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A Mechanistic Study of S_N2 Reaction in a Diol Solvent

Suk Im, Sung-Woo Jang, Hye-Rim Kim, Young-Ho Oh, Sung-Woo Park, and Sungyul Lee*

College of Environmental Science and Applied Chemistry (BK 21), Kyunghee University, Kyungki 446-701, S. Korea

Dae Yoon Chi*

Department of Chemistry, Sogang University, Seoul 121-742, S. Korea

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We present calculations for the mechanism of S_N2 reactions in ethylene glycol, focusing on the role of two protic functional groups (−OH) in the solvent molecule. We find that some hydroxyl groups act as Lewis base to interact with the cation, whereas others affect the reaction as Lewis acid to the nucleophile. We predict that the nucleophile (F^-) reacts as an ion pair rather than as a solvent-separated ion when metal cation (Cs^+) is used as a counterion. The overall influence of ethylene glycol manifests itself as the reaction barrier ($E^\ddagger = 20.0$, $G^\ddagger_{353K} = 21.5$ kcal/mol) that is a bit smaller than that in *tert*-butyl alcohol, which proved to be a very efficient solvent for S_N2 reactions [Kim, D. W., et al. *J. Am. Chem. Soc.* 2006, *128*, 16394]. We therefore show that a small protic solvent such as ethylene glycol may be as efficient as a bulky alcohol for S_N2 reactions.

I. Introduction

The bimolecular nucleophilic substitution (S_N2) reactions[1−17] have long been envisaged by a simple backside attack of the nucleophile on the substrate via a single transition state. Recent reports, however, propose that this simple view may not be true in certain situations; for example, Uggerud[7] recently discussed a S_N2 mechanism involving a frontal attack by the nucleophile. Since most S_N2 reactions occur in solution, the role of solvent is also expected to be critical for the efficiency of the reaction, as systematically discussed very recently by Pliego.[8] Conventional wisdom is that protic solvents are inefficient due to the hydrogen bonding with the nucleophile. Recently, however, Chi and co-workers[9,11] observed that bulky protic solvents such as *tert*-butyl alcohol can be very efficient for S_N2 reactions. They also observed that S_N2 reactions in ionic liquid can occur readily,[10] indicating that ionic species may affect the reaction rates in an intricate fashion that has so far not been considered. To elucidate this observation, Lee and co-workers[9a] proposed a S_N2 reaction in which the nucleophile reacts in the form of an ion pair (M^+X^-). In this mechanism, the protic solvent molecules (acting as Lewis *base*) interact with the cation rather than with the nucleophile, thereby reducing the unfavorable Coulombic influence of the cation on the nucleophilicity. The size of the protic solvent proved to be a critical factor for the efficiency of S_N2 reaction.

In the present work, we investigate the S_N2 reactions in a diol possessing two protic groups (−OH). Our motivation is that the efficiency of the reaction depends highly on whether the two hydroxyl groups in the solvent molecule may act as Lewis acid or base. We find that the ethylene glycol molecule acts as a bifunctional solvent. That is, the hydroxyl group may interact with the nucleophile both as a Lewis acid, forming hydrogen bonds (retarding the reaction), and as a Lewis base binding to the cation (promoting the reaction) by reducing the unfavorable Coulombic influence of the cation on the nucleophile.[9a] We examine the structures, energies, and Gibbs free energies of various conformers of $[Cs^+F^-\cdots C_3H_7{-}OMs]$ and $[F^-\cdots C_3H_7{-}OMs]$ (Ms = mesylate) systems under the influence of two ethylene glycol molecules to determine their thermodynamic stability. We suggest that the nucleophile (F^-) would react as a contact ion pair (CIP) rather than as a solvent-separated ion pair (SSIP) when metal cation (Cs^+) is used as a counterion. The calculated overall reaction barrier is slightly lower than that in *tert*-butyl alcohol that proved to be a very efficient protic solvent for S_N2 reactions,[9b] indicating that a small protic solvent with multiple −OH groups such as ethylene glycol may be as efficient as a bulky alcohol for S_N2 reactions, in agreement with recent experimental observations.[18]

II. Computational Methods

Density functional theory method (MPW1K)[16,17] is employed with the 6-311++G** basis set and the effective core potential for Cs (Hay−Wadt VDZ(n+1)),[19] as implemented in Gaussian 03 set of programs.[20] The MPW1K method, which we employ to compare the calculated barrier in this work with those of other reacting systems previously studied,[9a,11] is known to give barrier heights that are 2−3 kcal/mol smaller than those obtained by more accurate correlated ab initio method (MP2/6-311++G** or /aug-cc-pvdz). 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.

III. Results and Discussion

Table 1 and Figure 1 present the structures of conformers of $[Cs^+F^-\cdots C_3H_7{-}OMs]$ system under the influence of two molecules of ethylene glycol.[21] The most stable conformer is

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* Corresponding authors. Tel: +82-31-201-2423. Fax: +82-31-202-7337. E-mail: sylee@khu.ac.kr (S.L.); dychi@sogang.ac.kr (D.Y.C.).

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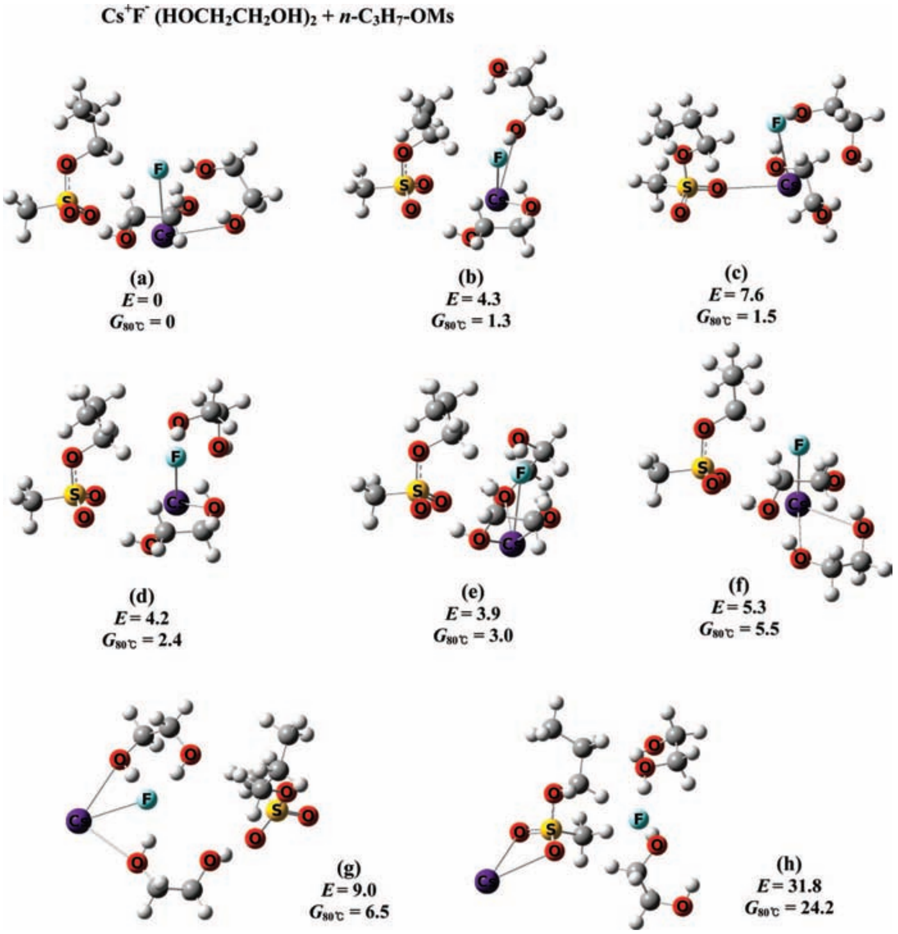


Figure 1. Structures, relative energy and Gibbs free energy of conformers of [$Cs^+F^- \cdots C_3H_7-OMs$] system under the influence of two ethylene glycol molecules (relative energy and Gibbs free energy in kcal/mol, bond lengths in Å; MPW1K/6-311++G**; ECP for Cs, Hay−Wadt VDZ(n+1)).

TABLE 1: Electronic *E* (hartrees), Zero-Point Energy (ZPE) (kcal/mol), Relative Energy Δ*E* (kcal/mol) Gibbs Free Energy ΔG_{353K} (hartrees) of the Conformers of the [$Cs^+F^- \cdots C_3H_7-OMs$] System under the Influence of Two Ethylene Glycol Molecules

	E	ZPE	Δ*E*	ΔG_{353K}
(a)	−1362.65701	209.7	0	0
(b)	−1362.64948	209.3	4.3	1.3
(c)	−1362.64224	208.0	7.6	1.5
(d)	−1362.64920	208.9	4.2	2.4
(e)	−1362.65040	209.4	3.9	3.0
(f)	−1362.64817	209.5	5.3	5.5
(g)	−1362.642918	209.8	9.0	6.5
(h)	−1362.60473	208.7	31.8	24.2

predicted to be (a). The OH groups in the reacting complex are found to play several different roles: in the ethylene glycol molecules located away from the reactant C_3H_7-OMs, one of the OH groups interacts with the cation Cs^+ (R_{O-Cs} = 3.243 Å) and the nucleophile F^- (R_{O-F} = 1.585 Å) (as a Lewis acid), whereas the other interacts with Cs^+ as a Lewis base (R_{O-Cs} = 3.155 Å) simultaneously forming a hydrogen bond (1.839 Å) with a OH group in the other ethylene glycol molecule. On the other hand, the role of the hydroxyl groups in the other ethylene glycol molecule, lying closer to C_3H_7-OMs, seems somewhat different. One of them binds both to the leaving group (R_{H-O} = 1.929 Å) and Cs^+ (R_{O-Cs} = 3.225 Å), whereas the other OH forms a hydrogen bond with the nucleophile F^- (R_{H-F} = 1.506 Å) and binds to the cation Cs^+ (R_{O-Cs} = 3.288 Å). Thus, when the OH group interacts with Cs^+, it acts as a Lewis base, whereas its role is considered as a Lewis acid when it forms hydrogen bond with the nucleophile F^-, promoting and retarding the S_N2 reaction, respectively.[9a] In the complex (a), there exist four such O−Cs^+ interactions and two H−F^- hydrogen bonds to affect the efficiency of the S_N2 reaction. In (b), the two OH groups, each from the two ethylene glycol molecules, bind to both Cs^+ (R_{O-Cs} = 3.113, 3.151 Å) and the nucleophile F^- (R_{H-F} = 1.597, 1.484 Å). One of the two remaining OH groups seems to be too far to influence the reaction, whereas the other interacts with the leaving group (R_{H-O} = 1.931 Å). In complex (c), one of the OH groups of each ethylene glycol molecules binds to F^- (R_{H-F} = 1.495 and 1.529 Å) and to Cs^+ (R_{O-Cs} = 3.221 and 3.193 Å). The other OH group of the respective ethylene glycol molecules exhibits weaker interaction with Cs^+ (R_{O-Cs} = 3.261, 3.258 Å). Complexes (d) and (e) are similar to each other except for the direction of a OH group interacting only with Cs^+. The H−F^- hydrogen bond (R_{H-F} = 1.483 Å) in (d) seems to be stronger than (e) (R_{H-F} = 1.525 Å), but the influence of OH as a Lewis base is estimated to be weaker (R_{O-Cs} = 3.253 Å vs 3.187 Å). The two ethylene glycol molecules are at a similar distance from the reactant C_3H_7-OMs in complex (e) lying 3 kcal/mol higher than (a). The OH groups in this complex also affect the reaction in various ways. In one the ethylene glycol molecules, two OH groups interact with Cs^+ (R_{O-Cs} = 3.187 Å) and with F^- (R_{O-F} = 1.525 Å), respectively. A OH group in the other solvent molecule binds both to Cs^+ (R_{O-Cs} = 3.109 Å) and F^- (R_{O-F} = 1.592 Å), whereas the other OH forms a weak hydrogen bond (R_{H-O} = 1.938 Å) with an oxygen atom

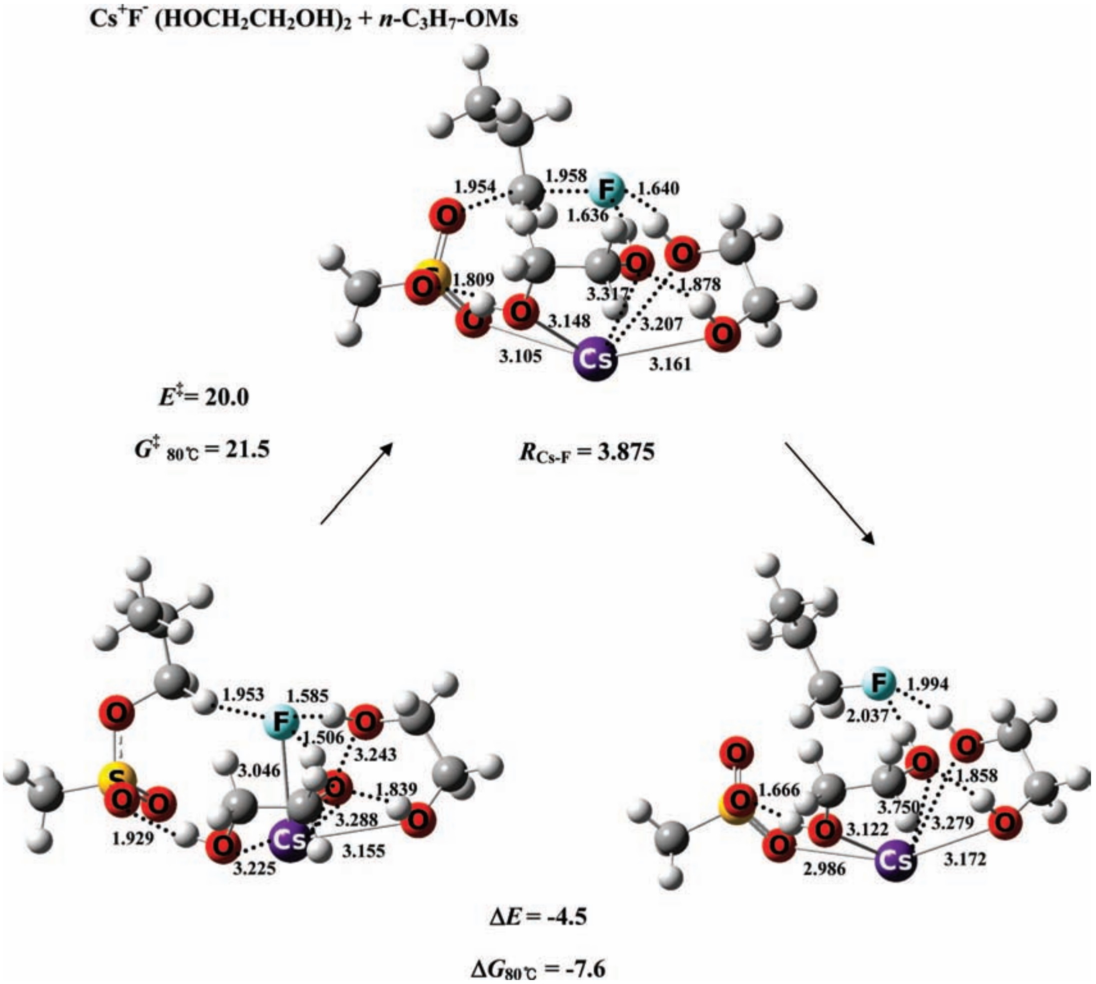


Figure 2. Calculated mechanism of ion-pair reaction $[Cs^+F^- \cdots C_3H_7{-}OMs]$ in ethylene glycol. Barriers in kcal/mol and bond lengths in Å (MPW1K/6-311++G**; ECP for Cs, Hay−Wadt VDZ(n+1)).

of the leaving group while also interacting with Cs^+ ($R_{O-Cs} = 3.176$ Å). In complex (f), one of the ethylene glycol molecules is located closer to F^-, while another sits near Cs^+. The two OH groups in the former ethylene glycol molecule interacts with F^- ($R_{H-F} = 1.430$ Å), and with an oxygen atom of the leaving group ($R_{H-O} = 1.897$ Å), respectively. Two OH groups of the other solvent molecule form a bridge with Cs^+ ($R_{O-Cs} = 3.187$ and 3.126 Å), while forming hydrogen bonds with the other ethylene glycol molecule ($R_{H-O} = 1.788$, 1.771 Å). In conformer (g), the cation Cs^+, the nucleophile F^-, and the reactant form more or less linear configuration with the energy substantially higher (by 8.0 kcal/mol) than (a). It seems that the two solvent molecules influence the reacting system such that the $Cs^+{-}F^-{-}C$ configuration is significantly bent as in (a). We also obtained the structure (h) to examine the thermodynamic stability of the conformer in which Cs^+ cation is separated from F^-, but find that its energy is much higher (by ~32 kcal/mol) than (a).

In addition to being useful to envisage the interactions among the participants of the reaction (cation, nucleophile, reactant, leaving group, and the solvent molecules), these prereaction complexes also indicate how the S_N2 reactions would proceed in ethylene glycol. For example, the conformer (a) possesses four such $O{-}Cs^+$ interactions resulting from the OH groups acting as Lewis base, and this structural characteristic may facilitate the S_N2 reaction by reducing the unfavorable Coulombic influence of Cs^+ on the nucleophilicity of F^-.[9a] Figure 2 depicts the calculated mechanism in which the nucleophile reacts in the form of ion pair (M^+X^-) in the most stable prereaction complex (a) presented in Table 2. As described above, the OH groups influence the reaction in various fashion, as a Lewis acid, base, or both. The formation of hydrogen bond between the hydroxyl hydrogen atom and the nucleophile F^- is expected to deter the S_N2 reaction (this is considered to be the origin of the inefficiency of protic solvents), and overall, two such hydrogen bonds form in (a). On the other hand, interactions between an oxygen atom (acting as a Lewis base) in the OH group and the cation Cs^+ would increase the reaction rate, because it alleviates the positive charge of Cs^+ that exerts a strong Coulombic influence on F^- to reduce its nucleophilicity. It is difficult to analyze the effects of each type of interaction on the reaction separately, but the complicated interplay among the participants of the reaction yields an overall activation barrier $E^‡$ of 20.0 ($G^‡_{353K} = 21.5$) kcal/mol.

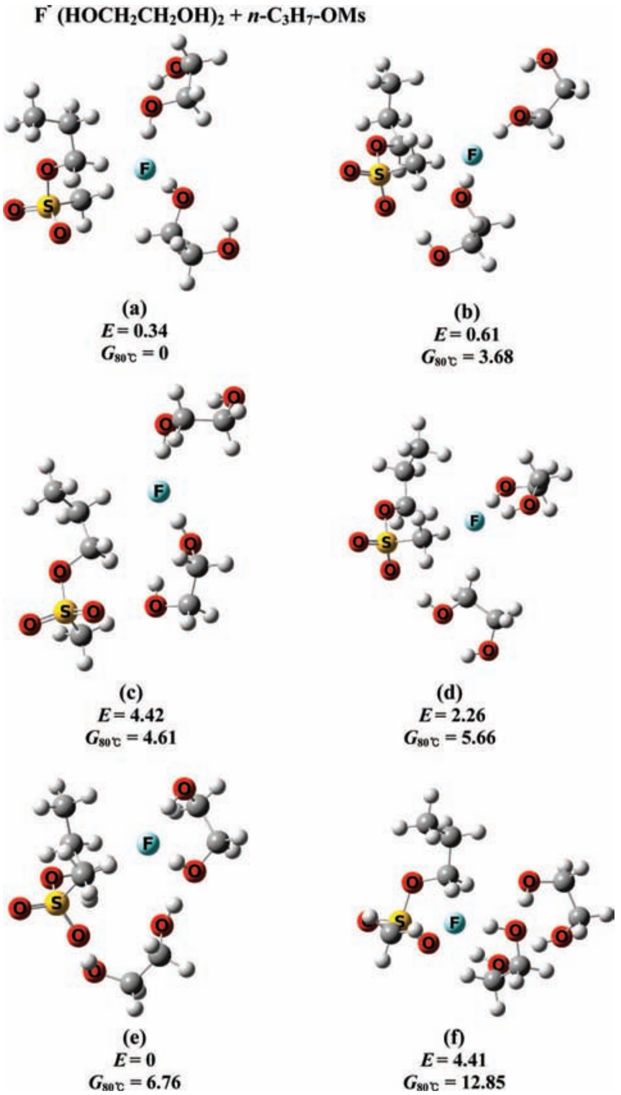
TABLE 2: Electronic E (hartrees), Zero-Point Energy (ZPE) (kcal/mol), Relative Energy ΔE (kcal/mol), and Gibbs Free Energy ΔG_{353K} (hartrees) of the Conformers of the $[F^- \cdots C_3H_7{-}OMs]$ System under the Influence of Two Ethylene Glycol Molecules

	E	ZPE	ΔE	ΔG_{353K}
(a)	−1342.74666	208.3	0.34	0
(b)	−1342.74659	208.6	0.61	3.68
(c)	−1342.73975	208.1	4.42	4.61
(d)	−1342.74441	208.8	2.26	5.66
(e)	−1342.74839	209.1	0	6.76
(f)	−1342.74092	208.8	4.41	12.85

TABLE 3: Comparison of Ion-Pair Reaction [$Cs^+F^- \cdots C_3H_7-OMs$] and Reaction of Naked Nucleophile [$F^- \cdots C_3H_7-OMs$]: Electronic Energy (E), Gibbs Free Energy G_{353K} (in hartrees), and Zero-Point Energy (ZPE) (in kcal/mol) of Prereaction Complex, Transition State, and Postreaction Complex; Activation Barrier ($E^{\ddagger}$ and $G^{\ddagger}_{353K}$) (in kcal/mol)

		prereaction complex	transition state	postreaction complex	$E^{\ddagger}$	$G^{\ddagger}_{353K}$
ion pair	E	−1362.65701	−1362.62433	−1362.66352		
	G	−1362.06641	−1362.03216	−1362.07847	20.0	21.5
	ZPE	209.7	209.2	209.3		
naked nucleophile	E	−1342.74666	−1342.70375	−1342.73812		
	G	−1342.16571	−1342.12412	−1342.15812	26.0	26.1
	ZPE	208.3	207.4	208.1		

Protic solvents have long been considered as being unfavorable for S_N2 reactions, because the OH groups were thought to form hydrogen bond with the nucleophile as a Lewis acid. Therefore, very bulky cations (such as *tert*-butylammonium) were usually employed to produce a "naked" nucleophile in aprotic solvents. Since the S_N2 mechanism presented above involves the protic solvent molecules as Lewis base and the nucleophile reacting as a CIP, it will be extremely instructive to compare this ion-pair mechanism with the conventional one in which the nucleophile is solvent-separated from the cation. This latter type of S_N2 reaction in diol has recently been studied by Pliego and co-workers,[12] who suggested that the reaction rates may increase by selective solvation of the nucleophile and leaving group by forming two cooperative hydrogen bonds with diol in the transition state. Figure 3 depicts the calculated structures of the [$F^- \cdots (HOCH_2CH_2OH)_2 \cdots n\text{-}C_3H_7-OMs$] system, in which the bare nucleophile F^- forms complexes (Table 3) with the reactant $n\text{-}C_3H_7-OMs$ and the two ethylene glycol molecules. As expected, in all these complexes the OH groups in the solvent molecule interact with F^- as a Lewis acid, exerting electrostatic influence (hydrogen bonding) that is unfavorable for S_N2 reaction. Figure 4 shows the mechanism of the reaction from the lowest energy structure of the [$F^- \cdots (HOCH_2CH_2OH)_2 \cdots n\text{-}C_3H_7-OMs$] system. It can be seen that the two OH groups are in direct contact with F^-, thus retarding the S_N2 reaction, whereas the other two are more or less indifferent. Although the nucleophile does not receive the unfavorable influence of cation, the acidic OH groups in the protic solvent molecules interact with the nucleophile more strongly due to the absence of the cation. This can be seen from the fact that while one of the H$\cdots$$F^-$ distances is similar (1.511 and 1.506 Å) in Figure 2 and in Figure 4, the other decreases notably from 1.585 Å in Figure 2 to 1.539 Å in Figure 4. As a result of these differences, the activation barrier now increases considerably to $E^{\ddagger} = 26.0$ ($G^{\ddagger}_{353K} = 26.1$) kcal/mol, indicating that the favored mechanism is the ion-pair reaction depicted in Figure 2. The calculated reaction barrier ($E^{\ddagger}= 20.0$, $G^{\ddagger}_{353K} =$



(a) $E = 0.34$ $G_{80℃} = 0$

(b) $E = 0.61$ $G_{80℃} = 3.68$

(c) $E = 4.42$ $G_{80℃} = 4.61$

(d) $E = 2.26$ $G_{80℃} = 5.66$

(e) $E = 0$ $G_{80℃} = 6.76$

(f) $E = 4.41$ $G_{80℃} = 12.85$

Figure 3. Structures and relative energy and Gibbs free energy of conformers of [$F^- \cdots C_3H_7-OMs$] system under the influence of two ethylene glycol molecules (relative energy and Gibbs free energy in kcal/mol, bond lengths in Å; MPW1K/6-311++G**).

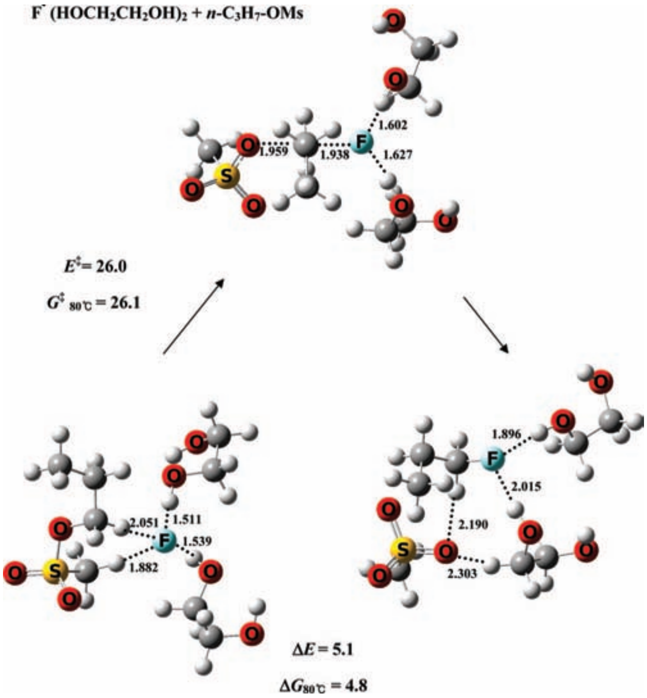


Figure 4. Calculated mechanism of naked nucleophile [$F^- \cdots C_3H_7-OMs$] in ethylene glycol. Barriers in kcal/mol and bond lengths in Å (MPW1K/6-311++G**).

21.5 kcal/mol) in ethylene glycol is slightly lower than that ($E^\ddagger = 20.4$, $G^\ddagger_{353K} = 22.4$ kcal/mol) in *tert*-butyl alcohol[9b] that proved to be a very efficient protic solvent for S_N2 reactions. This is in agreement with recent experimental observations.[18]

In summary, we showed that a small protic solvent with multiple −OH groups may be as efficient as a bulky alcohol for S_N2 reactions and that the nucleophile would react as a contact ion pair.

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Supporting Information Available: Full tables of electronic energies, ZPE, and the structures of the stationary states and the transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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