Origin of Salt Effects in $S_N2$ Fluorination Using KF Promoted by Ionic Liquids: Quantum Chemical Analysis

Young-Ho Oh and Sungyul Lee *

Department of Applied Chemistry, Kyung Hee University, Deogyeong-daero 1732, Yongin City 446-701, Korea; chem_yhoh@daum.net
* Correspondence: sylee@khu.ac.kr; Tel.: +82-31-201-2698

Abstract: Quantum chemical analysis is presented, motivated by Grée and co-workers’ observation of salt effects [Adv. Synth. Catal. 2006, 348, 1149–1153] for $S_N2$ fluorination of KF in ionic liquids (ILs). We examine the relative promoting capacity of KF in [bmim]PF$_6$ vs. [bmim]Cl by comparing the activation barriers of the reaction in the two ILs. We also elucidate the origin of the experimentally observed additional rate acceleration in IL [bmim]PF$_6$ achieved by adding KPF$_6$. We find that the anion PF$_6^-$ in the added salt acts as an extra Lewis base binding to the counter-cation K$^+$ to alleviate the strong Coulomb attractive force on the nucleophile F$^-$, decreasing the Gibbs free energy of activation as compared with that in its absence, which is in good agreement with experimental observations of rate enhancement. We also predict that using 2 eq. KF together with an eq. KPF$_6$ would further activate $S_N2$ fluorination.

Keywords: $S_N2$ fluorination; salt effect; ionic liquid; mechanism

1. Introduction

Besides the numerous advantages as solvents, ionic liquids (ILs) [1–9] are being used as extremely versatile and efficient organocatalysts/promoters in many chemical reactions [10–20]. This role of ILs for accelerating chemical reaction rates is due to the ionic nature of IL cations and anions, which exert strong electrostatic (Coulombic) forces on the participants in the reaction system. This seems to be especially notable for $S_N2$ reactions [10,11,20–27], because in this fundamental process the nucleophile may possess negative charges (halides, CN$^-$, NH$_2^-$, OH$^-$ etc.) that strongly interact with the relation counter-cations (alkali metal cations, tetraalkyl ammonium cations, etc.) and substrates. IL anions and cations may also interact with the substrates via hydrogen bonding. Elucidating the mechanism of ILs for enhancing the rates and yields of $S_N2$ reactions would certainly help to design task-specific ILs by monitoring these interactions. As for $S_N2$ fluorination, many schemes have been employed using ILs comprising the 1-butyl-3-methylimidazolium (bmim$^+$) or derivatives as the IL cation and IL anion such as OMs$^-$, Br$^-$, OTf$^-$ or PF$_6^-$ and the fluorinating agents such as CsF or KF. This class of ILs are called “phase transfer catalysts” because it looks as if the nucleophile F$^-$ takes the place of the IL anion for efficient $S_N2$ fluorination. The mechanism of this scheme was elucidated previously by Lee and co-workers [10,22–27]. It was observed in numerous studies that the capacity of ILs as catalysts/promoters for $S_N2$ reactions depend strongly on the structure of ILs. Kim and co-workers [11,26], for example, found that $S_N2$ fluorination may be promoted or suppressed depending on the structure of IL cation: While $S_N2$ fluorination may proceed well (yield = 90% in 2 h) in [bmim]PF$_6$, the reaction is completely suppressed in [hexaethylene glycol-mim]PF$_6$. They also observed that [bmim]PF$_6$ is a much better catalyst than [bmim]OMs or [bmim]OTs, demonstrating the conspicuous influence of the IL anion.

Grée and co-workers’ experimental study of $S_N2$ fluorination by KF in ILs is of high interest in this field. They observed [28] that addition of salts such as KPF$_6$ produced notable salt effects in $S_N2$ fluorination promoted by imidazolium ionic liquids using KF as
Grée and co-workers’ experimental study of SN2 fluorination by KF in ILs [28].

2.1. SN2 Fluorination without Salt Effects: Using 1 eq. of KF in [bmim]PF6

Figure 1. Fluorination by KF in ILs [28].

Scheme 1. SN2 fluorination of trichlorotoluene by KF [28].

Here we present quantum chemical calculations for model systems to theoretically analyze Grée and co-workers’ experiments. We provide a possible explanation for the origin of the experimentally observed additional rate enhancement in ionic liquid [bmim]PF6 achieved by adding the salt KPF6. We find that the anion PF6− in the added salt acts as an extra Lewis base binding the counter-cation K+ to the nucleophile, mitigating its strong Coulomb attractive force on F−. The effects of the added salt are revealed as decreased Gibbs free energy of activation as compared with that in the absence of salt effects (using 1 eq. of KF). We also show that using 2 eq. of the reactant KF produces effects similar to adding an eq. of KPF6. The fluoride in the extra KF acts not as a nucleophile but as an additional Lewis base binding to the counter-cation K+ to activate the reaction.

2. Results

Scheme 1 and Figure 1 present SN2 fluorination experimentally observed by Grée and coworkers. Of the ILs used, [bmim]PF6 seems to give better performance as the promoter of the reaction, resulting in a reaction yield of ~86% in 5 h. The corresponding yield in [bmim]Cl was only ~30%, indicating that the latter IL is much less efficient. Figure 1 also shows the activation of fluorination process by adding the salt KPF6, by which the reaction essentially completes in 2 h.

First, we study the case of using a substrate:KF ratio of 1:1, in which the metal salt acts only as fluorinating agent, that is, as the source of F−, thus no salt effects may be ascribed to this situation. Figure 2 presents the transition states (TSs) and energetics for this process (for coordinates and structures of pre- and post-reaction complexes, see Supplementary Materials. The reference for the zero of the free energy is taken as the ‘free’ reactants, for which the substrate, the CIPs KF, [bmim]PF6 or [bmim]Cl are all separated from one another
in solution phase). The IL [bmim]PF$_6$ and KF are used as the promoter and fluorinating agent, respectively, in the same amount as the substrate (substrate:KF:[bmim]PF$_6$ = 1:1:1). We found two reaction routes, case 1 and case 2 with Gibbs free energy of activation $G^\ddagger$ of 22.8 and 21.4 kcal/mol, respectively. The energetics of the reaction depicted in Figure 2 predicts that the reaction would proceed by the mechanism with lower $G^\ddagger$ (case 2) according to the Curtin–Henderson principle (When no equilibrium occurs between the free reactants and pre-reaction complex, the reaction proceeds preferably via the path with the lowest Gibbs free energy TS, irrespective of the Gibbs free energies of pre-reaction complexes) [29]. Here, the metal salt KF reacts as a contact ion pair, and electronegative F atoms in the IL anion PF$_6^-$ act as Lewis base coordinating to the counter-cation K$^+$, alleviating the latter’s adverse Coulombic influence on the nucleophile F$^-$. The main difference between the two mechanisms is the position of the counter-cation K$^+$. It seems that in (Case 2), K$^+$ is further stabilized by interacting with the electron abundant phenyl ring.

Figure 2. Calculated (a) transition states and (b) energetics of $S_N2$ fluorination in [bmim]PF$_6$ with substrate: KF = 1:1.

Figure 3 depicts the TSs and the energetics of $S_N2$ fluorination under the promoting effects of [bmim]Cl. Again, with a substrate:KF ratio of 1:1. We obtained two alternative routes, of which the (case 2) is more favorable with lower $G^\ddagger$ (23.9 kcal/mol). The higher $G^\ddagger$ than that (21.4 kcal/mol) for the $S_N2$ fluorination in [bmim]PF$_6$ seems to be in agreement with the experimentally observed lower reaction yield (~30%) as compared with that (~90%) in [bmim]PF$_6$. This difference in the promoting influence of the two ILs may result from the difference in the ability of the IL anions Cl$^-$ and PF$_6^-$: More electronegative and
numerous F atoms in PF$_6^-$ may donate partial negative charges to the counter-cation K$^+$ much better than Cl$^-$. Figure 3. Calculated (a) transition states and (b) energetics of S$_N$2 fluorination in [bmim]Cl with substrate: KF = 1:1.

2.2. Salt Effects: Adding KPF$_6$ or Using 2 Eq. of KF

The most proper question to ask would be: What is the mechanism of S$_N$2 rate enhancement by the added salt by KPF$_6$? Figure 4 presents the TSs and energetics for S$_N$2 fluorination promoted by [bmim]PF$_6$ and activated by KPF$_6$. The role of the added salt may be seen clearly from the structures of the TSs: In both TSs the anion PF$_6^-$ binds to the two K$^+$, acting as an additional Lewis base on the counter-cation K$^+$ to the nucleophile F$^-$. As a result, the Gibbs free energy of activation now decreases to 16.4 kcal/mol from that (21.4 kcal/mol) in the absence of salt effects given in Figure 2. We think that this is the origin of rate enhancement by adding KPF$_6$ observed by Grée and co-workers. In the presence of additional KPF$_6$, more electrostatic interactions are allowed (PF$_6^-$ . . . K$^+$ . . . F$^-$, PF$_6^-$ . . . bmim$^+$ ring, and PF$_6^-$ . . . K$^+$ . . . PF$_6^-$) than in its absence, thus stabilizing the TS. For example, the natural bond orbital charge of the H atom nearest to PF$_6^-$ decreases from +0.283 (Figure 2a) to +0.264 (Figure 2a), clearly showing the electrostatic influence of the anion.
Figure 4. Calculated (a) transition states and (b) energetics of S_N2 fluorination in [bmim]PF_6 activated by KPF_6, with substrate:KF:KPF_6 = 1:1:1.

If this is the case, then it can be expected that any salt, including KF, may also do, as long as its anion is capable of influencing the reaction as a Lewis base. Indeed, Grée and co-workers used 2 eq. of KF in their experiments with excellent S_N2 yields. In order to examine this case, we carried out calculations for S_N2 fluorination in [bmim]PF_6 with a substrate:KF ratio of 1:2. Figure 5 shows the TS for the most feasible reaction pathway and the corresponding energetics for S_N2 fluorination. The role of additional eq. KF is clearly seen: The extra F^- acts not as a nucleophile, but as an extra Lewis base on the counter-cation K^+ to the nucleophile, with the two K^+s and two F^-s forming a rectangular configuration.
2.3. Salt Effects: Using 2 KF plus 1 Eq. KPF$_6$ in [bmim]PF$_6$

Finally, we examine the most complicated system, in which two eq. KF and 1 eq. KPF$_6$ are used for S$_N$2 fluorination in [bmim]PF$_6$. In this situation, KF and KPF$_6$, each of 1 eq., may activate the reaction in collaboration. Figure 6 describes the TS for the most favorable mechanism and the corresponding energetics. The two anions F$^-$ and PF$_6^-$ now help to reduce the Coulombic influence of the counter-cation K$^+$, further lowering the $G^\ddagger$ to 9.1 kcal/mol.

3. Computational Details

The M06-2X/6-311G** method [30–32] was employed as implemented in Gaussian16 [33]. We adopted the cluster/continuum approximation [8] (accounting for the full solvent effect [34]) would require a molecular dynamics approach incorporating a few hundred explicit solvent molecules under periodic boundary condition), including the effects of the solvent continuum by the SMD-PCM method [35]. For the values of the dielectric constants of [bmim]Cl and [bmim]PF$_6$, we used 15.0 and 14.0, respectively [36]. We carried out an extensive search for stationary states over the potential energy surface of the system (substrate plus 1 or 2 IL unit). Pre-reaction and post-reaction complexes were obtained by verifying that all harmonic frequencies be real. Transition states were obtained by ascertaining the imaginary frequency of the reaction coordinate, and also by performing the intrinsic reaction coordinate analysis.
4. Conclusions

We presented a quantum chemical analysis to account for the activation of SN\textsubscript{2} fluorination by added salts. The role of the anion (F\textsuperscript{−} or PF\textsubscript{6}\textsuperscript{−}) of the added salt KF or KPF\textsubscript{6}\textsuperscript{−} seems to be an extra Lewis base acting on the counter-cation K\textsuperscript{+} to enhance the rate constants. These features of fluorination are in line with our proposed SN\textsubscript{2} mechanism in which the metal salt reacts as a contact ion-pair \cite{37-40} and the counter-cation (alkali metal cation) is ‘neutralized’ by the Lewis base promoter.

Supplementary Materials: The following are available online, Figure S1. Structures of pre- and post- reaction complexes for SN\textsubscript{2} fluorination in [bmim]PF\textsubscript{6} with substrate: KF = 1:1. Figure S2. Structures of pre- and post- reaction complexes Structures of pre- and post- reaction complexes for SN\textsubscript{2} fluorination in [bmim]Cl with substrate: KF = 1:1. Figure S3. Structures of pre- and post- reaction complexes for SN\textsubscript{2} fluorination in [bmim]PF\textsubscript{6}, with substrate: KF : KPF\textsubscript{6} = 1:1. Figure S4. Structures of pre- and post- reaction complexes for SN\textsubscript{2} fluorination in [bmim]PF\textsubscript{6}, with substrate: KF : KPF\textsubscript{6} = 1:2. Figure S5. Structures of pre- and post- reaction complexes for SN\textsubscript{2} fluorination in [bmim]PF\textsubscript{6}, with substrate: KF : KPF\textsubscript{6} = 1:2:1. Cartesian coordinates.

Author Contributions: Conceptualization; S.L., Y.-H.O.; methodology, Y.-H.O.; software, Y.-H.O.; formal analysis, S.L., Y.-H.O.; investigation, Y.-H.O.; resources, S.L.; writing—original draft preparation, Y.-H.O.; writing—review and editing, S.L.; visualization, Y.-H.O.; project administration, S.L.; funding acquisition, S.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by National Research of Korea (NRF-2019R1F1A1057609).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

References
1. Sheldon, R. Catalytic reactions in ionic liquids. Chem. Commun. 2001, 2399–2407. [CrossRef] [PubMed]
2. Wasserscheid, P.; Keim, W. Ionic Liquids—New “Solutions” for Transition Metal Catalysis. Angew. Chem. 2000, 39, 3772–3789. [CrossRef]
3. Welton, T. Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis. Chem. Rev. 1999, 99, 2071–2083. [CrossRef] [PubMed]
4. Dupont, J.; De Souza, R.F.; Suarez, P.A.Z. Ionic liquid (molten salt) phase organometallic catalysis. Chem. Rev. 2002, 102, 3667–3692. [CrossRef] [PubMed]
5. Dupont, J.; Suarez, P.A.Z. Physico-chemical processes in imidazolium ionic liquids. Phys. Chem. Chem. Phys. 2006, 8, 2441–2452. [CrossRef]
6. Binnemans, K. Ionic liquid crystals. Chem. Rev. 2005, 105, 4148–4204. [CrossRef] [PubMed]
7. Miao, W.; Tak, H.C. Ionic-liquid-supported synthesis: A novel liquid-phase strategy for organic synthesis. Acc. Chem. Res. 2006, 39, 897–908. [CrossRef] [PubMed]
8. Pliego, J.R.; Riveros, J.M. The cluster-continuum model for the calculation of the solvation free energy of ionic species. J. Phys. Chem. A 2001, 105, 7241–7247. [CrossRef]
9. Hallett, J.P.; Welton, T. Room-temperature ionic liquids: Solvents for synthesis and catalysis. 2. Chem. Rev. 2011, 111, 3508–3576. [CrossRef]
10. Oh, Y.H.; Jang, B.H.; Im, S.; Song, M.J.; Kim, S.Y.; Park, S.W.; Chi, D.Y.; Song, C.E.; Lee, S. SN2 Fluorination reactions in ionic liquids: A mechanistic study towards solvent engineering. Org. Biomol. Chem. 2011, 9, 418–422. [CrossRef]
11. Kim, D.W.; Song, C.E.; Chi, D.Y. New method of fluorination using potassium fluoride in ionic liquid: Significantly enhanced reactivity of fluoride and improved selectivity. J. Am. Chem. Soc. 2002, 124, 10278–10279. [CrossRef]
12. Xu, L.; Chen, W.; Ross, J.; Xiao, J. Palladium-catalyzed regioselective arylation of an electron-rich olefin by aryl halides in ionic liquids. Org. Lett. 2001, 3, 295–297. [CrossRef]
13. Böhm, V.P.W.; Herrmann, W.A. Nonaqueous ionic liquids: Superior reaction media for the catalytic Heck-Vinylation of chloroarenes. Chem. Eur. J. 2000, 6, 1017–1025. [CrossRef]
14. Min, B.K.; Lee, S.S.; Kang, S.M.; Kim, J.; Kim, D.W.; Lee, S. Mechanism of Nucleophilic Fluorination Facilitated by a Pyrene-tagged Ionic Liquids: Synergistic Effects of Pyrene–Metal Cation π-Interactions. Bull. Korean Chem. Soc. 2018, 39, 1047–1053. [CrossRef]
15. Lee, S.; Kim, D.W. Sustainable Catalysis in Ionic liquids; CRC Press Publishing: New York, NY, USA, 2018.
16. Lee, J.W.; Shin, J.Y.; Chun, Y.S.; Jang, B.H.; Song, C.E.; Lee, S.G. Toward understanding the origin of positive effects of ionic liquids on catalysis: Formation of more reactive catalysts and stabilization of reactive intermediates and transition states in ionic liquids. Acc. Chem. Res. 2010, 43, 985–994. [CrossRef]
17. Newington, I.; Perez-Arlandis, J.M.; Welton, T. Ionic liquids as designer solvents for nucleophilic aromatic substitutions. Org. Lett. 2007, 9, 5247–5250. [CrossRef]
18. Jadhav, V.H.; Jang, S.H.; Jeong, H.J.; Lim, S.T.; Sohn, M.H.; Kim, J.Y.; Lee, S.; Lee, J.W.; Song, C.E.; Kim, D.W. Oligoethylene glycols as highly efficient multifunctional promoters for nucleophilic-substitution reactions. Chem. Eur. J. 2012, 18, 3918–3924. [CrossRef]
19. Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. Diels-Alder Reactions in Room-Temperature Ionic Liquids. Tetrahedron Lett. 1999, 40, 793–796. [CrossRef]
20. Gauchot, V.; Schmitzer, A.R. Asymmetric aldol reaction catalyzed by the anion of an ionic liquid. J. Org. Chem. 2012, 77, 4917–4923. [CrossRef]
21. Xu, L.; Chen, W.; Xiao, J. Heck reaction in ionic liquids and the in situ identification of N-heterocyclic carbene complexes of palladium. Organometallics 2000, 19, 1123–1127. [CrossRef]
22. Oh, Y.H.; Choi, H.; Park, C.; Kim, D.W.; Lee, S. Harnessing ionic interactions and hydrogen bonding for nucleophilic fluorination. Molecules 2020, 25, 721. [CrossRef]
23. Shinde, S.S.; Lee, B.S.; Chi, D.Y. Synergistic effect of two solvents, tert-alcohol and ionic liquid, in one molecule in nucleophilic fluorination. Org. Lett. 2008, 10, 733–735. [CrossRef]
24. Lee, J.W.; Oliveira, M.T.; Jang, H.B.; Lee, S.; Chi, D.Y.; Kim, D.W.; Song, C.E. Hydrogen-bond promoted nucleophilic fluorination: Concept, mechanism and applications in positron emission tomography. Chem. Soc. Rev. 2016, 45, 4638–4650. [CrossRef]
25. Lee, J.W.; Yan, H.; Jang, H.B.; Kim, H.K.; Park, S.; Lee, S.; Chi, D.Y.; Song, C.E. Bis-Terminal Hydroxy Polyethers as All-Purpose, Multifunctional Organic Promoters: A Mechanistic Investigation and Applications. Angew. Chem. 2009, 121, 7819–7822. [CrossRef]
26. Jadhav, V.H.; Kim, J.Y.; Chi, D.Y.; Lee, S.; Kim, D.W. Organocatalysis of nucleophilic substitution reactions by the combined effects of two promoters fused in a molecule: Oligoethylene glycol substituted imidazolium salts. Tetrahedron 2014, 70, 533–542. [CrossRef]
27. Oh, Y.-H.; Ahn, D.-S.; Chung, S.-Y.; Jeon, G.-H.; Park, S.; Oh, S.J.; Kim, D.W.; Kil, H.S.; Chi, D.Y.; Lee, S. Facile Sn2 reaction in protic solvent: Quantum chemical analysis. J. Phys. Chem. A 2007, 111. [CrossRef]
28. Anguille, S.; Garayt, M.; Schanen, V.; GREE, R. Activation of nucleophilic fluorination by salts in ionic liquids and in sulfolane. Adv. Synth. Catal. 2006, 348, 1149–1153. [CrossRef]
29. Seeman, J.I. Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin-Hammett-Winstein-Holness kinetics. Chem. Rev. 1983, 83, 83–134. [CrossRef]
30. Zhao, Y.; Truhlár, D.G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other function. Theor. Chem. Acc. 2008, 120, 215–241. [CrossRef]
31. McLean, A.D.; Chandler, G.S. Contracted Gaussian basis sets for molecular calculations. I. Second row atoms, Z= 11–18. J. Chem. Phys. 1980, 72, 5639–5648. [CrossRef]
32. Krishnan, R.; Binkley, J.S.; Seeger, R.; Pople, J.A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. J. Chem. Phys. 1980, 72, 650–654. [CrossRef]
33. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Petersson, G.A.; Nakatsuji, H.; et al. Available online: https://gaussian.com/g09citation/ (accessed on 2 June 2016).
34. Chiappe, C.; Mennucci, B.; Pomelli, C.S.; Angelo Sanzone, A.; Marra, A. A theoretical study of the copper(ii)-catalyzed 1,3-dipolar cycloaddition reaction in dabcro-based ionic liquids: The anion effect on regioselectivity. Phys. Chem. Chem. Phys. 2010, 12, 1958–1962. [CrossRef]
35. Marenich, A.V.; Cramer, C.J.; Truhlar, D.G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and constant atomic surface tensions. J. Phys. Chem. B 2009, 113, 6378–6396. [CrossRef] [PubMed]
36. Singh, T.; Kumar, A. Static dielectric constant of room temperature ionic liquids: Internal pressure and cohesive energy density approach. J. Phys. Chem. B 2008, 112, 12968–12972. [CrossRef] [PubMed]
37. Laloo, J.Z.A.; Rhyman, L.; Larrañaga, O.; Ramosami, P.; Bickelhaupt, F.M.; de Cózar, A. Ion-Pair SN2 Reaction of OH- and CH3Cl: Activation Strain Analyses of Counterion and Solvent Effects. Chem. Asian J. 2018, 13, 1138–1147. [CrossRef] [PubMed]
38. Streitwieser, A.; Jayasree, E.G.; Hasanayn, F.; Leung, S.S.H. A theoretical study of the S22 reaction of allylic halides: Role of ion pairs. J. Org. Chem. 2008, 73, 9426–9434. [CrossRef] [PubMed]
39. Bouvet, S.; Pegot, B.; Marrot, J.; Magnier, E. Solvent free nucleophilic introduction of fluorine with [bmim][F]. Tetrahedron Lett. 2014, 55, 826–829. [CrossRef]
40. Kim, S.K.; Sessler, J.L. Calix[4]pyrrole-Based Ion Pair Receptors. Acc. Chem. Res. 2014, 47, 2525–2536. [CrossRef]