Facile S_N2 Reaction in Protic Solvent: Quantum Chemical Analysis

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We study the effects of protic solvent (water, methanol, ethanol, and *tert*-butyl alcohol) and cation (Na^+, K^+, Cs^+) on the unsymmetrical S_N2 reaction $X^- + RY \rightarrow RX + Y^-$ ($X = F, Br$; $R = CH_3, C_3H_7$; $Y = Cl, OMs$). We describe a series of calculations for the S_N2 reaction mechanism under the influence of cation and protic solvent, presenting the structures of pre- and postreaction complexes and transition states and the magnitude of the activation barrier. An interesting mechanism is proposed, in which the protic solvent molecules that are shielded from the nucleophile by the intervening cation act as a Lewis *base* to reduce the unfavorable Coulombic influence of the cation on the nucleophile. We predict that the reaction barrier for the S_N2 reaction is significantly lowered by the cooperative effects of cation and protic solvent. We show that the cation and protic solvent, each of which has been considered to retard the S_N2 reactivity of the nucleophile, can accelerate the reaction tremendously when they interact with the fluoride ion in an intricate, combined fashion. This alternative S_N2 mechanism is discussed in relation to the recently observed phenomenal efficiency of fluorination in *tert*-alcohol media [Kim, D. W.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 16394].

I. Introduction

The bimolecular nucleophilic substitution (S_N2) reaction[1−20] is one of the fundamental and most useful chemical reactions. Recent progress in experimental technique such as the spectroscopy of low-temperature gas-phase clusters and quantum chemical methods has allowed this very important class of reaction to be studied in detail at the molecular level. For example, it is now well-known that there exist intermediate pre- and postreaction complexes that are distinct from the transition state.[21−24] These complexes may be regarded as the starting and ending structures in the low-temperature gas-phase S_N2 reaction, respectively, although their role would diminish at elevated temperatures and vanish in the solution phase. The prototypical unsymmetrical S_N2 reaction[14−16,25−29] $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$ has been studied by several groups. The anion F^- is one of the most basic nucleophiles, and the reaction proceeds almost with unit probability by a nucleophilic attack of F^- on CH_3Cl via a very small activation barrier of about 2 kcal/mol in the gas phase.[16] This highly simplified version of the S_N2 reaction may, however, not explain why fluorination has been considered difficult to occur in the organic chemistry community. Several factors must be considered to elucidate the true nature of the S_N2 reaction in the solution phase. First, solvent molecules are expected to play a very important role on the reaction. Protic solvents such as water are usually regarded as retarding the S_N2 reaction. O'Hair et al.[15] for example, measured that the rate constant of the reaction of the hydrated F^- decreases by a factor of about 100 from that of the bare F^- ion. The inefficacy of protic solvent for S_N2 reaction is based on the idea that the solvent molecules, acting as a proton donor (Lewis acid), may form hydrogen bonds with the nucleophile to seriously reduce its nucleophilicity. This view of protic solvent has long been evoked to explain the low reactivity of the strong base F^- in the solution phase. Second, the effects of counterion (cation) must also be taken into account for the simple reason that one may not include the nucleophilic agent alone in the solution phase. Due to very strong Coulombic influence on the nucleophile, cation may decrease the S_N2 reaction rates, especially when it is close to the nucleophile as in a contact ion pair (CIP). For this reason, this latter form of the cation−nucleophile complex has been considered as being much less favorable for the solution-phase S_N2 reaction than solvent-separated ion pair (SSIP) and has not been studied systematically except the pioneering works by Streitwieser and co-workers.[10]

In a recent report,[30] we described a new type of S_N2 reaction characterized by several striking observations. First, bulky protic solvents (*tert*-butyl alcohol or *tert*-amyl alcohol) are extremely good for the S_N2 reaction. Second, product yield is highly dependent on the cation (Cs^+ is much better than K^+). Third, the relative reactivity of the halide ion nucleophile appears to be reversed (F^- much more reactive than Br^-) from that typical for halide ions in protic solvents ($F^- < Cl^- < Br^-$, etc). Our observations clearly demonstrated that large and polarizable cation and bulky *tert*-butyl alcohol may exhibit catalytic activity, and the phenomenal efficacy of fluorination seems to require a fundamental revision to the role of protic solvent and cation in the S_N2 reaction. The *combined* effects of cation and solvent may be quite complicated and intricate, and their mode of interactions may only be elucidated by scrutinizing their role in a variety of configurations on the potential energy surface of the S_N2 reaction.

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In the present work we systematically analyze the influence of cation and protic solvent on the S$_N$2 reactions $X^- + RY \rightarrow RX + Y^-$ (R = CH_3,C_3H_7; X = F, Br; Y = Cl, OMs). We calculate and compare the reaction barriers of the S$_N$2 reactions in water and methyl, ethyl, and *tert*-butyl alcohols to study the effects of the size of the protic solvent. Two halide nucleophiles, F^- and Br^-, are employed to elucidate the observed relative reactivity of F^- and Br^-, and a number of cations (Na^+, K^+, Cs^+) are compared to determine their influence on the S$_N$2 reactions. The effects of the leaving group are also briefly discussed by calculating the mechanism and the barrier for the model S$_N$2 reaction Cs^+F^-(*tert*-butyl alcohol)$_n$ + C_3H_7OMs (n = 1, 2). We find that, in the absence of solvent, cation is shown to retard the reaction tremendously, increasing the reaction barrier in the order of $Cs^+ < Rb^+ < K^+ < Na^+$. When cation is not present, protic solvent (acting as a Lewis acid) also decreases the S$_N$2 reaction rate by interacting (forming hydrogen bond) with the nucleophile. These findings are in line with the conventional thinking of the role of cation and protic solvent in S$_N$2 reactions. We propose an alternative mechanism in which cation and protic solvent molecules *cooperate* to accelerate the S$_N$2 reaction, respectively. In this situation, solvent molecules are shielded from the nucleophile by the cation and act as a Lewis *base* on the cation to alleviate its unfavorable Coulombic influence of cation on the nucleophile. We show that bulky solvent and bulky and polarizable cation are highly favorable for the proposed catalysis by demonstrating that *tert*-butyl alcohol and Cs^+ may profoundly lower the reaction barrier of the S$_N$2 reaction $F^- + C_3H_7OMs \rightarrow C_3H_7F + OMs^-$, as observed in this phenomenally efficient fluorination process.[30]

II. Computational Methods

MP2 and density functional theory methods (B3LYP[31,32] and the MPW1K[33,34]) are employed with the 6-311++G** basis set and the effective core potential for Cs (Hay-Wadt VDZ-(n+1)),[35] as implemented in the Gaussian 98[36] and Gaussian 03[37] set of programs. Stationary structures are confirmed by ascertaining that all the harmonic frequencies are real. The structure of the TS is obtained by verifying that one and only one of the harmonic frequencies is imaginary and also by carrying out the intrinsic reaction coordinate analysis (IRC) along the reaction pathway. Zero-point energies (ZPE) are taken into account, and default criteria are used for all optimizations.

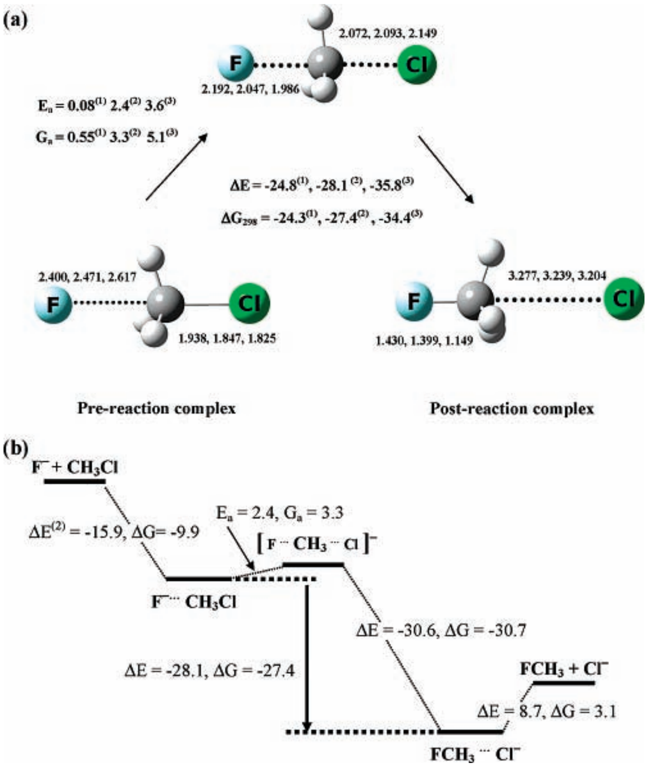

Figure 1. Gas-phase reaction $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$ of the free F^- ion: Formation of pre- and postreaction complexes (energy and Gibbs function in kcal/mol and bond lengths in Å): (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**, (3)MP2/6-311++G**.

TABLE 1: Comparison of Theoretical Methods Used for the Gas-Phase Reaction $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$ (barrier E_a, G_a, and reaction energy ΔE in kcal/mol)

method	E_a[a]	G_a[a]	ΔE[b]	ΔG_{298}
B3LYP/6-311++G**	0.08	0.55	−24.8	−24.3
B3LYP/aug-cc-PVDZ	0.10	0.56	−24.5	−24.0
B3LYP/aug-cc-PVTZ	0.37	0.83	−24.8	−24.5
MPW1K/6-311++G**	2.44	3.31	−28.1	−27.4
MPW1K/aug-cc-PVDZ	1.89	2.69	−28.1	−27.5
MPW1K/aug-cc-PVTZ	2.67	3.53	−28.2	−27.6
MP2/6-311++G**	3.60	5.07	−35.8	−34.4
MP2/aug-cc-PVDZ	2.85	3.76	−35.4	−34.6

[a] Energy (Gibbs function) of TS − energy (Gibbs function) of prereaction complex (ZPE-corrected). [b] Energy of postreaction complex − energy of prereaction complex (ZPE-corrected).

III. Results and Discussion

III-1. $F^-(H_2O)_n + CH_3Cl$ (n = 0−2). Figure 1 presents the gas-phase S$_N$2 reaction $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$.[15,16,25−29] It is useful to note that the negative activation barrier frequently coined in the S$_N$2 halogen exchange reaction refers to the energy of the transition state (TS) relative to the reacting species at infinite separation. Since the intermediate complexes become important in low-temperature gas phase, it would be more appropriate to compute the activation barrier as the difference in energy between the prereaction complex and the TS. The activation barrier thus defined is calculated to be quite small in all the calculations presented in Table 1. We employ the B3LYP, MPW1K, and MP2 methods with a series of basis sets (6-311++G**, aug-cc-PVDZ, and aug-cc-PVTZ). It seems that the B3LYP method gives the reaction barrier that is somewhat (by ∼2 kcal/mol) smaller than that obtained by the MP2 method. MPW1K/6-311++G** and MPW1K/aug-cc-PVTZ methods predict quite similar magnitude of the barrier, which is close (to within ∼0.5 kcal/mol) to that obtained by the MP2/aug-cc-PVDZ level of theory. We find that the MPW1K method gives more accurate barrier heights than B3LYP, as observed by Truhlar and co-workers.[38a] The energy and Gibbs function of reaction calculated by the MPW1K method are also a bit more accurate (closer to the MP2 values) than those obtained by the B3LYP theory, as observed by Zhao and Truhlar.[38b] Since we want to treat the system with big solvent molecules (*tert*-butyl alcohol) influencing the rate of S$_N$2 reaction, we employ in this work the MPW1K/6-311++G** technique that is demonstrated to give a quite accurate barrier (Table 1), unless noted otherwise. The prereaction complex is calculated to be 15.9 kcal/mol lower in energy than the reactants $F^- + CH_3Cl$, while the corresponding change in Gibbs function (at 298 K) is −9.9 kcal/mol by the MPW1K/6-311++G** method. The postreaction complex is 8.7 (3.1) kcal/mol lower in energy (Gibbs function) than the products [$CH_3F + Cl^-$]. It must be noted that the role of these complexes would diminish at elevated temperatures and vanish in the solution phase.

Figure 2a,b presents the calculated results for the effects of hydration.[6,14,15] We obtain two TS's connecting the same

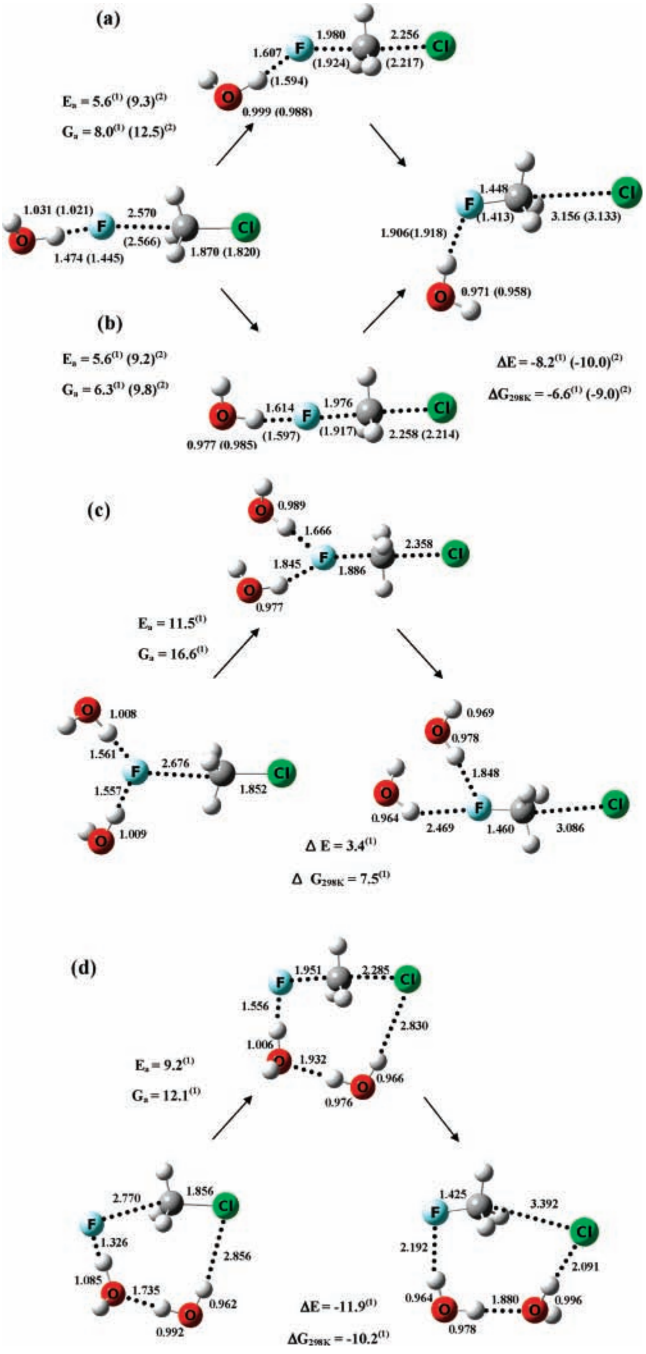

Figure 2. S_N2 reaction $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$ under the influence of a water molecule (a, b) and two water molecules (c, d). Energy and Gibbs function in kcal/mol and bond lengths in Å. (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**.

prereaction and postreaction complexes with similar activation barriers [5.6 (9.2−9.3) kcal/mol by B3LYP (MPW1K) theory], but slightly different Gibbs function of activation [8.0 (12.5) and 6.3 (9.8) kcal/mol]. We find that the MPW1K theory gives the barrier that is consistently larger (by 3−4 kcal/mol) than that obtained by the B3LYP method for all the reacting systems (Figures 1−8) studied in this work.

Structures of the TS's presented in Figure 2a are somewhat different: One of the OH bonds of the water molecule in the TS in path a is distorted away from the F−C−Cl axis, whereas it is more or less in line with the axis in path b. The solvating water molecule is being kept close to fluorine throughout the reaction. In both cases, the activation barriers are significantly larger (by ~7 kcal/mol) than that for the reaction of free F^- and CH_3Cl depicted in Figure 1. This increase in activation barrier results from hydrogen bonding of the water molecule with F^-, decreasing its nucleophilicity. The calculated barrier, however, still seems to be small, suggesting that the effects of a water molecule directly interacting with F^- are not sufficient to explain the difficulty of fluorination in the solution phase. Figure 2c depicts the situation in which two protic solvent molecules interact as a Lewis acid with the nucleophile, raising the barrier from 0.1 to 11.5 kcal/mol (B3LYP/6-311++G**). The barrier of the reaction is expected to increase further as a function of the number of water molecules. The water molecule may also assist the detachment of Cl^-, and Figure 2d presents a situation in which a water molecule interacts with F^-, while another binds to the leaving group. The effects of a water molecule interacting with the leaving group are estimated to lower the barrier slightly (by ~2 kcal/mol) from the situation depicted in Figure 2c. It seems that the smaller distance (1.326 Å) between the hydrogen atom in H_2O and F^- in Figure 2d than that in Figure 2a,b (1.474 Å) may overwhelm the effects of assisting the leaving group.

These predictions are in agreement with experiments. O'Hair et al.[15] measured that the rate constant of the reaction $F^-(H_2O)_{1,2} + CH_3Cl$ decreases by a factor of about 100 and by almost 4 orders of magnitude, respectively, from that for the bare F^- ion. The rate constant of the corresponding reaction in aqueous solution, on the other hand, drastically drops from the gas-phase value by almost 20 orders of magnitude with the increase in the barrier height to 27 kcal/mol.[25] Recently, Morokuma, Tomasi and co-workers[6] employed ONIOM−PCM methods to study the reaction $Cl^- + CH_3Cl$ in aqueous solution, and the net influence of solvation in the *absence* of the cation was considered as increasing the reaction barrier from the gas-phase reaction $Cl^-(H_2O) + CH_3Cl$ by 14−15 kcal/mol. Adopting this estimation, the barrier of the reaction $F^-(aq) + CH_3Cl$ may amount to about 20 kcal/mol.

III-2. $Na^+F^- + CH_3Cl$. Figure 3a depicts the situation in which the cation interacts with F^- in the *absence* of the solvating water molecules. When Na^+, F,$^-$ and CH_3Cl are arranged in an approximately collinear fashion, the S_N2 reaction may not occur because of too strong Coulombic interactions between Na^+ and F^-. When Na^+F^- and CH_3Cl are complexed in the π-type configuration, on the other hand, the reaction may proceed but only with considerable activation barrier [~35 (38) kcal/mol by the B3LYP/6-311++G** (MPW1K/6-311++G**) method] that is much larger than that (~27 kcal/mol) experimentally measured for the solution-phase reaction. The situation depicted in Figure 3 is similar to the ion pair S_N2 reaction studied by Streitwieser and co-workers[10] and may be considered an extreme case, in the sense that Na^+ exerts a strong Coulombic influence on F^- at closest distance, with Na^+F^- in the form of CIP. In actuality, the radial distribution function of the cation Na^+ in the aqueous NaX solution exhibits successive peaks with decreasing probability around the anion X^-,[39] and thus, some of the complex Na^+F^- may exist in the form of SSIP. Obviously, the cation Na^+ farther from F^- is expected to exert a diminishing influence, and the net effects of cation may be described as a weighted average of those of CIP and SSIP, increasing the barrier to less than predicted in Figure 3. When the complex Na^+F^- exists as the SSIP form, the cation is shielded from the nucleophile by the intervening solvent molecules.

III-3. $Na^+F^-(H_2O)_n + CH_3Cl$ (n = 1, 2). Acknowledging that the protic solvent molecules and the cation tend to decrease the rate of the S_N2 reaction when they *separately* influence the reacting system, one may ask: what would the effects of protic

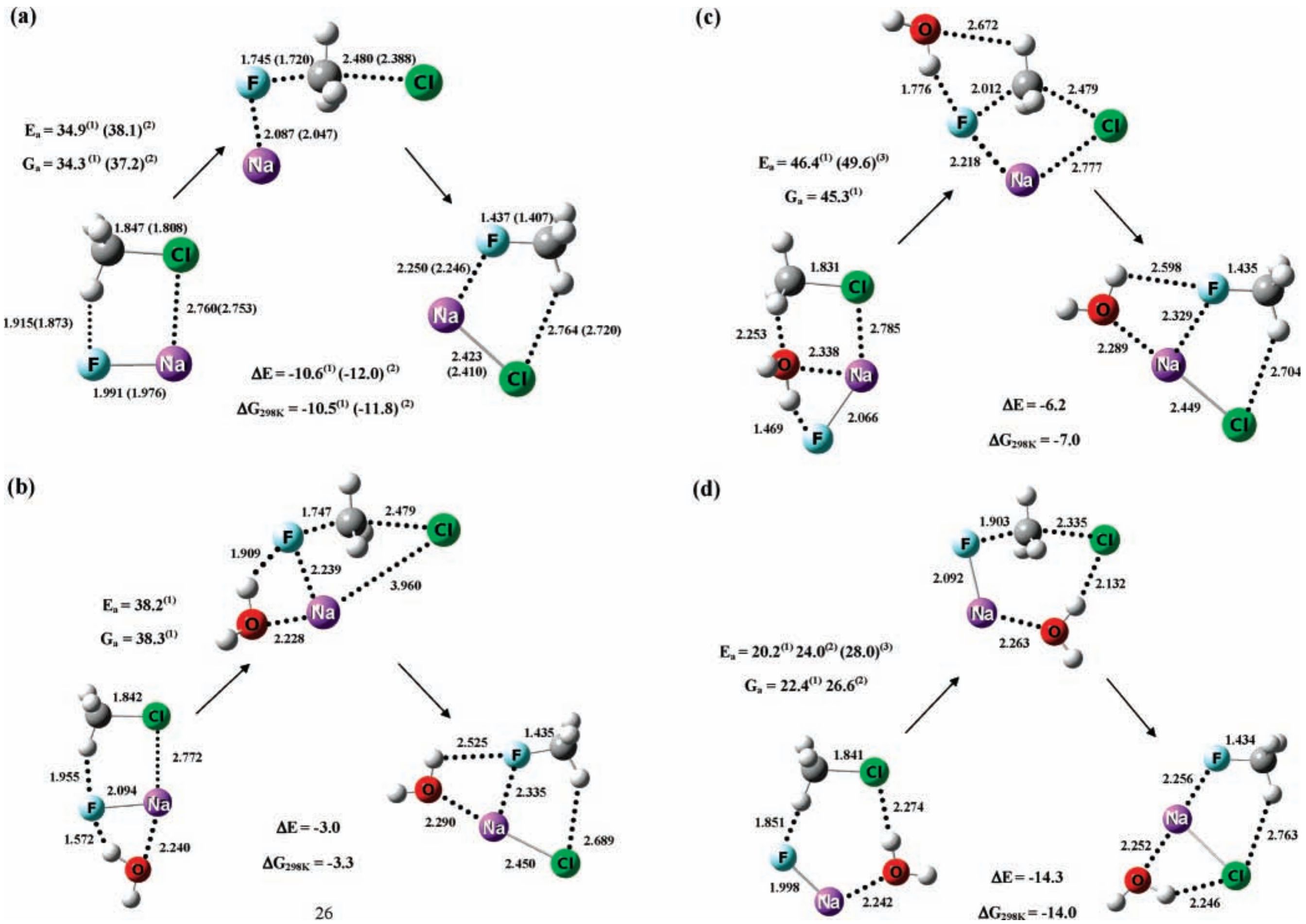

Figure 3. S_N2 reaction $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$ (a) under the influence of Na^+, and (b−d) under the influence of Na^+ and a water molecule. Energy and Gibbs function in kcal/mol and bond lengths in Å. (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**, (3) effective barrier, starting from the global minimum energy complex.

solvent be when partaking in combination with cation in the solution phase? Figure 3 illustrates the situations under the influence of Na^+ *and* a water molecule. In Figure 3b, a water molecule bridges Na^+ and F^- in the prereaction complex, partially neutralizing the Coulombic attractive force of Na^+ on F^-, but also decreasing the nucleophilicity of F^- itself. This role of water (proton-donating to F^- and accepting positive charge from Na^+) is maintained throughout the reaction, with the water molecule being kept far from CH_3Cl. These two contrasting effects seem to more or less cancel out, giving the activation barrier (38.2 kcal/mol) that is similar to (but a bit higher than) that (34.9 kcal/mol, B3LYP/6-311++G**) for the corresponding reaction without the binding water molecule (Figure 3a). In the prereaction complex depicted in Figure 3c, the water molecule is located between Na^+ F^- and CH_3Cl, bridging CH_3, Na^+, and F^-. The water molecule breaks away from Na^+, but still binds and reduces the nuclephilicity of F^- in the TS, producing a much larger barrier (46.4 kcal/mol, B3LYP/6-311++G**). It is useful to note that H_2O remains far from the Cl moiety throughout the reaction. The most interesting situation, in which the water molecule bridges Na^+ and the leaving group Cl^-, alleviating the effects of Na^+ on the nucleophile F^- and also assisting the detachment of Cl^-, is depicted in Figure 3d. This cooperative influence of Na^+ and H_2O lowers the activation barrier drastically to 20.2 (24.0) kcal/mol by the B3LYP/6-311++G** (MPW1K/6-311++G**) method. Since the prereaction complex in the mechanism depicted in Figure 3d is ~7.8 kcal/mol higher in energy than the lowest energy prereaction complex in Figure 3b, the effective barrier (also given in Figure 3) is ~28 kcal/mol, which is still very low compared with the mechanism in Figure 3b. The activation barrier for the reverse reaction, on the other hand, is significantly larger than that for the forward reaction. The solvent-assisted S_N2 mechanism shown in Figure 3d involves quite vigorous movements of the nuclei during the reaction, and the water molecule initially bridging Na^+ and Cl^- as part of the ring structure is eventually pushed away from CH_3F. It should be noted, however, that substantial movements of water molecules predicted in the gas-phase reaction here would not really describe those in the solution-phase reaction, in which numerous water molecules may restrict their motion.[40]

Figure 4 presents the structures of the prereaction complexes and the mechanism of the S_N2 reaction under the influence of Na^+ and the *two* water molecules, and again we predict very interesting effects of cation and protic solvent. In the prereaction complex in Figure 4a, the two water molecules bridge Na^+ and F^-, slightly increasing the barrier from that in Figure 3b involving a water molecule. The S_N2 reaction via this mechanism seems quite unrealistic due to the large reaction barrier ($E_a = 43.6$ kcal/mol, MPW1K/6-311++G**). A more interesting situation is depicted in Figure 4b, in which a water molecule interacts with Na^+ and F^-, while another water molecule bridges Na^+ and Cl. By partially reducing the positive charge of the Na^+ ion and by assisting the detachment of the leaving group Cl^- ion, the latter water molecule seems to lower the barrier from the case without its influence (Figure 3b) significantly by ~16 kcal/mol to 27.3 kcal/mol. In Figure 4c, the two water molecules also act to give a low barrier ($E_a = 28.1$, $G_a = 29.0$

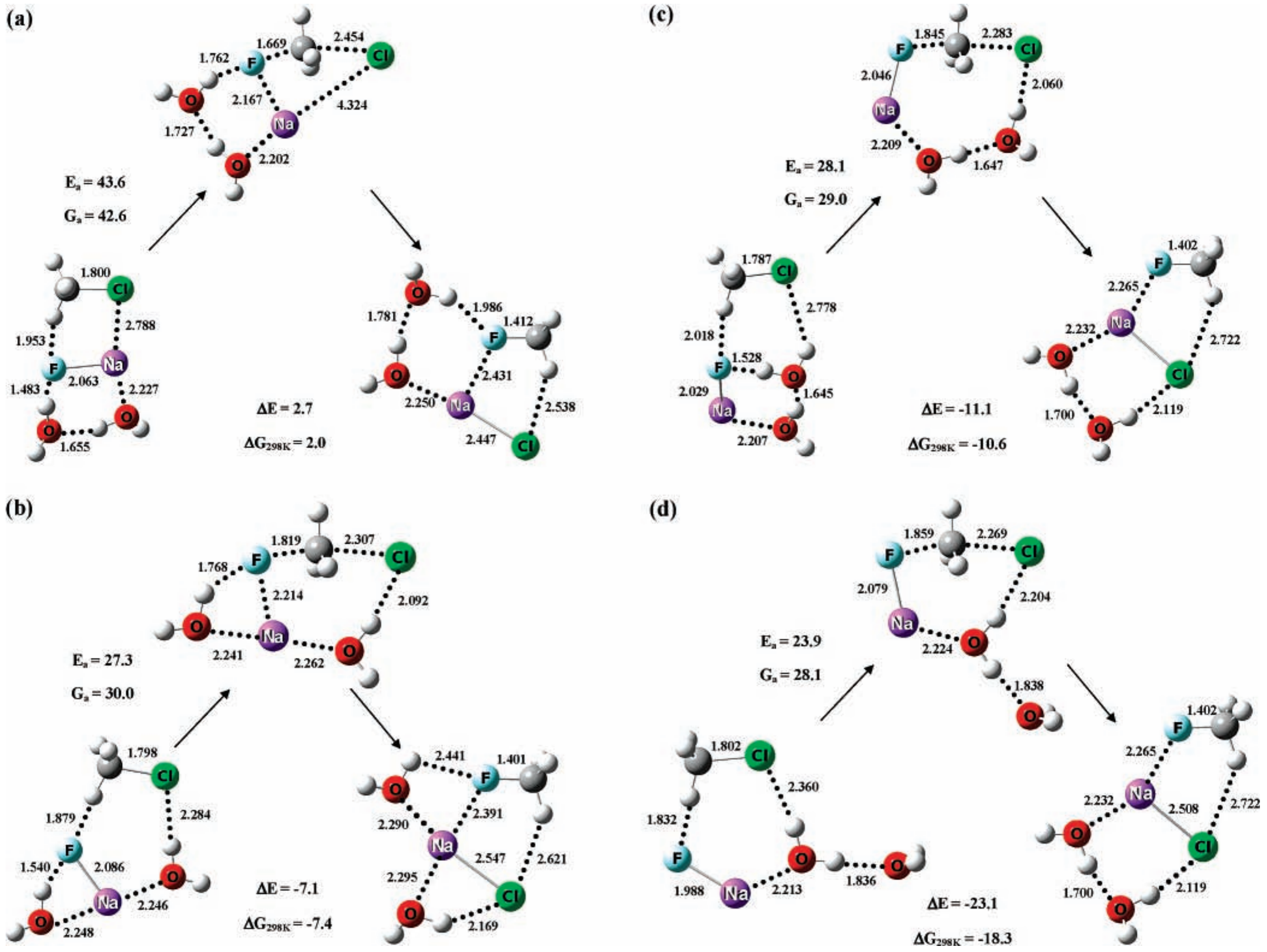

Figure 4. S_N2 reaction $F^- + CH_3Cl \rightarrow CH_3F + Cl^-$ under the influence of Na^+ and two water molecules. Energy and Gibbs function in kcal/mol and bond lengths in Å (MPW1K/6-311++G**).

kcal/mol) for the S_N2 reaction. In this situation, a water molecule bridges F^-, Cl, and H_2O, while another water molecule interacts with Na^+. The magnitude of the reaction barrier for the mechanism illustrated in Figure 4d is similar to that in Figure 3d, with another water molecule located at the far side exerting minimal influence. Thus, it seems that a single water molecule directly interacting with the cation may essentially be responsible for the predicted effects.

This predicted role of water molecule (acting as a Lewis base) in the gas-phase S_N2 reaction is in high contrast with the situation (either in the gas phase or in solution) in which protic solvent is generally considered to retard the S_N2 reaction, acting as Lewis acid and forming a hydrogen bond with the nucleophile. It also seems that this lowering of the reaction barrier predicted above by interacting protic solvent and cation is a new feature of the S_N2 reaction in the sense that the cation here remains close to the nucleophile in the form of CIP during the reaction (the SSIP form has been considered to be best for the reaction with the cation being kept as far as possible from the nucleophile in the conventional S_N mechanism). This mechanism of promoting the reaction by protic solvent is different from the solvent-mediated chemical reaction such as the multiple proton-transfer processes[41] via the solvent molecule(s), in which a part (proton) of the solvent molecule creates or annihilates chemical bonds with the reacting molecules. In the present situation, the solvent molecule remains intact, acting as a mediator of the chemical reaction. Lowering of the reaction barrier by the combined effects of cation and protic solvent to 20−23 kcal/mol, however, is far short for catalytic effects, because the barrier is still 10−18 kcal/mol higher than that for reactions in which only the protic solvent influences it (Figure 2). It seems that the effects of water molecules on Na^+ to reduce the strong Coulombic influence of Na^+ on F^- are not sufficient. The mechanism illustrated in Figures 3d and 4b−d, however, may give useful insights to devising a scheme by which the cation and solvent may catalyze the S_N2 reaction. For example, a highly polarizable cation such as Cs^+ or ammonium would be more favorable, because it will be affected by the protic solvent more easily and to a larger degree.

III-4. $Na^+Br^-(H_2O)_n$ + CH_3Cl (n = 0, 1). Since the fluorination reaction is generally thought to be more difficult than bromination, it will be interesting to examine how the proposed mechanism would predict the relative reactivity of F^- and Br^-. Figure 5 shows the mechanism of bromination under the influence of Na^+ and a water molecule. It is interesting to note that the barrier (27.3 kcal/mol, MPW1K/6-311++G**) is now higher than that (24.0 kcal/mol) for fluorination (Figure 3d), indicating that bromination may occur less readily than fluorination under these circumstances, that is, when a water molecule acts as a base to alleviate the retarding effects of cation. This prediction is clearly distinct from the effects of solvation that have been invoked to explain the difficulty of fluorination relative to bromination in the solution phase (F^- is solvated more extensively than Br^-). It seems rather that the difference

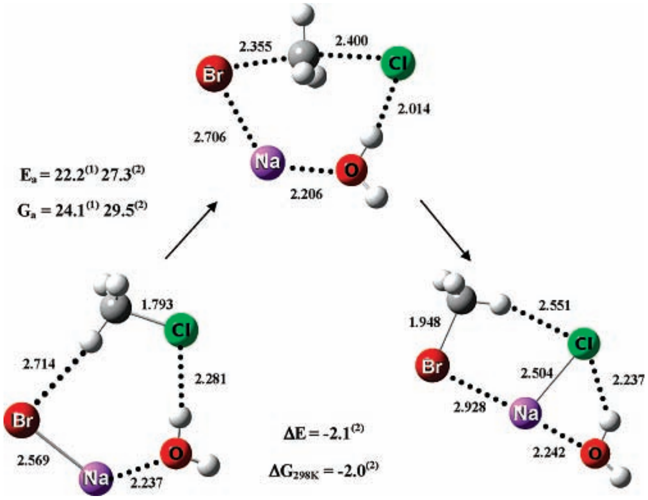

Figure 5. S_N2 reaction (a) $Br^- + CH_3Cl \rightarrow CH_3F + Cl^-$ and (b) $Br^-(H_2O) + CH_3Cl \rightarrow CH_3F + Cl^-$. Energy and Gibbs function in kcal/mol and bond lengths (MPW1K/6-311++G**) in Å. (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**.

in the inherent basicity of F^- and Br^- (F^- is more basic than Br^-) makes fluorination more favorable than bromination due to the role of water molecule as a Lewis base here.

III-5. $M^+F^-(H_2O)_n + CH_3Cl$ (M = K, Rb, and Cs; $n = 0, 1$). Since the metal cation may interact with the nucleophile and the solvent molecules, the barrier and the rate constant of the S_N2 reaction may also be profoundly affected by the properties of the cation. When a larger metal cation interacts with F^-, the Coulombic effects are expected to be smaller than that of Na^+. Indeed, the barriers of the reaction $M^+F^- + CH_3Cl$ (Figure 6a depicts the mechanism for M = Cs) are calculated to be 29.5, 23.0, and 20.7 kcal/mol (B3LYP/6-311++G**) for M = K, Rb, and Cs, respectively, which are progressively much smaller than that (34.9 kcal/mol) for the reaction [$Na^+F^- + CH_3Cl$] depicted in Figure 3a. When a water molecule interacts with the nucleophile F^- and larger metal cation (Figures 6b describes such a case for M = Cs, corresponding to Figure 3d for M = Na), the barriers of the reaction $M^+F^-(H_2O) + CH_3Cl$ are calculated to be 22.3, 20.3, and 20.3 for M = K, Rb, and Cs, respectively, quite similar to that (20.2 kcal/mol) for the reaction $Na^+F^-(H_2O) + CH_3Cl$. It seems that the bulky cation is pushed away from the reactants, allowing F^- and H_2O to get close to each other (their distance in Figure 6b is only 1.491 Å). This proximity of H_2O to F^- may decrease the nucleophilicity of F^- to a larger degree than in the reaction $Na^+F^-(H_2O) + CH_3Cl$, and therefore, the smaller Coulombic effects of the larger cation are more or less offset by the larger electrostatic influence of the water molecule on F^- to give the barriers that are almost independent of the metal cation. Thus, water does not seem to be a good protic solvent to harness the predicted effects of the large and polarizable cations to lower the activation barrier. Bulky solvent molecules, which may be alienated from the nucleophile more easily, would be much better, as described in the next section.

III-6. Cs^+F^-(*tert*-butyl alcohol)$_n$ + C_3H_7OMs ($n = 1, 2$). Our calculated results for a series of reactions $F^- + CH_3Cl \rightarrow FCH_3 + Cl^-$ in water and under the influence of cation may provide a fundamental insight into the mechanism of the phenomenally efficient fluorination in protic solvent described in a previous report.[30] The observed characteristics of the nucleophilic substitution reaction were in stark contrast with aspects associated with the conventional S_N2 reaction in several respects. First, hindered protic solvents (*tert*-butyl alcohol and *tert*-amyl alcohol in the present work) are extremely good for the S_N2 reaction. This finding is striking, because in conventional S_N2 reactions polar, aprotic solvents are known to be much more efficient. Second, product yield is highly dependent on the cation (Cs^+ is much better than K^+), which provides experimental evidence for the important influence of Coulombic interactions of the cation on the reaction. Third, the relative reactivity of the halide nucleophile appears to be the reverse (F^- much more reactive than Br^-) of that ($F^- < Cl^- < Br^-$, etc.) typical for halide in conventional S_N2 reactions in aprotic solvents predicted by simply considering the differential solvation of the nucleophile. Fourth, the effect of the leaving group seems to be much larger than in the conventional S_N2 reactions, suggesting that some sort of interaction between the leaving group and the other constituents of the reaction (the nucleophile, cation, or the solvent molecule) is affecting the reaction rate. The pronounced effect of the cation suggests that it may be in proximity to the nucleophile. On the other hand, the OH group of the protic solvent molecule and the nucleophile should remain as remote as possible during the progress of the reaction, because hydrogen bonding between them would certainly reduce the reactivity of the nucleophile. We propose that protic solvent molecules may play a critical role in promoting the reaction by alleviating the unfavorable Coulombic influence of the metal cation on the nucleophile, without forming a hydrogen bond with the nucleophile. The size of the solvent molecule would be an important property in this case, because the bulkier solvent

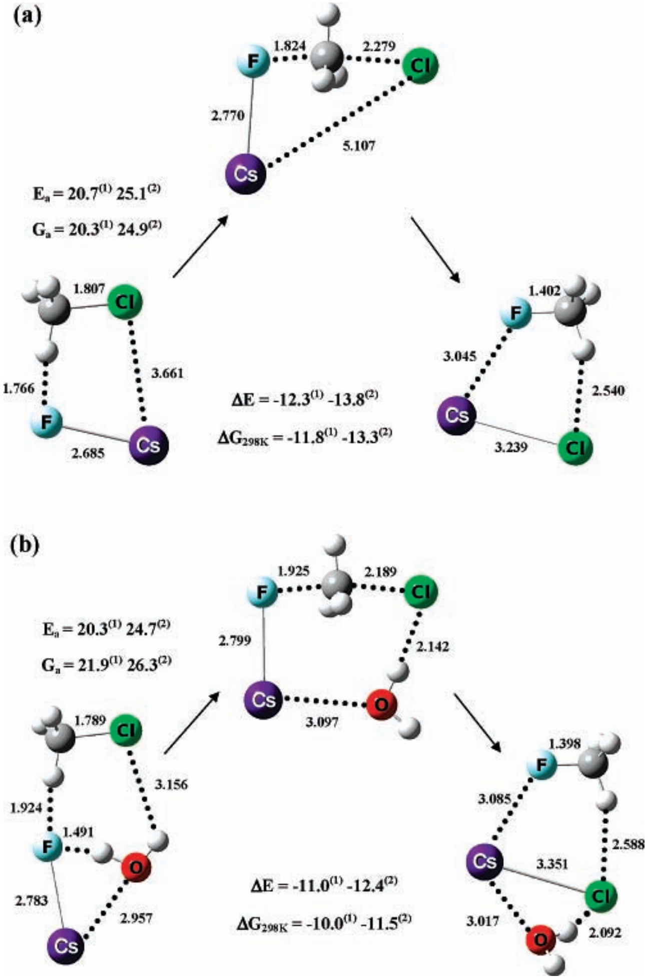

Figure 6. S_N2 reactions of (a) $Cs^+F^- + CH_3Cl$ and (b) $Cs^+F^-(H_2O) + CH_3Cl$. Energy and Gibbs function in kcal/mol and bond lengths in Å (MPW1K/6-311++G**; ECP for Cs, Hay-Wadt VDZ(n+1)). (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**.

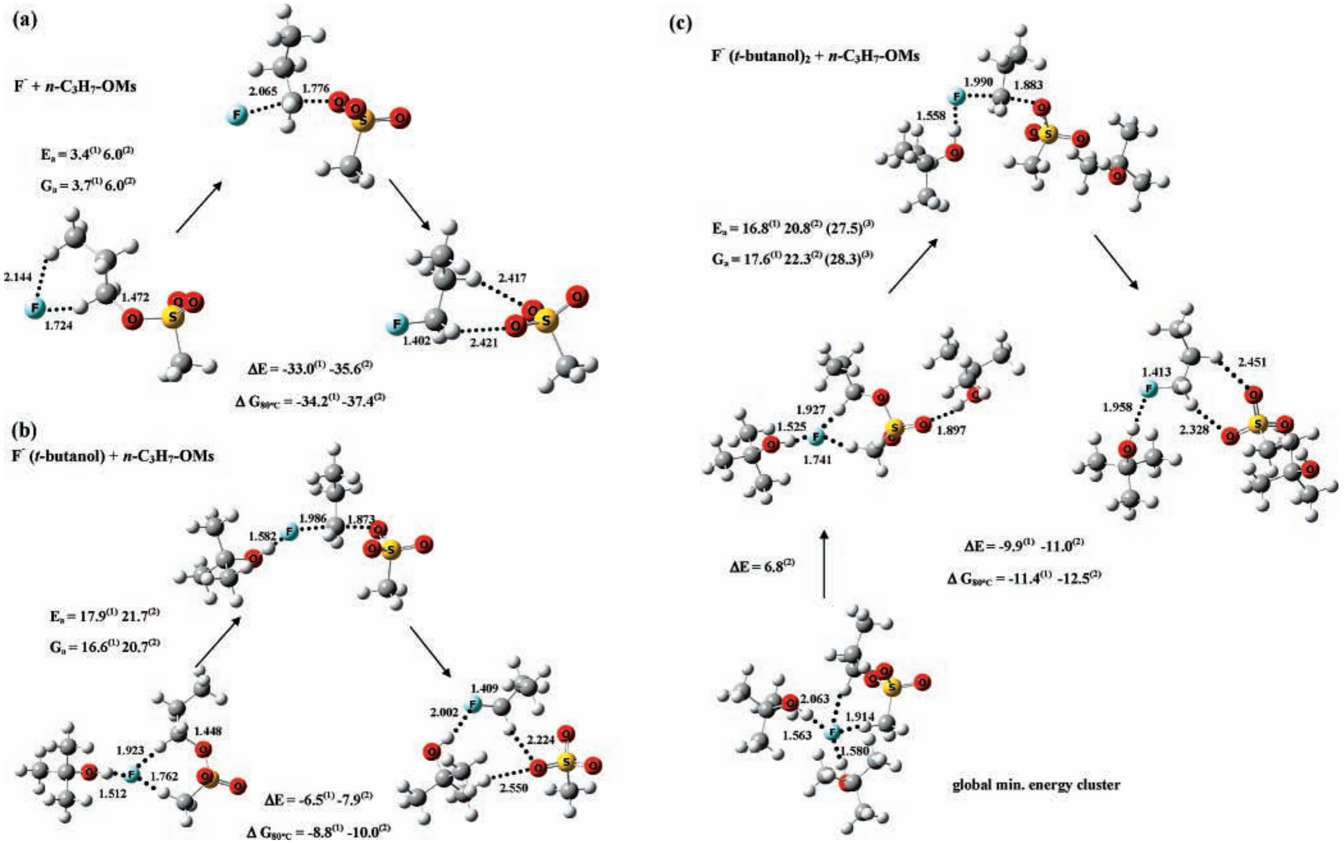

Figure 7. Calculated S_N2 mechanism in which bare F^- reacts. Protic solvent acts as a Lewis acid. Energy and Gibbs function in kcal/mol and bond lengths in Å. (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**, (3) effective barrier from the global minimum energy complex.

molecules are, the more difficult it will be for them to penetrate between cation and nucleophile. The size and polarizability of the cation would also be critical: bulky cation may better shield the solvent from the nucleophile, and the influence (reducing the positive charge of the cation) of solvent molecules on cation may be maximal when it is easily polarizable. For small solvent protic solvent molecules, methanol and ethanol, we find that the barriers of ∼20.2 (24.0) kcal/mol by the B3LPY (MPW1K) method are quite similar to the case of the reaction mediated by water. Larger solvent molecules would certainly be more effective, and we carry out calculations for the S_N2 reaction in *tert*-butyl alcohol. The structure of the leaving group may also be critical when the protic solvent molecule may interact with the leaving group to produce a stable transition state and low activation barrier. We choose the mesylate group possessing multiple oxygen atoms that may interact with OH in the bulky *tert*-butyl alcohol molecule.

Figure 7a depicts the S_N2 reaction $F^- + n\text{-}C_3H_7OMs$ in the absence of cation and solvent. The extremely low activation barrier (6 kcal/mol, MPW1K/6-311++G**) indicates that this reaction would proceed almost with gas kinetic rate constant. Figure 7b,c demonstrates the effects of protic solvent on the S_N2 reaction in which the "naked" nucleophile F^- interacts with *tert*-butyl alcohol. Our calculations show that the net effects of a *tert*-butyl alcohol molecule are to raise the reaction barrier by ∼16 kcal/mol, indicating that the protic solvent, acting as a Lewis acid, may retard the reaction tremendously. The prereaction complex given in Figure 7b is the global minimum energy structure in the F^-(*tert*-butyl alcohol) + $n\text{-}C_3H_7OMs$ system, whereas that in Figure 7c is not, lying 6.8 kcal/mol above the global minimum energy complex in the F^-(*tert*-butyl alcohol)$_2$ + $n\text{-}C_3H_7OMs$ system. In this latter case, the effective barrier for the reaction F^-(*tert*-butyl alcohol)$_2$ + $n\text{-}C_3H_7OMs$ may be obtained as the sum of the barrier from the prereaction complex in Figure 7b *and* the relative energy (6.8 kcal/mol) of this complex with respect to the global minimum energy structure given. The effective barrier thus obtained is 27.5 kcal/mol, as given in Figure 7c.

Noting the retarding effects of *tert*-butyl alcohol, interactions with more protic solvent molecules would further *increase* the already high barrier in this conventional S_N2 mechanism. Presence of another protic solvent interacting with the leaving group (Figure 7c) yields only a slight change in the barrier. This latter situation looks similar to the very interesting mechanism recently proposed by Pliego and Piló-Veloso,[42−46] in which the reaction rate increases by selective solvation of the nucleophile and leaving group by forming two cooperative hydrogen bonds with diol in the transition state. The barrier of the reaction depicted in Figure 7c is, however, calculated to be larger than that of the ion pair reaction proposed below, indicating that the interesting mechanism proposed by Pliego and co-workers is not effective here. It must be noted that the *tert*-butyl alcohol molecule near the leaving group moves vigorously during the course of reaction, and this prediction may be prone to change when more solvent molecules affect in solution. In this latter case, the movements of solvent molecules are expected to be seriously restrained, accompanied with the increase in reaction barrier. Since the barriers for the mechanisms depicted in Figure 7b,c are quite similar (the difference is only ∼1 kcal/mol), it seems that the *tert*-butyl alcohol molecule interacting with the nucleophile primarily determines the magnitude of the reaction barrier, and that vigorous movement of the *tert*-butyl alcohol molecule near the leaving group may not be a significant factor, at least with respect to the reaction barrier.

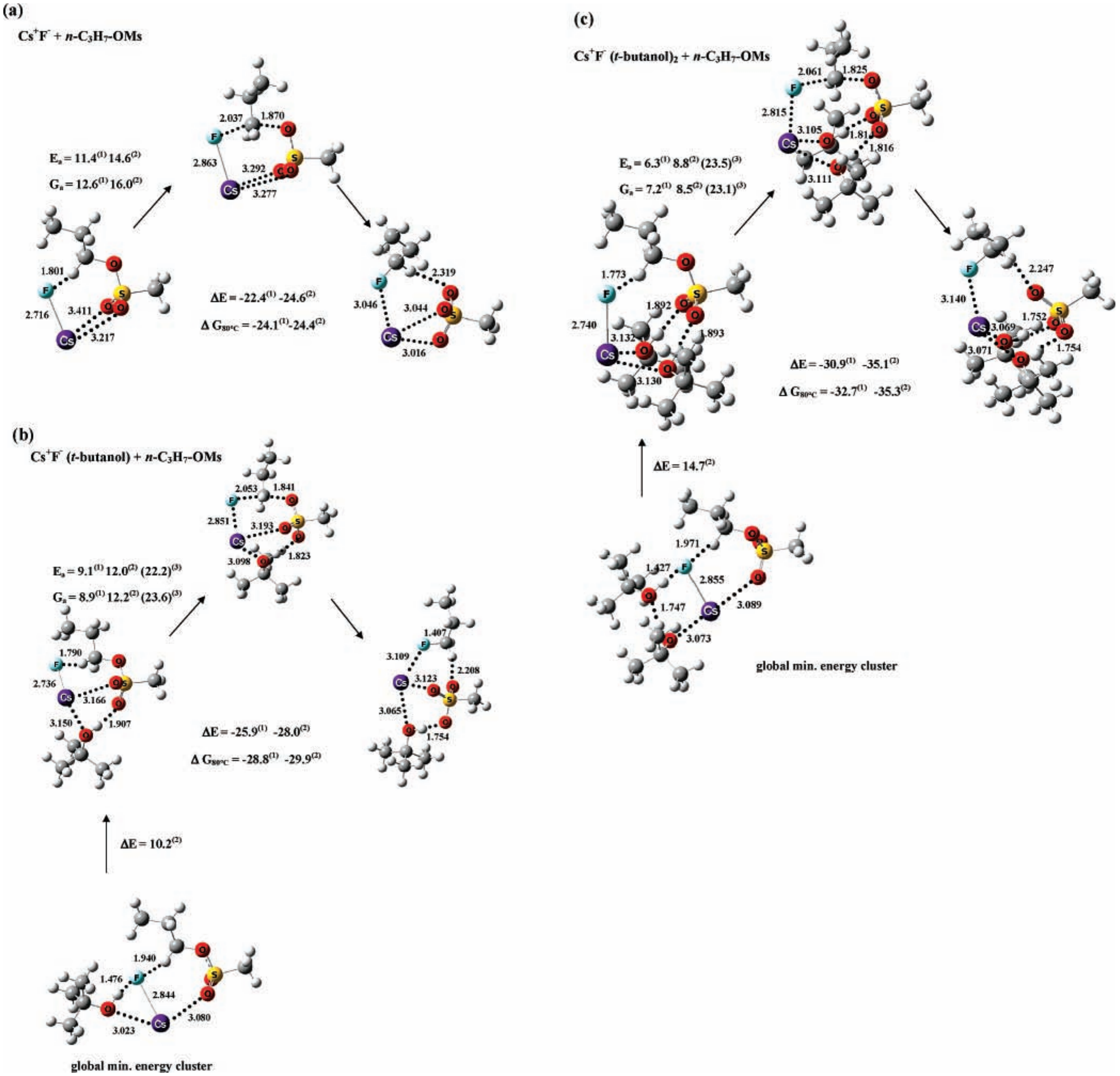

Figure 8. Calculated S_N2 mechanism in which Cs^+F^- reacts as an ion pair. Protic solvent acts as a Lewis base. Energy and Gibbs function in kcal/mol and bond lengths in Å. (1) B3LYP/6-311++G**, (2) MPW1K/6-311++G**, (3) effective barrier from the global minimum energy complex.

The effects of the cation Cs^+ on the reaction $F^- + n\text{-}C_3H_7\text{-}OMs$, on the other hand, are to raise the barrier only by ~9 kcal/mol (Figure 8a), which is much less pronounced than those of *tert*-butyl alcohol (Figure 7b). We find that the configuration of the reacting species depicted in Figure 8b,c for the reaction Cs^+F^-(*tert*-butyl alcohol)$_{1,2}$ + $n\text{-}C_3H_7OMs$ lowers the barrier by the combined effects of *tert*-butyl alcohol and cation Cs^+. The activation barrier ($E_a = 14.6$, $G_a = 16.0$ kcal/mol, MPW1K/6-311++G**) of the S_N2 reaction $Cs^+F^- + n\text{-}C_3H_7OMs$ in the absence of protic solvent now decreases to $E_a = 12.0$ ($G_a = 12.2$) kcal/mol (MPW1K/6-311++G**) under the influence of a *tert*-butyl alcohol molecule (Figure 8b). Comparing with the gas-phase S_N2 reaction between a *bare* F^- and the comparable halide (for example, $E_a = \sim 10$ kcal/mol for Cl^- + neopentyl-Cl),[5] this indicates that the unfavorable Coulombic influence of Cs^+ on F^- has essentially been nullified by a *tert*-butyl alcohol molecule. Considering that the prereaction complex given in Figure 8b is 10.2 kcal/mol higher in energy than the global minimum energy complex in the Cs^+F^-(*tert*-butyl alcohol) + $n\text{-}C_3H_7OMs$ system, the effective barrier is 22.2 kcal/mol, which is slightly larger (by ~0.5 kcal/mol) than that given in Figure 7b for the reaction of bare nucleophile F^- in the presence of protic solvent acting as a Lewis acid in the conventional S_N2 mechanism. Therefore, the S_N2 reaction of the naked F^- (Figure 7b) and the CIP form of F^- (Figure 8b) seems to proceed with very similar rate constants under the influence of a single *tert*-butyl alcohol molecule.

Figure 8c shows that a second *tert*-butyl alcohol molecule further reduces the activation barrier to $E_a = 8.8$ kcal/mol, approaching that (6.0 kcal/mol) for the reaction $F^- + n\text{-}C_3H_7\text{-}OMs$ (Figure 7a) that would proceed nearly with gas kinetic rate constant. The prereaction complex presented in Figure 8c is 14.7 kcal/mol higher in energy above the global minimum energy complex for the Cs^+F^-(*tert*-butyl alcohol)$_2$ + $n\text{-}C_3H_7\text{-}$

OMs system, and thus, the effective barrier is calculated to be 23.5 kcal/mol. Comparing with the barrier (27.5 kcal/mol) obtained for the conventional mechanism for F^-(*tert*-butyl alcohol)$_2$ + *n*-C_3H_7OMs depicted in Figure 7c, it can be seen that our proposed mechanism via the CIP form of the metal−halide is much more favorable than the conventional mechanism. The difference of ∼5.3 kcal/mol in the barrier of the two mechanism amounts to 200 times difference in rate constants. Interactions with more solvent molecules may still lower the barrier by "pulling" the positive charge of the cation and also possibly by assisting the detachment of the leaving group to a larger degree. Although our comparison of the two mechanisms would become more rigorous if the influence of the other infinite number of solvent molecules could be shown to be similar in the two cases, and if the effects of dynamic polarization[47] are included in our calculations, our proposed alternative mechanism (Figure 8b,c) would be much more feasible than the conventional mechanism depicted in Figure 7b,c, when we consider the already large difference in the reaction barriers of the two mechanisms under the influence of two solvent molecules (due to the bulkiness of *tert*-butyl alcohol, only a few solvent molecules are expected to interact directly with the reactants). Therefore, we suggest that this alternative mechanism, in which the *tert*-butyl alcohol molecule acts as a Lewis base to the cation Cs^+ (and as a Lewis acid to the leaving group −OMs, bridging the two) may indeed account for the experimentally observed phenomenal efficiency of fluorination in *tert*-alcohol medium in the presence of bulky and polarizable cation such as Cs^+.[30]

The different degree of solvation for nucleophiles (more solvation for F^- than for larger I^-) has usually been invoked to explain the smaller reaction rates of smaller halides in protic solvent. However, this is not the case here, because it was observed that the relative rate constants are in reverse order ($F^- > Br^-$) to that predicted for the nucleophilicity of the solvated halide in protic solvent ($F^- < Cl^- < Br^-$, etc). The observed higher reactivity of F^- is better explained by differences in the interactions in the CIP form of cation−halide. Our calculations for the reactions Cs^+X^- + *n*-C_3H_7OMs (X = F, Br) predict that the softer Br^- is less negative (−0.9693) than F^- (−0.9856), due to the larger effects of the cation Cs^+, indicating that the nucleophilicity is parallel to the basicity in the S_N2 reaction in the protic solvent (F^- more reactive than Br^-).

In summary, we have carried out a systematic analysis for the effects of cation and protic solvent on S_N2 reactions. We have demonstrated that bulky protic solvent (*tert*-butyl alcohol) may enormously promote the reaction when affecting the reaction in combination with bulky and polarizable cation (Cs^+) in an intricate fashion, proposing a new class of S_N2 reaction.

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Supporting Information Available: Full tables of electronic energies, ZPE, Gibbs function at 80 °C, and the atomic coordinates of the stationary states and the transition states presented in Figures 7 and 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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