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The Competition between Elimination Pathways in the Reactions of a Wide Variety of Bases with 2-Fluoro- and 2-Chlorobutane in the Gas Phase

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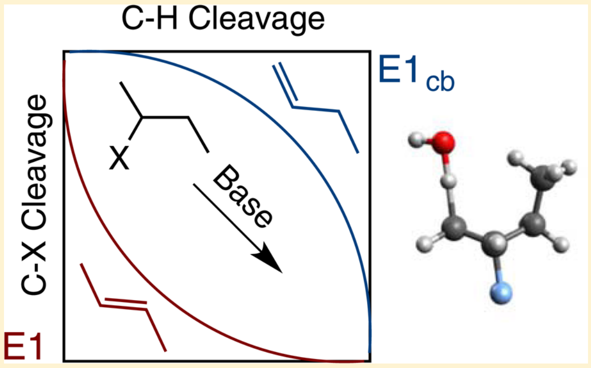
S *Supporting Information*

ABSTRACT: *Ab initio* methods are used to examine the regio- and stereoselectivities of the elimination reactions of 2-fluorobutane and 2-chlorobutane with a series of nucleophiles (F^-, HO^-, CH_3O^-, $(CH_3)_3CO^-$, NH_2^-, CH_3^-, H^-, Cl^-, HS^-, and PH_2^-). The data suggest that regiochemistry is most closely related to the nature of the transition state on the E2 spectrum with $E1_{cb}$-like reactions favoring the least-substituted alkene product and E1-like reactions favoring the most-substituted alkene product. There appears to be no correlation between the extent of π-bond formation (as measured by the $C_\alpha-C_\beta$ distance) and the preference for forming the more highly substituted alkene. The stereochemistry (*E* vs *Z*) is less sensitive to the nucleophile and is relatively constant with the exception of a few systems that appear to have long-range interactions that reduce the bias against the *Z* product. Comparisons with experimental results in solution show, with a few exceptions, similar reactivity trends in solution and the gas phase.



INTRODUCTION

Elimination reactions from a single substrate that lead to two or more product olefins have yielded much useful information on relative reactivities.[1] A simple analysis of the product composition, usually by gas chromatography, provides results quickly and easily. While the results would seem to avoid complicating factors by comparing two very similar reactions proceeding from a single substrate, the conclusions from the data are strictly applicable only under the conditions of that reaction and may not be applicable under other conditions. Changing conditions may lead to differences in solvent effects, the nature of the base (free vs ion paired), stereochemistry (syn vs anti), and temperature effects. As a result, there has been much interest in studying these systems in solvent-free environments.[2−15] In the present contribution, we have employed *ab initio* calculations to study the intrinsic effects of the base and leaving group on orientation in eliminations in the gas phase. Past studies have shown that fundamental patterns in condensed-phase elimination reactivity are reproduced in the gas phase as well as examining the competition between substitution and elimination.[11,16,17] However, there have not been definitive experimental studies of the regioselectivity of the E2 reactions of simple alkyl halides in the gas phase.

This approach eliminates the solvent effect and the ion-pairing nature of the base. It allows us to use a wider range of bases than would be feasible in any one solvent, and it ensures that the preferred stereochemistry of the reaction is anti. As long as the base is a free anion, anti is preferred over syn by 6−13 kcal/mol (in the presence of a metal ion that can coordinate with the leaving group as the anion attacks the β-hydrogen, syn elimination is preferred by at least 8 kcal).[5−7,18−20] Building on earlier computational results that focused on the reactions of 2-fluoro- and 2-chlorobutane with fluoride and chloride ions,[18] the present study examines a much broader variety of nucleophiles in terms of basicity and hardness (i.e., charge density and polarizability). The set produces a full spectrum of predicted product distributions and transition state geometries, which allows for a deeper analysis of the reaction system (Scheme 1).

METHODS

We chose to use the MP2/6-31+G* level of theory with the Gaussian03 suite of quantum mechanical programs.[21] While this relatively simple approach would be unsuitable for calculating absolute energies to the accuracy required for meaningful results, we felt that inadequacies of the method would largely cancel in the comparison of reactions at different sites in the same substrate. Earlier work on the reactions of 2-fluorobutane and 2-chlorobutane with the fluoride ion suggested that rational results were obtainable.[18] We prefer an ab initio approach because density functional theory approaches have been shown to be problematic in characterizing E2 processes.[22] Reactions yielding *E*-2- and *Z*-2-butene can utilize only one conformation of the

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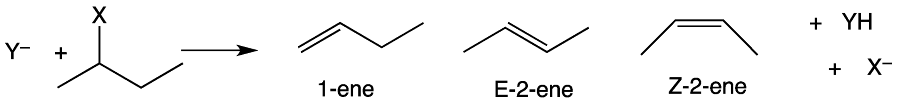
Scheme 1. Reaction Systems



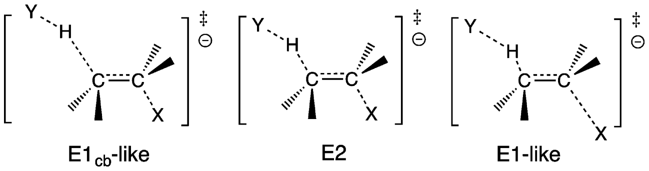
Y = F, Cl, HO, CH_3O, $(CH_3)_3CO$, NH_2, CH_3, H, SH, PH_2
X = F, Cl

transition state for each. Reactions yielding 1-butene, however, can utilize any one of three transition state conformations. Consequently, we calculated one transition state for each of the three staggered conformations (of the ethyl group relative to the leaving group).

RESULTS

Given the breadth of the data, it is best to group them into sets that exhibit similar selectivity behavior. The two substrates are markedly different because their leaving groups have very different basicities and their overall exothermicities differ by over 20 kcal/mol in the gas phase. The poor leaving group, fluoride, will shift the transition states toward $E1_{cb}$-like processes (Scheme 2), whereas more balanced transition states are expected for the reactions with chloride as the leaving group. As for the nucleophiles, some are small and basic (e.g., F^-, HO^-, and NH_2^-) and others in the group are less basic and have low charge densities (e.g., Cl^-, HS^-, and PH_2^-). The former will favor early transition states with $E1_{cb}$-character, and the latter will give later transition states with no tendency toward $E1_{cb}$-character in the transition state.

Scheme 2. Spectrum of E2 Transition States



2-Fluorobutane with Hard Nucleophiles. Data for the reactions of 2-fluorobutane with the various nucleophiles are given in Table 1 as relative enthalpies of activation. The set of hard nucleophiles includes entries 1−5 in Table 1; CH_3^- is on the borderline because although it is very basic, it is also a diffuse anion with a very low electron binding energy.[23] In any case, this set presents a relatively coherent picture. Formation of the 1-ene and E-2-ene are competitive, with barriers that are within roughly 1 kcal/mol of each other. The 1-ene is generally favored with the oxygen bases, HO^-, CH_3O^-, and $(CH_3)_3CO^-$, whereas the E-2-ene is favored for F^- and NH_2^-. The preferences for the *E* isomer over the *Z* isomer are from 0.9 to 1.6 kcal/mol. The computed preference in the product, *E*-2-butene vs *Z*-2-butene, is 1.6 kcal/mol at the MP2/6-31+G* level (experimental value is 0.75 kcal/mol).[24]

Table 1. Data for Elimination Reactions of 2-Fluorobutane[a]

entry	nucleophile	PA[b]	ΔΔH‡ (kcal/mol) 1-ene	E-2-ene	Z-2-ene	ΔH_{rxn}[c]
1	F^-	372	0.9	0.0	1.2	−1.4
2	HO^-	390	−0.4	0.0	1.2	−19.4
3	CH_3O^-	382	0.0	0.0	1.6	−11.4
4	$(CH_3)_3CO^-$	375	−0.6	0.0	0.9	−4.4
5	NH_2^-	403	0.4	0.0	1.2	−32.4
6	CH_3^-	417	0.9	0.0	1.1	−46.4
7	H^-	400	1.7	0.0	0.5	−29.4
8	Cl^-	333	2.6	0.0	1.7	37.6
9	HS^-	351	2.0	0.0	1.2	19.6
10	PH_2^-	364	1.4	0.0	1.0	6.6

[a] Computed at the MP2/6-31+G* level. [b] Proton affinity of the nucleophile (kcal/mol).[25] [c] Heat of reaction. Data from refs 24−26.

The geometries of the transition states for this set are more diverse, in part due to variations in exothermicity. To illustrate this effect, Table 2 gives geometric data for the transition states leading to the 1-enes and Figure 1 shows the corresponding transition state for the reaction of HO^- and 2-fluorobutane. The oxygen nucleophiles all give similar transition states where the proton transfer to the nucleophile is well advanced (O−H = 1.10−1.18 Å and C−H = 1.50−1.65 Å), but there is little extension of the C−F bond (C−F = 1.53−1.57 Å). These systems are exhibiting classic $E1_{cb}$ behavior. Although fluoride is a hard base, the elimination reaction is only slightly exothermic and results in a very late transition state with almost complete cleavage of the C−H (1.75) and C−F (1.97 Å) bonds, so any $E1_{cb}$ character in the process is not manifested in the transition state (see below). With NH_2^-, the strong basicity of the nucleophile shifts the system to a very early transition state that has $E1_{cb}$ character. The C−F bond is hardly stretched (1.51 Å), whereas the proton transfer has progressed, but not to the extent seen with the oxygen nucleophiles. These geometric effects are mirrored in the computed Natural Population Analysis (NPA) charges calculated for the transition states (Table 3). With the exception of the late transition state with fluoride as the base, all of the transition states exhibit little

Table 2. Bond Distances in TS for Forming 1-Ene from 2-Fluorobutane[a]

nucleophile (Y)	*r*(Y---H)	*r*(H---C)	*r*(C---C)	*r*(C---F)
F^-	1.01	1.75	1.38	1.97
HO^-	1.18	1.50	1.46	1.53
CH_3O^-	1.11	1.61	1.45	1.56
$(CH_3)_3CO^-$	1.10	1.65	1.45	1.57
NH_2^-	1.37	1.40	1.47	1.51
CH_3^-	1.56	1.36	1.47	1.51
H^-	1.09	1.40	1.46	1.53
Cl^-	1.49	1.74	1.36	2.19
HS^-	1.46	1.79	1.39	1.85
PH_2^-	1.59	1.73	1.42	1.65

[a] Computed at the MP2/6-31+G* level. The corresponding bond lengths in $CH_3CHFCH_2CH_3$ at this level of theory are H−C = 1.10 Å, C−C = 1.52 Å, and C−F = 1.43 Å. Experimental bond lengths for Y−H are HF, 0.92 Å; H_2O, 0.96 Å; CH_3OH, 0.96 Å; $(CH_3)_3COH$, 0.96 Å; NH_3, 1.01 Å; CH_4, 1.09 Å; 0.74 Å; HCl, 1.28 Å; H_2S, 1.34 Å; and PH_3, 1.42 Å.[27]

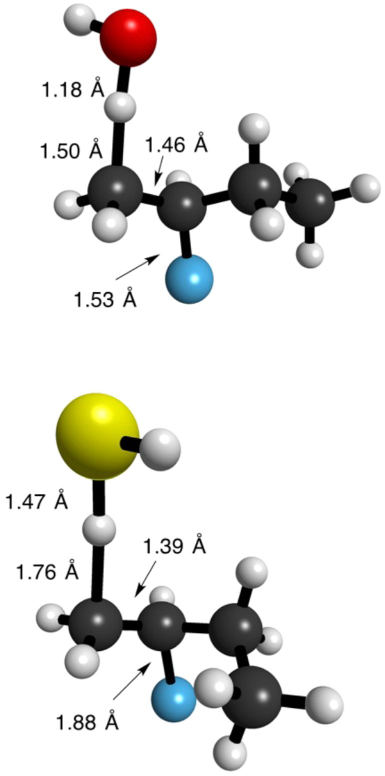


Figure 1. MP2/6-31+G* optimized transition states for the reactions of (top) HO^- and (bottom) HS^- reacting with 2-fluorobutane to produce 1-butene. Fluoride is blue, sulfur is yellow, oxygen is red, carbon is gray, and hydrogen is white.

Table 3. NPA Charges in TS for Forming 1-Ene from 2-Fluorobutane[a]

Nucleophile (Y)	Y	H	C_1	C_2	F
F^-	−0.7	0.58	−0.82	0.15	−0.83
HO^-	−0.74	0.47	−0.91	0.23	−0.56
CH_3O^-	−0.71	0.49	−0.93	0.22	−0.58
$(CH_3)_3CO^-$	−0.68	0.46	−0.91	0.10	−0.53
NH_2^-	−0.73	0.39	−0.86	0.24	−0.55
CH_3^-	−0.71	0.32	−0.83	0.24	−0.54
H^-	−0.53	0.2	−0.86	0.23	−0.56
Cl^-	−0.48	0.31	−0.72	0.11	−0.91
HS^-	−0.37	0.21	−0.83	0.16	−0.77
PH_2^-	−0.31	0.11	−0.89	0.19	−0.64
$CH_3CHFCH_2CH_3$[b]		0.23	−0.68	0.25	−0.47

[a] Computed at the MP2/6-31+G* level. [b] Substrate.

additional charge development on the fluoride leaving group (~ −0.55 vs −0.47 in the substrate).

2-Fluorobutane with Soft Nucleophiles. We have roughly categorized entries 6−10 as soft nucleophiles in this study (Table 1). Of this set, CH_3^- and H^- are quite different in that they are much more basic and do not involve third-period centers. With the exception of CH_3^-, all of these nucleophiles (entries 6−10) have a significant preference (1.4−2.6 kcal/mol) for 2-enes. With CH_3^-, the preference is only 0.9 kcal/mol, but as noted above, this nucleophile is on the edge of the two categories. The preference for *E*-2-butene over *Z*-2-butene with the soft nucleophiles varies more widely, and H^- gives a very small preference (0.5 kcal/mol).

The geometries of the transition states for 1-ene formation for these nucleophiles (Table 2) are also sensitive to the exothermicity of the process. The reactions with CH_3^- and H^- are highly exothermic and give transition states with significant $E1_{cb}$ character and little extension of the C−F bond (1.51 and 1.53 Å, respectively). In the endothermic reactions, the proton transfers are nearly complete at the transition states (C−H = 1.73−1.79 Å). As an example, the transition state for the reaction of HS^- with 2-chlorobutane is given in Figure 2. Only in the reaction with PH_2^- is the transition state early enough to see evidence of $E1_{cb}$ character in the set of endothermic processes. Here the proton transfer is nearly complete, but the C−F bond is only stretched to 1.65 Å. The charges on the leaving groups (Table 3) tend to reflect the position of the transition state on the reaction coordinate (early or late).

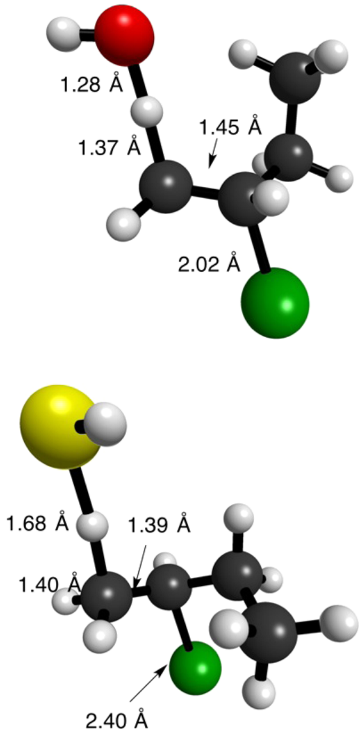


Figure 2. MP2/6-31+G* optimized transition states for the reactions of (left) HO^- and (right) HS^- reacting with 2-chlorobutane to produce 1-butene. Chlorine is green, sulfur is yellow, oxygen is red, carbon is gray, and hydrogen is white.

2-Chlorobutane with Hard Nucleophiles. Data for the reactions with 2-chlorobutane are shown in Table 4. With chloride as the leaving group, all of the reactions are exothermic with the exception of chloride as the nucleophile. Again, we will begin by examining the hard nucleophiles (entries 1−5). Unlike the reactions with 2-fluorobutane, there is a stronger preference for the 2-ene (1.5−1.9 kcal/mol) with this substrate. The preference for the *E*-2-butene over the *Z*-2-butene product is less variable than with 2-fluorobutane, ranging from 0.7 to 1.2 kcal/mol.

Geometric data for the transition states for 1-ene formation from 2-chlorobutane are shown in Table 5 and indicate that the transition states are very sensitive to the exothermicity of the reaction, with NH_2^- having the earliest transition state and F^- having the latest. In all cases, proton transfer is well advanced (C−H distances from 1.33−1.42 Å) and leaving group

Table 4. Data for the Elimination Reactions of 2-Chlorobutane[a]

entry		PA[b]		$\Delta\Delta H^{\ddagger}$ (kcal/mol)		
			1-ene	E-2-ene	Z-2-ene	ΔH_{rxn}[c]
1	F^-	372	1.6	0.0	1.1	−23.5
2	HO^-	390	1.5	0.0	1.1	−41.5
3	CH_3O^-	382	1.6	0.0	0.9	−33.5
4	$(CH_3)_3CO^-$	375	1.7	0.0	0.7	−26.5
5	NH_2^-	403	1.9	0.0	1.2	−54.5
6	CH_3^-	417	2.1	0.0	1.1	−68.5
7	H^-	400	2.5	0.0	0.6	−51.5
8	Cl^-	333	3.0	0.0	1.0	15.5
9	HS^-	351	3.2	0.0	0.8	−2.5
10	PH_2^-	364	3.1	0.0	0.8	−15.5

[a] Computed at the MP2/6-31+G* level. [b] Proton affinity (kcal/mol).[25] [c] Heat of reaction. Data from refs 24 and 25.

Table 5. Bond Distances in TS for Forming 1-Ene from 2-Chlorobutane[a]

Nucleophile (Y)	r(Y---H)	r(H---C)	r(C---C)	r(C---Cl)
F^-	1.16	1.42	1.42	2.17
HO^-	1.28	1.37	1.45	2.02
CH_3O^-	1.25	1.39	1.44	2.04
$(CH_3)_3CO^-$	1.26	1.40	1.44	2.06
NH_2^-	1.44	1.33	1.46	1.99
CH_3^-	1.65	1.29	1.46	1.97
H^-	1.21	1.29	1.45	2.02
Cl^-	1.58	1.41	1.37	2.63
HS^-	1.66	1.41	1.39	2.42
PH_2^-	1.82	1.37	1.41	2.26

[a] Computed at the MP2/6-31+G* level. The corresponding bond lengths in $CH_3CHClCH_2CH_3$ at this level of theory are H−C = 1.10 Å, C−C = 1.52 Å, and C−Cl = 1.80 Å. Experimental bond lengths for Y−H are HF, 0.92 Å; H_2O, 0.96 Å; CH_3OH, 0.96 Å; $(CH_3)_3COH$, 0.96 Å; NH_3, 1.01 Å; CH_4, 1.09 Å; 0.74 Å; HCl, 1.28 Å; H_2S, 1.34 Å; and PH_3, 1.42 Å.[27]

Table 6. NPA Charges in TS for Forming 1-Ene from 2-Chlorobutane[a]

Nucleophile (Y)	Y	H	C_1	C_2	Cl
F^-	−0.79	0.22	−0.86	0.04	−0.58
HO^-	−0.78	0.45	−0.84	−0.04	−0.43
CH_3O^-	−0.78	0.45	−0.84	−0.03	−0.45
$(CH_3)_3CO^-$	−0.73	0.41	−0.82	−0.14	−0.41
NH_2^-	−0.75	0.39	−0.82	−0.07	−0.38
CH_3^-	−0.75	0.32	−0.79	−0.09	−0.35
H^-	−0.61	0.24	−0.81	−0.06	−0.41
Cl^-	−0.64	0.32	−0.76	0.18	−0.86
HS^-	−0.58	0.25	−0.77	0.12	−0.76
PH_2^-	−0.56	0.20	−0.78	0.06	−0.63
$CH_3CHClCH_2CH_3$[b]		0.23	−0.65	−0.21	−0.11

[a] Computed at the MP2/6-31+G* level. [b] Substrate.

expulsion is lagging (C−Cl distances from 1.99−2.17 Å). Although not as pronounced as with 2-fluorobutane as the substrate, these nucleophiles are exhibiting $E1_{cb}$ character with 2-chlorobutane. The transition state for the reaction of HO^- with 2-chlorobutane is given in Figure 2. NPA charges are shown in Table 6 and mirror trends in the geometric parameters.

2-Chlorobutane with Soft Nucleophiles. With the soft nucleophiles, the preference to form the 2-ene is considerably greater, and this is most apparent in the least exothermic processes. For many of this set, the transition state preference for the 2-ene exceeds the computed thermodynamic preference to form *E*-2-butene (2.6 kcal/mol), suggesting that features in the transition state are biasing the system toward forming *E*-2-butene. The preference for *E* stereochemistry is somewhat smaller than that in the reactions of the hard nucleophiles with 2-chlorobutane and drops to 0.6 kcal/mol with H^- as the nucleophile.

The transition state geometries for the soft nucleophiles are also sensitive to the exothermicity of the reaction. In reactions that are weakly exothermic (or endothermic), there is substantial extension of the C−Cl bond. These reactions exhibit shorter C_1−C_2 distances and less C−H bond cleavage than was seen in the 2-fluorobutane system. Overall, they appear to have more synchronicity in the bond-breaking and -forming processes. A sample transition state for the reaction of HS^- with 2-chlorobutane is shown in Figure 2. The NPA charges highlight the shift in the nature of the mechanism with the soft nucleophiles. For Cl^-, HS^-, and PH_2^-, there is substantial positive charge on C-2 relative to the substrate. This suggests that C−Cl cleavage is getting ahead of proton transfer and that these transition states are showing some mild E1 character.

Reaction Profiles. To better characterize the nature of the reaction pathways, intrinsic reaction coordinate (IRC) calculations were completed for selected systems. These are presented in Figures 3 and 4 for the reactions of 2-fluorobutane and 2-chlorobutane, respectively, leading to 1-butene. In Figure 3, reactions with HO^-, HS^-, and F^- are shown. The process with HO^- is $E1_{cb}$-like with the early reaction coordinate completely dominated by proton transfer. The reaction is at the edge of becoming $E1_{cb}$, but the 2-fluoroethyl anion is only stable when hydrogen-bonded to the departing H_2O and is not a true intermediate.[4,9] At the other extreme in this set is the reaction of HS^-. Here the process begins with C−F extension, and then as the system approaches the transition state, proton transfer rapidly dominates. It should be noted that the transition state occurs late because it is an endothermic reaction. The process clearly has some E1 character early on the reaction path despite the poor leaving group. With F^-, proton transfer dominates the early portion of the reaction coordinate, but C−F cleavage is also important as the system reaches the transition state. Here, the system has features that favor an E1cb path (hard base, poor leaving group), but the limited exothermicity of the process requires some C−F cleavage in the transition state. The result is a process that gives a transition state that suggests a synchronous reaction, but is reached by a somewhat asynchronous path.

In Figure 4, IRCs are shown for the reactions of HO^- and HS^- with 2-chlorobutane. With HO^-, the reaction exhibits a transition state with some $E1_{cb}$ character, but early on the reaction coordinate, proton transfer, and C−Cl extension are relatively synchronous—only near the transition state does proton transfer begin to dominate the pathway. In contrast, the pathway with HS^- is dominated from the start by C−Cl cleavage and only near the transition state does proton transfer begin to play a large role.

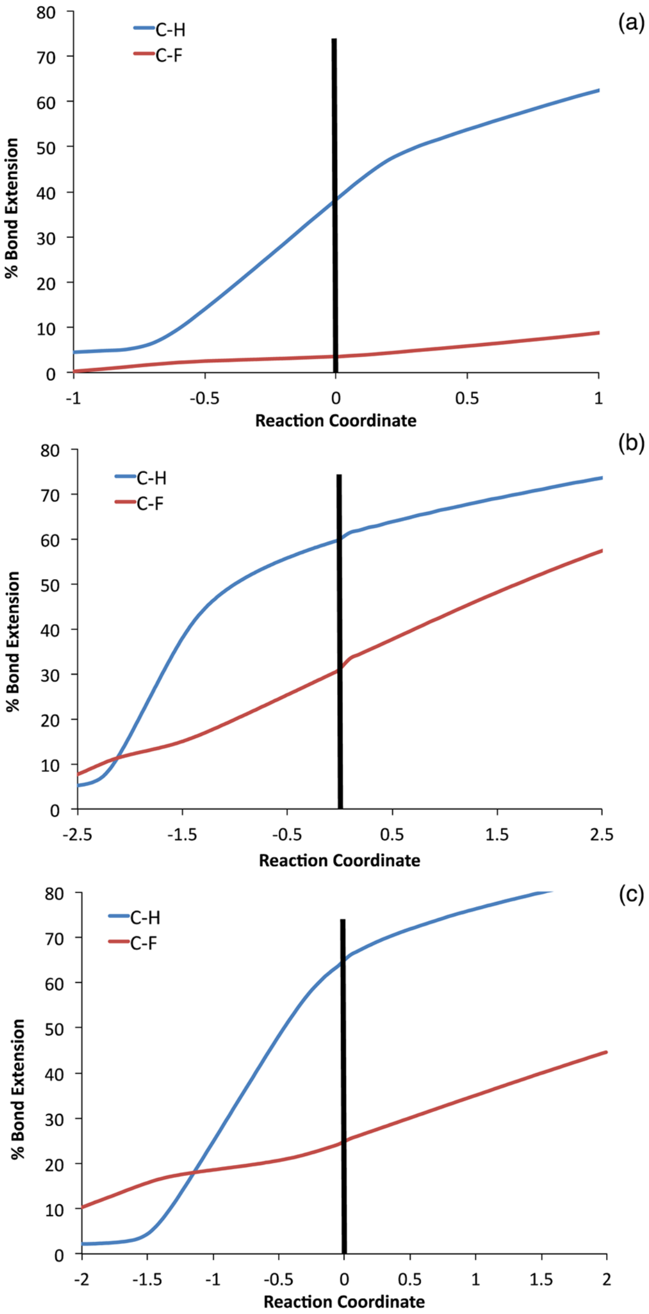


Figure 3. MP2/6-31+G* IRC calculations for the reactions of 2-fluorobutane with (a) HO$^-$, (b) F$^-$, and (c) HS$^-$. The black vertical line indicates the transition state.

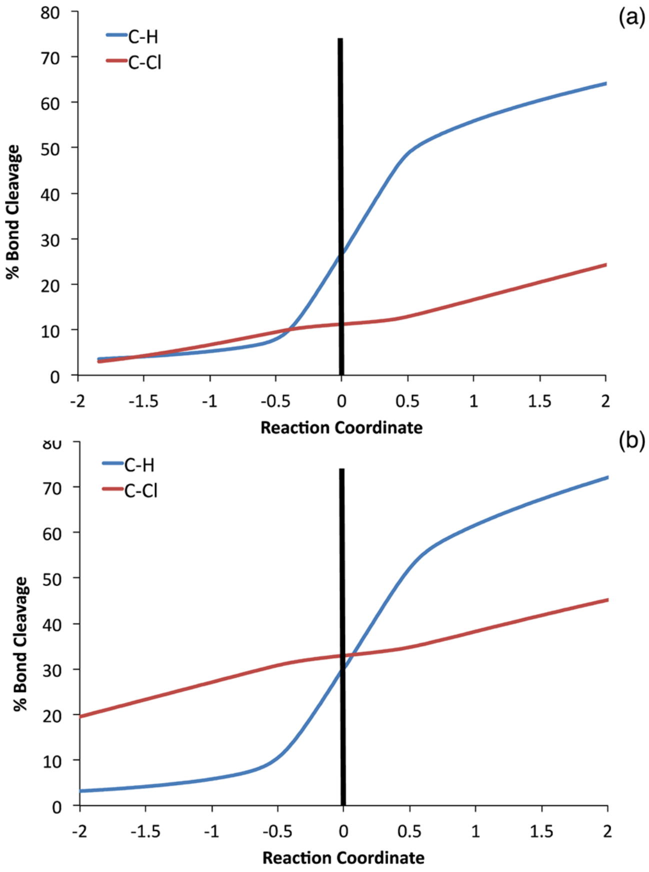


Figure 4. MP2/6-31+G* IRC calculations for the reactions of 2-chlorobutane with (a) HO$^-$ and (b) HS$^-$. The black vertical line indicates the transition state.

■ DISCUSSION

The reactions span a reasonable portion of the E2 spectrum of concerted transition states. With a weak leaving group, the 2-fluorobutane reactions are biased toward E1$_{cb}$-like processes. The IRC for HO$^-$ indicates a strongly E1cb-like pathway, and this is likely the case for the other oxygen-centered nucleophiles and the highly basic nucleophiles. With F$^-$, the reaction is barely exothermic and the transition state incorporates some C−F cleavage. So despite asynchronicity in reaching the transition state, it gives a transition state with significant double bonding and a prototypical E2 structure. Finally, the third period nucleophiles exhibit late transition states with 2-fluorobutane and, based on the IRC for HS$^-$, have some E1-character early in their reaction pathways. It has been shown that third-period nucleophiles are poor bases in E2 processes, so the E1-character is not surprising.[5] As expected, the better leaving group in 2-chlorobutane leads to earlier transition states and reduces the bias toward E1$_{cb}$ reactions. HO$^-$ and HS$^-$ present two general pathways with this substrate. In the former, the highly basic nucleophile is able to tilt the system to an E1$_{cb}$-like transition state, but early on the reaction coordinate, there is significant extension of the C−Cl bond. This pattern seems to extend across the transition states of all the highly basic nucleophiles. With HS$^-$, there is a dramatic shift toward an asynchronous pathway with E1 character. C−Cl cleavage dominates the early part of the reaction pathway, and there is considerable extension of the C−Cl bond in the transition state. Similar transition states are seen with the other third period nucleophiles.

From a transition state structure perspective, the reactions tend to separate into groups based on the nature of the nucleophilic atom. With second period nucleophiles (and the highly basic H$^-$), the pathways are dominated early by proton transfer and retain some E1$_{cb}$ character in the transition state. The extent of π-bonding in the transition state (as measured by the C_1−C_2 distance) depends partly on how early it occurs on the reaction coordinate and is most significant with the weakest base, F$^-$. With the third period nucleophiles, proton transfer is retarded due to their weak kinetic basicity and E1 character is more apparent in the transition states and pathways. These systems tend to be the least exothermic in this set, and they have considerably more π-bond formation (i.e., shorter C_1-C_2 distances) in their transition states.

With respect to regioselectivity, the data from Tables 1 and 4 lead to a few general conclusions. First, hard nucleophiles have a much weaker preference for producing 2-enes and when paired with a poor leaving group can favor the production of the 1-ene. For the reactions of the soft nucleophiles (with the exception of the borderline species, CH_3^-), little 1-ene product is expected in the gas phase. The preference for forming the 1-ene is also closely linked to the degree of $E1_{cb}$ character in the transition state. This is reasonable because the 1° center is expected to be more acidic than the 2° center. For example, the 1° C−H bonds in propane are estimated to be 3.8 kcal/mol more acidic in the gas phase than the 2° C−H bonds.[28] This preference for the 1-ene is most evident in the reactions of the oxygen-centered nucleophiles with 2-fluorobutane; however, almost all the transition states with high $E1_{cb}$ character either prefer the 1-ene or have only a small preference for the 2-ene (less than 1 kcal/mol). The one exception is the reaction of H^- with 2-fluorobutane. As has been well documented, an advantage of forming the 1-ene is reduced steric repulsion when the base attacks the least-hindered C−H bond.[1] With its small nucleophilic center, H^- has little steric impact and the inherent preference for 2-ene formation is more evident. The opposite effect is not observed with the bulky base, *tert*-butoxide, and it shows a 1-ene preference roughly similar to the other oxygen-centered nucleophiles. The *tert*-butyl group is well removed from the substrate in the gas-phase transition state, so it is not surprising that its steric bulk does not impact the barriers. In going to 2-chlorobutane as the substrate, $E1_{cb}$ character is reduced in all of the transition states, including those of the strong bases. Proton transfer is not near completion and is coupled to leaving group expulsion. Here, the E2 transition states do not incorporate significant carbanion character and the enhanced acidity of the 1° center is not able to tip the balance to the 1-ene. In these cases, the elimination transition states reflect product stability, though the advantage of the 2-ene is not fully realized in the transition states.

In the reactions with E1 character in their transition states, there is a strong preference for the 2-ene. This can reach or exceed the computed thermodynamic advantage seen in the products. This is most pronounced in the reactions of 2-chlorobutane and seems to correlate with the E1 character in the transition states. Surprisingly, the extent of π-bond formation in the transition states seems to have no impact on the preference for the 2-ene. For example, a graph of the 2-ene preference against the C_1-C_2 distances in the transition states produces a scatter plot with no visible correlation (see Supporting Information). This result suggests that the common argument that the relative stability of E2 transition states is driven mainly by the stability of the nascent alkene is tenuous. The controlling factor appears to be the location of the transition state on the E2 spectrum. When the transition state lies on the $E1_{cb}$ side of the spectrum, the carbanion character of the transition state will favor reactions involving the most acidic site, which is the least substituted β-carbon. This tilts the system toward the 1-ene in this case. When the transition state lies on the E1 side of the spectrum, the carbocation character that develops in the transition state will lead to hyperconjugation to hydrogens on adjacent carbons. In analogy to isolated carbocations, this will be most important on the most-substituted carbon and drive the system to the 2-ene.[29] An attractive aspect of this argument is that the kinetic preference for the 2-ene is not capped by the thermodynamic preference for the 2-ene, and with sufficient carbocation character, this form of transition state stabilization could exceed the preference for the 2-ene found in the product. In any case, the extent of π-bond formation in the transition state does not correlate with the preference for the 2-ene and other factors are at play.

The preference for *E* stereochemistry is less variable in these systems and tends to be roughly 1 kcal/mol in most cases (about 2/3 the computed preference in 2-butene). There are a few exceptions, and the most notable ones, with low preferences. These include the reactions of H^- with both substrates, the E1-like reactions with 2-chlorobutane, and the *tert*-butoxide reaction with 2-chlorobutane. The reasons for these low E-stereochemistry preferences are likely varied, but probably linked to long-range interactions. For example, it is possible that H^- and *tert*-butoxide could benefit from favorable van der Waals interactions with the terminal methyl groups in the cis transition state.

Although long sets of experimental results under comparable conditions are not available, key comparisons of calculation and experiment can still be made. For the reaction of sodium ethoxide with 2-pentyl halides in ethanol, the proportion of 1-pentene increases in the order I < Br < Cl < F, ranging from 20% for the iodide to 82% for the fluoride.[30] The same progression is observed for 2-methyl-2-butyl bromide and chloride under the same conditions. This is the order to be expected from our calculated comparisons of fluoride and chloride, indicating no qualitative difference between gas and solution phase. The *E*/*Z* ratio for the 2-pentene from the 2-pentyl halides is variable, from 4.1 for the iodide to 2.6 for the fluoride, in contrast to the small differences in the 2-butene ratios found in the present work.

For oxygen bases, a change in base usually involves a concomitant change in solvent, so that both base strength and solvation are varying. The reaction of a series of alkyl bromides with alkoxides in the corresponding alcohols show a marked increase in the percent of 1-ene in the order $EtO^- < t\text{-}BuO^- < Me_2EtCO^- < Et_3CO^-$.[31] The effects are substantial, ranging for 2-methyl-2-butyl bromide from 30% to 88%. Our contrasting results show $\Delta\Delta H^\ddagger$ for 1-butene formation varying by only about 0.1 kcal/mol from HO^- to CH_3O^- to $t\text{-}BuO^-$, with $t\text{-}BuO^-$ showing no special behavior compared to the other two bases. It thus is unlikely that there is any steric effect in the sense of direct steric interference between the base and substrate in the transition state. The results of Brown and Okamoto must reflect a solvent effect, possibly steric hindrance of solvation or the effect of solvation on the kinetic basicity of the alkoxide or on the extent of ion pairing with the counterion.

The reactions of tetrabutylammonium chloride and bromide in acetone with a number of alkyl bromides and an alkyl tosylate give the intriguing result of very low 1-ene products: the largest proportion of 1-ene (9%) is from 2-methyl-2-butyl bromide with tetrabutylammonium chloride, and some of the reactions yield less than 1% of 1-ene.[32] These results are similar to ours for the reactions of the softer bases with 2-butyl chloride and, to a lesser extent, with 2-butyl fluoride. Winstein proposed a very product-like transition state with the base coordinating with the β-hydrogen and the α-carbon at the same time, the E2C mechanism. Although our results show low preferences for 1-ene, the geometries of the transition states reveal them to belong to the normal E2 spectrum, tending toward the E1-like end. There is no reason to believe that the transition state in solution is qualitatively different.

CONCLUSIONS

Here we have surveyed the regioselectivity of a variety of nucleophiles in the base-induced eliminations of 2-fluorobutane and 2-chlorobutane. In these reactions, the nature of the transition state does not always reflect the pathway, and with the late transition states, the geometry can suggest greater synchronicity than is present in the path leading to it (i.e., one component, such as proton transfer, could lead early on the reaction coordinate but be caught at a late transition state by leaving group expulsion). The most novel result is that the position of the transition state on the E2 continuum is the greatest determinant in regioselectivity and outweighs factors related to the position of the transition state (i.e., early vs late) and the extent of π-bond formation. In E1$_{cb}$-like reactions, the higher intrinsic acidity of the least substituted β-carbon outcompetes product stability in determining the preferred pathway. In the reactions with E1 character, a hydrogen on the most highly substituted β-carbon is most engaged in hyperconjugation with the transient carbocation character at the α-center, making it the most acidic and driving the elimination toward the 2-ene. The length of the $C_\alpha-C_\beta$ bond (i.e., extent of π-bond formation) at the transition state seems to have little effect on the regioselectivity. Apparently the relative stability of the transition states is most closely related to factors that affect the stability of the center (α or β) that has experienced the greatest bond-breaking at the transition state, not the product of the reaction. This is not surprising because the relative stabilities of true E1$_{cb}$ and E1 intermediates are expected to be more sensitive to variations in substitution patterns than the alkene products. Overall, the data support the notion that the E2 spectrum (Scheme 1) is key to understanding the selectivity of elimination reactions. Comparisons with pertinent experimental results in solution reveal similar trends in reactivity between the gas phase and solution with a few exceptions. The most notable is the absence of a significant change in the 1-ene/*E*-2-ene ratio with increasing size of the oxygen base in the gas phase, suggesting that the change in solution is a solvation rather than a steric effect.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01983.

> Tables of all the transition state geometries in .xyz format along with the associated enthalpies and imaginary frequencies. The complete citation for ref 21 is also included (PDF)

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REFERENCES

(1) Saunders, W. H.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; Wiley: New York, NY, 1973.

(2) Glad, S. S.; Jensen, F. *J. Org. Chem.* **1997**, *62* (2), 253−260.

(3) Glad, S.; Jensen, F. *J. Am. Chem. Soc.* **1994**, *116* (20), 9302−9310.

(4) Gronert, S.; Kass, S. R. *J. Org. Chem.* **1997**, *62* (23), 7991−8000.

(5) Gronert, S. *J. Am. Chem. Soc.* **1991**, *113* (16), 6041−6048.

(6) Gronert, S. *J. Am. Chem. Soc.* **1993**, *115* (2), 652−659.

(7) Gronert, S. *J. Org. Chem.* **1994**, *59* (23), 7046−7050.

(8) Wu, W.; Shaik, S.; Saunders, W. H. *J. Org. Chem.* **2010**, *75* (11), 3722−3728.

(9) Saunders, W. H. *J. Org. Chem.* **1997**, *62* (2), 244−245.

(10) Saunders, W. H. *J. Org. Chem.* **1999**, *64* (3), 861−865.

(11) Conner, K. M.; Gronert, S. *J. Org. Chem.* **2013**, *78* (17), 8606−8613.

(12) Gronert, S.; Fagin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, *129* (17), 5330−5331.

(13) Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126* (40), 12977−12983.

(14) Chung, D. S.; Kim, C. K.; Lee, B. S.; Lee, I. *J. Phys. Chem. A* **1997**, *101* (48), 9097−9104.

(15) Minato, T.; Yamabe, S. *J. Am. Chem. Soc.* **1988**, *110* (14), 4586−4593.

(16) Flores, A. E.; Gronert, S. *J. Am. Chem. Soc.* **1999**, *121* (11), 2627−2628.

(17) Gronert, S. *Acc. Chem. Res.* **2003**, *36* (11), 848−857.

(18) Saunders, W. H. *J. Org. Chem.* **2000**, *65* (3), 681−684.

(19) Borchardt, J. K.; Saunders, W., Jr. *J. Am. Chem. Soc.* **1974**, *96* (12), 3912−3918.

(20) Borchardt, J. K.; Swanson, J.; Saunders, W. *J. Am. Chem. Soc.* **1974**, *96* (12), 3918−3920.

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

(22) Gronert, S.; Merrill, G. N.; Kass, S. R. *J. Org. Chem.* **1995**, *60* (3), 488−489.

(23) Ellison, G.; Engelking, P.; Lineberger, W. *J. Am. Chem. Soc.* **1978**, *100* (8), 2556−2558.

(24) Afeefy, H. Y.; Liebman, J. F.; Stein, S. E. *NIST Standard Reference Database Number 69*; National Institute of Standards and Technology (http://webbook.nist.gov): Gaithersburg, MD, 2015.

(25) Bartmess, J. E. *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, 2014.

(26) Kormos, B. L.; Liebman, J. F.; Cramer, C. J. *J. Phys. Org. Chem.* **2004**, *17* (8), 656−664.

(27) Johnson III, R. D. *NIST Computational Chemistry Comparison and Benchmark Database*, NIST Standard Database Number 101 (http://cccbdb.nist.gov): September 2015.

(28) Depuy, C. H.; Gronert, S.; Barlow, S. E.; Bierbaum, V. M.; Damrauer, R. *J. Am. Chem. Soc.* **1989**, *111* (6), 1968−1973.

(29) This effect is most pronounced in the H−C−C angles of the 2-butyl cation. For the hydrogens most engaged in hyperconjugation with the cationic center, the $H-C_1-C_2$ angle is 102.6° and the $H-C_3-C_2$ angle is 90.6° at the MP2/6-31+g* level. This suggests a much stronger interaction with the hydrogen at the most substituted site.

(30) Saunders, W. H.; Fahrenholtz, S. R.; Caress, E. A.; Lowe, J. P.; Schreiber, M. *J. Am. Chem. Soc.* **1965**, *87* (15), 3401−3406.

(31) Brown, H. C.; Moritani, I.; Okamoto, Y. *J. Am. Chem. Soc.* **1956**, *78* (10), 2193−2197.

(32) Parker, A. J.; Biale, G.; Cook, D.; Lloyd, D. J.; Stevens, D. R.; Takahashi, J.; Winstein, S. *J. Am. Chem. Soc.* **1971**, *93* (19), 4735−4749.