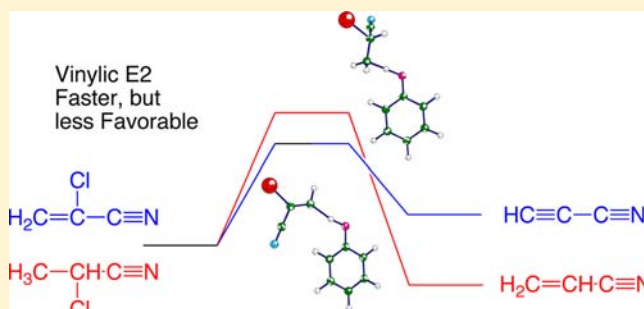# The Impact of Substituents on the Transition States of S$_N$2 and E2 Reactions in Aliphatic and Vinylic Systems: Remarkably Facile Vinylic Eliminations

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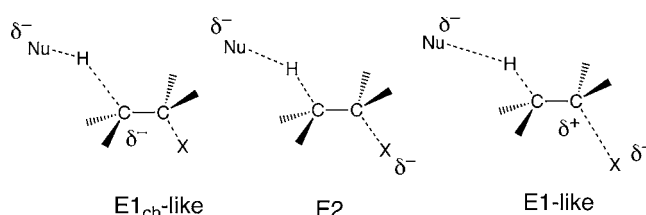
S *Supporting Information*

ABSTRACT: For a series of α and β substituted haloethanes and haloethenes, gas-phase experiments and computational modeling have been used to characterize their nucleophilic substitution and elimination reactions. Despite being less thermodynamically favorable, the vinylic eliminations have rate constants and computed barriers that are similar to those of analogous aliphatic eliminations. This is the result of the vinylic systems shifting to more E1$_{cb}$-like transition states and exploiting the inherent greater acidity of vinylic hydrogens. In general, the α-substituents have a greater impact on the S$_N$2 pathways and stabilize the transition states via field and polarizability effects. Substantial stabilization is also provided to the E2 transition states by the α-substituents, but they have surprisingly little impact on the geometries of the transition states of either pathway. The β-substituents generally lead to a strong bias toward elimination and greatly affect the synchronicity of the elimination (more E1$_{cb}$-like) as well as its location on the reaction coordinate (early). The experimental and computational data are in good accord, and the full data set provides a comprehensive picture of substituent effects on solvent-free S$_N$2 and E2 processes.
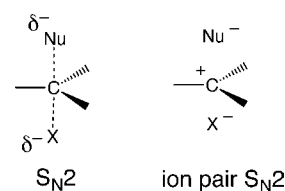
■ INTRODUCTION

Substitution and elimination reactions have proven to be excellent testing grounds for fundamental principles in physical organic chemistry.[1−5] A variety of substituent effects have been explored in these systems over a long period of time, and it is clear that the solvent can play a major role in determining both the sign and magnitude of substituent effects. For example, we previously have shown that β-halogen substituents enhance gas-phase S$_N$2 reactions whereas they are known to retard them in solution.[6] The difference in behavior can be attributed to subtle differences in the ionic structures of the transition states in the two media. As a part of this effort, mass spectrometric studies have revealed a wealth of mechanistic information about anionic S$_N$2 and E2 processes.[7−16] Here, we explore the impact of three general substituent types (phenyl, carbonyl, and cyano) at the α and β carbons of alkyl and vinyl halides undergoing S$_N$2 and E2 reactions in the gas phase. In this work, we investigate the interplay between energetic and geometric impacts. The transition states for these processes are known to be reasonably malleable, particularly the E2 reaction, where a spectrum of transition states from E1$_{cb}$-like to E1-like is available (Scheme 1).[2] Variations in the S$_N$2 transition states are also known and involve the introduction of S$_N$1 character, resulting in a transition state with ion pair properties (Scheme 2).[17] Key questions in the present study are how will the substituents at the α and β carbons shift the transition state geometries among these options, and will the extent of

Scheme 1. E2 Spectrum of Transition States

Scheme 2. S$_N$2 Transition State Variants

transition state distortion correlate with the amount of transition state stabilization. The data presented here also provide insight into the impact of unsaturation on E2 processes and highlight the ease of eliminations in vinylic halides. The experimental data was obtained in a quadrupole ion trap mass

spectrometer and are complemented by computational results on model systems.

■ METHODS

Mass Spectrometry. All experiments were completed in modified ThermoFinnigan LCQ or Deca quadrupole ion trap mass spectrometers equipped with electrospray ionization (ESI). Potassium salts of the dianion precursors to **1** and **2** were dissolved in HPLC-grade acetonitrile or methanol (10^{-4} to 10^{-5} M) and pumped through the electrospray interface at flow rates from 3 to 10 μL/min. Typical ESI conditions involved needle potentials from 3.5 to 4.5 kV and heated capillary temperatures from 125 to 200 °C. A notched waveform was applied to isolate the dianion in the ion trap. Once a steady signal was obtained, the neutral reagent was introduced into the helium system via a custom gas-handling system. The system has been described previously,[18,19] but a brief overview is given here. The liquid reagent was delivered to a measured flow of helium (1–2 L/min) by a syringe pump. With reagent flows of 30–300 μL/h, rapid evaporation occurs at the syringe needle to give mixing ratios of ~10^2 to 10^4 (He/reagent). For less volatile substrates, the mixing region was heated to 50–75 °C. Most of the gas mixture is diverted to an exhaust system, and ~0.25 mL/min is carried through the LCQ's restriction capillary to the ion trap to establish a helium pressure of $1.75 \pm 0.2 \times 10^{-3}$ Torr. At these pressures, the mean free path of the molecules is considerably longer than the dimensions of the trap and the loss of gases out of the end-cap holes of the trap can be treated as an effusion process. The lighter helium atoms effuse more quickly than the reagent molecules, and the mixing ratio must be corrected for differential effusion (square root of the mass ratio correction). The equation describing the reagent pressure (torr) is given below:

$$P_{RX} = (1.75 \times 10^{-3})F_{RX}d_{RX}/MW_{RX}/F_{He}(MW_{RX}/MW_{He})^{1/2} \quad (1)$$

where F_{RX} is the reagent flow rate (liquid, mL/min), d_{RX} is the reagent density, MW_{RX} is the reagent molecular weight, F_{He} is the helium flow rate (gas, mol/min), and MW_{He} is the atomic weight of He. Typical reagent pressures were between 10^{-5} and 10^{-7} Torr. The system is routinely calibrated against the known rate constants of Br$^-$ with iodomethane or $CF_3CF_2CH_2O^-$ with bromoethane.[16]

Once an appropriate flow of the neutral reagent was established, the system was given several minutes for the reagent pressure to equilibrate to a steady state. Kinetic measurements were completed by varying the time delay between dianion isolation and the expulsion of all ions to obtain a mass spectrum. During the delay time, the dianion was held in the trap with a q_z value of 0.5 to ensure that the expected products would experience stable trapping fields. In most cases, nine different time delays were used in each run. Time delays and reagent flows were adjusted to obtain plots that covered two to three half-lives of the reactant ion. Reported rate constants are the average of at least six kinetic runs using at least three different reagent flow rates and were obtained on at least two different days. Kinetic plots showed good linearity and gave correlation coefficients (r^2) greater than 0.98. Other work from our laboratory indicates that the ion trap provides an environment that is effectively at ambient temperature (~300 K).[20] No evidence for secondary reactions was observed, and the product distributions varied little as a function of reaction extent. Product ratios were not corrected for mass discrimination, which is expected to be modest in the mass ranges evaluated in the study.

All the neutral reagents were obtained in the highest purity commercially available and used without further purification aside from an extraction to remove any traces of acid in the samples. Just before use, the neutral reagents were added to an aqueous $NaHCO_3$, the mixture was shaken, and the organic layer was removed and then used for the mass spectrometric studies. In some cases the reagent was diluted with cyclohexane or toluene. The cyclohexane or toluene (and any trace H_2O) has no effect on the experiment, and appropriate dilution factors were used in the analysis of the kinetic data.
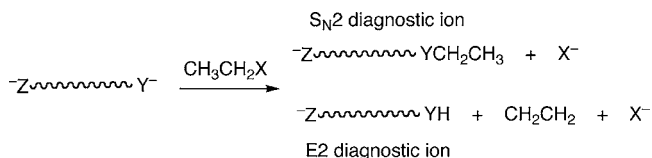
Computational. Calculations were completed with the GAUS-SIAN03[21] quantum mechanical package. Geometries were initially optimized at the HF/6-31+G* level, and frequency calculations were also completed at this level. All of the species in the study exhibited the proper number of imaginary frequencies. In addition, optimizations were completed at the MP2/6-31+G(d) level. Energies reported in the text are at the MP2/6-311+G(d,p) level corrected for zero-point vibrational energies (ZPE, scaled by 0.9135).[22] Given that the computational work on the model systems is to provide qualitative comparisons to the experiments, no thermal corrections were made. Multiple rotamers were considered, and data for only the most stable ones are listed in the tables. For the E2 reactions, only anti orientations were considered because there is ample evidence that they are preferred in the gas phase eliminations of simple halides.[23−25]
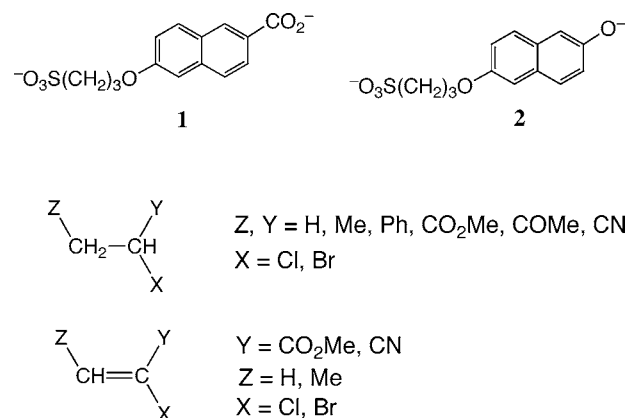
■ RESULTS AND DISCUSSION

Reaction Systems. For these studies, we have applied an approach based on dianion nucleophiles.[9] The rationale for using dianions is that, with singly charged nucleophiles, the only charged product is the leaving group, which is the same for S_N2 and E2 processes. By introducing a second, inert anionic site on the nucleophile, diagnostic, charged products are formed (Scheme 3). Specifically, an alkylated dianion is formed

Scheme 3. Dianion Strategy in S_N2/E2 Competition

in the S_N2 channel and the protonated dianion in the E2 channel. The dianions used in this study are shown in Scheme 4. Both employ the same backbone and only differ in the

Scheme 4. Reaction Systems

nucleophilic site, a carboxylate in dianion **1** and a 2-naphthoxide in dianion **2**. The inert anionic site in each case is a sulfonate. Electrostatic repulsion in the dianions greatly increases their gas phase proton affinity, but we have shown in the past that only a small portion of this energy is available at the transition state of an S_N2 reaction, so they behave much like singly charged analogues.[26] Dianion **2** is somewhat more basic than **1**, and its proton affinity is calculated to be 9 kcal/mol greater than that of the carboxylate (376 vs 367 kcal/mol) at the MP2/6-31+G(d,p)//MP2/6-31+G(p) level. For comparison, 2-naphthoxide and benzoate have experimental proton affinities of 344 and 340 kcal/mol, respectively (342 and 339 kcal/mol at the MP2/6-31+G(d,p)//MP2/6-31+G(p) level).[27]

This suggests about 30 kcal/mol of electrostatic repulsion in the dianions and is consistent with the expected charge separations (computed to be 13−14 Å from the carboxylate oxygens to the sulfonate oxygens in **1** and ~13 Å from the naphthoxide oxygen to the sulfonate oxygens in **2**).[28] In Scheme 4, the neutral halides are also shown. The leaving groups, Cl⁻ and Br⁻, have experimental proton affinities of 333 and 323 kcal/mol, a difference similar to the calculated difference in the proton affinities of **1** and **2**.[27] As a result, the combination of dianion **1** with the bromides and of dianion **2** with the chlorides will have very similar reaction energies in the E2 processes. In S_N2 reactions, a similar situation is anticipated though some modest variation in the alkyl group affinities of the dianions/leaving groups is expected.

α-Substituents. S_N2 *Reactions in α-Substituted Aliphatic Systems.* The data for the substituents at the α-position are given in Tables 1 and 2. The former pairs the weaker

Table 1. Rate Constants for Dianion 1 with α-Substituted Bromoethanes[a]

substituent	k	$k(S_N2)$[b]	S_N2 barrier	$k(E2)$[b]	E2 barrier	$\%S_N2$
Me	NR[c]		2.1		6.9	
Ph	0.5	0.45	−4.6	0.05	0.2	90
CO₂Me	9.7	9.7	−5.7		1.6	100
CN	34	24	−7.6	10	−2.1	71

[a]Rate constants in units of 10^{-10} cm³ molecule⁻¹ s⁻¹ and computed barriers in kcal/mol. [b]Partial rate constants for each reaction channel. [c]Reaction too slow to characterize, $<1 \times 10^{-12}$ cm³ molecule⁻¹ s⁻¹.

Table 2. Rate Constants for Dianion 2 with α-Substituted Chloroethanes[a]

substituent	k	$k(S_N2)$[b]	S_N2 barrier	$k(E2)$[b]	E2 barrier	$\%S_N2$
Me	NR[c]		6.7		7.4	
Ph	NR[c]		−3		0.2	
CO₂Me	0.43	0.37	−4.6	0.06	−0.8	86
CN	6.9	0.6	−4.3	6.3	−2.7	9
COMe	10.4	5.7	−7.6	4.7	−1.7	54

[a]Rate constants in units of 10^{-10} cm³ molecule⁻¹ s⁻¹ and computed barriers in kcal/mol. [b]Partial rate constants for each reaction channel. [c]Reaction too slow to characterize, $<1 \times 10^{-12}$ cm³ molecule⁻¹ s⁻¹.

nucleophile (**1**) with the better leaving group (Br⁻), and the latter pairs the better nucleophile (**2**) with the poorer leaving group (Cl⁻). The alternative pairings generally lead to reactions that are too fast (collision-controlled rate[29,30]) or too slow to obtain useful data. In the S_N2 reactions, both reaction systems show an increase in the experimental rate constant along the series CH₃ < Ph < CO₂Me < CN < COMe (Cl system only). The least reactive system, CH₃, gave rates too slow to be characterized in our system ($<1 \times 10^{-12}$ cm³ molecule⁻¹ s⁻¹). This pattern is in good accord with early, condensed-phase data.[31−33] Although the exothermicities of the comparable reactions in Tables 1 and 2 are estimated to be roughly similar, the combination of dianion **1** with the bromides gives significantly higher reaction rate constants. This is anticipated because some of the enhanced basicity of **2** is a result of greater internal electrostatic repulsion in the dianion, which we have shown is only partially available at the transition state of an S_N2 reaction.[26] With 3-chloro-2-butanone, there is evidence of proton transfer to give an enolate (<5% yield).[34] It is not possible to experimentally differentiate between the possible

enolates (carbon 1 or carbon 3), and computations at the MP2/6-31+G(d,p)//MP2/6-31+G(d) level indicate almost no difference in the acidity of these sites (359.1 and 359.2 kcal/mol, respectively). The appearance of the enolate is driven by the release of substantial Coulomb energy because singly charged 2-naphthoxide (PA = 344 kcal/mol)[27] is not nearly basic enough to deprotonate 3-chloro-2-butanone.

We have completed MP2/6-31+G(d,p)//MP2/6-31+G(d) calculations on the reactions of benzoate and phenoxide, as models for **1** and **2**, respectively, with the substituted alkyl halides (the actual dianions are too large for effective computational modeling). The computational barriers in Tables 1 and 2 are in accord with the experimental results but suggest that, in the alkyl chlorides, CO₂Me should be a slightly better activating group than CN. Overall, the impact of these α-substituents on the S_N2 channels is significant, and they provide rate enhancements of over 1000-fold and computed transition state stabilizations from 6 to 14 kcal/mol relative to an α-methyl group. In the case of α-bromopropionitrile, the rate is at or near the collision-controlled limit.[29] These results are not unexpected and parallel existing data in the gas phase and the condensed phase for these substituents.[6,31−33] It is noteworthy that the largest impact is for the polar, electron-withdrawing groups (CO₂Me, CN, and COMe) where the substituent's dipole likely plays a major role in stabilizing the anionic transition state. In the α-position, the highly polarizable phenyl group has a smaller impact. The effect of the substituents on the transition state geometries can be seen in the data in Tables 3 and 4. Two conclusions are evident. First, the transition states

Table 3. Geometric Parameters for the Reactions of Benzoate with α-Substituted Bromoethanes[a]

	S_N2		E2		
substituent	C−O	C−Br	O−H	C−H	C−Br
Me	2.076	2.513	1.245	1.412	2.534
Ph	2.043	2.491	1.222	1.431	2.467
CO₂Me	2.012	2.429	1.23	1.424	2.377
CN	2.008	2.45	1.239	1.401	2.320

[a]Distances in Å.

Table 4. Geometric Parameters for the Reactions of Phenoxide with α-Substituted Chloroethanes[a]

	S_N2		E2		
substituent	C−O	C−Cl	O−H	C−H	C−Cl
Me	2.084	2.356	1.198	1.463	2.213
Ph	2.086	2.336	1.205	1.448	2.184
CO₂Me	2.011	2.289	1.202	1.459	2.089
CN	2.031	2.274	1.203	1.441	2.067
COMe	2.015	2.354	1.218	1.419	2.112

[a]Distances in Å.

are only mildly perturbed by the substituents despite the large energetic stabilizations. For example, distances to the nucleophile and leaving group in the S_N2 transition states vary by less 0.07 Å across the series of substrates. This suggests that the interaction of the substituent with the reaction center is more likely through dipole and polarizability interactions rather than direct orbital interactions with the reaction center. Second, the strong electron-withdrawing groups (EWGs) lead to more compact transition states with shorter distances to the

nucleophile and leaving group. This is not related to reduced crowding in the transition state because compaction is also seen relative to the reaction of an unsubstituted ethyl halide system (data in Supporting Information). The net effect of compacting the transition state is to slightly increase the localization of charge near the substituent group as well as reduce the contribution of an ion pair resonance descriptor for the transition state (Scheme 2). This is a reasonable response and minimizes the unfavorable interactions of the electron-withdrawing group with the α-carbon. As expected, compaction of the TS is not appreciable with the phenyl substituent, where polar effects are less important.

E2 Reactions in α-Substituted Aliphatic Systems. The α-substituents have a slightly different impact on the E2 reactions (Tables 1 and 2). All of them are computed to be stabilizing relative to a methyl group, but the pattern shifts, with the CO_2Me group providing slightly less stabilization than a phenyl group in the bromo system and slightly more in the chloro system. In addition, the COMe group is less activating than the CN group in the E2 reaction. Like the S_N2 reactions, the substituents provide significant stabilization (5.3−10.1 kcal/mol) relative to a methyl group. Despite the stabilization of the E2 transition states by these groups, the partial rate constants for this pathway remain relatively low in most of the systems. Here, the E2 reaction of the methyl-substituted system has a high barrier relative to the S_N2 path and only the CN and COMe groups activate the E2 path enough to allow for competition with the S_N2 path. Brauman and co-workers have looked at the competition between substitution and elimination in the reaction of cyanide with 2-chloropropionitirile.[35] They estimated about a 7% yield in the S_N2 channel, which matches closely our value with dianion **2**. As in the S_N2 reactions, the impact on the E2 transition state geometries is small, with the greatest change occurring in the C−X bonds (Tables 3 and 4). It appears that leaving group departure is slightly delayed with the strong electron-withdrawing groups, likely because it limits the development of carbocation character at the α-carbon (i.e., E1-character; see Scheme 1). Despite the known plasticity of E2 transition states and the significant stabilizations found in these systems, there is surprisingly little variation across this series with respect to the E1 => E2 => E1$_{cb}$ spectrum of transition states. Again, the substituents appear to act mainly via through-space interactions with little perturbation of the transition state geometry.

When comparing the E2 data with the S_N2 data, it is clear that a different correlation is observed between the observed rate constants and the computed barriers. Although there is insufficient data for a quantitative analysis, the plot in Figure 1 highlights the differences qualitatively. If we arbitrarily set a threshold of 1×10^{-10} cm^3 molecule^{-1} s^{-1} as the transition point from a slow to fast reaction (∼5% efficiency), the S_N2 reactions for the α-substituents cross this threshold with a computed barrier of roughly −5 kcal/mol, whereas the E2 reactions cross this threshold with a computed barrier of roughly −1.5 kcal/mo1. This suggests that the known entropic bottleneck in S_N2 reactions[7,36] amounts to approximately a 3 kcal/mol disadvantage to the reaction from the $T\Delta S^{\ddagger}$ term (computed barrier correlates with $\Delta H^{\ddagger}$) in these systems.[37]

Cyclic Systems. With the carbonyl substituent, we also briefly examined the impact of a cyclic carbon framework on the S_N2 and E2 pathways. With 2-chlorocyclopentanone and 2-chlorocyclohexanone, substitution is not observed. The rate constants with dianion **2** are 4.3 and 3.0 × 10^{-9} cm^3 molecule^{-1}

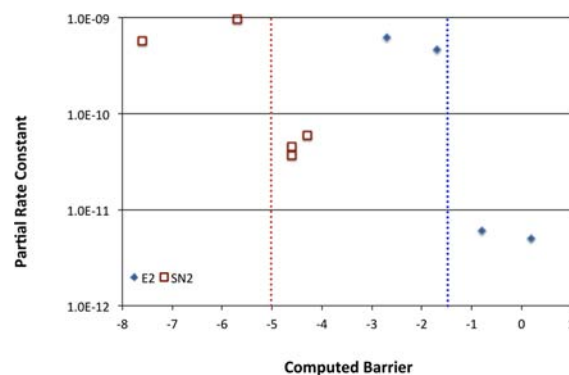**Figure 1.** Partial rate constants (cm^3 molecule^{-1} s^{-1}) plotted vs computed barriers (kcal/mol) for reactions in Tables 1 and 2. Only systems with measurable rate constants are plotted. Vertical red and blue lines are guides that separate S_N2 and E2 rate constants, respectively, that are greater than or less than 1 × 10^{-10} cm^3 molecule^{-1} s^{-1}.

s^{-1}, respectively. These rate constants are 3−4 times larger than that observed in the acyclic analogue, 3-chloro-2-butanone (Table 2) and are close to the expected collision rate. The computed data for these reactions indicate that the major impact of cyclization is in the E2 transition states, which are stabilized by 4.2 and 3.9 kcal/mol, respectively, relative to the acyclic system, whereas the S_N2 transition states are destabilized by 1.4 and 2.6 kcal/mol, respectively. There are four driving forces at play here. First, the cyclic systems have a CH$_2$ at the β-carbon, which should activate the E2 pathway. This effect amounts to 2.3 kcal/mol of stabilization for the E2 pathway of 1-chloropropane compared to chloroethane with phenoxide. Second, the ring systems favor conformations that are well-suited for eliminations. For example, the unactivated ring systems, chlorocyclopentane and chlorocyclohexane, give E2 activation energies with phenoxide that are 2 kcal/mol smaller than that of 1-choropropane.[38] Third, the preferred S_N2 pathway in 3-chloro-2-butanone involves an anti conformation for the carbon backbone. This is not possible in the ring systems and provides about 2 kcal/mol of stabilization to the acyclic system (relative to 3-chloro-2-butanone locked in a syn conformation from start to finish). Fourth, the cyclohexyl structure leads to a sterically crowded pathway for the backside attack of the S_N2 process. This has been observed computationally in the past,[25] and the present calculations put the S_N2 barrier for phenoxide with unactivated chlorocyclohexane at 2.4 kcal/mol above that of chlorocyclopentane. All combined, this leads to unusually low barriers for the E2 reactions in the cyclic systems and a strong bias against S_N2 reactions. As with the acyclic ketone, proton transfer is also seen here. The 2-chlorocyclopentanone and 2-cholorocyclohexanone systems give proton transfer yields of 25% and 15%, respectively. In the 5-membered ring, computations indicate that deprotonation is favored at carbon 2 (PA of 355.9 vs 356.8 kcal/mol), whereas, in the 6-membered ring, it is favored at carbon 6 (PA of 357.0 vs 360.0 kcal/mol). The slightly lower PA found in 2-cyclopentanone is consistent with the slightly higher enolate yield.

Vinylic Systems. Eliminations of vinylic halides are well-known and have been studied in the gas phase,[39−41] but the overall energetics of the processes are less favorable than those in aliphatic systems by approximately 10 kcal/mol. This poses a problem with our dianions because the inherent basicity of the

nucleophilic center is insufficient to produce an exothermic elimination process. For example, the reaction of 2-naphthoxide with Z-1-bromopropene to give propyne is endothermic by approximately 5 kcal/mol. The corresponding reaction of a vinylic chloride is endothermic by nearly 15 kcal/mol. For these reactions to occur in our system, they must take advantage of the release of Coulomb energy that results from the conversion from a dianion to two monoanions. Although Z-1-chloropropene fails to react with dianion **2**, an activated system, 2-chloroacrylonitrile does and produces exclusively elimination products at near the collision-controlled limit. Despite the inherent endothermicity of the elimination process, the release of Coulomb energy efficiently drives this process and taps into much of the potential thermodynamic basicity of the dianion (~30 kcal/mol). With bromide as the leaving group, even an unactivated substrate, Z-1-bromopropene, gives a slow elimination reaction with dianion **2** (2.4×10^{-11} cm^3 molecule^{-1} s^{-1}). As expected given the preference for anti eliminations, E-1-bromopropene does not give an elimination at a measurable rate. With the addition of an electron-withdrawing group at the α-position (CO$_2$Me), the rate for the vinylic bromide jumps to 5.5×10^{-10} cm^3 molecule^{-1} s^{-1}, nearly the same rate as the E2 pathway of dianion **2** with methyl 2-bromopropanoate, the aliphatic analogue (5.3×10^{-10} cm^3 molecule^{-1} s^{-1}). In none of the vinylic halide reactions was there any evidence of a substitution pathway. Computational data are consistent with the rate constants, and barriers of −0.7, −3.9, and −7.2 kcal/mol are estimated for the reactions of phenoxide with Z-1-bromopropene, methyl 2-bromoacrylate, and 2-chloroacrylonitrile, respectively. The remarkable aspect of the results is that despite being much less favorable thermodynamically, the barriers of these reactions are similar to those of aliphatic analogues reacting with phenoxide: 1-bromopropane (−1.4 kcal/mol), methyl 2-bromopropanoate (−4.4 kcal/mol), and 2-chloropropionitrile (−2.7 kcal/mol). The 2-chloroacrylonitrile system stands out in that the vinylic barrier is much lower than that of the aliphatic system. The vinylic systems offer more acidic hydrogens and, therefore, aid the proton transfer component of the process.[42,43] For example, the computed acidity (ΔH_{acid}) of acrylonitrile at the β-position (386 kcal/mol) is 15 kcal/mol lower than that of the β-position of propionitrile (401 kcal/mol)—in the alkene, deprotonation is computed as cis to the cyano group, which corresponds to the location in the elimination process. This effect is much smaller with an ester, and the β-position of methyl acrylate has a computed ΔH_{acid} of 396 kcal/mol. On the other hand, the vinylic systems are disfavored, as the leaving group is expelled and an alkyne rather than an alkene is formed. By shifting to an E1$_{cb}$-like pathway, the reactions exploit the advantage of the more acidic hydrogen and minimize the impact of alkyne formation. This is illustrated in Figure 2. With 2-chloroacrylonitrile, the C$_\beta$-H distance in the proton transfer is stretched to 1.635 Å and the O−H distance is only 1.085 Å in the transition state with phenoxide. The corresponding distances in 2-chloropropionitrile, which gives a more synchronized E2 reaction, are 1.441 Å and 1.203 Å. In fact, the transition state involving 2-chloroacrylonitrile has a more advanced proton transfer component and greater degree of E1$_{cb}$ character than any of the aliphatic phenoxide/chloride systems with strong electron-withdrawing groups at the β-carbon that we have studied (cyano or ester; see Tables 7 and 8 below). It does not appear that the ease of vinylic eliminations has been highlighted to this extent in the past, and previous gas-phase work has not
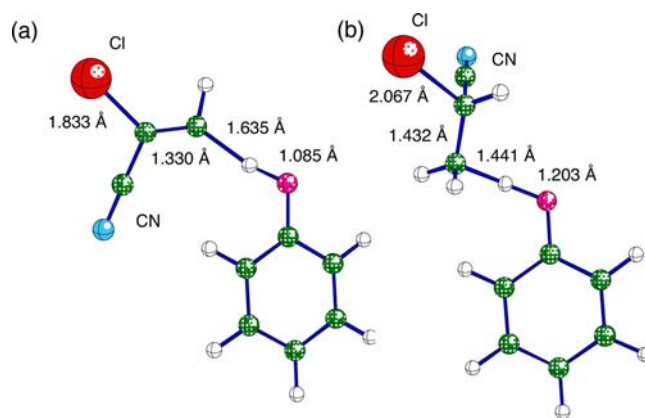

Figure 2. MP2/6-31+G(d) geometries of the transition states for the reactions of phenoxide with (a) 2-choroacrylonitrile and (b) 2-chloropropionitrile.

provided rate data that would expose the unusually high kinetic reactivity of the vinylic halides toward elimination (relative to aliphatic analogues).[39–41]

β-Substituents. S$_N$2 Reactions in β-Substituted Aliphatic Systems. Data for the β-substituted systems are given in Tables 5−8. Here, the methoxy substituent was included with

Table 5. Rate Constants for Dianion 1 with β-Substituted Bromoethanes[a]

substituent	k	k(S$_N$2)[b]	S$_N$2 barrier	k(E2)[b]	E2 barrier	%S$_N$2
Me	0.15	0.15	−2.1	0	4.6	100
Ph	8	3.2	−8.3	4.8	−5.7	40
CO$_2$Me	53		−5	53	−8.6	0
CN	[d]		−8.1		−11.4	

[a]Rate constants in units of 10^{-10} cm^3 molecule^{-1} s^{-1} and computed barriers in kcal/mol. [b]Partial rate constants for each reaction channel. [c]Reaction too slow to characterize, $<1 \times 10^{-12}$ cm^3 molecule^{-1} s^{-1}. [d]Reaction not studied experimentally.

Table 6. Rate Constants for Dianion 2 with β-Substituted Chloroethanes.[a]

substituent	k	k(S$_N$2)[b]	S$_N$2 barrier	k(E2)[b]	E2 barrier	%S$_N$2
Me	NR[c]		4.5		6	
Ph	6.9		−0.4	6.9	−6.4	0
CO$_2$Me	50		−1.8	50	−12.6	0
CN	50		−2.5	50	−15.4	0
OMe	0.06		4.6	0.06	3.9	0

[a]Rate constants in units of 10^{-10} cm^3 molecule^{-1} s^{-1} and computed barriers in kcal/mol. [b]Partial rate constants for each reaction channel. [c]Reaction too slow to characterize, $<1 \times 10^{-12}$ cm^3 molecule^{-1} s^{-1}.

Table 7. Geometric Parameters for the Reactions of Benzoate with β-Substituted Bromoethanes[a]

substituent	S$_N$2		E2		
	C−O	C−Br	O−H	C−H	C−Br
Me	2.026	2.449	1.238	1.424	2.445
Ph	2.026	2.426	1.176	1.494	2.237
CO$_2$CH$_3$	2.021	2.420	1.084	1.666	2.153
CN	1.993	2.412	1.080	1.675	2.193

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[a]Distances in Å. Calculations at MP2/6-31+G(d) level.

Table 8. Geometric Parameters for the Reactions of Phenoxide with β-Substituted Chloroethanes[a]

substituent	S_N2		E2		
	C−O	C−Cl	O−H	C−H	C−Cl
Me	2.024	2.288	1.214	1.439	2.179
Ph	2.031	2.273	1.173	1.489	1.940
CO_2Me	2.013	2.277	1.206	1.440	1.867
CN	1.996	2.247	1.166	1.489	1.877
OMe	2.015	2.263	1.163	1.517	2.107

[a]Distances in Å. Calculations at the MP2/6-31+G(d) level.

nucleophile **2**. Experimentally, these systems present a simpler picture because the substituents bias the reactions toward elimination. Only two substrates, 1-bromopropane and 2-phenethyl bromide, give an S_N2 product with nucleophile **1**, and none of them do with nucleophile **2**. As a result, the S_N2 rate information is very limited in this series. The computed barriers indicate that, at the β-carbon, the substituents provide considerably less stabilization to S_N2 transition states. The stabilizations vary from 2.0 to 7.0 kcal/mol (relative to Me) whereas they were in the 6−12 kcal/mol range in the α-series (OMe actually destabilizes the S_N2 transition state by 0.1 kcal/mol). Obviously the longer distance between the substituent and the reaction center is a key explanation for the attenuation of the substituent effects. Craig and Brauman have examined the reactions of chloride with chloroacetonitrile and 3-chloropropionitrile.[44] As in the present study, they found that the cyano group was more effective at the α-position in activating the S_N2 reaction. The result with methoxy is interesting and points to the delicate balance between the inductive effects of electron-withdrawing groups that can destabilize the transition state and field effects that should stabilize it. In this case, they almost perfectly cancel. The relative impacts of the substituents are slightly more complicated at the β-position because they are able to engage in direct interactions with the nucleophile. As a result, the two reaction systems do not produce the same order of reactivity for the substituents. This is most evident in the relative stabilizations provided by the phenyl and ester groups, which are sensitive to the nature of the nucleophile. The phenyl group is more effective in stabilizing the S_N2 transition state in the benzoate/bromide system, and the ester is more effective in the phenoxide/chloride system. Examination of the transition states reveals that these combinations allow for stacking-type interactions with the phenyl group of the nucleophile— interactions that are not possible with the alternative nucleophile. In Figure 3a, the phenyl of the benzoate is capable of a favorable interaction with the phenyl substituent of the substrate. With phenoxide as the nucleophile, the bond angles do not allow for this interaction. In contrast, the phenoxide's ring is well placed to interact with the ester substituent of the methyl haloacetates (Figure 3b). In this case, preferred bond angles prevent the benzoate from a similar interaction with the ester substituent. These interactions do not appear to be particularly strong but are sufficient to switch the order of reactivity in the two series. The electron-withdrawing groups at the β-position also lead to compaction of the transition state, but the effect is much more subtle than with the α-substituents and amounts to only a few hundredths of an angstrom in the forming/breaking bonds (Tables 7 and 8).

E2 Reactions in β-Substituted Aliphatic Systems. The situation in the E2 reactions is much different, and as expected,
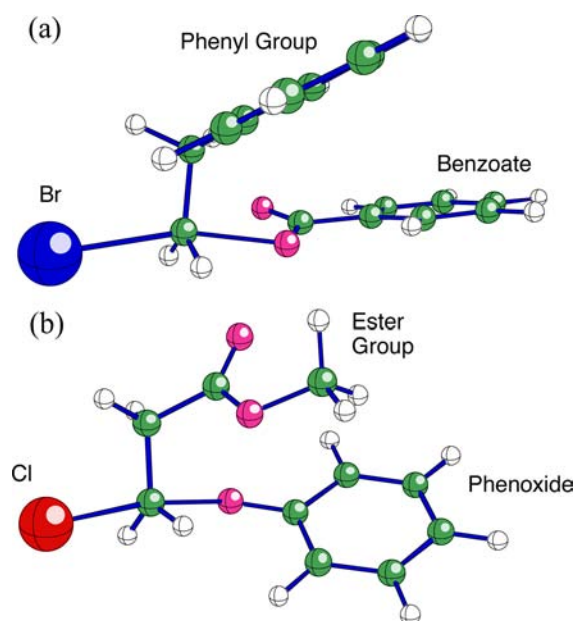

Figure 3. MP2/6-31+G(d) geometries of the transition states for the reactions of (a) benzoate with 1-bromo-2-phenylethane and (b) phenoxide with methyl 3-chloropropanoate.

the β-substituents have a very large impact on the reaction rate constants, transition state energies, and geometries. The E2 rate constants build along the following series: Me < OMe < Ph < Cl < CO_2Me ~ CN. The ester and cyano groups both lead to reactions at roughly the collision-controlled rate.[29] As noted above, the S_N2 channel is competitive in only two reaction pairings. The calculated transition state energies in the model systems are consistent with this result, as are previous calculations by Chung and co-workers.[45] Excluding MeO, the substituents stabilize the E2 transition states by 10−20 kcal/mol relative to a methyl group, leading to situations where the E2 path is favored by as much as 13 kcal/mol over the S_N2 path. The β-substituents provide considerably more stabilization in the E2 reactions of the phenoxide/alkyl chloride system, and there is a strong shift in the transition state energies toward eliminations with this nucleophile/leaving group combination. The greater impact of the β-substituent in the phenoxide/alkyl chloride systems is not a surprise because one expects more $E1_{cb}$-character and greater charge development at the β-carbon with the combination of a stronger base and a weaker leaving group (see below). The geometric impacts of the β-substituents on E2 transition states are very significant, particularly in the benzoate/alkyl bromide systems. As anticipated, the charge-stabilizing groups at the β-carbon push the reactions toward $E1_{cb}$-like pathways. This is particularly clear in the proton transfer component of the reaction, and unusually long $C\beta−H_\beta$ and short $O−H_\beta$ distances are seen in the transition states with the ester and cyano substituents. In the benzoate/alkyl bromide system, the $C_\beta−H_\beta$ distance stretches from 1.42 Å to 1.67 Å in the shift from a methyl to an ester substituent. Shortening of the $C_\alpha−Br$ bond is also observed in the activated transition states (2.44 Å vs 2.15 Å for methyl vs ester). An interesting point is that the phenyl group in this reaction system has almost as large a stabilizing effect as an ester (10.3 vs 13.2 kcal/mol), but the geometric impact is much smaller—the $C_\beta−H_\beta$ distance in the phenyl system is only stretched by 0.07 Å relative to the case of a methyl group substituent. The situation

in the phenoxide/alkyl chloride systems is surprisingly different. First, the $C_\beta-H_\beta$ distances do not stretch nearly as much with the strong electron-withdrawing groups. The $C_\beta-H_\beta$ distance reaches a maximum of 1.49 Å with the cyano system, and with the ester substituent, the $C_\beta-H_\beta$ distance is shorter than with a phenyl substituent. At first glance, this suggests that the phenoxide/alkyl chloride system is adopting less $E1_{cb}$-character in its transition states. This is counter to expectations because the combination of a stronger base with a weaker leaving group should advance the proton transfer component of the E2 process and favor an $E1_{cb}$-like path. The most reasonable rationale is that here the substituents are shifting the position of the transition state on the reaction coordinate as well as altering the synchronicity of the reaction. The transition states for the phenoxide/alkyl chloride systems with strong electron-withdrawing groups appear to be extremely early with almost no stretching of the $C_\alpha-Cl$ bond. As a result, there is still very high asynchronicity in the bond changing processes ($C_\beta-H_\beta$ vs $C_\alpha-Cl$ cleavage) despite the limited progression of the proton transfer component of the reactions. The reactions of the phenoxide/alkyl chloride and the benzoate/alkyl bromide systems have similar exothermicities (the proton affinities of benzoate and phenoxide differ by 10 kcal/mol, as do the proton affinities of Br^- and Cl^-), so one might not expect a shift of the transition state along the reaction coordinate between these two systems, but these reactions are highly asynchronous, and therefore, there is a near complete separation of the reaction processes (proton transfer and leaving group expulsion). There is a significant energetic advantage in the proton transfer component of the reaction of the more basic nucleophile (the phenoxide/alkyl chloride system), and consequently, its transition state should occur earlier on the reaction coordinate despite the fact that the reaction systems have similar overall energetics. The net result for the phenoxide/alkyl chloride system is shorter $C_\beta-H_\beta$ distances and E2 transition states that appear, at first glance, to have less, rather than more, $E1_{cb}$-character.

SUMMARY

This study provides a comprehensive investigation of the effect of α- and β-substituents on the rate constants and transition states of solvent-free S_N2 and E2 reactions. An overview of the substituent effects is shown in Figure 4. In general, charge-stabilizing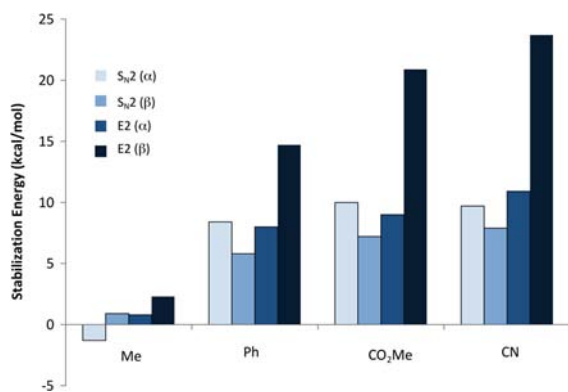 substituents at the α-carbon provide roughly similar stabilization to S_N2 and E2 transition states, but those at the β-carbon provide much more stabilization to E2 transition states. Although the electron-withdrawing groups have large effects on the rate constants and barriers, the impact on the transition state geometries is minor, except in the case of β-substituents in E2 reactions. Here, there is a large shift toward an $E1_{cb}$-like pathway with extensive proton transfer at the transition state. The electron-withdrawing groups on the β-carbons not only alter the synchronicity of the process but also are capable of shifting the system to an earlier transition state. In the eliminations, vinylic systems react at the same rate constants (and have similar barriers) as aliphatic analogs despite being considerably less exothermic processes. The vinylic systems adopt early, $E1_{cb}$-like transition states and exploit the advantage of more acidic β-hydrogens while minimizing the impact of forming a weaker π-bond. Finally, the data point to about a 3 kcal/mol advantage to E2 reactions from the entropy component of the free energy of activation at the temperature of the experiment (~300 K).[20]

ASSOCIATED CONTENT

Ⓢ Supporting Information

Energies and geometries for all relevant species in the computational study are available as well the complete citation for ref 21. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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REFERENCES

(1) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins Publishers: New York, 1987.
(2) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; John Wiley & Sons: New York, 1973.
(3) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962.
(4) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1969.
(5) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970.
(6) Gronert, S.; Pratt, L. M.; Mogali, S. *J. Am. Chem. Soc.* **2001**, *123*, 3081.
(7) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.
(8) Gronert, S. *Chem. Rev.* **2001**, *101*, 329.
(9) Gronert, S. *Acc. Chem. Res.* **2003**, *36*, 848.
(10) DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650.
(11) Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 9663.
(12) Regan, C. K.; Craig, S. L.; Brauman, J. I. *Science* **2002**, *295*, 2245.
(13) Ren, J. H.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 2640.
(14) Vayner, G.; Houk, K. N.; Jorgensen, W. L.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 9054.

Figure 4. Computed stabilization energies for substituents at the α and β positions in S_N2 and E2 reactions of phenoxide with substituted ethyl chlorides.

(15) Chen, X.; Walthall, D. A.; Brauman, J. I. *J. Phys. Chem. A* **2010**, *114*, 1392.

(16) Gronert, S.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1991**, *113*, 4009.

(17) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46.

(18) Gronert, S. *Mass Spectrom. Rev.* **2005**, *24*, 100.

(19) Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 12977.

(20) Gronert, S. *J. Am. Soc. Mass. Spectrom.* **1998**, *9*, 845.

(21) Frisch, M. J. et al. *Gaussian 03*, Revision B04; Gaussian, Inc.: Pittsburgh, PA, 2003.

(22) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345.

(23) Gronert, S. *J. Am. Chem. Soc.* **1991**, *113*, 6041.

(24) Gronert, S. *J. Am. Chem. Soc.* **1992**, *114*, 2349.

(25) Gronert, S. *J. Org. Chem.* **1994**, *59*, 7046.

(26) Gronert, S.; Fong, L. M. *Int. J. Mass Spectrom.* **1999**, *192*, 185.

(27) Bartmess, J. E. *Negative Ion Energetics Data*. In NIST Standard Reference Database Number 69; Mallard, W. G., Linstrom, P. J., Eds.; National Institute of Standards and Technology (http://webbook.nist.gov): Gaithersburg, MD, 2012.

(28) Gronert, S. *Int. J. Mass Spectrom.* **1999**, *185*, 351.

(29) The collision rates of these systems are problematic to characterize by standard approaches. The dianions have two, widely spaced charge sites, and the application of ADO theory with a charge of 2 is not a realistic representation of the situation. Using ADO as a general guide, these reactions give predicted collision rates in the range $(2-4) \times 10^{-9}$ cm^3 molecule^{-1} s^{-1}.

(30) Su, T.; Bowers, M. T. *In Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. *1*, pp 83.

(31) Sisti, A. J.; Lowell, S. *Can. J. Chem.* **1964**, *42*, 1896.

(32) Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645.

(33) Conant, J. B.; Kirner, W. R. *J. Am. Chem. Soc.* **1924**, *46*, 232.

(34) The ion trap has a limited mass window, so we are not able to simultaneously trap chloride along with the reactant/product ions, which have much higher m/z values. With bromide, a signal is observed, but the operative qz value causes discrimination and an attenuated signal intensity. In this study, ions with $m/z > 100$ had good trapping/detection efficiencies.

(35) Wladkowski, B. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 10643.

(36) Li, C.; Ross, P.; Szulejko, J. E.; McMahon, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 9360.

(37) Although entropies of activation can be produced in ab initio calculations (from single conformations at each stationary point), a full dynamics study would be needed given the nature of these surfaces.

(38) This is an overestimate because the cyclic systems have an alkyl group at the α-carbon. By analogy to other systems in this study, that provides about 1 kcal/mol of stabilization.

(39) Sullivan, S. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1977**, *99*, 5017.

(40) Rabasco, J. J.; Kass, S. R. *J. Am. Soc. Mass. Spectrom.* **1992**, *3*, 91.

(41) Kennedy, R. A.; Mayhew, C. A.; Peverall, R.; Watts, P. *Phys. Chem. Chem. Phys.* **2000**, *2*, 3145.

(42) Chou, P. K.; Kass, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 4357.

(43) Anderson, K. K.; Kass, S. R. *Tetrahedron Lett.* **1989**, *30*, 3045.

(44) Craig, S. L.; Brauman, J. I. *J. Am. Chem. Soc.* **1999**, *121*, 6690.

(45) Chung, D. S.; Kim, C. K.; Lee, B.-S.; Lee, I. *J. Phys. Chem. A* **1997**, *101*, 9097.