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Synthesis and Characterization of 5-[Methoxypoly(oxyethylene)]-(3*E*)-1,3-pentadiene and Its Diels−Alder Reactions

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Introduction. Poly(ethylene glycols) (PEGs) are well-known to be nontoxic, biocompatible, and soluble in water and many organic solvents.[1−3] PEG and its derivatives, PEGXs, are employed in a wide variety of biotechnical and chemical applications,[1,2,4−7] and interest continues in the preparation of new reactive PEGXs with novel properties.[1b,8−11]

Diels−Alder polymerizations have proven useful in the synthesis and elaboration of polymers.[12,13] This spurred our interest in PEGXs containing a diene moiety.

In the present work, we describe the synthesis and characterization of a novel PEG derivative, 5-[methoxypoly(oxyethylene)]-(3*E*)-1,3-pentadiene, **Ia,** and demonstrate its reactivity toward *N*-phenylmaleimide. **Ia** should be useful for the preparation of a vast array of mPEG derivatives with potentially useful biomedical applications, and as a macromonomer in homo- and copolymerization reactions. To facilitate characterization of **Ia** and its Diels−Alder adducts, a model compound, 5-methoxyethoxy-(3*E*)-1,3-pentadiene, **Ib**, has been synthesized, and its reactivity toward *N*-phenylmaleimide has been investigated.

Experimental Section. Reagents were purchased from Aldrich. Methoxypoly(ethylene glycol) (mPEG-2000) was purified conventionally.[8] 2-Methoxyethanol (anhydrous) and DMSO-d_6 were used as received. 5-Bromo-(3*E*)-1,3-pentadiene was prepared by published methods.[14,15] *N*-Phenylmaleimide was recrystallized from ethanol/water (1:2 by volume).

All ^{1}H NMR spectra were recorded at room temperature on a Varian Gemini-200 spectrometer operating at 200 MHz, using DMSO-d_6 as solvent. Chemical shifts are referenced to internal TMS and reported in ppm. Gel permeation chromatography (GPC) was performed on a Waters liquid chromatograph system equipped with a differential refractometer, Styragel columns, and tetrahydrofuran (THF) as eluent. Elemental analyses were performed by Atlantic Microlab (Norcross, GA).

Synthesis of Ib. Under a nitrogen atmosphere, to a stirred solution of sodium (0.53 g, 23 mmol) in 2-methoxyethanol (50 mL) at room temperature was added 5-bromo-(3*E*)-1,3-pentadiene (3.38 g, 23 mmol). The mixture was stirred overnight and then refluxed for 3 h more. Excess 2-methoxyethanol was removed by distillation. Water was added to the cooled reaction mixture, which was then extracted with diethyl ether. The diethyl ether solution was dried over $MgSO_4$, then stripped off at reduced pressure. Distillation at 87−88 °C, 31 mmHg (water aspirator), yielded 2.46 g (75%) of **Ib**. ^{1}H NMR: δ 3.25 (s, 3H, CH_3O−), 3.47(m, 4H, −OCH_2CH_2O−), 4.00 (dd, 2H, $J = 1.2$ and 6.0 Hz, C_5−H), 5.09−5.16 (dm, 1H, $J = 9.7$ Hz, C_1−H), 5.19−5.31 (dm, 1H, $J = 16.0$ Hz, C_1-H), 5.73−5.90 (td, 1H, $J = 6.0$ and 14.4 Hz, C_4−H), 6.19−6.48 (m, 2H, C_2−H and C_3−H).

Synthesis of Ia. mPEG-2000 (8.0 g, 4 mmol) in 120 mL of anhydrous THF, under a nitrogen atmosphere, was converted to the corresponding alkoxide by dropwise addition of *n*-butyllithium (2.5 M in hexane) in the presence of triphenylmethane, as indicator, until the pink color of triphenylmethyl anion persisted. 5-Bromo-(3*E*)-1,3-pentadiene (1.5 g, 10.2 mmol) was added and the mixture stirred overnight and then refluxed for 3 h more. THF was removed by distillation. The residue was dissolved in water, extracted with CH_2Cl_2, and dried over $MgSO_4$. The CH_2Cl_2 solution was added to dry diethyl ether. The precipitated product was collected and dried under vacuum; yield 5.95 g (72%). ^{1}H NMR: δ 3.25 (s, 3H, CH_3O−), 3.50 (s, mPEG backbone), 4.00 (dd, 2H, $J = 1.2$ and 6.0 Hz, C_5−H), 5.09−5.16 (dm, 1H, $J = 9.7$ Hz, C_1−H), 5.19−5.31 (dm, 1H, $J = 16.0$ Hz, C_1−H), 5.73−5.90 (td, 1H, $J = 6.0$ and 14.4 Hz, C_4−H), 6.19−6.48 (m, 2H, C_2−H and C_3−H).

Reaction of Ib with *N*-Phenylmaleimide. Ib (2.3 g, 16 mmol) and *N*-phenylmaleimide (2.44 g, 14 mmol) in benzene (50 mL) were refluxed overnight. Evaporation of benzene and removal of unreacted **Ib** under vacuum (<0.05 mmHg) left a slightly yellow viscous liquid; yield 4.19 g (95%).

Cycloadduct **IIb** (Scheme 1). ^{1}H NMR: δ 2.18−2.73 (overlapping multiplets, 3H, C_4-H and 2 C_7-H), 3.25 (s, 3H, CH_3O−), 3.37−3.47 (m, 4H, C_{7a}−H, C_{3a}−H, and −OCH$_2$CH_2OCH$_3$), 3.54−3.59 (m, 2H, −OCH_2CH$_2$-OCH$_3$), 3.72 and 3.84 (two dd, 2H, ABX pattern with $J_{AB} = 9.4$ Hz, $J_{AX} = 6.1$ Hz, and $J_{BX} = 7.7$ Hz, −CH_2-OCH$_2$CH$_2$OCH$_3$), 5.84−6.05 (m, 2H, C_5−H and C_6−H), 7.16−7.54 (m, 5H, *Ph*). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 67.88; H, 6.53; N, 4.33.

Reaction of Ia with *N*-Phenylmaleimide. Ia (2.0 g, 0.97 mmol) and *N*-phenylmaleimide (0.26 g, 1.5 mmol) in benzene (50 mL) were refluxed overnight. The mixture was cooled and the product precipitated by addition to dry diethyl ether. The product was filtered, washed with diethyl ether, and dried under vacuum (<0.05 mmHg) overnight; yield 1.95 g (90%).

Cycloadduct **IIa.** ^{1}H NMR: δ 2.18−2.73 (overlapping multiplets, 3H, C_4−H and 2 C_7−H), 3.25 (s, 3H, CH_3O−), 3.50 (s, mPEG backbone), 5.83−6.02 (m, 2H, C_5−H and C_6−H), 7.14−7.52 (m, 5H, *Ph*). The two diastereotopic hydrogens (centered at 3.72 and 3.84 ppm for **IIb**) as well as the protons on C_{7a} and C_{3a} were buried under the spinning sidebands of the mPEG backbone.

Results and Discussion. The reaction of sodium methoxyethoxide with 5-bromo-(3*E*)-1,3-pentadiene in 2-methoxyethanol proceeded in a straightforward manner, resulting in 5-methoxyethoxy-(3*E*)-1,3-pentadiene (**Ib**). The relative integration of protons on the methoxyethoxy and pentadienyl units are consistent with the proposed structure, and the coupling constant for protons on C_3 and C_4 was consistent with a trans configuration ($J = 14.4$ Hz). The ^{1}H NMR spectrum also indicated that the resonances at 4.20 ppm due to the methylene protons of 5-bromo-(3*E*)-1,3-pentadiene had been replaced with a new doublet of doublets at 4.00

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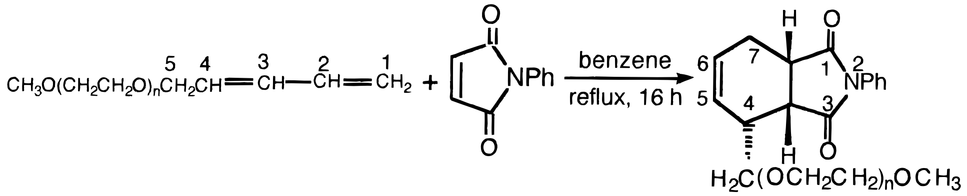
Scheme 1



Ia, n=44.7
Ib, n=1

IIa, n=44.7
IIb, n=1

ppm for the oxymethylene protons attached to the diene moiety.

Similarly, 5-[methoxypoly(oxyethylene)]-(3*E*)-1,3-pentadiene, **Ia**, was prepared from the reaction of mPEG alkoxide with 5-bromo-(3*E*)-1,3-pentadiene in THF. In the ^{1}H NMR spectrum of **Ia,** resonances assignable to the pentadienyl moiety are nearly identical to those on the model compound, **Ib**. The relative integration of the peaks for the terminal methoxy protons from the mPEG to the dienyl protons was consistent with a 1:1 mPEG to dienyl ratio. Further, the proton spectrum showed no observable resonance for hydroxyl proton at 4.56 ppm, demonstrating that substitution was complete.

The reactions of **Ia** and **Ib** with *N*-phenylmaleimide were then examined (Scheme 1).

In the ^{1}H NMR spectrum of **IIb**, the ratios of integrations were consistent with a 1:1 **Ib**:*N*-phenylmaleimide adduct. The four olefinic resonances assignable to the diene moiety of **Ib** were replaced by two olefinic proton signals at 5.84−6.05 ppm. Similarly, the peaks assigned to $-OCH_2-$diene at 4.00 ppm were replaced by two second-order doublets of doublets for the same methylene group centered at 3.72 and 3.84 ppm. In principle, the *N*-phenylmaleimide could add to the diene via either an *endo* or *exo* transition states, so two enantiomeric pairs of products are possible. However, the ^{1}H NMR is consistent with a single pair of enantiomer, and literature precedence suggests that *endo* addition should be preferred in this case.[16]

The ^{1}H NMR spectrum of **IIa** was similar to that of **IIb**. The ratios of methoxy protons to either olefinic protons or the aromatic protons were as required by the structure. However, spinning sidebands from the mPEG backbone overlapped with resonances from the methylene attached to the mPEG, preventing complete analysis.

The GPC analyses of **Ia** and **IIa** confirmed that the PEG backbone maintained its integrity throughout the reactions and that no polymerization of the diene occurred.

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