

# Gas Phase Studies of the Competition between Substitution and Elimination Reactions

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## ABSTRACT

Gas phase studies allow for the examination of organic reaction mechanisms in the absence of solvation effects and therefore probe the intrinsic reactivity of the reaction partners. The competition between substitution and elimination reactions has been a topic of interest for decades, but it has been difficult to examine in the gas phase because both pathways generally lead to the same ionic product and cannot be distinguished by mass spectrometry. By using dianions as nucleophiles, the reactions produce two ionic products, one of which identifies the mechanism. With this approach, we have examined a variety of substituent effects on the gas phase competition between substitution and elimination. In addition, we have found that similar processes occur during collisional activation of salt complexes that contain a dianion and a tetraalkylammonium cation. Overall, the results show that the gas phase studies probe the same fundamental features found in the condensed phase and provide valuable insights into reaction mechanisms.

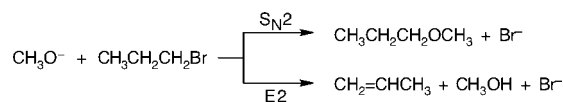
## Introduction

Over the past 30 years, gas phase studies of ionic organic reaction processes have provided a wealth of mechanistic information.<sup>1</sup> In the absence of solvation and ion pairing effects, the intrinsic reactivity of systems can be probed in great detail. Moreover, comparisons of gas phase to condensed phase data provide insights into the role that solvent and counterions play in determining reaction rates and product distributions. Many fundamental reaction mechanisms have been studied in the gas phase by mass spectrometric methods, but none has received more attention than the  $S_N2$  substitution. As in solution, gas phase  $S_N2$  reactions are often accompanied by competing E2 elimination reactions, so it is convenient to group them together in mechanistic studies.

Unfortunately, it is difficult to characterize the competition between  $S_N2$  and E2 pathways in gas phase studies because they lead to the same ionic product, and therefore cannot be distinguished directly by mass spectrometry. This is illustrated in Scheme 1 for the reaction of methoxide with propyl bromide. One sees a decrease

Scott Gronert received a Ph.D. from the University of California, Berkeley, working in the lab of Dr. Andrew Streitwieser, Jr. His introduction to mass spectrometry came as a postdoctoral fellow working with Drs. Charles DePuy and Veronica Bierbaum at the University of Colorado, Boulder. Gronert joined the faculty at San Francisco State University in 1990, and his research focuses on using mass spectrometry and computational methods to study fundamental organic reaction mechanisms.

Scheme 1



in the signal for  $\text{CH}_3\text{O}^-$  and the appearance of  $\text{Br}^-$ , but it is not possible to determine the branching between substitution and elimination because the neutral products are invisible in the instrument. To overcome this problem, a number of logical, clever, and sometimes heroic approaches have been applied.<sup>2–6</sup> In this Account, early attempts to investigate the gas phase competition between these mechanisms will be reported followed by a description of an approach recently developed in our laboratory that allows for the direct detection of diagnostic products in these reactions. First however, a brief description of the general features of gas phase ion/molecule reactions is warranted.

## Gas Phase Potential Energy Surfaces: $S_N2$ and E2 Reactions

In pioneering work, Brauman<sup>7</sup> showed that gas phase  $S_N2$  reactions were governed by a double-well potential energy surface where two stable complexes flank the transition state barrier (Figure 1). Brauman observed that gas phase  $S_N2$  reactions proceed at rates below the collision-controlled limit and reasoned that a barrier must exist on the surface; however, the long-range interaction of a charged nucleophile with a polar species such as an alkyl halide must initially be attractive. The simplest surface to fit these requirements is a double-well potential where the initial ion/dipole attraction leads to a stable complex that must overcome a barrier (i.e.,  $S_N2$  transition state) to yield a new complex between the reaction products. The two complexes on the surface are characterized by relatively long range ion/dipole interactions and have binding energies of roughly 10–25 kcal/mol.<sup>8</sup> Because collisions are rare at the pressures typically used in mass spectrometers, the system retains all of its energy, so if the overall reaction is exothermic, the product complex has more than enough energy to dissociate to give the free substitution products. Because most organic reactions have some intrinsic barrier, double-well potentials are ubiquitous in ion chemistry and a similar surface can be used to analyze gas phase E2 elimination reactions.

## Previous Approaches

Given the widespread interest in substitution and elimination reactions, there have been many attempts to characterize the competition in the gas phase. The most obvious and direct is to probe the structure of the neutral products. However, this strategy presents a formidable analytical challenge. To obtain rates that are compatible with the practical limitations of mass spectrometers, the neutral reagent is used in an enormous excess relative to the ionic reactant (~1 000 000:1). Consequently, the neu-

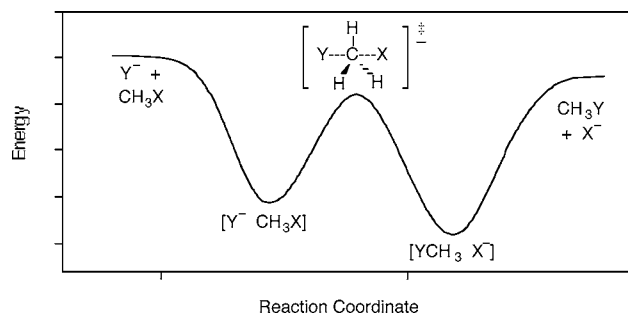
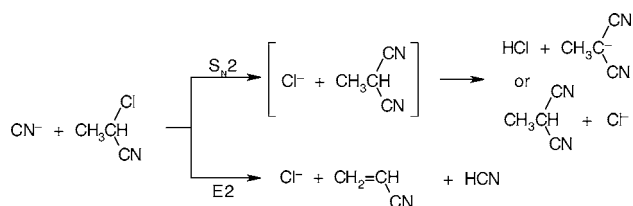


FIGURE 1. Double-well potential energy surface for reaction of Y<sup>-</sup> with CH<sub>3</sub>X.

Scheme 2

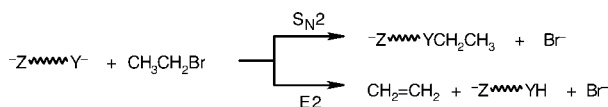


tral products are essentially tiny impurities in a sea of unreacted, neutral reagent. Despite this difficulty, two groups<sup>2,3</sup> have successfully characterized neutral products in gas phase reactions of anionic nucleophiles with alkyl halides.<sup>9</sup> Jones and Ellison<sup>2</sup> were able to trap the neutral gases from the reaction in Scheme 1, and using standard analytical approaches, found only evidence for elimination. Lieder and Brauman<sup>3</sup> employed a photoionization scheme and were able to identify fluoroethane as a product in the reaction of fluoride with ethyl chloride; however, the method had no ability to detect the possible E2 product, ethene. Although neutral detection methods have provided useful information, the experimental difficulties and limitations associated with them have prevented them from becoming general approaches. Instead, most of the available data are from indirect approaches that, for the most part, provide only qualitative information about the competition between substitution and elimination in the gas phase. A sampling of these studies is outlined below.

Wladkowski and Brauman<sup>4</sup> found that in the reaction of cyanide with 2-chloropropionitrile, chloride and the deprotonated substitution product are observed (Scheme 2). The latter is the result of a secondary reaction in the product ion/molecule complex. With an assumption based on previous work with regard to the partitioning of the S<sub>N</sub>2 pathway's products, it was possible to estimate an E2/S<sub>N</sub>2 ratio of roughly 10:1.

Lum and Grabowski<sup>5</sup> used the reactions of nucleophiles with ethyl dimethyl phosphate to gather information about the competition between S<sub>N</sub>2 and E2 reactions. In their approach, they reasoned that S<sub>N</sub>2 reactions would mainly occur at the methyl groups and therefore reactivity at the ethyl group would be indicative of an elimination pathway. Although not quantitative, the data reveal reasonable reactivity patterns. In general, localized bases favored elimination and delocalized, carbon-centered nucleophiles favored substitution. DePuy and co-workers<sup>10</sup>

Scheme 3



have also analyzed the competition in terms of reactivity patterns. They found that, in reactions with alkyl halides, some nucleophiles gave increasing rate constants as the alkyl halide became more highly substituted (i.e., 1° ≥ 2° ≥ 3°) whereas others gave decreasing rate constants across the same series of alkyl halides. Because one expects a sharp decrease in S<sub>N</sub>2 rates with more highly substituted alkyl halides, they interpreted these data as evidence that some of the nucleophiles were giving eliminations with higher rate constants than substitutions. The nucleophiles limited to S<sub>N</sub>2 processes gave the expected rate decrease with more highly substituted alkyl halides. This analysis was later supported by labeling studies that yielded significant primary deuterium isotope effects in systems where E2 reactions were suspected.<sup>6</sup>

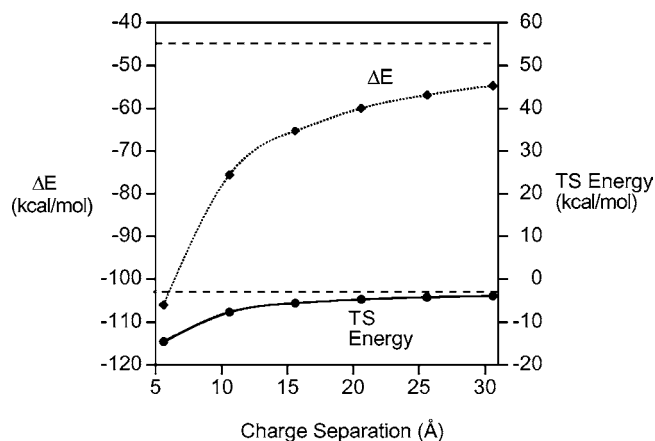
Although the indirect studies have yielded useful information, it is clear that it would be more desirable to have an approach that directly provides a quantitative measure of the competition. To this end, we have developed a method that employs dianions as the nucleophiles and leads to the formation of charged products that identify the reaction mechanism.

## Ionic Platform Approach

One way to force these gas phase nucleophilic reactions to provide charged, diagnostic products is to begin with a dianion. In this case, two charged products are formed in each pathway, one of which identifies the mechanism. This is illustrated in Scheme 3 where a second, chemically inert anionic site, Z<sup>-</sup>, has been appended to the nucleophilic anionic site, Y<sup>-</sup>.

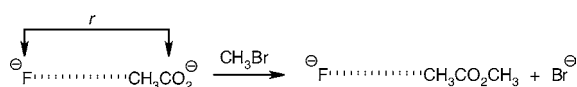
The appearance of the ethylated and protonated dianion in the product spectrum allows for a direct analysis of the ratio of S<sub>N</sub>2 to E2 products. This ionic platform approach is related to one used extensively by Kenttamaa to study radical reactivity.<sup>11</sup> In the past, it was impossible to pursue an ionic platform approach such as this because it depends on the selective formation of dianions in the gas phase, something that only became a realistic possibility with the development of electrospray ionization.

One important issue that must be addressed, however, is the impact of the second charge on the reactivity of the nucleophilic site. The presence of two, like charges in a single molecule can lead to significant electrostatic repulsion,<sup>12</sup> and the release of this energy during a reaction could possibly perturb the potential energy surface of the process. Because we wish to model the reactivity of singly charged nucleophiles (i.e., the second charge should only be a spectator that aids in detection), it is important to show that electrostatic repulsion in the dianion has only a modest effect on the potential energy surfaces of the reactions of interest.<sup>13</sup>



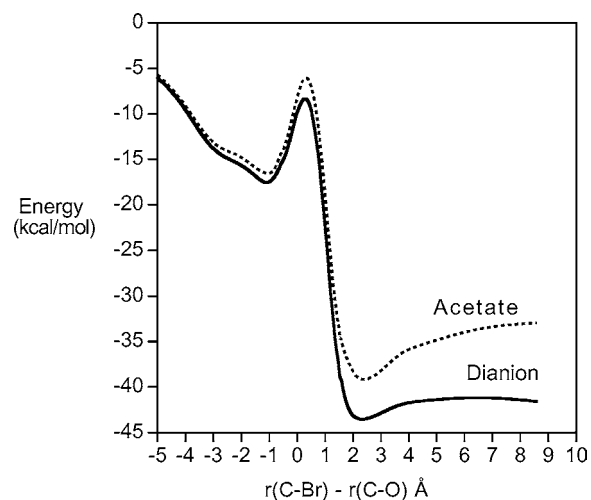
**FIGURE 2.** Plot of reaction energy,  $\Delta E$  (dotted line), and transition state energy,  $E_{TS}$  (solid line), as a function of charge separation in the dianion model. Dashed lines represent the values for acetate + methyl bromide (singly charged analogue). Calculations at the MP2/6-31+G(d,p) level.

**Scheme 4**



To examine the effect of electrostatic repulsion on the potential energy surface of an S<sub>N</sub>2 reaction, we have used *ab initio* calculations to study the reactions of model dianions with methyl bromide.<sup>14</sup> To reduce the computational demands, the dianion was modeled by an acetate ion with a point charge (fluoride) held at a fixed distance (Scheme 4).

Using distances of 5, 10, 15, 20, 25, and 30 Å, the overall energy change of the reaction ( $\Delta E$ ) as well as the transition state energy (relative to the reactants) was calculated (Figure 2). First, consider the effect of the charge separation on  $\Delta E$ . At 5 Å, there is over 60 kcal/mol electrostatic repulsion in the dianion and the S<sub>N</sub>2 reaction is exceptionally exothermic. As the charge separation in the dianion increases, the exothermicity of the process drops sharply, but even at 30 Å, the reaction is still 10 kcal/mol more exothermic than that of a singly charged analogue, acetate. In contrast,  $r$  has a much smaller effect on the transition state energy, and at distances of 15 Å or more, there is little difference between the transition state energy of the dianion and that of the singly charged analogue. The reason that the transition state is much less sensitive to the electrostatic repulsion in the dianion is that, in reaching it, the charge separation has only increased by a small amount because the departing charge is still localized near the initial nucleophile. As a result, only a small fraction of the internal electrostatic repulsion is released at the transition state with the majority of it being released later on the reaction coordinate as the singly charged products separate. In Figure 3, full potential energy surfaces are given for the reactions of methyl bromide with acetate and a dianion ( $r = 15$  Å). Both give double-well potential energy surfaces, and the surfaces have very similar shapes leading up to the transition state. The barrier with the dianion is somewhat lower because

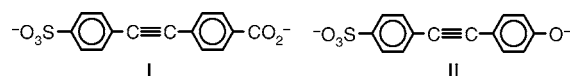


**FIGURE 3.** Potential energy surfaces for reactions of methyl bromide with dianion model (solid line) and acetate (dashed line). The charge separation in the dianion is 15 Å. Calculations at the MP2/6-31+G(d,p) level. The reaction coordinate corresponds to the difference between the breaking (C–Br) and forming (C–O) bond lengths (breaking – forming).

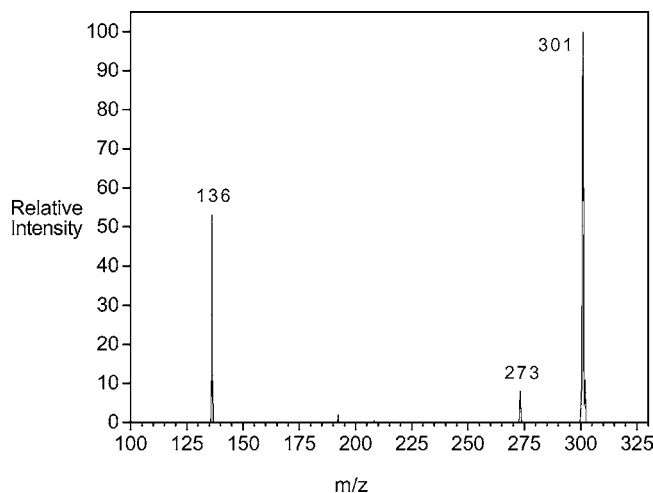
some electrostatic repulsion has been released, but this is a minor effect. The major differences on the surface occur after the transition state. Consequently, dianions with charge separations of approximately 15 Å can be used as surrogates to study the nucleophilic behavior of singly charged analogues.

## Gas Phase Reactions of Dianions with Alkyl Halides

The majority of our work has centered on a pair of dianion nucleophiles that share a common architecture. They both employ a diphenylacetylene spacer and a sulfonate as the inert anionic spectator charge. With alkyl halides, any reaction at the sulfonate center would be endothermic. The diphenylacetylene spacer provides a charge separation of at least 14 Å, so the effects of electrostatic repulsion on the potential energy surfaces will be modest. As nucleophilic sites, they bear either a benzoate or a phenolate. Unfortunately, there is not an effective way to experimentally measure the gas phase basicity of a dianion,<sup>13</sup> but the relative basicities of these nucleophiles can be estimated from the protonation free energies of singly charged analogues, benzoate and phenolate (333 and 342 kcal/mol, respectively).<sup>15</sup> Therefore, we can assume that **II** is about 9 kcal/mol more basic than **I**.



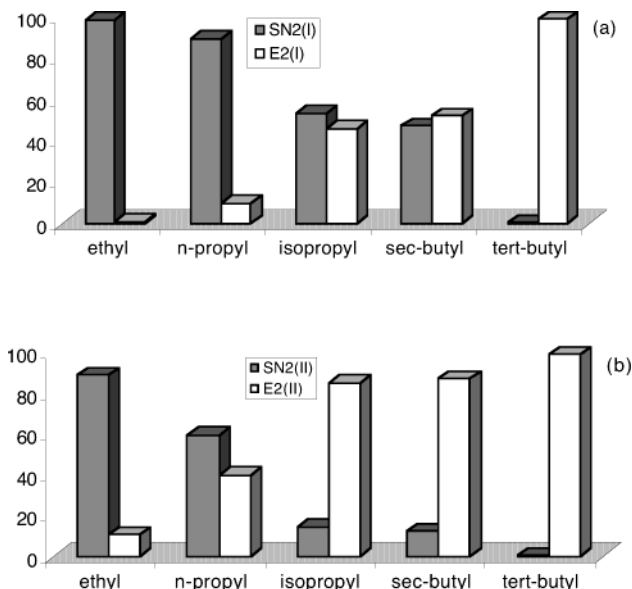
In our studies we have exclusively used a quadrupole ion trap mass spectrometer (modified Finnigan LCQ) to monitor the gas phase reactions. These instruments trap ions with alternating electric fields and are suitable for probing reactions at thermally equilibrated energies.<sup>16</sup> In a typical experiment, dianions are generated by electro-spray ionization, transferred to the ion trap by a series of



**FIGURE 4.** Spectrum from reaction of dianion **II** with ethyl bromide. Dianion **II** is at  $m/z = 136$ , and the E2 and S<sub>N</sub>2 products appear at  $m/z = 273$  and  $301$ , respectively. Small peak at  $m/z = 192$  corresponds to loss of SO<sub>3</sub> and an electron during the ion isolation process.

octapole ion guides, isolated by the application of a notched waveform (i.e., unwanted ions are ejected), and then allowed to react with a neutral reagent that has been added to the helium buffer gas in the trap. After a set time delay, all the ions are scanned out of the trap to provide a mass spectrum. By varying the time delay, kinetics can be measured. Details of the instrument and its operation have been presented previously.<sup>17</sup>

In Figure 4, a sample spectrum is presented for the reaction of the phenolate dianion (**II**) with ethyl bromide. The dianion appears in the spectrum at a mass-to-charge ratio ( $m/z$ ) of 136. The E2 product (i.e., protonated dianion) appears at  $m/z = 273$  (the large mass shift is the result of the conversion to a singly charged species,  $z = 1$  instead of 2). Substitution leads to the transfer of an ethyl group and gives an ion at  $m/z = 301$ . Integration of the area under the peaks gives the ratio of S<sub>N</sub>2 to E2 products. In Figure 5a, data are presented for the reaction of the benzoate dianion (**I**) with a series of simple 1°, 2°, and 3° alkyl bromides.<sup>18</sup> The primary bromides, ethyl and propyl, give mainly substitution, and the secondary bromides, isopropyl and *sec*-butyl, give roughly an even mixture of substitution and elimination. Only elimination is seen with *tert*-butyl bromide. In Figure 5b, data are given for the reactions of the phenolate dianion (**II**) with the same alkyl bromides. As noted above, this dianion is more basic so it is not a surprise that more elimination products are formed. Although substitution still dominates with primary bromides, elimination prevails for the secondary bromides. Overall, the data in Figure 5 are in perfect accord with the expectations that have been developed on the basis of condensed phase experiments over the past 70 years.<sup>19,20</sup> Although the potential energy surfaces are somewhat different, the gas phase experiments are probing the same fundamental features that are evident in condensed phase experiments, and thus offer another avenue to gain information about these important processes.



**FIGURE 5.** (a) Product distributions from reaction of dianion **I** with alkyl bromides. (b) Product distributions from reaction of dianion **II** with alkyl bromides.

**Table 1. Rates of Reactions and Branching Ratios of **II** with Alkyl Bromides<sup>a</sup>**

substrate	$k$	$k(\text{S}_{\text{N}}2)^b$	$k(\text{E}2)^b$
ethyl	$6.4 \pm 1.0$	5.9	0.5
<i>n</i> -propyl	$8.2 \pm 0.3$	4.8	3.3
isopropyl	$3.2 \pm 0.4$	0.5	2.7
<i>sec</i> -butyl	$13.1 \pm 1.5$	1.6	11.5
<i>tert</i> -butyl	$10.8 \pm 1.2$	0.0	10.8

<sup>a</sup> Units are  $10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ . Precisions listed are one standard deviation. Absolute uncertainties are expected to be  $\pm 25\%$ . <sup>b</sup> Partial rates for each pathway.

Kinetic data for the reactions of **II** with the alkyl bromides are given in Table 1.<sup>18</sup> The rate constants tend to be around  $10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ , which corresponds to roughly one successful reaction in every few hundred collisions of the reactants. It is most interesting to compare the partial rate constants for substitution and elimination. In the substitutions, there is the expected drop in rate constant in going from 1° to 2° bromides. In contrast to condensed phase work, the data indicate that methylation at the  $\beta$ -carbon leads to rate enhancements; propyl is more reactive than ethyl bromide and *sec*-butyl is more reactive than isopropyl bromide. A similar effect has been observed by Kebarle<sup>21</sup> in previous gas phase experiments and is also predicted by computational work.<sup>22</sup> It can be rationalized in the following way. Nucleophiles in the condensed phase are solvated and as a result are larger and much more sensitive to remote steric effects than bare gas phase nucleophiles. For example, many gas phase nucleophiles react readily with neopentyl halides,<sup>10</sup> whereas this substrate is nearly unreactive in solution.<sup>20</sup> Assuming that steric effects are not important, then the addition of a  $\beta$ -methyl provides a polarizable group that can stabilize the charged transition state. As for the E2 rates, there is also a correlation with the substitution pattern and generally the rate constants increase from 1° to 2° to 3° bromides. However, the effect



**Table 2. Partial Rate Constants for the S<sub>N</sub>2 and E2 Reactions of Dianions with Alkyl Bromides<sup>a</sup>**

	I		II	
	S <sub>N</sub> 2	E2	S <sub>N</sub> 2	E2
CH <sub>3</sub> CH <sub>2</sub> Br	3.5	0.0	5.9	0.5
FCH <sub>2</sub> CH <sub>2</sub> Br	20	0.0	33	16
ClCH <sub>2</sub> CH <sub>2</sub> Br	48	12	<i>b</i>	1880
BrCH <sub>2</sub> CH <sub>2</sub> Br	125	60	<i>b</i>	2730
EtCH <sub>2</sub> CH <sub>2</sub> Br	9.8	1.4		

<sup>a</sup> Units are 10<sup>-12</sup> cm<sup>3</sup> molecule<sup>-1</sup> s<sup>-1</sup>. <sup>b</sup> Yield too low for accurate partial rate measurements.

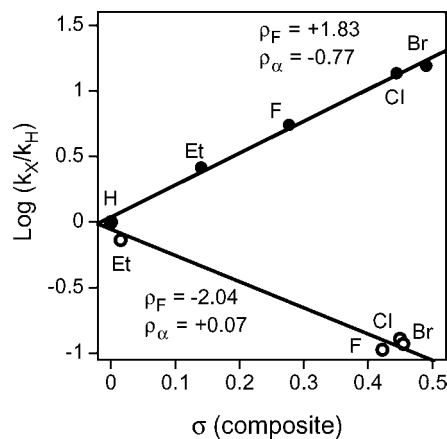
of methyl substitution at the β-carbon is most significant and large rate increases are seen in going from ethyl to propyl bromide and from isopropyl to *sec*-butyl bromide. Apparently, the addition of a methyl group at the β-carbon helps stabilize the partial charge on that center in the transition state. Moreover, the β-methylation increases the exothermicity of the reaction more than the α-methylation does. The enhanced effect of β-methylation is also evident in computational modeling on related systems. Using acetate as a nucleophile, MP2/6-31+G(d,p)//MP2/6-31+G(d) calculations indicate that the E2 barrier is 2.3 kcal/mol lower for *n*-propyl than for isopropyl bromide.<sup>23</sup>

The effect of β-halogenation has also been studied. Because one expects negative charge to build up on the β-carbon in an E2 transition state, β-halogenation should stabilize the transition state. However, the situation is not so clear in an S<sub>N</sub>2 transition state because there is the possibility of some positive charge building up on the α-carbon, leading to destabilization. Data for the reactions of I and II with β-halogenated substrates are listed in Table 2.<sup>17</sup> The impact on the elimination rates is clear, especially with the phenolate, II. There is a dramatic increase, roughly 5000-fold relative to ethyl, across the series from F to Cl to Br as the β-substituent. A similar, but less dramatic effect is seen with dianion I. The S<sub>N</sub>2 rate constants also increase with the addition of halogens at the β-carbon. For example, the S<sub>N</sub>2 reaction of I with 1,2-dibromoethane is about 30 times faster than the reaction with bromoethane. Clearly, the electron-withdrawing groups are stabilizing the S<sub>N</sub>2 transition state.

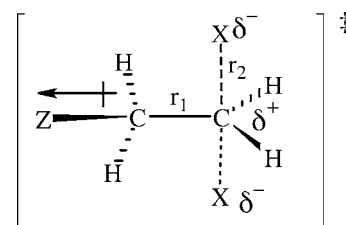
The S<sub>N</sub>2 data can be analyzed using a two-parameter, linear free energy relationship suggested by Taft that includes contributions from field effects and polarizability (eq 1).<sup>24</sup>

$$\log(k_X/k_H) = \rho_\alpha \sigma_\alpha + \rho_F \sigma_F \quad (1)$$

Here,  $\sigma_\alpha$  is the substituent's polarizability parameter and  $\sigma_F$  is its field-effect parameter. The  $\rho$  values are the scaling factors for each of the effects. A least-squares fit of the data results in  $\rho$  values of +1.83 and -0.77 for the field and polarizability effects in the gas phase. The significant, positive  $\rho_F$  value confirms that electron-withdrawing groups stabilize the S<sub>N</sub>2 transition state. Not surprisingly for a gas phase reaction, the substituent's polarizability is also important in stabilizing the transition state.<sup>25</sup> A graphical representation of the analysis is given in Figure 6. Data obtained in methanol using thiophenolate as the

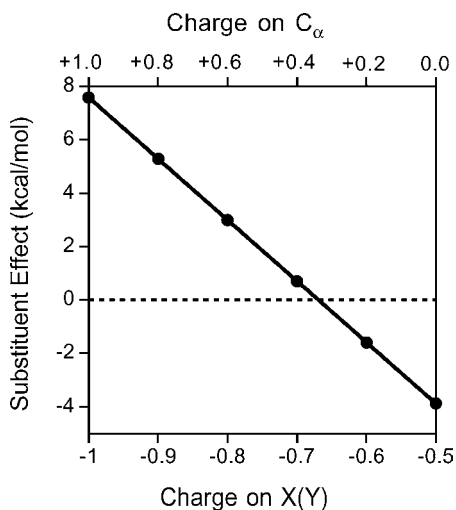


**FIGURE 6.** Hammett plots for S<sub>N</sub>2 reactions of β-substituted ethyl bromides in the gas phase (solid circles) and methanol (open circles).<sup>26</sup> Composite  $\sigma$  values are the  $\rho$  weighted averages of  $\sigma_\alpha$  and  $\sigma_F$ . The rates for dibromoethane were divided by 2.

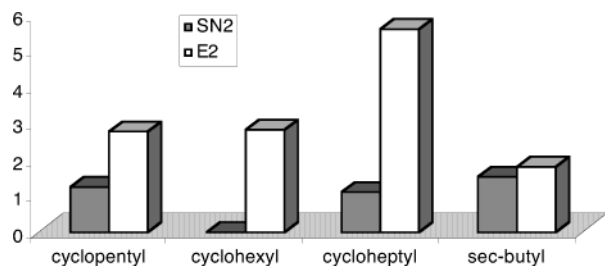
**Scheme 5**

nucleophile also are shown in the figure.<sup>26</sup> In this case,  $\rho_F = -2.04$  and  $\rho_\alpha = +0.07$ . Focusing on  $\rho_F$ , this is a striking reversal of a substituent effect. It is common to see exalted substituent effects in the gas phase because the low dielectric enhances electrostatic interactions, but these results suggest that the polarity of the transition state can be reversed by switching the medium. This is not unprecedented, but the magnitude of the effect in this case is highly unusual. Fortunately, it can be rationalized with the simple electrostatic model shown in Scheme 5 (for simplicity, an identity reaction is employed).

Three important electrostatic interactions are incorporated in this transition state model. There are two favorable interactions between the substituent's dipole and the entering and leaving groups (X) and one unfavorable interaction of the dipole with the partial positive charge on the α-carbon. Therefore, it is the balance of these interactions that determines whether the substituent is stabilizing or destabilizing. There are two limiting cases in terms of the polarity of the S<sub>N</sub>2 transition state. At one extreme, no charge develops on the α-carbon and each X group has a -1/2 charge. With no positive charge on the α-carbon, there are only favorable electrostatic interactions and the substituent must be stabilizing. At the other extreme is a transition state that is fully ionized where the α-carbon has a charge of +1 and the X groups each have a charge of -1. Sneen<sup>27</sup> referred to these as ion pair transition states. Using a reasonable transition state geometry and assuming the dipole expected for a C-Br bond, the electrostatic effect of the substituent can be estimated. Figure 7 illustrates how the transition state charge distribution controls the energetic effect of the



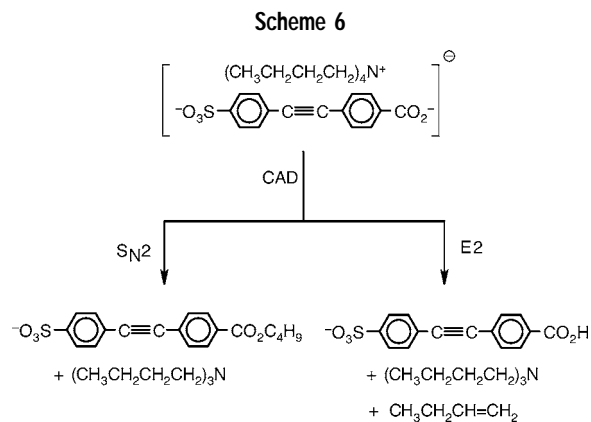
**FIGURE 7.** Plot of substituent effect as a function of charge on X in the model shown in Scheme 5. Model assumes a C–Z bond moment of 1.38 D with  $r_1$  set at 1.5 Å and  $r_2$  set at 2.5 Å. Negative values imply stabilization of the transition state.



**FIGURE 8.** Rate constants for the reactions of dianion I with cyclic bromides. Units are  $10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ .

substituent's dipole. On the far right of the graph is the first situation where no charge develops on the  $\alpha$ -carbon. Moving to the left, the transition state becomes more highly ionized and the effect of the substituent's dipole smoothly shifts from stabilizing to destabilizing. The close proximity of the substituent to the  $\alpha$ -carbon allows the destabilizing interaction to dominate in even a moderately ionized transition state. Figure 7 suggests that in the low dielectric of the gas phase, the S<sub>N</sub>2 transition state is only slightly ionized and lies to the right side of the graph such that electron-withdrawing substituents are stabilizing. In a solvent like methanol, hydrogen bonding to charged species is energetically favorable. Under these circumstances, the transition state is more highly ionized (left side of the graph) and electron-withdrawing substituents become destabilizing. Overall, the  $\beta$ -halogen substituents appear to be a very sensitive probe of the charge distribution in the transition state and therefore are able to highlight the fairly subtle electronic changes that occur upon transferring the S<sub>N</sub>2 transition state from one medium to another.

Ring size is another structural effect on the S<sub>N</sub>2/E2 competition that has been explored in the gas phase with the ionic platform approach. Data for the reaction of I with cyclopentyl, cyclohexyl, and cycloheptyl bromide as well as *sec*-butyl bromide are presented in Figure 8



(smaller rings are unreactive with I and II). The results suggest that ring structures tend to inhibit S<sub>N</sub>2 reactions. Cyclopentyl and cycloheptyl give S<sub>N</sub>2 reactions that are somewhat slower than *sec*-butyl bromide, but no S<sub>N</sub>2 products are seen with cyclohexyl bromide. This is consistent with condensed phase data<sup>28</sup> and of course is related to the difficult path required for backside attack by a nucleophile on a six-membered ring.<sup>29</sup> In the eliminations, cycloheptyl gives an unusually high rate constant. In condensed phase work, Bordwell<sup>30</sup> also has observed high E2 rates for cycloheptyl systems and computational modeling in our lab suggests that the seven-membered ring allows for a nearly strain-free E2 transition state.

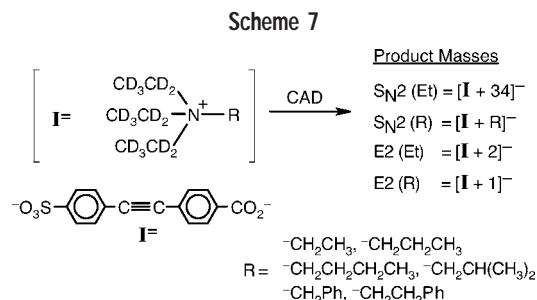
## Dianion Reactions in Gas Phase Salt Complexes

While carrying out the studies outlined above, we found that complexes between a dianion and one tetraalkylammonium counterion are formed in the electrospray process. These complexes have a net charge of  $-1$ , and when they are subjected to collisionally activated dissociation (CAD) conditions in the ion trap mass spectrometer, they fragment via two, distinct pathways.<sup>31</sup> This is illustrated in Scheme 6 for the complex of I and a tetrabutylammonium cation. One pathway corresponds to a substitution reaction where a butyl group is transferred to the nucleophilic carboxylate and tributylamine is the leaving group. Substitution reactions of this type have been seen before in salt complexes, but with the opposite polarity (i.e., dication/anion).<sup>32</sup> The other pathway corresponds to an elimination where the dianion becomes protonated, 1-butene is formed, and tributylamine again acts as the leaving group. This is a gas phase example of a Hofmann elimination. These processes are general, and data for complexes of a variety of tetraalkylammonium cations with I are given in Table 3.<sup>31</sup>

Tetrapropylammonium and tetrabutylammonium are the simplest in the series and give about a 2.5:1 ratio of substitution to elimination. The low yield of elimination products is probably related to the weak basicity of the benzoate nucleophile. In the condensed phase, Hofmann eliminations give high yields of alkenes, but stronger bases are involved in those reactions.<sup>19</sup> The benzytriethylam-

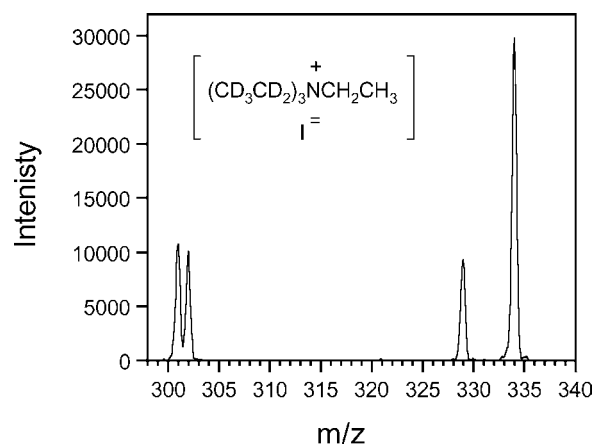
**Table 3. Reaction Yields (%) from CAD on the Tetraalkylammonium Complexes of I**

cation	S <sub>N</sub> 2	E2
tetrabutyl	70	30
tetrapropyl	75	25
benzyltriethyl	55/15 <sup>a</sup>	30
cetyltrimethyl	8/91 <sup>b</sup>	1

<sup>a</sup> Percentages of benzylation/ethylation in the S<sub>N</sub>2 process.<sup>b</sup> Percentages of cetylation/methylation in the S<sub>N</sub>2 process.

monium system is interesting because two substitution reactions are possible, transfer of a benzyl or an ethyl group. Taking into account the statistical advantage of three ethyl groups, substitution at the benzyl group is favored by over a factor of 10. This is not surprising because benzyl is known to yield faster S<sub>N</sub>2 reactions than ethyl in solution.<sup>20</sup> The data for this complex also indicate that elimination is favored over substitution by a factor of 2:1 on the ethyl group. A high elimination yield with ethyl is consistent with Hofmann elimination reactivity patterns.<sup>19</sup> Finally, the cetyltrimethylammonium salt gives almost exclusively substitution on the methyl group. This provides added support for the assumption that the substitution follows an S<sub>N</sub>2 pathway. One could suggest that collisional activation of the salt leads to an S<sub>N</sub>1-like mechanism where the energy is used to cleave a C–N bond to give a transient carbocation that is captured by the dianion in the complex. That would be unlikely with a methyl group, so it appears that an S<sub>N</sub>2 mechanism is operative.

One limitation of the tetraalkylammoniums discussed above is that as the reactive alkyl group is changed, so is the leaving group. For example, the change from tetrapropylammonium to tetrabutylammonium also shifts the leaving group from tripropylamine to tributylamine. For a careful analysis of structure/reactivity relationships, it would be preferable to have a system with a constant leaving group. This is possible with the systems outlined in Scheme 7.<sup>33</sup> Focusing on the unique group, “R”, the leaving group is always triethylamine-*d*<sub>15</sub>. The deuterium labeling is needed to distinguish between the four possible reaction pathways open to the cation, S<sub>N</sub>2 and E2 on the ethyl and the “R” group. The S<sub>N</sub>2 reactions are easily distinguished by the masses of the transferred group, but without the labels, the two E2 reactions would give products at the same mass. For example, Figure 9 shows the CAD spectrum of the complex of I with the cation where “R” is ethyl. This is an interesting case because it is tetraethylammonium where three of the ethyl groups are deuterated. At *m/z* = 301 and 302 are the products



**FIGURE 9.** CAD spectrum of complex with R = CH<sub>2</sub>CH<sub>3</sub>. Peaks at *m/z* = 329 and 334 represent S<sub>N</sub>2 reactions at the CH<sub>2</sub>CH<sub>3</sub> and CD<sub>2</sub>-CD<sub>3</sub> groups, respectively. The peaks at *m/z* = 301 and 302 represent E2 reactions on the CH<sub>2</sub>CH<sub>3</sub> and CD<sub>2</sub>CD<sub>3</sub> groups, respectively.

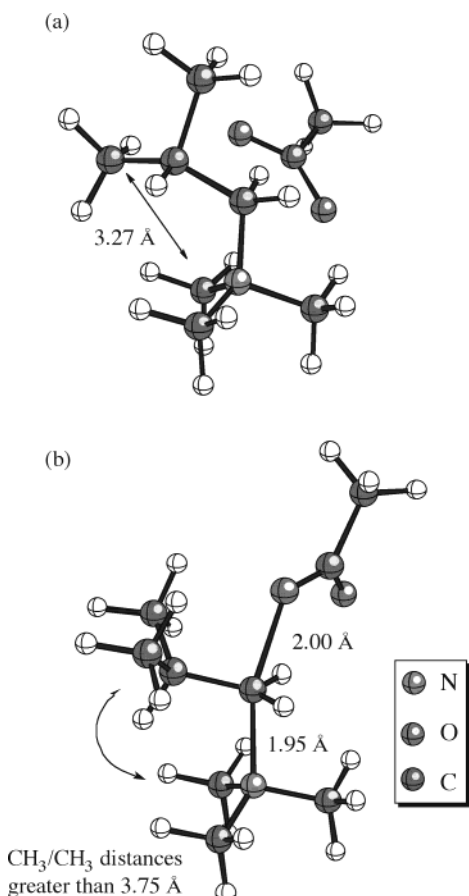
**Table 4. Product Distributions from the CAD Reactions of the Tetraalkylammonium Complexes of Dianion I (Scheme 7)**

R	E2(R)	S <sub>N</sub> 2(R)	E2(Et- <i>d</i> <sub>5</sub> )	S <sub>N</sub> 2(C <sub>2</sub> D <sub>5</sub> )	E2(R)/S <sub>N</sub> 2(R)
ethyl	0.186	0.157	0.158	0.500	1.19
propyl	0.049	0.127	0.230	0.594	0.38
butyl	0.036	0.119	0.236	0.610	0.30
isobutyl	0.042	0.297	0.176	0.486	0.14
benzyl	0.000	0.340	0.630 <sup>a</sup>	0.030 <sup>a</sup>	na <sup>b</sup>
2-phenethyl	0.934	0.023	0.023	0.019	40.6

<sup>a</sup> In this case, ethyl group is not deuterated. <sup>b</sup> Not applicable.

from the transfer of a proton and deuteron to the dianion during the activation process (i.e., E2 reactions). The yields are roughly the same, but there is a 3:1 statistical advantage for reaction at the deuterated ethyl group. Taking this into account, the data indicate a primary deuterium isotope effect of *k<sub>H</sub>/k<sub>D</sub>* = 3.5 ± 0.2. This value is very reasonable for a reaction where the rate-determining step involves the removal of a proton and is in accord with an E2 mechanism.<sup>19</sup> At *m/z* = 329 and 334 are the S<sub>N</sub>2 products of the reaction. Here, there is about a 3:1 ratio of C<sub>2</sub>D<sub>5</sub> to C<sub>2</sub>H<sub>5</sub> transfer. The peak areas indicate a *k<sub>H</sub>/k<sub>D</sub>* value of 0.95 ± 0.05. One expects a relatively small secondary deuterium isotope effect in an S<sub>N</sub>2 reaction and previous gas phase work on S<sub>N</sub>2 reactions has led to slightly inverse values;<sup>6</sup> however, the experimental uncertainties in the present value preclude a definitive statement about the secondary isotope effect.

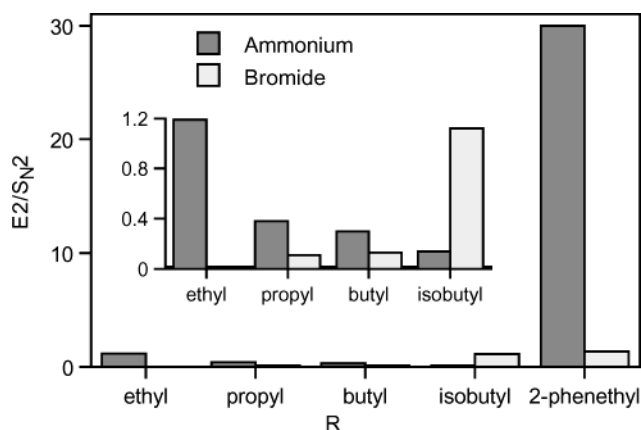
In Table 4, data are listed for the dissociation of several complexes of I with ammonium ions having the general structure shown in Scheme 7.<sup>33</sup> Several things are evident from the data. First, ethyl gives the most elimination and its E2 yields are 3 times greater than those of the other alkyl groups. This is expected for a Hofmann elimination.<sup>19</sup> Second, the 2-phenethyl group gives an exceptional E2 yield, presumably because the phenyl substituent greatly stabilizes the transient negative charge on the β-carbon. Third, the isobutyl group gives a surprisingly large S<sub>N</sub>2 yield. In fact, isobutyl gives a larger S<sub>N</sub>2 yield than the deuterated ethyl groups in this ammonium cation (sta-



**FIGURE 10.** Structures of isobutyltrimethylammonium/acetate (a) complex and (b) S<sub>N</sub>2 transition state from optimizations at the MP2/6-31+G(d) level.

tistically corrected). The origin of this effect is steric crowding in the cation caused by a close interaction between the isobutyl group and the large leaving group. Calculations on a model system, isobutyltrimethylammonium, indicate that there is a steric repulsion of 3–4 kcal/mol built into the cation (Figure 10a). The calculations also indicate that S<sub>N</sub>2 reactions on these ammonium ions involve exploded transition states with long distances from the  $\alpha$ -carbon to the entering and leaving groups (Figure 10b). As a result, the transition state is nearly strain free. Counter to the typical situation in S<sub>N</sub>2 reactions,<sup>20</sup> this represents a system where steric strain is released at the transition state and lowers the S<sub>N</sub>2 barrier for the isobutyl system.

Finally, it is possible to compare the results that we have obtained in the dissociation of the salt complexes with those that we have obtained in the bimolecular reactions of the dianions with alkyl bromides. We have used the same dianion and alkyl groups in these studies, so a direct comparison of leaving group effects is possible (i.e., bromide vs amine). Data for the two leaving groups are presented in Figure 11. Focusing on the simple alkyl groups, the ammonium data show that branching on the alkyl group causes a sharp reduction in the E2 yield. This is in accord with data for condensed phase Hofmann eliminations of ammonium salts.<sup>19</sup> In contrast, branching causes an increase in the E2 yields when the leaving group



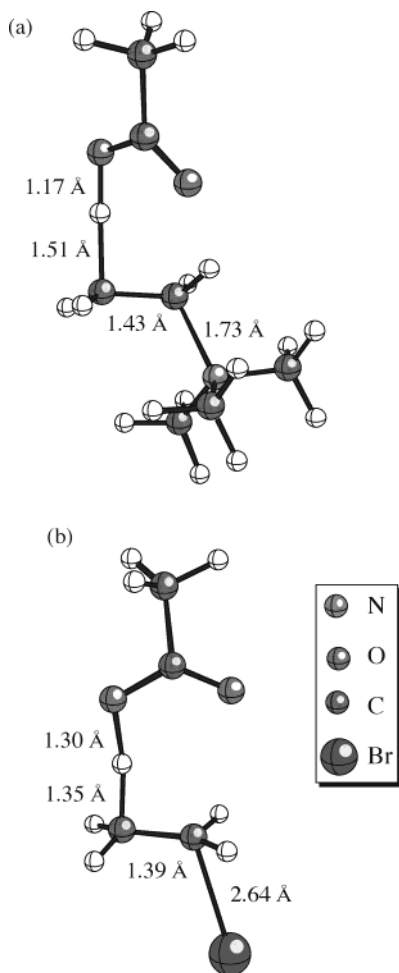
**FIGURE 11.** E2/S<sub>N</sub>2 ratios for gas phase reactions of I with tetraalkylammoniums (CAD of salt complex) and with alkyl bromides (bimolecular reactions). Insert shows an expanded view of the data for the first four groups.

is bromide. This is consistent with the Zaitzev pattern seen in condensed phase eliminations of alkyl halides.<sup>19</sup> Therefore, similar processes as well as subtle reactivity patterns are retained in the gas phase. This result suggests that the origin of these reactivity patterns is in the intrinsic properties of the transition states and is not an artifact of differences in solvation. The last substituent in Figure 11, 2-phenethyl, leads to an increase in the elimination yield that is much more dramatic for the ammonium system. It has been assumed that Hofmann eliminations have transition states with E1<sub>cb</sub> character and a significant negative charge on the  $\beta$ -carbon.<sup>19</sup> This has been confirmed by ab initio calculations on model systems, the reactions of acetate with the ethyltrimethylammonium cation and with ethyl bromide (Figure 12). In the Hofmann elimination, the proton is almost completely transferred from the  $\beta$ -carbon to the acetate, yet the C–N bond to the leaving group is only slightly stretched (about 12%). This geometry suggests extensive negative charge buildup on the  $\beta$ -carbon. In contrast, the reaction of acetate with ethyl bromide involves a more synchronous transition state where the cleavages of the C <sub>$\beta$</sub> –H and C–Br bonds are more evenly matched so less charge will develop on the  $\beta$ -carbon. This explains the greater stabilizing effect of a  $\beta$ -phenyl group on the Hofmann elimination transition state. The geometries also show that the C–C bond is shorter in the alkyl bromide transition state, indicating greater  $\pi$ -bond development. This is consistent with the Zaitzev reactivity pattern in that the formation of the more stable alkene (i.e., more highly substituted) is favored.

## Summary

Gas phase studies of organic reaction mechanisms can provide valuable information, but in some instances, such as the competition between substitution and elimination reactions, the characteristic products are not charged so conventional mass spectrometry cannot be used to probe them directly. Dianion nucleophiles can overcome this problem because the second charge is retained in a





**FIGURE 12.** Structures of transition states for E2 reactions of acetate with (a) ethyltrimethylammonium and (b) ethyl bromide from optimizations at the MP2/6-31+G(d) level.

species that identifies the mechanism. With these nucleophiles, we have shown that gas phase substitution and elimination reactions generally are governed by the same substituent effects as those in solution. However, there are notable exceptions such as the lack of significant steric effects from  $\beta$ -substituents and the lesser degree of ionization in gas phase  $S_N2$  transition states.

Salt complexes between dianions and singly charged cations offer another system for probing organic reactivity in the gas phase. When complexed with dianion nucleophiles, tetraalkylammonium cations undergo both substitution and elimination reactions during collision-activated dissociation. The latter process is a gas phase analogy of a Hofmann elimination, and it exhibits a similar reactivity pattern with respect to branched alkyl groups.

Overall, the results show that important insights into the intrinsic reactivity of organic systems can be gained through gas phase studies. In the absence of solvation and ion pairing, all of the observed effects can be attributed to the nature of the reaction partners. This allows for a very clear exploration of substituent effects. When combined with condensed phase data, it is possible to develop a comprehensive picture of the mechanism and a good

understanding of how solvation might perturb the potential energy surface and alter substituent effects.

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