

**Gas Phase Negative Ion Chemistry: Reactivity and Mechanism
in Fundamental Organic Reactions**

by

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Gas Phase Negative Ion Chemistry: Reactivity and Mechanism in Fundamental Organic Reactions

Thesis directed by Professor Veronica M. Bierbaum

Abstract:

Numerous experimental and theoretical studies have probed reactions using gas phase ion chemistry to develop an intrinsic understanding of kinetics, mechanisms and structure-energy relationships. The fundamental knowledge gained from these studies allows predictive tools to be developed for understanding chemical systems (earth's atmosphere, biological, etc.). This thesis describes the reactive characteristics and competitive processes within several organic ion-molecule reactions. An overview of the basic principles of gas phase ion-molecule reactions and the experimental methods employed in our studies are given in Chapters 1-2.

In Chapter 3, comparisons of the reactivity and mechanistic pathways between the reactions of alkyl iodides with CN^- in the gas phase and several solvents are reported. The mechanistic results are strikingly similar; however, a tighter gas phase transition state is suggested.

In Chapter 4, competition between the substitution ($\text{S}_{\text{N}}2$) and elimination ($\text{E}2$) reactions of alkyl iodides with Cl^- , CN^- , and HS^- is evaluated. Contrary to previous studies, our results reveal competition between the $\text{S}_{\text{N}}2$ and $\text{E}2$ pathways. Discussions cover reaction efficiencies, kinetic isotope effects, linear basicity-reactivity relationships, electrostatic models, and transition state looseness parameters.

In Chapter 5, our investigation of the α -effect in the gas phase shows enhanced validating an intrinsic origin of the effect. Variations in electron affinities and bond strengths between the normal and α -anions indicate that HOO^- has distinctive thermochemical properties.

In Chapter 6, we apply Marcus theory in an attempt to resolve discrepancies between experimental and computational studies on the existence of the α -effect in S_N2 reactions with CH_3Cl . Marcus theory indicates that the intrinsic differences between normal and α -nucleophiles are small and can be easily masked by thermodynamic driving forces.

In Chapter 7, we explore the intrinsic behavior of α -nucleophiles in competitive reaction mechanisms. The α -effect is not seen in the E2 mechanism, but is reported for nucleophilic attack at both sp^2 and sp^3 carbon sites. This is rationalized by “soft” base behavior.

In Chapter 8, the reactivity of 1,3,5-triazine is investigated. Significant hydride acceptor properties are observed. Anion-arene binding modes and their influence on reaction pathways are discussed.

Dedicated to My Family:

Gretchen, Zach, Tyler,
Nick and Anna

You are a gift from God.
Thank you for the inspiration, comfort,
and joy you bring to my life every day.

*Nothing in the world can take the place of Persistence.
Talent will not; nothing is more common than unsuccessful
men with talent. Genius will not; unrewarded genius is
almost a proverb. Education will not; the world is full of
educated derelicts. Persistence and determination alone
are omnipotent. The slogan 'Press On' has solved and
always will solve the problems of the human race.*

- Calvin Coolidge
(30th president of US, 1872 - 1933)

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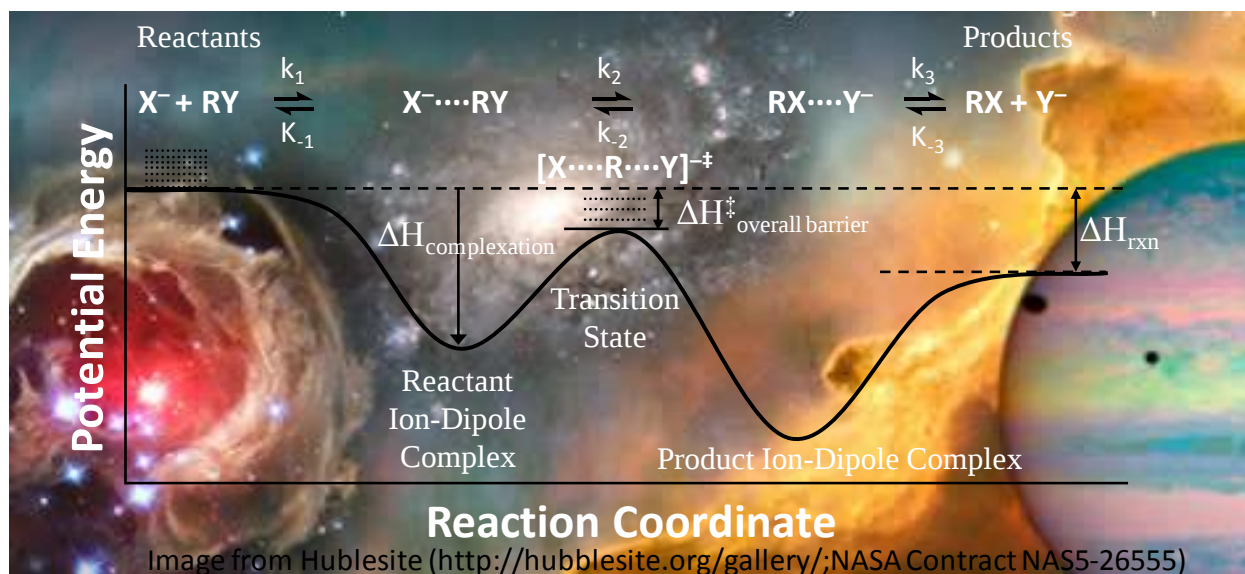
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Publications

1. Garver, J. M.; Fang, Y. R.; Eyet, N.; Villano, S. M.; Bierbaum, V. M.; Westaway, K. C., A Direct Comparison of Reactivity and Mechanism in the Gas Phase and in Solution. *Journal of the American Chemical Society* **2010** 132 (11), 3808-3814.
2. Garver, J. M.; Eyet, N.; Villano, S. M.; Yang, Z.; Bierbaum, V. M. Mechanistic investigation of S_N2 dominated gas phase alkyl iodide reactions. *International Journal of Mass Spectrometry*, **2011** 301 (1-3), 151-158.
3. Garver, J. M.; Eyet, N.; Villano, S. M.; Yang, Z.; Kato, S.; Wren, S. W.; Vogelhuber, K. M.; Lineberger, W. C.; Bierbaum, V. M. Gas Phase Reactions of 1,3,5-Triazine: Proton Transfer, Hydride Transfer, and Anionic σ -Adduct Formation. *Journal of the American Society for Mass Spectrometry*, **2011** 22 (7), 1260-1272.
4. Garver, J. M.; Gronert, S.; Bierbaum, V. M. Experimental Validation of the α -Effect in the Gas Phase, *submitted as a Communication to the Journal of the American Chemical Society*.
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6. Garver, J. M.; Yang, Z.; Wehres, N.; Nichols C.; Worker, B.; Gronert, S.; Bierbaum, V. M. Intrinsic Reactivity and the α -effect in Elimination Reactions and Competing Mechanisms in the Gas Phase, *In preparation*.
7. Wren, S. W.; Vogelhuber, K. M.; Garver, J. M.; Kato, S.; Sheps, L.; Bierbaum, V. M.; Lineberger, W. C. Nitrogen Proximity Effects in Azines: How Nitrogen Atoms Affect the C-H Bond Strengths and Anion Stability, *In preparation*.

CHAPTER 1

Gas-Phase Ion-Molecule Reactions



Overview

Life, Universe and Everything. The studies of gas phase ion-molecule reactions have played an important role in our fundamental understanding of physical organic chemistry. The relevance of this work is stressed and future applications highlighted. The fundamental physical organic principles that govern reaction mechanisms and reactivity are reviewed and the relevant chapters of the thesis in which they are employed are placed in brackets following the discussion, i.e., (see Chap 1-8).

1.1 Introduction

Historically, physical organic chemists have sought to identify meaningful trends in chemical reactivity and to relate these patterns with molecular parameters.¹ Early work focused on reaction mechanisms in solution and analyzed the effects of structural variations in terms of linear free-energy relationships and kinetic isotope effects. These experimental studies provided a solid foundation in kinetics, mechanisms and structure-energy relationships; however, for many classical organic reactions scientists have yet to resolve the role of solvent interactions from intrinsic reactivity. It is known that reaction rates and mechanisms can be influenced by solvent effects, which are even more pronounced in reactions involving ionic species due to strong electrostatic interactions with the solvent.² Thus, the fundamental nature of ion-molecule interactions should be derived from chemical behavior in a solvent-free environment. Gas phase studies provide insight into the intrinsic nature of a reaction without the interference of solvent effects and the presence of counter ions. In fact, the study of supramolecular chemistry and biological systems is increasingly performed with the aid of gas phase techniques.^{3,4} The gas phase has proven a valuable environment to establish the properties and reactivity of the non-polar interior of biological molecules (proteins and DNA), as well as provide insight into the role of solvent influences on nucleobase selectivity and recognition.⁵⁻⁷ Furthermore, gas phase data enable the molecular modeling of energies, structures, and electronic properties of molecules without having to account for the complexities of solute-solvent interactions.

The study of the products, distribution, rates, and equilibria of ionic reactions in the gas phase is well-suited to provide detailed information on reaction mechanisms, energetics, and solvent effects.^{8,9} Cations, anions, and even transient ionic intermediates can be generated, detected, isolated, and characterized in the gas phase. These completely unsolvated ions undergo

a large number of reactions that are analogous to those in solution. By comparing the gas phase results with those of condensed-phase experiments, the intrinsic behavior of these processes may be studied and the role of solvent exposed. Many common synthetic organic schemes (substitutions, eliminations, Grignard additions, aldol condensations, hydrolysis of esters, etc.) involve anions.¹ Many of these mechanisms not only play a central role in organic chemistry, but also in biological, atmospheric, and interstellar systems. A detailed and quantitative analysis of the effects of structural variation on the properties of molecules and reactions can be expanded to multidisciplinary areas such as supramolecular chemistry, nanotechnology, surfactant and membrane mimetic chemistry, catalytic processes, biochemical processes, and organic materials with specialized (super)conducting, optical, and magnetic properties.¹⁰

1.2 Fundamentals of Physical Organic Chemistry

Physical organic chemistry is concerned with the study of factors (structural or environmental) that affect the rates of reactions (kinetics), the way that light and matter interact (spectroscopy), how electrons are arranged in atoms and molecules (quantum mechanics), and the stabilities of compounds and processes (thermodynamics) of organic reactions.¹ Through the basic principles of classical and quantum mechanics, a method of describing microscopic atomic forces and molecular interactions is achieved. Statistical treatment of these concepts enables the prediction of the macroscopic properties and behavior of chemical systems. Chemical kinetics and reaction dynamics applies these concepts to explain the transformation of substances and the energy changes that accompany reactions. Within this framework the fundamental physical principles that govern reaction mechanisms and reactivity can be understood.

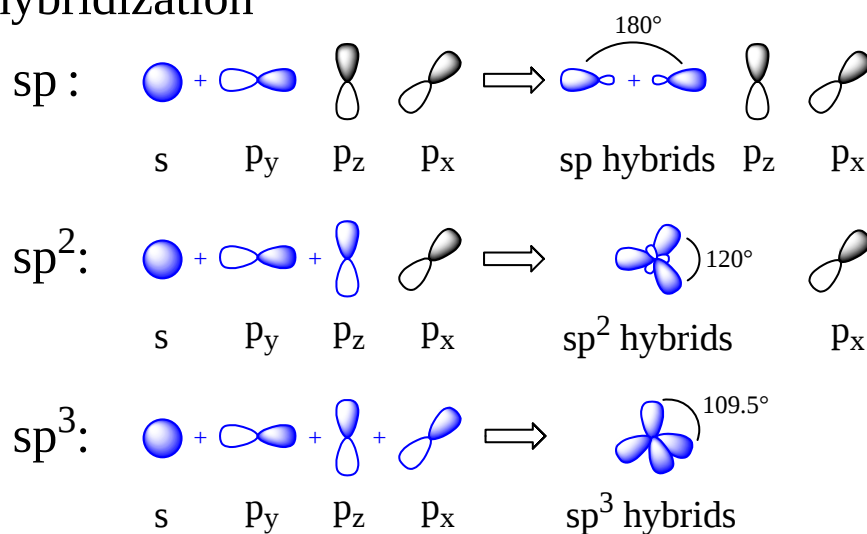
1.2.1 *Models of Chemical Bonding*¹

Since chemical reactions involve breaking and forming of chemical bonds, an understanding of the structural theory of organic chemistry will provide insights into physical properties of molecules and how they might interact. An atom consists of a dense, positively charged central nucleus surrounded by a cloud of negatively charged electrons held in place by electrostatic forces. The wave-like behavior of these electrons can be obtained from basic quantum mechanics via solution of the Schrödinger equation. In general, each solution or wavefunction describes the energy, size, shape, and the directionality of the atomic orbitals for a given nucleus. The geometries of these orbitals (s , p_x , p_y , p_z , etc.) determine the three dimensional structure of molecules and are the foundation of bonding models.

1.2.1.1 *Hybridized Orbitals*

The concept of hybridization arises from a "mixing" of the energy levels of the atomic orbitals during covalent bond formation. This perturbation of the atomic orbital wavefunctions results in new orbitals with geometries determined by the component atomic orbitals. Organic chemistry is primarily concerned with the sp^3 , sp^2 , and sp hybrid orbitals generated from the s and p orbitals. The geometries and shifts in electron distributions associated with the superposition of an s orbital with one, two, or three p orbitals are depicted in Figure 1.1a. These hybrid states are often invoked to describe molecular or transition state geometries (see Chap 3-8). The ideal geometries (sp^3 = tetrahedral, 109.5° ; sp^2 = trigonal planar, 120° ; sp = linear, 180°) are approximate and molecules deviate from ideal angles based on the actual percentage of s and p character used to form the hybrid orbitals. Hybrid orbitals also provide a picture of

a) hybridization



b) bonding

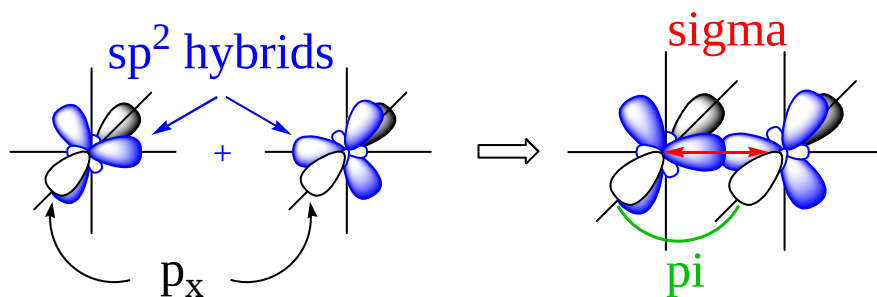


Figure 1.1 Hybridization. a) Forming sp , sp^2 and sp^3 hybrid orbitals and b) sigma (σ) and pi (π) bonding in hybrid orbitals.

bonding based on overlap of these orbitals along the bond axis to generate sigma (σ) bonds and between the orthogonal p orbitals on adjacent atoms to form pi (π) bonds (Figure 1.1b). Double bonds consist of a σ -bond and a π -bond and triple bonds consist of a σ -bond and two π -bonds. In structures with alternating single and multiple bonds (conjugated system), delocalization of charge density across the π -bonds may lower the overall energy and increase stability. The greater the delocalization of π -electrons across all the adjacent aligned p-orbitals (resonance) the greater the stability of the structure.¹ The continuous overlap of π bonds above and below the plane of the ring in a conjugated cyclic system (Hückel $4n+2$ electron rule)¹ is typically

associated with aromaticity (enhanced stabilization from cyclic delocalization and resonance). “Aromatic” systems tend to exhibit thermodynamic and kinetic stability; however, shifts in electron density within the σ and π bonds can significantly influence chemical properties as well as the forces that govern reaction pathways (see Chap 8).

1.2.1.2 *Electrostatic Models*

As mentioned above, the charge distribution within a molecule or anion is a key characteristic for predicting reactivity. Most of the gas phase anion-molecule reactions in our studies can be considered acid-base reactions in which a nucleophile (electron rich ion) attacks the site of an electron deficient atom (electrophilic center) within a molecule. Electronegativity and bond polarization provide a means to define the electron density within a structure. Electronegativity scales (measure of the attraction of an atom for electrons in a covalent bond) assess the energy of the orbitals that an atom uses to accept electrons. When a σ -bond forms between atoms (X-Y), the electrons will preferentially reside near the more electronegative atom (Y), producing a partial negative ($Y^{\delta-}$) and partial positive charge ($X^{\delta+}$) on the atoms. While the bonds are still covalent in nature, this bond polarization is often used to understand stability in electrostatic models (see Chap 3-8). Often the electronegativity and polarization effects can be felt along adjacent σ bonds (inductive effect) and across space between structures (field effects). In complex structures, electrostatic potential surfaces (see Chap 7 and 8 overview art) provide a better picture of the degrees of polarity across a molecule (red for negative and blue for positive). The polarizability of the anion also plays a key role in reactivity and selectivity. Whereas the energies of interaction for non-polarizable (hard) anions are primarily controlled by electrostatic attractions, polarizable (soft) anions are dependent on orbital mixing interactions.¹¹ Hard-Lewis-base-type nucleophiles tend to bind to hard-Lewis-acid-type electrophilic sites and soft-Lewis-

base-type nucleophiles tend to bind to soft-Lewis-acid-type electrophilic sites (see Chap 6 and 7). Molecular orbital theory provides a better context to understand the principle of hard and soft acids and bases.

1.2.1.3 Molecular Orbital Theory

While hybridization provides a simplistic picture of the interaction of atomic orbitals, molecular orbital theory considers the interactions of all the orbitals within a structure. Molecular orbitals (MOs) give us a deeper understanding of the electronic structure, orbital energies, and reactivity patterns of organic molecules. MOs are formed from the addition and

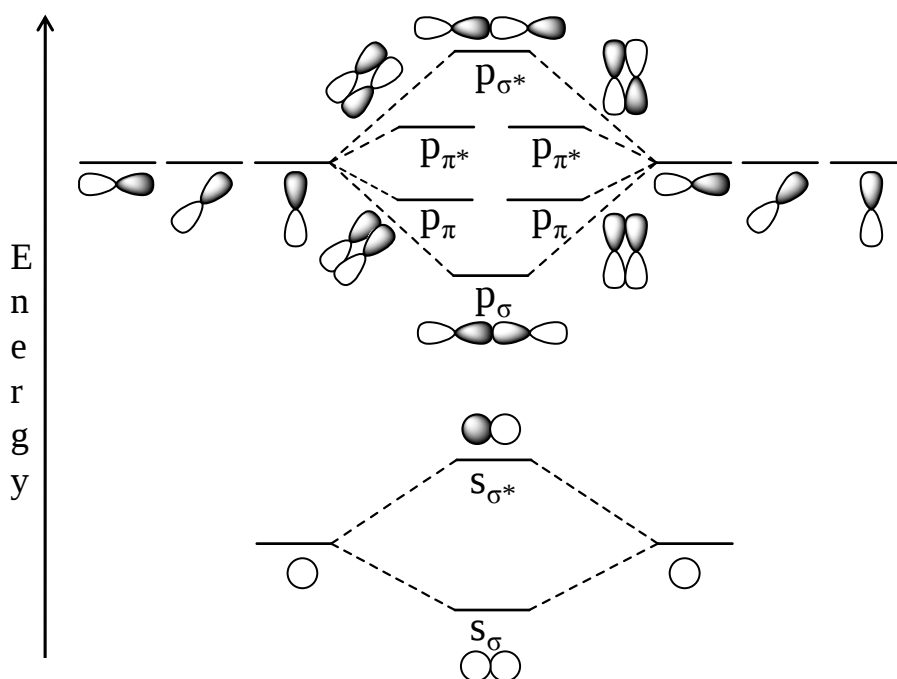


Figure 1.2 Generic MO diagram depicting the in-phase and out-of-phase interactions of the atomic s and p orbitals to form bonding and antibonding (*) MOs.

subtraction (linear combination method) of atomic and group orbitals. Conceptually, the formation of MOs can be visualized by the in-phase and out-of-phase interactions of atomic orbitals of similar symmetry and energy shown in the generic MO diagram, Figure 1.2. A constructive “bonding” interaction (lower in energy) occurs when the combination of the

wavefunctions is in-phase (overlap of two shaded or two unshaded orbital lobes) and an antibonding (*) interaction (higher in energy) is generated when the combination of the wavefunctions is out-of-phase (a shaded orbital lobe overlapping with an unshaded orbital lobe) (see Chap 8). Computer programs such as Gaussian¹² have enabled efficient calculations of MOs in order to predict the structures and energetics of many of the reactants, transition states, and products studied in this thesis (see Chap 3-8).

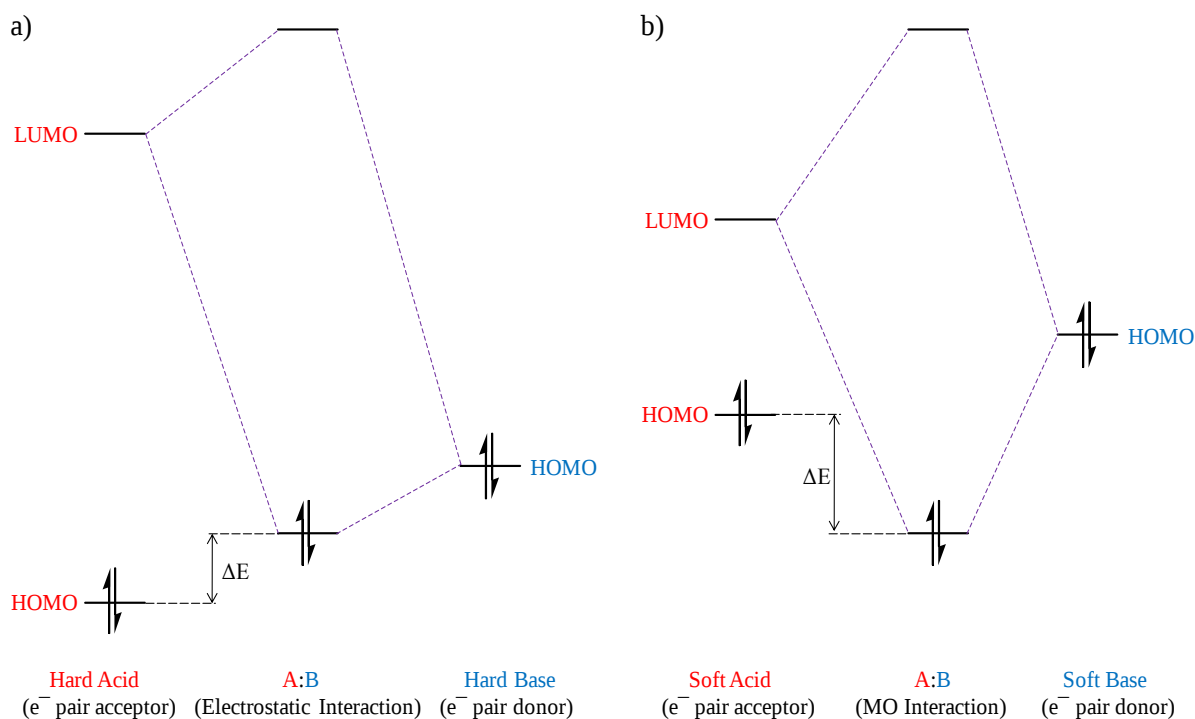


Figure 1.3 Hard Soft Acid Base (HSAB) interactions using frontier molecular orbital theory. a) Hard/Hard = HOMO-LUMO energies are far apart, reactivity influenced by electrostatic interactions. b) Soft/Soft = HOMO and LUMO are close in energy, reactivity governed by the formation of energetically favorable new MOs.

Since chemical bonding involves the interaction of the frontier molecular orbitals (FMO Theory) of the reactants, reactivity can be understood by focusing on the Highest Occupied Molecular Orbital (HOMO) of one species and the Lowest Unoccupied Molecular Orbital

(LUMO) of the other.¹¹ One application of the HOMO-LUMO argument is the description of acid-base behavior. Orbitals of similar symmetry and energy combine easily to form an acid-base adduct. Symmetry, energy, and occupation of frontier orbitals allow us to understand hard soft acid base theory (Figure 1.3). Hard acid-hard base reactions have HOMO-LUMO energies that are far apart; therefore, electrostatics (δ^+/δ^- charge attractions) primarily influence the bonding interactions. Soft acid-soft base reactions have similar HOMO and LUMO energies promoting the formation of energetically favorable new MOs. Hard-soft reactions do not generate stable interactions and reactivity is generally very low.¹³ The principles behind the hard (non-polarizable) and soft (polarizable) behavior can be used to rationalize the reactivity and mechanistic selectivity of anions (see Chap 5-7).

1.3 Gas Phase Kinetics and Thermodynamics

Knowledge of accurate reaction rates and thermochemical properties is of great importance in many branches of chemistry, in particular, combustion,¹⁴ atmospheric,¹⁵ prebiotic,¹⁶ and astrochemical (interstellar medium and planetary atmospheres)¹⁷ modeling. Much of the kinetic and thermochemical data available have been obtained from gas phase spectroscopic, kinetic, and equilibrium experiments and related through positive or negative ion thermochemical cycles.¹⁸ Our research group measures rate constants and product distributions of organic reactions in the gas phase revealing the details of how one molecule is transformed into another. The analysis of our data is understood in the context of a double-well potential energy surface and predicated on statistical rate theory.^{15,19} Thermodynamic information about the reactants, products and intermediate complexes can often be obtained from reaction rate constants or directly from collision-induced dissociation studies.

1.3.1 Double-Well Potential Energy Surface

Gas phase kinetic data can be interpreted by use of the double-well potential energy model proposed by Olmstead and Brauman²⁰ (Figure 1.4). Upon collision of the reactants X^- and RY , an intermediate reaction ion-dipole complex is formed, where k_1 is the collision

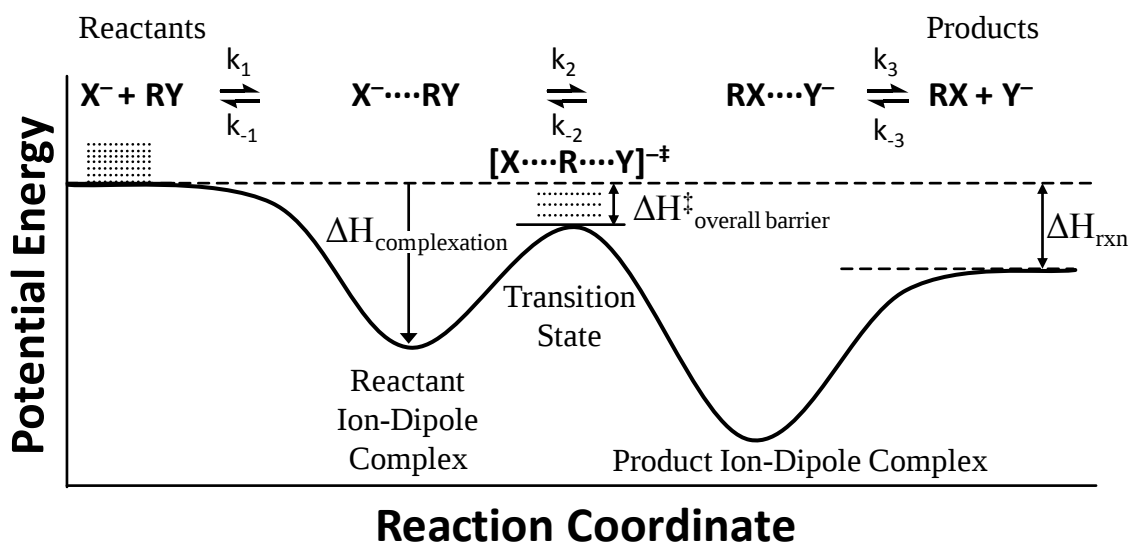


Figure 1.4 Gas Phase Double-Well Potential Energy Model.

rate constant. We typically describe the collision rate constant using the trajectory calculation parameterized method of Su and Chesnavich²¹ (This method employs an empirical function to determine the collision rate constant based on the ratio of the dipole moment of the neutral species to the square root of the polarizability). The ion-dipole complex is stabilized relative to the energy of the reactants by the “complexation” energy ($\Delta H_{\text{complexation}}$) of the ion, $X^- \cdots RY$. This energy is randomized within the internal modes of the reactant ion-dipole complex generating an energized species that can either proceed through a transition state to give a product complex (k_2) or dissociate to regenerate reactants (k_{-1}). The product ion-dipole complex may re-isomerize across the central barrier (k_{-2}) or dissociates into products (k_3). Assuming k_{-2} is negligible (exothermic reactions energetically favored), the overall bimolecular rate is given by

$$k_{\text{rxn}} = \frac{k_1 k_2}{k_{-1} + k_2} \quad (1.1)$$

The ability to extract meaningful information from our data is based on the statistical behavior of the reactant ion-dipole complex. In order for statistical rate theory to hold, a few assumptions must be valid: (1) collisions must not result in direct reactions or nonreactive elastic scattering, (2) the complexation energy is randomized within the internal modes (rotational and vibrational) of the complex on the time scale of the reaction, and (3) the transition state controls the reaction.¹⁹ Generally, ion-molecule reactions behave statistically because the deep well of the reactant ion-dipole complex generates long-lived intermediates; however, smaller reaction systems with fewer internal modes for energy distribution are more prone to non-statistical behavior. In extremely exothermic reactions and in reactions with extremely low activation energies, the central barrier has little effect on the reactant ion-dipole complex and the overall reaction transitions from kinetically to thermodynamically controlled. In these cases, mechanistic selectivity is significantly influenced by reaction dynamics and the interactions associated with molecular collisions (see Chap 5-7).

1.3.2 Negative Ion Cycle/Gas Phase Acidity

The energy required to homolytically break (or form) a chemical bond of a neutral molecule can be related to its gas phase acidity (basicity) and the electron affinity of the radical through the gas phase negative ion thermochemistry cycle (Figure 1.5). While the term gas phase “acidity”, $\Delta G_{\text{acid}}(\text{XH})$, of a molecule is uniformly defined as the Gibbs energy change of deprotonation ($\text{XH} \rightarrow \text{X}^- + \text{H}^+$), the terminology for the Gibbs energy change of the reverse reaction ($\text{X}^- + \text{H}^+ \rightarrow \text{XH}$), “basicity”, can sometimes need further elaboration. An additional modifier, “carbon basicity”, is employed in cases where the equilibrium involves the formation

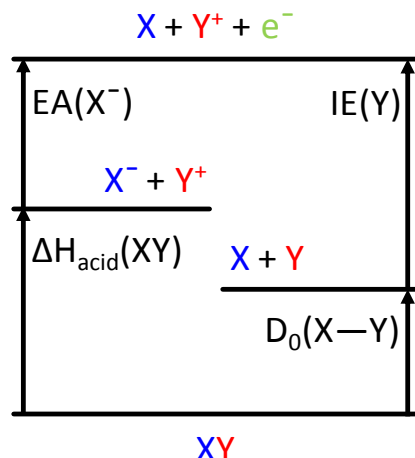


Figure 1.5 Gas Phase Negative Ion Thermochemical Cycle relating enthalpy of heterolytic bond cleavage (ΔH_{acid} , when $Y=H$), electron affinity (EA), ionization energy (IE), and bond dissociation energy (D_0).

of a bond by the base to carbon, ($X^- + RC^+ \rightarrow RCX$).²² This point is emphasized because the negative ion cycle can be used to calculate either hydrogen [$D_0(X-H)$] or carbon [$D_0(X-C)$] bond energies (see Chap 5). Therefore, the term ΔH_{acid} in Figure 1.5 can be used to describe either the enthalpy associated with heterolytic bond cleavage with hydrogen ($XH \rightarrow X^- + H^+$) or carbon ($RCX \rightarrow X^- + RC^+$). To avoid confusion in terminology, “proton affinity” is used to describe the enthalpy of protonation of the anion ($X^- + H^+ \rightarrow XH$) and “cation affinity” (e.g. CH_3^+ , methyl cation affinity; see Chap 4-7) describes the enthalpy of the anion reacting with the cation ($X^- + RC^+ \rightarrow RCX$).

1.3.3 Linear Free-Energy Relationships

Since many of our discussions employ proton affinities to evaluate trends and predict reactivity (see Chap 3-7), the basis of this association is provided. Figure 1.6 shows a Marcus-type rate-energy relationship applied to a gas phase double-well potential energy surface depicting the correlation between kinetics and thermodynamics.²³ The rate-controlling central barrier ($\Delta H_{\text{activation}}^\ddagger$) can be viewed as an intrinsic barrier ($\Delta H_{\text{intrinsic}}^\ddagger$) modified by an exothermic driving force ($\Delta H_{\text{driving force}}$). This relationship indicates that the enthalpies and free-energies of

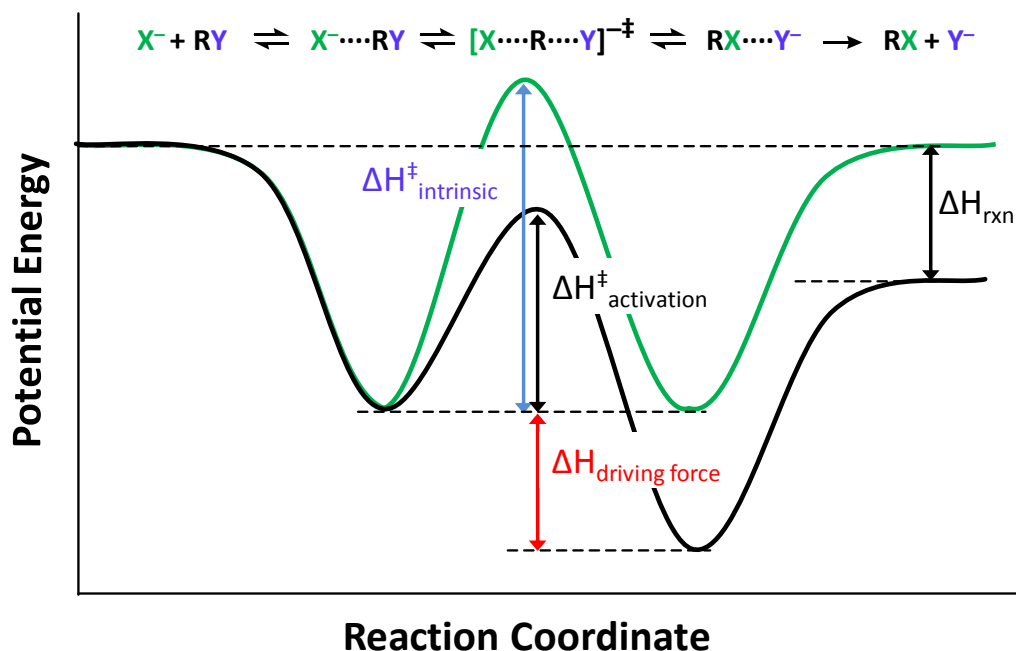


Figure 1.6 Marcus-type rate-energy relationship applied to a gas phase double-well potential energy surface depicting the correlation between kinetics and thermodynamics. The rate-controlling central barrier ($\Delta H^\ddagger_{\text{activation}}$) can be viewed as an intrinsic barrier ($\Delta H^\ddagger_{\text{intrinsic}}$) modified by an exothermic driving force ($\Delta H_{\text{driving force}}$).

activation for a reaction should have a strong correlation with the heats of reaction in the gas phase (i.e., the more exothermic, the lower the barrier). In general, the exothermicity of a nucleophilic reaction is equal to the difference in the cation affinity of the nucleophile and nucleofuge. Since both nucleophilicity and basicity involve the donation of electrons to an electrophile, a strong linear correlation also exists between proton affinities and cation affinities.²² These relationships establish a link between proton affinity and reactivity. “Linear” free-energy relationships tend to exist within a family of anions.²² Deviations from linearity in reactivity-basicity correlations can reflect the influence of additional variables or significant differences in the intrinsic nature of the anion. Based on this, the proton affinity (PA) is the most useful thermodynamic parameter for correlating reactivity patterns and evaluating intrinsic differences in anions.

1.4 References

1. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*. University Science Books: United States, **2006**.
2. Hynes, J. T. *Annu. Rev. Phys. Chem.* **1985**, *36*, 573-597.
3. Schalley, C. A. *Int. J. Mass Spec.* **2000**, *194*, 11-39.
4. Hoaglund-Hyzer, C.S.; Counterman, A.E.; Clemmer, D.E. *Chem. Rev.* **1999**, *99*, 3037-3079.
5. Lundegaard, C.; Jensen, K. F. *Biochem.* **1999**, *38*, 3327-3334.
6. Jordan, F.; Li, H.; Brown, A. *Biochem.* **1999**, *38*, 6369-6373.
7. Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 6258-6262.
8. Gronert, S. *Chem. Rev.* **2001**, *101*, 329-360.
9. Bohme, D. K. *Can. J. Chem.* **2008**, *86*, 177-198.
10. Engberts, J. B. F. N. *Pure Appl. Chem.* **1997**, *69*, 231-233.
11. Bradley, J. D.; Gerrans, G. C. *J. Chem. Educ.* **1973**, *50*, 463-466.
12. Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.
13. Chattaraj, P. K. *J. Phys. Chem. A* **2001**, *105*, 511-513.
14. Miller, J. A.; Kee, R. J.; Westbrook, C. K., *Annu. Rev. Phys. Chem.* **1990**, *41*, 345-387.
15. Steinfeld, J. I.; Francisco, J. S.; Hase, W. L. *Chemical Kinetics and Dynamics*; Prentice-Hall: Englewood Cliffs, NJ, **1989**.
16. Balucani, N. *Int. J. Mol. Sci.* **2009**, *10*, 2304-2335.
17. KIDA (*KInetic Database for Astrochemistry*, <http://kida.obs.u-bordeaux1.fr>).
18. NIST Chemistry WebBook, National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>.
19. Chabinyc, M. L.; Craig, S. L.; Regan, C. K.; Brauman, J. I. *Science* **1998**, *279*, 1882-1886.
20. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.
21. Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183-5185.
22. Uggerud, E. *Pure Appl. Chem.* **2009**, *81*, 709-717.
23. Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 2672-2680.

CHAPTER 2

Experimental Methods and Techniques



Overview

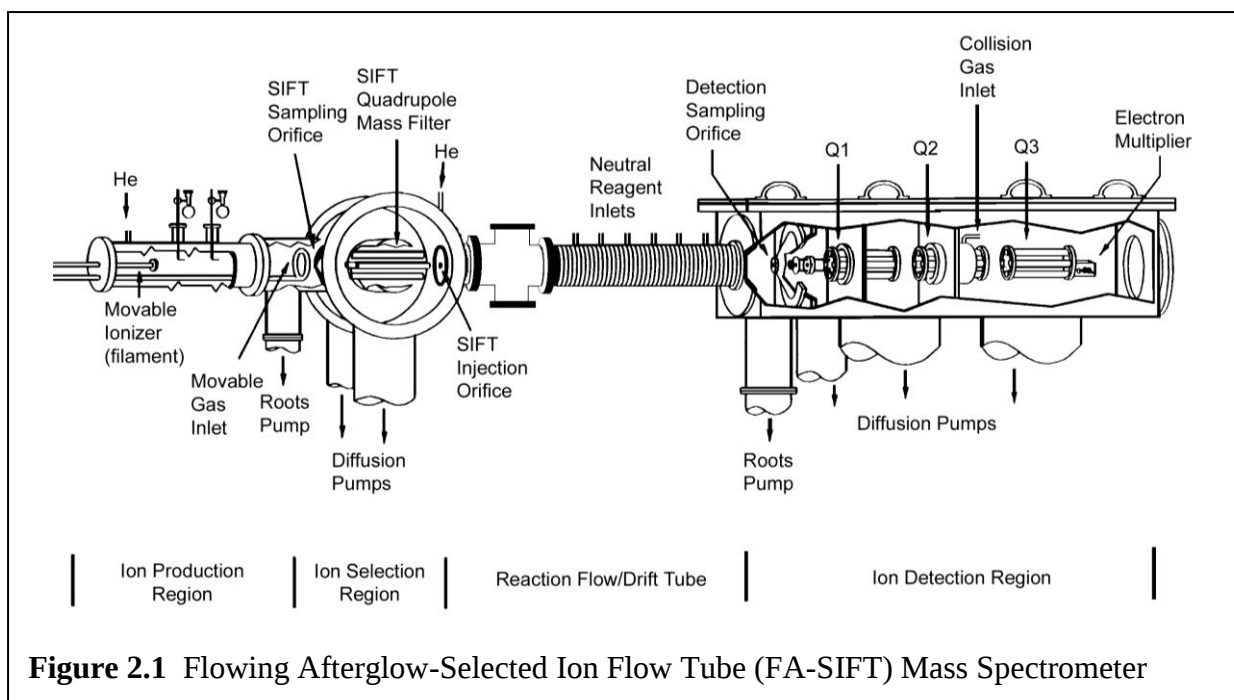
Flowing Afterglow-Selected Ion Flow Tube Mass Spectrometer (FA-SIFT MS). A multitude of scientists have pioneered a variety of gas phase methods and techniques to study molecular anion chemistry.¹ One of the principal methods of investigating gas phase kinetics and mechanisms has been the use of flowing afterglow instruments coupled with a mass spectrometer. The following sections provide an overview of the Flowing Afterglow-Selected Ion Flow Tube Mass Spectrometer, how rate constants and branching fractions are determined, and the background on the methodology employed to probe structures and assess gas phase acidity.

2.1 Introduction

A multitude of scientists have pioneered a variety of gas phase methods and techniques to study molecular anion chemistry.¹ One of the principal methods of investigating gas phase kinetics and mechanisms has been the use of flowing afterglow instruments coupled with a mass spectrometer. The correlation of kinetic data and isotope effects with thermodynamic and structural parameters has proven to be a valuable approach for interpreting transition state structures. Collision-induced dissociation methods allow structural information or gas-phase acidities to be obtained from energy-resolved competitive fragmentation. Gas phase acidities and proton affinities can be determined by the ion-molecule bracketing method, the equilibrium method ($K_{eq} = k_f/k_r$) or the kinetic method.

2.2 Flowing Afterglow-Selected Ion Flow Tube Mass Spectrometer

Ferguson, Fehsenfeld, and Schmeltekopf pioneered the use of the flowing afterglow technique to study atmospherically relevant ion-molecule reactions.² Flowing afterglow mass spectrometry provides the capability to make a variety of ions in situ and study their reactions under well characterized conditions (laminar flow behavior, viscous gas flow, thermalized ions, etc.). Due to the possibility of generating multiple reactant ions, in 1989 our lab designed and built a tandem flowing afterglow-selected ion flow tube (SIFT)³ instrument (Figure 2.1), which allows the ions of interest to be generated in a source flow tube and mass-selected prior to injection into the reaction flow tube.⁴ Our instrument consists of four sections: an ion source, an ion selection region, a reaction flow tube, and a detection system.



2.2.1 Ion Source Region

Primary reactant ions (e.g., HO^- and NH_2^-) are generated by electron impact on trace gases in the source flow tube (traditional flowing afterglow source with helium buffer gas). Secondary reactant ions can be produced through ion-molecule reactions with the primary reactant ions by adding another neutral reagent further downstream through moveable gas inlets. The moveable ionizer consists of a repeller plate, a rhenium filament (applied voltage, 5 V [2.5 A]; 25 mA electrons produced [~ 70 eV]), and an extracting grid that provides a feedback loop to regulate the emission current. All of these elements float at the voltage of the source flow tube. At the end of the source flow tube the ions are extracted into the ion selection region by an attractive potential relative to the source flow tube by a cone shaped extractor through a 2 mm orifice in a molybdenum nosecone. Once inside the selection chamber (10^{-4} torr, 10-inch diffusion pump), the ions are focused and guided by a series of six adjustable electrostatic lenses into the SIFT quadrupole mass filter. The SIFT quadrupole (Extrel # 4-270-9, four rods 1.6 cm x

22 cm) powered by an Extrel power supply (# 011-1) with a 1.5 MHz High-Q head (Extrel # 011-14) is mounted in a separate smaller chamber (10^{-6} torr, 6-inch diffusion pump), which allows transmission of ions up to 367 amu. The SIFT quadrupole is set to pass the ion of interest with a specific mass-to-charge ratio. Following mass selection, the ions are focused by three electrostatic lenses into an ion injection orifice and a concentric Venturi gas inlet just downstream of the orifice. Helium buffer gas is forced through two small, circularly symmetric inner and outer inlets by a high backing pressure. The resulting Venturi effect lowers the pressure near the ion orifice and backstreaming into the ion selection region, and increases ion transmission from a region of low pressure to high pressure.

2.2.2 *Reaction Flow Tube*

The reaction flow tube is 117 cm in length, composed of a 40 cm entry region and 77 cm reaction region. The entry region allows time for the He buffer gas to transition from turbulent flow to laminar flow and the reactant ion to be collisionally cooled (vibrationally and rotationally relaxed to a room temperature Boltzman distribution). Neutral reagents can be added to the reaction flow tube through a manifold containing seven fixed radial inlets; the first inlet is positioned at a distance of 13.5 cm from the downstream nosecone. Inlets are spaced at 9.7 cm increments. The reactant ions and neutral reagents are entrained in helium buffer gas maintained at a flow rate of 12.0 std L/min by a Tylan flow controller.

2.2.3 *Detection Region*

Reactant and product ions are gently extracted into the detection region through a 0.5 mm orifice in a molybdenum plate (< 10 V) mounted on a stainless steel carrier plate. The carrier plate voltage (1-10 V) is typically negative to focus the ions toward the nosecone. Once inside the detection region, sampled ions are focused into a triple quadrupole mass spectrometer by a

series of five electrostatic lenses. The triple quadrupole (Extrel C50 TQMS system: 1.2 MHz RF oscillator, 300 W DC power level for Q1 and Q3, and 200 W power level for Q2, 1.9 cm diameter rods capable of transmission up to 500 amu) can be operated in a MS-MS mode using Q1 and Q2 to scan or in a MS mode where Q1 and Q2 are used as ion pipes and Q3 scans. For the experiments described in this thesis, the instrument was operated in the MS mode using Q3 as the mass analyzer. The triple quadrupole is coupled to an electron multiplier with a gain of 10^8 . The output pulses are amplified, discriminated, and processed by the Extrel Merlin data system software package. The lensing and triple quadrupole/electron multiplier are housed in three separate chambers that are differentially pumped by two 10-inch and one 6-inch diffusion pumps maintaining pressures ranging from 10^{-6} to 10^{-7} torr.

2.2.4 Rate Constant Determination and Error Analysis

Since the velocity profile of our reactants and helium buffer gas are well-defined and well-characterized, the reaction time and distance can be related and incorporated into a second-order rate law describing the change in ion concentration as a function of distance (Eq 2.1),

$$\frac{d[X^-]}{dt} = \alpha v_{\text{He}} \frac{d[X^-]}{dz} = -k^{\text{II}}[X^-][N] \quad (2.1)$$

where $[X^-]$ is the concentration of reactant ion, $[N]$ is the concentration of the neutral reagent, z is the reaction distance, α is the ion velocity correction factor of 1.6,² and v_{He} is the average helium velocity. The integrated rate law of Equation 2.1 can be rearranged into a linear expression (Eq 2.2) allowing the slope (m) of a semilogarithmic plot of the ion concentration versus the reaction distance to be related to the reaction rate constant (k_{rxn}) by Equation 2.3.

$$\ln[X^-] = -k_{\text{rxn}}[N] \frac{z}{\alpha v_{\text{He}}} + \ln[X^-]_0 \quad (2.2)$$

$$k_{\text{rxn}} = -m \frac{\alpha v_{\text{He}}}{[N]} \quad (2.3)$$

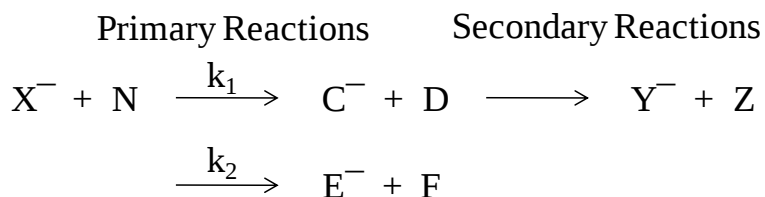
The concentration of neutral, [N], in particles cm^{-3} is determined using a known flow of neutral, F_N (determined by a change in pressure in a constant volume over time) in $\text{atm cm}^3 \text{s}^{-1}$, He velocity in cm s^{-1} , and the flow tube area using a radius of $a = 3.65 \text{ cm}$ and the conversion shown in Equation 2.4.

$$[N] \left(\frac{\text{particles}}{\text{cm}^3} \right) = \frac{F_N \left(\text{atm} \frac{\text{cm}^3}{\text{s}} \right)}{v_{\text{He}} \left(\frac{\text{cm}}{\text{s}} \right) \pi a^2 (\text{cm}^2)} \times \frac{3.535 \times 10^{16} \text{ particles}}{\text{cm}^3 \text{ torr}} \times \frac{760 \text{ torr}}{\text{atm}} \quad (2.4)$$

An extensive evaluation of systematic and random error has been reported in reference 5. From this work, the error in our measurements primarily arises from errors in the slope (1-3%), the ion velocity correction (12.5%), He buffer flow (0.9%), temperature (0.4%) measurements, and neutral flow determination (~3%). Propagating this error results in an accuracy of $\pm 14\%$ for each measurement; however, we conservatively give an overall accuracy of $\pm 20\%$. In addition, our rate constant measurements include error bars of one standard deviation of the mean of three or more measurements.

2.2.5 Branching Fractions

Competitive reaction pathways may exist within the ion-dipole complexes (Scheme 2.1); therefore, studies of gas phase ion-molecule reactions not only seek to identify relationships of reactant properties with reactivity and mechanism, but with product distributions as well.



Scheme 2.1

Secondary reactions or clustering between the product ions and the neutral reagent do not affect the overall rate constant measurement ($k_{\text{rxn}} = k_1 + k_2$), but need to be considered when

determining product branching fractions. Shifts in the relative abundance of primary ions due to secondary processes can be accounted for by using a plot of product ion intensity (C^- , E^- , and Y^-) as a function of inlet distance and extrapolating to product ion concentrations at “zero reaction distance” (before secondary processes can occur). Once secondary processes are accounted for the branching fractions can be used to determine the relative rate constants (k_1 and k_2) from the overall reaction rate constant ($k_{\text{rxn}} = k_1 + k_2$). The branching fractions (BR) are determined from a ratio of a given ionic product (C^- or E^-) to the total product ion concentration and related to the relative rate constants according to Equation 2.5.

$$BR_{C^-} = \frac{[C^-]}{[C^-] + [E^-]} = \frac{k_1}{k_1 + k_2} \quad \text{and} \quad BR_{E^-} = \frac{[E^-]}{[C^-] + [E^-]} = \frac{k_2}{k_1 + k_2} \quad (2.5)$$

2.3 Kinetic Isotope Effects

Deuterium Kinetic Isotope Effects (KIEs) are often employed to probe the structure of the transition state and relative reaction pathways. A deuterium KIE is the ratio of rate constants of an undeuterated reactant to the deuterated reactant ($KIE = k_H/k_D$). These KIEs are primarily due to the changes in the vibrational frequencies as a reaction proceeds from reactants to the transition state, Figure 2.2. The effects can be evaluated by comparing the relative differences in zero point energy between the hydrogen and deuterium labeled reactions. The electronic nature of the isotopic atoms is nearly identical; however, bonds to the heavier deuterium atoms will have lower vibrational frequencies. The relative change in vibrational energy, as the bonds in the reactant are modified to either a loose (longer bond) or tight (shorter bond) transition state, can be interpreted as an activation barrier for the respective isotopic reaction. A “normal” KIE (>1), [$E_a(H) < E_a(D)$ therefore $k_D < k_H$], is observed when bonds are loosened from reactants to

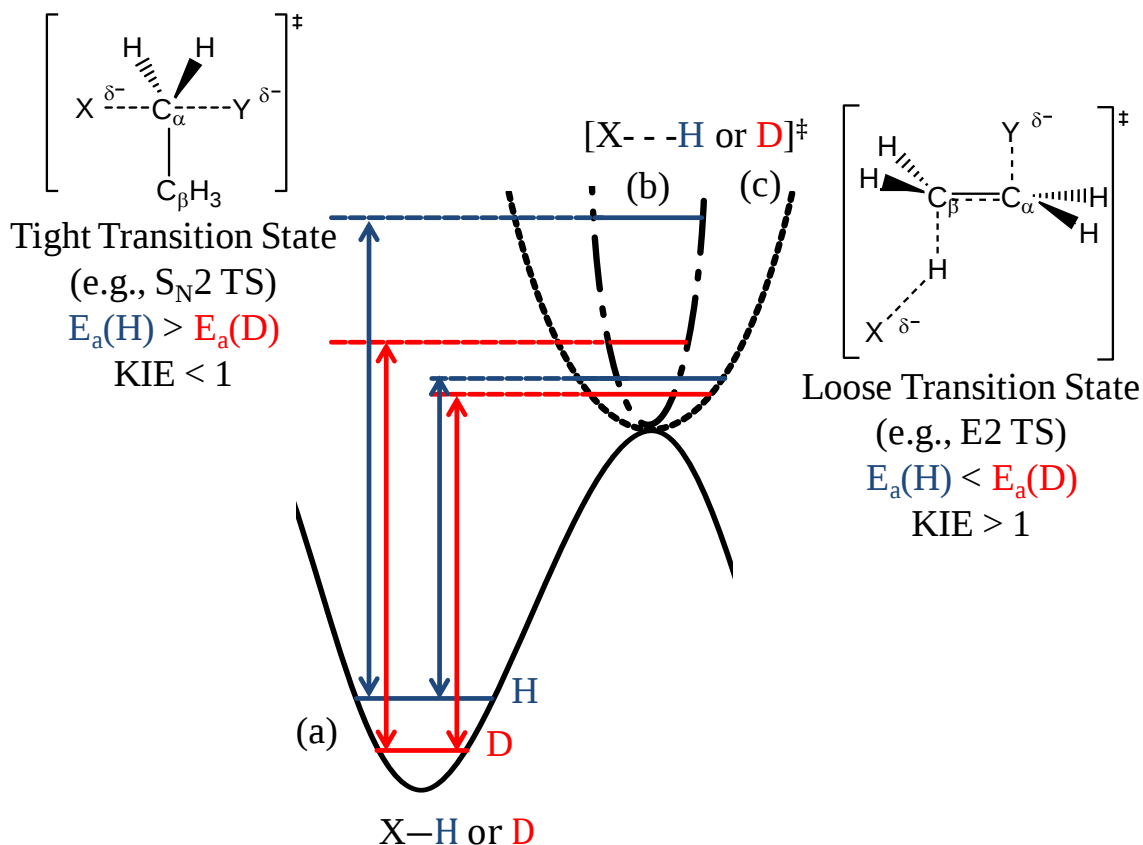


Figure 2.2 Schematic diagram of potential energy surfaces indicating the E_a or the “activation barrier” for hydrogen and deuterium labeled compounds and associated transition states (TS) upon transition from (a) reactant to (b) a tight TS (e.g., S_N2 TS) or (c) a “loose” transition state (e.g., $E2$ TS).

the transition state (e.g., loose $E2$ transition state, see Chap 3 and 4). An “inverse” KIE (< 1 , $[E_a(\text{H}) > E_a(\text{D}) \text{ therefore } k_D > k_H]$), results from the tightening of bonds on going to the transition state (e.g., sp^3 to sp^2 geometries in S_N2 transition state, see Chap 3 and 4). Although inverse KIEs are characteristic of “tight” transition states (e.g., S_N2 reactions) and normal KIEs are typical of “loose” transition states (e.g., $E2$ reactions), this interpretation must be tempered due to minor contributions from all modes (translational, vibrational, rotational). For our studies we determine the overall KIEs using a ratio of undeuterated to deuterated activation barriers (a more in depth analysis of the contributions from the various modes to the overall KIE can be accomplished by using transition state theory and partition functions⁶). For reactions that

proceed by both an E2 and S_N2 mechanism an overall KIE is measured, which provides qualitative insight into the competition between these two mechanisms.

2.4 Collision-Induced Dissociation

Structural information and bond dissociation energies can be evaluated by mass spectrometry via collision-induced dissociation (CID).^{7,8} In CID, precursor ions are accelerated by an electrical potential to a higher kinetic energy and then allowed to collide with a neutral collision gas (helium in our studies). At low impact energies (< 100 eV) some of the kinetic energy is converted into internal energy and dissociation occurs by vibrational and rotational excitation of the ions. Structural features of the precursor ion can be identified based on the fragmentation pattern observed in the mass spectrum. Under controlled ion translational energy conditions, thermochemical properties can be determined from the appearance energy for dissociation. By plotting ion signal as a function of this energy-resolved data, the observation of the onset of specific ions can be fitted to locate a threshold dissociation energy. The relevant energy for analysis must be converted from the lab frame (E_{lab}) to the center-of-mass (E_{com}) frame of reference. Figure 2.3 depicts the relative yield of precursor and fragment ions from collision-induced dissociation as a function of relative kinetic energy and an estimate of the threshold dissociation energy from the onset of fragmentation.

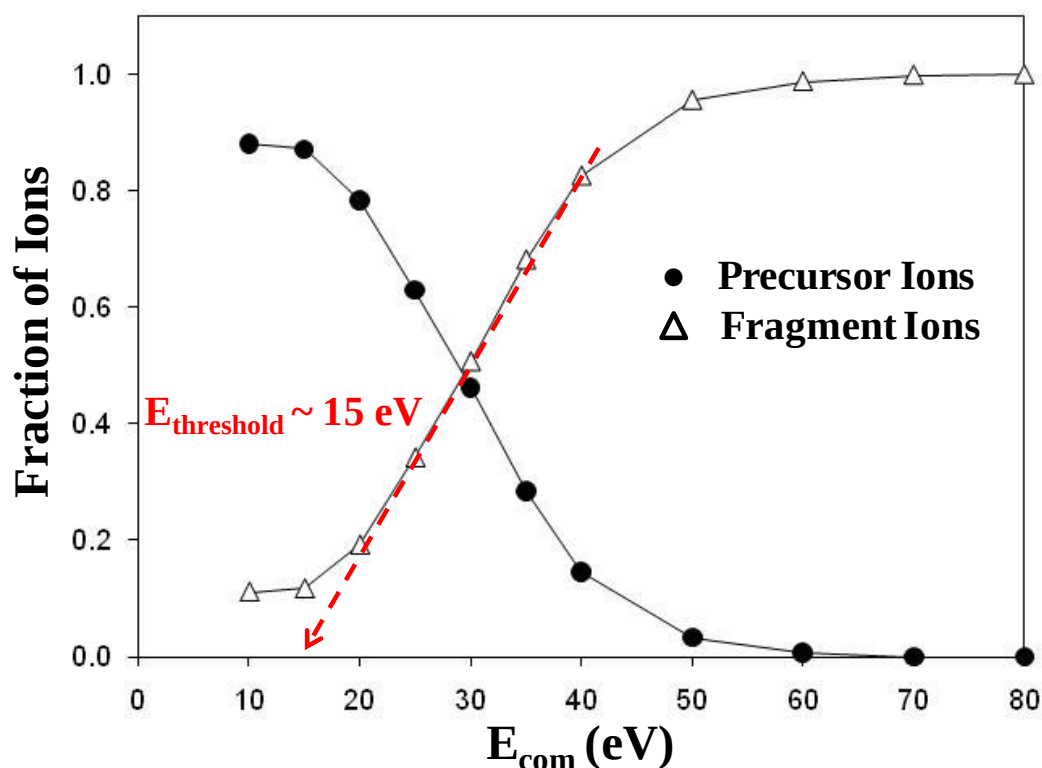


Figure 2.3 Relative yield of precursor and fragment ions from collision-induced dissociation as a function of relative kinetic energy and an estimate of the threshold dissociation energy from the onset of fragmentation.

2.5 Determining Gas Phase Acidity/Proton Affinity

A variety of mass spectrometry techniques (e.g., bracketing method, equilibrium method, kinetic method, etc.) have been developed to evaluate gas phase acidities and proton affinities.⁸ These methods typically assess acidity relative to the acidity of one or more reference molecules. Unfortunately, only a few acidities of reference acids have been accurately determined by high-resolution spectroscopic or calorimetric methods in combination with the negative ion cycle.⁹ Ideally a well-defined reference acid can be used to determine a forward and reverse reaction rate constant for use in the equilibrium method; however, because of gaps in acidity scales bracketing methods are often employed to estimate a range for relative acidity. Since we

measure reaction rates, we can experimentally assess the Gibbs energy associated with gas-phase acidity. In order to calculate proton affinities we computationally calculate an entropic contribution to the free energy (Eq 2.6)

$$\Delta_{\text{acid}}H_{298} = \Delta_{\text{acid}}G_{298} + T\Delta S, \text{ where } T = 298 \text{ K} \quad (2.6)$$

2.5.1 Equilibrium Method ($K_{\text{eq}} = k_f/k_r$)

In general, a forward ($k_f : A_{\text{ref}}^- + HA_{\text{unknown}} \rightarrow HA_{\text{ref}} + A_{\text{unknown}}^-$) and reverse ($k_r : A_{\text{unknown}}^- + HA_{\text{ref}} \rightarrow HA_{\text{unknown}} + A_{\text{ref}}^-$) proton transfer rate constant can be measured relative to a reference molecule when the reference acid is similar in acidity to the unknown acid (if not, either the forward or reverse rate is outside the detection limits of our instrument). The forward/reverse rate constant ratio gives the proton transfer equilibrium constant ($K_{\text{eq}} = k_f/k_r$). The relative change in Gibbs energy of the proton transfer reaction can be related to the equilibrium constant through the Gibbs free energy expression in Equation 2.7.

$$\Delta(\Delta_{\text{acid}}G_{298}) = -RT \ln(K_{\text{eq}}) \quad (2.7)$$

The reported accuracy for this method can be fairly high since the error involves the root sum square of the uncertainty in the reference acid and the error in the measurements.

2.5.2 Bracketing Method

If an equilibrium measurement cannot be made for a molecule, the bracketing technique allows the acidity of the ion of interest to be estimated by using a series of reference reactions. Both the forward and reverse reactions between the unknown and reference acids are monitored for the occurrence of a reaction (Fig 2.4). Reactivity is based on the assumption that an endothermic reaction will not be observed or will occur only at a low efficiency. If a reaction does occur, an upper or lower limit of acidity is set for the unknown acid. In Figure 2.4, the

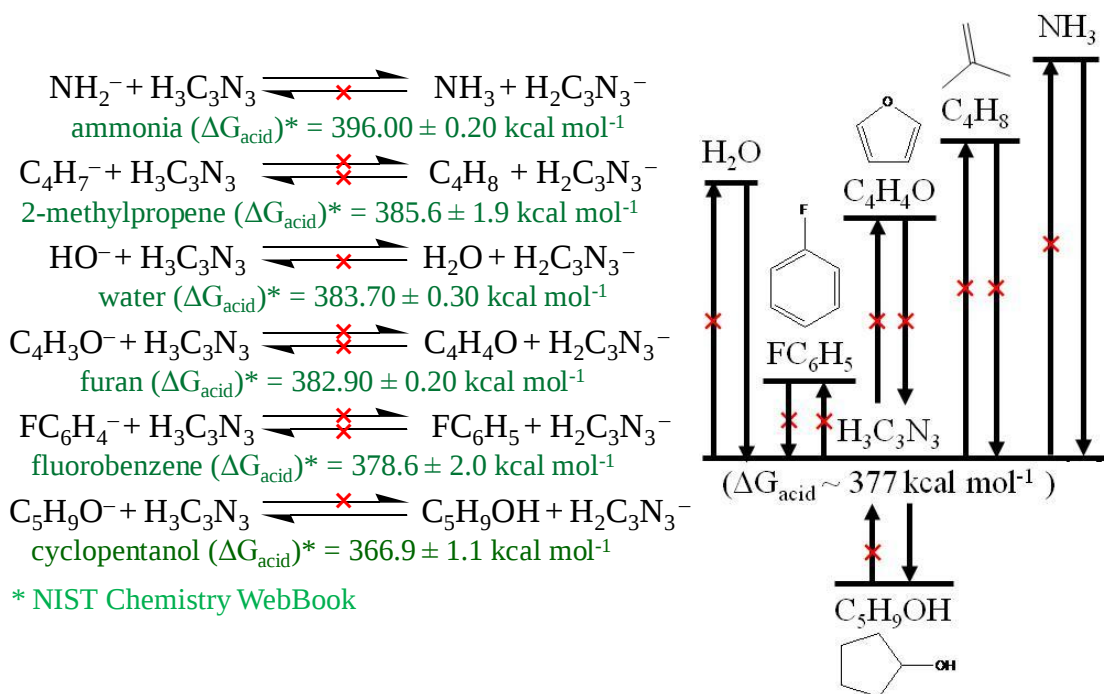


Figure 2.4 Bracketing Method. The reactivity of 1,3,5-triazine, $\text{H}_3\text{C}_3\text{N}_3$, lies between water and cyclopentanol; therefore $\text{H}_3\text{C}_3\text{N}_3$ is assigned a gas phase acidity of $374.9 \pm 9.1 \text{ kcal mol}^{-1}$.

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2.5.3 Kinetic Method

Although thermodynamic parameters have been assessed by various forms of the kinetic method (the simplest forms do not account for variations in entropy and therefore are less precise), they are all based on competitive bond cleavages using CID.^{10,11} The ratio of ions from the competitive fragmentation of an activated proton bound dimeric ion has been shown to reflect the thermochemical stability of the product ions (Fig 2.5). The ratio of the fragment ion abundances is related to the difference in proton affinities (ΔH_{acid}) of the two bases (A_1^- and A_2^-). The rate constants (k_{A1H} and k_{A2H}) for the two competitive dissociation channels for the activated proton bound cluster is related to the relative abundance of ions and proton affinity

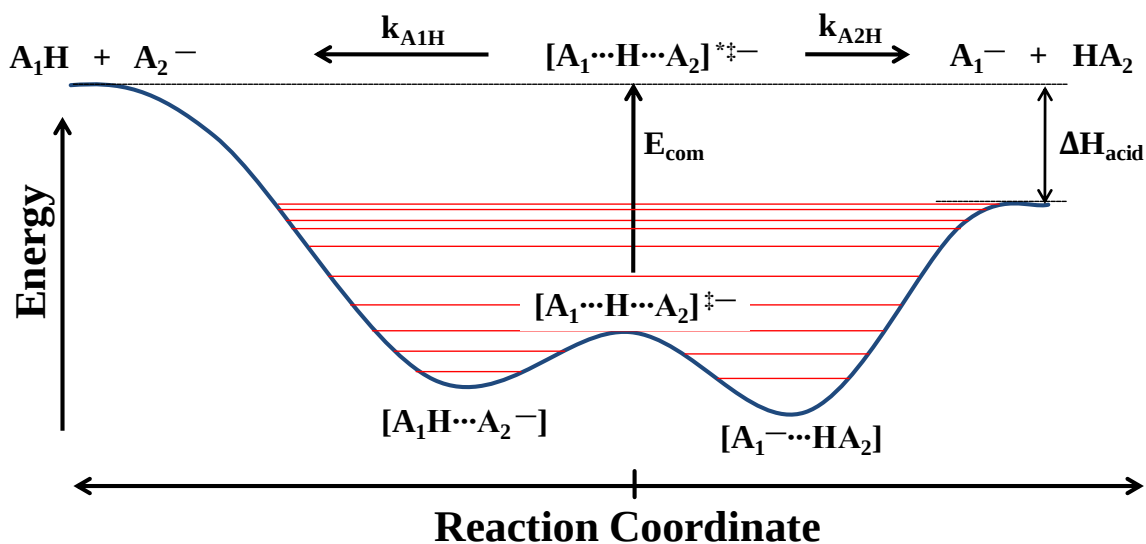


Figure 2.5 Kinetic Method. Potential energy surface for the proton bound dimeric ion depicting competitive dissociation between acids (A_1H and A_2H) upon collision-induced activation.

difference by Equation 2.8, where T_{eff} is the effective temperature (energy) of the activated

$$\ln \frac{k_{A1H}}{k_{A2H}} = \ln \frac{[A_2^-]}{[A_1^-]} \approx \frac{\Delta(\Delta H_{\text{acid}})}{RT_{\text{eff}}} \quad (2.8)$$

dimer.^{10,11} A calibration line based on the ion ratios of the unknown acid (AH_{unknown}) to reference acids as a function of the proton affinity of the reference acids provides a slope of $[-1/RT_{\text{eff}}]$ and an intercept of $[\Delta H_{\text{acid}}(AH_{\text{unknown}})/RT_{\text{eff}}]$.

2.6 References

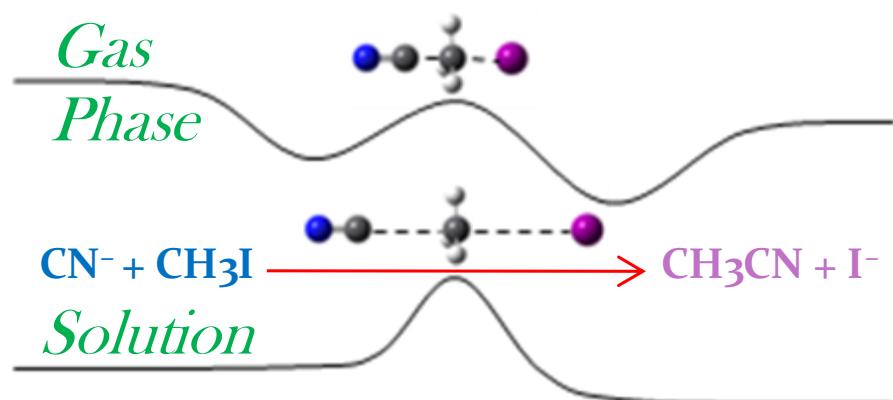
1. Simons, J. Molecular Ions Web Site, <http://www.hec.utah.edu/anions>.
2. Ferguson, E. E.; Fehsenfeld, F.C.; Schmeltekopf, A.L. *Adv. At. Mol. Phys.* **1969**, 5, 1-69.
3. Smith, D.; McIntosh, B. J.; Adams, N. G. *J. Chem. Phys.* **1989**, 90, 6213-6219.
4. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Processes* **1987**, 81, 85-100.
5. Van Doren, J. M. The Tandem Flowing Afterglow-SIFT-DRIFT: Developments and Applications to Gas Phase Ion Chemistry, PhD Thesis, Department of Chemistry and Biochemistry, University of Colorado at Boulder **1983**.
6. Davico, G. E.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2000**, 122, 1740-1748.
7. Schalley, C.; Armentrout, P. Threshold Collision-Induced Dissociations for the Determination of Accurate Gas-Phase Binding Energies and Reaction Barriers. In *Modern Mass Spectrometry*, Springer Berlin / Heidelberg: **2003**; 225, 233-262.
8. Ervin, K. M. *Chem. Rev.* **2001**, 101, 391-444.
9. Ervin, K. M.; DeTuro, V. F. *J. Phys. Chem. A* **2002**, 106, 9947-9956.
10. Cooks, R. G.; Wong, P. S. H. *Acc. Chem. Res.* **1998**, 31, 379-386.
11. Cooks, R. G.; Koskinen, J. T.; Thomas, P. D. *J. Mass Spectrom.* **1999**, 34, 85-92.

CHAPTER 3

A Direct Comparison of Reactivity and Mechanism in the Gas Phase and in Solution

Adapted from

Garver, J. M.; Fang, Y; Eyet, N.; Villano, S. M.; Bierbaum, V. M.; Westaway, K. C. *J. Am. Chem. Soc.*,
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Overview

Direct comparisons of the reactivity and mechanistic pathways for anionic systems in the gas phase and in solution are presented. Rate constants and kinetic isotope effects for the reactions of methyl, ethyl, *i*-propyl, and *t*-butyl iodide with cyanide ion in the gas phase, as well as for the reactions of methyl and ethyl iodide with cyanide ion in several solvents, are reported. In addition to measuring the perdeutero kinetic isotope effect (KIE) for each reaction, the secondary α - and β -deuterium KIEs were determined for the ethyl iodide reaction. Comparisons of experimental results with computational transition states, KIEs, and branching fractions are explored to determine how solvent affects these reactions. The KIEs show that the transition state does not change significantly when the solvent is changed from dimethyl sulfoxide/methanol (a protic solvent) to dimethyl sulfoxide (a strongly polar aprotic solvent) to tetrahydrofuran (a slightly polar aprotic solvent) in the ethyl iodide–cyanide ion $\text{S}_{\text{N}}2$ reaction in solution, as the “Solvation Rule for $\text{S}_{\text{N}}2$ Reactions” predicts. However, the Solvation Rule fails the ultimate test of predicting gas phase results, where significantly smaller (more inverse) KIEs indicate the existence of a tighter transition state. This result is primarily attributed to the greater electrostatic forces between the partial negative charges on the iodide and cyanide ions and the partial positive charge on the α carbon in the gas phase transition state. Nevertheless, in evaluating the competition between $\text{S}_{\text{N}}2$ and E2 processes, the mechanistic results for the solution and gas phase reactions are strikingly similar. The reaction of cyanide ion with ethyl iodide occurs exclusively by an $\text{S}_{\text{N}}2$ mechanism in solution and primarily by an $\text{S}_{\text{N}}2$ mechanism in the gas phase; only ~1% of the gas phase reaction is ascribed to an elimination process.

3.1 Introduction

The influence of solvent on reactions has intrigued chemists for many years. Ions in the gas phase often react differently than the same ions in solution, where coordinating solvent molecules stabilize charges. These effects are evident in the large differences between reaction rate constants of identical gas and condensed phase reactions,^{1,2} in the reversal of ordering of acidities and basicities in solution versus the gas phase,^{3,4} as well as in the enhanced nucleophilicity of polarizable nucleophiles in solution versus the gas phase.⁵ While gas phase studies allow one to probe the intrinsic reactivity of a molecule, a comparison of these results to solution allows one to directly probe the role of the solvent. For example, Figure 3.1 shows a potential energy diagram for an S_N2 reaction in the gas phase (curve a), in an aprotic solvent

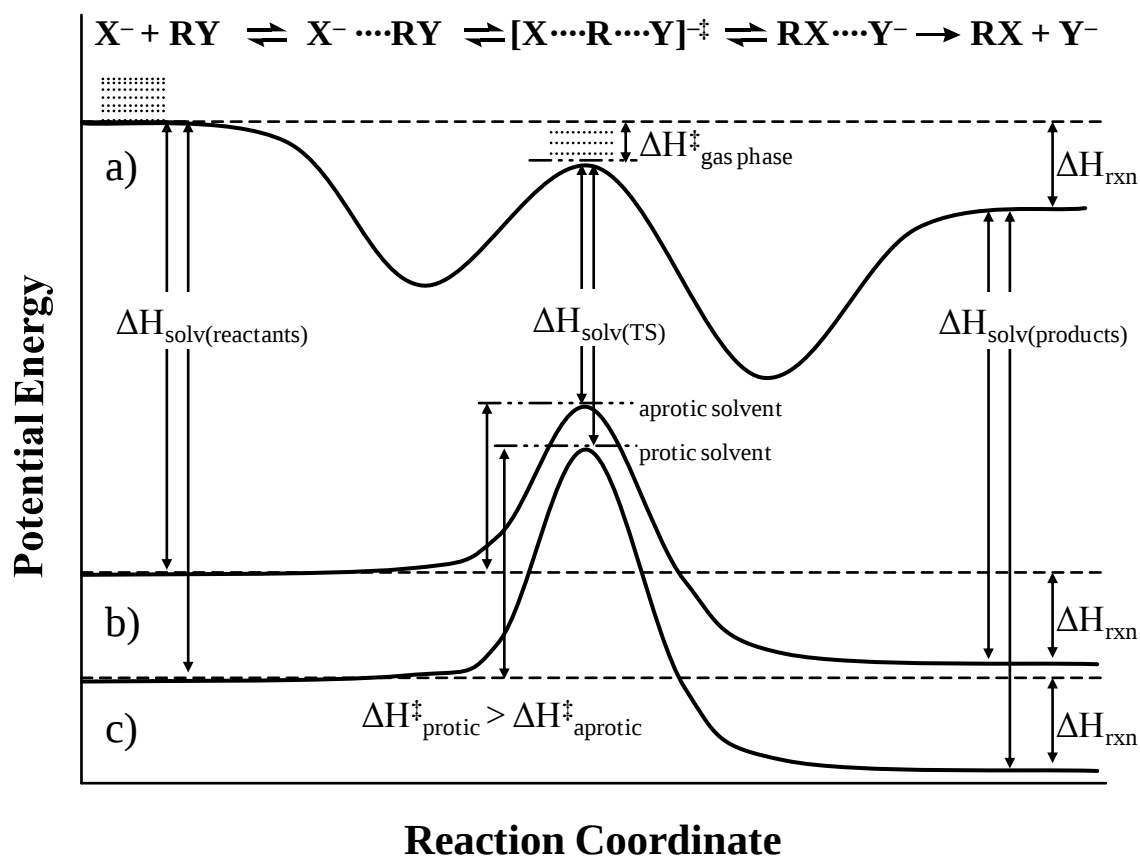
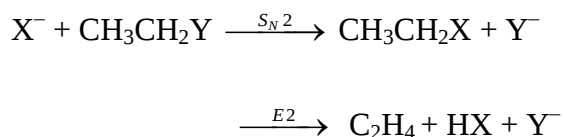


Figure 3.1. Potential energy diagram of a generic S_N2 reaction in the gas phase (curve a), in an aprotic solvent (curve b), and in a protic solvent (curve c).

(curve b), and in a protic solvent (curve c). In the gas phase, the ion and neutral molecule are attracted by ion-dipole and ion-induced-dipole forces, resulting in the formation of an encounter complex. Because the energy ($\sim 15\text{--}20 \text{ kcal mol}^{-1}$)⁶ released in forming the new bonds is converted to internal energy, the complex has sufficient energy to overcome the reaction barrier and form a product complex, which dissociates into the separated products. While there is ample energy for reaction, an ordered transition state slows the process, and hence not every collision results in reaction. The barrier height, and therefore the sum of states above the barrier, can be dramatically different for different ion-neutral pairs. The vertical separation between curves (a) and (b) and between curves (a) and (c) reflects the solvation energy of the reactants, products, and transition state, in the aprotic and protic solvents, respectively. When the reactants and products for the S_N2 reaction in Figure 3.1 are placed in solution, considerable energy is released due to solvation of the localized charge on the anion and to a lesser extent, the dipole in the substrate. In the transition state, on the other hand, the charge is dispersed and the solvation energy is much smaller. As a result, the central barrier ($\Delta H^\ddagger$) to reaction is much higher (the reactions are much slower) in solution than in the gas phase; as indicated in Figure 3.1, reaction barriers are higher in protic solvents relative to aprotic solvents. Figure 3.1 also defines $\Delta H^\ddagger$ for the gas phase transition state relative to the reactants; a more negative $\Delta H^\ddagger$ represents a lower energy barrier.

Studies of ion-molecule reactions in both solution and the gas phase have focused on how various nucleophiles, leaving groups, and substituents affect the reactivity of alkyl halides, and how various factors determine kinetics, mechanisms, and relative product distributions.⁷⁻¹² In particular, competition between base-induced elimination (E2) and nucleophilic substitution

(S_N2) mechanisms is significantly influenced by the nature of the attacking group (X⁻), leaving group abilities (Y), substrate properties, and solvent effects.¹³⁻¹⁶



Substituent effects on transition state structure indicate that both electronic and geometric (steric hindrance) effects influence the S_N2/E2 ratio.^{11, 17} Condensed and gas phase data show a transition from a predominantly substitution pathway to a predominantly elimination pathway as the steric hindrance around the α-carbon is increased (CH₃CH₂Y to (CH₃)₂CHY to (CH₃)₃CY). This shift in reaction pathway occurs because the additional methyl groups increase the steric crowding in the S_N2 transition state, thereby increasing the activation barrier and reducing the reaction rate. In contrast, the activation barrier for the E2 pathway, which is less affected by crowding in the transition state, appears to be lowered by the additional methyl groups producing faster rates.¹⁷

In previous work, the study of microsolvated ions has been undertaken as a way to bridge the gap between gas phase and solution. Extensive experimental¹⁸⁻²² and theoretical²³⁻²⁷ work has been carried out to understand S_N2 reactions, while fewer studies have examined E2 reactions.²⁸⁻³¹ While these experiments have provided valuable insight, they are typically limited to processes with a reaction efficiency greater than 10⁻³. The direct comparison of gas phase and solution results in this study provides additional insight into this problem.

Deuterium KIEs were employed in our gas and condensed phase reactions to probe the structure of the transition state and relative reaction pathways. A deuterium KIE is the ratio of the rate constant for an undeuterated reactant to the rate constant for a particular deuterated reactant, (KIE = k_H/k_D.) These KIEs are primarily due to changes in the vibrations of bonds

involving the isotopes as a reaction proceeds from reactants to products. A normal KIE (>1) is observed when these bonds are loosened on going from reactants to the transition state. This causes a decrease in zero point energy as the reaction proceeds from separated reactants to the transition state. An inverse KIE (<1) results from the tightening of these bonds on going to the transition state, causing an increase in the difference in zero point energy as the reaction proceeds. Although normal KIEs are characteristic of E2 reactions and inverse KIEs are typical of S_N2 reactions, this interpretation must be tempered due to minor contributions from all modes (translational, vibrational, rotational). For reactions that proceed by both an E2 and S_N2 mechanism an overall KIE is measured, which provides qualitative insight into the competition between these two mechanisms.

In this study, the reactivity, KIEs, and substituent effects for a series of alkyl iodide-cyanide ion reactions in the gas phase and in solution are evaluated. The reaction rate constants and KIEs for methyl, ethyl, *i*-propyl, and *t*-butyl iodide with cyanide ion in the gas phase, and of methyl and ethyl iodide with cyanide ion in solution, are reported. The reactions in solution were carried out in three different solvents – a methanol/dimethyl sulfoxide mixture ($\text{CH}_3\text{OH}/\text{DMSO}$), dimethyl sulfoxide (DMSO), and tetrahydrofuran (THF). CH_3OH is a protic solvent that is capable of forming strong hydrogen bonds to the negatively charged nucleophile in the ground state and transition state, DMSO is a very polar aprotic solvent, and THF is a weakly polar aprotic solvent that will solvate ions only very weakly. These solvents provide a smooth gradual transition to the gas phase conditions. In addition to measuring the perdeutero KIE, $(k_{\text{H}}/k_{\text{D}})_{\text{D}_5}$, for the ethyl iodide reaction, the secondary α -deuterium, $(k_{\text{H}}/k_{\text{D}})_{\alpha\text{-D}_2}$, and secondary β -deuterium, $(k_{\text{H}}/k_{\text{D}})_{\beta\text{-D}_3}$ KIEs were determined for the ethyl iodide reaction. Computational transition states, KIEs, and branching fractions for these reactions provide additional support for our conclusions.

3.2 Experimental

3.2.1 Gas Phase Experimental

These reactions were carried out in a flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer.³² The reactant anion, CN^- , is produced by electron impact on CNBr , mass-selected using a quadrupole mass filter, and injected into the reaction flow tube where it becomes thermally equilibrated to room temperature through collisions with He buffer gas (~ 0.5 torr, $\sim 10^4 \text{ cm s}^{-1}$). A known flow of neutral reagents was added to the reaction flow tube through a series of fixed inlets at various distances along the flow tube, and the depletion of the reactant ions and formation of the product ions were monitored using the detection quadrupole mass filter coupled to an electron multiplier. Reaction rate constants were determined under pseudo-first order conditions, where the concentration of the alkyl halide ($\sim 10^{11} \text{ molecules cm}^{-3}$) was significantly greater than the concentration of cyanide ion ($\sim 10^5 \text{ ions cm}^{-3}$). The reactant ion signal was monitored as the position of the neutral reagent addition was varied, thereby changing the reaction distance and time. The reaction rate constant is obtained from the slope of a plot of the $\ln [\text{ion}]$ as a function of the reaction distance and other measured experimental parameters. The reported values are the averages of at least three individual measurements. Absolute uncertainties in these rate measurements are $\pm 20\%$, however some systematic errors (pressure, temperature, He flow rate, etc.) cancel in the rate constant ratio, so that the error bars for KIEs are significantly smaller. Neutral reagents [CH_3I , Aldrich 99.5%; CD_3I , Cambridge Isotope Laboratories 99.5% D; $\text{CH}_3\text{CH}_2\text{I}$, Aldrich 99%; $\text{CD}_3\text{CD}_2\text{I}$, Isotec 99.5% D; $\text{CD}_3\text{CH}_2\text{I}$, Isotec 98% D; $\text{CH}_3\text{CD}_2\text{I}$, Isotec 98% D; $(\text{CH}_3)_2\text{CHI}$, Aldrich 99%; $(\text{CD}_3)_2\text{CDI}$, CDN Isotopes 99.1% D; $(\text{CH}_3)_3\text{CI}$, Aldrich 95%; $(\text{CD}_3)_3\text{CI}$, CDN Isotopes 99.5% D] were obtained from commercial vendors and purified by several freeze-pump-thaw cycles before use. The reagents

were protected from light and stored under vacuum. Helium buffer gas (99.995%) was purified by passage through a molecular sieve trap immersed in liquid nitrogen. Parallel reactions of deuterated and undeuterated reactants were carried out under identical conditions.

3.2.2 *Condensed Phase Experimental*

The rate constants were measured using the procedure outlined for the reaction of ethyl iodide in a previous study,¹² except that the stock solutions were prepared as follows. The alkyl iodide stock solutions for the reactions of ethyl iodide in DMSO and THF were prepared by adding approximately 18 μL of the alkyl iodide to 10 mL of the solvent. For the reaction of ethyl iodide in 90% $\text{CH}_3\text{OH}/10\%$ DMSO (v/v), the ethyl iodide stock solution was prepared by adding 36 μL of ethyl iodide to 10 mL of the solvent. The methyl iodide stock solution for the reaction in 40% $\text{CH}_3\text{OH}/60\%$ DMSO (v/v) was prepared by adding approximately 8 μL of methyl iodide to 10 mL of solvent. The tetrabutylammonium cyanide stock solutions for the ethyl iodide reactions in DMSO and THF and for the methyl iodide reactions in 40% $\text{CH}_3\text{OH}/60\%$ DMSO (v/v) were prepared by dissolving 75 mg of tetrabutylammonium cyanide (accurately weighed) in 50.00 mL of solvent. The tetrabutylammonium cyanide stock solution for the ethyl iodide reaction in 90% $\text{CH}_3\text{OH}/10\%$ DMSO (v/v) was prepared by dissolving approximately 0.170 g of tetrabutylammonium cyanide (accurately weighed) in 25.00 mL of solvent. Twenty mL of the tetrabutylammonium cyanide stock solution was transferred into a reaction flask fitted with a serum cap and the reaction flask and the alkyl iodide stock solutions were temperature equilibrated for at least one hour. The reaction was started by injecting 5 mL of the appropriate ethyl iodide stock solution into the reaction flask and 1.00 mL aliquots of the reaction mixture were taken throughout the reaction and injected into 30 mL of 0.013 M nitric acid. This quenched the reaction by protonating the nucleophile making it unreactive. After the acidic

solution containing HCN from the unreacted cyanide ion had been stirred in the fume hood for at least an hour to remove the hydrogen cyanide, the iodide ion in the sample was analyzed using a potentiometric titration and a 0.0005 M silver nitrate solution. The rate constants were calculated using the standard kinetic equation for a second order reaction that is first order in both reactants. The iodide reagents [CH_3I , 99.5%; CD_3I , 99.5% D; $\text{CH}_3\text{CH}_2\text{I}$, 99%; $\text{CD}_3\text{CD}_2\text{I}$, 99.5% D; $\text{CH}_3\text{CD}_2\text{I}$, 98% D] were purchased from Sigma-Aldrich. The reported rate constants are the averages of at least three individual measurements.

3.2.3 Computational Methods

Electronic structure calculations were carried out using the Gaussian 03³³ suite of programs to provide additional insight into the experimental results. Since it has been shown that the calculated KIEs for the ethyl iodide–cyanide ion $\text{S}_{\text{N}}2$ reaction vary markedly with the level of theory,¹² several levels of theory and basis sets were investigated. The MP2³⁴ level of theory with the 6-311++G(2d,p) basis set^{35,36} for C, N, and H and the LanL2DZ effective core potential³⁷ for I correctly predicted the magnitude of the observed $(k_{\text{H}}/k_{\text{D}})_{\alpha\text{-D}_3}$ for the methyl iodide–cyanide ion reaction, which can only occur by the $\text{S}_{\text{N}}2$ mechanism. Therefore, this level of theory was used in all subsequent calculations and scaling was not applied. Although Merrick, Moran, and Radom have not recommended optimal scaling factors for this level of theory, similar theoretical methods have zero point vibrational energy, enthalpy, and entropy scaling factors near unity.³⁸ Application of these factors might slightly change the absolute KIE values. However, work on similar reactions by Nielson, Glad, and Jensen indicates scaling does not affect the relative KIEs.³⁹ Therefore, we expect the magnitude and relative changes in our calculated KIEs to provide consistent interpretation of transition state structures without scaling.

The KIEs were calculated using transition state theory, formulated by assuming that any variational or tunneling effects are insignificant:

$$\frac{k_H}{k_D} = \exp\left(\frac{\Delta G_D^\ddagger - \Delta G_H^\ddagger}{RT}\right)$$

where $\Delta G^\ddagger = G^\ddagger - G^r$

$\Delta G^\ddagger$ is the difference between the zero point corrected free energy of the transition state relative to the separated reactants. Transition states were confirmed by the existence of one imaginary frequency along the reaction coordinate. The k_H/k_D ratio for the S_N2 and $E2$ transition states provides relative KIEs for each pathway. The % S_N2 was determined using the same formula with the ratio of the theoretical rate constants for the perprotio reaction, $k_{S_N2}/(k_{S_N2} + k_{E2})$. All frequencies are treated using the harmonic approximation. Although harmonic treatment of low frequency modes can introduce error into the entropy term of the free energy, this effect appears to be minimized in our KIE calculations due to the relatively small changes in the lowest frequencies upon isotopic substitution.

3.3 Results and Discussion

3.3.1 Gas Phase Reactions

The experimental rate constants, reaction efficiencies, and deuterium KIEs for the reactions of cyanide ion with alkyl iodides in the gas phase are given in Table 3.1. With the exception of the reaction of CN^- with *i*-propyl iodide, the reaction rate constants were within the detectable range of 10^{-9} to 10^{-12} $\text{cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. The reaction efficiencies (k_{rxn}/k_{col} , where k_{col} is calculated using parameterized trajectory theory⁴⁰) are less than 7%; this low reactivity is consistent with the low proton affinity and delocalized nature of the anion. With efficiencies well below the collision-controlled limit, the KIEs are expected to reflect the intrinsic reactivity

and differences in transition state structure. All enthalpies of reaction for the S_N2 pathways are at least 29 kcal mol⁻¹ more exothermic than those for the E2 pathways. Although the E2 reactions are less exothermic, they are energetically accessible. In principle, the delocalization of charge density on CN⁻ allows the C or N atom to be the reactive site; however, thermochemical data⁴¹ indicate that attack of the neutral reactant by the carbon nucleophile is thermodynamically favored by approximately 18 kcal mol⁻¹ based on heats of formation for CH₃CN versus CH₃NC and CH₃CH₂CN versus CH₃CH₂NC. Therefore the alkyl cyanides were assumed to be the only products in our comparison of experimental and computational results.

Table 3.1 Rate Constants (10⁻¹¹ cm³ s⁻¹), Reaction Efficiencies,^a Kinetic Isotope Effects (k_H/k_D), and Enthalpies of Reaction (kcal mol⁻¹)^b for CN⁻ + RI in the Gas Phase

Substrate (RI)	k _{exp}	Reaction Efficiency		S _N 2	E2
		k _{exp} /k _{col}	k _H /k _D ^c	ΔH _{rxn}	ΔH _{rxn}
CH ₃ I	12.8 ± 0.3	0.0574		-48.3	---
CD ₃ I	15.2 ± 0.7	0.0683	0.84 ± 0.03		
CH ₃ CH ₂ I	2.99 ± 0.02	0.0115		-48.6	-16.0
CH ₃ CD ₂ I	3.34 ± 0.09	0.0129	0.90 ± 0.03		
CD ₃ CH ₂ I	2.98 ± 0.06	0.0114	1.01 ± 0.02		
CD ₃ CD ₂ I	3.38 ± 0.07	0.0131	0.89 ± 0.02		
(CH ₃) ₂ CHI	< 0.1 ^d	<0.0004	---	-49.8	-17.8
(CH ₃) ₃ CI	1.1 ± 0.1	0.004		-46.3	-17.2
(CD ₃) ₃ CI	0.12 ± 0.01	0.0004	> 8 ^e		

^aEfficiency is the ratio of the experimental rate constant to the collision rate constant calculated using parameterized trajectory collision theory.⁴⁰ ^bEnthalpies of reaction are calculated from thermochemical data.⁴¹ ^cAdditional significant figures used in calculations are not reflected in rounded k_{exp} values. ^dThe rate constant for CN⁻ reacting with *i*-propyl iodide is at the detection limits of the instrument. ^eThis value is a lower limit without corrections for trace association products and mass discrimination.

In previous studies, reactivity trends and KIEs were utilized to assess the mechanistic behavior of the alkyl halides; different nucleophiles show significant differences in S_N2 and E2 branching fractions.^{13, 42} “Typical” perdeutero KIE values for alkyl halides transition from inverse to normal as the amount of substitution on the α-carbon of the neutral reactant increases. Many ethyl halide reactions exhibit an increased efficiency when compared with methyl halides.

This has been attributed to either an increased stabilization of the S_N2 transition state and/or an E2 contribution to the reaction. Further substitution on the alpha carbon generates additional steric hindrance to the S_N2 reaction, which overcomes the S_N2 stabilizing electronic effects, leading to significant amounts of E2 reaction. Reactions of *t*-butyl halides proceed exclusively by the E2 mechanism.¹³

An inverse (k_H/k_D)_{α-D3} of 0.84 ± 0.03 for reaction of CN[−] with methyl iodide and an (k_H/k_D)_{α-D2} of 0.90 ± 0.03 for the reaction of CN[−] with ethyl iodide are consistent with previously reported values for systems that proceed primarily or exclusively by an S_N2 mechanism.^{42, 43} The unusually large KIE (> 8) measured for the reaction of *t*-butyl iodide with CN[−] indicates that the reaction probably proceeds exclusively by an E2 mechanism. However unlike typical reaction systems, the reaction efficiency decreases from methyl to *i*-propyl, and then increases for *t*-butyl iodide. The observed decrease in rate constant from methyl to *i*-propyl shows the typical decrease in the S_N2 channel, but an unusually small increase in the E2 channel relative to previous results.^{13, 17, 42, 43} The exceptionally large increase in the rate constant and efficiency from the *i*-propyl to the *t*-butyl iodide reaction may be due to significant release of steric strain in going to the transition state of the *t*-butyl iodide reaction, i.e., *t*-butyl iodide is especially strained due to the large iodine atom and the multiple methyl groups.

3.3.2 Condensed Phase Reactions

The rate constants expressed in both solution and gas phase units, and the perdeutero KIEs for the S_N2 reaction between cyanide ion and methyl iodide in 40% CH₃OH/60% DMSO and ethyl iodide in 90% CH₃OH/10% DMSO, DMSO, and THF are presented in Table 3.2. All values are consistent with an S_N2 mechanism for the reaction.⁴⁴ The smaller (more inverse) KIE found for the methyl iodide–cyanide ion reaction in 40% CH₃OH/60% DMSO, Table 3.2, is

expected if both substrates react by an S_N2 mechanism. These results suggest that the ethyl iodide–cyanide ion reaction in solution is an S_N2 process. This conclusion was confirmed by a gas chromatographic analysis of the neutral products; no ethylene, which would be produced in an E2 reaction, could be detected.¹²

Table 3.2 Rate Constants and Perdeutero KIEs (k_H/k_D) for the $\text{CN}^- + \text{CH}_3\text{I}$ and $\text{CN}^- + \text{CH}_3\text{CH}_2\text{I}$ Reactions in the Protic to Aprotic Solvent Series.

Solvent (Temp)	Reaction	k_H ($\text{M}^{-1} \text{s}^{-1}$)	k_H ($\text{cm}^3 \text{s}^{-1}$)	Perdeutero k_H/k_D
40% CH_3OH / 60% DMSO (20°C)	$\text{CN}^- + \text{CH}_3\text{I}$	$5.63 (\pm 0.02) \times 10^{-2}$	9.34×10^{-23}	0.902 ± 0.004
90% CH_3OH / 10% DMSO (30°C)	$\text{CN}^- + \text{CH}_3\text{CH}_2\text{I}$	$5.84 (\pm 0.13) \times 10^{-5}$	9.69×10^{-26}	1.02 ± 0.03
DMSO (20°C)	$\text{CN}^- + \text{CH}_3\text{CH}_2\text{I}$	0.2075 ± 0.004	3.44×10^{-22}	1.044 ± 0.002
THF (0°C)	$\text{CN}^- + \text{CH}_3\text{CH}_2\text{I}$	0.4051 ± 0.0007	6.72×10^{-22}	1.062 ± 0.003

The increase in the rate constant from $\text{CH}_3\text{OH}/\text{DMSO}$ to DMSO to THF is primarily due to the different solvation energies of the cyanide ion. The cyanide ion will be most stable in $\text{CH}_3\text{OH}/\text{DMSO}$ where it is solvated by hydrogen bonding, and the least stable (least solvated) in THF, the solvent with the lowest dielectric constant. The solvation energy of the transition state will increase from THF to DMSO to $\text{CH}_3\text{OH}/\text{DMSO}$. However, since the negative charge on the cyanide ion is dispersed (partially transferred to the developing iodide ion) in going to the transition state, the difference between the transition state energies in the different solvents will be smaller than that in the ground state. As a result, $\Delta H^\ddagger$ decreases (the rate constant increases) from $\text{CH}_3\text{OH}/\text{DMSO}$ to DMSO to THF (from protic to aprotic solvents) as depicted in Figure 3.1.

3.3.3 Comparison of Gas Phase and Solution Results

The transition states of the methyl and ethyl iodide reactions in solution and gas phase were further probed using secondary α - and β -deuterium KIEs. These KIEs, measured in the condensed and gas phase, as well as the calculated branching fractions and KIEs are given in Table 3.3. It has been assumed that the solution perdeutero KIE for the ethyl iodide reaction is the product of the $(k_H/k_D)_{\beta-D3}$ and $(k_H/k_D)_{\alpha-D2}$:

$$\frac{k_{CN^-+CH_3CH_2I}}{k_{CN^-+CD_3CD_2I}} = \frac{k_{CN^-+CH_3CH_2I}}{k_{CN^-+CD_3CH_2I}} \times \frac{k_{CN^-+CH_3CH_2I}}{k_{CN^-+CH_3CD_2I}} = (k_H/k_D)_{\beta-D3} \times (k_H/k_D)_{\alpha-D2}$$

Because the $(k_H/k_D)_{\beta-D3}$ values for the reactions in solution were expected to be near unity, they were calculated from this relationship rather than experimentally measured. While the current gas phase data as well as our computational results support the use of this multiplicative technique, other gas phase results^{29,45} indicate this relationship may only be an approximation rather than a rigid equality. To accommodate the inexact nature of the relationship, no error bars have been given for the $(k_H/k_D)_{\beta-D3}$ values in solution.

Because the rate of the ethyl iodide–cyanide ion reaction changed by a factor of 10^4 when the solvent was changed from $CH_3OH/DMSO$ to THF, the rate constants and the KIEs could not be measured at the same temperature in the three solvents, Table 3.3. In order to accurately compare the KIEs in the different solvents, a temperature correction for the KIE was needed. This was possible for the $(k_H/k_D)_{\alpha-D2}$ values. The average temperature dependence of $(k_H/k_D)_{\alpha-D2}$ from 34 reactions in three different laboratories^{44, 46, 47} was $1.0 (\pm 1.0) \times 10^{-3}/^\circ C$. Applying this correction to the $(k_H/k_D)_{\alpha-D2}$ in Table 3.3 gives the best estimate of the $(k_H/k_D)_{\alpha-D2}$ for the S_N2 reaction between cyanide ion and ethyl iodide in the three solvents at $20^\circ C$, column 6, Table 3.3. Although no temperature dependence could be found for the $(k_H/k_D)_{\beta-D3}$ or $(k_H/k_D)_{D5}$ KIEs, a

Table 3.3 A Comparison of Experimental and Theoretical^a Deuterium KIEs for the $\text{CN}^- + \text{CH}_3\text{I}$ and $\text{CN}^- + \text{CH}_3\text{CH}_2\text{I}$ Reactions in the Gas Phase^b and in Solution^c.

Reaction Phase	CN [−] + CH ₃ I	CN [−] + CH ₃ CH ₂ I					
	(k _H /k _D) _{α-D3}	(k _H /k _D) _{D5}	Corrected (k _H /k _D) _{D5} (20°C)	(k _H /k _D) _{α-D2}	Corrected (k _H /k _D) _{α-D2} (20°C)	(k _H /k _D) _{β-D3}	Corrected (k _H /k _D) _{α-D3} (20°C)
40% CH ₃ OH/ 60% DMSO	0.902 ± 0.004 ^d	---	---	---	---	---	---
90% CH ₃ OH/ 10% DMSO	---	1.02 ± 0.03 ^e	1.03 ± 0.04	1.015 ± 0.02 ^e	1.03 ± 0.03	1.005 ^g	1.00 ^g
DMSO	---	1.044 ± 0.002 ^d	1.044 ± 0.002	1.032 ± 0.004 ^d	1.032 ± 0.004	1.012 ^g	1.012 ^g
THF	---	1.062 ± 0.003 ^f	1.04 ± 0.02	1.040 ± 0.003 ^f	1.02 ± 0.02	1.021 ^g	1.02 ^g
Gas Phase	0.84 ± 0.03	0.89 ± 0.02		0.90 ± 0.03		1.01 ± 0.02	
Theoretical S _N 2							
Gas Phase	0.83	0.89		0.91		0.97	
THF	---	1.087		1.059		1.028	
Theoretical E2							
Gas Phase	---	8.4		1.1		7.8	

^a Theoretical $\text{S}_{\text{N}}2$ and E2 KIEs used conventional transition state theory and $\Delta G^\ddagger$ at the MP2 level of theory with the 6-311++G(2d,p) basis set for C, N, and H and the LanL2DZ effective core potential for I at 298 K. ^b The error in the gas phase KIEs is one standard deviation of at least three measurements. Experiments conducted at 298 K. ^c The error in the solution KIEs is $1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2 \times (\Delta k_{\text{D}})^2]^{1/2}$, where Δk_{H} and Δk_{D} are the standard deviations for the average rate constants for the reactions of the undeuterated and deuterated substrates, respectively. ^d Experiments conducted at 20°C. ^e Experiments conducted at 30°C. ^f Experiments conducted at 0°C. ^g The $(k_{\text{H}}/k_{\text{D}})_{\beta\text{-D3}}/\text{corrected } (k_{\text{H}}/k_{\text{D}})_{\beta\text{-D3}}$ was calculated by dividing the experimental/corrected experimental $(k_{\text{H}}/k_{\text{D}})_{\text{D5}}$ by the experimental /corrected experimental $(k_{\text{H}}/k_{\text{D}})_{\alpha\text{-D2}}$.

comparison of the magnitude of these KIEs suggests a relatively small correction factor for the $(k_H/k_D)_{\beta-D3}$. Therefore, using the single component $(k_H/k_D)_{\alpha-D2}$ correction should provide a good estimate of the actual $(k_H/k_D)_{D5}$ values in solution; the corrected $(k_H/k_D)_{D5}$ values at 20°C are given in column 4, Table 3.3.

Computations were carried out to provide additional insight into the experimental results. The MP2³⁴ level of theory with the 6-311++G(2d,p) basis set for C, N, and H and the LanL2DZ effective core potential for I correctly predicted the observed $(k_H/k_D)_{\alpha-D3}$ for the methyl iodide–cyanide ion reaction that can only occur by the S_N2 mechanism, i.e., the computational $(k_H/k_D)_{\alpha-D3}$ of 0.83 found for the CN[−] + CH₃I reaction is in excellent agreement with the experimental gas phase $(k_H/k_D)_{\alpha-D3}$ of 0.84 ± 0.03. Therefore, this level of theory was used in all subsequent calculations. Solvent calculations were conducted at the same level of theory employing the polarizable continuum model with a THF dielectric parameter for the ethyl iodide reactions. Since standard dielectric parameters for mixed solvents are not available in the Gaussian database, condensed phase KIE calculations for the CN[−] + CH₃I reaction were not carried out. Consistent with experimental data no transition state structures were found for the E2 reactions in the condensed phase. The direction of the calculated KIEs is in good agreement with experimental data. While the consistency of the calculated KIEs for both the gas phase and THF solvent provides support for our methodology and use of relative KIEs to infer branching fractions, the qualitative predictions are considered more reliable than quantitative interpretations.

The theoretical KIE for the methyl iodide–cyanide ion reaction (0.83) is significantly smaller (more inverse) than the theoretical S_N2 $(k_H/k_D)_{\alpha-D2}$ for the gas phase ethyl iodide–cyanide ion reaction (0.91). This larger (less inverse) KIE for ethyl iodide reflects the additional

stabilization of the transition state by the polarizable alkyl group,^{13, 15, 17} the looser transition states found for the S_N2 reactions of ethyl substrates,⁴⁸ and the fact that this isotope effect is now due to only two hydrogens rather than three as in the methyl iodide case. The large magnitude of the E2 (k_H/k_D)_{D5} calculated for the gas phase ethyl iodide–cyanide reaction (8.4) arises from a substantial primary (7.8) and a smaller secondary (1.1) KIE. It is consistent with the large primary hydrogen-deuterium KIE observed for the E2 reaction between cyanide ion and *t*-butyl iodide (>8). Although the calculated KIEs for the E2 reaction are large compared to those typically found for E2 reactions (KIE = 2-7), they are in good agreement with the KIEs found experimentally and computationally by Gronert et al.⁴⁹ for E2 reactions in the gas phase.

Our transition state theory calculations predict the ethyl iodide–cyanide ion reaction to be 99% S_N2 and 1% E2. The presence of a small amount of E2 elimination in the gas phase reaction is consistent within the error range of a comparison of experimental and computational KIEs. Consider first the gas phase experimental (k_H/k_D)_{β-D3} value of 1.01, which exceeds the computational S_N2 value (KIE = 0.97). A simple calculation, detailed in Appendix 1, shows that this experimental value can be reproduced by a 4% contribution of the E2 channel (KIE = 7.8). While the experimental (k_H/k_D)_{α-D2} and (k_H/k_D)_{D5} values suggest no contribution from the E2 channel, the error bars on these values definitely allow a small amount of elimination pathway. Thus, both the transition state theory calculations and the experimental KIEs suggest there is a small amount of E2 pathway in the gas phase reaction, whereas there is none in solution. The E2 channel probably competes more effectively with the S_N2 channel in the gas phase because the solvation energy decreases the basicity of the anion in solution.

An examination of the (k_H/k_D)_{D5} and (k_H/k_D)_{α-D2} values at 20°C in columns 4 and 6 of Table 3.3 show that neither KIE is affected significantly by the change in solvent from

CH₃OH/DMSO to THF even though the rate constant changes by approximately 10⁴. This indicates that the structure of the S_N2 transition state is not affected significantly by a change in solvent. This result is in agreement with Westaway's "Solvation Rule for S_N2 Reactions,"⁴⁴ which predicts that there will be little or no change in transition state structure in a Type I S_N2 reaction (where the nucleophile and the leaving group have the same charge, as is the case for CN⁻ and I⁻) when the solvent is changed. It is worth noting that there was only a slight tightening of transition state structure when the solvent was changed from DMSO to THF for the Type I S_N2 reaction between ethyl chloride and cyanide ion.⁵¹

A comparison of the (k_H/k_D)_{α-D2} and the (k_H/k_D)_{D5} values for the gas phase and solution results show that the KIEs in the gas phase are significantly smaller (more inverse) than those in solution. For example, the (k_H/k_D)_{α-D3} values for the gas phase and solution are 0.84 and 0.902 for the methyl iodide reaction and the (k_H/k_D)_{α-D2} values are 0.90 and 1.03 for the ethyl iodide reaction, respectively. The same trend is observed in the (k_H/k_D)_{D5} results for the ethyl iodide reaction, i.e., 0.89 in the gas phase and 1.04 in solution. The smaller KIEs indicate a considerably tighter transition state in the gas phase.^{48,52-54} Although the calculations in THF using the polarizable continuum model correctly predict the larger secondary alpha, beta and perdeutero KIEs for the ethyl iodide– cyanide ion reaction that are consistent with a looser transition state in solution, there is poorer agreement between experiment and theory than for the gas phase analogs. Comparison of transition state structures from our theoretical gas-phase and the polarizable continuum model (PCM) calculations display a longer C_α - I bond and a shorter NC - C_α bond for the condensed phase (See Appendix 1). Although the PCM model only accounts for electrostatic solute-solvent interactions, it is possible that solvent effects advance the CN⁻ + CH₃CH₂I reaction along the reaction coordinate towards a more product-like transition

state. However, experimental KIEs from studies⁵¹ for the ethyl chloride–cyanide ion S_N2 reaction in DMSO and THF suggest that both the NC- - C_α and the C_α - - Cl bonds are shorter in the transition state for the less polar (less solvating) solvent (THF). Clearly further computational studies are warranted.

It is important to note that Westaway's Solvation Rule, which holds in solution very well, fails the ultimate test because the transition state changes significantly on going to the gas phase. The tighter transition state in the gas phase probably occurs because the electrostatic attraction between the partial negative charges on the cyanide and iodide ions and the partial positive charge on the alpha carbon is much more important in determining transition state structure in the gas phase than when the charges on the cyanide and iodide ions are reduced by solvation in solution. The tighter transition state in the gas phase is evident in the 7% difference in our (k_H/k_D)_{α-D3} values for the gas phase and solution (0.84 and 0.902, respectively) for the methyl iodide reaction. This trend is even more evident in the ethyl iodide reaction, i.e., the (k_H/k_D)_{α-D2} and (k_H/k_D)_{D5} values in the gas phase and in solution differ by 15% and 17%, respectively. The significant difference between the KIEs and the transition state structures in the gas phase and solution was initially troubling since the use of THF was expected to approach gas phase conditions. However, Bogdanov and McMahon⁵⁵ have shown that even though THF has a low dielectric constant (κ = 7), it is far from the gas phase limit. Figure 3.2 shows their computed values for ΔE[‡] for the Cl⁻ + CH₃Cl reaction as a function of the dielectric constant of the solvent. Changing the solvent from CH₃OH/DMSO to THF for the S_N2 reaction between methyl chloride and chloride ion would reduce ΔE[‡] by only 2 kcal mol⁻¹; in contrast, going from CH₃OH/DMSO to the gas phase would reduce ΔE[‡] by over 17 kcal mol⁻¹. Given the large difference in ΔE[‡]

between the gas phase and THF (approximately 15 kcal mol⁻¹) the observation of a significantly tighter transition state in the gas phase is a reasonable result. The curve in Figure 3.2 also

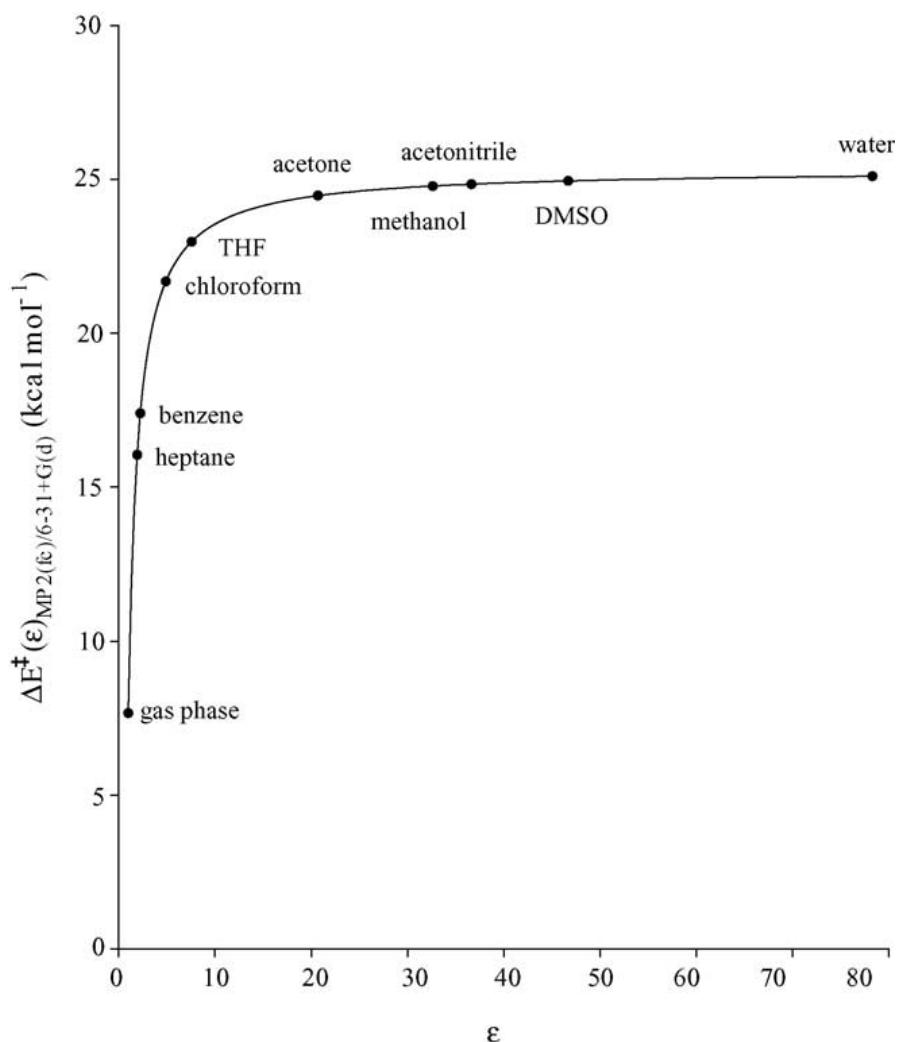


Figure 3.2. Plot of the dielectric constant (ϵ) vs. the activation energy for the $\text{Cl}^- + \text{CH}_3\text{Cl}$ $\text{S}_{\text{N}}2$ reaction, $\Delta E^\ddagger(\epsilon)_{\text{MP2}(\text{fc})/6-31+\text{G}(\text{d})}$, in various solvents.⁵⁶

explains why the reaction is between 10^{11} and 10^{15} times faster in the gas phase than in solution (see Tables 3.1 and 3.2 and Figure 3.1). Finally, the magnitudes of the electrostatic attraction between the partial negative charges on the nucleophiles in the transition state (cyanide ion and iodide ion) and the partial positive charge on the alpha carbon are much larger in the gas phase than in THF where solvation will reduce the electrostatic attraction between the ions in the

transition state. This greater electrostatic attraction in the gas phase transition state is likely responsible for the tighter transition state and more inverse KIEs observed in the gas phase.⁴⁹

3.4 Conclusion

The reaction of cyanide ion with ethyl iodide provides an ideal system for comparing gas phase and solution data. Both gas phase and solution reactions are dominated by the S_N2 pathway and have reactivities that are measurable and sensitive to isotopic substitution. In addition, the system is a Type I S_N2 reaction where changes in solvent are predicted to have minimal or no effect on transition state structure and the KIEs. A direct comparison of KIEs between the gas phase and solution showed that the KIEs in the gas phase are significantly smaller (more inverse) than those in solution. This result indicates that the transition state is significantly tighter in the gas phase. Thus, although the “Solvation Rule for S_N2 Reactions” has successfully predicted the change in transition state structure for a wide range of S_N2 reactions in solution,⁵⁴ it fails the ultimate test of predicting the effect of removing the solvent completely. The tighter transition state in the gas phase is primarily attributed to bond changes due to the greater electrostatic forces between the partial negative charges on iodide and cyanide ions and the partial positive charge on the alpha carbon in the gas phase.

3.5 References

1. Bohme, D. K.; Mackay, G. I. *J. Am. Chem. Soc.* **1981**, *103*, 978-979.
2. Bohme, D. K.; Raksit, A. B.; Mackay, G. L. *J. Am. Chem. Soc.* **1982**, *104*, 1100-1101.
3. Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986-5987.
4. Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247-350.
5. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.
6. DePuy, C. H. *J. Org. Chem.* **2002**, *67*, 2393-2401.
7. Gronert, S. *Chem. Rev.* **2001**, *101*, 329-360.
8. Almerindo, G. I.; Pliego, J. R. *Org. Lett.* **2005**, *7*, 1821-1823.
9. Tondo, D. W.; Pliego, J. R. *J. Phys. Chem. A* **2005**, *109*, 507-511.
10. Kahn, K.; Bruce, T. C. *J. Phys. Chem. B* **2003**, *107*, 6876-6885.
11. Westaway, K. C.; Fang, Y. R.; MacMillar, S.; Matsson, O.; Poirier, R. A.; Islam, S. M. *J. Phys. Chem. A* **2007**, *111*, 8110-8120.
12. Westaway, K. C.; Fang, Y. R.; MacMillar, S.; Matsson, O.; Poirier, R. A.; Islam, S. M. *J. Phys. Chem. A* **2008**, *112*, 10264-10273.
13. DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650-8655.
14. Uggerud, E. *Pure Appl. Chem.* **2009**, *81*, 709-717.
15. Gronert, S. *Acc. Chem. Res.* **2003**, *36*, 848-857.
16. Wladkowski, B. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 10643-10644.
17. Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 12977-12983.
18. Bohme, D. K.; Raksit, A. B. *Can. J. Chem.* **1985**, *63*, 3007-3011.
19. Kato, S.; Hacaloglu, J.; Davico, G. E.; DePuy, C. H.; Bierbaum, V. M. *J. Phys. Chem. A* **2004**, *108*, 9887-9891.
20. O'Hair, R. A. J.; Davico, G. E.; Hacaloglu, J.; Dang, T. T.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1994**, *116*, 3609-3610.
21. Thomas, J. M.; Viggiano, A. A. *J. Phys. Chem. A* **1999**, *103*, 2720-2722.
22. Viggiano, A. A.; Arnold, S. T.; Morris, R. A. *Int. Rev. Phys. Chem.* **1998**, *17*, 147-184.
23. Davico, G. E. *J. Phys. Chem. A* **2006**, *110*, 13112-13121.
24. Hu, W. -P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1994**, *116*, 7797-7800.
25. Ohta, K.; Morokuma, K. *J. Phys. Chem.* **1985**, *89*, 5845-5849.
26. Tachikawa, H. *J. Phys. Chem. A* **2001**, *105*, 1260-1266.
27. Glad, S. S.; Jensen, F. *J. Phys. Chem.* **1996**, *100*, 16892-16898.
28. Bickelhaupt, F. M.; Baerends, E. J.; Nibbering, N. M. M. *Chem. Eur. J.* **1996**, *2*, 196-207.
29. Eyet, N.; Villano, S. M.; Bierbaum, V. M. *J. Am. Soc. Mass Spectrom.* **2008**, *19*, 1296-1302.
30. Eyet, N.; Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1046-1051.
31. Wu, Y.-R.; Hu, W.-P. *J. Am. Chem. Soc.* **1999**, *121*, 10168-10177.
32. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Proc.* **1987**, *81*, 85-100.
33. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.;

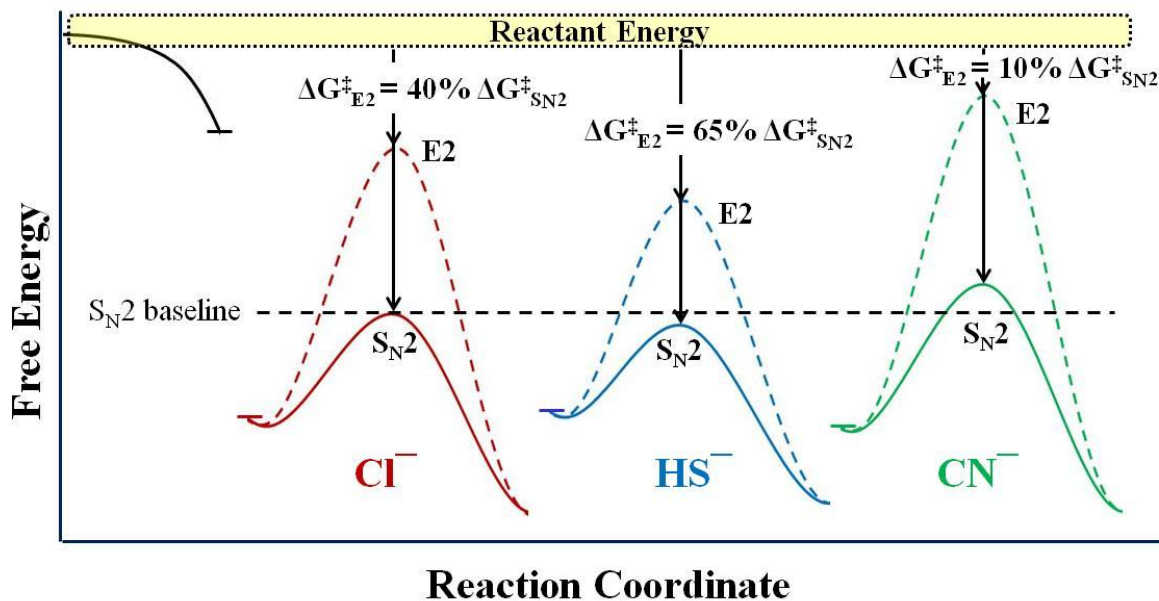
- Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision B.05*, Gaussian, Inc.: Pittsburgh, PA, 2004.
34. Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, 46, 618-622.
 35. Zhang, Q. Z.; Wang, H. N.; Sun, T. L.; Wang, W. X. *Chem. Phys.* **2006**, 324, 298-306.
 36. Hadad, C. M.; Rablen, P. R.; Wiberg, K. B. *J. Org. Chem.* **1998**, 63, 8668-8681.
 37. Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 270-283.
 38. Merrick, J. P.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007**, 111, 11683-11700.
 39. Nielson, P. A.; Glad, S. S.; Jensen, F. J. *J. Am. Chem. Soc.* **1996**, 118, 10577-10583.
 40. Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, 76, 5183-5185.
 41. P.J. Linstrom and W.G. Mallard, Eds., **NIST Chemistry WebBook, National Institute of Standards and Technology, NIST Standard Reference Database Number 69**, Gaithersburg MD, 20899, <http://webbook.nist.gov>; (retrieved October 23, 2009.)
 42. Gronert, S.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1991**, 113, 4009-4010.
 43. Bierbaum, V. M.; Grabowski, J. J.; DePuy, C. H. *J. Phys. Chem.* **1984**, 88, 1389-1393.
 44. Westaway, K. C.; Waszczylo, Z. *Can. J. Chem.* **1982**, 60, 2500-2520.
 45. Villano, S. M.; Eyet, N.; Lineberger, W. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2009**, 131, 8227-8233.
 46. Koshy, K. M.; Robertson, R. E. *J. Am. Chem. Soc.* **1974**, 96, 914-916.
 47. Shiner, V. J. Jr.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessick, M. A.; Milakofs, L.; Rapp, M. W. *J. Am. Chem. Soc.* **1969**, 91, 4838-4939.
 48. Poirier, R. A.; Wang, Y. L.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, 116, 2526-2533.
 49. Gronert, S.; Fagin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, 129, 5330-5331.
 50. Westaway, K. C. *Can. J. Chem.* **1978**, 56, 2691-2699.
 51. Fang, Y. R.; MacMillar, S.; Eriksson, J.; Kolodziejska-Huben, M.; Dybala-Defratyka, A.; Paneth, P.; Matsson, O.; Westaway, K. C. *J. Org. Chem.* **2006**, 71, 4742-4747.
 52. Kato, S.; Davico, G. E.; Lee, H. S.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2001**, 210, 223-229.
 53. Glad, S. S.; Jensen, F. J. *J. Am. Chem. Soc.* **1997**, 119, 227-232.
 54. Westaway, K. C. *Adv. Phys. Org. Chem.* **2006**, 41, 217-273.
 55. Bogdanov, B.; McMahon, T. B. *Int. J. Mass Spectrom.* **2005**, 241, 205-223.
 56. "Reprinted from *Int. J. Mass Spectrom.*, 241, Bogdanov, B. and McMahon, T.B., *Thermochemistry and structures of solvated S_N2 complexes and transition states in the gas phase: experiments and theory*, 205-223, Copyright (2005), with permission from Elsevier."

CHAPTER 4

Mechanistic Investigation of S_N2 Dominated Gas Phase Alkyl Iodide Reactions

Adapted from

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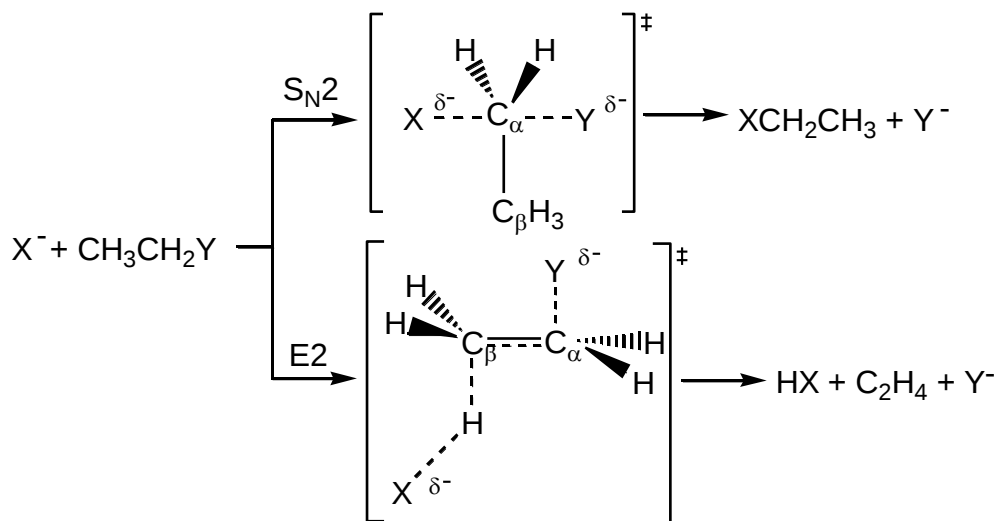
Overview

The competition between substitution (S_N2) and elimination (E2) has been studied for the reactions of methyl, ethyl, *i*-propyl, and *t*-butyl iodide with Cl⁻, CN⁻, and HS⁻ in the gas phase. Previous studies have shown a dominance of the S_N2 mechanism for sulfur anions and for some cyanide-alkyl iodide reactions. Although our results support this conclusion for the reactions studied, they reveal that competition between the S_N2 and E2 pathways exists for the *i*-propyl reactions. Steric and electronic effects, upon alkyl group substitution, produce looser and less stable S_N2 transition states; however, they can favor the E2 process. These opposing effects on barrier heights produce E2/S_N2 competition as steric hindrance increases around the α-carbon; however, the relative differences in intrinsic barrier heights lead to significantly different branching ratios. This interpretation is discussed in terms of reaction efficiencies, kinetic isotope effects, linear basicity-reactivity relationships, electrostatic models, and transition state looseness parameters.

4.1 Introduction

Studies of bimolecular nucleophilic substitution (S_N2) and base-induced elimination reactions (E2) have made significant contributions to the fundamental knowledge of prototypical organic reactions^{1, 2} and the conceptual framework for understanding biological systems.^{3, 4} In these experimental⁵⁻¹⁴ and theoretical investigations,¹⁵⁻²⁰ wide-ranging relationships connecting structure and reactivity parameters to reaction rates and mechanistic pathways have been established. These structure-energy relationships form the basis of efforts to predict and control the predominant reaction channel between the two competitive processes. Even within the current conceptual construct, transition state energetics^{9, 21} and solvent effects²²⁻²⁵ produce exceptions to expected reactivity and mechanistic selectivity. Of interest for our current research is the apparent dominance of the S_N2 mechanism for sulfur anions^{9, 21} and for some cyanide-alkyl iodide reactions²⁶ in the gas phase. By investigating the electronic and structural properties of systems that deviate from typical reactivity patterns, valuable insight can be gained to provide a more detailed picture of kinetics, mechanisms, and product distributions.

Studies of ion-molecule reactions have shown competition between S_N2 and E2 mechanisms (Scheme 4.1) to be significantly influenced by the nature of the attacking group (X^-), leaving group abilities (Y), substrate properties, and solvent effects.^{9, 27-29} The most influential factors on the E2/ S_N2 ratio are the presence of β -hydrogens, the degree of α - and β -branching, and the nucleophilicity vs. basicity of the reactant anion. For an E2 elimination to occur, there must be periplanar β -hydrogens allowing orbital overlap during double bond formation. This sp^3 to sp^2 transformation from reactants to products reduces steric strain between substituents producing a driving force for the E2 process in highly substituted systems. In contrast, increasing alkyl group substitution at the α -carbon or on the attacking group hinders



Scheme 4.1

the approach of the nucleophile during the S_N2 process, thus increasing the activation barrier and decreasing contributions from this channel. Experimental investigations into substituent effects around the α -carbon of alkyl halide substrates have shown a transition from predominantly substitution products for primary alkyl halides to exclusively elimination products for tertiary alkyl halides.^{17, 28, 30} In addition to structural influences, strong nucleophilicity (carbon cation affinity measured by kinetics) enhances the S_N2 pathway, while strong basicity (proton affinity measured by thermodynamics) enhances the $E2$ pathway. Distinguishing between the relative nucleophilic or basic character of an attacking group is not straightforward due to a linear free-energy relationship between these properties. Rationalized in the context of Marcus theory, the intrinsic transition state barrier height is lowered by the exothermicity of reaction.^{31, 32} Although gas-phase basicity is often an excellent predictive tool for S_N2 reactivity, deviations in the correlation between S_N2 and $E2$ barriers arise for attacking atoms outside the same row or group in the periodic table.^{9, 29} Alternative correlations utilizing transition state geometries, electronegativity, exothermicity and energy barriers have proven insightful.^{20, 33-36}

Intrinsic competition in gas phase ion-molecule reactions probed through mass spectrometry is often used to evaluate structure-energy relationships. However, the ability to differentiate between nucleophilic substitution and base-induced elimination is limited, since the competitive reactions typically produce the same ionic product. While alternate techniques and unique reaction schemes with differentiable products have garnered quantitative information on the competition between S_N2 and E2 pathways,^{14, 28, 30} most of the structure-reactivity data have been derived from indirect approaches, such as kinetic isotope effects (KIEs). A deuterium KIE is the ratio of the rate constant for an undeuterated reactant to the rate constant for a particular deuterated reactant ($\text{KIE} = k_{\text{H}}/k_{\text{D}}$). Deuterium KIEs enable the structure of the transition state and relative reaction pathways to be probed through relative energy changes in transition state barrier heights due to isotopic substitution. Since these KIEs are primarily due to changes in the vibrations, a normal KIE (>1) is observed when bonds are loosened on going from reactants to the transition state and an inverse KIE (<1) results from the tightening of bonds on going to the transition state. The magnitude of these effects is sometimes evaluated in terms of transition-state “looseness” or “crowdedness.”³⁵

Numerous groups have employed the use of KIEs derived from theoretical calculations and transition-state theory to elucidate a structural and energetic basis for reactivity.^{35, 37-39} Various attempts have been made to relate trends in KIEs with the degree of steric crowding on transition-state vibrational energy through a looseness parameter.⁴⁰⁻⁴² Almost all of these methods have defined the transition-state looseness parameter as a function of nucleophile-leaving group distance. Evaluation of the effectiveness of looseness parameters to predict KIEs indicates that the R_{TS} model (Eq 4.1) works well for S_N2 reactions with the same leaving group⁴³

$$R_{\text{TS}} = R_{\text{Nu-C}}^{\ddagger} + R_{\text{LG-C}}^{\ddagger} \quad (4.1)$$

and simple monatomic or diatomic nucleophiles:³⁵ Where $R_{\text{Nu-C}}^\ddagger$ refers to the nucleophile- C_α bond length at the transition state and $R_{\text{LG-C}}^\ddagger$ refers to the leaving group- C_α bond length at the transition state. In S_N2 processes, the C_α -H(D) out-of-plane bending vibrations will be of higher energy as the looseness parameter decreases contributing to an increased (more inverse) kinetic isotope effect. Studies of ethyl halide reactions indicate that the bending contribution accounts for the magnitude of KIEs in more complex substrates.⁴³

While the magnitude of the KIE in a reaction that occurs exclusively by S_N2 or by E2 mechanisms can be easily correlated to structure-energy relationships, evaluation of the KIE for a competitive reaction is complicated by contributions from both pathways. Relative contributions can be inferred from the overall KIE as a fraction of E2 reaction with high deuterium kinetic isotope effects ($k_H/k_D \approx 2$ -6) and a fraction of S_N2 reaction with slightly inverse KIEs ($k_H/k_D \approx 0.7$ -1.0).^{18, 44} Such interpretations can be facilitated with a computational KIE for each pathway. Corollary data have also been used to show linear relationships for barrier heights and structural changes with Mulliken charge on the leaving group³⁶ and with electronegativity of the attacking atom.²⁰ Assessing these relationships in conjunction with experimental KIEs investigates other factors determining S_N2 and E2 reactivity in addition to basicity.

In this work, we report on a series of substituted alkyl iodide reactions that display a predominance of the S_N2 mechanism and evaluate structure-energy relationships that correlate with competition between substitution and elimination pathways. We expand our earlier work²⁶ on alkyl iodide-cyanide ion reactions in the gas phase by investigating the reactions of methyl, ethyl, *i*-propyl, and *t*-butyl iodide with hydrogen sulfide and chloride ions. Reactivity patterns are discussed in conjunction with estimated relative barrier heights derived from linear basicity-

reactivity relationships. A multipole electrostatic model and transition-state looseness parameters are employed to garner insight into geometric and electronic effects during alkyl group substitution.

4.2 Experimental

4.2.1 Ion-Molecule Reactions

These reactions were carried out in a flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer.⁴⁵ In the source chamber, chloride and cyanide ions were generated by electron impact on chloroform and cyanogen bromide, respectively, and hydrogen sulfide ions were produced by electron impact on a mixture of carbon disulfide and methane. The reactant anions were then mass-selected using a quadrupole mass filter, and injected into the reaction flow tube where they become equilibrated to room temperature through collisions with He buffer gas (~ 0.5 torr, $\sim 10^4$ cm s⁻¹). A known flow of neutral reagents was added to the reaction flow tube through a series of fixed inlets at various distances along the flow tube, and the depletion of the reactant ions and formation of the product ions were monitored using a detection quadrupole mass filter coupled to an electron multiplier. Reaction rate constants were determined under pseudo-first order conditions, where the concentration of the alkyl halide ($\sim 10^{11}$ molecules cm⁻³) was significantly greater than the concentration of the reactant ion ($\sim 10^5$ ions cm⁻³). The reactant ion signal (intensities of 10^4 - 10^5 counts s⁻¹ with noise levels of ~ 1 count s⁻¹) was monitored as the position of the neutral reagent addition was varied, thereby changing the reaction distance and time. The reaction rate constant is obtained from the slope of a plot of the ln [ion counts] as a function of the neutral reaction distance and other measured experimental parameters; the measured ion decay was at least one order of magnitude. Reported rate constants are the averages of at least three individual measurements.

Absolute uncertainties in these rate measurements are $\pm 20\%$, however some systematic errors (pressure, temperature, He flow rate, etc.) are cancelled in the rate constant ratio, so that the error bars for KIEs are significantly smaller. Neutral reagents [CH_3I , Aldrich 99.5%; CD_3I , Cambridge Isotope Laboratories 99.5% D; $\text{CH}_3\text{CH}_2\text{I}$, Aldrich 99%; $\text{CD}_3\text{CD}_2\text{I}$, Isotec 99.5% D; $(\text{CH}_3)_2\text{CHI}$, Aldrich 99%; $(\text{CD}_3)_2\text{CDI}$, CDN Isotopes 99.1% D; $(\text{CH}_3)_3\text{CI}$, Aldrich 95%; $(\text{CD}_3)_3\text{CI}$, CDN Isotopes 99.5% D] were obtained from commercial vendors and purified by several freeze-pump-thaw cycles before use. The reagents were protected from light and stored under vacuum. Helium buffer gas (99.995%) was purified by passage through a molecular sieve trap immersed in liquid nitrogen. Parallel reactions of deuterated and undeuterated reactants were carried out under identical conditions.

4.2.2 Computational Methods

Electronic structure calculations were carried out using the Gaussian 03⁴⁶ suite of programs to provide additional insight into the experimental results. The MP2/6-311++G(2d,p) level of theory⁴⁷⁻⁴⁹ for carbon, nitrogen, and hydrogen and the LanL2DZ effective core potential⁵⁰ for iodine were employed based on accurate correlations of $\text{S}_{\text{N}}2$ KIEs for the methyl iodide–cyanide ion reaction in previous work.²⁶ Due to the systematic error of some electronic structure theory, it is very common to scale the Gaussian calculation of vibrational frequencies to obtain better results with respect to the experiments. Since optimal scaling factors for similar theoretical methods have zero point vibrational energy, enthalpy, and entropy scaling factors near unity,⁵¹ scaling was not employed in our experiments. Transition states were determined by the existence of one imaginary frequency along the reaction coordinate. The KIEs were calculated using transition-state theory (Eq 4.2), neglecting any variational or tunneling effects:

$$\frac{k_H}{k_D} = \exp\left(\frac{\Delta G_D^\ddagger - \Delta G_H^\ddagger}{RT}\right) \quad (4.2)$$

where $\Delta G^\ddagger = G^\ddagger - G^r$

$\Delta G^\ddagger$ is the difference between the zero point corrected free-energy of the transition state relative to the separated reactants. The k_H/k_D ratio for the S_N2 and E2 transition states provides a predicted KIE for each pathway. The S_N2 branching fraction ($BR_{S_N2} = k_{S_N2}/(k_{S_N2} + k_{E2})$) was determined using transition state theory and the ratio of the theoretical rate constants for the perprotio reactions. All frequencies are treated using the harmonic approximation. Although the harmonic treatment of low-frequency modes can introduce error into the entropy term of the free-energy, this effect appears to be minimized in our S_N2 KIE calculations due to the relatively small changes in the lowest frequencies upon isotopic substitution. Charges were calculated by natural population analysis (NPA) at the same level of theory on the optimized geometries.

4.3 Results and Discussion

4.3.1 Experimental Data

The experimental rate constants, reaction efficiencies, and deuterium KIEs for the gas phase reactions of chloride, hydrogen sulfide, and cyanide ions with a series of alkyl iodides are given in Table 4.1. The results for methyl iodide are consistent with previously reported rates and KIEs.⁵² With the exception of the reaction of CN^- with *i*-propyl iodide, the reaction rate constants are within the detectable range of 10^{-9} to 10^{-12} $cm^3 s^{-1}$ for our FA-SIFT. Due to variations in collision rates, reaction efficiencies (k_{rxn}/k_{col} , where k_{col} is calculated using parameterized trajectory theory⁵³) are employed in comparisons. These values represent the fraction of collisions that result in a reaction. The efficiencies are well below the collision-controlled limit indicating the ability to reflect relative differences in barrier heights ($\Delta G^\ddagger$); thus,

the rate constants and measured KIEs reflect structure-reactivity differences in the reactions. Both S_N2 and E2 pathways are energetically accessible (see Appendix 2) for all reactions. Although CN^- is an ambident nucleophile, the S_N2 and E2 pathways forming nitrile products are thermodynamically favored and assumed to occur exclusively. Recent work^{54, 55} has discussed the role of single-electron-transfer (SET) character in S_N2 transition states. While an analysis of this relationship for our reaction efficiencies versus ionization potentials suggests trends, the limited data do not allow a complete evaluation of SET.

4.3.2 *Reactivity Trends*

Since the reactions with methyl halides only proceed by the S_N2 pathway, a comparison of the reactivity of different nucleophiles provides a direct evaluation of nucleophilicity in terms of methyl cation affinity. The experimental ordering of efficiencies was found to be $HS^- > Cl^- > CN^-$. Proton affinities provide a measure of gas phase basicity for correlations with reactivity. While the relative reactivity of HS^- and Cl^- follows a linear free-energy relationship with Brønsted-type basicity (see Figure 4.1a), this correlation breaks down for CN^- . This reduced reactivity relative to basicity can be attributed to the delocalized charge on the attacking anion and the required reorganization of charge densities in the transition state influencing the barrier height. It is worth noting that the possible alpha-nucleophilic nature of CN^- (an enhanced reactivity of nucleophiles with a lone pair of electrons adjacent to the attacking atom) is not observed here. This result is perhaps expected since, unlike most alpha-nucleophiles, the lone electron pair in CN^- is isolated from the nucleophilic site by the presence of the triple bond.

Table 4.1 Reaction Rate Constants^a (k_H) in Units of $10^{-10} \text{ cm}^3 \text{ s}^{-1}$, Reaction Efficiencies^b (k_H/k_{col}), and Isotope Effects (KIE_{exp}).

Substrate	Cl^-		HS^-		CN^-^c	
	(Proton Affinity = 333 kcal mol ⁻¹)		(Proton Affinity = 351 kcal mol ⁻¹)		(Proton Affinity = 351 kcal mol ⁻¹)	
	k_H (k_H/k_{col})	KIE_{exp}	k_H (k_H/k_{col})	KIE_{exp}	k_H (k_H/k_{col})	KIE_{exp}
CH_3I	1.42 ± 0.01 (0.072)	0.86 ± 0.01	6.39 ± 0.03 (0.316)	1.03 ± 0.03	1.28 ± 0.03 (0.057)	0.84 ± 0.03
$\text{C}_2\text{H}_5\text{I}$	2.74 ± 0.02 (0.120)	0.96 ± 0.02	7.52 ± 0.20 (0.320)	0.99 ± 0.03	0.30 ± 0.02 (0.012)	0.89 ± 0.02
$(\text{CH}_3)_2\text{CHI}$	0.42 ± 0.01 (0.019)	1.29 ± 0.03	2.60 ± 0.03 (0.101)	1.05 ± 0.05	<0.01	
$(\text{CH}_3)_3\text{CI}$	0.77 ± 0.02 (0.030)	2.61 ± 0.10	5.35 ± 0.07 (0.204)	1.91 ± 0.04	0.11 ± 0.01 (0.004)	>8 ^d

^aError bars represent one standard deviation of the mean of 3 or more measurements; absolute accuracy is $\pm 20\%$. ^bEfficiency is the ratio of the experimental rate constant to the collision rate constant calculated using parameterized trajectory collision theory.⁵³ ^cPreviously reported values.²⁶ ^dThis value is a lower limit without corrections for trace association products and mass discrimination.

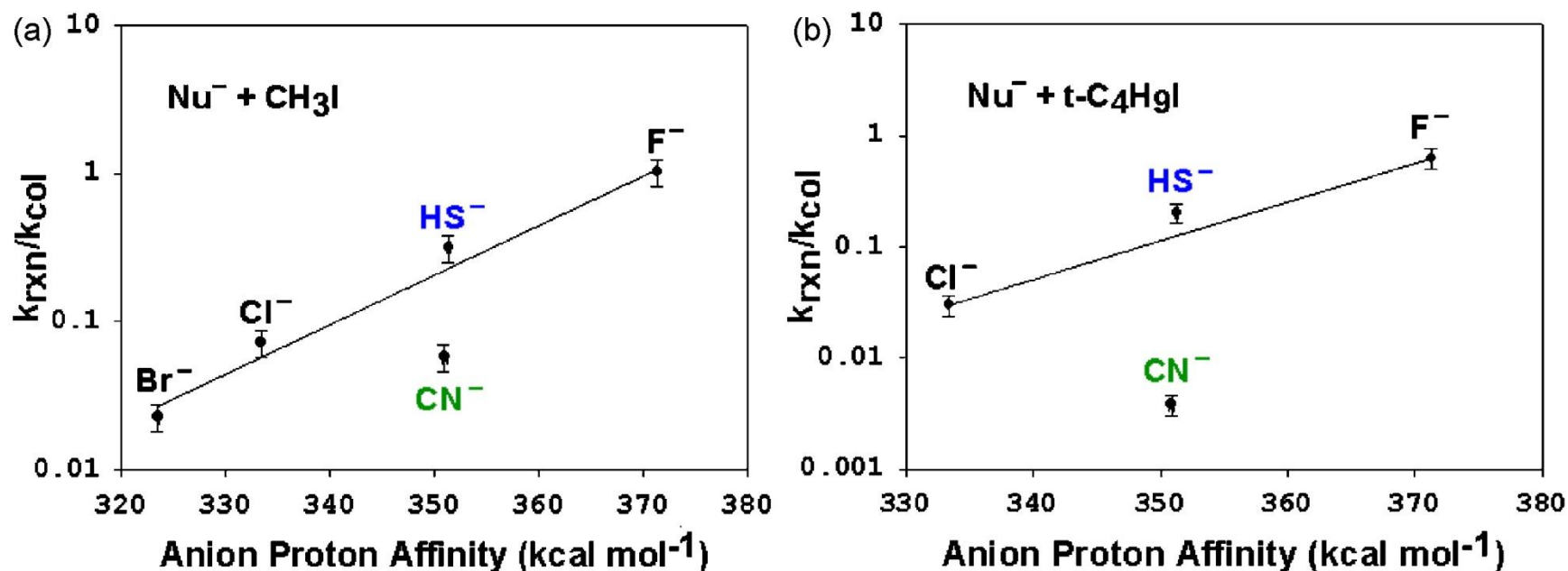


Figure 4.1 The logarithm of reaction efficiency ($k_{\text{rxn}}/k_{\text{col}}$) at 298 K versus the anion proton affinity (ΔH_{298}) for (a) the S_N2 reaction of Nu^- with CH_3I and (b) the E2 reaction of Nu^- with $t\text{-C}_4\text{H}_9\text{I}$. The linear trends are fit to the monatomic halide anions due to stronger linear correlations with basicity^{20, 29, 54, 55} (S_N2 : $y = 0.0334x - 12.39$; $r^2 = 0.989$ and E2: $y = 0.0348x - 13.13$). Experimental data from this work and ref 52 updated using parameterized trajectory theory⁵³ to calculate k_{col} . The reaction rate constant for F^- with $\text{C}_4\text{H}_9\text{I}$ was measured as $2.09 (\pm 0.02) \times 10^{-9}$ (this work where the error bars represent one standard deviation of the mean of 3 or more measurements; absolute accuracy is $\pm 20\%$); the reaction of Br^- with $t\text{-C}_4\text{H}_9\text{I}$ is not energetically accessible. Proton affinity data are from ref 61. Error bars for the plot represent an absolute accuracy of $\pm 20\%$ in efficiency.

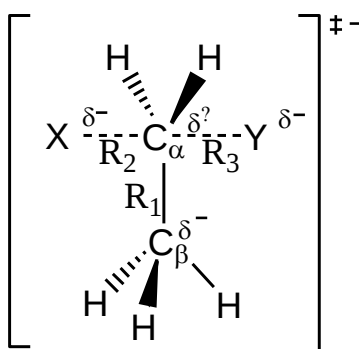
The relative correlation of basicity and E2 barrier heights can be accessed from the *t*-butyl iodide reactions since they have previously been shown to be dominated by the E2 mechanism.⁹ The experimental ordering of efficiencies was found to be $\text{HS}^- > \text{Cl}^- > \text{CN}^-$. Once again the reactivity of CN^- is below that expected for the associated basicity (see Figure 4.1b). Although similar trends in relative reactivity and Brønsted-type basicity are observed for both the $\text{S}_{\text{N}}2$ and E2 processes, comparison of the slopes for the halide anion with methyl iodide reactions (0.0334) and *t*-butyl iodide reactions (0.0348) reactions suggest that the E2 barrier is slightly more sensitive to basicity. Computational studies by Ren and Yamataka show a similar trend for competing barriers in $\text{CH}_3\text{CH}_2\text{Cl}$ reactions.⁵⁶ If the minor difference in slopes is interpreted as a reflection of the trends in barrier heights, the relative E2 to $\text{S}_{\text{N}}2$ efficiency increases at higher basicities (i.e., more similar $\text{S}_{\text{N}}2$ and E2 barrier heights). Analysis of the ratio of E2/ $\text{S}_{\text{N}}2$ (i.e., *t*- $\text{C}_4\text{H}_9\text{I}/\text{CH}_3\text{I}$) efficiencies shows an increase from Cl^- (41.7%) to F^- (60.1%). This relationship suggests that the $\text{S}_{\text{N}}2$ and E2 barriers for alkyl iodide reactions are not equivalent until extremely high anion basicities. If these trends in E2/ $\text{S}_{\text{N}}2$ barrier heights apply across the competitive series of ethyl and *i*-propyl iodide reactions, the $\text{S}_{\text{N}}2$ process should be the prominent pathway for all the nucleophiles in this study. This dominance of the $\text{S}_{\text{N}}2$ pathway is observed in dianion research with ethyl and *i*-propyl iodides by Gronert et al.²⁸ Further comparisons show that the CH_3I reaction efficiency of CN^- (0.057) is a factor of five below that of HS^- (0.316). However, the *t*- $\text{C}_4\text{H}_9\text{I}$ reaction efficiency of CN^- (0.004) is a factor of fifty below that of HS^- (0.204), a much greater deviation than in the $\text{S}_{\text{N}}2$ process. This result indicates that variations in electronic and structural changes for the CN^- reaction are magnified in the E2 transition state and that the E2 pathway is even more inhibited in these reactions.

Competing pathways as well as substituent effects complicate the analysis of the reactivity trends of the methyl, ethyl, *i*-propyl, and *t*-butyl iodide reactions. Therefore, established trends and a holistic approach must be employed. As C_α-branching increases, S_N2 processes will be inhibited and E2 processes will be enhanced. A decrease in reactivity down the series of alkyl iodides (i.e., 1° ≥ 2° ≥ 3°) would be indicative of large E2 barriers and a resulting dominance of the S_N2 pathway. In contrast, an increase in reactivity down the series of alkyl iodides (i.e., 1° ≤ 2° ≤ 3°) would be indicative of a major E2 contribution to the overall reaction rate. Applying these concepts to the data in Table 4.1, patterns emerge that support large barriers to the E2 process. For the Cl[−] and HS[−] nucleophiles, there is an increase in efficiency for the ethyl reaction followed by a sharp decrease for the *i*-propyl reaction. Although the increased reactivity in the primary iodide could be indicative of an E2 contribution, the sharp decrease for the secondary iodide dissuades this interpretation. Rather, the enhanced efficiency for the Cl[−] and HS[−] with ethyl iodide reactions is explained by stabilization of the S_N2 transition state through charge delocalization on the additional methyl group. It is more challenging to explain the dramatic decrease in efficiency along the series of alkyl iodides observed for CN[−] where the reaction efficiency drops below 2% for the ethyl reaction and continues to drop below the detection limit for the *i*-propyl reaction. In an effort to understand the anomalies between trends, we employ a slightly modified electrostatic model that has been effectively used by Gronert et al. for β-substituted alkyl halides.⁵⁷

4.3.3 *Multipole Electrostatic Model*

Variations in the magnitude of the efficiency between the methyl and ethyl reactions (67% increase for Cl[−], 1% increase for HS[−], and 79% decrease for CN[−]), reflect the combined capability of the methyl and attacking groups to shift electron density away from the α-carbon in

the transition state. This effect can be understood by applying a multipole electrostatic model⁵⁷ where the transition state is represented by the interaction of the partial charge on the attacking group, the leaving group, the β -carbon, and the α -carbon (Scheme 4.2). While the thermodynamic stability of the products can be reflected in shifts in the position of the geometry and amount of charge transferred in the transition state (early or late, i.e., reactant like or product like) used in our application of this model, the differences in the heat of reaction between the methyl and ethyl iodide reactions for a given nucleophile are all less than 1 kcal mol⁻¹. Therefore, relative variations in reaction efficiency are expected to be dominated by the intrinsic parameters that can be evaluated through bond lengths and the ionic nature of the transition state.



Scheme 4.2

Although methyl groups are commonly considered weak electron donors in solution, in gas phase reactions at saturated carbon centers they have a tendency to be weak electron acceptors.⁵⁸ Polarizability effects on anionic centers play a major role in reactivity and the ability to delocalize charge across alkyl groups significantly stabilizes the anionic S_N2 transition state. In the absence of an electron-withdrawing group on the methyl group to remove electron density, the β -carbon will maintain a partial negative charge. As the S_N2 reaction progresses, electron density from the nucleophile must transfer along the reaction coordinate to the leaving group. Depending on the electronegativity of the attacking and leaving groups, the electron

density of the transition state can range from a large partial negative charge on $X^{\delta-}$ and $Y^{\delta-}$ (strongly electronegative) with a slight positive charge on $C_{\alpha}^{\delta+}$ to a moderate partial negative charge on $X^{\delta-}$ and $Y^{\delta-}$ (weakly electronegative) with a slight negative charge on $C_{\alpha}^{\delta-}$. If a positive charge develops on C_{α} , attractive forces between $X^{\delta-}$, $Y^{\delta-}$, $C_{\beta}^{\delta-}$, and $C_{\alpha}^{\delta+}$ will significantly stabilize the transition state. On the opposite extreme, a negative charge on C_{α} generates repulsive forces between $X^{\delta-}$, $Y^{\delta-}$, $C_{\beta}^{\delta-}$, and $C_{\alpha}^{\delta-}$, destabilizing the transition state. Based on the covalent potential electronegativity scale⁵⁹ (see Appendix 2 for calculations), Cl^{-} (6.86) has a higher electronegativity than HS^{-} (5.83) or CN^{-} (5.74). As a result, more electron density will be shifted away from C_{α} in the chloride-ethyl iodide transition state leading to the observed enhanced reactivity compared to the chloride-methyl iodide reaction (further elaboration of this point is made below in conjunction with the computational atomic charges in Table 4.3). Electronegativity differences alone cannot explain the significant difference in efficiency between methyl and ethyl iodide reactions for CN^{-} and HS^{-} which have approximately the same electronegativity. However, if the relative R_1 , R_2 , R_3 bond distances of the model are taken into account in conjunction with electrostatic effects, shorter bonds would lead to larger repulsive forces and the observed reduced reactivity. A more inverse KIE for CN^{-} (KIE = 0.89) versus HS^{-} (KIE = 0.99) supports the presence of shorter bonds in the transition state. Therefore, the higher repulsive forces in the cyanide-ethyl iodide transition state would reduce efficiency. While based primarily on electrostatic field effects, this simple model seems to provide an effective explanation for variations in reactivity trends. Application of this model to other reactions is expected to hold, and computational studies by Wu et al. show a strong linear relationship between barrier heights and electronegativity for twelve nucleophiles.²⁰

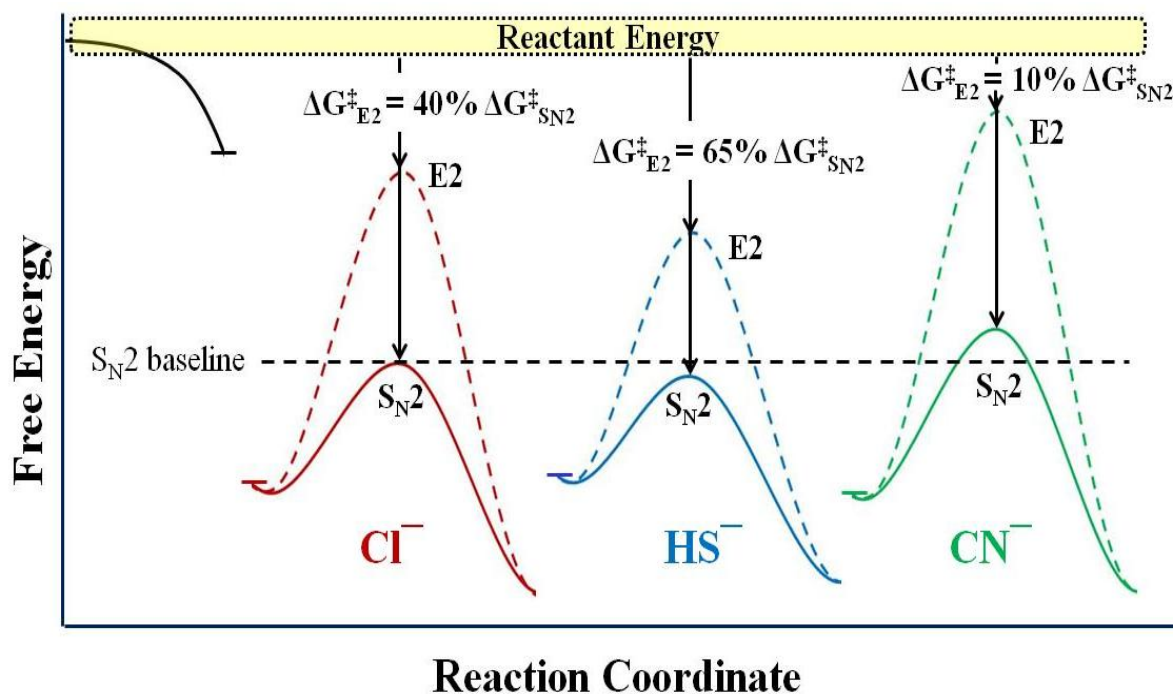


Figure 4.2 Qualitative depiction of relative S_N2 barrier heights for CH_3Cl and the E2 barrier heights for $t\text{-}C_4H_9I$ estimated from the basicity-reactivity baselines of Figure 4.1. The black dashed line (---) represents the linear fit of the S_N2 basicity-reactivity baseline.

4.3.4 Estimated Relative Free-Energy Barrier Heights

In an attempt to further discern the role of competition in these reactions, a qualitative analysis was made using estimated relative free-energy barrier heights from our E2/ S_N2 basicity-reactivity linear-fit baselines. To effectively analyze trends in reactivity relative to the free-energy barrier heights a common scale must be employed. Therefore the relative E2 to S_N2 free-energy barrier heights estimated from our E2/ S_N2 efficiencies are scaled to the linear S_N2 basicity-reactivity baseline. A qualitative depiction of the relationship of the free-energy barrier heights for and between anions is shown in Figure 4.2. The S_N2 free-energy barrier height for HS^- is slightly below the baseline reflecting slightly higher reactivity and the CN^- free-energy barrier height is significantly above the baseline reflecting substantially lower reactivity (this

correlates directly to Figure 4.1a). The E2 transition-state barrier height ($\Delta G^\ddagger_{\text{E2}}$) reflects a rough estimate of the variance between the lowest $\text{S}_{\text{N}}2$ and E2 free-energy barrier heights, which is related to the percent difference in $t\text{-C}_4\text{H}_9\text{I}$ and CH_3I reaction efficiencies ($\% \Delta G^\ddagger_{\text{S}_{\text{N}}2} = t\text{-C}_4\text{H}_9\text{I}$ efficiency divided by the CH_3I efficiency, although the linear proportionality is a simplification). While these approximations are based on experimental data, the use of efficiency ratios relies on many assumptions and is only intended to provide a plausible interpretation of branching ratios when used in conjunction with efficiencies and KIEs.

Upon transitioning from the methyl to the t -butyl iodide reactions, each additional methyl group will generate steric effects increasing the $\text{S}_{\text{N}}2$ free-energy barriers towards and above the E2 free-energy barriers. Examining the series of reactions in the context of these effects on the free-energy barrier heights, the $\text{S}_{\text{N}}2$ process is expected to dominate in the ethyl reactions with perhaps a small contribution of the E2 channel for HS^- . In the case of i -propyl, we would expect a small contribution of the E2 channel for Cl^- , competitive contributions from both the $\text{S}_{\text{N}}2$ and E2 channels for HS^- , and extremely small contributions from either channel for CN^- due to the high free-energy barriers for both channels. In the t -butyl reactions, significant steric hindrance will drive all the $\text{S}_{\text{N}}2$ free-energy barriers to be higher than the E2 free-energy barriers. The E2 mechanism will dominate; however, due to the higher E2 free-energy barrier for CN^- the efficiency would remain extremely low. The efficiencies and KIEs are in agreement with this assessment suggesting that the relationship between free-energy barrier heights established by the basicity-reactivity baselines is reasonable.

4.3.5 Kinetic Isotope Effects

If deuterium KIEs are used to rationalize the mechanisms for all three sets of anion reactions, the results also indicate a predominance of the $\text{S}_{\text{N}}2$ pathway for the ethyl and i -propyl

iodides. Across the methyl iodide reactions, the KIEs are inverse or near unity reflecting the expected vibrational changes during $sp^3 \rightarrow sp^2$ hybridization in an S_N2 transition state. This trend continues for the ethyl iodides indicating that the substitution channel is the dominant factor in the total KIE. The more normal effect for HS^- with methyl halides has been attributed to a small inverse vibrational contribution and a more normal rotational contribution (high moment of inertia due to larger size and higher mass) to the overall KIE.³⁵ This “loose” S_N2 transition state explains the relatively constant KIE (0.99-1.05) for the HS^- with methyl, ethyl, and *i*-propyl iodide series. It is not until the tertiary iodides that KIEs associated with the $E2$ channel are observed in all reactions.

A KIE significantly larger (> 8) than predicted by semi-classical theory (≈ 7) is observed for the CN^- with *t*-butyl iodide reaction. This value is established as a lower limit and is most likely higher due to mass discrimination and trace association products. The ability to more accurately assess the magnitude of this effect with confidence is limited by a combination of the larger error associated with smaller ion-signal changes due to the low reactivity and the high mass of the products. KIEs larger than the theoretical limit may be evidence of quantum mechanical tunneling; however, alternate explanations have been offered by Gronert et al.¹⁴ for observed KIEs of this magnitude in the gas phase. In reactions with barriers near the entrance channel, the pathways with the greater deuterium barrier height ($\approx 1 \text{ kcal mol}^{-1}$) are influenced by the lifetime of the collision complex leading to significantly lower rates. In reactions with competing pathways, a shift in barrier heights could push the deuterated system towards the S_N2 pathway. This explanation is interesting in light of the apparent dominance of the S_N2 channel in the ethyl and *i*-propyl iodide systems, but further discussion is beyond the scope of this work.

4.3.6 Computational Work

While higher levels of theory might improve the quantitative accuracy of the reaction barriers, our focus is on qualitative comparisons to experimental data. Therefore, our methodology only employs quantitative ratios of energies and discusses trends in geometry and charge distribution, which are less sensitive to the level of theory employed. To facilitate these comparisons, the isotope effect was computed using differences in enthalpy and free energy, as well as an estimate of the S_N2 branching fraction ($BR_{S_N2(\Delta G)}$) based on relative computational free-energy changes. Table 4.2 provides a summary of the results. Interpretation of the theoretical KIEs in the table should be tempered with an understanding of the calculations. As alkyl substitution increases, so do the number of low-frequency modes associated with the reactants and transition states. These low frequencies are difficult to model and can introduce error, especially in the entropic contribution to the free energy. However, this inaccuracy is minimized by small relative differences in the low frequency modes between the perprotio and perdeuterio reactions cancelling in the energy ratios. Reasonably good agreement between the free-energy (ΔG) and enthalpy (ΔH) computational KIEs for the series of alkyl iodide reactions was obtained, which indicates that significant variations in the low frequency modes do not occur except for the *t*-butyl iodide reactions. Although general comments can be made about the *t*-butyl iodide reactions, deviations between the experimental data and the *t*-butyl iodide calculations prevent the correlation of trend data. Since the experimental reactivity is governed by free-energy barriers, further discussions of KIEs will employ the free-energy computational values.

Reasonably good agreement of the computational $KIE_{S_N2(\Delta G)}$ with the experimental S_N2 KIEs and estimated product distributions indicates that the theoretical level is adequate for

Table 4.2 Experimental KIEs Compared to Computational KIEs and Branching Fractions

Reaction	KIE _{exp}	Theoretical				
		KIE _{SN2(ΔG)}	KIE _{E2(ΔG)}	BR _{SN2(ΔG)}	KIE _{SN2(ΔH)}	KIE _{E2(ΔH)}
Cl ⁻ + CH ₃ I	0.86 (±0.01)	0.87	---	---	0.86	---
Cl ⁻ + C ₂ H ₅ I	0.96 (±0.02)	0.97	9.50	0.99	1.00	11.0
Cl ⁻ + <i>i</i> -C ₃ H ₇ I	1.29 (±0.03)	1.05	9.83	0.97	1.08	10.8
Cl ⁻ + <i>t</i> -C ₄ H ₉ I	2.61 (±0.01)	---	a	0.00	---	9.5
CN ⁻ + CH ₃ I	0.84 (±0.03)	0.83	---	---	0.80	---
CN ⁻ + C ₂ H ₅ I	0.89 (±0.02)	0.89	8.43	0.99	0.87	8.13
CN ⁻ + <i>i</i> -C ₃ H ₇ I	---	0.93	8.72	0.20	0.94	8.41
CN ⁻ + <i>t</i> -C ₄ H ₉ I	> 8	---	b	0.00	---	7.72
HS ⁻ + CH ₃ I	1.03 (±0.03)	0.94	---	---	0.95	---
HS ⁻ + C ₂ H ₅ I	0.99 (±0.03)	1.02	9.56	0.99	1.05	10.0
HS ⁻ + <i>i</i> -C ₃ H ₇ I	1.05 (±0.05)	1.10	9.66	0.62	1.13	10.0
HS ⁻ + <i>t</i> -C ₄ H ₉ I	1.91 (±0.04)	---	c	0.00	---	9.17

^a 27.4 ^b 24.4 ^c 27.4; these values are not reliable due to contributions from low-frequency modes.

qualitative analysis and R_{TS} comparisons for the methyl, ethyl and *i*-propyl iodide reactions.

Calculating the expected total KIE using the magnitude of the theoretical KIEs and estimated

branching ratio for the Cl⁻ with *i*-propyl iodide reaction ($\text{KIE}_{\text{tot}} = \text{KIE}_{\text{E2}(\Delta\text{G})} \times \text{BR}_{\text{E2}(\Delta\text{G})} +$

$\text{KIE}_{\text{SN2}(\Delta\text{G})} \times \text{BR}_{\text{SN2}(\Delta\text{G})}$), gives a value of $\text{KIE}_{\text{tot}} = 1.31$. When compared to the $\text{KIE}_{\text{exp}} = 1.29$,

this combination of branching ratios and magnitudes of KIEs seems reasonable. In contrast,

meaningful branching ratios for the *t*-butyl iodide reactions cannot be deduced from the

computational KIEs due to their limited reliability. However, based on the large computational

KIEs for all the E2 reactions the low KIE_{exp} values for the reactions of Cl⁻ and HS⁻ with *t*-butyl

iodide pose the intriguing possibility of minor S_N2 contributions to these processes.

The BR_{SN2(ΔG)} values, as calculated from transition state theory and summarized in Table 4.2, support large contributions from the S_N2 channel in the primary and secondary iodides, but no contribution in the tertiary iodide. It is interesting to note the computed branching fractions

relative to the efficiency trends observed in the reaction. Upon switching from ethyl to *i*-propyl iodide, the efficiency of the Cl^- reaction decreases by 90%, while the efficiency of the HS^- reaction only decreases by 30%. The predicted $\text{S}_{\text{N}}2$ and E2 branching provides an interpretation of this effect based on two factors. First, the increase in steric hindrance around the α -carbon significantly inhibits the $\text{S}_{\text{N}}2$ process. Second, the E2 process is competitive for HS^- allowing a contribution to the overall rate from this channel. Our correlation of E2/ $\text{S}_{\text{N}}2$ barrier heights with basicity inferred from our *t*- $\text{C}_4\text{H}_9\text{I}/\text{CH}_3\text{I}$ efficiency ratios supports the E2 channel being more competitive for the more basic HS^- .

4.3.7 Looseness Parameters and Electrostatic Model

Correlations between experimental KIEs and looseness parameters have been primarily restricted to methyl and *t*-butyl halide reactions in the gas phase. Expansion of these concepts to the $\text{S}_{\text{N}}2$ dominated ethyl and *i*-propyl iodide reactions provides new insight into transition-state structures upon substitution. The looseness parameter (R_{TS}), theoretical $\text{S}_{\text{N}}2$ KIEs, and transition state α -carbon atomic charge are compiled in Table 4.3 for the $\text{S}_{\text{N}}2$ reactions. Although specific values are listed in the table, these numbers are not considered an actual measure of the molecular structures or charge. Rather, the parameters are interpreted qualitatively in order to access overall trends.

A key observation in Table 4.3 is a loosening of the transition states upon α -carbon substitution. A comparison of R_{TS} and KIE_{exp} clearly shows an increasingly normal isotope effect corresponding to longer bonds in the transition state upon progression from methyl through *i*-propyl iodide. This change in isotope effect could also be attributed to a reduction in the number of α -hydrogen/deuterium. However, scaling the isotope effect relative to the number of hydrogens does not fully account for the magnitude of the shift. Experimental condensed

Table 4.3 Looseness Parameter (R_{TS})^a, Theoretical S_N2 KIEs, and Transition State α -carbon atomic charge^b

S_N2 Reaction	R_{TS}	$KIE_{SN2(\Delta G)}$	C_α^δ
$Cl^- + CH_3I$	4.93	0.87	-0.2
$Cl^- + C_2H_5I$	5.02	0.97	0.0
$Cl^- + i-C_3H_7I$	5.15	1.05	0.4
$CN^- + CH_3I$	4.71	0.83	-0.3
$CN^- + C_2H_5I$	4.77	0.89	-0.1
$CN^- + i-C_3H_7I$	4.86	0.93	0.3
$HS^- + CH_3I$	4.75	0.94	-0.3
$HS^- + C_2H_5I$	5.07	1.02	-0.1
$HS^- + i-C_3H_7I$	5.17	1.10	0.3

^aUnits of Å ^bNatural charge distribution (units of elemental charge, e) in terms of Natural Population Analysis (NPA) calculations at the MP2/6-311++G(2d,p) level of theory for C, N, and H and the LanL2DZ effective core potential for I on the transition state geometries.

phase data have correlated looser S_N2 transition states for ethyl ($KIE \geq 1$) compared to methyl ($KIE \leq 1$) reactions.⁴² Even more compelling experimental evidence for larger (more normal) isotope effects and looser transition states (longer bonds) is the shift from inverse to normal S_N2 KIEs for ethyl to *i*-propyl dianion reactions in the gas phase.¹⁴ Connecting these effects between the condensed and gas phase further substantiates the recent use of KIEs to assess significantly tighter transition states in the gas phase versus solution.

Application of the electrostatic model⁵⁷ in conjunction with the electronegativity of the nucleophiles and R_{TS} to evaluate relative reactivity is bolstered by the trends in charge density predicted by NPA calculations. The transition states exhibit similar delocalization of charge upon alkyl-group substitution on the α -carbon. However, in the ethyl iodide reaction, the more electronegative Cl^- shifts enough electron density away from the α -carbon to significantly reduce

repulsive forces and stabilize the transition state. Based on a higher charge density on the α -carbon, tighter transition states ($R_{TS} = R_1 + R_2$) for CN^- have higher repulsive forces, which destabilize the transition state.

While this model predicts an even more stable transition state for the *i*-propyl reactions, the reduced efficiency indicates that other factors are destabilizing the transition state. An obvious feature absent in the model when applied across substrates is the effect of steric factors. Alkyl substitution generates steric hindrance which can suppress the S_N2 process, while the release of steric strain in branched substrates can favor the E2 reaction. These forces have the ability to drive changes in relative barrier heights and influence branching ratios. For the reactions studied, the steric and electronic effects do not display the ability to drive large deviations from the original E2/ S_N2 ratios established using the basicity-reactivity baseline. As a result computational branching ratios could be employed with estimated relative barrier heights to correlate reaction efficiencies for the different anions.

One final note of interest, when reviewing the atomic charges present in the transition states there is significantly more charge on the leaving group for the reaction of Cl^- and *i*-propyl iodide reaction, than for the analogous reactions. This is intriguing because the S_N2 process is predicted to dominate the branching ratio for this reaction relative to the other anions. Computational studies⁶⁰ have shown enhanced reactivity (lower S_N2 barrier heights) for nucleophiles with looser and more ionic transition states (i.e., $X^{\delta-}$, $Y^{\delta-}$, and $C_{\alpha}^{\delta+}$), such as those present in the Cl^- and *i*-propyl iodide reaction.

4.4 Conclusion

Our investigation of the apparent dominance of the S_N2 mechanism for some alkyl iodide reactions has provided a more detailed picture of kinetics, mechanisms, and product distributions

in the gas phase. Analysis of reactivity trends and the electronic and structural properties for the series of alkyl iodide reactions with Cl^- , HS^- , and CN^- have led to the following findings.

- (1) The relative E2/ $\text{S}_{\text{N}}2$ barrier heights for the ethyl and *i*-propyl iodide reactions appear to significantly favor the $\text{S}_{\text{N}}2$ pathway. Relative efficiencies indicate that the E2 pathway is more sensitive to basicity. At higher anion basicities the E2 pathway becomes more competitive with the $\text{S}_{\text{N}}2$ process.
- (2) A multipole electrostatic model⁵⁷ explains the relative reactivity for reactions with similar branching and steric factors. When employed in conjunction with the electronegativity of the nucleophile (to account for electron density on C_{α}) and the looseness of the transition state (assessed through KIEs or R_{TS}), all trends in the ethyl iodide reactions can be explained.
- (3) Larger (more normal) isotope effects and looser $\text{S}_{\text{N}}2$ transition states (longer bonds) are produced upon alkyl group substitution. These effects correlate with condensed phase studies.

The alkyl iodide reaction series has proven to be an ideal system for expansion of common techniques for evaluating exclusively $\text{S}_{\text{N}}2$ reactions and correlating the results of dianion studies. The halide ion-alkyl iodide reactions provide a simple monatomic basicity-reactivity baseline from which reactivity changes for various nucleophiles can be assessed. In addition, the reaction rate constants fall within the center of our experimental detection range. Future gas-phase studies on alkyl iodide reactions are certain to provide further insight into reactivity trends.

4.5 References

1. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanism*. 5th ed.; Springer: New York, **2007**.
2. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*. Harper and Row: New York, **1987**.
3. Bachrach, S. M.; Mulhearn, D. C. *J. Phys. Chem.* **1996**, *100*, 3535-3540.
4. Dmitrenko, O.; Thorpe, C.; Bach, R. D. *J. Org. Chem.* **2007**, *72*, 8298-8307.
5. Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 9663-9665.
6. Wladkowski, B. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 10643-10644.
7. Villano, S. M.; Eyet, N.; Lineberger, W. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2009**, *131* (23), 8227-8233.
8. Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 736-737.
9. DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650-8655.
10. Gronert, S. *Acc. Chem. Res.* **2003**, *36*, 848-857.
11. Haib, J.; Stahl, D. *Org. Mass Spectrom.* **1992**, *27*, 377-382.
12. Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 8568-8570.
13. Jones, M. E.; Ellison, G. B. *J. Am. Chem. Soc.* **1989**, *111*, 1645-1654.
14. Gronert, S.; Fagin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, *129*, 5330-5331.
15. Mugnai, M.; Cardini, G.; Schettino, V. *J. Phys. Chem. A* **2003**, *107*, 2540-2547.
16. Ermolaeva, L. V.; Appolonova, S. A.; Plemenkov, V. V.; Konovalov, A. I. *Theochem. J. Mol. Struct.* **1997**, *398*, 451-455.
17. Gronert, S.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1991**, *113*, 4009-4010.
18. Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 860-869.
19. Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114-128.
20. Wu, X. P.; Sun, X. M.; Wei, X. G.; Ren, Y.; Wong, N. B.; Li, W. K. *J. Chem. Theory Comput.* **2009**, *5*, 1597-1606.
21. Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 4488-4497.
22. Mackay, G. I.; Bohme, D. K. *J. Am. Chem. Soc.* **1978**, *100*, 327-329.
23. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.
24. O'Hair, R. A. J.; Davico, G. E.; Hacaloglu, J.; Dang, T. T.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1994**, *116*, 3609-3610.
25. Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 11073-11083.
26. Garver, J. M.; Fang, Y.; Eyet, N.; Villano, S. M.; Bierbaum, V. M.; Westaway, K. C. *J. Am. Chem. Soc.* **2010**, *132*, 3808-3814.
27. Uggerud, E. *Pure Appl. Chem.* **2009**, *81*, 709-717.
28. Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 12977-12983.
29. Gronert, S. *Chem. Rev.* **2001**, *101*, 329-360.
30. Flores, A. E.; Gronert, S. *J. Am. Chem. Soc.* **1999**, *121*, 2627-2628.
31. Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 2672-2680.
32. Laerdahl, J. K.; Uggerud, E. *Int. J. Mass Spectrom.* **2002**, *214*, 277-314.
33. Glad, S. S.; Jensen, F. *J. Org. Chem.* **1997**, *62*, 253-260.
34. Nielsen, P. A.; Glad, S. S.; Jensen, F. *J. Am. Chem. Soc.* **1996**, *118*, 10577-10583.
35. Davico, G. E.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2000**, *122*, 1740-1748.

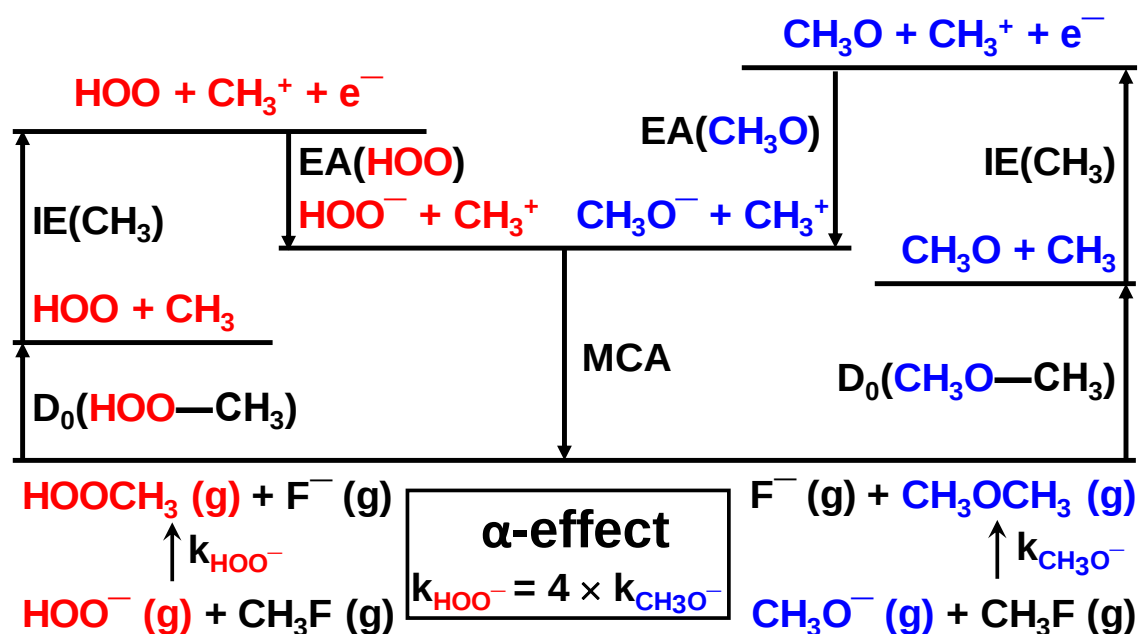
36. Glad, S. S.; Jensen, F. *J. Am. Chem. Soc.* **1994**, *116*, 9302-9310.
37. Viggiano, A. A.; Paschkewitz, J. S.; Morris, R. A.; Paulson, J. F.; Gonzalezlafont, A.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 9404-9405.
38. Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1995**, *117*, 10726-10734.
39. Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1994**, *116*, 7797-7800.
40. Glad, S. S.; Jensen, F. *J. Am. Chem. Soc.* **1997**, *119*, 227-232.
41. Wolfe, S.; Kim, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 8056-8061.
42. Poirier, R. A.; Wang, Y. L.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526-2533.
43. Westaway, K. C. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 989-1005.
44. Gronert, S.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1991**, *113*, 4009-4010.
45. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Proc.* **1987**, *81*, 85-100.
46. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision B.05*, Gaussian, Inc.: Pittsburgh, PA, 2004.
47. Zhang, Q. Z.; Wang, H. N.; Sun, T. L.; Wang, W. X. *J. Chem. Phys.* **2006**, *324*, 298-306.
48. Hadad, C. M.; Rablen, P. R.; Wiberg, K. B. *J. Org. Chem.* **1998**, *63*, 8668-8681.
49. Moller, C.; Plesset, M. S., *Phys. Rev.* **1934**, *46*, 618-622.
50. Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283.
51. Merrick, J. P.; Moran, D.; Radom, L., *J. Phys. Chem. A* **2007**, *111*, 11683-11700.
52. Bierbaum, V. M.; Grabowski, J. J.; DePuy, C. H., *J. Phys. Chem.* **1984**, *88*, 1389-1393.
53. Su, T.; Chesnavich, W. J., *J. Chem. Phys.* **1982**, *76*, 5183-5185.
54. Sauers, R. R. *J. Chem. Theory Comput.* **2010**, *6*, 602-606.
55. Shaik, S. S., *Acta Chem. Scand.* **1990**, *44*, 205-221.
56. Ren, Y.; Yamataka, H., *J. Comput. Chem.* **2009**, *30*, 358-365.
57. Gronert, S.; Pratt, L. M.; Mogali, S., *J. Am. Chem. Soc.* **2001**, *123*, 3081-3091.
58. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 4th ed.; John Wiley & Sons, Inc: New York, 1992.
59. Luo, Y. R.; Benson, S. W. *Acc. Chem. Res.* **1992**, *25*, 375-381.
60. Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660-5667.
61. P.J. Linstrom and W.G. Mallard, Eds., **NIST Chemistry WebBook, National Institute of Standards and Technology, NIST Standard Reference Database Number 69**, Gaithersburg MD, 20899, <http://webbook.nist.gov>; (retrieved October 23, 2009.)

CHAPTER 5

Experimental Validation of the α -Effect in the Gas Phase

Adapted from

Garver, J. M.; Gronert, S.; Bierbaum, V. M. *submitted for publication as a communication (J. Am. Chem. Soc.)*



Abstract

The α -effect, an enhanced nucleophilicity of an anion with lone pair electrons adjacent to the attacking atom, has been well documented in solution; however, there is continuing disagreement whether this effect is a purely solvent induced phenomenon or an intrinsic property of the α -nucleophiles. To resolve these discrepancies, we explore the α -effect in the bimolecular nucleophilic substitution ($\text{S}_{\text{N}}2$) reaction in the gas phase. Our results show enhanced nucleophilicity for HOO^- relative to “normal” alkoxides in three separate reaction series (methyl fluoride, anisole, and 4-fluoroanisole) validating an intrinsic origin of the α -effect. Caution must be employed when making comparisons of the α -effect between the condensed and gas phase due to significant shifts in anion basicity between these media. Variations in electron affinities and homolytic bond strengths between the normal and α -anions indicate that HOO^- has distinctive thermochemical properties.

5.1 Introduction

Gas-phase kinetic studies^{1,2} have provided an indispensable means to probe the energetics and intrinsic reactivity of prototypical organic reactions, free of solvent and counterion effects. Experimental and computational work³⁻¹⁰ has provided a wealth of knowledge on the dynamic, energetic, and steric factors inherent to bimolecular nucleophilic substitution (S_N2) reactions. Reaction rates are strongly influenced by non-covalent interactions, particularly the ion-stabilizing effect of solvents. These “solvent effects” can not only mask intrinsic differences, but can become the controlling factor that governs nucleophilicity. One of the most complex areas of interest with regard to these factors is the enhanced reactivity of α -nucleophiles. The term α -effect¹¹ has been used to describe the increased reactivity relative to a given basicity for nucleophiles with a lone pair of electrons adjacent to the attacking atom. Magnitudes of the α -effect ($k_\alpha/k_{\text{normal}}$) in the range of 5–1000 have been reported in solution for numerous reactions, and mysteriously absent in others.¹² Variations in the magnitude of the α -effect can be attributed to solvent effects generating differential transition state stabilization and ground state destabilization. Depending on the nucleophile-substrate system studied, either the transition state stabilization¹³ or ground state destabilization¹⁴ can dominate as the controlling factor in the overall effect. Differential solvation energies between normal and α -nucleophiles of 16 kJ mol⁻¹ and 24 kJ mol⁻¹ can lead to ground state α -effect rate enhancements by factors of 750 and 15000.^{12, 14} Due to this complexity, gas phase studies provide a vital link to resolving the intrinsic nature of the α -effect and providing insight into solvent effects.

Our research group has conducted several studies in an attempt to reveal the intrinsic nature and origin of the α -effect. Our initial work showed similar reactivity with methyl formate¹⁵ for the reagent pairing of HOO^- and HO^- (a standard reference employed in solution).

Patterson and Fountain¹⁶ suggest that the minor differences in these experimental data actually support an α -effect and rationalize enhanced reactivity in HOO^- due to a high degree of single-electron-transfer¹⁷ character. They argue that assessment of the α -effect in the gas phase requires strict adherence to the matched acidities in reagent pairing between the normal and α -nucleophiles. More recently, calculations by Ren and Yamataka^{18, 19} advocate for the existence of a large α -effect [i.e., $\Delta\Delta H^\ddagger(\text{HOO}^- \text{ vs } \text{X}^-) = 17.1 \text{ kJ mol}^{-1} \approx 960 \text{ times rate enhancement}$] in the gas phase reactions of α -nucleophiles with methyl chloride. However, we found no significant deviations in the Brønsted correlation for a series of $\text{S}_{\text{N}}2$ reactions of normal and α -nucleophiles with methyl chloride.²⁰ This result may reflect difficulties in experimentally examining the computed systems or an overestimation of the magnitude of the α -effect based on the series and range of anionic reactions used to define “normal” barrier heights. Interestingly, McAnoy et al.²¹ reported major differences in the branching ratios in the reactions of HOO^- and CD_3O^- with dimethyl methylphosphonate. Since HOO^- and CD_3O^- have similar proton affinities, this difference in branching ratios was attributed to greater nucleophilicity of HOO^- ; however, the absolute rate constants were not measured. It is not clear if the branching reflects differences in barriers or simply reaction dynamics. In an effort to resolve the conflicting results, we investigate the kinetics of $\text{S}_{\text{N}}2$ reactions of low exothermicity where a smaller thermodynamic component of the activation barrier may expose α -nucleophilicity. Our results clearly show enhanced reactivity for an α -nucleophile (HOO^-) relative to a series of normal nucleophiles (HO^- , CH_3O^- , $\text{C}_2\text{H}_5\text{O}^-$, and $i\text{-C}_3\text{H}_7\text{O}^-$) in the reactions of methyl fluoride, anisole, and 4-fluoroanisole. Our most definitive evidence is exhibited in the methyl fluoride reactions where only the $\text{S}_{\text{N}}2$ pathways are present, thus simplifying (versus competitive reaction systems) the identification of the α -effect.

5.2 Experimental

The overall reaction rate constants (300 ± 2 K) and branching fractions were measured using a tandem flowing afterglow-selected ion flow tube instrument, FA-SIFT.^{22, 23} Briefly, this instrument consists of an ion source, an ion selection region, a reaction flow tube, and a detection system (quadrupole mass filter coupled to an electron multiplier). Reaction rate constants are measured by monitoring ion signal as a function of reaction distance. Product branching ratios are determined by extrapolating the observed product yields to zero reaction distance in order to extract the initial ratios due to primary reactions. The reported reaction efficiencies are the experimental rate constant divided by the calculated collision rate constants; these values represent the fraction of collisions that result in reaction. Collision rate constants were calculated from parameterized trajectory collision rate theory.^{24, 25} Error bars represent one standard deviation of the mean in the averages of at least three individual measurements; absolute uncertainties in these rate constant measurements are $\pm 20\%$.

5.3 Results and Discussion

5.3.1 Kinetic Data

The proton affinity (PA)^{26, 27} of the anions, exothermicity of the S_N2 reaction (ΔH_{rxn}), overall experimental rate constant (k_{expt}), branching fractions, S_N2 reaction efficiency (Eff), and magnitude of the α -effect as a function of relative reaction efficiencies for the gas phase reactions of HOO^- relative to the normal oxyanions (HO^- , CH_3O^- , $C_2H_5O^-$, and $i-C_3H_7O^-$) with methyl fluoride (CH_3F), anisole ($CH_3OC_6H_5$) and 4-fluoroanisole ($CH_3OC_6H_4F$) are listed in Table 5.1. No observable reaction or association products occurred for the reaction of $C_2H_5O^-$ with methyl fluoride. Therefore, we place an upper limit for the rate constant and efficiency for this reaction. While the S_N2 mechanism is observed in most of the reactions, access to the proton

Table 5.1 Thermodynamic Parameters, Kinetic Data, and Branching Fractions to Evaluate the α -Effect for HOO^- Relative to Normal Oxyanions (HO^- , CH_3O^- , $\text{C}_2\text{H}_5\text{O}^-$, and $i\text{-C}_3\text{H}_7\text{O}^-$) in a Series of Bimolecular Nucleophilic Substitution ($\text{S}_{\text{N}}2$) Reactions

Reaction ($\text{X}^- + \text{M}$)	Thermodynamic Data ^a		Kinetic Data ^b $k_{\text{expt}} (\times 10^{-10})$	Branching Fraction (Eff) ^c			α -effect $\frac{\text{Eff}_{\text{HOO}^-}}{\text{Eff}_{\text{X}^-}}$
	PA (X^-)	ΔH_{rxn}		$\text{S}_{\text{N}}2$	PT	Association	
$\text{HO}^- + \text{CH}_3\text{F}$	1633	-91	0.120 ± 0.021	100% (0.0042)	---	---	0.62
$\text{CH}_3\text{O}^- + \text{CH}_3\text{F}$	1598 ± 2	-70	0.017 ± 0.001	100% (0.0007)	---	---	3.7
$\text{C}_2\text{H}_5\text{O}^- + \text{CH}_3\text{F}$	1585 ± 3	-60	< 0.001	< 0.00005	---	---	> 50
$\text{HOO}^- + \text{CH}_3\text{F}$	1575 ± 4	-65	0.060 ± 0.002	100% (0.0026)	---	---	
$\text{HO}^- + \text{CH}_3\text{OC}_6\text{H}_5$	1633	-162	13.1 ± 0.2	28% (0.13)	51%	20%	0.69
$\text{CH}_3\text{O}^- + \text{CH}_3\text{OC}_6\text{H}_5$	1598 ± 2	-141	2.74 ± 0.01	32% (0.04)	---	68%	2.3
$\text{C}_2\text{H}_5\text{O}^- + \text{CH}_3\text{OC}_6\text{H}_5$	1585 ± 3	-131	1.38 ± 0.10	10% (0.01)	---	90%	9.0
$\text{HOO}^- + \text{CH}_3\text{OC}_6\text{H}_5$	1575 ± 4	-135	3.49 ± 0.05	54% (0.09)	---	46%	
$i\text{-C}_3\text{H}_7\text{O}^- + \text{CH}_3\text{OC}_6\text{H}_5$	1576 ± 3	-121	---	---	---	100%	
$\text{HO}^- + \text{CH}_3\text{OC}_6\text{H}_4\text{F}$	1633	-174	23.0 ± 0.6	---	100%	---	
$\text{CH}_3\text{O}^- + \text{CH}_3\text{OC}_6\text{H}_4\text{F}$	1598 ± 2	-153	10.7 ± 0.4	32% (0.10)	10%	58%	2.3
$\text{C}_2\text{H}_5\text{O}^- + \text{CH}_3\text{OC}_6\text{H}_4\text{F}$	1585 ± 3	-143	6.88 ± 0.21	9% (0.02)	---	91%	12
$\text{HOO}^- + \text{CH}_3\text{OC}_6\text{H}_4\text{F}$	1575 ± 4	-147	10.4 ± 0.5	70% (0.23)	---	30%	
$i\text{-C}_3\text{H}_7\text{O}^- + \text{CH}_3\text{OC}_6\text{H}_4\text{F}$	1576 ± 3	-133	---	---	---	100%	

^aUnits of kJ mol^{-1} ; Proton Affinity (PA) from refs 26 and 27; Exothermicity of the $\text{S}_{\text{N}}2$ reaction (ΔH_{rxn}) calculated using heats of formation from ref 27 where ΔH_{rxn} for 4-fluoroanisole reactions estimated from anisole reactions based on proton affinity difference (12 kJ mol^{-1}). ^bOverall experimental rate constant (k_{expt}) in units of $\text{cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$; error bars represent one standard deviation of the mean of three or more measurements; absolute accuracy is $\pm 20\%$. ^c $\text{S}_{\text{N}}2$, proton transfer (PT), and association product branching fractions are determined by extrapolating the observed product yields to zero reaction distance in order to extract the initial ratios due to primary reactions; Efficiency (Eff) is the ratio of the branching rate constants ($k_{\text{S}_{\text{N}}2} = k_{\text{expt}} \times \text{branching fraction}$) to the collision rate constant (k_{col}) calculated using parameterized trajectory collision theory (ref 24) and dipole moments and polarizability from ref 25.

transfer (PT) channel is limited due to the relatively high proton affinities of anisole ($1637 \pm 2 \text{ kJ mol}^{-1}$)²⁸ and 4-fluoroanisole ($1614 \pm 3 \text{ kJ mol}^{-1}$)²⁹. Association products ($X^{\cdot-} \cdot M$) were observed in the larger reaction systems corresponding to the longer lifetimes of the reactant ion-dipole complex allowing for collisional stabilization by the He buffer gas. The reaction of $i\text{-C}_3\text{H}_7\text{O}^-$ with anisole and 4-fluoroanisole formed only association products and therefore did not provide insight into the S_N2 reactivity.

5.3.2 Evaluating the α -effect

The exothermicity of an S_N2 reaction is equal to the difference in the methyl cation affinity of the nucleophile and nucleofuge. Since both nucleophilicity and basicity involve the donation of electrons to an electrophile, it is not surprising that a strong linear correlation also exists between proton affinity ($X^- + H^+ \rightarrow HX$) and methyl cation affinity ($X^- + CH_3^+ \rightarrow CH_3X$).³⁰ Deviations from linearity in reactivity-basicity correlations can reflect the influence of additional variables or the manifestation of unique energetics in the transition state. The enhanced reactivity of an α -nucleophile is typically evaluated relative to normal anions of similar basicity through a Brønsted-type correlation or anionic reagent pairing ($k_\alpha/k_{\text{normal}}$). Trends in reaction efficiencies show enhanced nucleophilicity for HOO^- compared to the normal alkoxides (CH_3O^- and $\text{C}_2\text{H}_5\text{O}^-$) relative to their proton affinity. The relative α -effect, ($\text{Eff}_{\text{HOO}^-}/\text{Eff}_{X^-}$), more clearly reflects these trends and provides a method to assess the magnitude of the α -effect (Fig 5.1). As predicted by the Marcus relationship, the largest shifts in relative reactivity occur in the CH_3F system where intrinsic differences would be least masked by thermodynamic driving forces. The HOO^- reaction is 50 times more efficient than that of $\text{C}_2\text{H}_5\text{O}^-$ even though the proton affinity of ethoxide is 10 kJ mol^{-1} higher than that of the peroxide. This result most clearly reveals the α -effect in the gas phase. More modest enhancements are observed relative to

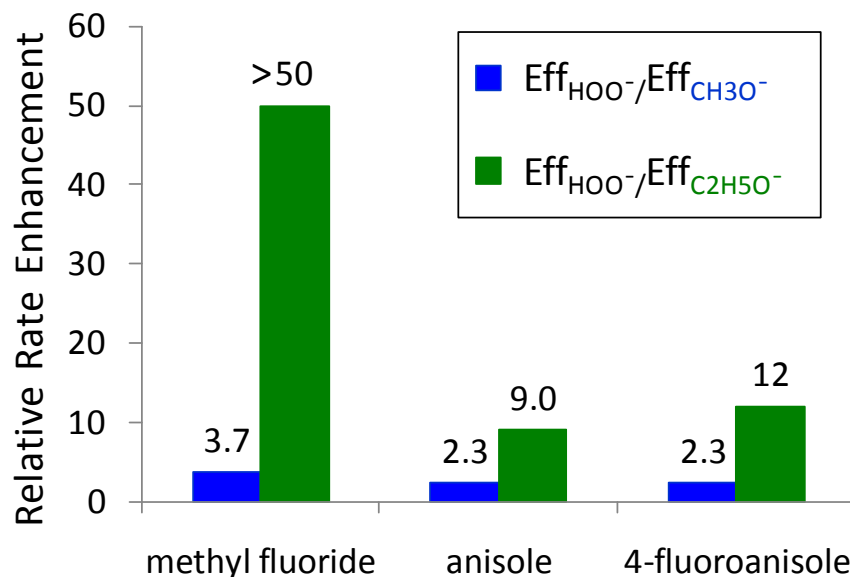


Figure 5.1 Magnitude of the α -effect for HOO^- (PA = 1575 kJ mol⁻¹) relative to CH_3O^- (PA = 1598 kJ mol⁻¹) and $\text{C}_2\text{H}_5\text{O}^-$ (PA = 1585 kJ mol⁻¹).

$\text{C}_2\text{H}_5\text{O}^-$ with anisole (9 times) and 4-fluoroanisole (12 times) and small comparative differences exist for all the CH_3O^- reactions (2.3-3.7 times). The ratio of rate constants of HOO^- to HO^- ($k_{\text{HOO}^-}/k_{\text{HO}^-}$) is a standard reference employed in solution to assess the magnitude of the α -effect. While HOO^- displays enhanced reactivity in the gas phase relative to alkoxides, the peroxide rate does not exceed that of HO^- . This is likely related to the much greater relative basicity of HO^- in the gas phase (see below).

5.3.3 Common Scale for Acidity/Basicity (Condensed and Gas Phase)

In the gas phase, acidity is defined as the free-energy change associated with the deprotonation ($\text{HX} \rightarrow \text{X}^- + \text{H}^+$) of a given chemical species. In contrast for solution, acidity is evaluated using the equilibrium constants of proton transfer. We can devise a common scale for acidity by translating aqueous pK_a values [$\text{pK}_{\text{HOH}} = 15.74$, $\text{pK}_{\text{CH}_3\text{OH}} = 15.54$, $\text{pK}_{\text{C}_2\text{H}_5\text{OH}} = 15.9$ (extrapolated), and $\text{pK}_{\text{HOOH}} = 11.64$]^{31, 32} to free energies of deprotonation at 298 K using the Gibbs free-energy relationship with equilibrium constants [$\Delta G_{\text{base}}(\text{HO}^-) = 89.84$, $\Delta G_{\text{base}}(\text{CH}_3\text{O}^-)$

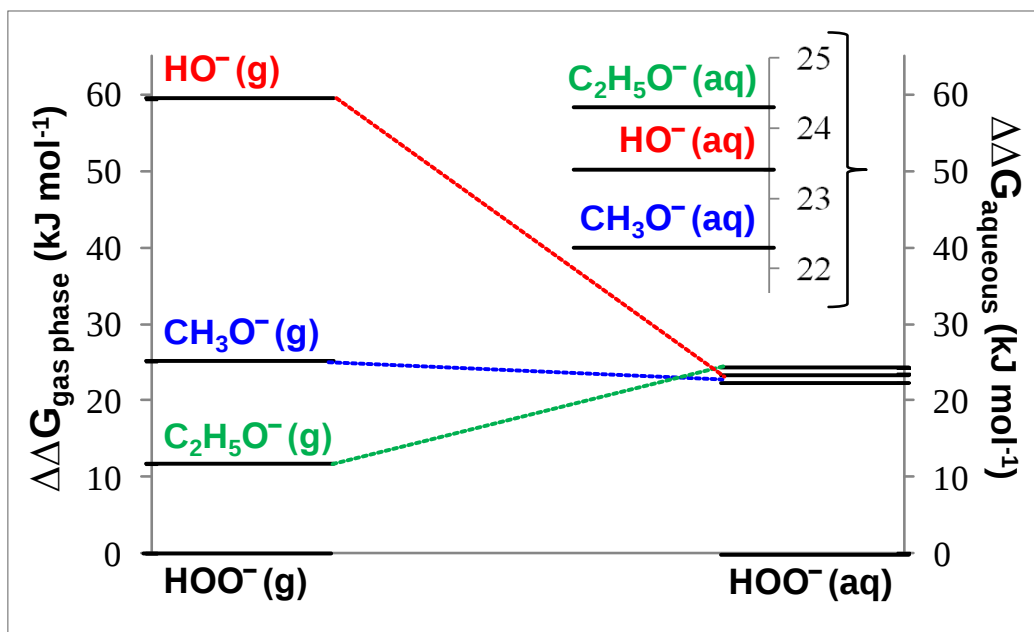


Figure 5.2 Suppression of the differences in relative free energies of deprotonation in aqueous solution [$\Delta\Delta G = \Delta G_{\text{base}}(\text{X}^-) - \Delta G_{\text{base}}(\text{HOO}^-)$ for both the gas phase and aqueous solution in kJ mol^{-1}].

$= 88.70$, $\Delta G_{\text{base}}(\text{C}_2\text{H}_5\text{O}^-) = 90.8$, and $\Delta G_{\text{base}}(\text{HOO}^-) = 66.44 \text{ kJ mol}^{-1}$]. Figure 5.2 depicts the relative free energy of deprotonation with respect to HOO^- for both the gas phase and aqueous solution. While there is little difference in free energies of deprotonation for the normal nucleophiles in solution relative to HOO^- [$\Delta\Delta G(\text{HO}^-) = 23.4$, $\Delta\Delta G(\text{CH}_3\text{O}^-) = 22.3$, and $\Delta\Delta G(\text{C}_2\text{H}_5\text{O}^-) = 24.3 \text{ kJ mol}^{-1}$], significant differences exist in the gas phase [$\Delta\Delta G(\text{HO}^-) = 59.4$, $\Delta\Delta G(\text{CH}_3\text{O}^-) = 25.1$, and $\Delta\Delta G(\text{C}_2\text{H}_5\text{O}^-) = 11.7 \text{ kJ mol}^{-1}$].^{26, 27} Methoxide is the nucleophile that maintains the most similar relative basicity to HOO^- in both media. On the other hand, HO^- is much more basic in the gas phase relative to HOO^- . Therefore, HO^- would act as a “super” nucleophile in the gas phase relative to solution and it is unlikely that an α -effect could overcome this difference in relative basicity in order for HOO^- to be more reactive in our studies.

5.3.4 Variations in Electron Affinities and Homolytic Bond Strengths

In Table 5.1, we note a large shift between the relative gas phase proton affinity (PA) and the exothermicity of reactions (ΔH_{rxn}) for HOO^- when compared to trends in the normal anions (14-15 kJ mol^{-1} versus $\text{C}_2\text{H}_5\text{O}^-$). While the α -nucleophile displays enhanced reactivity relative to proton affinity, part of this effect must be attributed to the larger exothermicity of reaction. Furthermore, this inversion would suggest there is a larger disparity between proton affinity and methyl cation affinity for the peroxide, than for the normal alkoxides. The methyl cation affinities of CH_3O^- (1140 kJ mol^{-1}) and HOO^- (1135 kJ mol^{-1}) are the same within experimental error (from heats of formation).¹⁵ If we use the gas phase thermochemical ion cycle (Table 5.2)

Table 5.2 Gas Phase Thermochemical Ion Cycle^a to Determine the Homolytic Bond Strength of CH_3OH and HOOH

	$\text{X}^- =$	CH_3O^-	HOO^-	
$\text{CH}_3\text{X} \rightarrow \text{CH}_3^+ + \text{X}^-$	-MCA	1140	1135	(1)
$\text{X}^- \rightarrow \text{X} + \text{e}^-$	EA (X)	151	104	(2)
$\text{CH}_3^+ + \text{e}^- \rightarrow \text{CH}_3$	-IE (CH_3)	-949	-949	(3)
$\text{CH}_3\text{X} \rightarrow \text{X} + \text{CH}_3$	$\text{D}_0 (\text{CH}_3\text{-X})$	342	290	(4)

^a methyl cation affinity [Eq (1)], electron affinity [Eq (2)], ionization energy [Eq (3)], and homolytic bond strength [Eq (4)] in kJ mol^{-1} ; refs 25, 26 and 27

to evaluate other factors associated with methyl cation affinity, we see the huge divergence in electron affinities reflected in the homolytic bond strengths. CH_3O^- has a higher electron binding energy ($\Delta\text{EA} = 47 \text{ kJ mol}^{-1}$)²⁵ that is balanced by the homolytic bond strength for CH_3OH which is about 52 kJ mol^{-1} higher than for the peroxy system. Shifts this large are the equivalent of HOO^- being in a completely different family of nucleophiles.

5.4 Conclusion

In summary, we report enhanced nucleophilicity for HOO^- relative to normal alkoxides in three reaction systems validating an intrinsic origin of the α -effect. Similarities in the relative basicities (in both the condensed and gas phase) and methyl cation affinities suggest the reagent pairing of CH_3O^- and HOO^- should be employed in the evaluation of the α -effect, as well as in drawing correlations with solution. Large shifts between the relative gas phase proton affinity and the exothermicity of reaction for HOO^- when compared to trends in the normal anions indicate differences between the natures of the nucleophiles. Variations in electron affinities and homolytic bond strengths between the methoxy and peroxy systems imply that significant variations would exist between electrostatic and orbital interactions within the transition states of normal and α -nucleophiles.

5.5 References

1. Gronert, S. *Chem. Rev.* **2001**, *101*, 329-360.
2. Bohme, D. K. *Can. J. Chem.* **2008**, *86*, 177-198.
3. Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 860-869.
4. Laerdahl, J. K.; Uggerud, E. *Int. J. Mass Spectrom.* **2002**, *214*, 277-314.
5. Shaik, S. S.; Schlegel, H. B.; Wolfe, S. *Theoretical Aspects of Physical Organic Chemistry: The S_N2 Reaction*. Wiley: New York, **1992**.
6. Viggiano, A. A.; Midey, A. J. *J. Phys. Chem. A* **2000**, *104*, 6786-6790.
7. Hase, W. L. *Science* **1994**, *266*, 998-1002.
8. Graul, S. T.; Bowers, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 3875-3883.
9. Hoz, S.; Basch, H.; Wolk, J. L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* **1999**, *121*, 7724-7725.
10. Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 12977-12983.
11. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16-24.
12. Buncel, E.; Um I. H. *Tetrahedron* **2004**, *60*, 7801-7825.
13. Um, I. H.; Shin, Y. H.; Han, J. Y.; Buncel, E. *Can. J. Chem.* **2006**, *84*, 1550-1556.
14. Kim, M. S.; Min, S. W.; Seo, J. A.; Um, I. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2913-2917.
15. DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481-2482.
16. Patterson, E. V.; Fountain, K. R. *J. Org. Chem.* **2006**, *71*, 8121-8125.
17. Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545-3547.
18. Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660-5667.
19. Ren, Y.; Yamataka, H. *Chem. Eur. J.* **2007**, *13*, 677-682.
20. Villano, S. M.; Eyet, N.; Lineberger, W. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 8227-8233.
21. McAnoy, A. M.; Paine, M. R. L.; Blanksby, S. *J. Org. Biomol. Chem.* **2008**, *6*, 2316-2326.
22. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **1987**, *81*, 85-100.
23. Bierbaum, V. M. In *Encyclopedia of Mass Spectrometry*; Editor, Gross, M. L., Caprioli, R., Eds.; Elsevier: Amsterdam, **2003**; Vol. 1, p 98.
24. Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183-5185.
25. *CRC Handbook of Chemistry and Physics*, 89th ed.; Editor, Lide, D. R., Ed.; CRC Press: Boca Raton, Fl., **2008**.
26. Ervin, K. M.; DeTuro, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947-9956.
27. Bartmess, J. E. "Negative Ion Energetics Data" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. Linstrom, P.J and Mallard, W.G., National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>, (retrieved 1 May, 2011).
28. This Work: $\text{HO}^- + \text{C}_6\text{H}_5\text{OCH}_3 \rightarrow \text{C}_6\text{H}_4\text{OCH}_3^- + \text{H}_2\text{O}$, $k_f = 6.7 \pm 0.2 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ and $\text{C}_6\text{H}_4\text{OCH}_3^- + \text{H}_2\text{O} \rightarrow \text{HO}^- + \text{C}_6\text{H}_5\text{OCH}_3$, $k_r = 5.00 \pm 0.03 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$; $\Delta_{\text{acid}}G_{298} = 1606 \pm 2 \text{ kJ mol}^{-1}$ and $\Delta_{\text{acid}}H_{298} = 1637 \pm 2 \text{ kJ mol}^{-1}$, where $T\Delta_{\text{acid}}S_{298} = 31 \text{ kJ mol}^{-1}$.

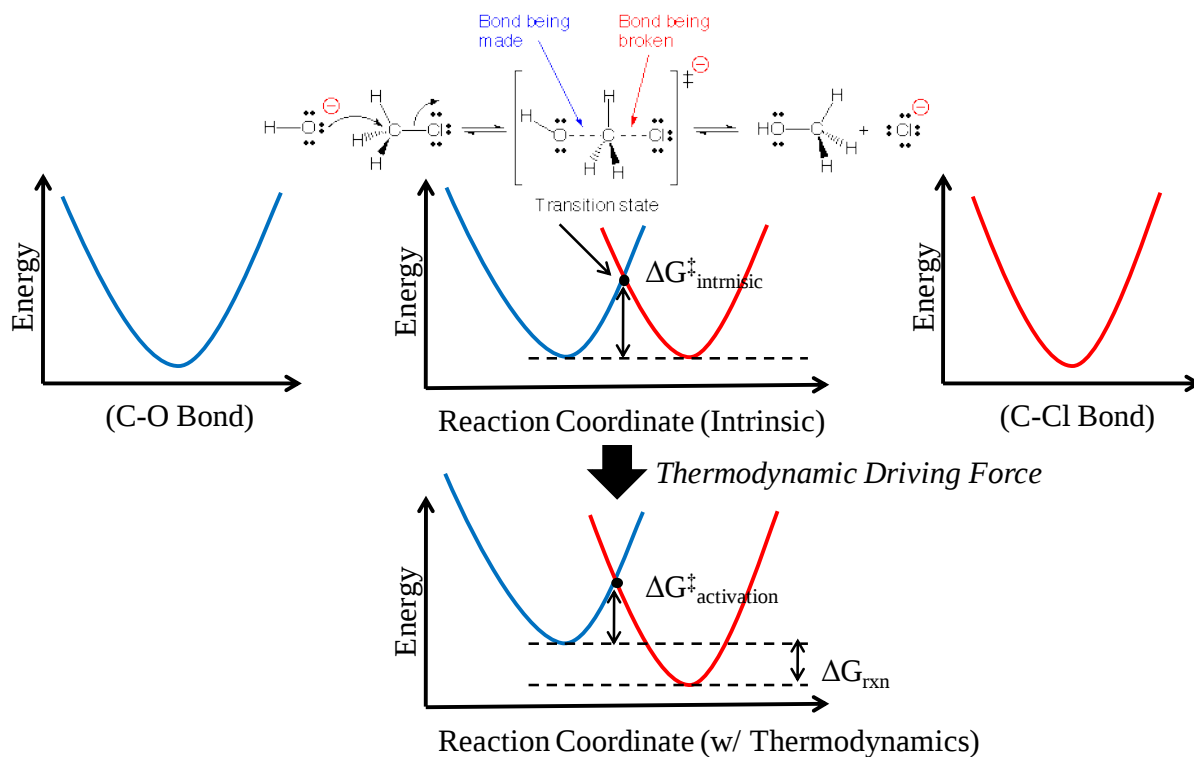
29. This Work: $\text{HO}^- + \text{FC}_6\text{H}_4\text{OCH}_3 \rightarrow \text{FC}_6\text{H}_3\text{OCH}_3^- + \text{H}_2\text{O}$, $k_f = 1.1 \pm 0.4 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$
and $\text{FC}_6\text{H}_3\text{OCH}_3^- + \text{H}_2\text{O} \rightarrow \text{HO}^- + \text{FC}_6\text{H}_4\text{OCH}_3$, $k_r = 7.85 \pm 0.12 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$;
 $\Delta_{\text{acid}}G_{298} = 1582 \pm 3 \text{ kJ mol}^{-1}$ and $\Delta_{\text{acid}}H_{298} = 1614 \pm 3 \text{ kJ mol}^{-1}$, where $T\Delta_{\text{acid}}S_{298} = 32 \text{ kJ mol}^{-1}$.
30. Uggerud, E. *Pure Appl. Chem.* **2009**, *81*, 709-717.
31. Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795-798.
32. Serjeant, E. P.; Dempsey, B. *Ionisation constants of organic acids in aqueous solution (IUPAC Chemical Data Series)*; Pergamon Press: Oxford; New York, **1979**.

CHAPTER 6

Resolving the α -effect in Gas Phase S_N2 Reactions: A Marcus Theory Approach

Adapted from

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Overview

Recently, we reported experimental validation of the α -effect in the gas phase. However, an earlier study by our group showed a lack of enhanced reactivity in a series of S_N2 reactions of α -nucleophiles with methyl chloride conflicting with computational predictions. [Ren, Y.; Yamataka, H. *Chem. Eur. J.* **2007**, 13, 677-682.] In an attempt to resolve these discrepancies, we investigate S_N2 reactions of low exothermicity where the smaller thermodynamic component of the activation barrier may expose α -nucleophilicity. The reaction efficiencies for the reactions of several normal nucleophiles [C₆H₅O⁻, HC(O)O⁻, CH₃C(O)O⁻] and alpha-nucleophiles [HC(O)OO⁻, CH₃C(O)OO⁻] with CH₃Cl are added to our previous Brønsted plot of normal and α -nucleophile reactions with methyl chloride. Further analysis of the methyl chloride data indicate that variations in intrinsic character are masked at higher exothermicities. Marcus theory indicates that converging thermodynamic driving forces allow a narrow window for resolving intrinsic differences in the gas phase. The presence of the α -effect is suggested in the

reactions of some α -nucleophiles with methyl chloride at lower basicities, however the normal alkoxides with similar proton affinities in these regions are limited and have non-homologous properties. Variations in the intrinsic Marcus barriers of the normal anion(s) defining “normal” reactivity will play a key role in the magnitude of the α -effect. Significantly lower electron affinities are associated with the formation of the α -oxyanions compared to the normal oxyanions ($X + e^- \rightarrow X^-$) suggesting that the ease of charge transfer between the nucleophile and transition state is responsible for the lower barriers of the α -nucleophiles.

6.1 Introduction

Gas phase kinetic studies have provided an indispensable means to probe the energetics and intrinsic reactivity of prototypical organic reactions. Recently, there has been renewed interest in these fundamental processes driven by the need to characterize solvent effects in new “green” solvents. Significant rate enhancements and control of mechanistic selectivity have been observed for nucleophiles in ionic liquids.¹⁻³ Related to this work is the attempt to resolve the origin of the enhanced reactivity of α -nucleophiles. These supernucleophiles have gained international interest for their potential use in chemical decontamination and environmental cleanup. The α -effect is well documented in solution; however, differential solvation energies between normal and α -nucleophiles can dominate as the controlling factor in the overall effect. Due to this complexity, gas phase studies provide a vital link to resolving the intrinsic nature of the α -effect and providing insight into solvent effects.

The term α -effect was coined by Pearson and Edwards in 1962 to describe a category of nucleophiles with a lone pair of electrons adjacent to the attacking atom that display enhanced reactivity.⁴ This enhanced reactivity is evaluated relative to the basicity of the anion and is predicated on rate-energy relationships. The typical magnitude of these rate enhancements in condensed phase studies is reported at 5 to 100 times faster for α -nucleophiles as compared to normal nucleophiles, however relative rates as high as 10^4 have been observed.⁴⁻¹⁴ While several theories (ground-state destabilization, transition-state stabilization, product stabilization, solvent effects, etc.) have been proposed to explain the origin of the α -effect, no conclusive evidence has been forwarded which identifies a dominant factor.¹⁵

Since static dielectric effects of solvents, as well as transport phenomena, can have significant influence on ionic reactions conducted in solution, gas phase studies provide a means of resolving solvent effects from intrinsic reactivity. Bimolecular ion-molecule gas phase

reactions are characterized by a classic double-well potential energy surface (PES) model¹⁶ where the central barrier reflects a complex interaction of dynamic, energetic, and steric factors inherent to the reactants. In solution, this barrier is modified by the differential charge stabilization energy between the delocalized transition state relative to the reactants and products resulting in a single-barrier PES. These “solvent effects” are evident in the large differences between reaction rate constants of identical gas and condensed phase reactions,^{17, 18} in the reversal of ordering of acidities and basicities in solution versus the gas phase,^{19, 20} as well as in the enhanced nucleophilicity of polarizable nucleophiles in solution versus the gas phase.¹⁶ Furthermore, experimental investigations probing the magnitude of the α -effect in mixed solvents reported separate ground-state desolvation and stabilization of transition-state effects, emphasizing the importance of solvent interactions as a factor in these reactivity trends.^{13, 21-24}

Although originally derived to describe barriers to electron-transfer reactions, Marcus rate theory has proven effective in separating the thermodynamic component of activation energy and allowing the "intrinsic" nature of anions to be studied in gas-phase S_N2 reactions.²⁵⁻³¹ Application of Marcus theory³² to a generic gas-phase S_N2 potential energy surface (Fig 6.1) provides a conceptual understanding of the relationship between kinetics and thermodynamics.^{26, 27} Marcus theory (Eq 6.1) allows the central barrier ($\Delta H^\ddagger_{\text{activation}}$) to be viewed primarily as an intrinsic barrier ($\Delta H^\ddagger_{\text{intrinsic}}$) modified by an exothermic driving force ($\Delta H_{\text{driving force}} = [\frac{1}{2} \Delta H_{\text{rxn}} + (\Delta H_{\text{rxn}})^2 / (16 \times \Delta H^\ddagger_{\text{intrinsic}})]$).^{30, 31}

$$\Delta H^\ddagger_{\text{activation}} = \Delta H^\ddagger_{\text{intrinsic}} + \frac{1}{2} \Delta H_{\text{rxn}} + (\Delta H_{\text{rxn}})^2 / (16 \times \Delta H^\ddagger_{\text{intrinsic}}) \quad (6.1)$$

Since experimental studies evaluate this activation barrier relative to the energy of separated reactants, this barrier is often referenced to the reactants ($\Delta H^\ddagger_{\text{overall}}$). For an identity reaction in which the attacking and leaving group are the same (a thermoneutral process), the activation

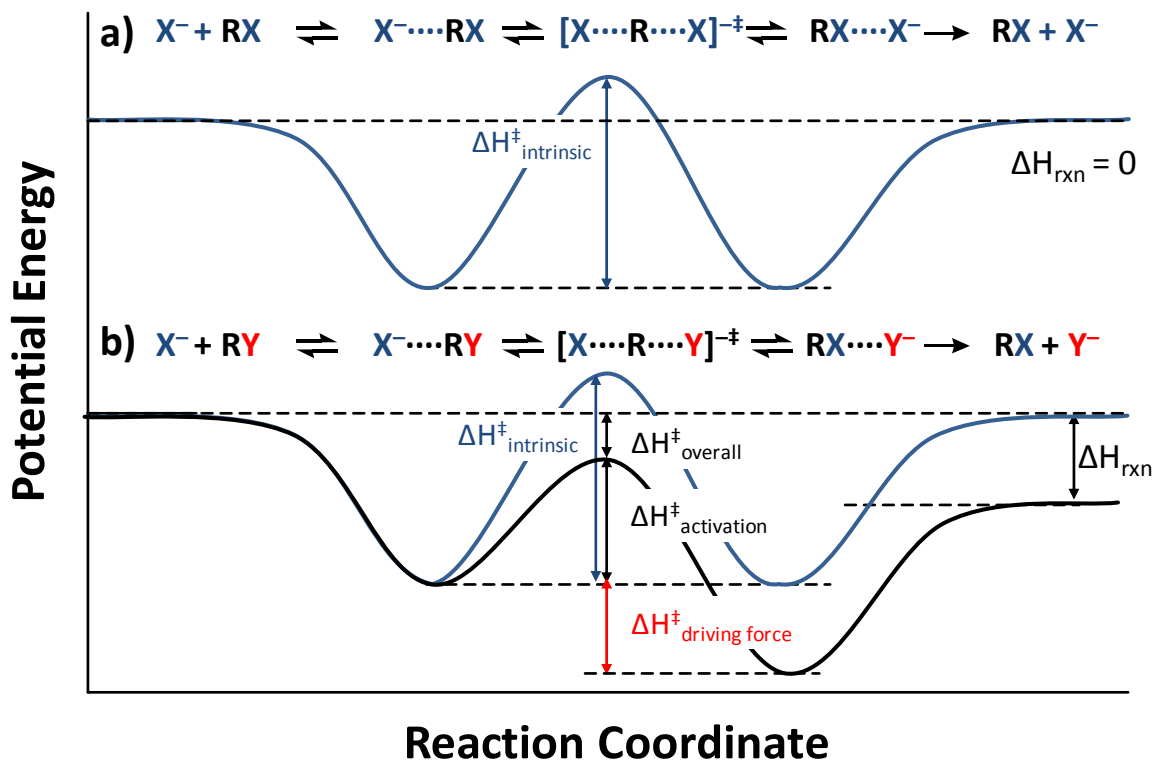


Figure 6.1. Application of Marcus theory to a generic gas-phase S_N2 potential energy surface depicting a) the “intrinsic” central barrier ($\Delta H^\ddagger_{\text{intrinsic}}$) of a thermoneutral identity reaction compared to b) the lowering of the intrinsic barrier by a thermodynamic driving force ($\Delta H^\ddagger_{\text{driving force}}$) in an exothermic non-identity reaction to produce a modified central barrier ($\Delta H^\ddagger_{\text{activation}}$). This activation barrier is often referenced to the energy of separated reactants ($\Delta H^\ddagger_{\text{overall}}$).

barrier is entirely a function of the intrinsic properties of the reactants. However, for a non-identity reaction where the attacking and leaving groups are different, there is a thermodynamic contribution to the activation barrier. For an exothermic reaction ($-\Delta H_{\text{rxn}}$), there is a driving force that lowers the intrinsic barrier, resulting in a smaller overall activation barrier. The parallels between the free energy of activation and the free energy of reaction allow correlations to be established between reactivity (kinetics) and basicity (thermodynamics). Based on these parallels, linear free-energy relationships tend to exist within exothermic reactions for a family of nucleophiles in which the attacking atom and steric effects remain the same.³³⁻³⁵ Deviations

from linearity in reactivity-basicity correlations can reflect the influence of additional variables or the manifestation of unique energetics in the transition state. The enhanced reactivity of the α -nucleophiles is typically evaluated from the deviations in the linearity of Hammett or Brønsted-type plots, where the log of the reactivity is plotted as a function of enthalpy of reaction.³⁶

Recent high-level computational studies^{15, 37, 38} by Ren and Yamataka have inferred an inherent stability of the S_N2 transition states for α -nucleophiles relative to normal nucleophiles in reactions with alkyl chlorides. However, the lack of enhanced reactivity in a series of S_N2 reactions of α -nucleophiles with methyl chloride in a gas phase investigation by Villano et al.³⁹ produce conflicting interpretations of the presence of an α -effect in this reaction system. In an attempt to resolve these discrepancies, we investigate the S_N2 processes in reactions of low exothermicity where the smaller thermodynamic component of the activation barrier may expose α -nucleophilicity. The reaction efficiencies for the reactions of several normal nucleophiles [$C_6H_5O^-$, $HC(O)O^-$, $CH_3C(O)O^-$] and alpha-nucleophiles [$HC(O)OO^-$, $CH_3C(O)OO^-$] with CH_3Cl are added to our previous Brønsted plot of normal and α -nucleophile reactions with methyl chloride. While the presence of the α -effect is suggested at lower basicities, a rapid drop in reaction efficiencies below the detection limits of our instrument hinders the ability to define “normal” reactivity trends. This result is perplexing, since definitive evidence of enhanced nucleophilicity for HOO^- relative to the proton affinities of normal alkoxides (HO^- , CH_3O^- , and $C_2H_5O^-$) in three separate reaction series (methyl fluoride, anisole, and 4-fluoroanisole) has been recently reported by our lab.⁴⁰ A Marcus theory approach to understanding the relationship between the intrinsic and thermodynamic contributions to the overall activation barrier reveals factors that influence both experimental and computational studies. Continuing in the Marcus context, we utilized the computational barriers to evaluate intrinsic differences. An “average”

intrinsic barrier is determined by computationally extracting an intrinsic barrier for HO^- , CH_3O^- , $\text{C}_2\text{H}_5\text{O}^-$, $i\text{-C}_3\text{H}_7\text{O}^-$, and HOO^- with methyl chloride, methyl fluoride, anisole, and 4-fluoroanisole at two different levels of theory.

6.2 Experimental

6.2.1 Ion-Molecule Reactions

These reactions were carried out in a flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer, which has been previously described.⁴¹ Briefly, this instrument consists of four sections: an ion source, an ion selection region, a reaction flow tube, and a detection system. A flowing afterglow ion source is used to produce ions, which are mass-selected using a quadrupole mass filter prior to injection into the reaction flow tube. Hydroxide was prepared by electron ionization (70 eV) of methane and nitrous oxide (2:1 ratio). Most other ionic reagents were generated by proton abstraction of neutrals by HO^- . The peroxyformate, HC(O)OO^- , and peroxyacetate anions, $\text{CH}_3\text{C(O)OO}^-$, were synthesized in a gas-phase Baeyer-Villiger reaction of HOO^- with methyl formate and methyl acetate as previously described.^{42, 43} Injected ions are entrained in a flow of helium ($200 \text{ std cm}^3 \text{ s}^{-1}$, 0.5 torr) and thermalized to $300 \pm 2 \text{ K}$ prior to reactions with neutral reagents that are added through multiple inlets along the length of the reaction flow tube. Ionic reactants and products are analyzed in the detection region using a triple-quadrupole mass filter and an electron multiplier. The reactions are carried out under pseudo-first order conditions (reactant ion $\sim 10^5 \text{ ions cm}^{-3}$; neutral reactant $\sim 10^{11} \text{ molecules cm}^{-3}$), and the reported branching ratios and reaction rate coefficients are the averages of at least three individual measurements. Product branching ratios are determined by extrapolating the observed product yields to zero reaction distance in order to extract the initial ratios due to primary reactions. The reported reaction efficiencies are the experimental rate constants divided by the

calculated collision rate constants. Collision rate constants were calculated from parameterized trajectory collision rate theory.⁴⁴ Error bars represent one standard deviation in the data; absolute uncertainties in these rate constant measurements are $\pm 20\%$. The detection system was tuned to minimize mass discrimination, and no further corrections were made in the analysis.

6.2.2 *Materials*

All compounds were obtained from commercial vendors. These compounds include anisole, $\text{C}_6\text{H}_5\text{OCH}_3$, Aldrich, 99.7% (anhydrous); 4-fluoroanisole, $\text{FC}_6\text{H}_4\text{OCH}_3$, Aldrich, 99%; methyl chloride, CH_3Cl , Matheson, 99.5%; methyl fluoride, CH_3F , Matheson, 99.99%; 2-propanol, $(\text{CH}_3)_2\text{CHOH}$, Aldrich, 99.9%; ethanol, $\text{C}_2\text{H}_5\text{OH}$, Decon Laboratories, 200 proof; methanol, CH_3OH , Aldrich, 99.9%; water, H_2O , distilled; methyl formate, HC(O)OCH_3 , Sigma-Aldrich, anhydrous, 99%; methyl acetate, $\text{CH}_3\text{C(O)OCH}_3$, Fluka, $>99.9\%$; phenol, $\text{C}_6\text{H}_5\text{OH}$, Sigma-Aldrich, $\sim 99\%$; formic acid HC(O)OH , Sigma-Aldrich, $\geq 95\%$; and acetic acid, $\text{CH}_3\text{C(O)OH}$, Sigma-Aldrich, $\geq 99\%$. The reagents were protected from light and stored under vacuum. Helium buffer gas (99.995%) was purified by passage through a molecular sieve trap immersed in liquid nitrogen.

6.2.3 *Computational Methods*

Ab initio molecular orbital calculations were carried out with the G3MP2 method using the Gaussian 09 suite of programs.⁴⁵ Frequency calculations were conducted for all species to establish their nature as local minima or transition states. Enthalpy changes were calculated from the energies of the optimized structures, and thermal corrections included for 298 K without scaling of the calculated vibrational frequencies.

6.2.4 Marcus Barrier Calculations

In order to correlate our computational barriers with Marcus theory, we reference the Marcus equation to the reactants by using a modified form of the Marcus Equation (Eq 6.2) defined by Dodd and Brauman.²⁷

$$\Delta E_{\text{overall}} = \Delta E_{\text{intrinsic}} + \frac{\Delta E_{\text{rxn}}}{2} + \frac{\Delta E_{\text{rxn}}^2}{16(\Delta E_{\text{intrinsic}} - \Delta E_{\text{well}})} \quad (6.2)$$

Where, $\Delta E_{\text{overall}}$ is the electronic energy difference between the separated reactants and the S_N2 transition state, $\Delta E_{\text{intrinsic}}$ is the intrinsic non-identity reaction barrier relative to the reactants, ΔE_{rxn} is the free energy of reaction, and ΔE_{well} is the complexation energy of the reactant ion-dipole complex. We employ G2(+) data from the work of Ren and Yamataka for the CH_3Cl and CH_3F reactions;^{15, 37, 38, 46} however, this work did not calculate the complexation energy of the reactant ion-dipole complex. We did compute the barrier heights and complexation energy for the reaction of $\text{C}_2\text{H}_5\text{O}^-$ in these systems. The G3MP2 complexation energies between the anions and both anisoles only varied by $\sim 4 \text{ kJ mol}^{-1}$. These variations did not influence the $\Delta E_{\text{overall}}$ using Equation 6.2. Therefore we choose to use an average complexation energy for all of the reaction systems (ΔH_{well} : $\text{CH}_3\text{Cl} = 60$, $\text{CH}_3\text{F} = 50$, $\text{CH}_3\text{OC}_6\text{H}_5 = 92$, $\text{CH}_3\text{OC}_6\text{H}_4\text{F} = 102 \text{ kJ mol}^{-1}$).

6.3 Results and Discussion

6.3.1 Brønsted Correlation

Based on Ren and Yamataka's computational work, we focus initially on a series of normal and α -nucleophile reactions with methyl chloride.^{39, 47-49} Attempts were made to examine many of the reactions used in Ren and Yamataka's computational study; however, several of the alkyl chloride reactions could not be studied experimentally (the reactions of Cl^- and Br^- are

below the detection limits of our instrument; HSO^- , FO^- , and $\text{ClCH}_2\text{CH}_2\text{O}^-$ could not be generated in measureable abundances). Since methyl chloride does not contain β -hydrogens, this reaction is assumed to proceed through a typical $\text{S}_{\text{N}}2$ process. The experimental data for these reactions are shown in terms of a Brønsted-type plot in Figure 6.2 where the y-axis is the logarithm of the reaction efficiency and the x-axis is the gas phase proton affinity of the anion. Blue represents the normal oxyanions and red the oxygen alpha nucleophiles.

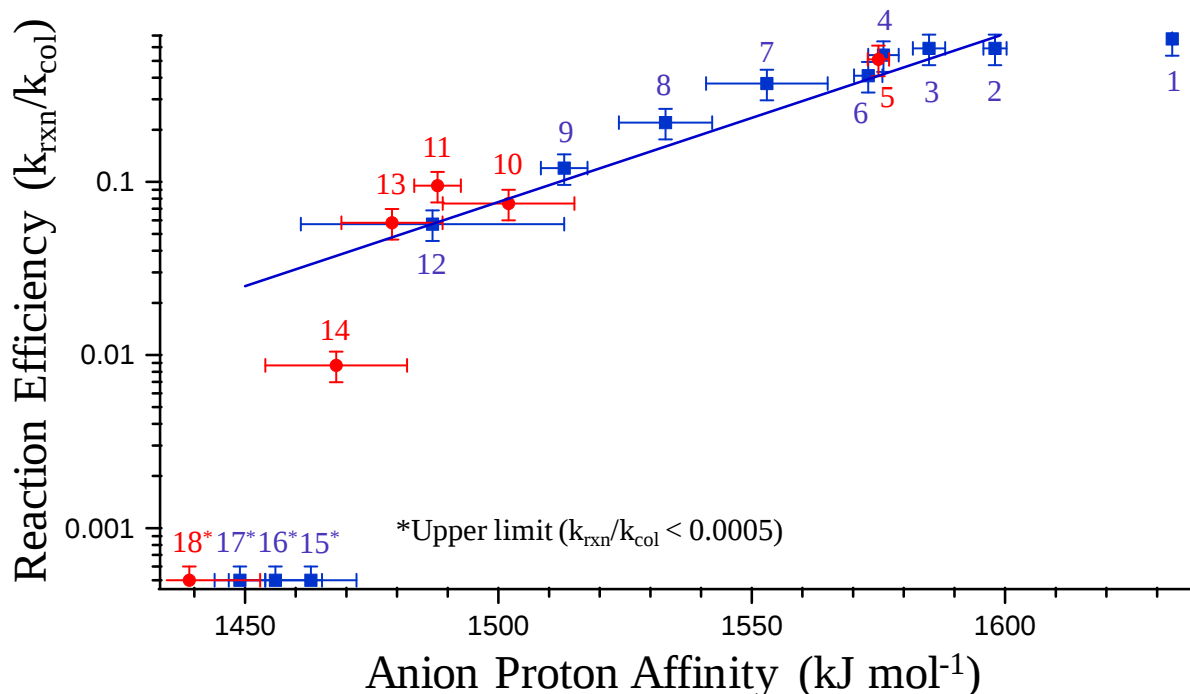


Figure 6.2. Brønsted-type plot where y-axis is the logarithm of the reaction efficiency ($k_{\text{rxn}}/k_{\text{col}}$) and the x-axis is the gas phase proton affinity of the anion (ΔH_{298}) for the $\text{S}_{\text{N}}2$ reaction of Nu^- with CH_3Cl . Experimental data at 300 ± 2 K from this work (anions 14-18) and references 39, 48, and 49 updated using parameterized trajectory theory (ref 44) to calculate k_{col} . (■ normal oxyanions, ● α -oxyanions): 1. HO^- 2. CH_3O^- 3. $\text{C}_2\text{H}_5\text{O}^-$ 4. $i\text{-C}_3\text{H}_7\text{O}^-$ 5. HOO^- 6. $t\text{-C}_4\text{H}_9\text{O}^-$ 7. $\text{CFH}_2\text{CH}_2\text{O}^-$ 8. $\text{CF}_2\text{HCH}_2\text{O}^-$ 9. $\text{CF}_3\text{CH}_2\text{O}^-$ 10. CH_3SO^- 11. ClO^- 12. $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}^-$ 13. BrO^- 14. HC(O)OO^- 15. $\text{C}_6\text{H}_5\text{O}^-$ 16. HC(O)O^- 17. $\text{CH}_3\text{C(O)O}^-$ 18. $\text{CH}_3\text{C(O)OO}^-$

In Figure 6.2, we note that in general the reactivity follows basicity trends; however, the plot flattens at the higher basicities as the reaction efficiency approaches the collision rate. At

the lower basicities there is a rapid drop in reaction efficiency. This result is attributed to the diminishing thermodynamic driving force contributions to the overall activation barrier. The rate constant for HC(O)OO^- is $1.77 \pm 0.05 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$. The changes in ion signal intensities were too low to measure an accurate rate constant for $\text{C}_6\text{H}_5\text{O}^-$, HC(O)O^- , $\text{CH}_3\text{C(O)O}^-$, and $\text{CH}_3\text{C(O)OO}^-$ (hence an upper limit of $1 \times 10^{-12} \text{ cm}^3 \text{ s}^{-1}$). The overall trends in Figure 6.2 do not show any significant deviations between the α -anions and the normal anions. Small shifts may hint that the α -anions are more reactive than normal anions at lower basicities (11, 13 and 14 versus 12 and 15). ClO^- and BrO^- are slightly more efficient than $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}^-$ and HC(O)OO^- is more efficient than $\text{C}_6\text{H}_5\text{O}^-$. However, the homologous properties and intrinsic barriers of the phenoxide ion deviate from other straight-chain alkoxides and fluoroalkoxides,²⁵ making the definition of “normal” reactivity more difficult. Despite this ambiguity, the presence of an α -effect is suggested in the reactions of other α -nucleophiles.

6.3.2 Marcus Theory (Variations in Intrinsic Nature of Anions)

Limitations associated with employing a reactivity-basicity relationship to evaluate intrinsic nucleophilicity are revealed within the context of the Marcus model. The intrinsic barriers (no thermodynamic driving force) for identity or exchange reactions ($\text{X}^- + \text{CH}_3\text{X}$) provide a direct measure of inherent nucleophilicity. Pellerite and Brauman found the intrinsic barriers for gas-phase $\text{S}_{\text{N}}2$ identity reactions correlate with methyl cation affinities (MCA), where $\text{MCA}(\text{X}^-)$ for $\text{CH}_3\text{X} \rightarrow \text{CH}_3^+ + \text{X}^-$ is defined by Equation 6.3.²⁹

$$\Delta H_{\text{intrinsic}}^\ddagger \propto \text{MCA}(\text{X}^-) = \Delta H^\circ = D^\circ(\text{CH}_3\text{-X}) - \text{EA}(\text{X}^\bullet) + \text{IE}(\text{CH}_3) \quad (6.3)$$

In this equation, D° is the homolytic dissociation energy of the $\text{CH}_3\text{-X}$ bond, $\text{EA}(\text{X}^\bullet)$ is the electron affinity of the X radical, and $\text{IE}(\text{CH}_3)$ is the methyl radical ionization energy. Based on this relationship, intrinsic barriers are larger for nucleophiles with strong bonds to carbon and

with low electron affinities. Expanding on this relationship, Streitwieser highlighted that differences in the strengths in carbon bonds versus hydrogen bonds for different classes of compounds can lead to large deviations in correlations between nucleophilicity and basicity. Therefore, any Brønsted-type correlations between basicity and nucleophilicity to resolve intrinsic reactivity must employ related groups of bases where the reacting atom is the same.

Ren and Yamataka use an S_N2 reaction barrier height-basicity relationship to estimate a 17.1 kJ mol^{-1} α -effect for HOO^- relative to a Brønsted correlation of normal nucleophiles with CH_3Cl .³⁸ However, this correlation was defined with a wide class of nucleophiles. If the normal anion Brønsted correlation is defined for only CH_3O^- and HO^- , the size of the α -effect for HOO^- drops to 9.8 kJ mol^{-1} . This suggests that the magnitude of the α -effect may be smaller than originally predicted and that the intrinsic differences in anions may be small or masked.

6.3.3 Marcus Theory (*Convergence of Overall Activation Barriers*)

It is instructive to use Marcus theory to take a more in-depth look at the magnitude of intrinsic barriers and their contribution to the overall activation barriers. While minor variations in intrinsic nucleophilicity exist for a given nucleophile (depending on the method employed to calculate the identity exchange reaction barrier), general trends in the energetics indicate that typical differences in intrinsic barriers within a homologous class of nucleophiles are small ($< 10 \text{ kJ mol}^{-1}$).^{25, 50} Computational and experimental studies^{31, 51, 52} have shown that the additive postulate of these intrinsic barriers utilized in determining the non-identity intrinsic barrier has excellent predictive power to determine overall activation barriers. The intrinsic barrier for a non-identity reaction is the average of the intrinsic exchange barriers for the reactant ion and product ion, $\Delta H^\ddagger_{\text{intrinsic}(X,Y)} = [(\Delta H^\ddagger_{\text{intrinsic}(X,X)} + \Delta H^\ddagger_{\text{intrinsic}(Y,Y)})/2]$. As a result, the intrinsic reactivity differences between a series of anions with a given substrate are halved.

This issue is further aggravated by the intrinsic difference averaging effect of the quadratic term in the thermodynamic driving force, $\Delta H_{\text{driving force}}^{\ddagger} = [\frac{1}{2} \Delta H_{\text{rxn}} + (\Delta H_{\text{rxn}})^2 / (16 \times \Delta H_{\text{intrinsic}}^{\ddagger})]$. While anions with similar intrinsic barriers experience equivalent thermodynamic lowering at a given exothermicity ($-\Delta H_{\text{rxn}}$), anions with lower intrinsic barriers have a smaller thermodynamic driving force contribution due to larger values in the quadratic term. The overall effect is that anions with higher intrinsic barriers have larger thermodynamic driving forces and anions with lower intrinsic barriers have smaller thermodynamic driving forces. Figure 6.3 depicts the relationship of the Marcus non-identity reaction activation barrier and the thermodynamic driving force at increasing exothermicity of reaction for hypothetical non-identity reaction intrinsic barrier heights of 40, 50, 60, and 80 kJ mol⁻¹. At lower

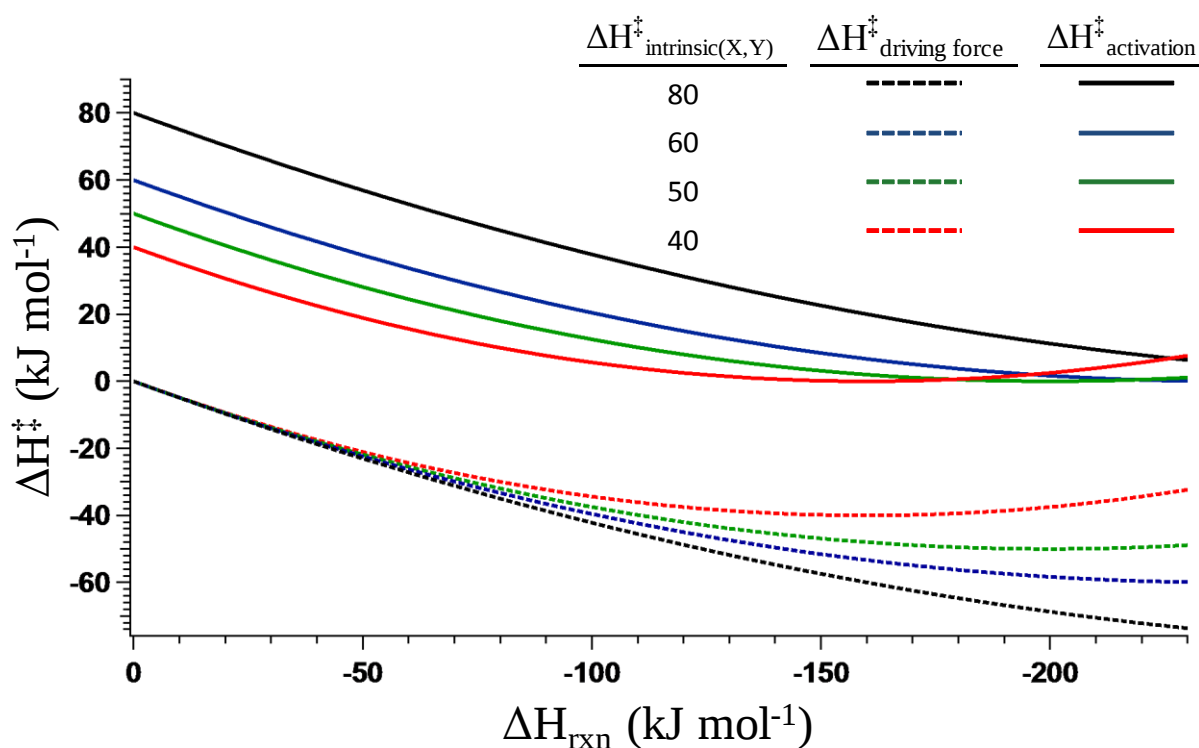


Figure 6.3. Relationship of the Marcus non-identity reaction activation barrier ($\Delta H_{\text{activation}}^{\ddagger} = \Delta H_{\text{intrinsic}}^{\ddagger}(\text{X,Y}) + \Delta H_{\text{driving force}}^{\ddagger}$) and the thermodynamic driving force ($\Delta H_{\text{driving force}}^{\ddagger} = \frac{1}{2} \Delta H_{\text{rxn}} + (\Delta H_{\text{rxn}})^2 / (16 \times \Delta H_{\text{intrinsic}}^{\ddagger})$) at increasing exothermicity of reaction (ΔH_{rxn}) for hypothetical non-identity reaction intrinsic barrier heights of 40, 50, 60, and 80 kJ mol⁻¹.

exothermicities, thermodynamic driving forces correlate almost directly to the exothermicity of reaction and the relative differences in intrinsic barriers are maintained in the overall activation barrier. As the exothermicity of reaction increases, the relative contributions from the thermodynamic driving force for the reactions with smaller intrinsic barriers diminish and the overall activation barriers begin to converge masking the differences in intrinsic barriers. The rate of convergence is delayed in reactions with higher intrinsic barriers due to the steeper curvature of the free-energy surfaces for the reactant and/or product states. Good nucleophiles (poor leaving groups) have low intrinsic barriers and converge quickly. Poor nucleophiles (good leaving groups) have large intrinsic barriers and maintain intrinsic differences over a wider range of exothermicities. With respect to this relationship, it is interesting to note that the magnitude of the α -effect for nucleophilic cleavage of esters in solution is marginal with poor leaving groups and increases with leaving group ability.⁵³

Hypothetically, the Marcus inversion region (Figure 6.3: $\Delta H^\ddagger_{\text{intrinsic}}(\text{X,Y}) = 40 \text{ kJ mol}^{-1}$ at $\Delta H_{\text{rxn}} > -150 \text{ kJ mol}^{-1}$) could be reached in extremely exothermic reactions with low barriers; however, under these conditions reactions in the gas phase are controlled by the collision rate and this aspect cannot be experimentally probed. At the lower end of the exothermicity scale, without a sufficiently high thermodynamic driving force to overcome endothermic intrinsic barriers ($\Delta H^\ddagger_{\text{driving force}} > \Delta H^\ddagger_{\text{intrinsic}}(\text{X,Y})$), the reaction rates are below the detection limits of our instrument ($\sim 1 \times 10^{-13} \text{ cm}^3 \text{ s}^{-1}$). In summary, there is a narrow window in the gas phase for which small variations in intrinsic reactivity can be effectively evaluated.

6.3.4 Overall and Intrinsic Barriers

Ultimately we are interested in the true intrinsic nature of the α -effect; therefore, we utilized the computational barriers to evaluate intrinsic differences for HO^- , CH_3O^- , $\text{C}_2\text{H}_5\text{O}^-$,

i-C₃H₇O[−], and HOO[−] with methyl chloride, methyl fluoride, anisole, and 4-fluoroanisole. Since the G2(+) method has been employed in several computational studies^{15, 37, 38} on the α -effect in methyl chloride and methyl fluoride systems, we made use of these barriers for comparison with our experimental data. However, in the larger anisole systems we chose to employ the G3MP2 method, which is still a high level of theory but less expensive computationally. Table 6.1 lists the anion proton affinities (PA), exothermicities of reaction (ΔH_{rxn}), reaction efficiencies (Eff), relative α -effects ($\text{Eff}_{\text{HOO}^-}/\text{Eff}_{\text{X}^-}$), overall activation barrier ($\Delta H_{\text{overall}}^\ddagger$), Marcus barriers [intrinsic barriers ($\Delta H_{(\text{X},\text{X})}^\ddagger$, $\Delta H_{(\text{Y},\text{Y})}^\ddagger$, and $\Delta H_{(\text{X},\text{Y})}^\ddagger$), the thermodynamic driving force ($\Delta H_{\text{driving force}}^\ddagger$), and activation barriers ($\Delta H_{\text{overall}}^\ddagger$)] for the S_N2 reactions. The ΔH_{rxn} was determined from experimental heats of formation.⁵⁴ The Marcus intrinsic barrier for the anions in each reaction, $\Delta H_{(\text{X},\text{X})}^\ddagger$, was extracted by matching the Marcus $\Delta H_{\text{overall}}^\ddagger$ to the G2(+)/G3MP2 $\Delta H_{\text{overall}}^\ddagger$ (full description of the method is given in the experimental section). Our use of Marcus barriers is an inverse variation of the method typically employed. Many studies use identity reactions to estimate an overall intrinsic barrier, then apply thermodynamic driving forces to generate an overall activation barrier. Computational barriers are very sensitive to the level of theory employed and any system limitations could be compounded in an identity reaction. We attempt to average out these errors by extracting intrinsic barriers for the anions from the computational overall activation barriers of three different systems and two different levels of theories.

We immediately note that there is a lack of correlation between the computational barrier heights in the methyl chloride reactions and our experimental data. While Marcus theory predicts intrinsic differences to converge in highly exothermic reactions, the similarities in

Table 6.1. The α -effect and Intrinsic Reactivity for the S_N2 Reactions of HO^- , CH_3O^- , $C_2H_5O^-$, and HOO^- with Methyl Chloride, Methyl Fluoride, Anisole and 4-Fluoroanisole (energies in units of kJ mol^{-1})

Reaction ($X^- + M$)	PA(X^-) ^a	ΔH_{rxn} ^b	S_N2 Eff	α -effect ^c	G2(+)/G3MP2 ^d	Marcus Barriers ^e (relative to reactants)				
				$\frac{\text{Eff}_{HOO^-}}{\text{Eff}_{X^-}}$		$\Delta H_{(X,X)}^\ddagger$	$\Delta H_{(Y,Y)}^\ddagger$	$\Delta H_{(X,Y)}^\ddagger$	$\Delta H_{\text{driving force}}^\ddagger$	$\Delta H_{\text{overall}}^\ddagger$
$HO^- + CH_3Cl$	1633	-210	0.67	0.76	-55.5	<u>10.5</u>	<u>9.8</u>	<u>10.2</u>	<u>-65.7</u>	<u>-55.5</u>
$CH_3O^- + CH_3Cl$	1598	-189	0.59	0.86	-50.6	<u>17.0</u>	<u>9.8</u>	<u>13.4</u>	<u>-64.0</u>	<u>-50.6</u>
$C_2H_5O^- + CH_3Cl$	1585	-179	0.59	0.86	-43.4	<u>33.7</u>	<u>9.8</u>	<u>21.8</u>	<u>-65.0</u>	<u>-43.3</u>
$HOO^- + CH_3Cl$	1575	-184	0.51		-56.6	<u>-9.5</u>	<u>9.8</u>	<u>0.2</u>	<u>-56.8</u>	<u>-56.6</u>
$HO^- + CH_3F$	1633	-91	0.0042	0.62	-15.6	56.7	-11.0	22.9	-38.5	-15.6
$CH_3O^- + CH_3F$	1598	-70	0.0007	3.7	-14.1	43.6	-11.0	16.3	-30.4	-14.1
$C_2H_5O^- + CH_3F$	1585	-60	<0.00005	>50	-5.2	52.9	-11.0	21.0	-27.0	-6.0
$HOO^- + CH_3F$	1575	-65	0.0026		-19.4	28.1	-11.0	8.6	-28.0	-19.4
$HO^- + CH_3OC_6H_5$	1633	-162	0.13	0.69	-28.6	40.5	39.2	39.9	-68.4	-28.6
$CH_3O^- + CH_3OC_6H_5$	1598	-141	0.04	2.3	-21.6	39.4	39.2	39.3	-60.9	-21.6
$C_2H_5O^- + CH_3OC_6H_5$	1585	-131	0.01	9.0	-11.2	53.8	39.2	46.5	-57.7	-11.2
$HOO^- + CH_3OC_6H_5$	1575	-135	0.09		-25.6	26.7	39.2	33.0	-58.6	-25.6
$HO^- + CH_3OC_6H_4F$	1633	-174	---	---	-36.6	38.1	35.2	36.7	-73.2	-36.6
$CH_3O^- + CH_3OC_6H_4F$	1598	-153	0.10	2.3	-29.6	37.2	35.2	36.2	-65.8	-29.6
$C_2H_5O^- + CH_3OC_6H_4F$	1585	-143	0.02	12	-19.2	51.8	35.2	43.5	-62.7	-19.2
$HOO^- + CH_3OC_6H_4F$	1575	-147	0.23		-33.9	23.8	35.2	29.5	-63.4	-33.9

^aProton affinities (PA), $H^+ + X^- \rightarrow HX$ in kJ mol^{-1} : HO^- (1633)⁵⁴, CH_3O^- (1598 $\pm$ 2)⁵⁸, $C_2H_5O^-$ (1585 $\pm$ 3)⁵⁸, HOO^- (1575 $\pm$ 2).⁵⁵ ^bExothermicity of reaction (ΔH_{rxn}) calculated using heats of formation from ref 54; ΔH_{rxn} for 4-fluoroanisole reactions estimated from anisole reactions based on proton affinity difference (12 kJ mol^{-1}). ^cRelative α -effect using a ratio of S_N2 reaction efficiencies ($\text{Eff}_{HOO^-}/\text{Eff}_{X^-}$). ^dG2(+) method: methyl chloride/fluoride ref 15, 36-38 ($C_2H_5O^-$ this work); G3MP2 method: anisoles. ^eMarcus barriers: non-identity reaction intrinsic barrier, $\Delta H_{(X,Y)}^\ddagger = [(\Delta H_{(X,X)}^\ddagger + \Delta H_{\text{intrinsic}(Y,Y)}^\ddagger)/2]$; thermodynamic driving force [$\Delta H_{\text{driving force}}^\ddagger = \frac{1}{2} \Delta H_{\text{rxn}} + (\Delta H_{\text{rxn}})^2/(16 \times (\Delta H_{\text{intrinsic}(X,Y)}^\ddagger + \Delta H_{\text{well}}))$] where ΔH_{well} ($CH_3Cl = 60$, $CH_3F = 50$, $CH_3OC_6H_5 = 92$, $CH_3OC_6H_4F = 102$ kJ mol^{-1}); activation barrier, $\Delta H_{\text{overall}}^\ddagger = (\Delta H_{\text{intrinsic}(X,Y)}^\ddagger + \Delta H_{\text{driving force}}^\ddagger)$; Marcus barriers for CH_3Cl unreliable due to dominance of thermodynamic contributions (see discussion). ^fNo S_N2 products; 100% proton transfer.

reaction efficiencies and the lack of an α -effect in methyl chloride is more likely a characteristic of gas phase reactions with low activation barriers. DePuy et al. concluded that extremely exothermic gas phase S_N2 reactions have low central barriers that have little influence on reaction rates.⁴⁸ In these cases, the probability of reaction is dominated by the volume in phase space that leads to products compared to the total volume, and reaction rate constants are not sensitive to small changes in barrier heights. This lack of sensitivity is reflected by the reactions of CH_3O^- and $\text{C}_2\text{H}_5\text{O}^-$ with methyl chloride, which have indistinguishable reaction efficiencies. While the Marcus theory method of determining barriers has proven to give excellent correlation with experimental and computational barriers, this relationship begins to breakdown in highly exothermic reactions with low barriers ($\Delta H_{\text{rxn}} \gg \Delta H_{\text{intrinsic}}^\ddagger$).⁵¹ Clearly there is a breakdown in the Marcus barriers for the methyl chloride reactions due to the overwhelming thermodynamic contributions; the intrinsic barriers are only listed to highlight this dominance.

The other computational barriers ($\Delta H_{\text{overall}}^\ddagger$ for both methods) compare well with our experimental efficiencies. While the methyl chloride series of reaction barriers and efficiencies are mostly a reflection of the exothermicity of reaction, the barrier heights for the methyl fluoride series lie close to the entrance channel resulting in high sensitivity of reaction efficiency relative to small changes in barrier heights. The similarities of exothermicity and structure for anisole and 4-fluoroanisole are reflected in a consistency of relative differences in barrier heights and efficiencies in both series (i.e., CH_3O^- vs HOO^- : $\Delta\Delta H^\ddagger \sim 4 \text{ kJ} = 2 \times \text{Eff}$ and $\text{C}_2\text{H}_5\text{O}^-$ vs HOO^- : $\Delta\Delta H^\ddagger \sim 14.5 \text{ kJ} = 10 \times \text{Eff}$). While the relative differences in the G2(+) results have similar trends with the G3MP2 values, the relative differences in barrier heights and efficiencies for HO^- and HOO^- are at odds in the methyl fluoride system. Based on trends in all of the systems, it appears that the G2(+) HO^- barrier is about 5 kJ mol^{-1} higher than would be expected to match

experimental efficiencies. Perhaps this difference is a true representation of the enthalpy barriers and significant differences exist in the entropic contributions to the overall free-energy barriers for the reactions of methyl fluoride with HO^- and HOO^- .

Since there is a strong correlation between the computational barriers and our experimental data, we would expect that the use of Equation 6.2 would allow us to separate the activation energy into thermodynamic and "intrinsic" components. Since the level of theory can lead to variations in the overall magnitude of activation barriers, the intrinsic differences between the anions, $\Delta H^\ddagger_{(X,X)}$, are considered more reliable than quantitative interpretations. The thermodynamic driving forces for methyl fluoride, anisole, and 4-fluoroanisole appear to retain a linear relationship with their exothermicity of reaction allowing relatively similar values for the estimated intrinsic barriers for the anions. The intrinsic barriers for CH_3O^- and HO^- are almost identical, however $\text{C}_2\text{H}_5\text{O}^-$ has a higher intrinsic barrier by approximately 14 kJ mol^{-1} . Overall, the true intrinsic nature of HOO^- , $\Delta H^\ddagger_{(X,X)}$, lies $13\text{-}15 \text{ kJ mol}^{-1}$ below that of CH_3O^- and HO^- ($\text{HO}^- + \text{CH}_3\text{F}$ has been omitted due to questionable reliability), and only $\sim 7 \text{ kJ mol}^{-1}$ difference with $\Delta H^\ddagger_{(X,Y)}$. Based on this result we would estimate the largest rate enhancement for a "standard" alpha effect in the gas phase to be around 20. This magnitude would exist in the absence of thermodynamic masking and therefore would be expected to be smaller in most reactions. If $\text{C}_2\text{H}_5\text{O}^-$ is used to define the normal baseline ($\Delta\Delta H^\ddagger_{(X,Y)} \sim 14 \text{ kJ mol}^{-1}$), an α -effect as large as 275 could be produced. Based on the intrinsic variations in our reference anions, defining "normal" will play a key role in assessing the magnitude of the α -effect and goes beyond simply matching proton affinities of anions.

Unfortunately, we cannot make a direct comparison to the intrinsic barriers of Chen and Brauman due to the lack of sensitivity of the RRKM calculations and our experimental

measurements in the highly exothermic CH_3Cl reactions. Still it is informative to apply their interpretation of some factors causing variations in intrinsic reactivity to our work. While Chen and Brauman rationalize higher barriers in some of their nucleophiles as a consequence of a concentrated charge in the nucleophile and a delocalized charge in the transition state, an opposite argument could be made for lower barriers in the peroxide anion.²⁵ The unique nature of HOO^- (two equally electronegative atoms adjacent in the attacking group with lone pair electrons) delocalizes charge to stabilize the anion and at the same time localizes the charge near the bond forming in the transition state. The similarities of charge distribution between the nucleophile and transition state lead to significantly lower barriers compared to normal nucleophiles. Furthermore, unlike normal nucleophiles, this minor shift in charge distribution would result in a more consistent transition in both thermodynamic and “kinetic” reactivity from a protic to a polar aprotic solvent based on the polar group and hydroxyl substitution model of Chen and Brauman.²⁵

6.3.5 *Molecular Electron Affinity (Ease of Electron Transfer for the Nucleophile to TS)*

It is important to note that there is approximately a 10 kJ mol^{-1} shift between the relative gas phase proton affinity (PA) and the exothermicity of reactions (ΔH_{rxn}) for HOO^- (see Table 6.1). This inversion would suggest that there is a larger disparity between proton affinities and methyl cation affinities for the peroxide, than for the normal alkoxides. One of the key parameters which influences both proton affinities and methyl cation affinities is the molecular electron affinities ($\text{X} + \text{e}^- \rightarrow \text{X}^-$). Upon inspection, there is a significant difference in electron affinity for the formation of the normal anions HO^- (1.83 eV), CH_3O^- (1.57 eV), $\text{C}_2\text{H}_5\text{O}^-$ (1.71 eV), and $i\text{-C}_3\text{H}_7\text{O}^-$ (1.85 eV) relative to the formation of HOO^- (1.08 eV).⁵⁵ Intriguingly, this lower electron affinity relative to gas phase anion basicity holds for other peroxy α -nucleophiles

CH₃OO⁻ (1.16 eV), C₂H₅OO⁻ (1.19 eV), (CH₃)₃COO⁻ (1.20 eV), and C₆H₅OO⁻ (1.06 eV) versus *t*-C₄H₉O⁻ (1.91 eV), FCH₂CH₂O⁻ (2.22 eV), and C₆H₅O⁻ (2.25 eV).⁵⁵ Perhaps the significantly lower electron affinity influences the intrinsic reactivity of the α -nucleophiles. This can be understood in terms of the ease of transferring an electron from the attacking group to the leaving group ($X^- \rightarrow TS^-$). As the electron binding energy of the attacking anion increases, more energy is required in the transition state to transfer the charge to the leaving group. A more rigorous assessment of this factor in S_N2 transition state stabilization can be found in several recent articles by Hoz,⁵⁶ Fountain,⁷ and Sauers⁵⁷ on ionization energies and single electron transfer (SET) character.

6.3.6 Variations in Solvent Effects

An interesting observation is the huge shift in vertical detachment energies (VDE) reported for HO⁻ when transitioning to solution ($\Delta VDE_{\text{gas phase}} = 10.8 \text{ eV}$ versus $\Delta VDE_{\text{aqueous}} = 0.7 \text{ eV}$).⁵⁷ With such a large solvent effect on ionization energy, we were curious to determine if there were any trends in properties based on electron affinities for the gas phase versus the condensed phase data. Figure 6.4 depicts our assessment of proton affinity in the gas phase versus the pK_a of the same anion in water. There is undoubtedly a differential solvation energy between normal nucleophiles and α -nucleophiles from their associated proton affinities in the gas phase. Although there is some scatter in the relationships, the aqueous normal anions are about three orders of magnitude more basic than the aqueous α -nucleophiles. Since we would expect the delocalized α -nucleophiles to be less solvated than normal nucleophiles, the higher acidity of the α -nucleophiles indicates weaker bonds to hydrogen than the normal nucleophiles. This interpretation is supported by the finding that oximate α -nucleophiles are less solvated than

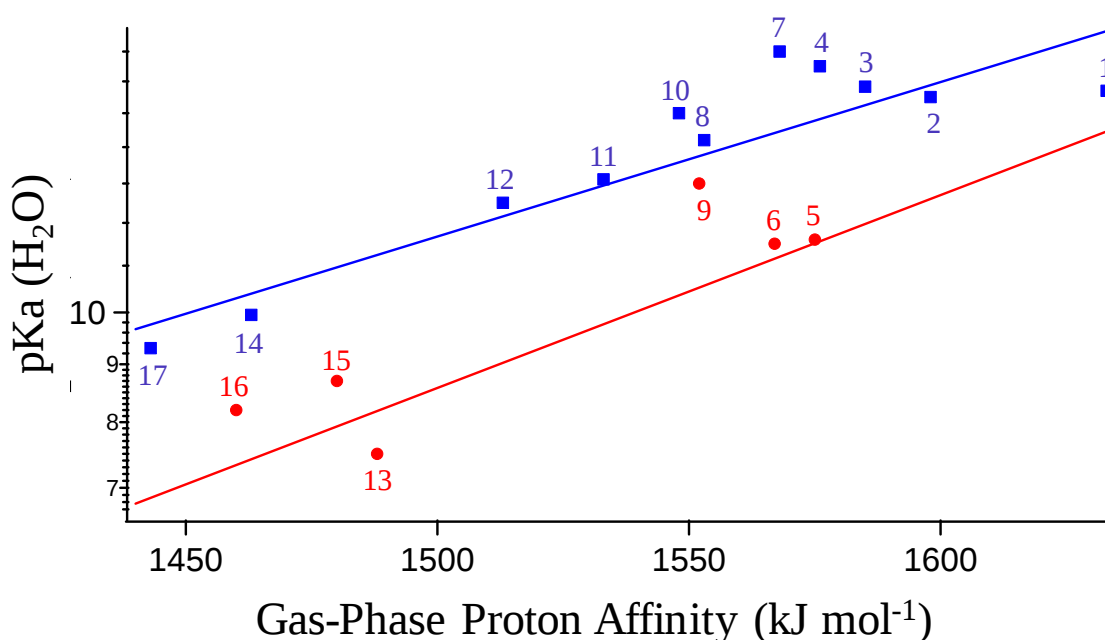


Figure 6.4. Differential solvation effects relative to gas-phase proton affinities (aqueous pKa versus gas phase proton affinity) between normal nucleophiles (■) and α -nucleophiles (●). 1. HO^- 2. CH_3O^- 3. $\text{C}_2\text{H}_5\text{O}^-$ 4. $i\text{-C}_3\text{H}_7\text{O}^-$ 5. HOO^- 6. CH_3OO^- 7. $t\text{-C}_4\text{H}_9\text{O}^-$ 8. $\text{CF}_3\text{CH}_2\text{O}^-$ 9. $t\text{-C}_4\text{H}_9\text{OO}^-$ 10. $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$ 11. $\text{CF}_3\text{CH}_2\text{O}^-$ 12. $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}^-$ 13. ClO^- 14. $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}^-$ 15. BrO^- 16. HC(O)OO^- 17. $\text{C}_6\text{H}_5\text{O}^-$

normal phenoxide nucleophiles in H_2O by about 16 kJ mol^{-1} (a ground state solvation α -effect of 750).¹³

6.4 Conclusion

Our investigation of the α -effect in gas phase $\text{S}_\text{N}2$ reactions provides insight into the intrinsic reactivity of α -nucleophiles and solvent effects on nucleophilicity. Our results are fully consistent with the current framework of computational and condensed phase studies of the α -effect. Our analysis of reactivity trends, acidity/basicity in the gas phase versus solution, and computational barriers has led to the following findings.

- (1) *Masking of intrinsic differences in the gas phase.* The overall trends in the magnitude of the α -effect in the gas phase are consistent with Marcus theory. Variations in intrinsic

character can be easily masked at higher exothermicities of reaction due to a convergence of overall activation barriers and the lack of sensitivity of the reactant ion-dipole complex to small central barriers. At lower exothermicities, the limit of detection restricts the range in which small intrinsic differences can be resolved.

- (2) *Intrinsic Marcus Barriers.* The reference anion(s) defining “normal” reactivity will play a key role in assessing the magnitude of the α -effect. Variations in the intrinsic barriers of the normal anions (~ 14 kJ) could produce a range of rate enhancements from 20 to 275 for HOO^- in a comparison of purely intrinsic reactions. Experimentally, we would expect the magnitude of the α -effect to be smaller and more consistent as thermodynamic contributions will mask intrinsic differences and cause overall barriers to converge.
- (3) *Lower Molecular Electron Affinity for the α -nucleophiles.* Significantly lower electron affinities (~ 0.6 eV) are associated with the formation of the α -oxyanions compared to the normal oxyanions ($\text{X} + \text{e}^- \rightarrow \text{X}^-$). Nucleophilicity is often correlated with electron affinity and bond-strength effects. The ease of charge transfer between the nucleophile and transition state is a key concept in explaining barrier heights. The lower barriers for the α -nucleophiles can be rationalized by a localized “softness” in the anion leading to similarities of charge distribution between the nucleophile and transition state when compared to the localized charge distribution of normal nucleophiles.
- (4) *Differential Solvation Effects for the α -Nucleophiles.* Significant differences in aqueous solvation energies ($\Delta\text{pK}_a \sim 3$) between normal nucleophiles and α -nucleophiles from their associated proton affinities in the gas phase suggests differential solvation plays a dominant role in the magnitude of the α -effect in solution.

6.5 References

1. Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 16394-16397.
2. Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281-4285.
3. Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278-10279.
4. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16-24.
5. Fountain, K. R.; Felkerson, C. J.; Driskell, J. D.; Lamp, B. D. *J. Org. Chem.* **2003**, *68*, 1810-1814.
6. Fountain, K. R.; Tad-y, D. B.; Paul, T. W.; Golynskiy, M. V. *J. Org. Chem.* **1999**, *64*, 6547-6553.
7. Fountain, K. R. *J. Phys. Org. Chem.* **2005**, *18*, 481-485.
8. Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052-2056.
9. Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 6592-6597.
10. Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 4400-4402.
11. Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327-2330.
12. Pratt, R. F.; Bruice, T. C. *J. Org. Chem.* **1972**, *37*, 3563-3564.
13. Buncel, E.; Um, I. H. *Tetrahedron* **2004**, *60*, 7801-7825.
14. Kirby, A. J.; Manfredi, A. M.; Souza, B. S.; Medeiros, M.; Priebe, J. P.; Brandao, T. A. S.; Nome, F. *Arkivoc* **2009**, *3*, 28-38.
15. Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660-5667.
16. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.
17. Bohme, D. K.; Rakshit, A. B.; Mackay, G. I., *J. Am. Chem. Soc.* **1982**, *104*, 1100-1101.
18. Bohme, D. K.; Mackay, G. I. *J. Am. Chem. Soc.* **1981**, *103*, 978-979.
19. Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986-5992.
20. Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247-350.
21. Um, I. H.; Han, J. Y.; Buncel, E. *Chem.-Eur. J.* **2009**, *15*, 1011-1017.
22. Um, I. H.; Buncel, E. *J. Org. Chem.* **1999**, *65*, 577-582.
23. Um, I. H.; Hwang, S.-J.; Buncel, E. *J. Org. Chem.* **2006**, *71*, 915-920.
24. Kim, M. S.; Min, S. W.; Seo, J. A.; Um, I. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2913-2917.
25. Chen, X.; Brauman, J. I. *J. Am. Chem. Soc.* **2008**, *130*, 15038-15046.
26. Dodd, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1984**, *106*, 5356-5357.
27. Dodd, J. A.; Brauman, J. I. *J. Phys. Chem.* **1986**, *90*, 3559-3562.
28. Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 5993-5999.
29. Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 2672-2680.
30. Laerdahl, J. K.; Uggerud, E. *Int. J. Mass Spectrom.* **2002**, *214*, 277-314.
31. Wladkowski, B. D.; Brauman, J. I. *J. Phys. Chem.* **1993**, *97*, 13158-13164.
32. Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891-899.
33. Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. *Advances in Chemistry Series* **1987**, *215*, 137-153.
34. Uggerud, E., *J. Phys. Org. Chem.* **2006**, *19*, 461-466.
35. Uggerud, E., *Chem.-Eur. J.* **2006**, *12*, 1127-1136.
36. Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511-527.
37. Ren, Y.; Yamataka, H. *Org. Lett.* **2006**, *8*, 119-121.
38. Ren, Y.; Yamataka, H. *Chem.-Eur. J.* **2007**, *13*, 677-682.

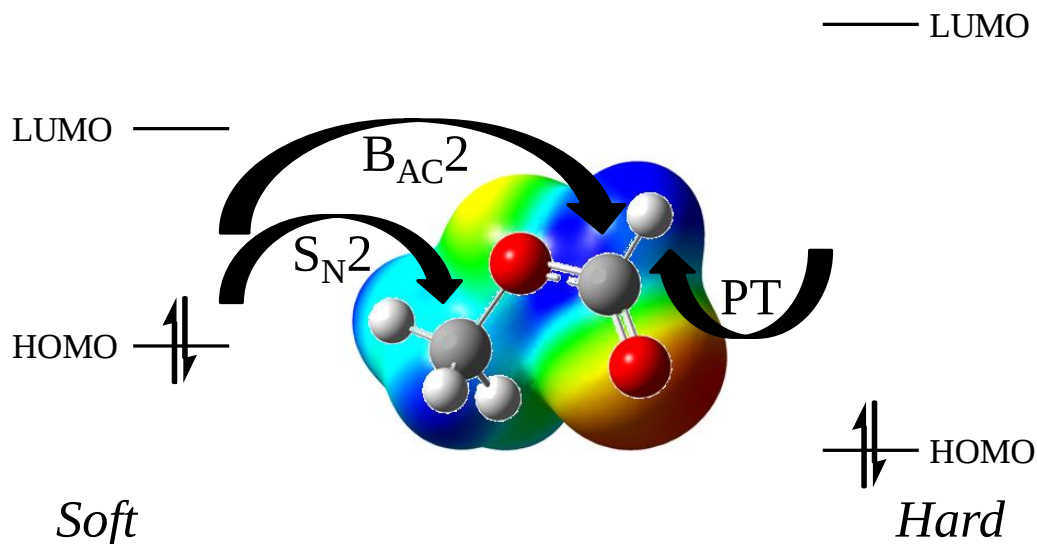
39. Villano, S. M.; Eyet, N.; Lineberger, W. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 8227-8233.
40. Garver, J. M.; Gronert, S.; Bierbaum, V. M. *submitted (J. Am. Chem. Soc.)*
41. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Proc.* **1987**, *81*, 85-100.
42. Villano, S. M.; Eyet, N.; Wren, S. W.; Ellison, G. B.; Bierbaum, V. M.; Lineberger, W. C. *Eur. J. Mass Spectrom.* **2010**, *16*, 255-268.
43. Villano, S. M.; Eyet, N.; Wren, S. W.; Ellison, G. B.; Bierbaum, V. M.; Lineberger, W. C. *J. Phys. Chem. A* **2010**, *114*, 191-200.
44. Su, T.; Chesnavich, W. J., *J. Chem. Phys.* **1982**, *76*, 5183-5185.
45. Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.
46. Ren, Y.; Yamataka, H. *J. Comput. Chem.* **2009**, *30*, 358-365.
47. Bohme, D. K.; Young, L. B. *J. Am. Chem. Soc.* **1970**, *92*, 7354-7358.
48. DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650-8655.
49. Downard, K. M.; Bowie, J. H.; O'Hair, R. A. J.; Krempp, M.; DePuy, C. H. *Int. J. Mass Spectrom. Ion Processes* **1992**, *120*, 217-229.
50. Hoz, S.; Basch, H.; Wolk, J. L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* **1999**, *121*, 7724-7725.
51. Glukhovtsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1996**, *118*, 6273-6284.
52. Gonzales, J. M.; Allen, W. D.; Schaefer, H. F. *J. Phys. Chem. A* **2005**, *109*, 10613-10628.
53. Nomura, Y.; Kubozono, T.; Hidaka, M.; Horibe, M.; Mizushima, N.; Yamamoto, N.; Takahashi, T.; Komiyama, M. *Bioorg. Chem.* **2004**, *32*, 26-37.
54. Bartmess, J. E. "Negative Ion Energetics Data" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. Linstrom, P.J and Mallard, W.G., National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>
55. Lide, D. R. *CRC Handbook of Chemistry and Physics, 89th Ed.* CRC Press: Boca Raton, FL, **2008**; p U552-U552.
56. Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545-3547.
57. Sauers, R. R. *J. Chem. Theory Comput.* **2010**, *6*, 602-606.
58. Adriaanse, C.; Sulpizi, M.; VandeVondele, J.; Sprik, M. *J. Am. Chem. Soc.* **2009**, *131*, 6046-6047.

CHAPTER 7

Intrinsic Reactivity and the α -effect in Elimination Reactions and Competing Mechanisms in the Gas Phase

Adapted from

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Overview

Recently, our studies of the α -effect (enhanced reactivity of nucleophiles with lone pair electrons adjacent to the attacking group) have shown increased nucleophilicity for HOO^- in a series of bimolecular substitution (S_N2) reactions in the gas phase supporting an intrinsic origin of the effect. Our current work continues to explore the behavior of α -nucleophiles by expanding to other reaction systems and mechanisms. We evaluate intrinsic reactivity differences in the elimination (E2) reactions of a series of anions with *tert*-butyl chloride by a Brønsted-type correlation. Additional analysis in the E2 reaction with *tert*-butyl chloride and the S_N2 reaction with methyl chloride is accomplished by reagent pairing of normal and α -nucleophiles of nearly identical proton affinities [$\text{FCH}_2\text{CH}_2\text{O}^-$, PhCH_2O^- , $(\text{CH}_3)_3\text{COO}^-$]. Finally, the relationship between product distributions and the magnitude of the α -effect in the competing reactions of dimethyl methylphosphonate (DMMP) and methyl formate is assessed by reagent pairing (HOO^- versus HO^- , CH_3O^- , $\text{C}_2\text{H}_5\text{O}^-$, and $(\text{CH}_3)_2\text{CHO}^-$). While our results do not indicate significant deviations between the α -anions and the normal anions for the E2 mechanism, enhanced nucleophilicity is observed for both $(\text{CH}_3)_3\text{COO}^-$ and HOO^- . Unlike condensed phase studies, the magnitude of the α -effect in the methyl formate reactions at the sp^3 carbon (nucleophilic substitution, S_N2) and the sp^2 carbon (addition-elimination at the carbonyl center, B_{AC2}) are nearly identical. The behavior of the α -nucleophiles can be rationalized by “soft” base behavior (in the context of hard and soft acids and bases).

7.1 Introduction

Gas phase kinetic studies have provided an indispensable means to probe the energetics and intrinsic reactivity of prototypical organic reactions. This work has led to significant insight on biochemical processes and the mechanism of substrate discrimination.¹⁻³ Other groups have focused on gas phase degradation reactions to evaluate the effectiveness of nucleophiles in the breakdown of neurotoxins and chemical warfare agents.^{4, 5} These efforts have allowed the intrinsic behavior of fundamental reactions to be revealed and extrapolated to solvents and biological environments. Chemical reaction rates are strongly influenced by noncovalent interactions, particularly the ion-stabilizing effect of solvents. Gas phase studies allow the factors inherent to the reactants to be revealed in the absence of solvent effects. When these factors are resolved, the true relationship between the intrinsic character and solvent effects can be understood. One of the most complex areas of interest with regard to these factors is the enhanced reactivity of α -nucleophiles. Recently, our studies of the α -effect have shown enhanced nucleophilicity for HOO^- relative to the proton affinities of normal alkoxides (HO^- , CH_3O^- , and $\text{C}_2\text{H}_5\text{O}^-$) in three separate series of gas phase bimolecular substitution ($\text{S}_{\text{N}}2$) reactions supporting an underlying intrinsic origin of the α -effect.⁶ Our current work focuses on the α -effect in other gas phase reaction mechanisms and systems to further elucidate the nature of the α -effect and to allow these effects to be compared to those in solution.

The term α -effect⁷ has been used to describe the increased reactivity relative to a given basicity for nucleophiles with a lone pair of electrons adjacent to the attacking atom. Magnitudes of the α -effect ($k_{\alpha}/k_{\text{normal}}$) in the range of 5–1000 have been reported in solution for numerous reactions, and mysteriously absent in others.⁸⁻¹⁴ A multifaceted puzzle, the rate enhancement of α -nucleophiles has been found to be highly dependent on the nature of the substrate and the

environment of the reaction. The α -effect has been shown to be small or absent for substrates in which there is a low correlation coefficient (β_{nuc}) in the Brønsted relationship.⁴⁷ The β_{nuc} value is taken as a measure of the extent of bond formation in the transition state (TS). Therefore it is understandable that a smaller TS stabilizing interaction between the α -nucleophile and substrate would be present in a more reactant-like TS. In the Hammond Postulate context, the TS will lower and shift towards product character with increasing leaving group stability, even if the TS more closely resembles the reactants. In some cases the magnitude of the α -effect becomes not only dependent on, but primarily driven by the basicity of the leaving group.¹⁵ The magnitude of the α -effect is also highly dependent on the hybridization ($\text{sp} > \text{sp}^2 > \text{sp}^3$)¹³ and polarizability¹⁶ of the electrophilic center. These interactions follow the principle of hard and soft acids and bases (HSAB),¹⁷ which can be understood by employing perturbation molecular orbital theory.¹⁸ Whereas the energies of interaction for hard acids and bases (non-polarizable) are primarily controlled by electrostatic attractions, soft acids and bases (polarizable) depend on orbital mixing interactions. Hard (normal) anions have a tendency to react poorly with more electronegative sp^2 and sp carbon atoms and polarizable electrophilic centers (softer electrophiles), while the diffuse nature of the nucleophilic center of the α -anions¹⁹ causes a local softness.²⁰

The joint efforts of the Buncl and Um groups have shed light on the α -effect in solution.^{13, 16, 21-26} Variations in the magnitude of the α -effect can be attributed to differential transition state (TS) stabilization and ground state (GS) destabilization effects. Depending on the nucleophile-substrate system studied, either the TS stabilization²² or GS destabilization²⁷ can dominate as the controlling factor in the overall effect. Differential solvation energies between normal and α -nucleophiles of 16 kJ mol^{-1} and 24 kJ mol^{-1} can lead to GS α -effects ($k_{\alpha}/k_{\text{normal}}$) of

750 and 15000.^{13, 27} Due to this complexity, gas phase studies provide a vital link to resolving the intrinsic nature of the α -effect and provide insight into solvent effects.

Gas phase anion chemistry probes the underlying factors that govern many of the common organic reaction schemes (substitutions, eliminations, Grignard additions, aldol condensations, hydrolysis of esters, etc.) and gives rise to a framework from which solvent effects can be understood. Bimolecular ion-neutral gas phase reactions are typically characterized by a classic double-well potential energy surface (PES) model²⁸ where the central barrier reflects a complex interaction of dynamic, energetic, and steric factors inherent to the reactants. In solution, this barrier is modified by the differential charge stabilization energy between the delocalized transition state relative to the reactants and products resulting in a single-barrier PES. These “solvent effects” are evident in the large differences between reaction rate constants of identical gas and condensed phase reactions,^{29, 30} in the reversal of ordering of acidities and basicities,^{31, 32} as well as in the enhanced nucleophilicity of polarizable nucleophiles in solution.²⁸

Recently our research group has reported an α -effect in the gas phase for HOO^- relative to the proton affinities of normal alkoxides (HO^- , CH_3O^- , and $\text{C}_2\text{H}_5\text{O}^-$) in three separate reaction series (methyl fluoride, anisole, and 4-fluoroanisole) validating an intrinsic origin of the effect.⁶ Based on these results, a Marcus theory³³ approach was employed to resolve discrepancies between experimental³⁴ and computational^{35, 36} studies on the existence of the α -effect in $\text{S}_{\text{N}}2$ reactions with CH_3Cl .³⁷ Marcus theory indicates that the intrinsic differences between normal and α -nucleophiles are small and can be easily masked by thermodynamic driving forces. Furthermore, large variations between the ionic character of the α -nucleophiles and normal nucleophiles can be magnified by solvent effects.

Based on our new understanding of the expected magnitude of the α -effect and the narrow window for resolving small intrinsic differences in the gas phase, we expand our studies of the behavior of α -nucleophiles to other reaction systems and mechanisms. Often gas phase nucleophilic substitution reactions are in competition with other processes, such as elimination and proton transfer reactions. Although all of these processes can be described with a double-well potential energy surface (Figure 7.1), differences in the transition states lead to variations in the controlling factors for the reaction pathways. The proton transfer TS has

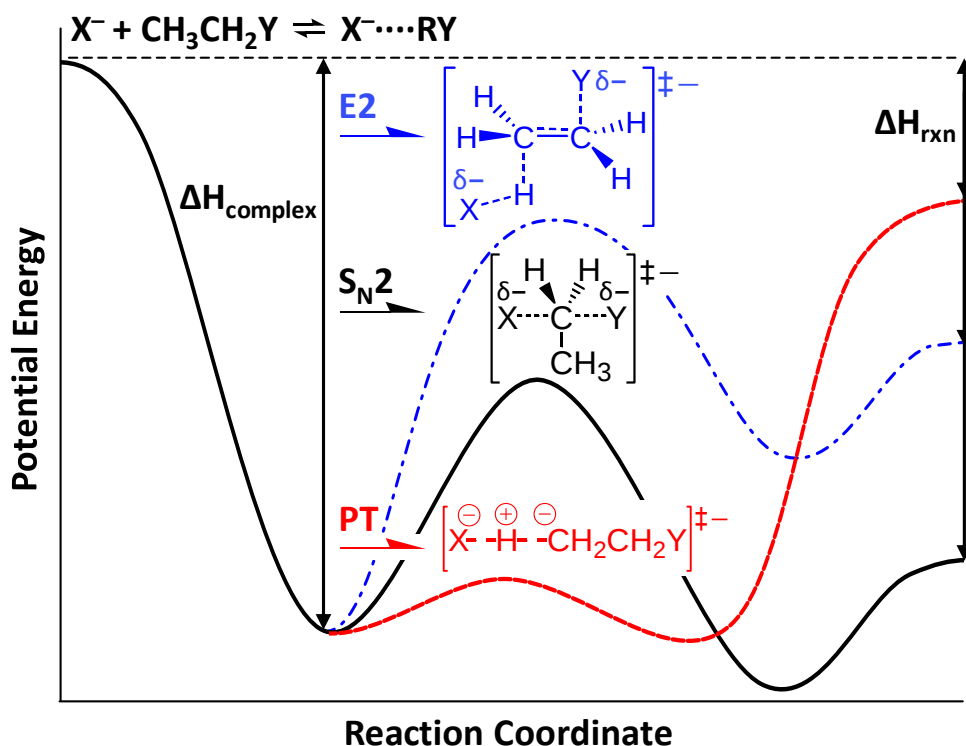


Figure 7.1 Generic gas phase double-well potential energy surfaces for competing bimolecular elimination (E2), bimolecular substitution (S_N2), and proton transfer (PT) reactions.

significant “ion-triplet” character,^{38, 39} $[X^- \cdots H^+ \cdots RY]$, where “loose” electrostatic forces result in a nearly barrierless reaction. Due to the shallow barrier, most proton transfer reactions have single-well reaction characteristics where the reactivity is primarily related to the exothermicity of reaction (ΔH_{rxn}). The bimolecular elimination (E2) and substitution (S_N2) reactions are

controlled by their central barriers. The highly structured E2 and S_N2 TS are entropically hindered raising the enthalpic barriers depicted in Figure 7.1 (The E2 TS is looser and has smaller entropic barriers than the S_N2 TS⁴⁰). In envisioning these entropic effects for the reactions depicted above, nearly equivalent controlling free-energy barriers and competing processes are expected. Proton transfer is often statistically favored over the S_N2 process and will dominate product distributions when proton transfer is thermodynamically favored. Even when 5 kJ mol⁻¹ endothermic, an “entropy-driven” proton transfer reaction will compete with an S_N2 channel with a central barrier that lies 29 kJ mol⁻¹ below the energy of the separated reactants.⁴¹ In fact, S_N2 entropic barriers are so large that the E2 channel will dominate in systems where the S_N2 barrier is marginally smaller (4–8 kJ mol⁻¹) than the E2 barrier.⁴² Seemingly small changes in the relative barrier heights (such as those in the α -effect) can have large effects on product distributions.

In this study, we investigate the reactivity trends and α -effect for a series of reactions in single-channel reaction substrates (*tert*-butyl chloride and methyl chloride), as well as two competitive reaction systems (dimethyl methylphosphonate and methyl formate). A Brønsted-type correlation is employed to discern differences in reactivity as a function of proton affinity in the E2 reactions of a series of anions with *tert*-butyl chloride. To refine our assessment of intrinsic differences, we narrowed our focus to reagent pairing of normal and α -nucleophiles (FCH₂CH₂O⁻, PhCH₂O⁻, (CH₃)₃COO⁻) in the E2 reaction with *tert*-butyl chloride and the S_N2 reaction with methyl chloride. We then expand our reagent pairing (HOO⁻ versus HO⁻, CH₃O⁻, C₂H₅O⁻, and (CH₃)₂CHO⁻) in the competing reactions of dimethyl methylphosphonate and methyl formate to assess the relationship between product distributions and the magnitude of the

α -effect. Computational transition state barriers and exothermicities of reaction are employed to aid in our discussions of intrinsic differences between anions.

7.2 Experimental

7.2.1 Ion-Molecule Reactions

These reactions were carried out in a flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer, which has been previously described.⁴³ Briefly, this instrument consists of four sections: an ion source, an ion selection region, a reaction flow tube, and a detection system. A flowing afterglow ion source is used to produce ions, which are mass-selected using a quadrupole mass filter prior to injection into the reaction flow tube. Hydroxide was prepared by electron ionization (70 eV) of methane and nitrous oxide (2:1 ratio). Most other ionic reagents were generated by proton abstraction of neutrals by HO^- . The peroxyformate, HC(O)OO^- , and peroxyacetate anions, $\text{CH}_3\text{C(O)OO}^-$, were synthesized in a gas-phase Baeyer-Villiger reaction of HOO^- with methyl formate and methyl acetate as previously described.^{44, 45} Injected ions are entrained in a flow of helium ($200 \text{ std cm}^3 \text{ s}^{-1}$, 0.5 torr) and thermalized to $300 \pm 2 \text{ K}$ prior to reactions with neutral reagents that are added through multiple inlets along the length of the reaction flow tube. Ionic reactants and products are analyzed in the detection region using a triple-quadrupole mass filter and an electron multiplier. The reactions are carried out under pseudo-first order conditions (reactant ion $\sim 10^5 \text{ ions cm}^{-3}$; neutral reactant $\sim 10^{11} \text{ molecules cm}^{-3}$), and the reported branching ratios and reaction rate coefficients are the averages of at least three individual measurements. Product branching ratios are determined by extrapolating the observed product yields to zero reaction distance in order to extract the initial ratios due to primary reactions. The reported reaction efficiencies are the experimental rate constant divided by the calculated collision rate constants. Collision rate constants were calculated from parameterized

trajectory collision rate theory.⁴⁶ Error bars represent one standard deviation in the data; absolute uncertainties in these rate constant measurements are $\pm 20\%$. The detection system was tuned to minimize mass discrimination, and no further corrections were made in the analysis.

7.2.2 Materials

All compounds were obtained from commercial vendors. These compounds include *tert*-butyl chloride, $(\text{CH}_3)_3\text{CCl}$, Aldrich, 99%; methyl chloride, CH_3Cl , Matheson, 99.5%; dimethyl methylphosphonate, $\text{CH}_3\text{PO}(\text{OCH}_3)_2$, Aldrich, 97%; methyl formate, HCOOCH_3 , Aldrich, 99% (anhydrous); *tert*-butyl hydrogenperoxide, $(\text{CH}_3)_3\text{COOH}$, Aldrich, 90% (10% H_2O); 2-fluoroethanol, $\text{FCH}_2\text{CH}_2\text{OH}$, Aldrich, 95%; benzyl alcohol, $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$, Aldrich, 99.8% (anhydrous); hydrogen peroxide, HOOH , Sigma-Aldrich, 50 wt. % solution in water; methanol, CH_3OH , Aldrich, 99.9%; methanol- d_4 , CD_3OD , CDN Isotopes, 99.8% D; ethanol, $\text{C}_2\text{H}_5\text{OH}$, Decon Laboratories, 200 proof; Ethyl-1,1- d_2 alcohol, $\text{CH}_3\text{CD}_2\text{OH}$, Aldrich, 98% D; 2-propanol, $(\text{CH}_3)_2\text{CHOH}$, Aldrich, 99%; methyl acetate, $\text{CH}_3\text{C}(\text{O})\text{OCH}_3$, Fluka, >99.9%; phenol, $\text{C}_6\text{H}_5\text{OH}$, Sigma-Aldrich, ~99%; formic acid $\text{HC}(\text{O})\text{OH}$, Sigma-Aldrich, $\geq 95\%$; and acetic acid, $\text{CH}_3\text{C}(\text{O})\text{OH}$, Sigma-Aldrich, $\geq 99\%$. The reagents were protected from light and stored under vacuum. Helium buffer gas (99.995%) was purified by passage through a molecular sieve trap immersed in liquid nitrogen.

7.2.3 Computational Methods

Ab initio molecular orbital calculations were carried out with the G3MP2 method using the Gaussian 09 suite of programs.⁴⁷ Frequency calculations were carried out for all species to establish their nature as local minima or transition states. Enthalpy changes were calculated from the energies of the optimized structures, and thermal corrections included for 298 K without scaling of the calculated vibrational frequencies.

7.3 Results and Discussion

7.3.1 Brønsted Correlation (E2 Mechanism)

Recent computational work by Ren and Yamataka indicate the existence of the α -effect in the gas phase for a series of E2 reactions with alkyl chlorides.^{48, 49} Since competition exists between the S_N2 and E2 processes within the ethyl and isopropyl chloride substrates and both reactions produce the same ionic product (non-distinguishable in mass spectrometry), we employed *tert*-butyl chloride as the substrate for our E2 investigation. Because of steric hindrance, the S_N2 reaction is severely inhibited for *tert*-butyl chloride and therefore the reactivity measured is directly related to the E2 process.^{42, 50-52} The experimental data for the reactions of the normal and α -anions are shown in terms of a Brønsted-type plot in Figure 7.2 where the y-axis is the logarithmic scale of the reaction efficiency and the x-axis is the gas phase proton affinity^{44, 45, 53, 54} of the anion. Due to variations in collision rates, reaction efficiencies are employed to normalize the reaction rate constants for comparisons. These values represent the fraction of collisions that result in a reaction. Blue represents the normal oxyanions and red the oxygen α -nucleophiles. Efficiencies are determined from previously reported experimental rate constants^{34, 55, 56} and this work (anions 11–15) at 300 ± 2 K. Our measured rate constants for $\text{HC(O)}\text{O}^-$, $\text{C}_6\text{H}_5\text{O}^-$, and $\text{HC(O)}\text{OO}^-$ were $6.23 \pm 0.35 \times 10^{-12}$, $4.00 \pm 0.21 \times 10^{-12}$, and $2.75 \pm 0.41 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$, respectively. The changes in ion signal intensities were too low to measure an accurate rate constant for $\text{CH}_3\text{C(O)}\text{O}^-$ and $\text{CH}_3\text{C(O)}\text{OO}^-$ (hence an upper limit of $1 \times 10^{-12} \text{ cm}^3 \text{ s}^{-1}$).

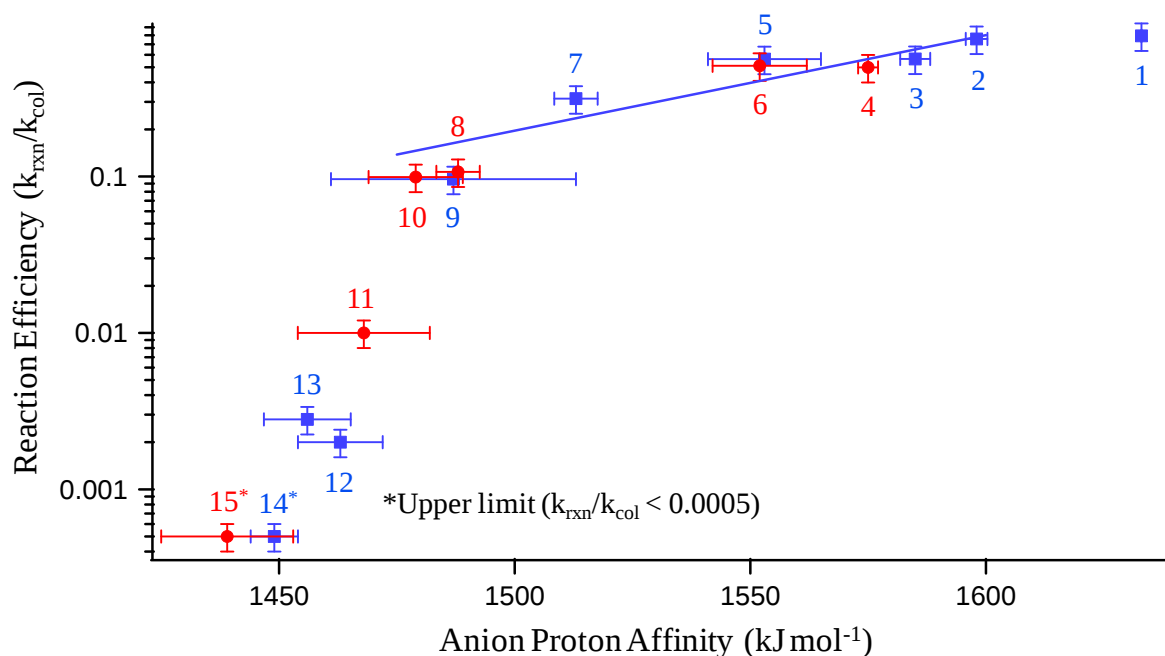


Figure 7.2 Brønsted correlation where y-axis is the logarithmic scale of the E2 reaction efficiency for the anion with $(\text{CH}_3)_3\text{CCl}$ and the x-axis is the gas phase proton affinity of the anion (refs 44, 45, 53, 54). Reaction efficiencies calculated with rate constants (k_{rxn}) from this work (anions 11-15) and refs 34, 55, 56 and parameterized trajectory theory (ref 46) collision rates (k_{col}). (■ normal oxyanions, ● α -oxyanions): 1. HO^- 2. CH_3O^- 3. $\text{C}_2\text{H}_5\text{O}^-$ 4. HOO^- 5. $\text{CFH}_2\text{CH}_2\text{O}^-$ 6. $(\text{CH}_3)_3\text{COO}^-$ 7. $\text{CF}_3\text{CH}_2\text{O}^-$ 8. ClO^- 9. $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}^-$ 10. BrO^- 11. HC(O)OO^- 12. $\text{C}_6\text{H}_5\text{O}^-$ 13. HC(O)O^- 14. $\text{CH}_3\text{C(O)O}^-$ 15. $\text{CH}_3\text{C(O)OO}^-$

In Figure 7.2, we note that the free-energy relationship between reactivity and basicity is predominantly linear; however, there is a slight curvature in the plot that increases at lower basicities. Although there is a strong correlation of reactivity with basicity, the non-linear behavior indicates significant contributions from other factors to the activation barrier. Such curvature has been attributed to minor shifts in TS structures.⁵⁷ The term “variable E2 transition state” has been used to describe the E2 mechanism due to the varying degrees of proton transfer from C_β to the attacking base, the formation of a π bond between C_α and C_β , and the departure of a leaving group Y^- from C_α in the TS.⁵⁸ For strong bases, very strong hydrogen bonding exists

between the anion and proton resulting in a TS with a large degree of carbanionic character at C_α . As the strength of the base decreases, larger shifts in electron density within the substrate are required to facilitate the departure of the leaving group resulting in more carbocation character at the C_α in the TS. This shift in the nature of the TS is perpendicular to the reaction coordinate and produces non-linear behavior in Brønsted correlations.⁵⁷ The Brønsted plot would be curved, concave downward, with increasing tangent angles for less reactive anions. This type of trend is supported by electron density shifts in the NPA (natural population analysis computational method) charge distributions and corresponding deformation energies reported by Ren and Yamataka.^{48, 49} This implies a dependence of the E2 mechanism on the charge distribution within the attacking group, as well as the proton affinity. A similar relationship was reported by means of a two-parameter (proton affinity and electronegativity) equation to estimate barrier heights in the E2 reactions.⁵⁹ It is important to attribute some of the curvature in our Brønsted correlations to a flattening at higher basicities as the reaction efficiencies approach the collision rate. However, the ability to resolve intrinsic differences in reagent pairs at a proton affinity of 1550 kJ mol^{-1} (see below), shows that the reactivity is still primarily controlled by barrier heights at the heart of the Brønsted plot.

While the ability to make linear correlations from our data is restricted, the overall trends in Figure 7.2 do not show any significant deviations between the α -anions and the normal anions. Small shifts may hint that the α -anions are more reactive than normal anions at lower basicities (anions 8 and 10 relative to 9) and less reactive than more basic normal anions (anions 6 and 4 relative to 3 and 5). It is interesting to note that Ren and Yamataka's data also suggest smaller shifts in NPA charge distributions and deformation energies for the α -anions when compared to the normal anions.^{48, 49} Based on the variable transition state model, smaller shifts would result

in a more linear relationship with proton affinity. If such a relationship exists, the variations in reactivity are extremely small (within the experimental uncertainty of our measurements) and cannot be confirmed without more definitive experimental evidence.

7.3.2 Reagent Pairing [$\text{FCH}_2\text{CH}_2\text{O}^-$, $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$, $(\text{CH}_3)_3\text{COO}^-$]

Due to the non-linear behavior in our Brønsted correlations, we attempted to find normal oxyanions and α -oxyanions of similar structure and proton affinities to evaluate as reagent pairs. The selection of the anion of *tert*-butyl hydroperoxide as the α -nucleophile allowed us to pair both the anion of benzyl alcohol and 2-fluoroethoxide in our α -effect evaluations. The proton affinities (PA), exothermicity of reaction (ΔH_{rxn}), reaction rate constants (k_{rxn}), reaction efficiency (Eff), α -effect ($\text{Eff}_\alpha/\text{Eff}_{\text{Normal}}$), and computational barrier heights ($\Delta H^\ddagger$) for these anions in the $\text{S}_{\text{N}}2$ reactions with methyl chloride and the E2 reactions with *tert*-butyl chloride are listed in Table 7.1. In both the $\text{S}_{\text{N}}2$ and E2 system the reaction rate constants are moderately fast resulting in similar reaction efficiencies ($\text{Eff} = 0.24\text{--}0.56$) which correspond well with the G3MP2 activation barriers.

7.3.2.1 $\text{S}_{\text{N}}2$ Reactions

Our reaction rate constants and efficiencies are slightly higher than those reported for CH_3Cl with $\text{FCH}_2\text{CH}_2\text{O}^-$ ($\text{Eff} = 0.19$) and $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$ ($\text{Eff} = 0.20$) by Chen and Brauman, but the agreement is reasonable considering the variations in the experimental techniques.⁶⁰

Differences in the experimental conditions (ΔT 50 K) between the Fourier transform ion cyclotron resonance spectrometer (FT-ICR) and FA-SIFT MS result in slight shifts in TS barriers due to the negative temperature dependence of the tight $\text{S}_{\text{N}}2$ TS in the double-well potential energy surface. The α -effect (1.6 and 2.1) is manifested in the relative reaction efficiencies for the $\text{S}_{\text{N}}2$ reactions. The limited magnitude of the effect (≤ 20) is consistent with earlier estimates

Table 7.1. Thermodynamic and Kinetic Data with Associated Barriers for the Reagent Pairing [$\text{FCH}_2\text{CH}_2\text{O}^-$, $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$, and $(\text{CH}_3)_3\text{COO}^-$] in the $\text{S}_{\text{N}}2$ Reactions with CH_3Cl and the E2 Reactions with $(\text{CH}_3)_3\text{CCl}$ to Evaluate the α -effect.

		Thermodynamic Data (kJ mol^{-1})		Kinetic Data		α -effect	$\Delta\text{H}^\ddagger$ (kJ mol^{-1})
Reaction ($\text{X}^- + \text{M}$)		PA (X^-) ^a	$\Delta\text{H}_{\text{rxn}}$ ^b (G3MP2)	k_{rxn} ($\times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$) ^c	Eff	$\left[\frac{\text{Eff}_\alpha}{\text{Eff}_{\text{normal}}} \right]$	G3MP2
$\text{S}_{\text{N}}2$	$\text{FCH}_2\text{CH}_2\text{O}^- + \text{CH}_3\text{Cl}$	1553 ± 12	-130 (-149)	6.28 ± 0.20	0.31	1.6	-37.4
	$\text{C}_6\text{H}_5\text{CH}_2\text{O}^- + \text{CH}_3\text{Cl}$	1548 ± 9	-125 (-148)	4.46 ± 0.09	0.24	2.1	-31.8
	$(\text{CH}_3)_3\text{COO}^- + \text{CH}_3\text{Cl}$	1552 ± 9	-141 (-164)	9.74 ± 0.20	0.51		-44.9
E2	$\text{FCH}_2\text{CH}_2\text{O}^- + (\text{CH}_3)_3\text{CCl}$	1553 ± 12	-88.3 (-80.0)	12.3 ± 0.2	0.56	0.9	-35.1
	$\text{C}_6\text{H}_5\text{CH}_2\text{O}^- + (\text{CH}_3)_3\text{CCl}$	1548 ± 9	-83.3 (-73.7)	5.17 ± 0.10	0.27	1.9	-32.2
	$(\text{CH}_3)_3\text{COO}^- + (\text{CH}_3)_3\text{CCl}$	1552 ± 9	-87.3 (-82.3)	10.2 ± 0.2	0.51		-39.6

^aproton affinities from ref 53; G3MP2 proton affinities (kJ mol^{-1}): $\text{FCH}_2\text{CH}_2\text{O}^-$ (1544), $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$ (1538), $(\text{CH}_3)_3\text{COO}^-$ (1547). ^bExothermicity of reaction ($\Delta\text{H}_{\text{rxn}}$) calculated from gas phase heats of formation (ΔH_f) from ref 53 and an estimated ΔH_f for the $\text{S}_{\text{N}}2$ neutral products using additivity rules; numbers in parentheses are calculated $\Delta\text{H}_{\text{rxn}}$ using the G3MP2 method. ^cError bars represent one standard deviation of the mean of three or more measurements; absolute accuracy is $\pm 20\%$; efficiency (Eff) is the ratio of the branching rate constants ($k_{\text{PT or SN2}} = k_{\text{rxn}} \times \text{BR}$) to the collision rate constant (k_{col}) calculated using parameterized trajectory collision theory (ref 46).

of nucleophilic intrinsic differences ($\sim 7 \text{ kJ mol}^{-1}$) between α -peroxyanions and normal oxyanions.³⁷ Our computational S_N2 barriers support both a slightly higher intrinsic barrier for $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$ relative to $\text{FCH}_2\text{CH}_2\text{O}^-$ and a lower barrier for $(\text{CH}_3)_3\text{COO}^-$ relative to both normal anions. While the α -nucleophile displays enhanced reactivity relative to proton affinity, part of this effect must be attributed to the larger exothermicity of reaction ($>10 \text{ kJ mol}^{-1}$). A similar disparity between the proton affinities and methyl cation affinities of the hydrogen peroxide anion compared to normal alkoxides has been reported in our earlier work.⁶

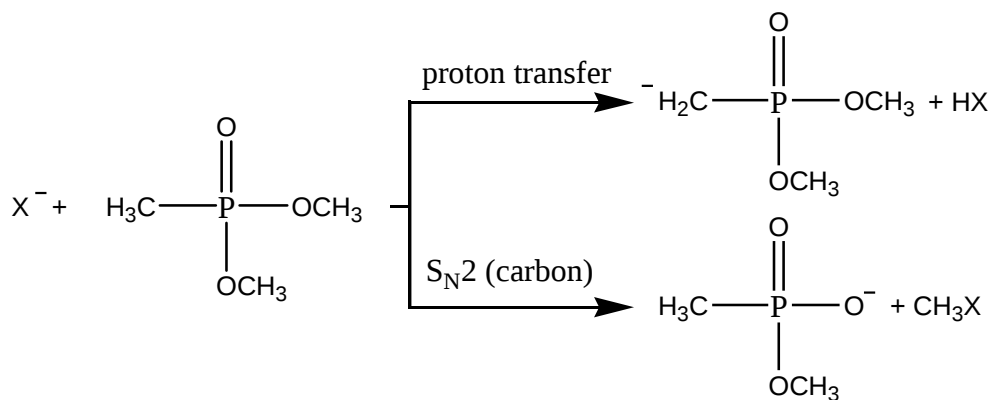
7.3.2.2 E2 Reactions

Our experimental reaction efficiencies correlate extremely well with the proton affinities and exothermicities of reaction, which is expected due to the deprotonation component of the E2 mechanism. Such strong correlations show a high sensitivity in reactivity to proton affinities. The proton affinity of $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$ is about 5 kJ mol^{-1} lower than that of the other anions, therefore $\text{FCH}_2\text{CH}_2\text{O}^-$ and $(\text{CH}_3)_3\text{COO}^-$ provide the best reagent pairing to evaluate the α -effect in the E2 system. The reaction efficiency of $(\text{CH}_3)_3\text{COO}^-$ is slightly less than that of $\text{FCH}_2\text{CH}_2\text{O}^-$; however, the efficiencies are the same within experimental error. Even though our computational E2 barriers are higher than those for the S_N2 reactions, our overall reaction rate constants are slightly larger due to a smaller entropic barrier in the E2 TS. The differences between the E2 barriers are also smaller than those of the S_N2 system, suggesting more similar reaction efficiencies and smaller intrinsic differences between anions. A lower computational barrier for $(\text{CH}_3)_3\text{COO}^-$ relative to $\text{FCH}_2\text{CH}_2\text{O}^-$ suggests the existence of an α -effect that is not reflected in our experimental data. Assuming our capability to resolve reactivity differences of $\pm 20\%$, the reaction efficiencies should be able to reflect differences in overall activation barrier heights greater than 1 kJ mol^{-1} . In more exothermic reactions smaller barriers will have less

influence on the reactant ion-dipole complex and this sensitivity will decrease. Work by Chen and Brauman using RRKM fitting to estimate barrier heights from reaction efficiencies suggests that at similar barrier heights to those in our reaction studies this sensitivity decreases to around 4 kJ mol⁻¹.⁶⁰ While we are attempting to understand differences in experimental data and trends in computational data, we recognize that the barrier heights have the inherent chemical inaccuracy (~ 10 kJ mol⁻¹) of any computational method. If an α -effect does exist in the E2 reaction, intrinsic differences between (CH₃)₃COO⁻ and FCH₂CH₂O⁻ must be small (≤ 4 kJ mol⁻¹) to be experimentally masked at the given computational barrier levels and measured reaction efficiencies.

7.3.3 Dimethyl Methylphosphonate

Several gas phase studies of negative ions reacting with the organophosphate nerve agent (GX) surrogate, dimethyl methylphosphonate (DMMP), have been performed.^{5, 61, 62} As the basicity of the anions approaches the proton affinity of DMMP (1560 ± 12 kJ mol⁻¹)⁶², both the S_N2 and PT channels become active (Scheme 7.1). McAnoy et al. reported significant



Scheme 7.1

differences in the branching ratios (S_N2:PT) in the reactions of HOO⁻ (89%:11%) and CD₃O⁻ (3%:97%) with DMMP. Since HOO⁻ and CD₃O⁻ have similar proton affinities, this difference

in branching ratios was attributed to a greater nucleophilicity of HOO^- ; however, the absolute rate constants were not measured, which may have allowed an assessment of the α -effect. In an effort to further resolve the intrinsic reactivity of the HOO^- anion, we have measured the overall reaction rate constants (k_{rxn}) and branching fractions (BR) for the reactions of HOO^- , CD_3O^- , and $(\text{CH}_3)_2\text{CHO}^-$ with DMMP. These results and the associated exothermicities of reaction (ΔH_{rxn}) and $\text{S}_{\text{N}}2$ barriers ($\Delta H^\ddagger$) relative to the reactants calculated by the G3MP2 method are listed in Table 7.2.

The reported branching fractions in Table 7.2 are consistent with previously reported values.^{5,62} The overall rate constants are relatively large for gas phase reactions, yet the reaction efficiencies are less than 50% of the collision rate. This is surprising given that all the reactions have access to a barrierless PT channel, especially in the more exothermic CD_3O^- reaction. McAnoy et al. estimated Arrhenius pre-exponential factors that favored the $\text{S}_{\text{N}}2$ (carbon) process over the PT channel.⁵ If the $\text{S}_{\text{N}}2$ process is favored in reaction dynamics, the PT transfer efficiency could be significantly reduced. It does not appear that the PT reactions of CD_3O^- and $(\text{CH}_3)_2\text{CHO}^-$ reach the collision controlled limit and non-statistical dynamics may play a role.

The most striking feature in the data is the large shift in partitioning to favor the $\text{S}_{\text{N}}2$ products for HOO^- relative to the normal anions supporting the conclusion of McAnoy et al. that the α -effect does exist in this system. Our computational $\text{S}_{\text{N}}2$ barriers support this enhanced nucleophilicity for HOO^- . The shift in exothermicities of the $\text{S}_{\text{N}}2$ reaction reflects a disparity between the proton affinities and methyl cation affinities of the α -nucleophile relative to the normal anions in our study. In the reactions studied by Lum and Grabowski, the branching ratios

Table 7.2 Kinetic Data and Branching Fractions with Relevant Thermodynamic Data (kJ mol⁻¹) for the Reactions of CD₃O⁻, HOO⁻, and (CH₃)₂CHO⁻ with Dimethyl Methylphosphonate (DMMP)

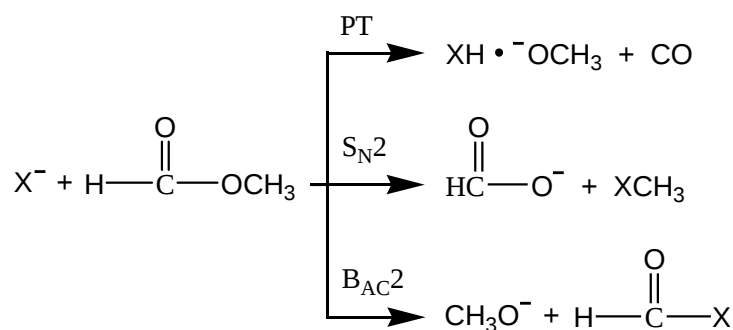
Reaction (X ⁻ + DMMP)	PA (X ⁻) ^a	Kinetic Data	S _N 2			PT	
		k _{rxn} (x10 ⁻⁹) ^b	BR (Eff) ^c	ΔH ^{‡d}	ΔH _{rxn} ^e	BR (Eff) ^c	ΔH _{rxn} ^e
CD ₃ O ⁻ + DMMP	1598 ± 2	1.80 ± 0.02	3% (0.01)	-45.7	-214	97% (0.47)	-40.1
HOO ⁻ + DMMP	1575 ± 2	1.73 ± 0.01	83% (0.38)	-53.7	-198	17% (0.08)	-17.1
(CH ₃) ₂ CHO ⁻ + DMMP	1576 ± 4	1.55 ± 0.01	7% (0.04)	-31.7	-185	93% (0.48)	-14.6

^aProton affinity (PA) from refs 53 and 54. ^bOverall rate constant (k_{rxn}) in units of cm³ s⁻¹; error bars represent one standard deviation of the mean of three or more measurements; absolute accuracy is ± 20%. ^cBimolecular nucleophilic substitution (S_N2) and proton transfer (PT) product branching fractions (BR); efficiency (Eff) is the ratio of the branching rate constants (k_{PT or SN2} = k_{rxn} × BR) to the collision rate constant (k_{col}) calculated using parameterized trajectory collision theory (ref 46); dipole moment (μ = 3.76 D) and polarizability (α = 1.01 × 10⁻²³ cm³) of DMMP from ref 61. ^dBarrier heights (ΔH[‡]) are relative to the reactants calculated by G3MP2 method. ^eExothermicity of reaction (ΔH_{rxn}) calculated by G3MP2 method.

(S_N2:PT) shift slightly towards the S_N2 products as the proton affinity of the anion decreases approaching the proton affinity of DMMP. This result indicates a slowing of the PT process relative to the S_N2 reaction with decreasing anion basicity. The overall rate constant and partitioning is clearly dominated by the proton transfer channel in our studies of the CD₃O[−] reaction. Any attempt to evaluate the magnitude of the α-effect from these data would be flawed. However, the increase in the S_N2 products in the (CH₃)₂CHO[−] reaction (even with a higher barrier), suggests that the PT process has slowed enough to allow the S_N2 barrier to be reflected in partitioning and therefore in the overall rate constant and efficiencies. The S_N2 barrier heights indicate a significant intrinsic difference in the nucleophilicity of HOO[−] relative to (CH₃)₂CHO[−]. If we were to evaluate the α-effect (Eff_{HOO[−]}/Eff_{(CH₃)₂CHO[−]}) with DMMP of this reagent pair, HOO[−] is 9.5 times more efficient. While this is a fairly significant effect for a gas phase reaction, it is difficult to separate the true effect of the PT channel on partitioning. Furthermore, the possible influence of non-statistical dynamics makes the situation more complex and the analysis problematic.

7.3.4 Methyl Formate

Several gas phase studies have examined nucleophilic reactions with methyl formate.⁶³⁻⁶⁷ While secondary reactions lead to variations in products, there are three primary reaction channels (Scheme 7.2): proton transfer (PT), bimolecular nucleophilic substitution (S_N2), and addition-elimination at the carbonyl center (B_{AC}2). Since the direct proton transfer channel for most of our reactions is endothermic, the dominant PT process observed in our studies is driven by the formation of CO and solvated anionic clusters (Riveros reaction⁶⁸). While the α-effect has been reported for nucleophilic ester cleavage in solution,¹⁵ the reactions of esters in solution are



Scheme 7.2

dominated by the B_{AC}2 mechanism.⁶³ In an earlier gas phase study, similar branching fractions (S_N2:PT:B_{AC}2) in the reactions of HOO[−] (8%:64%:28%) and HO[−] (5%:61%:34%) with methyl formate were found.⁶⁵ Based on this typical reagent pairing used in evaluating the α-effect, the conclusion was reached that no α-effect existed in the gas phase. Patterson and Fountain have suggested that these experimental gas phase methyl formate data do support an α-effect and rationalize enhanced reactivity in HOO[−] due to a high degree of single-electron-transfer character.⁶⁹ They argue that assessment of the α-effect in the gas phase requires strict adherence to the matched acidities in reagent pairing between the normal and α-nucleophiles. In order to more effectively evaluate intrinsic differences in the methyl formate reactions, we have expanded the reagent pairing of HOO[−] with HO[−], CH₃O[−], C₂H₅O[−], and (CH₃)₂CHO[−]. Deuterated analogs were employed when necessary to differentiate reaction pathways. Kinetic data and branching fractions with relevant thermodynamic data (kJ mol^{−1}) for the reactions of HOO[−], CD₃O[−], CH₃CD₂O[−] and (CH₃)₂CHO[−] with methyl formate are listed in Table 7.3.

Our branching fractions and overall reaction rate constants are in good agreement with previously reported values.^{64, 65} While earlier work⁶⁴ suspected a B_{AC}2 pathway with CD₃O[−], no undeuterated methoxide was observed as a product. Our current work reports observations of an ionic mass corresponding to the production of CH₃O[−] and a secondary reaction of CH₃O[−]

through a PT channel to produce a $\text{CH}_3\text{O}^- \cdot \text{CH}_3\text{OH}$ cluster in both the CD_3O^- and the $\text{CH}_3\text{CD}_2\text{O}^-$ reactions. We attribute this formation of CH_3O^- to the $\text{B}_{\text{AC}2}$ channel because the PT channel capable of producing the non-solvated CH_3O^- for both anions is more endothermic by approximately 45 kJ mol^{-1} (see appendix 3). Based on this assumption, we report branching fractions and efficiencies for the $\text{B}_{\text{AC}2}$ channel in these reactions. A trace ($< 1\%$) of $\text{S}_{\text{N}2}$ products (HCOO^-) is observed in the reaction of methyl formate with $\text{CH}_3\text{CD}_2\text{O}^-$; however, we could not effectively extrapolate the small yield to zero reaction distance to determine an exact branching fraction. Therefore, we place an upper limit of 1% and approximate an α -effect at this limit for $\text{CH}_3\text{CD}_2\text{O}^-$.

All of the reactions with methyl formate have a high efficiency. While the total reaction efficiency of HO^- is 72%, the other anions span a narrow range of 61-64%. Trends in branching fractions and associated efficiencies indicate that the relative differences in barriers are influencing the partitioning of products and the data can be used to evaluate intrinsic differences in each channel. Computational analysis of the methyl formate reaction system by Pliego and Riveros indicates that the PT channel follows a single-well potential, the $\text{S}_{\text{N}2}$ reaction occurs by a double-well potential, and the $\text{B}_{\text{AC}2}$ reaction progresses through a multi-well potential with the controlling barrier being the formation of a tetrahedral intermediate.⁷¹ Table 7.3 displays the controlling barriers for the $\text{S}_{\text{N}2}$ and $\text{B}_{\text{AC}2}$ processes and the exothermicity of reaction for the PT formation of the solvated products determined by the G3MP2 method. The $\text{S}_{\text{N}2}$ and $\text{B}_{\text{AC}2}$ reaction efficiencies track nicely with the corresponding barrier heights; however, the efficiencies of the PT channel seem low for the given exothermicities of reaction. The PT pathway has been described as a direct formation of a methoxide ion bound to two neutral molecules ($\text{CH}_3\text{O}^- \cdot \text{CO} \cdot \text{HX}$), rather than a step-wise proton abstraction from the formyl group.⁷¹

Table 7.3 Kinetic Data and Branching Fractions with Relevant Thermodynamic Data (kJ mol⁻¹) for the Reactions of HO⁻, CD₃O⁻, CH₃CD₂O⁻, HOO⁻ and (CH₃)₂CHO⁻ with methyl formate

Reaction		Kinetic Data	S _N 2			PT		B _{AC} 2		
(X ⁻ + HCOOCH ₃)	PA (X ⁻) ^a	k _{rxn} (x10 ⁻⁹) ^b	BR (Eff) ^c	ΔH ^{‡d}	α-effect	BR (Eff) ^c	ΔH _{rxn} ^d	BR (Eff) ^c	ΔH ^{‡d}	α-effect
HO ⁻ + HCOOCH ₃	1633 ± 0	1.73 ± 0.03	8% (0.05)	-39.3	1.0	59% (0.47)	-83.1	33% (0.20)	-52.6	0.9
CD ₃ O ⁻ + HCOOCH ₃	1598 ± 2	1.33 ± 0.03	3% (0.02)	-31.6	2.5	79% (0.48)	-64.3	18% (0.11)	-47.8	1.5
CH ₃ CD ₂ O ⁻ + HCOOCH ₃	1585 ± 3	1.25 ± 0.02	< 1%	-21.8	~13.5	97% (0.62)	-52.5	3% (0.02)	-44.7	8.5
HOO ⁻ + HCOOCH ₃	1575 ± 2	1.34 ± 0.03	8% (0.05)	-35.7		64% (0.39)	-75.8	28% (0.17)	-55.2	
(CH ₃) ₂ CHO ⁻ + HCOOCH ₃	1576 ± 4	1.20 ± 0.02	---	-13.1	---	100% (0.64)	-47.3	---	-43.5	---

^aProton affinity (PA) from refs 53 and 54. ^bOverall rate constant (k_{rxn}) in units of cm³ s⁻¹; error bars represent one standard deviation of the mean of three or more measurements; absolute accuracy is ± 20%. ^cBimolecular nucleophilic substitution (S_N2), proton transfer (PT), and addition-elimination at the carbonyl center (B_{AC}2), product branching fractions (BR); efficiency (Eff) is the ratio of the branching rate constants (k_{S_N2, PT or B_{AC}2} = k_{rxn} × BR) to the collision rate constant (k_{col}) calculated using parameterized trajectory collision theory (ref 46); dipole moment (μ = 1.77 D) and polarizability (α = 5.05 × 10⁻²³ cm³) of methyl formate from ref 70. ^dBarrier heights (ΔH[‡]) and exothermicity of reaction (ΔH_{rxn}) are relative to the reactants calculated by G3MP2 method; PT products (XH•CH₃O⁻ + CO); B_{AC}2 TS barrier is conversion from reactant-ion dipole complex to the tetrahedral intermediate.

While this allows an energetically favorable single-well pathway, the overall process is less facile than the typical proton transfer process. Whereas the PT reaction proceeds through the formyl group proton, both the S_N2 and $B_{AC}2$ processes originate from the reactant ion-dipole complex hydrogen bonded to the methyl group of the ester. The relative branching ratios ($S_N2:B_{AC}2$) from RRKM calculations (15%:85%)⁷¹ for the decomposition of this complex in the reaction of HO^- with methyl formate show good agreement with our data (20%:80%). This indicates that competition between the S_N2 and the $B_{AC}2$ mechanisms behaves statistically and supports our use of relative differences in these channels to evaluate the α -effect.

As we review the magnitude of the α -effect for the S_N2 and $B_{AC}2$ reactions in Table 7.3, the relative change in reaction efficiencies definitely favors HOO^- compared to the normal anions as the proton affinity decreases. Unfortunately, the rate constant for these pathways in the most closely matched normal anion ($(CH_3)_2CHO^-$) is completely masked by the competing PT channel. This result prevents us from determining an upper limit for the rate constant and thereby estimating the relative magnitude of the α -effect. Nevertheless, the trends in both reaction efficiencies and computational barriers would suggest at least an order of magnitude enhancement in reactivity. We note that the $B_{AC}2$ process is a nucleophilic attack at a sp^2 carbon which in solution has shown a significantly higher enhanced reactivity with α -nucleophiles as compared to studies on the nucleophilic attack at the sp^3 carbon.¹³ It appears that the magnitude of the α -effect in the methyl formate system is the same or slightly higher at the sp^3 carbon when compared to the sp^2 carbon site of attack. Based on this result, we would suggest that a large component of the magnitude of the α -effect observed in sp^2 hybridized systems is due to solvent effects. This suggestion is consistent with the dominance of the $B_{AC}2$ mechanism in solution with esters, which is not observed in the gas phase. Pliego and Riveros have attributed the

reversal in the dominance of the PT to the B_{AC}2 mechanism from gas to condensed phase for HO[−] with methyl formate to a reduction in basicity upon solvation.⁷¹

While we do not observe a significant difference in the α -effect between sp² and sp³ hybridized carbon, the principles behind the hard (non-polarizable) and soft (polarizable) base rationale still seem to apply as an underlying factor in the reactivity of the α -nucleophiles. Lee and Grabowski have reported “hard” base behavior (preference for deprotonation/elimination) for alkoxides and a preference for nucleophilic attack in the “soft” base enolates.⁷² One could envision the diffuse nature of the nucleophilic center of the α -anions¹⁹ producing a local “softness”,²⁰ which would influence their reactivity relative to normal nucleophiles. Our observation of large disparities between the proton affinities and methyl cation affinities of the α -nucleophiles compared to the normal nucleophiles points to some variation in the hard/soft nature between the anions.

7.4 Conclusion

Our investigation of the α -effect for the elimination (E2) and substitution (S_N2 and B_{AC}2) mechanisms in the gas phase provides valuable insight into the intrinsic nature of the α -nucleophiles. Our analyses of the reactivity trends and associated thermodynamic factors for the reaction systems in our study have led to the following findings.

- (1) Brønsted correlations and reagent pairing for the E2 reactions of *tert*-butyl chloride do not indicate significant deviations between the α -anions and the normal anions. If an “ α -effect” does exist in the E2 reactions, intrinsic differences must be small ($\leq 4 \text{ kJ mol}^{-1}$) to be experimentally masked for the observed reaction efficiencies in our study.

- (2) The E2 reactions are very sensitive to the proton affinity/exothermicity and the nature of the attacking anion. Therefore Brønsted relationships should be restricted to a narrow range of proton affinities. Even small differences in proton affinities ($\sim 5 \text{ kJ mol}^{-1}$) for normal anions could generate large shifts in reactivity; therefore, the proton affinities of reagent pairs must be strongly correlated to assess intrinsic differences.
- (3) An α -effect was observed for the S_N2 reaction of $(\text{CH}_3)_3\text{COO}^-$ relative to $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$ (2.1) and $\text{FCH}_2\text{CH}_2\text{O}^-$ (1.5) with CH_3Cl . However part of this effect must be attributed to the greater exothermicity of reaction ($> 10 \text{ kJ mol}^{-1}$) of the α -nucleophile.
- (4) Reagent pairing in the reactions of HOO^- and $(\text{CH}_3)_2\text{CHO}^-$ with DMMP shows an enhanced S_N2 channel for the α -nucleophile that is 9.5 times more efficient. While this is a relatively large α -effect compared to the other reaction systems in this study, it is difficult to separate the effect of the PT channel on partitioning and the possible influence of non-statistical dynamics in this reaction system. In addition to enhanced reactivity within a reaction channel, the small shifts in barriers, as a result of the α -effect, in competitive reaction systems can generate significant shifts in product distributions and thereby mask channels.
- (5) Our data for the reactions of methyl formate show enhanced nucleophilicity for HOO^- in both the S_N2 and $B_{AC}2$ mechanisms. Unlike condensed phase studies, the magnitude of the α -effect is the same or smaller for attack at a sp^2 carbon (~ 10) versus a sp^3 carbon (~ 13.5). We propose that the difference in effects between media is driven by shifts in reactivity between reaction channels as a result of solvent effects.
- (6) Observation of large disparities between the proton affinities and methyl cation affinities of the α -nucleophiles compared to the normal nucleophiles in our study implies an

inherent difference in the nature of the attacking groups. We suggest that the diffuse nature of the attacking group of the α -nucleophiles produces a local softness (in the context of HSAB) that influences their reactivity relative to normal nucleophiles.

7.5 References

1. Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 6258-6262.
2. Sun, X.; Lee, J. K. *J. Org. Chem.* **2010**, *75*, 1848-1854.
3. Zhachkina, A.; Lee, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 18376-18385.
4. Creek, J. A. M.; McAnoy, A. M.; Brinkworth, C. S. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 3419-3424.
5. McAnoy, A. M.; Paine, M. R. L.; Blanksby, S. J. *Org. Biomol. Chem.* **2008**, *6*, 2316-2326.
6. Garver, J. M.; Gronert, S.; Bierbaum, V. M. *submitted (J. Am. Chem. Soc.)*
7. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16-24.
8. Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 6592-6597.
9. Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052-2056.
10. Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 4400-4402.
11. Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327-2330.
12. Pratt, R. F.; Bruice, T. C. *J. Org. Chem.* **1972**, *37*, 3563-3564.
13. Buncel, E.; Um, I. H. *Tetrahedron* **2004**, *60*, 7801-7825.
14. McIsaac, J. E.; Subbaraman, L. R.; Subbaraman, J.; Mulhausen, H. A.; Behrman, E. J., *J. Org. Chem.* **1972**, *37*, 1037-1041.
15. Nomura, Y.; Kubozono, T.; Hidaka, M.; Horibe, M.; Mizushima, N.; Yamamoto, N.; Takahashi, T.; Komiyama, M. *Bioorg. Chem.* **2004**, *32*, 26-37.
16. Um, I. H.; Han, J. Y.; Buncel, E. *Chem.-Eur. J.* **2009**, *15*, 1011-1017.
17. Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827-1836.
18. Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223-234.
19. Heaton, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 2004-2008.
20. Pearson, R. G. *Proceedings of the National Academy of Sciences* **1986**, *83*, 8440-8441.
21. Um, I. H.; Buncel, E. *J. Am. Chem. Soc.* **2001**, *123*, 11111-11112.
22. Um, I. H.; Hwang, S. J.; Buncel, E. *J. Org. Chem.* **2006**, *71*, 915-920.
23. Um, I. H.; Shin, Y. H.; Han, J. Y.; Buncel, E. *Can. J. Chem.* **2006**, *84*, 1550-1556.
24. Um, I. H.; Buncel, E. *J. Org. Chem.* **1999**, *65*, 577-582.
25. Um, I. H.; Hwang, S. J.; Buncel, E. *J. Org. Chem.* **2006**, *71*, 915-920.
26. Um, I. H.; Im, L.-R.; Buncel, E. *J. Org. Chem.* **2010**, *75*, 8571-8577.
27. Kim, M. S.; Min, S. W.; Seo, J. A.; Um, I. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2913-2917.
28. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.
29. Bohme, D. K.; Rakshit, A. B.; Mackay, G. I. *J. Am. Chem. Soc.* **1982**, *104*, 1100-1101.
30. Bohme, D. K.; Mackay, G. I. *J. Am. Chem. Soc.* **1981**, *103*, 978-979.
31. Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986-5992.
32. Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247-350.
33. Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891-899.
34. Villano, S. M.; Eyet, N.; Lineberger, W. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 8227-8233.
35. Ren, Y.; Yamataka, H. *Org. Lett.* **2006**, *8*, 119-121.
36. Ren, Y.; Yamataka, H. *Chem.-Eur. J.* **2007**, *13*, 677-682.
37. Garver, J. M.; Yang, Z.; Nichols, C. M.; Worker, B. B.; Gronert, S.; Bierbaum, V. M. (*in preparation*)

38. Gronert, S.; Keeffe, J. R. *J. Org. Chem.* **2006**, *71*, 5959-5968.
39. Keeffe, J. R.; Gronert, S.; Colvin, M. E.; Tran, N. L. *J. Am. Chem. Soc.* **2003**, *125*, 11730-11745.
40. Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 860-869.
41. Ren, J.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 2640-2646.
42. Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 12977-12983.
43. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Proc.* **1987**, *81*, 85-100.
44. Villano, S. M.; Eyet, N.; Wren, S. W.; Ellison, G. B.; Bierbaum, V. M.; Lineberger, W. C. *Eur. J. Mass Spectrom.* **2010**, *16*, 255-268.
45. Villano, S. M.; Eyet, N.; Wren, S. W.; Ellison, G. B.; Bierbaum, V. M.; Lineberger, W. C. *J. Phys. Chem. A* **2010**, *114*, 191-200.
46. Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183-5185.
47. Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.
48. Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660-5667.
49. Ren, Y.; Yamataka, H. *J. Comput. Chem.* **2009**, *30*, 358-365.
50. Gronert, S.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1991**, *113*, 4009-4010.
51. Gronert, S.; Fagin, A.; Okamoto, K.; Pratt, L. M.; Mogali, S. *Abstr. Pap. Am. Chem. Soc.* **2003**, 226, U181-U181.
52. Gronert, S.; Fagin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, *129*, 5330-5331.
53. Bartmess, J. E. "Negative Ion Energetics Data" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. Linstrom, P.J and Mallard, W.G., National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>.
54. Ervin, K. M.; DeTuro, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947-9956.
55. Bohme, D. K.; Young, L. B. *J. Am. Chem. Soc.* **1970**, *92*, 7354-7358.
56. DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650-8655.
57. Kurz, J. L. *Chem. Phys. Lett.* **1978**, *57*, 243-246.
58. Bartsch, R. A.; Zavada, J., *Chem. Rev.* **1980**, *80*, 453-494.
59. Wu, X. P.; Sun, X. M.; Wei, X. G.; Ren, Y.; Wong, N. B.; Li, W. K. *J. Chem. Theory Comput.* **2009**, *5*, 1597-1606.
60. Chen, X.; Brauman, J. I. *J. Am. Chem. Soc.* **2008**, *130*, 15038-15046.

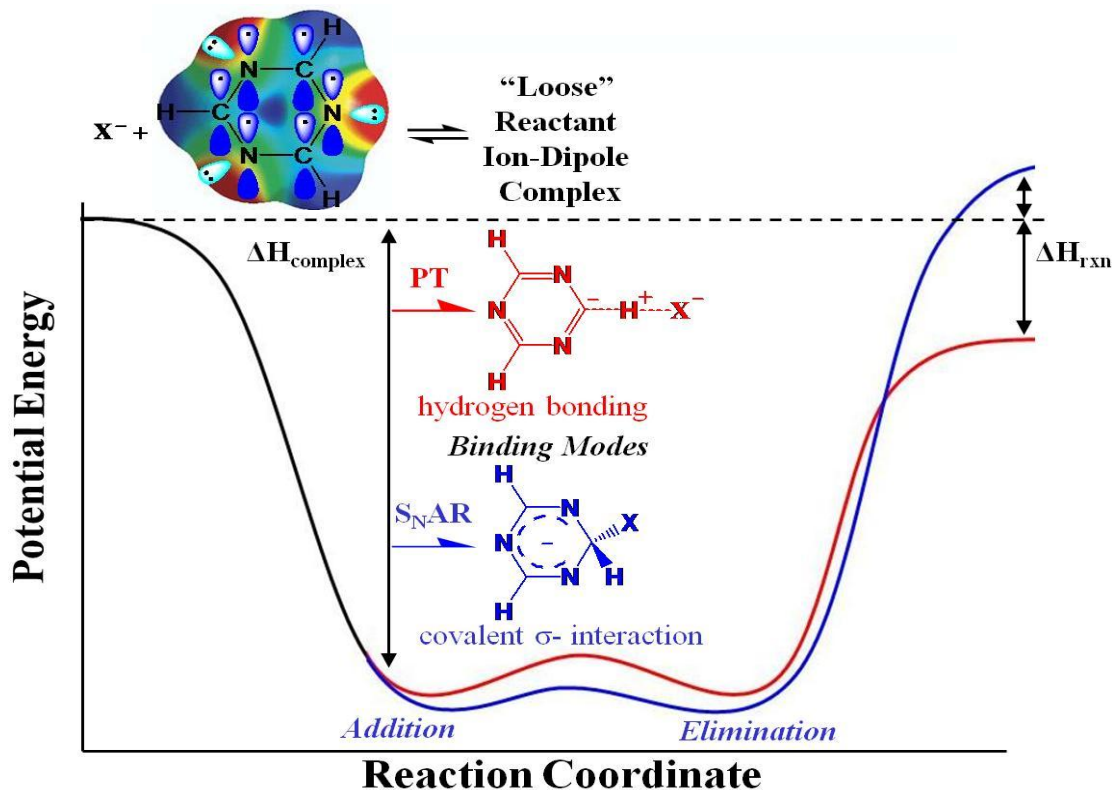
61. Midey, A. J.; Miller, T. M.; Viggiano, A. A. *J. Phys. Chem. A* **2009**, *113*, 4982-4989.
62. Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 7823-7832.
63. Frink, B. T.; Hadad, C. M. *J. Chem. Soc., Perkin Trans. 2* **1999**, *31*, 2397-2407.
64. DePuy, C. H.; Grabowski, J. J.; Bierbaum, V. M.; Ingemann, S.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1985**, *107*, 1093-1098.
65. DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481-2482.
66. Takashima, K.; Riveros, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 6128-6132.
67. Johlman, C. L.; Wilkins, C. L. *J. Am. Chem. Soc.* **1985**, *107*, 327-332.
68. Isolani, P. C.; Riveros, J. M. *Chem. Phys. Lett.* **1975**, *33*, 362-364.
69. Patterson, E. V.; Fountain, K. R. *J. Org. Chem.* **2006**, *71*, 8121-8125.
70. Lide, D. R. *CRC Handbook of Chemistry and Physics, 89th Ed.* CRC Press: Boca Raton, FL, 2008; p U552-U552.
71. Pliego, J. J. R.; Riveros, J. M. *Chem.–Eur. J.* **2001**, *7*, 169-175.
72. Lee, J. K.; Grabowski, J. J. *J. Org. Chem.* **1996**, *61*, 9422-9429.

CHAPTER 8

Gas Phase Reactions of 1,3,5-Triazine: Proton Transfer, Hydride Transfer and Anionic σ -Adduct Formation

Adapted from

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Overview

The gas phase reactivity of 1,3,5-triazine with several oxyanions and carbanions, as well as amide, was evaluated using a flowing afterglow-selected ion flow tube mass spectrometer. Isotopic labeling, H/D exchange, and collision-induced dissociation experiments were conducted to facilitate the interpretation of structures and fragmentation processes. A multi-step ($\rightarrow \text{HCN} + \text{HC}_2\text{N}_2^- \rightarrow \text{CN}^- + 2 \text{HCN}$) and/or single-step ($\rightarrow \text{CN}^- + 2 \text{HCN}$) ring-opening collision-induced fragmentation process appears to exist for 1,3,5-triazinide. In addition to proton and hydride transfer reactions, the data indicate a competitive nucleophilic aromatic addition pathway ($S_N\text{Ar}$) over a wide range of relative gas phase acidities to form strong anionic σ -adducts (Meisenheimer complexes). The significant hydride acceptor properties and stability of the anionic σ -adducts are rationalized by extremely electrophilic carbon centers and symmetric charge delocalization at the electron-withdrawing nitrogen positions. The types of anion-arene binding modes and their influence on reaction pathways are discussed.

8.1 Introduction

The chemical compound 1,3,5-triazine, ($C_3N_3H_3$), also known as s-triazine, is a symmetric six-membered N-heterocyclic aromatic ring consisting of alternating carbon and nitrogen atoms. N-heterocycles are important constituents of many natural and synthetic products (plastics, drugs, petrochemicals, food, paints, etc.) and offer the high-energy, high-density properties desired in energetic materials (explosives, pyrotechnics, propellants, and fuels).¹ Furthermore, nitrogen ring compounds are biologically relevant as model nucleobases due to their H-acceptor abilities² and their role in bioactivity.³ Triazine derivatives are commonly used in herbicides,⁴ pharmaceutical products,^{5, 6} and as light stabilizers in polymers.^{7, 8} Many of the unique chemical and physical properties of the triazine compounds arise from the interaction of the carbon atoms with the electron-withdrawing nitrogen atoms within the aromatic ring.^{2, 9} While the structure-reactivity relationships of nitroaromatics have been extensively studied, more recently the electrostatic interaction of anions with electron-deficient arenes and heteroarenes has gained interest.^{10, 11} Our investigation of the gas phase reactivity of the electrophilic 1,3,5-triazine and the complexes formed during these reactions has revealed significant hydride acceptor properties and proven insightful into anion-arene interactions.

Polycyclic or heterocyclic conjugated systems tend to exhibit thermodynamic and kinetic stability.¹² This “aromatic” stability can influence physicochemical properties, as well as the forces that govern reaction pathways.¹³ While the incorporation of nitrogen within an aromatic ring has little effect on aromaticity, there are significant effects on reactivity.¹⁴ Typically the π -electron density of an aromatic ring makes it susceptible to reactions by electrophilic agents, however the addition of an electron-withdrawing group activates the compound to nucleophilic

attack via an S_NAr mechanism.¹⁵ The S_NAr mechanism is believed to be a two-step addition-elimination pathway which proceeds through a Meisenheimer complex (anionic σ-adduct) intermediate. In solution, these complexes typically serve as reaction intermediates; however, in the gas phase these species can be isolated and characterized in the absence of complicating solvent interactions.^{16, 17}

Both transition states¹⁸ and stable intermediates¹⁹ of anionic σ-adducts have been reported in the gas phase reaction. To understand the reactivity of the prototypical S_NAr reaction Fernández et al.²⁰ conducted a theoretical investigation of the stability of these structures relative to intrinsic nucleophilicity. Interestingly, unlike aliphatic nucleophilic substitution reactions (S_N2), the identity S_NAr reactions (where nucleophile and leaving group are the same) for aromatics with nucleophiles belonging to the same period of the periodic table have almost identical barrier heights. However, in non-identity reactions the exothermicity of reaction provides a thermodynamic driving force which influences barrier heights. The intrinsic stability of the complex is dominated by the electronic nature of the aromatic substrate. During the formation of the anionic σ-adduct, a critical balance between the stabilization due to bond formation and destabilization from the destruction of aromaticity dictates the relative potential energy (minimum or transition state) of the complex. Less stable structures gain stability through more planar orientations through distortions of the typical tetrahedral (sp³) Meisenheimer-type geometry. These findings correlate nicely with the anion-arene interactions described by Hay and Bryantsev²¹ and the experimental results of Hiraoka et al.²²

To ensure common nomenclature in discussions of anion-arene interactions, Hay and Bryantsev have proposed characterization of complexes by geometric features and the degree of covalency.²¹ Figure 8.1 depicts the primary binding motif categories as (a) aryl H-bonding

(when acidic hydrogens are present), (b) noncovalent anion– π complexes, (c) weakly covalent σ -adducts, and (d) strongly covalent σ -adducts. “Strongly covalent σ -adducts” have extensive mixing of the anion and arene-type molecular orbitals (MOs) to form the typical tetrahedral (sp^3) Meisenheimer-type structures. “Noncovalent anion- π complexes” exhibit ring-centered geometries which are bound with electrostatic forces. Moderate interaction between the anion and arene MOs yields “weakly covalent σ -adducts” with off-center configurations. Employing these definitions, true electrostatic binding of anions with aryl rings is rare and most supramolecular bonding and solid state interactions display off-center arrangements.¹⁰

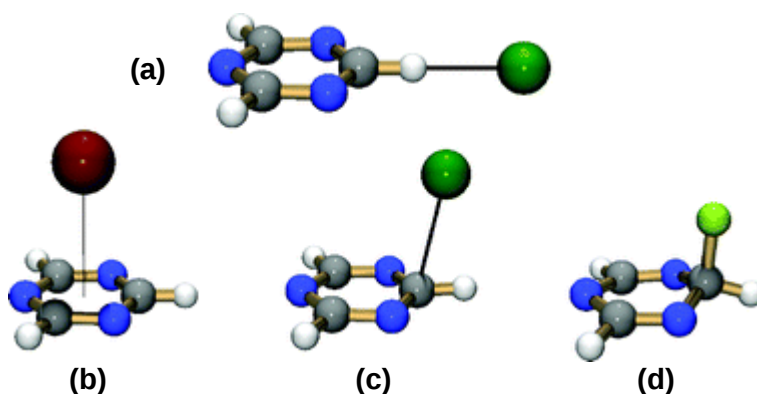


Figure 8.1 Binding modes for complexes of anions with charge-neutral arenes (a) C–H hydrogen bonding, (b) noncovalent anion– π interaction, (c) weakly covalent σ -interaction, and (d) strongly covalent σ -interaction.²¹ - Reproduced by permission of The Royal Chemical Society.

Computations suggest that strong nucleophiles produce strongly covalent σ -adducts, while less nucleophilic anions form weakly covalent σ -adducts depending on electron deficiency in the aromatic ring.²¹ Gas phase spectroscopic evidence of these two types of structural motifs supports this relationship.²³ The amount of interaction between the electrons of the anion and the π -system is enhanced and stabilized by electron deficiencies in the aromatic ring. The degree of

electron deficiency in aryl compounds can be modulated through substitution of electron withdrawing groups, such as $-F$, $-CN$ and $-NO_2$. However, electron-withdrawing groups can inductively weaken the strength of hydrogen bonds which enhances the proton transfer processes. Therefore when aryl C–H groups are present, both hydrogen bound anion complexes and anionic σ -adducts must be considered. Studies of substituted benzenes suggest that gas phase nucleophilic attack on the ring is feasible only when the acidity of the aromatic compounds is lower than or comparable to that of the nucleophile.^{24, 25} While hydrogen bound complexes may be present at a wide range of relative acidities, the proton transfer channel does not become active until about the same relative acidity range as that of nucleophilic substitution. For highly basic nucleophiles, the proton transfer reaction is significantly favored over the substitution reaction.^{24, 26}

Depending on the nature of the anion and arene, gas phase reactions have shown the aromatic nucleophilic substitution channel to be in competition with multiple pathways (proton transfer, E2 elimination, S_N2 , etc.).²⁶⁻²⁹ Of particular interest to our current work is the presence of a hydride transfer channel with 1,3,5-triazine to form a hydride-Meisenheimer complex. Recently, these complexes have been identified in the biodegradation of nitroaromatics.³⁰⁻³⁴ Although fragmentation patterns of the hydride-Meisenheimer complex of trinitrotoluene, $[TNT + H]^-$, were studied by Yinon et al., reduction and hydrolysis in their heated source prevented identification of stable hydride σ -adducts.³⁵ Other hydride transfer mechanisms for the anionic reductions of carbonyls and activated olefins have been observed in the gas phase;³⁶⁻⁴⁰ however, to our knowledge hydride transfer to neutral aromatics and stable anionic hydride σ -adducts have not been reported in the gas phase. A computational study by Gronert and Keeffe on factors influencing hydride transfer indicates that electron withdrawing groups increase hydride ion

affinity and reaction rates, while resonance lowers barriers to hydride transfer.⁴¹ From this perspective, electrophilic aromatic rings offer intriguing hydride donor and acceptor properties.

In the present study, we investigate the reactivity of 1,3,5-triazine with amide and several oxyanions and carbanions, as well as evaluate the reaction products using collision-induced dissociation. A flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer was utilized to measure kinetic data and analyze the dissociation process. Isotopic labeling and H/D exchange experiments were conducted to facilitate the interpretation of fragmentation processes and the structures of products. In addition, theoretical calculations were carried out to elucidate the structures of the intermediates/transition states/products and the driving energetics behind the mechanistic processes. Our results are discussed in terms of relative gas phase acidities, anion-arene interactions, and σ -adduct stability.

8.2 Experimental

8.2.1 Ion-Molecule Reactions

All reactions were carried out using a flowing afterglow-selected ion flow tube (FA-SIFT) mass spectrometer, which has been previously described.⁴² Briefly, this instrument consists of four sections: an ion source, an ion selection region, a reaction flow tube, and a detection system. A flowing afterglow ion source is used to produce ions, which are mass-selected using the ion selection region quadrupole mass filter prior to injection into the reaction flow tube. Primary anions were prepared by electron ionization (70 eV) of methane and nitrous oxide (2:1 ratio) to produce hydroxide or of ammonia to produce amide. Other ionic reagents were generated by proton abstraction of neutrals by either NH_2^- or HO^- . Injected ions are entrained in a flow of helium ($200 \text{ std cm}^3 \text{ s}^{-1}$, 0.5 torr) and thermalized to $300 \pm 2 \text{ K}$ prior to reactions with neutral reagents that are added through multiple inlets along the length of the

reaction flow tube. Ionic reactants and products are analyzed in the detection region using a triple-quadrupole mass filter and an electron multiplier. The reactions are carried out under pseudo-first order conditions (reactant ion $\sim 10^5$ ions cm^{-3} ; neutral reactant $\sim 10^{11}$ molecules cm^{-3}), and the reported branching ratios and reaction rate coefficients are the averages of at least three individual measurements. Product branching ratios are determined by extrapolating the observed product yields to zero reaction distance in order to extract the initial ratios due to primary reactions. The reported reaction efficiencies are the experimental rate constant divided by the calculated collision rate constant ($\text{Eff} = k_{\text{expt}}/k_{\text{col}}$). Collision rate constants were calculated from parameterized trajectory collision rate theory.⁴³ Error bars represent one standard deviation in the data; absolute uncertainties in these rate constant measurements are $\pm 20\%$. The detector was tuned to minimize mass discrimination, and no further corrections were made in the analysis.

8.2.2 Collision-Induced Dissociation

The source and selection region of the FA-SIFT mass spectrometer has been previously employed in collision-induced dissociation experiments to investigate fragmentation pathways and estimate dissociation energies.⁴⁴⁻⁴⁶ Collisional activation is accomplished by injecting the anion or adduct at varied injection energies (E_{lab}) of 10-80 eV, defined as the voltage difference between the source flow tube and the injection orifice. Collisions with helium take place in the vicinity of the injection orifice (i.e., SIFT-CID) that connects the quadrupole region and the second flow tube. Nominal center-of-mass collision energies (E_{cm}) can be calculated using the relation $E_{\text{cm}} = E_{\text{lab}} \times m_{\text{He}}/(m_{\text{He}} + m_{\text{ion}})$, where m_{He} and m_{ion} are the masses of He and the reactant ion, respectively. However, SIFT-CID occurs under multiple-collision conditions thereby enabling fragmentation at collision energies that are lower than threshold energies. The E_{cm} should thus be taken as the lower bound for the actual internal excitation of the anions. The

mass spectra of the precursor and fragment ions were analyzed to elucidate the chemical structures of molecules.

8.2.3 *H/D Exchange*

Hydrogen/deuterium (H/D) exchange reactions of gas phase ions have proven to be powerful tools for probing ion structures in the FA-SIFT.^{47, 48} In our H/D exchange analysis, gaseous D₂O was added near the middle of our reaction flow tube downstream of the first four neutral reactant inlets. The extent of H/D exchange for reactant and product ions was evaluated by m/z shifts in the mass spectra.

8.2.4 *Materials*

All compounds were obtained from commercial vendors and liquid samples were purified by several freeze-pump-thaw cycles before use. These compounds include 1,3,5-triazine, C₃N₃H₃, 97%; ammonia, NH₃, Airgas, 99.9995%; 2-methylpropene, CH₂=C(CH₃)₂, Phillips 66, 99+%; 1,4-diazine, C₄H₄N₂, Aldrich, 99+%; furan, C₄H₄O, Aldrich, 99+%; pyridine, C₅H₅N, Fluka, 99.8%; difluoromethane, F₂CH₂, Aldrich 99.7%; fluorobenzene, C₆H₅F, Aldrich, 99%; difluorobenzene, C₆H₄F₂, Aldrich, 99%; 2-methylfuran, (CH₃)C₄H₃O, Aldrich 99%; 1,4-dimethylbenzene, (CH₃)₂C₆H₄, EM Science, 98%; cyclopentanol, C₅H₉OH, Aldrich, 99%; ethanol, C₂H₅OH, Decon Laboratories, 200 proof; methanol, CH₃OH, Aldrich, 99.9%; methanol-d₄, CD₃OD, CDN Isotopes, 99.8% D; water, H₂O, distilled; water, H₂¹⁸O, Cambridge Isotope Laboratories, 80% ¹⁸O; D₂O, Cambridge Isotope Laboratories, 99.9% D. Helium buffer gas (99.995%) was purified by passage through a molecular sieve trap immersed in liquid nitrogen.

8.2.5 *Computational Methods*

Ab initio molecular orbital calculations were carried out with the B3LYP method using the 6-311++G(d,p) and aug-CC-pVTZ basis sets using the Gaussian 09 suite of programs.⁴⁹

Frequency calculations were carried out for all species to establish their nature as local minima or transition states. Enthalpy changes were calculated from the energies of the optimized structures, and thermal corrections were included for 298 K without any scaling of the calculated vibrational frequencies.

8.3 Results and Discussion

The bimolecular ion-neutral reactions between the conjugate base and neutral species of 1,3,5-triazine, oxygen-centered reactants (water, methanol, cyclopentanol, and ethanol), carbon-centered reactants (2-methylpropene, 1,4-dimethylbenzene, 1,4-diazine, pyridine, fluorobenzene, difluorobenzene, furan, and 2-methylfuran) and a nitrogen-centered reactant (ammonia) were investigated by using FA-SIFT mass spectrometry. Proton and hydride transfer reactions were observed; however, the formation of a collision stabilized adduct/cluster dominated most of the reactions studied. Of significant interest was the type of anion-arene binding motif present within these complexes and the influence of this interaction on reaction pathways.

8.3.1 *Elucidation of Structure, Mechanisms, and Energetics*

Collision-induced dissociation (CID) mass spectrometry was employed to investigate the key structural features, energetics, and thermochemical properties of our gas-phase ion-molecule reactions. In CID, selected precursor ions are activated by multiple collisions with a buffer gas which increases the internal vibrational and rotational energy of the ion until dissociation occurs. Mass shifts corresponding to isotopic labeling and fragmentation patterns allow the elucidation of structure and insight into reaction and dissociation mechanisms. In a simple bond-breaking process, the dissociation product intensities yield information regarding bond energies within the precursor ion. Coarse decomposition threshold energies can be extracted from energy-dependent precursor ion breakdown curves. However, in more complex processes, the product intensities

will be associated with activation energies that reflect bond breaking and bond formation. Application of the extended kinetic method to the fragmentation ratios of proton-bound ion complexes allows the relative proton affinity of an unknown to be determined relative to a series of reference bases.

Figure 8.2a displays the FA-SIFT mass spectrum for the reaction of $\text{HO}^- + 1,3,5\text{-triazine}$. The major product ion of the reaction is deprotonated 1,3,5-triazine (m/z 80); a small contribution from the stabilized ion-dipole complex is observed at m/z 98 ($[\text{HO}\cdot\text{C}_3\text{H}_3\text{N}_3]^-$). Minor ion peaks at m/z 26 (CN^-), m/z 44, and m/z 71 suggest either appreciable contributions from impurities or a fragmentation pathway. Similar ion peaks from CID of the hydroxide-1,3,5-triazine cluster, $[\text{HO}\cdot\text{C}_3\text{H}_3\text{N}_3]^-$ (Figure 8.2b) are observed. This suggests that the $\text{HO}^- + 1,3,5\text{-triazine}$ product ion peaks at m/z 26, 44, and 71 originate from the reactant ion-dipole cluster, $[\text{HO}\cdot\text{C}_3\text{H}_3\text{N}_3]^-$, as opposed to impurities. Further supporting this interpretation is the observed isotopic shift (inset, Figure 8.2a) of m/z 44 to 46 and m/z 71 to 73 when H^{18}O^- was utilized in both the reaction and cluster generation. Clearly ^{18}O is incorporated into the products and fragments; however this result can be explained through either an electrostatic clustering interaction (m/z 44, $[\text{CN}^-\cdots\text{H}_2\text{O}]$ and m/z 71, $[\text{C}_2\text{HN}_2^-\cdots\text{H}_2\text{O}]$) or a covalent bonding interaction (m/z 44, $[\text{NH}=\text{CHO}^-]$ and m/z 71, $[\text{C}_2\text{N}_2\text{H}_3\text{O}^-]$).

To resolve the nature of these peaks, the m/z 44 ion was generated in the source from the reaction of $\text{HO}^- + 1,3,5\text{-triazine}$; unfortunately, the m/z 71 ion could not be generated in sufficient quantities to study. Mass selection and injection of the m/z 44 ion over an E_{cm} injection energy range of 1-2 eV, resulted only in an ion peak at m/z 42. If the m/z 44 ion were a water cluster a peak at m/z 26 should have been observed. The peak at m/z 42 (NCO^-) is consistent with loss of H_2 from $\text{NH}=\text{CHO}^-$. CID of the m/z 96 ion produced the same m/z 42

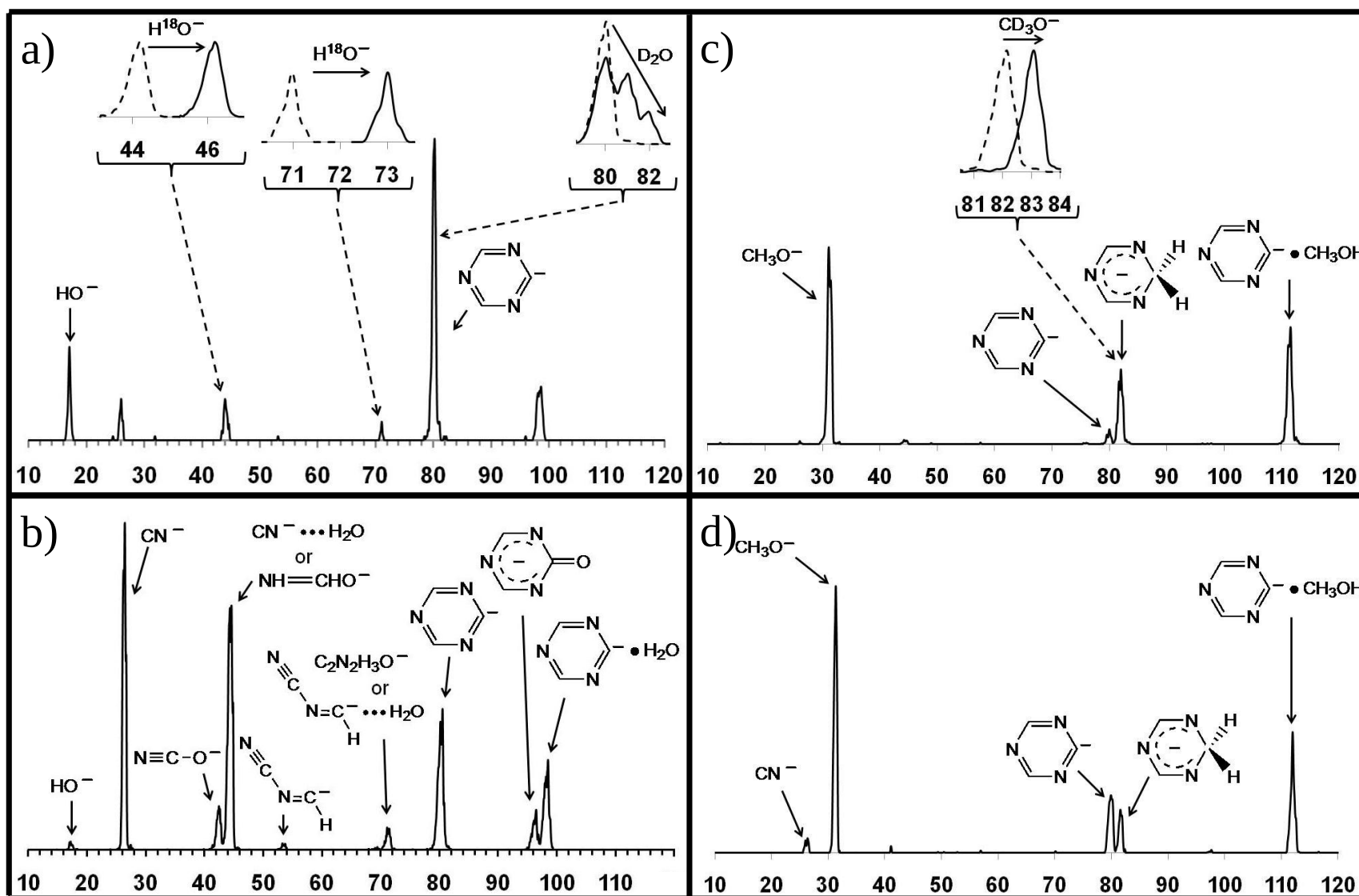
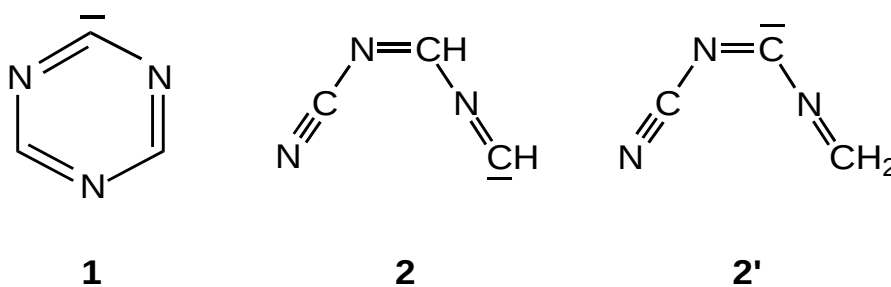


Figure 8.2 FA-SIFT Mass Spectra of (a) the reaction of HO^- + 1,3,5-triazine with insets of isotopic shift studies. (b) CID of the hydroxide-1,3,5-triazine species, $[\text{HO} \cdot \text{C}_3\text{H}_3\text{N}_3]^-$, at an E_{cm} injection voltage of 1.2 eV. (c) The reaction of CH_3O^- + 1,3,5-triazine with insets of isotopic shift studies. (d) CID of the methoxide-1,3,5-triazine species, $[\text{CH}_3\text{O} \cdot \text{C}_3\text{H}_3\text{N}_3]^-$, at E_{cm} of 0.65 eV.

peak, implying that this ion has a keto-type structure generated from the loss of H₂ from an m/z 98 covalently bound adduct. Therefore, the peaks at m/z 26 (CN⁻), m/z 44 (NH=CHO⁻), and m/z 71 (C₂N₂H₃O⁻) indicate an addition mechanism prior to a ring-opening fragmentation process, signifying the presence of a covalent σ-adduct motif within the stabilized ion-dipole complex.

Figure 8.2c displays the mass spectrum of the reaction of CH₃O⁻ + 1,3,5-triazine. The major product ion of the reaction is the hydride transfer product of 1,3,5-triazine to produce a hydride-Meisenheimer complex, C₃H₄N₃⁻ (m/z 82). This product was confirmed by an isotopic shift (inset, Figure 8.2c) of m/z 82 to 83 for the reaction of CD₃O⁻ with 1,3,5-triazine. Additional peaks show the presence of deprotonated 1,3,5-triazine at m/z 80, a stabilized species at m/z 112, and minor peaks at m/z 26 and 44. CID of the stable species (Figure 8.2d) does not reveal additional fragmentation pathways.

The presence of a ring-opening fragmentation pathway led to concerns that the C₃H₂N₃⁻ (m/z 80) species (Scheme 8.1) could be the intact 1,3,5-triazinide (1) and/or its ring-opened structure (2). Hydrogen migration during ring opening may give rise to a second ring-opened species (2').



Scheme 8.1

Producing 1,3,5-triazinide, $\text{C}_3\text{H}_2\text{N}_3^-$, in the source through the reactions of CH_3O^- and HO^- with 1,3,5-triazine allowed the structure of the m/z 80 product to be probed by CID and H/D exchange.

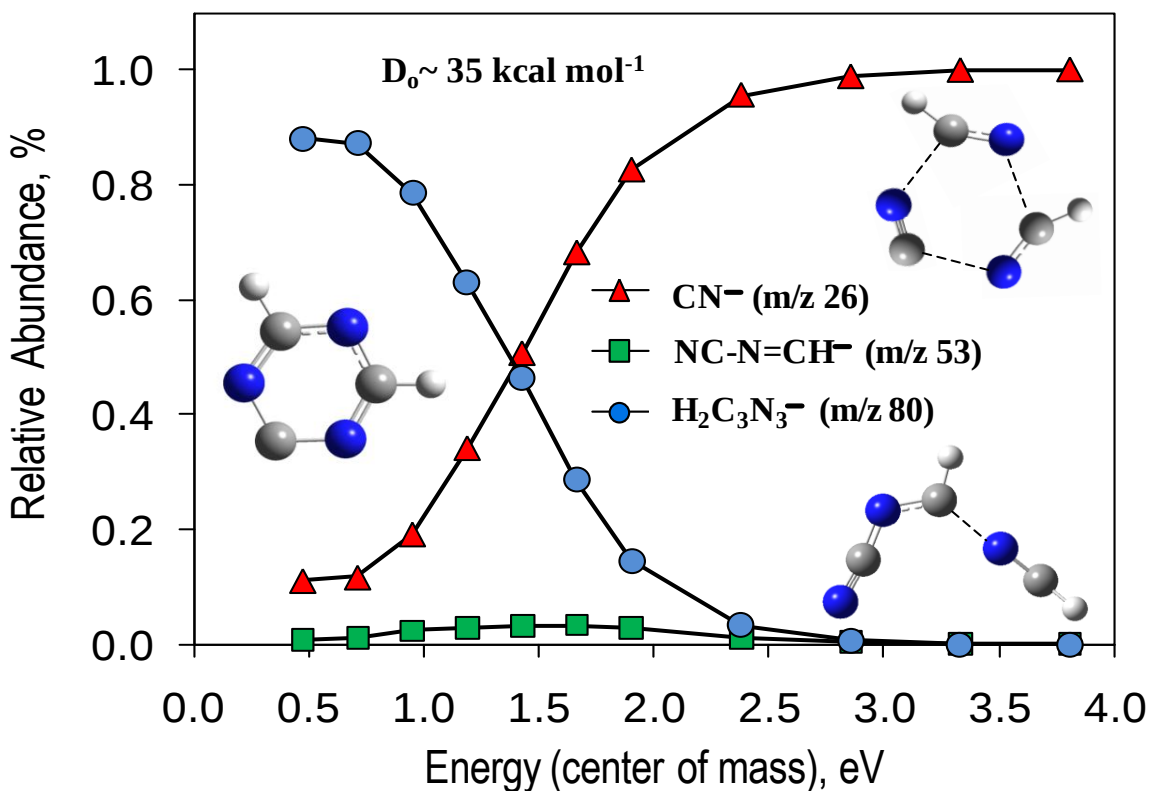
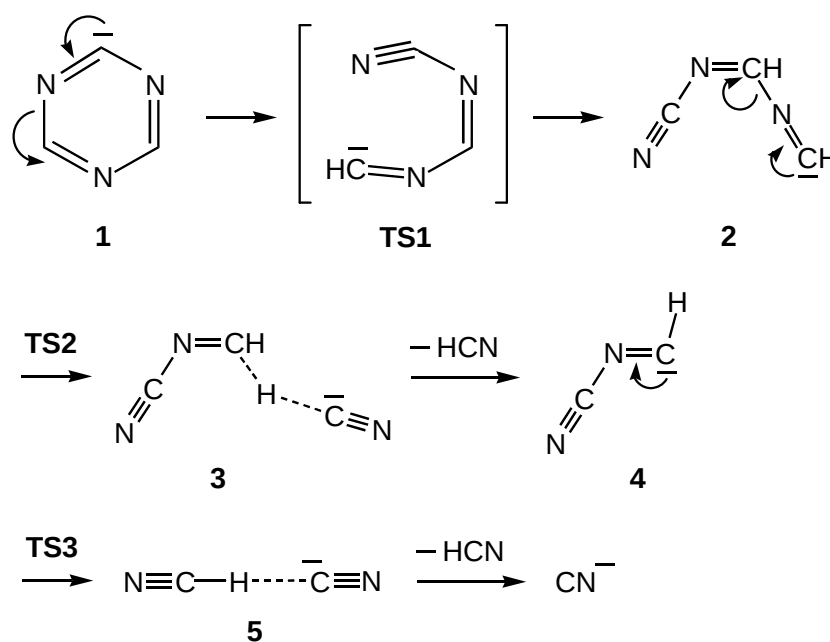


Figure 8.3 Relative yield of the product ions from the SIFT collision-induced dissociation of 1,3,5-triazinide, $\text{C}_3\text{H}_2\text{N}_3^-$, as a function of translational energy in the center-of-mass frame.

The injection of 1,3,5-triazinide yielded about 10% CN^- ions even at the lowest injection energy ($E_{\text{cm}} \sim 0.5$ eV). Figure 8.3 shows the relative yields of the product ions in CID of the 1,3,5-triazinide anion as a function of SIFT injection energy. As the injection energy increases, more CN^- ions are observed together with a minor amount of m/z 53 ions. A nominal CID threshold energy has been estimated from the decomposition behavior of 1,3,5-triazinide to be roughly 1.5 eV (35 kcal mol^{-1}) following the calibration procedure described earlier for SIFT-

CID involving multiple collisions.⁵⁰ The derived value compares qualitatively well with our calculated rate-determining barrier (44.3 kcal mol⁻¹) and the experimental dissociation energy for 1,3,5-triazine (40 kcal mol⁻¹).⁵¹

The photodissociation of neutral 1,3,5-triazine to produce three HCN molecules has been attributed to two reaction channels, a simultaneous three-body dissociation mechanism and a consecutive two-body process from a ring-opened structure, which proceeds by the initial formation of HCN and H₂C₂N₂.⁵² A similar dissociation scheme (Scheme 8.2) can be used to



Scheme 8.2 Dissociation scheme for the fragmentation of 1,3,5-triazinide.

describe the fragmentation of 1,3,5-triazinide. The reagent anion proceeds through a ring-opening transition state **TS1**. The ring-opened anion **2** can further fragment via **TS2** to an ion-neutral adduct **3**. After loss of HCN the NC-N=CH⁻ anion **4** (*m/z* 53) transforms via **TS3** to an ion-neutral adduct **5**, which loses HCN to yield the terminal product ion **CN⁻**.

An energy diagram for the decomposition of 1,3,5-triazinide is shown in Figure 8.4. The ring-opened transition state TS1 has a relatively low bond energy of 29.9 kcal mol⁻¹. The diagram assumes that the HCN molecules have been sequentially lost. Interestingly, the observed yield of the NC-N=CH⁻ anion is minor and the decomposition of 1,3,5-triazinide proceeds primarily to form the terminal anion CN⁻ even at the lowest collision energy studied.

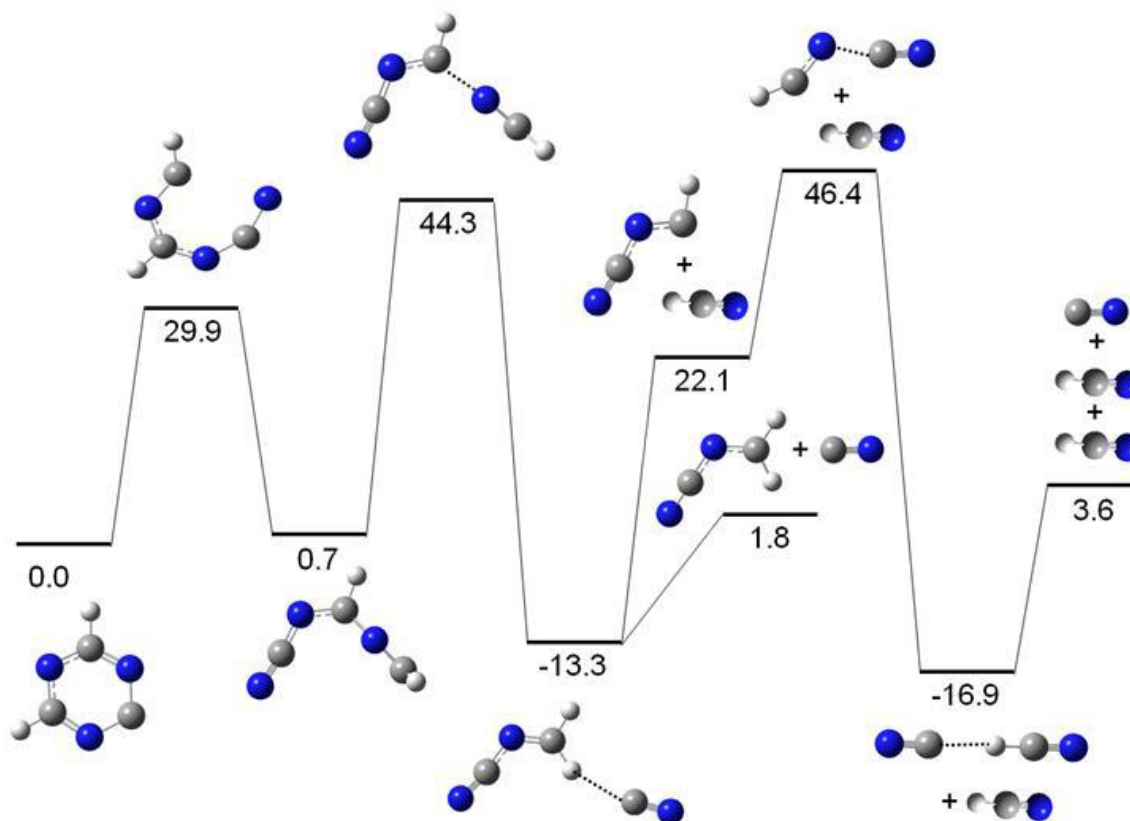


Figure 8.4 Energy diagram for the decomposition of 1,3,5-triazinide. Calculations performed at the B3LYP/6-311++G(d,p) level of theory.

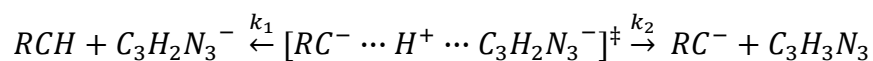
Since anions 1, 2, and 2' are the same mass, the only way to differentiate between the structures was through shifts in reaction rate constants and deuterium exchange reactions. Based on these studies,⁵³ the yield of the ring-opened anion 2 and 2' is negligibly small following injection of the 1,3,5-triazinide; it is possible that collisions with helium sequentially destroy the intermediate species. Alternatively and more probably, the energized species can fragment by a

multi-step and/or single-step process in which the species are stabilized by the complexation energy of the fragment ion and neutral product. This stabilizing effect will significantly lower the energy barriers in Figure 8.4.

The presence of a ring-opened structure was further evaluated using H/D exchange. This technique allows the barrier for internal proton transfer or the proton affinity difference between the two deprotonated species (i.e., DO^- and $\text{C}_3\text{H}_2\text{N}_3^-$) to be assessed. An endothermic gas phase H/D exchange process can be driven by the complexation energy ($\Delta H_{\text{complexation}} \sim 15\text{-}20$ kcal mol⁻¹) within an ion-dipole complex. Based on the computational proton affinities at the B3LYP/6-311++G** level of theory for the isomeric forms of 1,3,5-triazinide [386.7 kcal mol⁻¹ for (1), 356.8 kcal mol⁻¹ for (2), and 356.1 kcal mol⁻¹ for (2')] relative to the experimental proton affinity of hydroxide [390.3 kcal mol⁻¹] the only ion-dipole complex capable of undergoing H/D exchange is the ring-closed form (1) as shown in Scheme 8.1. Experimentally, the $\text{C}_3\text{H}_2\text{N}_3^-$ anion formed from both HO^- and CH_3O^- deprotonation showed two H/D exchanges with D_2O (inset, Figure 8.2a) strongly suggesting that the ring-closed structure (1) is the dominant species. The experimental and computational data indicate that the mechanistic reaction pathways most likely proceed through an intact 1,3,5-triazinide or triazine structure.

All of the carbanion [C_4H_7^- , $\text{C}_4\text{H}_3\text{N}_2^-$, $\text{C}_4\text{H}_3\text{O}^-$, $\text{C}_5\text{H}_4\text{N}^-$, FC_6H_4^- , $\text{F}_2\text{C}_6\text{H}_3^-$, $(\text{CH}_3)_2\text{C}_6\text{H}_3^-$, $(\text{CH}_3)\text{C}_4\text{H}_2\text{O}^-$] reactions with 1,3,5-triazine resulted almost exclusively in the formation of a stabilized ion-dipole complex. CID of these carbanion complexes did not display an addition-fragmentation pathway, only deprotonated forms of the anionic species. However, the ratio of CID fragment ions did not correlate with relative proton affinities as would be expected by kinetic method techniques. The method generally assumes that the peak intensities

reflect the difference in Gibbs free energy between the transition state of a proton-bound complex and the two competing dissociation channels.



One would expect a decreasing ratio of carbanions to 1,3,5-triazinide as the proton affinity of the carbanion increases; nonetheless, in all cases, a majority of the 1,3,5-triazinide (>90%) retained the proton (see Appendix 3 for relative abundances). This deviation from thermodynamic relationships indicates either a significant barrier to proton transfer or a non-proton bound form of ion-dipole complex (this aspect is discussed below).

8.3.2 Reactivity of 1,3,5-Triazine

The gas phase reactions formed a number of primary and secondary products; the latter tend to be anionic clusters with the neutral reactant. Table 8.1 lists the series of 1,3,5-triazine (M) reactions along with the corresponding proton affinity⁵⁴ of the reactant anion (X^-), the overall rate constant, reaction efficiency, and the initial product ion distribution. The primary product ions in Table 8.1 correspond to a proton transfer reaction, $(M-H)^-$, a stabilized anion-arene complex ($X^- \cdots M$), a hydride transfer reaction $(M+H)^-$, and a fragmentation pathway (m/z 26, 44, 71) originating from an S_NAr process. The carbanion reactions displayed only traces (< 1%) of deprotonated 1,3,5-triazine $(M-H)^-$. The m/z 44 peak is only observed in reactions with oxyanions. The additional peak observed at m/z 71 for the reaction with HO^- corresponds to a loss of HCN from the reactant ion-dipole complex (m/z 98).

Our data show both the proton transfer and the addition S_NAr pathways to be active. This is expected since the acidities of 1,3,5-triazine and the nucleophiles are similar as discussed in the introduction. Variations in product ion distribution can be interpreted as a competition between the exit channel for proton transfer and conversion within the ion-dipole complex.

Table 8.1 1,3,5-Triazine (M) Reactions at 300 ± 2 K with Proton Affinity (kcal mol^{-1}), Overall Rate Constant (k_{expt})^a in Units of $10^{-10} \text{ cm}^3 \text{ s}^{-1}$, Reaction Efficiency ($\text{Eff} = k_{\text{expt}}/k_{\text{col}}$)^b, and Initial Product Ion Distribution.

Reaction	Proton Affinity(X^-) ^c	Kinetic Data		Product Ions (%)				
		k_{expt}	Eff	(M-H) ⁻	(X ⁻ ·M)	(M+H) ⁻	(m/z 71)	(m/z 44)
$\text{NH}_2^- + \text{C}_3\text{N}_3\text{H}_3$	403.4 ± 0.1	15.1 ± 0.3	0.85	92	8			
$\text{OH}^- + \text{C}_3\text{N}_3\text{H}_3$	390.3 ± 0.3	14.5 ± 0.5	0.83	60	25		2	10
$\text{CH}_3\text{O}^- + \text{C}_3\text{N}_3\text{H}_3$	381.5 ± 0.6	8.40 ± 0.08^d	0.61	7	49	31		12
$\text{C}_2\text{H}_5\text{O}^- + \text{C}_3\text{N}_3\text{H}_3$	378.3 ± 0.8	7.20 ± 0.01	0.60		60	40		
$\text{C}_5\text{H}_9\text{O}^- + \text{C}_3\text{N}_3\text{H}_3$	375.0 ± 1.1^e	---	---		75			25
carbanion ^f + $\text{C}_3\text{N}_3\text{H}_3$	381.9-393.0	---	---	1	99			
$\text{C}_3\text{N}_3\text{H}_2^- + \text{H}_2\text{O}^g$	386.1 ± 0.7	---	---		100			
$\text{C}_3\text{N}_3\text{H}_2^- + \text{CH}_3\text{OH}^g$	386.1 ± 0.7	10.7 ± 0.1^d	0.53	100				

^aError bars represent one standard deviation of the mean of three or more measurements; absolute accuracy is $\pm 20\%$. ^bEfficiency is the ratio of the experimental rate constant to the collision rate constant calculated using parameterized trajectory collision theory[43]. ^cNIST Chemistry WebBook, NIST Standard Reference Database Number 69 [54]. ^dPrevious work [53]. ^eThis work ^fCarbanions [C_4H_7^- , $\text{C}_4\text{H}_3\text{N}_2^-$, $\text{C}_4\text{H}_3\text{O}^-$, $\text{C}_5\text{H}_4\text{N}^-$, FC_6H_4^- , $\text{F}_2\text{C}_6\text{H}_3^-$, $(\text{CH}_3)_2\text{C}_6\text{H}_3^-$, $(\text{CH}_3)\text{C}_4\text{H}_2\text{O}^-$]. ^gFragmentation upon injection of 1,3,5-triazinide produced $\sim 10\% \text{CN}^-$, however, this ion did not participate in the primary reactions.

Normally this competition is between exit channels, however the elimination step of the S_NAr mechanism for 1,3,5-triazine is thermodynamically inhibited since hydride is such a poor leaving group. We will simplify our discussion by treating the stabilized anion-arene complex, $(X^{\cdot-} \cdot M)$, as a single isomer composed of the anionic σ -adduct. Although a small amount of the proton-bound isomer exists, computations (see below) suggest that the Meisenheimer complex is significantly lower in energy (consistent with the strong stabilizing effect of electron-withdrawing nitrogen) than the H-bonded complex and would dominate a Boltzmann distribution at equilibrium.

The product ion distributions for the gas phase anionic reactions with 1,3,5-triazine can be interpreted as a competition between a proton transfer pathway and the addition mechanism of the S_NAr reaction. Most gas phase ion-molecule reaction mechanisms are represented by a double-well potential energy curve⁵⁵ where ion-dipole interactions form a potential minimum before significant changes in chemical bonding occurs in the central barrier. Often, there is more than one energetically accessible potential minimum within the reactant-ion dipole complex. As the nucleophile ($X^{\cdot-}$) approaches the arene, either a H-bonding or an electrostatic interaction develops along a minimum energy reaction pathway leading to two different reactant ion-dipole complexes, an aryl H-bonded complex and a Meisenheimer complex. Most proton transfer reactions have very low transition state barriers producing single-well reaction characteristics. Based on this single-well feature, the reactivity of proton transfer has direct correlations with the relative proton affinity of an anion. On the other hand, the S_NAr (addition-elimination) reaction proceeds by nucleophilic attack on an electrophilic carbon to produce a resonance-stabilized Meisenheimer complex. (The hydride transfer reaction is an alternate pathway from the H-bonded complex driven by the exothermic formation of an aldehyde, see pathway below.) A

conversion barrier between the two pathways is highly likely based on previously reported calculations which suggest that large barriers may exist between binding motifs.⁵⁶ The presence of a conversion barrier is reasonable based on the large geometry changes and shifts in electron density between the σ -adduct and H-bonded complexes. Based on this overall picture, when an ion-dipole complex is formed there are three possible outcomes: dissociation back into reactants, an ensuing proton/hydride transfer (if the exit barrier is low enough), or stabilization through collisions with the carrier gas (if the lifetime of the complex is long enough).

As anticipated, there is a strong correlation between the degree of proton transfer and the relative gas phase proton affinity between 1,3,5-triazinide ($\Delta_{\text{acid}}H_{298} = 386.1 \pm 0.7 \text{ kcal mol}^{-1}$)⁵³ and the anions (non-carbon centered). The high proton affinity of NH_2^- ($\Delta_{\text{acid}}H_{298} = 403.40 \pm 0.10 \text{ kcal mol}^{-1}$)⁵⁴ generates a highly exothermic pathway to the ammonia and triazinide products. The proton transfer rate constant for reaction of amide with 1,3,5-triazine is $k_{\text{PT}} = 1.42 \times 10^{-9} \text{ cm}^3 \text{ s}^{-1}$ ($k_{\text{PT}} = k_{\text{expt}} \times \text{branching fraction}$) with a reaction efficiency of 80%. With this large thermodynamic driving force of $17.3 \text{ kcal mol}^{-1}$ one would expect near collision rate reaction efficiency. The lower reaction efficiency observed and the presence of a stable complex suggest that conversion between the two reaction pathways is inhibited and reaction rates can be influenced by the type of anion-arene complexes that are energetically accessible.

The proton transfer rate constant for reaction of HO^- ($\Delta_{\text{acid}}H_{298} = 390.3 \pm 0.03 \text{ kcal mol}^{-1}$)⁵⁴ with 1,3,5-triazine is $k_{\text{PT}} = 8.70 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ with a reaction efficiency of 50%. This reaction is exothermic by only $4.2 \text{ kcal mol}^{-1}$ and formation of the anionic σ -adduct becomes competitive; the product ion ratios are 60% proton transfer and 40% Meisenheimer complex (25% stable complex and 15% fragmentation). Proton transfer becomes endothermic by 4.6 kcal

mol⁻¹ for CH₃O⁻ ($\Delta_{\text{acid}}H_{298} = 381.5 \pm 0.6 \text{ kcal mol}^{-1}$)⁵⁸ and $k_{\text{PT}} = 5.5 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$ with a reaction efficiency of 4%.

The reaction of cyclopentoxide does not result in proton transfer, however, our forward and reverse rate measurements relative to isopropanol ($k_f = 2.4 \pm 0.6 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$; $k_r = 3.28 \pm 0.14 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$) give thermodynamic values of $\Delta_{\text{acid}}G_{298} = 366.9 \pm 1.1 \text{ kcal mol}^{-1}$ and $\Delta_{\text{acid}}H_{298} = 375.0 \pm 1.1 \text{ kcal mol}^{-1}$. These measurements indicate that cyclopentanol is considerably more acidic than reported by previous studies ($\Delta_{\text{acid}}H_{298} = 383.0 \pm 4.6 \text{ kcal mol}^{-1}$).⁵⁹ Therefore, when the endothermicity is greater than 4.6 kcal mol⁻¹, proton transfer for anions with 1,3,5-triazine is below the detection limits of our instrument ($k_{\text{PT}} < 1 \times 10^{-12} \text{ cm}^3 \text{ s}^{-1}$).

The dominance of the proton transfer channel when the reaction is highly exothermic is consistent with other gas phase work.^{24, 26} For example, Briscese and Riveros observed exclusive proton transfer and complete inhibition of the S_NAr reaction in their fluorobenzene systems when proton transfer was about 9 kcal mol⁻¹ exothermic. It is therefore intriguing that the Meisenheimer complex was observable in our studies of NH₂⁻ + 1,3,5-triazine where the acidity difference is 17 kcal mol⁻¹; this result suggests inhibition from conversion barriers and/or a more stable Meisenheimer complex. The enhanced stabilization is consistent with computations that have shown significant stabilization energies for anionic σ -complexes containing nitro groups relative to other electron-withdrawing groups.^{20, 60}

A hydride transfer channel becomes active for methoxide and is the only product channel for ethoxide. The hydride transfer rate constant (k_{HT}) for reaction of CH₃O⁻ with 1,3,5-triazine is $k_{\text{HT}} = 2.6 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ ($k_{\text{HT}} = k_{\text{expt}} \times \text{branching fraction}$) with a reaction efficiency of 19%. The hydride transfer rate constant for reaction of C₂H₅O⁻ with 1,3,5-triazine is $k_{\text{HT}} = 2.9 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ with a reaction efficiency of 24%.

Another insightful trend in the data shows that as the proton transfer channel is less available there is an increase in both a stabilized anion-arene complex ($X^{\cdot-} \cdot M$) and fragmentation products. Based on the diagram of the reaction system (Figure 8.5), one may envision the increase in a stabilized complex due to an increase in “trapped” H-bonded complex. However, the increase in fragmentation products from an additive pathway (m/z 44, see CID section) indicates an increase in Meisenheimer complex. While the amide results indicate that conversion between binding motifs is inhibited, an increase in Meisenheimer complexes in less exothermic or more endothermic reactions suggests that although inhibited, conversion between anion-arene complexes is energetically accessible.

8.3.3 *Potential Energy Surface of 1,3,5-Triazine Reactions*

To help characterize the mechanisms in the reactions of 1,3,5-triazine, DFT calculations were conducted. Due to the wide variation in the ions and molecules studied, we were unable to find a level of theory that was capable of accurately reproducing enthalpies of deprotonation for all species. However, the B3LYP/aug-cc-pVTZ calculations for the cyclic compounds (1,3,5-triazine and furan) and the relative values for H_2O versus CH_3OH were within 1 kcal mol^{-1} of the experimental gas phase acidity values; therefore, differences between calculated energies should be fairly accurate. Reaction coordinate plots with optimized structures and associated energies at 0 K for the reaction of 1,3,5-triazine with (a) hydroxide, (b) amide, (c) methoxide, and (d) furanide are shown in Figure 8.5.

The reaction profile for $HO^{\cdot-} + C_3H_3N_3$ (Figure 8.5a) clearly depicts potential energy minima for an aryl H-bonded complex and a relatively more stable Meisenheimer complex along different reaction pathways that lead to the same products, deprotonated triazine and water. Although not depicted, a hydrogen migration from the oxygen to the nitrogen in the

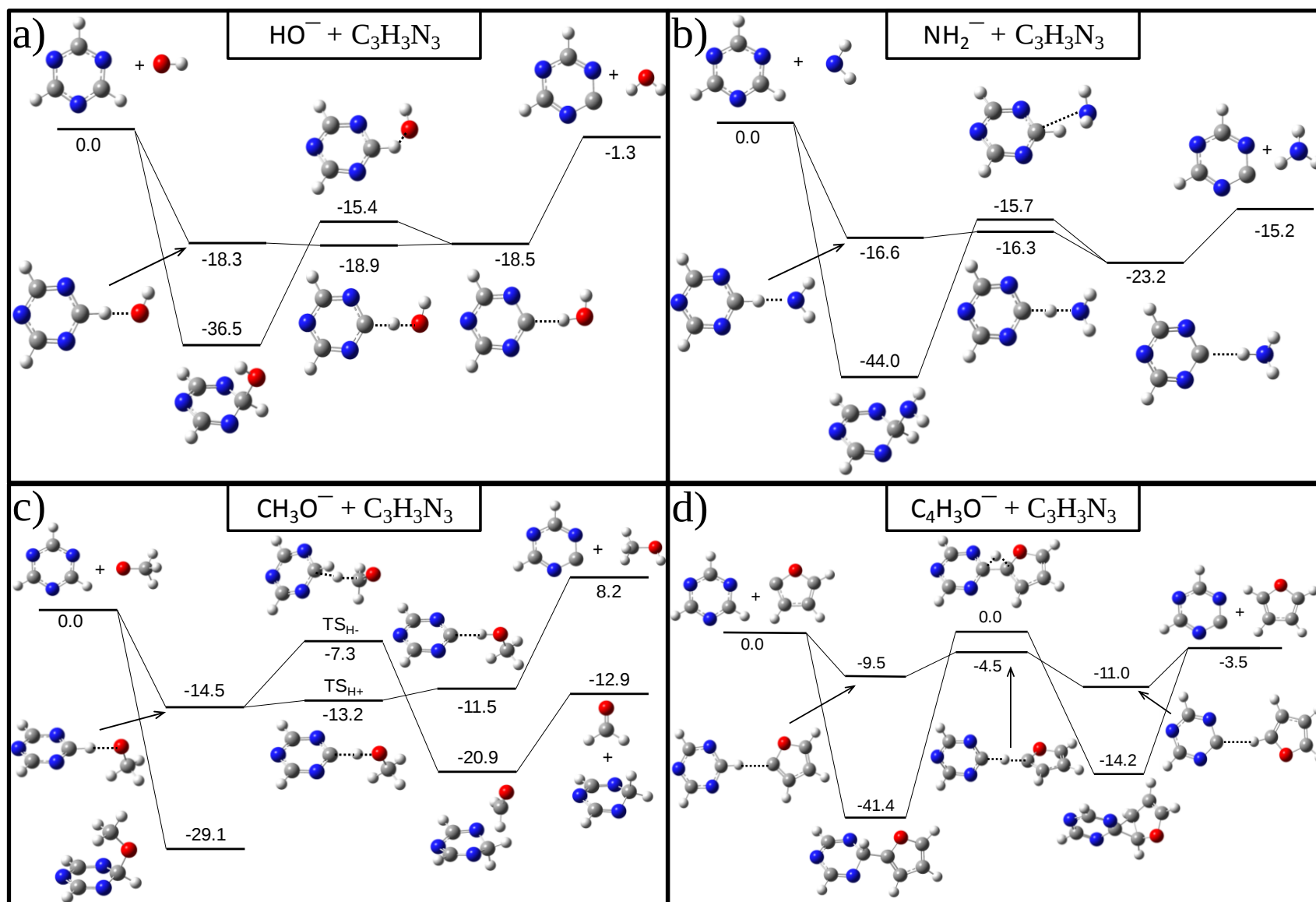


Figure 8.5. Reaction coordinate plots for the reaction of 1,3,5-triazine with (a) hydroxide, (b) amide (c) methoxide, and (d) furanide. Calculations at the B3LYP/aug-cc-pVTZ level of theory. Energy values at 0 K are relative to separated reactants (kcal mol^{-1}).

Meisenheimer complex similar to those seen by Mukherjee and Ren,⁶¹ produces a stable keto-like ring opened structure ($-40.2 \text{ kcal mol}^{-1}$). The barrier to this process lies $7.3 \text{ kcal mol}^{-1}$ below the total energy of reactants and may be the pathway that leads to the observed fragmentation products. The H-bonded complex proceeds through the typical “single-well” proton transfer pathway, while the anionic σ -adduct follows a gas-phase ion–molecule reaction double-minimum potential. The transition state for the proton transfer channel ($-18.9 \text{ kcal mol}^{-1}$) and the central barrier ($-15.4 \text{ kcal mol}^{-1}$) for the double-well are close in energy and well below the product energy ($-1.3 \text{ kcal mol}^{-1}$). This suggests that both channels contribute to products and display single-well characteristics controlled primarily by the exothermicity of reaction.

Before collisional stabilization, the ion-dipole complex should be able to freely convert between binding motifs given the potential energy surface for the hydroxide-triazine reaction (Figure 8.5a) and the conversion barrier should have no influence on the reaction. We would expect a similar conversion barrier for the amide-triazine reaction, however this does not explain the experimental data that suggest an inhibited reaction. A reasonable explanation accounting for the presence of a collisionally stabilized complex and inhibited efficiency originates from the large exothermicity of reaction. While hydroxide participates in a slightly exothermic proton transfer process, proton transfer with amide is highly exothermic. As a result of the stability of the products, proton transfer through the anionic σ -adduct for amide has double-well characteristics with the conversion barrier inhibiting and controlling the reaction pathway. Computations for $\text{NH}_2^- + 1,3,5\text{-triazine}$ support this view (Figure 8.5b) with the anionic σ -adduct ($-44.0 \text{ kcal mol}^{-1}$) and H-bonded product ion-dipole complex ($-23.2 \text{ kcal mol}^{-1}$) lying below the conversion barrier ($-15.7 \text{ kcal mol}^{-1}$).

The reaction profile for $\text{CH}_3\text{O}^- + \text{C}_3\text{H}_3\text{N}_3$ (Figure 8.5c) also indicates the presence of an aryl H-bonded complex and a relatively more stable Meisenheimer complex. The H-bonded complex and anionic σ -adduct follow single-well characteristics to proton transfer products and a double-well potential leading to hydride transfer products. The proton transfer process is endothermic and is expected to be extremely slow. The alternate hydride transfer pathway is exothermic by $12.9 \text{ kcal mol}^{-1}$ and should be the dominant channel kinetically controlled by the slightly higher central barrier ($-7.3 \text{ kcal mol}^{-1}$). This relationship is observed in the product ion ratios of 7% proton transfer and 31% hydride transfer.

The presence of a hydride transfer pathway is intriguing, since often competing processes can interfere with detection of this mechanism. Hydride transfer involves motion of a proton with an electron pair between electron deficient sites. The hydride affinities for closed shell neutrals range from 6 to $106 \text{ kcal mol}^{-1}$.⁶² Our computations suggest that the hydride affinity of 1,3,5-triazine is 52 kcal mol^{-1} (similar to acrylonitrile, $\text{C}_3\text{H}_3\text{N}$, at 56 kcal mol^{-1})⁶² indicating a moderately strong bonding interaction between the $1s^2$ electrons of the hydride and the π^* orbitals. Gronert and Keeffe discuss this “in phase” interaction within a three-nuclei ($\text{C}\cdots\text{H}\cdots\text{C}$) transition state framework in terms of maxim overlap to account for non-linear geometries.⁴¹ Our calculated bond angle (157°) and HOMO for the methoxide reaction depict this type of constructive interaction. Weak hydrogen bonding between the oxygen of the anion and the hydrogen attached to the carbon at the site of attack may facilitate this orientation of the transition state as well as lower the overall energy. In addition to high hydrogen binding energies, hydride acceptors tend to have high electron binding energies. Computations suggest that the electron-withdrawing character of $-\text{CN}$ and $-\text{NO}_2$ groups produce very stable hydride adducts corresponding to positive electron affinities ($2.4 \text{ kcal mol}^{-1}$ and $27.7 \text{ kcal mol}^{-1}$,

respectively).⁶³ The nitrogen atoms in the 1,3,5-triazine ring should have a similar effect on the electron affinity by shifting electron density away from the nearby reaction center reducing the Coulombic repulsive forces and increasing the effective nuclear charge. Furthermore, negative charge delocalization at the nitrogen positions and resonance within the ring help stabilize the additional electron density in the anionic product and transition state structures.

The reaction profile for $\text{C}_4\text{H}_3\text{O}^- + \text{C}_3\text{H}_3\text{N}_3$ (Figure 8.5d) provides insight into the lack of proton transfer for the carbanion reactions. The potential energy profile for the proton transfer reaction displays double-well characteristics. Analogous to the hydride transfer process, the proton transfer can also be viewed as a three-nuclei array in which the HOMO is antibonding resulting in an electrostatically controlled reaction (shuttling of the proton between two atoms with electron pairs).⁴¹ The degree of stability in this “ionic” transition state $[\text{Ar}^- \cdots \text{H}^+ \cdots \text{X}^-]^\ddagger$ correlates with the electronegativity of the attacking atom of the nucleophile.⁶⁴ Due to high electronegativity, amide and oxyanions concentrate electron density to generate strong electrostatic attractions and low transition state barriers. Carbanions are less capable of shifting electron density, which results in weak electrostatic forces in the transition states and barriers to proton transfer. Furthermore, while electron-withdrawing nitrogen and delocalization in 1,3,5-triazine weakens the C-H bond, this also reduces the stabilizing electrostatic/H-bonding interactions (very small δ^- on the carbon site in Ar^-) in the transition state. These factors combine to generate activation barriers to proton transfer between carbon centers. Thus, even with a large thermodynamic driving force, the furanide ($\Delta_{\text{acid}}\text{H}_{298} = 391.10 \pm 0.40 \text{ kcal mol}^{-1}$)⁶⁵ reaction has a transition state barrier of 5 kcal mol^{-1} above the H-bonded complex inhibiting and slowing the reaction. Essentially the ion-dipole complex is trapped in either a H-bonded complex well or an anionic σ -adduct. The energy diagram indicates the anionic σ -adduct is over

30 kcal mol⁻¹ more stable than the H-bonded complex, and therefore is statistically favored. This trapping of the ion-dipole complex prohibits thermodynamically controlled conversion between proton bound forms resulting in the lack of deprotonated 1,3,5-triazine in our CID studies.

One final aspect revealed in our computations (see Appendix 4 for specific bond lengths and angles of the Meisenheimer complexes) is the slight distortion of the aromatic ring (sp³ bond angle character range of the Nu—C—H bonds was 99-108°, and the dihedral angle range of the C_{Nu}—plane of ring was 7-10°, where C_{Nu} is the site of nucleophilic addition) and the short adduct bond lengths (< 1.5 Å, covalent). Therefore, all of the Meisenheimer complexes formed are in the strong σ -adduct category. This result is expected due to the high bond energies associated with C-N, C-C, and C-O bonds. In addition, the exceptionally high stability of these adducts is generated by the symmetric nature of the ring where most of the electron density is localized at the nitrogen positions, thereby delocalizing the charge over the entire ring.

8.4 Conclusion

Our investigation of the reactions of 1,3,5-triazine has provided a more detailed understanding of the influence of anion-arene interactions on mechanisms and product distributions in the gas phase. Analysis of reactivity trends, collision-induced fragmentation processes and H/D exchange experiments revealed intriguing structure-reactivity relationships generated by the electron-withdrawing character of the heteroaromatic nitrogen. The major conclusions drawn from this work include the following.

- (7) A multi-step and/or single-step ring-opening collision-induced fragmentation appears to exist for 1,3,5-triazinide, similar to the photodissociation pathways reported for neutral 1,3,5-triazine.

- (8) The electron-withdrawing nitrogen atoms in the 1,3,5-triazine ring significantly reduce Coulombic repulsive forces to generate extremely electrophilic carbon centers. The presence of a major hydride transfer process indicates the strength of this effect.
- (9) The symmetric nature of the nitrogen atoms in the ring allows stabilization of the negative charge density in the anionic products through delocalization over the entire ring. This effect is manifested in the high stability of the strong covalent σ -adducts.
- (10) The S_NAr addition pathway in 1,3,5-triazine is competitive over a wider range of relative gas phase acidity differences than previously reported for other aromatic systems.
- (11) Our data suggest that the type of interactions initially formed in the loose anion-arene complexes and the transition state barriers between binding motifs can significantly influence competition between different channels which may be operative in gas-phase reactions.

8.5 References

1. Agrawal, J. P. *Progr. Energy Combust. Sci.* **1998**, *24*, 1-30.
2. Alves, W. A. *Vib. Spectrosc.* **2010**, *53*, 285-288.
3. Ali, T. E. S. *Eur. J. Med. Chem.* **2009**, *44*, 4385-4392.
4. Pelizzetti, E.; Maurino, V.; Minero, C.; Carlin, V.; Pramauro, E.; Zerbini, O.; Tosato, M. L. *Environ. Sci. Technol.* **1990**, *24*, 1559-1565.
5. Eisa, H. M.; Tantawy, A. S.; Elkerdawy, M. M. *Pharmazie* **1991**, *46*, 182-184.
6. Klenke, B.; Stewart, M.; Barrett, M. P.; Brun, R.; Gilbert, I. H. *J. Med. Chem.* **2001**, *44*, 3440-3452.
7. Valet, A. *Prog. Org. Coat.* **1999**, *35*, 223-233.
8. Rogers, J.; Moyer, B.; Kalscheur, G.; Emig, N. *JCT Coatingstech* **2007**, *4*, 82-86.
9. Turker, L.; Atalar, T.; Gumus, S.; Camur, Y. *J. Hazard. Mater.* **2009**, *167*, 440-448.
10. Berryman, O. B.; Johnson, D. W. *Chem. Commun.* **2009**, *22*, 3143-3153.
11. Wheeler, S. E.; Houk, K. N. *J. Phys. Chem. A* **2010**, *114*, 8658-8664.
12. Ciesielski, A.; Krygowski, T. M.; Cyranski, M. K.; Dobrowolski, M. A.; Balaban, A. T. *J. Chem. Inf. Model.* **2009**, *49*, 369-376.
13. Katritzky, A. R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7-15.
14. Schlosser, M.; Ruzziconi, R. *Synthesis-Stuttgart* **2010**, *13*, 2111-2123.
15. Mąkosza, M. *Russ. Chem. Bull.* **1996**, *45*, 491-504.
16. Dillow, G. W.; Kebarle, P. *J. Am. Chem. Soc.* **1988**, *110*, 4877-4882.
17. Zheng, Y. J.; Ornstein, R. L. *J. Am. Chem. Soc.* **1997**, *119*, 648-655.
18. Girollo, T.; Xavier, L. A.; Riveros, J. M. *Angew. Chem.* **2004**, *43*, 3588-3590.
19. Chiavarino, B.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lemaire, J.; Maitre, P. *Angew. Chem.* **2007**, *46*, 1995-1998.
20. Fernandez, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* **2010**, *75*, 2971-2980.
21. Hay, B. P.; Bryantsev, V. S. *Chem. Commun.* **2008**, *21*, 2417-2428.
22. Hiraoka, K.; Mizuse, S.; Yamabe, S. *J. Phys. Chem.* **1987**, *91*, 5294-5297.
23. Chiavarino, B.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lemaire, J.; Maitre, P.; Scuderi, D. *Chem.-Eur. J.* **2009**, *15*, 8185-8195.
24. Briscese, S. M. J.; Riveros, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 230-231.
25. Schneider, H.; Vogelhuber, K. M.; Schinle, F.; Weber, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 13022-13026.
26. Chen, H.; Chen, H. W.; Cooks, R. G. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 998-1004.
27. Paul, G. J. C.; Kebarle, P. *J. Am. Chem. Soc.* **1991**, *113*, 1148-1154.
28. Danikiewicz, W.; Bienkowski, T.; Kozłowska, D.; Zimnicka, M. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1351-1363.
29. Ingemann, S.; Nibbering, N. M. M.; Sullivan, S. A.; DePuy, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 6520-6527.
30. Khan, H.; Harris, R. J.; Barna, T.; Craig, D. H.; Bruce, N. C.; Munro, A. W.; Moody, P. C. E.; Scrutton, N. S. *J. Biol. Chem.* **2002**, *277*, 21906-21912.
31. Behrend, C.; Heesche-Wagner, K. *Appl. Environ. Microbiol.* **1999**, *65*, 1372-1377.
32. Vorbeck, C.; Lenke, H.; Fischer, P.; Knackmuss, H. J. *J. Bacteriol.* **1994**, *176*, 932-934.

33. Ziganshin, A. M.; Gerlach, R.; Borch, T.; Naumov, A. V.; Naumova, R. P. *Appl. Environ. Microbiol.* **2007**, *73*, 7898-7905.
34. Rieger, P. G.; Sinnwell, V.; Preuss, A.; Francke, W.; Knackmuss, H. J. *J. Bacteriol.* **1999**, *181*, 1189-1195.
35. Yinon, J.; Johnson, J. V.; Bernier, U. R.; Yost, R. A.; Mayfield, H. T.; Mahone, W. C.; Vorbeck, C. *J. Mass Spectrom.* **1995**, *30*, 715-722.
36. Artau, A.; Ho, Y.; Kenttamaa, H.; Squires, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 7130-7137.
37. DePuy, C. H.; Bierbaum, V. M.; Schmitt, R. J.; Shapiro, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 2920-2921.
38. Ingemann, S.; Kleingeld, J. C.; Nibbering, N. M. M. *J. Chem. Soc., Chem. Commun.* **1982**, *17*, 1009-1011.
39. Bernasconi, C. F.; Stronach, M. W.; DePuy, C. H.; Gronert, S. *J. Phys. Org. Chem.* **1990**, *3*, 346-348.
40. Bernasconi, C. F.; Stronach, M. W.; DePuy, C. H.; Gronert, S. *J. Am. Chem. Soc.* **1990**, *112*, 9044-9052.
41. Gronert, S.; Keeffe, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 2324-2333.
42. Van Doren, J. M.; Barlow, S. E.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Processes* **1987**, *81*, 85-100.
43. Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183-5185.
44. Kato, S.; Lineberger, W. C.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2007**, *266*, 166-179.
45. Blanksby, S. J.; Kato, S.; Bierbaum, V. M.; Ellison, G. B. *Aust. J. Chem.* **2003**, *56*, 459-472.
46. Custer, T. G.; Kato, S.; Fall, R.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2003**, *223*, 427-446.
47. Kato, S.; DePuy, C. H.; Gronert, S.; Bierbaum, V. M. *J. Am. Soc. Mass Spectrom.* **1999**, *10*, 840-847.
48. DePuy, C. H.; Kato, S. H/D Exchange Reactions. In *Encyclopedia of Mass Spectrometry: Theory and Ion Chemistry*, Armentrout, P. B., Ed. Elsevier: Amsterdam, **2003**; Vol. 1, pp 670-674.
49. Gaussian 03 (Revision-B.05), Frish, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W. A., P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 2004.

50. Ichino, T.; Gianola, A. J.; Kato, S.; Bierbaum, V. M.; Lineberger, W. C. *J. Phys. Chem. A* **2007**, *111*, 8374-8383.
51. Wiberg, K. B.; Nakaji, D.; Breneman, C. M. *J. Am. Chem. Soc.* **1989**, *111*, 4178-4190.
52. Dyakov, Y. A.; Mebel, A. M.; Lin, S. H.; Lee, Y. T.; Ni, C. K. *J. Phys. Chem. A* **2007**, *111*, 9591-9599.
53. Wren, S. W.; Vogelhuber, K. M.; Garver, J. M.; Kato, S.; Sheps, L.; Bierbaum, V. M.; Lineberger, W. C. *In preparation*
54. Bartmess, J. E. "Negative Ion Energetics Data" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. Linstrom, P.J and Mallard, W.G., National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>.
55. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.
56. Dotterer, S. K.; Harris, R. L. *J. Org. Chem.* **1988**, *53*, 777-779.
57. Wickhamjones, C. T.; Ervin, K. M.; Ellison, G. B.; Lineberger, W. C. *J. Chem. Phys.* **1989**, *91*, 2762-2763.
58. Ervin, K. M.; DeTuro, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947-9956.
59. Alconcel, L. S.; Continetti, R. E. *Chem. Phys. Lett.* **2002**, *366*, 642-649.
60. Glukhovtsev, M. N.; Bach, R. D.; Laiter, S. J. *J. Org. Chem.* **1997**, *62*, 4036-4046.
61. Mukherjee, S.; Ren, J. H. *J. Am. Soc. Mass Spectrom.* **2010**, *21*, 1720-1729.
62. Goebbert, D. J.; Wenthold, P. G. *Int. J. Mass Spectrom.* **2006**, *257*, 1-11.
63. Vianello, R.; Peran, N.; Maksic, Z. B. *Eur. J. Org. Chem.* **2007**, *3*, 526-539.
64. Keeffe, J. R.; Gronert, S.; Colvin, M. E.; Tran, N. L. *J. Am. Chem. Soc.* **2003**, *125*, 11730-11745.
65. Clifford, E. P.; Wenthold, P. G.; Lineberger, W. C.; Ellison, G. B.; Wang, C. X.; Grabowski, J. J.; Vila, F.; Jordan, K. D. *J. Chem. Soc., Perkin Trans. 2* **1998**, *5*, 1015-1022.

Appendix 1

Calculation of the E2 Branching Fraction

The experimental rate constants and computational kinetic isotope effects can be used to estimate the branching fraction for the E2 pathway, designated as c in the derivation below.

$$k_{\text{Hexp}} = k_{\text{HS}} + k_{\text{HE}} \quad k_{\text{HE}} = c \cdot k_{\text{Hexp}}$$

$$k_{\text{HS}} = (1 - c) \cdot k_{\text{Hexp}}$$

$$k_{\text{Dexp}} = k_{\text{DS}} + k_{\text{DE}} \quad k_{\text{DE}} = \frac{k_{\text{HE}}}{\text{KIE(E2)}}$$

$$k_{\text{DS}} = k_{\text{Dexp}} - k_{\text{DE}} = k_{\text{Dexp}} - \frac{k_{\text{HE}}}{\text{KIE(E2)}}$$

$$\text{KIE}(S_N2) = \frac{k_{\text{HS}}}{k_{\text{DS}}} = \frac{(1 - c) \cdot k_{\text{Hexp}}}{k_{\text{Dexp}} - \frac{c \cdot k_{\text{Hexp}}}{\text{KIE(E2)}}}$$

Where

k_{Hexp} = experimental rate constant for the undeuterated reactant

k_{Dexp} = experimental rate constant for the appropriate deuterated reactant

k_{HS} = actual rate constant for substitution channel for the undeuterated reactant

k_{DS} = actual rate constant for substitution channel for the appropriate deuterated reactant

k_{HE} = actual rate constant for elimination channel for the undeuterated reactant

k_{DE} = actual rate constant for elimination channel for the appropriate deuterated reactant

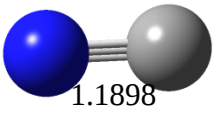
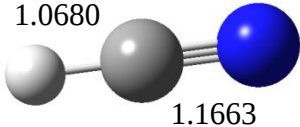
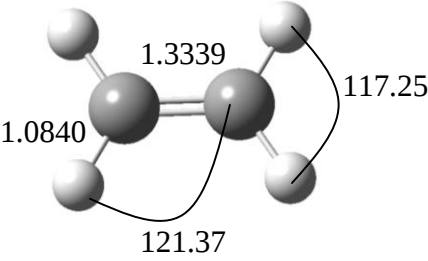
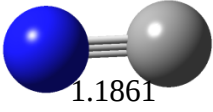
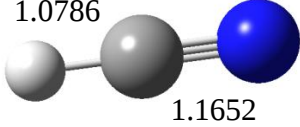
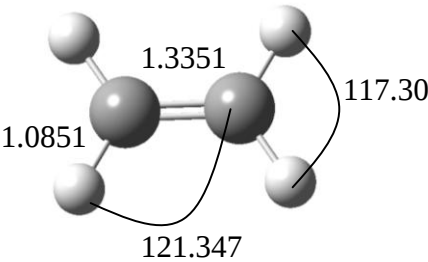
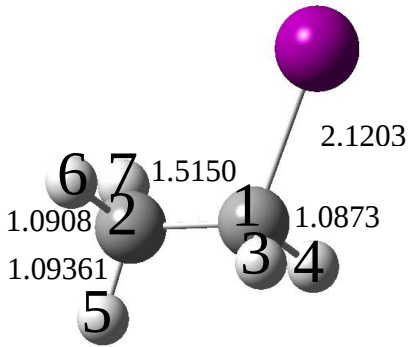
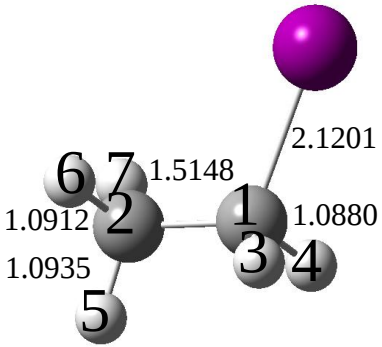
$\text{KIE}(S_N2)$ = computational KIE ($k_{\text{H}}/k_{\text{D}}$) for substitution channel

KIE(E2) = computational KIE ($k_{\text{H}}/k_{\text{D}}$) for elimination channel

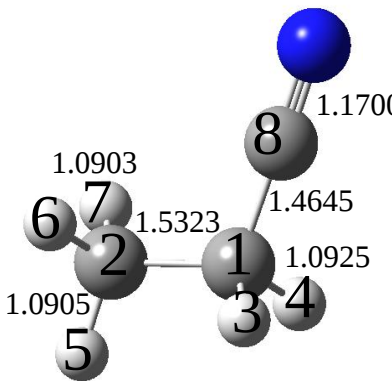
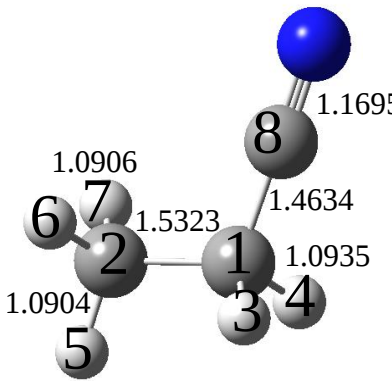
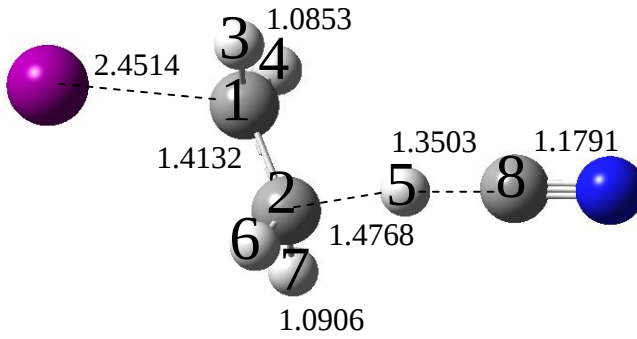
Optimized Geometry for the Reaction of CH₃I + CN⁻

Structures
CH ₃ I (gas phase)
108.36 1.0844 2.1128 110.56
CN ⁻ (gas phase)
1.1898
S _N 2 transition state (gas phase)
85.80 119.47 94.20 2.5078 2.2042 1.071
CH ₃ CN (gas phase)
109.93 1.1692 1.4614 1.0899 109.00

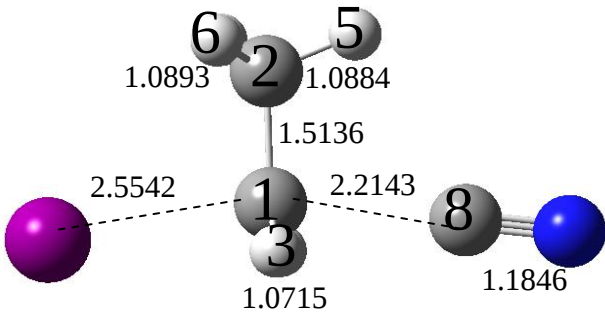
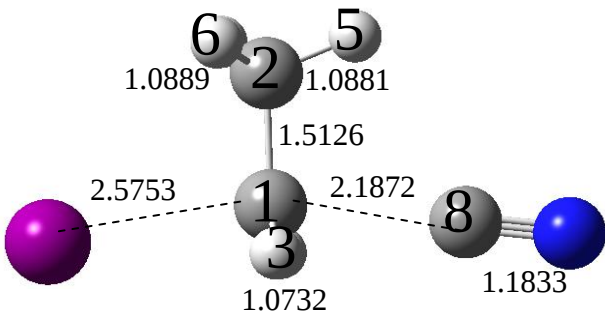
Optimized Geometry for the Reaction of $\text{CH}_3\text{CH}_2\text{I} + \text{CN}^-$

Structures		
CN^- (gas phase)	HCN (gas phase)	C_2H_4 (gas phase)
		
CN^- (THF)	HCN (THF)	C_2H_4 (THF)
		
$\text{C}_2\text{H}_5\text{I}$ (gas phase)		
		$\angle \text{IC1H3} = 105.79$ $\angle \text{IC1C2} = 113.09$ $\angle \text{H3C1H4} = 108.90$ $\angle \text{H3C1C2} = 111.46$ $\angle \text{H5C2C1} = 109.72$ $\angle \text{H6C2C1} = 111.31$ $\angle \text{H6C2H5} = 108.19$ $\angle \text{H6C2H7} = 108.01$
$\text{C}_2\text{H}_5\text{I}$ (THF)		
		$\angle \text{IC1H3} = 105.73$ $\angle \text{IC1C2} = 113.04$ $\angle \text{H3C1H4} = 109.02$ $\angle \text{H3C1C2} = 111.49$ $\angle \text{H5C2C1} = 109.50$ $\angle \text{H6C2C1} = 111.39$ $\angle \text{H6C2H5} = 108.16$ $\angle \text{H6C2H7} = 108.14$

Optimized Geometry for the Reaction of CH₃CH₂I + CN⁻

Structures	
C ₂ H ₅ CN (gas phase)	
	$\angle$ C8C1H3 = 108.14 $\angle$ C8C1C2 = 111.83 $\angle$ C1C8N = 179.02 $\angle$ H3C1H4 = 107.15 $\angle$ H3C1C2 = 110.71 $\angle$ H5C2C1 = 109.85 $\angle$ H6C2C1 = 110.69 $\angle$ H6C2H5 = 108.60 $\angle$ H6C2H7 = 108.32
C ₂ H ₅ CN (THF)	
	$\angle$ C8C1H3 = 107.83 $\angle$ C8C1C2 = 111.81 $\angle$ C1C8N = 179.29 $\angle$ H3C1H4 = 107.36 $\angle$ H3C1C2 = 110.91 $\angle$ H5C2C1 = 109.44 $\angle$ H6C2C1 = 110.79 $\angle$ H6C2H5 = 108.59 $\angle$ H6C2H7 = 108.59
E2 transition state (gas phase)	
	$\angle$ H6C2H7 = 112.77 $\angle$ H3C1H4 = 112.71 $\angle$ H6C2H5 = 101.31 $\angle$ C1C2H5 = 104.84 $\angle$ C2H5C8 = 172.48 $\angle$ H5C8N = 177.41 $\angle$ H3C1C2 = 116.06 $\angle$ H3C1I = 94.40

Optimized Geometry for the Reaction of $\text{CH}_3\text{CH}_2\text{I} + \text{CN}^-$

Structures	
$\text{S}_{\text{N}}2$ transition state(gas phase)	
	$\angle \text{C1C7H5} = 111.05$ $\angle \text{C1C2H6} = 109.98$ $\angle \text{H6C2H5} = 107.37$ $\angle \text{H3C1H4} = 117.82$ $\angle \text{H3C1C2} = 120.82$ $\angle \text{H3C1I} = 89.73$ $\angle \text{H3C1C8} = 82.88$ $\angle \text{C1C8I} = 165.58$ $\angle \text{NC8C1} = 178.82$
$\text{S}_{\text{N}}2$ transition state (THF)	
	$\angle \text{C1C2H5} = 111.17$ $\angle \text{C1C2H6} = 110.18$ $\angle \text{H6C2H5} = 108.67$ $\angle \text{H3C1H4} = 117.96$ $\angle \text{H3C1C2} = 120.91$ $\angle \text{H3C1I} = 89.72$ $\angle \text{H3C1C8} = 83.50$ $\angle \text{C1C8I} = 164.26$ $\angle \text{NC8C1} = 175.09$

Appendix 2

Exothermicities ($\Delta_f H_{298}$ taken from NIST WebBook) and Computational Reaction Barriers^a (MP2/6-311++G(2d,p) for C, N, and H and the LanL2DZ effective core potential for I) relative to the separated reactants.

Reaction	$\Delta H_{\text{rxn}} S_N2$ (kcal mol ⁻¹)	$\Delta H^\ddagger S_N2$ (kcal mol ⁻¹)	$\Delta H_{\text{rxn}} E2$ (kcal mol ⁻¹)	$\Delta H^\ddagger E2$ (kcal mol ⁻¹)	S_N2 preference (kcal mol ⁻¹)
Cl ⁻ + CH ₃ I	-13.9	6.2	---	---	---
Cl ⁻ + C ₂ H ₅ I	-14.8	9.4	1.5	16.0	6.6
Cl ⁻ + <i>i</i> -C ₃ H ₇ I	-14.6	11.9	-0.5	14.6	2.7
Cl ⁻ + <i>t</i> -C ₄ H ₉ I	-16.5	23.1	0.2	13.1	-10.0
CN ⁻ + CH ₃ I	-48.0	3.2	---	---	---
CN ⁻ + C ₂ H ₅ I	-48.3	7.5	-16.0	11.0	3.5
CN ⁻ + <i>i</i> -C ₃ H ₇ I	-49.5	12.1	-17.8	10.3	-1.8
CN ⁻ + <i>t</i> -C ₄ H ₉ I	-46.0	25.4	-17.2	14.5	-10.9
HS ⁻ + CH ₃ I	-34.3	0.1	---	---	---
HS ⁻ + C ₂ H ₅ I	-34.7	2.8	-16.2	9.0	6.2
HS ⁻ + <i>i</i> -C ₃ H ₇ I	-36.4	6.6	-18.1	8.2	1.6
HS ⁻ + <i>t</i> -C ₄ H ₉ I	-34.2	20.8	-17.4	6.6	-14.2

^aWhen the S_N2 barrier heights are above the energy of the reactants, the reaction rate constants are expected to be very low. Based on our reaction efficiencies the absolute values of the computational barrier heights are too high. While higher levels of theory might improve the quantitative accuracy of our reaction barriers, our focus is on qualitative comparisons to experimental data. Therefore, our methodology only employs quantitative ratios of energies and discusses trends in geometry and charge distribution which are less sensitive to the level of theory employed. Reasonably good agreement of the computational KIE with the experimental S_N2 KIEs and estimated product distributions indicates that the theoretical level is adequate for qualitative analysis and R_{TS} comparisons for the methyl, ethyl and isopropyl iodide reactions for a given nucleophile. Additionally, the relative S_N2 and E2 barrier heights (S_N2 preference = $\Delta H_{\text{rxn}} E2 - \Delta H_{\text{rxn}} S_N2$) are consistent with our experimental data.

Covalent Potential Electronegativity Scale

Covalent potential scale of EN (V_x) is defined

$$V_x = n_x/r_x$$

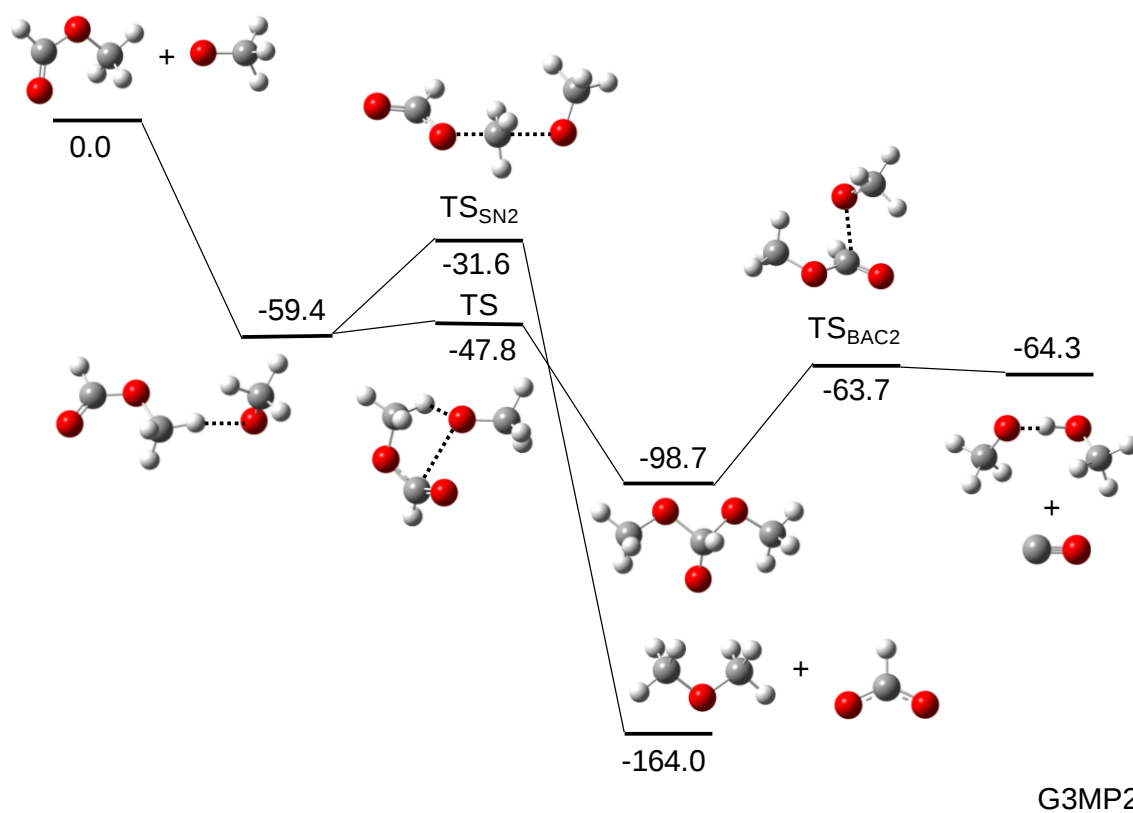
where n is the number of valence electrons in X (the central atom) and r is the covalent radius of X in the hybridized valence state (i.e., $N \equiv C - C \equiv N$, $C - C = 1.393 \text{ \AA}$, $r_C = 0.5 \cdot 1.393 \text{ \AA} = 0.6965 \text{ \AA}$).

$$V_{Cl} = 7/1.02 \text{ \AA} = 6.86$$

$$V_C = 4/0.697 \text{ \AA} = 5.74$$

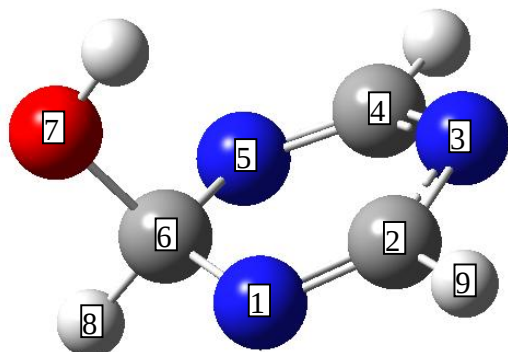
$$V_S = 6/1.03 \text{ \AA} = 5.83$$

Appendix 3



Reaction coordinate plot for the reaction of methoxide with methyl formate. Calculations using the G3MP2 method. Energy values at 0 K are relative to separated reactants (kJ mol⁻¹).

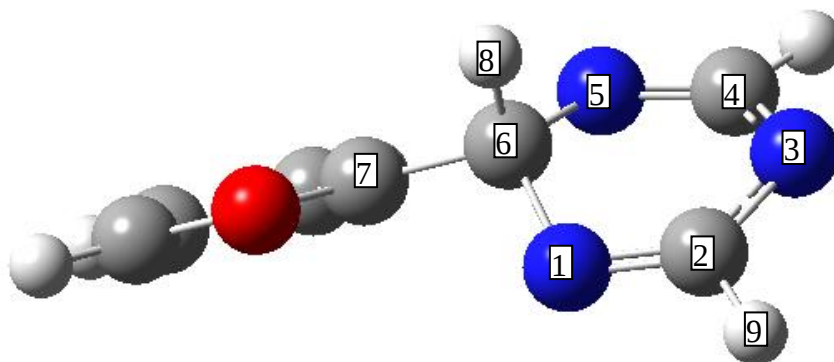
Geometry and bond lengths of the hydroxide-1,3,5-triazine adduct at the B3LYP/aug-cc-pVTZ level of theory



Bond	Bond Length (Å)	Bond	Bond Length (Å)	Bond Angle	Angle (°)	Bond Angle	Angle (°)
N1-C2	1.30168	N5-C6	1.44591	∠C6N1C2	114.83	∠N5C6N1	116.26
C2-N3	1.35441	C6-H8	1.09233	∠N1C2N3	128.87	∠N5C6O7	109.46
N3-C4	1.35444	C6-O7	1.46712	∠C2N3C4	111.45	∠N5C6H8	109.61
C4-N5	1.30166	C2-H9	1.09303	∠C6N1C2N3	8.08	∠O7C6H8	101.36

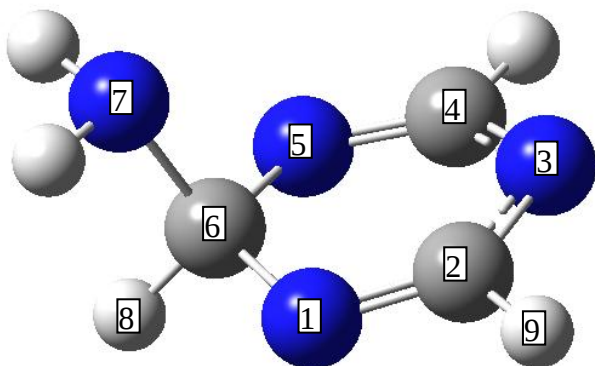
Bond	Bond Length (Å)	Bond	Bond Length (Å)	Bond Angle	Angle (°)	Bond Angle	Angle (°)
N1-C2	1.300	N5-C6	1.443	∠C6N1C2	115.37	∠N5C6N1	116.74
C2-N3	1.353	C6-H8	1.093	∠N1C2N3	129.02	∠N5C6O7	109.95
N3-C4	1.353	C6-O7	1.474	∠C2N3C4	111.51	∠N5C6H8	109.57
C4-N5	1.300	C2-H9	1.093	∠C6N1C2N3	6.67	∠O7C6H8	99.66

Geometry and bond lengths of the furanide-1,3,5-triazine adduct at the B3LYP/aug-cc-pVTZ level of theory



Bond	Bond Length (Å)	Bond	Bond Length (Å)	Bond Angle	Angle (°)	Bond Angle	Angle (°)
N1-C2	1.296	N5-C6	1.461	∠C6N1C2	111.06	∠N5C6N1	116.74
C2-N3	1.362	C6-H8	1.112	∠N1C2N3	128.63	∠N5C6C7	109.38
N3-C4	1.359	C6-C7	1.498	∠C2N3C4	110.54	∠N5C6H8	108.32
C4-N5	1.297	C2-H9	1.092	∠C6N1C2N3	10.30	∠C7C6H8	106.39

Geometry and bond lengths of the amide-1,3,5-triazine adduct at the B3LYP/aug-cc-pVTZ level of theory



Bond	Bond Length (Å)	Bond	Bond Length (Å)	Bond Angle	Angle (°)	Bond Angle	Angle (°)
N1-C2	1.298	N5-C6	1.454	∠C6N1C2	114.28	∠N5C6N1	116.96
C2-N3	1.355	C6-H8	1.101	∠N1C2N3	129.16	∠N5C6N7	107.89
N3-C4	1.355	C6-N7	1.497	∠C2N3C4	111.74	∠N5C6H8	107.57
C4-N5	1.298	C2-H9	1.093	∠C6N1C2N3	7.58	∠N7C6H8	108.73

SIFT-CID ratios for reference acid/1,3,5-triazinide clusters

		$A_{\text{ref}}^- : 1,3,5\text{-triazinide}^-$			
	E_{com}	$[\text{F}_2\text{C}_6\text{H}_3 \cdots \text{H} \cdots \text{H}_2\text{C}_3\text{N}_3]^-$	$[\text{C}_5\text{H}_5\text{O} \cdots \text{H} \cdots \text{H}_2\text{C}_3\text{N}_3]^-$	$[\text{FC}_6\text{H}_4 \cdots \text{H} \cdots \text{H}_2\text{C}_3\text{N}_3]^-$	$[\text{C}_4\text{H}_3\text{O} \cdots \text{H} \cdots \text{H}_2\text{C}_3\text{N}_3]^-$
(eV)	kcal mol ⁻¹	($\Delta H_{\text{acid}} = 380.2 \pm 2.1$) ^a	($\Delta H_{\text{acid}} = 383.9 \pm 3.1$) ^a	($\Delta H_{\text{acid}} = 386.8 \pm 2.1$) ^a	($\Delta H_{\text{acid}} = 391.1 \pm 0.4$) ^a
0.16	3.6		95:5		
0.18	4.2		94:6		94:6
0.21	4.8		93:7		95:5
0.26	6.0		93:7		96:4
0.31	7.2	98:2		90:10	
0.34	7.7	98:2		90:10	
0.39	8.9	98:2		91:9	96:4
0.44	10.1	98:2		91:9	

^aProton Affinities from Bartmess, J. E. "Negative Ion Energetics Data" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. Linstrom, P.J and Mallard, W.G., National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>

Bibliography

- Adriaanse, C.; Sulpizi, M.; VandeVondele, J.; Sprik, M. *J. Am. Chem. Soc.* **2009**, *131*, 6046-6047.
- Agrawal, J. P. *Progr. Energy Combust. Sci.* **1998**, *24*, 1-30.
- Alconcel, L. S.; Continetti, R. E. *Chem. Phys. Lett.* **2002**, *366*, 642-649.
- Ali, T. E. S. *Eur. J. Med. Chem.* **2009**, *44*, 4385-4392.
- Almerindo, G. I.; Pliego, J. R. *Org. Lett.* **2005**, *7*, 1821-1823.
- Alves, W. A. *Vib. Spectrosc.* **2010**, *53*, 285-288.
- Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*. University Science Books: United States, **2006**.
- Artau, A.; Ho, Y.; Kenttamaa, H.; Squires, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 7130-7137.
- Bachrach, S. M.; Mulhearn, D. C. *J. Phys. Chem.* 1996, *100*, 3535-3540.
- Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795-798.
- Balucani, N. *Int. J. Mol. Sci.* **2009**, *10*, 2304-2335.
- Bartmess, J. E. "Negative Ion Energetics Data" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. Linstrom, P.J and Mallard, W.G., National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>.
- Bartsch, R. A.; Zavada, J., *Chem. Rev.* **1980**, *80*, 453-494.
- Behrend, C.; Heesche-Wagner, K. *Appl. Environ. Microbiol.* **1999**, *65*, 1372-1377.
- Bernasconi, C. F.; Stronach, M. W.; DePuy, C. H.; Gronert, S. *J. Phys. Org. Chem.* **1990**, *3*, 346-348.
- Bernasconi, C. F.; Stronach, M. W.; DePuy, C. H.; Gronert, S. *J. Am. Chem. Soc.* **1990**, *112*, 9044-9052.
- Berryman, O. B.; Johnson, D. W. *Chem. Commun.* **2009**, *22*, 3143-3153.
- Bickelhaupt, F. M.; Baerends, E. J.; Nibbering, N. M. M. *Chem. Eur. J.* **1996**, *2*, 196-207.
- Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114-128.

- Bierbaum, V. M.; Grabowski, J. J.; DePuy, C. H. *J. Phys. Chem.* **1984**, *88*, 1389-1393.
- Bierbaum, V. M. In *Encyclopedia of Mass Spectrometry*; Editor, Gross, M. L., Caprioli, R., Eds.; Elsevier: Amsterdam, **2003**; Vol. 1, p 98.
- Blanksby, S. J.; Kato, S.; Bierbaum, V. M.; Ellison, G. B. *Aust. J. Chem.* **2003**, *56*, 459-472.
- Bogdanov, B.; McMahon, T. B. *Int. J. Mass Spectrom.* **2005**, *241*, 205-223.
- Bohme, D. K.; Young, L. B. *J. Am. Chem. Soc.* **1970**, *92*, 7354-7358.
- Bohme, D. K.; Mackay, G. I. *J. Am. Chem. Soc.* **1981**, *103*, 978-979.
- Bohme, D. K.; Raksit, A. B.; Mackay, G. L. *J. Am. Chem. Soc.* **1982**, *104*, 1100-1101.
- Bohme, D. K.; Raksit, A. B. *Can. J. Chem.* **1985**, *63*, 3007-3011.
- Bohme, D. K. *Can. J. Chem.* **2008**, *86*, 177-198.
- Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. *Advances in Chemistry Series* **1987**, *215*, 137-153.
- Bradley, J. D.; Gerrans, G. C. *J. Chem. Educ.* **1973**, *50*, 463-466.
- Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986-5992.
- Briscese, S. M. J.; Riveros, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 230-231.
- Buncel, E.; Um I. H. *Tetrahedron* **2004**, *60*, 7801-7825.
- Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanism*. 5th ed.; Springer: New York, **2007**.
- Chabiny, M. L.; Craig, S. L.; Regan, C. K.; Brauman, J. I. *Science* **1998**, *279*, 1882-1886.
- Chattaraj, P. K. *J. Phys. Chem. A* **2001**, *105*, 511-513.
- Chen, X.; Brauman, J. I. *J. Am. Chem. Soc.* **2008**, *130*, 15038-15046.
- Chen, H.; Chen, H. W.; Cooks, R. G. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 998-1004.
- Chiavarino, B.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lemaire, J.; Maitre, P. *Angew. Chem.* **2007**, *46*, 1995-1998.
- Chiavarino, B.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lemaire, J.; Maitre, P.; Scuderi, D. *Chem.-Eur. J.* **2009**, *15*, 8185-8195.

- Ciesielski, A.; Krygowski, T. M.; Cyranski, M. K.; Dobrowolski, M. A.; Balaban, A. T. *J. Chem. Inf. Model.* **2009**, *49*, 369-376.
- Clifford, E. P.; Wenthold, P. G.; Lineberger, W. C.; Ellison, G. B.; Wang, C. X.; Grabowski, J. J.; Vila, F.; Jordan, K. D. *J. Chem. Soc., Perkin Trans. 2* **1998**, *5*, 1015-1022.
- Cooks, R. G.; Koskinen, J. T.; Thomas, P. D. *J. Mass Spectrom.* **1999**, *34*, 85-92.
- Cooks, R. G.; Wong, P. S. H. *Acc. Chem. Res.* **1998**, *31*, 379-386.
- CRC Handbook of Chemistry and Physics*, 89th ed.; Editor, Lide, D. R., Ed.; CRC Press: Boca Raton, Fl., **2008**.
- Creek, J. A. M.; McAnoy, A. M.; Brinkworth, C. S. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 3419-3424.
- Custer, T. G.; Kato, S.; Fall, R.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2003**, *223*, 427-446.
- Danikiewicz, W.; Bienkowski, T.; Kozłowska, D.; Zimnicka, M. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1351-1363.
- Davico, G. E.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2000**, *122*, 1740-1748.
- Davico, G. E. *J. Phys. Chem. A* **2006**, *110*, 13112-13121.
- DePuy, C. H.; Bierbaum, V. M.; Schmitt, R. J.; Shapiro, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 2920-2921.
- DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481-2482.
- DePuy, C. H.; Grabowski, J. J.; Bierbaum, V. M.; Ingemann, S.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1985**, *107*, 1093-1098.
- DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650-8655.
- DePuy, C. H. *J. Org. Chem.* **2002**, *67*, 2393-2401.
- DePuy, C. H.; Kato, S. "H/D Exchange Reactions." In *Encyclopedia of Mass Spectrometry: Theory and Ion Chemistry*, Armentrout, P. B., Ed. Elsevier: Amsterdam, **2003**; Vol. 1, pp 670-674.
- Dillow, G. W.; Kebarle, P. *J. Am. Chem. Soc.* **1988**, *110*, 4877-4882.
- Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 6592-6597.

Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052-2056.

Dmitrenko, O.; Thorpe, C.; Bach, R. D. *J. Org. Chem.* **2007**, *72*, 8298-8307.

Dodd, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1984**, *106*, 5356-5357.

Dodd, J. A.; Brauman, J. I. *J. Phys. Chem.* **1986**, *90*, 3559-3562.

Dotterer, S. K.; Harris, R. L. *J. Org. Chem.* **1988**, *53*, 777-779.

Downard, K. M.; Bowie, J. H.; O'Hair, R. A. J.; Krempp, M.; DePuy, C. H. *Int. J. Mass Spectrom. Ion Processes* **1992**, *120*, 217-229.

Dyakov, Y. A.; Mebel, A. M.; Lin, S. H.; Lee, Y. T.; Ni, C. K. *J. Phys. Chem. A* **2007**, *111*, 9591-9599.

Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16-24.

Eisa, H. M.; Tantawy, A. S.; Elkerdawy, M. M. *Pharmazie* **1991**, *46*, 182-184.

Engberts, J. B. F. N. *Pure Appl. Chem.* **1997**, *69*, 231-233.

Ermolaeva, L. V.; Appolonova, S. A.; Plemenkov, V. V.; Konovalov, A. I. *Theochem. J. Mol. Struct.* **1997**, *398*, 451-455.

Ervin, K. M. *Chem. Rev.* **2001**, *101*, 391-444.

Ervin, K. M.; DeTuro, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947-9956.

Eyet, N.; Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1046-1051.

Eyet, N.; Villano, S. M.; Bierbaum, V. M. *J. Am. Soc. Mass Spectrom.* **2008**, *19*, 1296-1302.

Fang, Y. R.; MacMillar, S.; Eriksson, J.; Kolodziejska-Huben, M.; Dybala-Defratyka, A.; Paneth, P.; Matsson, O.; Westaway, K. C. *J. Org. Chem.* **2006**, *71*, 4742-4747.

Ferguson, E. E.; Fehsenfeld, F.C.; Schmeltekopf, A.L. *Adv. At. Mol. Phys.* **1969**, *5*, 1-69.

Fernandez, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* **2010**, *75*, 2971-2980.

Flores, A. E.; Gronert, S. *J. Am. Chem. Soc.* **1999**, *121*, 2627-2628.

Fountain, K. R.; Tad-y, D. B.; Paul, T. W.; Golynskiy, M. V. *J. Org. Chem.* **1999**, *64*, 6547-6553.

Fountain, K. R.; Felkerson, C. J.; Driskell, J. D.; Lamp, B. D. *J. Org. Chem.* **2003**, *68*, 1810-1814.

Fountain, K. R. *J. Phys. Org. Chem.* **2005**, *18*, 481-485.

Frink, B. T.; Hadad, C. M. *J. Chem. Soc., Perkin Trans. 2* **1999**, *31*, 2397-2407.

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.1*, Gaussian, Inc., Wallingford CT, **2009**.

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision B.05*, Gaussian, Inc.: Pittsburgh, PA, **2004**.

Garver, J. M.; Fang, Y.; Eyet, N.; Villano, S. M.; Bierbaum, V. M.; Westaway, K. C. *J. Am. Chem. Soc.* **2010**, *132*, 3808-3814.

Garver, J. M.; Gronert, S.; Bierbaum, V. M. *submitted as a communication (J. Am. Chem. Soc.)*

Garver, J. M.; Yang, Z.; Nichols, C. M.; Worker, B. B.; Gronert, S.; Bierbaum, V. M. (*in preparation*)

Giroldo, T.; Xavier, L. A.; Riveros, J. M. *Angew. Chem.* **2004**, *43*, 3588-3590.

Glad, S. S.; Jensen, F. *J. Am. Chem. Soc.* **1994**, *116*, 9302-9310.

Glad, S. S.; Jensen, F. J. *Phys. Chem.* **1996**, *100*, 16892-16898.

Glad, S. S.; Jensen, F. J. *Am. Chem. Soc.* **1997**, *119*, 227-232.

Glad, S. S.; Jensen, F. J. *Org. Chem.* **1997**, *62*, 253-260.

Glukhovtsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1996**, *118*, 6273-6284.

Glukhovtsev, M. N.; Bach, R. D.; Laiter, S. *J. Org. Chem.* **1997**, *62*, 4036-4046.

Goebbert, D. J.; Wenthold, P. G. *Int. J. Mass Spectrom.* **2006**, *257*, 1-11.

Gonzales, J. M.; Allen, W. D.; Schaefer, H. F. *J. Phys. Chem. A* **2005**, *109*, 10613-10628.

Graul, S. T.; Bowers, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 3875-3883.

Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 4400-4402.

Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327-2330.

Gronert, S.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1991**, *113*, 4009-4010.

Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 4488-4497.

Gronert, S.; Pratt, L. M.; Mogali, S., *J. Am. Chem. Soc.* **2001**, *123*, 3081-3091.

Gronert, S. *Chem. Rev.* **2001**, *101*, 329-360.

Gronert, S. *Acc. Chem. Res.* **2003**, *36*, 848-857.

Gronert, S.; Fagin, A.; Okamoto, K.; Pratt, L. M.; Mogali, S. *Abstr. Pap. Am. Chem. Soc.* **2003**, *226*, U181-U181.

Gronert, S.; Fagin, A. E.; Okamoto, K.; Mogali, S.; Pratt, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 12977-12983.

Gronert, S.; Keefe, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 2324-2333.

Gronert, S.; Keefe, J. R. *J. Org. Chem.* **2006**, *71*, 5959-5968.

Gronert, S.; Fagin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, *129*, 5330-5331.

Hadad, C. M.; Rablen, P. R.; Wiberg, K. B. *J. Org. Chem.* **1998**, *63*, 8668-8681.

Haib, J.; Stahl, D. *Org. Mass Spectrom.* **1992**, *27*, 377-382.

Hase, W. L. *Science* **1994**, 266, 998-1002.

Hay, B. P.; Bryantsev, V. S. *Chem. Commun.* **2008**, 21, 2417-2428.

Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 270-283.

Heaton, M. M. *J. Am. Chem. Soc.* **1978**, 100, 2004-2008.

Hiraoka, K.; Mizuse, S.; Yamabe, S. *J. Phys. Chem.* **1987**, 91, 5294-5297.

Hoaglund-Hyzer, C.S.; Counterman, A.E.; Clemmer, D.E. *Chem. Rev.* **1999**, 99, 3037-3079.

Hoz, S. *J. Org. Chem.* **1982**, 47, 3545-3547.

Hoz, S.; Basch, H.; Wolk, J. L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* **1999**, 121, 7724-7725.

Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1994**, 116, 7797-7800.

Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1995**, 117, 10726-10734.

Hu, W. P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1996**, 118, 860-869.

Hynes, J. T. *Annu. Rev. Phys. Chem.* **1985**, 36, 573-597.

Ichino, T.; Gianola, A. J.; Kato, S.; Bierbaum, V. M.; Lineberger, W. C. *J. Phys. Chem. A* **2007**, 111, 8374-8383.

Ingemann, S.; Nibbering, N. M. M.; Sullivan, S. A.; DePuy, C. H. *J. Am. Chem. Soc.* **1982**, 104, 6520-6527.

Ingemann, S.; Kleingeld, J. C.; Nibbering, N. M. M. *J. Chem. Soc., Chem. Commun.* **1982**, 17, 1009-1011.

Isolani, P. C.; Riveros, J. M. *Chem. Phys. Lett.* **1975**, 33, 362-364.

Jencks, W. P. *Chem. Rev.* **1985**, 85, 511-527.

Johlman, C. L.; Wilkins, C. L. *J. Am. Chem. Soc.* **1985**, 107, 327-332.

Jones, M. E.; Ellison, G. B. *J. Am. Chem. Soc.* 1989, 111, 1645-1654.

Jordan, F.; Li, H.; Brown, A. *Biochem.* **1999**, 38, 6369-6373.

Kahn, K.; Bruice, T. C. *J. Phys. Chem. B* **2003**, 107, 6876-6885.

- Kato, S.; DePuy, C. H.; Gronert, S.; Bierbaum, V. M. *J. Am. Soc. Mass Spectrom.* **1999**, *10*, 840-847.
- Kato, S.; Davico, G. E.; Lee, H. S.; DePuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2001**, *210*, 223-229.
- Kato, S.; Hacaloglu, J.; Davico, G. E.; DePuy, C. H.; Bierbaum, V. M. *J. Phys. Chem. A* **2004**, *108*, 9887-9891.
- Kato, S.; Lineberger, W. C.; Bierbaum, V. M. *Int. J. Mass Spectrom.* **2007**, *266*, 166-179.
- Katritzky, A. R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7-15.
- Keeffe, J. R.; Gronert, S.; Colvin, M. E.; Tran, N. L. *J. Am. Chem. Soc.* **2003**, *125*, 11730-11745.
- Khan, H.; Harris, R. J.; Barna, T.; Craig, D. H.; Bruce, N. C.; Munro, A. W.; Moody, P. C. E.; Scrutton, N. S. *J. Biol. Chem.* **2002**, *277*, 21906-21912.
- KIDA (KInetic Database for Astrochemistry, <http://kida.obs.u-bordeaux1.fr>).
- Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 16394-16397.
- Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281-4285.
- Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278-10279.
- Kim, M. S.; Min, S. W.; Seo, J. A.; Um, I. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2913-2917.
- Kirby, A. J.; Manfredi, A. M.; Souza, B. S.; Medeiros, M.; Priebe, J. P.; Brandao, T. A. S.; Nome, F. *Arkivoc* **2009**, *3*, 28-38.
- Klenke, B.; Stewart, M.; Barrett, M. P.; Brun, R.; Gilbert, I. H. *J. Med. Chem.* **2001**, *44*, 3440-3452.
- Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223-234.
- Koshy, K. M.; Robertson, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 914-916.
- Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 6258-6262.
- Kurz, J. L. *Chem. Phys. Lett.* **1978**, *57*, 243-246.
- Laerdahl, J. K.; Uggerud, E. *Int. J. Mass Spectrom.* **2002**, *214*, 277-314.

- Lee, J. K.; Grabowski, J. J. *J. Org. Chem.* **1996**, *61*, 9422-942
- Lide, D. R. *CRC Handbook of Chemistry and Physics, 89th Ed.* CRC Press: Boca Raton, Fl., **2008**; p U552-U552.
- Linstrom, P.J.; Mallard, W.G. Eds., *NIST Chemistry WebBook, National Institute of Standards and Technology, NIST Standard Reference Database Number 69*, Gaithersburg MD, 20899, <http://webbook.nist.gov>;
- Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*. Harper and Row: New York, 1987.
- Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 9663-9665.
- Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 7823-7832.
- Luo, Y. R.; Benson, S. W. *Acc. Chem. Res.* **1992**, *25*, 375-381.
- Lundegaard, C.; Jensen, K. F. *Biochem.* **1999**, *38*, 3327-3334.
- Mackay, G. I.; Bohme, D. K. *J. Am. Chem. Soc.* **1978**, *100*, 327-329.
- Mąkosza, M. *Russ. Chem. Bull.* **1996**, *45*, 491-504.
- March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 4th ed.; John Wiley & Sons, Inc: New York, 1992.
- Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891-899.
- McAnoy, A. M.; Paine, M. R. L.; Blanksby, S. *J. Org. Biomol. Chem.* **2008**, *6*, 2316-2326.
- McIsaac, J. E.; Subbaraman, L. R.; Subbaraman, J.; Mulhausen, H. A.; Behrman, E. J., *J. Org. Chem.* **1972**, *37*, 1037-1041.
- Merrick, J. P.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007**, *111*, 11683-11700.
- Midey, A. J.; Miller, T. M.; Viggiano, A. A. *J. Phys. Chem. A* **2009**, *113*, 4982-4989.
- Miller, J. A.; Kee, R. J.; Westbrook, C. K., *Annu. Rev. Phys. Chem.* **1990**, *41*, 345-387.
- Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618-622.
- Mugnai, M.; Cardini, G.; Schettino, V. *J. Phys. Chem. A* **2003**, *107*, 2540-2547.
- Mukherjee, S.; Ren, J. H. *J. Am. Soc. Mass Spectrom.* **2010**, *21*, 1720-1729.

Nielson, P. Aa.; Glad, S. S.; Jensen, F. J. *J. Am. Chem. Soc.* **1996**, *118*, 10577-10583.

NIST Chemistry WebBook, National Institute of Standards and Technology, Gaithersburg MD, 20899, <http://webbook.nist.gov>

Nomura, Y.; Kubozono, T.; Hidaka, M.; Horibe, M.; Mizushima, N.; Yamamoto, N.; Takahashi, T.; Komiyama, M. *Bioorg. Chem.* **2004**, *32*, 26-37.

O'Hair, R. A. J.; Davico, G. E.; Hacaloglu, J.; Dang, T. T.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1994**, *116*, 3609-3610.

Ohta, K.; Morokuma, K. *J. Phys. Chem.* **1985**, *89*, 5845-5849.

Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219-4228.

Patterson, E. V.; Fountain, K. R. *J. Org. Chem.* **2006**, *71*, 8121-8125.

Paul, G. J. C.; Kebarle, P. *J. Am. Chem. Soc.* **1991**, *113*, 1148-1154.

Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827-1836.

Pearson, R. G. *Proceedings of the National Academy of Sciences* **1986**, *83*, 8440-8441.

Pelizzetti, E.; Maurino, V.; Minero, C.; Carlin, V.; Pramauro, E.; Zerbinati, O.; Tosato, M. L. *Environ. Sci. Technol.* **1990**, *24*, 1559-1565.

Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 5993-5999.

Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1983**, *105*, 2672-2680.

Pliego, J. J. R.; Riveros, J. M. *Chem.–Eur. J.* **2001**, *7*, 169-175.

Poirier, R. A.; Wang, Y. L.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526-2533.

Pratt, R. F.; Bruice, T. C. *J. Org. Chem.* **1972**, *37*, 3563-3564.

Ren, J.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 2640-2646.

Ren, Y.; Yamataka, H. *Org. Lett.* **2006**, *8*, 119-121.

Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660-5667.

Ren, Y.; Yamataka, H. *Chem. Eur. J.* **2007**, *13*, 677-682.

Ren, Y.; Yamataka, H., *J. Comput. Chem.* **2009**, *30*, 358-365.

- Rieger, P. G.; Sinnwell, V.; Preuss, A.; Francke, W.; Knackmuss, H. J. *J. Bacteriol.* **1999**, *181*, 1189-1195.
- Rogers, J.; Moyer, B.; Kalscheur, G.; Emig, N. *JCT Coatingstech* **2007**, *4*, 82-86.
- Sauers, R. R. *J. Chem. Theory Comput.* **2010**, *6*, 602-606.
- Schalley, C. A.; Armentrout, P. Threshold Collision-Induced Dissociations for the Determination of Accurate Gas-Phase Binding Energies and Reaction Barriers. In *Modern Mass Spectrometry*, Springer Berlin/Heidelberg: **2003**, 225, 233-262.
- Schalley, C. A. *Int. J. Mass Spec.* **2000**, *194*, 11-39.
- Schlosser, M.; Ruzziconi, R. *Synthesis-Stuttgart* **2010**, *13*, 2111-2123.
- Schneider, H.; Vogelhuber, K. M.; Schinle, F.; Weber, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 13022-13026.
- Serjeant, E. P.; Dempsey, B. *Ionisation constants of organic acids in aqueous solution (IUPAC Chemical Data Series)*; Pergamon Press: Oxford; New York, **1979**.
- Shaik, S. S., *Acta Chem. Scand.* **1990**, *44*, 205-221.
- Shaik, S. S.; Schlegel, H. B.; Wolfe, S. *Theoretical Aspects of Physical Organic Chemistry: The S_N2 Reaction*. Wiley: New York, **1992**.
- Shiner, V. J. Jr.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessick, M. A.; Milakofs, L.; Rapp, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 4838-4939.
- Simons, J. Molecular Ions Web Site, <http://www.hec.utah.edu/anions>.
- Smith, D.; McIntosh, B. J.; Adams, N. G. *J. Chem. Phys.* **1989**, *90*, 6213-6219.
- Steinfeld, J. I.; Francisco, J. S.; Hase, W. L. *Chemical Kinetics and Dynamics*; Prentice-Hall: Englewood Cliffs, NJ, **1989**.
- Su, T.; Chesnavich, W. J. *J. Chem. Phys.* **1982**, *76*, 5183-5185.
- Sun, X.; Lee, J. K. *J. Org. Chem.* **2010**, *75*, 1848-1854.
- Tachikawa, H. *J. Phys. Chem. A* **2001**, *105*, 1260-1266.
- Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247-350.
- Takashima, K.; Riveros, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 6128-6132.

- Thomas, J. M.; Viggiano, A. A. *J. Phys. Chem. A* **1999**, *103*, 2720-2722.
- Tondo, D. W.; Pliego, J. R. *J. Phys. Chem. A* **2005**, *109*, 507-511.
- Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 11073-11083.
- Turker, L.; Atalar, T.; Gumus, S.; Camur, Y. *J. Hazard. Mater.* **2009**, *167*, 440-448.
- Uggerud, E., *J. Phys. Org. Chem.* **2006**, *19*, 461-466.
- Uggerud, E., *Chem.–Eur. J.* **2006**, *12*, 1127-1136.
- Uggerud, E. *Pure Appl. Chem.* **2009**, *81*, 709-717.
- Um, I. H.; Buncel, E. *J. Org. Chem.* **1999**, *65*, 577-582.
- Um, I. H.; Buncel, E. *J. Am. Chem. Soc.* **2001**, *123*, 11111-11112.
- Um, I. H.; Hwang, S. J.; Buncel, E. *J. Org. Chem.* **2006**, *71*, 915-920.
- Um, I. H.; Shin, Y. H.; Han, J. Y.; Buncel, E. *Can. J. Chem.* **2006**, *84*, 1550-1556.
- Um, I. H.; Han, J. Y.; Buncel, E. *Chem.–Eur. J.* **2009**, *15*, 1011-1017.
- Um, I. H.; Im, L.-R.; Buncel, E. *J. Org. Chem.* **2010**, *75*, 8571-8577.
- Valet, A. *Prog. Org. Coat.* **1999**, *35*, 223-233.
- Van Doren, J. M. *The Tandem Flowing Afterglow-SIFT-DRIFT: Developments and Applications to Gas Phase Ion Chemistry*, PhD Thesis, Department of Chemistry and Biochemistry, University of Colorado at Boulder **1983**.
- Van Doren, J. M.; Barlow, S. E.; Depuy, C. H.; Bierbaum, V. M. *Int. J. Mass Spectrom. Ion Processes* **1987**, *81*, 85-100.
- Vianello, R.; Peran, N.; Maksic, Z. B. *Eur. J. Org. Chem.* **2007**, *3*, 526-539.
- Viggiano, A. A.; Paschkewitz, J. S.; Morris, R. A.; Paulson, J. F.; Gonzalezlafont, A.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 9404-9405.
- Viggiano, A. A.; Arnold, S. T.; Morris, R. A. *Int. Rev. Phys. Chem.* **1998**, *17*, 147-184.
- Viggiano, A. A.; Midey, A. J. *J. Phys. Chem. A* **2000**, *104*, 6786-6790.
- Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 736-737.

- Villano, S. M.; Eyet, N.; Lineberger, W. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 8227-8233.
- Villano, S. M.; Eyet, N.; Wren, S. W.; Ellison, G. B.; Bierbaum, V. M.; Lineberger, W. C. *Eur. J. Mass Spectrom.* **2010**, *16*, 255-268.
- Villano, S. M.; Eyet, N.; Wren, S. W.; Ellison, G. B.; Bierbaum, V. M.; Lineberger, W. C. *J. Phys. Chem. A* **2010**, *114*, 191-200.
- Vorbeck, C.; Lenke, H.; Fischer, P.; Knackmuss, H. J. *J. Bacteriol.* **1994**, *176*, 932-934.
- Westaway, K. C. *Can. J. Chem.* **1978**, *56*, 2691-2699.
- Westaway, K. C.; Waszczylo, Z. *Can. J. Chem.* **1982**, *60*, 2500-2520.
- Westaway, K. C. *Adv. Phys. Org. Chem.* **2006**, *41*, 217-273.
- Westaway, K. C.; Fang, Y. R.; MacMillar, S.; Matsson, O.; Poirier, R. A.; Islam, S. M. *J. Phys. Chem. A* **2007**, *111*, 8110-8120.
- Westaway, K. C. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 989-1005.
- Westaway, K. C.; Fang, Y. R.; MacMillar, S.; Matsson, O.; Poirier, R. A.; Islam, S. M. *J. Phys. Chem. A* **2008**, *112*, 10264-10273.
- Wheeler, S. E.; Houk, K. N. *J. Phys. Chem. A* **2010**, *114*, 8658-8664.
- Wiberg, K. B.; Nakaji, D.; Breneman, C. M. *J. Am. Chem. Soc.* **1989**, *111*, 4178-4190.
- Wickhamjones, C. T.; Ervin, K. M.; Ellison, G. B.; Lineberger, W. C. *J. Chem. Phys.* **1989**, *91*, 2762-2763.
- Wladkowski, B. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 10643-10644.
- Wladkowski, B. D.; Brauman, J. I. *J. Phys. Chem.* **1993**, *97*, 13158-13164.
- Wolfe, S.; Kim, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 8056-8061.
- Wren, S. W.; Vogelhuber, K. M.; Garver, J. M.; Kato, S.; Sheps, L.; Bierbaum, V. M.; Lineberger, W. C. *In preparation*
- Wu, Y.-R.; Hu, W.-P. *J. Am. Chem. Soc.* **1999**, *121*, 10168-10177.
- Wu, X. P.; Sun, X. M.; Wei, X. G.; Ren, Y.; Wong, N. B.; Li, W. K. *J. Chem. Theory Comput.* **2009**, *5*, 1597-1606.

Yinon, J.; Johnson, J. V.; Bernier, U. R.; Yost, R. A.; Mayfield, H. T.; Mahone, W. C.; Vorbeck, C. *J. Mass Spectrom.* **1995**, *30*, 715-722.

Zhachkina, A.; Lee, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 18376-18385.

Zhang, Q. Z.; Wang, H. N.; Sun, T. L.; Wang, W. X. *Chem. Phys.* **2006**, *324*, 298-306.

Zheng, Y. J.; Ornstein, R. L. *J. Am. Chem. Soc.* **1997**, *119*, 648-655.

Ziganshin, A. M.; Gerlach, R.; Borch, T.; Naumov, A. V.; Naumova, R. P. *Appl. Environ. Microbiol.* **2007**, *73*, 7898-7905.