Transetherification on Polyols by Intra- and Intermolecular Nucleophilic Substitutions

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Abstract
Transetherification on polyols involving intra- and intermolecular nucleophilic substitutions is reported. Di- or trialkoxide formation of propane-1,3-diol or 2-(hydroxymethyl)propane-1,3-diol derivatives by NaH triggers the reaction via oxetanes formation, where the order to add NaH and a polyol significantly influences the yields of products. It was demonstrated that the protective group on the pentaerythritol skeleton is apparently transferred to the hydrophilic and hydrophobic chain molecules bearing a leaving group in one-step, and a protective group conversion from tosyl to benzyl was successful using a benzyl-appending trial to afford a desired product in 67% yield.

Introduction
An ether synthesis is one of key reactions in preparation of materials including long hydrophilic or hydrophobic tails [1–10]. Usually, an alkoxy anion, generated by the hydrogen abstraction from an alcohol with a strong base, reacts with the target long chain molecule bearing a leaving group, like tosyl and halide moieties. This methodology is also applicable for preparation of branched molecules bearing multiple chains like dendrimers, amphiphiles, or liquid crystalline molecules, where a polyol, such as pentaerythritol, provides one of the fundamental skeletons to construct such branched structures [11–22]. Transetherification is also a useful reaction for the ether synthesis to develop functional molecules and hyperbranched polymers [23–32]. However, transetherification can also be an adverse side reaction in a multi-step reaction scheme [33–35]. Here we report our serendipitous discovery of transetherification, which proceeds by intra- and intermolecular nucleophilic substitutions starting from protected pentaerythritols coupled with chain molecules bearing a leaving group. This reaction scheme would offer a possible route for preparation of ethers and also predict a side reaction in the synthesis of branched compounds.

Results and Discussion
In our research project to develop structured poly(ethylene glycols) [36], we tried Williamson ether synthesis [37] between a propane-1,3-diol derivative 1 and a tosylate 2a with NaH in tetrahydrofuran (THF; Figure 1, Table 1, Entry 1). Initially 1 was mixed with NaH in anhydrous THF, and the mixture was heated under reflux for generation of the alkoxide. The resulting mixture gave a deep red solution, where 2a was added at 0°C (Procedure A). Actually, this reaction afforded the expected product 3a in 13% yield. Meanwhile, 4a (21% yield) was unexpectedly obtained as the major product with a comparable amount of 5a (12%). Apparently, transetherification of benzyl and trisopropylsilyl (TIPS) groups of 1 to 2a took place by substitution with the tosyl group, together with the formation of the ether linkage at the hydroxy group of 1 to give 3a. A product due to one-to-one coupling between 1 and 2a was not detected. Such unexpected products were obtained not only with the oligoethylene glycol tosylate, but also with tosylate 2b having a hydrophobic alkyl chain, where the reaction under similar condition resulted in the formation of 4b and 5b in 21% and 6% yield, respectively, in addition to 3b (Table 1, Entry 2).

Here, it is of importance that, the MALDI-TOF-MS spectrum of the crude product with γ-cyano-4-hydroxycinnamic acid as a matrix (Figure 2), extracted with CHCl3 from the reaction mixture (Table 1, Entry 1), shows molecular ion peaks corresponding to oxetane derivatives 6 and 7 (Figure 3) (Calcd for C12H15KNaO3: 269.0556, C12H15Na2O3: 253.0817, C12H15O3: 231.0997, (7+Na)7, C12H15Na3O3Si: 269.0536, 297.1862, (7+Na+K – H)5), C12H15NaO3Si: 297.1862, C12H15KO3Si: 313.1601, (6+K)7). The MALDI-TOF-MS spectrum of the crude product with gentisic acid as a matrix also showed molecular ion peaks corresponding to oxetane derivatives 6 and 7 (Found: 231.616 ([7+Na]7), 253.397 ([7+2Na – H]7), 269.390 ([7+Na+K – H]5), 297.097 ([6+Na]7), and C12H15KO3Si: 313.1601 ([6+K]7)).

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This likely accompanies the formation of nucleophilic benzyloxy or siloxy anions, which finally react with 2a to yield 4a or 5a, respectively.

Noteworthy here is that the order of the addition of reagents, namely that of NaH, 2a and 1, significantly influenced on the yields of the products. When NaH was added to the mixture of 1 and 2a, followed by refluxing (Procedure B), 3a was obtained in 93% yield, while the formation of 4a and 5a was negligible (Table 1, Entry 3). Under this condition, the reaction mixture remained colorless, unlike Procedure A, indicating formation of monokoxide of 1. Furthermore, when the reaction was carried out with a half concentration of 1, 2 and NaH in Procedure A (Table 1, Entry 4), the yield of 3a was increased (37%), while yields of 4a and 5a were decreased (10% and 9% yield, respectively). The dilute condition is likely favorable for the formation of the monokoxide of 1. Hence, these results suggest that the suppression of dialkoxide formation from 1 would be advantageous for the formation of 3a, while being disadvantageous for the formation of 4a and 5a. Indeed, a reaction between monoalcohol 8 and 2a with NaH, following Procedure A, afforded 9 in 34% yield, while 4a, 5a, and 10 were not detected (Figure 4a). Thus, the intra- and intermolecular nucleophilic substitutions to prompt the transetherification are likely triggered by a dianion formation from 1.

A tosyl group functions as a protecting group for alcohols [38,39]. Hence, this transetherification can be regarded as a one-step method to convert the protecting group from tosyl to another such as benzyl or TIPS. To demonstrate the protecting group conversion from tosyl to benzyl, 2,2-bis(benzyloxy)methylpropane-1,3-diol 11 and 2-(benzyloxy)methyl-2-(hydroxymethyl)propane-1,3-diol 13 were reacted with tosylate 2a (Figures 4b and 4c). A reaction between 11 and 2a with NaH in THF following Procedure A afforded 4a in 27% yield with the formation of 12 in 6% yield. Importantly, a reaction between 13 and 2a resulted in the formation of 4a in much higher yield (67%), with a trace amount of 14. Products due to one-to-one and one-to-two coupling between 13 and 2a were not detected. The neighboring three hydroxy groups in 13 are likely advantageous for the formation of dialkoxide or trialkoxide to encourage the transetherification. Thus, the triol 13 is a useful reagent for the protecting group transfer to the tosyl group through the transetherification by intra- and intermolecular nucleophilic substitutions.

**Figure 1. Ether formation between 1 and 2.**
doi:10.1371/journal.pone.0091912.g001

**Table 1. Ether formation between 1 and 2.**

| Entry | R     | Procedure | [1] (mM) | [2] (mM) | Yields (% vs. 1) |
|-------|-------|-----------|----------|----------|-----------------|
| 1     | R-a   | A         | 32.5     | 65.0     | 13 21 12        |
| 2     | R-b   | A         | 32.5     | 65.0     | 33 21 6         |
| 3     | R-a   | B         | 32.5     | 65.0     | 93 2 1          |
| 4     | R-a   | A         | 16.5     | 33.0     | 37 10 9         |

*a)*Reaction conditions: 30 mL THF, 0.972 mmol 1, 1.94 mmol 2, 9.72 mmol NaH; reflux (ca. 339 K); reaction time: 12 h. *b)*Reaction conditions: 30 mL THF, 0.486 mmol 1, 0.972 mmol 2, 4.86 mmol NaH; reflux (ca. 339 K); reaction time: 12 h. *c)*Isolated yields.

doi:10.1371/journal.pone.0091912.t001

**Figure 2. MALDI-TOF-MS spectrum of the crude product extracted by CHCl₃ for the reaction in Table 1, Entry 1.**

Structures of 6 and 7 are shown in Figure 3. Matrix: α-cyano-4-hydroxycinnamic acid.
doi:10.1371/journal.pone.0091912.g002
In this work, transetherification of polyols involving intra- and intermolecular reactions was reported. It is strongly likely that the di- or trialkoxide formation triggers the transetherification. These results are considered not only to lead to new synthetic routes for preparing ethers and branched compounds, but also to be useful to avoid adverse side reactions related to Williamson ether synthesis \[40-44\]. Using this reaction, one-step transfer of a hydroxy-protecting group from benzyl to tosyl was also successfully demonstrated.

**Experimental Part**

**General**
Column chromatography: with silica gel (SiO\(_2\); 63–210 \(\mu\m\); Kanto Chemical). \(^1\)H-NMR spectra: Bruker BioSpin AVANCE III 400 and BioSpin AVANCE III 500 FT-NMR spectrometers; in CDCl\(_3\); \(\delta\) in ppm rel. to Me\(_4\)Si as an internal standard, \(J\) in Hz.

**Ether Formation**

**Procedure A:** A mixture of \(1\) (0.372 g, 0.972 mmol) and NaH (0.233 g, 9.72 mmol) in anhydrous THF (15 mL) was refluxed (about 339 K) under Ar for 30 min in the dark, where the reaction mixture turned into deep red from a colorless suspension. After the mixture was cooled to 273 K, an anhydrous THF solution (15 mL) of \(2a\) (0.911 g, 1.94 mmol) was added dropwise to the resulting mixture. After the reaction mixture was refluxed for 12 h in the dark, water (50 mL) was added to the resulting mixture at 0°C, and organic components were extracted with CHCl\(_3\) (3×50 mL). The organic extract was dried over Na\(_2\)SO\(_4\) and filtered off from insoluble substances. The filtrate was evaporated to dryness under reduced pressure at 313 K, and the residue was purified by column chromatography (EtOAc/hexanes/MeOH 90:10:0 to 100:0:0 to 90:0:10) to afford \(1\) (recovered, 0.134 g, 0.350 mmol, 36%), \(3a\) (0.123 g, 0.126 mmol, 13%), \(4a\) (0.083 g, 0.204 mmol, 21%), and \(5a\) (0.055 g, 0.117 mmol, 12%).

**Procedure B:** To an anhydrous THF (30 mL) solution of \(1\) (0.371 g, 0.972 mmol) and \(2a\) (0.909 g, 1.94 mmol) was added NaH (0.234 g, 9.72 mmol) at 0°C under Ar. After the reaction mixture was refluxed (about 339 K) for 12 h in the dark, water (50 mL) was added to the resulting mixture at 273 K, and organic components were extracted with CHCl\(_3\) (3×50 mL). The organic extract was dried over Na\(_2\)SO\(_4\) and filtered off from insoluble substances. The filtrate was evaporated to dryness under reduced pressure at 313 K, and the residue was purified by column chromatography (EtOAc/hexanes/MeOH 90:10:0 to 100:0:0 to 90:0:10) to afford \(1\) (recovered, 0.007 g, 2%), \(3a\) (0.882 g, 0.904 mmol, 93%), \(4a\) (0.008 g, 0.019 mmol, 2%), and \(5a\) (0.005 g, 0.0097 mmol, 1%).

For characterization of \(1\), \(2a\), \(3a\), \(8\) and \(13\), see \[36\].

**Data of \(2b\):** \(^1\)H-NMR: 1.21–1.35 (\(\delta\), 14H); 1.56–1.64 (\(\delta\), 4H); 2.45 (\(\delta\), 3H); 3.43 (\(\delta\), \(J\) = 6.5, 2H); 3.80 (\(\delta\), 3H); 4.02 (\(\delta\), \(J\) = 6.5, 2H); 4.43 (\(\delta\), 2H); 6.88 (\(\delta\), \(J\) = 8.0, 2H); 7.27 (\(\delta\), \(J\) = 7.0, 2H); 7.34 (\(\delta\), \(J\) = 8.0, 2H); 7.79 (\(\delta\), \(J\) = 7.0, 2H). MALDI-TOF-MS: 485.30 ([M+Na]+, C\(_{26}\)H\(_{38}\)NaO\(_5\)S\(_2\); calc. 485.23).

**Data of \(3b\):** \(^1\)H-NMR: 1.02–1.08 (\(\delta\), 18H); 1.26–1.35 (\(\delta\), 28H); 1.51 (\(\delta\), 3H); 1.56–1.61 (\(\delta\), 8H); 3.33–3.46 (\(\delta\), 16H); 3.80 (\(\delta\), 6H); 4.43 (\(\delta\), 2H); 6.87 (\(\delta\), \(J\) = 8.5, 2H); 7.25–7.31 (\(\delta\), 9H).
HR-ESI-TOF-MS: 985.6926 ([M+Na]+, C59H98NaO8Si+; calc. 985.6929).

Data of 4a: 1H-NMR: 3.58–3.68 (m, 16H); 3.80 (s, 3H); 4.49 (s, 2H); 4.56 (s, 2H); 6.87 (d, J = 8.5, 2H); 7.27 (m, 4H); 7.33 (m, 3H).

HR-ESI-TOF-MS: 427.2098 ([M+Na]+, C23H32NaO6+; calc. 427.2097).

Data of 4b: 1H-NMR: 1.07–1.36 (m, 14H); 1.57–1.63 (m, 4H); 3.36–3.48 (m, 4H); 3.80 (s, 3H); 4.43 (s, 2H); 4.51 (s, 2H); 6.88 (d, J = 8.5, 2H); 7.26 (d, J = 8.5, 2H); 7.27–7.31 (m, 5H).

HR-ESI-TOF-MS: 421.2718 ([M+Na]+, C26H38NaO3Si+; calc. 421.2719).

Data of 5a: 1H-NMR: 1.02–1.11 (m, 21H); 3.56–3.68 (m, 4H); 3.80 (s, 3H); 3.83 (s, 3H); 4.43 (s, 2H); 4.49 (s, 2H); 6.87 (d, J = 8.5, 2H); 7.26 (d, J = 8.5, 2H).

HR-ESI-TOF-MS: 493.2965 ([M+Na]+, C25H46NaO6Si+; calc. 493.2961); 509.2704 ([M+K]+, C25H46KO6Si+; calc. 509.2701).

Data of 5b: 1H-NMR: 1.03–1.08 (m, 18H); 1.26–1.35 (m, 16H); 1.55–1.59 (m, 5H); 3.43 (t, J = 7.0, 2H); 3.75 (t, J = 7.0, 2H); 3.80 (s, 3H); 4.43 (s, 2H); 4.48 (s, 2H); 6.87 (d, J = 8.5, 2H); 7.29 (d, J = 8.5, 2H).

HR-ESI-TOF-MS: 487.3585 ([M+Na]+, C28H52NaO3Si+; calc. 487.3583).

Data of 6: 1H-NMR: 1.04 (s, 6H); 1.05 (s, 12H); 1.57 (m, 3H); 3.70 (s, 2H); 3.94 (s, 2H); 4.45 (d, J = 6.0, 2H); 4.48 (d, J = 6.0, 2H).

MALDI-TOF-MS: 297.189 ([M+Na]+, C14H30NaO3Si+; calc. 297.186); 313.165 ([M+K]+, C14H30KO3Si+; calc. 313.160).

Data of 7: 1H-NMR: 3.70 (s, 2H); 3.95 (s, 2H); 4.45 (d, J = 6.0, 2H); 4.49 (d, J = 6.0, 2H); 4.54 (s, 2H); 7.29–7.35 (m, 5H).

MALDI-TOF-MS: 231.101 ([M+Na]+, C12H16NaO3+; calc. 231.100).

Data of 9: 1H-NMR: 0.92–1.01 (m, 21H); 1.36–3.69 (m, 16H); 3.55 (s, 6H); 3.63 (s, 2H); 4.43 (s, 2H); 4.47 (s, 2H); 6.85 (d, J = 8.5, 2H); 7.17–7.27 (m, 20H); 7.40 (d, J = 8.0, 2H).

HR-ESI-TOF-MS: 943.5151 ([M+Na]+, C56H76NaO9Si+; calc. 943.5156); 959.4890 ([M+K]+, C56H76KO9Si+; calc. 959.4896).

Data of 11: 1H-NMR: 2.59 (t, J = 6.0, 2H); 3.57 (s, 4H); 3.69 (s, 4H); 4.50 (s, 4H); 7.26–7.33 (m, 10H).

HR-ESI-TOF-MS: 339.1576 ([M+Na]+, C19H24NaO4+; calc. 339.1572).

Data of 12: 1H-NMR: 3.54–3.68 (m, 40H); 3.80 (s, 3H); 4.49 (s, 2H); 4.50 (s, 2H); 6.87 (d, J = 8.5, 2H); 7.26–7.30 (m, 14H).

MALDI-TOF-MS: 931.46 ([M+Na]+, C51H72NaO14+; calc. 931.464); 947.43 ([M+K]+, C51H72KO14+; calc. 947.45).

Data of 14: 1H-NMR: 3.37–3.67 (m, 48H); 3.793 (s, 6H); 3.802 (s, 3H); 4.46 (s, 2H); 4.485 (s, 4H); 4.494 (s, 2H); 6.86–6.88 (m, 10H).

Figure 4. Ether formation between tetraethylene glycol tosylate 2a and a) monoalcohol 8, b) propane-1,3-diol 11 and c) 2-(hydroxymethyl)propane-1,3-diol 13. Reaction time was 12 h. Yields were calculated based on the isolated amounts. ND: not detected.
doi:10.1371/journal.pone.0091912.g004

PLOS ONE | www.plosone.org 4 March 2014 | Volume 9 | Issue 3 | e91912
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Author Contributions
Conceived and designed the experiments: KK. Performed the experiments: RC KA. Analyzed the data: TM RC KK. Wrote the paper: TM KK.