# MALDI-TOF in the Characterizations of Dendritic−Linear Block Copolymers and Stars

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ABSTRACT: Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry was utilized to study simple poly(ethylene glycol)s (PEG) and a series of amphiphilic copolymers prepared from PEG and dendritic molecules. For the amphiphilic copolymers with branched dendritic structures, MALDI-TOF spectrometry affords more accurate molecular weight data than the conventional gel-permeation chromatography (GPC). For mass lower than 10 000, the molecular weight distribution of the polymer is well-resolved into individual peaks. Using MALDI-TOF in the linear mode, copolymers with molecular masses of up to 43 000 Da were analyzed. For various dendrons attached to the same PEG, a good correlation was observed between calculated and measured data for the expected incremental increase as a function of dendrimer generation. End-group analysis using MALDI-TOF mass spectrometry proved very useful for the analysis of polymers with relatively low molecular weights. The experimental results agree well with the calculated masses of selected oligomers. Such end-group analysis can differentiate between the AB dendritic−linear diblocks, ABA triblocks, and linear PEG. These analyses support our earlier finding that the Williamson ether synthesis utilized in the PEG−dendron coupling reaction indeed converts all of the PEG to the desired block copolymer products.

## Introduction

MALDI-TOF mass spectrometry is fast becoming a technique of choice for the analysis of synthetic polymers. This powerful technique allows the direct analysis of polymers without the complication of fragmentation due to the combination of a soft ionization process with the use of a variety of MALDI matrices.[1] MALDI has been used most extensively in the analysis of biopolymers such as proteins while other innovative applications such as the evaluation of peptide combinatorial libraries have also emerged.[2] It is only recently that synthetic polymers as well as dendrimers have been successfully analyzed by this technique.[3,4] A growing number of synthetic polymers including polystyrene (PS), poly(methyl methacrylate) (PMMA), and poly(ethylene glycol) (PEG) have been studied using MALDI-TOF mass spectrometry. We have previously reported[5−7] on a series of block and star amphiphilic copolymers that consist of hydrophilic PEGs and hydrophobic poly(aryl ether) dendritic blocks. The polymers were characterized by various techniques including GPC. However, conventional GPC with linear polymers used for calibration is not an ideal tool to measure the molecular weights of such hybrid copolymers. This is due to both the highly branched nature of the dendritic blocks and also the tendency of these amphiphilic polymers to form micellar aggregates in different solvents. These polymers with their unique chemical and topological features behave quite differently from normal linear polymers. An additional degree of difficulty is introduced in the analysis of these hybrid polymers by the fact reactions on polymer chain ends are frequently hard to monitor and quantify. This applies to the functionalization of PEG chain ends with dendrimers, as GPC may not distinguish the difference between a fully functionalized triblock copolymer and a mixture of triblock and monosubstituted diblock copolymers. This difficult analytical task along with the accurate monitoring of polymer molecular weight changes that accompany block copolymer formation can be tackled using MALDI-TOF mass spectrometry. After ionization, the singly charged and structurally intact ions of polymer detected by MALDI-TOF may provide a bell-shaped distribution of oligomers. Thus, the mass of each oligomer can be identified, and average molecular weights as well as polydispersities of polymers can also be determined. The oligomers are equally spaced in a way that normally reflects the mass of polymer repeat unit. As the molecular weight and polydispersity of samples increase, MALDI-TOF analysis of MW distribution becomes less reliable since it cannot be ascertained that the entire molecular weight distribution travels equally through the spectrometer tube. Simultaneous molecular weight measurement and end-group analysis in MALDI-TOF mass spectrometer is an obvious advantage over other analytical methods.[8,9] In this paper, we report detailed analyses of PEG and their block or star copolymers using MALDI-TOF mass spectrometry.

## Experimental Section

**Materials.** Poly(ethylene glycol) methyl ether (MPEG) with nominal molecular weight (MW) of 5000 was purchased from Aldrich. Poly(ethylene glycol) with MW 4000 was obtained from Scientific Polymer Products (Sp$^2$), Inc. Four-arm star poly(ethylene glycol) with MW = 20 000 was obtained from Shearwater Polymers, Inc. Polyether dendrons of generations 2−4 ([G-2], [G-3], and [G-4]) were prepared according to the literature procedure.[11] Their copolymers with a variety of PEGs were synthesized according to a method already described.[6−8]

**Sample Preparation.** The matrices used in MALDI-TOF mass spectrometry were α-cyano-4-hydroxycinnamic acid, *trans*-indoleacrylic acid (IAA), and 2,5-dihydroxybenzoic acid (DHBA). The solvent used for both matrix and sample was tetrahydrofuran (THF). All of three matrices afford good MALDI results for polymers with relatively low molecular weights, but α-cyano-4-hydroxycinnamic acid gave MALDI signals with the strongest intensity when the same conditions were applied in parallel measurements. As the molecular weights approach 10 000, the resolution decreases, and the 2,5-dihydroxybenzoic acid matrix affords best results. A typical

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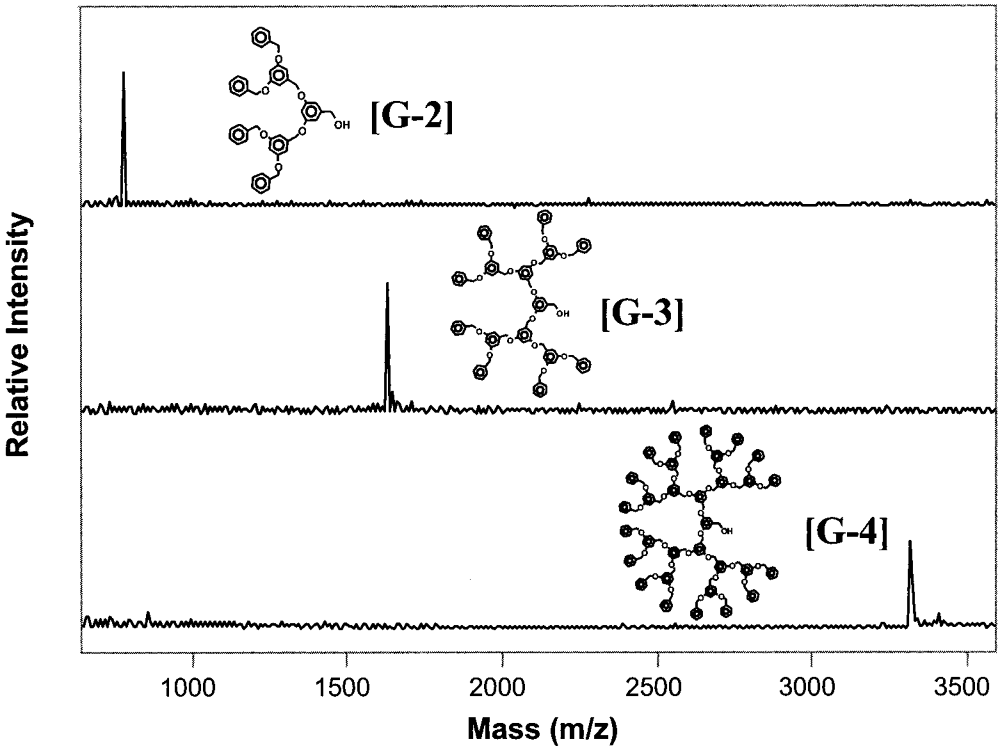


**Figure 1.** MALDI-TOF mass spectra of different generation dendrons.

procedure used for sample preparation was as follows. The matrix (20−30 mg) was dissolved in 1 mL of THF, a lengthy process with α-cyano-4-hydroxycinnamic acid. The concentration used for the various polymer samples (either PEGs or hybrid block copolymers) was ca. 5−10 mg/mL. The matrix solution (20 $\mu$L) and the sample solution (5 $\mu$L) were mixed well, and then 1 $\mu$L of the resulting solution was loaded into a single well of a gold-coated MALDI plate and dried before inserting into the vacuum chamber of the MALDI instrument.

**Instrumentation.** MALDI-TOF mass spectrometry was carried out on a PerSeptive Biosystems-Voyager-DE mass spectrometer operating in linear mode. The spectrometer equipped with a nitrogen laser (337 nm) was calibrated using bovine insulin as standard (two sharp peaks at 2867.80 and 5734.59). The laser steps and voltages applied were adjusted as a function of the polymer molecular weights and molecular weight distribution as well as the nature of the different molecular compositions. In general, high molecular weight polymeric species required higher laser power in order to fly in the MALDI tube.

GPC measurements were carried out using a Waters 150CV plus gel permeation chromatograph equipped with a set of four 5 $\mu$m PL gel columns (Polymer Laboratories) with porosities of 100 Å, 500 Å, 1000 Å, and Mixed C. The mobile phase was THF eluting at 1 mL/min. Calibration was accomplished using 18 polystyrene standards obtained from Polymer Laboratories.

## Results and Discussion

Three generations of monodisperse[10] Fréchet-type dendrons [G-2], [G-3], and [G-4] with increasing branching structures were prepared by the conventional convergent approach.[11] Their MALDI-TOF mass spectra are shown in Figure 1. Peaks with highest intensity are attributed to the sodium ion adducts of these dendrons $[M + Na]^+$. The cationization by sodium is due to arbitrary sodium impurities in the samples. The calculated masses for [G-2], [G-3], and [G-4] are 744.88, 1593.87, and 3291.86 Da. The experimental results and the calculated molecular masses of the sodium ion adducts are well matched (Table 1). These data suggest that convergent dendrimers being size monodisperse could be used as standards to calibrate the MALDI-TOF spectrometer.

**Table 1. MALDI-TOF Molecular Weight Data of G2−G4 Polyether Dendrons**

| dendron | calcd mol wt | exptl mol wt |
|---|---|---|
| [G-2]−OH | 767.9 $[M + Na]^+$ | 768.2 |
| [G-3]−OH | 1616.9 $[M + Na]^+$ | 1616.9 |
| [G-4]−OH | 3314.9 $[M + Na]^+$ | 3314.0 |

Monomethyl ether terminated PEG was utilized for the preparation of the diblock copolymers. The dendrons were covalently attached to MPEG 5000 via a typical Williamson ether synthesis.[5,6] MPEG 5000 and the corresponding AB diblock hybrids with different generation dendrons are shown schematically in Figure 2.

Figure 3 depicts the MALDI-TOF mass spectra of the resulting hybrid diblock copolymers. The mass difference between each adjacent peak is 44 Da, which corresponds to the mass of the PEG's oxyethylene repeat unit. The spectrum of MPEG 5000 contains oligomer peaks extending from approximately $m/z = 3500$ to 6500. Attachment of different generation dendrons to the MPEG 5000 shifted the whole mass distribution curves to higher molecular weights while the shape of the curves shows no significant changes. If some unreacted MPEG were left after the coupling reaction, the shape would no longer be the same. In addition, the presence of a single set of peaks in the MALDI-TOF-MS also provides strong support for the existence of only one kind of polymeric species in the system. The increases in mass measured at the maximum of MALDI-TOF distribution curves correspond to the addition of the masses of the [G-2], [G-3], and [G-4] dendrons.

The average molecular weights (both number-average and weight-average molecular weights), peak molecular weights, and polydispersities can be derived from the MALDI-TOF-MS. The results are listed in Table 2. The molecular weights shown in brackets are calculated from the molecular weights of the corresponding native

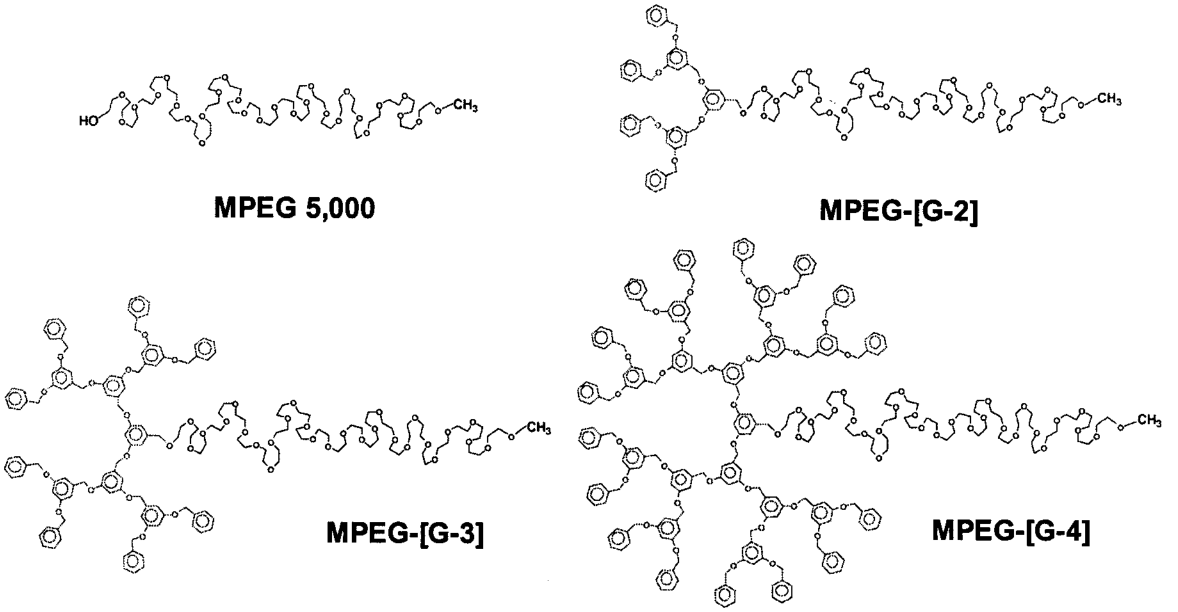


**Figure 2.** Structures of MPEG 5000 and its hybrid diblocks MPEG−[G-2], MPEG−[G-3], and MPEG−[G-4].

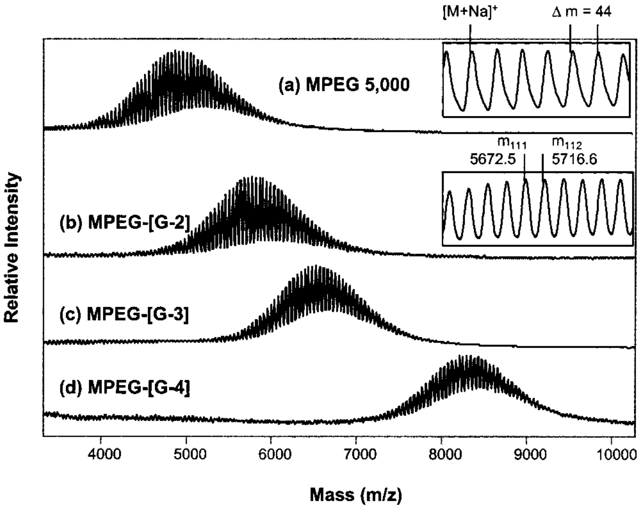


**Figure 3.** MALDI-TOF mass spectra of the hybrid diblock copolymers.

**Table 2. Molecular Weights of PEG and PEG−Dendron Block or Star Copolymers Obtained from MALDI-TOF Measurements**

| polymer | $M_n$ | $M_w$ | $M_p$ | PDI |
|---|---|---|---|---|
| MPEG 5000 | 4960 | 5030 | 4900.1 | 1.01 |
| MPEG−[G-2] | 5700 [5690][a] | 5760 | 5673.2 [5628.0] | 1.01 |
| MPEG−[G-3] | 6560 [6540] | 6610 | 6519.0 [6477.0] | 1.01 |
| MPEG−[G-4] | 8250 [8220] | 8290 | 8291.4 [8175.0] | 1.01 |
| PEG 4000 | 4390 | 4500 | 4184.2 | 1.02 |
| [G-2]−PEG−[G-2] | 5830 [5840] | 5890 | 5590.1 [5638.0] | 1.01 |
| [G-3]−PEG−[G-3] | 7540 [7540] | 7630 | 7258.8 [7335.9] | 1.01 |
| [G-4]−PEG−[G-4] | 11000 [10900] | 11200 | 10900.2 [10731.9] | 1.01 |
| star PEG | 25700 | 25900 | 25495 | 1.01 |
| PEG−$[G-2]_4$ | 28800 [28600] | 29000 | 28403 [28402] | 1.01 |
| PEG−$[G-3]_4$ | 31700 [32000] | 31800 | 31740 [31800] | 1.01 |
| PEG−$[G-4]_4$ | 38900 [38800] | 39100 | 38925 [38590] | 1.01 |

[a] Numbers in brackets are calculated based on the measured molecular weights of native PEGs.

**Table 3. Molecular Weights and Polydispersities of Polymers Obtained from GPC Measurements**

| polymer | $M_n$ | $M_w$ | $M_p$ | PDI |
|---|---|---|---|---|
| MPEG 5000 | 6860 | 7120 | 7180 | 1.04 |
| MPEG−[G-2] | 8020 [7590][a] | 8330 | 8530 [7910] | 1.04 |
| MPEG−[G-3] | 8590 [8440] | 8930 | 9330 [8760] | 1.04 |
| MPEG−[G-4] | 9880 [10100] | 10400 | 10800 [10400] | 1.05 |
| PEG 4000 | 4380 | 4600 | 4620 | 1.05 |
| [G-2]−PEG−[G-2] | 6730 [5830] | 6940 | 7000 [6070] | 1.03 |
| [G-3]−PEG−[G-3] | 8320 [7530] | 8690 | 9230 [7770] | 1.04 |
| [G-4]−PEG−[G-4] | 9740 [10900] | 10000 | 10500 [11100] | 1.03 |
| star PEG | 11800 | 14100 | 14600 | 1.20 |
| PEG−$[G-2]_4$ | 12600 [14700] | 15300 | 16800 [17500] | 1.22 |
| PEG−$[G-3]_4$ | 16100 [18100] | 19800 | 21400 [20900] | 1.23 |
| PEG−$[G-4]_4$ | 17100 [24900] | 20600 | 21800 [27700] | 1.21 |

[a] Numbers in brackets are calculated based on the measured molecular weights of native PEGs.

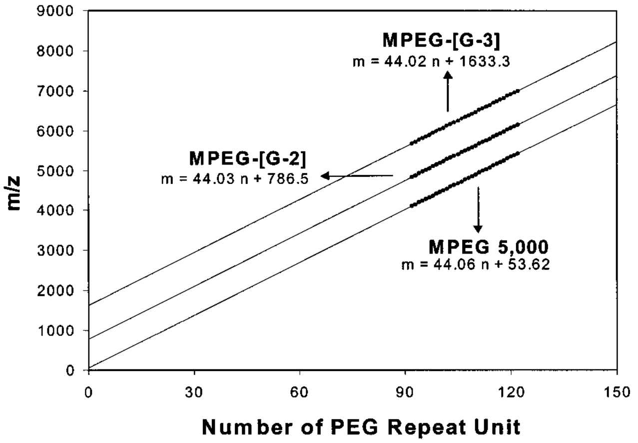


**Figure 4.** Plot of *m*/*z* values from MALDI-TOF vs number of PEG repeat unit for MPEG 5000, MPEG−[G-2], and MPEG−[G-3].

PEGs. For example, the number-average molecular weight of MPEG 5000 is 4960 Da. After the attachment of [G-2] dendron, the number-average molecular weight of MPEG-[G-2] is expected to be 5690 Da. The experimental mass (5700 Da) is well within the expected range. For both MPEG-[G-3] and MPEG-[G-4] diblocks, the experimental results are also in good agreement with the calculated values. The experimental peak molecular weights $M_p$ (corresponding to the peak with highest intensity in the distribution) only deviate slightly from the calculated values for MPEG-[G-2] and MPEG-[G-3] diblocks. There is a mismatch in the case

**Table 4. Molecular Weights of MPEG and Its Diblock Copolymers with Dendrons**

| polymer | formula | mol wt $m(n)$: $n \times m_{\text{monomer}} + m_{\text{end groups}} + m_{\text{cation}}$ | $m(111)^a$ | $m(111)^b$ |
|---|---|---|---|---|
| MPEG 5000 | $CH_3O-(CH_2CH_2O)_n-H$ | $n \times 44.05 + 32.04 + 23.00$ | 4944.6 | 4944.7 |
| MPEG−[G-2] | $CH_3O-(CH_2CH_2O)_n-$[G-2] | $n \times 44.05 + 758.91 + 23.00$ | 5671.5 | 5672.5 |
| MPEG−[G-3] | $CH_3O-(CH_2CH_2O)_n-$[G-3] | $n \times 44.05 + 1{,}607.90 + 23.00$ | 6520.4 | 6519.7 |
| MPEG−[G-4] | $CH_3O-(CH_2CH_2O)_n-$[G-4] | $n \times 44.05 + 3{,}305.88 + 23.00$ | 8218.4 | 8204.6 |

[a] Calculated mass of 111mer of the polymer based on the formula. [b] Experimental mass of 111mer of the polymer.

**Table 5. Molecular Weights of Telechelic PEG and Its Triblock Copolymers with Dendrons**

| polymer | formula | mol wt $m(n)$: $n \times m_{\text{monomer}} + m_{\text{end groups}} + m_{\text{cation}}$ | $m(96)^a$ | $m(96)^b$ |
|---|---|---|---|---|
| PEG 4000 | $HO-(CH_2CH_2O)_n-H$ | $n \times 44.05 + 18.02 + 23.00$ | 4269.8 | 4271.5 |
| [G-2]−PEG−[G-2] | [G-2]$-O-(CH_2CH_2O)_n-$[G-2] | $n \times 44.05 + 1471.74 + 23.00$ | 5723.5 | 5721.7 |
| [G-3]−PEG−[G-3] | [G-3]$-O-(CH_2CH_2O)_n-$[G-3] | $n \times 44.05 + 3169.72 + 23.00$ | 7421.5 | 7434.9 |
| [G-4]−PEG−[G-4] | [G-4]$-O-(CH_2CH_2O)_n-$[G-4] | $n \times 44.05 + 6565.70 + 23.00$ | 10817.1 | N/A |

[a] Calculated mass of 96mer of the polymer. [b] Experimental mass of 96mer of the polymer.

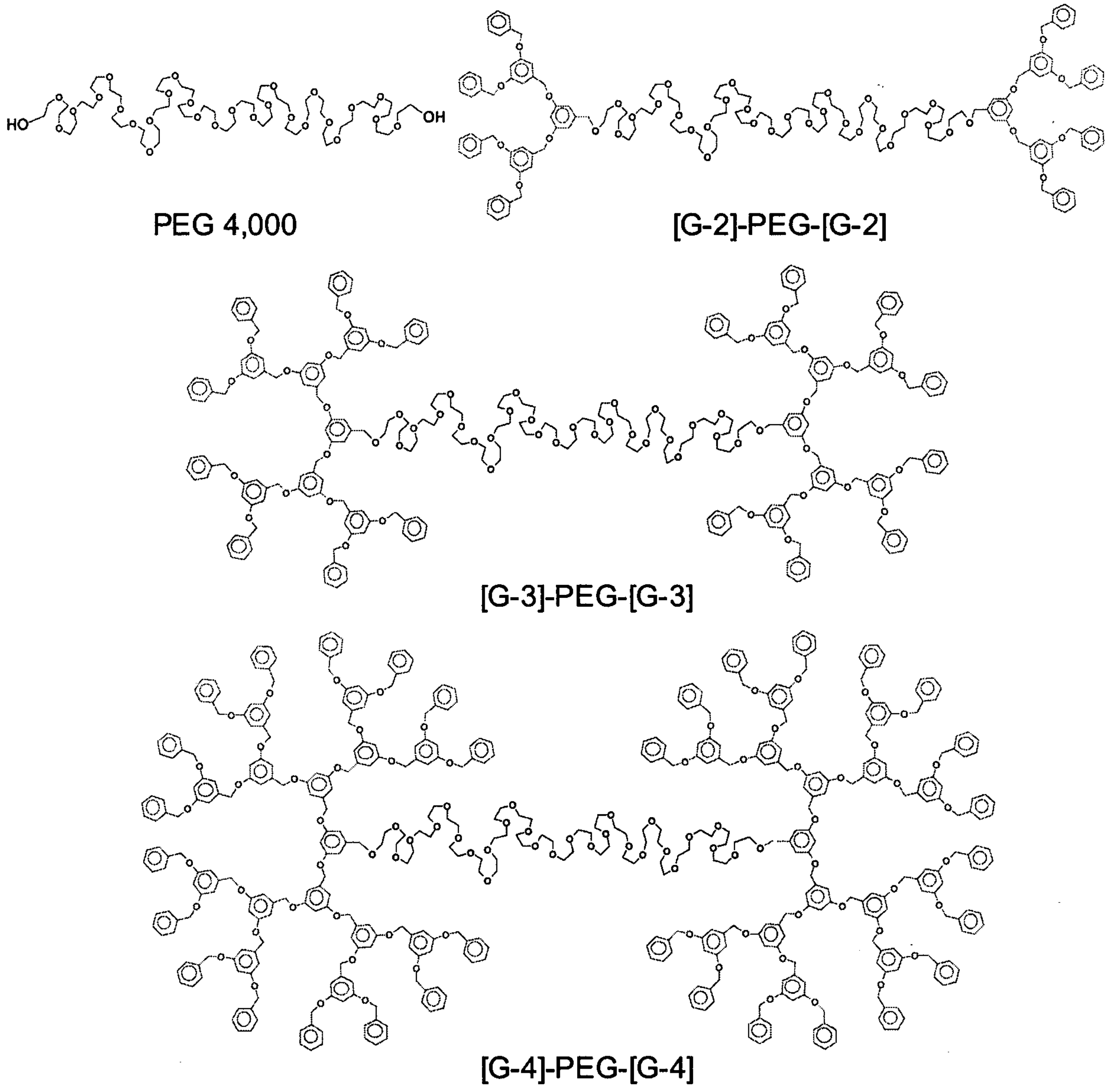


**Figure 5.** Chemical structures of telechelic PEG and its triblock copolymers.

of MPEG-[G-4] for which the baseline of the MALDI-TOF-MS is less perfect than is the case for the previous two copolymers. The polydispersities measured in MALDI are generally lower than those determined from GPC measurements, especially for those polymers with broad distributions. This phenomenon has been investigated by Müllen and co-workers.[12] High molecular weight polymers require higher laser power for the desorption/ionization process than do low molecular weight polymers. For a polydisperse polymer, the above effect may cause smaller peak areas for the high mass component and thus narrower polydispersity in MALDI. As shown in Table 3, the molecular weight data obtained from GPC measurements for the same set of polymer samples characterized by MALDI, though still meaningful, show wider discrepancies from the calculated data. This is not unexpected for such hybrid linear–globular macromolecules given the very different hydrodynamic properties of the linear standards used for calibrations of the GPC. Unlike MALDI-TOF, the molecular weight increment measured by GPC for each copolymer does not match the additional mass of each dendron, as shown by a comparison of the numbers inside and outside of the brackets in Table 3.

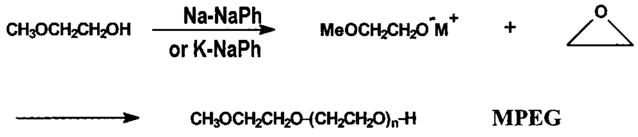
A significant advantage of the MALDI-TOF-MS technique is its ability to assist in the analysis of polymer end groups. By considering the calculated mass and the experimental mass of a single oligomer, the functional groups at both ends of the polymer can be analyzed. The calculated mass $m(n)$ of single peak of the molecular weight distribution is a linear function of number of polymer repeat unit $n$,

$$m(n) = n \times m_{\text{monomer}} + m_{\text{end groups}} + m_{\text{cation}} \tag{1}$$

where $m_{\text{monomer}}$ is the mass of the monomer, $m_{\text{end groups}}$ is the residue mass of both end groups, and $m_{\text{cation}}$ is the mass of the alkali cation ($Na^+$ or $K^+$).

Figure 4 shows a correlation of the mass ($m/z$) measured in MALDI-TOF for MPEG 5000, MPEG-[G-2], and MPEG-[G-3] with the number of PEG repeat units. The slope of the fitted line is the mass of ethylene oxide, and the intercept is the sum of the mass of the end groups and the mass of the cation. The slopes for three copolymers are very close to the actual mass of ethylene oxide (44.05 Da). The values for three intercepts (53.62, 786.5, and 1633.3 Da) are fairly close to the expected masses of 55.04, 781.9, and 1630.9 Da, respectively.

It is likely that the commercial sample of monomethyl ether terminated PEG (MPEG) was prepared via anionic polymerization. One of its chain ends is capped with a methoxy group while the other chain end is a hydroxyl group that is used in the subsequent reaction with a dendritic bromide in a Williamson ether synthesis.



If $CH_3OCH_2CH_2O$ and H are taken as the two end groups, $m_{\text{end groups}}$ is 76.09; alternatively, the value is 32.04 if $CH_3O$ and H are considered to be the end groups. According to eq 1, the peaks of Figure 3a are associated with the sodium ion adducts $[M + Na]^+$ at mass $44.05n + 76.09 + 23$ or $44.05n' + 32.04 + 23$, where $n$ is the degree of polymerization and $n'$ is the number of repeat units. For instance, the peak with mass number 4944.7 is assigned to the 111mer of MPEG 5000. The calculated mass for this specific oligomer is 4944.6, almost the same value as the observed molecular weight (Table 4).

The molecular weight of a single oligomer after different dendrons are attached to MPEG 5000 may be predicted in a similar fashion. The calculated mass for the 111mer obtained after attachment of [G-2] to MPEG ($CH_3O-(CH_2CH_2O)_{111}-$[G-2]) is 5671.5, and the experimental value is 5672.5. If the copolymer were a mixture of MPEG-[G-2] with some unreacted MPEG 5000, a peak would be observed at 5693.5 (128mer of MPEG 5000) between two oligomers of MPEG-[G-2] (111mer at 5672.5 and 112mer at 5716.6). Such a peak is not observed in the inset of Figure 3b. On the basis of the above argument, it is concluded that the diblock copolymer is a pure polymer uncontaminated by the starting MPEG.

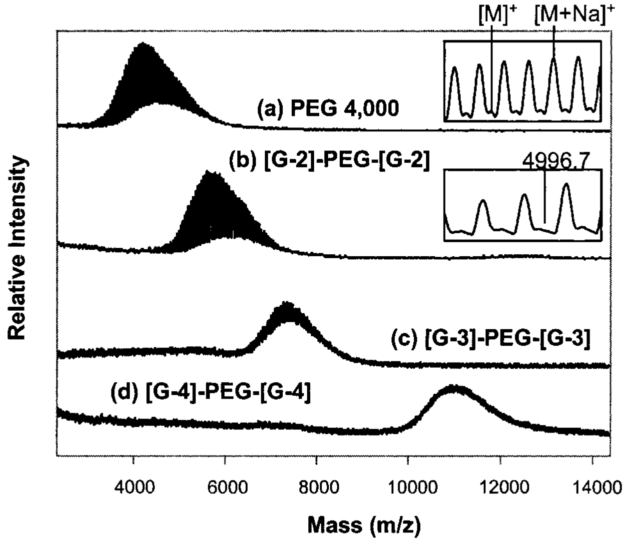


**Figure 6.** MALDI-TOF mass spectra of telechelic PEG and triblock copolymers.

The calculated mass of the 111mer of MPEG-[G-3], with the formula $CH_3O-(CH_2CH_2O)_{111}-$[G-3], is 6520.4 Da. while is the experimental value is 6519.7 Da. However, this near exact agreement is not observed with some higher molecular weight species. There is a nonnegligible deviation between the calculated and the experimental mass (~14 Da) for MPEG-[G-4]. The quality of the baseline of its MALDI-TOF mass spectrum is degraded as a result of the higher laser power applied, and peak resolution is also significantly lessened although individual peaks are still visible in the spectrum. Or, this deviation could be explained by the cationization of lithium ion instead of sodium ion. In the case of $[M + Li]^+$, the experimental mass 8204.6 is close to the calculated value 8202.4.

Telechelic PEG with the formula $HO-(CH_2CH_2O)_n-H$ differs from MPEG by the nature of one of its end groups. Therefore, the formula used to derive its molecular weight is different: $m(n) = n \times 44.05 + 18.02 + 23$ (for the sodium ion adduct) (see Table 5). Indeed, the observed molecular weights of homotelechelic PEG do not appear in the spectrum of MPEG, and vice versa. The chemical structures of telechelic PEG and its hybrid triblock copolymers with [G-2], [G-3], and [G-4] dendrons are shown in Figure 5.

Figure 6 displays the MALDI-TOF mass spectra of triblock copolymers of PEG and dendrons. In Figure 6a, a second set of peaks of much lower intensity is attributed to molecular ions of the original PEG $HO-(CH_2CH_2O)_n-H$ without $Na^+$. A similar phenomenon is also observed in the mass spectra of [G-2]–PEG–[G-2].

In the triblock copolymers, a dendron is attached to each end of PEG. Given the nature of the reaction used

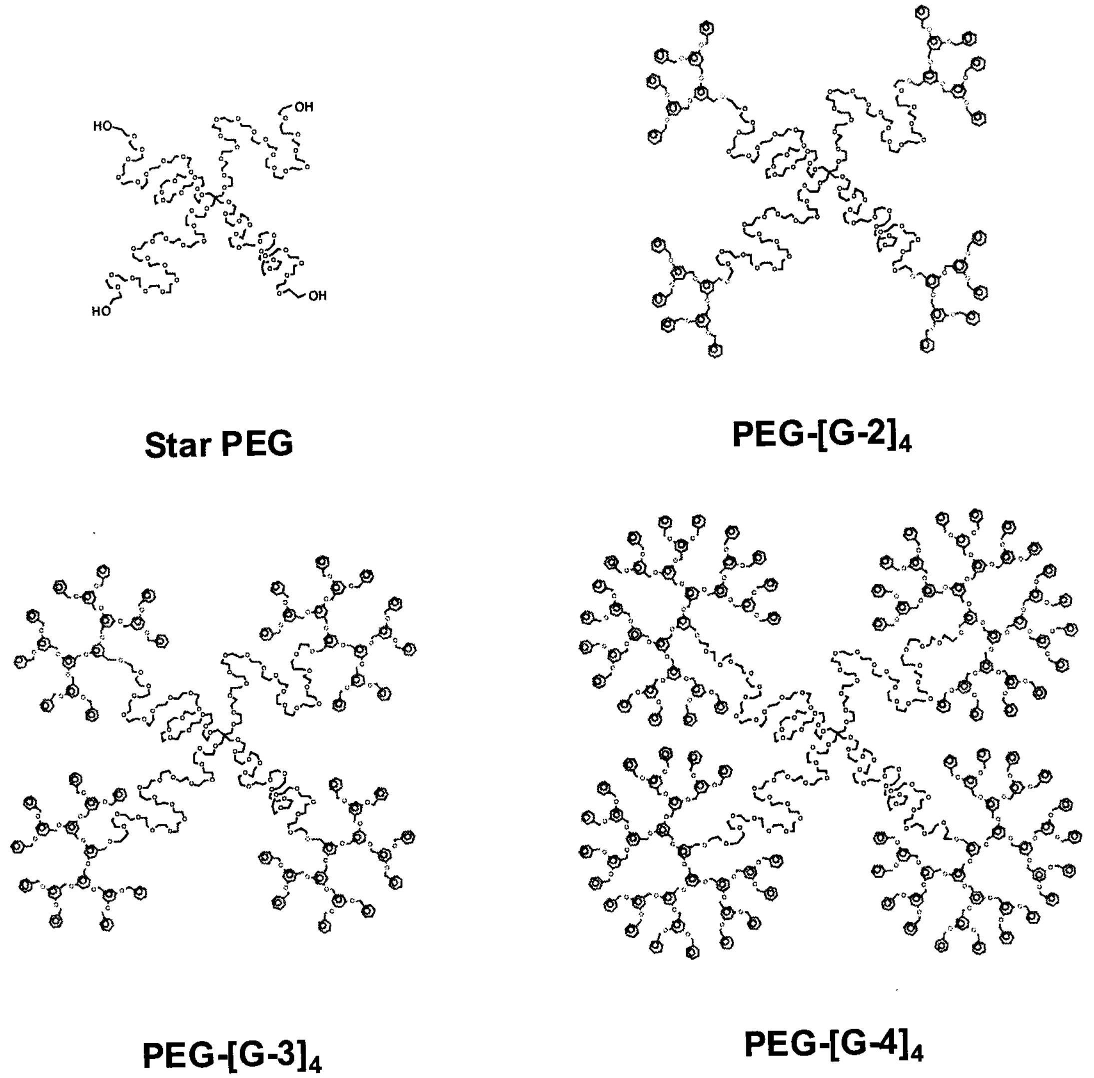


**Figure 7.** Structures of the PEG and its starlike hybrid copolymers.

to prepare these triblock hybrid structures, it is conceivable and even likely that some of the molecules present in the distribution might be functionalized by a single dendron rather than two. The molecular weights of such diblocks would be different from those of hybrid PEG triblocks. For example, the observed molecular weight of the 96mer of [G-2]–PEG–[G-2] is 5721.7, close to the calculated value of 5723.5 (Table 5). If only one end of PEG were functionalized with [G-2], the formula used to calculate the molecular weight of HO–$(CH_2CH_2O)_n$–[G-2] would be $m(n) = n \times 44.05 + 744.88 + 23$ ($Na^+$ adduct). According to this formula, the mass of the 96mer of HO–$(CH_2CH_2O)_n$–[G-2] would be 4996.7. However, there is no peak of mass 4996.7 in the MALDI-TOF mass spectrum of [G-2]–PEG–[G-2] (see the inset of Figure 6b). This suggests that [G-2]–PEG–[G-2] is a pure triblock structure without any noticeable contamination by the hybrid diblock copolymer. Such a conclusion could not have been reached on the basis of conventional gel-permeation chromatography only. In the case of triblock [G-3]–PEG–[G-3], the resolution problem encountered earlier with the higher MW sample MPEG–[G-4] surfaces again as the deviation between calculated and experimental mass becomes larger for the reason discussed above or due to the cationization of $K^+$ instead of $Na^+$. When two [G-4] dendrons are attached to PEG, the whole MALDI-TOF spectrum becomes a single broad peak (Figure 6d) with no individual peak resolution corresponding to oligomers.

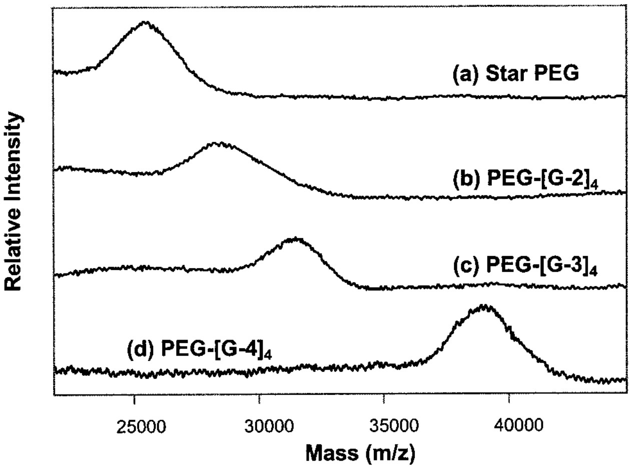


**Figure 8.** MALDI-TOF mass spectra of 4-arm star PEG and its copolymers.

Therefore, at the present time, and with the equipment available to us, end-group analysis by MALDI-TOF mass spectrometry is only successful with polymers of relatively low molecular weights for which fine resolution can be obtained.

The average molecular weights for the telechelic PEG and the triblock copolymers have been measured both by MALDI-TOF and by GPC, and the results are shown in Tables 2 and 3. The experimental and calculated results are in good agreement.

Figure 7 shows a 4-arm star PEG along with its three starlike hybrid copolymers, each containing four terminal dendrons. The molecular weight of the star PEG is quite high as shown in Figure 8a. Although the resolution of the MALDI-TOF-MS is less satisfactory for higher MW samples, a significant range of molecular weights is still measurable. The number- and weight-average molecular weights are derived from the whole peak area. The average molecular weights obtained from GPC measurements (see Table 3) underestimates the real molecular weights of star copolymers since they have rather globular structures. By comparing the mass shift and the shape of the series of peaks, it is concluded that four dendrons are covalently attached to the four ends of the star PEG. The highest mass measured for the star copolymers of this study reaches 43 000.

## Conclusion

MALDI-TOF mass spectrometry has been used to characterize PEGs and their block or starlike copolymers. Average molecular weights and polydispersities were obtained from the mass spectra. The results that show various polymers with molecular weights up to almost 40 000 can be accurately analyzed. End-group analysis has been performed on lower molecular weight polymers, and end-group functionality of PEG was determined. The experimental data agree well with the calculated values. The copolymer structures of PEG and dendrimers have been confirmed by MALDI-TOF measurements. MALDI-TOF mass spectrometry provides an efficient method for the characterization of polymer functionalization.

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