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Synthesis and Investigation of Novel Branched PEG-Based Soluble Polymer Supports

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Abstract: The efficient synthesis of a number of novel poly(ethylene glycol)-based branched soluble polymer supports with high loading capacities has been developed. These compounds are characterized and tested for their loading levels utilizing a number of coupling reactions.

Soluble polymer supports offer certain advantages over insoluble polymers in terms of ease of analysis and monitoring and, most importantly, the establishment of homogeneous conditions, which are most conducive to bimolecular processes.[1] Poly(ethylene glycol)s (PEGs) have been successfully used as polymer supports in the synthesis of oligopeptides,[2] oligosaccharides,[3] and oligonucleotides[4] since the 1970s, but the first small molecule assembly on a PEG was reported only in 1995.[5] Since then, interest in PEGs for soluble polymer support applications in combinatorial, general organic synthesis, and especially, medicinal chemistry[6] has seen an exponential growth. However, because each molecule of PEG possesses only two attachment sites, represented by the terminal OH groups, PEGs suffer from their inherent low loading capacities, and this considerable drawback limits their efficient use as soluble polymer supports. A number of attempts to increase the loading capacity of PEG through chemical modifications have been attempted.[7a,b] Among the most recent are PEGs with pendant end groups based on etherified 5-hydroxyisophthalic acid,[7c] and star polymers based on PEG and cyclotriphosphazine[7d] have been reported in order to increase the number of anchoring functional groups and thus the loading capacity. Although these compounds are versatile for general coupling and decoupling reactions, the preparation of such modified PEGs is not as efficient and cost-effective as those with dendrimeric end-groups or branches based on glycerol and pentaerythritol. Furthermore, as we required the use of such soluble supports in photochemical processes, the interfering chromophores associated with the aryl end groups can potentially complicate such reactions.

The attachment of dendrimeric units with multiple alcohol functionalities has been reported and used in various medical and engineering applications[8−15] and in combinatorial chemistry.[14,15] A variety of hybrid dendritic-linear polymers have been developed recently, based on the amide and ester linkages,[15,16] but these are not stable to acidic or basic conditions, which limits their use in many synthetic applications.

We have developed a variety of hybrid branched and dendrimeric PEG derivatives and other PEG-derivatized polymers based on glycerol, pentaerythritol, and pentaerythritol derivatives. Such structural modifications with saturated ether functions would make these dendrimers much more stable in both acids and bases and would not interfere with their use as support agents in photochemical reactions.[17] We report in this investigation a series of modified PEGs that exhibit significantly higher loading capacities relative to commercial PEGs.

One of the methods we used for structure identification of the modified polymers is MALDI-MS. Although this method does not always give quantitative results, it is useful in qualitatively assessing the extent to which structural modification has occurred.

Commercially available PEGs come as relatively pure[18] polydispersed mixtures, as readily revealed by the MALDI-MS. The spectrum reveals both molecular ions as well as those associated with dehydration (data available in Supporting Information). This dehydration is associated with the ionization method for spectrum acquisition and not with sample contamination, as evident in the ^{1}H NMR spectrum of the mixture by of the complete absence of olefinic proton signals.

Functionalization of commercial PEG is usually achieved starting with mesylation or tosylation of the terminal alcohol groups. Mesylation of PEG proceeded with high yields (>98%). The commonly used procedure was modified by using tripentylamine (TPA) in place of triethylamine (TEA). The use of larger amines is preferred[19] because the triethylamine hydrogen chloride byproduct

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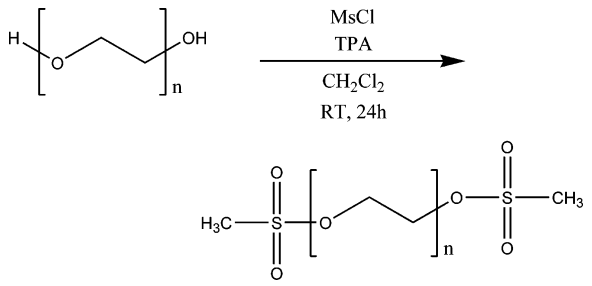


is difficult to separate from PEG dimesylate. Replacement of TEA with the much more lipophilic TPA provides an efficient solution to this problem, since TPA·HCl, unlike TEA·HCl, is soluble in diethyl ether, the common solvent used for precipitating PEGs.

Complete tosylation of PEG is more difficult to achieve and is usually done with pyridine under reflux.[20] However, two-phase tosylation of PEG using a water/NaOH/CH_2Cl_2 system proceeded much faster with quantitative yields.

The preparation of first and second generation modified PEGs based on glycerol followed a convergent approach as illustrated in Scheme 1.

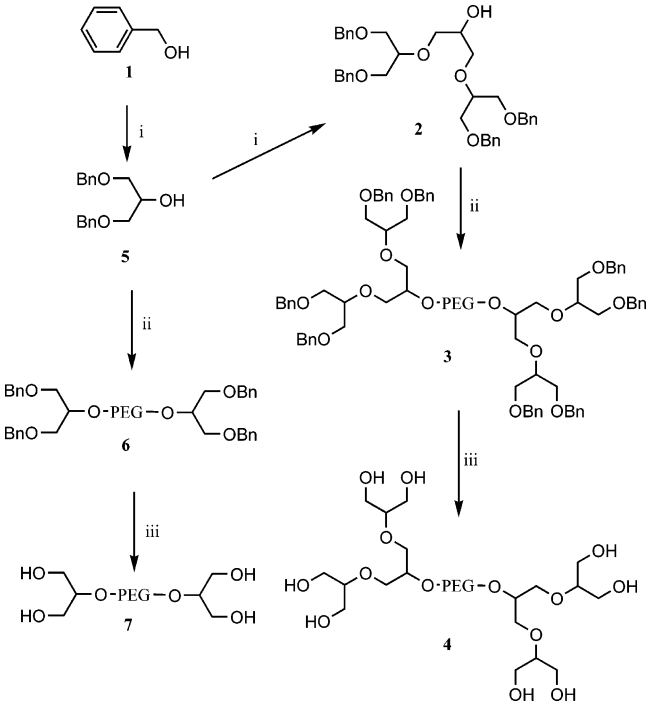
Benzyl alcohol (**1**) was sequentially reacted with epichlorohydrin via alcohol **5** to give 1,3-bis(1,3-*O*,*O*-dibenzyl-2-glyceroxy)-2-propanol[21] (**2**), which was purified by flash chromatography. Coupling of **2** with PEG gave **3**, which was deprotected with palladium(0) on carbon to give PEG_{3400}-$(OH)_8$ (**4**). PEG_{3400}-$(OH)_4$ (**7**) was prepared in a similar fashion by coupling 1,3-dibenzyl glycerol (**5**) with PEG and subsequent deprotection with palladium-(0). These reactions proceeded with high yields (88−92%), but lengthy purifications of **2** and **5** by flash chromatography made the large-scale synthesis of **4** and **7** not very practical. The theoretical loading capacity is increased from 0.58 mmol/g for commercial PEG_{3400}-$(OH)_2$ to 1.12 mmol/g for PEG_{3400}-$(OH)_4$ (**7**) and 2.07 mmol/g for PEG_{3400}-$(OH)_8$ (**4**), which is comparable to commercially available polystyrene- and PEG-cross-linked Merrifield and Wang resins (typical loading capacities of 0.5−1.5 mmol/g). The products were characterized by ^{1}H NMR and IR spectroscopy, as well as MALDI-MS.

To extend these modifications to include triply branched polymers, we were interested in incorporating pentaerythritol units to the termini of PEG. Two approaches were developed for coupling pentaerythritol to PEG. The first sequence (Scheme 2) was partially based on a synthetic protocol reported earlier by a French group, involving triallylation of pentaerythritol[22] (**8**) and subsequent coupling of the product with PEG dimesylate. However, this method is impractical if applied to a large-scale synthesis because the preparation of triallyl pentaerythritol (**9**) involves lengthy purification steps using high-temperature vacuum distillation and flash chromatography and, in addition, deallylation in the following step involves a costly palladium(0) reagent.

An alternative method involved direct coupling of pentaerythritol and PEG. This was initially complicated by the low solubility of pentaerythritol in nonaqueous solvents but was finally accomplished by heating to reflux the reagents in dry DMF for 24 h in the presence of tetrabutylammonium iodide. The possibility for the formation of the cross-linked polymerized product was minimized by the use of a large excess of pentaerythritol (about 10−12 equiv per hydroxyl group of PEG). The absence of the cross-linked product was confirmed by MALDI-MS. This method was found to be far superior to the one involving protecting group chemistry. It eliminates five reaction steps and dramatically improves the efficiency of the process. This approach enables efficient large-scale preparation of PEG-$(OH)_6$ (**11**), with overall yields approaching 90%. The theoretical loading capacity is increased from 0.58 mmol/g for PEG-$(OH)_2$ to 1.643 mmol/g for PEG-$(OH)_6$ (**11**).

These novel polymers were coupled to a number of substrates in order to evaluate their loading levels, and their products were analyzed by ^{1}H NMR spectroscopy, MALDI-MS, chlorine elemental analysis (for the chlorinated substrates), and acid-catalyzed methanolysis and recovery of substrate. The data are summarized in Table 1. For PEG-$(OH)_6$ (**11**), the loading levels, although higher than those for commercial PEG, were significantly lower than the corresponding theoretical loading capacities. The loading levels diminish significantly as the molecular size of the substrate is increased. This phenomenon can be attributed to a combination of steric hindrance due to proximity effects of the alcohol anchoring groups and intramolecular hydrogen bonding. To overcome this problem, a number of modified PEGs with spatially separated OH functions were prepared (Scheme 3).

SCHEME 1[a]



[a] Reagents and conditions: (i) NaH, epichlorohydrin, THF; (ii) (1) NaH, THF, (2) MsO-PEG-OMs; (iii) Pd/C, MeOH, HCOOH (17% of CH_3OH by weight).

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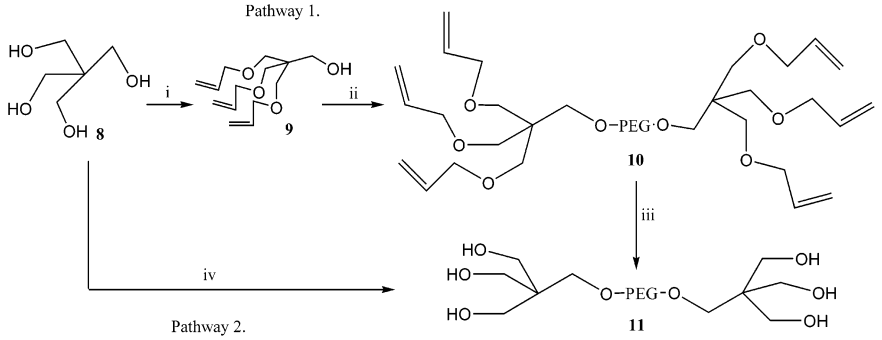
SCHEME 2[a]



[a] Reagents and conditions: (i) KOH, H_2O, CH_2CHCH_2Br; (ii) NaH, MsO-PEG-OMs; (iii) Pd/C, MeOH, HCOOH (17% in CH_3OH by weight); (iv) NaH, MsO-PEG-OMs, $(^tBu)_4NI$, DMF, ca. 130 °C, 48 h.

TABLE 1. Loading Levels for Commercial and Modified PEGs (mmol/g)[e]

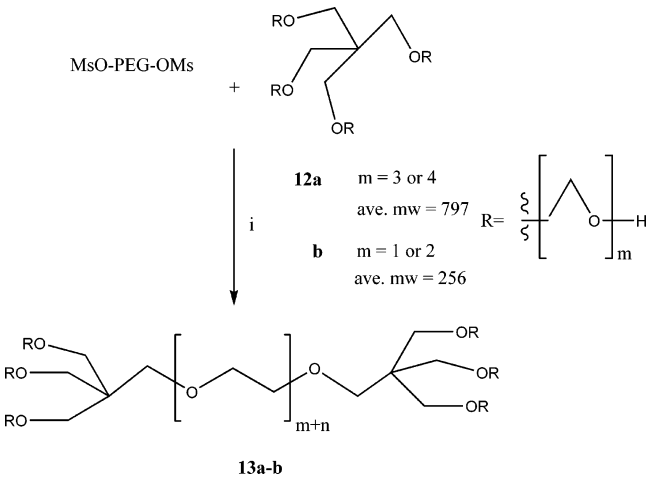
Polymer	Theoretical loading capacity	R= –S(=O)(=O)–CH3	–S(=O)(=O)–C6H4–CH3	–C(=O)–C6H5	–C(=O)–C6H3Cl2	–C(=O)–C10H7
PEG-(OH)$_2$	0.588	0.58 [a] 0.58 [b]	0.58 [a]	0.58 [a] 0.5 [c]	0.58 [a] 0.5-0.6 [b] 0.58 [d]	0.58 [a] 0.5-0.6 [b]
PEG-(OH)$_4$ (7)	1.122	1.10 [a]	1.02 [a]	1.03 [a] 0.9 [c]	1.01 [a] 1.0-1.1 [b*] 0.9 [d]	0.91 [a]
PEG-(OH)$_6$ (11)	1.643	1.37 [a]	1.24 [a]	1.40 [a] 1.2 [c]	1.29 [a] 0.9-1.3 [b*] 0.94 [d]	0.93 [a] 0.6-0.9 [b*]
PEG-(OH)$_8$ (4)	2.073	1.99 [a]	n/a	1.84 [a] 1.6 [c]	1.78 [a] 1.6 [c]	1.04 [a]
PEG-(PEE)$_2$ (13b)	1.534	1.33 [a]	1.18 [a]	1.21 [a]	1.10 [a]	0.86 [a]

[a] Determined by ^1H NMR integration, with backbone methylene hydrogens signals as internal standard. [b] Determined by MALDI-MS. (*) Some of the MALDI-MS data were difficult or impossible to interpret due to the appearance of several mass distributions appearing in the same spectrum [c] Determined by methanolysis cleavage and recovery of substrate. [d] Determined by chlorine elemental analysis. [e] Six equivalents of R-Cl used per OH group, THF, 48 h, room temperature. Variation of solvent polarity (from DMF to CH_2Cl_2) did not result in statistically significant changes in yields for the tabulated esterification reactions.

To increase the distance between the terminal alcohol groups, PEG was coupled to commercially available pentaerythritol ethoxylates (PEE) (**12a,b**) of differing molecular sizes (average molecular weights 797 and 256) (Scheme 3). The loading levels for the resulting polymers PEG-(PEE)$_2$ **13a,b** were evaluated (Table 1). As expected, the relative loading efficiencies (% of theoretical) for these polymers were among the highest of the supports tested. However, the synthesis of **13a** was difficult because of the complexity of separating PEG-(PEE)$_2$ (**13a**) from unreacted PEE (**12a**). The use of smaller, more water soluble pentaerythritol ethoxylates (**12b**) resolved this problem, allowing for their easy separation by extraction. The theoretical loading capacity was increased from 0.588 mmol/g for PEG-(OH)$_2$ to 1.206 mmol/g for PEG-(PEE)$_2$ (**13a**) and 1.534 mmol/g for PEG-(PEE)$_2$ (**13b**).

To further evaluate their efficiency in a small-molecule synthesis, compounds **7**, **11**, and **13b** were esterified to completion with benzoyl chloride and transesterified with sodium methoxide in methanol (24 h, reflux). Isolated methyl benzoate yields of 85%, 76%, and 84% based on theoretical loading capacities, respectively, were obtained, showing significant increases in efficiency when compared to the unmodified linear polymer.

SCHEME 3[a]



13a-b

[a] Reagents and conditions: (i) NaH, $(^tBu)_4NI$, DMF, ca. 130 °C, 48 h or excess PEE, NaH, ca. 120 °C, 48 h.

Coupling of MeO-PEG-OH of different molecular weights (2000 and 5000) with PEE_{256} under similar conditions yielded a product (MeO-PEG-PEE_{256}) with three alcohol functionalities.

The second generation dendrimer PEG-$(OH)_{18}$ was synthesized via mesylation of **13b** and subsequent coupling of the resulting PEG-$(OMs)_6$ with PEE_{256}. The resulting dendrimer was found not to be useful as a soluble polymer support because of its highly hygroscopic nature, which made it difficult to handle at ambient conditions.

As can be seen from the data in Table 1, the loading levels of these novel soluble polymer supports are significantly increased relative to commercial PEG. The physical and crystallization properties of the branched polymers described were typically very similar to those of the linear poly(ethylene glycol)s, allowing for easy crystallization from ether, filtering and handling. Compounds **11** and **13b** combine the optimal advantages of ease of preparation and increased loading capacity, and can find application in many reactions involving PEGs where low loading capacity is a limitation. The simplicity and low cost of preparation allows for the large-scale synthesis of a variety of dendrimeric poly(ethylene glycol)s with high loading capacities. The non-UV absorbing properties of these polymers also permit their potential use as soluble polymer supports in photochemical reactions as described in one example of a nucleoside synthesis.[17]

Experimental Section

The preparation of 1,3-bis(1,3-*O*,*O*-dibenzyl-2-glyceroxy)-2-propanoldibenzyl glycerol (**2**) and dibenzyl glycerol (**5**) were adopted from ref 21. Triallyl pentaerythritol (**9**) was prepared according to a procedure described in ref 22.

Mesylation of PEG. PEG_{3400} (5 g, 1.47 mmol) was dried under vacuum at 40 °C and then dissolved in dry CH_2Cl_2 (100 mL). Tripentylamine (2 g, 8.8 mmol) was added, and the mixture was cooled to 0 °C with stirring. Mesyl chloride (1.82 g, 14.7 mmol) was added slowly, and the mixture was stirred for 24 h at room temperature. The CH_2Cl_2 was than evaporated under reduced pressure. The dry brown residue was redissolved in a minimal amount of water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, and their volume was reduced by 95% under reduced pressure. The remaining CH_2Cl_2 was cooled to 0 °C, and 150 mL of anhydrous ether was slowly added with stirring. After 4 h, 5.04 g (96% yield) of white powder was recovered by filtration and washed twice with 25 mL of diethyl ether: ^{1}H NMR δ 4.40 (d, 4H), 3.83−3.47 (m, 308H), 3.10 (s, 6H); MALDI-MS M^+ peaks *m*/*z* 2726 to 4398.

Tosylation of PEG. To solution of 30% NaOH in water (10 mL) and 25 mL of CH_2Cl_2 (25 mL) was added PEG_{3400} (5 g, 1.47 mmol). To the vigorously stirred mixture was added dropwise a solution of 8 g (38.8 mmol) of tosyl choride in CH_2Cl_2 (20 mL) over 15 min. The organic layer was then separated and washed with water (2 × 10 mL). The volume of CH_2Cl_2 was reduced by 95% under reduced pressure. The remaining CH_2Cl_2 was cooled to 0 °C, and 150 mL of anhydrous ether was slowly added with stirring. After 4 h, 4.96 g (1.30 mmol, 96% yield) of white powder was recovered by filtration and washed twice with 25 mL of diethyl ether: ^{1}H NMR δ 7.81 (d, 12H), 7.12 (d, 12H), 4.40 (d, 4H), 3.83−3.47 (m, 308H); MALDI-MS M^+ peaks *m*/*z* 2878 to 4374.

General Coupling of PEG Dimesylate with Pentaerythritol and Pentaerythritol Ethoxylates. Pentaerythritol (5 g, 0.037 mol) and 0.25 g of ^{t}Bu_4NI were dissolved in 50 mL of dry DMF. NaH (2.00 g, 0.08 mol) was slowly added to the mixture, which was heated to reflux for 2 h. PEG dimesylate (8 g, 0.00225 mol) was added to the solution and refluxed for 48 h, after which DMF was evaporated under reduced pressure. The brown residue was redissolved in water (50 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The volume of CH_2Cl_2 was reduced by 95% under reduced pressure, and the product **11** was crystallized by slow addition of diethyl ether at 0 °C.

PEG-$(OH)_6$ (11): ^{1}H NMR δ 3.83−3.48 (m, methylene protons); MALDI-MS M^+ peaks from *m*/*z* 2718 to 4038, $M^+ - 18$ peaks from *m*/*z* 2700 to 4020.

PEG-$(OH)_6$ (13a): ^{1}H NMR δ 3.83−3.48 (m, methylene protons); MALDI-MS M^+ peaks from *m*/*z* 2982 to 4610, $M^+ - 18$ peaks from *m*/*z* 2964 to 4592.

PEG-$(OH)_6$ (13b)L ^{1}H NMR δ 3.83−3.48 (m, methylene protons); MALDI-MS M^+ peaks from *m*/*z* 4038 to 5666, $M^+ - 18$ peaks from *m*/*z* 4020 to 5648.

Typical Procedure for Coupling of 2, 5, and 9 To Give Corresponding PEG Complexes 3, 6, and 10, Respectively. Triallyl pentaerythritol (**9**) (2.15 g, 8.26 mmol) was dissolved in 100 mL of dry THF. To this solution was added 0.3 g (12.7 mmol) of NaH, and the resulting mixture was stirred for 30 min, after which 5 g of dimesyl PEG were added. The solution was refluxed for 24 h, and THF was evaporated under reduced pressure. The brown residue was redissolved in a minimal amount of water and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, and their volume was reduced by 95% under reduced pressure. The remaining CH_2Cl_2 was cooled to 0°, and 150 mL of dry diethyl ether was slowly added with stirring. White crystals were formed and filtered after 4 h: 4.2 g, 74.8% yield; ^{1}H NMR δ 5.94−5.84 (m, 6H), 5.26−5.11 (dd, 12H), 3.94−3.43 (m, 324H); MALDI-MS M^+ peaks *m*/*z* 3484 to 4320.

PEG-$(OBn)_4$ (6): ^{1}H NMR δ 7.33−7.38 (m, 20H), 4.55 (s, 8H), 3.83−3.43 (m, 318H); MALDI-MS M^+ peaks from 3254 to 4266.

PEG-$(OBn)_8$ (3): ^{1}H NMR δ 7.42−7.29 (m, 40H), 4.56 (s, 16 H), 3.94−4.12 (m, 2 H), 3.85−3.43 (m, 326 H); MALDI-MS M^+ peaks from 3690 to 5470.

Typical Procedure for Deprotection of 3, 6, and 10 to 4, 7 and 11, Respectively. A solution of 5 g of **10** in 150 mL of dry methanol was cooled to 0 °C, and 10% Pd (0) on activated carbon (0.41 g, 0.385 mmol) was slowly added to the mixture, followed by slow addition of formic acid (5 mL). The mixture was allowed to stir for 16 h, after which it was filtered. The methanol was evaporated, and the light yellow residue was dissolved in a minimal amount of water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, and their volume was reduced by 95% under reduced pressure. The remaining CH_2Cl_2 was cooled to 0°, and 150 mL of dry diethyl ether was slowly added with stirring.

PEG-$(OH)_8$ (4): ^{1}H NMR δ 4.02−4.06 (m, 2H), 3.83−3.48 (m, 326); MALDI-MS M^+ *m*/*z* 2794 to 4510, $M^+ - 18$ *m*/*z* 2776 to 4492.

PEG-$(OH)_4$ (7): ^{1}H NMR δ 3.76 (m, 4H), 3.72−3.58 (m, 312H), 3.52 (m, 4H); MALDI-MS M^+ *m*/*z* 2850 to 4390, $M^+ - 18$ peaks from *m*/*z* 2832 to 4372.

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Supporting Information Available: MALDI-MS of the PEG_{3400} and of the modified PEG-$(OH)_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

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