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Oligoethylene Glycols as Highly Efficient Mutifunctional Promoters for Nucleophilic-Substitution Reactions

Vinod H. Jadhav,[a] Seung Ho Jang,[a] Hwan-Jeong Jeong,[a] Seok Tae Lim,[a] Myung-Hee Sohn,[a] Ju-Young Kim,[b] Sungyul Lee,*[b] Ji Woong Lee,[c] Choong Eui Song,*[c] and Dong Wook Kim*[a]

Abstract: Herein, we report the promising use of *n*-oligoethylene glycols (oligoEGs) as mutifunctional promoters for nucleophilic-substitution reactions employing alkali metal salts. Among the various oligoEGs tested, pentaethylene glycol (pentaEG) had the most efficient catalytic activity. In particular, when compared with other nucleophiles examined, a fluorine nucleophile generated from CsF was significantly activated by the pentaEG promoter. We also performed various facile nucleophilic-displacement reactions, such as the halogenation, acetoxylation, thioacetoxylation, nitrilation, and azidation of various substrates with potassium halides, acetate, thioacetate, cyanide, and sodium azide, respectively, in the presence of the pentaEG promoter. All of these reactions provided their desired products in excellent yields. Furthermore, the combination of pentaEG and a *tert*-alcohol medium showed tremendous efficiency in the nucleophilic-displacement reactions (fluorination and methoxylation) of base-sensitive substrates with basic nucleophiles (cesium fluoride and potassium methoxide, respectively). The catalytic role of oligoEGs was examined by quantum-chemical methods. The oxygen atoms in oligoEGs were found to act as Lewis bases on the metal cations to produce the "flexible" nucleophile, whereas the two terminal hydroxy (OH) groups acted as "anchors" to orientate the nucleophile and the substrate into an ideal configuration for the reaction.

Keywords: alkali metals · oligoethylene glycol · fluorine · nucleophilic substitution · multifunctional promoter

Introduction

Nucleophilic substitution is a fundamental transformation for functional-group interconversion in organic synthesis.[1,2] Although alkali-metal fluorides are a readily available source of fluoride ions, their applications have been limited owing to their low solubilities in organic solvents.[3] Over the past few decades, a number of useful procedures,[4] such as ionic-liquid systems,[5] have been developed to enhance the reactivity and solubility of alkali-metal salts in organic media and thereby accelerate the reaction rate.[4] Although the use of alkali-metal-salts/[18]crown-6-ether complexes[6] and tetra-alkylammonium salts[7] are representative methods that have been employed in various procedures, these methods still have some drawbacks. For example, [18]crown-6 systems have shown poor performance when the metal cation and nucleophile form a tight ion-pair, such as alkali-metal/fluoride pairs, and some tetra-alkylammonium salts are thermally unstable.[6–8]

It is also well-known that polar aprotic solvents, such as acetonitrile, dimethyl sulfoxide (DMSO), and *N,N*-dimethyl formamide (DMF), are effective reaction media for nucleophilic-substitution reactions with alkali-metal salts as the nucleophile sources because these solvents allow the nucleophilicities of metal salts to be enhanced by the selective solvation of metal cations, and the lack of a proton for hydrogen bonding, which leaves the anion (nucleophile) "naked".[9] However, it has recently been reported that the use of a bulky, non-polar, protic *tert*-alcohol, such as *tert*-butyl alcohol or *tert*-amyl alcohol, can significantly increase the reactivity of alkali-metal fluorides because the "flexible" fluoride that is produced from the protic solvent molecules acts as a Lewis base towards the counterion (metal cation)

[a] Dr. V. H. Jadhav, S. H. Jang, Dr. H.-J. Jeong, Dr. S. T. Lim, Dr. M.-H. Sohn, Prof. Dr. D. W. Kim
Department of Nuclear Medicine
Cyclotron Research Center
Research Institute of Clinical Medicine
Chonbuk National University Medical School
Jeonju, Jeonbuk 561-712 (Korea)
Fax: (+82) 63-255-1172
E-mail: kimdw@chonbuk.ac.kr

[b] J.-Y. Kim, Prof. Dr. S. Lee
Department of Applied Chemistry
Kyung Hee University
Gyeonggi 446-701 (Korea)
E-mail: sylee@khu.ac.kr

[c] J. W. Lee, Prof. Dr. C. E. Song
Department of Chemistry and the
Department of Energy Science
Sungkyunkwan University
300 Cheoncheon, Jangan, Suwon, Gyeonggi 440-746 (Korea)
E-mail: s1673@skku.edu

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to neutralize the strong Coulombic influence of the latter on the nucleophile.[10] In a recent significant advance, we observed that short-chain oligoethylene glycol (oligoEG) solvents, such as triethylene glycol (triEG) and tetraethylene glycol (tetraEG) showed high efficiencies in nucleophilic-fluorination reactions with potassium fluoride compared with long-chain polyethylene glycols (PEGs).[11,12] More recently, we reported a heterogeneous catalytic system using pentaethylene glycol (pentaEG) that showed a highly efficient catalytic activity in fluorination reactions with cesium fluoride, as well as a number of other synthetic and practical merits.[13] This result prompted us to expand our study on the possible use of various *n*-oligoEGs as bifunctional catalysts for nucleophilic-displacement reactions using alkali-metal salts. Herein, we examined *n*-oligoEGs of various lengths with regard to their effectiveness as promoters in various nucleophilic-substitution reactions, including fluorination, with the corresponding alkali-metal salts.

Results and Discussion

Screening of *n*-oligoethylene glycols: To investigate the effect of chain-length on the catalytic activities of *n*-oligoEGs in nucleophilic-substitution reactions, we carried out the nucleophilic fluorination with CsF as the nucleophile source (100 °C for 1.5 h) and the nucleophilic acetoxylation with KOAc (80 °C for 2.5 h) in the presence of *n*-oligoEGs of different chain-lengths, such as triEG, tetraEG, pentaEG, hexaEG, octaEG, and PEG_{600} in CH_3CN (Figure 1). In the fluorination reaction, *n*-oligoEGs of a specific chain-length (in particular, pentaEG) showed significant catalytic activity in increasing the nucleophilicity of CsF (Figure 1 A). However, in the acetoxylation reaction, long-chain oligoEGs (longer than pentaEG) also showed catalytic activity similar to that of pentaEG; pentaEG showed slightly better performance compared to other long-chain oligoEGs (Figure 1 B). These results revealed that the fluorination reaction using these *n*-oligoEGs as promoters was much more sensitive to the length of *n*-oligoEGs than other nucleophilic-substitution reactions. This result was taken into consideration as we performed further studies on nucleophilic-substitution reactions, including fluorination, with pentaEG.

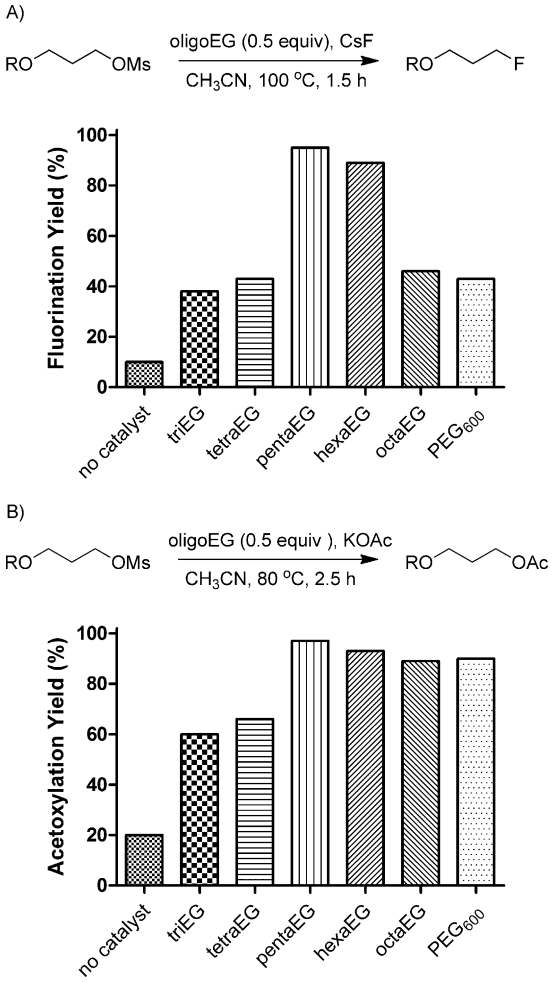


Figure 1. Effect of chain-length on the catalytic activity of *n*-oligoEGs in nucleophilic-substitution reactions. A) Fluorination with CsF in the presence of various *n*-oligoEGs. B) Acetoxylation with KOAc. The quantity of product was determined by ^1H NMR spectroscopy. R = 2-naphthyl, EG = ethylene glycol.

Influence of bis-terminal hydroxy groups of pentaEG on nucleophilic-substitution reactions: To investigate the influence of the two terminal hydroxy groups of pentaEG, which might form hydrogen bonds with nucleophiles, on various nucleophilic-substitution reactions, we performed three types of displacement reactions (nucleophilic fluorination with CsF, acetoxylation with KOAc, and bromination with KBr) in the presence of pentaEG, monomethylated pentaEG, and dimethylated pentaEG in CH_3CN. Standard control reactions were also performed in the absence of any catalyst (Figure 2). The fluorination reaction with CsF and 0.5 equivalents of pentaEG, which had two terminal hydroxy groups, proceeded approximately two-fold faster than that with 0.5 equivalents of monomethylated pentaEG, which only had one hydroxy group. Moreover, dimethylated pentaEG, which was methylated at both terminal hydroxy groups to prevent hydrogen bonding with nucleophiles such as fluoride, showed very low activity in the same fluorination reaction compared with both pentaEG and monomethyl pentaEG (Figure 2 A). These results were similar to those reported previously by ourselves.[11–13] Hydrogen-bonding interactions between a terminal OH group and the fluoride ion of MF could provide a "flexible" fluoride effect[10] to increase its nucleophilicity and increase the initial interactions between pentaEG and CsF to more effectively form the CsF/ether complex. The other nucleophilic-displacement reactions, such as acetoxylation using KOAc and bromination using KBr, in the presence of pentaEG, momomethyl pentaEG, and dimethyl pentaEG, showed similar trends (Figure 2). However, the hydroxy groups of pentaEG did not significantly influence these displacement reactions through hydrogen-bonding effects, perhaps owing to the

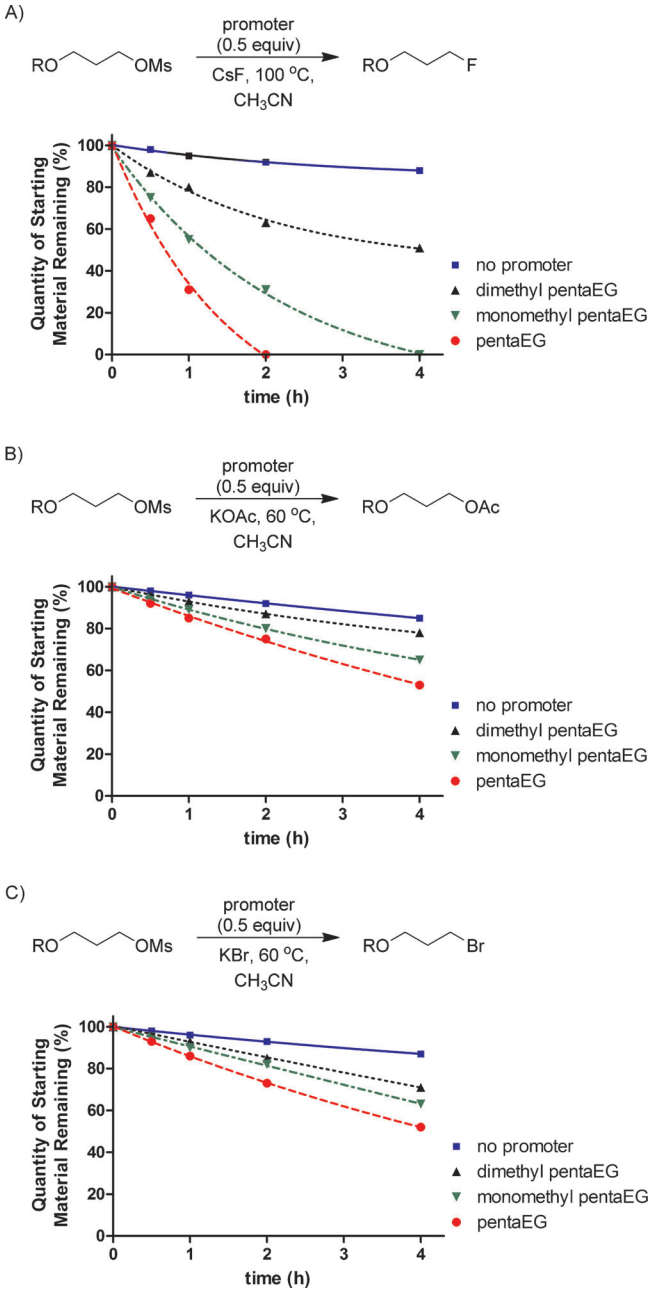
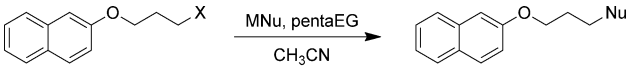


Figure 2. A) Nucleophilic fluorination with CsF and pentaEG, dimethylpentaEG, monomethylpentaEG, or no promoter. B) Nucleophilic acetoxylation with KOAc and pentaEG, dimethylpentaEG, monomethylpentaEG, or no promoter. C) Nucleophilic bromination with KBr and pentaEG, dimethylpentaEG, monomethylpentaEG, or no promoter. The quantity of starting material remaining was determined by ^{1}H NMR spectroscopy. R = 2-naphthyl.

higher nucleophilicity of these nucleophiles compared to fluoride.

Nucleophilic-substitution reactions with pentaEG: Table 1 shows the results for the nucleophilic-substitution reactions of model compounds 2-(3-methanesulfonyloxypropyl)naphthalene (**1**) and 2-(3-bromopropoxy)naphthalene (**2**) with various alkali-metal salts (MNu) in the presence of pentaEG

Table 1. Nucleophilic-displacement reactions with various alkali-metal salts (MNu) using pentaEG or the stated alternative reagents.[a]



1: X = OMs
2: X = Br

3: Nu = F, **2**: Nu = Br, **4**: Nu = I,
5: Nu = OAc, **6**: Nu = SAc,
7: Nu = CN, **8**: Nu = N_3

Entry	X	pentaEG [equiv]	MNu	T [°C]	t [h]	Yield [%][b] Product	Alkene
1	OMs	1.0	CsF	100	1	96	trace
2	OMs	0.5	CsF	100	1.5	95	trace
3	OMs	0.25	CsF	100	5	81[c]	19[c]
4	OMs	[18]crown-6[d]	CsF	100	4	75[c]	25[c]
5	OMs	0.5	KBr	90	1	97	–
6	OMs	0.5	KI	90	1	98	–
7	Br	0.5	KI	90	1	98	–
8	OMs	0.5	KOAc	90	1.5	98	–
9	Br	0.5	KOAc	90	1.5	98	–
10	OMs	0.5	KSAc	90	1	98	–
11	Br	0.5	KSAc	90	1	97	–
12	OMs	0.5	KCN	90	2.5	93	–
13	Br	0.5	KCN	90	5	92	–
14	OMs	0.5	NaN_3	90	3	97	–
15	Br	0.5	NaN_3	90	2	98	–

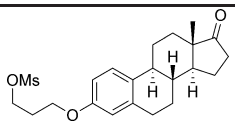
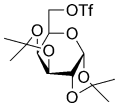
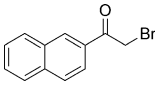
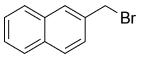
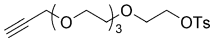
[a]All reactions were carried out on a 1.0 mmol reaction scale of substrate **1** or **2**, with 3 mmol MNu in 4.0 mL of solvent; [b] yield of isolated product; [c] yields were determined by ^{1}H NMR spectroscopy; [d] 0.5 equiv of [18]crown-6 was used. Ms = methanesulfonyl, Ac = acetyl.

under various reaction conditions. The fluorination of mesylate **1** with CsF in the presence of [18]crown-6 (0.5 equiv) as a conventional phase-transfer catalyst (PTC) at 100 °C in CH_3CN only provided the desired fluorinated product (**3**) in 75 % yield, along with 25 % of alkene by-product, which was formed from an elimination side-reaction that was facilitated by the "naked"-fluoride effect (Table 1, entry 4). However, the same reaction in the presence of stoichiometric or sub-stoichiometric amounts of pentaEG (1.0 or 0.5 equiv) proceeded in almost-quantitative yield (Table 1, entries 1 and 2). This result clearly indicated that the pentaEG efficiently enhanced the reactivity of CsF, whilst suppressing the formation of byproducts during the fluorination reaction through a "flexible"-fluoride effect. However, the use of 0.25 equivalents of pentaEG showed poor performance in the same reaction (81 % fluoroalkane **3**, with 19 % alkene; Table 1, entry 3) because the "flexible"-fluoride effect was not possible with low amounts of pentaEG. Diverse nucleophilic transformations were also attempted with various potassium salts as nucleophile sources in the presence of 0.5 equivalents of pentaEG. Table 1, entries 5–7 show that the halogenation reactions of mesylate **1** or bromoalkane **2** were complete within 1 h, thereby affording their corresponding halogenated products in very high yield (97–98 %). A single oxygen or sulfur nucleophile, generated by pentaEG from the corresponding potassium salt, was introduced into aliphatic organic compounds during the corresponding transformation in almost-quantitative yields (97–98 %; Table 1, entries 8–11). The transformation of methanesulfonate or bromide groups into an azide by using sodium azide,

which has recently received much attention owing to the utility of click chemistry,[14] proceeded smoothly, thereby affording azido-product **8** in 97–98% yield (Table 1, entries 14 and 15).

Nucleophilic-substitution reactions of various substrates: Table 2 shows the results for the nucleophilic-displacement reactions of halide and sulfonate substrates with various

Table 2. Nucleophilic-substitution reactions of various substrates.[a]

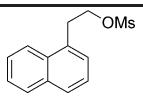
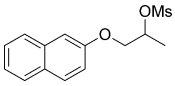
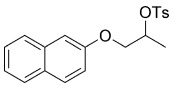
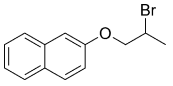
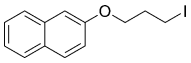
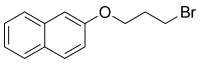
Entry	Substrate	MNu	T [°C]	t [h]	Yield [%][b]
1		CsF	100	6	94
2		NaN_3	90	3	96
3		KOAc	90	4	98
4		KSAc	90	4	96
5		KBr	80	1	94
6		NaN_3	80	1.5	92
7		KOAc	80	1	96
8		KSAc	80	1	93
9		CsF	100	1.5	88
10		CsF	100	1	96
11		CsF	100	2	94

[a]All reactions were carried out on 1.0 mmol substrate, with MNu (3.0 equiv) and PentaEG (0.5 equiv) in CH_3CN (4.0 mL); [b] yield of isolated product.

alkali-metal salts in the presence of pentaEG (0.5 equiv) in CH_3CN, thereby demonstrating that pentaEG was an efficient promoter for the nucleophilic-substitution reactions of various substrates. Fluoro-, azido-, acetoxy-, and thioacetoxy-substituted estrone derivatives, which play crucial roles in biological systems, were synthesized from the nucleophilic-substitution reactions of an estrone mesylate substrate in excellent yields (94–98%) by using the corresponding alkali-metal salts with pentaEG (Table 2, entries 1–4). Several displacement reactions, such as fluorination, azidation, acetoxylation, and thioacetoxylation, of a sugar-triflate substrate also proceeded well to afford their corresponding desired products in high yields (94, 92, 96, and 93%, respectively; Table 2, entries 5–8). α-Fluoroacetonaphthone was produced from the fluorination of α-bromoacetonaphthone in 88% yield (Table 2, entry 9). The reaction of benzylic bromide gave the benzylic fluoride product in 96% yield (Table 2, entry 10). A fluoro-substituted acetylene derivative was prepared from the corresponding tosylate substrate in high yield in the presence of pentaEG (Table 2, entry 11).

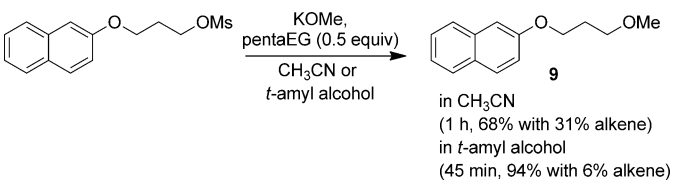
Selective nucleophilic-fluorination reactions: Table 3 shows the results for the highly chemoselective nucleophilic fluorination of various base-sensitive substrates, which were prone to the elimination side-reactions under basic reaction conditions that are associated with the conventional "naked" fluoride reagents, owing to the synergistic effect between pentaEG and the bulky protic *tert*-alcohol solvent.

Table 3. Selective nucleophilic-fluorination reactions using CsF in the presence of pentaEG in *tert*-alcohol solvent.[a]

Entry	Substrate	t [h]	Ratio [%][b] Product	Alkene
1		1	93	7
2		2	94	6
3		1.5	88	12
4		8	73	21[c]
5		4	73	27
6		5	88	12

[a] All reactions were carried out on 1.0 mmol substrate with CsF (3.0 equiv) and PentaEG (0.5 equiv) in *tert*-amyl alcohol (4.0 mL); [b] ratio was determined by ^1H NMR spectroscopy; [c] with 6% of alcohol byproduct.

The fluorination of 1-(2-mesylethyl)naphthalene to afford 1-(2-fluoroethyl)naphthalene using CsF in the presence of pentaEG in *tert*-amyl alcohol proceeded efficiently and gave the corresponding fluoride in 93% yield, with the styrene byproduct being formed in only 7% yield (Table 3, entry 1). A *sec*-fluoroalkane was produced from the *sec*-alkyl-mesylate or -tosylate in excellent yield through the synergistic pentaEG- *tert*-alcohol media effect (Table 3, entries 2 and 3). The transformation of *sec*-alkyl bromide into the fluoride by using the conventional PTC is very difficult because of a competing β-elimination side-reaction. Nevertheless, the fluorination of *sec*-bromoalkane to afford the desired *sec*-fluoroalkane in the pentaEG/*tert*-alcohol media proceeded in high yield (73%; Table 3, entry 4). Substrates that contained primary iodo- and bromoalkanes showed similar trends (73 and 88%, respectively; Table 3, entries 5 and 6). These results indicated that the protic atmosphere created by the *tert*-alcohol solvent and the "flexible"-fluoride effect afforded by hydrogen-bonding interactions between the fluoride ion, pentaEG, and *tert*-alcohol allowed these nucleophilic-fluorination reactions of the base-sensitive substrates to proceed selectively and in excellent yields. The comparative data (Scheme 1) highlights the important role of the synergistic effect of pentaEG and *tert*-alcohol solvent in the nucleophilic-substitution reaction with another strongly basic



Scheme 1. Methoxylation with KOMe in the presence of pentaEG.

nucleophile, such as methoxide. Whereas the methoxylation of the mesylate **1** with potassium methoxide in the presence of pentaEG in CH_3CN provided the methoxylated product in 68% yield (together with 31% of alkene byproduct), the same reaction in *tert*-amyl alcohol proceeded more selectively, thereby providing the product in 94% yield (with only 6% alkene).

Mechanistic features: The origin of the catalytic role of *n*-oligoEGs (see above) was similar to that of the fluorination reactions of KF in the presence of bis-terminal hydroxy polyethers.[11] We used density functional theory (MPWPW1K[15]) with the 6-311++G(d,p)) basis set and the (Hay–Wadt VDZ(n+1)) effective core potential for Cs[16] as implemented in Gaussian 09[17] to obtain the pre-reaction complexes, transition states, and post-reaction complexes. Table 4 shows the calculated reaction barriers of the model reaction $CsF+C_3H_7OMs \rightarrow CsOMs+C_3H_7F$, which was extremely useful in elucidating the mechanism of the observed S_N2 fluorination reactions[10a,b,11] in the presence of oligoEGs. The activation barriers ($E^{\ddagger}$ and $G^{\ddagger}_{373K}$) decreased progressively from triEG to pentaEG, which was in good agreement with the observed increasing yields. These calculated barriers ($E^{\ddagger} \approx 21.3$–$22.6$ kcal mol^{-1}) were slightly smaller than that for the very effective S_N2 fluorination reaction in tert-butyl alcohol ($E^{\ddagger} = 23.5$ kcal mol^{-1}),[10a,b] [$Cs^+F^- + C_3H_7OMs \rightarrow Cs^+OMs^- + C_3H_7F$], thus accounting for the phenomenal efficiency of this system.

Table 4. Calculated activation barriers $E^{\ddagger}$ and $G^{\ddagger}_{373K}$ [kcal mol^{-1}] for the nucleophilic-fluorination reactions in the presence of *n*-oligoEG (MPWPW1K/6-311++G(d,p)), in comparison with their corresponding yields.

	$E^{\ddagger}$	$G^{\ddagger}_{373K}$	Yield [%][a]
$CsF+C_3H_7OMs$ (triEG)	22.61	24.70	38
$CsF+C_3H_7OMs$ (tetraEG)	22.06	24.05	43
$CsF+C_3H_7OMs$ (pentaEG)	21.30	23.15	95

[a] oligoEG (0.5 equiv), 100 °C, CH_3CN, 1.5 h.

Figure 3 shows the calculated transition states in the S_N2 fluorination reactions in the presence of tri-, tetra-, and pentaEG, and shows their catalytic roles in detail. The O atoms in the oligoEGs formed a hollow "pocket" surrounding the ion-pair Cs^+F^-, thereby acting as a Lewis base toward the Cs^+ ions and neutralizing the electrostatic effects of the cation on, and "freeing", the nucleophile (F^-). The decreasing barrier heights (and increasing yields) from triEG to pentaEG were presumably due to the increased stabilization of the transition state. Figure 3 shows that the Cs^+ counterions interacted with the increasing number of oxygen atoms (4, 5, and 6 O atoms for tri-, tetra- and pentaEG, respectively), thus resulting in "freer" F^- ions (note the increasing Cs–F distance: 3.898, 3.921, and 4.180 Å, respectively).

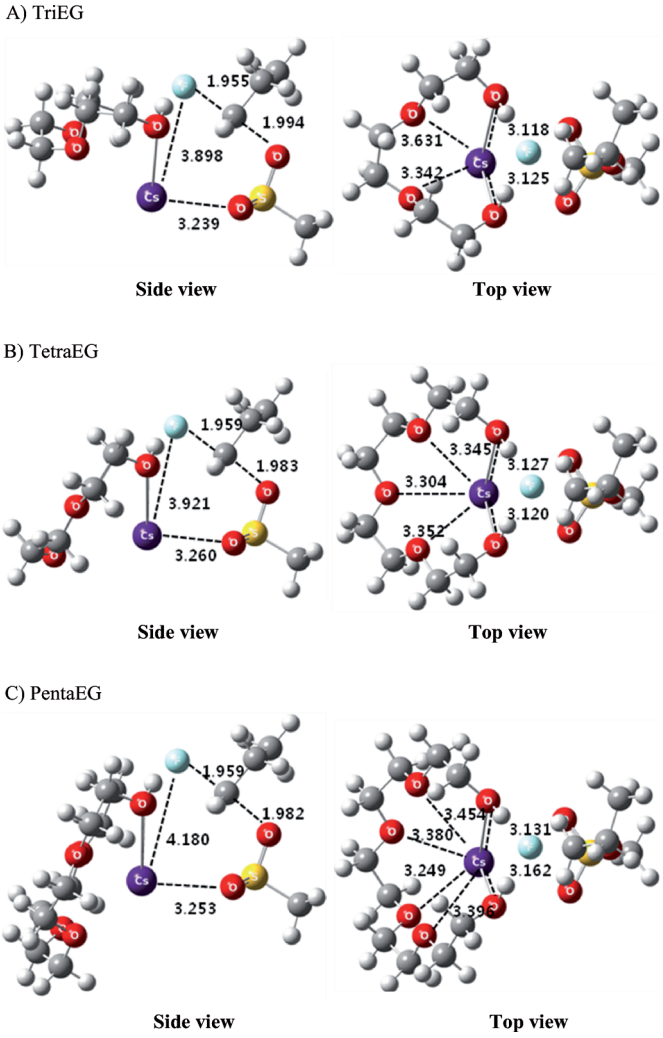


Figure 3. Transition states in nucleophilic-fluorination reactions in the presence of *n*-oligoEG (MPWPW1K/6-311++G(d,p)).

Conclusion

We have demonstrated the catalytic activities of *n*-oligoEGs of various lengths in nucleophilic-substitution reactions, such as fluorination and acetoxylation reactions. Among various *n*-oligoEGs, pentaEG showed the highest efficiency; in particular, the fluorination reaction was very sensitive and dependent on the chain-length of the *n*-oligoEGs. In the pentaEG catalytic system, the bis-terminal hydroxy group played an important role in enhancing the reactivity of alkali-metal salts, in particular CsF. The use of pentaEG as a promoter also showed good performance in other nucleophilic-displacement reactions of various substrates with halides, nitrogen, oxygen, and sulfur nucleophiles that were activated by pentaEG from the corresponding alkali-metal salts in a polar aprotic solvent, such as CH_3CN. Moreover, the nucleophilic reaction of various base-sensitive substrates by using strong basic nucleophiles, such as fluoride and methoxide, in *tert*-alcohol media proceeded much more selectively and at a faster rate owing to a "flexible"-fluoride

effect that was generated by hydrogen-bonding interactions between pentaEG, the nucleophiles, and *tert*-alcohol. We studied the mechanism of the catalytic reaction to elucidate the role of *n*-oligoEGs and we found that the oxygen atoms acted as Lewis bases towards CsF and the terminal OH groups acted as effective anchors for the F^- ions and the leaving groups. Our current work focuses on the development of more-efficient promoters that contain a pentaEG moiety generated by structural modification.

Experimental Section

General: Unless otherwise noted, all reagents and solvents were commercially available. Reaction progress was followed by TLC on 0.25 mm silica gel glass plates containing F-254 indicator. Visualization on TLC was conducted by UV light. Column chromatography on silica gel was performed with 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer, and chemical shifts (δ) are reported in ppm relative to tetramethylsilane. Low- and high-resolution electron impact (EI, 70 eV) MS were obtained.

Typical procedure of the fluorination reaction (Table 1, entry 2): CsF (456 mg, 3 mmol) was added to a mixture of mesylate **1** (281 mg, 1.0 mmol), pentaEG (119 mg, 0.5 mmol), and MeCN (4 mL) in a vial. The mixture was heated for 1.5 h at 100 °C. The reaction time was determined by checking TLC. The mixture was filtered and washed with Et_2O, and the filtrate was evaporated under reduced pressure. Column chromatography on silica gel (10% EtOAc/hexanes) afforded 195 mg (0.95 mmol, 95%) of 2-(3-fluoropropoxy)naphthalene (**3**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.39 (m, 2H), 4.24 (t, J = 6.2 Hz, 2H), 4.72 (dt, J = 46.8, 5.8 Hz, 2H), 7.16–7.22 (m, 2H), 7.34–7.53 (m, 2H), 7.76–7.83 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4 (d, J = 20.1 Hz), 63.6 (d, J = 25.3 Hz), 80.8 (d, J = 163.9 Hz), 106.8, 118.8, 123.6, 126.4, 126.7, 127.6, 129.1, 129.4, 134.6, 156.7; MS (EI): *m/z*: 204 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{13}H_{13}FO$: 204.0950 $[M]^+$; found: 204.0932. Registry No. provided by the author: 398–53–8.

Typical procedure for the halogenation reaction (Table 1, entries 5 and 6): The procedure for fluorination (see above) was followed except that KNu (Nu = Br, I) was used at 90 °C.

2-(3-Bromopropoxy)naphthalene (**2**): 257 mg (0.97 mmol, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.36–2.43 (m, 2H), 3.67 (t, J = 6.6 Hz, 2H), 4.23 (t, J = 5.6 Hz, 2H), 7.14–7.17 (m, 2H), 7.34–7.49 (m, 2H), 7.74–7.80 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.1, 32.2, 65.2, 106.6, 118.8, 123.7, 126.4, 126.7, 127.6, 128.9, 129.4, 134.4, 156.5 ppm; MS (EI): *m/z* (%):both 264 and 266 $[M]^+$, 144 (100), 115; HRMS (EI): *m/z* calcd for $C_{13}H_{13}O^{79}Br$: 264.0150 $[M]^+$; found: 264.0151. Registry No. provided by the author: 3245–62–3.

2-(3-Iodopropoxy)naphthalene (**4**): 306 mg (0.98 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$): 2.32–2.38 (m, 2H), 3.43 (t, J = 6.6 Hz, 2H), 4.16 (t, J = 5.8 Hz, 2H), 7.15–7.17 (m, 2H), 7.35–7.49 (m, 2H), 7.49–7.80 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 2.7, 32.8, 67.1, 106.6, 118.8, 123.6, 126.4, 126.7, 127.6, 128.1, 129.4, 134.4, 156.5 ppm; MS (EI): *m/z* (%): 312 $[M]^+$, 185, 144, 115 (100); HRMS (EI): *m/z* calcd for $C_{13}H_{13}OI$: 312.0011 $[M]^+$; found: 312.0006. Registry No. provided by the author: 380363–99–5.

Typical procedure for the acetoxylation reaction Table 1, entry 8): Potassium acetate (295 mg, 3 mmol) was added to a mixture of mesylate **1** (281 mg, 1.0 mmol), pentaEG (119 mg, 0.5 mmol), and MeCN (4 mL) in a vial. The reaction mixture was heated for 1.5 h at 90 °C. The reaction mixture was filtered and washed with Et_2O (15 mL). The filtrate was evaporated under reduced pressure. Column chromatography on silica gel (10%, EtOAc/hexanes) afforded 2-(3-acetoxypropoxy)naphthalene (**5**): 239 mg (0.98 mmol, 98%); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.18–2.22 (m, 2H), 4.17 (t, J = 6.18 Hz, 2H), 4.31 (t, J = 6.18 Hz, 2H), 7.10–7.15 (m, 2H), 7.33 (t, J = 7.56 Hz, 1H), 7.43 (t, J = 6.90 Hz, 1H), 7.71–7.77 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.1, 28.7, 61.5, 64.4, 106.6, 118.9, 123.7, 126.5, 126.8, 127.7, 129.0, 129.5, 134.6, 156.8, 171.2 ppm; MS (EI): *m/z*: 244 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{15}H_{16}O_3$ 244.1099 $[M]^+$; found 244.1096. Registry No. provided by the author: 876485–90–4.

Typical procedure for the thioacetoxylation reaction (Table 1, entry 10): The procedure for acetoxylation (see above) was followed except that potassium thioacetate was used.

2-(3-Thioacetoxypropoxy)naphthalene (**6**): 255 mg (0.98 mmol, 98%) was obtained; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.11–2.16 (m, 2H), 2.34 (s, 3H), 3.10 (t, J = 6.84 Hz, 2H), 4.13 (t, J = 6.18 Hz, 2H), 7.11–7.15 (m, 2H), 7.33 (t, J = 6.84 Hz, 1H), 7.44 (t, J = 6.90 Hz, 1H), 7.71–7.76 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.1, 29.3, 30.8, 66.2, 106.7, 118.9, 123.7, 126.5, 126.8, 127.7, 129.0, 129.5, 134.6, 156.8, 195.9 ppm; MS (EI): *m/z*: 260 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{15}H_{16}O_2S$: 260.0871 $[M]^+$; found: 260.0874.

Typical procedure for the nitrilation reaction (Table 1, entry 12): The procedure for acetoxylation (see above) was followed except that potassium cyanide was used.

2-(3-Cyanopropoxy)naphthalene (**7**): 196 mg (0.93 mmol, 93%); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.18–2.23 (m, 2H), 2.63 (t, J = 6.90 Hz, 2H), 4.19 (t, J = 6.18 Hz, 2H), 7.12–7.14 (m, 2H), 7.35 (t, J = 6.90 Hz, 1H), 7.45 (t, J = 8.22 Hz, 1H), 7.72–7.78 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 25.6, 65.4, 106.9, 118.8, 119.3, 124.0, 126.7, 126.9, 127.7, 129.2, 129.6, 134.5, 156.4 ppm; MS (EI): *m/z*: 211 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{14}H_{13}NO$: 211.0997 $[M]^+$; found: 211.0998. Registry No. provided by the author: 727429–81–4.

Typical procedure for the azidation reaction (Table 1, entry 14): Sodium azide (195 mg, 3 mmol) was added to a mixture of mesylate **1** (281 mg, 1.0 mmol), pentaEG (119 mg, 0.5 mmol), and MeCN (4 mL) in a vial. The mixture was heated for 3 h at 90 °C. The reaction time was determined by TLC. The reaction mixture was filtered and washed with Et_2O (15 mL). The filtrate was evaporated under reduced pressure. Column chromatography on silica gel (10% EtOAc/hexanes) afforded 220 mg (0.97 mmol, 97%) of 2-(3-azidopropoxy)naphthalene (**8**). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.10–2.14 (m, 2H), 3.57 (t, J = 6.9 Hz, 2H), 4.17 (t, J = 6.2 Hz, 2H), 7.13–7.16 (m, 2H), 7.32–7.35 (m, 1H), 7.42–7.45 (m, 1H), 7.71–7.77 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.9, 48.4, 64.6, 106.7, 118.8, 123.8, 126.5, 126.8, 127.7, 129.1, 129.5, 134.6, 156.7 ppm; MS (EI): *m/z* (%): 227 $[M]^+$, 169, 143 (100), 115; HRMS (EI): *m/z* calcd for $C_{13}H_{13}N_3O$: 227.1059 $[M]^+$; found: 227.1060. Registry No. provided by the author: 1199811–23–8.

Typical procedure for the methoxylation reaction (Scheme 1): Potassium methoxide (211 mg, 3 mmol) was added to a mixture of mesylate **1** (281 mg, 1.0 mmol), pentaEG (119 mg, 0.5 mmol), and *tert*-amyl alcohol (4 mL) in a vial. The reaction mixture was heated for 45 min at 90 °C. The reaction time was determined by TLC. The mixture was filtered and washed with Et_2O (15 mL). The filtrate was evaporated under reduced pressure. Column chromatography on silica gel (10% EtOAc/hexanes) afforded 203 mg (0.94 mmol, 94%) of 2-(3-methoxypropoxy)naphthalene (**9**). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.09–2.16 (s, 2H), 3.37 (S, 3H), 3.60 (t, J = 6.18 Hz, 2H), 4.18 (t, J = 6.18 Hz, 2H), 7.13–7.15 (m, 2H), 7.31 (t, J = 6.84 Hz, 1H), 7.42 (t, J = 6.84 Hz, 1H), 7.71–7.77 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 29.7, 58.9, 64.9, 69.4, 106.7, 119.0, 123.6, 126.4, 126.8, 127.7, 128.9, 129.4, 134.7, 157.0 ppm; MS (EI): *m/z*: 216 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{14}H_{16}O_2$: 216.1150 $[M]^+$; found: 216.1149. Registry No. provided by the author: 1006374–27–1.

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