Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 418

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PAPER

S_N2 Fluorination reactions in ionic liquids: a mechanistic study towards solvent engineering†‡

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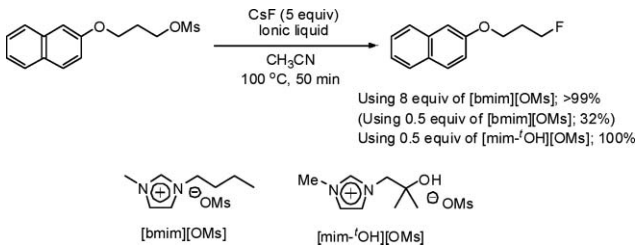
Received 15th July 2010, Accepted 16th September 2010
DOI: 10.1039/c0ob00426j

In the catalysis of S_N2 fluorination reactions, the ionic liquid anion plays a key role as a Lewis base by binding to the counterion Cs^+ and thereby reducing the retarding Coulombic influence of Cs^+ on the nucleophile F^-. The reaction rates also depend critically on the structures of ionic liquid cation, for example, n-butyl imidazolium gives no S_N2 products, whereas n-butylmethyl imidazolium works well. The origin of the observed phenomenal synergetic effects by the ionic liquid [mim-^{t}OH][OMs], in which *t*-butanol is bonded covalently to the cation [mim], is that the *t*-butanol moiety binds to the leaving group of the substrate, moderating the retarding interactions between the acidic hydrogen and F^-. This work is a significant step toward designing and engineering solvents for promoting specific chemical reactions.

Introduction

Ionic liquids have found a wide range of applications in all fields of chemistry because of their useful physicochemical properties. Besides being ideal solvent for a variety of chemical reactions due to high polarity, low volatility, and easy recovery, ionic liquids are also gaining tremendous importance as catalysts.[1] Many reactions that proceeded *via* reactive intermediates (alkyl, vinyl, arenium carbocations and oxygen radical anion) showed pronounced positive ionic liquid effects such as rate acceleration and increased regio- and stereoselectivity, originating from the stabilization of the reactive intermediates.[2] In addition to these multi-step reactions, significantly enhanced reactivity and selectivity have also been observed in a concerted reaction such as nucleophilic substitution reactions in ionic liquids.[2,3] As shown from the examples[3j] in Scheme 1, the use of an ionic liquid such as [bmim][OMs] for the S_N2 reaction[4] with CsF proceeds with remarkable rate acceleration and high chemoselectivity, in contrast to the corresponding reactions in common organic solvents. The efficiency of nucleophilic fluorination was further improved by employing the modified ionic liquid [mim-^{t}OH][OMs], which can complete the reaction within 1 h with catalytic amounts.[3j] However, the detailed mechanism and the role of ionic species



Scheme 1 S_N2 fluorination with CsF in ionic liquids.

(cation and anion) of ionic liquids for promoting these reactions have not been elucidated yet. Understanding of the origin of the positive role of ionic liquids[5] will give a significant impact for predicting their effects on other organic reactions and, moreover, for designing new catalytic reactions that do not work efficiently in conventional organic solvents.

In this work, we present a mechanistic detail of catalytic activity of ionic liquids for S_N2 reactions,[6–8] focusing on the role of ionic species in S_N2 fluorination reaction in various ionic liquids. For S_N2 reactions in [bmim][OMs] (bmim = n-butylmethyl imidazolium), we show that the ionic liquid anion plays a key role as a Lewis base by binding to the counterion Cs^+ and thereby reducing the retarding Coulombic influence of Cs^+ on the nucleophile. The F^- reacts as an ion pair (Cs^+F^-) rather than as a naked nucleophile here. We also carry out experiments using n-butyl thaizolium instead of n-butyl imidazolium, to examine the role of the ionic liquid cation, especially that of the acidic C2-hydrogen.[9] We elucidate the origin of oberved synergetic effects[3j] in catalysis of ionic liquid [mim-^{t}OH][OMs], in which *t*-butanol is bonded covalently to the cation [mim]. We find that the *t*-butanol moiety binds to the leaving group of the substrate, and also moderates the retarding interactions between the acidic hydrogen and F^-.

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† This publication is part of the web themed issue on fluorine chemistry.

‡ Electronic supplementary information (ESI) available: Calculation method, figures and tables. See DOI: 10.1039/c0ob00426j

Although we focus on fluorination reaction in this work, our findings will apply to other S_N2 reactions as well. We hope our work will constitute a significant step toward designing and engineering solvents for specific chemical reactions.

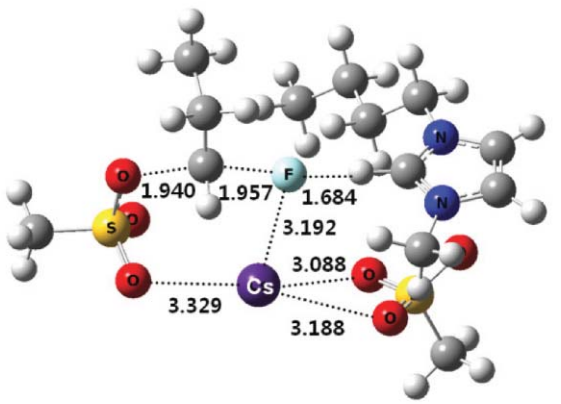
We employ the density functional theory method MPW1K[10,11] with the 6-311++G** basis set and the effective core potential for Cs (Hay-Wadt VDZ(n+1)),[12] as implemented in GAUSSIAN 03 set of programs.[13] Full intrinsic reaction coordinate (IRC) analysis is carried out to calculate the barriers and to confirm the reaction pathways. Zero point energies (ZPE) are taken into account, and default criteria are used for all optimizations. In order to reduce computational efforts, we adopt C_3H_7OMs as the model substrate for 3-(naphthalene-2-yloxy)-propyl-methanesulfonate, after finding that the naphthalene ring and the ether group do not play any significant role in the S_N2 fluorination reactions studied here.

Results and discussion

Fig. 1(a) presents the calculated mechanisms of S_N2 fluorination reaction [$Cs^+F^- + C_3H_7OMs \rightarrow C_3H_7F + Cs^+OMs^-$] in ionic liquid [bmim][OMs]. The cation [bmim], anion [OMs], nucleophile F^-, counterion Cs^+ and the leaving group of the substrate form a very stable and compact cyclic structure. The counterion Cs^+ binds both to F^- and the leaving group, allowing an ideal configuration for the nucleophilic attack. The role of the ionic liquid cation [bmim] and anion [OMs] for accelerating the reaction is clearly seen in [OMs] (and the leaving group) interacts with the counterion Cs^+, reducing the retarding Coulombic influence of Cs^+ on F^- (thus "freeing" F^-), whereas [bmim] 'collects' [OMs], Cs^+ and F^- for this ideal arrangement. The role of Cs^+ promoting the approach of F^- to the leaving group (the substrate) and that of [OMs] (acting as a Lewis base) to neutralize the Coulombic influence of Cs^+ on F^- seems to be the key factor in this mechanism, suggesting that choice and 'design' of the ionic liquid anion and the counterion will be critical. Binding of [bmim] to F^- may partially decrease the nucleophilicity of F^-, but the stronger influence of [OMs] on Cs^+ seems to overcome this, giving the reaction barrier ($E^‡$ = 20.3, $G^‡_{100°c}$ = 20.8 kcal mol^{-1}) that is quite similar to those in the very efficient S_N2 reactions in protic solvents *t*-butanol (20.4 kcal mol^{-1}) and ethylene glycol (20.0 kcal mol^{-1}) presented in earlier works. Based on these results, we demonstrate that the S_N2 rate constants in *t*-butanol,[9] ethylene glycol,[10] and in [bmim][OMs] are quite comparable, in good agreement with the observed excellent S_N2 rates in ionic liquids.[3e,f,g,j] According to the S_N2 mechanism depicted in Fig. 1(a), it seems that an ionic liquid with strong coordinating ability (*via* stronger influence on Cs^+) would be favourable.

	$E^‡$	$G^‡_{100°C}$	E	$G_{100°C}$
(a)	20.3	20.8	0	0
(b)	12.5	16.1	10.0	8.3

(a) S_N2 Mechanism I in [bmim][OMs]



(b) S_N2 Mechanism II in [bmim][OMs]

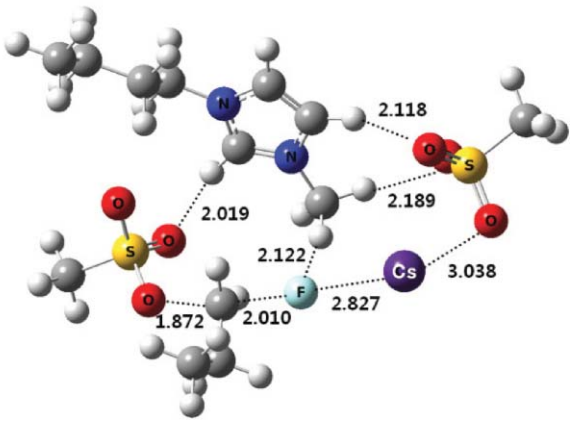
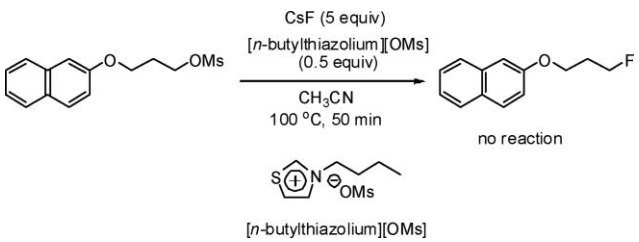


Fig. 1 Calculated transition states in S_N2 reaction in [bmim][OMs]. Energy and Gibbs free energy in kcal mol^{-1}, and bond lengths in Å (MPW1K/6-311++G**; ECP for Cs, Hay-Wadt VDZ(n+1)).

An alternative structure for the pre-reaction complex may be proposed in which the acidic hydrogen in the imidazolium ring may interact with the leaving group rather than with F^-, and this configuration is depicted in Fig. 1(b). The energy (Gibbs free energy) of this complex is calculated to be 10.0 (8.3) kcal mol^{-1} higher than that depicted in Fig. 1(a). Thus, although the reaction barrier ($E^‡$ = 12.5, $G^‡_{100°c}$ = 16.1 kcal mol^{-1}) is smaller than that depicted in Fig. 1(a), this mechanism is far less favourable on thermodynamic and kinetic grounds (the overall reaction barrier, $G^‡_{100°c}$ = 24.4 kcal mol^{-1}, starting from the most stable pre-reaction complex in Fig. 1(a) to the product in Fig. 1(b) is much larger than that ($G^‡_{100°c}$ = 20.8 kcal mol^{-1}) for the mechanism I). Therefore, the S_N2 mechanism presented in Fig. 1(a) seems to be far more feasible.

If the acidic hydrogen in the ionic liquid interacts with F^-, (the leaving group), then introducing a hydrogen with stronger acidity would decrease (increase) the reaction rate. We carried out the reaction using a thiazolium bearing a more acidic C2-proton than the imidazolium,[9] finding that S_N2 fluorination do *not* proceed at all (Scheme 2). Fig. 2 shows the calculated mechanism of S_N2 fluorination in [*N*-butylthiazolium][OMs]. The pre-reaction



Scheme 2 S_N2 fluorination with CsF in [*N*-butylthiazolium][OMs].

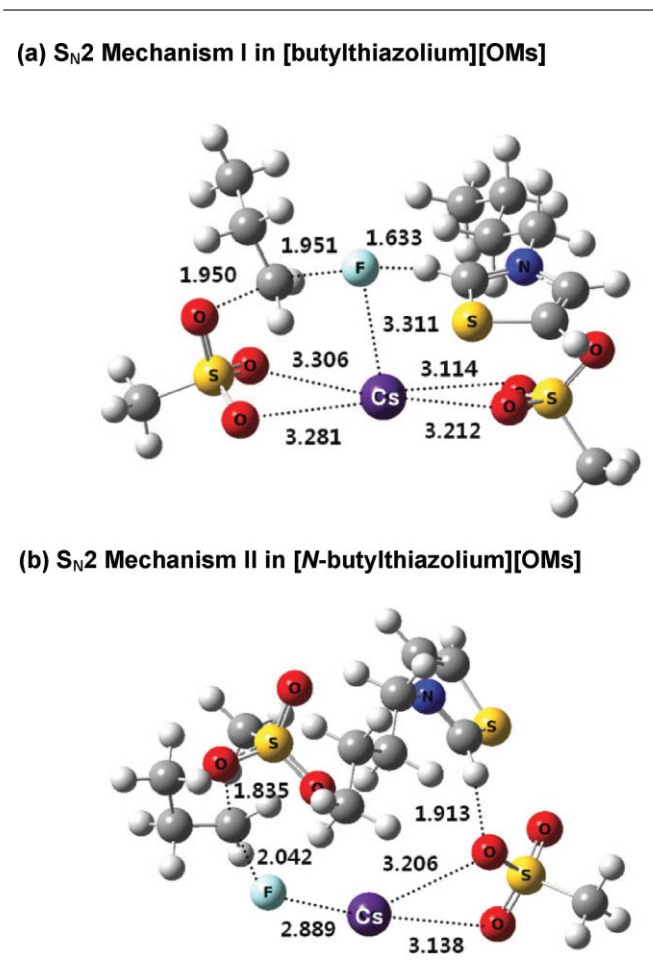


Fig. 2 Calculated transition states of S_N2 reaction in [*N*-butylthiazolium][OMs]. Energy and Gibbs free energy in kcal mol^{-1}, and bond lengths in Å (MPW1K/6-311++G**; ECP for Cs, Hay-Wadt VDZ(n+1)).

complex in which the acidic hydrogen binds to F^- is far more stable (ΔE = 10.9, ΔG = 12.4 kcal mol^{-1}) than the one where it interacts with the leaving group, overwhelming the relative kinetic feasibility of the pathway from the latter complex (barrier of the S_N2 reaction being ~6 kcal mol^{-1} smaller). The S_N2 barrier ($E^‡$ = 21.5, $G^‡_{100°c}$ = 23.2 kcal mol^{-1}) presented in Fig. 2(a), which is larger than that in Fig. 1(a) by ~1.2 kcal mol^{-1}, is also in agreement with the observed inefficiency of the liquid ion [*N*-butylthiazolium][OMs]. Considering these experimental and theoretical observations, we conclude that the acidic hydrogen in imidazolium binds to F^- rather than to the leaving group, as illustrated in Fig. 1(a). We also carry out calculations for S_N2 fluorination in [bmin][BF_4] to examine the effects of the ionic liquid anion. The barrier $G^‡_{100°c}$ is calculated to be 21.9 kcal mol^{-1}, a bit larger than that (20.8) in [bmin][BF_4], in excellent agreement with the observed smaller S_N2 yield in [bmin] [BF_4] than in [bmin][OMs]. These are summarized in Tables 1 and 2.

It is useful to note that the role of the ionic liquid anions discussed here is quite analogous to that of protic solvent[14–16] and bis-terminal hydroxypolyethers previously reported by us.[17] That is, they act on the counterion Cs^+ as a Lewis base, alleviating the Coulombic influence of Cs^+ on F^- and thus "freeing" from Cs^+. If these effects of ionic liquid anion and the –OH group of protic solvent are "combined", the catalytic effects of ionic liquid may be

Table 1 Calculated barriers of S_N2 reactions [Cs^+F^- + C_3H_7OMs → C_3H_7F + Cs^+OMs^-] (energy and Gibbs free energy in kcal mol^{-1}) in ionic liquids

Ionic liquids	$E^‡$	$G^‡_{100°c}$	Observed S_N2 Yield (%)
[*N*-butylthiazolium][OMs]	21.5	23.2	0[a]
[bmim][BF_4]	19.8	21.9	24[b]
[bmim][OMs]	20.3	20.8	32[b]
[mim-^{t}OH][OMs]	16.0	19.1	100[b]

[a] Reaction was carried out on a 0.2 mmol scale of 3-(naphthalen-2-yloxy)propyl methanesulfonate with 5 equiv. of CsF using 8 equiv. of [*N*-butylthiazolium][OMs] in CH_3CN (0.6 mL) for 50 min at 100 °C. [b] From Ref. 3j: Reactions were carried out on a 1.0 mmol scale of substrate 3-(naphthalen-2-yloxy)propyl methanesulfonate with 5 equiv. of CsF using 0.5 equiv. of ionic liquid in CH_3CN (3.0 mL) for 50 min at 100 °C.

Table 2 Activation barriers $E^‡$ and $G^‡_{100°c}$, and relative energies E an Gibbs free energies $G_{100°c}$ of the pre-reaction complexes of S_N2 reaction in [*N*-butylthiazolium][OMs] (kcal mol^{-1}). (MPW1K/6-311++G**; ECP for Cs, Hay-Wadt VDZ(n+1))

	$E^‡$	$G^‡_{100°c}$	E	$G_{100°c}$
(a)	21.5	23.2	0	0
(b)	15.1	16.8	10.9	12.4

enhanced by synergetic effects (*i.e.*, the counter anion of the ionic liquid acts as a Lewis base toward Cs^+, drastically reducing its electrostatic effects and thereby "freeing" the F^- nucleophile, and the acidic –OH proton interacts with the mesylate leaving group, helping it to detach from the reactant). Based on this idea, Chi and co-workers[3j] synthesized the ionic liquids [mim-^{t}OH][OMs] (Scheme 1), in which *t*-BuOH is combined to the imidazolium by covalent bonding. The ionic liquid [mim-^{t}OH][OMs] was found to be remarkably efficient, making the S_N2 fluorination proceed to completion in less than an hour as presented in the last entry in Table 1. Fig. 3 gives a mechanistic detail to elucidate the nature of the 'synergetic' effects, presenting the two alternative mechanisms in which the role of *t*-BuOH differs: In Mechanism I, the –OH group acts as additional Lewis base binding to the counterion Cs^+ to further reduce its Coulombic influence on the nucleophile F^-, whereas in Mechanism II it interacts with the leaving group. We find that the reaction barriers ($E^‡$ = 15~16, $G^‡_{100°c}$ = 17~19 kcal mol^{-1}) for both mechanisms are far smaller than that ($E^‡$ = 20.3, $G^‡_{100°c}$ = 20.8 kcal mol^{-1}) in [bmim][OMs], in excellent agreement with the experimentally observed phenomenal efficiency of the ionic liquid [mim-^{t}OH][OMs] for accelerating S_N2 fluorination. The Mechanism II depicted in Fig. 3(b) would be overwhelmingly favoured, because the calculated energy (Gibbs free energy) of the pre-reaction complex presented in Fig. 3(a) is found to be much higher (by 11.9 (10.7) kcal mol^{-1}). Therefore, it is concluded that the *t*-BuOH moiety acts as an 'anchor' to the leaving group for facile nucleophilic attack by F^-, rather than as a Lewis base to Cs^+. It is also worth noting that the distance between the acidic hydrogen and F^- (1.704 Å) in the pre-reaction complex in Fig. 3(b) is much larger than that (1.537 Å) in Fig. 1(a), indicating that the *t*-BuOH group helps to decrease the retarding effects of the H–F^- interaction. In Fig. 3(c) we describe the mechanism of the corresponding E2 process. It is calculated to proceed *via* the

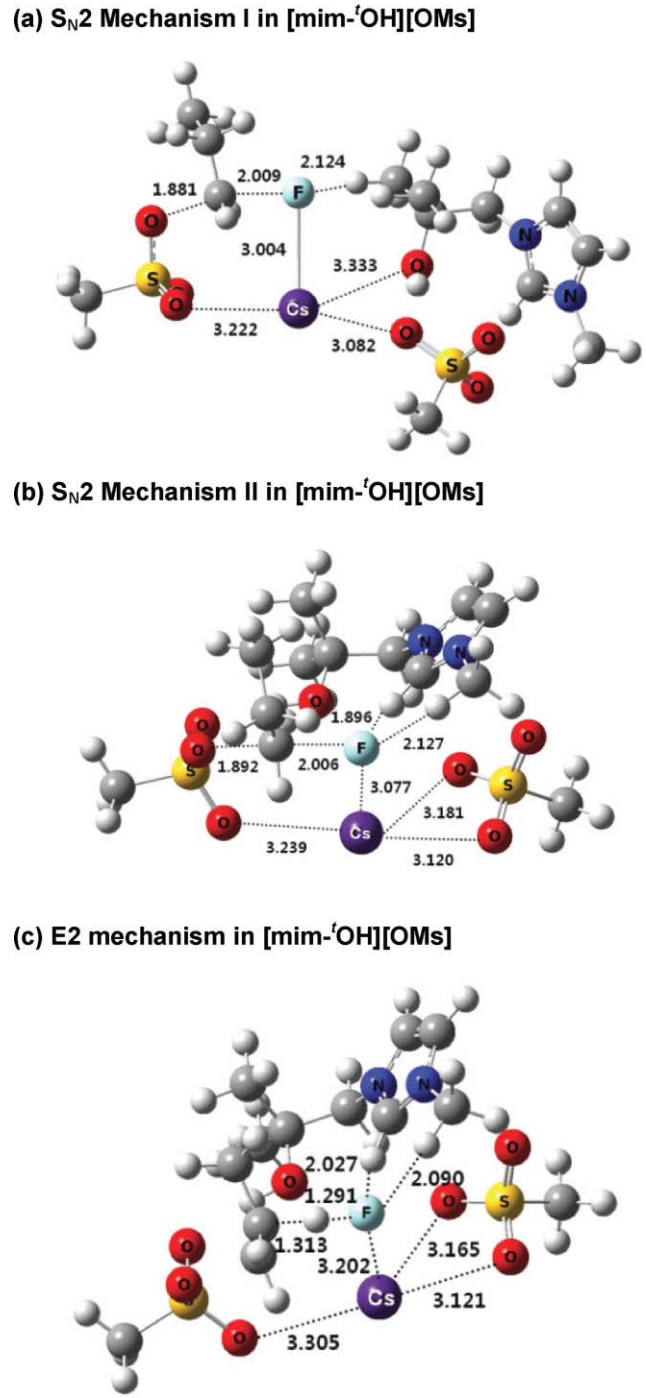


Fig. 3 Calculated transition states in S_N2 reaction (a), (b) and E2 reaction (c) in [mim-^{t}OH][OMs]. Energy and Gibbs free energy in kcal mol^{-1}, and bond lengths in Å (MPW1K/6-311++G**; ECP for Cs, Hay-Wadt VDZ(n+1)).

activation barrier of $E^{\ddagger} = 24.9$, $G^{\ddagger}_{100°c} = 26.1$ kcal mol^{-1} (Table 3), which is much larger than that of S_N2 fluorination, in excellent agreement with the experimentally observed complete (100%) S_N2 fluorination with no E2 by-product. This is in contrast with the 4% yield for the E2 product obtained in the S_N2 fluorination reaction in [bmim][OMs].

Table 3 Activation barriers $E^{\ddagger}$ and $G^{\ddagger}_{100°c}$, and relative energies E and Gibbs free energies $G_{100°c}$ of the pre-reaction complexes of S_N2 and E2 reactions in [mim-^{t}OH][OMs] (kcal mol^{-1}). (MPW1K/6-311++G**; ECP for Cs, Hay-Wadt VDZ(n+1))

	$E^{\ddagger}$	$G^{\ddagger}_{100°c}$	E	$G_{100°c}$
(a)	15.6	17.3	11.9	10.7
(b)	16.0	19.1	0	0
(c)	24.9	26.1	0	0

Conclusions

We have presented the mechanism of S_N2 reactions in ionic liquids that fully accounts for the newly developed catalytic capacity of ionic liquids. We have elucidated the origin of remarkable efficiency of [mim-^{t}OH][OMs] as the combined synergetic efforts of the ionic liquid anion and the –OH group acting as an 'anchor' to the substrate. Our work demonstrates that one may indeed "tailor" the solvent to promote a specific chemical reaction, by systematically designing the structures of ionic liquids. We hope that our present work will open a new perspective in solvent engineering.

Acknowledgements

This work was supported by grants from the Ministry of health, welfare and family affairs of Korea, NRF-20090085824 (Basic Science Research Program), NRF-20090094024 (Priority Research Centers Program), R11-2005-008-00000-0 (SRC program of MEST /KOSEF), R31-2008-000-10029-0 (WCU program), and the Ministry of Education, Science and Technology (Converging Research Program, 2010K001050 and 2010K001203).

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