Polymer Bulletin 48, 221–224 (2002)

Polymer Bulletin

New syntheses of methoxypoly(oxyethylene) vinyl ether and its oligo analog

M. Reza Sedaghat-Herati (✉), Michael Tyndall, Richard N. Biagioni

Department of Chemistry, Southwest Missouri State University, Springfield,
Missouri 65804 USA
e-mail: mrs837f@smsu.edu, Fax: (417) 836-5507

Received: 27 November 2001/Revised version: 13 March 2002/ Accepted: 18 March 2002

Summary

A new method to synthesize vinyl ethers of methoxyoligooxyethylene, **I**, and methoxypoly(oxyethylene), **II**, is described. In this work, these derivatives were prepared by reacting the alkoxide of ethylene glycol vinyl ether with the tosylate (or mesylate) of oligo-/or methoxypoly(oxyethylene) in tetrahydrofuran.

Introduction

Poly(ethylene glycol) (PEG) and its monomethyl ether (mPEG) are water soluble polymers that exhibit interesting properties. These properties include biocompatibility, lack of toxicity and immunogenicity, and ease of excretion from living organisms. Consequently, PEG and its derivatives have been widely used in various chemical and biotechnical applications [1-5].

Various copolymers of PEG have been widely used in applications such as phase transfer catalysts, ionic conductors for battery applications, polymeric emulsifiers, drug delivery materials, carriers for gene delivery, and biomaterials [6-13]. For example, alternating copolymers of PEG derived from oligooxyethylene vinyl ether and/or poly(oxyethylene) vinyl ether with maleic anhydride have been used as ion-conducting polymers, as biocompatible matrixes for the formulation of nanoparticle delivery systems for targeted administration of protein drugs [14-16], and alternating copolymers of PEG and lysine have been implicated as carriers of low molecular weight drugs [17]. Mathias and co-workers [18] have reported the syntheses of mono- and divinyl ethers of oligooxyethylenes and their cationic homo- and copolymerization reactions. The synthesis involved reaction of the alkoxide of oligomeric poly(oxyethylene) with acetylene at high temperatures (175-185 ^{0}C). Chain shortening was observed in the conversion of oligomeric poly(oxyethylenes) to the corresponding vinyl ethers. However, fractional distillation allowed isolation of essentially one compound. Later, Suzuki and Tomono [19] devoted a major part of a report to the synthesis of mPEG-vinyl ether. Their synthesis was similar to that reported by Mathias et. al. [18]. However, purification of the resulting mPEG-vinyl ethers having high boiling points involved treatment with (a) charcoal, (b) anion-exchange resin of Cl^- type, (c) anion exchange resin of OH^- type (all at pH > 7), (d) mixed anion / cation exchange resin (this treatment was carried out at pH = 7), and finally (e) extraction of the polymer with chloroform and precipitation in ether/petroleum ether.

In this work, we present a simple and more convenient method for the preparation of vinyl ethers of oligooxyethylene and mPEG.

Experimental

Materials

Reagents were purchased from Aldrich. Methoxypoly(ethylene glycols) (mPEG 750 and mPEG 2000) were dried by azeotropic distillation in benzene. Ethylene glycol vinyl ether, 2-(2-methoxyethoxy)ethanol, and DMSO-d_6 were used as received. Tetrahydrofuran (THF) was refluxed with $LiAlH_4$ and then distilled. mPEG-mesylate (mPEG-Ms), and 2-(2-methoxyethoxy)ethyl tosylate, were prepared according to methods previously published [20,21].

Measurements

NMR spectra were recorded at room temperature on a Varian Gemini-200 spectrometer operating at 200 MHz for ^1H and 50.3 MHz for ^{13}C in DMSO-d_6. Chemical shifts were recorded in ppm and are referenced to internal TMS. GPC was performed on a Waters liquid chromatograph system equipped with a differential refractometer, columns (Styragel HR 1 and HR 4E), 1.0 mL/min, 25 °C, and THF as eluent.

^{13}C NMR of mPEG in DMSO-d_6: 57.99, 60.17, 68.72, 69.56, 69.75, 71.24, 72.31.

Synthesis

Synthesis of 2-methoxytriethoxyethylene, I

Ethylene glycol vinyl ether (19.00 g, 216 mmol) in 100 mL of anhydrous THF, under a nitrogen atmosphere, was converted to the corresponding alkoxide by slow addition of sodium hydride (1.68 g, 60% in mineral oil, 42 mmol). After the complete reaction of sodium hydride, 2-(2-methoxyethoxy)ethyl tosylate (11.60 g, 42 mmol) was added and the mixture stirred at room temperature overnight. THF was removed by distillation. The residue was dissolved in methylene chloride (150 mL), washed with brine (2 x 10 mL), and dried over anhydrous $MgSO_4$. Methylene chloride was removed and the product was distilled at 82–85 ^0C at 0.8 mmHg. Yield 6.10 g. $CH_3OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH=CH_2$: ^1H NMR: 3.23(s, 3H, CH_3O-), 3.39-3.56(m, 8H, $CH_3OCH_2CH_2OCH_2CH_2O$-), 3.57-3.65(m, 2H, -$OCH_2CH_2OCH=CH_2$), 3.72-3.82(m, 2H, -$OCH_2CH_2OCH=CH_2$), 3.96(dd, 1H, J = 1.4 and 7 Hz, *cis* =CH_2), 4.17(dd, 1H, J = 1.4 and 14.3 Hz, *trans* =CH_2), 6.49(dd, 1H, J = 7.0 and 14.3 Hz, OCH=). ^{13}C NMR: 58.06, 67.30, 68.87, 69.61, 69.79, 69.87, 71.28, 86.89, 151.90.

Synthesis of 2-[Methoxypoly(oxyethylene)]ethylene (mPEG-vinyl ether), II

Ethylene glycol vinyl ether (8.82 g, 100 mmol) in 150 mL of anhydrous THF, under a nitrogen atmosphere, was converted to the corresponding alkoxide by slow addition of sodium hydride (2.00 g, 60% in mineral oil, 50 mmol). After the complete reaction of sodium hydride, mPEG-Ms derived from mPEG 750 (21.00 g, 25 mmol) was added and the mixture stirred at room temperature for twenty four hours. THF was removed by distillation. The residue was dissolved in methylene chloride (100 mL) and washed with distilled water (4x 10 mL) and centrifuged before separation. Methylene chloride was removed and the residue was dissolved in benzene (75 mL) and dried azeotropically for five hours. The benzene solution containing **II** was concentrated and added to dry diethyl ether (350 mL) at 0 ^{0}C. The precipitated product was collected and dried under vacuum. Yield 12.0 g. $CH_3O(CH_2CH_2O)_nCH=CH_2$: ^{1}H NMR: 3.23(s, 3H, C*H*$_3$O-), 3.50(bs, PEG backbone), 3.70-3.80(m, 2H, -OCH$_2$C*H*$_2$OCH=CH$_2$), 3.96(dd, 1H, J = 1.8, 6.6 Hz, *cis* C*H*2=), 4.17(dd, 1H, J = 1.8, 14.3 Hz, *trans* C*H*2=), 6.50(dd, 1H, J = 6.6, 14.3 Hz, =C*H*-). ^{13}C NMR 57.93, 67.18, 68.74, 69.48, 69.68, 71.18, 86.72, 151.77.

Synthesis and purification of **II** involving mPEG 2000 was carried out in the same manner as for mPEG 750. In general, higher yields were obtained for mPEG 2000 as compared to mPEG 750. Our initial synthesis of **II** (employing mPEG 2000) involved drying the methylene chloride solution containing the product with anhydrous magnesium sulfate. However, it was noted that the product underwent hydrolysis after short periods of time. This was ascribed to the acidic nature of the drying agent and thus the azeotropic method of drying was adopted.

Results and discussion

The reaction of the alkoxide derived from ethylene glycol vinyl ether with 2-(2-methoxyethoxy)ethyl tosylate in THF proceeded in a straightforward manner, resulting in **I**. The ^{1}H NMR spectrum was consistent with structure **I** as the only species present.

Similarly, the reaction of the alkoxide derived from ethylene glycol vinyl ether with mPEG-Ms in THF resulted in the corresponding vinyl ether, **II**. In the ^{1}H NMR spectrum of either compound, the relative integration of protons on the methoxy and vinyl units were consistent with a 1:1 mPEG to vinyl ratio. The ^{1}H NMR spectrum also indicated the resonances due to the tosylate (or mesylate) protons had been replaced with three new doublet of doublets for the vinyl group, demonstrating that substitution was complete. In addition, no observable resonance at 4.56 ppm (diagnostic of terminal –OH for mPEG)**,** meaning that no elimination occurred during the reaction [22].

Bayer and co-workers [23] have shown that ^{13}C NMR can detect as little as 2% unsubstituted PEG in the presence of other PEG derivatives. From the work of Barelle and co-workers [24] on PEG, the resonance of carbon attached to hydroxyl appears at 61.4 ppm in $CDCl_3$. From our work on mPEG, the resonance of this carbon in dmso-d$_6$ appears at 60.2 ppm. Consistent with proton NMR, the ^{13}C NMR spectra of I and II show no resonances corresponding to 2-(2-methoxyethoxy)ethanol or mPEG, consistent with complete or nearly complete substitution.

GPC analyses of II and mPEG indicated almost identical retention volumes for both, confirming that the PEG backbone maintained its integrity during its preparation. This is in contrast with the earlier method of synthesizing vinyl ether of oligooxyethylene by reacting the alkoxide of oligooxyethylene with acetylene, in which the process involved chain shortening [18]. However, it is interesting to note that, while synthesis of the monomethyl ether of oligo- and poly(oxyethylene) vinyl ether was carried out by a similar method no chain shortening has been reported [19]. While we have used methoxyoligooxyethylene (and its polymer analog) to prepare the vinyl ether derivative, the same method is applicable to the preparation of vinyl ethers of oligo- and poly(oxyethylene).

Acknowledgements. M. R. Sedaghat-Herati wishes to acknowledge SMSU for a faculty grant.

References

1. Harris JM (ed) (1992) Poly(ethylene glycol) Chemistry. Biotechnical and Biomedical Applications, Plenum: New York
2. Harris JM, Zalipsky S (eds) (1997) Poly(ethylene glycol): Chemistry and Biological Applications; ACS Symposium Series: American Chemical Society: Washington, DC
3. Zalipsky S (1995) Adv Drug Delivery 16: 157
4. Lewanski C R, Stewart S (1999) Pharm Sci Technol Today 2: 473
5. Ohya Y, Cai R, Nishizawa H, Hara K, Ouchi T (2000) Preparation of PEG-Grafted Chitosan Nanoparticles as Peptide Drug Carriers. S T P Pharma Sci 10: 77
6. Kimura Y, Regen SL (1983) J Org Chem 48: 195
7. Lauter U, Meyer WH, Wegner G (1997) Macromolecules 30: 2092
8. Drescher B, Scranton AB, Klier J (2000, Volume date 2001) Polymer 42: 49
9. Sawada H, Ariyoshi Y, Lee K, Kyokane J, KawaseT (2000) Eur Polym J 36: 2523
10. Ouchi T, Hirano T, Maruhashi S, Nishizawa H, Shizuno K, Ohya Y (2000) Polym Prepr (Am Chem Soc, Div Polym Chem) 41(2): 1548
11. Vanderkerken S, Vanheede T, Toncheva V, Schacht E, Wolfert MA, Seymour L, Urtti A (2000) J Bioact Compat Polym 15: 115
12. Allen C , Han J,Yu Y, Maysinger D, Eisenberg A (2000) J Controlled Release 63: 275

13. Yasugi K, Nakamura T, Nagasaki Y, Kato M, Kataoka K (1999) Macromolecules 32: 8024
14. Ding LM, Shi J, Yang CZ (1997) Synth Met 87: 157
15. Chiellini E, Chiellini EE, Chiellini F, Solaro R (1998) Polym Prepr (Am Chem Soc, Div Polym Chem) 39(2): 182
16. Reiche A, Dlubek G, Weinkauf A, Sandner B, Fretwell HM, Alam AA, Fleischer G, Rittig F, Kaerger J, Meyer M (2000) J Phys Chem B 104: 6397
17. Yalpani M (ed.) (1996) Biomedical Functions and Biotechnology of Natural and artificial Polymers, ATL Press Page 63
17. Seymour RB, Harris FH, Branum I (1945) Industrial and Engineering Chemistry 41: 1701
18. Mathias LJ, Canterberry JB, South M (1982) J Polym Sci Polym Lett Ed 20: 473
19. Suzuki T, Tomono T (1984) J Polym Sci Polym Chem Ed 22: 2829
20. Zalipsky S, Gilon C, Zilkha A (1983) Eur Polym J 19: 1177
21. Morpurgo M, Veronese FM, Kachensky D, Harris JM (1996) Bioconjugate Chem 7:363
22. Sedaghat Herati MR, Miller P, Kozlowski A, Harris JM (1999) Polymer Bulletin 43: 35
23. Bayer E, Zheng H, Albert K, Geckeler K (1983) Polymer Bulletin 10: 231
24. Barelle M, Bequin C, Tessier S (1982) Org Magn Reson 19: 102