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Efficient and Chemoselective Synthesis of ω,ω-Heterodifunctional Polymers

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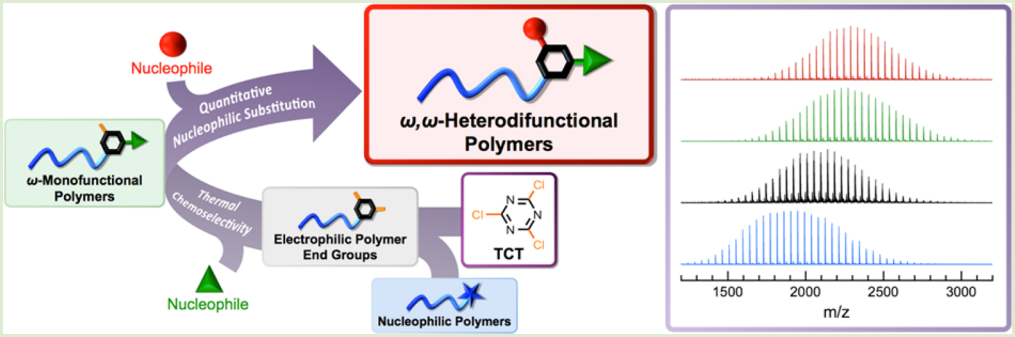
Supporting Information



ABSTRACT: We report a strategy for the preparation of semitelechelic polymers containing two distinct functionalities at one chain end by consecutive and chemoselective nucleophilic aromatic substitution reactions on 2,4,6-trichloro-1,3,5-triazine (TCT). Because of its commercial availability, well-defined nature, and ubiquity in biological applications, monomethyl ether poly(ethylene glycol) (mPEG) was chosen to demonstrate the utility of this ω,ω-heterodifunctional end-group modification strategy. TCT-functionalized mPEG underwent highly efficient ω,ω-heterodisubstitution via sequential chemoselective substitution with model thiols and amines. The efficiency of nucleophile conjugation to the polymer end group was confirmed by ^{1}H NMR spectroscopy and matrix assisted laser desorption-ionization time-of-flight mass spectrometry. In addition, density functional theory calculations provided insight into the importance of nucleophile addition order. This route introduces TCT derivatization as a powerful and facile tool to achieve specific polymeric end-group complexity and efficient heterogeneous functionalization.

Telechelic polymers allow access to a variety of macromolecular architectures (e.g., polymer−protein conjugates,[1] multiblock polymers,[2] and star polymers[3]) through polymer end-group functionalization.[4] Inefficient transformations on polymers can lead to functionally disperse mixtures of chains that are difficult to purify and demonstrate heterogeneous properties. Therefore, efficient postpolymerization modification techniques that provide near-quantitative yields, such as "click" chemistry and multicomponent reactions, have been exploited to obtain homogeneous polymers.[5−15] These modular and orthogonal reactions have become particularly prevalent in polymer end-group modifications, wherein their inherent efficiency circumvents the onerous purification processes often required during the synthesis of telechelic polymers.[16−22]

This report details our investigations in using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine (TCT)) as a convenient means to synthesize semitelechelic ω,ω-heterodifunctionalized polymers through the installation of two functional groups at the hydroxyl terminus of the commodity polymer monomethyl ether poly(ethylene glycol) (mPEG). TCT is frequently used as an organic synthesis building block to access complex molecular architectures due to its efficient reactivity with a variety of nucleophiles.[23] As the electrophilicity of TCT and its partially functionalized dichlorotriazine (DCT) and monochlorotriazine (MCT) analogues are markedly different, nucleophilic aromatic substitution of the three chlorine atoms on TCT generally requires higher temperatures and/or stronger nucleophiles for each consecutive step (Figure 1A). This differential reactivity is attributed to the increased electron delocalization in the aromatic ring after substitution of each electron-withdrawing substituent (i.e., chlorine) with electron-donating groups from the nucleophile residue. Consequently, we recognized that TCT's ability to undergo sequential nucleophilic aromatic substitutions provides an ideal strategy for synthesizing complex macromolecular architectures.

Simanek and co-workers have extensively exploited the chemoselective nature of TCT to minimize the number of functional group modifications and circumvent the protecting group chemistry typically required during dendrimer synthesis.[24−33] TCT has also been conjugated to polymer end

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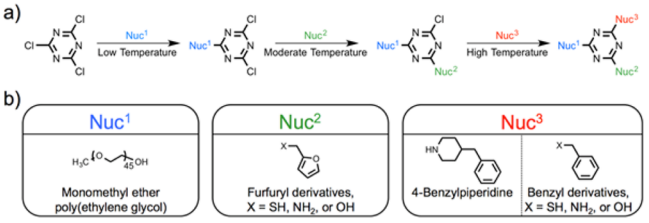


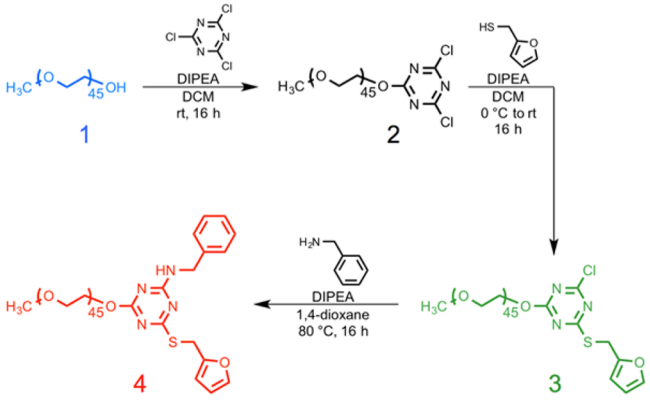
Figure 1. General approach to 2,4,6-trichloro-1,3,5-triazine (TCT) functionalization. (a) Varying temperatures allow chemoselective nucleophilic functionalization. (b) Model nucleophiles employed for sequential TCT functionalization.

groups, but relatively minimal characterization and/or incomplete consumption of its reactive sites has hindered its widespread applicability.[34−37] However, other synthetic approaches toward the end-group functionalization of mPEG have received considerable attention, primarily due to mPEG's important role in providing hydrophilicity and biocompatibility in a variety of biomedical applications.[38−40] Given that mPEG contains no sites amenable to functionalization along its backbone, efficient end-group derivatization is critical for preparing the polymers needed for many of these applications. Traditional routes for mPEG end-group modification can require tedious multistep syntheses and typically install only one reactive site per chain end.[41−44] Additionally, there are few reports on the efficient ω,ω-heterodifunctionalization of mPEG.[45−47]

Therefore, we sought to establish a straightforward and methodical TCT conjugation approach to construct ω,ω-heterodifunctional mPEG while generally investigating TCT functionalization more broadly as a powerful route to achieving specific polymeric end-group complexity. Herein, we report the efficient transformation of commercially available mPEG to ω,ω-heterodifunctionalized mPEG conjugates by chemoselective reactions with model thiol, amine, and alcohol nucleophiles (Figure 1b). The reaction conditions we identified resulted in the desired selective nucleophilic substitutions and avoided the variety of possible byproducts that could result from over/under consumption of reactive sites during each consecutive step (Figure S1). In all cases, end-group functionalization was confirmed via ^{1}H NMR spectroscopy and matrix assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-ToF MS). Moreover, using density functional theory (DFT) calculations, electrostatic potential maps were constructed to provide insight into the electronic structure and differential reactivity of the triazine ring of TCT and DCT.

Amines are commonly used for TCT functionalization due to their high nucleophilicity and the resulting delocalization of the amine lone pair electrons after substitution. Previous model nucleophile/TCT reactivity studies have suggested that the reaction of a primary amine followed by a more reactive cyclic secondary amine can result in quantitative, consecutive nucleophilic substitutions.[24] However, we sought to investigate the potential of using TCT as a facile strategy to orthogonally and efficiently install two functional groups on a hydroxyl-terminated polymer (i.e., the ω-terminus of 2000 g/mol mPEG). When mPEG (**1**) was treated with 2.5 equiv of TCT at room temperature for 16 h, the hydroxyl group was quantitatively transformed to the DCT derivative (i.e., 2-mPEG-4,6-dichloro-1,3,5-triazine (**2**)) (Scheme 1). Product conversion of **1** to **2** was monitored using ^{1}H NMR spectroscopy by the appearance of peaks attributed to the

Scheme 1. Nucleophilic Substitutions to 2,4,6-Trichloro-1,3,5-triazine Using *N,N*-Diisopropylethylamine (DIPEA), Yielding an ω,ω-Heterodifunctional Monomethyl Ether Poly(ethylene glycol) Conjugate



$-CH_2-O-$triazine protons at δ = 4.65 ppm as shown in Figure 2. To investigate the nucleophilic scope of this approach for

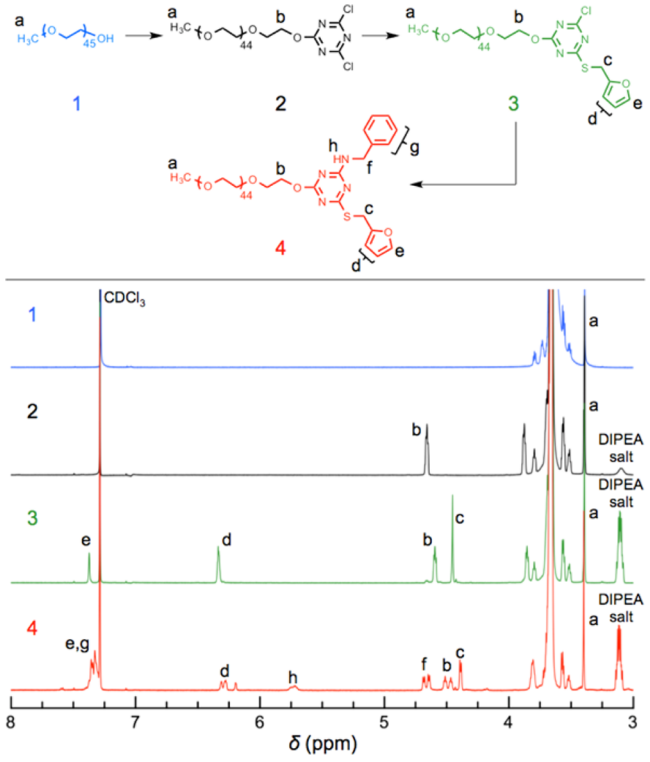


Figure 2. ^{1}H NMR spectra of monomethyl ether poly(ethylene glycol) (**1**, blue) and its derivatives after reaction with 2,4,6-trichloro-1,3,5-triazine (**2**, black), 2-furylmethanethiol (**3**, green), and 1-phenylmethanamine (**4**, red).

mPEG functionalization, model thiol, amine, and alcohol nucleophiles were reacted with the DCT-mPEG derivative (**2**) and various MCT derivatives (Table 1).

The second nucleophilic substitution on the DCT ring of **2** with the model thiol 2-furylmethanethiol required a temperature where efficient conversion to 2-mPEG-4-(2-furylmethanethiol)-6-chloro-1,3,5-triazine (**3**) could be achieved without under or over consumption of the nucleophile. We observed that when a solution of **2** in dichloromethane (DCM) was

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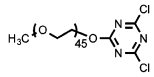
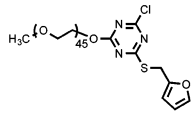
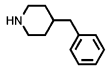
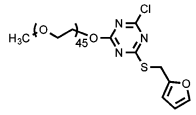
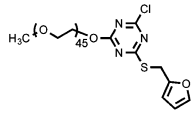
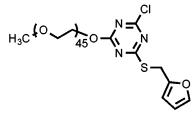
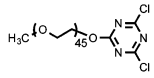
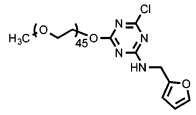
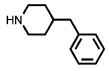
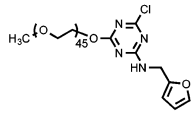
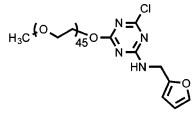
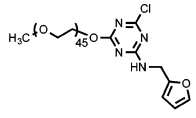
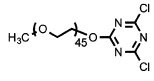
Table 1. Nucleophilic Aromatic Substitution Conversions on Monomethyl Ether Poly(ethylene glycol) Triazine-Based End Groups Using Thiol, Amine, and Alcohol Nucleophiles

Entry	Electrophile	Nucleophile	Temp. (°C)	Conv.[a] (%)
1			0 – 25[b]	>95
2			80	>95
3			80	16
4			80	92
5			80	<5
6			0 – 25[b]	>95
7			80	>95
8			80	24
9			80	>95
10			80	<5
11			100	8

[a]After 16 h using 1.0 equiv of nucleophile to polymer, conversion determined by ^{1}H NMR spectroscopy. [b]Reactions held at 0 °C for 3 h, then warmed to 25 °C and stirred for 13 h.

treated with 1.00 equiv of 2-furylmethanethiol at 0 °C for 3 h, and allowed to stir at room temperature for another 13 h near-quantitative substitution of the second chlorine with the thiol occurred. Conversion was determined using ^{1}H NMR spectroscopy by observing the appearance of peaks at δ = 4.45 ppm, attributed to the furfuryl methylene protons, and δ = 6.43 and 7.34 ppm, attributed to the aromatic furyl protons. For the final substitution on the MCT, 1.00 equiv of 1-phenylmethanamine was added to **3** and allowed to react at 80 °C for 16 h to achieve 2-mPEG-4-(2-furylmethanethiol)-6-(1-phenylmethanamine)-1,3,5-triazine (**4**). ^{1}H NMR spectroscopy of the products indicated a conversion of 92%, as evidenced by the appearance of new peaks attributed to the benzyl methylene protons at δ = 4.63−4.67 ppm and the aromatic phenyl protons at δ = 7.29−7.38 ppm. Notably, the proton signals of the mPEG conjugate **4** suggested the presence of conformational isomers, which can likely be attributed to restricted nitrogen−triazine bond rotation due to partial double bond character.[48] The presence of conformational isomers, which was also observed for other amine−TCT adducts (SI), further supports the stabilizing effect of nitrogen's considerable electron delocalization into the triazine ring.

Although ^{1}H NMR spectroscopy showed the successful functionalization of the mPEG conjugate **2** with 2-furylmethanethiol and 1-phenylmethanamine, these data alone did not provide insight into the exact end-group composition. Therefore, MALDI-ToF MS was used to confirm that predominantly ω,ω-heterodifunctionalized mPEG was present (Figure 3). The MALDI-ToF MS spectrum of **2** showed a main distribution attributed to the **2** + Na^+ adduct with an increased mass of 146.9 g/mol, which was corroborated using isotope prediction calculations (SI). Minor distributions of **2** + K^+ and an unidentifiable ionization degradation product were also visible. Single addition of 2-furylmethanethiol was confirmed via a mass increase of 77.99 g/mol, a major **3** + Na^+ distribution, and a minor **3** + K^+ distribution. Addition of 1-phenylmethanamine resulted in a mass increase of 71.10 g/mol with major **4** + Na^+ and minor **4** + K^+ distributions visible, confirming mPEG ω,ω-heterodifunctionalization. Importantly, no residual byproducts from inefficient nucleophilic substitution were observed during the MALDI-ToF MS characterization.

Throughout our studies, we realized the importance of considering the order in which different nucleophiles were added to the triazine ring. To elucidate the effect of triazine electronics during different nucleophile additions, DFT calculations using analogous amine, alcohol, and thiol substituents were performed on model DCT and MCT compounds (Figure 4, B3LYP 6-311+G** basis set). The electrostatic potential maps revealed that upon substitution of the first chlorine on TCT with an alcohol nucleophile (i.e., mPEG, Figure 4a) the resulting DCT remains relatively electron deficient because of the high electronegativity of oxygen. This observation is consistent with the low temperatures required to conjugate thiol (Table 1, entry 1) and amine (Table 1, entry 6) nucleophiles to **2** (i.e., a DCT compound).

Although a thiol nucleophile reacted near quantitatively with **2**, subsequent addition of another thiol to the resulting MCT was inefficient (Table 1, entry 3), despite the relatively low electron density levels on the triazine ring observed in the electrostatic potential maps for the analogous model MCT with oxygen and sulfur substituents (Figure 4b). Therefore, even though sulfur has a relatively low electronegativity, its larger size likely limits orbital overlap and π-orbital delocalization within the triazine ring, resulting in an electron-deficient MCT that was deactivated toward the addition of thiols as a third nucleophile.

Conjugating two amine nucleophiles to **2** required the same experimental reaction conditions as shown in Scheme 1, where each nucleophilic aromatic substitution resulted in >95% conversion, as determined by ^{1}H NMR spectroscopy (Table 1, entries 7 and 9). MALDI-ToF MS further confirmed the singular presence of the MCT−mPEG intermediate and ω,ω-heterodifunctionalized mPEG products (SI). The electrostatic potential map of a model MCT compound containing oxygen and nitrogen substituents showed increased electron density within the ring, suggesting significant π-orbital delocalization of

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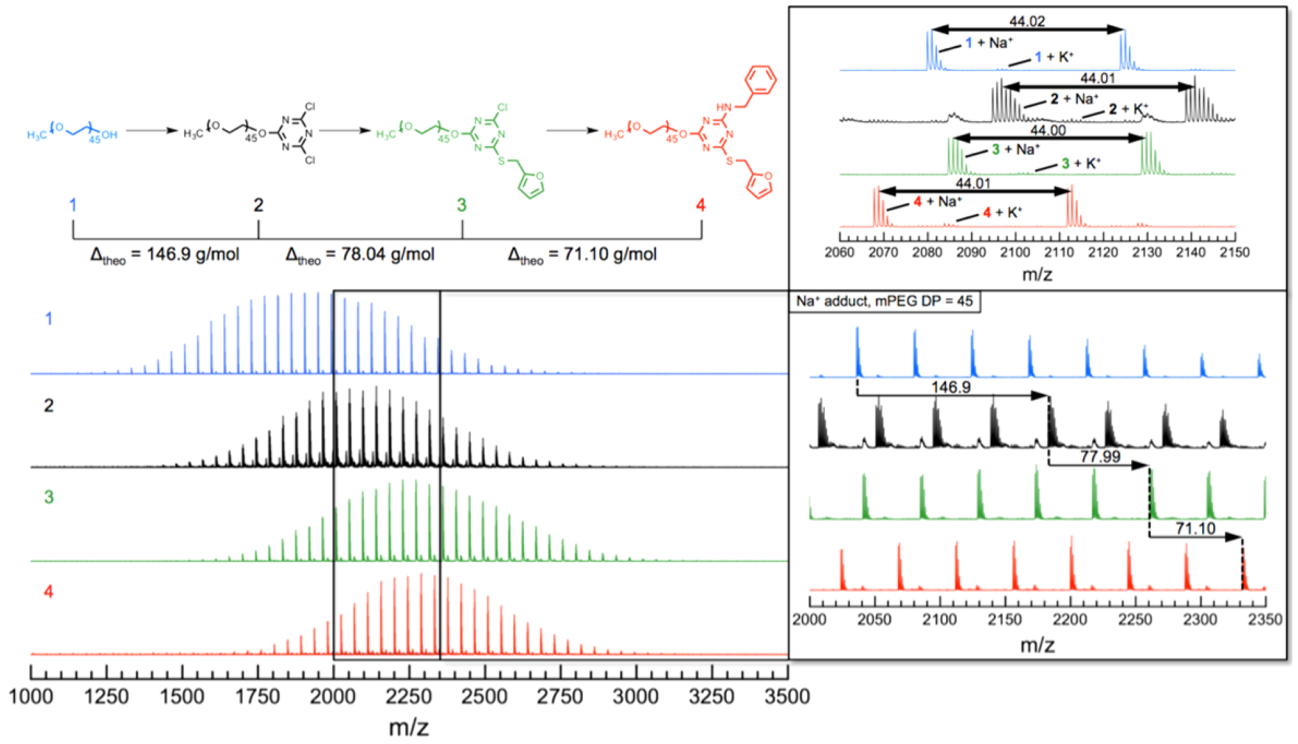

Figure 3. Matrix assisted laser desorption-ionization time-of-flight mass spectra confirming the ω,ω-heterodifunctionalization of monomethyl ether poly(ethylene glycol) via incorporation of 2,4,6-trichloro-1,3,5-triazine and subsequent reactions with model nucleophiles.

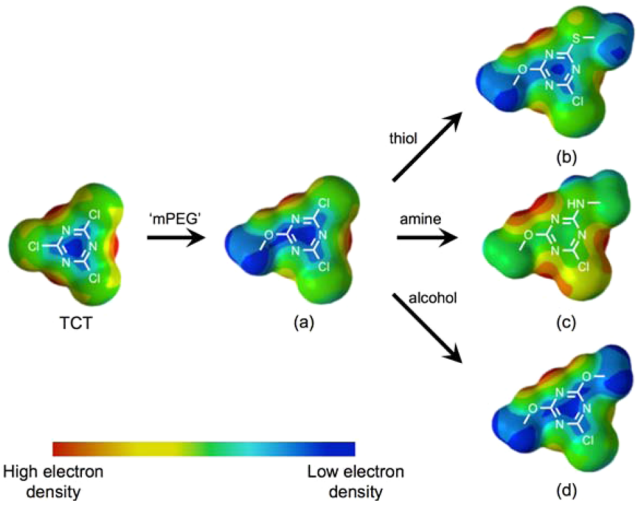

Figure 4. Electrostatic potential maps from density functional theory calculations of 2,4,6-trichloro-1,3,5-triazine (TCT) substituted with (a) a model alcohol (i.e., an analogue of monomethyl ether poly(ethylene glycol) (mPEG)), followed by model (b) thiol, (c) amine, and (d) alcohol substituents (B3LYP 6-311+G** basis set).

the nitrogen substituent (Figure 4c). The stabilization that results from nitrogen substituents may deactivate the MCT-mPEG adducts toward addition of poorly stabilizing nucleophiles, such as thiols (e.g., phenylmethanethiol, Table 1, entry 8), while allowing amine nucleophiles to be good third nucleophiles regardless of the second nucleophile (Table 1, entries 2, 4, 7, and 9).

We were unable to conjugate additional alcohol nucleophiles to any triazine product that resulted after the initial TCT–mPEG conjugation (Table 1, entries 5, 10, and 11). The electrostatic potential map for a model MCT compound with two oxygen substituents suggests a highly electron-deficient triazine ring would result in this case. The electronic deficiency is believed to be from the high electronegativity of oxygen, which results in low π-orbital delocalization and high σ-bond electron withdrawal. Therefore, the electronic instability of the triazine ring that would result after substituting two chlorines with two alcohol nucleophiles appears too high to overcome during mPEG functionalizations.

These experimental and theoretical results provide insight into a preferred nucleophilic substitution order for TCT. Namely, to ensure efficient functionalization, the order of substitution should be (1) alcohol, (2) thiol, and (3) amine when these three different nucleophiles are required for polymer end-group functionalization. It should be emphasized that these experiments were conducted using a 1:1 ratio of nucleophile to the DCT–mPEG conjugate and that manipulating stoichiometry of less active nucleophiles would presumably lead to increased conversions of nucleophilic substitution reactions.

In summary, hydroxyl-terminated polymers were shown to be successfully ω,ω-heterodifunctionalized employing the readily available compound TCT. Given the wide variety of available nucleophiles and established utilization of mPEG in numerous biological applications (e.g., protein conjugation), end-group modification using TCT provides unprecedented access to semitelechelic heterodifunctional architectures. Moreover, the facile ability of TCT to undergo sequential nucleophilic aromatic substitution reactions suggests it is a promising and versatile tool for polymer functionalization with applications well beyond the synthesis of (semi)telechelic polymers, specifically in the areas of macromolecular design and materials synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and supporting figures (PDF)

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Notes

The authors declare no competing financial interest.

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