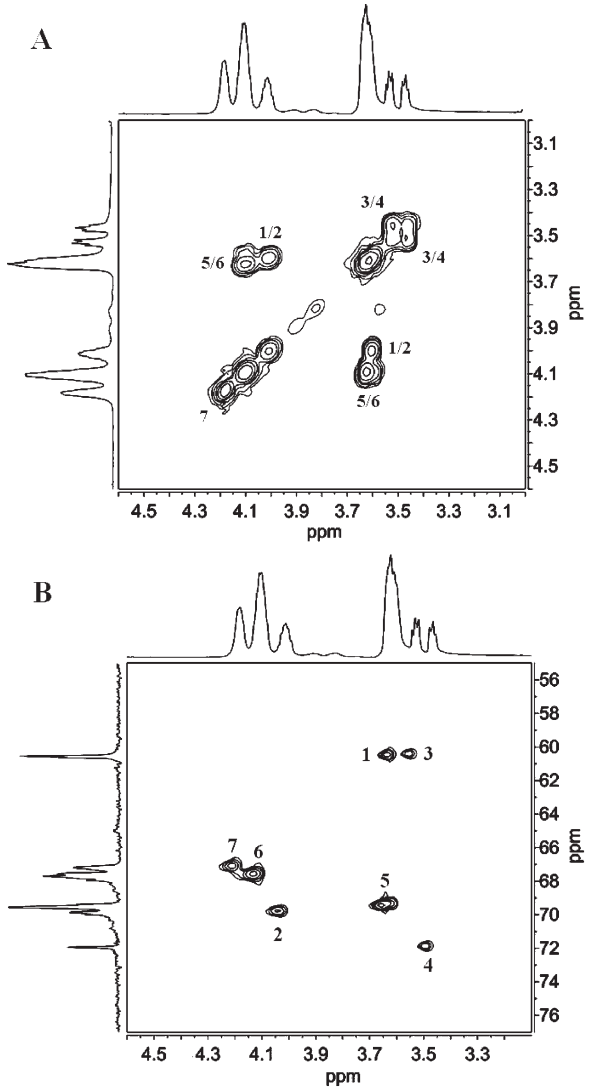


Figure 4. 2D NMR spectra of HPHEEP in D_2O: (A) $^1H,^1H-COSY$; (B) $^{13}C,^1H$-HSQC.

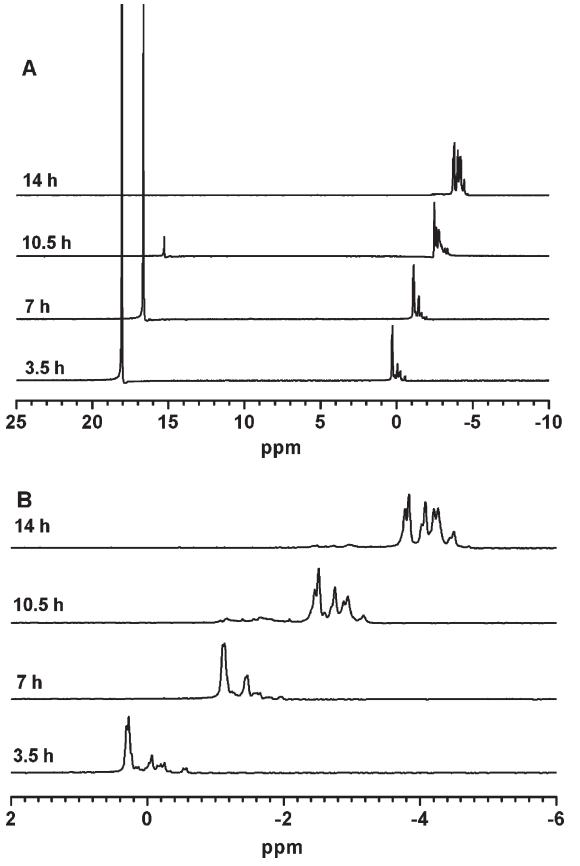


Figure 5. ^{31}P NMR spectra of HPHEEP at the different polymerization time at 60 °C.

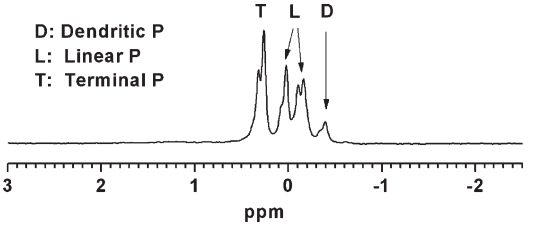


Figure 6. ^{31}P NMR spectra of HPHEEP for the calculation of DB.

The degree of branching (DB) is the most important molecular structure parameter for hyperbranched polymers, which was defined originally by Hawker, Lee, and Fréchet. It is expressed as DB = (no. of dendritic units + no. of terminal units)/(no. of dendritic units + no. of terminal units + no. of linear units).[53] The techniques of ^1H NMR and quantitative ^{13}C NMR spectra are usually utilized to determine DB.[53,54] After carefully analyzing the microstructure of HPHEEP **IV**, we considered that there are two kinds of dendritic units, two kinds of terminal units and four kinds of linear units in HPHEEP as shown in Figure 3. Various kinds of carbon and hydrogen atoms were labeled by numbers. Then we try to adopt $^1H,^1H-COSY$ and $^{13}C,^1H$-HSQC techniques to distinguish the structural units of HPHEEP **IV** completely.[55] The typical $^1H,^1H-COSY$ and $^{13}C,^1H$-HSQC spectra of HPHEEP **IV** are shown in Figure 4. Clearly, Figure 4A reveals that 1-H/2-H, 3-H/4-H, and 5-H/6-H are in different spin systems. Combining the cross peaks in Figure 4B allows the assignment of the signals in these systems to be facilitated. In detail, the resonances at 3.53 and 3.46 ppm can be easily assigned to the methylene protons of $-OCH_2CH_2OCH_2C\boldsymbol{H}_2OH$ and $-OCH_2CH_2OC\boldsymbol{H}_2-CH_2OH$, respectively. On the basis of the ^1H NMR spectrum of the inimer HEEP, the signals appear at 4.10 and 3.62 ppm can be identified with the methylene protons of $-POC\boldsymbol{H}_2-CH_2OCH_2CH_2O-$ and $-POCH_2C\boldsymbol{H}_2OCH_2CH_2O-$, respectively. Furthermore, the peak at 4.18 ppm is assured the characteristic absorptions of methylene protons ($-POC-\boldsymbol{H}_2C\boldsymbol{H}_2OP-$). Unfortunately, the signals of methylene protons and carbons in various structural units (i.e., **1**, **2**, **3**, **4**, **5**, **6**, or **7** in dendritic units, linear units, or terminal units) could not be distinguished here even by using $^1H,^1H-COSY$ and $^{13}C,^1H$-HSQC techniques. Thereby the DB of the resulting HPHEEP cannot be obtained by the routine techniques of ^1H NMR and quantitative ^{13}C NMR spectra.

Fortunately, we found that the signals of phosphorus atoms in dendritic, linear, or terminal units can be identified in the ^{31}P NMR spectrum of the resulting HPHEEP. So the ^{31}P NMR spectra were used to monitor the diversification of the phosphorus atom signals in the polymerization. Figure 5 displayed the ^{31}P NMR spectra of the HPHEEP samples obtained at 60 °C and the different polymerization time. It shows that the strong peak at 18.04 ppm belong to the phosphorus atom in inimer HEEP decreased gradually with polymerization time and disappeared absolutely when the

polymerization proceeded to 14 h. Simultaneously, some new peaks appeared at −0.41 to −0.31 ppm, which belong to phosphorus atoms in HPHEEP, and their relative intensity changed continuously in the polymerization process (Figure 5A). In order to highlight the signal changes of the phosphorus atom in dendritic, linear and terminal units and identified them, the ^{31}P NMR spectra of the same four samples in the region from −6 to +2 ppm were enlarged and are shown in Figure 5B. According to the SCROP mechanism in Scheme 2 and various microstructures in Figure 3, most cyclic phosphates in inimer HEEP were opened to form dimers at the initial stage of the polymerization, which have the same structure as the terminal units in HPHEEP. Therefore the strong resonance appeared at 0.25 ppm can be attributed to the two kinds of terminal phosphorus atoms. The middle-strong resonances at 0.01 and −0.18 ppm increased gradually with further polymerizing, and they can be attributed to the four kinds of linear phosphorus atoms. Meanwhile the weak but discernible peak at −0.41 ppm can be assigned naturally to the dendritic phosphorus atoms. Such subtle changes and differences in the monitored ^{31}P NMR spectra were in good agreement with what happened in the polymerization process.

Finally, the DB of the resulting HPHEEP (see Figure 6) can be facilely calculated according to the corresponding integrals of the peak areas of various structural units in the quantitative ^{31}P NMR spectrum on the basis of the following formula:

$$DB = \frac{S_D + S_T}{S_D + S_T + S_L}$$

Here S_D = integral area of dendritic units, S_T = integral area of terminal units, and S_L = integral area of linear units.

As the result, the degree of branching of HPHEEP is determined to be 0.47.

Conclusions. A novel hydroxyl-functionalized cyclic phosphate inimer HEEP was prepared successfully by molecular design and the corresponding hyperbranched polyphosphate was obtained by its SCROP in bulk without catalysts. The SCROP of HEEP at different temperatures was investigated and the results showed the polymerization process at 60 °C was finished in 14 h and the corresponding $\overline{M}_w$ of HPHEEP reached 5200 with PDI of 1.75 on the basis of NMR and GPC characterizations. Furthermore the SCROP of HEEP can also proceed slowly at 20 °C without catalysts and the side reactions can be alleviated at such a low polymerization temperature. The DB of the resulting HPHEEP is determined to be 0.47 by the aid of quantitative ^{31}P NMR spectrum. Due to the facile polymerization without catalysts, the resulting product is very pure and would be a perfect material for biomedical applications.

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Supporting Information Available: Text giving full experimental details and characterization data, including a figure showing the NMR spectra of 2-(2-hydroxyethoxy)ethoxy-2-oxo-1,3,2- dioxaphospholane. This material is available free of charge via the Internet at http://pubs.acs.org.

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