

## Intermediate Complexes in S<sub>N</sub>2 Reaction: [Na<sup>+</sup>, F<sup>-</sup>, H<sub>2</sub>O, CH<sub>3</sub>Cl] System

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Received September 2, 2005

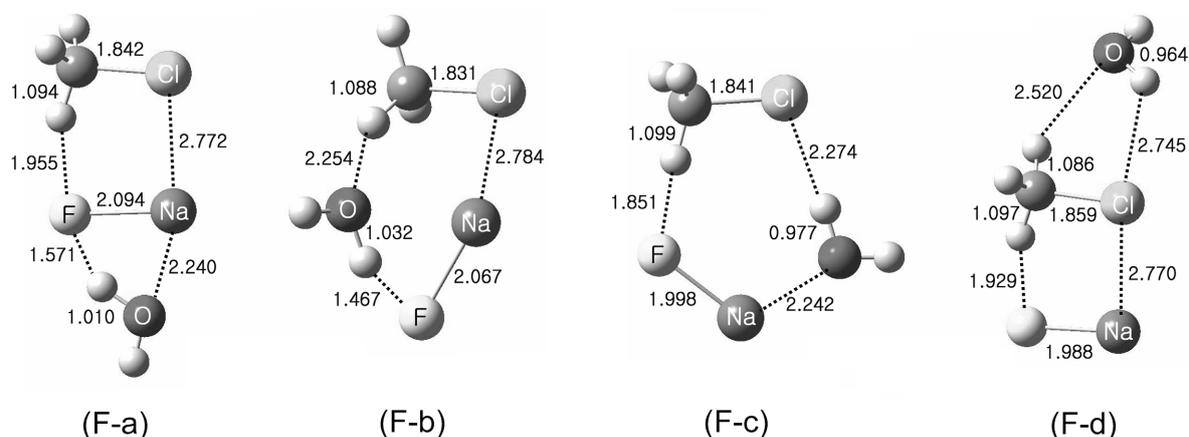
**Key Words :** Intermediate complex, S<sub>N</sub>2 reaction

The unsymmetrical S<sub>N</sub>2 reaction<sup>1-9</sup> [F<sup>-</sup> + CH<sub>3</sub>X → CH<sub>3</sub>F + X<sup>-</sup>] has been studied in the gas phase by several groups to interrogate the mechanism in solution. The F<sup>-</sup> anion is one of the most reactive nucleophiles in the gas phase, and the reaction proceeds very fast almost to completion with very small activation barrier of about 2 kcal/mol.<sup>4</sup> This highly simplified version of the S<sub>N</sub>2 reaction may not explain why the fluorination reaction has been considered to be quite difficult to occur in the solution phase in the organic chemistry community. The solvent is expected to influence the rate of the reaction profoundly: For example, protic solvent is usually known to be unfavorable for the S<sub>N</sub>2 reaction. Studying the reaction mechanism in the solution phase either experimentally or theoretically is, however, difficult for several reasons. First, in the solution phase S<sub>N</sub>2 reaction, there exist no discernible intermediate pre- and post-reaction complexes that are considered to be the configurations of the reacting and the produced species in the gas phase. Second, it is very difficult to study the structures of the transition state in the solution phase. Third, it is virtually impossible to examine the effects of infinite number of solvent molecules on the reaction accurately (that is, on the molecular level). Quantum chemical calculations would be very useful in this regard for elucidating the mechanism by adopting a cluster model comprising the reacting species and a number of solvent molecules.

Several factors must be considered to elucidate the true nature of the S<sub>N</sub>2 reaction. First, the solvent molecules are

expected to play very important role on the reaction in condensed phase. It is generally considered that polar solvents such as water may retard the S<sub>N</sub>2 reaction in the solution phase. O'Hair *et al.*,<sup>3</sup> for example, measured that the rate constant of the reaction of the hydrated F<sup>-</sup> ion [F<sup>-</sup>(H<sub>2</sub>O) + CH<sub>3</sub>Cl] decreases by a factor of about 100 from that of the bare F<sup>-</sup> ion. Second, the effects of the counterion (cation) must also be taken into consideration for the simple reason that one may not introduce the nucleophilic agent (negative ion) alone in the reaction system in the solution phase. Although the cation may profoundly affect the S<sub>N</sub>2 reaction due to the very strong and long-range Coulombic influence on the nucleophile, it is quite surprising to notice that detailed accounts for its effects have rarely been delineated even for the gas phase S<sub>N</sub>2 reaction.

In the present work we study the [Na<sup>+</sup>, F<sup>-</sup>, CH<sub>3</sub>Cl, H<sub>2</sub>O] and the [Na<sup>+</sup>, Cl<sup>-</sup>, CH<sub>3</sub>F, H<sub>2</sub>O] system to calculate the structures of the intermediate complexes in prototypical unsymmetrical S<sub>N</sub>2 reaction [F<sup>-</sup> + CH<sub>3</sub>Cl → CH<sub>3</sub>F + Cl<sup>-</sup>] and its reverse reaction under the influence of a water molecule.<sup>10-13</sup> The role of metal cation and solvent molecule in the complex are examined in detail. Calculations are carried out by the GAUSSIAN 03 set of programs.<sup>14</sup> The density functional theory method B3LYP/6-311++G\*\* is employed. The stationary structures are confirmed by ascertaining that all the harmonic frequencies be real. We take zero point energies into consideration. Default criteria are employed for optimization.



**Fig. 1.** Calculated structures of the complexes for the forward reaction [F<sup>-</sup> + CH<sub>3</sub>Cl → CH<sub>3</sub>F + Cl<sup>-</sup>] under the influence of Na<sup>+</sup> and a water molecule.

**Table 1.** Electronic energy ( $E$ ), zero point energy ( $ZPE$ ) and relative energy  $\Delta E$  of the complexes for the reaction  $[F^- + CH_3Cl \rightarrow CH_3F + Cl^-]$ , and the Mulliken partial charge  $q_F$  of  $F^-$ 

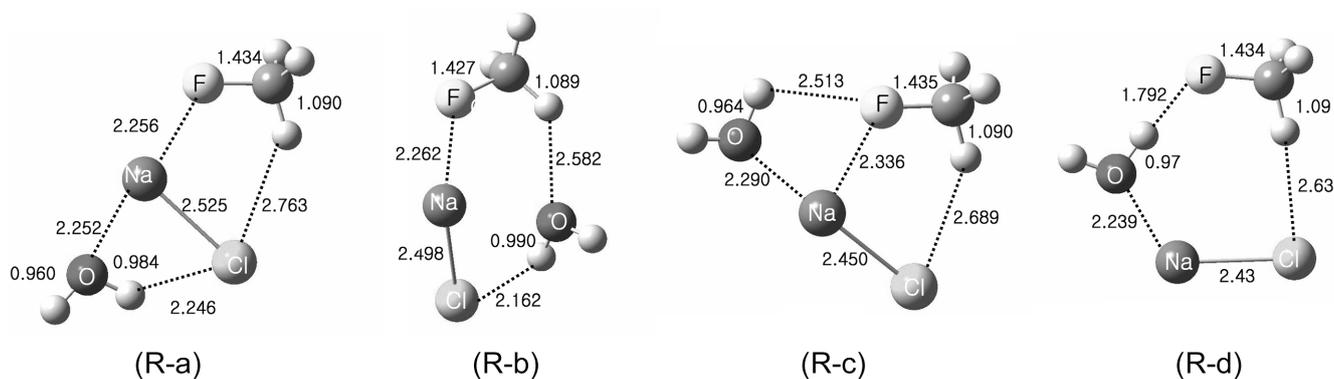
Complex	$E$ (Hartree)	$ZPE$ (kcal/mol)	$\Delta E$ (kcal/mol)	$q_F$
(F-a)	-838.88802	40.48	0	-0.679
(F-b)	-838.88293	40.49	3.21	-0.657
(F-c)	-838.87566	40.49	7.77	-0.743
(F-d)	-838.85655	39.60	18.87	-0.738

Figure 1 and Table 1 list the structures and energies of the stationary structures of the  $[Na^+ - F^- - CH_3Cl - H_2O]$  system obtained in our present study. In all the calculated structures,  $Na^+$  and  $F^-$  lie close to each other, due to their strong Coulombic interaction. This is to be easily understood by the fact that only a water molecule is available in these gas phase model complexes for solvating the ions. The situation roughly corresponds to that in the solution phase in which the metal cation and the nucleophilic anion remains as a contact ion pair rather than as a solvent-separated ion pair. Although it is known that the strong solvation by water renders considerable portion of the  $Na^+$  and  $F^-$  ions to exist as solvent-separated ion pair, we intend to put the solvent-separated ion pair to model the situation in which the cation exerts maximum Coulombic interactions that are unfavorable for the reaction. This latter case may hold for the  $S_N2$  reactions occurring in less polar solvent.

The cation  $Na^+$ , the nucleophile  $F^-$ , the substrate  $CH_3Cl$ , and the solvent molecule  $H_2O$  interact in several different ways in these intermediate complexes. In the lowest energy structure (F-a), the  $Na^+$  ion exerts electrostatic influence on the nucleophile  $F^-$ , while also interacting with  $Cl$  and the water molecule. The strong Coulombic force of  $Na^+$  on  $F^-$  would result in very low probability of reaction compared with the case where the cation is far from the nucleophile. The water molecule bridges  $Na^+$  and  $F^-$  in the far side of  $CH_3Cl$ , partially neutralizing the Coulombic attractive force by  $Na^+$  on  $F^-$ , but also decreasing the nucleophilicity of  $F^-$  itself. The role of the water is proton-donating to  $F^-$ , and positive charge-accepting from  $Na^+$ . The  $F^-$  ion is seen to form weak hydrogen bonding with the methyl hydrogen in this complex. The thermodynamic stability of this complex

results from the fact that every electronegative atom interacts with electropositive atom. In the structure (F-b), the water molecule locates between  $Na^+$  and  $F^-$ , bridging the methyl,  $Na^+$  and  $F^-$ . Both the water molecule and the  $Na^+$  ion also interact to reduce the nucleophilicity of  $F^-$  in this complex. The nucleophile  $F^-$  is quite far from the substrate  $CH_3Cl$ , so the reaction would involve very extensive movement of  $F^-$  toward  $CH_3Cl$ . The complex (F-b) is 3.2 kcal/mol higher in energy than (F-a). In the complex (F-c) the nucleophile  $F^-$  ion interacts with methyl and  $Na^+$ , while the water molecule bridges  $CH_3Cl$  and  $Na^+$ . Since the water molecule does not bind to  $F^-$ , the nucleophile is only influenced by  $Na^+$ , in contrast with the other complexes (F-a) and (F-b). The energy of (F-c) is, however, quite higher (by 7.77 kcal/mol) than (F-a) obviously due to the lack of electrostatic interactions between  $F^-$  and  $H_2O$ .

It is useful to note that the water molecule forms hydrogen bond with  $Na^+$ , thus moderating the Coulombic influence of  $Na^+$  on the nucleophile  $F^-$  in (F-c). Consequently, the nucleophilicity of  $F^-$  may be the largest in this complex, making the  $S_N2$  reaction more favorable. This can also be seen from the partial charge of -0.743 that are the largest of all the complexes presented in Table 1. Therefore, on the basis of the nucleophilicity of  $F^-$ , the complex (F-c) may be considered to be the most favorable for the  $S_N2$  reaction  $[F^- + CH_3Cl \rightarrow CH_3F + Cl^-]$  under the influence of  $Na^+$  and a water molecule. It is also instructive to observe that the difference in the bonding in (F-a) and (F-c) is that the water molecule interacts with  $F^-$  in the former complex, whereas it forms hydrogen bond with the leaving group  $Cl$  in (F-c). Stronger interactions between  $F^-$  and  $H_2O$  obviously render the structure (F-a) to be of lower energy relative to (F-c). If the complex of the latter type is allowed to be of sufficiently low energy, for example, by selecting the solvent and the leaving group in such a way to make the solvent-leaving group interaction stronger than that between the solvent and the nucleophile, the  $S_N2$  reaction may proceed more readily *via* the configuration similar to (F-c) with more active nucleophile. On the other hand, both the water molecule and the  $Na^+$  ion tend to reduce the nucleophilicity of  $F^-$  in (F-a) and (F-b), making the nucleophile less favorable for the reaction. This can also be seen in smaller partial charges of

**Fig. 2.** Calculated structures of the complexes for the reverse reaction  $[Cl^- + CH_3F \rightarrow CH_3Cl + F^-]$  under the influence of  $Na^+$  and a water molecule.

**Table 2.** Electronic energy ( $E$ ), zero point energy ( $ZPE$ ) and relative energy  $\Delta E$  of the complexes for the reaction  $[Cl^- + CH_3F \rightarrow CH_3Cl + F^-]$ , and the Mulliken partial charge  $q_{Cl}$  of Cl

Complex	$E$ (Hartree)	$ZPE$ (kcal/mol)	$\Delta E$ (kcal/mol)	$q_{Cl}$
(R-a)	-838.89918	40.96	0	-0.548
(R-b)	-838.89631	41.18	2.02	-0.533
(R-c)	-838.89325	40.81	3.57	-0.587
(R-d)	-838.89195	41.26	4.83	-0.561

the fluorine atom in (F-a) and (F-b) given in Table 1. Thus, the hydrogen bonding in the complex (F-a) between the nucleophile  $F^-$  and the water molecule seems to be the main reason that the  $S_N2$  reaction usually does not proceed well in the protic solvent. In the higher energy complex (F-d), the water molecule locates far from the nucleophile, exerting minimal influence on the  $S_N2$  reaction. This complex seems highly unfavorable for reaction both thermodynamically and kinetically.

Figure 2 and Table 2 present the corresponding structures of the complexes for the reverse reaction  $[Cl^- + CH_3F \rightarrow CH_3Cl + F^-]$  under the influence of  $Na^+$  and a water molecule. Some of these pre-reaction complexes for the reverse reaction may serve as the post-reaction complex in the forward reaction  $[F^- + CH_3Cl \rightarrow CH_3F + Cl^-]$ , being connected along the reaction path with the complex given in Figure 1.

The  $S_N2$  reaction pathways in solution would, of course, be somewhat different from those of the gas phase reactions, and the intermediate complexes presented in this study would lie in energy above the separated reactants. Study on the solution phase reaction may be carried out by including more solvent molecules in the cluster, and also by employing the continuum model to simulate the effects of the solvent continuum. The role of the cation and the solvent molecule(s) discussed above for the gas phase model reac-

tion may well give useful insight to the reaction mechanism in solution.

**Acknowledgments.** This work was supported by the Korea Science and Engineering Foundation Grant (R01-2005-000-10117-0).

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