

Leaving Group Effects in Gas-Phase Substitutions and Eliminations

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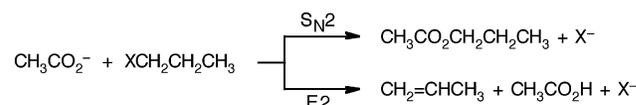
Abstract: Using a methodology recently developed for studying the product distributions of gas-phase S_N2 and E2 reactions, the effect of the leaving group on the reaction rate and branching ratio was investigated. Using a dianion as the nucleophile, reactions with a series of alkyl bromides, iodides, and trifluoroacetates were examined. The alkyl groups in the study are ethyl, *n*-propyl, *n*-butyl, isobutyl, isopropyl, *sec*-butyl, and *tert*-butyl. The data indicate that leaving group abilities are directly related to the exothermicities of the reaction processes in both the gas phase and the condensed phase. Gas-phase data give a reactivity order of iodide > trifluoroacetate > bromide for S_N2 and E2 reactions. Previous condensed phase data indicate a reactivity order of iodide > bromide > trifluoroacetate for substitution reactions; however, the basicities of bromide and trifluoroacetate are reversed in the condensed phase so this reactivity pattern does not reflect the relative reaction exothermicities. Aside from this variation, the gas-phase data parallel condensed phase data indicating that the substituent effects are rooted in the nature of the alkyl substrate rather than in differences in solvation. The experimental data are supported by calculations at the MP2/6-311+G(d,p)//MP2/6-31+(d) level.

Introduction

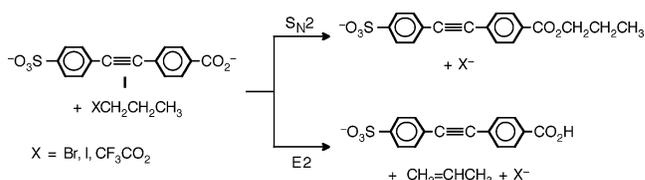
Substitution and elimination reactions have had a central role in the development of modern mechanistic organic chemistry.^{1–5} They share the same reactants, a nucleophile and substrate with a good leaving group, and often compete (for example, see Scheme 1). A tremendous amount of data is available for these reactions and generalizations have been put forward to explain the effects of the substrate's structure, the nucleophile, the leaving group, and the solvent on the absolute and relative rates of these processes.

More recently, these reactions have been studied in the gas phase by several research groups in an effort to simplify the systems and eliminate solvation effects.⁶ A major complication in the gas-phase study of substitution and elimination reactions is that they generally lead to the same ionic product (Scheme 1) and therefore cannot be distinguished directly by mass spectrometry. Novel approaches to deal with this issue have

Scheme 1



Scheme 2



been developed in the past but did not prove to be general.^{7,8} To allow for the direct detection of reaction products, we have turned to dianions as nucleophiles because their reactions lead to two ionic products, one of which is diagnostic of the mechanism.⁹ An example is shown in Scheme 2 using a dianion, **I**, with a carboxylate as the nucleophile and a sulfonate as a spectator ionic site. Only the carboxylate is reactive under these conditions and the second charge has a limited effect on the potential energy surfaces of substitution reactions.^{10–12} We have

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used this approach to study several factors that influence the competition between substitution and elimination including the structure of the alkyl halide substrate and the nature of the nucleophilic center.^{13,14} Here, we explore the effect of the leaving group on the rates of the reactions and the competition between the mechanisms. Three leaving groups have been investigated, bromide, iodide, and trifluoroacetate.¹⁵ The gas-phase proton affinity (PA)¹⁶ of iodide (314 kcal/mol) is 9 kcal/mol less than bromide so it is expected to be a better leaving group and to lead to faster reactions. Trifluoroacetate has essentially the same PA (323 kcal/mol) as bromide so similar rates might be expected; however, trifluoroacetate relies on resonance delocalization for some of its stability and this factor may not be fully realized in the transition states. Moreover, the reactions of alkyl trifluoroacetates tend to be more exothermic than those of the bromides.^{16–18} For the alkyl component of the substrates, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, and *tert*-butyl groups have been used. To support the experimental work, the reactions also have been studied computationally using acetate as a simplified model for the dianion nucleophile

Methods

Mass Spectrometry. All experiments were completed in a modified Finnigan LCQ quadrupole ion trap mass spectrometer equipped with electrospray ionization (ESI). The tetrabutylammonium salt of **I** was dissolved in HPLC-grade acetonitrile or methanol (10^{-4} – 10^{-5} M) and pumped through the electrospray interface at flow rates from 3 to 10 μ L/min. Typical ESI conditions involved needle potentials from 3.5 to 4.5 kV and heated capillary temperatures from 125 to 200 °C. In some cases, triethylamine (10^{-3} – 10^{-2} M) was added as a base to enhance the dianion signal. A notched waveform was applied to isolate the dianion in the ion trap. Once a steady signal was obtained, the neutral reagent was introduced into the helium system via a custom gas-handling system. The system has been described previously,^{9,13} but a brief overview is given here. The liquid reagent was delivered to a measured flow of helium (1–2 L/min) by a syringe pump. With reagent flows of 30–300 μ L/hr, rapid evaporation occurs at the syringe needle to give mixing ratios of $\sim 10^2$ – 10^4 (He/reagent). For less volatile substrates, the mixing region was heated to 50–75 °C. Most of the gas mixture is diverted to an exhaust system and ~ 0.25 mL/min is carried through the LCQ's restriction capillary to the ion trap to establish a helium pressure of $1.75 \pm 0.2 \times 10^{-3}$ Torr. At these pressures, the mean free path of the molecules is considerably longer than the dimensions of the trap and the loss of gases out of the end cap holes of the trap can be treated as an effusion process. The lighter helium atoms effuse more quickly than the reagent molecules and the mixing ratio must be corrected for differential effusion (square root of the mass

ratio correction). The equation describing the reagent pressure (Torr) is given below:

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

where F_{RX} is the reagent flow rate (liquid, mL/min), d_{RX} is the reagent density, MW_{RX} is the reagent molecular weight, F_{He} is the helium flow rate (gas, moles/min), and MW_{He} is the atomic weight of He. Typical reagent pressures were between 10^{-5} and 10^{-7} Torr.

Once an appropriate flow of the neutral reagent was established, the system was given several minutes for the reagent pressure to equilibrate to a steady state. Kinetic measurements were completed by varying the time delay between dianion isolation and the expulsion of all ions to obtain a mass spectrum. During the delay time, the dianion was held in the trap with a q_z value of 0.5 to ensure that the expected products would experience stable trapping fields. In most cases, 13 different time delays were used in each run. Time delays and reagent flows were adjusted to obtain plots that covered two to three half-lives of the reactant ion. Reported rates are the average of at least six kinetic runs using at least three different reagent flow rates and were obtained on at least two different days. Kinetic plots showed good linearity and gave correlation coefficients (r^2) greater than 0.98. To evaluate the absolute accuracy of the rate constant measurements, we previously have compared our data with results from flowing afterglow work and seen good correspondence.^{13,14} Other work from our laboratory indicates that the ion trap provides an environment that is effectively at ambient temperature (~ 300 K).¹⁹ Finally, product distributions were determined by integrating the areas under the appropriate peaks. No evidence for secondary reactions was observed and the product distributions varied little as a function of reaction extent.

All the neutral reagents were obtained in the highest purity commercially available and used without further purification with exception of the trifluoroacetates. The commercial samples were contaminated with traces of trifluoroacetic acid and required purification. Just before use, they were added to an aqueous NaHCO₃/cyclohexane mixture, the organic layer was removed and then used for the mass spectrometric studies. The cyclohexane (and any trace H₂O) has no effect on the experiment and appropriate dilution factors were used in the analysis of the kinetic data. The dianion precursor salt was available from a previous study.¹⁴

Computational. Calculations were completed with the GAUSSIAN98²⁰ or GAUSSIAN03²¹ quantum mechanical packages on a Digital

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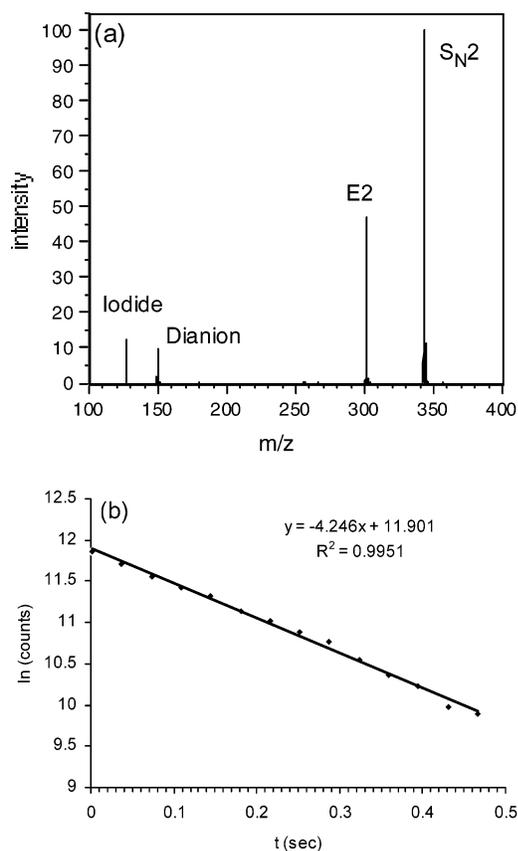


Figure 1. (a) Spectrum from the reaction of **I** with isopropyl iodide. The dianion, **I**, is at $m/z = 150$ and the E2 and S_N2 products appear at $m/z = 301$ and 343 , respectively. (b) Kinetic plot for the reaction of **I** with isopropyl iodide.

Alpha, an HP/Convex Exemplar, or a Pentium 4 computer. Geometries were initially optimized at the HF/6-31+G* level and frequency calculations were also completed at this level. All of the species in the study exhibited the proper number of imaginary frequencies. In addition, optimizations were completed at the MP2/6-31+G(d) level. Energies reported in the text are at the MP2/6-311+G(d,p) level corrected for zero-point vibrational energies (ZPE, scaled by 0.9135).²² For iodide, an all-electron basis set reported by Radom and co-workers was employed.²³ In some cases, larger basis sets and higher levels of correlation were employed to test the accuracy of the computed values.

Given that the computational work on the model systems is to provide qualitative comparisons to the experiments, no thermal corrections were made. Multiple rotamers were considered and data for only the most stable ones are listed in the tables. For the E2 reactions, only anti orientations were considered because there is ample evidence that they are preferred in the gas-phase eliminations of simple halides.^{24–26}

Results and Discussion

Figure 1a provides a sample mass spectrum for the reaction of **I** with isopropyl iodide. Dianion **I** appears at $m/z = 150$ and the S_N2 and E2 products appear at $m/z = 343$ and 301 , respectively. A rather small signal is observed for iodide under these conditions because the q_z value of the trap had been set

Table 1. Rate Constants for Reactions with **I**^a

alkyl group	Br	leaving group	
		TFA ^b	I
ethyl	0.44	1.3	28
<i>n</i> -propyl	0.67		41
<i>n</i> -butyl	1.39	1.6	59
isobutyl	0.32		26
isopropyl	0.12	0.4	7.2
<i>s</i> -butyl	0.56		47
<i>tert</i> -butyl	0.48		93

^a Units = 10^{-11} cm^3 molecule⁻¹ sec⁻¹. Expected absolute uncertainty is $\pm 20\%$ but relative values have smaller uncertainties, $\pm 5\%$. ^b TFA = trifluoroacetate.

to maximize the trapping efficiency of the higher mass products (301 and 349) at the expense of the low mass ions (i.e., iodide). A kinetic plot for this reaction is shown in Figure 1b and it has good linearity over more than two half-lives. In Table 1, overall rate constants are given for the reactions of **I** with the alkyl bromides, iodides, and trifluoroacetates. The rate constants range from as low as $\sim 1 \times 10^{-12}$ cm^3 molecule⁻¹ sec⁻¹ up to $\sim 9 \times 10^{-10}$ cm^3 molecule⁻¹ sec⁻¹. It is not straightforward to estimate collision rates for dianions such as **I**,⁹ but one expects values of about $2\text{--}5 \times 10^{-9}$ cm^3 molecule⁻¹ sec⁻¹.²⁷ Therefore, these rate constants correspond to efficiencies (reaction rate/collision rate) ranging from less than 0.001 to greater than 0.1. The rate constant data in Table 1 point to a clear pattern in leaving group ability: iodide > trifluoroacetate > bromide. This pattern does not match the gas-phase proton affinities of the leaving groups (iodide < bromide \sim trifluoroacetate) but does parallel the expected exothermicities of the reactions. For example, NIST data indicate that the gas-phase S_N2 reactions of methyl iodide are 2.2 kcal/mol more exothermic than those of methyl trifluoroacetate and 6.4 kcal/mol more exothermic than those of methyl bromide.^{16,18} Our computational work also indicates that the alkyl trifluoroacetate reactions generally are about 4 kcal/mol more exothermic than the alkyl bromide reactions. Therefore, the higher gas-phase reactivity of the trifluoroacetates compared to the bromides is reasonable given the reaction thermodynamics. However, a different pattern is found in solution. For example, Noyce reported a relative reactivity ranking of 1:7:43 for the series trifluoroacetate/bromide/iodide in solvolysis reactions.²⁸ An important difference is that in water, trifluoroacetate is a much stronger base than bromide (or iodide), so it is expected to be a poorer leaving group in that medium. The large shift in relative basicity between the media is easily rationalized. The resonance delocalization and diffuse nature of trifluoroacetate reduces its solvation energy relative to the halides and makes it a less stable anion in solution (i.e., more basic). The key point, however, is that leaving group ability appears to be controlled by the same factor in both phases, the exothermicity of the reaction process.

Product distributions from the reactions are presented in Table 2. The data are in accord with expectations from previous condensed- and gas-phase work.^{1,6} Substitution dominates with primary alkyl groups and a mixture of substitution and elimination is observed with secondary alkyl groups. Elimination is the only pathway with the tertiary alkyl group. Table 2 also

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Table 2. Partial Rate Constants for Reactions with I^a

alkyl Group	leaving group								
	Br			TFA ^b			I		
	S _N 2	E2 ^c	%S _N 2	S _N 2	E2 ^c	%S _N 2	S _N 2	E2 ^c	%S _N 2
ethyl	0.43	0.00	99	1.3	0.0	100	28	0.3 (0.1)	99
<i>n</i> -propyl	0.67	0.00	100				39	1.6 (0.8)	96
<i>n</i> -butyl	1.39	0.00	99	1.6	0.0	100	56	3.0 (1.5)	95
isobutyl	0.04	0.28 (0.28)	11				3.7	23 (23)	14
isopropyl	0.004	0.12 (0.02)	3	0.1	0.3 (0.05)	22	5.0	2.2 (0.4)	69
<i>s</i> -butyl	0.20	0.36 (0.18)	36				13	34 (17)	27
<i>tert</i> -butyl	0.00	0.48 (0.05)	0				0.0	92 (10)	0

^a Units = 10⁻¹¹ cm³ molecule⁻¹ sec⁻¹. ^b TFA = trifluoroacetate. ^c Parenthetic data is on per β-hydrogen basis.

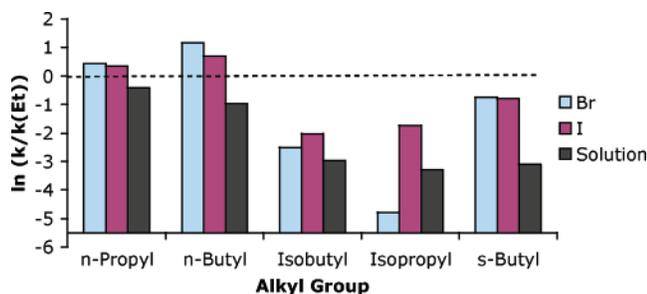


Figure 2. Relative rate data for the S_N2 reactions. Br and I refer to gas-phase data with I as the nucleophile. Solution data is for iodide exchange reactions in ethanol.³ All values relative to ethyl (represented by dashed horizontal line).

provides data on the partial rate constants for the S_N2 and E2 pathways and is useful for analyzing substituent effects.

S_N2 Rates. The bromides provide a good illustration of the effect of the alkyl group on the S_N2 rates. For the primary bromides, there is a general increase in the S_N2 rate as the chain length increases from ethyl to *n*-propyl and then to *n*-butyl. This pattern has been observed before and been attributed to the greater polarizability of the longer alkyl chains, which can stabilize the anionic S_N2 transition states.^{9,24,25,29–31} A similar effect is observed in the trifluoroacetates where *n*-butyl trifluoroacetate reacts slightly faster than ethyl trifluoroacetate. In the iodides, the same order of reactivity also is observed (*n*-butyl > *n*-propyl > ethyl). In Figure 2, the rate data for the gas-phase S_N2 reactions are presented along with representative data from solution.³ The rates in the figure are relative to the ethyl representative of each series (the rate constants for the ethyl systems are represented by the dashed line). It can be seen in the figure that chain lengthening retards the S_N2 reaction in solution (i.e., ethyl faster than *n*-propyl and *n*-butyl). In the condensed phase, polarizability effects are less important and apparently the longer alkyl chains interfere with the solvation of the transition state. In the isobutyl system, there is a sharp drop in the S_N2 rate constant for the gas-phase (bromide and iodide) and the condensed-phase systems. Kebarle and co-workers²⁹ had also noted this effect in early gas-phase work. Branching at the β-carbon is believed to cause steric crowding in the S_N2 transition state, and this factor appears to be nearly as important in the gas phase as in solution. This result suggests that the two additional methyl groups on the β-carbon can

directly interfere with the incoming nucleophile (not just with its solvation shell).

In secondary systems, the S_N2 rate constants naturally drop because of crowding in the transition states. The effect is most dramatic for isopropyl bromide where almost no S_N2 products are observed. For *sec*-butyl bromide and iodide, the S_N2 rate reduction in the gas phase is not nearly as large as in the isopropyl system; however, in solution, isopropyl and *sec*-butyl halides tend to give similar rates. The enhanced reactivity of the *sec*-butyl group relative to isopropyl in the gas phase can partially be explained by its greater polarizability. The computational modeling (see below) also suggests that *sec*-butyl has a significantly lower S_N2 barrier than isopropyl bromide.

Comparing the substituent effects across the series of leaving groups, it is clear that similar factors are at work but that the bromides are more sensitive to them. Bromide is the worst leaving group in the gas phase and therefore the alkyl bromides suffer the largest transition-state barriers. The barriers for the bromides may be close to the limit of energy available in the gas-phase collision complexes (see below), and therefore the rate constants could be very sensitive to small changes in the barriers. Aside from this difference, the data in Figure 2 and Table 2 show a remarkable consistency across the three leaving groups and the two media (gas phase and condensed phase). It does appear that the addition of methyl groups at the α- or β-carbons causes somewhat larger S_N2 rate reductions in solution. This effect is probably related to the fact that a solvated nucleophile is effectively larger and is more prone to steric crowding.

E2 Rates. For all the leaving groups, a clear trend is seen in the E2 rate constants (Table 2). The elimination rates are low for the straight-chain, primary alkyl groups, but much higher for the secondary and tertiary groups. However, the isobutyl substrates are much more reactive than the other primary substrates, and on a per β-hydrogen basis, are the most reactive of all. Because the E2 rate constants are very low for some of the primary bromides, the iodides are more useful for making quantitative comparisons. With the primary iodides, it is clear that addition of methyl groups at the β-carbon has a dramatic effect on the E2 rate constant. Almost no E2 products are seen with ethyl, low rate constants are observed with *n*-propyl and *n*-butyl, and a very high rate constant is observed with isobutyl. The rate constant ratio for this series (ethyl, *n*-propyl, isobutyl) is 1:5.2:240 on a per β-hydrogen basis. Moreover, the E2 rate for *sec*-butyl is nearly 15 times greater than that for isopropyl. Addition of methyl groups at the α-carbon also enhances the E2 rates. Going across the series ethyl/isopropyl/*tert*-butyl, the relative E2 rates (per β-hydrogen basis) increase sharply, 1:3.9:110. As with the β-methyl groups, it appears that the second addition of a methyl group has the greatest impact on the rate.³² In Figure 3, the gas-phase data for the iodides are compared to data obtained in ethanol for alkyl bromides.³³ The same order of reactivities is observed in both phases (propyl < isopropyl < isobutyl < *sec*-butyl < *tert*-butyl) and therefore it appears that similar factors are at work in determining the relative rates.

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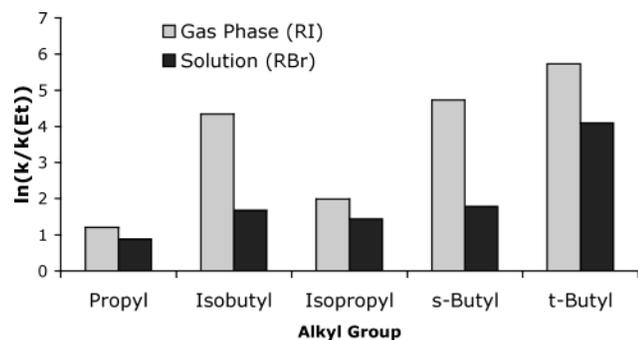


Figure 3. Relative rate data for the E2 reactions (relative to ethyl). Gas phase refers to the reactions of **I** with alkyl iodides. Solution data refers to the reactions of ethoxide/ethanol with alkyl bromides.³³ Condensed-phase data originally were reported at 25 and 55 °C but were converted to a single temperature of 40 °C using an assumed E_a of 22.9 kcal/mol (the average value from systems measured at multiple temperatures). This conversion adds relatively little uncertainty to the plot.

Table 3. Energies of Transition States for the Reactions of Acetate with Ethyl Bromide and Ethyl Iodide^a

species	level			
	MP2 6-31+G(d,p)	MP4 6-31+G(d,p)	MP2 6-311+G(d,p)	MP4 6-311+G(d,p)
EtI/S _N 2	3.7	1.6	-0.7	-2.4
EtI/E2	5.2	5.0	-0.4	-0.5
S _N 2 preference (I)	1.4	3.3	0.2	1.9
EtBr/S _N 2	-3.1	-5.4	1.5	-0.9
EtBr/E2	2.9	3.1	4.8	5.0
S _N 2 preference (Br)	6.0	8.5	3.4	5.9
S _N 2 (I vs Br) ^b	6.8	7.0	-2.1	-1.5

^a kcal/mol. ^b Iodide S_N2 transition-state energy – bromide S_N2 transition-state energy.

The major difference is that the gas-phase data are more sensitive to substituents and greater rate effects are observed. Because steric crowding is not especially important in E2 reactions, it appears that the added polarizability of the additional methyl groups is the key to enhancing the rates. Polarizability effects are less important in solution so smaller substituent effects are observed.

Computational Modeling. To gain greater insight into the reactions, ab initio calculations were used to model the transition states. As in our previous work, acetate was used as a simple model for the dianion nucleophile. In these studies, the iodides proved to be problematic. Initial attempts at the MP2/6-31+G(d,p) level suggested that the iodides had *higher* barriers than the bromides (Table 3). After several trials with various basis sets, we concluded that the all-electron basis set that we had chosen for iodide was sufficient,²³ but that at least a triple- ζ basis set was needed for the other atoms (6-311+G(d,p)). With this basis set, the barriers for ethyl iodide are lower than those of ethyl bromide; however, the S_N2 and E2 barriers were nearly the same for ethyl iodide, which is inconsistent with the experimental data.^{34,35} Ethyl iodide required a shift to the MP4 level to resolve this inconsistency.³⁶ Given the scope of this

(34) Because S_N2 reactions are expected to have large entropic barriers, an S_N2 reaction must have a lower enthalpic barrier to dominate over an E2 reaction. In fact, one expects E2 to dominate in systems where the S_N2 barrier is marginally smaller (1–2 kcal/mol) than the E2 barrier. See ref 35.

(35) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.

(36) We were not able to test this level thoroughly in these systems. It may be satisfactory, but it is possible that higher levels would be needed to obtain data that is consistent with all the iodide experiments.

Table 4. Energies of Transition States for the Reactions of Acetate with Alkyl Bromides and Trifluoroacetates (MP2/6-311+G(d,p)//MP2/6-31+G(d))^a

species ^b	S _N 2	E2	S _N 2 preference
EtBr	1.4	4.6	3.2
<i>n</i> -PrBr	-0.1	1.6	1.7
<i>n</i> -BuBr	-1.0	0.8	1.8
ⁱ BuBr	1.0	-1.8	-2.8
ⁱ PrBr	3.5	3.0	-0.5
<i>s</i> -BuBr	1.3	0.1	-1.2
<i>t</i> -BuBr	9.5	1.3	-8.2
EtTFA	-1.5	3.1	4.6
<i>n</i> -PrTFA	-2.9	1.1	4.0
<i>n</i> -BuTFA	-3.6	1.0	4.5
ⁱ BuTFA	-2.1	0.1	2.2
ⁱ PrTFA	1.8	2.4	0.7
<i>s</i> -BuTFA	-2.0	-1.0	1.0
<i>t</i> -BuTFA	4.7	-1.1	-5.8

^a kcal/mol. ^b TFA = trifluoroacetate.

study, MP4 calculations on all the systems with the 6-311+G(d,p) basis set were not practical. As a result, the computational data is limited to the bromides and trifluoroacetates at the MP2/6-311+G(d,p) level. Because we are examining model systems, the limited quantitative accuracy of this level is not a major concern and we are only seeking qualitative trends in the computational data.

In Table 4, transition-state energies are presented for the alkyl bromides and trifluoroacetates reacting with acetate. In some cases, negative transition-state energies have been obtained. This is common in gas-phase reactions and implies that the transition state is more stable than the separated reactants. This does not always lead to a collision-controlled reaction rate because entropic bottlenecks are possible, especially with tight transition states such as that of an S_N2 process.³⁵ With a negative transition-state energy, a barrier can still exist on the potential energy surface because the reaction initially passes through a stabilized ion/dipole complex on the way to the transition state. These complexes are generally 10–15 kcal/mol more stable than the reactants³⁰ so a significant barrier on the surface could still lead to a transition state that is more stable than the reactants. If the transition state is considerably less stable than the separated reactants (3–5 kcal/mol), very low rate constants are expected in the gas phase.⁶

A comparison of the data in Tables 2 and 4 indicates that the computational barriers are in reasonable accord with the observed rate constants for the S_N2 and E2 reactions. For example, the computed reactivity order for the S_N2 reactions of the bromides is *n*-butyl > *n*-propyl > isobutyl > *sec*-butyl ~ ethyl > isopropyl. Experimentally, the order is *n*-butyl > *n*-propyl > ethyl > *sec*-butyl > isobutyl > isopropyl. The only significant difference involves isobutyl bromide, which is predicted to be relatively more reactive than it is experimentally. This discrepancy may be related to an underestimation of steric effects because of the small size of the model nucleophile (acetate). We have much less experimental data for the trifluoroacetates, but the data are also in good accord with the computations. For the E2 reactions, there again is reasonable consistency between the experimental and computational data, but only if one uses rates that are on a per β -hydrogen basis (the appropriate comparison).

It is interesting to evaluate the effect of substituents on the E2 transition-state structures. It is well-known that E2 transition

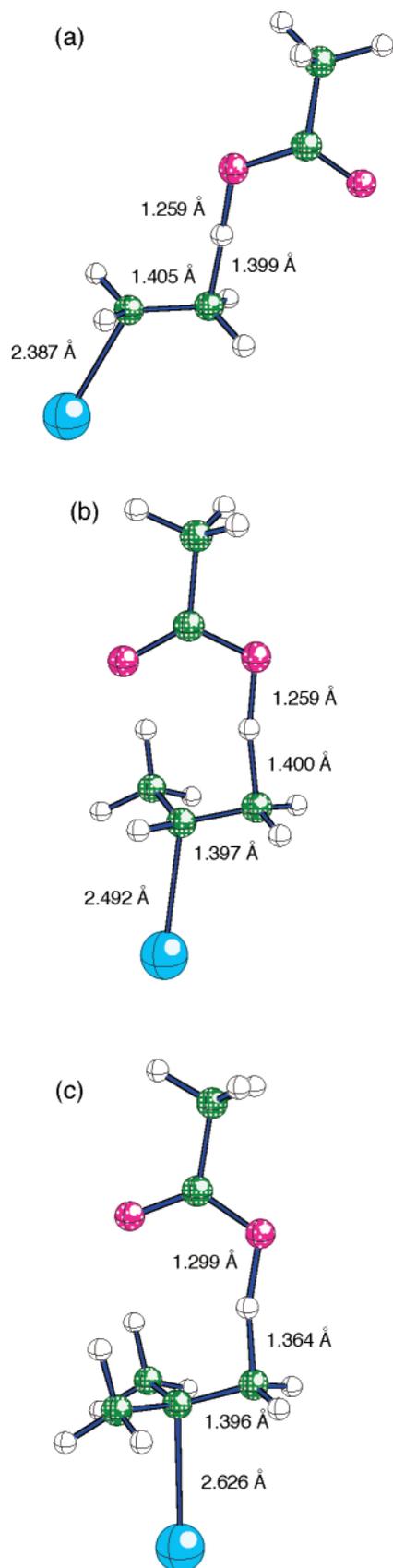


Figure 4. E2 transition states (MP2/6-31+G(d)) for the E2 reactions of acetate with (a) ethyl, (b) isopropyl, and (c) *tert*-butyl bromide. In all cases, acetate is on the upper right and bromide is on the lower left.

states can span a range of profiles from E1_{CB}-like (high β -carbanion character) to E1-like (high α -carbocation charac-

ter).² The E2 transition states for ethyl, isopropyl, and *tert*-butyl bromide are shown in Figure 4. Across this series, there is a consistent elongation of the C $_{\alpha}$ -Br distance in the transition state as methyl groups are added to the α -carbon. Also, the O-H distance (transferring proton) becomes longer and the C $_{\beta}$ -H distance becomes shorter in the *tert*-butyl system. These changes imply that the leaving group expulsion component of the reaction progresses to a greater extent and the proton-transfer component to a lesser extent when methyl groups are added to the α -carbon (i.e., more E1-like). Despite these subtle geometric shifts across the series, proton transfer and leaving group expulsion are both well advanced in all of the transition states in Figure 4 and therefore they are best classified as prototypical E2 transition states. The isopropyl and *tert*-butyl systems prefer a conformation where the acetate carbonyl is above the breaking C-Br bond. This conformation suggests a weak, stabilizing interaction between the nucleophile and the α -carbon in the more E1-like systems and has some of the characteristics of the E2C transition state proposed by Winstein;³⁷ however, the energetic impact is less than 1 kcal/mol (relative to a conformation similar to that found for ethyl). In terms of energies, the addition of methyl groups at the α -carbon reduces the E2 barrier by 1.4 kcal/mol for the first addition and 1.9 kcal/mol for the second addition.

A less pronounced pattern is observed in the transition-state geometries when methyl groups are added to the β -carbon (Figure 5). However, from ethyl to *n*-propyl and then isobutyl, there is a shift toward a less advanced proton-transfer component and a slightly more advanced leaving group expulsion component in the transition state. Despite the smaller impact on the geometries, the addition of methyl groups to the β -carbon has a larger effect on the transition-state energies. The first addition reduces the E2 barrier by 3 kcal/mol and the second by 3.4 kcal/mol. The larger energetic impact of β -methyl groups is also seen in the reaction exothermicities. For example, the elimination reaction of *n*-propyl bromide is 3 kcal/mol more exothermic than that of ethyl bromide whereas the elimination reaction of isopropyl bromide has essentially the same exothermicity as that of ethyl bromide.¹⁸ These data point out that the methyl groups have a twofold effect on the transition-state energies. For α -methylation, the charged transition state benefits from the added polarizability of the substrate even though the methylation has little effect on the exothermicity of the process. For β -methylation, the transition state benefits from the added polarizability as well as from a portion of the additional exothermicity of the reaction. This combination creates a situation where the energetic effect of the substituent on the transition state can be equal to or greater than its effect on the reaction product. The strong influence of polarizability on the methyl substituent effect is in accord with the larger rate enhancements observed in the gas-phase experiments (Figure 3).

In all cases, the trifluoroacetates are computed to have lower S_N2 barriers than the bromides. This is consistent with the rate data. For the E2 reactions, the computed barriers are generally lower for the trifluoroacetates, which is in accord with the observation that isopropyl trifluoroacetate has a higher E2 rate constant than isopropyl bromide. The other difference between

(37) Beltrame, P.; Biale, G.; Lloyd, D. J.; Parker, A. J.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2240.

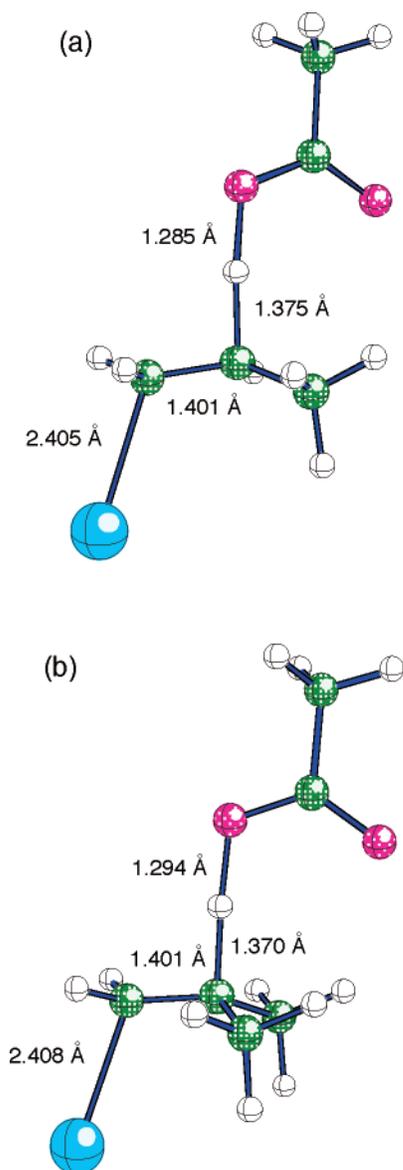


Figure 5. E2 transition states (MP2/6-31+G(d)) for the E2 reactions of acetate with (a) *n*-propyl, (b) isobutyl bromide. In both cases, acetate is on the upper right and bromide is on the lower left.

the leaving groups is that the computed S_N2 preferences are greater for the trifluoroacetates. Again, there is limited experimental data for comparison, but in isopropyl, considerably more S_N2 products are observed for the trifluoroacetate than the

bromide. This trend seems to correlate with leaving group ability and isopropyl iodide gives the most S_N2 product in the series (however, *sec*-butyl iodide gives somewhat less S_N2 product than *sec*-butyl bromide). One explanation is that the bond to the leaving group is cleaved to a greater extent in the S_N2 transition state so the process is more sensitive to leaving group ability. For example, the breaking C–O distances in the S_N2 and E2 transition states of ethyl trifluoroacetate are computed to be 1.912 and 1.885 Å, respectively.

Conclusions

As in solution, gas-phase leaving group abilities correlate with the exothermicities of S_N2 and E2 reactions. In the gas phase, the observed order of reactivity is iodide > trifluoroacetate > bromide. This order differs from that found in solution because the alkyl cation affinities of bromide and trifluoroacetate are reversed in the two phases. Nonetheless, these results confirm that variations in reaction energetics play a similar role in determining the rates of gas-phase and condensed-phase S_N2 and E2 reactions. In comparison to condensed-phase data, the gas-phase S_N2 reactions appear to be less sensitive to substituent effects whereas the gas-phase E2 reactions appear to be more sensitive to substituent effects. In S_N2 reactions, steric crowding is a key component of the substituent effect (at least with alkyl substituents) and this will be less important in the gas phase because the nucleophile does not bring a solvation shell with it. Steric effects are not particularly important in E2 reactions so other factors come into play. In particular, polarizability effects are much more important in the gas phase and are probably the root of the larger substituent effects observed in gas-phase E2 reactions. The effect of methylation on the E2 rates is greatest at the β -position, and the computational data suggest that the energetic effect of methylation on the transition states can be equal to or greater than its effect on the reaction products.

As has been noted before,³⁸ the gas phase provides data that are complementary to that obtained in solution and that reveal similar reactivity trends. Consequently, it is a very useful medium for probing the details of fundamental organic reaction mechanisms and unraveling the origins of reactivity trends without interference from factors related to solvation effects.

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(38) DePuy, C. H. *J. Org. Chem.* **2002**, *67*, 2393.