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Determining the Efficacy of the Extended Kinetic Method for Determination of Thermochemical Properties of Small, High-Entropy, Organic Molecules

Mary Grace Pisano

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Determining the efficacy of the extended kinetic method for determination of thermochemical properties of small, high-entropy, organic molecules

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Woodstock, Georgia

BS, Kennesaw State University, 2013

A Thesis presented to the Graduate Faculty of the College of William and Mary in Candidacy for the Degree of Master of Science

Department of Chemistry

The College of William and Mary
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Master of Science

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ABSTRACT

The efficacy of the extended kinetic method (EKM) for determining thermochemical quantities of small, high-entropy, organic molecules is tested via repeated measurements on multiple mass spectrometers (including a triple quad, a quadrupole ion-trap, and a flowing afterglow triple quad) and support from high-accuracy theoretical calculations. Currently accepted values of proton affinity (PA) reported on NIST.gov for the following molecules are brought into question based on statistically significant differences from theoretical determinations that are followed by experimental results in agreement: 1,2-ethanediol (NIST: 815.9 kJ/mol, this work: 802.8 kJ/mol), 1,4-butanediol (NIST: 915.6 kJ/mol, this work: 906.3), and 4-amino-1-butanol (NIST: 984.5 kJ/mol, this work: 975.7 kJ/mol). Experimental and theoretical data for 2-amino-1-ethanol, ethylenediamine, and 3-amino-1-propanol are also compared with NIST values.
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Finally, the writer would like to thank her friends and family for their endless chants of “You can do this!” and “What is it you do again?” who, without their influence, would not be here.
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Chapter 1 - Introduction

1.1 Gas-Phase Thermochemistry

Studies of compounds in the gas-phase became viable in chemistry labs around the world more than one hundred years ago with JJ Thomson’s “Rays of Positive Electricity and their Application to Chemical Analysis” in 1913. Molecules are studied in the gas phase to allow for analysis of the “intrinsic” properties of the substances in question. Without environmental effects, characteristics inherent to the substance being studied on a molecular level are able to be analyzed, and its chemical properties are able to be experimentally determined with great accuracy.

The determination of thermochemical properties of gas-phase ions such as proton affinity, gas-phase basicity, and ionization potential have been reported since 1957, starting with the publication of Field and Franklin’s book, “Electron Impact Phenomena and the Properties of Gaseous Ions”. Since 1957, the study of gas-phase ion thermochemistry and the use of mass spectrometers has proliferated; from the study of single atoms to conformer-selective dissociation of folded proteins, imaging of the spatial distribution of ions, and the study of structural integrity of membrane proteins.

Proton affinity, ionization potential, and gas-phase acidity are a few examples of the properties studied in gas-phase ion thermochemistry. Proton affinity (PA) is defined as the energy required to remove a proton from a compound and is quantitatively described by Equation 1. It ranges from 691.0 kJ/mol (water) to 1051.0 kJ/mol (arginine).
$M + H^+ \rightarrow MH^+ \quad \Delta H_{rxn} = -PA$ \hspace{1cm} (1)

Ionization potential (IP), the energy needed to remove an electron from an atom or molecule,\textsuperscript{6} is quantitatively defined by Equation 2. It ranges from 6.80 eV (N-phenylpyrrolidine) to 12.74 eV (hydrochloric acid).

$M \rightarrow M^+ + e^- \quad \Delta H_{rxn} = IP$ \hspace{1cm} (2)

Gas-phase acidity (GA) is defined as the Gibbs free energy change of the dissociation of a neutral compound to the molecular ion plus a proton\textsuperscript{6} (Equation 3). It has a range from 1354.4 kJ/mol (hydrochloric acid) to 1641.8 kJ/mol (benzene).

$AH \rightarrow A^- + H^+ \quad \Delta G_{acid} = GA$ \hspace{1cm} (3)

For the purpose of comparison, ethanediol is a weak base, and has values for PA, IP, and GA of 815.9 kJ/mol, 10.55 eV, and 1510.0 kJ/mol, respectively.

Thermochemical properties such as these are studied using various techniques and instrumentation, one of which is the extended kinetic method which utilizes mass spectrometers for analysis.

1.2 Measurement of Thermochemical Properties in the Gas-Phase

1.2.1 Extended Kinetic Method (EKM)

R. Graham Cooks developed and published his first paper on the kinetic method,\textsuperscript{7} in which he proposed the possibility of a relative approach to thermochemical determinations, in 1977. As it was first described, the kinetic method treats the competitive dissociation of a proton-bound heterodimer (Equation 4) as a way to measure the difference between $k_1$ and $k_2$. In mass
spectrometry, this difference manifests itself as a difference in peak heights for the mass to charge ratios (m/z) of $A-H^+$ and $B_i-H^+$.

$$[A-H-B_i]^+$$

$\begin{align*}
  k_1 & \quad A-H^+ + B_i \\
  k_2 & \quad A + B_i-H^+
\end{align*}$$

(A) represents the analyte of interest, and $B_i$ refers to a series of structurally similar reference bases for which the thermochemical property of interest is already known. Following experimentation, the peak intensities are compared and the following calculations and assumptions are made (Equations 5 and 6).

$$k = \frac{RT}{h} \frac{Q^*}{Q} e^{\frac{\epsilon_0}{RT}}$$

$$ln \left( \frac{k_2}{k_1} \right) \approx ln \left( \frac{l_{B_i-H^+}}{l_{A-H^+}} \right) \approx \frac{\Delta \epsilon_0}{RT_{eff}} \approx \frac{(\Delta H_{B_i} - \Delta H_A)}{RT_{eff}}$$

Derivation of the kinetic method is described above with $k$ being the rate constant for the competing dissociation reactions, $R$ being the gas constant (8.314 J/mol*K), $h$ being Planck’s constant (6.626*10^{-24} m²kg/s), $Q$ being the partition function of the heterodimer ion, $Q^*$ being the partition function of the transition state, $\epsilon_0$ being the activation energy of formation of the fragment ion, $l$ being peak intensity, $H$ being reaction enthalpy, and $T$ being the effective temperature of the complex. Because the products of the dissociation come from the same reactant, $Q$ drops out of the equation, and $Q^*$ can be assumed to drop as a result of minimal differences in transition state entropy between the species.
The kinetic method as it was first published was a strong analytical technique, but lacked consideration for key factors such as entropic effects. Development of the kinetic method continued from its inception, with one of the most notable and cited alterations being consideration of entropic differences between the analyte and reference bases, as suggested by Wesdemiotis, Armentrout, and Feneslau. With these considerations, the extended kinetic method (EKM) was established. The EKM is the method currently used when employing Cooks’ kinetic method. The EKM differs from the kinetic method only in that it accounts for the possible entropic differences between the analyte and a given reference base (Equation 7).

\[
\ln \left( \frac{k_2}{k_1} \right) \approx \frac{(\Delta H_{B_i} - \Delta H_A)}{RT_{eff}} - \frac{(\Delta S_A - \Delta S_{B_i})}{R} \quad (7)
\]

With consideration of entropy, the EKM produces two plots which allow for the determination of the thermochemical property of interest. For example, if one were to substitute \( \Delta H \) in (4) with proton affinity (PA), by graphing \( \ln (k_2/k_1) \) vs. \( PA_{Br} - PA_{avg} \) (referred to as KM Plot 1), a visualization of the estimated PA of the analyte is observed as a crossing point for each line connecting the value of peak ratio at a given collision energy for each reference compound. Additionally, by creating a plot of negative intercept vs. slope of the lines in Plot 1 at different energies (KM Plot 2), the enthalpy difference \( (\Delta H_A - \Delta H_{\text{avg of references}}) \) and associated entropy divided by the gas constant \( (\Delta S/R) \) for the analyte in question appear as the slope and intercept of a line of best-fit of the data. Thus,
the EKM is a strong technique for measuring thermochemical properties of non-volatile species.

1.2.2 Equilibrium Methods

Other methods for determination of thermochemical values using mass spectrometry include ion/molecule equilibrium measurements as well as bracketing.\textsuperscript{17} Equilibrium methods use equilibrium constant calculations along with estimation of entropy changes in order to determine changes in enthalpy and therefore the thermochemical values of interest.\textsuperscript{18} Entropy changes in this case either come from a Van’t Hoff plot of data taken at varying temperatures, or from statistical mechanics calculations. In previous accounts, equilibrium measurements have been regarded as more accurate for thermochemical determinations\textsuperscript{19-21} than the EKM. These methods are challenging to compare as equilibrium methods cannot be used when the analyte of interest is non-volatile or not thermally labile. As only around 2\% of compounds in the world are volatile, the necessity of a method to measure non-volatile compounds is key; this is where the EKM trumps equilibrium methods.

1.3 Theoretical Computation

Thermochemical properties of each analyte used in this project were theoretically calculated prior to experimentation by \textit{ab initio} (DFT) studies. Every relevant theoretical method utilizes a linear combination of basis functions (referred to as a basis set) to approximate the valence structure. Split-valence
basis sets allow for more fluidity in electron density which gives way to more realistic modeling of structure for a given system.

Each split valence basis set consists of specified numbers of primitive Gaussian functions for each core and valence atomic orbital, those for the valence being split into multiple sets with the additional possibility of adding polarizing and/or diffusing functions. Polarizing functions are denoted in Pople’s basis sets\textsuperscript{22} as asterisks (*), and signify an increase of flexibility in the electron cloud by way of additional (and atom-appropriate) orbitals. Diffuse (or augmentation) functions are denoted in Pople’s basis sets as plus signs (+), and allow for more accurate approximation of “fluffy” atoms such as anions.

The Hartree-Fock (HF) method, also known as the self-consistent field (SCF) method, allows for approximation of the energy of a given system by means of solving a Schrodinger equation with a simplified Hamiltonian that ignores most electron correlation. The HF method is a simplified method that can be solved exactly. Relevant assumptions arise from utilization of the Born-Oppenheimer Approximation (allows for treatment of the electronic and nuclear coordinates as separate entities), ignorance of relativistic effects, and use of the mean field approximation (eliminates the variable of electron correlation). Despite the various assumptions made by the HF method, it is widely used as a starting point for theoretical computations because of its relatively low computational cost and reasonably accurate approximations.

Density functional theory (DFT) is an approach which uses functionals of electron density to make its determination. B3LYP, a DFT method developed in
1993, is referred to as a hybrid functional. While all DFT methods utilize functionals of electron density, hybrid functionals take into account exchange and/or correlation functions from other methods in order to optimize accuracy; B3LYP takes into account HF exchange functions for its approximation.

The Gaussian 2 (G2) method of analysis, introduced in 1991, is based on *ab initio* molecular orbital theory. It uses Møller-Plesset perturbation theory in its treatment of correlation, and a quadratic configuration interaction (QCISD) calculation as its computational coup de grâce.\(^{23}\) M06-2X, introduced in 2007, has become widely used in computation of properties of organic compounds.\(^{24}\) M06-2X is a hybrid meta exchange-correlation functional that factors in twice the nonlocal exchange of M06.

1.4 Instrumentation

Quantitation of thermochemical properties relies heavily on constant temperature and low pressure, to provide consistent kinetic environments. Mass spectrometers are well-suited for study of molecules in the gas phase, as they are typically held at pressures near \(1 \times 10^{-5}\) torr and allow for measurement of temperature throughout experimentation. A mass spectrometry experiment involves ionization followed by fragmentation and detection; in tandem mass spectrometry (MS/MS), initial detection is followed by selection of a specific mass which is then subsequently fragmented and detected.

Generally, mass spectrometers are distinguished by ionization source, method of mass separation, and mechanism of fragmentation. The instruments
described in this work are an electrospray ionization-enabled triple quadrupole (ESI-ESI-QQQ), electrospray ionization-enabled quadrupole ion-trap (ESI-ESI-LCQ), and a flowing-afterglow triple quadrupole (FA-QQQ). Electrospray ionization involves a known and constant flow rate of sample injected through a high voltage needle to create a pseudo-gaseous state of the analyte, and the resulting sample is drawn through a heated capillary which leads to the detector. For a flowing-afterglow instrument, the sample is floated down a river of helium in plasma form with a known and constant flow rate down a flow-tube, eventually passing through a low voltage nose cone which leads to the mass analyzer.

Generally, mass analyzers within a mass spectrometer are varied combinations of ion-traps and/or quadrupoles. In a ESI-QQQ, the first and third quadrupoles are traditionally used for mass filtration and/or analysis, while the second quadrupole is maintained as an r.f.-only quad, allowing it to act as a collision cell instead of a mass analyzer. For MS/MS studies involving a ESI-QQQ in this work, ions enter Q1 and are filtered to only allow the heterodimeric (parent) mass into Q2. After collision-induced dissociation, the resulting fragment ions were sent into Q3 for mass analysis.

A quadrupole ion-trap, however, consists of a pair of hyperbolic electrodes and a ring electrode in between to create a literal trap, with filtered ions leaked in through a small hole in the hyperbolic electrode closest to the quadrupole. The ions are held in the center of the trap with the assistance of a damping (or sheath) gas in addition to the alternating voltages on each electrode, and are
isolated, fragmented, and analyzed within the trap. The resulting ions are then ejected using mass-specific waveforms to the detector.

1.5 Establishment of Necessity and Guide to Thesis

The efficacy of the EKM continues to be actively questioned in the chemistry literature.\textsuperscript{29-31} Experiments done in instruments with high, unaccounted-for effective temperatures give determinations that are unreasonable, and these values are compared with determinations via the EKM. Without consideration for the high effective temperatures in some previous experiments, values determined using the EKM are proposed to be inaccurate.

The work described in this thesis comprises the calculation of thermochemical data for varying types of small, high-entropy organic molecules from both theoretical computation and experimental data collected from multiple types of mass spectrometers. The results of analysis are compared to reported reference values from NIST.gov, and the efficacy of the extended kinetic method for polyfunctional molecules is described.

Chapter 2: Experimental Details

2.1 Experimental Parameters

Three types of instruments were used for the experiments described in this thesis: an ESI triple-quad mass spectrometer (ESI-QQQ), an ESI quadrupole
ion-trap mass spectrometer (ESI-LCQ), and a flowing-afterglow triple-quad mass spectrometer (FA-QQQ). The triple-quad mass spectrometer used is a Thermo ESI-LCQ TSQ-Quantum Discovery, the ion-trap mass spectrometer used is a Finnigan ESI-LCQ Deca, and the flowing afterglow was independently constructed. All FA-QQQ experimental data was collected by previous lab members, and is therefore not described here.

The ESI-LCQ and ESI-QQQ use similar solution for analysis, but have slightly different methods of data acquisition. Solutions of each analyte and reference were made to be approximately $5 \times 10^{-5} M$ with 50:50 MeOH:H$_2$O and 1% formic acid, and dimer solutions were made with a 1:1 ratio of reference to analyte as seen in Table 1.

For analysis in the ESI-LCQ, the resulting solutions were injected into the mass spectrometer at a flow rate of 10 microliters/minute, capillary temperature of 125°C, with nitrogen as a sheath gas, and helium as the collision gas. The heterodimeric peak was mass selected in the ion trap, allowing only those molecules within a small, specific mass range to be stable in the trap. Then, via MS/MS, the selected peak was fragmented further, and a spectrum was collected for each heterodimer and its known fragments in a normalized collision energy scan from 0% to 100% collision energy in steps of 2%.

For analysis in the ESI-QQQ, the resulting solutions were injected into the mass spectrometer at a flow rate of 7 microliters/minute, a capillary temperature of 100°C, with nitrogen as a sheath gas, and argon as the collision gas (at 0.3 microliters/min). The resulting heterodimeric peak mass was isolated in Q1,
<table>
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<th>References</th>
<th>Proton Affinity (kJ/mol)(^a)</th>
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<td>2-aminoethanol</td>
<td>amylamine</td>
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<td></td>
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\(^a\): all proton affinity values above are reported from [27].

injected into an r.f.-only quad (traditionally Q2), and then fragmented in Q3. Spectra were collected at collision energies that varied from 0V to 30V in intervals of 3V.
For each instrument, data was collected for each analyte-reference heterodimer on a minimum of three different days to ensure scientifically and statistically significant results. Data used for analysis reflected a linear relationship between effective temperature and applied collision energy, as is expected within EKM theory due to less reliable estimations of effective temperature as collision energy increases after a certain point. Orthogonal distance regression (ODR) was run following data concatenation which allowed for quantitation of how statistically sound results were by way of calculation of error associated with the selected data.

ODR is used instead of least squares regression because it can treat variables as separate entities despite calculating error of a value that is found by use of the variables in conjunction with one another. ODRFit (developed by Ervin and Armentrout) was used to carry out calculations in this work. ODR works through utilization of a Monte Carlo simulation with a given window of energetic “possibility”. All thermochemical properties being reported in this work are post-ODR, and therefore include any reasonable error.

2.2 Theoretical Calculations

Theoretical calculations of the thermochemical properties to be measured in this experiment were completed using Gaussian09\textsuperscript{25}/Gaussian98\textsuperscript{26} and PCModel 9.2 (Serena Software, Bloomington, IN). Structures of each analyte were drawn in PCModel and a GMMX search was run to find the most probable, unique conformers. The resulting files were transferred to Unix work stations and
RHF/3-21G optimizations were computed for each conformer. Conformers considered to be unique survived elimination, and were then optimized at the RB3LYP/3-21G level, and so on through each method in Table 2; this approach to computation allows for minimization of computational cost without foregoing the benefits of higher-level theory.

Table 2: Theoretical Methods of Calculation Used

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<thead>
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<th>Method</th>
<th>Job</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHF/3-21G</td>
<td>opt*</td>
</tr>
<tr>
<td>RB3LYP/3-21+G*</td>
<td>opt</td>
</tr>
<tr>
<td>RB3LYP/6-31+G*</td>
<td>opt+freq*</td>
</tr>
<tr>
<td>RB3LYP/6-311++G**</td>
<td>energy</td>
</tr>
<tr>
<td>G2/6-311++G**</td>
<td>opt+freq</td>
</tr>
<tr>
<td>M06-2X/6-31+G*</td>
<td>opt+freq</td>
</tr>
<tr>
<td>M06-2X/6-311++G**</td>
<td>energy</td>
</tr>
</tbody>
</table>

*: opt = optimization, freq=frequency

Chapter 3: Results

3.1 Reference Base Trial and Error

The EKM was used to experimentally calculate the proton affinities and gas-phase basicities of ethanediol, ethylenediamine, 2-aminoethanol, 3-aminopropanol, 1,4-butanediol, and 4-aminobutanol with use of a quadrupole ion-trap mass spectrometer (ESI-LCQ), a triple-quadrupole mass spectrometer (ESI-QQQ) and a flowing afterglow triple-quadrupole mass spectrometer (FA-QQQ). Each of these analytes were studied using identical reference bases and solution concentration from instrument to instrument. Reference bases were selected to be structurally similar to the analyte in question as is required with
use of the EKM; Table 3 lists each reference base investigated for use with each analyte.

Table 3: List of Used and Unused References for Reported Analytes

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Used References</th>
<th>Unused References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-amino-1-ethanol</td>
<td>amylamine</td>
<td>isopropylamine</td>
</tr>
<tr>
<td></td>
<td>n-butylamine</td>
<td>phenethylamine</td>
</tr>
<tr>
<td></td>
<td>pyridazine</td>
<td>pyrrolidine</td>
</tr>
<tr>
<td></td>
<td>sec-butylamine</td>
<td>tert-butylamine</td>
</tr>
<tr>
<td>ethylenediamine</td>
<td>3-picoline</td>
<td>phenethylamine</td>
</tr>
<tr>
<td></td>
<td>4-picoline</td>
<td>sec-butylamine</td>
</tr>
<tr>
<td></td>
<td>diethylamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pyrrolidine</td>
<td></td>
</tr>
<tr>
<td>1,2-ethanediol</td>
<td>1-hexanol</td>
<td>1-heptanol</td>
</tr>
<tr>
<td></td>
<td>1-pentanol</td>
<td>2-butanol</td>
</tr>
<tr>
<td></td>
<td>1-propanol</td>
<td>2-butanone</td>
</tr>
<tr>
<td></td>
<td>2-propanol</td>
<td></td>
</tr>
<tr>
<td>3-amino-1-propanol</td>
<td>2-aminopyridine</td>
<td>acetone</td>
</tr>
<tr>
<td></td>
<td>3-methoxypyridine</td>
<td>benzonitrile</td>
</tr>
<tr>
<td></td>
<td>piperidine</td>
<td>cyclopentanone</td>
</tr>
<tr>
<td></td>
<td>pyrrolidine</td>
<td>isobutyronitrile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>benzylamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N,N-dimethylaniline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pyridine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tert-butylamine</td>
</tr>
</tbody>
</table>

Note: 1,4-butanediol and 4-aminobutanol were investigated with only the references used by previous lab members, so no unused references were tested.

3.2 Diol Results

When analyzing plots from the kinetic method, it is important to note that each grouping of markers in an EKM Plot 1 represents the branching ratios of one reference compound at various energies. Although the associated error with
some measurements post-ODR is relatively high, analysis of the raw data, done traditionally in the extended kinetic method with EKM Plot 2, gives evidence of feasibility of these estimations. EKM Plot 2 provides a measure of consistency within the data, as well as quantifiable estimations of associated entropy by way of the intercept term for the equation of a best-fit line; the equation for said line being as follows (Equation 8):

$$y = \frac{\Delta H_{\text{Analyte}} - \Delta H_{\text{Average}} - T_{\text{eff}} \Delta S}{R T_{\text{eff}}}$$  \hspace{1cm} (8)$$

The slope for Equation 8 gives the estimated difference in proton affinity from analyte to reference base average.

The data collected for ethanediol, a low-proton-affinity molecule in comparison to the other analytes studied, produced an estimated proton affinity of 794.4 ± 8.4 kJ/mol via the ESI-LCQ (Figure 1) and 800.6 ± 24.4 kJ/mol via the ESI-QQQ (Figure 3). The results of analysis via ESI-LCQ and ESI-QQQ mass spectrometry were in excellent agreement with each other, and the post-ODR KM Plot 1 for each instrument displays relatively high statistical probability of accuracy of the results determined.

Figure 1 displays the isothermal proton affinity of ethanediol falling well within the boundaries of interpolation, and gives a visual representation of the minimal error associated with this determination. Figure 3 shows a crossing point slightly out of range of the reference bases, this extrapolation accounts for the increased error seen in this measurement. This disparity between mass
spectrometers has been determined to be due to difference of temperatures within each instrument, leading to differing activity of reference bases from instrument to instrument. Data from EKM Plot 2 for each instrument (Figures 2 and 4) gives $R^2$ values of 0.894 and 0.9969, giving evidence for the accuracy of these determinations despite the relatively high levels of associated error post-ODR.

Figure 1: EKM Plot 1 for 1,2-Ethanediol via ESI-LCQ Post-ODR
Figure 2: EKM Plot 2 for 1,2-Ethanediol via ESI-ESI-LCQ

1,2-Ethanediol EKM Plot 2 (LCQ)

\[ y = 1.1816x + 1.1664 \]
\[ R^2 = 0.894 \]

Figure 3: EKM Plot 1 for 1,2-Ethanediol via ESI-ESI-QQQ Post-ODR

\[ \ln\left(\frac{[B(H^+)]}{[A(H^+)]}\right) \]

[Graph showing various alcohols and their corresponding PA values]
Data was reported from previously completed experiments on the ESI-LCQ and FA-QQQ for 1,4-butanediol. Data collected for 1,4-butanediol produced estimated proton affinities of: $893.9 \pm 32.5$ kJ/mol via the ESI-LCQ (Figure 5), 890.6 ± 24.8 kJ/mol via the ESI-QQQ (Figure 7), and 885.5 ± 20.8 kJ/mol via the FA-QQQ (Figure 9) with insignificant agreement between the estimates due to somewhat high margins of error. The error associated with these measurements is most likely due to the extrapolation necessary for approximation via ODR. As seen in Figures 5 and 9, the isothermal PA (the crossing point) is outside of the range of the data, and in Figure 7, the large differences in branching ratio among the reference bases used account for somewhat large associated error.
However, EKM Plot 2 for each instrument (Figures 6, 8, and 10), show correlation values of 0.9517, 0.9858, and 0.9842. High correlation between estimated difference in proton affinity and associated entropy in EKM Plot 2 gives evidence to the viability of measurements determined in EKM Plot 1. So, despite large associated error in the PA estimation, the actual estimation is thought to be highly accurate.

Figure 5: EKM Plot 1 for 1,4-Butanediol via ESI-LCQ Post-ODR
Figure 6: EKM Plot 2 for 1,4-Butanediol via ESI-LCQ

![1,4-Butanediol KM Plot 2](image)

\[ y = 26.153x - 7.5593 \]
\[ R^2 = 0.9517 \]

Figure 7: EKM Plot 1 for 1,4-Butanediol via ESI-QQQ Post-ODR

![1,4-Butanediol KM Plot 1](image)
Figure 8: EKM Plot 2 for 1,4-Butanediol via ESI-QQQ

1,4-Butanediol EKM Plot 2 (QQQ)

\[ y = -0.0277x - 1.7169 \]
\[ R^2 = 0.9858 \]

Figure 9: EKM Plot 1 for 1,4-Butanediol via FA-QQQ Post-ODR
3.3 Diamine Results

Results for ethylenediamine are shown in Figure 11. Proton affinity values for the references vary minimally, and the difference in effective temperature among them varies similarly; this relationship leads to inflated error in ODR analysis as error estimates for each reference conflate (and thus leave more room for possible error despite the visibly high accuracy of the measurement). Proton affinity determinations via ESI-LCQ and ESI-QQQ (Figures 11 and 13) were 950.4 ± 16.4 kJ/mol and 946.9 ± 8.4 kJ/mol, respectively. Figures 12 and 14 give evidence to the accuracy of determination with correlations of 0.9526 and 0.9877.
Figure 11: EKM Plot 1 for Ethylenediamine via ESI-LCQ Post-ODR

![EKM Plot 1](image)

Figure 12: EKM Plot 2 for Ethylenediamine via ESI-LCQ

![EKM Plot 2](image)

\[ y = 3.5499x - 3.4867 \]

\[ R^2 = 0.9526 \]
Figure 13: EKM Plot 1 for Ethylenediamine via ESI-QQQ Post-ODR

Figure 14: EKM Plot 2 for Ethylenediamine via ESI-QQQ

Ethylenediamine EKM Plot 2 (QQQ)

\[ y = -1.0591x - 1.5522 \]

\[ R^2 = 0.9877 \]
The unexpected negative slope of Figure 14 is most likely due to the references chosen. Because the estimated entropy within the system is plotted on the y-axis and differences in applied basicity are measured on the x-axis, the negative slope here indicates that the basicity of ethylene diamine is lower than that of most of the references.

3.4 Alcoholamine Results

Proton affinity determinations for 2-aminoethanol were determined with the FA-QQQ (Figures 19 and 20) by a previous lab member. Data collected for 2-aminoethanol produced estimated proton affinities of: 925.3 ± 10.5 kJ/mol via the ESI-LCQ (Figure 15), 921.3 ± 8.0 kJ/mol via the ESI-QQQ (Figure 17), and 928.3 ± 9.0 kJ/mol via the FA-QQQ (Figure 19), with excellent agreement between the estimates.

EKM Plot 2 for data via the ESI-LCQ (Figure 16) produces an $R^2$ value of 0.962, a relatively high amount of correlation which speaks to relatively high accuracy for this approximation. The EKM Plot 2 for data via the ESI-QQQ (Figure 18) gives an $R^2$ value of 0.7621. This value, although still moderately high in terms of correlation, is markedly lower than any other value reported in this work. The post-ODR margin of error for this same data is low, indicating that although the accuracy of estimated entropy is subject to some doubt, the reported approximation for proton affinity is statistically sound (with 95% confidence). $R^2$ for data collected via FA-QQQ was 0.815 (Figure 20) which gives reasonable statistical power to this approximation.
Figure 15: EKM Plot 1 for 2-aminoethanol via ESI-LCQ Post-ODR

Figure 16: EKM Plot 2 for 2-aminoethanol via ESI-LCQ
Figure 17: EKM Plot 1 for 2-aminoethanol via ESI-QQQ Post-ODR

Figure 18: EKM Plot 2 for 2-aminoethanol via ESI-QQQ
Figure 19: EKM Plot 1 for 2-aminoethanol via FA-QQQ Post-ODR

![EKM Plot 1](image)

Figure 20: EKM Plot 2 for 2-aminoethanol via FA-QQQ

2-Amino-1-ethanol EKM Plot 2 (FAQQQ)

![EKM Plot 2](image)

\[
\ln \left[ \frac{[B]+H^+}{[A]+H^+] \right] = 5.0522x - 3.4144
\]

\[R^2 = 0.815\]
The experimental data for 3-aminopropanol determined using the FA-QQQ was completed by a previous lab member. Data collected for 3-aminopropanol produced estimated proton affinities of: 953.0 ± 17.9 kJ/mol via the ESI-LCQ (Figure 21), 961.9 ± 36.4 kJ/mol via the ESI-QQQ (Figure 23), and 963.8 ± 26.2 kJ/mol via the FA-QQQ (Figure 25). Significant variation between the estimates is likely due to high margins of error.

With the proton affinities of the references being very close in Figure 21, error is quantitatively inflated with use of ODRfit. Statistically speaking, if the values used for a determination are all very close, the error within the data has the ability to compound in Monte Carlo simulations and can falsely inflate associated error. In Figure 22, an $R^2$ value of 0.9904 is calculated, giving evidence to the false inflation of error seen in Figure 21 by giving evidence to its accuracy. In Figures 23 and 25, the isothermal proton affinity falls outside of the range of the references being used for 3-aminopropanol; this can be due to many factors, but is certainly a notable contributing factor to the margin of error observed for this measurement. A comparably large amount of extrapolation for the determination in Figure 23 is observed graphically as well as in the associated error, 36.4 kJ/mol, but the data is given evidence of viability in Figure 24 with a correlation of 0.944. The existence of “high” associated error as well as high correlation can be thought of in terms of percentage: despite appearing “high”, 36.4 kJ/mol is only 4% error in 961.9 kJ/mol. Figure 26 gives an $R^2$ value of 0.8858, and thus gives evidence of moderately high accuracy for this determination.
Figure 21: EKM Plot 1 for 3-aminopropanol via ESI-LCQ Post-ODR

Figure 22: EKM Plot 2 for 3-aminopropanol via ESI-LCQ

3-Amino-1-propanol EKM Plot 2 (LCQ)

\[ y = 4.8884x - 1.9776 \]

\[ R^2 = 0.9904 \]
Figure 23: EKM Plot 1 for 3-aminopropanol via ESI-QQQ Post-ODR

Figure 24: EKM Plot 2 for 3-aminopropanol via ESI-QQQ
Figure 25: EKM Plot 1 for 3-aminopropanol via FA-QQQ Post-ODR

Figure 26: EKM Plot 2 for 3-aminopropanol via FA-QQQ
Post-ODR plots of 4-aminobutanol from the ESI-LCQ (Figure 27) and FA-QQQ (Figure 31) give values within 1 kJ of each other, 964.5 ± 11.2 kJ/mol and 964.2 ± 27.2 kJ/mol, while measurements from the ESI-QQQ (Figure 29) give a PA value of 976.6 ± 45.6 kJ/mol. The accuracy of these approximations is supported by EKM plot 2 for each instrument, Figures 28, 30 and 32, respectively. R² values for the ESI-LCQ, ESI-QQQ, and FA-QQQ data were 0.9936, 0.9988, and 0.9625.

In Figures 29 and 31, large amounts of extrapolation are visibly necessary to estimate the isothermal point; this extrapolation is the most likely culprit for the moderately large error associated with this determination. Figure 32 gives a correlation of 0.9625, which gives evidence to the accuracy of the determination made with raw data, the estimation of proton affinity pre-ODR for 4-aminobutanol being 969.9 kJ/mol. This discrepancy of high accuracy versus high error is most likely due to limitations of statistical analysis in terms of extrapolation.
Figure 27: EKM Plot 1 for 4-aminobutanol via ESI-LCQ Post-ODR

![EKM Plot 1 for 4-aminobutanol via ESI-LCQ Post-ODR](image)

Figure 28: EKM Plot 2 for 4-aminobutanol via ESI-LCQ

![EKM Plot 2 for 4-aminobutanol via ESI-LCQ](image)
Figure 29: EKM Plot 1 for 4-aminobutanol via ESI-QQQ Post-ODR

Figure 30: EKM Plot 2 for 4-aminobutanol via ESI-QQQ
Figure 31: EKM Plot 1 for 4-aminobutanol via FA-QQQ Post-ODR

Figure 32: EKM Plot 2 for 4-aminobutanol via FA-QQQ

$$y = 7.6897x - 1.1597$$
$$R^2 = 0.9625$$
3.5 Theoretical Results

As previously mentioned, theoretical calculations were done at varying levels of assumption and power; the structures displayed in this section are produced from an optimization at the 6-31+G* level of theory, and differences in enthalpies and Gibb’s free energies are reported from a single-point energy calculation at the B3LYP/6-311++G** level. In Figure 33, the lowest-energy conformers for protonated diols, diamines, and alcoholamines are displayed. Each optimized structure for the protonated species is cyclic and indicates that hydrogen bonding is likely to occur within the lowest-energy structure.

Figure 33: Lowest Energy Protonated Conformers for 2-4 Diols, Diamines, and Alcoholamines*

* Red: oxygen atom, Blue: nitrogen atom, Dotted Line: hydrogen bonding
In Figure 34, the optimized neutral conformers for 2-4 carbon diols are shown in order of increasing enthalpy from left to right. The lowest enthalpy conformer for each of the diols was determined to be cyclic with a single point energy calculation at the B3LYP/6-311++G** level based on the optimized structure from B3LYP/6-31+G*. Enthalpies and Gibb’s free energies for the conformers of 1,4-butanediol were reported in kcal/mol, and give differing indications of the lowest energy structure. Note: by enthalpy, the conformers are pictured in the appropriate order, but by Gibb’s free energy, the second conformer for 1,4-butanediol would be preeminent.

Figure 34: Lowest Energy Neutral Conformers for 2-4 Diols
In Figure 35, the optimized neutral conformers for 2-4 carbon diamines are shown in order of increasing enthalpy from left to right. The lowest enthalpy conformer for 2-3 diamines was determined to be cyclic with a single point energy calculation at the B3LYP/6-311++G** level based on the optimized structure from B3LYP/6-31+G*, while the trans, straight-chain form was found for 4 diamine. The straight-chain form was most likely found to be the lowest energy structure due to steric hindrance. There was agreement between enthalpy and Gibb’s free energy for each of the diamines.

Figure 35: Lowest Energy Neutral Conformers for 2-4 Diamines
In Figure 36, the optimized neutral conformers for 2-4 carbon alcoholamines are shown in order of increasing enthalpy from left to right. The lowest enthalpy conformer for each of the alcoholamines was determined to be cyclic. Enthalpies and Gibb's free energies for the conformers of 3-aminopropanol were reported in kcal/mol, and give differing indications of the lowest energy structure. Note: by enthalpy, the conformers are pictured in the appropriate order, but by Gibb's free energy, the second conformer for 3-aminopropanol would be preeminent.

Figure 36: Lowest Energy Neutral Conformers for 2-4 Alcoholamines
Chapter 4: Discussion

4.1 Discussion of Results

The results in this work give evidence of the relevance and importance of the EKM based on statistically-founded ODR analysis of error, as well as support of theoretical values that are in close agreement with experimental results which were at times within the bounds of chemical accuracy (± 8.0 kJ/mol). Variation between instruments being used provided valuable insight in that no instrument was found to be more apropos of this analysis- meaning the EKM is relatively suitable for most instruments regardless of analyte (with higher-energy instruments being understood and considered in analysis).\textsuperscript{36,37}

Previously and presently determined experimental results, when compared with their respective reported NIST values,\textsuperscript{27} paint a picture of the issues relevant to fundamental chemistry. Reported values alongside NIST values and theoretical determinations are seen in Table 4, with associated error for theoretical determinations found in Table 5. The lack of agreement between the values for PA determined in this paper and those currently reported on NIST requires explanation.

When one investigates the values currently listed on NIST for PA of most small organic molecules, one finds that a review compiled by Hunter and Lias in 1998\textsuperscript{32} is frequently cited. The values reported by Hunter and Lias used in this experiment were all from Bowers' “Gas Phase Ion Chemistry” published in 1979,\textsuperscript{33} except for the value reported for ethanediol which was reported from Chen and Stone’s 1995 publication.\textsuperscript{34} The values reported by Bowers were from
a paper he and Aue did in 1973\textsuperscript{35} as well as a paper Aue and Yamdagni did in the same year. Some of the reported NIST values for analytes in this work are from evaluations done more than 40 years ago, with the most recently evaluated being 20 years old, and it is obvious that some of these older values on NIST are becoming obsolete.

One of the frequently referenced works in Hunter and Lias’ review, and thus NIST, is Mautner’s 1980 publication\textsuperscript{38} on polyfunctional ions. Mautner’s work was not very different from the values determined in this work, except that his determination for polyfunctional bases (specifically alcoholamines) was that proton affinity would rise with chain length due to the molecule’s ability to create an intramolecular hydrogen bond. His trend from ethanolamine to butanolamine was 923.4, 961.5, to 984.5 kJ/mol, calculated using equilibrium methods on a sector instrument. The difference from propanolamine to butanolamine in this work is less than 4 kJ/mol both theoretically (by G2) and experimentally (using each instrument), speaking to a more starkly asymptotic relationship between chain-length and proton affinity in polyfunctional bases than Mautner describes.

A recent review by Bouchoux in 2012,\textsuperscript{30} states the relationship between aliphatic chain length and proton affinity in polyfunctional bases is strongly correlated. The author references Aue and Bowers as well as Yamdagni and Kebarle’s work in the 1970’s reflecting this same characteristic; polyfunctional bases will form intramolecular hydrogen bonds which will result in lower-entropy, higher-proton affinity conformers. In this same publication, Bouchoux goes on to reference Armentrout,\textsuperscript{9} Drahos and Vekey,\textsuperscript{40} Ervin and Armentrout,\textsuperscript{39} and
Table 4: Quantitative Results (all values reported in kJ/mol)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>1,2-ethanediol</th>
<th>2-aminoethanol</th>
<th>ethylenediamine</th>
<th>3-aminopropanol</th>
<th>1,4-butenediol</th>
<th>4-aminobutanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>800.5</td>
<td>920.7</td>
<td>952.2</td>
<td>964.4</td>
<td>901.7</td>
<td>965.8</td>
</tr>
<tr>
<td>G2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>798.4</td>
<td>921.5</td>
<td>947.7</td>
<td>958.2</td>
<td>881.5</td>
<td>962.2</td>
</tr>
<tr>
<td>M06-2X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>796.5</td>
<td>915.1</td>
<td>943.9</td>
<td>953.5</td>
<td>891.7</td>
<td>955.9</td>
</tr>
<tr>
<td>KM (IT)</td>
<td>794.4 +/- 8.4</td>
<td>925.3 +/- 10.5</td>
<td>950.4 +/- 16.4</td>
<td>953.0 +/- 17.9</td>
<td>893.9 +/- 32.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>964.5 +/- 11.2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>KM (ESI-QQQ)</td>
<td>801.7 +/- 24.4</td>
<td>921.3 +/- 8.0</td>
<td>946.9 +/- 8.4</td>
<td>961.9 +/- 36.4</td>
<td>890.6 +/- 24.8</td>
<td>976.6 +/- 45.6</td>
</tr>
<tr>
<td>KM (FA-QQQ)</td>
<td>928.3 +/- 9.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>963.8 +/- 26.2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>885.5 +/- 20.8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>964.2 +/- 27.2&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIST&lt;sup&gt;e&lt;/sup&gt;</td>
<td>815.9</td>
<td>930.0</td>
<td>951.6</td>
<td>962.5</td>
<td>915.6</td>
<td>984.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>: [28], <sup>b</sup>: [23], <sup>c</sup>: [24], <sup>d</sup>: completed by previous member of lab, <sup>e</sup>: [27]

Table 5: Error in Theoretical Calculations (all values reported in kJ/mol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Associated Error (kJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0</td>
</tr>
<tr>
<td>G2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.4</td>
</tr>
<tr>
<td>M06-2X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>: [28], <sup>b</sup>: [23], <sup>c</sup>: [24]
himself\textsuperscript{19} as previous works questioning the efficacy of the extended kinetic method as a whole. In each of the papers referenced, the argument made is not that the EKM is impossibly inaccurate; it is simply that the EKM requires careful assessment and selection of references.

Previous comparisons of EKM values to values found with varying methods and in instruments that use much higher energy fields than the instruments used here are not necessarily comparable. Sector instruments, widely used in mass spectrometry and in many of the more notable equilibrium methods, use high-energy fields for analysis and have been paired with hard ionization sources such as chemical ionization.\textsuperscript{37} The efficacy of the EKM is supported by the findings of this work; values determined experimentally are in agreement with values calculated theoretically.

The NIST value reported for each analyte was not within the bounds of associated error for G2 and M06-2X calculations, which brings into question the relevance of any of NIST’s “older” values. Despite the fact that no experimentally-determined value is going to be perfectly in line with theoretical values, the majority of the NIST values noted were not within the bounds of chemical accuracy (8-10 kJ/mol) with theoretical values. 1,2-ethanediol, 2-aminoethanol, and 4-aminobutanol all produced at least one set of post-ODR results from one of the instruments utilized that did not contain the NIST value reported for that analyte. The reported discrepancies in this work give sufficient evidence to the necessity of questioning the currently reported NIST values for thermochemical properties of small, high-entropy, organic compounds.
4.2 Conclusion

Analytical chemistry has come a long way in the last two to four decades, and the fundamental values for intrinsic properties, the values that are used for modeling of larger systems and making estimations of more complicated structures, should reflect that. The results of this work are reasonable approximations for thermochemical properties of the molecules in question, and their accuracy is proven statistically using ODRfit. In more general terms, the EKM is robust and can be used with success. The robust nature of the EKM is in part because it is relative in its approach: meaning, although reported values for any given compound may be multiple decades old and differ from currently determined values, the relative differences between similar compounds (2-aminoethanol, 3-aminopropanol, 4-aminobutanol) will not differ significantly. In closing, the EKM is not only powerful, but resilient, and data resulting from its use can be compared with that of varying instrumentation with appropriate understanding of environmental factors specific to the instrument being used.


8. Wesdemiotis, C., and B. A. Cerda. "Li⁺, Na⁺, and K⁺ Binding to the DNA and RNA Nucleobases. Bond Energies and Attachment Sites from the


15. Poutsma, J. C., et al. "Gas-Phase Acid-Base Properties of Homocysteine, Homoserine, 5-Mercaptonorvaline, and 5-Hydroxynorvaline from the


