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Single Electron Transfer and S_N2 Reactions: The Importance of Ionization Potential of Nucleophiles

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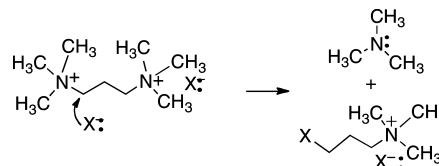
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Abstract: The importance of single electron transfer energetics in promoting S_N2 reactions was probed by a density functional computational study on substitution reactions of quaternary ammonium ion complexes with anionic nucleophiles. Good correlations were found between the ionization potentials (IP) of the nucleophiles when plotted against density functional theory (DFT)-computed reaction activation enthalpies ($\Delta H_{\text{rxn}}^\ddagger$) over a range of 15 eV. Poor correlations were found between IPs or proton affinities and central barrier heights ($\Delta H_{\text{cmp}}^\ddagger$). Examples of inverted values of $\Delta H_{\text{rxn}}^\ddagger$ of primary vs secondary systems were found.

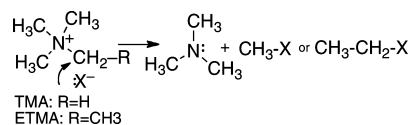
Introduction

Bimolecular nucleophilic substitution reactions at saturated carbon atoms likely represent the most highly studied organic mechanism both experimentally and computationally. The pioneering work of the Ingold school established the bimolecular nature of the reaction in solution.¹ The work of Brauman et al.² laid the theoretical groundwork for study of gas phase S_N2 reactions in terms of a double minimum potential energy profile to form ion–molecule complexes that either revert to starting components or pass over “central” S_N2 transition energy barriers. The reaction products also form a complex that ultimately dissociates to individual products. Recent work by McMahon and co-workers has provided direct experimental verification of these ideas.³ Bento and Bickelhaupt have carried a detailed analysis of methyl halide/halide reactions, Si, and group 14 elements and have concluded that HOMO/LUMO orbital interactions are of paramount importance.⁴ Shaik and others⁵ have stressed the importance of single electron transfer from the nucleophile to the substrate as an important feature of the

Scheme 1. Nucleophilic Substitution by Halogen on a bis-Quaternary Ammonium Salt



Scheme 2. Reactions of TMA/ETMA with Nucleophile X^-



electronic nature of S_N2 transition states. In this context, the transition state for simple S_N2 reactions involving a single electron transfer can be symbolized as shown below.



This study probes the idea that energies of S_N2 transition structures should correlate with ionization potentials (IPs) of attacking nucleophiles.

This work evolved from experimental and computational studies with bis-ammonium alkyl dihalides that were shown to undergo substitution and elimination reactions in the gas phase (Scheme 1).⁶ An unexpected result was the relative insensitivity of the computed central barrier ($\Delta H_{\text{cmp}}^\ddagger$) to the nature of the halogen. It was also shown that the second positive center had little effect on the computed S_N2 activation enthalpies compared to simple tetraalkylammonium ion salts. These results stimulated a desire to extend the survey of S_N2 reactivity to a much broader range of nucleophiles and in particular to assess the relationship between nucleophile ionization potential on transition structure energy and S_N2 barriers. Scheme 2 describes this approach that compares the energetics of reactions of nucleophilicities at primary and secondary carbon centers of ethyltrimethyl (ETMA) and tetramethyl (TMA) ammonium salts with trimethylamine as the common leaving group.

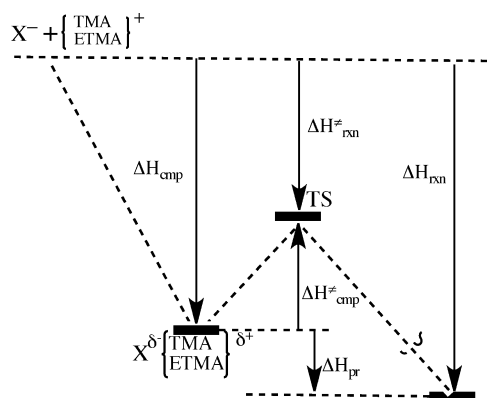
The abbreviated enthalpy diagram in Scheme 3 outlines the computational analysis invoked in this study given the expectation that complex formation between neutral products trimethylamine and alkylX would not affect the overall objectives. ΔH_{pr} represents the sum of the enthalpies of R-X and trimethylamine.

Computations and Methodology

All structures were fully optimized by analytical gradient methods using the Gaussian03 suite⁷ and DFT calculations at

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Scheme 3. Enthalpy Diagram for Nucleophilic Substitution Reactions of the Tetramethylammonium Ion (TMA) and Ethyltrimethylammonium Ion (ETMA) with Nucleophile X^-



the RB3LYP/6-31+G(d) level,⁸ the exchange functional of Becke,⁹ and the correlation functional of Lee, Yang, and Parr.¹⁰ Vibrational analyses established the nature of all stationary points as either energy minima (no imaginary frequencies) or first-order transition structures (one imaginary frequency). In some cases, IRC calculations verified that the TS connected initial and product structures. In other cases, we relied on animations of the vectors associated with the imaginary frequencies as a guide. Reported enthalpies (unscaled) were corrected for zero-point energy and temperature effects at 298.14 K. In the first stage of this project, the enthalpies of complex formation (ΔH_{comp}) between the anions and TMA and ETMA were evaluated. S_N2 transition structures ($\Delta H_{\text{comp}}^\ddagger$) were located for reactions at methyl groups in the TMA series and at the methylene groups in the ETMA series, i.e., reactions at primary and secondary carbons with trimethylamine as a leaving group (Scheme 2). These data are summarized in Table 1 along with derived values for the transition structure enthalpies $\Delta H_{\text{rxn}}^\ddagger$.

Because few experimental IPs for many of the ions are available, they were computed using DFT at the (U)B3LYP/

Table 2. Ionization Potentials^a and Proton Affinities:^b (U)B3LYP/aug-cc-pVDZ^c

anion	ionization potential, eV	proton affinity, kcal mol ⁻¹	anion	ionization potential, eV	proton affinity, kcal mol ⁻¹
F ⁻	3.56	371.3	OCi ⁻	2.34	349.4
Cl ⁻	3.72	333.4	CO ₃ ⁻²	-3.55	476.5
HCO ₂ ⁻	3.48	345.3	H ⁻	0.89	394.6
NO ₃ ⁻	3.90	327.5	CH ₃ CH ₂ O ⁻	1.67	378.6
OH ⁻	1.85	390.8	HOB ₂ ⁻²	-2.52	486.9
CH ₃ O ⁻	1.53	381.7	BO ₃ ⁻³	-8.38	592.8
CN ⁻	4.04	351.1	(HO) ₂ PO ₂ ⁻	4.15	325.4
HOO ⁻	1.03	368.5	HOPO ₃ ⁻²	-1.84	452.7
N ₃ ⁻	2.67	337.6	PO ₄ ⁻³	-7.21	573.1
SH ⁻	2.36	351.1	HSiO ₄ ⁻³	-7.13	573.5
HOCO ₂ ⁻	3.56	330.4	SiO ₄ ⁻⁴	-11.1	664.7

^a DFT methodology has been shown to give good results for IPs: Rienstra-Kiracofe, J. C.; Tschumper, G. S.; Schaefer, H. F., III. Atomic and Molecular Electron Affinities: Photoelectron Experiments and Theoretical Computations. *Chem. Rev.* **2002**, *102*, 231–282. ^b Some proton affinity data is taken from tables in the NIST data bank: Bartmess, J. E. In *NIST Standard Reference Database Number 69*; Mallard, W. G., Linstrom, P. J., Eds.; National Institutes of Standards and Technology (http://webbook.nist.gov): Gaithersburg, MD, 1999. ^c See Supporting Information Table S5 for primary data.

aug-cc-pVDZ level. Computed values agreed within 2–3 kcal/mol with available experimental values. Proton affinities were compiled from the literature or computed. Table 2 displays the relevant ionization energies and the proton affinities.

Discussion

Figure 1 shows a plot of central barrier heights ($\Delta H_{\text{comp}}^\ddagger$) for the S_N2 reactions of ETMA vs IPs. The widely scattered data points reveal no meaningful correlations.¹¹ Similar results were obtained for reactions of TMA (not shown). In part, these findings reflect the consequences of the small range of $\Delta H_{\text{comp}}^\ddagger$ compared to the large variations in IP. Likewise, plots of $\Delta H_{\text{comp}}^\ddagger$ vs proton affinities (PA) for ETMA (Figure 2; and TMA)

Table 1. Computed Data for Complex Energy Formation (ΔH_{comp}), Transition Structure Barriers ($\Delta H_{\text{comp}}^\ddagger$), and Reaction Transition Structure Enthalpy Changes ($\Delta H_{\text{rxn}}^\ddagger$) for ETMA and TMA Systems at 298.15 K: B3LYP/6-31+G(d)

anion	tetramethylammonium systems			ethyltrimethylammonium systems		
	ΔH_{comp} , kcal mol ⁻¹	$\Delta H_{\text{comp}}^\ddagger$, kcal mol ⁻¹	$\Delta H_{\text{rxn}}^\ddagger$, kcal mol ⁻¹	ΔH_{comp} , kcal mol ⁻¹	$\Delta H_{\text{comp}}^\ddagger$, kcal mol ⁻¹	$\Delta H_{\text{rxn}}^\ddagger$, kcal mol ⁻¹
F ⁻	-114.33	22.3	-92.02	-112.75	22.6	-90.15
Cl ⁻	-91.98	19.4	-75.59	-90.66	21.5	-69.12
HCO ₂ ⁻	-95.28	27.4	-67.89	-93.44	28.1	-65.34
NO ₃ ⁻	-85.15	21.2	-63.92	-83.70	21.2	-62.50
OH ⁻	-117.25	24.1	-93.20	-111.40	19.3	-92.10
CH ₃ O ⁻	-107.94	19.5	-88.43	-102.40	17.1	-85.30
CN ⁻	-88.69	18.1	-70.60	-83.77	19.3	-64.47
HOO ⁻	-109.10	16.7	-92.39	-107.65	17.2	-90.45
N ₃ ⁻	-85.87	16.2	-69.68	-84.56	16.7	-67.86
SH ⁻	-89.65	14.8	-74.85	-85.24	14.3	-70.94
HOCO ₂ ⁻	-92.46	19.8	-72.68	-88.83	18.1	-70.73
OCi ⁻	-99.58	16.4	-83.16	-95.24	14.3	-80.94
CO ₃ ⁻²	-192.33	19.2	-173.12	-186.72	12.2	-174.53
H ⁻	-142.10	14.0	-128.06	-140.36	15.4	-124.97
CH ₃ CH ₂ O ⁻	-104.92	12.6	-92.35	-99.37	16.9	-82.47
HOB ₂ ⁻²	-200.64	21.8	-178.82	-203.85	22.9	-180.96
BO ₃ ⁻³	-314.87	20.0	-294.86	-311.44	14.2	-297.27
(HO) ₂ PO ₂ ⁻	-88.88	23.6	-65.23	-85.87	21.8	-64.05
HOPO ₃ ⁻²	-178.86	19.3	-159.52	-174.09	13.6	-160.48
PO ₄ ⁻³	-282.44	22.1	-260.38	-280.22	11.3	-268.95
HSiO ₄ ⁻³	-289.90	23.5	-266.44	-280.66	11.7	-268.94
SiO ₄ ⁻⁴	-419.02	19.4	-399.57	-418.38	15.3	-403.08

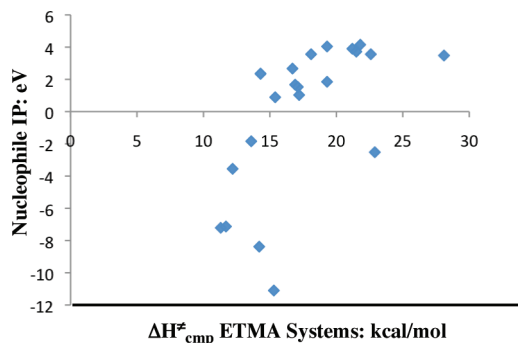


Figure 1. Plot of IP vs $\Delta H_{\text{cmp}}^{\circ}$ for ETMA.

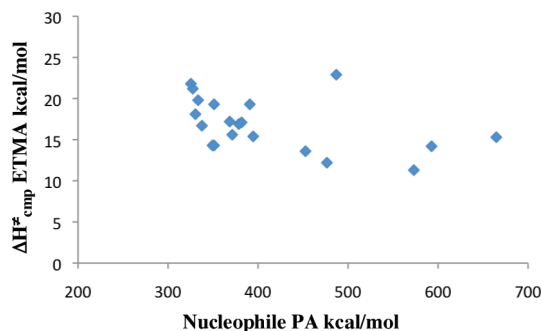


Figure 2. Plot of $\Delta H_{\text{cmp}}^{\circ}$ vs PA for ETMA.

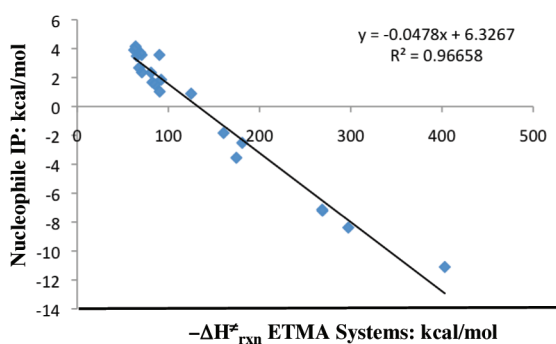


Figure 3. Plot of IP of nucleophiles vs $-\Delta H_{\text{rxn}}^{\circ}$ for tetramethylammonium systems.

systems gave rise to widely scattered arrays of data points. Similarly, attempts to find significant correlations for plots of $-\Delta H_{\text{cmp}}^{\circ}$ of monoanions vs IP and plots of $-\Delta H_{\text{cmp}}^{\circ}$ vs IP for oxygen-centered nucleophiles failed. On the other hand, plots of $-\Delta H_{\text{rxn}}^{\circ}$ vs IP gave good correlations for both methyl and ethyl substitutions (Figures 3 and 4).

These remarkable trends are consistent with the concept of single electron transfer as an important electronic factor in initiating bimolecular nucleophilic substitution reactions at primary and secondary saturated carbon atoms. In addition, these correlations validate the concept that it is the stability of the transition structure relative to the separate reactants that is the kinetically relevant term as opposed to central barrier heights, per se.¹²

Some unexpected results were the findings that $\Delta H_{\text{cmp}}^{\circ}$ for substitution at the methyl carbon was not always more favorable than that for substitution at the ethyl carbon (Table 1, Figure 5). These unprecedented discrepancies showed up not only with the polyionic anions but also with simple nucleophiles, e.g., hypochlorite ion, hydroxide ion, et al. That these disparities are

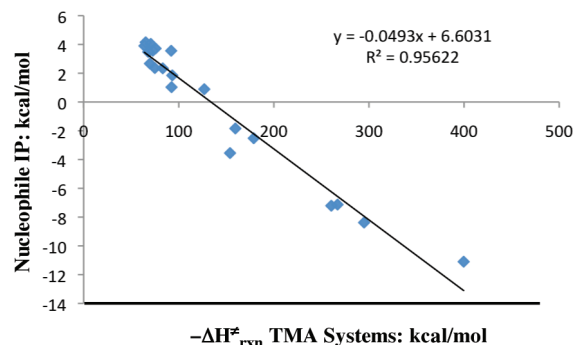


Figure 4. Plot of IP of nucleophiles vs $-\Delta H_{\text{rxn}}^{\circ}$ for ethyltrimethylammonium systems.

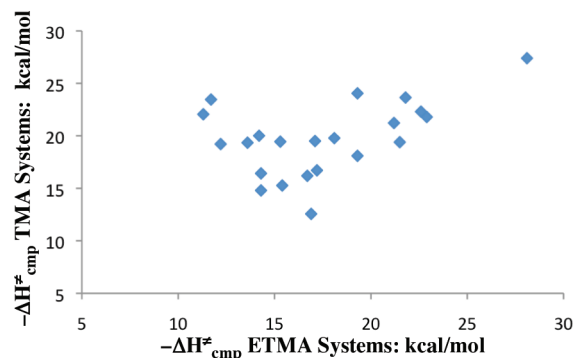


Figure 5. Plot of $-\Delta H_{\text{cmp}}^{\circ}$: TMA vs ETMA.

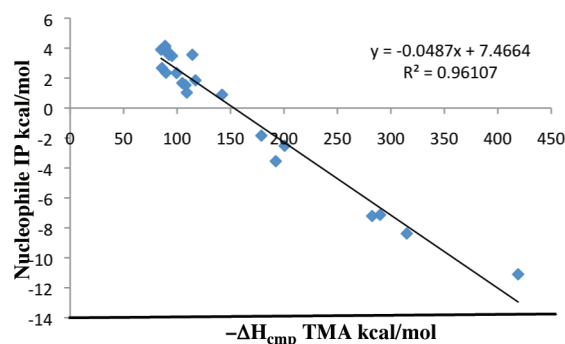


Figure 6. Plot of IP of nucleophiles vs $-\Delta H_{\text{cmp}}^{\circ}$ for tetramethylammonium ions.

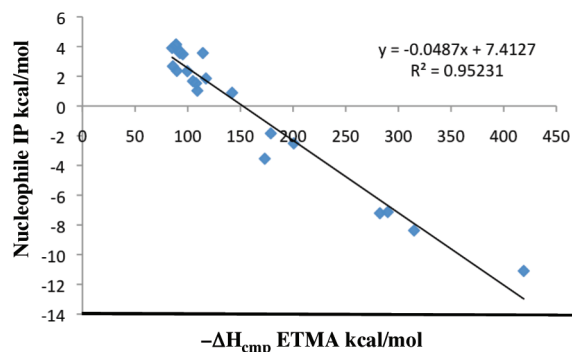


Figure 7. Plot IP of nucleophiles vs $-\Delta H_{\text{cmp}}^{\circ}$ for ethyltrimethylammonium ions.

not anomalies associated with complex formation is shown by plots of IP vs $\Delta H_{\text{cmp}}^{\circ}$ (Figures 6 and 7).

Apparently the electronic forces and steric and/or entropic¹³ factors involved in complex formation vs the transition structures

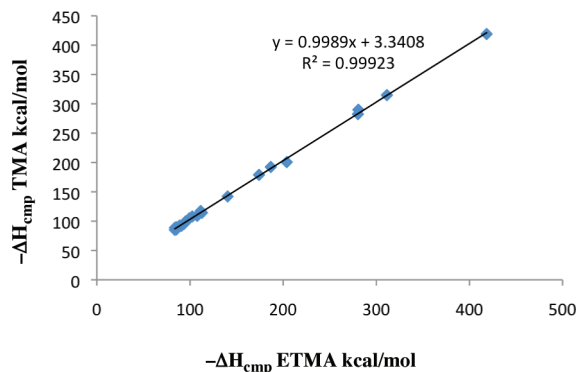


Figure 8. Comparison of $-\Delta H_{\text{cmp}}$: TMA vs ETMA.

for certain of these systems can be significantly disparate. Similarly, comparisons of the enthalpies of the complex formation did not show any major anomalies as shown by the data in Figure 8. An excellent correlation was obtained: in almost all cases, methyl systems give rise to tighter, lower enthalpy complexes than ethyl analogs. The only exception was HBO_3^{2-} : the TMA complex was less stable than the ETMA complex by $\sim 3 \text{ kcal mol}^{-1}$. It would appear that irregularities in binding energies/structures do not give rise to anomalous methyl/ethyl reversals.^{12,13} Comparisons of the TMA vs ETMA transition structures in general showed that the TMA transition structures were somewhat “earlier” in that average $\text{X}\cdots\text{C}$ and $\text{C}\cdots\text{N}$ bond lengths were shorter (1.774 and 2.254 Å, respectively) than those in the corresponding ETMA TSs (1.875 and 2.305 Å, respectively). No trends were noted that resolved the reactivity reversals, however (see Supporting Information Table S6).

Detailed studies by Bento and Bickelhaupt⁴ with combinations of $\text{S}_{\text{N}}2$ reactions of methyl halide/halide ions support our results in that these workers describe nucleophilic character in terms of charge transfer and HOMO/LUMO interactions.

In related studies, Uggerud¹⁴ recently estimated potential energy profiles for 18 identity $\text{S}_{\text{N}}2$ reactions using G2 quantum methods and found a linear correlation between nucleophile ionization potential (1–4 eV range) and barrier heights. It is interesting to note that the slope of the plot of IP vs $\Delta H_{\text{cmp}}^\ddagger$ was much steeper than the ones we found in Figures 3 and 4. This is probably due to the fact that identity reactions do not involve an overall energy change, whereas the systems studied herein are all strongly exothermic (Supporting Information Tables S4 and S5).

The alkyl ammonium systems examined in this study represent one extreme of structure–reactivity behavior in that the reactant bears a positive charge that is partially neutralized in the transition structure unlike most of the previous studies. For example, Brauman and Olmstead found that the cyanide ion is virtually unreactive toward methyl chloride.¹⁵ In this study, $\Delta H_{\text{rxn}}^\ddagger$ for CN^- is not atypical compared to other uncharged nucleophiles, and the transition structure has a “typical” geometry.

In many cases, the high degree of exothermicity of these reactions, -61 to $-400 \text{ kcal mol}^{-1}$ (see Supporting Information Tables S4 and S5), may serve to compress the range of activation enthalpies because the geometry of the transition structures resides close to that of the starting components (vide infra) in contrast to “identity $\text{S}_{\text{N}}2$ reactions” in which the transition structure involves equal bonding of the nucleophile

and leaving group. Still, there are some exceptions and inconsistencies with this argument. The TSs for attack of the nitrate ion on both methyl and ethyl centers are nearly symmetrical, and the $\Delta H_{\text{cmp}}^\ddagger$'s are essentially the same. Yet, in both cases, the overall reactions are highly exothermic: 88.8 vs $91.1 \text{ kcal mol}^{-1}$, respectively.

In a recent computational study of reactions of substituted p-X-phenoxides with methyl halides, Li and Xue¹⁶ found good correlations of both barrier heights and central barriers with the phenoxide substituent (σ) constants. These workers did not examine correlations with ionization potential, but it is likely that IPs would parallel nucleophilicity of the phenoxides.

Conclusions

The reported correlations of IP with transition structure energy serve as a useful predictor of $\Delta H_{\text{rxn}}^\ddagger$.¹⁷ Clearly, there are subtleties, e.g., entropy, steric effects, and orbital shapes, that modulate the behavior of the complexes and that are not understood at this time. It is clear that barrier heights $\Delta H_{\text{cmp}}^\ddagger$ are not useful predictors of relative reactivity in these systems. The generality of these correlations and exceptions remains to be explored in other systems.⁴

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Supporting Information Available: Transition structure bond distances, ΔH_{rxn} data, ΔH_{pr} data, ionization potential calculations, and enthalpy data for all reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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