

Very Efficient Nucleophilic Aromatic Fluorination Reaction in Molten Salts: A Mechanistic Study[†]

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We report a quantum chemical study of an extremely efficient nucleophilic aromatic fluorination in molten salts. We describe that the mechanism involves solvent anion interacting with the ion pair nucleophile M^+F^- ($M = Na, K, Rb, Cs$) to accelerate the reaction. We show that our proposed mechanism may well explain the excellent efficiency of molten salts for S_NAr reactions, the relative efficacy of the metal cations, and also the observed large difference in rate constants in two molten salts ($n\text{-C}_4\text{H}_9\text{N}^+\text{CX}_3\text{SO}_3^-$, ($X=H, F$) with slightly different sidechain ($-\text{CH}_3$ vs. $-\text{CF}_3$).

Key Words : Mechanism, S_NAr , Molten salt

Introduction

Although the nucleophilic aromatic substitution (S_NAr)¹⁻⁷ reactions have been less popular than the electrophilic counterpart in synthetic organic chemistry, the introduction of some nucleophilic groups such as alkoxides, phenoxides, sulfides, amines and fluoride ion,⁸⁻¹⁰ to aromatic rings may still necessitate the employment of this type of reaction. There are also situations in which the S_NAr reactions are much more advantageous. For example, the S_NAr procedure is known to be far more selective than electrophilic substitution for producing highly specific ¹⁸F compounds to be used as noninvasive imaging agents to study and probe the molecular and biological processes in living systems with positron emission tomography (PET).¹¹⁻¹⁵

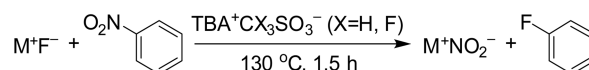
Since the S_NAr reactions usually occur in solution, solvent would affect the efficiency to a large extent. The counterion (cation) may also profoundly affect the efficiency and yields of the reaction. It is well known that the nucleophilic reactions of M^+X^- ($M = \text{metal}$, $X = \text{nucleophile}$) in organic solvents are extremely sluggish because of the strong Coulombic influence of the metal cation on the nucleophile. Various schemes were employed to separate the nucleophile from the metal cation, but even strong bases such as the crown ether are not very good for that purpose. Ionic liquids and molten salts¹⁶⁻²⁴ have recently been found to be quite useful for some organic reactions. For example, D'Anna and co-workers found that in S_NAr reactions amines react faster in ionic liquids than in molecular solvents by almost 1 or 3 orders of magnitude.¹⁹ Systematic investigations of the underlying mechanism, however, have been quite rare. Elucidation of the mechanistic principle

based on the detailed interactions among the nucleophile, counter cation, substrate, and the ionic species (cation and anion) of ionic liquids and molten salts, and their effects on the reaction would certainly help to “design” the ionic liquids for specific S_NAr reactions, as recently exemplified by several groups.²⁰⁻²⁴

In this work, we describe the role and the efficiency of molten salts in nucleophilic aromatic fluorination reactions. We describe a S_NAr mechanism that is consistent with the excellent efficiency of the reaction, and also with the observed large difference in the reaction rates for a series of metal cations (Na^+ , K^+ , Rb^+ , Cs^+) in two tetra-*n*-butylammonium (TBA^+) sulfonates – $\text{TBA}^+\text{CH}_3\text{SO}_3^-$ and $\text{TBA}^+\text{CF}_3\text{SO}_3^-$ differing slightly in sidechain ($-\text{CH}_3$ vs. $-\text{CF}_3$). Although we focus on nucleophilic aromatic fluorination, our findings will apply to other S_NAr reactions as well.

Computational Methods

Density functional theory method (B3LYP)^{25,26} is employed with the 6-311++G** basis set and the effective core potential for Rb^+ , Cs^+ (LANL2DZ)ECP,²⁷ as implemented in GAUSSIAN 09 set of programs.²⁸ We model the cation TBA^+ by tetramethyl ammonium (TMA^+) to reduce computational efforts. Stationary structures are confirmed by ascertaining that all the harmonic frequencies are real. Structures of the transition state (TS) are obtained by only one imaginary harmonic frequency, and also by carrying out the intrinsic reaction coordinate (IRC) analysis along the reaction pathway. Zero point energies (ZPE) are taken into



Scheme 1

[†]This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

Table 1. Experimentally observed yields and calculated activation barriers (kcal/mol) of S_NAr fluorination in molten salts

M^+F^-	Solvent anion	yield	$E^\ddagger (G^\ddagger_{130^\circ C})$ from pre-reaction complex	$E^\ddagger (G^\ddagger_{130^\circ C})$ from most stable complex
NaF	$CH_3SO_3^-$	0	22.7 (22.4)	28.3 (26.9)
KF	$CH_3SO_3^-$	15	21.9 (21.3)	27.3 (26.1)
RbF	$CH_3SO_3^-$	76	16.8 (18.9)	25.3 (24.8)
CsF	$CH_3SO_3^-$	82	16.0 (16.5)	24.2 (23.1)
CsF	$CF_3SO_3^-$	6	16.9 (18.2)	24.2 (27.3)

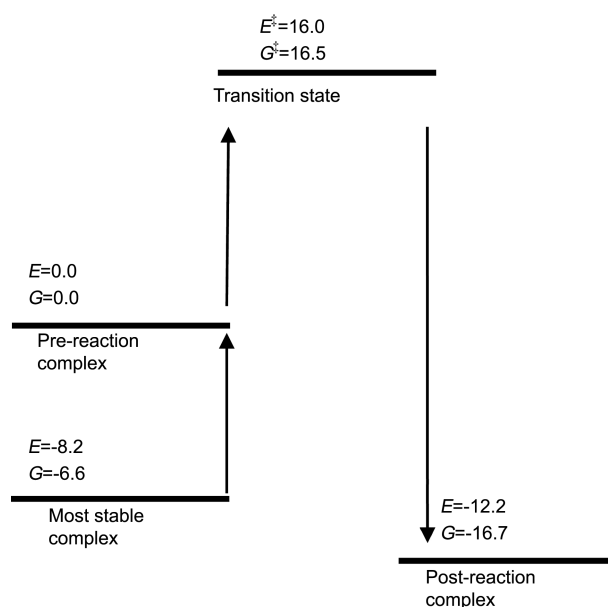
account. Gibbs free energies are computed at 130 °C, thermal corrections included, for the supramolecular complex [MX, substrate, ionic liquid anion and cation]. No effects of the ionic liquid continuum were taken into account. Default criteria are used for all optimizations.

Results

Table 1 presents the observed yields²⁹ (%) and calculated activation barriers of S_NAr fluorination in two molten salts. Several features are notable: First, the S_NAr reactions are found to proceed very rapidly (especially for CsF in solvent $TBA^+CH_3SO_3^-$); Second, the yields are highly dependent on the metal cation (Cs^+ is much better than Na^+); Third, solvents $TBA^+CH_3SO_3^-$ and $TBA^+CF_3SO_3^-$ give very different product yields (82 and 6%, respectively), although their structural difference is quite minor ($-CH_3$ vs. $-CF_3$).

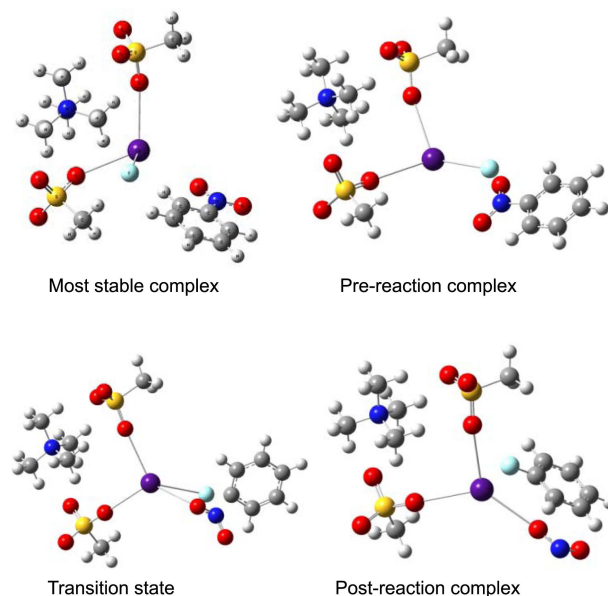
These observations may give several important clues to elucidate the mechanism of the S_NAr fluorination in molten salts, concerning the interactions among the metal counterion, F^- , molten salt cation and anion, and the substrate nitrobenzene. Very strong dependence of the product yields on the counterion M^+ indicates that it may influence the reaction in the vicinity of the nucleophile F^- . The smaller the metal cation is, the stronger Coulombic influence it will exert on F^- , thereby reducing the nucleophilicity of F^- and retarding the reaction. Notable difference in the reaction rates in solvents $TBA^+CH_3SO_3^-$ and $TBA^+CF_3SO_3^-$ is also striking, since it indicates that a small difference in the inductive effects of the solvent sidechain may cause a significant variation in yields. Since the molten salt anion $CX_3SO_3^-$ ($X = H, F$), is not expected to interact directly with another anion (F^-), the retarding effects of the electron-withdrawing $-CF_3$ group in solvent $TBA^+CF_3SO_3^-$ in comparison with solvent $TBA^+CH_3SO_3^-$ with $-CH_3$ suggest that the molten salt anion may influence the reaction through the counterion (metal cation) in the vicinity of F^- .

Based on these observations, we carried out a series of quantum chemical calculations for the S_NAr fluorination reaction. We tried a variety of configurations of the nucleophile, counterion, and the substrate by extensively searching over the potential energy landscape of the [CsF + nitrobenzene + molten salt] system with varying number of molten salt cations and anions. We find that two anions and a cation of the molten salt form the first shell around the nucleophile,

**Figure 1.** Energy diagram of reaction $[Cs^+F^- + \text{nitrobenzene} \rightarrow Cs^+NO_2^- + \text{F-benzene}]$ in $TMA^+CH_3SO_3^-$ (Energy in kcal/mol).

counterion, and substrate, directly affecting the reaction barrier and rate constant. The calculated energetic of the reaction $[CsF + \text{nitrobenzene} \rightarrow CsNO_2 + \text{F-benzene}]$ in $TMA^+CH_3SO_3^-$ is depicted in Figure 1. The barrier $G^\ddagger_{130^\circ C}$ (16.5 and 23.1 kcal/mol from the pre-reaction complex and the most stable complex, respectively) of the reaction is quite low, and the reaction Gibbs energy (-16.7 kcal/mol) is highly negative.

The structures of the pre-reaction complex, transition state, and the post-reaction complex are given in Figure 2, along with the most stable (lowest energy) from which the effective overall reaction barrier is evaluated. In the lowest energy complex, the nucleophile is located approximated

**Figure 2.** Calculated structures involved in S_NAr fluorination reaction $[Cs^+F^- + \text{nitrobenzene} \rightarrow Cs^+NO_2^- + \text{F-benzene}]$ in $TMA^+CH_3SO_3^-$.

parallel to the phenyl ring, and away from the leaving group $-\text{NO}_2$, far from being amenable to S_NAr fluorination. The reaction proceeds from the pre-reaction complex, in which the nucleophile lies above the phenyl ring to attack the carbon center. In the pre-reaction complex, whose energy (Gibbs free energy) of the pre-reaction complex is 8.2 (6.6) kcal/mol higher than that of the lowest energy complex, TMA^+ , CH_3SO_3^- , Cs^+ , F^- , and the substrate nitrobenzene form a very stable and compact ring due to strong Coulomb forces. The nucleophile F^- reacts in the vicinity of the metal cation as an ion-pair, well describing the observed strong effects of the latter ionic species. The anion (CH_3SO_3^-), on the other hand, binds to Cs^+ as a Lewis base³⁰ alleviating the positive charge that is the retarding Coulombic influence of Cs^+ on F^- , thereby “freeing” F^- . The role of bulky TMA^+ is to pull together the two CH_3SO_3^- anions acting on Cs^+ . The reaction mechanism involving $\text{TMA}^+\text{CF}_3\text{SO}_3^-$ or other metal cation (Na^+ , K^+ , Rb^+) is essentially equivalent to that depicted in Figure 2.

The calculated reaction barriers (energy and Gibbs free energy) presented in Table 1 may well elucidate the observed features of aromatic fluorination in molten salts. First, the barrier ($E^\ddagger = 16.0$, $G^\ddagger = 16.5$ kcal/mol) for the reaction [$\text{Cs}^+\text{F}^- + \text{nitrobenzene} \rightarrow \text{Cs}^+\text{NO}_2^- + \text{F-benzene}$] in solvent and $\text{TMA}^+\text{CH}_3\text{SO}_3^-$ is very low, well accounting for the observed efficiency of the ionic liquid for S_NAr fluorination reactions. Second, the reaction of F^- as an ion pair (M^+F^-) accounts for the strong dependence of the reaction on metal cation M^+ . This trend in yields as a function of metal cation indicates that lighter metal cation such as Na^+ acts as a hard acid with smaller polarizability, retarding the reaction to a larger extent through stronger Coulombic influence on F^- . As presented in Table 1, the barriers are calculated to significantly decrease from $E^\ddagger = 22.7$, $G^\ddagger = 22.4$ kcal/mol for Na^+ to $E^\ddagger = 16.0$, $G^\ddagger = 16.5$ kcal/mol for Cs^+ , in complete agreement with the experimentally observed reaction yields that decrease rapidly from 82% for Cs^+ to 0% for Na^+ . The observed trend in yields also agrees with the effective barriers (for example, $E^\ddagger = 24.2$, $G^\ddagger = 23.1$ kcal/mol for CsF in solvent M) calculated from the lowest energy complex given in Figure 1. Third, the S_NAr barrier ($E^\ddagger = 16.9$, $G^\ddagger = 18.2$ kcal/mol) of the reaction of CsF in solvent $\text{TMA}^+\text{CF}_3\text{SO}_3^-$ is calculated to be higher than that ($E^\ddagger = 16.0$, $G^\ddagger = 16.5$ kcal/mol) in solvent $\text{TMA}^+\text{CH}_3\text{SO}_3^-$. The more electron-withdrawing $-\text{CF}_3$ than $-\text{CH}_3$ decreases the negative charge of the $-\text{SO}_3^-$ moiety to a larger degree by inductive effects, resulting in weaker capability of CF_3SO_3^- to coordinate to Cs^+ as a Lewis base.

Traditionally, the counterion (cation) has usually been considered to be harmful for nucleophilic reactions by exerting strong Coulombic influence on the nucleophile. Various efforts have been focused to decrease this retarding effect of the counterion, for example, using the large cations such as tetrabutyl ammonium, or employing the agents such as crown ethers to “capture” the cation away from the nucleophile. Our work presented here, however, suggests that small metal cation such as Cs^+ may also be very

efficient for nucleophilic reactions in contrast with the conventional wisdom, when the effects of the counterion can be “neutralized” by the strong Lewis base such as shown here for the anion of the molten salt. The ionic species (cation and anion) of the molten salts promote the S_NAr reaction by helping to form pre-reaction complex in which the nucleophile, counterion, and the substrate are arranged in an ideal configuration for the reaction, rendering the nucleophile as “free” as possible (Figure 2). The leaving group (NO_2^-) is also stabilized by this compact arrangement in the post-reaction complex, by interacting with the counterion and the phenyl ring of the substrate, giving a large decrease in Gibbs free energy ($\Delta G = -16.7$ kcal/mol) and rendering the reaction highly favorable thermodynamically. This role of the molten salt anion (CH_3SO_3^- and CF_3SO_3^-) as Lewis base coordinating to the counterion (Na^+ , K^+ , Rb^+ , Cs^+) is essentially equivalent to that of the protic solvents³¹ and the ionic liquid anions³²⁻³⁴ to promote S_N2 reactions in which the nucleophile reacts as an ion pair.^{35,36} Various discussions were given in numerous reports on the role of ionic liquids for promoting the nucleophilic substitution reactions, which could not be described only by means of the usual solvent parameters.¹⁹ Although in the present work we have calculated the reaction by adopting the supramolecular model excluding the effects of the ionic liquid continuum, our results clearly show the detailed interactions between the substrates and ionic liquids are responsible for promoting the S_NAr reactions. More comprehensible mechanistic study will involve the cluster approach combined with the polarizable continuum model, but this is left as a future work.

Conclusion

In summary, we have described the mechanism of highly efficient S_NAr reaction in molten salts that accounts for all experimental observations. The nucleophile reacts as an ion pair, and the molten salt anion interacts with the counterion to reduce its strong Coulombic influence on the nucleophile, rendering the nucleophile “free”. We believe that our mechanistic study will contribute significantly to the development of solvent engineering to design and use solvent catalysts for specific chemical reactions.

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