Postpolymerization Modifications of Poly(ethylene oxide) through C–H Functionalization: Embracing Functionality, Degradability, and Molecular Delivery

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ABSTRACT

This study presents a novel organocatalytic approach for direct modification of poly(ethylene oxide) (PEO) by attaching functional groups using C-H bond functionalization, yielding functionalized PEO with degradability and molecular delivery capabilities. Direct functionalization of PEO has been a challenging task due to the difficulty in finding versatile polymerization conditions that can accommodate various functional epoxides. The presented method overcomes these limitations and allows for a broad substrate scope including biologically active carboxylic acids such as ibuprofen and glycyrrhetinic acid. The modification process preserves the parent PEO structure throughout the highly reactive radical and oxocarbenium intermediate. The resulting functional PEO contains a degradable acetal unit, making it desirable for molecular delivery applications. Hydrolysis studies confirm the steady release of fragmented PEO and carboxylic acid. The drug-loaded PEO demonstrates cytoprotective activity in RAW264.7 cells stimulated with lipopolysaccharide (LPS). The hydrophobic drug moieties taken up by cells and released via the acid-triggered cleavage of acetal linkages in the acidic environment of endosomes. Crosslinked PEO is also demonstrated with a dicarboxylic acid, which loses its gel architecture upon contact with water. The presented method offers a versatile and efficient way to modify PEO, with potential applications in drug delivery and tissue engineering.
Introduction

Poly(ethylene oxide) (PEO)/poly(ethylene glycol) (PEG) is a synthetic polymer that is hydrophilic and has a wide range of applications in various fields, including energy harvesting devices, everyday consumables, and specialized medical treatments.\textsuperscript{1−4} Researchers have shown an interest in functionalized PEO that possesses both the desirable characteristics of PEO and functional molecules. For example, the attachment of biologically relevant molecules at the ends of PEG chains, known as PEGylation, has been used to impact medicines such as the recent COVID-19 vaccines.\textsuperscript{5−7}

Connecting functional molecules to PEO presents a synthetic challenge (Scheme 1).\textsuperscript{8−10} While copolymerization of ethylene oxide and functional epoxide has been pursued to introduce functionality on PEO chains (Scheme 1A), the inherent steric and electronic difference between unsubstituted ethylene oxide (EO) and substituted epoxide makes efficient copolymerizations difficult. Furthermore, finding versatile polymerization conditions that accommodate various functional epoxides has been challenging. Consequently, end-group modification of terminal hydroxy groups (PEGylation, Scheme 1B) has been predominantly employed. However, the installation of multiple functionalities is restricted due to the limited number of hydroxyl groups per chain. Moreover, the modification site is limited to the chain's end.
Scheme 1. General strategies for functionalized PEO synthesis.

Polymer functionalization through postpolymerization modification (PPM) is a promising route for rapid and efficient polymer modification.\textsuperscript{11–12} However, direct C–H bond functionalization of poly(ethylene oxide) (PEO) has been challenging and not extensively explored. Historically, C–H bonds have been regarded as inert and crucial for providing molecular stability. Nonetheless, recent advances in synthetic methodologies have enabled the
precise manipulation of C–H bonds with high efficiency and precision.\textsuperscript{13–14} Among hydrocarbons, the relatively weak C–H bond strength of ether units has led to the development of methods for activating and attaching various structures to ethereal C–H bonds.\textsuperscript{15–17} However, successful modification of polymeric ethers remains limited. Although some PEO PPMs have focused on direct oxidation to enhance degradability, only a few reports have been published. For instance, Reid and Elisseeff reported the incorporation of hydrolytically degradable hemiacetals into low molecular weight PEO templates using Fenton oxidation.\textsuperscript{18} Meanwhile, Bielawski and Liu demonstrated the direct conversion of poly(ethylene glycol) (PEG) to poly[(ethylene glycol)-co-(glycolic acid)] via RuO$_4$-mediated oxidation to form degradable ester groups.\textsuperscript{19} However, these methods had limitations in accommodating other functionalities. Parent and Wu reported PEO functionalization via a reactive radical formed by dicumyl peroxide, which was then trapped with an alkyne moiety to avoid undesirable chain-coupling or chain-scission.\textsuperscript{20} However, this report only demonstrated the functionalization of ethyl propionate. Recently, Zeng and coworkers developed a method for controllable C–H alkylation of polyethers using iron photocatalysis, leading to a successful versatile functionalization. The intermediate radicals generated under mild photocatalytic conditions coupled with electron deficient alkenes, while endured undesired degradations.\textsuperscript{21}

In this paper, we disclose a condition for the direct attachment of carboxylic acids to PEO. The fully organocatalytic system can accommodate a broad scope of structurally diverse aromatic and aliphatic carboxylic acids, including biologically active ones. The resulting functional PEO now features a degradable acetal unit. The chemical and biological study of degradation and molecular delivery successfully demonstrate the hydrolysis of the acetal unit, which yields short PEO fragments and a carboxylic acid, making it highly desirable for PEO-based drug delivery.
Results and Discussion

Among numerous examples of direct C–H functionalization of ethers, Wan's condition exhibited PEO functionalization with low backbone degradation and gelation.\textsuperscript{22} The method involves the formation of a C–O bond between ether and carboxylic acid using tert-butyl ammonium iodide (TBAI) and tert-butyl hydrogen peroxide (TBHP), and it demonstrates simple operation and a broad substrate scope, including acyclic ethers (Scheme 2). The proposed mechanism involves the formation of an oxocarbenium intermediate from radical generation and oxidation by the TBAI catalyst, followed by the attachment of a nucleophilic carboxylic acid to form the desired C–O bond. The method's fully organocatalytic feature makes it highly desirable for medicinal applications.

Scheme 2. Direct oxidative C–O bond formation of ethers by Wan and coworkers

The initial conditions for PEO modification involved the use of benzoic acid (0.5 mmol), PEO 6K (10 mmol based on repeat units), TBHP (1.0 mmol), and TBAI (0.1 mmol) in ethyl acetate (2 mL) at 80 °C (Table 1, entry 1). The reaction resulted in the quantitative attachment of benzoic acid to the PEO chain, indicating 5% functionalization of repeating units. However, the reaction also caused undesirable chain scissions from an intermediate radical or oxonium cation before they react with a nucleophilic carboxylic acid, resulting in decreased molecular weight and broadened dispersity of a number average molecular weight ($M_n$) of 3.6 kg/mol and dispersity ($D$) of 1.38. To balance activation and attachment rates, the TBHP
loadings were decreased in subsequent experiments. At TBHP = 0.7 equiv., the conversion rate was 79%, and the functionalization ratio was 3.9 mol% (entry 2). The crude mixture showed nominal dispersity broadening and good conversion ($M_n = 5.1$ kg/mol, $D = 1.23$). After dialysis in acetone, the purified functional PEO had a functionalization ratio of 3.3 mol%, $M_n = 5.5$ kg/mol, and $D = 1.29$ (entry 2-1). The conversion rates decreased to 49% and 15% at TBHP loadings of 0.5 and 0.25 equiv., respectively (entries 3 and 4). The $^1$H NMR and FT-IR spectra confirmed the successful introduction of the benzoyloxy group to PEO 6.0k (Figure 1). Aromatic proton peaks of 2:1:2 ratio (7.30 – 8.20 ppm, orange dot) and triplet acetal proton peak (6.25 ppm, red dot) in $^1$H-NMR and an ester vibration signal (1720 cm$^{-1}$) in FT-IR were placed with PEO signals.

The subsequent experiments involved examining various reagent ratios. Increasing the amount of benzoic acid hampered functionalization (21% conv., entry 5). Adding more TBAI catalyst had a slight impact, resulting in 83% conv. (0.20 equiv., entry 6) and 72% conv. (0.30 equiv., entry 7). Doubling all reagents except PEO decreased efficiency and increased chain deterioration (61% conv., $D = 1.36$, entry 8). The progress of the reaction was monitored over time (entries 2, 9, and 10). Both C–H functionalization and chain alteration proceeded consistently. Once benzoic acid was mostly consumed, chain damage became a significant process, leading to a broader chain length dispersity (92% conv., $D = 1.41$, entry 11).
Table 1. Optimization results with PEO 6K.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a  (mmol)</th>
<th>TBHP (mmol)</th>
<th>TBAI (mmol)</th>
<th>Time</th>
<th>Conv. (%)a</th>
<th>Portion of Functionalization (%)a</th>
<th>$M_n$ (kg/mol)b</th>
<th>$D^b$</th>
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<td>PEO 6 k</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>92</td>
<td>4.6</td>
<td>5.6</td>
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a. Determined using $^1$H NMR spectroscopy using CH$_2$Br$_2$ standard. b. Determined using size exclusion chromatography (SEC) with PEO standards in tetrahydrofuran (THF) at 40 °C.
Figure 1. $^1$H NMR and FT-IR of benzyloxylated PEO, Table 1, entry 2-1.
Table 2. Optimization results with PEO 20k

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzoic acid (mmol)</th>
<th>TBAI (mmol)</th>
<th>TBHP (mmol)</th>
<th>Time</th>
<th>Conv.</th>
<th>Portion of Substitution</th>
<th>Mn (kg/mol)</th>
<th>D&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>67</td>
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a. Determined using <sup>1</sup>H NMR spectroscopy using CH<sub>2</sub>Br<sub>2</sub> standard. b. Determined using size exclusion chromatography (SEC) with PEO standards in THF at 40 °C.

A series of experiments was conducted on a longer chain, PEO 20K (M<sub>n</sub> = 19.6 Kg/mol) (Table 2). The reactivity remained unchanged, but there was an enhancement in the degree of dispersity broadening. Although chain scission may have occurred at the same rate, it was more frequent per chain compared to PEO 6K. Under the same conditions as entry 2 of Table 1, a significant increase in dispersity was observed, resulting in a value of 1.42 (entry 1). However, by reducing TBHP to 0.5 equiv., a narrow dispersity was restored (entries 2 and 3), and the efficiency of PPM was improved by increasing TBAI (67%, entry 3).

Assorted carboxylic acids were used under optimized conditions of PEO 6K (entry 2, Table 1) and PEO 20K (entry 3, Table 2) to synthesize functionalized PEO. The measured properties of the isolated functionalized PEO are presented in Scheme 3. The conversion was calculated based on the theoretical maximum functionalization of repeat units (5%).
The change in the electronic nature of benzoic acid followed the proposed reaction mechanism. The key C–O bond formation occurs between the carboxylate anion and oxonium cation, and the nucleophilicity of carboxylate directly influenced the efficiency. Electron-withdrawing substitutions at the para position reduced reactivity. 4-Chloro-benzoic acid (1b) exhibited 46% conversion with PEO 6K (2b-6k) and 54% conversion with PEO 20K (2b-20k). Strong withdrawing 4-cyano-benzoic acid (1c) was only incorporated in 24% (PEO 6K, 2c-6k) and 30% (PEO 20K, 2c-20k). In contrast, a mild electron donation, such as the methyl group (1d), resulted in a similar conversion of 83% with PEO 6K (2d-6k) and 56% with PEO 20K (2d-20k). Other aromatic carboxylic acids reacted with similar efficiencies. Extended conjugation, such as 2-naphthoic (1e) and cinnamic (1f) acids, exhibited comparable reactivities to benzoic acid (2e and 2f). The introduction of a click moiety, azide group (1g), was successful, providing further opportunities for functionalization (2g). Electron-rich heterocycles reacted with mixed efficiency. 3-thiophenecarboxylic acid (1h) was attached to PEO with 68% (PEO 6K, 2h-6k) and 60% (PEO 20K, 2h-20k) conversions similar to benzoic acid. However, 2-furoic acid (1i) exhibited reduced attachment ratios of 24% (PEO 6K, 2i-6k) and 36% (PEO 20K, 2i-20k), respectively. Conversely, the electron-deficient 2-pyridine carboxylic acid (1j) displayed good efficiency at 62% (2j-6k) and 68% (2j-20k), respectively. Aliphatic acids were investigated, and primary palmitic acid (1k) was found to give good conversions of 94% (2k-6k) and 54% (2k-20k). Secondary cyclohexane carboxylic acid (1l) and tertiary 1-adamantane carboxylic acid (1m) showed comparable reactivity, indicating no significant steric effects. Finally, PEO with biologically active units were synthesized successfully with ibuprofen (1n) and glycyrrhetinic acid (1o). PEO-ibuprofen (2n) was obtained with good efficiency (77% with PEO 6K and 49% with PEO 20K). Glycyrrhetinic acid functionalized PEO exhibited similar incorporation ratio (71%, 2o-6k and 53%, 2o-20k).
Scheme 3. Scope of carboxylic acids

2a-6k  Conv. = 64%, x = 3.2 mol%  
Mₚ = 5.5 kg/mol D = 1.29

2b-6k  Conv. = 46%, x = 2.3 mol%  
Mₚ = 5.7 kg/mol D = 1.22

2c-6k  Conv. = 24%, x = 1.2 mol%  
Mₚ = 5.9 kg/mol D = 1.25

2a-20k Conv. = 58%, x = 2.9 mol%  
Mₚ = 14.7 kg/mol D = 1.27

2b-20k Conv. = 52%, x = 2.6 mol%  
Mₚ = 15.0 kg/mol D = 1.27

2c-20k Conv. = 30%, x = 1.5 mol%  
Mₚ = 11.8 kg/mol D = 1.68

2d-6k  Conv. = 86%, x = 4.3 mol%  
Mₚ = 5.6 kg/mol D = 1.25

2e-6k  Conv. = 64%, x = 3.2 mol%  
Mₚ = 5.6 kg/mol D = 1.26

2f-6k  Conv. = 68%, x = 3.4 mol%  
Mₚ = 5.6 kg/mol D = 1.29

2d-20k Conv. = 56%, x = 2.8 mol%  
Mₚ = 13.3 kg/mol D = 1.31

2e-20k Conv. = 58%, x = 2.9 mol%  
Mₚ = 14.5 kg/mol D = 1.28

2f-20k Conv. = 54%, x = 2.7 mol%  
Mₚ = 14.9 kg/mol D = 1.29

2g-6k  Conv. = 50%, x = 2.5 mol%  
Mₚ = 5.7 kg/mol D = 1.20

2h-6k  Conv. = 68%, x = 3.4 mol%  
Mₚ = 5.8 kg/mol D = 1.26

2i-6k  Conv. = 24%, x = 1.2 mol%  
Mₚ = 6.2 kg/mol D = 1.32

2g-20k Conv. = 62%, x = 3.1 mol%  
Mₚ = 16.6 kg/mol D = 1.20

2h-20k Conv. = 60%, x = 3.0 mol%  
Mₚ = 14.0 kg/mol D = 1.30

2i-20k Conv. = 36%, x = 1.8 mol%  
Mₚ = 18.9 kg/mol D = 1.13

2j-6k  Conv. = 62%, x = 3.1 mol%  
Mₚ = 4.7 kg/mol D = 1.41

2k-6k  Conv. = 94%, x = 4.7 mol%  
Mₚ = 4.3 kg/mol D = 1.29

2l-6k  Conv. = 88%, x = 4.4 mol%  
Mₚ = 4.9 kg/mol D = 1.26

2j-20k Conv. = 62%, x = 3.1 mol%  
Mₚ = 13.4 kg/mol D = 1.38

2k-20k Conv. = 54%, x = 2.7 mol%  
Mₚ = 10.7 kg/mol D = 1.43

2l-20k Conv. = 56%, x = 2.8 mol%  
Mₚ = 12.7 kg/mol D = 1.32

2m-6k  Conv. = 84%, x = 4.2 mol%  
Mₚ = 4.1 kg/mol D = 1.27

2n-6k  Conv. = 77%, x = 3.9 mol%  
Mₚ = 5.1 kg/mol D = 1.18

2o-6k  Conv. = 71%, x = 3.6 mol%  
Mₚ = 5.3 kg/mol D = 1.25

2m-20k Conv. = 56%, x = 2.8 mol%  
Mₚ = 9.7 kg/mol D = 1.43

2n-20k Conv. = 49%, x = 2.5 mol%  
Mₚ = 15.0 kg/mol D = 1.23

2o-20k Conv. = 53%, x = 2.7 mol%  
Mₚ = 13.7 kg/mol D = 1.39
The resulting functionalized PEO derivatives contain an $\alpha$-acyloxy ether linkage that is susceptible to hydrolysis, leading to the generation of fragmented PEO and the regeneration of a carboxylic acid (Scheme 4). Given PEO's extensive use in biomedical applications, its facile degradation and quick excretion from the body are highly desirable.\textsuperscript{23−24} Additionally, the modified PEO can serve as a delivery vehicle for hydrophobic carboxylic acid-based drug molecules.

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme4.png}
\end{center}

**Scheme 4.** Hydrolysis of functionalized PEO with $\alpha$-acyloxy ethers units

To validate this hypothesis, we tested the degradation of the modified PEO and the detection of carboxylic acid under hydrolysis conditions. Specifically, we placed benzoic acid-attached PEO ($M_n = 13.4$ kg/mol, 3.1 mol% benzoic esters) in D$_2$O and monitored the release of benzoic acid via $^1$H NMR spectroscopy (Figure 2). The resulting spectra of the functionalized PEO featured broad aromatic peaks (green dots) from the polymeric benzoates. However, the slow appearance of sharp peaks corresponding to benzoic acid (red dots) and the simultaneous disappearance of the broad aromatic peaks confirmed carboxylic acid release. Additionally, the hydrolysis of the PEO resulted in the formation of an aldehyde at the end of the PEO fragments. The triplet peak at 5.2 ppm (purple dot) corresponded to the acetal structure, which experienced a favorable shift to acetal of aliphatic aldehyde in water. A tiny singlet signal at 9.6 ppm (yellow dot) presented a minor equilibrium product, the aldehyde. Furthermore, the release of benzoic acid and the formation of PEO fragments led to an imminent reduction in molecular weight, which we monitored over time. The steady liberation of benzoic acid was observed from 39% at 24 h to 87% at 96 h, accompanied by a reduction in molecular weight.
from 13.4 kg/mol to 3.5 kg/mol at 24 h and 2.2 kg/mol at 96 h.

**Figure 2.** $^1$H NMR and molecular weight changes of benzyloxy-PEO in water.

We investigated the potential of modified polyethylene oxide (PEO) as a drug carrier for biologically active molecules such as ibuprofen and glycyrretinic acid. The cytoprotective activity of PEO-ibuprofen (2n-6k) and PEO-glycyrretinic acid (2o-6k) was evaluated using RAW264.7 cells that were stimulated with lipopolysaccharide (LPS) (Figure 3A). Our results showed that both 2n-6k and 2o-6k effectively reduced the LPS-mediated cytotoxicity in a concentration-dependent manner. Interestingly, the cytoprotective activity of 100 μg/mL of both polymers was comparable to those of the equivalent amount of ibuprofen (4.3 μg/mL) and glycyrretinic acid (12.7 μg/mL), indicating that the drugs were released from PEO in cells to exert their therapeutic actions.

To further substantiate the release of ibuprofen and glycyrretinic acid in the cellular environment, we subjected cells treated with 2o-6k and 2n-6k to mass spectroscopy (Figure
Our data showed that both drugs were detected in cells incubated with 2o-6k and 2n-6k for 10 hours, but at a lower concentration compared to those treated with free equivalent ibuprofen and glycyrrhetinic acid. The slower cellular uptake of polymeric 2o-6k and 2n-6k compared to their free counterparts was attributed to their hydrophilic nature and higher molecular weight. However, our results demonstrate that the hydrophobic drug moieties (ibuprofen or glycyrrhetinic acid) of 2o-6k and 2n-6k can be taken up by cells and released via the acid-triggered cleavage of acetal linkages in the acidic environment of endosomes, which are a nexus for endocytic pathways for foreign substances. Overall, these findings suggest that PEO-based drug carriers may have great potential for targeted drug delivery in various biomedical applications.

Figure 3. A) Evaluation of anti-inflammatory effect of drug-loaded PEOs, B) Detection of effect drugs in the cells.
Next, we explored the application of the PPM technique for synthesizing crosslinked PEO with degradability. We used dodecanedioic acid and performed PPM of PEO under identical conditions. The resulting product was a gel that was insoluble in acetone and water (as shown in Figure 4A). However, when the gel was treated with water, it gradually dissolved, and complete dissolution was achieved after 2 hours (as shown in Figure 4B). We are currently investigating the potential of this gel for use as a removable hydrogel patch and drug delivery.

![Chemical reaction and gel images](image)

**Figure 4.** Crosslinked-PEO via the PPM method and its degradability test.
Conclusion

In this paper, we present a novel post-polymerization modification strategy for the synthesis of highly functionalized PEO. Our approach utilizes a mild organocatalytic oxidative reaction pathway with carboxylic acids, which avoids unwanted PEO cleavage and allows for the attachment of a broad range of carboxylic acids, up to 5 mol% of repeat units. Unlike other methods, this approach does not impact the PEO structure, and the location of attachment is not limited to the end groups, thus enabling new types of applications. In our study, we demonstrated the potential of the modified PEO for drug delivery, as it contains an acetal unit that leads to steady hydrolysis and the release of carboxylic acids upon degradation in water. Our results suggest that this modified PEO has great potential for future use in drug delivery applications.

Supporting Information

General considerations, procedure, and $^1$H-NMR, SEC, FT-IR characterization data (PDF)

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Notes

The authors declare the following competing financial interest(s): Two patent applications KR1020210143769 and KR 1020230052300, submitted by the Jeonbuk National University.

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