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Substituent Effects in Gas-Phase Substitutions and Eliminations: β-Halo Substituents. Solvation Reverses S_N2 Substituent Effects

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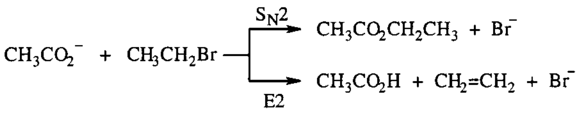
Abstract: The gas-phase reactions of benzoate and phenolate containing dianions with a series of β-substituted alkyl bromides ($X\text{-}CH_2CH_2Br$, X = H, F, Cl, Br) have been studied in a quadrupole ion trap mass spectrometer. Branching ratios between S_N2 and E2 products were measured and rate constants were determined. The β-halogens increase both the S_N2 and E2 rates, but the effect is greater for the latter process and therefore these substituents lead to an increase in the amount of elimination. The kinetic data for the S_N2 reactions can be analyzed via a two-parameter, linear free-energy relationship and the results indicate that field-effects (i.e., electron-withdrawing groups) strongly favor the reaction ($\rho_F = 1.83$). In contrast, analysis of the available condensed phase data for these substrates indicates that halogens strongly retard the reaction ($\rho_F = -2.04$). The dramatic reversal in substituent effects can be explained by a simple electrostatic model which suggests that solvation causes the system to shift to a more highly ionized S_N2 transition state.

Introduction

One of the key elements in the development of physical organic chemistry has been the investigation of the effect of substituents on the rates and product distributions of reactions.[1,2] Over the past 75 years, there have been numerous studies that have explored a variety of substituent effects in substitution and elimination reactions. Despite the success of previous studies in probing the mechanisms of these two fundamental processes, some details have been obscured by complications involving solvation effects. For example, it is often difficult to determine whether a change in a nucleophile's structure has a greater effect on its intrinsic reactivity or on its solvation properties. To avoid such complications, organic chemists have turned to gas-phase studies in the past 20 years.[3−5] In the total absence of solvation, all of the observed reactivity patterns are clearly related to the intrinsic properties of the reaction partners.

Gas-phase studies of nucleophilic reactions generally have relied on mass spectrometry for manipulating the reactant ions and detecting the products. For simple S_N2 reactions (e.g., methyl halides),[6−9] this has proven to be a very powerful approach, but complications in product identification arise with substrates that are capable of both S_N2 and E2 reactions because both the reactions lead to the same ionic product. This is illustrated below in the reaction of acetate with ethyl bromide (eqs 1 and 2). It can easily be seen that both pathways lead to



$$CH_3CO_2^- + CH_3CH_2Br \xrightarrow{S_N2} CH_3CO_2CH_2CH_3 + Br^- \quad (1)$$

$$CH_3CO_2^- + CH_3CH_2Br \xrightarrow[E2]{} CH_3CO_2H + CH_2{=}CH_2 + Br^- \quad (2)$$

bromide as the sole ionic product and would be indistinguishable by mass spectrometry. A number of approaches have been employed to overcome this problem,[9−18] including efforts to physically characterize the neutral products.[19,20] Unfortunately, direct characterization of the products has not proven to be a general technique and most of the data in the literature on the competition between gas-phase S_N2 and E2 reactions has resulted from indirect approaches such as secondary reactions, reactivity trends, or isotope effects.

Recently, we presented a method that allows for the direct detection of the products of gas-phase S_N2 and E2 reactions.[21] It involves appending a second, nonreactive ionic site to the nucleophile. This site acts as an "ionic handle" that allows for the detection of a diagnostic product in the reaction with an alkyl halide. We have used this approach to investigate the

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(1) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970.

(2) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1969.

(3) Gronert, S. *Chem. Rev.* **2001**, in press.

(4) Nibbering, N. M. M. *Adv. Phys. Org. Chem* **1988**, *24*, 1.

(5) Riveros, J. M.; Jose, S. M.; Takashima, K. *Adv. Phys. Org. Chem* **1985**, *21*, 197.

(6) Bohme, D. K.; Young, L. B. *J. Am. Chem. Soc.* **1970**, *92*, 7354.

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

(8) Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 2672.

(9) DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650.

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

(11) Grabowski, J. J.; Lum, R. C. *J. Am. Chem. Soc.* **1990**, *112*, 607.

(12) Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 8619.

(13) Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 9663.

(14) Lum, R. C.; Grabowski, J. J. *J. Org. Chem.* **1993**, *58*, 2029.

(15) Noest, A. J.; Nibbering, N. M. M. *Adv. Mass Spectrom.* **1980**, *8*, 227.

(16) Occhiucci, G.; Speranza, M.; De Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1989**, *111*, 7387.

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

(18) Haib, J.; Stahl, D. *Org. Mass Spectrom.* **1992**, *27*, 377.

(19) Lieder, C. A.; Brauman, J. I. *Int. J. Mass Spectrom. Ion Phys.* **1975**, *16*, 307.

(20) Jones, M. E.; Ellison, G. B. *J. Am. Chem. Soc.* **1989**, *111*, 1645.

(21) Flores, A. E.; Gronert, S. *J. Am. Chem. Soc.* **1999**, *121*, 2627.

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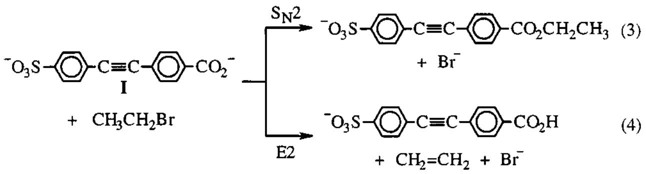
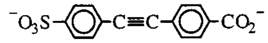
Scheme 1



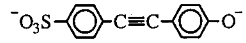
reactions of two dianion nucleophiles with a series of simple halides and representative reactions are outlined in Scheme 1. It can be seen that by starting with a doubly charged nucleophile, each pathway leads to two ionic products. The alkylated (S_N2) and protonated (E2) nucleophiles still retain charges and therefore can be used to identify the reaction mechanism (eqs 3 and 4).

A key assumption of the method is that the second charge does not radically distort the reactivity of the nucleophilic center so that the dianion can provide a good model for the properties of a singly charged nucleophile. The potential problem with a dianion is that it contains a significant amount of internal electrostatic repulsion that will be released in the course of a reaction with an alkyl halide as the charged species separate. This issue has been explored by computational methods, and for dianions with fairly large initial charge separations (~15 Å or more), the second charge has only a modest effect on the potential energy surface of a nucleophilic reaction such as an S_N2 substitution.[22] The effect of the second charge is limited because in reaching the transition state of an S_N2 reaction, there is a relatively small increase in the charge separation so only a small amount of the internal electrostatic repulsion is released. The majority of the internal electrostatic repulsion is released after the transition state and has no effect on the kinetics or product distribution of the reaction. As a result, dianion nucleophiles can provide realistic models of singly charged analogues in these reactions.[23]

In a previous communication,[21] we demonstrated the utility of the method and applied it to a series of alkyl bromides with varying substitution patterns at the α-carbon (i.e., 1°, 2°, and 3°). Here, we describe an investigation of the effect of placing electron-withdrawing groups at the β-carbon of the substrate. Specifically, the reactions of dianions **I** and **II** with a series of



I



II

2-haloethyl bromides (fluoro, chloro, and bromo) have been examined. Both of these dianions were used in our previous study and the diphenylacetylene framework provides a reasonable charge separation (~14 Å) that limits the effects of internal electrostatic repulsion. It is well-known that electron-withdrawing groups at the β-carbon should enhance E2 rates because they stabilize the incipient negative charge that develops on the β-carbon in the E2 transition state.[2,24] Much of the previous condensed phase work has focused on systems with either a substituted aryl group or a powerful electron-withdrawing group such as nitro or cyano at the β-carbon.[25−29] Less has been reported on the effects of simple electron-withdrawing groups such as halogens. In a very early study, Olivier and Weber showed that 1,2-dibromoethane was over 100 times more reactive than 1,1-dibromoethane under elimination conditions.[30] Goering and Espy[31] also found that halogens and other groups at the β-carbon increase the E2 rate. In contrast, Okamoto and co-workers[32] found that alkoxy and chloro substituents at the β-carbon caused a reduction in E2 rates in aqueous solution. They rationalized this result as a steric effect. As for S_N2 reactions, there is evidence from condensed phase studies that electron-withdrawing groups at the β-carbon (including halogens) lead to rate reductions.[32−35] In the present study, we test the validity of the generalization that electron-withdrawing groups at the β-carbon *increase* E2 rates and *decrease* S_N2 rates by determining the S_N2 and E2 rate constants of the reactions of the 2-haloethyl bromides with **I** and **II**. In addition, we evaluate the relative abilities of the various halogens to stabilize/destabilize the transition states.

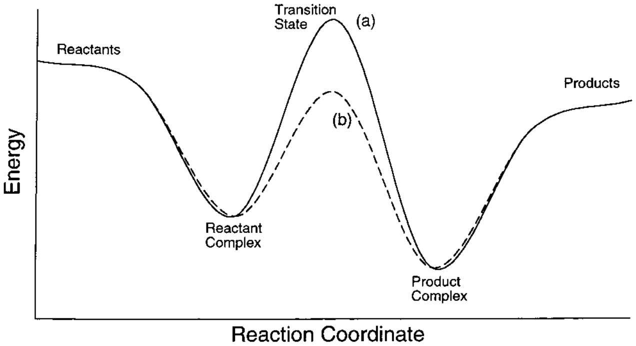


Figure 1. Double-well potential for gas-phase ion−molecule reactions: (a) positive activation energy (solid line) and (b) negative activation energy (dashed line).

To support the experimental work, ab initio calculations have been completed. Given the size of the dianions, it is impractical to pursue calculations on the actual experimental systems. Instead, we have used two types of model systems. The reaction of acetate with the 2-haloethyl bromides provides a reasonable model of the reactions of the benzoate dianion, **I**. The other model system uses methoxide as the nucleophile. Of course, methoxide does not provide a realistic model of the phenolate nucleophile, **II**, because it is a much stronger gas-phase base, but it does offer insight into the effects of base strength and charge localization on the competition between S_N2 and E2 reactions in the β-substituted systems. The S_N2 and E2 reactions involve a single barrier and lead to a double-well potential energy surface originally proposed by Brauman (Figure 1).[7] For each reaction, we have computationally characterized four stationary points on the surface: the reactants, the reactant ion−dipole complex, the transition state, and the products. On this type of gas-phase potential energy surface, the activation energy is defined as the energy difference between the transition state and the separated reactants. As a result, positive (Figure 1a) and negative (Figure 1b) activation energies are possible.

Experimental Section

Mass Spectrometry. All experiments were completed in a modified Finnigan LCQ quadrupole ion trap mass spectrometer equipped with

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(22) Gronert, S.; Fong, L.-M. *Int. J. Mass Spectrom.* **1999**, *192*, 185.
(23) Gronert, S. *J. Mass Spectrom.* **1999**, *34*, 787.
(24) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; John Wiley & Sons: New York, 1973.
(25) Bunnett, J. F.; Sridharan, S.; Cavin, W. P. *J. Org. Chem.* **1979**, *44*, 1463.
(26) Crosby, J.; Stirling, C. J. M. *J. Am. Chem. Soc.* **1968**, *90*, 6869.
(27) Gandler, J. R.; Yokoyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 130.
(28) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1914.
(29) Saunders: W. H., Jr. *Acc. Chem. Res.* **1976**, *9*, 19.
(30) Olivier, S. C. J.; Weber, A. P. *Recl. Trav. Chim.* **1934**, *53*, 1087.
(31) Goering, H. L.; Espy, H. H. *J. Am. Chem. Soc.* **1956**, *78*, 1454.
(32) Okamoto, K.; Kita, T.; Araki, K.; Shingu, H. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1913.
(33) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; MacGraw-Hill: New York, 1962.
(34) Hine, J.; Brader, W. H. *J. Am. Chem. Soc.* **1953**, *75*, 3964.
(35) Tutwiler, F. B.; McKee, R. L. *J. Am. Chem. Soc.* **1954**, *76*, 6342.

electrospray ionization (ESI). Tetraalkylammonium salts of the dianion precursors were dissolved in HPLC-grade acetonitrile ($10^{-4}-10^{-5}$ M) and pumped through the electrospray interface at flow rates from 3 to 10 μL/min. Typical ESI conditions involved needle potentials from 3.5 to 4.5 kV and heated capillary temperatures from 125 to 200 °C. In some cases, a small amount of tetramethylammonium hydroxide ($10^{-4}-10^{-5}$ M) was added 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 (alkyl bromide) was introduced into the helium system via a custom gas-handling system. The system has been described previously,[21,36] but a brief overview is given here. The liquid alkyl bromide was delivered to a measured flow of helium (1−2 L/min) by a syringe pump. With alkyl bromide flows of 30−300 μL/h, 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.[37] 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:

$$P_{\mathrm{RX}} = (1.75 \times 10^{-3}) F_{\mathrm{RX}} d_{\mathrm{RX}} / \mathrm{MW}_{\mathrm{RX}} / F_{\mathrm{He}} (\mathrm{MW}_{\mathrm{RX}} / \mathrm{MW}_{\mathrm{He}})^{1/2} \quad (5)$$

where F_{RX} is the reagent flow rate (liquid, mL/min), d_{RX} is the reagent density, $\mathrm{MW}_{\mathrm{RX}}$ is the reagent molecular weight, F_{He} is the helium flow rate (gas, mol/min), and $\mathrm{MW}_{\mathrm{He}}$ 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.[38] In most cases, 13 different time delays were used in each run. Time delays and reagent flows were adjusted to obtain plots that covered 2−3 half-lives of the reactant ion. Reported rates are the average of at least 6 kinetic runs with at least 3 different reagent flow rates and were obtained on at least two different days. Kinetic plots showed excellent linearity and gave correlation coefficients (r^2) greater than 0.98. Since the original communication,[21] we have shifted to using the "Scan Activation Parameters" option of the LCQ software to obtain kinetic data. In this mode, the computer monitors the signal intensity of several masses at set delay times (i.e., time between reactant ion isolation and mass scan). Although one does not obtain full spectra at each delay time, this method allows for more rapid data acquisition and has improved the quality of the kinetic plots. To evaluate the absolute accuracy of the rate constant measurements, we have studied two reactions where data are available from flowing afterglow work. Using the present approach, we have obtained rate constants of $(9.4 \pm 0.9) \times 10^{-12}$ cm^3/molecule/s and $(5.8 \pm 0.3) \times 10^{-12}$ cm^3/molecule/s for the reactions of $(CF_3)_2CHO^-$ with ethyl bromide and isopropyl bromide, respectively.[39] These are in reasonable accord with the flowing afterglow values ($(7.83 \pm 0.33) \times 10^{-12}$ and $(4.24 \pm 0.17) \times 10^{-12}$ cm^3/molecule/s, respectively).[17] Other work from our laboratory indicates that the ion trap provides an environment that is effectively at ambient temperature (~300 K).[36] 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.

Table 1. Rates of Reactions and Branching Ratios of Dianions with Alkyl Bromides[a]

	I		**II**	
substrate	*k*	$S_N2/E2$	*k*	$S_N2/E2$
CH_3CH_2Br	0.35 ± 0.04	>200	0.64 ± 0.10	12.5
FCH_2CH_2Br	2.0 ± 0.3	>200	4.9 ± 0.3	2.0
$ClCH_2CH_2Br$	6.0 ± 0.5	4.0	188 ± 10	<0.005
$BrCH_2CH_2Br$	18.5 ± 1.5	2.1	273 ± 40	<0.005
$EtCH_2CH_2Br$	1.1 ± 0.1	7.7		

[a] Units are 10^{-11} cm^3/molecule/s. Precisions listed are one standard deviation. Absolute uncertainties are expected to be ±25%.

All alkyl halides were obtained in the highest purity commercially available and used without further purification. The dianion precursor salts were available from a previous study.[21]

Computational. Calculations were completed with the GAUSSIAN94[40] or GAUSSIAN98[41] quantum mechanical packages on an SGI Octane, an IBM 39H, an HP 735, a Digital Alpha, an HP/Convex Exemplar, or a Pentium 3 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 for the reactions of both nucleophiles and at the B3LYP/6-31+(d) level for only the reactions of methoxide. Energies reported in the text are at the MP2/6-31+G(d) level corrected for zero-point vibrational energies (ZPE, scaled by 0.9135).[42] Given that the computational work on the model systems is to provide qualitative comparisons to the experiments, no thermal corrections were made. For the neutral species, complexes, and transition states, multiple rotamers were considered and data for only the most stable ones are listed in the tables.

Results

Kinetic and product distribution data for the reactions of dianions **I** and **II** with the 2-haloethyl bromides are given in Table 1. A representative spectrum for the reaction of **II** with 2-fluoroethyl bromide is shown in Figure 2a. In the spectrum, dianion **II** appears at *m/z* 136. The reaction produces protonated **II** (E2) at *m/z* 273 and 2-fluoroethylated **II** (S_N2) at *m/z* 319. The ratio of the areas under the two peaks gives the $S_N2/E2$ product distribution. A representative kinetic plot for this reaction is shown in Figure 2b.

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

(37) The restriction capillary is designed to provide this pressure when a helium pressure of 3 psi is applied to it externally (Thermoquest/Finnigan Corp.).

(38) Stable trapping fields are obtained with q_z values down to about 0.15. Since there is an inverse relationship between mass and q_z, this value allows for efficient detection of ions with *m/z* values up to about 3 times the starting ion. This is adequate for the present studies.

(39) These values are somewhat different than those obtained in our previous study (ref 21). A signal normalization scheme was used in the previous analysis, but after concluding that this approach introduced unnecessary errors, we now use the absolute reactant ion signal intensity in the kinetic plots.

(40) Gaussian 94, Revision B.3: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, W. P. M.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 1995.

(41) Gaussian 98, Revision A.7; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; J. Tomasi; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Morokuma; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 1998.

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

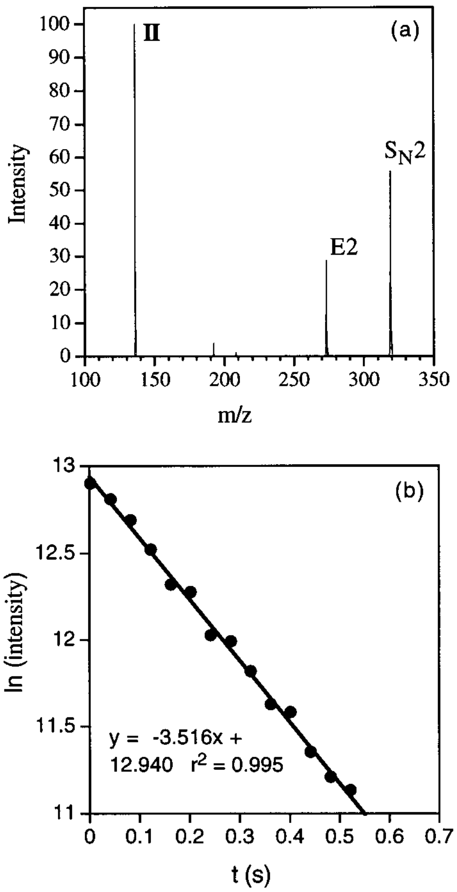

Figure 2. (a) Spectrum obtained for the reaction of **II** with 2-fluoroethyl bromide. **II** appears at *m/z* 136 and the products are at *m/z* 273 (E2) and 319. Small peaks at *m/z* 192 (**II** − SO_3^-) and 208 (**II** − SO_2^-) arise as fragmentation products during the ion isolation process, but do not interfere with the kinetic measurements. (b) Representative kinetic plot for the reaction of **II** with 2-fluoroethyl bromide.

In the reaction of the benzoate, **I**, with ethyl bromide, a slow rate is obtained and only S_N2 products are observed (Table 1). The addition of a β-fluoro group leads to a rate increase (>5-fold) although only S_N2 products are observed. The switch from fluoro to chloro as the β-substituent leads to another overall rate increase (about 3-fold) and the emergence of E2 products (S_N2/E2 = 80/20). Finally, 1,2-dibromoethane gives the highest rate and there is a greater elimination yield, yet substitution still dominates (S_N2/E2 = 68/32). Phenolates are stronger bases than benzoates in the gas phase[43] and the data in Table 1 reflect this fact. First, the rate constants with **II** are larger (in some cases dramatically) for each of the substrates. Second, there is strong shift toward E2 pathways. For example, the chloro- and bromo-substituted systems give almost exclusively E2 products with the phenolate. It is also striking that these substrates give very large rate constants that must be close to the collision-controlled limit.[44,45]

Table 2. Computational Results for the Reactions of Acetate with Substituted Ethyl Bromides (ZCH_2CH_2Br)[a]

Z	species	HF	MP2	ZPE	MP2 rel energy[b]	S_N2 pref[b]
H	substrate	−2648.5548	−2648.9330	0.0709		
	complex	−2875.8294	−2876.8438	0.1242	−16.8	
	S_N2 TS	−2875.8107	−2876.8221	0.1238	−3.4	
	E2 TS	−2875.7816	−2876.8034	0.1180	5.0	8.4
	S_N2 products	−305.8839	−306.7626	0.1270	−20.4	
	E2 products	−78.0358	−78.2912	0.0547	−1.3	
F	substrate	−2747.4085	−2747.9585	0.0639		
	complex	−2974.6908	−2975.8786	0.1172	−22.6	
	S_N2 TS	−2974.6666	−2975.8520	0.1171	−6.0	
	E2 TS	−2974.6342	−2975.8324	0.1105	2.6	8.5
	S_N2 products	−404.7368	−405.7868	0.1200	−19.6	
	E2 products	−176.8914	−177.3207	0.0475	−3.9	
Cl	substrate	−3107.4571	−3107.9644	0.0623		
	complex	−3334.7372	−3335.8784	0.1090	−22.6	
	S_N2 TS	−3334.7132	−3335.8577	0.1154	−5.9	
	E2 TS	−3334.6916	−3335.8401	0.1097	1.9	7.7
	S_N2 products	−764.7830	−765.7909	0.1184	−18.5	
	E2 products	−536.9369	−537.3235	0.0461	−1.8	
Br	substrate	−5217.8799	−5218.3694	0.0616		
	complex	−5445.1638	−5446.2922	0.1149	−24.4	
	S_N2 TS	−5445.1410	−5446.2682	0.1149	−9.3	
	E2 TS	−5445.1213	−5446.2565	0.1096	−5.0	4.3
	S_N2 products	−2875.2067	−2876.1968	0.1177	−19.0	
	E2 products	−2647.3575	−2647.7258	0.0454	−0.2	
CN	substrate	−2740.2902	−2740.9472	0.0708		
	complex	−2967.5770	−2968.8727	0.1238	−26.1	
	S_N2 TS	−2967.5539	−2968.8489	0.1240	−11.0	
	E2 TS	−2967.5446	−2968.8487	0.1185	−14.1	−3.0
	S_N2 products	−397.6166	−398.7742	0.1269	−18.7	
	E2 products	−169.7734	−170.3086	0.0548	−3.1	

[a] Calculations using the 6-31+G(d) basis set. Absolute energies in hartrees and relative energies in kcal/mol. [b] MP2 level. Includes Hartree−Fock ZPE correction scaled by 0.9135.

Computational data for the model reactions of acetate and methoxide with the substituted ethyl bromides are given in Tables 2 and 3, respectively. To test the quality of the computational approach, the thermochemistry for the reaction of acetate with ethyl bromide can be compared with experimentally derived values.[46,47] Reasonably good agreement is seen for the reaction energies of the S_N2 and E2 processes in this system (computed, −20.4 kcal/mol and −1.3 kcal/mol vs experimental, −21.5 kcal/mol and −5.8 kcal/mol). Consistency with experiment is also seen in the data on the methoxide reactions with ethyl bromide (computed, −58.3 kcal/mol and −38.1 kcal/mol vs experimental, −55.3 kcal/mol and −39.1 kcal/mol). These results suggest the theoretical level is adequate for the qualitative purposes of this study. In comparing the MP2 and B3LYP data for the methoxide reactions, they produce similar errors, but in different processes. MP2 does poorly in the S_N2 reaction and B3LYP does poorly in the E2 reaction. Overall, the two theoretical methods give qualitatively similar results, but B3LYP predicts somewhat more stable transition structures. In some reactions, B3LYP (with zero-point energy corrections) predicts that the transition states are actually more

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(43) It is not possible to measure directly the acid/base properties of a multiply charged ion (see ref 23). However, given the structural similarities of the two ions, singly charged analogues should provide a reasonable estimate of the relative proton affinities.

(44) Models for collision rates are well developed for systems with localized charges and one could calculate a collision rate for a dianion using the Su and Bowers method (ADO) by simply setting the charge value at 2 (see ref 45). However, the present systems have two distant charge centers and are not suitable for such models. Assuming that the dianions should give collision rates greater than a simple anion, but smaller than a localized dianion, it is reasonable to assume that collision rates between 2×10^{-9} and 5×10^{-9} cm^3/molecule/s are operative in these systems.

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

(46) Afeefy, H. Y.; Liebman, J. F.; Stein, S. E. In *NIST Chemistry WebBook, NIST Standard Reference Database Number 69 (http://webbook.nist.gov)*; Mallard, W. G., Linstrom, P. J., Eds.; National Institute of Standards and Technology: Gaithersburg, MD, 2000 (http://webbook.nist.gov).

(47) Bartmess, J. E. In *NIST Standard Reference Database Number 69*; Mallard, W. G., Linstrom, P. J., Eds.; National Institute of Standards and Technology: Gaithersburg MD, 2000 (http://webbook.nist.gov).

Table 3. Computational Results for the Reactions of Methoxide with Substituted Ethyl Bromides (ZCH_2CH_2Br)[a]

Z	species	HF	MP2	B3LYP	ZPE	MP2 rel energy[b]	B3LYP rel energy[b]	S_N2 pref[c]
H	substrate	−2648.5548	−2648.9330	−2650.9529	0.0709			
	complex	−2762.9950	−2763.7099	−2766.0949	0.1110	−19.5	−18.2	
	S_N2 TS	−2762.9896	−2763.7058	−2766.0945	0.1113	−16.7	−17.8	
	E2 TS	−2762.9712	−2763.6986	−2766.0918	0.1059	−15.2	−19.2	1.5
	S_N2 products	−193.1098	−193.6870	−194.3538	0.1163	−58.3	−54.2	
	E2 products	−78.0358	−78.2912	−78.5933	0.0547	−38.1	−35.7	
F	substrate	−2747.4085	−2747.9585	−2750.1893	0.0639			
	complex	−2861.8568	−2862.7444	−2865.3395	0.1041	−25.1	−23.3	
	S_N2 TS	−2861.8470	−2862.7376	−2865.3371	0.1046	−20.5	−21.6	
	E2 TS	−2861.8302	−2862.7294	−2865.3328	0.0987	−18.7	−22.2	1.8
	S_N2 products	−291.9632	−292.7117	−293.5898	0.1094	−57.7	−53.9	
	E2 products	−176.8914	−177.3207	−177.8355	0.0475	−40.7	−39.5	
Cl	substrate	−3107.4571	−3107.9644	−3110.5491	0.0623			
	complex	−3221.9046	−3222.7498	−3225.6985	0.1024	−24.8	−22.9	
	S_N2 TS	−3221.8919	−3222.7427	−3225.6951	0.1026	−20.2	−20.7	
	E2 TS	−3221.8874	−3222.7420	−3225.6961	0.0977	−22.6	−24.1	−2.4
	S_N2 products	−652.0119	−652.7167	−653.9482	0.1078	−57.1	−53.0	
	E2 products	−536.9369	−537.3235	−538.1910	0.0461	−38.6	−36.7	
Br	substrate	−5217.8799	−5218.3694	−5222.0728	0.0616			
	complex	−5332.3301	−5333.1581	−5337.2247	0.1018	−26.8	−24.4	
	S_N2 TS	−5332.3206	−5333.1519	−5337.2222	0.1024	−22.6	−22.5	
	E2 TS	−5332.3156	−5333.1527	−5337.2229	0.0971	−26.1	−26.0	−3.5
	S_N2 products	−2762.4350	−2763.1220	−2765.4721	0.1072	−57.3	−53.1	
	E2 products	−2647.3575	−2647.7258	−2649.7127	0.0454	−37.0	−35.4	
CN	substrate	−2740.2902	−2740.9472	−2743.1946	0.0708			
	complex[d]							
	S_N2 TS	−2854.7352	−2855.7342	−2858.3490	0.1114	−25.5	−25.8	
	E2 TS[e]							
	S_N2 products	−284.8458	−285.7002	−286.5952	0.1161	−57.6	−54.1	
	E2 products	−169.7734	−170.3086	−170.8403	0.0548	−39.9	−38.9	

[a] Calculations using the 6-31+G(d) basis set. Absolute energies in hartrees and relative energies in kcal/mol. [b] Includes Hartree−Fock ZPE correction scaled by 0.9135. [c] MP2 level. [d] No ion−dipole complex was found. The structure either collapses through E2 TS or to an addition product (at CN group). [e] No barrier was found for the E2 process and the system smoothly progressed from reactant to product complex.

stable than the ion/dipole complexes. This simply indicates that the barrier on the electronic potential energy surface is smaller than the differences in vibrational energies of these species. In addition to the tables, molecular representations of the S_N2 and E2 transition states for the reactions of the acetate ions are shown in Figures 3 and 4. A key feature of the S_N2 transition states is their great similarity with less than a 0.05 Å variation across the series of compounds in the forming and breaking bond lengths. Clearly, the β-halogen is a remote substituent in the S_N2 reactions and does not greatly perturb the gas-phase reaction path. In contrast, there is a definite variation in the transition state geometries for the E2 reactions. Across the series (H, F, Cl, Br) there is a smooth shift from a central E2 transition state (Z = H) to one with a high degree of $E1_{cb}$ character (Z = Br). This is clearly seen in the bond lengths involved in the proton transfer. For ethyl bromide, the forming O−H bond is nearly as long as the breaking C_β−H bond (1.302 Å vs 1.354 Å). In contrast, proton transfer is nearly complete in the reaction with 1,2-dibromoethane (O−H = 1.092 Å and C_β−H = 1.581 Å). Changes in the breaking C_α−Br bond lengths also reflect a shift toward more $E1_{cb}$ character with the larger halogens.

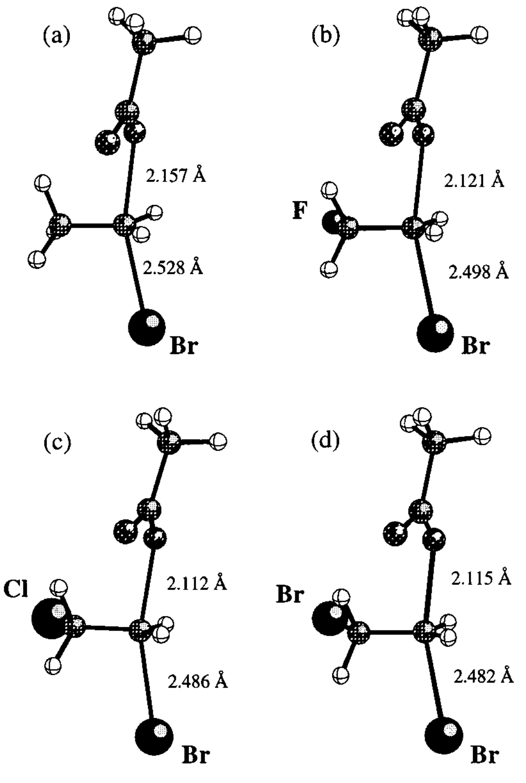

Figure 3. MP2/6-31+G(d) optimized geometries for the S_N2 transition states of the reactions of acetate with (a) ethyl bromide, (b) 2-fluoroethyl bromide, (c) 2-chloroethyl bromide, and (d) 2-bromoethyl bromide. In each drawing, acetate is at the top. The substituent groups are labeled.

Discussion

S_N2 Rates. Relative rate constants for substitution and elimination are shown in Table 4 and are most instructive in analyzing the results. In the S_N2 partial rates for **I**, one observes a smooth increase across the substituent series: H < F < Cl < Br. With nucleophile **II**, an S_N2 rate increase is seen with the addition of a β-fluoro group, but useful data cannot be obtained for β-chloro and β-bromo groups because the E2 channel

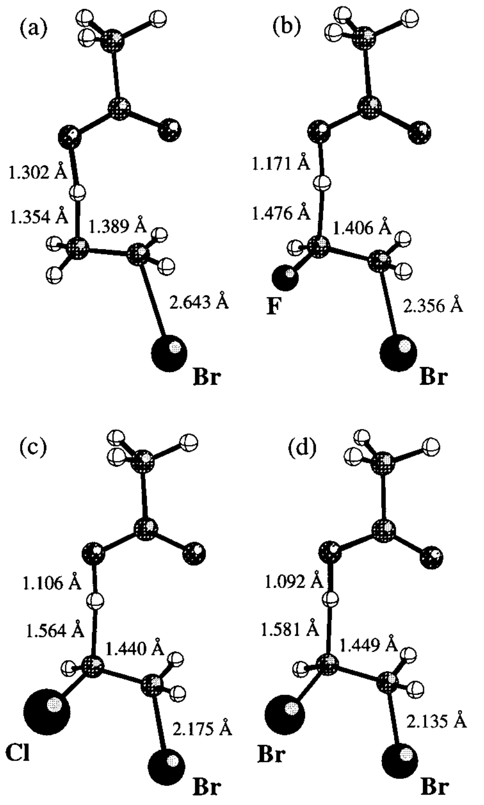

Figure 4. MP2/6-31+G(d) optimized geometries for the E2 transition states of the reactions of acetate with (a) ethyl bromide, (b) 2-fluoroethyl bromide, (c) 2-chloroethyl bromide, and (d) 2-bromoethyl bromide. In each drawing, acetate is at the top. The substituent groups are labeled.

Table 4. Relative Rates for the S_N2 and E2 Reactions of Dianions with Alkyl Bromides

	I		II	
	S_N2	E2	S_N2	E2
CH_3CH_2Br	1.0	0.0	1.7	0.1
FCH_2CH_2Br	5.7	0.0	9.3	4.7
$ClCH_2CH_2Br$	13.7	3.5	*a*	530
$BrCH_2CH_2Br$	35.8	17.1	*a*	780
$EtCH_2CH_2Br$	2.8	0.4		

[a] The yield was too low for accurate partial rate measurements.

overwhelms the S_N2 channel in these substrates. The computed data for the reactions of acetate with these substrates also show that the β-halogens stabilize the S_N2 transition states relative to the unsubstituted system (Table 2). Across the series (H, F, Cl, Br) the transition state energies smoothly drop from −3.4 to −9.3 kcal/mol relative to the separated reactants. A similar, but less dramatic trend is also seen in the computational work with methoxide (Table 3). Clearly, simple electron-withdrawing groups at the β-carbon stabilize the S_N2 transition state and can *increase* the substitution rate in the gas phase. However, the opposite effect is well documented in solution. For example, Hine and Brader[34] found that with thiophenolate in methanol, the S_N2 reactions of 2-haloethyl bromides are from 8 to 10 times slower than those of ethyl bromide. This represents a striking reversal in substituent effects caused by solvation. It is not an artifact of comparing different nucleophiles (benzoate vs thiophenolate) because in solution, S_N2 rate reductions from electron-withdrawing groups at the β-position are seen with a range of nucleophiles including acetate and halides.[32,33]

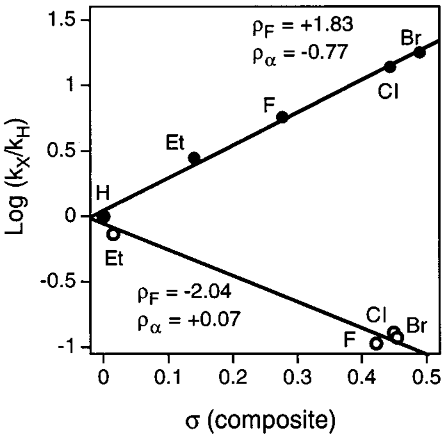

Figure 5. Hammett plots for the S_N2 reactions of the β-substituted ethyl bromides in the gas phase (solid circles) and methanol (open circles). Composite σ values are the ρ weighted averages of σ_α and σ_F ($[\rho_\alpha\sigma_\alpha + \rho_F\sigma_F]/[\mathrm{Abs}(\rho_\alpha) + \mathrm{Abs}(\rho_F)]$). The use of the composite σ values allows for a convenient graphical presentation of the two-parameter data. The displayed ρ values were obtained by a conventional least-squares fit of the data to eq 6. The rates for dibromoethane were divided by two.

To better understand this unusual result, we have analyzed the kinetic data for nucleophile **I** using a two-parameter, linear free-energy relationship suggested by Taft.[48] An assumption in applying a linear free-energy analysis to gas-phase data is that the rate is controlled by the reaction barrier height rather than a dynamics bottleneck.[49] Although it appears that the rates of gas-phase S_N2 reactions in small systems can be heavily influenced by dynamics issues,[50−52] this does not appear to be the case for larger systems with many degrees of freedom.[53] In the Taft analysis, each substituent is characterized by a polarizability and field-effect parameter (eq 6). Here, σ_α is the

$$\log(k_X/k_H) = \rho_\alpha\sigma_\alpha + \rho_F\sigma_F \qquad (6)$$

substituent's polarizability parameter and σ_F is its field-effect parameter. These values were taken from Taft's set[48] for gas-phase systems.[54] The ρ values are the scaling factors for each of the effects. In Figure 5, least-squares fits to the equation are presented graphically for the gas-phase data as well as for the methanol data from Hine and Brader.[34] In each plot, a good fit is seen with an r^2 value greater than 0.982. In the gas phase, both polarizability and field effects are important and values of $\rho_\alpha = -0.77$ and $\rho_F = +1.83$ are obtained. The results imply that field effects are most important in this system and that electron-withdrawing groups increase the rate (i.e., stabilize the transition state). The most straightforward explanation is that the dipole of the substituent at the β-carbon has a favorable electrostatic interaction with the anionic reaction center ensemble

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(48) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(49) Fundamentally, there is no problem applying a linear free-energy analysis to gas-phase data. The only question is whether the results truly represent effects on the transition state energy. There is evidence that this is true in the present case. First, the reaction efficiencies are relatively low, suggesting that a barrier affects the rate. Second, a substrate similar to those in this study (chloroacetonitrile, ref 53) appears to behave statistically. Third, the computational data support the conclusion that halogens reduce the S_N2 barrier.

(50) Hase, W. L.; Wang, H.; Peslherbe, G. H. *Adv. Gas-Phase Ion Chem.* **1998**, *3*, 125.

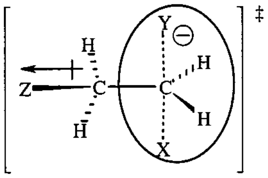
(51) Viggiano, A. A.; Morris, R. A.; Paschkewitz, J. S.; Paulson, J. F. *J. Am. Chem. Soc.* **1992**, *114*, 10477.

(52) Graul, S. T.; Carpenter, C. J.; Bushnell, J. E.; van Koppen, P. A. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1998**, *120*, 6785.

(53) Viggiano, A. A.; Morris, R. A.; Su, T.; Wladkowski, B. D.; Craig, S. L.; Zhong, M.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 2213.

(54) The following values were used: F ($\sigma_F = 0.44$ and $\sigma_\alpha = 0.13$), Cl ($\sigma_F = 0.45$ and $\sigma_\alpha = -0.43$), Br ($\sigma_F = 0.45$ and $\sigma_\alpha = -0.59$), and Et ($\sigma_F = 0.0$ and $\sigma_\alpha = -0.49$).

Scheme 2



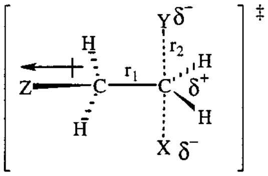
(nucleophile/leaving group/α-carbon) at the transition state (Scheme 2). A similar rationalization has been presented already by Brauman and co-workers[55] to explain rate enhancements observed in the gas-phase S_N2 reactions of benzyl chlorides containing electron-withdrawing groups on the ring.

The ρ_α value is also significant (−0.77) and implies that polarization of the substituent group also stabilizes the transition state in the gas phase (the negative sign is an artifact of how the σ_α values are defined). This is not surprising and it is well-known that polarizability plays an important role in determining gas-phase properties such as acidities and basicities.[56−58] In fact, polarization must be included in eq 6 to get a good fit for these systems because each of the halogen substituents has a similar σ_F value so the variation in rates from F < Cl < Br must be a result of increasing polarizability along the series. To provide further evidence of the importance of polarizability in these systems (as well as the validity of the analysis) we have also studied the reaction of nucleophile **I** with *n*-butyl bromide (i.e., substituent = ethyl group). This provides an example of a substituent without a field effect ($\sigma_F = 0$), but with significant polarizability ($\sigma_\alpha = 0.49$). Data for this substrate are included in Tables 1 and 4. It can be seen in Figure 5 that the ethyl substituent fits into the same linear free-energy relationship as the halogens.

When an identical analysis is applied to the previous condensed phase data (Figure 5), the fit to eq 6 indicates that field effects are the dominant factor ($\rho_F = -2.04$) and that polarizability plays almost no role in solution ($\rho_\alpha = 0.07$). The striking difference is that in going from the gas phase to the condensed phase, ρ_F shifts from being significantly positive to significantly negative. In other words, solvation completely reverses the role of field effects in the S_N2 reaction. A reversal in ρ is not unprecedented for S_N2 reactions, but the large shift in this case is striking. For example, the condensed phase S_N2 reactions of ring-substituted benzyl chlorides give a slightly negative ρ (−0.3) for treatment with hydroxide in H_2O, but a slightly positive ρ (+0.8) for treatment with iodide in acetone.[59] The data from Brauman's study[55] of the gas-phase S_N2 reactions of ring-substituted benzyl chlorides with chloride ions can also be investigated with the two-parameter analysis presented above and a ρ_F value of +3.5 is obtained ($\rho_\alpha = -0.8$).[60] Again, one sees that the shift to the gas phase leads to a significant increase in ρ.

To explain the large reversal in substituent effects for the β-halogens, there are two options: (i) the electron-withdrawing substituents reduce the solvation energy of the transition state relative to the reactant or (ii) solvation alters the electronic structure of the S_N2 transition state. It is difficult to find support for the first option, particularly because this effect must overcome the intrinsic stabilization that these substituents provide to the gas-phase transition state. One might want to invoke steric effects, but the kinetic data in solution provide no evidence for this. Clearly, the substituent size increases across the series F < Cl < Br, but addition of any of these halogens at the β-position leads to approximately the same S_N2 rate in methanol. As suggested from the linear free-energy analysis, the effect of these substituents is definitely a polar one in both the gas phase and solution. It is known that the halogen substituents moderately increase the aqueous solvation energies of these substrates (i.e., increase their Henry's law constants[61]), but there is no reason to doubt that they would have a similar effect on the solvation energies of the transition states. Moreover, this effect is simply too small to explain the experimental results. A more likely explanation is that solvation alters the S_N2 transition state in such a way that the polar effects of the substituents are dramatically changed.

Scheme 3



The situation outlined in Scheme 2 approximates the transition state as simply a diffuse anionic sphere around the reaction center. Under all circumstances, the interaction of this anionic sphere with the bond moment of an electron-withdrawing substituent would lead to stabilization. Of course, this is a gross simplification. A more realistic approach would be to represent the transition state as an "ion triplet" with the nucleophile and leaving group bearing partial negative charges, and the α-carbon bearing a partial positive charge (Scheme 3).[33] This leads to a more complicated electrostatic analysis because the substituent's dipole will have a destabilizing interaction with the charge at the α-carbon, but stabilizing interactions with the charges at the nucleophile and leaving group. By using this type of model, the substituent can either stabilize or destabilize the transition state depending on the magnitude of the partial charges and the geometry (particularly the distance from the dipole to the reaction center, r_1). Given the geometric constraints of a β-substituted system, the partial charges are the most important variables. As a simple example, consider an identity reaction (i.e., bromide on an alkyl bromide) where it can be assumed that the entering and leaving groups have the same charges and bond lengths. As rough approximations, the distances in Scheme 3 can be set to $r_1 = 1.5$ Å and $r_2 = 2.5$ Å with a C−Z bond moment of 1.38 D (C−Br bond[62]).[63] The two reasonable limiting cases in terms of polarity are (i) a transition state where no charge develops on the α-carbon (X = Y = −1/2 and $C_\alpha = 0$) and (ii) one where the C_α−X bond is completely ionized (X = Y = −1 and $C_\alpha = +1$). The latter situation has been referred

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[55] Wladkowski, B. D.; Wilbur, J. L.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 2471.

[56] Taft, R. W.; Taagepera, M.; Abboud, J. L. M.; Wolf, J. F.; DeFrees, D. J.; Hehre, W. J.; Bartmess, J. E.; McIver, R. T., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 7765.

[57] Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247.

[58] Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311.

[59] Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.

[60] In this analysis, four meta substituents were used (methyl, methoxy, fluoro, and chloro) along with the parent system. The trifluoromethyl group was omitted because it gave a fairly poor fit to eq 6. If included, a ρ_F value of +4.0 is obtained.

[61] Sander, R. In *NIST Chemistry WebBook, NIST Standard Reference Database Number 69*; Mallard, W. G., Linstrom, P. J., Eds.; National Institute of Standards and Technology: Gaithersburg, MD, 2000 (http://webbook.nist.gov).

[62] Smyth, C. P. *Dielectric Behavior and Structure*; McGraw-Hill: New York, 1955.

[63] The C−Br dipole was simulated by a positive and negative charge (+0.144 and −0.144) held 2 Å apart. This leads to a dipole moment of 1.38 D. The bond moment is oriented as if it is attached to a tetrahedral carbon at the β-position.

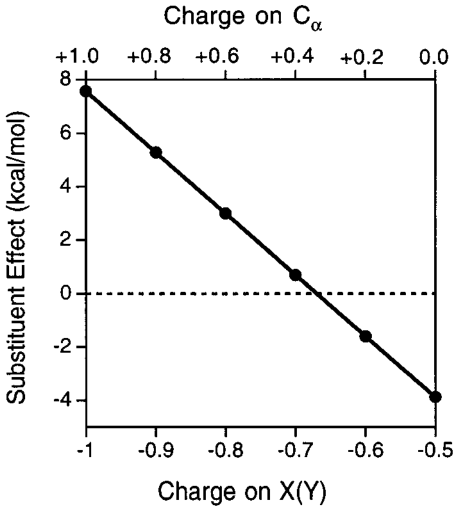

Figure 6. Plot of substituent effect as a function of charge on X(Y) in the model shown in Scheme 3. The model assumes a C$-$Z bond moment of 1.38 D with r_1 set at 1.5 Å and r_2 set at 2.5 Å. In the graph, negative values imply stabilization of the transition state. The horizontal, dashed line represents a "zero" substituent effect.

to as an "ion pair" transition state.[64] The simple electrostatic model outlined in Scheme 3 predicts very different substituent effects from these two limiting cases. If no charge develops on the α-carbon (case i), there are only attractive ion/dipole interactions and the electron-withdrawing substituent significantly stabilizes the transition state. If the α-carbon has a full positive charge (case ii), the repulsive ion/dipole interaction with the α-carbon dominates and the electron-withdrawing group destabilizes the transition state. This is graphically illustrated in Figure 6 where the substituent effect is plotted as a function of the charge on X(Y). A balance of these factors occurs for a transition state with partial charges of approximately $X = Y = -0.65$ and $C_\alpha = +0.3$, and the model predicts that the substituent dipole would have essentially no effect on a transition state with this charge distribution. If the magnitudes of the charges increase from this balance point (e.g., $C_\alpha > +0.3$), the dipole of an electron-withdrawing substituent causes a net destabilization of a few kcal/mol (i.e., negative ρ). In contrast, if the charges are smaller (i.e., $C_\alpha < +0.3$), the substituent's dipole stabilizes the transition state (i.e., positive ρ).

Although the model is exceptionally simple, it provides a good foundation for rationalizing the condensed-phase and gas-phase results. In the gas phase, the low dielectric and lack of solvation disfavor a highly ionized transition state. The positive charge on the α-carbon is limited and therefore the electron-withdrawing substituent stabilizes the transition state. In the condensed phase, increasing the charge on the nucleophile and leaving group should increase the solvation energy of the transition state (i.e., stronger hydrogen bonding and charge/dipole interactions with solvent molecules). Of course, this is balanced by an intrinsic destabilization of the transition state (it prefers the gas-phase charge distribution). Nonetheless, the condensed-phase transition state should be more highly ionized. Examination of Figure 6 shows that the substituent effect is very sensitive to the charges and going from a charge distribution of ($X = Y = -0.6$ and $C_\alpha = +0.2$) to one of ($X = Y = -0.7$ and $C_\alpha = +0.4$) leads to more than a 2 kcal/mol shift in the effect of the substituent's dipole on the transition state energy (-1.6 to $+0.7$ kcal/mol). The model is based on a C$-$Br bond providing the dipole, and by using the σ_F value for Br, this change in substituent effect would be equivalent to a shift in ρ_F from $+2.6$ to -1.1 at 300 K. The model is certainly too crude to be considered quantitative, but the important point is that subtle changes in the charge distribution can have a major impact on the substituent effect. Given the very large energy associated with the solvation of a charged species, it is not unreasonable to assume that solvation could lead to an increase in the polarity of the S_N2 transition state by 0.1 electrons on the nucleophile and leaving group. This type of rationalization also works well with the data quoted above for the reactions of ring-substituted benzyl chlorides with various nucleophiles. Here, one sees a smooth progression in ρ values in going from the most ionizing to the least ionizing environments: $\rho(H_2O, HO^-) = -0.3 < \rho(\text{acetone}, I^-) = +0.8 < \rho(\text{gas phase}, Cl^-) = +3.5$. Changes in the nucleophile complicate this comparison, but at least the progression fits the model.

Overall, this analysis points to variable transition states for the S_N2 process depending on the environment. The concept of variable transition states has been most often couched in terms of changes in geometry, but in the present case, our data only probe variations in the electronic structure of the transition state. Jorgensen and co-workers[65] have used molecular simulation techniques to probe the effect of solvation on the geometry of an S_N2 transition state. In the reaction of chloride with methyl chloride, they found that water had little effect on the geometry and caused only a small increase in the C$-$Cl distances. However, the apparent insensitivity of the geometry to solvation does not preclude the small shift in charge distribution needed to reverse the substituent effect. In fact, this analysis reaffirms that care must be taken in using electronic effects as evidence for geometric changes in transition structures.

There are two areas where the present model is particularly relevant to previous work presented by Brauman and co-workers.[55,66] First, their data for the identity S_N2 reactions of ring-substituted benzyl chlorides[55] indicate that substituents have nearly the same effect on the stability of the ion/dipole complexes as on the transition states (i.e., a one-to-one correspondence in the increases in the ion/dipole complex and transition state stability). As a result, all the reactions have approximately the same barrier relative to the ion/dipole complex. They have argued that the substituents essentially "pull down" the entire potential energy surface in these reactions. Our ab initio data for the reactions of the 2-haloethyl bromides (Tables 2 and 3) show a reasonable correlation between the effect of the substituent on the stability of the complex and the transition state; however, the magnitude of the substituent effect is clearly greater on the ion/dipole complex in these systems. For example, the 2-halo substituents increase the stabilities of the acetate complexes by 5.8$-$7.6 kcal/mol, but the transition states by only 2.5$-$5.9 kcal/mol. Consequently, the substituted systems have higher barriers relative to the ion/dipole complexes. It is important to remember that in gas-phase reactions, it is the stability of the transition state relative to the separated reactants that is the kinetically relevant term, so observations about the relative energies of the complexes and transition states are interesting in terms of the shape of the potential energy surface, but are generally not important in determining observed rate constants. The difference between the ethyl bromide and benzyl chloride systems is probably a result of the substituent being closer to the reaction center in the 2-haloethyl bromides. The shorter distance (i.e., r_1 in Scheme 3) increases the importance of the repulsive interaction of the dipole with the

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

(65) Jorgensen, W. L.; Buckner, J. K. *J. Phys. Chem.* **1986**, *90*, 4651.

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

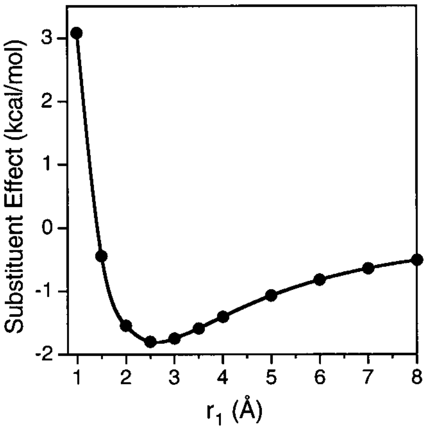

Figure 7. Plot of substituent effect as a function of distance r_1 in the model shown in Scheme 3. The model assumes a C−Z bond moment of 1.38 D with r_2 set at 2.5 Å and the charge on X(Y) set to −0.65. In the graph, negative values imply stabilization of the transition state.

partial charge on the α-carbon and reduces its overall stabilizing effect on the transition state. At longer distances, the attractive interaction with the charges on X and Y better offsets the repulsive interaction with the charge on the α-carbon. In fact, the simple electrostatic model in Scheme 3 predicts that for large r_1 values, the substituent effect is fairly insensitive to the charge distribution at the reaction center (i.e., the situation approaches the anionic sphere model in Scheme 2) and therefore one expects that substituents would equally stabilize complexes and transition states. For example, at $r_1 = 4$ Å, there is just over a 1 kcal/mol variation in the substituent effect across the entire range of reasonable transition state charge distributions (i.e., charge on X and Y varying from −0.5 to −1.0). In another study, Craig and Brauman[66] have investigated the S_N2 reactions of chloride with a series of alkyl chlorides that have electron-withdrawing groups at varying distances from the reaction center ($Cl(CH_2)_nZ$, $n = 1$ to 5, Z = Cl, CN, and OH). In this work, they found compelling evidence that the substituents electrostatically stabilized the transition states by through-space interactions (internal solvation). A key result is that the effect of the substituent dipole does not drop off monotonically and is maximized for intermediate distances ($n = 3$). For example, the chloro-substituted series gives the following reactivity order:

$$Cl(CH_2)_3Cl > Cl(CH_2)_4Cl \gg Cl(CH_2)_2Cl$$

This may be related to an orientation effect (i.e., geometric constraints preventing the dipole from aligning itself with the charge), but it is also a predicted outcome from the model in Scheme 3. This is illustrated in Figure 7 with the charge on X and Y set at −0.65.[67] In the model, the stabilizing effect of the dipole of an electron-withdrawing group is maximized at a distance (r_1) of about 2.5 Å and slowly diminishes for longer distances, but quickly shifts to destabilizing for shorter distances. This pattern matches Brauman's data very well and a distance of $r_1 = 2.5$ Å is reasonably close to what one would expect for the halogenated $n = 3$ species in the study (i.e., $ClCH_2CH_2CH_2Cl$). Therefore, our model fully supports Brauman's conclusion that these substituent effects can be explained on the basis of through-space electrostatic interactions.

E2 Rates. The quantitative analysis of the E2 rates is compromised by competition with substitution and by the dynamic range of gas-phase reactions (Table 4). With nucleophile **I**, E2 products are not observed with ethyl bromide or 2-fluoroethyl bromide (S_N2 only). With the stronger base (**II**), the elimination rate approaches the collision-controlled limit for 2-chloroethyl and 2-bromoethyl bromide so these substrates cannot be safely included in a kinetic analysis. As a result, only qualitative observations can be made.

First, the E2 rates are much more sensitive than the S_N2 rates to the addition of substituents at the β-carbon and a rate increase of over a 1000-fold is observed for the reactions of **II** with the chloro- and bromo-substituted systems. This is not surprising given that the β-substituent is on a reaction center that is expected to bear a partial negative charge in the transition state of the E2 process. The larger substituent effects are also consistent with the larger geometric variations in the calculated E2 transition states (Figure 4). Second, as one moves across the series there is a systematic increase in E2 rates: H < F < Cl < Br. The effective acidity of the β-carbon is probably an important factor in determining this reactivity order. The acidifying effect of the substituents can be judged by using CH_3Z compounds as models (eq 7). The gas-phase acidities (ΔH_{acid}) of these species are known and an identical order is observed (least to most acidic): H (417 kcal/mol) > F (409 kcal/mol) > Cl (400 kcal/mol) > Br (397 kcal/mol).[47] It is interesting to

$$CH_3Z \xrightarrow{\Delta H_{acid}} {}^{-}CH_2Z + H^+ \qquad (7)$$

note that for both nucleophiles, it appears that the most dramatic E2 rate increases occur in going from the fluoro-substituted to the chloro-substituted alkyl bromide. This is also consistent with the greater acidifying effects of chlorine and bromine. The computational data (Tables 2 and 3) indicate the same reactivity order with increasingly stable E2 transition states across the series. It appears that product stability has little to do with the kinetic reactivity and the reaction exothermicities (all of which are calculated to be near zero for the acetate reactions) do not correlate with the observed rates (a similar effect is seen for the S_N2 reactions). To provide data for a highly acidifying group at the β-carbon, we have considered 2-cyanoethyl bromide. The calculations with acetate as the nucleophile predict a very stable E2 transition state and with methoxide, the E2 barrier disappears and a single well potential is observed. This is not surprising because methoxide is a strong enough base in the gas phase to deprotonate nitriles without the aid of a leaving group.[47] Experimentally, this substrate gives only E2 products at rates near the collision-controlled limit with nucleophiles **I** and **II**.

There is fairly limited data on the effect of β-halogens on condensed-phase E2 reaction rates. Hine and Langford[68] have shown that for alkyl bromides ($Z\text{-}CH_2CH_2Br$) in H_2O/dioxane, the E2 rate with hydroxide increases along the series F (0.052) < Cl (0.68) < Br (1.00). It is interesting to note that they also found that the largest rate change occurred in going from F to Cl as the substituent. Unfortunately, they did not include a simple alkyl halide in their data set. Goering and Espy[31] have found that the addition of a β-halogen greatly increases the E2 rate in HO^-/EtOH/H_2O solution. For example, *cis*-1-bromo-2-chlorocyclohexane and *cis*-1,2-dibromocyclohexane react 39 and 120 times faster than bromocyclohexane under the same conditions. In contrast, Okamato et al.[32] found a sharp rate decrease (60-fold) for $ClCH_2CH_2Cl$ compared to that for CH_3CH_2Cl in E2 reactions with acetate in H_2O. In fact, they found that all electron-withdrawing groups at the β-carbon retarded the E2 reaction rate. Moreover, their data indicated that the chloro substituent led to a higher S_N2/E2 ratio than in the

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[67] The shape of the curve is not very sensitive to the charge on X(Y), but the magnitude of stabilization at any particular distance is.

[68] Hine, J.; Langford, P. B. *J. Am. Chem. Soc.* **1956**, *78*, 5002.

unsubstituted system. They argued that the base (acetate) favors Hofmann-like elimination behavior[69] and steric effects control the E2 reaction rate. However, our gas-phase and computational data with carboxylate bases clearly show that the β-halogens can dramatically stabilize E2 transition states and favor elimination over substitution. It is unclear why acetate in H_2O gives the opposite result, but this does not appear to be a general characteristic of condensed-phase eliminations.

S_N2 vs E2 Reactions. Although the β-halo substituents increase both the S_N2 and E2 rates, the impact is greater on the elimination process. As a result, the substituents led to an increase in the E2 yields. For example, nucleophile **I** gives only S_N2 products with ethyl and 2-fluoroethyl bromide, whereas the more activating substituents, chloro and bromo, lead to modest yields of E2 products. This pattern can be explained in the following way. For the unsubstituted system, it is likely that the E2 transition state is significantly less stable than the reactants and therefore gives a very low (unobservable) reaction rate. The S_N2 process must have a more stable transition state and substitution products are observed. This type of situation is reflected in the calculations on the model system, the reaction of acetate with ethyl bromide. First, the E2 transition state is computed to be over 5 kcal/mol less stable than the reactants. Although an activation energy of ~5 kcal/mol may appear small by condensed-phase standards, it translates to a very slow reaction by gas-phase standards. Practical limitations in mass spectrometry necessitate a kinetic window limited to reactions that have very high efficiencies (observed rate/collision rate). In most cases, observable reactions are limited to an efficiency range from 1 (reaction at every collision) to about 0.0001 (reaction once in every 10 000 collisions). As a result, activation energies of about 5 kcal/mol are around the limit for the slowest ion/molecule reactions that can be observed. Second, the S_N2 transition state for the reaction of acetate with ethyl bromide is calculated to be 8 kcal/mol more stable than the E2 transition state. In addition, it is slightly more stable than the separated reactants (negative activation energy). Negative activation energies are a common occurrence in gas-phase ion/molecule reactions because of the initial complexation energy and they generally result in fast reactions. However, Brauman[7,70] has pointed out that reactions with negative activation energies do not always proceed at the collision-controlled limit because entropic effects (particularly in the highly ordered S_N2 transition state) can reduce the efficiency significantly. In any case, the computed results are consistent with the unsubstituted system giving only substitution products. Moving down the series of halogens, the calculations show a steady decrease in the transition state energies as well as in the S_N2 preference with acetate as the nucelophile. However, the S_N2 process is always preferred by at least 4 kcal/mol. Again, this pattern is in good accord with the experimental results for nucleophile **I** where rates increase and E2 reactions emerge, but do not dominate with the chloro- and bromo-substituted substrates.

Nucleophile **II** is a stronger base than **I** and therefore should be more prone to elimination reactions. For example, our calculations on the reactions with methoxide (stronger base) as the nucleophile (Table 3) show smaller S_N2 preferences than the reactions with acetate (weaker base) as the nucleophile (Table 2). In fact, the E2 transition state is more stable than the S_N2 transition state for the reactions of methoxide with the chloro- and bromo-substituted systems. Experimentally, nucleophile **II** gives small to moderate elimination yields with ethyl bromide and 2-fluoroethyl bromide whereas nucleophile **I** gives only substitution products with these substrates. The greatest difference occurs for the chloro- and bromo-substituted systems. These substrates give very high rates and almost exclusively elimination products with nucleophile **II**. The best explanation for this behavior is that in the reactions of **II**, the β-chloro and β-bromo substituents stabilize the E2 transition state to the point where it is at a lower energy than the reactants (i.e., a negative activation energy). Because E2 transition states are not highly constrained, the reaction rate can approach the collision-controlled limit under these conditions. The near absence of substitution products with these substrates should not be viewed as evidence for high barriers in their S_N2 reactions. All of our data (experimental and computational) suggest that the β-substituents should stabilize the S_N2 transition states, and with methoxide as the nucleophile (Table 3), the halogens are predicted to stabilize the S_N2 transition states by up to 10 kcal/mol. Therefore, it is likely that the S_N2 reactions with these substrates also have negative activation energies, but that the entropic disadvantage of the highly ordered S_N2 transition state makes it much less competitive. Although both channels (S_N2 and E2) could be enthalpically accessible in the reactions of **II** with 2-chloroethyl and 2-bromoethyl bromide, entropic factors funnel nearly all the reactions through the elimination pathway. As noted above, Brauman[7,70] has clearly shown that entropic effects can severely limit the efficiencies of S_N2 reactions.

The most relevant condensed-phase data on the effect of β-halogens on S_N2/E2 competition comes from Hine and Langford's study of the reactions of hydroxide in aqueous dioxane.[68] Although their analytical method produced rather large uncertainties in S_N2 rates, they found that a chlorine or a bromine at the β-position greatly increases the E2 yield. For example, $BrCH_2CH_2Br$ gives an E2/S_N2 ratio of greater than 18:1 whereas the ratio with FCH_2CH_2Br is only 0.27:1.

Conclusions

The present data show that in the absence of solvation, β-halogens increase the rates of both S_N2 and E2 reactions. The effect is most pronounced in the E2 pathway and as a result, the β-halogens shift the systems toward greater elimination yields. In comparisons to condensed-phase data, the results with the S_N2 reaction point to a large, solvation-induced reversal in substituent effects. In the gas phase, β-halogens have a strong stabilizing effect ($\rho_F = +1.83$) whereas the opposite is true in methanol ($\rho_F = -2.04$). This reversal in substituent effects can be explained by a simple electrostatic model that approximates the transition state as a positively charged carbon sandwiched between negatively charged entering and leaving groups (i.e., $X^{\delta-}$- -$C_\alpha^{\delta+}$- -$X^{\delta-}$). In this model, the effect of a nearby dipole goes from stabilizing to destabilizing as the transition state becomes more highly ionized (i.e., larger charges on X and C_α). It seems reasonable that solvation by a polar solvent would shift the system to a more ionized transition state and therefore reverse the substituent effect. The model also indicates that this type of behavior is limited to situations where the internal dipole is very near to the reaction center and will be most apparent in β-substituted systems.[71]

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[69] Systems giving Hofmann elimination are generally characterized by positive ρ values because electron-withdrawing groups stabilize the charge at the β-carbon (see ref 24). Consequently, the rate reduction observed with the chloro substituent is not typical of Hofmann eliminations.

[70] Chabinyc, M. L.; Craig, S. L.; Regan, C. K.; Brauman, J. I. *Science* **1998**, *279*, 1882.

[71] It is difficult to apply this simple model to α-substituted systems because orbital overlap (conjugation) and steric effects could play dominant roles.

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