Formyl-Ended Heterobifunctional Poly(ethylene oxide): Synthesis of Poly(ethylene oxide) with a Formyl Group at One End and a Hydroxyl Group at the Other End

Yukio Nagasaki, Takahiko Kutsuna, Michihiro Iijima, Masao Kato, and Kazunori Kataoka*

Department of Materials Science and Technology, Science University of Tokyo, Noda 278, Japan

Shigeru Kitano and Yoshihito Kadoma

Tsukuba Research Center, Nippon Oil and Fat Company, Toko-dai, Tsukuba 300-26, Japan.
Received September 6, 1994®

Well-defined poly(ethylene oxide) (PEO) with a formyl group at one end and a hydroxyl group at the other terminus was synthesized by the anionic ring opening polymerization of ethylene oxide (EO) with a new organometallic initiator possessing an acetal moiety, potassium 3,3-diethoxypropyl alkoxide. Hydrolysis of the acetal moiety produced a formyl group-terminated heterobifunctional PEO with a hydroxyl group at the other end.

Poly(ethylene oxide) (PEO) chemistries have been widely studied by numerous researchers in terms of synthetic methods and mechanisms, properties, and applications (*1*, *2*). In particular, the applications of PEO have become attractive in a variety of fields such as biology, biomedical science, surface chemistry, and electrochemistry, due to their unique properties such as solubility and flexibility of the chains and basicity of the ether oxygens in the main chain. Recently, end-functionalized PEOs have become very important in controlling these properties. For example, an end-functionalized PEO can be used as a surface modifier to change surface properties, *e.g.*, for biocompatible surfaces (*3*) and for capillary electrophoresis (*4*). An end-functionalized PEO is also utilized for protein modifications (*5*), conjugation (*6*), and crosslinking (*7*). For example, a protein–PEO conjugate increases the solubility and stability in water and decreases the antigenicity of the protein in general (*2*). Most of the end-functionalized PEOs, however, are semitelechelic (*8*) or homotelechelic oligomers. To expand the utility of PEO's, convenient synthesis of heterotelechelic oligomers (*9*) is needed. If such heterotelechelics are easily synthesized, these materials can be utilized as heterocrosslinkers of different substances with defined spacer lengths, surface modifiers with the remaining reactive moieties at the free end, etc. There are several reports on the synthesis of heterobifunctional PEOs using homotelechelic PEOs as the starting materials (*6*, *10*). The synthetic methods, however, are complicated because they have to use several reaction steps to derivatize the PEO terminus. In addition, the efficiency for derivatizations is not very high, meaning the resulting PEO is a mixture of the starting homotelechelics and the resulting heterotelechelics to some extent.

Our strategy for heterotelechelic synthesis is to create a novel polymerization route of EO using new initiators containing defined functionalities. So far, we have synthesized heterotelechelics with a primary amino group at one end and a hydroxyl group at the other end by an anionic ring opening polymerization of EO using silyl-protected potassium amide (*11*, *12*). In this paper, we report the synthesis of PEO with a formyl group at one end and a hydroxyl group at the other end.

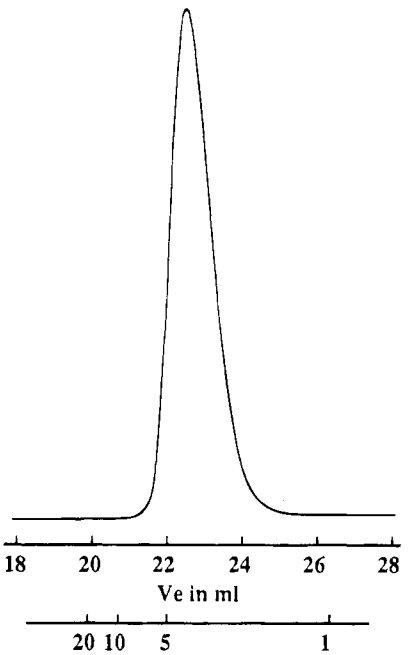

Figure 1. Gel permeation chromatogram of poly(ethylene oxide) prepared by the anionic ring opening polymerization initiated with PDA [a Shimadzu 6A liquid chromatograph was used (column: TSK-Gel G4000H8 + G3000H8 + G2500H8)].

A formyl group is very useful for conjugation with protein due to its stability in water and its rapid reactivity with primary amino groups. In addition, no charge variation takes place by the modification because the resulting Schiff base can be easily converted to a *sec*-amino group by reduction. The variation in charge distribution in protein sometimes induces denaturation. There are several published reports on the synthesis of formyl group-terminated PEOs. Harris and his coworkers reported the synthesis of a formyl group-ended semitelechelic PEO starting from a hydroxyl-terminated semitelechelic PEO (methoxy group at the other terminus (*13*)). A formyl group-terminated heterobifunctional PEO

® Abstract published in *Advance ACS Abstracts*, February 1, 1995.

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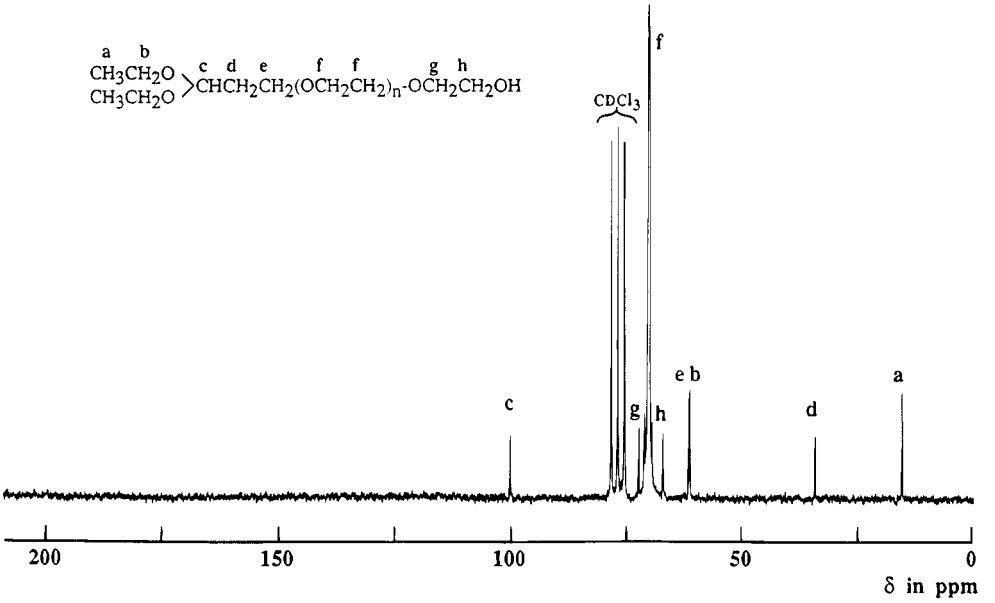


Figure 2. ^{13}C NMR spectrum of hetero-PEO prepared by the anionic ring opening polymerization initiated with PDA (the same sample as in Figure 1).

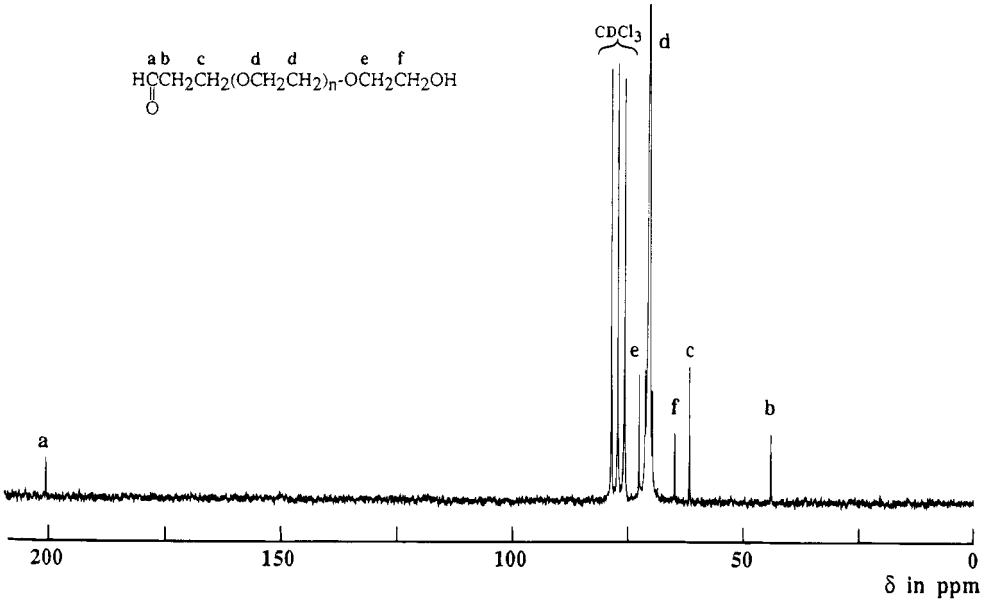
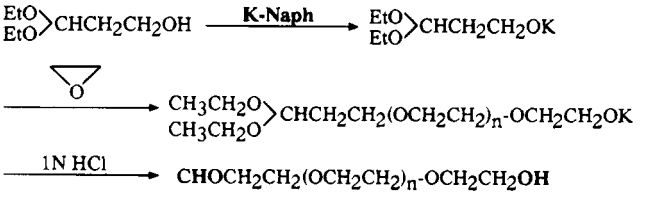


Figure 3. ^{13}C NMR spectrum of heteroPEO after acid treatment (the same polymerization conditions as in Figure 1).

was synthesized by a coupling reaction (*13*, *14*) and an oxidation reaction (*15*) starting from a hydroxyl group-ended homotelechelic PEO. The PEO thus obtained still retained the above-mentioned problems such as purity and yield.

To quantitatively synthesize a formyl group-ended heterobifunctional PEO, the anionic ring opening polymerization of EO was carried out using potassium alkoxide with an acetal moiety as an initiator, *e.g.*, potassium (3,3-diethoxypropyl)alkoxide (PDA). To THF (16 mL) in a 100 mL flask with a three-way stopcock under argon atmosphere were added 3,3-diethoxypropyl alcohol (DA; 1 mmol) and potassium naphthalene (1 mmol) to form PDA. After liquid EO (70 mmol; below 0 °C) was added via a cooled syringe, the mixture was allowed to react for 2 days at room temperature. Figure 1 shows the gel permeation chromatogram (GPC) of the reaction mixture, in which it can be seen that the polymer was obtained with a narrow molecular weight distribution (M_w/M_n = 1.05; M_w and M_n denote weight average and number average molecular weights, respectively). M_n of the polymer determined from GPC (M_n = 3100) agreed well with that calculated using an initial monomer/initiator ratio (M_n = MW(EO)[[EO]$_0$/[PDA]$_0$] + MW(DA) = 44(70/1) + 148 = 3200), indicating that is PDA the sole initiating species for this polymerization (Scheme 1).

Scheme 1



To obtain information on the end group of the polymer thus obtained, ^{13}C NMR analysis was carried out. Figure 2 shows the ^{13}C NMR spectrum of the polymer after purification of the polymer by precipitation in ether and freeze-drying in benzene. By referring to the literature on hydroxyl-terminated PEO (*16*) and diethoxypropyl

Table 1. ^{13}C NMR Chemical Shift Data of PEO Initiated with PDA (ppm)

carbon	a	b	c	d	e	f	g	h
obsd	15.1	61.2	100.3	33.9	61.5	70.4	72.4	67.1
calcd	14.7	57.1	118.4	39.5	60.3	70.6	72.8	63.7

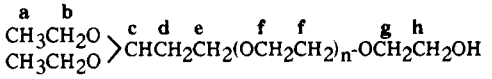


Table 2. Results of Anionic Polymerizations of Ethylene Oxide (EO) with PDA as an Initiator[a]

run	$[EO]_0/[PDA]_0$	time (h)	yield (%)	$10^{-3} \times M_n$[b] obsd[c]	$10^{-3} \times M_n$[b] calcd[e]	M_w/M_n[c,d]
1	40	50	99.3	1.8	1.8	1.08
2	70	50	97.7	3.1	3.2	1.05
3	120	50	93.5	5.3	4.6	1.09

[a] Solvent: THF. Temperature: rt. [b] M_n denotes number average molecular weight. [c] Determined from the GPC results. [d] M_w denotes weight average molecular weight. [e] Determined from the following equation: $M_n(calc) = MW(EO)[[EO]_0/[PDA]_0] + MW(PDA) = 44[[EO]_0/[PDA]_0] + 148$.

alcohol as reference compounds, the assignments of these signals were carried out and are described in Figure 2. The assignments of these signals were in good accordance with the calculated data (*17*) as shown in Table 1. Further results of the anionic polymerizations under the several conditions are summarized in Table 2. The yield of the polymers was almost quantitative, and their molecular weight can be easily controlled by the monomer/initiator ratio.

Transformation of the acetal group at the polymer end to an aldehyde group was carried out by the addition of 15 mL of 1 N HCl to the reaction mixture after a 2-day polymerization. From the ^{13}C NMR spectrum of the purified polymer shown in Figure 3, it was found that the signals derived from the acetal moiety completely diminished and the three signals derived from the aldehyde moiety appeared at 43.6, 64.6, and 200.9 ppm, which are assignable to $-CH_2CH_2CHO$, $-CH_2CH_2CHO$, and $-CH_2CH_2CHO$ at the end of the polymer chain, respectively. ^1H NMR of this polymer in DMSO-d_6 shows the aldehyde proton at 9.8 ppm and the alcohol proton in 4.5 ppm, an indication of complete transformation of the acetal end group to an aldehyde group.

On the basis of the reported results, it is concluded that a heterobifunctional PEO with an aldehyde moiety at one end and a hydroxyl group at the other end was quantitatively synthesized in one pot.

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(8) The term *telechelic oligomer* was defined as oligomer with reactive groups at the chain ends.
(9) The term *heterotelechelics* was defined in our previous paper (*11*), which denotes the telechelic oligomer with a functional group at one end and another functional group at the other end.
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BC940102C