

¹H-NMR Investigation of Quantitative Functionalization of Poly(ethylene glycol)s

K. JANKOVA¹ and J. KOPS²

¹Bourgas University of Technology, "Prof. Dr. Assen Zlatarov" Department of Polymers, BG-8010, Bourgas, Bulgaria;

²Technical University of Denmark, Department of Chemical Engineering, DK-2800 Lyngby, Denmark

SYNOPSIS

Poly(ethylene glycol)s, with different molecular weights (4,000–20,000) and a monomethoxy-substituted poly(ethylene glycol) (molecular weight 5,000) have been quantitatively end group functionalized with bromo and amino groups. The bromination was carried out with thionyl bromide in toluene. ¹H-NMR was used for the determination of the degree of substitution by monitoring the characteristic signals for the —CH₂Br protons in relation to the signals from the remaining hydroxyl groups. Under the conditions used, qualitative substitution was obtained after repeating the bromination reaction. The results were in agreement with elemental analysis. The bromo end group could be quantitatively converted into amino groups by reaction in absolute ethanol with excess of ammonia or ethylenediamine. Also in this case, ¹H-NMR was used to determine the quantitative substitution by the characteristic signals for the aminomethyl protons and the simultaneous disappearance of the bromomethyl proton signals. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Block polymers are of considerable interest for the development of technologically important materials. One of the methods of obtaining these is by coupling reactive end groups of two prepolymers. The application of mono- and bifunctional poly(ethylene glycol)s (PEGs) as starting materials for the preparation of di- or triblock copolymers, containing well-defined PEG segments have led to amphiphilic block copolymers, which are of great interest, because of their unique emulsifying, thickening, foaming, and other properties.^{1,2} In connection with the preparation of such polymers it is of primary importance that pure mono- or difunctional (telechelic) prepolymers are used.

In the present communication we report methods for quantitative functionalization of PEG and monomethoxy-PEG (MPEG) with bromo and amino end groups and analysis of these by ¹H-NMR spectroscopy and by chemical methods. The PEG derivatives, containing one or two bromo or amino end groups are soluble in water and for that reason

they are of interest for the synthesis of new amphiphilic block copolymers.

Several investigations are reported in the literature concerning the functionalization of PEG with bromine^{3–5} and amino end groups.^{4–8} Degrees of substitution of more than 90% have been reported, however, experimental evidence for quantitative functionalization is lacking specially concerning bromo end groups.

EXPERIMENTAL

Materials

Poly(ethylene glycol)s (PEG 4000, 6000, 10,000, and 20,000) were commercial products (Merck) and the monomethoxy-poly(ethylene glycol) (MPEG 5000) was purchased from Aldrich. Triethylamine and dioxane were from Fluka, 1,6-dibromhexane from EGA, and the activated carbon from Merck. All the other chemicals and the solvents were purchased from Aldrich-Chemie and were reagent grades. Solvents were used after usual drying and distillation without further pretreatment unless otherwise stated.

Substitution Reactions of Poly(ethylene glycol) (1a)

The procedures are described for the case of PEG4000 and are representative for substitution reactions of the other types of PEG as well as for MPEG.

α -(2-Bromoethyl)- ω -Bromopoly(ethylene glycol) (2a)

PEG 4000, 34 g (8.5 mmol) (m.p. 59–60°C), was dissolved in 250 mL of dry toluene and 50 mL of toluene was distilled off to remove traces of moisture. After cooling down to 30–40°C, 5.6 mL (40.8 mmol) of freshly distilled anhydrous triethylamine was added. A solution of 2.8 mL SOBr₂ in 30 mL dry toluene was added dropwise at 35°C with continuous stirring under a dry nitrogen atmosphere. After refluxing for 1–3 h, the hot brown dispersion was passed through a sintered glass funnel with a 2–3 cm thick layer of Standard Super Cell diatomaceous earth and left at room temperature for 2–4 h. The solution was then heated to 50°C, treated with 4 g activated carbon, and filtered through a diatomaceous earth layer. The solution was stored at 5°C overnight to crystallize the product. The toluene was removed by filtration and the solid product was dissolved in absolute ethanol at 50°C. After treatment with active carbon, filtration through a warm layer of diatomaceous earth, the ethanolic solution was stored overnight at 5°C to recrystallize the product. The solid material was filtered off, washed with cold ethanol and ether, and dried in vacuum. The degree of substitution was determined to 87.2%. After reacting once more with SOBr₂ and using the described procedure the substitution of the hydroxyl groups by bromine was quantitative. For purification, the powder was dissolved in tetrahydrofuran (THF) or dioxane and reprecipitated twice with ether. Yield: 69.4% 2a (4000), m.p. 58–59°C.

α -[(2-Aminoethylamino)ethyl]- ω -[2-Aminoethylamino]Poly(ethylene glycol) (4a)

The procedure for the reaction of ethylenediamine with 2a (4000) is representative for the synthesis of other α -(2-aminoalkylaminoethyl)- ω -aminoalkylaminopoly-(ethylene glycol)s. 3 g (0.75 mmol) of 2a (4000) was dissolved in 60 mL absolute ethanol and 0.3 g (5 mmol) ethylenediamine was added. The solution was refluxed overnight. After treatment with 0.5 g of active carbon, the product was filtered and left overnight for crystallization. The crystals

were filtered, washed with cold ethanol and ether, and dried in vacuum. The powder was dissolved in THF or dioxane and twice reprecipitated in ether. Yield: 2.3 g 4a (4000), m.p. 56–57°C. The substitution was complete, and was proved by ¹H-NMR, elemental analysis and potentiometric titration.

α -(2-Aminoethyl)- ω -Aminopoly(ethylene glycol) (5a)

3 g (0.75 mmol) of 2a (4000) was dissolved in 53 mL of absolute ethanol in a 150 mL glass bottle, which was cooled to –40°C, after which 30 g (1.76 mol) NH₃ was condensed in the bottle. The bottle was put in a 250 mL metal autoclave, which was tightly closed and placed in an oil bath at 100°C. After 1 h the autoclave was cooled down and carefully opened. After evaporation more ethanol was added several times and removed by rotatory evaporation until no NH₃ could be detected. The solution was left overnight at 5°C for crystallization. After filtration, the crystals were washed with cold ethanol and ether, and dried in vacuum. For purification the powder was dissolved in THF and reprecipitated with ether. Yield: 2.7 g 5a (4000), m.p. = 54–55°C. The substitution of amino for the bromo end groups was quantitative as proved by ¹H-NMR, elemental analysis and potentiometric titration.

Instrumental Analysis

GPC Analysis

The molecular weights of polymer samples were determined by gel permeation chromatography (GPC) (Waters Model 200) in THF solvent. As the calibration is based on PS standards the calculated values were obtained by correcting with ratio of the molecular weight of the repeating units.

¹H-NMR Analysis

The ¹H-NMR spectra were recorded on a 250 MHz Bruker spectrometer. The polymers and model compounds were dissolved in DMSO-*d*₆, dried over molecular sieves 4 Å.

The degree of substitution by bromine was calculated from NMR data (Fig. 1, spectrum 2) from the integrated area for the CH₂Br triplet (3.75 ppm) as compared to that for the OH triplet (4.56 ppm) taking into consideration the different number of protons in the two groups. The signal at 4.56 ppm was found to disappear at 100% substitution.

The quantitative substitution of amino for the

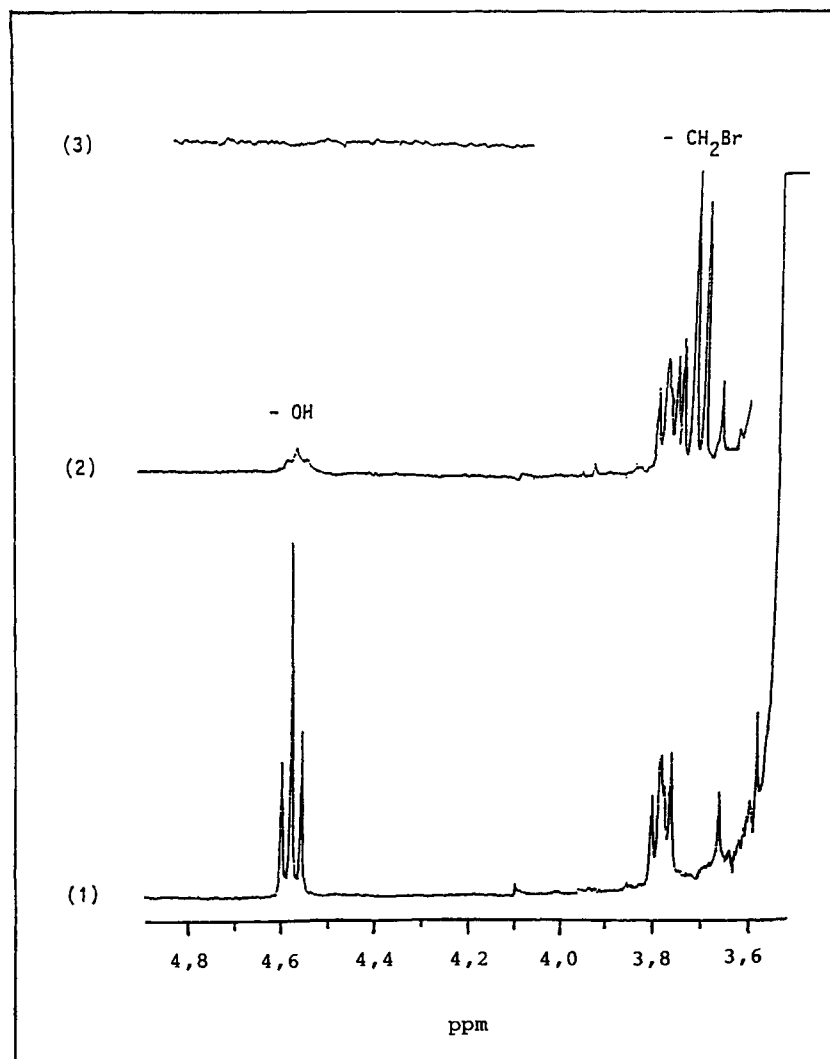


Figure 1 $^1\text{H-NMR}$ -spectra of end group brominated poly(ethylene glycol) 4000. (1) Starting PEG 4000. (2) α -(2-bromoethyl)- ω -bromopoly(ethylene glycol) with degree of substitution of 87.2%. (3) Completely brominated product.

bromo end groups was indicated by reaction of 2a with ammonia and the recorded $^1\text{H-NMR}$ spectrum (Fig. 2) of the resulting polymer. In this case it is seen that the triplet signal of the CH_2Br group at 3.75 ppm in the partially (75.3%) brominated product spectrum (1) has disappeared completely and the CH_2NH_2 signal at 3.00 ppm appears instead in spectrum 2. Internal agreement was found in the ratios of the areas related to OH, CH_2Br , and CH_2NH_2 .

For the molecular weight determination by the $^1\text{H-NMR}$ data the sum of the integrals for the polymer backbone around 3.51 ppm was compared to the area the CH_2NH_2 end groups at 3.00 ppm and a

degree of polymerization could be calculated on this basis.

RESULTS AND DISCUSSION

PEG, MPEG, and their derivatives have been analyzed by the $^1\text{H-NMR}$ spectroscopy in several solvents. In CCl_4 , CDCl_3 , and others, the OH appears as a singlet at a position and a sharpness which is highly dependent upon the solvent, PEG concentration (due to intermolecular hydrogen bonding), and concentrations of acidic or basic impurities in

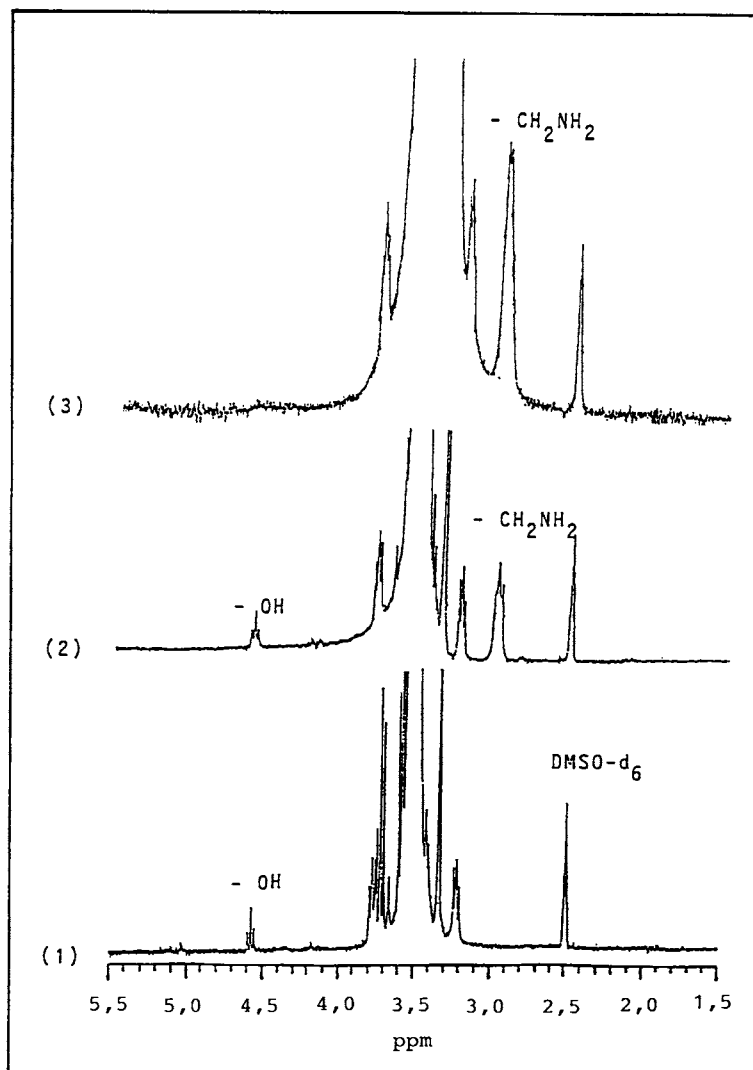


Figure 2 $^1\text{H-NMR}$ -spectra of aminated products from partially and fully brominated PEG 4000. (1) Partially brominated (75.3%) PEG 4000 and (2) the aminated product thereof. (3) The completely aminated product α -(2-aminoethyl)- ω -aminopoly(ethylene glycol).

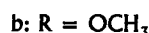
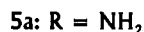
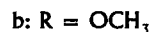
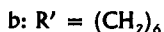
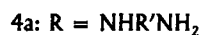
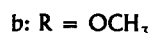
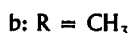
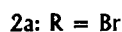
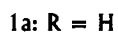
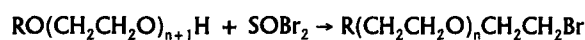
the solvent.⁹ The $^1\text{H-NMR}$ of the PEG, MPEG, and derivatives in $\text{DMSO-}d_6$ shows a signal for the OH as a triplet as a result of a coupling with the adjacent methylene.¹⁰ The triplet is confined to a limited chemical shift range 4.56 ± 0.05 ppm and is readily distinguishable from the spinning side bands or other peaks not only on the basis of the observed multiplicity but also as a result of the chemical shifts. This way the area of the hydroxyl PEG peak in $\text{DMSO-}d_6$ can be used in a quantitative way to obtain information about PEG molecular weight and degree of substitution.

Based on the work of Johansson et al.¹¹ substitution by bromine in PEG (2a) and MPEG (2b) were carried out by reactions of 1a and 1b with thionyl bromide in toluene in the presence of triethylamine (Scheme 1). The modified products showed a triplet at 3.75 ppm, due to the methylene protons in the CH_2Br endgroups (Fig. 1, spectrum 2). In the model compound 1,6-hexamethylenediamine this triplet appears in CCl_4 by 3.37 ppm and in $\text{DMSO-}d_6$ by 3.51 ppm.

For the determination of the degree of substitution three methods have been used: (1) $^1\text{H-NMR}$,

(2) determination of bromine after oxygen flask combustion and titration with 0.04 N $\text{Hg}(\text{NO}_3)_2$, and (3) absorption of the combustion products (HBr) 1 h by 0.2 N KOH , adding HNO_3 and potentiometric titration of the KBr solution with 0.1 N AgNO_3 .¹² Results in a range of 75–93% bromine end groups were found after bromination. Only by a second bromination with SOBr_2 the terminal hydroxyl groups could be substituted by bromine completely. The NMR signal of the OH groups by 4.56 ppm disappears (Fig. 1, spectrum 3) and the determination of the bromine by the two chemical reactions¹² of 2a and 2b show a content of bromine very close to 3.68 and 1.59 weight %, respectively, which is in accordance with a complete substitution of the hydroxyl end groups by bromine. Elemental analysis found for Br-PEG 4000: Calc. C 52,64, H 8,77, Br 3,59, Found C 52,38, H 8,96, Br 3,68. For Br-MPEG 5000: Calc. C 53,80, H 8,99, Br 1,58, Found C 53,66, H 9,00, Br 1,59. (Bromine contents determined by the first method above).

From the brominated PEG and MPEG, according to the Scheme 1 we have obtained the aminated products 4a, b and 5a, b by reaction with diamines or ammonia. The Hoffmann reaction with the model compound 1,6-dibromohexane and ammonia gives low molecular weight polyamines, containing two



Scheme 1

primary (3.06 ppm) and three secondary (2.76 ppm) amino groups, which appears in the $^1\text{H-NMR}$ spectra in $\text{DMSO-}d_6$, respectively, as a triplet and quartet. The methylene protons (CH_2)₄ away from the CH_2NH_2 end groups are in the range 1.1–1.8 ppm. The same position (3.06 ppm) for the CH_2NH_2 protons have been reported for the sample $\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$ in $\text{DMSO-}d_6$.¹³

In case of the brominated polymers 2a and 2b the reactions with ammonia or ethylene diamine proceeds rapidly without formation of longer chains. Thus the substitution is complete after less than 0.5 h. The CH_2Br signal at 3.75 ppm disappears and a new signal appears at 3.00 ppm, which is assigned to primary amino groups. In case of reaction of 2a and 2b with ethylene diamine a signal also appears around 2.62 ppm which is assigned to secondary amino groups in products 4a and 4b. The absence of the latter signal in the samples 5a, b and GPC analysis shows that no chain formation takes place. This fact has also been found by other authors.¹¹ Nitrogen determination gave the following results, NH_2 -PEG 4000 (NH_3): Calc. N 0,70, Found 0,80. NH_2 -PEG 4000 (EDA): Calc. N 1,39, Found N 1,50.

The quantitative substitution of amino for the bromo end groups in the PEG and MPEG was confirmed by a sample of 2a with a bromine substitution of 75.3% which was reacted with ammonia under conditions for completely substitution. The calculation on the basis of the $^1\text{H-NMR}$ spectrum shown in (Fig. 2, spectrum 2) shows the presence of nearly 25% of unreacted OH groups and 75% CH_2NH_2 groups which is in accordance with a quantitative substitution. The complete substitution of amino for the bromo end groups was also proved by elemental analysis of the nitrogen and potentiometric titration of the amino end groups with 0,1 N HCl .

The number-average molecular weights of the amino modified PEGs were calculated on the basis of the signals around 3.00 ppm compared to the total signal from the backbone. The calculated value was in agreement with that obtained by GPC.

The modified polymers are soluble in many solvents (e.g., water, ethanol, pyridine, THF, dioxane, benzene, toluene, chloroform, dichloromethane) however, are insoluble in diethylether and petroleum ether.

The substituted PEG with two functional groups can be used for the synthesis of triblocks with other monofunctional prepolymers, or to get block copolymers by polycondensation [block copolymers of type $(\text{A-B})_n$]. The modified MPEGs are useful for making triblocks, where the center block is another

difunctional polymer, or for making star polymers. Studies on the application of these functionalized soluble polymers will be reported later.

CONCLUSION

Quantitative functionalization of poly(ethylene glycol)s including monomethoxy-poly(ethylene glycol) with bromo and amino end groups can be obtained by reaction with thionyl bromide and subsequent reaction with ammonia or ethylene diamine.

The quantitative substitution with bromine was determined by the use of $^1\text{H-NMR}$ analysis based on the appearance of characteristic signals for the bromomethyl protons. The results were in agreement with elemental analysis. The quantitative substitution was under the conditions used only obtained after a second bromination with thionyl bromide.

The substitution of amino for the bromo groups was found to be quantitative by $^1\text{H-NMR}$ analysis on the basis of the appearance of aminomethyl protons and the simultaneous disappearance of the bromomethyl protons.

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REFERENCES

1. J. P. Kennedy and Y. Hongu, *Polym. Bull.*, **13**, 115 (1985).
2. J. P. Kennedy and B. Iván, *Designed Polymers by Carbocationic Macromolecular Engineering: Theory and Practice*, Hanser Publishers, Munich, Vienna, New York, Barcelona, 1992.
3. A. Chaabouni, P. Hubert, E. Dellacherie, and J. Neel, *Makromol. Chem.*, **179**, 1135 (1978).
4. M. Mutter, *Tetrahedron Lett.*, **31**, 2839 (1978).
5. A. Bückmann and M. Morr, *Makromol. Chem.*, **182**, 1379 (1981).
6. K. Geckeler, *Polym. Bull.*, **1**, 727 (1979).
7. S. Zalipsky, C. Gilou, and A. Zilkha, *Eur. Polym. J.*, **19**, 1177 (1983).
8. A. Gehrhardt and M. Mutter, *Polym. Bull.*, **18**, 187 (1987).
9. J. B. Lambert, H. F. Shurvell, L. Vebit, R. G. Cooks, and G. H. Stout, *Organic Structural Analysis*, Macmillan, New York, 1976.
10. J. M. Dust, Z.-h. Fang, and J. M. Harris, *Macromolecules*, **23**, 3742 (1990).
11. G. Johansson, A. Hartman, and P. A. Albertsson, *Eur. J. Biochem.*, **33**, 379 (1973).
12. W. Schöniger, *Mikrochimica Acta*, **74** (1954); 869 (1956).
13. $^1\text{H-NMR}$ Sadtler Katalog No. 45587.

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