



Polymer-supported oligoethylene glycols as heterogeneous multifunctional catalysts for nucleophilic substitution

Vinod H. Jadhav^a, Hwan-Jeong Jeong^a, Seok Tae Lim^a, Myung-Hee Sohn^a,
Choong Eui Song^{b,c,*}, Dong Wook Kim^{a,*,†}

^a Department of Nuclear Medicine, Cyclotron Research Center, Research Institute of Clinical Medicine, Chonbuk National University Medical School, Jeonju, Jeonbuk 561-712, Republic of Korea

^b Department of Chemistry, Sungkyunkwan University, 300 Cheoncheon, Jangsan, Suwon, Gyeonggi 440-746, Republic of Korea

^c Department of Energy Science, Sungkyunkwan University, 300 Cheoncheon, Jangsan, Suwon, Gyeonggi 440-746, Republic of Korea

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ABSTRACT

We investigated various structurally modified polystyrene-supported oligoethylene glycols (PSoligoEG) in order to find an optimized PSoligoEG by examining the dependence of their catalytic activity on the oligoethylene glycol chain length and the loading level of the oligoethylene glycol portion on the polystyrene support. From this, we found that the PSpentaEG with the highest pentaEG loading had the best catalytic efficacy among the various PSoligoEGs in nucleophilic substitutions. This PSpentaEG absorbed both polar aprotic solvents, such as DMSO, DMF, and acetonitrile, as well as protic media, such as *tert*-amyl alcohol and aqueous acetone, and swelled considerably. To expand the scope of the PSpentaEG as a heterogeneous catalyst for diverse nucleophilic displacement reactions, we carried out the thioacetoxylation, nitrilation, azidation, iodination, bromination, chlorination, and methoxylation using the corresponding alkali metal salts in the presence of PSpentaEG in various solvents; all the reactions proceeded smoothly, affording the corresponding products in high yields.

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1. Introduction

Solid-phase chemistry using polymeric supports has played an important role in the synthesis of bioactive oligomers, as well as the eco-friendly catalyst-immobilization research field.¹ In particular, since catalysts tethered on various insoluble supports, such as silica gel, metal particles, and polystyrenes, provide many merits, including ease of recycling and separation, ease of handling, and the unique microenvironment caused by the reactants within the supports, they have received much attention in many chemical processes.² Among the various polymeric supports, the favorable characteristics of polystyrene, such as chemical inertness, good stability, facile functionalization, and low expense, garner it frequent use as a polymeric support for just such purposes.³

Nucleophilic substitution using alkali metal salts as nucleophiles is known to be one of the most essential chemical reactions for organic transformations, despite the low solubility of alkali metal salts in organic media.⁴ In order to enhance their nucleophilicity and solubility, various phase-transfer catalysts, such as tetraalkylammonium

salts and crown ether derivatives, are commonly used in nucleophilic displacement reactions.^{5–7} Moreover, over the past several decades, various phase-transfer catalysts immobilized on polymeric supports also have been developed to enable catalyst recovery and facilitate product purification by simple filtration.^{8,9} However, these immobilized phase-transfer catalyst systems generally show inefficient activity in nucleophilic substitution reactions when compared with the corresponding non-immobilized catalyst systems.⁸

Recently, it was reported that nucleophilic substitution reactions, including fluorination, using the corresponding alkali metal salts, could proceed very quickly in oligoethylene glycol reaction solvents, such as tetraethylene glycols.¹⁰ In this reaction method, the oligoethylene glycol could act as a multifunctional catalyst through metal cation chelation with the ether groups, as well as through protic medium effects caused by the controlled hydrogen bonding between the nucleophiles and oligoethylene glycol. However, due to their high boiling points, the use of these short chain oligoethylene glycols as reaction solvents can often be inconvenient in chemical processes.^{9,11} More recently, a polystyrene-supported pentaethylene glycol (PSpentaEG) was introduced as a highly efficient heterogeneous catalyst for nucleophilic fluorination reactions.¹² This PSpentaEG not only demonstrated good performance in nucleophilic fluorination using CsF in *tert*-alcohol media, but also outlined many practical merits, such as ease of handling, separation, and

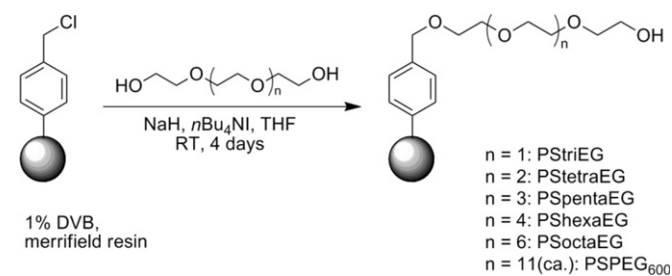
* Corresponding authors. E-mail addresses: s1673@skku.edu (C.E. Song), kimdw@chonbuk.ac.kr, kimdw@inha.ac.kr (D.W. Kim).

† Current address: Department of Chemistry, Inha 100 Namgu, Incheon 402-751, Republic of Korea. Tel.: +82 63 250 2396; fax: +82 63 255 1172.

recovery. In this paper, we not only expand on studies of the structural modifications of polymer-supported oligoethylene glycols (PSoligoEGs) by variation of their ethylene glycol chain lengths and the loading level of the oligoethylene glycol portion on polystyrene, but also further their applications in various nucleophilic substitution reactions using corresponding alkali metal salts in the presence of PSoligoEGs. We also surveyed the swelling properties of the PSoligoEG systems in several solvents.

2. Results and discussion

Scheme 1 illustrates the preparation of PSoligoEGs using a simple one-step reaction. We prepared various PSoligoEGs with different lengths of oligoethylene glycol portions and different loading levels of pentaEG (EG=ethylene glycol) portions on polystyrene supports. Treatment of Merrifield resin¹³ (1% divinylbenzene) with either triEG, tetraEG, pentaEG, hexaEG, octaEG, or polyEG₆₀₀ in anhydrous THF for 4 days afforded PStriEG (2.4 mmol of triEG portion/g of polymer-supported product obtained), PStetraEG (2.2 mmol tetraEG portion/g), PSpentaEG (1.9 mmol pentaEG portion/g), PShexaEG (1.7 mmol hexaEG portion/g), PSocetaEG (1.4 mmol octaEG portion/g), or PSpolyEG₆₀₀ (1.1 mmol PEG₆₀₀ portion/g), respectively. All PSoligoEGs were characterized by ¹³C NMR (solid state) spectroscopy and elemental analysis.



Scheme 1. Preparation of polymer-supported oligoethylene glycols: PSoligoEGs. DVB=divinylbenzene; PS=polymer support; EG=ethylene glycol.

The catalytic activities of the PSoligoEGs toward nucleophilic substitution reactions according to oligoethylene glycol chain length in the PSoligoEG system were examined by carrying out fluorination with CsF and acetoxylation with KOAc in the presence of various PSoligoEGs, under uniform reaction conditions (fluorination: at 100 °C for 2.5 h; acetoxylation: at 80 °C for 3.5 h) and in CH₃CN, as shown in **Fig. 1**. Interestingly, specific lengths of oligoEGs,

such as pentaEG and hexaEG, in the PSoligoEG system play a crucial role in supporting the catalytic activity. PSpentaEG and PShexaEG showed the most efficient catalytic activities toward nucleophilic fluorination using CsF. It is speculated that the ether groups of PSpentaEG, which act as a Lewis base toward the metal cation, are of an optimized length for chelation with metal cations (in particular, Cs⁺) to generate 'naked' (free) fluorides, thereby enhancing the nucleophilicity and solubility of the MF. Considering these results, we undertook further studies with the PSpentaEG system. The catalytic activities of these PSoligoEGs in the acetoxylation reaction using KOAc showed similar trends. However, the catalytic effects of the PSoligoEGs, according to oligoethylene glycol chain length, toward the acetoxylation reaction were not dramatic when compared with those toward the fluorination reaction.

Table 1 illustrates the swelling properties of PSpentaEG (100–200 mesh, 0.9 mmol pentaEG portion/g), together with the reported swelling degree of the Merrifield resin (100–200 mesh, 0.9 mmol Cl/g).¹⁴ Immobilization of the pentaEG onto the polystyrene beads gave the PSpentaEG remarkably increased swelling constants in polar aprotic solvents, such as DMSO, CH₃CN, and DMF, in comparison with the parent Merrifield resin. Moreover, this PSpentaEG was also quite swollen in protic media, such as *tert*-amyl alcohol, methanol, and aqueous acetone, compared with the Merrifield resin. However, the swelling properties of the PSpentaEG were poor in benzene and ether-type solvents, such as 1,4-dioxane and THF. Based on these results, it is expected that this PSoligoEG catalytic system might be efficient in polar aprotic and protic reaction media.

Table 1
Volume of swollen PSpentaEG (mL/g)^a

Entry	Solvent	Merrifield resin	PSpentaEG
1	THF	6.4 (6.4 ^b)	4.5
2	Acetone	2.7	2.8
3	H ₂ O/Acetone (1:1)	1.9	2.3
4	Benzene	6.3 (6.6 ^b)	3.7
5	CH ₃ CN	1.6 (1.8 ^c)	2.6
6	DMF	4.7 (4.8 ^b)	6.5
7	1,4-Dioxane	6.0 (6.0 ^b)	3.9
8	CH ₂ Cl ₂	6.1 (6.0 ^b)	5.6
9	Methanol	1.7 (1.8 ^b)	2.6
10	DMSO	1.7 (1.8 ^b)	6.7
11	<i>tert</i> -Amyl alcohol	0.5	1.2

^a Volumes were measured in syringes equipped with a sintered frit, after equilibrating for 1 h using 100 mg of Merrifield resin (0.9 mmol/g) or PSpentaEG (0.9 mmol/g). Both resins had dry volumes of approximately 1.5 mL/g.

^b Ref. 14b.

^c Ref. 14a.

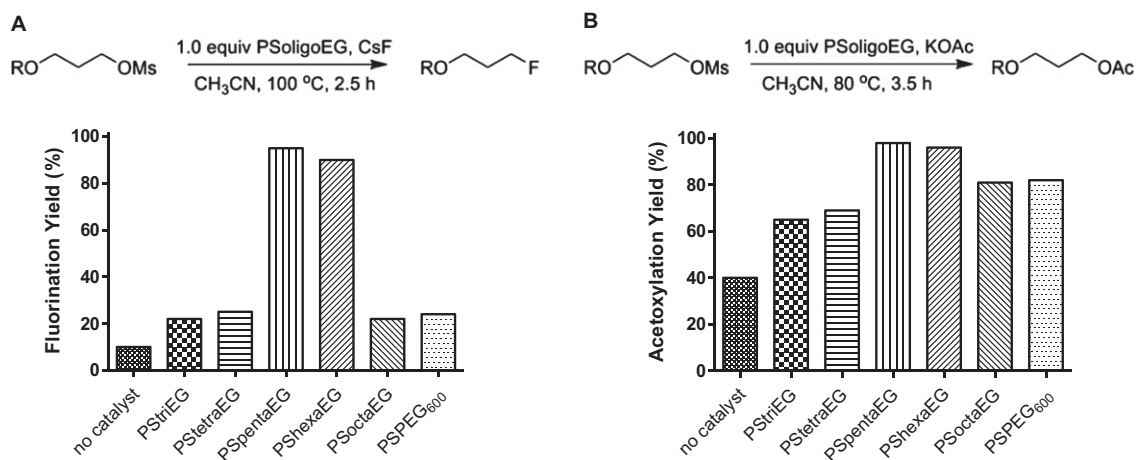


Fig. 1. Catalytic activity of PSoligoEGs in nucleophilic substitutions according to oligoethylene glycol length. (A) Fluorination using CsF in the presence of various PSoligoEGs. (B) Acetoxylation using KOAc. Product quantity determined by ¹H NMR. R=2-naphthyl.

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