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Tailor-Made Hexaethylene Glycolic Ionic Liquids as Organic Catalysts for Specific Chemical Reactions

Vinod H. Jadhav, Hwan-Jeong Jeong, Seok Tae Lim, Myung-Hee Sohn, and Dong Wook Kim*

Department of Nuclear Medicine, Cyclotron Research Center, Chonbuk National University Medical School, Jeonju, Jeonbuk 561-712, Korea

kimdw@chonbuk.ac.kr

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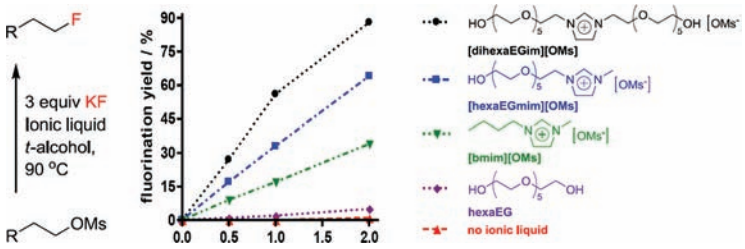
ABSTRACT



Hexaethylene glycol substituted imidazolium based ionic liquids (hexaEGILs) were designed and prepared well-tailored to a specific organic reaction using alkali-metal fluorides (MFs) as multifunctional organic catalysts. These hexaEGIL catalysts could significantly enhance the reactivity of MF, even KF. Furthermore, the hexaEGIL systems showed tremendous efficiency in the nucleophilic fluorination of base-sensitive substrates.

Due to several attractive properties, room temperature ionic liquids (ILs) containing bulky organic cations paired with their counteranions have attracted interest as eco-friendly alternative reaction solvent systems (compared to conventional volatile solvent systems) for a variety of applications in chemistry, including reaction acceleration, separation, and nanotechnology.[1] Moreover, because ILs are highly tunable, they can be tailored to meet specific needs by making simple structural modifications on either the cation or anion component.[1,2] It is well-known that imidazolium based IL solvent systems perform well in nucleophilic substitutions (including fluorination), when using alkali-metal salts as nucleophile sources, through the phase transfer catalyst (PTC) effect of IL reaction media.[3]

Among various organic transformations, the use of nucleophilic fluorination to introduce a single fluorine atom at a specific molecular site is regarded as an important organic transformation reaction in the field of medicinal chemistry and, in particular, the area of [^{18}F]radiopharmaceutical research involved with positron emission tomography (PET) studies.[4] For this purpose, alkali metal fluorides (MFs) such as KF are generally used with various PTCs in polar aprotic solvents (e.g., CH_3CN, DMF).[5] However, due

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to recent advances, this fluorination reaction using MF in the absence of PTCs can be accelerated in protic media, such as *tert*-alcohols[6] and short-chain polyethylene glycols (PEGs),[7] through the "flexible" fluoride[8] effect, resulting from the controlled hydrogen bonding between MF and the protic solvents.[6–8] Moreover, it was found that the specific length of PEGs such as pentaEG (EG = ethylene glycol), tethered by polymer support, could provide PTC-like activity for enhancing the reactivity of CsF in the fluorination reaction.[9] However, these protic media protocols are still not sufficient to enhance the reactivity of KF for this nucleophilic displacement reaction due to the strong Coulombic influence of the potassium cation on fluoride, and the protocols might be inconvenient for the chemical processes due to the high boiling point of PEG solvents.[6–9]

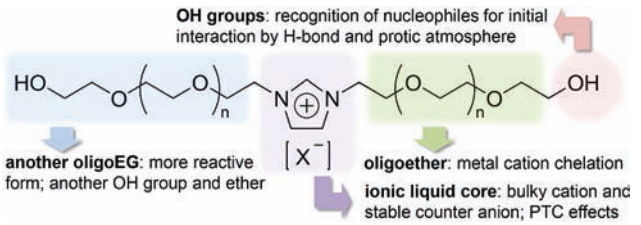
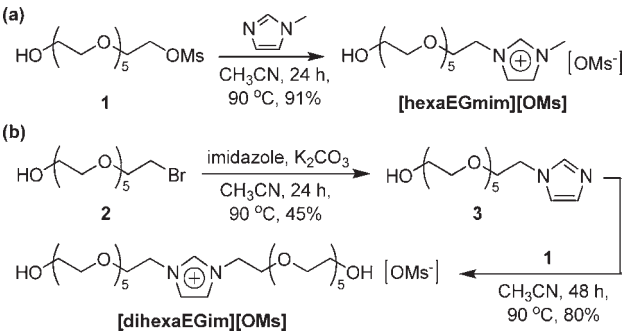


Figure 1. Concept of tailor-made ionic liquids: oligoether substituted imidazolium salts.

Catalysis has played a crucial role in chemical science, and the design and application of new catalysts is an important research topic. Based on these observations and needs, we have designed oligoether substituted imidazolium based ILs as multifunctional organic catalysts, in anticipation that (i) their imidazolium salt core might have a PTC-like activity;[3] (ii) the oligoether moiety might act as a Lewis base toward metal cations, allowing the fluoride nucleophile to become "free" and active;[7] (iii) the terminal hydroxyl group might provide the recognition of the nucleophile (fluoride) for initial interaction by H-bonding as well as a "flexible" fluoride effect with *tert*-alcohol solvents;[6] (iv) another oligoEG component might make MFs more reactive (Figure 1). Herein, we introduce tailor-made hexaethylene glycolic ionic liquid (hexaEGIL) systems as extremely efficient organic catalysts designed for nucleophilic fluorination using KF including radiofluoride [^{18}F].

The hexaEGILs [hexaEGmim][OMs] and [dihexaEGim][OMs] (hexaEGmim = 1-hexaethylene glycolic 3-methylimidazolium cation; dihexaEGim = 1,3-dihexaethylene glycolic imidazolium cation; OMs = mesylate anion) were prepared using a simple procedure as shown in Scheme 1. Among various lengths of oligoEG, hexaEG was used to prepare the hexaEGILs because of its metal cation chelation efficiency (after *N*-alkylation, hexaEGILs could have six-membered oxygen atoms on either branch, similar to pentaEG). An *N*-alkylation reaction of 1-methylimidazole with hexaEG mesylate **1** in CH_3CN for 24 h afforded [hexaEGmim][OMs] in 91% yield. [dihexaEGim][OMs] was prepared by *N*-alkylation of imidazole with hexaEG bromide **2** in the presence of K_2CO_3, followed by treatment of **3** with hexaEG mesylate **1** for two days.

Scheme 1. Preparation of Hexaethylene Glycol Substituted Imidazolium Salts (a) [hexaEGmim][OMs] and (b) [dihexaEGim][OMs]



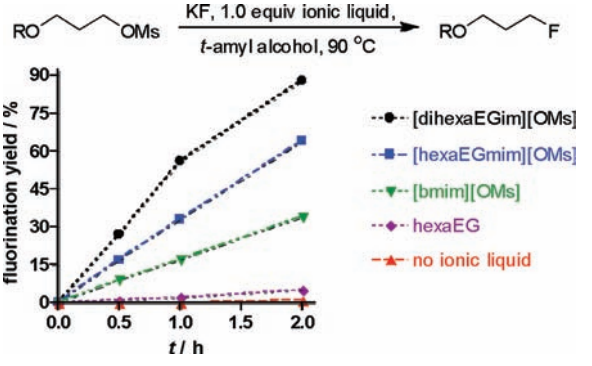


Figure 2. Catalytic activity of hexaEGILs, [hexaEGmim][OMs] and [dihexaEGim][OMs], in a nucleophilic fluorination reaction with KF. The quantity of product was determined by ^{1}H NMR. R = naphthyl.

To investigate the catalytic activity of these two hexaEGILs, we carried out the nucleophilic fluorination using 3 equiv of KF in the presence of the hexaEGILs (1.0 equiv) in a *tert*-amyl alcohol medium under uniform reaction conditions (at 90 °C for 2 h) and compared these results with results of the same reaction in the presence of a conventional IL [bmim][OMs] (bmim = 1-*n*-butyl-3-methylimidazolium) or hexaEG, or in the absence of any catalyst, as shown in Figure 2. Whereas KF was inactive in the fluorination, even in a *tert*-alcohol system without PTCs, the reactivity of KF

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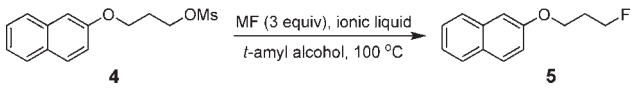
could be enhanced by all ILs in the same reactions. In particular, hexaEG substituted IL systems [hexaEGmim][OMs] and [dihexaEGim][OMs] showed much faster reaction rates than the conventional IL [bmim][OMs] system in the fluorination reaction. Furthermore, [dihexaEGim][OMs] containing two hexaEG components had highly efficient catalytic activity compared with monosubstituted [hexaEGmim][OMs]. These results were highly consistent with our hypothesis depicted in Figure 1 and showed that these hexaEGILs were well tailored to the specific organic reactions using alkali-metal fluoride.

Table 1. Fluorinations including [^{18}F]Radiofluorination of Mesylate **4** with Alkali-Metal Fluorides (MF) in the Presence of hexaEGILs[a]



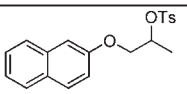
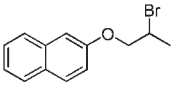
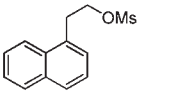
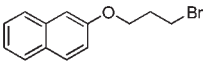
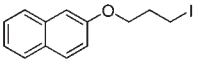
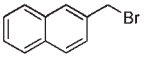
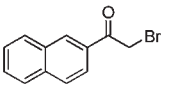
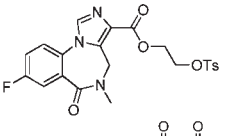
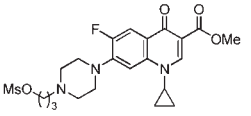
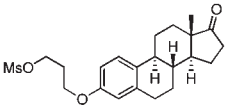
4 **5**

entry	ionic liquid (equiv)	MF (3 equiv)	time (h)	yield (%)[b]
1	1.0 mL of [hexaEGmim][OMs]	KF	45 min	95
2	[hexaEGmim][OMs] (2.0)	KF	1.5	96
3	[hexaEGmim][OMs] (1.0)	KF	2	96
4	[hexaEGmim][OMs] (0.5)	KF	3	98 (95)[c]
5	[hexaEGmim][OMs] (0.25)	KF	8	91
6	–	KF	12	10
7	[dihexaEGim][OMs] (0.5)	KF	2	98
8	[dihexaEGim][OMs] (0.5)	CsF	15 min	98 (95)[c]
9	[dihexaEGim][OMs] (0.5)	RbF	1	90
10	10 mg of [dihexaEGim][OMs]	$^{18}F^-/Cs_2CO_3$	15 min	98[d] (88)[e]
11[f]	–	[^{18}F]TBAF	15 min	85[d] (72)[e]

[a] All reactions were carried out on a 1.0 mmol reaction scale of mesylate **4** using 3 equiv of MF in 4.0 mL of *tert*-amyl alcohol at 100 °C. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Yields of isolated product in parentheses. [d] Yield determined by radio TLC. [e] Radiochemical yield. [f] Reference 3c.

Table 1 illustrates the nucleophilic fluorination (including [^{18}F]radiofluorination) of a model mesylate compound **4** with 3 equiv of various alkali-metal fluorides, such as KF, RbF, and CsF, employing the hexaEGILs as cosolvents, promoters, and catalysts in a *tert*-amyl alcohol medium at 100 °C. In entries 1–3, when using [hexaEGmim][OMs] as a cosolvent or promoter (0.1 mL, 2.0 and 1.0 equiv amounts, respectively), the fluorination reaction with KF proceeded smoothly, affording the desired fluoro-product **5** in excellent yields (95–96%). It should be noted that the use of catalytic amounts (0.5 and 0.25 equiv) of [hexaEGmim][OMs] was enough to complete the reaction within reasonable time periods (3 and 8 h) and to provide the product **5** in high yields (entries 4 and 5, 98 and 91%, respectively). In comparison, a *tert*-amyl alcohol system in the absence of any catalyst; this reaction proceeded remarkably slowly, converting only 10% of the mesylate **4** to the fluoro-compound **5** after extended reaction times (12 h, entry 6). Moreover, as shown in entry 7, the use of 0.5 equiv of [dihexaEGim][OMs], which is the best condition for this type reaction, allowed the same reaction with KF to proceed almost quantitatively within 2 h. Furthermore, the same fluorination using CsF in

Table 2. Nucleophilic Fluorinations of the Various Substrates with 3.0 equiv of KF Using [dihexaEGim][OMs] (0.5 equiv) ss a Catalyst

entry	substrate	method[a]	time (h)	yield (%)[b] product	yield (%)[b] alkene
1		A	4	91	9
2		B	1	59	41
3		A	12	72	28
4[c]		B	3	19	81
5		A	2.5	92	8
6		A	7	91	8
7		A	6	86	10
8		A	1	90	-
9		A	1	94	-
10		A	3	86	-
11		A	8	92	-
12		A	3	97	-

[a] Method A: reactions were carried out on a 1.0 mmol scale of substrate with 3.0 equiv of KF and 0.5 equiv of [dihexaEGim][OMs] in 4.0 mL of *tert*-amyl alcohol. Method B: with TBAF in *tert*-amyl alcohol. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Reference 9.

the presence of [dihexaEGim][OMs] proceeded to completion, in very high yield (98%), within only 15 min (entry 8). The other alkali-metal fluoride (RbF) also can be efficiently activated by the [dihexaEGim][OMs] organic catalyst in this substitution reaction (entry 9). To demonstrate that [dihexaEGim][OMs] can be used to introduce fluorine-18 into organic molecules for a PET study, we conducted the nucleophilic [^{18}F]radiofluorination with [^{18}F]fluoride generated from a cyclotron using [dihexaEGim][OMs], instead of conventional PTCs under no-carrier-added conditions. A comparison of entries 10 and 11 shows that when compared with the conventional method using tetrabutylammonium [^{18}F] fluoride ([^{18}F]TBAF), a radiolabeled compound [^{18}F]**5** was produced in higher radiochemical yield (88%, decay corrected) with a 15 min reaction time by this [dihexaEGim][OMs] labeling protocol.

Table 2 shows the fluorination of various substrates using 3 equiv of KF in the presence of 0.5 equiv of [dihexaEGim][OMs] in *tert*-amyl alcohol, thereby demonstrating that

[dihexaEGim][OMs] is generally applicable for various other substrates. In entries 1−4, the fluorination reaction of secondary alkyl tosylate and bromide, as base-sensitive substrates, using KF/[dihexaEGim][OMs] in *tert*-amyl alcohol proceeded with significant chemoselectivity, providing the desired secondary alkyl fluoride in high yield (91 and 78%, entries 1 and 3, respectively, Method A) compared with the same reaction using the conventional TBAF (entries 2 and 4). In these reactions, we anticipated that their chemoselectivity might be enhanced by the "flexible" fluoride effect generated from the controlled H-bonding between the terminal OH groups of [dihexaEGim][OMs], KF, and *tert*-alcohol media. Another base-sensitive substrate, 1-(2-mesyloxyethyl)naphthalene, could be converted to 1-(2-fluoroethyl)naphthalene in 92% yield, with the alkene byproduct being formed in only 8% yield by this KF/[dihexaEGim][OMs] protocol (entry 5). The displacement reactions of the primary alkyl bromide and iodide to the primary alkyl fluoride **5** using KF/[dihexaEGim][OMs] in *tert*-amyl alcohol also proceeded very selectively, affording **5** in excellent yield (91 and 86%, entries 6 and 7, respectively). The fluorination reaction of a benzylic bromide afforded the benzylic fluoride with 90% reaction yield (entry 8). An α-fluoroacetophenone was synthesized in 94% yield through the fluorination of the α-bromoacetophenone (entry 9). Various bioactive molecules such as fluoro-flumazenile,[10] fluoropropyl ciprofloxacin,[11] and fluoropropyl estrone, which can be molecular probes for PET, were produced in excellent yield by reactions with the corresponding tosylate and mesylate precursors (entries 10−12).

In summary, we have prepared new tailor-made hexaethylene glycolic imidazolium based ionic liquids (hexaEGILs) that act as highly efficient multifunctional organic catalysts designed for specific organic reactions such as nucleophilic fluorination with KF or [^{18}F]fluoride, which is known to be a particularly difficult chemical process. These hexaEGIL catalytic systems could not only significantly enhance the reactivity of KF but also reduce the formation of byproducts. Further studies are currently underway to develop more efficient oligoEGILs through structural modifications and to apply these unusual catalysts to other chemical reactions, including rapid ^{18}F labeling of radiopharmaceuticals for PET.

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Supporting Information Available. Experimental procedures and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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