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Effects of Ion and Protic Solvent on Nucleophilic Aromatic Substitution (S_NAr) Reactions

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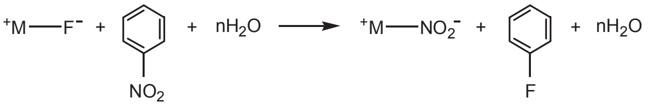
We investigate the mechanism of S_NAr fluorination reactions under the influence of protic solvents and ions. We find that counterion or protic solvent alone retards the S_NAr reactions, but together they may promote the reaction. In this mechanism, the protic solvent acts on the counterion as a Lewis base, and the nucleophile reacts as an ion pair. We also show that an anion (mesylate) may exhibit catalytic effects, suggesting the role of ionic liquids for accelerating the S_NAr reactions.

Key Words: Ion, Protic solvents, S_NAr

Introduction

Nucleophilic substitution, which has not been popular for aromatic reactions, proved much more efficient for producing 18[F]-labeled biomolecules than electrophilic aromatic substitution.[1-7] Although the fluoride anion is very reactive in gas phase in nucleophilic processes, the reactivity drops dramatically in solution phase due to strong effects of counterion (cation) and solvent. It has been considered that protic solvents retard the S_N2 reactions because of hydrogen bonding with the nucleophile. Recently, however, Chi and co-workers[8] observed that bulky protic solvents such as *tert*-butyl alcohol can be very efficient for S_N2 reactions, in stark contrast with conventional belief. To elucidate this observation, Lee and co-workers[9-12] proposed a new S_N2 mechanism, in which the nucleophile reacts in the form of an ion pair (M^+X) and the protic solvent interacts as a Lewis *base* with the counterion rather than with the nucleophile.

Pliego and Piló-Veloso[13] recently suggested in their computational work of S_NAr reactions that the more F^- ion is naked, the more facilitated is the S_NAr reaction. In this conventional wisdom for nucleophilic aromatic substitution reaction, hydration is sure to retard the reaction through hydrogen bonding with the nucleophile. In the present work, we study whether the protic solvent could be efficient for S_NAr reactions. We systematically analyze the influence of cation (alkali metal ions Na^+ and Cs^+) and protic solvent (water) on the S_NAr reactions [M^+F^- + *nitro*benzene + nH_2O → *fluoro*benzene + $M^+NO_2^-$ + nH_2O ($M^+ = Na^+, Cs^+$, n = 0, 2)] depicted in Scheme 1. We investigate the mechanistic process of S_NAr fluorination by quantum chemical methods. We calculate and compare the reaction barriers of S_NAr reactions under the influence of counterion and/or protic solvent, and find that cation or water molecule (acting as Lewis acid) alone retards the reaction considerably. These findings are in line with conventional thinking of the role of cation and protic solvent in S_NAr reactions. We propose, however, an alternative mechanism in which cation and protic solvent molecules cooperate to accelerate the S_NAr reaction. In this situation, solvent molecules are shielded from the nucleophilie by the cation, acting as a Lewis base on the cation to reduce its unfavorable Coulombic influence on the nucleophile. Based on this observation, we also propose a mechanism in which solvent anion (for example, mesylate in ionic liquid) may promote the S_NAr process.



Scheme 1. S_NAr fluorination by the salt MF under the influence of water molecules

Computational Methods

Density functional theory method (MPW1K) is employed with the 6-311++G** basis set and the effective core potential for Cs (Hay-Wadt VDZ(n+1)),[14] as implemented in GAUSSIAN 03 set of programs.[15] Stationary structures are confirmed by ascertaining that all the harmonic frequencies are real. Structures of the transition state (TS) are obtained by verifying that one and only one of the harmonic frequencies is imaginary, and also by carrying out the intrinsic reaction coordinate (IRC) analysis along the reaction pathway. Zero point energies (ZPE) are taken into account, and default criteria are used for all optimizations.

Results

Figure 1 presents the gas-phase S_NAr fluorination [F^- + *nitro*benzene → *fluoro*benzene + NO_2^-]. One of the central questions concerning the S_NAr process is whether the reaction proceeds in a single step with a transition state, or in a two-step mechanism with an intermediate. Our calculations demonstrate that the S_NAr reaction F^- with nitrobenzene occurs in a single-step without formation of a stable σ-complex, in line with the agree with the report by Glukhovtsev.[4] The pre-reaction complex is very stable with the energy lower by ~16 kcal/mol than that of the separate reactants. The activation barrier is calculated to be very low (~4 kcal/mol), indicating that the reaction is instantaneous, in the absence of counterion and solvent.

Figure 2 presents the effects of hydration. It models the aque-

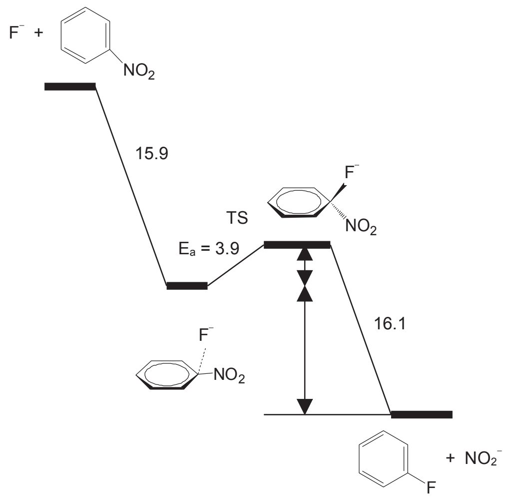


Figure 1. Energy profile and mechanism of the reaction [F^- + *nitro*benzene → *fluoro*benzene + NO_2^-]. Energy in kcal/mol.

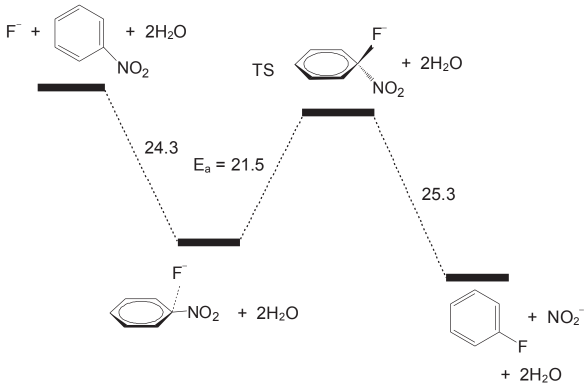


Figure 2. Energy profile and mechanism of the reaction [F^- + *nitro*benzene + $2H_2O$ → *fluoro*benzene + NO_2^- + $2H_2O$]. Energy in kcal/mol.

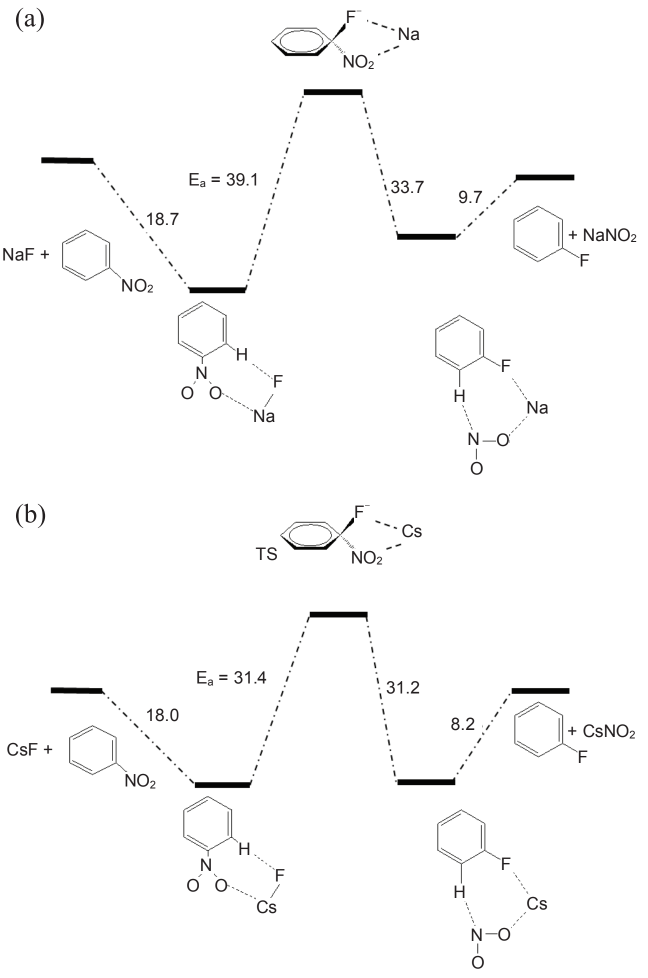


Figure 3. Energy profile and mechanism of the reactions [M^+F^- + *nitro*benzene → *fluoro*benzene + $M^+NO_2^-$] (a) M = Na (b) M = Cs. Energy in kcal/mol.

ous solution phase as a cluster of water molecules to explicitly probe the effects of water molecules on the reaction barrier. In the most stable pre-reaction complex, the two water molecules, nitro and fluoride ion form a ring through hydrogen bonding. A water molecule interacts with F^-, while another binds to the leaving group. The activation barrier significantly increases to ~21.5 kcal/mol, clearly demonstrating the retarding effects of water.

In conventional concept of S_NAr reactions, counterions (cations) are considered to be harmful due to strong Coulombic influence on the nucleophile. Figure 3(a) presents the reaction [Na^+F^- + *nitro*benzene → *fluoro*benzene + $Na^+NO_2^-$] in the absence of solvating water molecules. In the pre-reaction complex, the ion pair Na^+F^- and the nitro group are arranged in a coplanar fashion. This is quite different from the pre-reaction complexes depicted in Figure 1 and Figure 2, in which the nucleophile F^- is located off the phenyl ring. It seems that the counterion Na^+ bridges F^- and the leaving group NO_2 in the pre-reaction complex in Figure 3(a), rendering a stronger interaction between F^-, NO_2, and the hydrogen atom in a planar configuration. Whereas the ion pair locates perpendicular to the benzene ring in the transition state. Due to strong Coulombic interaction between Na^+ and F^-, the activation barrier dramatically increases to ~39.1 kcal/mol. Figure 3(b) presents the corresponding reaction [Cs^+F^- + *nitro*benzene → *fluoro*benzene + $CsNO_2$], in which the larger and more polarizable counterion Cs^+ is used. The activation barrier is much smaller (~31.4 kcal/mol), as a result of weaker Coulombic influence of Cs^+ on F^-.

Observing that the protic solvent molecules or the cation tend to increase (decrease) the barrier (rate) of the S_NAr reaction, one may ask: what would the effects of protic solvent be when partaking in combination with cation? Figure 4(a) illustrates the situation under the influence of Na^+ and two water molecules. In the pre-reaction complex, one water molecule bridges Na^+ and NO_2^-, partially neutralizing the Coulombic attractive force by Na^+ on F^- and also assisting the detachment of the leaving group NO_2^-. It is worth noting that F^- is located again off the phenyl ring plane in the pre-reaction complexes in Figure 4(a) due the influence of the two water molecules. The nucleophile F^- distances away from the hydrogen atom and the counterion Na^+, attacking the carbon atom and removing the leaving group.

The combined efforts of the water molecules and the counterion now lower the barrier significantly (by 12.6 kcal/mol)

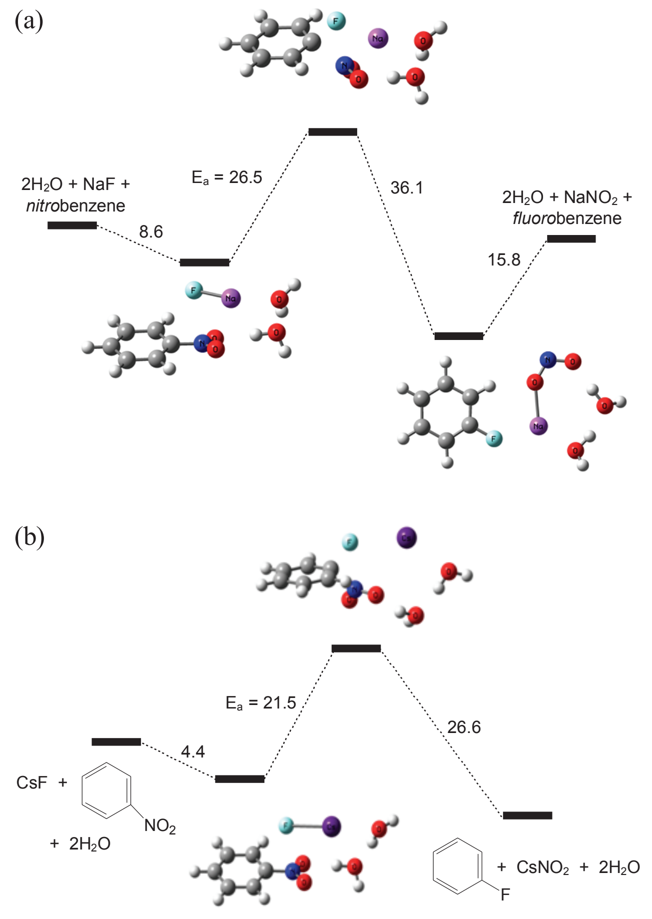


Figure 4. Energy profile and mechanism of the reaction [M^+F^- + *nitro*benzene + $2H_2O$ → *fluoro*benzene + $M^+NO_2^-$ + $2H_2O$] (a) M = Na (b) M = Cs. Energy in kcal/mol.

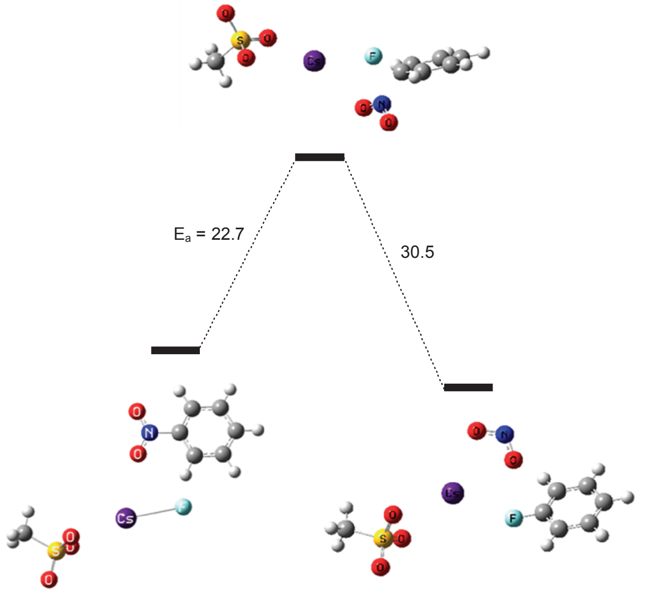


Figure 5. Energy profile and the mechanism of the reaction [Cs^+F^- + *nitro*benzene + mesylate → *fluoro*benzene + $Cs^+NO_2^-$ + mesylate]. Energy in kcal/mol.

to ~26.5 kcal/mol. Figure 4(b) presents the similar reaction [Cs^+F^- + *nitro*benzene + $2H_2O$ → *fluoro*benzene + $Cs^+NO_2^-$ + $2H_2O$]. In this case, the activation barrier is further lowered to ~21.5 kcal/mol. Therefore, our calculated results imply that when the nucleophile reacts as an ion-pair (Na^+F^- or Cs^+F^-) under the influence of water molecules, the synergetic effects of the cation and protic solvent may help to reduce the barrier significantly, suggesting a possible means of promoting the S_NAr reaction rates by deliberately choosing the counterion and solvent.

If protic solvents could promote the S_NAr reaction by acting as a Lewis base, solvent anions may also function in a similar fashion. The ion-pair S_NAr reaction [Cs^+F^- + *nitro*benzene → $Cs^+NO_2^-$ + *fluoro*benzene] under the influence of a mesylate anion $CH_3SO_3^-$ is depicted in Figure 5. The calculated activation barrier is ~22.7 kcal/mol, similar to that of the reaction in water, indicating that the anion may also be employed as a promoter of S_NAr reactions. Since the ionic liquids would be a natural source of solvent anion, prudent design and use of ionic liquids may be useful to facilitate the S_NAr reactions, as exemplified by Welton.[16]

In conclusion, we demonstrated by quantum chemical calculations that the combined effects of counterion and protic solvent may accelerate the S_NAr reactions. By examining the influence of a mesylate anion, we also suggested that the ionic liquids can be employed to facilitate the S_NAr reactions.

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