Activation Strain Analysis of $S_N2$ Reactions at C, N, O, and F Centers

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ABSTRACT: Fundamental principles that determine chemical reactivity and reaction mechanisms are the very foundation of chemistry and many related fields of science. Bimolecular nucleophilic substitutions ($S_N2$) are among the most common and therefore most important reaction types. In this report, we examine the trends in the $S_N2$ reactions with respect to increasing electronegativity of the reaction center by comparing the well-studied backside $S_N2$ Cl$^-$ + CH$_3$Cl with similar Cl$^-$ substitutions on the isoelectronic series with the second period elements N, O, and F in place of C. Relativistic (ZORA) DFT calculations are used to construct the gas phase reaction potential energy surfaces (PES), and activation strain analysis, which allows decomposition of the PES into the geometrical strain and interaction energy, is employed to analyze the observed trends. We find that $S_N2$@N and $S_N2$@O have similar PES to the prototypical $S_N2$@C, with the well-defined reaction complex (RC) local minima and a central barrier, but all stationary points are, respectively, increasingly stable in energy. The $S_N2$@F, by contrast, exhibits only a single-well PES with no barrier. Using the activation strain model, we show that the trends are due to the interaction energy and originate mainly from the decreasing energy of the empty acceptor orbital ($\sigma^*$$_{N,Cl}$) on the reaction center A in the order of C, N, O, and F. The decreasing steric congestion around the central atom is also a likely contributor to this trend. Additional decomposition of the interaction energy using Kohn–Sham molecular orbital (KS-MO) theory provides further support for this explanation, as well as suggesting electrostatic energy as the primary reason for the distinct single-well PES profile for the FCl reaction.

1. INTRODUCTION

Understanding chemical reactions and reactivity is one of the central goals of chemistry and, more broadly, all natural science. The ability of molecular species to react and form new, more complex ones is responsible for the evolution and existence of the Universe, Earth, and biological life. In modern society, design and production of new compounds and materials is key for technological advances that help sustain the growing and expanding human population. Fundamental insights into the underlying physical principles behind key chemical processes are therefore critical for further progress in their future development, control, and optimization.

One of the most important prototypes of chemical reactions is bimolecular nucleophilic substitution ($S_N2$, see Scheme 1). Due to its significance, numerous experimental and theoretical studies have been focused on providing detailed, fundamental understanding of the $S_N2$ reactions. Perhaps the best-known model for $S_N2$ reactions is the symmetric, thermoneutral $S_N2$ reaction between the chloride anion and chloromethane, Cl$^-$ + CH$_3$Cl in the gas phase (Scheme 1). This reaction proceeds preferentially through backside nucleophilic attack of the chloride anion at the carbon atom ($S_N2@C$) with concerted expulsion of the leaving group. A well-known feature of gas phase $S_N2@C$ reactions is their double-well potential energy surface (PES) along the reaction coordinate, as illustrated in Figure 1. This PES is characterized by a central barrier, provided by a trigonal bipyramidal transition state (TS, see also Scheme 1), that separates two energy minima, associated with the reactant and product ion–molecule complexes (RC and PC).

Among the most powerful approaches to understanding reactivity is examining trends with respect to some selected properties of the reacting species. Although many trends could be explained using chemical intuition or empirical understanding, when combined with modern quantum chemical calculations it is possible to uncover the details of the electronic structure and its changes associated with the observed trends, thereby providing the fundamental explanations. Bento and Bickelhaupt recently used relativistic DFT calculations together with analysis by the activation strain model to examine...
the effects of the nucleophile and the leaving group on methyl chloride (CH$_3$Cl) S$_{N}$2 reactions, both backside and frontside. This study demonstrated that the nucleophile is determined by the electron-donor capability of the nucleophile, while the leaving group ability is associated primarily with the carbon—leaving group bond strength.

The same authors also investigated the S$_{N}$2 reactions according to Scheme 1 with the central C atom substituted by heavier group-14 atoms (Si, Ge, Sn, Pb). An interesting feature of the PES for the S$_{N}$2@Si, @Ge, @Sn, and @Pb reactions is that the central barrier disappears, giving rise to a single-well reaction profile. They showed that the disappearance of the central barrier is due to the decrease in steric repulsion for the larger atoms along with more stabilizing orbital interactions due to better chloride HOMO/substrate LUMO overlap.

The next level of the quest for a more complete understanding of the S$_{N}$2 reactions is the examination of trends with respect to substitutions on atoms other than carbon and its group-14 congeners. Several theoretical reports compare various aspects of S$_{N}$2@C reactions to S$_{N}$2@N, S$_{N}$2@P, S$_{N}$2@O, and S$_{N}$2@F. However, these studies often focus on thermochemistry, molecular geometries, solvent, or comparison of different computational methods, and few seek a systematic examination of trends with respect to the properties of the central atom and their significance in the S$_{N}$2 reactivity. Here we take the first step in this direction by considering on the S$_{N}$2 reactions for all substrates of the second period elements that are isoelectronic to the CH$_3$Cl prototype, namely, NH$_3$Cl, OHCl, and FCl (Scheme 2). This series provides a potentially very rich model set for understanding the roles of several key factors in the S$_{N}$2 reactivity which may be further representative of the corresponding groups of the periodic table. In particular, there is a strong trend of increasing electronegativity from C to F which goes with a more negatively charged electrophilic central atom. Intuitively, one might expect that higher electronegativity will lead to higher barriers due to repulsion with the approaching nucleophile. On the other hand, the valence of the central element decreasing in the same order results in different geometry of the reacting species and transition states, which may manifest itself via geometry strain and steric effects. The resulting PESs are therefore expected to reflect, to a greater or lesser extent, an interplay of both these fundamental contributions. To sort out the roles of each of these individual PES components, we take advantage of the activation strain model, which has been specifically designed for this purpose (see Methods for details), and use this powerful methodology to identify the underlying physical reasons and explanations for the observed trends in the S$_{N}$2 reactivity.

2. METHODS

2.1. Computational Details. All calculations were performed with the Amsterdam Density Functional (ADF) program. The molecular orbitals (MOs) were expanded in a large uncontracted set of Slater-type orbitals (STOs) containing diffuse functions, TZ2P. This basis is of triple-$\zeta$ quality and has been augmented by two sets of polarization functions: 2p and 3d on hydrogen and 3d and 4f on all heavier atoms. An auxiliary set of s, p, d, f, and g STOs was used to 2p and 3d on hydrogen and 3d and 4f on all heavier atoms. An auxiliary set of s, p, d, f, and g STOs was used to

2.2. Analysis of the Potential Energy Surfaces. Insight into how the activation barriers arise is obtained through activation strain analyses of the various S$_{N}$2 reactions. The activation strain model, also known as distortion/interaction model, is a fragment approach to understanding chemical reactions, in which the height of reaction barriers is described in terms of the original reactants. Thus, the potential energy surface $\Delta E(\zeta)$ is decomposed, along the reaction coordinate $\zeta$, into the strain $\Delta E_{\text{strain}}(\zeta)$ associated with deforming the individual reactants plus the actual interaction $\Delta E_{\text{int}}(\zeta)$ between the deformed reactants:

$$\Delta E(\zeta) = \Delta E_{\text{strain}}(\zeta) + \Delta E_{\text{int}}(\zeta)$$
The strain $\Delta E_{\text{strain}}(\zeta)$ is determined by the rigidity of the reactants and by the extent to which groups must reorganize in a particular reaction mechanism, whereas the interaction $\Delta E_{\text{int}}(\zeta)$ between the reactants depends on their electronic structure and on how they are mutually oriented as they approach each other. It is the interplay between $\Delta E_{\text{strain}}(\zeta)$ and $\Delta E_{\text{int}}(\zeta)$ that determines if and at which point along the $\zeta$ a barrier arises. The activation energy of a reaction $\Delta E^\ddagger = \Delta E^\ddagger_{\text{strain}} = \Delta E^\ddagger_{\text{strain}}(\zeta_{\text{TS}})$ plus the TS interaction $\Delta E^\ddagger_{\text{int}} = \Delta E^\ddagger_{\text{int}}(\zeta_{\text{TS}})$:

$$\Delta E^\ddagger = \Delta E^\ddagger_{\text{strain}} + \Delta E^\ddagger_{\text{int}}$$

In the graphical representations shown below, $\zeta$ is then projected onto the stretch of the central atom—leaving group (A−Cl, A = C, N, O, and F) bond, which is generally one of the dominant components of the reaction coordinate and undergoes a well-defined change from an intact to a dissociated bond.

The interaction $\Delta E_{\text{int}}(\zeta)$ between the strained reactants is further analyzed in the conceptual framework provided by the Kohn–Sham molecular orbital (KS-MO) model, according to which it is decomposed into three physically meaningful terms:

$$\Delta E_{\text{int}}(\zeta) = \Delta V_{\text{delat}}(\zeta) + \Delta E_{\text{Pauli}}(\zeta) + \Delta E_{\text{vcl}}(\zeta)$$

The term $\Delta V_{\text{delat}}(\zeta)$ corresponds to the classical electrostatic interaction between the unperturbed charge distributions of the deformed reactants and is usually attractive. The Pauli repulsion $\Delta E_{\text{Pauli}}(\zeta)$ comprises the destabilizing interactions between occupied orbitals and is responsible for any steric repulsion (see ref. 44 for an exhaustive discussion). The orbital interaction $\Delta E_{\text{vcl}}(\zeta)$ accounts for charge transfer (interaction between occupied orbitals on one moiety with unoccupied orbitals of the other, including HOMO–LUMO interactions) and polarization (empty–occupied orbital mixing on one fragment due to the presence of another fragment).

The activation strain analysis was performed with the aid of the PyFrag program at discrete points on the reaction coordinate, sampled from the computed IRC paths (see above), except Cl− + FCl, where due to the absence of a TS a relaxed energy scan (linear transit) along the F−Cl bond was used.

### 3. RESULTS AND DISCUSSION

#### 3.1. Reaction Profiles

The computed energies of the reaction complexes (RC), transition states (TS), and transition complex (TC) with respect to the free reactants are summarized in Table 1. Also shown in Table 1 are the A−Cl− distances (where A stands for the central atom; A = C, N, O, F) at the respective stationary points. The corresponding reaction profiles are superimposed in Figure 2. Our ZORA-OLYP/TZ2P computations show that all the model reactions proceed via a Cl−−A−Cl symmetric transition structure which is either a labile transition state (for A = C, N, O) or a stable intermediate transition complex (for A = F). Furthermore, there is a systematic trend in the energy of this symmetric TS or TC relative to the reactants: along A = C, N, O, and F, it decreases from −3.0 kcal/mol to −16.8 kcal/mol, respectively (Table 1).

The Cl− + CH3Cl reaction exhibits the characteristic double-well PES involving local minima corresponding to the reaction complexes (RC) and a central barrier for the transition state (TS), in line with previous studies. Specificaly, the RCs are respectively 7 and 25 kcal/mol lower, while the TSs are 9 and 23 kcal/mol below the computed values for the CH3Cl + Cl− reaction (all values relative to the reactants). The height of the reaction barrier with respect to the RC, however, does not follow the same trend. It is computed to be 9, 7, and 12 kcal/mol for the reactions with CH3Cl, NH3Cl, and OHCl, respectively.

By contrast, the Cl− + FCl reaction profile is qualitatively different, with only a single minimum corresponding to the symmetric [Cl−−F−−Cl]− transition complex and no separate, asymmetric RC. The TC is stable by 17 kcal/mol compared to the individual reactants (Table 1). This species features a strong halogen bond and electron-rich hypervalent fluorine.

Similar single-well profiles were identified for S2 substitution on heavier group-14 atoms: Si, Ge, Sn, and Pb. In fact, under certain conditions, they may also exist for S2 substitution on carbon.

Another trend apparent from Table 1 is the systematic decrease in bond distances between the central atom and the Cl− leaving group for both RC and transition structure (TS or TC) in the order C, N, O, and F. The differences are somewhat greater for the TS (by ~0.02 Å) and also decrease more significantly from S2@N to S2@O than from S2@C to S2@N, by about 0.04 Å for both RC and TS. The trend continues for the S2 substitution at F although, as mentioned above, no asymmetric RC exists, only a stable TC. In this stable [Cl−−F−−Cl]− complex the F−Cl bond lengths are greater than in the RCs for the other compounds. However, when compared...
to the TS, the bond again shortens from O–Cl to F–Cl (Table 1).

For completeness, in Table 2 we present the thermochemistry activation parameters for the studied reactions, calculated

|                | Cl + CH3Cl | Cl− + NH2Cl | Cl− + OHC | Cl− + FCl |
|----------------|------------|------------|-----------|-----------|
| ΔU£            | −0.6       | −9.6       | −12.5     | −16.3     |
| ΔH£            | −1.2       | −10.2      | −13.1     | −16.9     |
| −TΔS£          | 7.5        | 7.5        | 7.6       | 6.5       |
| ΔG£            | 6.3        | −2.7       | −5.5      | −10.4     |

Computed at ZORA-OLYP/TZ2P for 1 atm, 298.15 K.

Table 2. Thermochemistry of Activation (in kcal/mol) for the Studied S2 reactions

Figure 3. Activation strain analysis of the S2 reaction profiles. Total energy (black), decomposed into strain (blue) and interaction (red) components plotted as a function of the A−Cl stretch coordinate with respect to its equilibrium value for (a) Cl− + NH2Cl reaction (A = C), (b) Cl− + NH2Cl reaction (A = N), (c) Cl− + OHC reaction (A = O), and (d) Cl− + FCl reaction (A = F). The pale blue vertical lines indicate the position of the transition state.

for 1 atm, 298.15 K. The trends in the activation thermodynamic energy (i.e., electronic energy plus ZPVE plus thermal energy of translation, rotation, and vibration) and enthalpy parallel the electronic energy presented in Table 1. All ΔH£ are negative, implying that the reaction rates would exhibit an anti-Arrhenius behavior in the gas phase, i.e., they would decrease with the increasing temperature. The activation entropy (given as −TΔS£) is essentially constant for CH3Cl, NH2Cl, and OHC reactions, and only 1 kcal·mol−1 lower for the FCl, yielding quantitatively very similar progression in the activation Gibbs free energies. Note, however, that there is a qualitative difference: the ΔG£ for the Cl− + CH3Cl reaction is slightly positive, therefore presenting an actual activation barrier, while all others are negative. Thus, at low-pressure conditions, the gas-phase S2 substitution at C still experiences an entropy bottleneck whereas gas-phase S2 substitution at N, O, and F proceeds spontaneously. Note that at higher pressure, as energy dissipation becomes important, the central barrier (i.e., relative to the RC or TC) becomes decisive.

At first sight, the mechanism behind the above trends may not be entirely obvious. Why should the relative energy of the TS or TC go down, if the nucleophile attacks a more electronegative and thus more negatively charged (vide infra) central atom if one goes from A = C to A = N, O, and F? By contrast, the interaction energies (Figure 4b, see also Table 3) show a clear trend of stabilization in the order of C, N, O, F. The explanation can be found from the examination of the dominant frontier orbital interaction between the occupied Cl− 3p AO and the backside lobe of the empty σ*A−Cl orbital. As shown in Table 4, the σ*A−Cl energy monotonically decreases with the increasing electronegativity of the central atom, respectively, for along C, N, O, and F. This reflects the decreasing orbital energy of the central atom’s 2p AOs in this order. The monotonic decrease of the σ*A−Cl orbital energy along CH3Cl, NH2Cl, and OHC, and FCl causes the HOMO–LUMO gap ∆ε between nucleophile Cl− 3p AO and substrate σ*A−Cl to become smaller and thus the orbital interactions to become more stabilizing. This is what we see in the systematic trend in interaction curves, in perfect agreement with the relationship ∆Eint ∼ S/E where S represents the overlap integral (Table 4) and ∆ε is the energy difference between the interacting orbitals. Note that the orbital overlap, shown in Table 4 for the TS (TC), decreases slightly with the increasing electronegativity of A (with the exception of N and O), consistently with the generally greater wave function rather than the strain (Figure 4a). In Table 3, we list the values of the ∆Estrain and ∆Eint at the TS or, for SN2@F, TC. Although the strain energy does destabilize the TS of the Cl− + CH3Cl with respect to NH2Cl and OHC ones by ∼5 kcal·mol−1, the latter two have virtually the same TS strain energy and the Cl− + FCl reaction complex has again slightly higher strain, counter to the progression in the total energy (Figure 2). These differences in the ∆Estrain correlate well with the order of A−Cl bond dissociation energies, that is, stronger bonds go with more destabilizing strain curves (Table 4). By contrast, the interaction energies (Figure 4b, see also Table 3) show a very clear trend of stabilization in the order of C, N, O, F. The explanation can be found from the examination of the dominant frontier orbital interaction between the occupied Cl− 3p AO and the backside lobe of the empty σ*A−Cl orbital. As shown in Table 4, the σ*A−Cl energy monotonically decreases with the increasing electronegativity of the central atom, respectively, for along C, N, O, and F. This reflects the decreasing orbital energy of the central atom’s 2p AOs in this order. The monotonic decrease of the σ*A−Cl orbital energy along CH3Cl, NH2Cl, and OHC, and FCl causes the HOMO–LUMO gap ∆ε between nucleophile Cl− 3p AO and substrate σ*A−Cl to become smaller and thus the orbital interactions to become more stabilizing. This is what we see in the systematic trend in interaction curves, in perfect agreement with the relationship ∆Eint ∼ S/E where S represents the overlap integral (Table 4) and ∆ε is the energy difference between the interacting orbitals. Note that the orbital overlap, shown in Table 4 for the TS (TC), decreases slightly with the increasing electronegativity of A (with the exception of N and O), consistently with the generally greater wave function.
amplitude on the more electropositive element of the A–Cl bond, which opposes the stabilization effect of the HOMO–LUMO gap. The Δε is therefore clearly the decisive factor in determining the interaction energy, as evidenced particularly by the greatest amount of stabilization in F–Cl (Figure 4b, Table 4).

That the orbital interaction is indeed the dominant contribution to the ΔEint trend is further confirmed by the examination of the decomposition of ΔEint according to our quantitative analysis associated with the KS-MO model (see Methods). The individual components, ΔEPauli, ΔVelec, and ΔEelstat are overlaid for all four studied SN2 reactions in Figure 5. Both the Pauli repulsion term (ΔEPauli, Figure 5a) and the electrostatic interaction (ΔVelec, Figure 5b) oppose the trend; although the ΔVelec trend is further conformed by the overall progression of the transition states, the pink square for Cl+ + FCl the position of the stable transition complex.

**Table 3. Activation Strain Analysis (in kcal mol⁻¹) at the TS of the Studied SN2 Reactions**

| Reaction                  | ΔE⁻¹ | ΔEstrain | ΔEelstat |
|---------------------------|------|----------|----------|
| Cl− + CH3Cl              | -0.1 | 31.6     | -9.2     |
| Cl− + NH2Cl              | -11.8| 25.7     | -26.1    |
| Cl− + OHCl               | -16.8| 26.1     | -27.7    |
| Cl− + FCl                | -44.5| 34.9     | -37.9    |

*Computed at the ZORA-OLYP/TZ2P level.

**Table 4. Properties of the Substrates in Studied SN2 Reactions: A–Cl Bond Strengths (in kcal mol⁻¹), σ⁺A–Cl Orbital Energy (in eV), and A Atomic Charge (in au)*

| Substrate | BDE⁻¹ | σ⁺A–Cl | Q_{HOMO}(A⁻¹) | Δen⁺⁺ | Δσ⁺⁺ |
|-----------|-------|--------|---------------|-------|-------|
| CH3−Cl    | 84.2  | -5.13  | -0.031        | -0.61 | 0.215 |
| NH3−Cl    | 63.4  | -6.96  | -0.143        | -0.12 | 0.174 |
| OH−Cl     | 58.6  | -8.95  | -0.152        | 0.28  | 0.183 |
| F−Cl      | 65.3  | -11.08 | -0.072        | 0.82  | 0.131 |

*Computed at ZORA-OLYP/TZ2P. *Bond dissociation energy. *VDD atomic charge. *Pauling electronegativity difference of central atom relative to Cl. *Overlap integral between HOMO (3p) of Cl− and LUMO (σ⁺A–Cl) of each substrate at the TS (TC).
of the steric congestion by hydrogens bound to the central carbon for a series of Cl\textsuperscript{−}-induced S\textsubscript{2}2@C reactions with CH\textsubscript{3}Cl, CH\textsubscript{2}Cl\textsuperscript{*}, CHCl\textsuperscript{*}, and CCl\textsuperscript{***} \textsuperscript{**} which have the same number of central atom bound hydrogens as our model series. They found that the central activation barrier becomes systematically lower with the decreasing number of hydrogens bound to the central atom and vanishes completely for the CCl\textsuperscript{***} \textsuperscript{**} parallelizing our result for S\textsubscript{2}2@F.

Finally, the difference in shape between the PES for S\textsubscript{2}2@C, S\textsubscript{2}2@N, and S\textsubscript{2}2@O and that for S\textsubscript{2}2@F is also codetermined by the strength of the hydrogen bonds that promote the occurrence of a stable RC and PC. Note that the relative energy of the S\textsubscript{2}2@F TC complex exactly fits the trend of the TS energetics for the other reactions: the symmetric TS or TC systematically decreases in energy relative to separate reactants along C, N, O, and F. However, the central barrier, that is, the TS energy relative to the RC energy, behaves less systematically. This is because it is dependent not only on the trend in stability of the symmetric transition species (TS or TC) but also on the stability or even the availability of the Cl\textsuperscript{−}···H−AH\textsubscript{···}Cl hydrogen bond in the RC or PC. This hydrogen bond becomes stronger as the H–A bond becomes more polar, along Cl\textsuperscript{−}···H–CH\textsubscript{3}Cl, Cl\textsuperscript{−}···H–NH\textsubscript{2}Cl, and Cl\textsuperscript{−}···H–OCl (see Table 1 and Figure 2). The hydrogen bonding in the RC (and PC) for S\textsubscript{2}2@N and S\textsubscript{2}2@O is evident from the geometries where, in contrast to the RC for S\textsubscript{2}2@C, the Cl\textsuperscript{−} clearly aligns with the N–H or O–H bond. This pronounced H-bonding interaction is reflected also in the distinct downward curvature of the ΔE\textsubscript{int} (Figure 4b) below d(A–Cl) of ~0.1 Å for S\textsubscript{2}2@N and S\textsubscript{2}2@O. But it ceases to exist as soon as there is no hydrogen-bond donor anymore, namely, for FCl; and so vanishes the RC and PC in the case of S\textsubscript{2}2@F.

4. CONCLUSIONS

The analyses of the S\textsubscript{2}2 reactions of Cl\textsuperscript{−} + CH\textsubscript{3}Cl, NH\textsubscript{2}Cl, OHCl, and FCl based on relativistic density functional theory reveal a consistent trend, whereby the overall reaction barriers are progressively lower in energy with the increasing electronegativity of the reaction center. The reaction complexes (RC) likewise become increasingly stabilized the more electronegative the central atom, with the exception of FCl, which yields a single-well PES with no central barrier.

Analyses based on the activation strain model show that the trend is entirely due to the increasingly stabilizing interaction energy between nucleophile and substrate, with minimal contribution from the geometric strain. The origin of this trend lies predominantly (although not exclusively) in the lower energy of the unoccupied acceptor orbital (σ\textsuperscript*nH–C\textsubscript{···}Cl) as the electronegativity of the substitution center A (= C, N, O, and F) increases. This σ\textsuperscript*nH–C\textsubscript{···}Cl orbital-energy lowering leads to a stronger HOMO–LUMO orbital interaction with the 3p lone-pair orbital of the Cl\textsuperscript{−} nucleophile.

These results underline the importance of the reaction center electronegativity and orbital interactions in shaping the S\textsubscript{2}2 reaction profiles. They also demonstrate the great utility of relativistic DFT calculations and activation strain analyses for understanding the fundamentals of chemical reaction mechanisms.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.6b12240.
of the Model System F+ + CH₂H₂F + nHF. Chem. - Eur. J. 1996, 2, 196–207.

(18) Bento, A. P.; Bickelhaupt, F. M. Nucleophilic Leav- ing-Group Ability in Frontside and Backside SN₂ Reactions. J. Org. Chem. 2008, 73, 7290–7299.

(19) Bento, A. P.; Bickelhaupt, F. M. Frontside versus Backside SN₂ Substitution at Group 14 Atoms: Origin of Reaction Barriers and Reasons for Their Absence. Chem. - Asian J. 2008, 3, 1783–1792.

(20) Bento, A. P.; Bickelhaupt, F. M. Nucleophilic Substitution at Silicon (Sn₂@Si) via a Central Reaction Barrier. J. Org. Chem. 2007, 72, 2201–2207.

(21) Ren, Y.; Chu, S. Y. Recent Development in the Study of SN₂ Reactions at Heteroatoms and Ion Pair Systems. J. Theor. Comput. Chem. 2006, 5, 121–140.

(22) Xie, J.; Otto, R.; Mikosch, J.; Zhang, J.; Wester, R.; Hase, W. L. Identification of Atomic-Level Mechanisms for Gas-Phase X+ + CH,Y SN₂ Reactions by Combined Experiments and Simulations. Acc. Chem. Res. 2014, 47, 2960–2969.

(23) Diefenbach, A.; de Jong, G. T.; Bickelhaupt, F. M. Activation of H-H, C-H, C-C and C-Cl Bonds by Pd and PdCl₂. Understanding Anion Assistance in C-X Bond Activation. J. Chem. Theory Comput. 2005, 1, 286–298.

(24) Diefenbach, A.; Bickelhaupt, F. M. Oxidative Addition of Pd to C-H, C-C and C-Cl Bonds: Importance of Relativistic Effects in DFT Calculations. J. Chem. Phys. 2001, 115, 4030–4040.

(25) de Jong, G. T.; Bickelhaupt, F. M. Transition-State Energy and Position along the Reaction Coordinate in an Extended Activation Strain Model. ChemPhysChem 2007, 8, 1170–1181.

(26) Fernando, I.; Bickelhaupt, F. M. The Activation Strain Model and Molecular Orbital Theory: Understanding and Designing Chemical Reactions. Chem. Soc. Rev. 2014, 43, 4953–4967.

(27) Wolters, L. P.; Bickelhaupt, F. M. The Activation Strain Model and Molecular Orbital Theory. Wiley Interdiscip. Rev. Comput. Mol. Sci. 2015, 5, 324–343.

(28) Baerends, E. J.; Ziegler, T.; Autschbach, J.; Bashford, D.; Béres, A.; Bickelhaupt, F. M.; Bo, C.; Boerrigter, P. M.; Cavallo, L.; Chong, D. P.; et al. Computer Code ADF 2015.01 SCM, Theoretical Chemistry and Molecular Orbital Theory: Understanding and Designing Chemical Reactions. Chem. Soc. Rev. 2014, 43, 4953–4967.

(29) Bento, A. P.; Sola, M.; Bickelhaupt, F. M. Ab Initio and DFT Benchmark Study for Nucleophilic Substitution at Carbon (Sn₂@C) and Silicon (Sn₂@Si). J. Comput. Chem. 2005, 26, 1497–1504.

(30) Swart, M.; Sola, M.; Bickelhaupt, F. M. Energy Landscapes of Nucleophilic Substitution Reactions: A Comparison of Density Functional Theory and Coupled Cluster Methods. J. Comput. Chem. 2007, 28, 1551–1560.

(31) van Lenthe, E.; Baerends, E. J.; Snijders, J. G. Relativistic Total Energy Using Regular Approximations. J. Chem. Phys. 1994, 101, 9783–9792.

(32) Lee, C. T.; Yang, W. T.; Parr, R. G. Development of the Colle-Salvetti Correlation Energy Formula into a Functional of Electron Density. Phys. Rev. B: Condens. Matter Matter. Phys. 1988, 37, 785–789.

(33) Handy, N. C.; Cohen, A. J. Left-Right Correlation Energy. Mol. Phys. 2001, 99, 403–412.

(34) Bento, A. P.; Sola, M.; Bickelhaupt, F. M. Ab Initio and DFT Benchmark Study for Nucleophilic Substitution at Carbon (Sn₂@C) and Silicon (Sn₂@Si). J. Comput. Chem. 2005, 26, 1497–1504.

(35) Swart, M.; Sola, M.; Bickelhaupt, F. M. Energy Landscapes of Nucleophilic Substitution Reactions: A Comparison of Density Functional Theory and Coupled Cluster Methods. J. Comput. Chem. 2007, 28, 1551–1560.

(36) Bento, A. P.; Sola, M.; Bickelhaupt, F. M. E2 and Sn₂ Reactions of X+ + CH₂CH₂X (X = F, Cl); an Ab Initio and DFT Benchmark Study. J. Chem. Theory Comput. 2008, 4, 929–940.

(37) Swart, M.; Sola, M.; Bickelhaupt, F. M. Density Functional Calculations of E2 and Sn₂ Reactions: Effects of the Choice of Method, Algorithm, and Numerical Accuracy. J. Chem. Theory Comput. 2010, 6, 3145–3152.

(38) Gonzales, J. M.; Allen, W. D.; Schafer, H. F. Model Identity Sn₂ Reactions CH₂X + X⁻ (X = F, Cl, CN, OH, SH, NH₂, PH₂); Marcus Theory Analyzed. J. Phys. Chem. A 2005, 109, 10613–10628.