Mechanism Elucidation

A Unified Framework for Understanding Nucleophilicity and Protophilicity in the S\textsubscript{N}2/E2 Competition

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Abstract: The concepts of nucleophilicity and protophilicity are fundamental and ubiquitous in chemistry. A case in point is bimolecular nucleophilic substitution (S\textsubscript{N}2) and base-induced elimination (E2). A Lewis base acting as a strong nucleophile is needed for S\textsubscript{N}2 reactions, whereas a Lewis base acting as a strong protophile (i.e., base) is required for E2 reactions. A complicating factor is, however, the fact that a good nucleophile is often a strong protophile. Nevertheless, a sound, physical model that explains, in a transparent manner, when an electron-rich Lewis base acts as a protophile or a nucleophile, which is not just phenomenological, is currently lacking in the literature. To address this fundamental question, the potential energy surfaces of the S\textsubscript{N}2 and E2 reactions of X\textsuperscript{−} + C\textsubscript{2}H\textsubscript{5}Y model systems with X, Y = F, Cl, Br, I, and At, are explored by using relativistic density functional theory at ZORA-OLYP/TZ2P. These explorations have yielded a consistent overview of reactivity trends over a wide range in reactivity and pathways. Activation strain analyses of these reactions reveal the factors that determine the shape of the potential energy surfaces and hence govern the propensity of the Lewis base to act as a nucleophile or protophile. The concepts of “characteristic distortivity” and “transition state acidity” of a reaction are introduced, which have the potential to enable chemists to better understand and design reactions for synthesis.

Introduction

The ability to rationally design chemical reactions is one of the fundamental challenges in chemistry. Unraveling the processes that dictate the course reactants take along a potential energy surface (PES) paves the way to such design and may lead to the discovery of new chemistry. Two prototypical reactions in organic chemistry that feature in many routes in organic synthesis are bimolecular nucleophilic substitution (S\textsubscript{N}2) and base-induced elimination (E2). S\textsubscript{N}2 reactions (i.e., nucleophilic attack) are in principle always in competition with E2 reactions (i.e., protophilic attack), which opens the possibility and the necessity to actively tune reactivity toward the desired path to maximize the formation of the targeted compound and to avoid unwanted side products (see Scheme 1).

Over the past decades, valuable insights have emerged from experimental\textsuperscript{[3]} and theoretical studies\textsuperscript{[14]} on the trends in S\textsubscript{N}2 and E2 reactivity, as well as the nature of the reactions’ potential energy surfaces.\textsuperscript{[20]} The direct competition between substitution and elimination pathways of anionic Lewis bases with alkyl substrates is a fundamental problem and the factors that influence this competition in solution have been studied extensively.\textsuperscript{[20b, 5, 6]} Recently, Wu et al.\textsuperscript{[17]} explored the competition between gas phase S\textsubscript{N}2 and E2 pathways for a range of anionic Lewis bases reacting with ethyl chloride. They consolidated our earlier finding that the unfavorably high activation strain, \(\Delta E^{\ddagger}\)\textsubscript{strain}, of the E2 pathway can be overruled by a strongly sta...
Nucleophilicity and leaving group ability in $S_2$ reactions have been related to various properties of $X$ (the nucleophile) and $Y$ (the leaving group), such as electronegativity, size, polarizability, and others. Nonetheless, the state of the art is to some extent still phenomenological. More recently, it was established that the height of $S_2$ reaction barriers is directly determined by the stability of the nucleophile’s ($X'$) highest occupied molecular orbital (HOMO) and by the strength of the substrate’s carbon–leaving group bond (C–Y): a higher electron-donating capability of the X–Y bond leads to a lower barrier and vice versa. The same relations were found by Shaik et al. by using the valence bond (VB) model, which predicted that the height of the $S_2$ barrier depends on the vertical ionization energy of the nucleophile ($E_{I(X)}$) minus the electron affinity of the C–Y bond ($E_{A(C-Y)}$).

Main trends in reactivity

Herein, we develop, based on quantum chemical analyses, a unified model that provides chemists with the tools to readily understand the duality of Lewis bases, that is their nucleophilic or protophilic character. To this end, we have explored and analyzed the potential energy surfaces along the reaction coordinates of the $S_2$ substitution, anti-$E_2$ elimination (E2-a), and syn-$E_2$ elimination (E2-s) reactions of $X' + C_2H_5Y$, with $X, Y = F, Cl, Br, I, At$, and by using relativistic density functional theory (DFT) at ZORA-OLYP/TZ2P. The $C_2H_5Y$ substrate allows us to probe the direct competition between $S_2$ and $E_2$, and our findings can be extended to any substrate where the acidic hydrogen and the leaving group are electronically coupled. In the first place, these explorations provide us with a consistent overview of reactivity trends over a wide range of reactivities and pathways. More importantly, analyses of these consistent reactivity data based on the activation strain model (ASM) of reactivity reveal the factors that determine the shape of the potential energy surfaces and hence govern the propensity of the Lewis base to act as a nucleophile or protophile, namely: (i) the “characteristic distortivity” of the substrate, which is associated with a particular reaction mechanism; (ii) the electron-donating capability of the Lewis base, which enters into an acid–base like interaction with the substrate; and (iii) the strength of the C–Y leaving group bond.

Results and Discussion

The results of our ZORA-OLYP/TZ2P computations on the $S_2$ and $E_2$ reactions in Scheme 1 are collected in Table 1, in Figure 1–Figure 8, and in the Supporting Information. Table 1 contains the energies of stationary points along the various reaction profiles relative to the energy of the infinitely separated reactants. Structural data of stationary points are shown in Figure 1 for the two representative reactions 1b and 2a; full structural data for all stationary points are provided in Figure S1 and Table S1 in the Supporting Information.

In most cases, the $S_2$ anti-$E_2$, and $syn-E_2$ model reactions proceed via a reactant complex (RC) and a transition state (TS) towards a product complex (PC), which may eventually dissociate into products (see Table 1 and Figure 1); exceptions are discussed later on. Schematic representations of such reaction profiles are shown in Figure 2a for an exothermic reaction. In the case of anti-$E_2$ elimination, the initial transition state (TS1) constitutes the actual elimination process and leads to an intermediate complex (INT) in which the conjugated acid forms an H–X complex with the newly formed ethylene and the leaving group $Y^-$ hydrogen binds to an ethylene C–H bond (see Figure 1 for selected structures and Figure 2b for a schematic anti-$E_2$ reaction profile). From here, migration of XH to the leaving group leads, via a second transition state (TS2), to the PC, $H_2C=CH^-\cdot Y\cdot X$, which, for our model reactions, is identical to that of $syn-E_2$ elimination. In all cases, TS1 is higher in energy than TS2 and, therefore, rate-determining for the
Table 1. Energies relative to reagents (in kcalmol⁻¹) of the stationary points occurring in S₂2, anti-E2, and syn-E2 reactions of X + CH₆Y[4c]

| X⁻  | species | F (d) | Cl (b) | Br (c) | I (d) | At (e) |
|-----|---------|-------|--------|--------|-------|--------|
| F  (1) | RC-a    | −20.0 | −23.3 |
|      | RC-s    | −15.2 | −16.5 |
|      | S₂-2TS  | −4.2  | −17.5 |
|      | E₂-a-TS₁| −8.0  | −23.3 |
|      | E₂-a-INT| −12.5 | −37.0 |
|      | E₂-a-TS₂| −12.3 | −36.7 |
|      | E₂-s-TS | −4.9  | −12.6 |
|      | E₂-PC   | −41.4 | −52.2 |
|      | S₂-2PC  | −20.0 | −46.6 |
|      | S₂-2P   | 0.0   | −38.3 |
|      | E₂-P    | 12.9  | −25.4 |
| Cl⁻ (2) | RC-a    | −8.4  | −9.7  |
|      | RC-s    | [a]   | [a]   |
|      | S₂-2TS  | 26.5  | 8.5   |
|      | E₂-a-TS₁| 46.0  | 21.4  |
|      | E₂-a-INT| 44.4  | [a]   |
|      | E₂-a-TS₂| 45.0  | [a]   |
|      | E₂-s-TS | 50.9  | 27.8  |
|      | E₂-PC   | −8.8  | −4.7  |
|      | S₂-2PC  | −0.1  | −8.2  |
|      | S₂-2P   | 48.4  | 10.1  |
|      | E₂-P    | 66.4  | 28.1  |
| I⁻ (4) | RC-a    | −5.5  | −6.4  |
|      | RC-s    | [a]   | [a]   |
|      | S₂-2TS  | 32.1  | 12.4  |
|      | E₂-a-TS₁| 54.5  | 31.1  |
|      | E₂-a-INT| 29.6  | 21.3  |
|      | E₂-a-TS₂| 45.0  | [a]   |
|      | E₂-s-TS | 35.0  | 27.6  |
|      | E₂-PC   | −4.9  | 0.3   |
|      | S₂-2PC  | 6.8   | −1.0  |
|      | S₂-2P   | 50.6  | 17.7  |
|      | E₂-P    | 75.4  | 37.1  |
| At⁻ (5) | RC-a    | −5.0  | −5.8  |
|      | RC-s    | [a]   | [a]   |
|      | S₂-2TS  | 33.6  | 13.0  |
|      | E₂-a-TS₁| 33.9  | 25.7  |
|      | E₂-a-INT| 32.4  | 24.0  |
|      | E₂-a-TS₂| 32.4  | 24.0  |
|      | E₂-s-TS | 28.9  | 23.0  |
|      | E₂-PC   | −3.2  | 2.0   |
|      | S₂-2PC  | 8.6   | 0.7   |
|      | S₂-2P   | 57.4  | 19.1  |
|      | E₂-P    | 77.2  | 38.9  |

[a] Computed at ZORA-OLYP/TZ2P (see Scheme 1 for designation of species). [b] Nonexistent: encounter of reactants induces S₂2 or E₂-a reaction without barrier. [c] Nonexistent: optimization yields RC-a. [d] No stationary point obtained due to an extremely shallow PES. [e] Nonexistent: expelled leaving group induced barrierless E₂ reaction.

overall anti-E2 pathway. The energetically favored products for both anti-E2 and syn-E2 pathways are C₅H₅-YH[X, that is, the olefin plus the leaving group, microsolvated by the conjugate acid. A number of clear and general trends in reactivity can be discerned. Reaction barriers always increase as the Lewis base X⁻ becomes less basic, along F⁻, Cl⁻, Br⁻, I⁻, and At⁻ (see Table 1). Note that in the gas phase, it is possible to have negative barriers with respect to the separate reactants, because under these conditions, in many cases, the nucleophile forms an encounter complex (sometimes referred to as an ion-dipole complex) with the substrate, which is stabilized by both electrostatic and donor–acceptor orbital interactions. Interestingly, reaction barriers rise more rapidly along this series for E₂ than for S₂2 reactions (note that TS₁ is rate-determining for all anti-E2 reactions). This trend can be found for all of the C₅H₅Y substrates. As a consequence, the preferred reaction pathway switches from anti-E2, in the cases where F⁻ attacks the substrate, to S₂2 for the heavier halide anions. For example, along F⁻, Cl⁻, Br⁻, I⁻, and At⁻ + C₅H₅Cl, the S₂2 reaction barrier (S₂-2TS in Table 1) moderately increases from −17.5 to +4.0, +8.5, +12.4, and +13.0 kcalmol⁻¹, respectively, whereas the anti-E2 barrier (E₂-a-TS₁ in Table 1) rises more steeply from −23.3 to +10.7, +21.4, +31.1, and +33.9 kcalmol⁻¹, respectively. Thus, although anti-E2 prevails for the more basic halide F⁻, with a reaction barrier that is 5.8 kcalmol⁻¹ lower than the S₂2 pathway, the S₂2 pathway dictates for all heavier, less basic, halides, with an anti-E2 barrier for At⁻ that is 20.9 kcalmol⁻¹ higher than the S₂2 pathway. This is in line with the work of Shai et al., who showed, with the use of valence bond (VB) theory, that strong Lewis bases prefer the E₂ pathway. The syn-E2 pathway is in all cases less reactive than anti-E2.

Our S₂2 barriers for X + C₅H₅Y are consistently a few kcalmol⁻¹ higher than the corresponding barriers for X + CH₃Y obtained at the same level of theory in an earlier study. For example, along F⁻, Cl⁻, Br⁻, and I⁻ + CH₃Cl, the S₂2 barrier increases comparatively moderately from −19.2 to −0.2, +4.1, and +7.9 kcalmol⁻¹. This is consistent with the slight increase of steric hindrance in the S₂2 reactions of C₅H₅X compared with those of CH₃X. On the other hand, reaction barriers decrease for both S₂2 and anti-E2 pathways as the leaving group Y in the substrate C₅H₅Y varies along F⁻, Cl⁻, Br⁻, and At⁻. Thus, along Cl⁻ + C₅H₅F, C₅H₅Cl, C₅H₅Br, C₅H₅I, and C₅H₅At, the S₂2 barrier (S₂-2TS in Table 1) decreases from +20.8 to +4.0, −1.6, −5.3, and −6.1 kcalmol⁻¹ whereas the anti-E2 barrier (E₂-TS₁ in Table 1) goes from +36.4 down to +10.7, +3.6, −1.3, and −2.4 kcalmol⁻¹. Our computations show that less basic halides, that is, those with a lower proton affinity, are both worse nucleophiles and worse protophiles, in the sense that they lead to higher barriers for substitution (nucleophilic attack) as well as for elimination (protophilic attack) reactions along the series F⁻ < Cl⁻ < Br⁻ < I⁻ < At⁻. Thus, if there were no competing E₂ channels, for example, in the aforementioned reaction systems X + CH₃Y, a stronger Lewis base is a better nucleophile. This is what we designate as “intrinsic nucleophilicity”. However, our computations also show that the lowering of reaction barriers for the protophilic attack benefits more from increasing the basicity than that for the nucleophilic attack. Thus, if the basicity becomes strong enough, the protophilic character

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of \( X \) prevails. In this situation of mechanistic competition, we speak about the “apparent nucleophilicity”. Note that weaker Lewis bases proceed with a reduced intrinsic nucleophilicity (i.e., higher \( S_{\text{p}2} \) barrier) but an enhanced apparent nucleophilicity (i.e., more favorable \( S_{\text{p}2} \) barrier compared with \( E_2 \) barrier). The origin of these trends is explained later on, on the basis of the activation strain model (ASM) of reactivity\(^{14c,10}\) and quantitative molecular orbital (MO) theory.\(^{15}\)

**Special features of particular reactions**

The prior discussed trends in \( S_{\text{p}2} \) versus \( E_2 \) reactivity hold for all reaction systems. But the precise shape of the PES differs in

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a few instances to the extent that the process becomes spontaneous, the reverse barrier disappears, or the product complex becomes labile and leads to a spontaneous follow-up reaction.

In the case of the rather exothermic reactions that occur between $F^-$ and $C_2H_xBr$, $C_2H_xI$, or $C_2H_xAt$, the barrier for the anti-E2 pathway disappears and $F^-$ spontaneously abstracts a $\beta$-proton from $C_2H_xX$ ($X = Br$, I, At) to form the product complex E2-a-PC, $C_2H_x-$YHX, without the occurrence of a stable reactant complex or transition state. The latter has become a shoulder on the PES along the reaction coordinate, as schematically depicted in Figure 2c. The barrier for the $S_2$ reaction has also disappeared for these reactants, which is in line with our previously obtained results for the $S_2$ reactions $F^- + CH_xBr$ and $CH_xI$. However, the steepest descent path upon the encounter of the $F^- + CH_xX$ reactants leads into the anti-E2 and not the $S_2$ channel.

The highly endothermic nucleophilic substitutions between $Br^-$, I$, and At$ $\cdot C_2H_xF$ have, by symmetry, no reverse barrier (see Figure 2d, red dotted curve). Interestingly, when following the three forward $S_2$ processes, we nevertheless do find saddle-points at 26.5, 32.1, and 33.6 kcal mol$^{-1}$, respectively (listed in Table 1, as $S_2$-TS). This transition state is achieved after the actual substitution stage, as the reaction systems begin to deviate from the actual $S_2$ path. What happens is that the emerging leaving group, $Y^-$, is a relatively strong Lewis base, which induces a barrier-free E2 elimination from the comparatively reactive $C_2H_xX$ molecule ($X = Br$, I, At) formed in the $S_2$ reaction (Scheme 2). This is schematically depicted in Figure 2d, blue curve. Successive $S_2$+$E_2$ multi-step reactions have also been observed by using mass spectrometric techniques in other reaction systems. Eventually, the same E2-a-F product, $C_2H_x-$FHX$^-$, is formed as in a direct E2 reaction between the original reactants. For example, in the case of $Br^- + C_2H_xF$, the $S_2$ pathway, with a barrier of only 26.5 kcal mol$^{-1}$, dominates the direct anti-E2 reaction, with a barrier of 46.0 kcal mol$^{-1}$. Yet, also the $S_2$ pathway leads, via a concerted $S_2$+$E_2$ mechanism, to the formation of $C_2H_x$ and $FHB^-\cdot$ and not $C_2H_xBr$ and $F^-$.

**Activation strain analyses**

The results of our activation strain analysis (ASA)$^{[4c,10]}$ for the representative $S_2$ and anti-E2 reactions of $X^-$ and $C_2H_xY$ ($X,Y = F,Cl$) are collected in Figure 3 and Figure 5 (see Figure S2 in the Supporting Information for all data). The activation strain model involves the decomposition of the electronic energy ($\Delta E$) into two distinct energy terms, namely, the strain energy ($\Delta E_{strain}$) and the interaction energy ($\Delta E_{int}$). The strain energy results from the deformation of the individual reactants and the interaction energy between the deformed reactants along the reaction coordinate, defined, in this case, as the stretch of the $\alpha$-carbon–leaving group ($C\equiv Y$) bond. This critical reaction coordinate undergoes a well-defined change during the reaction from the reactant complex via the transition state to the product and is shown to be a valid reaction coordinate for studying substitution reactions. Note that the syn-E2 pathway always goes with a higher reaction barrier than the anti-E2 pathway and, therefore, is excluded from this analysis. In Figure 3, we show how the nature of the Lewis base $X^-$ (left column) and the leaving group $Y$ (right column) influences the decomposition of the potential energy surface (PES) along the reaction coordinate ($z$), cf. Eq. (1), for the $S_2$ reaction (upper row) and anti-E2 reaction (lower row). The solid curves represent the PES ($\Delta E$), whereas the dashed and dotted curves represent the strain ($\Delta E_{strain}$) and interaction ($\Delta E_{int}$) energy, respectively. Panels (a) and (c) compare curves of $F^- + C_2H_xF$ (black) and $Cl^- + C_2H_xF$ (red) for $S_2$ and anti-E2 reactions, respectively, whereas panels (b) and (d) compare curves of $Cl^- + C_2H_xF$ (red) and $Cl^- + C_2H_xCl$ (blue) for $S_2$ and anti-E2 reactions, respectively. Note that the left and right columns share reaction 1a, that is, $Cl^- + C_2H_xF$. This series is representative for the observed effects induced by Lewis base and/or leaving group variations along the various model reactions. Figure 3a indicates that, in the $S_2$ reaction, a stronger nucleophile enhances, in agreement with its increased intrinsic nucleophilicity, the stabilizing interaction energy over the entire course of the reaction, whereas the strain energy is minimally affected. The reason for this more stabilizing interaction energy is the stability of the $X^-$ np atomic orbital (AO), which decreases along $At^-$, I$, Br^-$, $Cl^-$, and $F^-$ and reduces the corresponding HOMO–LUMO energy gap with the substrate (Figure 4)$^{[4i,17]}$. This effect can be explained by the size of the AOs of the nucleophile. $F^-$ has a less stable HOMO owing to the compactness of fluorine AOs, which experience more destabilizing coulombic repulsion between the electrons compared with the heavier and larger halides. A better leaving group, on the other hand, results in a weaker carbon–leaving group bond, that is, lower carbon–leaving group bond enthalpy$^{[19]}$ which manifests in less destabilizing strain energy, whereas the interaction energy is hardly affected by varying the leaving group (Figure 3b).

**Scheme 2.** Multi-step reaction found for highly endothermic nucleophilic substitutions.
Similar trends are observed for the E2 reaction. In Figure 3c, the variation of the protophile, the situation is slightly more complicated as a stronger protophile results in an earlier proton abstraction, that is, an earlier jump in interaction and strain energy, along the reaction coordinate. The interaction energy is largely influenced by the nature of the protophile, because a stronger protophile, due to its enhanced intrinsic nucleophilicity, results in a more stabilizing interaction and, therefore, a lower transition barrier (see above). Furthermore, the nature of the protophile affects the strain energy by abstracting the proton at different moments along the reaction coordinate, which can be seen as the different positions of the sudden jump in strain energy. The stronger the base, the earlier it abstracts the proton. Note that the strain energy around the reactant and product complexes (i.e., start and end of the activation strain diagram) are nearly consistent and hence not influenced by the nature of the protophile. In line with the S_N2 systems, a better leaving group reduces the strain curves, as a result of the prior discussed weaker carbon–leaving group bond, whereas the stabilizing interaction energy remains nearly unchanged (Figure 3d). Thus, a better Lewis base or leaving group results in both a lower S_N2 and E2 reaction barrier.

To directly analyze and compare the S_N2 and E2 pathways, Figure 5 shows four panels displaying the S_N2 and E2 pathways of the model reaction: F− + C_2H_5F (1a), F− + C_2H_5Cl (1b), Cl− + C_2H_5F (2a), and Cl− + C_2H_5Cl (2b). Going down a column, we
vary the Lewis base, and along a row, we change the nature of the leaving group. Note that, for all reactions, the strain and interaction energy curves for the E2 reaction display a profound difference compared to the S_N2 analog. As mentioned above, a sudden jump in strain and interaction energy is observed during the E2 reaction. This jump can be attributed to the proton abstraction by the Lewis base, which, in E2 reactions, acts as a protophile. The deprotonation of the substrate by the protophile requires a large deformation in the geometry of the substrate but also results in a more stabilizing interaction (see below).

The S_N2 pathway intrinsically has a less destabilizing strain energy than the E2 analog, because along the former reaction pathway only one bond (C-C) is being broken, while for the latter two bonds are being broken (C-C and C-H). Thus, the distortion, characteristic for the S_N2 pathway, is inherently lower than the E2 pathway. At the same time, the “characteristic distortivity” for both pathways also has direct implications on the electronic structure of the substrate. The LUMO of the substrate has antibonding character in the C-C and C-H bonds. The deformation along the S_N2 pathway (elongation of C-C) reduces the antibonding overlap for C-C, which, in turn, stabilizes the LUMO (see Figure 6). For the E2 reaction, this effect is more pronounced as the antibonding overlap of both the C-C and C-H bonds are being reduced. For the S_N2 pathway, this results in an intrinsically larger HOMO–LUMO gap than for the E2 pathway, and therefore a significantly less stabilizing interaction energy between the Lewis base and the substrate, regardless of the Lewis base.

Our activation strain analysis reveals that, similar to the strain energy, the interaction energy may also be translated into a simple concept, that is, it corresponds directly to the strength of the Lewis acid or base. A more basic Lewis base (higher-energy HOMO) interacts more strongly. In addition, a more acidic substrate (lower-energy LUMO) also interacts more strongly. Consequently, we propose the novel concept of effective acidity of the deformed substrate in the transition state, or “transition state acidity”. For an E2 pathway, the substrate in the transition state is more acidic (lower-energy LUMO), whereas in an S_N2 pathway it is less acidic (higher-energy LUMO). As a result, the E2 pathways will always dominate the S_N2 pathway in the limit of a strong interaction (more basic Lewis base), which we have observed for the reactions where X = F.

Changing the Lewis base from X = F to X = Cl has a profound effect on the preferred reaction pathway, shifting the preference from E2 for F (Figure 5a and b) to S_N2 for Cl (Figure 5c and d). As previously discussed, when going from F to Cl, both the C-C and C-H bond interactions decrease, which leads to a decrease in the stabilizing interaction energy between the Lewis base and the substrate.

**Figure 5.** Activation strain analysis of the differences between the PESs of S_N2 (red) and anti-E2 (blue) reactions of X+C_2H_5Y with X, Y = F, Cl. Trends down columns (a–c) or b–d) show how variation of the Lewis base influences the competition, whereas trends along rows (a–b or c–d) show the effect of leaving group variation. Solid lines correspond to the PES, dashed lines to the strain energy, and dotted lines to the interaction energy. Transition states are indicated with dots. Computed at ZORA-OLYP/TZ2P.
Cl− the basicity is reduced, which manifests in a less stabilizing interaction energy for both the $S_N2$ and $E2$ reaction pathways. This enhances the apparent nucleophilicity, because the $S_N2$ barrier becomes more favorable compared with the $E2$ barrier.

The weaker Lewis base Cl− has a lower-energy HOMO (Figure 4), resulting in a larger HOMO–LUMO gap and hence a weaker interaction with the substrate. Due to this weaker interaction, Cl− is unable to overcome the highly destabilizing characteristic distortivity that inextricably accompanies the $E2$ reaction.

On the other hand, substituting Y for a better leaving group, by going from $Y = F$ to $Y = Cl$, reduces the strain curves for the $S_N2$ and $E2$ pathway to a similar extent, making the strain a less important factor, whereas the interaction curves, which are always in favor of $E2$, remain essentially constant for both pathways. As predicted by our model, this has the effect of reducing the apparent nucleophilicity. Thus, the preference for the $E2$ pathway is further enhanced (e.g., from $F^- + C_2H_5F$ to $F^- + C_2H_5Cl$) or the preference for the $S_N2$ pathway is reduced (e.g., from $Cl^- + C_2H_5F$ to $Cl^- + C_2H_5Cl$); see also Table 1 and Figure 5. At last, we were able to extrapolate the strain and interaction curves of our model reactions to a simplified $S_N2$ and $E2$ limit (see Figure 7a). This plot clearly displays the interaction of the Lewis base with the acidic substrate to be the dominant effect that determines the propensity towards the $S_N2$ or $E2$ reaction pathway.

Our herein presented model also explains the effect of solvation on the $S_N2$ versus $E2$ competition. Solvation stabilizes the lone-pair electrons of a Lewis base and, thus, lowers the
HOMO of $X^-$ and reduces its electron-donating capability or basicity. As a response, the acid–base, that is, HOMO–LUMO interaction between the Lewis base and substrate goes from a stronger interaction, for example, in the case of $F^-$ (Figure 7c), to a weaker interaction (Figure 7d) and, hence, changes the preferred reaction pathway from E2 in the gas phase to $S_2$ in solution.\(^{3,4,6,11}\) In addition, also for weaker Lewis bases ($X = \text{Cl}^-, \text{Br}^-, I^-, \text{At}^-$), solvation will enhance the apparent nucleophilicity as it increases the E2 reaction barrier to a larger extent than the $S_2$ reaction barrier. These effects will be more pronounced when the polarity of the solvent increases.\(^{[21]}\)

### Evaluating the generality of the model

Next, we seek to test our proposed general model and have, therefore, studied the $S_2$/E2 competition of the following three, commonly used, Lewis bases $\text{H}_2\text{CHN}^-$, $\text{H}_2\text{CO}^-$, and $\text{H}_2\text{CS}^-$ with $\text{C}_2\text{H}_5\text{Cl}$.\(^{6,7,22}\) As previously discussed, strong Lewis bases will have a more favorable interaction with the substrate than weak Lewis bases and, therefore, the former will be able to overcome the characteristic high distortivity accompanied with the E2 reaction. Thus, based on the strength of the Lewis base, that is, the stability of the HOMO, one can predict the preferred reaction pathway. The energy of the HOMO of the three Lewis bases decreases from $\text{H}_2\text{CHN}^-$ ($E_{\text{HOMO}} = 3.3$ eV), to $\text{H}_2\text{CO}^-$ ($E_{\text{HOMO}} = 2.4$ eV), to $\text{H}_2\text{CS}^-$ ($E_{\text{HOMO}} = 1.7$ eV), which indicates that the Lewis base becomes increasingly weaker. This implies that the strong Lewis base $\text{H}_2\text{CHN}^-$ will be prone to undergo an E2 reaction and that the intrinsic nucleophilicity reduces along the series from $\text{H}_2\text{CHN}^-$, to $\text{H}_2\text{CO}^-$, to $\text{H}_2\text{CS}^-$. 

Table 2 displays the energies of the stationary points of the $S_2$ and E2 reaction between $\text{H}_2\text{CX}^-$ ($X = \text{HN}, \text{O}, \text{S}$) and $\text{C}_2\text{H}_5\text{Cl}$. As predicted, based on the stability of the HOMO of the Lewis base, $\text{H}_2\text{CHN}^-$ is the most reactive Lewis base, to the extent that both the $S_2$ and E2 reactions are barrierless. We note that the $S_2$ reaction occurs with a TS-like structure at $-13.7$ kcal mol$^{-1}$ but this is a shoulder on the reactions’ potential energy surface, as shown in Figure 2c, not a saddle point. Interestingly, even though $\text{H}_2\text{CO}^-$ is a moderate Lewis base, it is strong enough to result in a lower energy barrier for the E2 reaction compared to the $S_2$ reaction, $-12.1$ and $-9.2$ kcal mol$^{-1}$, respectively. Contrarily, the weakest Lewis base of the series, $\text{H}_2\text{CS}^-$, undergoes, not unexpectedly, an $S_2$ reaction, with a barrier that is $3$ kcal mol$^{-1}$ lower than the E2 reaction. Thus, changing the Lewis base from $\text{H}_2\text{CHN}^-$ to $\text{H}_2\text{CO}^-$ to $\text{H}_2\text{CS}^-$ reduces the intrinsic nucleophilicity, as the $S_2$ reaction barrier steadily increases, but enhances the apparent nucleophilicity, because the $S_2$ reaction barrier becomes consistently more favorable compared with the E2 barrier.

At last, we applied the activation strain model (ASM) of reactivity to examine if the behavior of the Lewis base, that is, nucleophilic or protophilic, is indeed determined by the Lewis acid–base-like interaction between the Lewis base and the substrate. In Figure 8, we focus on the $S_2$/E2 competition of $\text{H}_2\text{CO}^-$ and $\text{H}_2\text{CS}^-$, which prefer an E2 and $S_2$ reaction, respectively. It can clearly be seen that the more basic Lewis base $\text{H}_2\text{CO}^-$ interacts strongly with the more acidic E2 transition state, which, in turn, manifests in a more stabilizing interaction energy (Figure 8a). As a result, $\text{H}_2\text{CO}^-$ is able to overcome the highly destabilizing characteristic distortivity along the E2 pathway and hence making $\text{H}_2\text{CO}^-$ a protophile. On the other hand, $\text{H}_2\text{CS}^-$ is a weaker Lewis base and, for that reason, has a less stabilizing Lewis acid–base-like interaction with $\text{C}_2\text{H}_5\text{Cl}$, resulting in reaction barriers that are determined by the strain energy (Figure 8b). As the $S_2$ reaction occurs with less destabilizing strain energy, i.e., a lower characteristic distortivity, than the E2 pathway, $\text{H}_2\text{CO}^-$ will act as a nucleophile following the $S_2$ reaction. The herein presented results show that our proposed model is indeed general and can be used to elucidate the $S_2$/E2 competition of a plethora of Lewis bases.

### Conclusion

Bimolecular nucleophilic substitution ($S_2$; nucleophilic attack) and base-induced elimination (E2; protophilic attack) reactions are both accelerated when the electron-donating capability of the Lewis base increases, but the E2 pathway benefits more and therefore is favored in the case of stronger Lewis bases. Solvation, in general, stabilizes the HOMO, decreasing the electron-donating capability of the Lewis base and thus reduces the preference for E2 or enhances the preference for $S_2$ (enhanced apparent nucleophilicity), even though the barrier of the latter is also raised (reduced intrinsic nucleophilicity). These insights emerge from a detailed and consistent quantum chemical exploration of a vast range of archetypal model systems $X^- + \text{C}_2\text{H}_5\text{Y}$ ($X, Y = \text{F, Cl, Br, I, At}$) displaying a wide range in reactivity and pathways.

We highlight the main factors determining the shape of the potential energy surface, and hence the propensity of the Lewis base to act as a nucleophile or protophile, to be the structural deformation of the substrate during the course of the reaction in combination with the nature of the Lewis base and the nature of the leaving group. Each pathway is associated with a characteristic distortivity: high and associated with a more destabilizing strain for the E2 pathway, in which two bonds are broken ($\text{C}^-\equiv\text{Y}, \text{C}^-\equiv\text{H}$), versus, low and associated with a less destabilizing strain for the $S_2$ pathway, in which

### Table 2. Energies relative to reactants (in kcal mol$^{-1}$) of the stationary points occurring in $S_2$ and E2 of $\text{H}_2\text{CX}^- + \text{C}_2\text{H}_5\text{Cl}$ ($X = \text{HN}, \text{O}, \text{S}$).[a]

|        | $\text{H}_2\text{CHN}^-$ | $\text{H}_2\text{CO}^-$ | $\text{H}_2\text{CS}^-$ |
|--------|---------------------------|--------------------------|--------------------------|
| $R\text{C}$ | -13.1                     | -8.7                     |                           |
| $S_2\text{-TS}$ | -9.2                     | -1.8                     |                           |
| $E\text{2-TS}$ | -12.1                     | 1.5                      |                           |
| $S_2\text{-PC}$ | -77.4                     | -47.3                    | -34.1                    |
| $E\text{2-PC}$ | -66.4                     | -48.3                    | -21.9                    |
| $S_2\text{-P}$ | -88.0                     | -43.0                    | -25.1                    |
| $E\text{2-P}$ | -54.0                     | -29.7                    | -6.8                     |

[a] Computed at ZORA-OLYP/TZ2P. [b] Nonexistent; encounter of reactions induces $S_2$ and E2 reactions without barrier. [c] An IRC analyses reveals a shoulder along the $S_2$ potential energy surface at $-13.7$ kcal mol$^{-1}$, which is characterized by forming the new C$^-$–Y bond and breaking the old C$^-\equiv$Y.
only one bond is broken (C\textsubscript{2}–Y). At the same time, the LUMO of the substrate is C\textsubscript{2}–Y and C\textsubscript{2}–H antibonding and therefore assumes a lower orbital energy along the more distortive E2 pathway, rendering effectively a higher electron-accepting capability. We refer to this circumstance as the “transition state acidity” of the substrate, which is stronger for E2 than S\textsubscript{2}.

Thus, the Lewis acid–base-like interaction between the Lewis base and the substrate in the transition state determines the outcome of the competition: (i) in a regime of weak interaction, that is, if the Lewis base is weak, the strain determines the barrier and this factor is always more favorable, i.e., less destabilizing, for the less distortive pathway, S\textsubscript{2}; (ii) in a regime of strong interaction, that is, if the Lewis base is strong, the interaction overrules the strain and determines the barrier, and this factor is always more favorable, i.e., more stabilizing, for the more distortive pathway, E2. These findings show that the nucleophilic or protophilic behavior of a Lewis base towards a Lewis-acidic substrate is fundamentally co-determined by the latter.

The introduced concepts of “characteristic distortivity” and “transition state acidity”, together with the distinction between apparent and intrinsic nucleophilicity, provide a vital, qualitative approach for understanding organic reactions in the framework of both MO theory and Lewis’ theory of acids and bases.\textsuperscript{[15,20]} This approach rationalizes in a physically sound and intuitive manner why strong Lewis bases prefer the protophilic pathway, whereas weak Lewis bases behave as nucleophiles in S\textsubscript{2} reactions, and why (stronger) solvation pushes the mechanistic competition from E2 towards S\textsubscript{2}. The insights provided herein elucidate a plethora of experimental findings and can serve as powerful tools for a more rational design of synthetic routes. We envisage that the scope of our findings extends well beyond the competition between nucleophilic and protophilic reactivity.

**Figure 8.** Activation strain diagram of the difference in the PESs of the S\textsubscript{2} (red) and E2 (blue) reactions of (a) H\textsubscript{3}CO\textsuperscript{-} and (b) H\textsubscript{3}CS\textsuperscript{-} with C\textsubscript{2}H\textsubscript{5}Cl. Solid lines correspond to the PES, dashed lines to the strain energy, and dotted lines to the interaction energy. Transition states are indicated with dots. Computed at ZORA-DZVP/TZ2P.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** activation strain model, bond theory, density functional calculations, nucleophilicity, protophilicity

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