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How Alkyl Halide Structure Affects E2 and S_N2 Reaction Barriers: E2 Reactions Are as Sensitive as S_N2 Reactions

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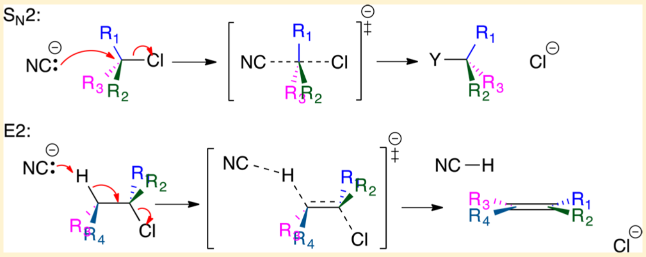
Ⓢ *Supporting Information*

ABSTRACT: High-level electronic structure calculations, including a continuum treatment of solvent, are employed to elucidate and quantify the effects of alkyl halide structure on the barriers of S_N2 and E2 reactions. In cases where such comparisons are available, the results of these calculations show close agreement with solution experimental data. Structural factors investigated include *α*- and *β*-methylation, adjacency to unsaturated functionality (allyl, benzyl, propargyl, *α* to carbonyl), ring size, and *α*-halogenation and cyanation. While the influence of these factors on S_N2 reactivity is mostly well-known, the present study attempts to provide a broad comparison of both S_N2 and E2 reactivity across many cases using a single methodology, so as to quantify relative reactivity trends. Despite the fact that most organic chemistry textbooks say far more about how structure affects S_N2 reactions than about how it affects E2 reactions, the latter are just as sensitive to structural variation as are the former. This sensitivity of E2 reactions to structure is often underappreciated.



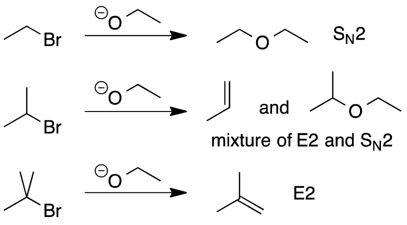
■ INTRODUCTION

The S_N2 (bimolecular nucleophilic substitution) and E2 (bimolecular elimination) reactions are among the most fundamental in organic chemistry, and students learning the subject typically encounter these two reactions very early in their journey.[1−3] Indeed, these two reactions have been the subject of innumerable investigations, including solution- and gas-phase experimental studies as well as computational explorations, over the past 70 years. There is insufficient space in this paper to mention or even reference any but a tiny fraction of these studies, but that is not to diminish the profound importance of all this work in establishing the nature of these reactions.[4]

Already in the 1940s, Hughes and Ingold established that the S_N2 reaction is sensitive to steric hindrance.[5−7] About a decade ago, gas-phase experiments threw into question whether this effect is inherent to the reaction, or mostly a result of differential solvation,[8] but the issue now appears resolved that most of the tendency exists even in the gas phase.[9−11] Organic chemistry students learn early in their careers about this characteristic of S_N2 reactions and about the competition by elimination reactions that leads to the typical behavior outlined in Scheme 1.

Textbooks typically say little about how the structures of alkyl groups affect E2 reactions, leading students to conclude that the pattern shown in Scheme 1 results from the fact that E2 remains a relatively constant alternative as the S_N2 reaction becomes progressively less favorable.[12] That is, in the absence of information about how structure affects E2 barriers, the intuitive assumption is that such effects are minor, at least compared to those for the S_N2 reaction.

Scheme 1



However, this assumption is incorrect. Connor and Gronert, in particular, have investigated how *α*- and *β*-methylation affect the barriers of substitution and elimination reactions in the gas phase using both experimental and computational approaches.[13] They have demonstrated that both *α*- and *β*-substitution not only decrease the rates of substitution reactions but also increase the rates of elimination reactions, at least in the gas phase.[14]

Apart from Connor and Gronert's work (and numerous solution-phase Hammett studies of *p*-substituted benzyl cases[15−17]), the research literature reveals comparatively little direct information about the variation of E2 reaction rates with the structure of alkyl halides,[18] especially in solution, although Saitsev's rule, the tendency of E2 to favor the more substituted alkene when more than one elimination pathway is possible,

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clearly implies an effect. It would thus seem valuable to establish, in a consistent quantitative fashion and for a solution environment, how the pattern in Scheme 1 arises, considering the dependence of *both* S_N2 *and* E2 barriers on structure.

S_N2 reactions are known to be accelerated by adjacent conjugation, as in the allyl and benzyl cases, and by adjacent carbonyl functionality, as in chloroacetone, and to be affected by ring size (e.g., cyclopropyl and cyclobutyl halides react rather slowly).[19,20] However, quantitative data illustrating these effects in solution are limited, and this is even more the case for elimination reactions.[21] It would therefore seem useful to quantify how typical structural variations affect both substitution and elimination reaction barriers, as this might teach us how large and how general or transferable these effects are. It is commonly assumed that elimination is favored in cases yielding conjugated alkene products, but is that really so, and by how much? Do the effects of alkyl substitution remain the same when other functionality is present? What is the effect of additional halogenation or cyanation?

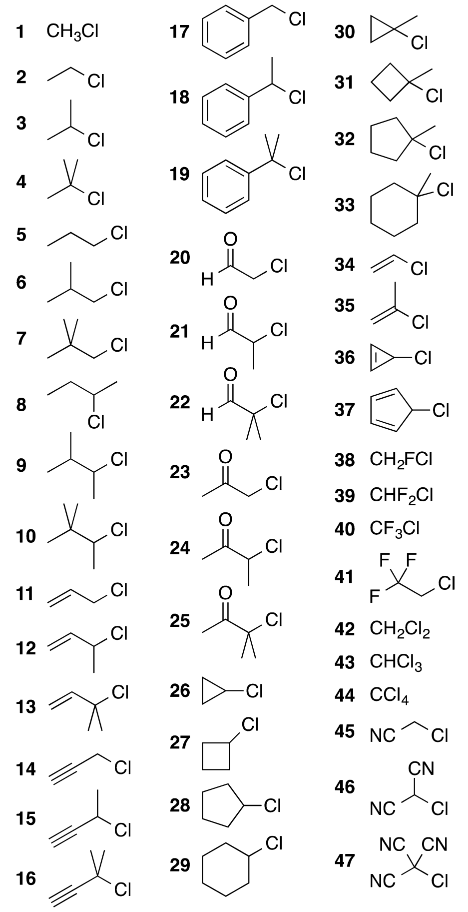
Such an internally consistent collection of data does not currently exist, likely because performing the necessary experiments—for many, highly varied structures under a single set of conditions—would be enormously laborious or even impossible. However, state of the art electronic structure calculations now provide rather reliable reaction and activation energies, and economical continuum models can provide a reasonable correction for nonspecific solvation effects. Thus, it is the goal of the present work to use such an approach to (a) determine whether changes in E2 as well as S_N2 barriers cause the general reactivity pattern illustrated in Scheme 1 and (b) provide a broad quantitative picture of how typical variations in alkyl halide structure affect both S_N2 and E2 reaction rates. Relative free energies for forming carbocations and for substitution and elimination reactions are also provided for comparison and context.

■ RESULTS AND DISCUSSION

Chart 1 lists the structures that were chosen in order to provide a broad view of substituent effects on the relative barriers of S_N2 and E2 reactions. The S_N2 products are unambiguous (replace Cl with CN), but Scheme 2 depicts the E2 products, of which more than one are sometimes possible. In such cases, "cis" indicates a *cis* alkene (where *trans* is preferred); "as" refers to an anti-Saitsev product (disfavored, except in the case of **30**); and "al" refers to an allene product (disfavored). Table 1 tabulates the free energy barriers for these reactions, as well as the free energies for forming carbocations. Overall reaction enthalpies and free energies appear in the Supporting Information. Where possible, calculations were carried out using the W1 procedure, which emulates CCSD(T,Full)/aug-cc-pVQZ+2df//B3LYP/cc-pVTZ+d.[22−24] In cases where W1 proved too costly, calculations were performed at the G4 level[25] (which emulates CCSD(T)/6-311+G(3df,2p)//B3LYP/6-31G(2df,p)), and then energies were corrected to be "effectively" W1 by taking advantage of the extremely high correlation between G4 and W1 energies for each individual class of reaction ($r^2 \approx 0.99$). The procedure is described in more detail in the Supporting Information.

Although many gas-phase calculations were performed as part of the study, we report here only calculations carried out using a simulated acetonitrile solvent. This choice represents a typical polar aprotic solvent, for which continuum solvation models should provide a fairly accurate accounting.[26] Our goal is not to reproduce a single, exact set of experimental conditions but to provide a consistent and reasonably representative set of conditions to allow for meaningful comparisons.

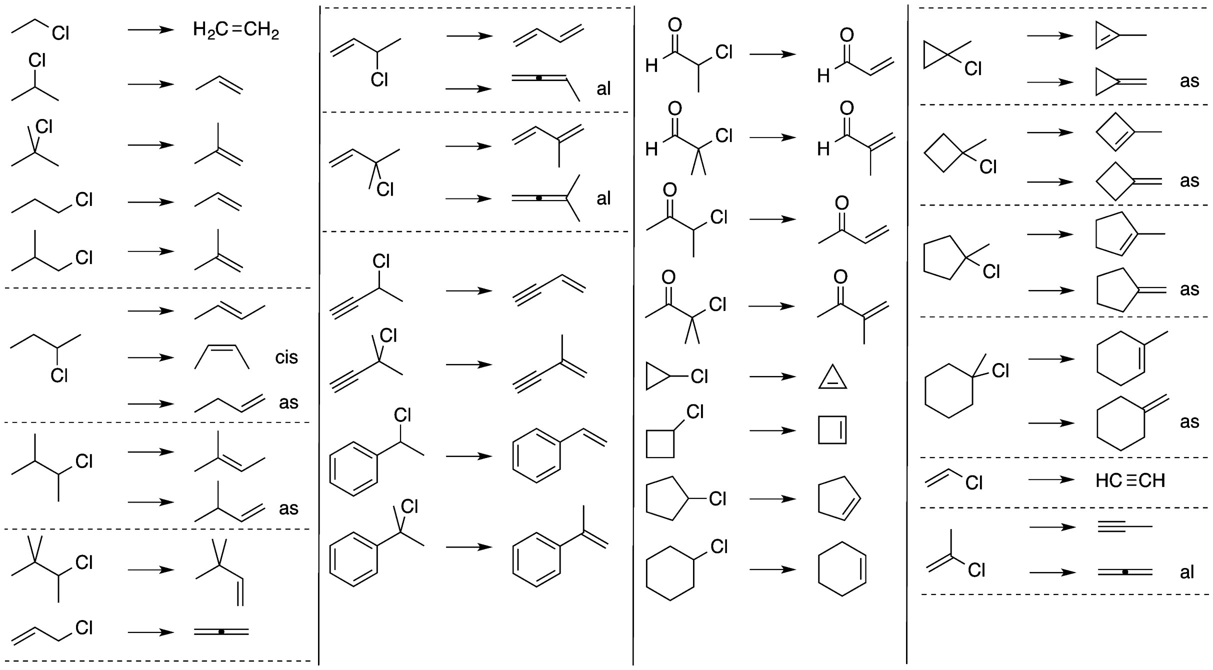
Chart 1. Compounds Studied[a]



[a]Substitution products are the same structures, with CN replacing Cl.

For reasons of computational economy, chloride was chosen as the leaving group (nucleofuge). Both chloride and cyanide were investigated as nucleophiles/bases, but we focus here on the case of cyanide. While studying the case of chloride is theoretically interesting for the substitution reaction, since the resulting identity reactions have no thermodynamic component to their barriers in the sense of Marcus Theory, the exothermic reactions involving cyanide ion likely represent a more typical example of a "real" reaction. Similarly, chloride is too weak a base to make a very realistic E2 reaction partner, but cyanide is not unreasonable, and indeed the eliminations using cyanide are generally exothermic (while those with chloride are not). Cyanide might not seem an obvious choice to model the base in an E2 reaction, but it is computationally economical, and using the same species to model both the S_N2 and E2 reactions permits more straightforward comparisons.

To refer to the E2 reaction as a single mechanism represents somewhat of a simplification, since the transition state can vary in character across the E2H-E2C spectrum.[27] The extreme ends of this spectrum refer to an $E1_{cb}$ reaction and an E1 reaction, respectively. Reactions at the E2H end are known to behave somewhat differently than reactions elsewhere on this spectrum (the Hofmann versus the Saitsev elimination patterns). The intention here is to focus on Saitsev-type elimination reactions, Scheme 2. E2 Reactions



with transition structures ranging in character from rather central to somewhat carbocationic. The choice of a good leaving group (chloride), a modest base (cyanide), and substrates that lack especially acidic *β*-hydrogens should enforce this reactivity pattern.

The information collected in Table 1 addresses the questions raised in the Introduction, as well as some others. Table 1 represents the central result of this investigation and may serve as a useful reference for future purposes.

Do the calculations agree with experiment? It is possible to investigate how well the present calculations reproduce changes in S_N2 barriers for the modest number of cases where the kinetics have been studied experimentally under comparable sets of conditions. Table 2 lists the available experimental data, along with the calculated values. Free energy barriers are presented relative to methyl. The experimental data include several different sources and several different sets of reaction conditions, none of which correspond exactly to those on which the computations are based. The calculated barriers in Table 2 represent the identity reactions in which chloride displaces chloride, since that corresponds more closely to the actual experiments (typically, a halide displacing a halide) than when cyanide is the nucleophile. Figure 1 demonstrates that an excellent correlation exists between the experimental and calculated barriers ($r^2 = 0.96$), lending confidence to the value of the calculations. The case of 2-chloroacetonitrile appears to be somewhat of an outlier,[28] and the correlation increases to 0.99 if that case is omitted. The difference in reactivity calculated for neopentyl versus ethyl also agrees closely with that computed by Vayner, Houk, Jorgensen, and Brauman.[9]

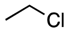
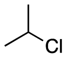
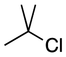
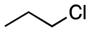
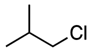
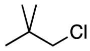
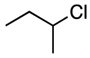
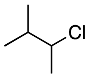
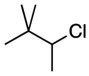
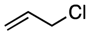
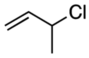
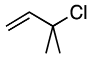
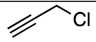
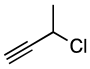
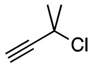
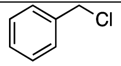
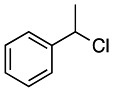
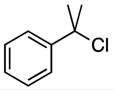
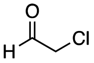
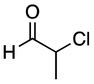
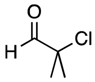
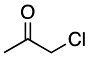
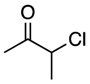
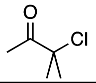
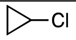
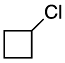
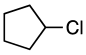
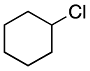
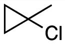
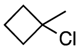
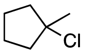
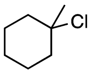
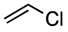
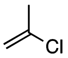
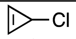
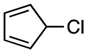
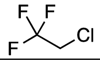
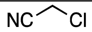
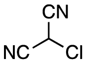
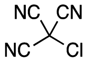
Although solution quantitative kinetic data for elimination reactions resembling those studied here are mostly lacking, at least two reasonable comparisons are possible. Froemsdorf observed a ratio of *trans*-2-butene to *cis*-2-butene of 3.35:1 when 2-bromobutane was treated with potassium ethoxide in ethanol at 55 °C.[29] That ratio implies a difference in barriers of 0.8 kcal/mol (favoring *trans*), in reasonable agreement with the difference of 0.5 kcal/mol reported here. Similarly, treatment of 2-iodobutane with *p*-nitrobenzoate in DMSO yielded 5.8% 1-butene vs 94.2% 2-butene at 50 °C.[30] Assuming the same trans/cis ratio as before, and taking into account statistical factors (three methyl H's leading to 1-butene, as opposed to one type of methylene H each leading to *trans*- and *cis*-2-butene), this ratio implies that the barrier leading to 1-butene is 2.3 kcal/mol higher than that leading to *trans*-2-butene. This value compares reasonably well to the value of 3.0 kcal/mol reported here, especially since the experimental conditions do not match those simulated computationally.

Alkyl Substitution and the Changing Ratio of S_N2 vs E2. The first few entries of Table 1 clearly illustrate that as methylation of the *α*-carbon increases, the barrier to the E2 reaction decreases by the same amount as the barrier to S_N2 increases. Figure 2 illustrates this point graphically. Contrary to what has often been assumed, the classic reactivity pattern of Scheme 1 derives just as much from the increasing rate of the E2 reaction as from the decreasing rate of the S_N2 reaction.

Why does increasing alkyl substitution enhance the rate of the E2 reaction? It might result from increasing product stability, as has been invoked to rationalize the Saitsev pattern of regiochemical preference.[31−33] Alkyl substitution does stabilize alkenes, and some of this stabilization should manifest itself already in the transition structure. The first comparison in Scheme 3 illustrates this point: the E2 barrier for 2-chlorobutane lies 2.4 kcal/mol lower in energy than that for 2-chloropropane, despite the fact that both alkyl chlorides are secondary.

This observation can be rationalized in terms of the greater stabilization of a disubstituted alkene (*trans*-2-butene) compared to a monosubstituted alkene (propene). However, the second comparison demonstrates that alkene product stability cannot be the only reason for the observed trends, as both reactions yield the same product. Although the first reaction is more exergonic, the barrier for the *second* reaction is

Table 1. W1U/SCRF Barriers for S_N2 and E2 Reactions and for Carbocation Formation (Free Energies, kcal/mol)[a]

Species	**S_N2**	**E2[b]**	**Carbocation**
	$\Delta G^{\ddagger}$ (298K) solution	**$\Delta G^{\ddagger}$ (298K) solution**	**ΔG (298K) solution**
CH_3Cl	**24.6**	--	**80.9**
	**28.5**	**38.0 (42.7 syn)**	**50.5**
	**31.6**	**34.6**	**40.4**
	**34.1**[c]	**30.1**	**28.8**
	**27.8**	**35.5**	rearranges
	**29.6**	**33.0**	rearranges
	34.6	--	rearranges
	**30.8**	**32.2 (33.1 cis) (35.0 as)**	**40.4**
	31.7	29.6 (35.0 as)	37.9
	35.5	35.8	rearranges
	**26.0**	**40.4**	**41.8**
	**29.4**	**33.1 (39.7 al)**	**30.9**
	32.8	29.3 (36.0 al)	24.5
	**26.0**	--	**54.8**
	**30.4**	**34.6**	**41.7**
	36.4	32.0	32.5
	24.1	--	**34.5**
	27.9	31.8	27.7
	28.8	27.9	22.5
	**22.1**	--	rearranges
	**24.2**	**34.9**	rearranges
	28.5	32.0	48.3
	**21.9**	--	rearranges
	23.9	34.5	rearranges
	29.0	32.1	42.8
	**41.7**	**48.2**	rearranges
	**34.0**	**37.5**	**46.3**
	30.8	32.2	37.7
	34.0	32.4	40.5
	**49.1**	**(47.3) 41.3 as**	rearranges
	38.5	32.7 (34.0 as)	33.0
	32.2	28.0 (30.7 as)	27.0
	37.3	28.6 (31.1 as)	30.4
	**44.8**	**38.0**	**70.7**
	**52.7**	**38.6 (43.3 al)**	**51.8**
	**14.6**	--	**12.4**
	**28.0**	--	anti-aromatic
CH_2FCl	**28.6**	--	**65.1**
CHF_2Cl	**34.7**	--	**58.9**
CF_3Cl	**48.9**	--	**67.9**
	**33.7**	--	rearranges
CH_2Cl_2	**30.6**	--	**58.4**
$CHCl_3$	**37.2**	--	**47.5**
CCl_4	**43.2**	--	**39.8**
	**24.3**	--	**86.1**
	**22.5**	--	**89.0**
	**18.2**	--	**89.8**

[a] Values in bold are W1; others are G4, with a correction based on the W1/G4 correlation relationship. The base or nucleophile is cyanide ion, and the simulated solvent is acetonitrile. [b] Abbreviations: "as" means TS leading to anti-Saitsev elimination product; "al" means TS leading to allene-type elimination product; "cis" means TS leading to *cis* (rather than *trans*) alkene product; "syn" specifies the *syn*, rather than the usual *anti*, TS. [c] This is the C_3 structure, which has three imaginary frequencies. However, two of the three frequencies are very small (<100 cm^{-1}), and a proper transition state with lower symmetry and only one imaginary frequency could not be located.

lower, by 2.9 kcal/mol. This finding can be explained by assuming that, although E2 reactions do not involve a carbocation intermediate, the transition structure nonetheless has some carbocation character and is therefore stabilized by α-carbon substituents.[34,35] The much longer C−Cl bond length in the transition structure for 2-chloro-2-methylpropane (2.88 Å) compared to 1-chloro-2-methylpropane (2.40 Å) speaks to the larger extent of carbocation character in the former transition structure.[36]

A statistical analysis supports the arguments exemplified in Scheme 3. The calculated E2 reaction barriers parallel the reaction exergonicity with a correlation coefficient (r^2) of 0.58

Table 2. Comparison of Experimental and Calculated S_N2 Reaction Barriers (kcal/mol)

	experimental			calculated[a]	
R	*k*	$\Delta\Delta G^\ddagger$	ref	$\Delta G^\ddagger$	$\Delta\Delta G^\ddagger$
methyl	1.0	0.00	*b,c*	28.2	0.0
ethyl	3.3×10^{-2}	2.02	*b*	30.0	1.8
	1.7×10^{-2}	2.43	*c*		
propyl	1.3×10^{-2}	2.57	*b*	29.9	1.7
	1.1×10^{-2}	2.69	*c*		
isopropyl	8.3×10^{-4}	4.20	*b*	32.0	3.8
isobutyl	2.5×10^{-3}	3.55	*c*	31.8	3.6
t-butyl	5.5×10^{-5}	5.81	*d*	34.3	6.1
neopentyl	3.3×10^{-7}	8.84	*b*	37.8	9.6
	4.3×10^{-7}	8.68	*c*		
allyl	1.3	−0.16	*b*	27.8	−0.4
benzyl	4.0	−0.82	*b*	26.9	−1.3
methyl	1.0	0.00	*e*	28.2	0.0
acetyl	3.7×10^{1}	−2.14	*e*	25.2	−3.0
cyanomethyl	3.2×10^{1}	−2.05	*e*	28.0	−0.2

[a] Calculated values: W1U/G4 in acetonitrile solution, for chloride displacing chloride. [b] Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; p 13. [c] Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3694−3697. [d] Cook, D.; Parker, A. J. *J. Chem. Soc. B* **1968**, 142−148. Kinetic data for R-Br reacting with LiCl in acetone. [e] Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645−4650. Kinetic data for R-Cl reacting with iodide ion. The reference reaction in this case was with 1-chlorobutane, and so relative rates had to be converted to a scale relative to chloromethane by assuming the rate constant for 1-propyl is the same as for 1-butyl.

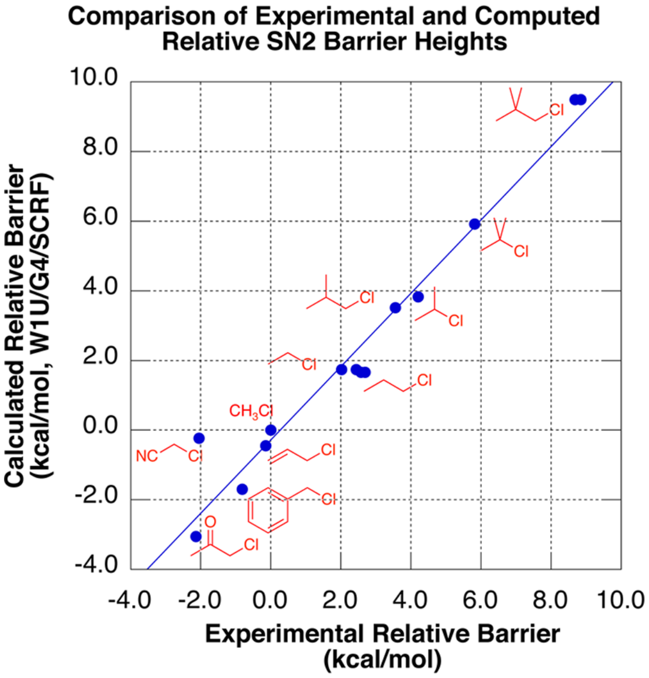


Figure 1. Comparison of calculated and experimental relative barriers of S_N2 reactions. The least-squares line has the equation $y = -0.274 + 1.053x$ and a correlation coefficient r^2 of 0.957. The correlation coefficient increases to 0.989 with the point for CH_2CNCl removed.

(Figure S1, Supporting Information), and parallel the stability of the associated carbocation with a correlation coefficient of 0.39 (Figure S2, Supporting Information). However, a two-parameter regression including both factors yields a much

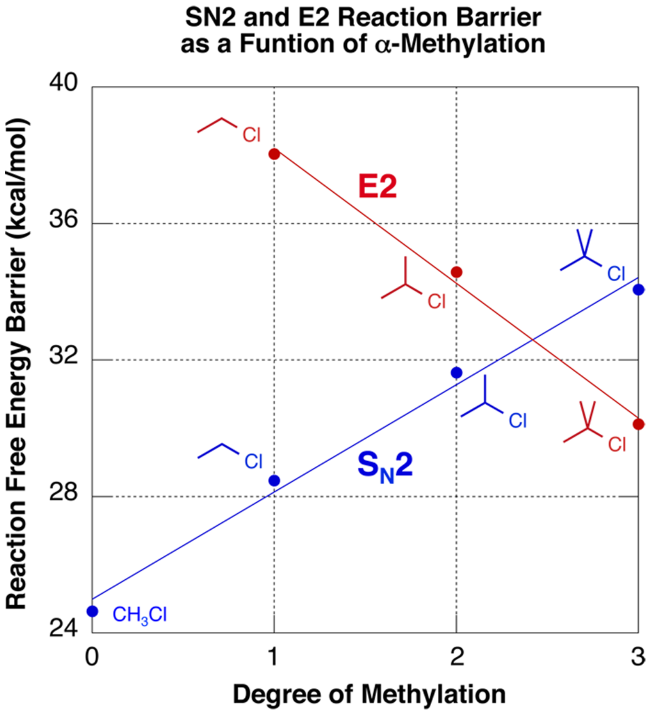
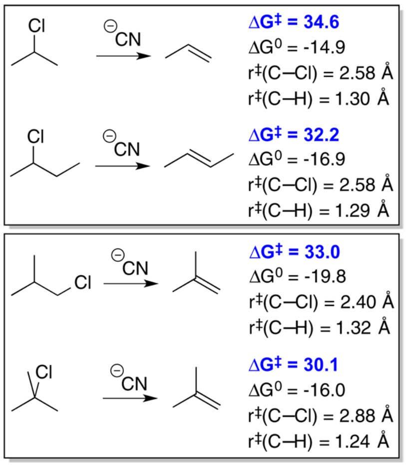


Figure 2. Effect of increasing *α*-methylation on the barriers of S_N2 and E2 reactions. The preference for elimination over substitution with increasing substitution results as much from the decrease in E2 barrier as from the increase in S_N2 barrier.

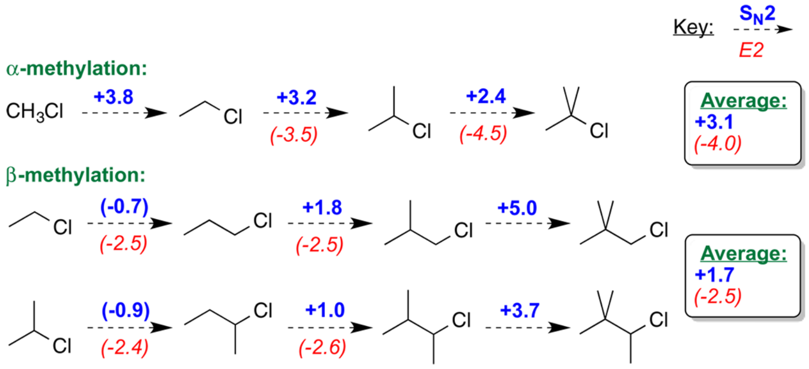
Scheme 3. Comparison of E2 Reactions (energies in kcal/mol)



superior correlation of 0.77 (Figure S3, Supporting Information).

The data in Table 1 also support a more general statement about how both *α*- and *β*-methylation affect the rates of S_N2 and E2 reactions. Chart 2 is the first in a series that depicts how reaction barriers change as a result of structural modification. Each dashed arrow represents a structural perturbation. The blue number above the arrow represents how the S_N2 barrier changes in response to this perturbation, while the red number below the arrow represents how the E2 barrier changes. The boxes on the right side summarize the average result for the series of structural perturbations to their left. Negative numbers are placed in parentheses for additional clarity. Thus, for instance, adding successive methyl groups to the *α*-carbon of

Chart 2. ***Relative*** **Free Energy Barriers (kcal/mol) Caused by the Structural Perturbations Shown (*α*- and *β*-Methylation)**



chloromethane raises the S_N2 barrier by 3.8, 3.2, and then 2.4 kcal/mol, or 3.1 kcal/mol on average.

Chart 2 demonstrates that, for otherwise unfunctionalized alkyl chlorides, each successive *α*-methylation increases the S_N2 barrier by about 3 kcal/mol and decreases the E2 barrier by 4 kcal/mol. Each successive *β*-methylation also decreases the E2 barrier by 2−3 kcal/mol. Methylation of the *β*-carbon has a more complicated effect on the S_N2 reaction barrier. The first *β*-methylation in fact slightly *decreases* the barrier, while the second modestly increases it, and the third dramatically increases it. Brauman and co-workers have also observed this pattern, in both solution and the gas phase,[10] as have Connor and Gronert in the gas phase, attributing it to a combination of polarizability and steric effects.[13] The variety of compounds in Chart 1 also permits an analysis of *α*-methylation when various other functional groups are present. The nearly parallel lines in Figure 3, which link series of compounds that differ only in the number of *α*-methyl substituents, demonstrate that the effect is fairly constant (with the propargyl and cyclopentyl cases deviating slightly): each *α*-methyl raises the S_N2 barrier by 3−4 kcal/mol, consistent with the more limited analysis in Chart 2.[37] A similar analysis for the E2 reaction shows that *α*-methylation consistently reduces the E2 barrier by 3−4 kcal/mol (3.3 kcal/mol on average), and is illustrated as the inset in Figure 3.[38]

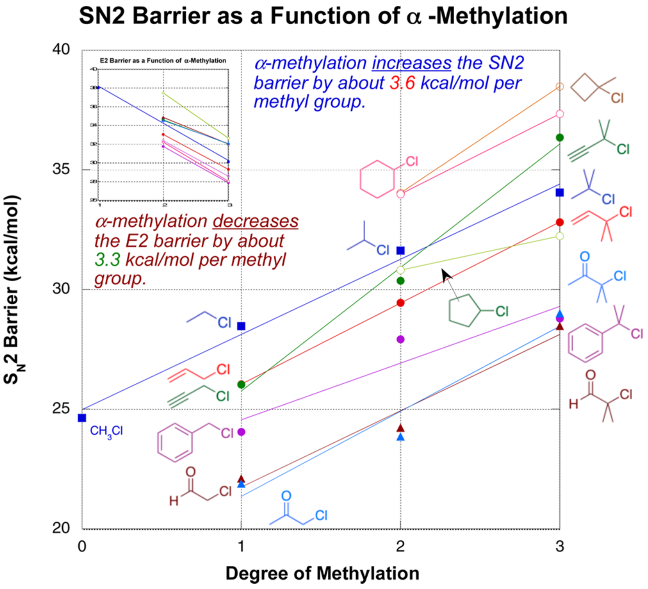


Figure 3. Effect of *α*-methylation on the S_N2 reaction barriers of various classes of compounds. Inset: effect of *α*-methylation on the E2 reaction. Both plots omit the chlorocyclopropane/1-chloro-1-methylcyclopropane case, which is far off scale.

As mentioned previously, E2 transition structures can vary in structure, more so than S_N2 transition structures. One might therefore worry particularly in the case of E2 about how generalizable are the reactivity patterns described by the present data. The results would surely differ for $E1_{cb}$-like E2 reactions at the E2H end of the E2H−E2C spectrum. Sterically hindered bases would also likely yield rather different preferences. However, there is reason to believe that the patterns elucidated from the present investigation apply reasonably broadly to E2 reactions of compounds that have good leaving groups, fit the Saitsev reactivity profile, and whose transition structures lie more in the middle of the spectrum, or toward the E2C end. For instance, in the present study, the changes in barrier heights that accompany *α*- and *β*-methylation are much the same when instead of cyanide the base is chloride (a weaker base). Furthermore, Connor and Gronert observed effects of very similar size and direction, albeit in the gas phase, when using naphthoate and phenoxide, which are somewhat stronger bases than cyanide.[13] Nonetheless, it remains an open question how, and how much, the dependence of E2 reaction barrier on alkyl halide structure itself depends on the strength of the base.[39]

Conjugation. Allyl and benzyl halides are known to react particularly rapidly by the S_N2 mechanism.[40−44] Chart 3 demonstrates that the effect is modest for the allyl case, typically resulting in a barrier decreased by 2 kcal/mol, small and inconsistent for the propargyl case but quite substantial for the benzyl case, where the barrier decreases by 4−5 kcal/mol. The effect on E2 reactions follows the same trend but is only about half as great. Allylation decreases the E2 barrier by about 1 kcal/mol,[45] whereas benzylation decreases the barrier by 2−3 kcal/mol. The stabilization of the conjugated alkene products and of the conjugated carbocations derived by loss of chloride rationalizes this observation. The propargyl case is more difficult to understand; the E2 barrier increases, although only slightly.

Carbonyl Substituents. Chloroacetone and other *α*-halo carbonyls are known to undergo very rapid S_N2 reactions, and this observation has been attributed in the past either to conjugative[44,46] or to dipolar[11,47,48] stabilization of the transition structure. Chart 4 demonstrates that this effect is very large: the S_N2 barrier decreases by 5−8 kcal/mol (6.5 kcal/mol on average). One might have expected the E2 barrier also to decline, as in the allyl and benzyl case, since *α*,*β*-unsaturated carbonyl compounds enjoy conjugative stablilization. However, Chart 4 shows that the effect of an *α*-carbonyl on the E2 barrier

Chart 3. *Relative* Free Energy Barriers (kcal/mol) Caused by the Structural Perturbations Shown

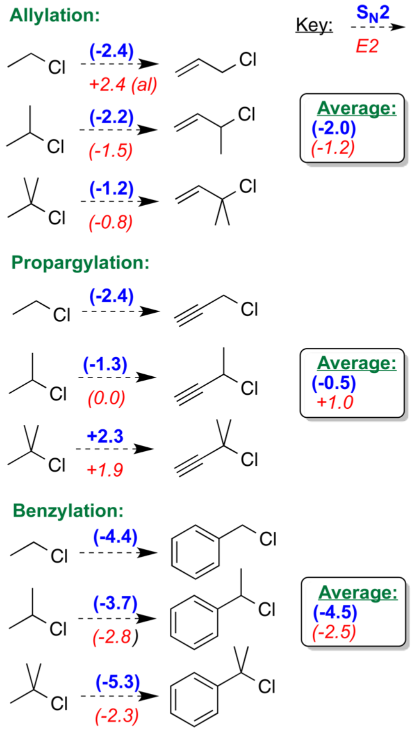
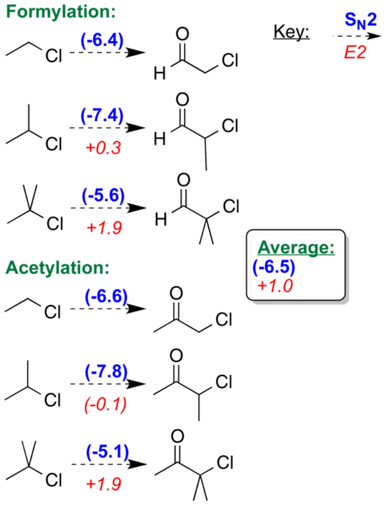


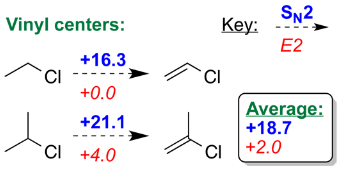
Chart 4. *Relative* Free Energy Barriers (kcal/mol) Caused by the Structural Perturbations Shown



is generally small but positive! Upon reflection, however, this finding is not surprising. We have seen that E2 barriers correlate reasonably well with incipient carbocation stability, as well as with product alkene stability. The α-carbonyl will clearly destabilize positive charge on the reacting carbon in the E2 transition structure, and this effect overpowers the conjugative stabilization of the product. Accordingly, the C−Cl bond lengths in the transition structures are somewhat shortened when a carbonyl is present, indicative of reduced carbocation character.[49]

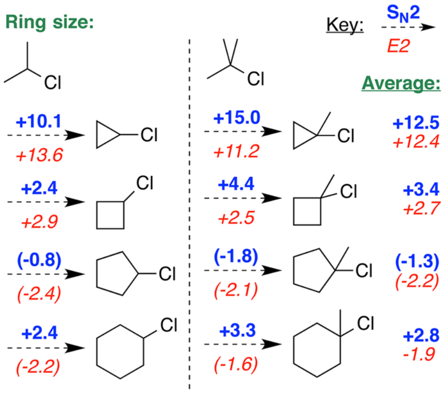
Vinyl Chlorides. Chart 5 shows that the barrier to S_N2 reaction for vinyl chlorides is extremely high, 16−21 kcal/mol higher than in saturated analogues.[50] The E2 barrier, on the other hand, increases only modestly, by 0−4 kcal/mol. These values are consistent with the known behavior of vinyl halides, which at least under harsh conditions undergo elimination, but not substitution (unless by an addition−elimination mechanism, in the case of vinyl halides conjugated to an electron-withdrawing group such as cyano or carbonyl). Gronert has observed similar behavior in the gas-phase, and has attributed the comparative facility of the E2 reaction at vinyl centers to a shift toward an $E1_{cb}$-like mechanism, resulting from the greater acidity of sp^2-hybridized C−H bonds.[51]

Chart 5. *Relative* Free Energy Barriers (kcal/mol) Caused by the Structural Perturbations Shown



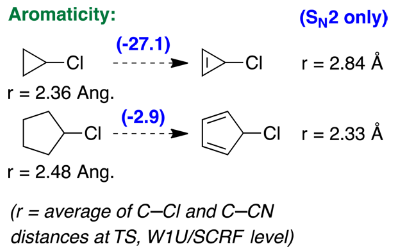
Ring Size. Both substitution and elimination convert a tetrahedral sp^3 center with 109.5° idealized bond angles into a trigonal planar sp^2 center with 120° idealized bond angles. Both transformations thus increase the angle strain in a cyclopropyl or cyclobutyl system. Accordingly, as Chart 6 demonstrates, the barriers for both S_N2 and E2 rise enormously for cyclopropyl chlorides (by 10−15 kcal/mol, 12 on average)[52] and significantly for cyclobutyl chlorides (by 1−5 kcal/mol, 3 on average), as is well recognized. On the other hand, cyclopentyl cases accelerate both reactions, with barriers reduced by 1−2 kcal/mol in comparison to an acyclic reference. Cyclohexyl cases are unusual in having a differential effect on substitution and elimination: the S_N2 barrier increases by 2−3 kcal/mol compared to isopropyl chloride, but the E2 barrier decreases by about 2 kcal/mol. Cyclohexyl cases thus exhibit a bias toward elimination rather than substitution, in comparison to acyclic reference cases. These observations concur with Gronert's earlier gas-phase computational analysis showing that elimination barriers are somewhat reduced in 5- and 6-membered rings and that substitution barriers are lower in 5-membered rings than in 6-membered rings.[53]

Chart 6. *Relative* Free Energy Barriers (kcal/mol) Caused by the Structural Perturbations Shown



Effect of Aromaticity. Chart 7 illustrates the effect of potential aromaticity on S_N2 transition structures. 3-Chlorocyclopropene yields an aromatic carbocation upon departure of the chloride ion. Accordingly, the transition structure is very carbocation-like, with much longer C−Cl and C−CN bonds

Chart 7. *Relative* **Free Energy Barriers (kcal/mol) Caused by the Structural Perturbations Shown**



(2.86 and 2.82 Å, respectively) than in the corresponding transition structure for chlorocyclopropane (2.37 and 2.34 Å), and the barrier is therefore extraordinarily low.[54] 5-Chloro-1,3-cyclopentadiene, on the other hand, would yield a highly unstable carbocation, but, at least in principle, a very stable anion. Accordingly, the transition structure has unusually short bonds (2.29 Å and 2.38 Å instead of 2.49 Å and 2.48 Å for the saturated analogue), accumulating negative charge on the reacting carbon atom. The barrier is again lower than one would otherwise expect. Thus, stabilization of *either* positive *or* negative charge can lower the energy of the transition structure.

Halogenation and Cyanation. Fluorination raises the S_N2 barrier in a successively increasing fashion: the first α-fluorine increases the barrier by 4 kcal/mol, but the next one raises it by another 6 kcal/mol, and the third by another 14 kcal/mol. Fluorination in the β-position raises the barrier to a somewhat smaller degree: three β-fluorines have about the same effect as two α-fluorines. Chlorine behaves somewhat differently, although broadly in the same sense. α-Chlorination raises the barrier to a rather similar degree, but in a linear fashion. That is, each successive chlorine raises the barrier by 6−7 kcal/mol. The effect of fluorine is presumably polar and/or electronic in character, while in the case of chlorine sterics likely play a role as well. Unsurprisingly, the cyano group has an effect broadly similar to that of a carbonyl,[11] although not nearly as strong. A single cyano substituent has a small effect,[55] but a second one reduces the barrier by 2 kcal/mol, and a third one reduces it by another 4 kcal/mol. In all three cases, fluorination, chlorination, and cyanation, the S_N2 reactivity pattern bears no discernible relation to the pattern of carbocation stability, but does seem to follow the analysis of Kost and Aviram, who found that π-donors raise the S_N2 barrier while π-acceptors lower it.[56]

Syn Transition Structures. In the case of elimination from chloroethane, the transition structure with a *syn* orientation was computed as well as that with the preferred *anti* orientation. The preference for *anti* is almost 5 kcal/mol, consistent with the general experimental observation that *anti* elimination is strongly favored,[57−59] such that significant amounts of *syn* elimination only occur under rather unusual circumstances.[60]

Summary of Chemical Effects. Figure 4 summarizes in a compact form the effects of the various structural perturbations discussed in the preceding paragraphs on the calculated S_N2 and E2 reaction barriers.

Further Patterns in Transition Structures. The present study provides a wealth of structural as well as energetic information that allowed us to reach some interesting general correlations. However, most of the geometric parameters of the transition structures that were investigated did not show particularly strong, useful, or interesting correlations with barrier heights, at least that held true over the entire set of substitution or elimination reactions explored.[61] Nevertheless, we found a meaningful correlation between the E2 barrier height and the increase in the length of the β C−H bond in the transition structure, which is depicted in Figure 5. The distance from the attacking cyanide to the hydrogen is also strongly correlated with the barrier height, but with the opposite sign, so this geometric parameter represents the extent to which the

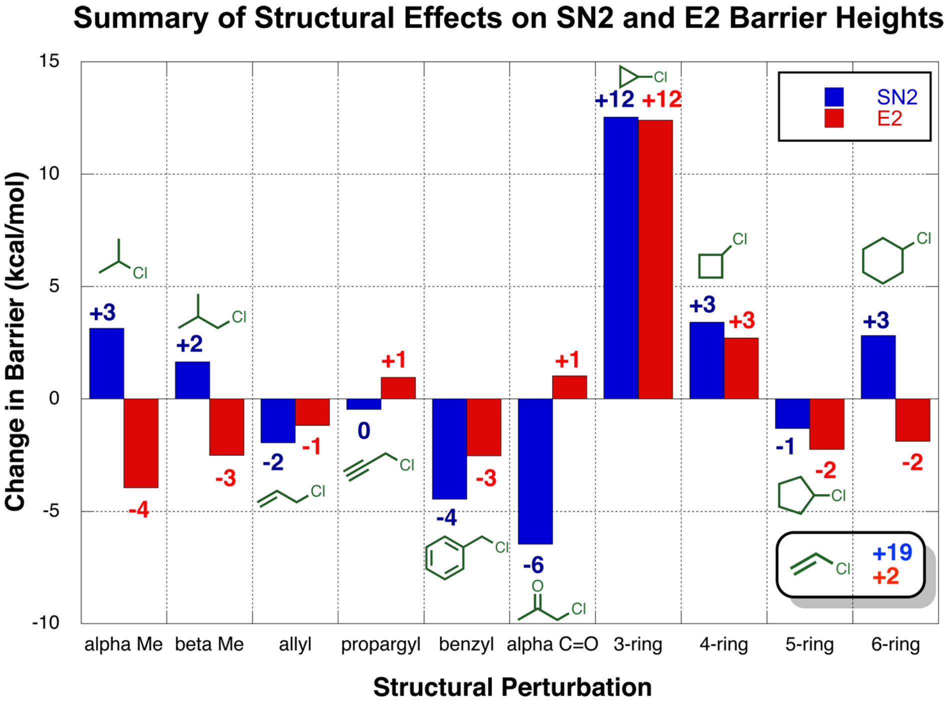


Figure 4. Summary of the main structural effects on S_N2 and E2 reaction barriers. Each bar indicates the perturbation *represented* by the compound shown, but based on the average of *all* the relevant comparisons illustrated in Charts 2−6 (i.e., the averages reported in these charts).

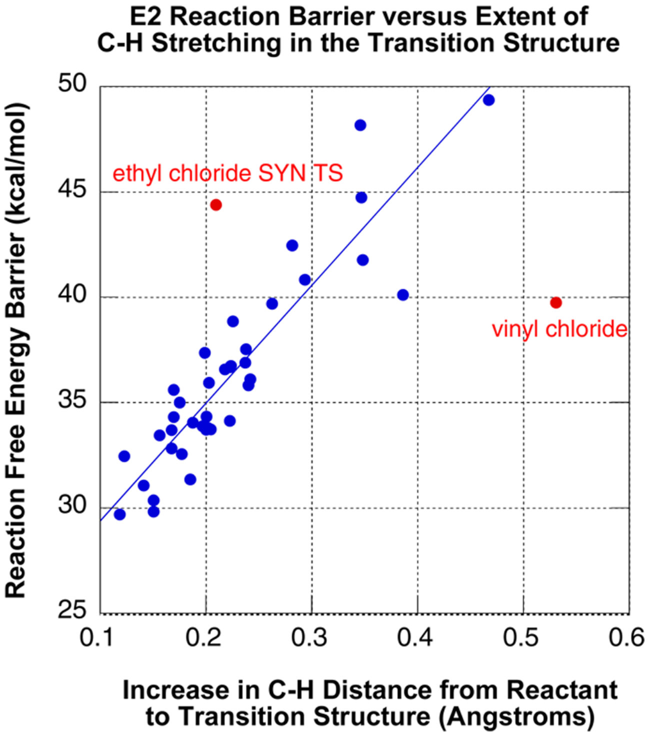


Figure 5. Correlation between $\Delta G^{\ddagger}$ (298 K) and extent of C−H bond stretching in the transition structure (compared to the reactant) for E2 reactions. The least-squares line has the equation $y = 23.79 + 55.92x$ and a correlation coefficient r^2 of 0.84. The correlation coefficient decreases to 0.61 if the two outlier points shown in red are included.

proton is transferred from the alkyl chloride to the cyanide in the transition structure.

Perhaps somewhat more surprisingly, the extent of C−H bond lengthening is negatively, not positively, correlated with the extent of C−Cl bond cleavage. Greater C−H lengthening in the transition structure thus seems to indicate not a later but rather a less cationic transition structure in which extensive C−H bond cleavage is required before the chloride begins to depart. In that light, Figure 5 can be interpreted as showing that E2 barriers are low when the transition structure is comparatively cationic in character (such that leaving group departure occurs well ahead of C−H cleavage) and are high when the transition structure is not so cationic in character (such that extensive C−H cleavage is necessary in order to entice the chloride to depart).

Finally, Marcus theory suggests that the barrier for a reaction can be decomposed into an intrinsic and a thermodynamic component. Substitution reactions to some degree provide a test of the theory. Marcus theory can be used to predict the barriers of S_N2 reactions in which cyanide displaces chloride from the barriers of the identity reactions (chloride displacing chloride and cyanide displacing cyanide) and the exothermicity of the nonidentity reaction. Figure 6 plots the barriers for all the S_N2 reactions investigated here computed in this manner against the actual (ab initio calculated) values. The agreement is indeed superb, as has been observed in other Marcus theory analyses of S_N2 reaction barriers.[62,63]

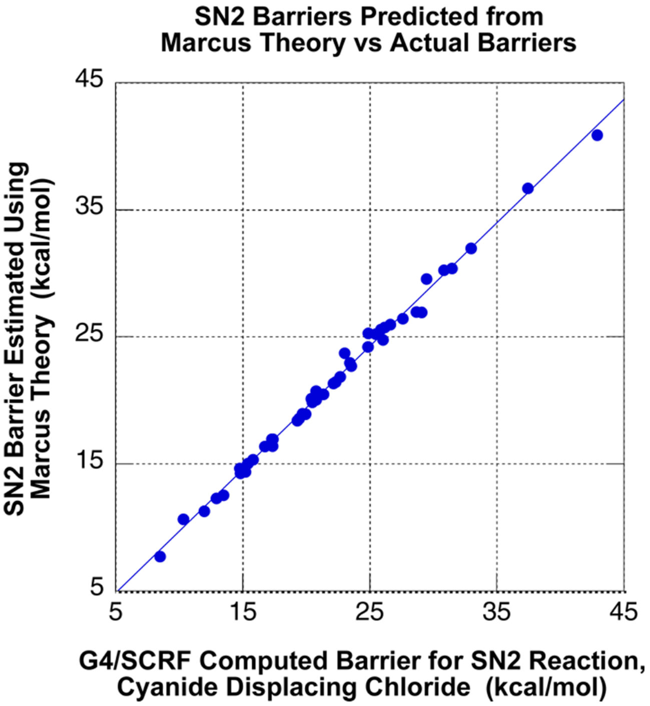


Figure 6. Plot of S_N2 barrier ($\Delta H^{\ddagger}$, 0 K) estimated using Marcus theory versus the actual (ab initio calculated) barrier. The horizontal axis represents the G4/SCRF barriers computed for S_N2 reactions in which cyanide displaces chloride. The vertical axis represents estimates obtained using Marcus theory from the computed barriers for the corresponding identity reactions (chloride displacing chloride and cyanide displacing cyanide) and the computed overall enthalpies of the nonidentity reactions. The equation is

$$B_{\mathrm{CNCl}} = \frac{B_{\mathrm{CNCN}} + B_{\mathrm{ClCl}} + E_{\mathrm{CNCl}}}{2}$$

where B_{CNCl} is the estimated barrier for the reaction in which cyanide displaces chloride; B_{CNCN} and B_{ClCl} are the barriers for the identity displacement reactions; and E_{CNCl} is the overall enthalpy change (exoerthmicity) of the nonidentity displacement (in which cyanide displaces chloride). The least-squares line has the equation $y = -0.020 + 0.971x$ and a correlation coefficient r^2 of 0.995. The correlation coefficient decreases to 0.988 if free energies at 298 K are used instead of enthalpies at 0 K (and the resulting slope is 0.973, and the intercept is +0.57 kcal/mol).

Enthalpy vs Free Energy, Solvent Effects, and Choice of Base and Nucleophile. All of the patterns of reactivity described above were deduced from free energy barriers for substitution and elimination reactions in which cyanide is the nucleophile or base, calculated in the presence of a simulated acetonitrile solvent. Under different conditions, the barriers would surely be somewhat different. Can the qualitative patterns, which are the central result of this paper, nevertheless be generalized? We hope so, and there is some evidence to support this notion.

For instance, the decision to use free energies rather than enthalpies makes virtually no difference. A plot of $\Delta G^{\ddagger}$ (298 K) versus $\Delta H^{\ddagger}$ (0 K) (Figure S4, Supporting Information) for all S_N2 and E2 reactions yields a correlation coefficient r^2 of 0.97 and a slope of 0.94.[64] Along the same lines, inclusion of solvation clearly makes an enormous difference for the absolute magnitude of the barriers, but the effect on relative barriers is far smaller. A comparison between the barriers computed in the presence and absence of a solvent shows a fairly high correlation of r^2 = 0.84 (at least if three outliers are omitted[65]) (Figure S5, Supporting Information). It therefore seems fair to say that polar, aprotic solvation has some effect on the reactivity, but that the trends and patterns mostly reflect inherent (gas-phase) behavior rather than differential solvation.

The choice of reaction partner is more fraught. The S_N2 barriers computed with cyanide as the nucleophile correlate with those for chloride rather closely, with $r^2 = 0.93$ and a slope of 1.06 (Figure S6, Supporting Information). The patterns of S_N2 reactivity are thus broadly similar with the two different nucleophiles, and there is reason to believe that the results are fairly general. The E2 barriers computed with chloride and cyanide as the base, on the other hand, are very poorly correlated (Figure S7, Supporting Information). That is likely because chloride is an unrealistically weak base, and in fact, the eliminations promoted by chloride are endothermic rather than exothermic. The reactions with cyanide, which are exothermic, serve as a more reasonable basis for comparisons. However, it must be conceded that the patterns of reactivity reported here for E2 reactions are probably not as generalizable as the S_N2 patterns. In particular, these patterns are probably typical of reactions at the E2C end of the traditional E2H-E2C spectrum: those E2 reactions characterized by good leaving groups and somewhat softer bases, in which there is a certain amount of carbocation character at the α-carbon (as opposed to carbanion character on the β-carbon at the E2H end of the spectrum).[27,34]

COMPUTATIONAL METHODS

All calculations were performed using the Gaussian 09 package.[66] G4 calculations were performed on all reactants, transition structures, carbocations, and products, both in the gas phase and in a simulated acetonitrile solvent, although only the latter results are reported here. The solvent simulation was accomplished using the default solvation model in Gaussian 09: the Polarizable Continuum Model implemented via integral equation formalism (IEF-PCM).[67−69] Ionic species were modeled as free ions, lacking counterions. Although this approach is imperfect, the good agreement with experiment (e.g., Figure 1) suggests it is sufficient for the present purposes.[70] The G4 procedure is documented elsewhere[25] but begins with a B3LYP/6-31G(2df,p) geometry optimization and frequency calculation. Minima (reactants, products, carbocations) were confirmed to have no imaginary frequencies, while transition structures were confirmed to have one. In a very small number of symmetrical cases (e.g., S_N2 of chloride on 2-chloro-2-methylpropane), one or two excess imaginary frequencies were present but had very small magnitudes and corresponded to rotations of methyl groups with very low barriers.[71] Free energies are all reported at 298 K.

W1 calculations were also carried out where possible, generally for reactants with four or fewer carbon atoms, and the associated transition structures, products, and carbocations.[22−24] In the gas phase, W1BD calculations were used, and in solution, W1U calculations.[72] As explained in the Supporting Information, the G4 barriers were converted to a scale comparable to the W1U barriers using the extremely close correlation between the two for any single reaction class ($r^2 = 0.993$ or better for all reaction types).

Many of the structures, both minima and transition structures, have more than one thermally accessible conformation. In such cases, all the reasonable conformations were computed, and the lowest energy structure was used for analysis.[73] Conformational averaging was not included in the calculations of free energy, but for these fairly small and simple structures, we believe this omission will not have a large effect on the predicted reactivity differences.[74]

Calculations were also performed at a number of other levels of theory, some of which are substantially less expensive than W1 or G4. While computational methodology is not the focus of this paper, we nonetheless provide some comparisons in Table 3, which describes the correlations between reaction barriers computed at various levels.[75] The W1U, G4, G3B3, and CBS-QB3 procedures in particular all give very closely correlated reaction barriers.

Table 3. Comparison of Reaction Barriers Computed at Various Levels of Theory[a] [75]

method	r^2	1-r^2	slope	intercept (kcal/mol)
compared to W1U:				
G4	0.988	0.012	1.030	−0.71
G3B3	0.986	0.014	1.023	−1.70
CBS-QB3	0.993	0.007	1.028	−1.50
B2PLYPD[b]	0.983	0.017	0.971	−3.20
M062X sp[c]	0.983	0.017	0.936	+0.34
M062X[d]	0.984	0.016	0.942	+0.39
compared to G4:				
G3B3	0.988	0.012	0.991	−0.87
CBS-QB3	0.984	0.016	0.988	−0.42
B2PLYPD[b]	0.965	0.035	0.946	−2.95
M062X sp[c]	0.930	0.070	0.904	+0.64
M062X[d]	0.932	0.068	0.906	+0.86

[a]Based on free energies of activation at 298 K in simulated acetonitrile solvent, for all S_N2 and E2 reactions. The cases with both chloride and cyanide as the reaction partner are included. [b]B2PLYPD/6-311+G(2df,2p)//B3LYP/6-31G(d). [c]M062X/6-311+G(2df,2p)//M062X/6-31+G(2df,p). [d]M062X/6-31+G(2df,p).

CONCLUSION

A systematic comparison of the free energies of transition structures for S_N2 and E2 reactions has been carried out at the W1 and G4 levels of electronic structure theory and in the presence of a simulated solvent. This makes it possible to elucidate the effects of alkyl halide structure on these canonical reactions in a more consistent manner than previously. While the conclusions depend to some degree on the present choice of nucleophile or base (cyanide ion), leaving group (chloride), solvent (acetonitrile), etc., there is nonetheless reason to believe that the findings offer some insight that has a degree of generality for typical substitution and elimination reactions in which the leaving group is good (and in which elimination mechanisms do not begin to resemble $E1_{cb}$).

Some key findings are as follows:

- α-Methylation raises the S_N2 barrier by approximately 3 kcal/mol per methyl group; β-methylation raises the barrier by a somewhat smaller amount on average, but the effect is highly nonlinear (the last methyl group makes by far the biggest difference).
- The effect of α- and β-methylation on E2 barriers is even larger and of opposite sign: each α-methylation decreases the barrier by roughly 4 kcal/mol, and each β-methylation decreases the barrier by about 3 kcal/mol.
- The first two points together demonstrate that the preference for elimination over substitution as alkyl substitution increases results at least as much from the decrease in the E2 barrier as from the increase in the S_N2 barrier.
- Compared to saturated analogues, allyl derivatives show moderately increased S_N2 reactivity (barriers decreased by ~2 kcal/mol), and slightly increased E2 reactivity (barriers decreased by ~1 kcal/mol). Propargyl derivatives exhibit reactivity very similar to that of saturated analogues (S_N2 barriers decreased and E2 barriers increased by ~1 kcal/mol).
- Benzyl derivatives show greatly enhanced S_N2 reactivity (barriers decreased by ~5 kcal/mol), as well as substantially increased E2 reactivity (barriers decreased by ~3 kcal/mol).

- Allyl, propargyl, and benzyl systems thus all show a pronounced bias toward substitution over elimination.
- Carbonyl substituents hugely enhance S_N2 reactivity (barriers lowered by ~7 kcal/mol) while slightly decreasing E2 reactivity (barriers raised by ~1 kcal/mol). These systems are thus ideally suited for substitution; i.e., they have an enormous bias toward substitution over elimination.
- Vinyl derivatives show enormously decreased S_N2 reactivity (barriers raised by ~19 kcal/mol) but only slightly decreased E2 reactivity (barriers raised by ~2 kcal/mol).
- Strained rings show very similar amounts of decreased reactivity in both substitution and elimination: barriers increase by ~12 kcal/mol for cyclopropyl systems and ~3 kcal/mol for cyclobutyl systems.
- Cyclopentyl systems show slightly greater reactivity than acyclic analogues in both S_N2 and E2 (barriers lower by 1–2 kcal/mol).
- Cyclohexyl systems exhibit enhanced E2 reactivity (barriers drop by ~2 kcal/mol) but significantly decreased S_N2 reactivity (barriers increase by ~3 kcal/mol), strongly biasing these systems toward elimination.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full Gaussian 09 reference; selected recent references about S_N2 and E2 reactions; plots of $\Delta G^{\ddagger}$ versus ΔG^0, versus carbocation stability, and versus a composite of both parameters for E2 reactions; plot of $\Delta G^{\ddagger}$ versus $\Delta H^{\ddagger}$; plot of $\Delta G^{\ddagger}$ in solution versus gas phase; plots of $\Delta G^{\ddagger}$ for cyanide versus chloride for both S_N2 and E2 reactions; description of procedure for interpolating W1 energies from G4 energies; plots comparing W1U and G4 energies for all reaction types; correlations between all levels of theory; comments on imaginary frequencies; W1, G4, CBS-QB3, G3B3, M062X/6-31+G(2df,p), M062X/6-311+G(2df,2p), and B2PLYPD/6-311+G(2df,2p) absolute and relative energies (all both SCRF and gas-phase); W1U/SCRF, G4/SCRF, W1BD (gas-phase), and G4 (gas-phase) optimized geometries. 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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(14) To be a little more precise, Gronert (ref 13) shows the effect of *β*-substitution on the S_N2 reaction rate is not monotonic: the first methylation increases the reaction rate, although subsequent *β*-methylations decrease it. The same behavior is observed in the present study (vide infra). The effect on the E2 rate is more consistent.

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states, and the carbocation energies are provided only as a reference. The dielectric response of a continuum solvation model goes roughly as $(\varepsilon - 1)/(2\varepsilon + 1)$, and this factor quickly approaches its maximum as ε becomes greater than about 10 anyway, so the particular choice of polar solvent for such a model in fact makes little difference.

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(34) Carbocation character at the α-carbon is consistent with a transition state at the E2C end of the E2H−E2C spectrum, as expected for E2 reactions characterized by good leaving groups and relatively soft bases.

(35) Ground-state destabilization might also play a role here: some of the steric congestion of a tertiary alkyl chloride is relieved upon going to the E2 transition state, in which the α and β carbons are partially planarized.

(36) Calculated atomic charges reveal the same trend. The CCSD(T) calculations and other highly correlated levels of theory that underlie the compound procedures such as W1 and G4 do not yield wave functions and therefore do not allow computation of charges. However, the B3LYP/cc-pVTZ+d optimization that serves as the start of the W1U procedure yields the following values for the Mulliken atomic charge of the carbon bearing the chlorine, in the E2 transition structure, for the four cases in Scheme 3: +0.067; +0.052; +0.048; and +0.220. The tertiary case clearly has far more carbocation character in the transition structure than do the other three cases, and the primary case has the least carbocation character. The C(β)−H bond lengths (given in Scheme 3) tell a similar story: the tertiary case is clearly different from the others.

(37) The average reported for the effect of methylation also includes three series not shown in the plot (to reduce clutter): 1-chloropropane to 2-chlorobutane, 1-chloro-2-methylpropane to 2-chloro-3-methylbutane, and 1-chloro-2,2-dimethylpropane to 3-chloro-2,2-dimethylbutane.

(38) The averaging excludes cases that yield only allene or alkyne products and uses the E2 reaction yielding 1-methylcyclopropene (rather than the more stable methylenecyclopropane) from 1-chloro-1-methylcyclopropane as the reference case for 1-chlorocyclopropane.

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(73) Barriers are computed as the difference in energy between the lowest energy transition structure conformation and the lowest energy reactant conformation. It is assumed that barriers for conformational interconversion are lower than the substitution and elimination reaction barriers (the Curtin−Hammett condition).

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(75) Calculations reported here were in acetonitrile solvent in all cases. The set of barriers used for comparison consists of all the S_N2 and E2 barriers, with both chloride and cyanide as the reaction partner. Note that the correlations with W1 cannot be directly compared to those with G4, since W1 calculations were not possible for all structures, i.e., the top portion of the table corresponds to a different and substantially smaller set of comparisons than does the lower part of the table.

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