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Sequence-regulated oligomers and polymers by living cationic polymerization

1. Synthesis of sequence-regulated trimers and tetramers of functional vinyl ethers

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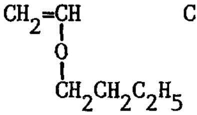
SUMMARY

A new trimer (**3**) and a tetramer (**4**) of vinyl ethers with controlled repeat unit sequences were prepared through the living cationic polymerization initiated with the hydrogen iodide/zinc iodide (HI/ZnI_2) system in toluene at -40^oC; for example, **4** consisted of the following sequence, $H-CH_2CH(O\underline{n}Bu)-CH_2CH[OCH_2CH_2CH(COOEt)_2]-CH_2CH(OCH_2CH_2OCOC_6H_5)-CH_2CH[OCH_2CH_2-OCOC(CH_3)=CH_2]-OCH_3$, and is a new methacrylate-type macromonomer. The synthesis involved sequential and successive reactions of the corresponding four vinyl ethers (each equimolar to hydrogen iodide) with the HI/ZnI_2-generated living oligomeric growing species, starting from the quantitative addition of hydrogen iodide to n-butyl vinyl ether and subsequent activation of the resulting adduct with ZnI_2. The structure and molecular weights of these sequence-regulated vinyl ether oligomers were verified by ^1H NMR and thermospray mass spectroscopy.

INTRODUCTION

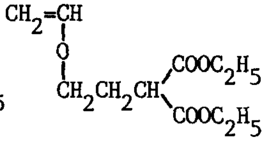
Except in the in-vivo synthesis of macromolecules like proteins and genes, regulation of repeat-unit sequence along the main chain is still beyond our reach in polymer synthesis. In contrast to the success and sophistication in the synthesis of polypeptide, DNA, RNA, etc. by polycondensation (e.g., Merrifield's method), the current status of the sequence control in addition polymerization remains rather primitive, at the best leading to •••AAABBB••• type block polymers and AB- or ABC-type alternating copolymers, where A, B, and C represent monomer repeat units. Such a truly regulated sequence as ABCDE••• may be obtained by a laborious and cumbersome stepwise synthesis but not by a one-pot polymerization process.

This preliminary paper reports the synthesis of a trimer and a tetramer of vinyl ethers (VEs) with controlled repeat-unit sequence. The four VEs that were employed for the synthesis are shown below, which have a common basic structure, $CH_2=CH-OCH_2CH_2-X$, but differ in the pendant functional group X: n-butyl vinyl ether (NBVE), ethyl 2-(vinyloxy)ethyl malonate (VOEM), 2-(benzoyloxy)ethyl vinyl ether (BzOVE), and 2-(vinyloxy)ethyl methacrylate (VEM). As illustrated in Scheme I, the synthesis of these



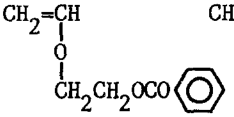
$CH_2=CH-O-CH_2CH_2C_2H_5$

NBVE



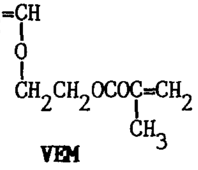
$CH_2=CH-O-CH_2CH_2CH(COOC_2H_5)_2$

VOEM



$CH_2=CH-O-CH_2CH_2OCOC_6H_5$

BzOVE



$CH_2=CH-O-CH_2CH_2OCOC(CH_3)=CH_2$

VEM

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Scheme I

"sequence-regulated oligomers" involves one-pot sequential reactions of the four VEs on the basis of the living cationic polymerization with the hydrogen iodide/zinc iodide (HI/ZnI_2) initiating system (1,2). The latter three VEs have polar functional pendant groups which can readily be converted into hydroxyl or carboxylic acid functions. We have already confirmed that all of them can be polymerized into living polymers under adequate conditions (4-8). It is important that, in the oligomers 2-4, the sequence of repeat units (or pendant functional groups) is regulated by the order of monomer addition. Though AB-type heterodimers of styrene derivatives have been prepared by stepwise reactions (9), this study provides the first example of the synthesis of sequence-regulated oligomers via one-pot sequential reactions based on living polymerization.

RESULTS AND DISCUSSION

Sequential Living Oligomerization

According to Scheme I, the synthesis of sequence-regulated oligomers 2-4 was carried out in toluene at -40°C with use of four separate batch reactors. In all of them, the sequential reaction was performed in an identical manner, but the four batches were quenched with methanol at different stages in order to separate and identify the products of each stage (i.e., the first batch for 1, the second batch for 2, and so on).

NBVE was first treated with an equimolar amount of HI to give adduct 1^*. The addition reaction was rapid and quantitative (see below) (4). Upon addition of VOEM (the second monomer) and ZnI_2 (activator), the second-stage reaction occurred without an induction phase and was completed in 30 min. Quenching the reaction at this stage led to dimer 2, whereas addition of BzOVE (the third monomer) to the solution of the intermediate 2^* induced a smooth consumption of BzOVE to give a 88% conversion in an additional 165 min. On further equimolar addition of VEM (the fourth monomer) to the resultant trimeric living species 3^*, the fourth-stage reaction ensued and reached 84% conversion in an additional 5 hr to afford living tetramer 4^*.

Product Distribution

The resultant living oligomers 1^*-4^* were quenched with methanol, and converted into more stable acetal forms 1-4. Figure 1 shows the product distribution curves for the respective steps. Curve (A) for the first stage consists of only a sharp and unimodal fraction. ^1H and ^{13}C NMR analysis of this fraction showed that the product is the acetal 1 without any by-products. The quantitative formation of NBVE-HI adduct 1^* in the first stage was thus confirmed.

The product distribution curve (B) for the second stage (quenched after the addition of VOEM) exhibits three major peaks a-c. According to the peak molecular weight and NMR structural analysis, the shadowed middle fraction b is due to the desired AB dimer 2 (NBVE-VOEM). The sharp fraction c indicates that, although the added VOEM monomer was completely consumed, a part of the monomeric intermediate 1^* remained unreacted. This incomplete reaction of 1^* in turn led to the formation of a trimer (NBVE-VOEM-VOEM; peak a) that involves a homo-sequence of VOEM. This probably resulted from the relatively high reactivity of VOEM (10), which was able to react with the resulting living species 2^* before complete consumption of NBVE-HI adduct 1^*.

The yield of 2 was about 70%, on the basis of comparing the peak areas of a and b. Since the refractive index (RI) of oligomers often depends on the degree of polymerization and on the structure of pendant substituents,

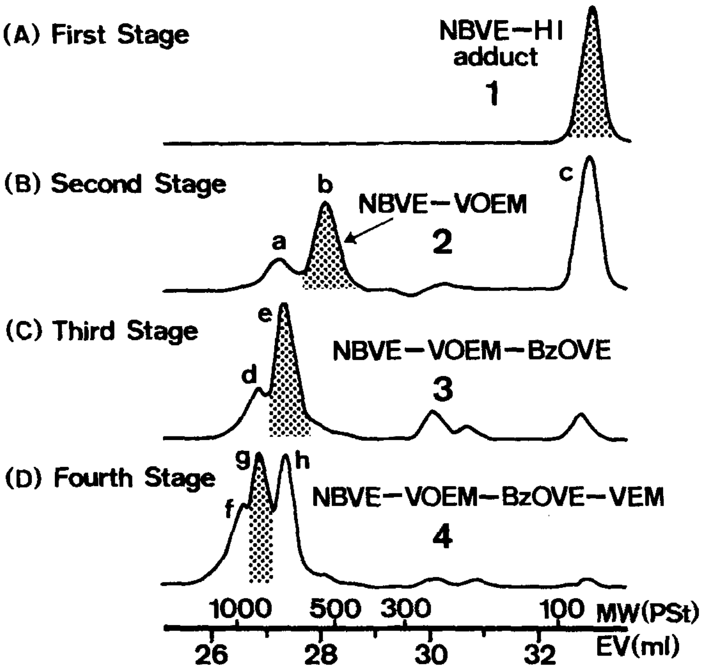

Figure 1. SEC curves of the products obtained in the four-stage sequential reaction of four vinyl ethers with HI/ZnI_2 in toluene at $-40^{\circ}C$: $[HI]_0 = [VE]_0 \cong 10$ mM; $[ZnI_2]_0 = 0.20$ mM. Conversions of added monomers: (A) NBVE, 100 %; (B) VOEM, 100 %; (C) BzOVE, 88 %; (D) VEM, 84 %.

this yield is a simple estimation that arbitrarily assumes the same RI-detection sensitivity for all oligomers.

The expected trimer 3 (NBVE-VOEM-BzOVE) was obtained as the main product in the third-stage reaction (Figure 1, curve C, peak e). After the addition of BzOVE (Scheme I), peak b of dimer 2 (Figure 1, curve B) disappeared almost completely and a new peak e of trimer 3 instead appeared in elution volume $\sim$ 27 ml. The yield of 3, based on the product peaks d + e ($\overline{M}_w > 400$; elution volume < 29 ml) was relatively good (ca. 70%). The trimer peak e was, however, accompanied by higher oligomer fractions, typically peak d, that apparently came from the trimeric intermediate NBVE-VOEM-VOEM*, which formed in the second stage (peak a, Figure 1, curve B) and might be capable of reacting further with added BzOVE. Some low-molecular-weight products were also obtained.

Curve (D) for the fourth-stage products possessed three major peaks (f-h). Although the chromatographic resolution for molecular weight > 600 was rather poor, the dotted area (g) was attributed to the target tetramer 4 (see below). The yield of 4 was ca. 30% (based on the peaks f-h); the remainders were higher-molecular-weight oligomers (peak f) and the unreacted trimer 3 (peak h). The tetramer 4 is interesting in structure, a methacrylate-type macromonomer having a sequence-regulated vinyl ether oligomer as the backbone.

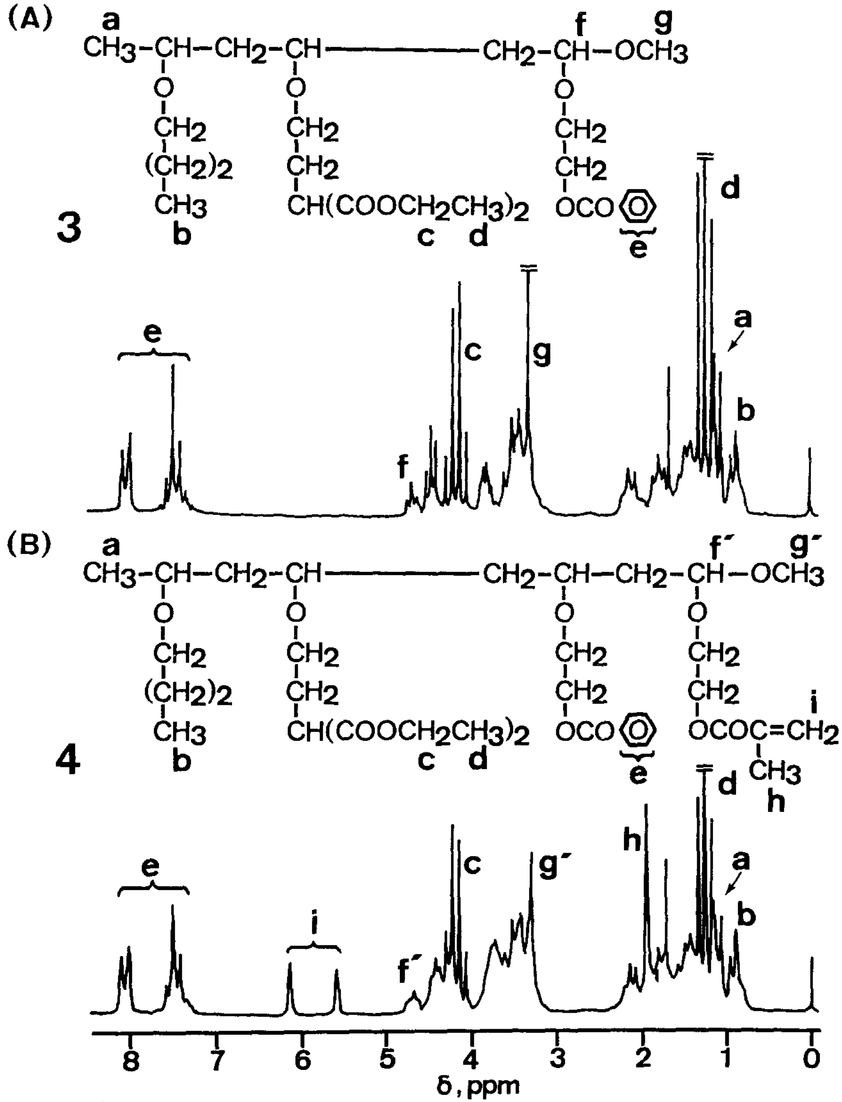

Figure 2. ^{1}H NMR spectra in $CDCl_3$: (A) trimer 3 (fraction e); (B) tetramer 4 (fraction g).

Structure of Sequence-Regulated Oligomers

The fractions of the dimer 2 (peak b), the trimer 3 (e), and the tetramer 4 (g) were isolated by preparative size-exclusion chromatography and analyzed by ^{1}H NMR spectroscopy. Figure 2 shows the ^{1}H NMR spectra of the isolated 3 (Figure 2A) and 4 (Figure 2B). Figure 2A exhibits four characteristic absorptions assignable to the three component units of the trimer 3: peak b (CH_3-, δ 0.9) for the pendant methyl of the NBVE unit; peak c ($COOCH_2$-, δ 4.2) and d ($COOCH_2\underline{CH_3}$, δ 1.3) for the malonic ester of the VOEM unit; and peak e (-C_6H_5, δ 7.3 - 8.2) for the phenyl group of the BzOVE unit. In addition to these four signals, Figure 2B exhibits new absorptions i (=CH_2, δ 5.6 and 6.1) and h [-$OCOC(CH_3)$=, δ 2.0], both of which are assignable to the VEM unit. The structure of the dimer 2 was also confirmed by ^{1}H NMR. All these spectra show no other peaks due to additional repeat units or by-products. As summarized in Table I, the number of each repeat unit (by ^{1}H NMR) is close to one per chain, with the peak (b) of the NBVE unit as reference.

Peaks f and f' (broad triplets at δ 4.7) are assigned to the methine proton of the acetal end group, $-C\underline{H}(OR)OCH_3$, that arises from the quenching reaction of methanol with the living growing end, $-CH(OR)-I\cdots ZnI_2$ (4). The amounts of this terminal group in the products were in the range of 85-100% relative to the NBVE unit (Table I). Evidently, the living growing ends in 2*, 3*, and 4* indeed survived, although the synthesis involved a relatively long reaction time (> 8 hr in total), highly diluted conditions, and a number of sequential additions of monomers, all of which may result in contamination of the reaction mixtures with hazardous impurities.

The NMR analysis thus showed the isolated fractions b, e, and g to be dimer 2, trimer 3, and tetramer 4, respectively.

TABLE I

Characterization of Sequence-Regulated Oligomers 2-4

product	unit ratio[a]				acetal end[b]	mol. wt., $[M+NH_4]^+$	
(fraction)	NBVE	VOEM	BzOVE	VEM	(%)	obd[c]	calcd
2 (b)	1.00	1.08	-	-	100	380	380
3 (e)	1.00	1.13	0.97	-	85	573	573
4 (g)	1.00	1.16	1.14	0.94	92	729	729

a) Determined by ^{1}H NMR assuming that one oligomer chain forms per unit NBVE-HI adduct 1*.
b) Measured by ^{1}H NMR.
c) Measured by thermospray mass spectroscopy; see text.

Molecular Weight Analysis by Thermospray Mass Spectroscopy

For further evidence for the formation of 2-4, the absolute molecular weights of the isolated products were determined by thermospray mass spectroscopy (see Experimental), which gives $[M+NH_4]^+$ as a parent peak (11) and is suited for the molecular weight determination of oligomers where extensive fragmentation must be avoided. As seen in Table I, the observed mass numbers ($[M+NH_4]^+$) of the fractions b, e, and g are all identical with the calculated values for 2, 3, and 4, respectively.

In conclusion, this study has demonstrated that the HI/ZnI_2 initiating system leads to the sequence-regulated oligomers by sequential reactions of three or four vinyl ethers. Synthesis of other sequence-regulated oligomers with different components is now in progress.

EXPERIMENTAL

Materials

VOEM, BzOVE, and VEM were prepared by the substitution reactions of 2-chloroethyl vinyl ether with the corresponding sodium salts, sodiomalonic ester (6), sodium benzoate (7), and sodium methacrylate (8), respectively. These monomers and commercial NBVE (4) were purified by distillation as reported previously. Toluene as polymerization solvent was purified by the usual methods and distilled twice over calcium hydride. Anhydrous hydrogen iodide was prepared as an n-hexane solution as already reported (4), and ZnI_2 (Aldrich, purity > 99.99%) was used as received (1).

Procedures

The synthesis of oligomers was carried out under dry nitrogen in a baked glass vessel equipped with a three-way stopcock and a stirrer bar. The mixture was magnetically stirred during the reaction. In the synthesis of trimer **3**, for example, a toluene solution (17 ml) of NBVE (0.2 mmol; 0.026 ml) was stirred at -40°C and then treated with an equimolar amount of HI to form adduct **1***. The second-stage reaction was initiated by adding a toluene solution (1.0 ml) of VOEM (0.2 mmol; 0.045 ml) and ZnI_2 (in diethyl ether; 4.0 mM, 1.0 ml) in this order. The reaction reached about 100% conversion in 30 min, followed by the addition of a toluene solution (1.0 ml) of BzOVE (0.2 mmol; 0.035 ml) to start the third reaction. After 165 min, the reaction was terminated with prechilled ammoniacal methanol. The quenched reaction mixtures were washed with 10% aqueous sodium thiosulfate solution and then with water, evaporated to dryness under reduced pressure to give **3** as an oil. The tetramer **4** was prepared in a similar way.

The product distribution of the reaction mixture was measured in chloroform by size-exclusion chromatography (SEC) on a Jasco Trirotar chromatograph equipped with three polystyrene gel columns (Shodex K-802, K-803, and K-804) that were calibrated against standard polystyrene samples in the molecular weight range 10^2 - 10^5. Oligomers were isolated by preparative SEC (column: Shodex H-2001, operational molecular weight range: $\leq$ 1000); then their ^1H NMR spectra were recorded in $CDCl_3$ on a Jeol FX-90Q. The molecular weights of the oligomers were determined by thermospray mass spectroscopy on a Shimadzu QP-1000 quadrapole mass spectrometer equipped with a Vestec Model 750B thermospray unit and a Shimadzu LC-6A precision pump (eluent: methanol containing 0.1 M ammonium acetate).

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