

S_N2/E2 Branching in Protic Solvents: A Mechanistic Study

Young-Ho Oh, Suk Im, Sung-Woo Park, Sungyul Lee,^{*} and Dae Yoon Chi^{†*}

Department of Applied Chemistry, Kyunghee University, Gyeonggi 446-701, Korea

^{*}E-mail: sylee@khu.ac.kr

[†]Department of Chemistry, Sogang University, Seoul 121-742, Korea. ^{*}E-mail: dychi@sogang.ac.kr

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We present calculations for S_N2/E2 reactions in protic solvents (*t*-butyl alcohol, ethylene glycol). We focus on the role of the hydroxyl (-OH) groups in determining the S_N2/E2 rate constants. We predict that the ion pair E2 mechanism is more favorable than the naked ion E2 reaction in ethylene glycol. E2 barriers are calculated to be much larger (~9 kcal/mol) than S_N2 reaction barriers in protic solvents, in agreement with the experimental observation [Kim, D. W. *et al. J. Am. Chem. Soc.* 2006, 128, 16394] of no E2 products in the reaction of CsF in *t*-butyl alcohol.

Key Words: S_N2/E2 branching, Protic solvent

Introduction

Although the bimolecular nucleophilic substitution (S_N2)¹⁻¹⁵ reaction has been known for very long, recent studies showed that the efficiency of the reaction may be significantly improved by careful and systematic investigation. The focus of these new developments in S_N2 reaction was on the role of counterion (cation) and solvent. Chi and co-workers^{9,11} demonstrated that employing bulky protic solvents such as *t*-butyl alcohol and amyl alcohol leads to very efficient S_N2 reactions, which is in direct contradiction with the conventional wisdom in S_N2 community. The mechanism of this new type of S_N2 reaction received a keen interest, and Lee and co-workers^{9(a),12} proposed that the nucleophile reacts as a contact ion pair rather than as a solvent-separated ion pair, and that the protic solvents act as a Lewis base. This mechanism was in agreement with the observed features of the reaction^{9(b)}, such as the strong dependence on cation (Cs⁺, K⁺, Na⁺) and the order of reactivity (F⁻ > Cl⁻ > Br⁻). Small bifunctional protic solvent (ethylene glycol) was also predicted to give highly efficient S_N2 reactions. The bimolecular elimination¹⁶⁻²⁶ (E2) rate constants are also of primary importance, because the E2 reactions usually compete with S_N2. It is well known that E2 reaction of a strong base such as F⁻ may occur as readily as S_N2. Detailed and systematic investigation for the mechanism of competing S_N2/E2 reactions at molecular level may yield invaluable information for elucidating the relative S_N2/E2 rate constants as a function of interactions between the cation, solvent, and leaving group. In this work, we investigate the S_N2/E2 branching in protic solvent (*t*-butyl alcohol and ethylene glycol) by calculating and comparing the barriers of the S_N2 [F⁻ + *n*-C₃H₇-OMs → *n*-C₃H₇-F + OMs⁻] and E2 [F⁻ + *n*-C₃H₇-OMs → C₃H₆ + HF + OMs⁻] reactions under the influence of the counterion Cs⁺ and protic solvents. We focus on the role of the hydroxyl groups in protic solvent in determining the S_N2/E2 rate constants.

Computational Methods

Density functional theory method (MPW1K)^{27,28} is em-

ployed with the 6-311++G** basis set and the effective core potential for Cs (Hay-Wadt VDZ(n+1)),²⁹ as implemented in GAUSSIAN 03 set of programs.³⁰ 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 and Discussion

Figure 1 presents the calculated E2 reactions of F⁻ in ethylene glycol. The most intriguing question concerning the mechanism of E2 reactions in protic solvents will be whether the nucleophile F⁻ reacts as an ion pair as in S_N2 reactions discussed in previous works,^{9,10,12} or as a naked ion.¹¹ The ion pair E2 reaction [Cs⁺F⁻...C₃H₇-OMs] shown in Figure 1(a) proceeds from the lowest energy pre-reaction complex from which S_N2 reaction also originate.^{9(c)} with the E2 barrier of 28.3 kcal/mol. On the other hand, the pre-reaction complexes for naked ion E2 reaction [F⁻ + *n*-C₃H₇-OMs] depicted in Figure 1(b) are different from the lowest energy complex for naked ion S_N2 reaction.^{9(c)} In the lowest energy complex for naked ion S_N2 reaction, the two OH groups (each from the two ethylene glycol molecules) bind to the nucleophile F⁻ (R_{H-F} = 1.511, 1.539 Å), and the nucleophile F⁻ also interacts with a hydrogen (R_{H-F} = 1.882, 2.051 Å) of methyl group in the leaving group and α -hydrogen (R_{H-F} = 1.882, 2.051 Å). In the naked ion E2 pre-reaction complexes, on the other hand, the two OH groups (each from the two ethylene glycol molecules) bind more strongly to the nucleophile F⁻ (R_{H-F} = 1.482, 1.449 Å), and the nucleophile F⁻ (R_{H-F} = 2.093 Å) interacts with the β -hydrogen. The energy of naked ion E2 complex presented in Figure 1 (b) is ~7.4 kcal/mol above the naked ion S_N2 pre-reaction complex. Since the barrier from this E2 pre-reaction complex is calculated to be 23.6 kcal/mol, the overall barrier from the lowest energy naked ion complex is calculated to be

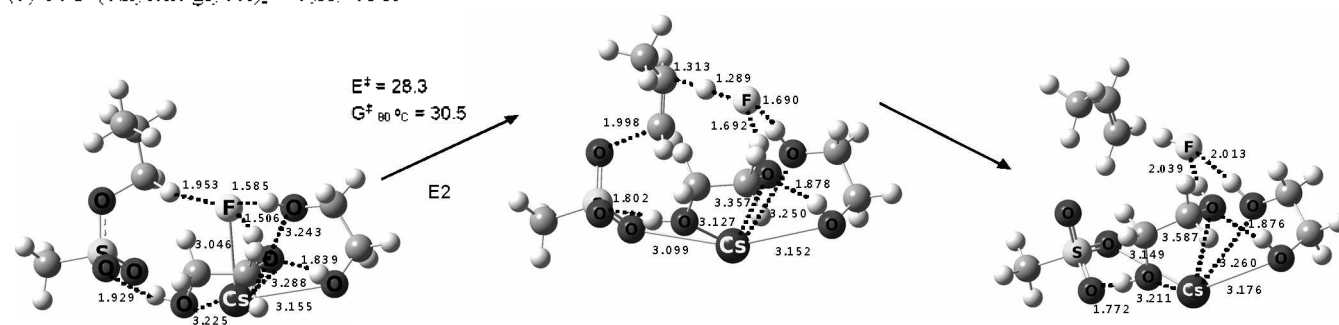
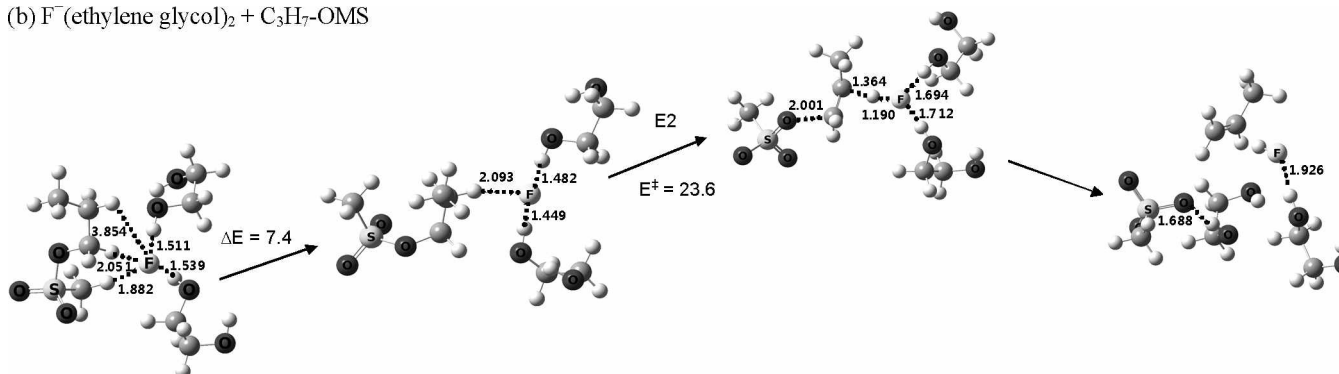
(a) $\text{Cs}^+\text{F}^-(\text{ethylene glycol})_2 + \text{C}_3\text{H}_7\text{-OMS}$ (b) $\text{F}^-(\text{ethylene glycol})_2 + \text{C}_3\text{H}_7\text{-OMS}$ 

Figure 1. Calculated E2 reactions in ethylene glycol. (a) ion pair mechanism [$\text{Cs}^+\text{F}^- \cdots \text{C}_3\text{H}_7\text{-OMS}$] (b) naked ion mechanism of E2 reaction [$\text{F}^- + n\text{-C}_3\text{H}_7\text{-OMS}$]. Energy and Gibbs free energy in kcal/mol and bond lengths in Å (MPW1K/6-311++G** ; ECP for Cs, Hay-Wadt VDZ(n+1)).

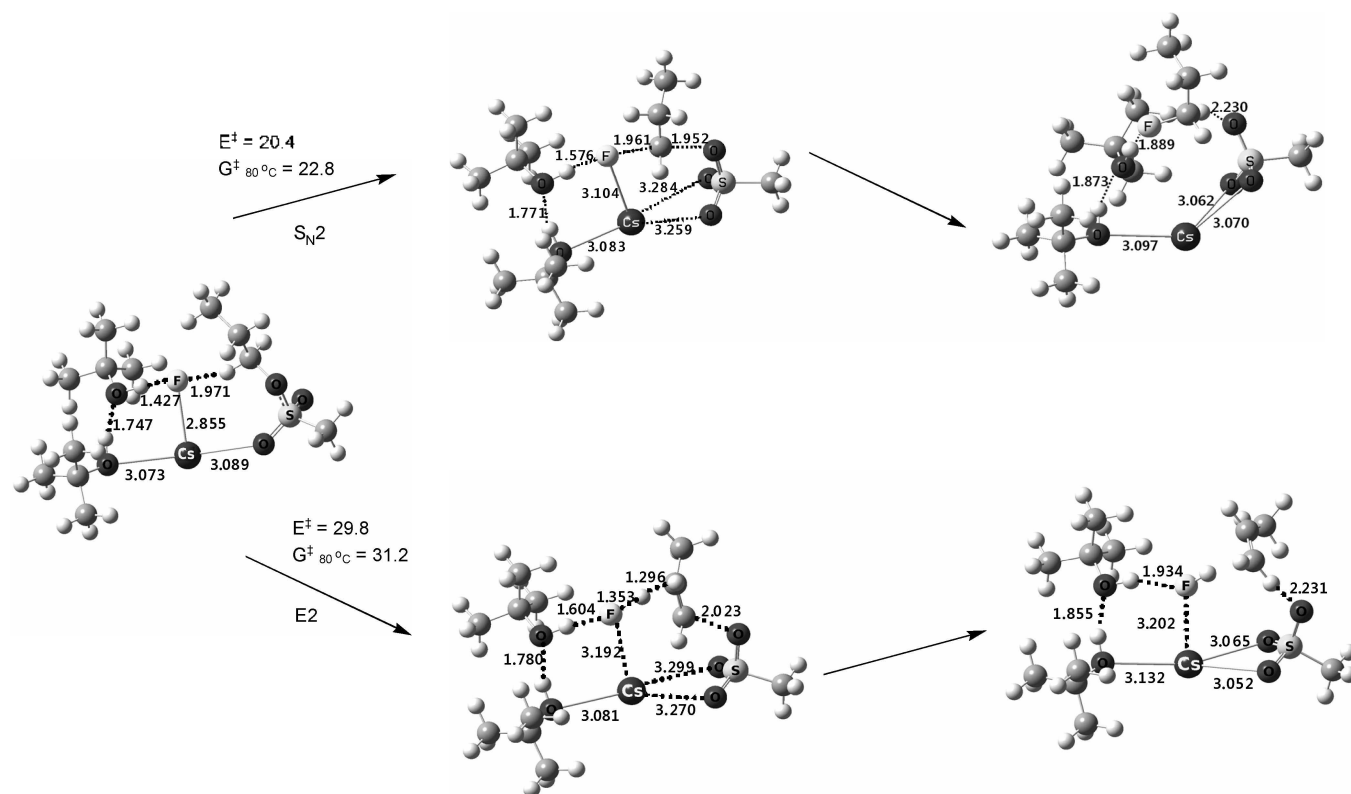
~ 31 kcal/mol. Comparing this barrier to that (28.3 kcal/mol) for ion pair E2 reaction shown in Figure 1(a), it seems that the ion pair mechanism is more favorable. Therefore, we discuss the ion pair E2 reactions only in comparison with the corresponding $\text{S}_{\text{N}}2$ reactions.

Figure 2 compares the mechanism and barriers of $\text{S}_{\text{N}}2/\text{E}2$ reactions in (a) *t*-butyl alcohol and in (b) ethylene glycol. E2 reaction in *t*-butyl alcohol depicted in Figure 2 (a) occurs from the pre-reaction complex whose structure is a bit different (in the orientation of the side chain) from that for $\text{S}_{\text{N}}2$ reaction.^{9(c)} The role of the counterion (Cs^+) and protic solvent in E2 reaction in *t*-butyl alcohol is quite similar to that in $\text{S}_{\text{N}}2$ reaction, F^- being in direct contact with the cation Cs^+ whose (retarding) Coulombic influence on F^- is alleviated by a -OH group (acting as a Lewis base, $R_{\text{O-Cs}} = 3.073$ Å) in one of the two *t*-butyl alcohol molecules. This OH group also forms a hydrogen bond with the oxygen of OH group in the other *t*-butyl alcohol molecule ($R_{\text{H-F}} = 1.747$ Å).

On the other hand, the other -OH (acting as a Lewis acid) binds to the nucleophile F^- ($R_{\text{H-F}} = 1.427$ Å), partially decreasing the nucleophilicity of F^- . These two opposing role of the -OH groups gives a low $\text{S}_{\text{N}}2$ barrier ($E^\ddagger = 20.4$, $G^\ddagger_{80^\circ\text{C}} = 22.8$ kcal/mol), indicating that its influence as a Lewis base overwhelms the effects as a Lewis acid. The overall E2 barrier (from the $\text{S}_{\text{N}}2$ pre-reaction complex) in *t*-butyl alcohol is calculated to be 29.8 kcal/mol, much higher than that (20.4 kcal/mol) of the $\text{S}_{\text{N}}2$ reaction, indicating that the retarding effects -OH as a Lewis acid are much larger for E2 reactions

compared with the $\text{S}_{\text{N}}2$ mechanism. This large difference between the barriers (rate constants) of $\text{S}_{\text{N}}2/\text{E}2$ reactions in *t*-butyl alcohol is in agreement with the experimental observation of no E2 products reported earlier.^{9(a)} E2 reaction in ethylene glycol proceeds from the most stable (lowest energy) pre-reaction complex from which $\text{S}_{\text{N}}2$ reactions also occur.^{9(c)} with the -OH groups playing a variety of role. When the OH group interacts with Cs^+ , it acts as a Lewis base, whereas its role is considered to be as a Lewis acid when it forms hydrogen bond with the nucleophile F^- , promoting and retarding the $\text{S}_{\text{N}}2$ reaction, respectively. There exist four such O- Cs^+ interactions and two H- F^- hydrogen bonds to affect the efficiency of the $\text{S}_{\text{N}}2$ reaction. Specifically, one of two OH groups interacts with Cs^+ as a Lewis base ($R_{\text{O-Cs}} = 3.225$ Å) simultaneously interacting with the leaving group ($R_{\text{H-O}} = 1.929$ Å), whereas the other OH group forms a hydrogen bond with the nucleophile F^- ($R_{\text{H-F}} = 1.506$ Å) and interacts with the cation Cs^+ ($R_{\text{O-Cs}} = 3.288$ Å) in the ethylene glycol molecules located closer to $\text{C}_3\text{H}_7\text{-OMS}$. On the other hand, the role of the OH groups in the other ethylene glycol molecule, lying far from $\text{C}_3\text{H}_7\text{-OMS}$, seems somewhat different. One of them binds both to cation Cs^+ ($R_{\text{O-Cs}} = 3.243$ Å) and the nucleophile F^- ($R_{\text{O-F}} = 1.585$ Å), whereas the other OH group interacts with Cs^+ as a Lewis base ($R_{\text{O-Cs}} = 3.155$ Å), forming a hydrogen bond (1.839 Å) with the oxygen of OH group in the other ethylene glycol molecule. The low $\text{S}_{\text{N}}2$ barrier ($E^\ddagger = 20.0$, $G^\ddagger_{80^\circ\text{C}} = 22.0$ kcal/mol) in ethylene glycol also seems to suggest that the role of the -OH groups as a Lewis base overcomes the retarding effects

(a) Cs^+F^- (*t*-butanol)₂ + $\text{C}_3\text{H}_7\text{-OMS}$



(b) Cs^+F^- (ethylene glycol)₂ + $\text{C}_3\text{H}_7\text{-OMS}$

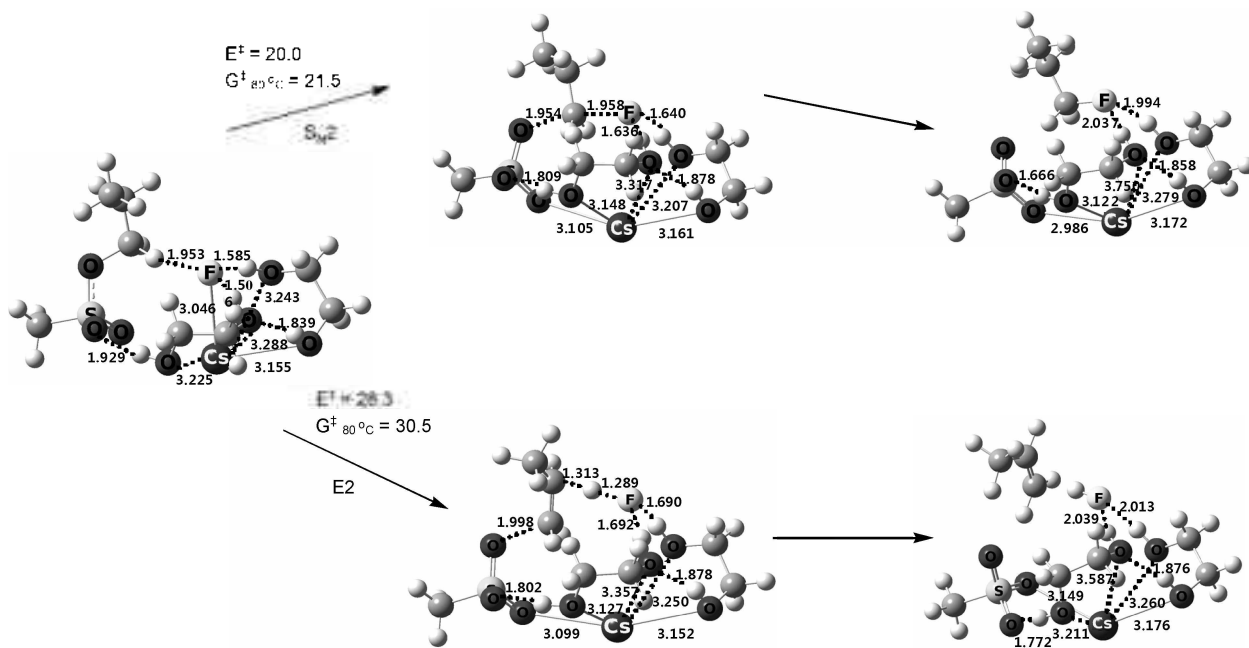


Figure 2. Calculated ion pair $\text{S}_{\text{N}}2/\text{E}2$ reactions [$\text{Cs}^+\text{F}^- \dots \text{C}_3\text{H}_7\text{-OMS}$] in (a) *t*-butyl alcohol and (b) ethylene glycol. Energy and Gibbs free energy in kcal/mol and bond lengths in Å (MPWIK/6-311++G** ; FCP for Cs, Hay-Wadt VDZ/(n+1)).

as Lewis acid on F^- , as discussed before.^{9(c)} The E2 barrier in ethylene glycol (28.3 kcal/mol) is found to be much higher than that (20.0 kcal/mol) of the corresponding S_N2 reaction. These large differences between the $S_N2/E2$ barriers in *t*-butyl alcohol and in ethylene glycol suggest that the E2 branching ratios are negligible, less than 1% at reaction temperature of 80 °C.

In summary, we showed that the E2 reaction barriers in protic solvents (*t*-butyl alcohol, ethylene glycol) are considerably higher than those for S_N2 reactions. We thus demonstrated the low E2 branching and extremely high S_N2 efficiency of protic solvents, which is in agreement with experimental observations.^{9(a)}

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