



# Article Effects of Methyl Substitution and Leaving Group on E2/S<sub>N</sub>2 Competition for Reactions of F<sup>-</sup> with RY (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, ${}^{i}C_{3}H_{7}$ , ${}^{t}C_{4}H_{9}$ ; Y = Cl, I)

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Abstract: The competition between base-induced elimination (E2) and bimolecular nucleophilic substitution (S<sub>N</sub>2) is of significant importance in organic chemistry and is influenced by many factors. The electronic structure calculations for the gas-phase reactions of  $F^- + RY$  (R = CH<sub>3</sub>,  $C_2H_5$ ,  ${}^{t}C_3H_7$ ,  ${}^{t}C_4H_9$ , and Y = Cl, I) are executed at the MP2 level with aug-cc-pVDZ or ECP/d basis set to investigate the  $\alpha$ -methyl substitution effect. The variation in barrier height, reaction enthalpy, and competition of  $S_N 2/E2$  as a function of methyl-substitution and leaving group ability has been emphasized. And the nature of these rules has been explored. As the degree of methyl substitution on  $\alpha$ -carbon increases, the E2 channel becomes more competitive and dominant with R varying from  $C_2H_5$ ,  ${}^{i}C_3H_7$ , to  ${}^{t}C_4H_9$ . Energy decomposition analysis offers new insights into the competition between E2 and  $S_N 2$  processes, which suggests that the drop in interaction energy with an increasing degree of substitution cannot compensate for the rapid growth of preparation energy, leading to a rapid increase in the S<sub>N</sub>2 energy barrier. By altering the leaving group from Cl to I, the barriers of both S<sub>N</sub>2 and E2 monotonically decrease, and, with the increased number of substituents, they reduce more dramatically, which is attributed to the looser transition state structures with the stronger leaving group ability. Interestingly,  $\Delta E_0^{\ddagger}$ exhibits a positive linear correlation with reaction enthalpy ( $\Delta H$ ) and halogen electronegativity. With the added number of substituents, the differences in  $\Delta E_0^{\ddagger}$  and  $\Delta H$  between Y = Cl and I likewise exhibit good linearity.

**Keywords:** base-induced elimination (E2); nucleophilic substitution (S<sub>N</sub>2);  $\alpha$ -methyl substitution; electronic structure calculation

## 1. Introduction

Two basic organic reactions in the development of modern physical organic chemistry, base-induced bimolecular elimination (E2) and bimolecular nucleophilic substitution ( $S_N$ 2) reactions, usually compete with each other in many cases. In the past few decades, E2 and  $S_N$ 2 reactions have been widely researched in the gas and condensed phase, both experimentally [1–3] and theoretically [4–19]. Since  $S_N$ 2 and E2 pathways generate the same ionic product, it is a serious challenge to distinguish between the two processes using conventional spectrometric techniques [20]. Kinetic isotope effects could qualitatively tell E2 and  $S_N$ 2 pathways apart, as it is observed that E2 reactions have normal KIEs ( $k_H/k_D > 1$ ), whereas  $S_N$ 2 reactions have inverse KIEs ( $k_H/k_D < 1$ ) [1]. In this regard, theoretical approaches have played an important role in probing the mechanisms. Extensive theoretical investigations have mainly focused on the reactions of the type of X<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Y (X = F, Cl, OH, ClO, et al.; Y = F, Cl, Br, I) over the years [13,14,16,17,21–29]. The competition between E2 and  $S_N$ 2 reaction pathways



Citation: Zhen, W.; Zhao, S.; Fu, G.; Wang, H.; Sun, J.; Yang, L.; Zhang, J. Effects of Methyl Substitution and Leaving Group on  $E2/S_N2$ Competition for Reactions of  $F^-$  with RY (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>,  ${}^{i}C_{3}H_{7}$ ,  ${}^{i}C_{4}H_{9}$ ; Y = Cl, I). *Molecules* **2023**, *28*, 6269. https://doi.org/10.3390/ molecules28176269

Academic Editor: Maofa Ge

Received: 3 August 2023 Revised: 22 August 2023 Accepted: 24 August 2023 Published: 27 August 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). caused by multiple factors, such as nucleophile, leaving groups, substrate characteristics, and environment, has been investigated in detail [10,16,17,25,28–31]. Mugnai et al. [10] analyzed the influence of temperature on the competition between E2 and  $S_N 2$  in  $F^- + CH_3CH_2Cl$  reaction by ab initio molecular dynamics, and found that  $S_N 2$  and E2 reaction mechanisms were favored at high and low temperatures, respectively. In addition, the ion-imaging experiments and quasi-classical trajectory simulations of this system conducted by Wester et al. [31] also showed that the  $S_N 2$  mechanism becomes more relevant as the collision energy is increased. Bickelhaupt and colleagues [22], founded on an activation-strain analysis, reported that  $F^-$  could participate in a more stabilizing orbital interaction with  $CH_3CH_2Cl$  than  $PH_2^-$ , owing to its augmented proton affinity, leading to the observed preference for E2. Shaik et al. [24]. from the VB perspective, revealed that essentially  $S_N 2$  was the preferred reaction pathway but the E2 pathway prevailed in many cases on account of the greater resonance stabilization in its transition-state (TS) region.

Among these factors, substituent effects have revealed an important function in studying the mechanisms and the competition between the E2 and  $S_N 2$  [32–37]. Gronert [28,29] measured fluoride reacting with  $CH_3Cl$  with a reaction efficiency of 0.56, and with the increased degree of substitution to ethyl, isopropyl, and tert-butyl chloride, the efficiency improved from 0.79 to 0.93 due to the presence of an E2 pathway, which was entropically favored [36]. Further theoretical calculations at the MP2/6-31 + G\*\* level for the reaction of  $F^-$  with CH<sub>3</sub>CHClCH<sub>3</sub> pointed out methyl substitution at the  $\alpha\text{-}carbon$  elevated the barrier of the  $S_N2$  pathway due to the crowded environment while stabilizing the transition state in E2 reactions [38]. Accordingly, Bierbaum et al. [1] explored the competition between E2 and  $S_N2$  pathways for BrO<sup>-</sup> and ClO<sup>-</sup> with RCl (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>,  $^{1}C_{3}H_{7}$ ,  $^{t}C_{4}H_{9}$ ) by using deuterium kinetic isotope effect (KIE) means. For each anion series, the trend that KIEs became increasingly more normal  $(k_H/k_D > 1)$  as the extent of substitution indicated that the E2 pathway became the predominant pathway and steric effects inhibited the S<sub>N</sub>2 pathway. A method calculating "steric hindrance (SH)" was proposed by Pendás and co-workers [39,40], which was consistent with the chemical intuition that the SH of the complex methylated alkyl system S<sub>N</sub>2 was greater than E2.

Recently, Wester et al. [41] presented a series of reactions  $X^- + RY$  (X = F, Cl, R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, <sup>i</sup>C<sub>3</sub>H<sub>7</sub>, <sup>t</sup>C<sub>4</sub>H<sub>9</sub> and Y = Cl, I), which displayed the transition from backward to forward scattering by the substitution of the  $\alpha$ -carbon. It is noticed that the changes following increasing methyl substitution are somewhat different for different leaving groups. Compared to the rich experimental studies, systematic and accurate PESs for complex methylated alkyl halides, especially <sup>i</sup>C<sub>3</sub>H<sub>7</sub>Y and <sup>t</sup>C<sub>4</sub>H<sub>9</sub>Y, are still lacking. In this paper, a series of F<sup>-</sup> + RY (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, <sup>i</sup>C<sub>3</sub>H<sub>7</sub>, <sup>t</sup>C<sub>4</sub>H<sub>9</sub>; Y = Cl, I) reactions as shown in Scheme 1 have been investigated with electronic structure calculations. We revisit these systems and try to address the following two issues. (1) The accurate PESs for a series of reactions are established and compared to explore how methyl substitution at the  $\alpha$ -carbon affects the E2/S<sub>N</sub>2 competing mechanisms. (2) It will be of interest to probe the role of the leaving group in E2/S<sub>N</sub>2 reactions of  $\alpha$ -methyl substitution.



**Scheme 1.** Pathways for reactants  $F^-$  + RY (R= CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, <sup>i</sup>C<sub>3</sub>H<sub>7</sub>, <sup>t</sup>C<sub>4</sub>H<sub>9</sub>, represented in red; Y = Cl, I, represented in blue).

#### 2. Results and Discussion

## 2.1. Potential Energy Surfaces of $F^-$ + RY Reactions

The relative energy of stationary points of  $F^-$  + RCl (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, <sup>i</sup>C<sub>3</sub>H<sub>7</sub>, <sup>t</sup>C<sub>4</sub>H<sub>9</sub> and Y = Cl, I calculated by the MP2 method are displayed in Table 1 together with the high-level CCSD(T)-F12b [16,42], CCSD(T) [17] benchmark values, and the available B97-1/aug-ccpVDZ values [43]. The average deviation from the benchmark is 0.11/0.48, 0.16/0.13, and 0.16/0.35 kcal/mol for CH<sub>3</sub>Cl/I, C<sub>2</sub>H<sub>5</sub>Cl/I, and <sup>1</sup>C<sub>3</sub>H<sub>7</sub>Cl/I, respectively, indicating that the MP2/aug-cc-pVDZ (ECP/d) level is reasonable. The profiles of PES for  $F^-$  + RY are presented in detail in Figures 1a,b and S1a,b together with the geometrical structures in Figure S2a,d. As shown in Figures 1 and S1, similar to the reaction of  $F^-$  with ethyl halide, for isopropyl and tert-butyl reactions, four traditional reaction pathways, including baseinduced anti and syn elimination (anti-E2 and syn-E2), as well as nucleophilic substitution with inversion and retention of configuration (inv- $S_N 2$  and ret- $S_N 2$ ), are predicted by MP2 theory. Inv- $S_N 2$  and anti-E2 reactions share the same reactant complex (a/bRC), and ret- $S_N 2$ and syn-E2 also utilize a common complex (c/dRC) along the reaction coordinate. With the increased methyl substitution, the difference in PES profiles of the series of reactions lies in the entrance channel. For  $F^-$  + RY (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, and Y = Cl, I), a hydrogenbonded F...HC<sup> $\alpha$ </sup>H<sub>2</sub>(CH<sub>2</sub>)Y complex (c/dRC<sub>H</sub>) is obtained, which can easily convert to an ion-dipole complex  $F \cdots H^{\beta} CH_2(CH_2)Y$  (a/bRC) via a low-energy  $TS_{RC}$  [16,29,42,44–52]. In contrast, for  $F^- + RCl$  ( $R = {}^{i}C_{3}H_{7}$ ,  ${}^{t}C_{4}H_{9}$  and Y = Cl, I) reactions, only an ion-dipole complex (a/bRC) is found, where  $F^-$  is situated between  $\alpha$ -carbon and  $\beta$ -hydrogen of iso-propyl or tert-butyl moiety, so that  $F^-$  can attack either target atom to form an inv- $S_N 2$ or anti-E2 channel. For the reactant complex  $F \cdots H^{\beta} H_2(CH_3)CHY$  (c/dRC) in syn-E2 and ret-S<sub>N</sub>2 channels,  $F^-$  and some hydrogen atoms in  $\beta$ -position, instead of  $\alpha$ -hydrogen of alkyl halides, have a mild hydrogen-bond interaction. There is no transition state available for the conversion of these two RCs.

			Cl			Ι	
R	Species	MP2	CCSD(T) <sup>a</sup>	Exptl <sup>c</sup>	MP2	CCSD(T) <sup>b</sup>	Exptl <sup>c</sup>
CH <sub>3</sub>	1dRC <sub>H</sub>	16.9	17.6		-18.9	-20.3	
	1TS <sub>RC</sub>	-15.1	-15.8		-15.8	-17.6	
	1bRC	-15.6	-16.1		-16.2	-18.3	
	1bTS	-12.3	-12.8		-15.6	-18.1	
	1dTS	32.1	30.7		22.8	18.3	
	1dPC	-40.7	-41.6		-49.6	-55.3	
	1bPC	-40.7	-41.6		-49.6	-55.3	
	1P2	-30.6	-31.8	-31.1	-40.9	-48.0	-42.3
C <sub>2</sub> H <sub>5</sub>	$2c/2dRC_{H}$	-17.8	-18.0		-18.7	-19.6	
	2a/2bRC	-17.5	-17.7		-19.4	-20.1	
	2aTS	-11.2	-11.1		-15.8	-16.0	
	2bTS	-11	-11.3		-15.4	-16.9	
	2cTS	-0.1	-6.8		-4.2	-4.9	
	2dTS	31.1	30.0		21.5	19.2	
	2aPC	-31.9	-33.6		-41.5	-42.7	
	2bPC	-42.4	-44.6		-51.8	-50.9	
	2cPC	-44.2	-41.6		-49.0	-54.0	
	2dPC	-42.4	-44.6		-51.8	-54.0	
	2P1	-15.5	-18.1	-22.5	-26.3	-26.2	-37.8
	2P2	-31.3	-34.0	-32.0	-42.1	-44.0	-48.7
<sup>i</sup> C <sub>3</sub> H <sub>7</sub>	3a/3bRC	-20.7	-21.4		-21.9	-22.8	
	3c/3dRC	-15.5	-16.3		-16.9	-17.9	
	3aTS	-11.6	-12.4		-16.9	-17.5	
	3bTS	-9.1	-11.0		-14.1	-16.3	
	3cTS	0.3	-1.0		-4.3	-5.4	
	3dTS	31.5	28.8		21.4	-	
	3aPC	-31.8	-33.8		-41.8	-44.4	
	3bPC	-43.9	-46.9		-54.0	-57.9	
	3cPC	-44.4	-47.3		-48.8	-52.8	
	3dPC	-44.4	-47.3		-54.0	-	
	3P1	-13.9	-16.5	-22.1	-24.8	-28.4	-37.7
	3P2	-31.8	-34.9	-30.3	-42.8	-46.8	-45.9
<sup>t</sup> C <sub>4</sub> H <sub>9</sub>	4a/4bRC	-23.1	-23.3		-24.4	-25.6	
	4c/4dRC	-15.6	-16.1		-17.2	-17.8	
	4aTS	-11.9	-17.6		-17.7	-24.4	
	4bTS	-2.3	-		-7.5	-	
	4cTS	0.8	-4.6		-3.9	-10.8	
	4dTS	39.9	-		28.8	-	
	4aPC	-33.4	-37.8		-43.4	-51.2	
	4bPC	-46.2	-		-56.1	-	
	4cPC	-44.0	-49.1		-49.1	-57.4	
	4dPC	-46.2	-		-56.1	-	
	4P1	-12.6	-18.2	-22.1	-23.9	-37.6	-37.6
	4P2	-31.9	-	-29.5	-43.3	-	-37.8

**Table 1.** The relative energies (kcal/mol) for stationary points of the E2 and  $S_N 2$  pathways on the  $F^-$  + RY with different methods.

<sup>a</sup> (1) Energies with respect to the F<sup>-</sup> + CH<sub>3</sub>Cl reactants at AE-CCSD(T)/aug-cc-pCVQZ level are from ref. [41]. (2) Energies for F<sup>-</sup> +C<sub>2</sub>H<sub>5</sub>Cl reaction are obtained at the CCSD(T)-F12b/aug-cc-pVQZ +  $\Delta$ core level of theory from ref. [16]. (3) Energies for F<sup>-</sup> + <sup>i</sup>-C<sub>3</sub>H<sub>7</sub>Cl reaction are calculated at CCSD(T)/aug-cc-pVTZ//MP2/aug-cc-pVDZ level of theory. (4) Energies For F<sup>-</sup> + <sup>t</sup>-C<sub>4</sub>H<sub>9</sub>Cl reaction obtained at B97-1/aug-cc-pVDZ level are from ref. [43]. <sup>b</sup> (1) Energies of F<sup>-</sup> + CH<sub>3</sub>I reaction at CCSD(T)-F12b/aug-cc-pVTZ-pp are from ref. [47]. (2) Energies of F<sup>-</sup> + C<sub>2</sub>H<sub>5</sub>I reaction at CCSD(T)/PP/t level are from ref. [17]. (3) Energies for F<sup>-</sup> + <sup>i</sup>-C<sub>3</sub>H<sub>7</sub>I reaction are calculated at CCSD(T)/pp/t//MP2/ECP/d level of theory. (4) Energies For F<sup>-</sup> + <sup>t</sup>-C<sub>4</sub>H<sub>9</sub>I reaction obtained at B97-1/aug-cc-pVDZ level are from ref. [43].



**Figure 1.** Potential energy curves and stationary points at MP2/aug-cc-pVDZ level for  $F^- + RCl$  reactions. The energy (in kcal/mol) is relative to  $F^- + CH_3Cl$  (**a**) and  $F^- + RCl$  (**b**) reactants at 0 K, and does not include ZPE. In (**b**), the black, blue, and pink numbers represent  $F^- + C_2H_5Cl$ ,  $F^- + {}^{i}C_3H_7Cl$ , and  $F^- + {}^{t}C_4H_9Cl$  reactions, respectively.

Resulting from the strong steric exclusion between the nucleophile and substrate, the ret-  $S_N 2$  TS usually gives a much higher overall barrier than other reaction pathways, suggesting it is the least favorable pathway. The barrier for the syn-E2 pathway is usually higher than inv- $S_N 2$  and anti-E2 for a similar hindrance effect. Therefore, in the following discussions, the most competitive inv- $S_N 2$  and anti-E2 pathways for the series of  $F^- + RY$  reactions are considered here, and their PES profiles obtained at the MP2 level of theory are characterized in Figure 2 for convenience of comparison. For the  $F^- + CH_3Y$  reaction,  $F^-$  attacks CH<sub>3</sub>Y on the back-side via a traditional path along a pre-reaction ion-dipole complex (1bRC), a Walden-inversion transition state (1bTS), and a post-reaction ion-dipole complex FCH<sub>3</sub>…Y<sup>-</sup> (1bPC). The E2 pathways appear with the successive addition of the methyl group besides the  $S_N 2$  pathways and show similar double well potential characters. The initial association of  $F^-$  and RY can form an ion-dipole complex a/bRC and, after going over a/bTS, the system drops down to the deep potential energy well a/bPC and then decomposes to products P1 (RF + Cl<sup>-</sup>/I<sup>-</sup>) and P2 (RCH<sub>2</sub> = CH<sub>2</sub> + HF + Cl<sup>-</sup>/I<sup>-</sup>), respectively.

#### 2.2. Effects of $\alpha$ -Methyl Substitution

To explore the effects of the addition of the  $\alpha$ -methyl group on the competition of E2 and S<sub>N</sub>2 mechanisms, the activation ( $\Delta E_0^{\ddagger}$ ) and the overall barrier ( $\Delta E^{\ddagger}$ ) are especially emphasized for discussion as presented in Scheme 2, and the calculated values of the relevant energies are summarized in Table 1. Here, Y = Cl is used as an example.

Exothermicity. As shown in Figure 2, it is clear that all E2 and  $S_N2$  paths for the reaction of  $F^- + RY$  (R = CH<sub>3</sub>,  $C_2H_5$ ,  ${}^iC_3H_7$ ,  ${}^tC_4H_9$ , and Y = Cl, I) are highly exothermic, and, for each reaction, the reaction enthalpy  $\Delta H$  of  $S_N2$  pathways is much more negative than that of E2 pathways, suggesting  $S_N2$  reactions are more exothermic than E2 reactions owing to the strong combination between the F atom and C atoms in the neutral products. By changing R from the methyl to the tert-butyl group, the  $\Delta H$  of  $S_N2$  pathways slightly drops, while the values of E2 pathways escalate, eventually widening the  $\Delta H$  gap between E2 and  $S_N2$ .



**Figure 2.** Schematic potential energy surface (PES) of the  $F^- + RY$  ( $R = CH_3$ ,  $C_2H_5$ ,  ${}^{t}C_3H_7$ ,  ${}^{t}C_4H_9$ ; Y = Cl, I) with stationary points along the anti-E2 (black) and inv-S<sub>N</sub>2 (red) channels at MP2/aug-cc-pVDZ(ECP/d) level. The reported energies (in kcal/mol) are relative to reactants without ZPE.



**Scheme 2.** Schematic of activation barrier ( $\Delta E_0^{\ddagger}$ ), overall barrier ( $\Delta E^{\ddagger}$ ), and reaction enthalpy  $\Delta H$ .

Barrier Height. The variation of  $\Delta E_0^{\ddagger}$ ,  $\Delta E^{\ddagger}$ , and the difference in  $\Delta E_0^{\ddagger}$  between inv- $S_N^2$  and anti-E2 along the methylation of the  $\alpha$ -carbon is illustrated in Figure 3a–c. The horizontal coordinate is the degree of methyl substitution of  $C^{\alpha}$ , named *n*, ranging from 0 to 3. As described in Figure 3a, successively adding methyl groups to the  $C^{\alpha}$  dramatically raises the activation barrier ( $\Delta E_0^{\ddagger}$ ) of inv-S<sub>N</sub>2 from 3.3 to 6.8 to 11.6 and finally to 20.8 kcal/mol, while the  $\Delta E_0^{\ddagger}$  of anti-E2 gently escalates from 6.6, 9.1 to 11.2 kcal/mol. Figure 3b depicts the activation barrier difference between the inv-S<sub>N</sub>2 and anti-E2 pathways  $(\Delta \Delta E_0^{\ddagger} = \Delta E_0^{\ddagger}_{inv-SN2} - \Delta E_0^{\ddagger}_{anti-E2})$  as *n* changes from 1 to 3, which is 0.2 and 2.5 kcal/mol for n = 1 and 2, respectively. The significant augment of  $\Delta \Delta E_0^{\ddagger}$  for the  $F^- + {}^{t}C_4H_9Cl$  reaction is observed in doubling the difference to 9.6 kcal/mol. All these results suggest that anti-E2 is becoming more and more competitive. Wester and coworkers [32] have disentangled the dynamics of the competition between anti-E2 and inv-S<sub>N</sub>2 in the reaction  $F^- + C_2H_5Cl$ , indicating that anti-E2 is more advantageous. In addition, Gronert [38] also predicted that in the reaction of  $F^- + {}^{i}C_{3}H_{7}Cl$  anti-E2 is completely dominated and substitution should be more competitive with ethyl halides. As the maximum difference between  $\Delta E_0^{\ddagger}(S_N 2)$  and  $\Delta E_0^{\ddagger}(anti-E2)$  of these three systems, the anti-E2 mechanism will also be the most favorable pathway for  $F^- + {}^{t}C_4H_9Cl$  (I).



**Figure 3.** (a) Activation barrier heights  $\Delta E_0^{\ddagger}$  (full line) and overall barrier heights (dashed line) of anti-E2 and inv-S<sub>N</sub>2 transition states as a function of methyl substitution degree *n* of C<sup> $\alpha$ </sup> (*n* = 0–3). (b) Barrier difference  $\Delta \Delta E_0^{\ddagger}$  between anti-E2 and inv-S<sub>N</sub>2 as a function of *n* (*n* = 1–3). Values of Y = Cl are reported. All the energies are in kcal/mol. (c) Energy decomposition analysis of the anti-E2 and inv-S<sub>N</sub>2 transition structure between F<sup>-</sup> + (CH<sub>3</sub>)<sub>n</sub>CCl (*n* = 0–3).

For the variation pattern of overall barriers ( $\Delta E^{\ddagger}$ ), the  $\alpha$ -methyl group slightly changes the  $\Delta E^{\ddagger}$  of an anti-E2 pathway with values gradually dropping from -11.2, -11.6 to -11.9 kcal/mol but significantly alters the barrier of inv-S<sub>N</sub>2 from -12.3 kcal/mol for F<sup>-</sup> + CH<sub>3</sub>Cl to -2.3 kcal/mol for F<sup>-</sup> +  ${}^{t}C_{4}H_{9}$ Cl. Rablen et al. [35] systematically compared the free energies of S<sub>N</sub>2/E2 transition states for CN<sup>-</sup> + RCl reactions at the W1 and G4 levels of electronic structure theory in the presence of a simulated acetonitrile solvent. Their results suggest that the barrier to the E2 reaction reduces by the same magnitude as the barrier to S<sub>N</sub>2 raises when methylation of the  $\alpha$ -carbon increases. Connor and Gronert [34] studied the impact of  $\alpha$ - and  $\beta$ -methylation on E2 and S<sub>N</sub>2 reactions between a series of alkyl bromides and nucleophiles in the gas phase using both mass spectrometer experiment and computational methods. They found the reduction in S<sub>N</sub>2 rate constant and the mounting in E2 rate constant when adding a methyl group to the  $\alpha$ -carbon position, which is in line with our findings.

To understand why the increasing alkyl substitution strikingly enhances the  $\Delta E^{\ddagger}$  of the  $S_N 2$  reaction and slightly lowers the E2 barrier, we decompose the transition state energy by referring to the activation strain analyses proposed by Bickelhaupt et al. [28,53,54] as shown in Figure 3b. Energy decomposition contributes to a quantitative understanding of how methyl substitution affects the inv- $S_N 2$ /anti-E2 reaction barrier. The total energy  $\Delta E^{\ddagger}$ , that is, the difference between reactants and transition states, can be decomposed

into preparation energy ( $\Delta E_{\text{prep}}$ ) and interaction energy ( $\Delta E_{\text{int}}$ ) based on the formula  $\Delta E^{\ddagger} = \Delta E_{\text{prep}} + \Delta E_{\text{int}}$ . The  $\Delta E_{\text{prep}}$  is the energy that is needed to overcome the deformation of individual reactants from their equilibrium structure into the geometries of the transition structure. And the interaction energy  $\Delta E_{int}$  is considered as the energy difference between the individual fragments of transition states' geometries and the transition states. For  $F^-$  + RCl reactions, the inv-S<sub>N</sub>2 goes with less preparation energy than anti-E2, which can be attributed to the different mechanisms. One bond breaking occurs in the inv-S<sub>N</sub>2 mechanism, whereas two bond breakings and one C-C bond shrinking occur along the anti-E2 pathway. Hence, the destabilizing distortion characteristic for the anti-E2 reaction pathway is by definition higher than the inv-S<sub>N</sub>2 reaction pathway. As previously proposed by Bickelhaupt [53], the C<sup> $\alpha$ </sup>-Y bond extension of inv-S<sub>N</sub>2 reduces the antibonding orbital overlap between  $C_{2p}$  and  $Y_{2p}$  orbitals, which makes the LUMO of the substrate more stable. Obviously, due to the antibonding orbital overlap of both the  $C^{\alpha}$ -Y and  $C^{\beta}$ -H bonds being diminished, this stabilization of the LUMO is more significant in the E2 reaction. For inv-S<sub>N</sub>2 transition structures, when the degree of CH<sub>3</sub> varies from 0 to 3,  $\Delta E_{prep}$  increases gradually, indicating the fragments in the transition structures distorted more violently, whereas  $\Delta E_{int}$  decreases, suggesting the interaction of two parts is stronger. The decline in  $\Delta E_{int}$  cannot pay for the rapid growth of  $\Delta E_{prep}$ , resulting in the overall rise in  $\Delta E^{\ddagger}$ . Especially in the  $F^- + {}^{t}C_4H_9Cl$  reaction, the increase in  $S_N 2 \Delta E^{\ddagger}$  is particularly significant. In comparison, the  $\Delta E_{\text{prep}}$  of the anti-E2 transition structure is higher but elevates more slowly than that of the inv-S<sub>N</sub>2. Accordingly, the results obtained suggest that, compared to the anti-E2 reaction, the inv- $S_N$ 2 reaction is more sensitive to structural changes in the substrate. Therefore, the barrier of inv-S<sub>N</sub>2 increases with the increased degree of substitution, resulting in less competitiveness compared to anti-E2, which is in agreement with previous research by Pendás et al. [39]. The  $\Delta E_{int}$  is further broken down into the steric term  $\Delta E_{\text{steric}}$  ( $\Delta E_{\text{steric}} = \Delta E_{\text{els}} + \Delta E_{\text{XC}} + \Delta E_{\text{Pauli}}$ ) and the orbital interaction term  $\Delta E_{\rm orb}$  in order to ascertain the primary contributor to the fluctuation in  $\Delta E_{\rm int}$  as shown in Figure S3 [55]. Obviously, the orbital interaction term  $\Delta E_{orb}$  is responsible for the interaction energy. The orbital interactions of both  $S_N2$  and E2 decrease as the number of substituents increases. It is noteworthy that the stronger orbital interaction favors the E2 reaction to lower  $\Delta E_{int}$  compared to its S<sub>N</sub>2 analog. This is consistent with the finding by Bickelhaupt et al. [22] for the  $F^-$  + CH<sub>3</sub>CH<sub>2</sub>Cl reaction.

These results suggest that, with the addition of  $\alpha$ -methyl substituent, the anti-E2 reaction is completely dominant considering the energetics from ethyl to butyl reactions in the gas phase. This is consistent with the scattering experimental phenomenon [41] that the character of forward scattering becomes more and more obvious with the increased size of residue R, where scattering into the forward hemisphere is a mechanistic fingerprint of E2 reactions. Further dynamics simulations are desired for revealing the variation in an aspect of dynamical factors.

#### 2.3. Effects of Leaving Group

It is of interest to explore the effect of the leaving group along the  $\alpha$ -methyl substitution. Figure 4a compares the activation barrier heights of F<sup>-</sup> + RCl and F<sup>-</sup> + RI; it can be seen that, as the enhanced leaving group ability varies from Cl to I, both S<sub>N</sub>2 and E2 reaction barriers are dropped by similar amounts. More significantly, with the increased number of substituents of n = 0-3 the barrier heights decrease more dramatically from 3.5/3.7, 3.8/4.1, to 3.9/4.5 kcal/mol for the S<sub>N</sub>2/E2 reaction pathways along Y = Cl to I. Their key TS structural character could be closely related to this change. Variation in the leaving group from Cl to I causes the elongation of the C<sup> $\alpha$ </sup>-Y bond  $\Delta$ L (L<sub>C $\alpha$ -I</sub> - L<sub>C $\alpha$ -Cl</sub>) ranging from 0.26, 0.29, 0.32 to 0.38Å with *n* going from 0 to 3 for the TS structure of inv-S<sub>N</sub>2. Similarly, the bond elongation  $\Delta$ L of C<sup> $\alpha$ </sup>-Y for anti-E2 TS also grows along with methyl substitution degree *n*. The looser transition states typically align with the reduced barrier heights, resulting in heightened reactivity [20,56,57].



**Figure 4.** (a) Comparison of activation barriers between inv-S<sub>N</sub>2 and anti-E2 TS in the  $F^-$  + RY reaction calculated by MP2 method. The correlation of (b) activation barrier heights  $\Delta E_0^{\ddagger}$  and reaction enthalpy  $\Delta H$ , (c) activation barrier difference  $\Delta \Delta E_0^{\ddagger}$  and reaction enthalpy  $\Delta AH$  between Y = Cl and I, and (d) activation barrier heights and electronegativity of leaving group Y.

Along the leaving group ability changing from Cl, Br to I, a good linear relationship is found between  $\Delta E_0^{\dagger}$  and  $\Delta H$  for both inv-S<sub>N</sub>2 and anti-E2 pathways of each F<sup>-</sup> + RY reaction as presented in Figure 4b. Obviously, the F<sup>-</sup> + RY reaction set obeys the expression  $\Delta E_0^{\dagger} = a\Delta H + C$ , which connects the barrier with the reaction enthalpy, following the Bell– Evans–Polanyi principle, which is a long-standing chemical theory [58]. Furthermore, good relevance is also found between activation barrier difference  $\Delta \Delta E_0^{\dagger}$  and enthalpy difference  $\Delta \Delta H$  for Y = Cl and I with the increased degree of substitution of the corresponding S<sub>N</sub>2 and E2 pathways as shown in Figure 4c. The above results indicate that, as the leaving group changes from Cl to I, the reaction becomes more exothermic and the barrier drops. Barriers of both inv-S<sub>N</sub>2 and anti-E2 reactions are found to exhibit good linear dependences with halogen electronegativity increasing in the order of I (2.66) < Br (2.96) < Cl (3.16) as shown in Figure 4d. The above results suggest the decreased electronegativity of Y is expected to lead to a looser TS structure (elongation of C-Y bond), and further a higher reaction reactivity.

### 3. Computational Methods

The stationary points for a series of  $F^- + RY$  (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, <sup>i</sup>C<sub>3</sub>H<sub>7</sub>, <sup>t</sup>C<sub>4</sub>H<sub>9</sub> and Y = Cl, I) reactions are studied by second-order Møller–Plesset perturbation MP2 [59,60] with the frozen core (FC) method. The atoms of H, C, F, and Cl are based on Dunning and Woons aug-cc-pVDZ [61,62] basis set. For I, the core electrons use the Wadt and Hay ECP [63] and the valence electrons use a 3s, 3p basis, plus a d-polarization function with a 0.262 exponent, and s, p, and diffuse functions with exponents of 0.034, 0.039, and 0.0873, respectively.

According to previous work, aug-cc-pVDZ basis set has the lowest systematic errors, while G\*\* and aug-cc-pVTZ tend to overestimate and underestimate the single-point energies [64]. Aug-cc-pVDZ basis set also showed good agreement with the experiment in previous research on similar reactions [17,30,42]. Vibrational analysis is used to determine

each stationary point under the harmonic oscillator mode in which balanced structures have no imaginary frequencies and transition states have one normal mode with an imaginary frequency. Furthermore, each transition state is calculated with the internal reaction coordinate (IRC) to make sure that it connects the assumed pre- and post-reaction complexes. The coupled cluster theory with triple excitations treated perturbatively CCSD(T) is often used as a benchmark due to its good accuracy [16,17,25,65]. Hence, the relative energies of the stationary points are compared with the high-level CCSD(T)-F12b [16,42] and CCSD(T) [17] benchmark values, and the available B97-1 values [43] for methyl, ethyl, and tert-butyl halide systems, to rationalize the dependability of the computing method. Since there is no report available previously for isopropyl halide reactions, the high-level CCSD(T)/aug-cc-pVTZ or CCSD(T)/ECP/d energy corrections based on MP2 geometries are performed. Gaussian 09 package [66] was used for all computations.

#### 4. Conclusions

In this paper,  $F^-$  ions with a series of  $\alpha$ -substituted alkyl chlorides and alkyl iodides in the gas phase are studied by using MP2/aug-cc-pVDZ or MP2/ECP/d methods, and the effect of methyl substituents and leaving group ability on the competition of E2 and  $S_N2$ pathways is investigated. As the degree of methyl substitution increases, the preference for anti-E2 over inv- $S_N2$  enlarges, and, till  $R = {}^tC_4H_9$ , anti-E2 becomes overwhelmingly dominant. The prediction of this reaction trend is consistent with the differential scattering experiment [41]. This can be explained by energy decomposition analysis. With the increased degree of substitution, the drop in the interaction energy between reactants cannot compensate for the rapid growth of preparation energy resulting from the more distorted transition state structure for the inv- $S_N2$  reaction pathway.

In the aspect of the leaving group, the barrier heights for both E2 and  $S_N2$  reactions drop more dramatically along Y = Cl to I with the increased number of substituents, which can be attributed to the relaxation of the key transition state structure. Variation in the leaving group from Cl to I results in the larger extension of the C<sup> $\alpha$ </sup>-Y for the TS structure of anti-E2 and inv-S<sub>N</sub>2 with the methyl group going from 0 to 3, and thus the larger reaction activity. Along the leaving group ability changing from Cl, Br to I, a notable linear relationship is found between  $\Delta E_0^{\ddagger}$  and  $\Delta H$  for both the inv-S<sub>N</sub>2 and anti-E2 channels of each F<sup>-</sup> + RY reaction, indicating the smaller the reaction barrier, the more negative the reaction enthalpy. These results correspond to the decreasing halogen electronegativity from Cl to I, which results in the more relaxed structural characters of TS and thus the larger reaction probability. This work lays the foundation for our subsequent dynamic simulations. Since it is known that the dynamics of the reaction may deviate from the potential energy surface, dynamics simulations are able to intensify our understanding of the effects of the substitution and leaving group on the competition mechanism between E2 and S<sub>N</sub>2 reactions.

**Supplementary Materials:** The following supporting information can be downloaded at: https: //www.mdpi.com/article/10.3390/molecules28176269/s1, Figure S1: Potential energy curves and stationary points at MP2/ ECP/d level for F- + RI reactions. The energy (in kcal/mol) is relative to F- + CH3I (a) and F- + RI (b) reactants at 0K, and does not include ZPE. For Figure S1b, the black, blue, and pink numbers represent F- + C2H5I, F- + iC3H7I, and F- + tC4H9I reactions, respectively; Figure S2: Stationary point structures of E2 and SN2 pathways for (a) F-+ CH3Y, (b) F-+ C2H5Y, (c) F-+ iC3H7Y, (d) F-+ tC4H9Y(Y = Cl, I) reaction optimized at the MP2/aug-cc-pVDZ(ECP/d) theoretical level. Bond distances are in Å, and black/pink line represents Y = Cl/I.; Figure S3: Interaction energy decomposition according to formula  $\Delta E_{int} = (\Delta E_{els} + \Delta E_{XC} + \Delta E_{Pauli}) + \Delta E_{orb} =$  $\Delta E_{steric} + \Delta E_{orb}$ .  $\Delta E_{els}$  is electrostatic interacton term,  $\Delta E_{XC}$  is the change of exchange-correlation energy during complexation process, and  $\Delta E_{Pauli}$  is the Pauli repulsion effect between electrons in occupied orbitals of the fragments and is invariably positive. They combine to form steric term  $\Delta E_{steric}$  (Dashed line).  $\Delta E_{orb}$  is orbital interaction term and represented by short dotted line. The full line represents  $\Delta E_{int}$ . **Author Contributions:** Conceptualization, J.Z. and L.Y.; Funding acquisition, J.S., L.Y. and J.Z.; Investigation, W.Z., S.Z., G.F. and H.W.; Resources, L.Y. and J.Z.; Supervision, J.S., J.Z. and L.Y.; Writing—original draft, W.Z.; writing—review and editing, J.Z. and L.Y. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work is supported by the State Key Lab of Urban Water Resource and Environment of Harbin Institute of Technology (No. ES202303, 2022TS25), the National Natural Science Foundation of China (No. 21972034), and Heilongjian Touyan Team (HITTY-20190033).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in Supplementary Material.

**Conflicts of Interest:** The authors declare no conflict of interest.

#### References

- Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. Reactions of α-Nucleophiles with Alkyl Chlorides: Competition between S<sub>N</sub>2 and E2 Mechanisms and the Gas-Phase α-Effect. *J. Am. Chem. Soc.* 2009, 131, 8227–8233. [CrossRef] [PubMed]
- Garver, J.M.; Fang, Y.R.; Eyet, N.; Villano, S.M.; Bierbaum, V.M.; Westaway, K.C. A Direct Comparison of Reactivity and Mechanism in the Gas Phase and in Solution. *J. Am. Chem. Soc.* 2010, 132, 3808–3814. [CrossRef] [PubMed]
- Carrascosa, E.; Meyer, J.; Michaelsen, T.; Stei, M.; Wester, R. Conservation of direct dynamics in sterically hindered S<sub>N</sub>2/E2 reactions. *Chem. Sci.* 2018, 9, 693–701. [CrossRef] [PubMed]
- 4. Gronert, S. Theoretical Studies of Elimination Reactions. 1. Reactions of F<sup>-</sup> and PH<sub>2</sub><sup>-</sup> with CH<sub>3</sub>CH<sub>2</sub>Cl. Competition between S<sub>N</sub>2 and E2 Mechanisms for First- and Second-Row Nucleophiles. *J. Am. Chem. Soc.* **1991**, *113*, 6041–6048. [CrossRef]
- Haib, J.; Stahl, D. Competition Between Substitution (S<sub>N</sub>2), Elimination (E2) and Addition Elimination (AE) Reactions in the Gas Phase. Org. Mass. Spectrom. 1992, 27, 377–382. [CrossRef]
- 6. Hu, W.P.; Truhlar, D.G. Factors Affecting Competitive Ion-Molecule Reactions: ClO<sup>-</sup> + C<sub>2</sub>H<sub>5</sub>Cl and C<sub>2</sub>D<sub>5</sub>Cl via E2 and S<sub>N</sub>2 Channels. *J. Am. Chem. Soc.* **1996**, *118*, 860–869. [CrossRef]
- Glad, S.S.; Jensen, F. Kinetic Isotope Effects and Transition State Geometries. A Theoretical Investigation of E2 Model Systems. J. Org. Chem. 1997, 62, 253–260. [CrossRef]
- Chung, D.S.; Kim, C.K.; Lee, I. Theoretical Studies of Competitive Gas-Phase S<sub>N</sub>2 and E2 Reactions of NCCH<sub>2</sub>CH<sub>2</sub>Cl with OH<sup>-</sup> and SH<sup>-</sup>. J. Phys. Chem. A 1997, 101, 9097–9104. [CrossRef]
- Bickelhaupt, F.M. Understanding Reactivity with Kohn-Sham Molecular Orbital Theory: E2-S<sub>N</sub>2 Mechanistic Spectrum and Other Concepts. J. Comput. Chem. 1999, 20, 114–128. [CrossRef]
- Mugnai, M.; Cardini, G.; Schettino, V. Substitution and Elimination Reaction of F<sup>-</sup> with C<sub>2</sub>H<sub>5</sub>Cl: An ab Initio Molecular Dynamics Study. J. Phys. Chem. A 2003, 107, 2540–2547. [CrossRef]
- Vayner, G.; Houk, K.N.; Jorgensen, W.L.; Brauman, J.I. Steric Retardation of S<sub>N</sub>2 Reactions in the Gas Phase and Solution. *J. Am. Chem. Soc.* 2004, 126, 9054–9058. [CrossRef]
- Ochran, R.A.; Uggerud, E. S<sub>N</sub>2 reactions with allylic substrates—Trends in reactivity. *Int. J. Mass. Spectrom.* 2007, 265, 169–175. [CrossRef]
- Bento, A.P.; Solà, M.; Bickelhaupt, F.M. E2 and S<sub>N</sub>2 Reactions of X<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>X(X = F, Cl); an ab Initio and DFT Benchmark Study. J. Chem. Theory Comput. 2008, 4, 929–940. [CrossRef] [PubMed]
- Wu, X.P.; Sun, X.M.; Wei, X.G.; Ren, Y.; Wong, N.B.; Li, W.K. Exploring the Reactivity Trends in the E2 and S<sub>N</sub>2 Reactions of X<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Cl (X = F, Cl, Br, HO, HS, HSe, NH<sub>2</sub>, PH<sub>2</sub>, AsH2,CH<sub>3</sub>, SiH<sub>3</sub>, and GeH<sub>3</sub>). *J. Chem. Theory Comput.* 2009, *5*, 1597–1606. [CrossRef]
- Wolters, L.P.; Ren, Y.; Bickelhaup, F.M. Understanding E2 versus S<sub>N</sub>2 Competition under Acidic and Basic Conditions. *Chemistry-Open* 2014, *3*, 29–36. [CrossRef]
- 16. Tajti, V.; Czakó, G. Benchmark ab Initio Characterization of the Complex Potential Energy Surface of the F<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Cl Reaction. *J. Phys. Chem. A* 2017, 121, 2847–2854. [CrossRef] [PubMed]
- 17. Yang, L.; Zhang, J.X.; Xie, J.; Ma, X.Y.; Zhang, L.Y.; Zhao, C.Y.; Hase, W.L. Competing E2 and S<sub>N</sub>2 Mechanisms for the F<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>I Reaction. *J. Phys. Chem. A* 2017, *121*, 1078–1085. [CrossRef]
- Hamlin, T.A.; Swart, M.; Bickelhaupt, F.M. Nucleophilic Substitution (S<sub>N</sub>2): Dependence on Nucleophile, Leaving Group, Central Atom, Substituents, and Solvent. *Chemphyschem* 2018, 19, 1315–1330. [CrossRef] [PubMed]
- Satpathy, L.; Sahu, P.K.; Behera, P.K.; Mishra, B.K. Solvent Effect on the Potential Energy Surfaces of the F<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Br Reaction. J. Phys. Chem. A 2018, 122, 5861–5869. [CrossRef]
- Garver, J.M.; Eyet, N.; Villano, S.M.; Yang, Z.; Bierbaum, V.M. Mechanistic investigation of S<sub>N</sub>2 dominated gas phase alkyl iodide reactions. *Int. J. Mass. Spectrom.* 2011, 301, 151–158. [CrossRef]
- Vermeeren, P.; Hansen, T.; Jansen, P.; Swart, M.; Hamlin, T.A.; Bickelhaupt, F.M. A Unified Framework for Understanding Nucleophilicity and Protophilicity in the S<sub>N</sub>2/E2 Competition. *Chem. Eur. J.* 2020, *26*, 15538–15548. [CrossRef] [PubMed]

- Vermeeren, P.; Hansen, T.; Grasser, M.; Silva, D.R.; Hamlin, T.A.; Bickelhaupt, F.M. S<sub>N</sub>2 versus E2 Competition of F<sup>-</sup> and PH<sub>2</sub><sup>-</sup> Revisited. J. Org. Chem. 2020, 85, 14087–14093. [CrossRef] [PubMed]
- Hansen, T.; Vermeeren, P.; Bickelhaupt, F.M.; Hamlin, T.A. Origin of the α-Effect in S<sub>N</sub>2 Reactions. *Angew. Chem. Int. Ed.* 2021, 60, 20840–20848. [CrossRef] [PubMed]
- Stuyver, T.; Shaik, S. Resolving Entangled Reactivity Modes through External Electric Fields and Substitution: Application to E2/S<sub>N</sub>2 Reactions. J. Org. Chem. 2021, 86, 9030–9039. [CrossRef] [PubMed]
- 25. Tasi, D.A.; Tokaji, C.; Czako, G. A benchmark ab initio study of the complex potential energy surfaces of the OH<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Y [Y = F, Cl, Br, I] reactions. *Phys. Chem. Chem. Phys.* **2021**, *23*, 13526–13534. [CrossRef]
- Hansen, T.; Roozee, J.C.; Bickelhaupt, F.M.; Hamlin, T.A. How Solvation Influences the S<sub>N</sub>2 versus E2 Competition. *J. Org. Chem.* 2022, 87, 1805–1813. [CrossRef]
- Li, Y.; Li, C.; Gao, D.; Wang, D. Atomic-Level Mechanism, Solvent Effect, and Potential of the Mean Force of the F<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Cl S<sub>N</sub>2 Reaction in Aqueous Solution. *J. Phys. Chem. A* 2022, *126*, 5527–5533. [CrossRef]
- 28. Wu, X.; Zhang, S.; Xie, J. Investigating the competing E2 and  $S_N 2$  mechanisms for the microsolvated HO<sup>-</sup> (H<sub>2</sub>O)<sub>n=0-4</sub> + CH<sub>3</sub>CH<sub>2</sub>X (X = Cl, Br, I) reactions. *Phys. Chem. Chem. Phys.* **2022**, 24, 12993–13005. [CrossRef]
- Zhao, S.; Fu, G.; Zhen, W.; Yang, L.; Sun, J.; Zhang, J. Reaction mechanism conversion induced by the contest of nucleophile and leaving group. *Phys. Chem. Chem. Phys.* 2022, 24, 24146–24154. [CrossRef]
- Tajti, V.; Czako, G. Vibrational mode-specific dynamics of the F<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Cl multi-channel reaction. *Phys. Chem. Chem. Phys.* 2022, 24, 8166–8181. [CrossRef]
- 31. Meyer, J.; Tajti, V.; Carrascosa, E.; Gyori, T.; Stei, M.; Michaelsen, T.; Bastian, B.; Czako, G.; Wester, R. Atomistic dynamics of elimination and nucleophilic substitution disentangled for the F<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Cl reaction. *Nat. Chem.* **2021**, *13*, 977–981. [CrossRef]
- Nettey, S.; Swift, C.A.; Joviliano, R.; Noin, D.O.; Gronert, S. The impact of substituents on the transition states of S<sub>N</sub>2 and E2 reactions in aliphatic and vinylic systems: Remarkably facile vinylic eliminations. *J. Am. Chem. Soc.* 2012, 134, 9303–9310. [CrossRef] [PubMed]
- 33. Martinez, H.; Rebeyrol, A.; Nelms, T.B.; Dolbier, W.R. Impact of fluorine substituents on the rates of nucleophilic aliphatic substitution and β-elimination. *J. Fluor. Chem.* **2012**, *135*, 167–175. [CrossRef]
- 34. Conner, K.M.; Gronert, S. Impact of alkyl substituents on the gas-phase competition between substitution and elimination. *J. Org. Chem.* **2013**, *78*, 8606–8613. [CrossRef] [PubMed]
- 35. Rablen, P.R.; McLarney, B.D.; Karlow, B.J.; Schneider, J.E. How alkyl halide structure affects E2 and S<sub>N</sub>2 reaction barriers: E2 reactions are as sensitive as S<sub>N</sub>2 reactions. *J. Org. Chem.* **2014**, *79*, 867–879. [CrossRef]
- DePuy, C.H.; Gronert, S.; Mullin, A.; Bierbaum, V.M. Gas-Phase S<sub>N</sub>2 and E2 Reactions of Alkyl Halides. J. Am. Chem. Soc. 1990, 112, 8650–8655. [CrossRef]
- Gronert, S.; DePuy, C.H.; Bierbaum, V.M. Deuterium Isotope Effects in Gas-Phase Reactions of Alkyl Halides: Distinguishing E2 and S<sub>N</sub>2 Pathways. J. Am. Chem. Soc. 1991, 113, 4009–4010. [CrossRef]
- Gronert, S. Theoretical Studies of Elimination Reactions. 3. Gas-Phase Reactions of F<sup>-</sup> with (CH<sub>3</sub>)<sub>2</sub>CHCl and CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>Cl. The Effect of Methyl Substituents. *J. Am. Chem. Soc.* 1993, 115, 652–659. [CrossRef]
- Gallegos, M.; Costales, A.; Pendás, Á.M. Does Steric Hindrance Actually Govern the Competition between Bimolecular Substitution and Elimination Reactions? J. Phys. Chem. A 2022, 126, 1871–1880. [CrossRef]
- Gallegos, M.; Costales, A.; Pendás, A.M. A real space picture of the role of steric effects in S<sub>N</sub>2 reactions. J. Comput. Chem. 2022, 43, 785–795. [CrossRef]
- Carrascosa, E.; Meyer, J.; Zhang, J.; Stei, M.; Michaelsen, T.; Hase, W.L.; Yang, L.; Wester, R. Imaging dynamic fingerprints of competing E2 and S<sub>N</sub>2 reactions. *Nat. Comun.* 2017, *8*, 25. [CrossRef] [PubMed]
- Szabo, I.; Czako, G. Revealing a double-inversion mechanism for the F<sup>-</sup> + CH<sub>3</sub>Cl S<sub>N</sub>2 reaction. *Nat. Commun.* 2015, *6*, 5972. [CrossRef] [PubMed]
- 43. Meyer, J.; Carrascosa, E.; Michaelsen, T.; Bastian, B.; Li, A.; Guo, H.; Wester, R. Unexpected Indirect Dynamics in Base-Induced Elimination. *J. Am. Chem. Soc.* 2019, 141, 20300–20308. [CrossRef] [PubMed]
- Zhang, J.; Hase, W.L. Electronic Structure Theory Study of the F<sup>−</sup> + CH<sub>3</sub>I → FCH<sub>3</sub> + I<sup>−</sup> Potential Energy Surface. J. Phys. Chem. A 2010, 114, 9635–9643. [CrossRef] [PubMed]
- 45. Szabó, I.; Császár, A.G.; Czakó, G. Dynamics of the F<sup>−</sup> + CH<sub>3</sub>Cl → Cl<sup>−</sup> + CH<sub>3</sub>F S<sub>N</sub>2 reaction on a chemically accurate potential energy surface. *Chem. Sci.* 2013, 4, 4362. [CrossRef]
- Stei, M.; Carrascosa, E.; Kainz, M.A.; Kelkar, A.H.; Meyer, J.; Szabo, I.; Czako, G.; Wester, R. Influence of the leaving group on the dynamics of a gas-phase S<sub>N</sub>2 reaction. *Nat. Chem.* 2016, *8*, 151–156. [CrossRef]
- Olasz, B.; Szabo, I.; Czako, G. High-level ab initio potential energy surface and dynamics of the F<sup>-</sup> + CH<sub>3</sub>I S<sub>N</sub>2 and proton-transfer reactions. *Chem. Sci.* 2017, *8*, 3164–3170. [CrossRef]
- Szabo, I.; Czako, G. Benchmark ab Initio Characterization of the Complex Potential Energy Surface of the Cl<sup>-</sup> + CH<sub>3</sub>I Reaction. J. Phys. Chem. A 2017, 121, 5748–5757. [CrossRef]
- Gyori, T.; Olasz, B.; Paragi, G.; Czako, G. Effects of the Level of Electronic Structure Theory on the Dynamics of the F<sup>-</sup> + CH<sub>3</sub>I Reaction. J. Phys. Chem. A 2018, 122, 3353–3364. [CrossRef]
- 50. Tasi, D.A.; Fabian, Z.; Czako, G. Benchmark ab Initio Characterization of the Inversion and Retention Pathways of the OH<sup>-</sup> + CH<sub>3</sub>Y [Y = F, Cl, Br, I] S<sub>N</sub>2 Reactions. *J. Phys. Chem. A* **2018**, *122*, 5773–5780. [CrossRef]

- 51. Tasi, D.A.; Fabian, Z.; Czako, G. Rethinking the  $X^- + CH_3Y$  [X = OH, SH, CN, NH<sub>2</sub>, PH<sub>2</sub>; Y = F, Cl, Br, I] S<sub>N</sub>2 reactions. *Phys. Chem. Chem. Phys.* **2019**, *21*, 7924–7931. [CrossRef] [PubMed]
- 52. Kerekes, Z.; Tasi, D.A.; Czako, G. S<sub>N</sub>2 Reactions with an Ambident Nucleophile: A Benchmark Ab Initio Study of the CN<sup>-</sup> + CH<sub>3</sub>Y [Y = F, Cl, Br, and I] Systems. *J. Phys. Chem. A* 2022, *126*, 889–900. [CrossRef] [PubMed]
- 53. Vermeeren, P.; Hamlin, T.A.; Bickelhaupt, F.M. Chemical reactivity from an activation strain perspective. *Chem. Commun.* 2021, 57, 5880–5896. [CrossRef] [PubMed]
- 54. Zhao, S.; Fu, G.; Zhen, W.; Wang, H.; Liu, M.; Yang, L.; Zhang, J. Nucleophile Effects on the E2/S<sub>N</sub>2 Competition for the X<sup>-</sup> + CH<sub>3</sub>CH<sub>2</sub>Cl Reactions: A Theoretical Study. *J. Phys. Chem. A* **2023**, *127*, 3381–3389. [CrossRef]
- 55. Lu, T.; Chen, F. Multiwfn: A Multifunctional Wavefunction Analyzer. J. Comput. Chem. 2012, 33, 580–592. [CrossRef]
- 56. Kim, C.K.; Li, H.G.; Lee, B.-S.; Kim, C.K.; Lee, H.W.; Lee, I. Gas-Phase Identity Nucleophilic Substitution Reactions of Cyclopropenyl Halides. J. Org. Chem. 2002, 67, 1953–1960. [CrossRef]
- 57. Ren, Y.; Yamataka, H. The α-Effect in Gas-Phase S<sub>N</sub>2 Reactions: Existence and the Origin of the Effect. *J. Org. Chem.* **2007**, *72*, 5660–5667. [CrossRef]
- 58. Chen, Y.; Chang, K.H.; Meng, F.Y.; Tseng, S.M.; Chou, P.T. Broadening the Horizon of the Bell–Evans–Polanyi Principle towards Optically Triggered Structure Planarization. *Angew. Chem. Int. Ed.* **2021**, *60*, 7205–7212. [CrossRef]
- 59. Head-Gordon, M.; Pople, J.A. MP2 Eenergy Evaluation By Direct Methods. Chem. Phys. Lett. 1988, 153, 503–506. [CrossRef]
- Frisch, M.J.; Head-Gordon, M.; Pople, J.A. Semi-Direct Algorithms for the MP2 Energy and Gradient. *Chem. Phys. Lett.* 1990, 166, 281–289. [CrossRef]
- 61. Dunning, T.H. Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen. *J. Chem. Phys.* **1989**, *90*, 1007–1023. [CrossRef]
- 62. Woon, D.E.; Dunning, T.H. Gaussian basis sets for use in correlated molecular calculations. III. The atoms aluminum through argon. J. Chem. Phys. 1993, 98, 1358–1371. [CrossRef]
- 63. Wadt, W.R.; Hay, P.J. Ab initio effective core potentials for molecular calculations. Potentials for main group elements Na to Bi. *J. Chem. Phys.* **1985**, *82*, 284–298. [CrossRef]
- 64. Zhang, L.; Yang, L.; Zhao, Y.; Zhang, J.; Feng, D.; Sun, S. Effects of Water Molecule on CO Oxidation by OH: Reaction Pathways, Kinetic Barriers, and Rate Constants. J. Phys. Chem. A 2017, 121, 4868–4880. [CrossRef]
- 65. Szucs, T.; Czako, G. Benchmark ab initio potential energy surface mapping of the F<sup>-</sup> + CH<sub>3</sub>NH<sub>2</sub> reaction. *Phys. Chem. Chem. Phys.* **2022**, *24*, 20249. [CrossRef]
- 66. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A.; Scalmani, G.; Barone, V.; Mennucci, B.; et al. *Gaussian 09*; Revision A.01; Gaussian Inc.: Wallingford, CT, USA, 2009.

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