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Synthesis of novel biodegradable poly(ethylene glycol) analogue: Water-soluble aliphatic polyester with pendant oligo(ethylene glycol) chains

Lei Feng [a,c], Jian Yuan Hao [a,b,*], Cheng Dong Xiong [a], Xian Mo Deng [a]

[a] Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, P.O. Box 415, Chengdu 610041, China
[b] School of Microeletronics and Solid State Electronics, University of Electronic Science and Technology of China, Chengdu 610054, China
[c] Graduate School of Chinese Academy of Sciences, Beijing 100039, China

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Abstract

A novel poly(ethylene glycol) (PEG) analogue composed of aliphatic polyester backbone and pendant oligo(ethylene glycol) short chains is reported. The PEG analogue is a copolymer synthesized by ring-opening alternating copolymerization of succinic anhydride with 2-((2-(2-metho xyethoxy)ethoxy)methyl)oxirane. The structure of the copolymer was confirmed by ^{1}H NMR spectrum. The effects of the monomer feed ratio on the copolymerization were studied and the polymerization mechanism was given. The PEG analogue disclosed is water-soluble and expected to have promising applications in biomedical fields as a substitute of PEG due to the existence of degradable ester bond in the backbone.

Keywords: Water-soluble; PEG analogue; 2-((2-(2-Methoxyethoxy)ethoxy)methyl)oxirane; Ring-opening alternating copolymerization; Polyester

Poly(ethylene glycol) (PEG) is a cheap, neutral, water-soluble, biocompatible, FDA-approved polymer and thus is probably the most widely applied synthetic polymer in biotechnology and medicine [1]. For instance, PEG is an excellent shielding agent for in vitro delivery of various bioactive compounds. Indeed, PEG allows a good solubility in physiological media and prevents the adsorption of plasma proteins, which can trigger immune response [2,3]. Thus, PEG was extensively used in delivery of low molecular weight drugs, active peptides, proteins, and genetic materials [4,5]. In this respect, two synthetic strategies exist for constructing PEG-based delivery vehicles. A first route is to directly covalently conjugate active substance with PEG. Another approach relies on the physical entrapment of active substances in the artificial nanocarriers made from PEG-polyester block copolymers. However, one potential limitation of PEG is the non-degradability of their backbone. This aspect could hamper the wide spread adoption of PEG in the biomedical field, in particular for in vivo applications. Thus, there is a need for polymers that have similar structure and can play a role as PEG, but could also be completely degraded in human environment [6,7].

* Corresponding author at: Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, P.O. Box 415, Chengdu 610041, China.
E-mail addresses: jyhao@uestc.edu.cn, j.hao@cioc.ac.cn (J.Y. Hao).

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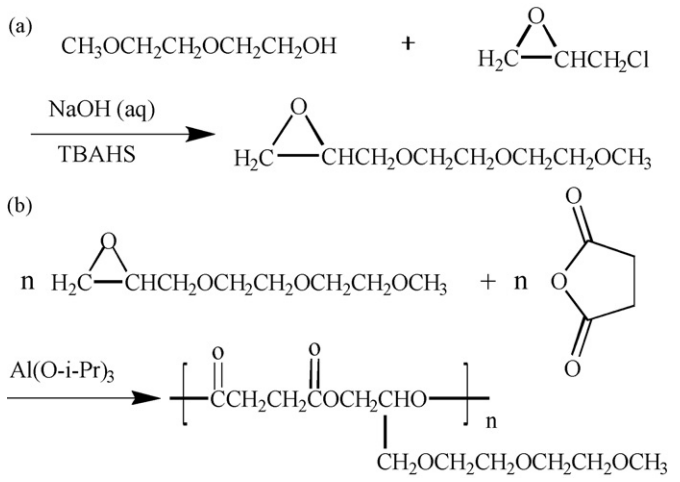


Scheme 1. Synthesis of MEEMO (a) and poly(SA-MEEMO) (b).

In the present paper, we report a novel PEG analogue with aliphatic polyester backbone and short oligo(ethylene glycol) pendant chains. The PEG analogue was synthesized by ring-opening copolymerization of cyclic aliphatic anhydride (succinic anhydride, SA) and functionalized epoxide bearing diethylene glycol monomethyl ether pendant group. The ethylene glycol ether pendant group is a short hydrophilic oligo(ethylene glycol) chain that is incorporated into the macromolecular construction and endowed the molecule with excellent water solubility.

Hydrophilic monomer [2-((2-(2-methoxyethoxy)ethoxy)methyl)oxirane, MEEMO] can be generally obtained by reaction of epichlorohydrin with diethylene glycol monomethyl ether in alkali condition. We describe here a single step synthesis of MEEMO using aqueous sodium hydroxide as alkali under phase-transfer condition (Scheme 1a). This method could be performed in large scale and is superior to the literature procedure using vivid NaH previously reported [8]. The detailed procedure is as follows: a mixture of aqueous sodium hydroxide (144 g, 1.8 mol, 50%, w/w), racemic epichlorohydrin (140 ml, 1.8 mol), and tetrabutylammonium hydrogen sulfate (TBAHS, 10.1 g, 5 mol%) was vigorously stirred at room temperature. Then, diethylene glycol monomethyl ether (72 ml, 0.6 mol) was added dropwisely. After stirred at room temperature for 3 h, the mixture was partitioned and the organic phase was washed with brine to neutrality and dried with sodium sulfate. After filtered, the filtrate evaporated to dryness and followed by vacuum distillation. MEEMO was obtained as a colorless liquid; yield 71.3 g (67.4%); bp 128 °C/12 mmHg. The structure of MEEMO was confirmed by ^{1}H NMR ($CDCl_3$) spectrum: δ 3.80, 3.76 (dd, 1H), 3.73–3.61 (m, 6H), 3.58–3.52 (m, 2H), 3.43 (q, 1H), 3.37 (s, 3H), 3.15 (m, 1H), 2.79 (t, 1H), 2.64 (q, 1H).

MEEMO and SA were copolymerized in bulk at 120 °C, 24 h, using aluminum isopropoxide (AIP) as an initiator in various monomer feed radios (Scheme 1b). The crude product was dissolved in chloroform and precipitated with petroleum–ether (1:1, v/v), then dried at 70 °C for 24 h under reduced pressure. The PEG analogue appears to be yellow oil and could dissolve into water in any proportion.

Fig. 1 shows the ^{1}H NMR spectrum of the PEG analogue synthesized at a SA/MEEMO monomer feed ratio of 50/50. From the integrated intensities of respective signals, the SA/MEEMO molar ratio in copolymer is determined to be 1:1, within the range of experimental error. The effects of the monomer feed radio on the copolymerization are listed in Table 1. It shows that the content of SA or MEEMO in the copolymers is almost constant as 50 mol% when varying the monomer feed ratio from 75/25 to 25/75. This confirms that SA and MEEMO were copolymerized in a strictly alternative way. As a result, the yield and Mw give the maximum values at the SA/MEEMO ratio of 50/50. Furthermore, homopolymerization of MEEMO or SA was both not initiated by aluminum isopropoxide. Thus, it can be concluded that the copolymerization was carried out alternatively between SA and MEEMO; once one of them had been consumed completely, the polymerization would be terminated.

Furthermore, in order to clarify the mechanism of the copolymerization, equi-molar reactions of SA and AIP as well as MEEMO and AIP were performed, respectively in toluene at 120 °C for 1 h. From the ^{1}H NMR spectra analysis of the reaction mixtures, SA was completely converted into isopropyl succinate while large amount of

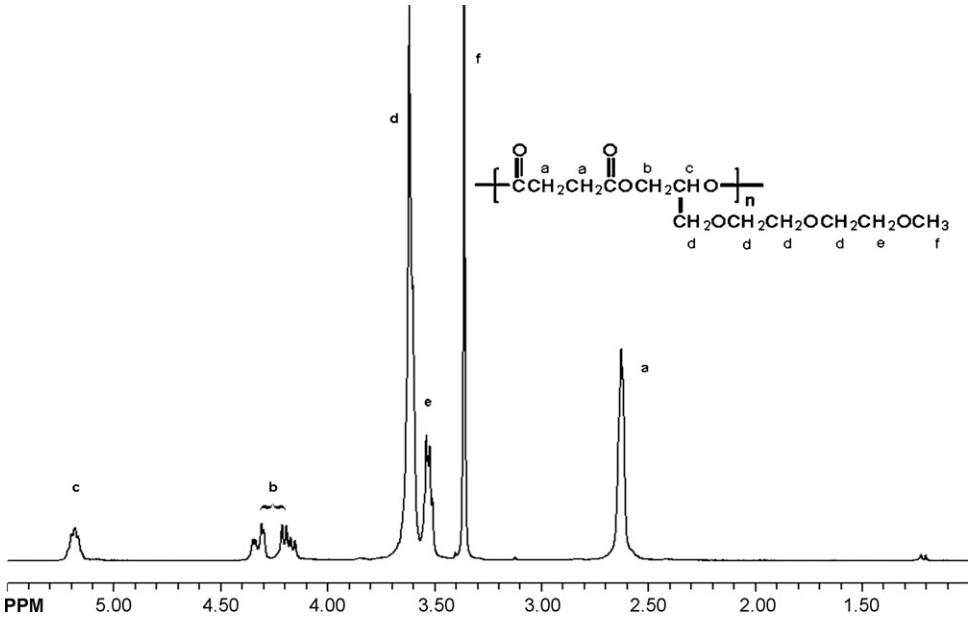


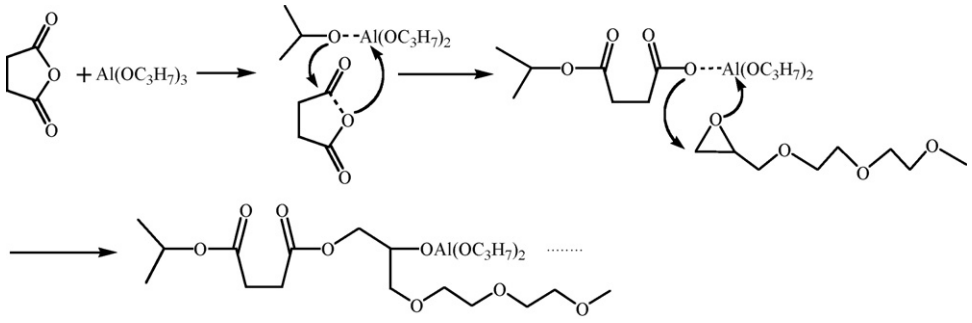
Fig. 1. ^{1}H NMR spectrum of poly(SA-MEEMO).

Table 1
The effects of the monomer feed radio on the copolymerization of SA and MEEMO[a].

Monomer feed ratio MEEMO/SA (mol%)	Yield (%)	Mw[b]	Mw/Mn[b]	Copolymer composition[c] MEEMO/SA (mol%)
100/0	–	–	–	–
75/25	59.5	3298	1.42	58/42
60/40	87.3	4566	1.46	54/46
50/50	98.6	5210	1.52	50/50
40/60	80.6	3995	1.56	49/51
25/75	54.4	3280	1.47	46/54

[a] Polymerization condition: 120 °C, 24 h in bulk using AIP as initiator.
[b] Determined by GPC; THF as solvent and polystyrene as standard.
[c] Determined by ^{1}H NMR spectra.

unreacted MEEMO was recovered. From these results, the mechanism of ring-opening copolymerization of SA and MEEMO is presumed in the following manner [9]: the AIP attacks acyl-oxygen bond of SA firstly to produce the active initiator; then, the processes of SA inserting into the O–Al bond and MEEMO inserting into the COO–Al bond are repeated alternately (Scheme 2).



Scheme 2. Mechanism of SA and MEEMO ring-opening copolymerization.

In this paper, we have disclosed a novel PEG analogue composed of aliphatic polyester backbone and pendant oligo(ethylene glycol) chains. This polymer is water-soluble and is expected to have promising applications in biomedical fields as a substitute of PEG due to existence of degradable ester bond in the backbone.

Acknowledgments

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References

[1] R. Duncan, Nat. Rev. Drug Disc. 2 (2003) 347.
[2] K.L. Prime, G.M.J. Whitesides, J. Am. Chem. Soc. 115 (1993) 10714.
[3] S. Stolnik, L. Illum, S.S. Davis, Adv. Drug Del. Rev. 16 (1995) 195.
[4] F.M. Veronese, Biomaterials 22 (2001) 405.
[5] R.B. Greenwald, Y.H. Choe, J. McGuire, C.D. Conover, Adv. Drug Del. Rev. 55 (2003) 217.
[6] J.F. Lutz, J. Polym, Sci. Part A: Polym. Chem. 46 (2008) 3459.
[7] B. Jeong, M.R. Kibbey, J.C. Birnbaum, et al. Macromolecules 33 (2000) 8317.
[8] S.J. Jungk, J.A. Moore, R.D. Gandour, J. Org. Chem. 48 (1983) 1116.
[9] Y. Maeda, A. Nakayama, N. Kawasaki, et al. Polymer 38 (1997) 4719.