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Enthalpy and entropy in chemical reactivity

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Publication Date
2012

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Enthalpy and Entropy in Chemical Reactivity: I. Temperature Dependence of Secondary Deuterium Isotope Effects on the Acidity of Carboxylic Acids and Phenols, and a Rejection of any Inductive Contribution II. Kinetic and Mechanistic Studies of Reactions of Malonic Anhydrides III. Developing an ITC Method to Measure Heats of Proton Transfer

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

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2012
The dissertation of Agnes Flach is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

2012
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ACKNOWLEDGEMENTS

I would like to sincerely thank Professor Charles Perrin for his advice, support, and guidance, which has enabled me to grow as a scientist. I am grateful to have worked for someone with such immense knowledge and expertise and I appreciate everything that he has taught me. I would also like to thank Dr. Phaneendrasai Karri for his help and encouragement along the way. Additionally, I am indebted to Dr. Anthony Mrse whose suggestions and insights were indispensable to the success of my NMR experiments. Also a special thanks goes out to Mark Olsen for his insightful discussions and sense of humor, Dr. Marlon Manalo for his contribution to the “Malonic Anhydrides” project, and my co-workers Gabriel Reyes-Rodriguez and Dr. Yanmei Dong for all of their help throughout the years.

Lastly, I would especially like to thank my husband Ryan, my family, Christine, Markovnikov, and Bettina for their love and support during the past few years.

The material in Chapter 1, in part, has been published in Angewandte Chemie, 2011, Perrin, C. L.; Flach, A., Wiley-VCH, 2011.
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PUBLICATIONS

Enthalpy and Entropy in Chemical Reactivity: I. Temperature Dependence of Secondary Deuterium Isotope Effects on the Acidity of Carboxylic Acids and Phenols, and a Rejection of any Inductive Contribution II. Kinetic and Mechanistic Studies of Reactions of Malonic Anhydrides III. Developing an ITC Method to Measure Heats of Proton Transfer

by

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Doctor of Philosophy in Chemistry

University of California, San Diego, 2012

Professor Charles L. Perrin, Chair

Secondary deuterium isotope effects on the acidities of carboxylic acids and phenols were measured at various temperatures using a highly accurate NMR titration method. Our measurements confirmed that deuteration decreases acidity. The contributions of enthalpy and entropy to the isotope effects were also determined to explore the origin of these secondary isotope effects on the acidities of carboxylic
acids and phenols. While it has previously been shown that these isotope effects are predominantly due to changes in bond vibrational frequencies and zero-point energies upon deprotonation (which would be manifested in enthalpy) it was not known if there is also a smaller contribution from an inductive effect. An inductive contribution to the isotope effect could arise from an electrostatic interaction between the negatively charged carboxylate and the dipole moment of the C-D or C-H bond, and would be manifested in entropy. Our results settle a question that has been unanswered for over 50 years and finally confirm that IEs originate only from changes in vibrational frequencies and zero-point energies upon deprotonation, and that there is no contribution from an inductive effect.

The rate constants and activation parameters for the thermal decomposition of malonic, methylmalonic, and dimethylmalonic anhydrides were reliably obtained using NMR spectroscopy. The highest rate of decomposition was found for methylmalonic anhydride and the lowest rate of decomposition was found for dimethylmalonic anhydride. The enthalpy of activation values provided additional evidence supporting the previously proposed [2+2] cycloreversion mechanism for the decomposition of the malonic anhydrides. Additionally, the enthalpy of activation values were used to determine the extent to which electronic and steric factors influence the rate of decomposition. Our results show that the dominant influence, on the rates of decomposition of malonic anhydrides, is the steric hindrance to the formation of the twisted Möbius transition state by the bulky methyl groups. We also found a smaller contribution from electronic effects due to the stabilization of the sp²
carbons forming in the transition state by the electron donating methyl groups. The entropy of activation values for the decomposition of the three anhydrides are also discussed. Finally, the reactions of methylmalonic anhydride with various hindered bases were monitored by NMR spectroscopy and the relative acidity of methylmalonic anhydride was estimated.

Preliminary work has been done towards developing a new isothermal titration calorimetry method to measure the enthalpies of proton transfer between isopropylamine and various large ring cycloalkylamines, which would ultimately allow us to dissect the relative basicities of these amines into enthalpic and entropic components. The enthalpic and entropic components to the relative basicities of cycloalkylamines and isopropylamine would clarify whether conformational effects or hindrance to the solvation of the cycloalkylammonium ions by additional carbons are responsible for the previously observed, unexpectedly low, basicities of large ring cycloalkylamines.
CHAPTER ONE

Temperature Dependence of Secondary Deuterium Isotope Effects on the Acidity of Carboxylic Acids and Phenols, and a Rejection of any Inductive Contribution
Abstract:

Secondary deuterium isotope effects on the acidity of carboxylic acids and phenols were measured at various temperatures using an NMR titration method applicable to a mixture of isotopologues and capable of very high accuracy. Analysis of formic-$d$ acid, acetic-$d$ and -$d_2$ acids, and 3,5-difluorophenol-2,4,6-$d_3$ isotopologue mixtures confirmed that deuteration decreases acidity. Isotope effects on the acidity of carboxylic acids and phenols have previously been shown to arise mainly from changes in bond vibrational frequencies and zero-point energies, which would be manifested in enthalpy. The question we address is whether there is a smaller inductive contribution to the isotope effect, which would be manifested in entropy. An inductive contribution to the isotope effect could arise from an electrostatic interaction between the negatively charged carboxylate and the dipole moment of the C-D vs. C-H bond, where more solvent organization would be required to stabilize the greater negative charge of the deutero isotopologue. Our variable temperature experiments confirm that these isotope effects are temperature dependent and lie entirely in enthalpy for the formic acid and difluorophenol samples, with no contribution from entropy. For the acetic acid samples, the contribution from entropy might seem to be statistically significant, but it is negative, and inconsistent with any inductive contribution. The isotope effect also appears to be additive in acetic-$d_1$ and acetic-$d_2$ acids, although a nonadditivity due to a stereoelectronic electron delocalization was estimated to be too small to be measured. In summary, these findings are consistent with the proposal that IEs originate only from changes in
vibrational frequencies and zero-point energies upon deprotonation, and that there is no contribution from an inductive effect.
Introduction:

Isotope Effects

Isotope effects (IEs) are observed when a reaction rate or equilibrium constant changes as a result of isotopic substitution. They can be used as valuable tools to provide insight into molecular reactivity and equilibria.\(^1,2,3,4\)

Isotope effects can be either kinetic or equilibrium. The effect of isotopic substitution on the rate of a reaction is a kinetic isotope effect.\(^2\) The effect of isotopic substitution on the position of an equilibrium is an equilibrium IE.\(^5\) Furthermore, isotope effects are either primary or secondary, depending on the distance of the isotopic substitution from the reaction site. Primary IEs are IEs that occur when a bond to the isotope is broken, whereas that bond remains intact if the IE is secondary. Both primary and secondary IEs originate from the differences in vibrational frequencies and zero-point energies (ZPEs) that arise when one isotope is substituted for another.\(^2\) Considering how the dissociation of a C-H bond differs from that of a C-D bond can demonstrate the ZPE origin of primary IEs. First, as can be seen in Figure 1-1, the dissociation energy of a C-H bond is smaller than that of a C-D bond. This is so because deuterium, the heavier isotope, causes a lowering of the zero-point vibrational energy of the bond, making it stronger than that with the protium. Equation 1-1 describes the ZPE \((E_0)\) of a harmonic potential, where \(h\) is Planck’s constant, \(\nu\) is the vibrational frequency, and \(k\) is the force constant.\(^3\) Equation 1-2 defines \(\mu\), the reduced mass, where \(m_1\) and \(m_2\) are the masses of the two atoms.
connected by the bond. When a proton is substituted by a deuterium, the reduced mass is increased, resulting in a lower ZPE and a stronger bond.

\[ E_o = \frac{h\nu}{2} = \frac{h}{4\pi} \left( \frac{k}{\mu} \right)^{1/2} \]  

1-1

\[ \mu = \frac{m_1m_2}{m_1 + m_2} \]  

1-2

Primary isotope effects are observed for reactions where the C-H or C-D bond is only partially broken in the transition state. In these cases the ZPE difference between the partially broken C-H and C-D bonds in the transition state is smaller than the ZPE difference between C-H and C-D bonds in the reactant and the magnitude of the IE will depend on this difference between the ZPE differences of the C-H and C-D bonds in the transition state and the C-H and C-D bonds in the reactants.
Figure 1-1. Zero-point energies and associated bond dissociation energies (BDEs) for C-H and C-D bonds. The zero-point energies of the C-H and C-D bonds are $E_0(H)$ and $E_0(D)$, respectively. The zero-point energy separation between them is $\Delta ZPE$.

Secondary IEs are IEs that occur even though the bond to the isotopic atom remains intact. Since the isotopic bond remains intact, the cleavage of a stronger bond cannot be the cause of the secondary IE. Secondary IEs are divided into groups based on the location of the isotope with respect to the reaction site. If the isotope is substituted on the atom where the reaction occurs, the effect is an $\alpha$-secondary IE. Secondary IEs are then named $\beta$, $\gamma$, and so on as the substitution is located on a neighboring atom, and then even farther away from the reaction site. Secondary $\alpha$-IEs are usually attributed to changes in vibrational modes associated with rehybridization.\(^2\) There is a large difference in force constants for out-of-plane bending modes between $sp^3$ and $sp^2$ hybridized carbons, with the $sp^3$ bend being much stiffer.\(^3\) In a reaction
involving rehybridization of a carbon from sp\(^3\) to sp\(^2\), such as formation of a carbocation, the force constant for the out-of-plane bending mode is larger in the reactant. The transition state, which is developing sp\(^2\) character, has a decreased ZPE separation compared to the reactant. This leads to a smaller activation barrier for the lighter isotope, and a reaction involving a C-H bond will be faster than that involving a C-D bond. On the other hand, if the reaction site is converted from sp\(^2\) to sp\(^3\), the ZPE difference is larger in the transition state, and deuteration increases the reaction rate.

The majority of work that has been done to study secondary β-IEs focuses on kinetic IEs in S\(_{N}1\) solvolysis reactions.\(^6\) In solvolysis, where there is a buildup of positive charge in the transition state, these IEs can generally be explained by changes in vibrational frequencies due to hyperconjugation.\(^7\) Any C-H bond which overlaps with the partially empty p orbital of the developing carbocation can release its electrons to provide stabilization. This delocalization of electron density reduces the C-H vibrational frequency and the ZPE. The reduction is larger for the C-H bond than the C-D bond, leading to a smaller activation barrier for the C-H isotopologue. A reaction with a C-H bond will therefore be faster than that with a C-D bond.

Our current work concerns secondary equilibrium IE on acidities. These are different from solvolysis because there is no rehybridization upon deprotonation and because they are not kinetic IEs. Also, the origin of these secondary equilibrium IEs is still unclear.
Evidence Supporting the Vibrational Origin of Isotope Effects

In the past 60 years, a great deal of work has been done to understand deuterium IEs on acidity and basicity. Research has consistently shown that deuteration reduces acidity and there is a lot of evidence to support the conclusion that isotopically induced changes in zero-point energies are the dominant contributor to these observed IEs. Upon deprotonation of the acid to the carboxylate, there is a net decrease in vibrational frequencies and zero-point energies. One or more bonds in the product conjugate base have a decreased vibrational frequency, and a smaller separation between H and D zero-point energies (Figure 1-2). This leads to a smaller energy difference for deprotonation of the protio acid, therefore favoring deprotonation for the H-substituted over the D-substituted acid.

![Figure 1-2](image)

**Figure 1-2.** Equilibrium isotope effect on acidity, which favors product with H. The larger energy difference $\Delta E^o_D$ is for the deuterio isotopologue.
One of the first quantitative attempts to explain the observed IE in terms of ZPEs was by Bell and Crooks,\textsuperscript{12} who calculated the IE of formic acid by using experimental vibrational frequencies of HCO$_2$H, HCO$_2^-$, DCO$_2$H, and DCO$_2^-$. Their calculated value was consistent with the experimental value, supporting the idea that the IE can be explained by differences in vibrational frequencies and zero point energies arising from isotopic substitution.

Additionally, in some more recent studies,\textsuperscript{10,13} the secondary IEs on acidity of several carboxylic acids, phenol and also on the basicity of pyridine were calculated from changes in vibrational frequencies. The calculated values were then compared with experimental results. Although all the individual vibrations responsible for the IEs could not be identified, the calculations showed that the IEs indeed originate from changes in vibrational frequencies and zero point energies. The computations reproduced the experimentally observed decrease of IE going from formic to acetic to pivalic acids, an increase of IE with distance in phenol as the site of deuteration was changed from ortho to para, and also an IE in benzoic acid that did not decrease with distance as the site of deuteration was changed from ortho to meta to para. Similarly, the computational and experimental results of the pyridine studies show an increase of IE as the site of deuteration was changed from the 2-position to the 3-position. An increase in IE was also observed as the site of deuteration was changed from the 2-position to the 4-position. While in both cases, the calculated values were found to be much larger than the experimental, it may be possible to correct them by using higher levels of computation or by accounting for solvation.\textsuperscript{13} The ability of these
computations to represent experimental values supports the interpretation that IEs originate from changes in vibrational frequencies and zero point energies.

**Vibrational Origin in Terms of Negative Hyperconjugation**

One factor that may contribute to the changes in vibrational frequencies upon deprotonation is negative hyperconjugation. As described above, in solvolysis, the partial cation developing in the transition state is stabilized by neighboring C-H bonds, which release their electrons and help stabilize the partially empty p orbital. This stabilizing delocalization of electrons from a bonding σ orbital into the partially empty p orbital is known as hyperconjugation.

A similar effect has been shown to explain secondary β isotope effects on amine basicity. In amines, the nitrogen lone pair is stabilized by the empty σ* orbital of the adjacent C-H bonds. This n-σ* delocalization is known as negative hyperconjugation. When the lone pair of electrons is delocalized into the σC-H* orbital, the extra electron density in the antibonding σ* orbital results in a weakening of the C-H bond, and its bond order, frequency, and zero-point energy are reduced. This reduction is more favorable for a C-H bond than a C-D bond. Upon protonation the zero-point energies of the C-H and C-D bonds increase. This increase is smaller for the C-D bond, and thus the deuto amine is more basic. In summary, the IEs on amine basicity are due to a greater reduction of the ZPE of the C-H than the C-D bond, because of delocalization of the lone pair.
Figure 1-3 shows molecular orbital diagrams of hyperconjugation and negative hyperconjugation. As illustrated in the diagram, the stabilization due to hyperconjugation is greater than that due to negative hyperconjugation. This is because the interaction of the $\sigma_{C-H}$ bonding orbital with the lower energy vacant $p$ orbital is stronger than the interaction between the lone pair and the higher energy $\sigma_{C-H^*}$ orbital. The contribution of negative hyperconjugation to the secondary $\beta$-deuterium IE is supported by computation.$^{11}$

![Molecular orbital diagrams of hyperconjugation and negative hyperconjugation.](image)

**Figure 1-3.** Molecular orbital diagrams of hyperconjugation and negative hyperconjugation.

Additional evidence supporting the contribution of negative hyperconjugation to the secondary $\beta$-deuterium IE on the basicity of amines was the discovery that the IE is maximum when the deuterium is in a position either antiperiplanar or (to a lesser extent) synperiplanar to the nitrogen lone pair.$^{15,11}$ This stereoelectronic IE originates
in ZPEs and can be attributed to isotope sensitive changes in vibrational frequencies caused by delocalization of the nitrogen lone pair into the empty $\sigma^*$ orbital of the adjacent C-H or C-D bonds. Since the delocalization of the lone pair by the C-H or C-D bond requires overlap between the lone pair and the C-H or C-D bond orbitals (which is greatest in the anti orientation), an amine having a C-H bond antiperiplanar to the lone pair has a lower vibrational frequency than an amine having a C-D bond antiperiplanar. Again, as explained above, negative hyperconjugation leads to a greater reduction of the ZPE of the C-H than the C-D bond (it is more stabilizing for the C-H) and so the protio amine would be less basic than the deutero. The stereoelectronic origin of the IE on amine basicities was demonstrated in an experiment measuring the relative basicities of the two isotopomers of 1-benzyl-4-methylpiperidine-2,2,6-$d_3$ (1 and 2, Figure 1-4).\textsuperscript{11} The value of $K_a^1/K_a^2$ was found to be 1.060 ± 0.006 (corresponding to a $\Delta pK_a$ of 0.0253 ± 0.0025), showing that the isotopomer with the deuterium that is antiperiplanar to the nitrogen lone pair is indeed more basic.

![Figure 1-4. Two isotopomers of 1-benzyl-4-methylpiperidine-2,2,6-$d_3$.](image)
As further support for the stereoelectronic IEs on amine basicity and their origin in ZPEs, nonadditivity of IEs on the basicities of trimethylamine isotopologues was confirmed.\textsuperscript{43} As discussed above, the hyperconjugative stabilization is more favorable for a C-H bond than a C-D bond and therefore the protio amine is less basic than the deutero. Compared to CD\textsubscript{3}NH\textsubscript{2}, the additional H in CD\textsubscript{2}HNH\textsubscript{2} should add the greatest amount of stabilization. One more H of CDH\textsubscript{2}NH\textsubscript{2} should provide slightly less stabilization because the second H must compete for the position antiperiplanar to the nitrogen lone pair. The H in the position that is antiperiplanar to the nitrogen lone pair will lead to the maximum decrease in basicity. The others will lead to a decrease in basicity, but to a smaller extent. Thus, the amine CDH\textsubscript{2}NH\textsubscript{2} should still be less basic than CD\textsubscript{2}HNH\textsubscript{2}, but the decreased basicity due to the additional H would be less than the decreased basicity going from CD\textsubscript{3}NH\textsubscript{2}, to CD\textsubscript{2}HNH\textsubscript{2}. In a recent study the secondary deuterium IE on the basicity of trimethylamine isotopologues was measured, and nonadditivity was observed.\textsuperscript{43} The IE when comparing (CD\textsubscript{3})\textsubscript{2}NCHD\textsubscript{2} vs. (CHD\textsubscript{2})\textsubscript{3}N was found to be larger than when comparing (CH\textsubscript{2}D)\textsubscript{3}N vs. (CHD\textsubscript{2})\textsubscript{3}N and likewise both of these were found to be larger than (CH\textsubscript{3})\textsubscript{3}N vs. (CH\textsubscript{2}D)\textsubscript{3}N. This data provides additional support for the stereoelectronic origin of the IE on the basicity of amines.
This type of delocalization can also contribute to the secondary IE on the acidity of carboxylic acids and phenols. In formic acid, HC(=O)OH, for example, the reduction of C-H frequency upon deprotonation can be attributed to delocalization of oxygen lone pairs that are antiperiplanar to the $\alpha_{\text{C-H}}^*$ orbital as shown in 3 of Figure 1-5. As described above for amines, this delocalization also leads to a decrease of the vibrational frequency and ZPE of the C-H bond and can contribute to the observed IE. Computations have shown that in formic acid the C-H stretching frequency in HCOOH, 3057 cm$^{-1}$, decreases to 2571 cm$^{-1}$ in HCO$_2^-$.

The experimental IR C-H stretching frequencies in HCOOH and HCO$_2^-$ are 2943 and 2825 cm$^{-1}$, respectively. For the deuterio isotopologue the C-D stretching frequency in DCOOH, 2274 cm$^{-1}$, decreases to 1876 cm$^{-1}$ in DCO$_2^-$.

The weakening of this stretching vibration is consistent with $n-\alpha^*$ delocalization. To further support the participation of $n-\alpha^*$ delocalization in stabilizing the formate anion, the C-H bond distance was calculated.
and found to increase from 1.097 Å in formic acid to 1.138 Å in the formate anion. Further computations on acetic acid revealed that upon deprotonation the C-C bond distance increases from 1.508 Å in acetic acid to 1.576 Å in the acetate anion. But not in agreement with what is expected for \( n-\sigma^* \) delocalization, the three C-H bond distances were also found to increase upon deprotonation. The greatest increase was seen for the bond in the molecular plane. The contribution of \( n-\sigma^* \) delocalization to the IE on the aromatic acids studied was even less clear. For example, computations performed on phenol have shown that upon deprotonation all 5 hydrogens gain electron density and the frequencies and zero-point energies decrease for all C-D bonds. However as shown in 5 of Figure 1-5, \( n-\sigma^* \) delocalization can account for an increase in electron density and a decrease in zero-point energy only at the meta position. The decrease of the ortho and para C-D frequencies and ZPEs upon deprotonation, however, cannot be explained by negative hyperconjugation and so the IEs in phenol could not be assigned to \( n-\sigma^* \) delocalization.

The Isotope Effect in Terms of Induction

An inductive effect is observed when an atom or group of atoms donates or withdraws electrons through \( \sigma \) bonds.\(^3\) For example, an electronegative atom will draw electrons toward itself. Electronegativity and induction are both factors that influence acidities. Figure 1-6 shows that acidity increases with a more electronegative substituent, so that chloroacetic acid is a stronger acid than acetic. Upon deprotonation the more electronegative chlorine is better able to draw electron
density away form the negatively charged oxygen than the hydrogen of the methyl substituent on acetic acid. This makes deprotonation of chloroacetic acid more favorable.

\[
\begin{align*}
\text{acetic acid} & \quad \text{p}K_a = 4.76 \\
3\text{-chloropropanoic acid} & \quad \text{p}K_a = 3.98 \\
\text{chloroacetic acid} & \quad \text{p}K_a = 2.87 \\
\text{trichloroacetic acid} & \quad \text{p}K_a = 0.64
\end{align*}
\]

**Figure 1-6.** Increasing acidity due to electronegativity and induction. Shown are pK\textsubscript{a} values for substituted carboxylic acids\textsuperscript{3,16}

One feature of induction is that the farther away the electronegative atom, the lower its ability to withdraw electrons through the σ system. In this case, the larger the distance between the electronegative chlorine and the carboxyl group, the lower its ability to stabilize the negative charge of the carboxylate via induction. Figure 1-6 shows that 3-chloropropanoic acid is less acidic than 2-chloroacetic acid. Finally, the effect increases with the number of substituents, so that trichloroacetic acid is more acidic than both chloroacetic and acetic acids.

One simplistic rationalization for an inductive contribution to the observed IE on acidity is that deuterium is more electron-donating than protium, making the deuterocarboxylates less stable. This simple reasoning is not valid because the Born-Oppenheimer Approximation states that since electrons move so much faster than
nuclei, the nuclear positions can be fixed and the electronic wave function is independent of nuclear mass. Therefore, the electronegativities of H and D are the same. The Born-Oppenheimer Approximation allows the molecular Schrödinger equation, eq. 1-3, to be replaced by two equations, an electronic and a nuclear Schrödinger equation. This allows for nuclear and electronic motion to be treated separately. The general molecular Hamiltonian, \( \hat{H}_{\text{mol}} \), for any molecule is given by equation 1-4. The symbols \( M \) and \( m \) represent the masses of the nuclei and electrons, respectively. The other symbols in the equation are nuclear charge, \( Z \), electron charge, \( e \), the distance between two electrons \( i \) and \( j \), \( r_{ij} \), the distance between nucleus A and electron \( i \), \( r_{Ai} \), and the kinetic energy operator, \( \nabla^2 \). The electronic Hamiltonian consists of terms three, four, and five of eq. 1-4, which represent the kinetic energy of the electrons, nuclear-electron attraction, and electron-electron repulsion, respectively. Terms one and two represent kinetic energy of the nuclei and nuclear-nuclear repulsion, respectively. In the solution of the electronic Schrödinger equation, the positions of the nuclei are fixed and the corresponding electronic energy eigenvalue is solved for at the fixed internuclear distance. This is done repeatedly at various internuclear separations to eventually give the potential energy function. As can be seen from eq. 1-4, terms three, four, and five, the three terms making up the electronic Hamiltonian, are independent of nuclear mass, and therefore the electronic energy eigenvalue is also isotope independent. Accordingly, as can be seen in Figure 1-1, the potential energy curves for C-H and C-D bonds are identical. If the Born-Oppenheimer Approximation holds, then only vibrational eigenvalues, the values of
the vibrational energy levels obtained by solving the vibrational Hamiltonian, can contribute to the IE.

\[
\hat{H}_{\text{mol}} \Psi_{\text{mol}} = E_{\text{mol}} \Psi_{\text{mol}}
\]

\[
\hat{H}_{\text{mol}} = -\frac{\hbar^2}{2} \sum_A N_A^{-1} \nabla^2_A + \sum_{A<B} e^2 Z_A Z_B e^{-r_{AB}} - \frac{\hbar^2}{2m} \sum_i \nabla^2_i - \sum_A e^2 Z_A e^{-r_A} + \sum_{i<j} e^2 e^{-r_{ij}} \quad (1-3)
\]

Another explanation for an inductive contribution is from a field effect. Field effects are similar to inductive effects, but the interaction does not happen through σ bonds but through space. Bond dipoles can produce an electric field that can have an electrostatic effect on distant atoms. The differences in acidities of the carboxylic acids in Figure 1-6 were explained above by the ability of substituents to withdraw electrons through the σ bonds. These differences in acidity could also be accounted for by a field effect. Replacing the three protons of the acetic acid methyl group by more electronegative chlorine atoms changes the magnitude and direction of the three bond dipoles. The resulting dipole moment, which is a sum of the individual bond dipoles of the three C-Cl bonds, points away from the negatively charged oxygens and stabilizes trichloroacetic acid upon deprotonation. The field effect produced by the C-H bond dipoles of acetic acid is not as stabilizing, and so deprotonation of acetic acid is less favorable.

The influence of a field effect on acidity, distinguished from an inductive effect, can be seen by comparing the acidities of compounds 6 and 7 (Figure 1-7).\(^2,17\) The electronegative chlorine is one bond closer to the carboxyl group in 7; however,
compound 6 is more acidic. One reasonable explanation for this is that the negative end of the C-Cl dipole is aligned toward the carboxylate in 7, making it less stable via a field effect.

\[ \text{p}K_a = 5.72 \pm 0.01 \quad \text{p}K_a = 5.90 \pm 0.01 \]

**Figure 1-7.** Decreasing acidity due to field effects.

It has been suggested that this type of electrostatic interaction between the negatively charged carboxylate and the dipole moments, \( \mu \), of C-H and C-D bonds may contribute to the observed IE on acidities.\(^9,18\) The bond dipole moment, \( \mu \), is a product of charge separation and bond length. The C-H bond is longer than the C-D bond, and thus the dipole moment of the C-H bond is larger than that of the C-D bond. The differences in bond length and dipole moment arise from the anharmonicities of C-H and C-D bond vibrations. The potential energy curve for a C-H or C-D bond is anharmonic, and therefore the vibrational wave function is skewed and not symmetric with respect to the minimum of the curve. The C-H wave function lies higher in the well than a C-D and thus its average displacement from the equilibrium position is larger. Figure 1-8 shows that the ground state vibrationally averaged bond distance of a C-H bond, \(<r_{CH}>\), lies slightly to the right of the vibrationally averaged bond
distance of a C-D bond, $<r_{CD}>$. Both of these average bond distances are to the right of the equilibrium bond distance, $r_e$, which corresponds to the minimum of the curve. As discussed above, according to the Born-Oppenheimer approximation the electronic wave function and the potential energy curve are independent of nuclear mass and the potential energy curves for C-H and C-D bonds are identical. But as seen in Figure 1-8 the potential energy curve is anharmonic and the vibrational wave functions of C-H and C-D are different. Therefore, the vibrationally averaged bond distances of C-H and C-D bonds are different, and the average positions of their nuclei are also different. This offset explains why a C-H bond is longer, on average, than a C-D bond.

![Figure 1-8](image.png)

**Figure 1-8.** Ground state vibrational wave functions of C-H and C-D on the anharmonic potential energy curve. The vertical bars represent the ground state vibrationally averaged bond distances of the C-H bond, $<r_{CH}>$, the C-D bond, $<r_{CD}>$, and the equilibrium bond distance, $r_e$, which corresponds to minimum potential energy.
In this case the direction of the dipole moment is assumed to be $C^+\text{H}^-$ (or $C^+\text{D}^-$) because only a dipole pointing in this direction can explain the decreased acidity of the deuterio isotopologue. This is opposite to the direction expected from the atomic electronegativities. The larger C-H dipole, which points away from both partially negatively charged oxygens of the anion withdrawing the electron density, is more stabilizing for the protio isotopologue then the deuterio. This greater stabilization of the negative charge in the protio anion (by its larger dipole moment) can account for the increased acidity of the protio when compared to the deuterio. In this way, deuterium might be more ‘electron donating’ because its smaller dipole moment leads to larger partial negative charge on the carbon of the C-D when compared to the carbon of the C-H. This explanation for how induction might contribute to the observed IE is more of a possibility than the one based on relative electronegativities of H and D.

**Experiments Supporting an Inductive Contribution**

In a study of secondary deuterium IEs on the acidity of formic, acetic, pivalic, and benzoic acids, Streitwieser and Klein\textsuperscript{18} reproduced the values obtained by Bell and Crooks for formic acid, and provided additional data for other carboxylic acids. While Streitwieser and Klein agreed with Bell and Crooks on the origin of the IE of formic acid, they concluded that an inductive effect could explain the IE for the other acids studied. Streitwieser and Klein estimated the contribution of the inductive effect to the IE of acetic acid. Equation 1-5\textsuperscript{10,18} relates differences in $pK_a$ to differences in
dipole moments, where $\mu$ represents dipole moment. For their estimate of $\Delta \mu$, Streitwieser and Klein used the difference between the dipole moments of (CH$_3$)$_3$CD and (CH$_3$)$_3$CH, which is 0.0086 D. The value of the derivative, $d\,pK_a/d\mu$, was 0.608 D$^{-1}$, determined from the effect on acidity of a C-Cl bond dipole. Using these values the $\Delta pK_a$ per D was calculated to be 0.005, which entirely accounts for the experimental observation in acetic-$d_3$ acid of a $\Delta pK_a$ of 0.014.

$$\Delta pK_a = \frac{\partial pK_a}{\partial \mu} \Delta \mu$$

In addition, the fall-off of the IE with distance was considered to be consistent with an inductive effect. Studies by Halevi, Nussim, and Ron$^{9,19}$ also support that induction is the dominant contributing factor to the observed IE. Their primary argument was based on the observation that the IE decreases with distance, and this ‘dampening’ of the IE is consistent with the falloff observed for normal inductive effects. In addition, some others have also accepted inductive effects as the source of isotope effects.$^{20}$

**Evidence Against an Inductive Contribution**

Besides Bell and Crooks, many others have argued that the origin of these IEs is from changes in vibrational frequencies and zero-point energies, and that induction is not the dominant contributing factor.$^{8,21}$ More recently Perrin and Dong$^{10}$ measured
the secondary deuterium isotope effects on the acidity of carboxylic acids and phenols using a remarkably accurate NMR titration method.\textsuperscript{22} They found, in agreement with previous studies, that deuteration decreases acidity for all compounds studied and that in formic, acetic, and pivalic acids the IE decreases as the site of deuteration moves farther from the OH. The authors did not agree that this decrease was related to a contribution from induction. Revisiting the previous calculation,\textsuperscript{18} which found the inductive effect to entirely account for the observed IE of acetic acid, they judged that the estimated value of $\Delta \mu$, 0.0086 D, was too high for such a nonpolar bond. The value of $\Delta \mu$ was recalculated by Perrin and Dong using the difference in C-H and C-D bond lengths $(r_{CH} - r_{CD} = 0.5 \text{ pm})$\textsuperscript{23} and the derivative of dipole moment with respect to C-H bond distance $(d\mu/dr_{CH} = 0.004 \text{ e})$, obtained from infrared intensities.\textsuperscript{24} Inserting the new more reasonable estimate of $\Delta \mu$, $1\times10^{-4}$ D, into eq. 1-5 the inductive contribution to the IE was found to be 0.00006 per D. This new value is much smaller than the previous 0.005.

Another interesting result in this work, questioning the inductive contribution, was for phenol and benzoic acid, where the IE does not decrease as deuterium substitution moves from ortho to meta to para.\textsuperscript{10} These cases where the IEs do not decrease with distance do not support the rationalization that IEs are of an inductive origin, which mandates that distance lowers the ability of the substituted isotope to affect the reaction. Furthermore, the dipole for the ortho position, which is opposite from the meta and para, might have produced the opposite IE. Finally, ab-initio calculations were performed to calculate the IEs from changes in vibrational
frequencies. These computations reproduced the observed IE, although the calculated values were much larger than the experimental values. This overestimate might be corrected by using higher levels of computation or by accounting for solvation, but the important thing is that only an underestimate of the IEs would have supported an inductive contribution. In addition, because the differences in dipole moment between C-H and C-D bonds arise from anharmonicity of bond vibrations, the inductive contribution depends on bond anharmonicity. The calculations performed by Perrin and Dong to calculate the IEs on the acidities of carboxylic acids and phenol and also the calculations mentioned previously calculating the IEs on the basicity of pyridines ignore anharmonicity and so their ability to reflect the experimental IE provides no support for an inductive contribution. Both of these studies, which show the failure of the IEs to diminish with distance in aromatic acids and bases, support the vibrational, not inductive, origin of IEs.

More evidence against an inductive contribution was presented when the IEs on amine basicity were found to be of stereoelectronic origin. The IE on the basicity of amines was found to be the greatest when the deuterium was placed in a position either antiperiplanar or synperiplanar to the nitrogen lone pair. This stereoelectronic IE was found to originate in ZPEs and was attributed to the reduction of the frequencies and ZPEs of adjacent C-H or C-D bonds. Since the reduction for a C-D bond is less favorable bond than for a C-H bond, a deuterium either antiperiplanar or synperiplanar to the nitrogen lone pair leads to the least amount of stabilization and should result in the largest increase in basicity when compared to the protonated
amine. An IE of stereoelectronic origin is evidence against an inductive contribution, which would be angle-independent.

As further support for the stereoelectronic origin of the IE on amine basicity, nonadditivity of IEs on the basicities of trimethylamine isotopologues (CH₃)₃N, (CH₂D)₃N, (CHD₂)₃N, and (CD₃)₂NCHD₂ was confirmed. An IE that is stereoelectronic should result in nonadditivity of the IEs. Nonadditivity of IEs provides even more evidence against an inductive contribution. Contrary to what was found, the inductive effect would cause each H to add the same amount of stabilization and as mentioned earlier would be angle-independent.

**Inductive Effect and Entropy**

Measuring the temperature dependence of the IEs should provide a definitive test of the inductive contribution. Much research has been done to study the temperature dependence of dissociation constants and related thermodynamic parameters on carboxylic acids and phenols. The enthalpies of ionization of formic and acetic acids in water at 25 °C are small and indistinguishable, 0.01 ± 0.05 and -0.02 ± 0.05 kcal/mol, respectively. However, the entropies of ionization of formic and acetic acids in water at 25 °C are -17.1 and -21.9 cal/K·mol, respectively, corresponding to free-energy contributions of -5.1 and -6.5 kcal/mol. The entropy contribution is due to two factors (which necessitate more solvent organization around the acetate than the formate ion) and is less favorable for the ionization of acetic than
formic acid. The first factor is that the acetate methyl group produces a larger steric hindrance to solvation of the acetate anion than the smaller H of the formate. The second is that the electron donating methyl group leads to a larger negative charge on acetate anion than that on the formate. Due to both of these factors the acetate anion requires more solvent organization than the formate and therefore acetic acid would have a less favorable entropy of ionization than formic acid. Harned and Ehlers determined the dissociation constant of acetic acid from 0 to 60 °C at 5 °C intervals. The smallest enthalpic contribution, at 20 °C, was found to be 13 cal/mol. The entropy contribution at 20 °C is -21.7 cal/K·mol (-6.36 kcal/mol). At 60 °C, where the contribution from enthalpy is the largest, -321 cal/mol, the contribution from entropy is -22.0 cal/K·mol (-7.33 kcal/mol). Therefore the greater acidity of formic acid is due to entropy, not enthalpy.

Studies on the ionization of benzoic acids show that benzoic acid is slightly more acidic than \textit{m}-methylbenzoic acid. At 25 °C the enthalpies of ionization of benzoic and \textit{m}-methylbenzoic acids in water are -67 ± 19 and -91 ± 13 cal/mol, respectively. Additionally, the entropy values of benzoic and \textit{m}-methylbenzoic acids found under the same conditions are -19.44 ± 0.04 cal/K·mol (-5.796 kcal/mol of free energy) and -19.75 ± 0.05 cal/K·mol (-5.888 kcal/mol of free energy), respectively. Thus, as in the examples above, the thermodynamic data show a very small enthalpic contribution and a larger contribution from entropy.

In this case it is possible to distinguish between the dominance of entropy on the overall acidity and the dominance of entropy with regard to the substituent effect.
The dominance of entropy on the overall acidity can be seen from the data above because the entropic contributions to the free energy of ionization of benzoic and m-methylbenzoic acids, -5796 and -5888 cal/mol, are much larger than the enthalpic contributions of -67 and -91 cal/mol. Entropy also dominates with regard to the substituent effect because the values of $\Delta S^\circ (\Delta S^\circ_{\text{benzoic}} - \Delta S^\circ_{\text{m-methylbenzoic}} = 92 \pm 19$ cal/mol) is larger than the value of $\Delta H^\circ$, which is zero ($\Delta H^\circ_{\text{benzoic}} - \Delta H^\circ_{\text{m-methylbenzoic}} = 24 \pm 23$ cal/mol).

The decrease in acidity due to methyl substitution at the meta position is due to an inductive field effect. The electric field created by the C-H and C-C bond dipoles leads to a destabilizing electrostatic interaction with the partial negative charges on the oxygens of the benzoate anion. This dipole interaction leads to a larger negative charge on the oxygens and requires more solvent organization. Hence this inductive field effect on the acidity of m-methylbenzoic acid is manifested in entropy.

Because entropy is the largest contributing factor to the inductive effect on dissociation constants of carboxylic acids it may also contribute to the IE on the acidity of these acids, if an inductive effect is responsible. Despite his argument for an inductive contribution to the IE, Halevi did not measure the temperature-dependence of the isotope effects, but implied that performing these measurements would clarify the extent to which inductive effects contribute. He claimed that "it should be noted that $\Delta H^\circ$ of ionization of weak carboxylic acids in water at 25º is generally close to zero. Therefore, if inductive effects determine acidity at all, they do so via changes in entropy, presumably entropy of solvation." He reasoned that because the enthalpy
contribution is small, the differences in acidity between carboxylic acid isotopologues must be due to entropy.

The focus of this work is to explore the origin of secondary IEs on the acidity of carboxylic acids and phenols. While it has been shown that zero-point energies are the dominant contributor, it is still unclear if there also is a smaller contribution from an inductive effect. Determining the contribution of enthalpy and entropy to the IE from its temperature dependence can be used to resolve this problem. A contribution from inductive effects would be manifested in entropy. If the IE is due to an electrostatic interaction between the negatively charged carboxylate and the less stabilizing dipole moment of the C-D bond, more organization of solvent would be required to stabilize the greater negative charge of the D-isotopologue. This would result in a less favorable (greater) entropy of reaction for the deprotonation of the deutero acid. Earlier attempts\textsuperscript{27,28} to measure the temperature dependence of the secondary deuterium IE on the acidity of acetic acid and calculate the associated thermodynamic parameters were unsuccessful due to large experimental error. More recent work\textsuperscript{11} showed that there is a large enthalpy contribution to the β-deuterium IE on amine basicity, contrary to previous claims of a temperature-independent IE.\textsuperscript{29} Again the experimental error was too large to conclude that ΔΔS° = 0. We have therefore undertaken to investigate this problem further by measuring the temperature dependence of the secondary deuterium IEs on the acidities of formic acid, acetic acid, and 3,5-difluorophenol. We will then evaluate the thermodynamic parameters from that temperature dependence.
Measurement of Isotope Effect and Separation into Enthalpy and Entropy

To achieve a better understanding of the contributions of enthalpy and entropy to the IE on acidities, the IE must be measured and the thermodynamic parameters evaluated from its temperature dependence. An equilibrium IE is observed when two isotopologues have different acidity constants, for example in our case the deutero acid has a different acid dissociation constant than the protio acid. The ratio of the acidity constants of the two isotopologues, $K_a^H/K_a^D$, is the IE on acidities because it is a measure of the change in acidity upon deuteration. Substituent effects are customarily defined as $k_{\text{modified}}/k_{\text{standard}}$, whereas IEs are defined as $K_a^H/K_a^D$. In this work the equilibrium IE is defined as $K_a^H/K_a^D$, rather than as $k_{\text{modified}}/k_{\text{standard}}$, and its value is greater than one.

The enthalpic contribution, $\Delta \Delta H^o$, is given by equation 1-6. The entropic contribution, $\Delta \Delta S^o$, is given in equation 1-7. A contribution from ZPEs that increases $K_a^H/K_a^D$ would be expected to lead to a negative $\Delta \Delta H^o$. This is because when the isotope sensitive bonds become weaker upon deprotonation, the difference between H and D ZPEs decreases. The decrease is more favorable for the H-substituted isotopologue. As a result the enthalpy difference for deprotonation of the protio isotopologue is smaller than that of the deutero. A contribution from the inductive effect that increases $K_a^H/K_a^D$ would be expected to lead to a positive $\Delta \Delta S^o$. An inductive contribution would arise from electrostatic interactions between carboxylate or phenoxide anions and dipole moments of C-H or C-D bonds. The smaller dipole...
moment of the C-D bond would have a less stabilizing effect on the negative charge of
the deprotonated acid than the larger C-H dipole moment. The D-anion, which has a
greater negative charge on the oxygen, would then require more solvent organization
to stabilize its negative charge than the H-isotopologue. This would result in a less
favorable (more negative) entropy of deprotonation for the deutero isotopologues than
the protio and therefore a positive $\Delta \Delta S^\circ$, eq. 1-7. In summary, if $K_a^H/K_a^D > 1$, the
correction to the IE from the enthalpy, $\Delta \Delta H^\circ$, arising from ZPEs, is expected to be
negative (as had been observed in amines\textsuperscript{11}), whereas the correction from the
entropy, $\Delta \Delta S^\circ$, arising from an inductive effect, is expected to be positive.

$$
\Delta \Delta H^\circ = \left( H^\circ - H^\circ \right) - \left( H^\circ - H^\circ \right)
$$

$$
\Delta \Delta S^\circ = \left( S^\circ - S^\circ \right) - \left( S^\circ - S^\circ \right)
$$

NMR titration methods\textsuperscript{22} make it possible to precisely determine ratios of
acidity constants. The method involves titrating a mixture of two compounds with
small aliquots of either acid or base and monitoring the changes in chemical shift upon
protonation or deprotonation. When a mixture of two acids with slightly different p$K_a$
values is titrated with base, the stronger acid will be deprotonated first. Thus, the
chemical shifts of the more acidic compound will change earlier than those of the less
acidic compound. To achieve a precise measurement, it is important to choose
reporter nuclei that undergo a sufficiently large change in chemical shift upon
ionization and for which the chemical shift changes for both compounds can be
observed from start to finish during the titration.
Equation 1-8 describes the equilibrium for the proton exchange between two acids, $A_1$ and $A_2$. The protonated and deprotonated forms of each acid are denoted as $AH$ and $A^-$, respectively. The ratio of acidity constants, $K_a^{A_1}/K_a^{A_2}$, of these two acids, along with the equilibrium constant, $K$, for the exchange, is given by equation 1-9. Since proton exchange is rapid on the NMR time scale$^{22}$, for each acid the chemical shift of a reporter nucleus as observed during NMR analysis is the weighted average of the chemical shifts of the resonances for the protonated and deprotonated species. Equation 1-10 relates how the observed chemical shift of acid $A_1$, $\delta_{A_1}$, depends on the extent to which the sample is protonated or deprotonated. The chemical shifts of the protonated and deprotonated species are $\delta_{A_{1H}}$ and $\delta_{A_{1-}}$, respectively. A similar equation can also be written for acid $A_2$.

$$A_1H + A_2^- \rightleftharpoons A_1^- + A_2H \quad 1-8$$

$$K = \frac{K_a^{A_1}}{K_a^{A_2}} = \frac{[A_1^-][A_2H]}{[A_1H][A_2^-]} \quad 1-9$$

$$\delta_{A_1} = \frac{\delta_{A_{1H}}[A_1^-] + \delta_{A_{1H}}[A_1H]}{[A_1^-]+[A_1H]} \quad 1-10$$

The relationship between $K$ and the chemical shifts of the two acids is expressed in equation 1-11,$^{22}$ which can be obtained by solving eq. 1-10 for $[A_1H]$ (and the corresponding equation for acid $A_2$ for $[A_2H]$) and then substituting those results for $[A_1H]$ and $[A_2H]$ into eq. 1-9. Equation 1-11 states that a plot of $(\delta_{A_2} - \delta_{A^-})(\delta_{A_{1H}} - \delta_{A_{1H}})$ vs. $(\delta_{A_1} - \delta_{A_1^-})(\delta_{A_{2H}} - \delta_{A_2})$ is a straight line with slope $K$ and intercept zero.
\[
(\delta_{A_2} - \delta_{A_2^-}) (\delta_{A_1H} - \delta_{A_1}) = K (\delta_{A_1} - \delta_{A_1^-}) (\delta_{A_2H} - \delta_{A_2})
\]

An equation for the IE, \( K_a^{H}/K_a^{D} \), can be obtained using similar logic and algebra, and has been used in the past to measure secondary isotope effects with great precision.\(^{10,11,13} \) The ratio of acidity constants, \( K_a^{H}/K_a^{D} \), and the observed chemical shift of the protio isotopologue, \( \delta_H \), are given in equations 1-12 and 1-13 (plus an equation similar to equation 1-13 for the chemical shift of the deutero isotopologue, \( \delta_D \)), and the relationship between \( K \) and the chemical shifts of the isotopologues is given in equation 1-14. In these equations the concentrations of the protonated and deprotonated species are \([H_o]\) and \([H_-]\), respectively, and the chemical shifts of the protonated and deprotonated species are \( \delta_{H_o} \) and \( \delta_{H_-} \), respectively, or \([D_o]\), \([D_-]\), \( \delta_{D_o} \), and \( \delta_{D_-} \) for the deuterium-containing isotopologues. Thus the IE, \( K_a^{H}/K_a^{D} \), can be measured as the slope of the straight-line plot of eq 1-14.

\[
K = \frac{K_a^{H}}{K_a^{D}} = \frac{[H_-][D_o]}{[H_o][D_-]}
\]

\[
\delta_H = \frac{\delta_{H_o} [H_-] + \delta_{H_o} [H_o]}{[H_-] + [H_o]}
\]

\[
(\delta_{D} - \delta_{D^-}) (\delta_{H_o} - \delta_{H_-}) = K (\delta_{H} - \delta_{H^-}) (\delta_{D_o} - \delta_{D_-})
\]

In this work, to simplify the task of obtaining \( K \) at many different temperatures, only three titration points were used, instead of the multi-point titration. Carrying out a full titration involves adding small aliquots of base repeatedly into the
NMR sample. Typically the sample must be ejected from the probe to make each addition or added with a continual addition titration apparatus.\textsuperscript{30} For titrations that are performed at various temperatures without the titration apparatus the sample and probe temperatures must be re-equilibrated after each addition when the sample is re-injected into the magnet. This process is very time consuming.

Equation 1-15 relates the IE, $K$, to $\Delta \Delta G^\circ$, which is a negative number that indicates how much more favorable the deprotonation of the H-substituted acid is than the deuterio ($\Delta \Delta G^\circ = \Delta G^\circ_H - \Delta G^\circ_D$). Equation 1-16 relates $\Delta \Delta G^\circ$ to $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$. According to equation 1-17 a plot of $\ln K$ versus inverse temperature has a slope equal to $-\Delta \Delta H^\circ/R$ and an intercept equal to $\Delta \Delta S^\circ/R$. According to the above discussion, when $K_a^H/K_a^D > 1$, $\Delta \Delta H^\circ$ is expected to be negative, owing to ZPE, whereas $\Delta \Delta S^\circ$ is expected to be positive if there is any inductive contribution to the IE.

\begin{equation}
\Delta \Delta G^\circ = -RT \ln \frac{K_a^H}{K_a^D}
\end{equation}

\begin{equation}
\Delta \Delta G^\circ = \Delta \Delta H^\circ - T \Delta \Delta S^\circ
\end{equation}

\begin{equation}
\ln K = -\frac{\Delta \Delta H^\circ}{RT} + \frac{\Delta \Delta S^\circ}{R}
\end{equation}

The three points used to determine $K$ according to eq. 1-14 could be obtained from the spectra of only three samples: fully protonated, 50% neutralized, and fully deprotonated. NMR analysis of each of these samples was performed across a range of temperatures, from -2 to 70 °C. Two of the points on the plot, corresponding to the
data obtained from the fully protonated and fully deprotonated samples, lie at the origin. The third point on the plot was obtained from the chemical shifts of a 50% neutralized sample. The values of $K$ obtained from these 3-point plots at different temperatures could be then substituted into equation 1-17. $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$ could be obtained from the slope and intercept of a plot of $\ln K$ versus $1/T$.

In summary, to further our understanding of the origin of the secondary deuterium IE on the acidity of carboxylic acids and phenols, and to test for a contribution from an inductive effect, we propose to determine the contributions of enthalpy and entropy to the IE from its temperature dependence. A three-point NMR titration was performed on a mixture of protio and deutero isotopologues of formic and acetic acids and 3,5-difluorophenol to find the IE, which is the ratio of the acidity constants, $K_a^H/K_a^D$. These titrations were performed at various temperatures from -2 °C and 70 °C to measure the temperature dependence of the IE, from which the enthalpy and entropy contributions were evaluated. An origin in ZPEs would be manifested in enthalpy, while any contribution from an inductive effect would be manifested in entropy.
Experimental

Materials

Formic acid, formic-$d$ acid, 3,5-difluorophenol, malonic-$d_2$ acid-$d_2$, D$_2$O, and all other reagents were obtained from commercial suppliers and used as received. The 3,5-difluorophenol-2,4,6-$d_3$ sample used in this work was previously synthesized by the Perrin lab. A mixture of acetic-$d_n$ acid isotopologues ($n = 0, 1, 2, 3$) was prepared according to previously reported methods.

Synthesis of a mixture of acetic-$d_n$ acid isotopologues ($n = 0, 1, 2, 3$)

Malonic-$d_2$ acid-$d_2$ (2.7g, 25mmol = 100 mmolD total) was melted at 140°C. At least 100 μL of water was then added under stirring. This mixture was then heated at 150 °C for 15 min. The product, a colorless liquid, was purified by fractional distillation at atmospheric pressure, b.p. 117-119 °C (lit. 117.9 °C). The $^1$H NMR spectrum (500 MHz, D$_2$O) showed peaks at 2.08 ppm (s, CH$_3$), 2.07 ppm (t, CDH$_2$), 2.06 ppm (qn, CD$_2$H). The product also contained acetic-$d_3$ acid, whose methyl group is invisible to $^1$H NMR. The $^1$H NMR peak integrations are in the ratio 7.3%:40.1%:52.6%, corresponding to acetic acid: acetic-$d$ acid: acetic-$d_2$ acid in molar ratio 1.0:8.3:21.6.

Synthesis of 3,5-difluorophenol-2,4,6-$d_3$

The Perrin Lab previously synthesized the material used. The choice of conditions was guided by a kinetic study of the acidity dependence of hydrogen exchange in 4-chlorophenol. A mixture of 3,5-difluorophenol (0.26g, 2mmol) and
60% D$_2$SO$_4$ in D$_2$O (1.0g, 6mmol) was heated under N$_2$ in an oil bath at 75°C with stirring. $^1$H and $^{19}$F NMR spectra were obtained every hour to monitor the exchange. After 6 hours the mixture was dropped slowly onto ice (2g) and extracted three times with diethyl ether (10mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under reduced pressure to yield 0.24g (92%) of product, whose $^{19}$F NMR showed two peaks at δ -114.3 and -114.6, in the ratio of 20:80. The mixture was again exchanged with 60% D$_2$SO$_4$ (1.0g, 6mmol) and treated as above. The white solid obtained was dried under vacuum overnight. mp. 46-49° (lit$^{33}$ 49.5-52.5°). $^{19}$F NMR indicated 92% 3,5-difluorophenol-2,4,6-$d_3$ δ -114.6 (s).

Sample Preparation

Three samples were prepared for each acid studied: fully protonated, fully deprotonated, and half neutralized. The samples were prepared at room temperature. For each sample the chemical shifts at all temperatures were measured on the same solution. To make these samples, stock solutions of the acids were first prepared by dissolving the mixture of isotopologues of each acid and the internal standard in D$_2$O. Proton chemical shifts were referenced to internal 1,4–dioxane. Carbon and fluorine chemical shifts were referenced to internal N,N-dimethylformamide and sodium tetrafluoroborate, respectively. The concentrations of the formic acid samples were approximately 2M (1:20 formic: formic-$d$). The concentrations of the 3,5-difluorophenol samples were approximately 0.01M (1:2 3,5-difluorophenol: 3,5-difluorophenol-2,4,6-$d_3$), and the acetic acid samples were approximately 0.05M (1:30 acetic acid: (acetic-$d$ acid+acetic-$d_2$)). The acetic acid sample was actually a mixture
of acetic, acetic-$d$, acetic-$d_2$, and acetic-$d_3$ acid. The concentration of acetic-$d_3$ acid is $>50\%$, as explained in the synthetic procedure above, but this does not interfere with our measurements because it is invisible to $^1$H NMR. The fully protonated, fully deprotonated, and half neutralized solutions for NMR analysis were then made from the stock solutions, as described below.

The fully protonated samples were prepared for each acid by adding the appropriate amount of a stock solution of the acid to an NMR tube. An initial spectrum of the sample was taken, and, to ensure complete protonation, 2 µL aliquots of DCl in D$_2$O were added to the sample NMR tubes until no peak movement was observed upon further addition. The concentration of DCl added to the acetic acid and 3,5-difluorophenol samples was 0.1 M and for the more concentrated formic acid samples 1 M DCl was used.

Each fully deprotonated sample was prepared by adding fresh stock solution to an NMR tube, followed by an amount of NaOD in D$_2$O, calculated as sufficient to fully deprotonate the known amount of total acid in the tube. To ensure complete deprotonation, smaller amounts of NaOD were then added until no peak movement in the NMR spectrum was observed upon further addition of base. The concentrations of NaOD used to prepare the formic acid, acetic acid, and the 3,5-difluorophenol samples were 14.8, 1, 0.25 M, respectively.

Before considering the method used to prepare the half-neutralized samples, it should be noted that due to the isotope effect on acidity, both isotopologues cannot be exactly 50%-deprotonated at the same time. Instead, the half-neutralized samples
were prepared so that the total solution was half-neutralized. At this point, the half-neutralization point, the total concentration of the protonated species ([H$_o$] + [D$_o$]) is equal to the total concentration of the deprotonated species ([H$_-$] + [D$_-$]), as given by equation 1-18. When the solution is exactly half-neutralized, the H-isotopologue is slightly more than 50% deprotonated and the D-isotopologue is slightly less than 50% deprotonated. Equations 1-19 and 1-20 give the total concentrations of both isotopologues. Equation 1-21 relates the concentrations of all species to the ratio of acidity constants, $K_a^H / K_a^D$.

$$[H_o] + [D_o] = [H_-] + [D_-]$$  \hspace{1cm} 1-18

$$[H_o] + [H_-] = [H]$$  \hspace{1cm} 1-19

$$[D_o] + [D_-] = [D]$$  \hspace{1cm} 1-20

$$K = \frac{K_a^H}{K_a^D} = \frac{[H_-][D_o]}{[H_o][D_-]}$$  \hspace{1cm} 1-21

The concentrations of all species in the solution at the half-neutralization point were obtained from equations 1-18, 1-19, 1-20, and 1-21 by finding the values of [H$_-$], [H$_o$], [D$_-$], and [D$_o$] that satisfy all four equations. Having four equations 1-18, 1-19, 1-20, and 1-21 and four unknowns [H$_-$], [H$_o$], [D$_-$], and [D$_o$] makes it possible to solve for all of the concentrations, most easily by using the Solver routine in an Excel spreadsheet. The Solver was used to obtain the concentrations of [H$_-$] and [D$_-$] that satisfy eq. 1-18, where the values of [H$_o$] and [D$_o$] were obtained from eqs. 1-19, and 1-20. Additionally, a constraint was applied to fix the ratio of acidity constants, eq. 1-
21, at the value determined experimentally in previous experiments at room temperature. The approximate values of the total concentrations, [H] and [D], are fixed by the preparation of the stock solutions, as given in the beginning of this section. These values do not need to be known exactly as we are not looking for exact concentrations of all the species, but only their relative concentrations. Next, from the values of [H₂], [H₂O], [D₂], and [D₂O], the chemical shifts at half-neutralization of the protio, δ_H_half, and deutero, δ_D_half, isotopologues can be found. The values of δ_H_half and δ_D_half can be found by entering the values of [H₂], [H₂O], [D₂], and [D₂O] at the half-neutralization point obtained by Solver into eq. 1-13.

Accordingly, the half neutralized samples can then be prepared for each acid by adding the appropriate amount of fresh stock solution of each acid to an NMR tube and then adding an appropriate amount of base until the chemical shifts of both isotopologues move as close as possible to the above calculated values of δ_H_half and δ_D_half. This method is more reliable than trying to add an amount of base to match the stoichiometry. The chemical shifts of the half neutralized samples, prepared as described here are denoted as δ_H and δ_D.

It should also be noted that the chemical shifts at half-neutralization do not lead to a maximum value of the x-coordinate, x (eq. 1-22), on the three point plot from which K is determined, eq. 1-23. The maximum value of the x-coordinate is important because it corresponds to the position, on the three-point plot, where the non-zero point extends the furthest in the x and y directions. This is where the error in the slope, K, is the smallest, as will be shown below. We call this the optimum
neutralization point. The chemical shifts of the H and D isotopologues at optimum neutralization are designated as $\delta_{\text{H opt}}$ and $\delta_{\text{D opt}}$, respectively. The values of $\delta_{\text{H opt}}$ and $\delta_{\text{D opt}}$, and the concentrations of all species in the mixture at optimum neutralization were calculated using another iterative method. Instead of solving for the concentrations $[\text{H}].$ and $[\text{D}].$ so that the total solution is exactly half neutralized, the concentrations giving the maximum value of $x$, eq. 1-22, were found using Solver. As stated above, the experimental samples were prepared so that the chemical shifts of the experimental sample moved as close as possible to the values of $\delta_{\text{H half}}$ and $\delta_{\text{D half}}$ rather than to $\delta_{\text{H opt}}$ and $\delta_{\text{D opt}}$. The implications of this method of sample preparation on the accuracy of our results will be discussed in detail below and in the ‘Results’ section.

$$x = (\delta_{\text{D}} - \delta) (\delta_H - \delta_{H^-})$$  \hspace{1cm} 1-22

$$ (\delta_D - \delta_{D^-})(\delta_{H^0} - \delta_H) = K (\delta_{H} - \delta_{H^-})(\delta_{D^0} - \delta_{D})$$  \hspace{1cm} 1-23

The starting (fully protonated, $\delta_{\text{H0}}$ and $\delta_{\text{D0}}$), experimental half neutralized ($\delta_{\text{H and D}}$), and ending (fully deprotonated, $\delta_{\text{H-}}$ and $\delta_{\text{D-}}$) chemical shifts at 22.9 °C are listed in Table 1-1. For all acids the calculated chemical shifts at half-neutralization, and at optimum neutralization, along with the experimentally obtained chemical shifts, repeated for comparison, are listed in Table 1-2. There are two sets of data listed for 3,5-difluorophenol. One sample was prepared so that it is relatively close to optimum neutralization, DFP-$d_3$, and another that deviates from optimum neutralization by about 15% and is 65% neutralized, DFP-$d_3 (65\%)$. This latter sample was prepared in order to test experimentally the effect of inexact neutralization.
Table 1-1. The starting, experimental half neutralized, and ending chemical shifts in Hz at 22.9 °C.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$\delta_{H_{\text{a}}}$</th>
<th>$\delta_{D_{\text{a}}}$</th>
<th>$\delta_{H}$</th>
<th>$\delta_{D}$</th>
<th>$\delta_{H_{\text{e}}}$</th>
<th>$\delta_{D_{\text{e}}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-$d$</td>
<td>20913</td>
<td>20890.1</td>
<td>21264.9</td>
<td>21232.4</td>
<td>21606.4</td>
<td>21587.8</td>
</tr>
<tr>
<td>Acetic-$d_1$</td>
<td>1040.4</td>
<td>1034.2</td>
<td>995.4</td>
<td>989.2</td>
<td>952.1</td>
<td>945.4</td>
</tr>
<tr>
<td>Acetic-$d_2$</td>
<td>1040.4</td>
<td>1028</td>
<td>995.4</td>
<td>982.9</td>
<td>952.1</td>
<td>938.6</td>
</tr>
<tr>
<td>DFP-$d_3$</td>
<td>-53643.9</td>
<td>-53925.3</td>
<td>-54308.6</td>
<td>-54575.3</td>
<td>-54953.2</td>
<td>-55233.3</td>
</tr>
<tr>
<td>DFP-$d_3$ $(65%)$</td>
<td>-53643.9</td>
<td>-53925.3</td>
<td>-54305.8</td>
<td>-54572.2</td>
<td>-54953.2</td>
<td>-55233.3</td>
</tr>
</tbody>
</table>

Table 1-2. The half ($\delta_{\text{half.}}$), optimum ($\delta_{\text{opt.}}$), and experimental ($\delta_{\text{H/D}}$) chemical shifts for the half neutralized samples, in Hz at 22.9 °C.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$\delta_{H_{\text{half.}}}$</th>
<th>$\delta_{D_{\text{half.}}}$</th>
<th>$\delta_{H_{\text{opt.}}}$</th>
<th>$\delta_{D_{\text{opt.}}}$</th>
<th>$\delta_{H}$</th>
<th>$\delta_{D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-$d$</td>
<td>21271.1</td>
<td>21238.3</td>
<td>21265.7</td>
<td>21232.9</td>
<td>21264.9</td>
<td>21232.4</td>
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<tr>
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<td>989.847</td>
<td>996.027</td>
<td>989.855</td>
<td>995.4</td>
<td>989.2</td>
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<tr>
<td>Acetic-$d_2$</td>
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<td>983.349</td>
<td>995.786</td>
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<td>995.4</td>
<td>982.9</td>
</tr>
<tr>
<td>DFP-$d_3$</td>
<td>-54308.1</td>
<td>-54574.5</td>
<td>-54305.8</td>
<td>-54572.2</td>
<td>-54308.6</td>
<td>-54575.3</td>
</tr>
<tr>
<td>DFP-$d_3$ $(65%)$</td>
<td>-54308.1</td>
<td>-54574.5</td>
<td>-54305.8</td>
<td>-54572.2</td>
<td>-54360.8</td>
<td>-54627.6</td>
</tr>
</tbody>
</table>

Table 1-3 contains the $[H_{a}]/[H_{e}]$ and $[D_{a}]/[D_{e}]$ ratios calculated at half and optimum neutralization and also the ratios attained in the experimental samples. The $[H_{a}]/[H_{\text{half.}}]$ and $[D_{a}]/[D_{\text{half.}}]$ ratios at half-neutralization and the $[H_{a}]/[H_{\text{opt.}}]$ and $[D_{a}]/[D_{\text{opt.}}]$ ratios at optimum neutralization were calculated using the concentrations of the protonated and deprotonated forms of the isotopologues determined by the iterative methods described above. The $[H_{a}]/[H_{\text{exp.}}]$ and $[D_{a}]/[D_{\text{exp.}}]$ ratios of the experimental neutralization samples were calculated from eq. 1-24\textsuperscript{34} using the chemical shifts observed. As can be seen from Table 1-3 the discrepancies between
the values of \([H_o]/[H_-]\)\text{half}, \([H_o]/[H_-]\)\text{opt}, and \([H_o]/[H_-]\)\text{exp} and therefore the deviations of the experimental sample from half-neutralization or from optimum neutralization are very small. A more detailed error analysis showing that these deviations do not significantly affect the experimental results will be presented in the ‘Results’ section.

\[
\frac{[H_-]}{[H_o]} = \frac{(\delta_H - \delta_{H^-})}{(\delta_{H^+} - \delta_H)}
\]

1-24

**Table 1-3.** Ratios of protonated to deprotonated acid expected at half and optimum neutralization and the ratios for the experimental half neutralized samples, at 22.9 °C.

<table>
<thead>
<tr>
<th>Acid</th>
<th>([H_o]/[H_-])</th>
<th>([D_o]/[D_-])</th>
<th>([H_o]/[H_-])</th>
<th>([D_o]/[D_-])</th>
<th>([H_o]/[H_-])</th>
<th>([D_o]/[D_-])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>half</td>
<td>half</td>
<td>opt</td>
<td>opt</td>
<td>exp</td>
<td>exp</td>
</tr>
<tr>
<td>Formic-d</td>
<td>0.9363</td>
<td>1.0033</td>
<td>0.9660</td>
<td>1.0351</td>
<td>0.9702</td>
<td>1.0382</td>
</tr>
<tr>
<td>Acetic-d</td>
<td>0.9904</td>
<td>1.0011</td>
<td>0.9907</td>
<td>1.0015</td>
<td>0.963</td>
<td>0.9734</td>
</tr>
<tr>
<td>Acetic-d</td>
<td>0.9800</td>
<td>1.0010</td>
<td>0.9800</td>
<td>1.0010</td>
<td>0.963</td>
<td>0.9832</td>
</tr>
<tr>
<td>DFP-d3</td>
<td>0.9711</td>
<td>1.0148</td>
<td>0.9781</td>
<td>1.0220</td>
<td>0.9697</td>
<td>1.0123</td>
</tr>
<tr>
<td>DFP-d3</td>
<td>0.9711</td>
<td>1.0148</td>
<td>0.9781</td>
<td>1.0220</td>
<td>0.8264</td>
<td>0.8625</td>
</tr>
</tbody>
</table>

Finally, the values of \(K\), eq. 1-12, were obtained from NMR chemical shifts in samples with different extents of protonation, starting with the fully protonated, then the half neutralized, and finally the fully deprotonated sample. These changes in chemical shifts upon deprotonation were analyzed as three-point plots, eq. 1-14, whose slope is equal to \(K\). Individual plots were made for each sample at each temperature point, and the values of \(K\) were obtained at 8-9 temperatures between -2 °C and 70 °C. The values of \(\ln K\) were then plotted versus \(1/T\), according to equation 1-17, and \(\Delta\Delta H^\circ\) and \(\Delta\Delta S^\circ\) were obtained from the slope and intercept of these plots, respectively.
NMR Spectroscopy

All spectra were recorded on a JEOL ECA 500-MHz spectrometer. $^1$H, $^{13}$C, and $^{19}$F NMR were used to record the acetic acid, formic acid, and 3,5-difluorophenol sample spectra, respectively. For the formic acid samples the reporter nucleus was the carboxyl carbon. In acetic acid the reporter nuclei were the $\alpha$-protons. The reporter nuclei in 3,5-difluorophenol were the two fluorine atoms.

The spectral window was reduced to 39 kHz (65,536 points) for $^{13}$C, 29 kHz (262,144 points) for $^{19}$F, and 2.5 kHz (131,072 points) for $^1$H. The data were zero-filled to increase digital resolution. The chemical shifts of the internal reference standards 1,4-dioxane, $N,N$-dimethylformamide, and sodium tetrafluoroborate are 3.75 ppm,$^{46}$ 165.53 ppm,$^{46}$ and -154 ppm,$^{47,10}$ respectively. Spectra were recorded at 8-9 temperatures between -2 °C and 70 °C, and the temperature was calibrated with 80% ethylene glycol in 20% dimethyl sulfoxide (DMSO).$^{35}$ WALTZ $^1$H decoupling was applied during the acquisition of the fully protonated formic acid and fully deprotonated formate $^{13}$C spectra. At each temperature the irradiation offset, which is the $^1$H irradiation frequency, was adjusted to produce the best spectrum. It was found to vary from 5.0 to 6.5 ppm relative to tetramethylsilane. The half neutralized formic acid sample was not decoupled because the CH singlet and the CD triplet overlap, making it difficult to obtain an accurate value for the peak position of the CH acid. Instead the value for the chemical shift of the CD acid was obtained from the position of the center peak of the CD triplet and the value for the chemical shift of the CH acid.
was obtained by taking the average position of the doublet in the undecoupled spectrum. The chemical shift of the amide carbon of the internal reference, \( N, N \)-dimethylformamide, was also evaluated in this way.

High salt concentrations in these samples led to poorly shimmed or split peaks and made it difficult to determine accurate peak positions in some spectra, especially at extreme temperature points. For example, the \( ^{19}F \) peaks in the spectra of some 3,5-difluorophenol samples were symmetric, but split. The chemical shift of each peak was taken as the average of the two frequencies, which were found at the half-height of the peak. The \( ^{1}H \) peaks of the acetic acid spectra, on the other hand, were not symmetric, and also overlapped, so it was not reliable to determine the peak positions by obtaining the midpoint of the two peak frequencies at half-height. For the acetic acid samples a 3 mm Shigemi tube (no. BMS-003, Shigemi Inc., Allison Park PA) whose susceptibility was matched for D2O, was used to reduce the sample volume to 150 \( \mu \)L, and thus the amount of salt interfering with the shimming. The Shigemi tube allowed us to achieve adequately shimmed peaks and accurate peak positions. The 3,5-difluorophenol and formic acid samples were analyzed in 3mm NMR tubes. The volume of solution added was about 300 \( \mu \)L for each 3 mm NMR tube, and 150 \( \mu \)L for the Shigemi tube. All data were processed using the JEOL Delta Software.
Ethylene Glycol Calibration Curve

The temperature was calibrated with 80 % ethylene glycol – 20 % DMSO.$^{36}$ This was done to compare the temperature set on the JEOL temperature controller with the actual temperature of the sample inside the probe. The actual temperature was determined by recording the $^1$H NMR chemical shift difference between the OH and CH$_2$ groups in ethylene glycol, $\Delta$. At room temperature the chemical shift of the CH$_2$ group is around 3.4 ppm, and the OH group around 4.9 ppm. As temperature increases, the amount of OH hydrogen bonding decreases, the OH proton becomes more shielded, and its resonance moves upfield toward the CH$_2$ peak. Because there is an adequately linear relationship between temperature and $\Delta$, the separation between the OH and CH$_2$ resonances, the actual temperature could be found from equation 1-25$^{36}$, which is reliable from about 25 to 107 °C. From temperature measurements between 25 and 85 °C a calibration curve of ‘actual temperature’ vs. ‘set temperature’ was made. The actual temperatures below 25 °C were then extrapolated from this graph. Our temperature calibration curve (Figure 1-9) was constructed using data (Table 1-4) acquired in duplicate.

$$T(\text{°K}) = (4.218 - \Delta)/0.009132$$  

1-25
Table 1-4. Duplicate temperature calibrations with 80 % ethylene glycol – 20 % DMSO, based on difference between OH and CH chemical shifts.

<table>
<thead>
<tr>
<th>T Set (°C)</th>
<th>Δ = δ_{OH} - δ_{CH3} (ppm)</th>
<th>Actual T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1.518</td>
<td>22.6</td>
</tr>
<tr>
<td>35</td>
<td>1.432</td>
<td>32.0</td>
</tr>
<tr>
<td>45</td>
<td>1.344</td>
<td>41.6</td>
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<tr>
<td>55</td>
<td>1.259</td>
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</tr>
<tr>
<td>85</td>
<td>1.002</td>
<td>79.0</td>
</tr>
</tbody>
</table>

Figure 1-9. Temperature calibration curve obtained with 80 % ethylene glycol – 20 % DMSO.

\[ y = 0.9335x - 0.4282 \]
\[ R^2 = 0.99987 \]
Results

Isotope Effects on the Acidities of Carboxylic Acids and Phenols

The chemical shifts for all compounds at each of the temperatures can be found in Tables 1-5, 1-6, 1-7, 1-8, and 1-9. For each acid mixture, chemical-shift changes upon deprotonation were observed from spectra of only three samples, starting with the fully protonated, then the experimental half neutralized, and finally the fully deprotonated. The chemical shifts for the fully protonated and fully deprotonated samples agree with those reported earlier. The data in the tables below reveal that, as reported previously, the chemical shifts of acetic acid and 3,5-difluorophenol move upfield upon deprotonation. The $^{13}$C signal of formic acid moves downfield upon deprotonation.

Table 1-5. Chemical shifts (Hz) of formic acid isotopologues.

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>$\delta_{H_0}$</th>
<th>$\delta_{D_0}$</th>
<th>$\delta_{H}$</th>
<th>$\delta_{D}$</th>
<th>$\delta_{H-}$</th>
<th>$\delta_{D-}$</th>
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<td>21245.0</td>
<td>21616.8</td>
<td>21597.8</td>
</tr>
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<td>20863.7</td>
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</table>
Table 1-6. Chemical shifts (Hz) of acetic acid isotopologues (acetic and acetic-$d_1$).

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>$\delta_{\text{Ho}}$</th>
<th>$\delta_{\text{Do}}$</th>
<th>$\delta_{\text{H}}$</th>
<th>$\delta_{\text{D}}$</th>
<th>$\delta_{\text{H-}}$</th>
<th>$\delta_{\text{D-}}$</th>
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<td>987.5</td>
<td>952.8</td>
<td>946.3</td>
</tr>
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<td>988.4</td>
<td>952.4</td>
<td>945.8</td>
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<td>945.1</td>
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<td>1038.0</td>
<td>997.2</td>
<td>990.9</td>
<td>951.7</td>
<td>944.8</td>
</tr>
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<td>991.7</td>
<td>951.5</td>
<td>944.6</td>
</tr>
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<td>992.5</td>
<td>951.4</td>
<td>944.4</td>
</tr>
</tbody>
</table>

Table 1-7. Chemical shifts (Hz) of acetic acid isotopologues (acetic and acetic-$d_2$).

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>$\delta_{\text{Ho}}$</th>
<th>$\delta_{\text{Do}}$</th>
<th>$\delta_{\text{H}}$</th>
<th>$\delta_{\text{D}}$</th>
<th>$\delta_{\text{H-}}$</th>
<th>$\delta_{\text{D-}}$</th>
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Table 1-8. Chemical shifts (Hz) of 3,5-difluorophenol isotopologues.

<table>
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<th>Temp. (°C)</th>
<th>δ_Ho</th>
<th>δ_Do</th>
<th>δ_H</th>
<th>δ_D</th>
<th>δ_H-</th>
<th>δ_D-</th>
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Table 1-9. Chemical shifts (Hz) of 3,5-difluorophenol (65%) isotopologues.

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>δ_Ho</th>
<th>δ_Do</th>
<th>δ_H</th>
<th>δ_D</th>
<th>δ_H-</th>
<th>δ_D-</th>
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<td>-54352.6</td>
<td>-54604.2</td>
<td>-55003.0</td>
<td>-55267.5</td>
</tr>
</tbody>
</table>

As can be seen from Tables 1-5, 1-6, 1-7, 1-8, and 1-9 and also Table 1-1, the change in chemical shift of the carboxyl carbon $^{13}$C signal of formic acid upon deprotonation is around 700 Hz (5.6 ppm). In acetic acid the shift of the $^1$H signal of the reporter $\alpha$-protons upon deprotonation is 90 Hz (0.2 ppm). Even though this change is much smaller than that of the $^{13}$C signal, it still allowed for an adequate
measurement of the IE, as shown in the error analysis below. The most remote reporter nuclei, the two fluorine atoms in 3,5-difluorophenol, are more sensitive to the state of protonation than both the $^1$H and $^{13}$C signals, because the shift of the $^{19}$F signal upon deprotonation is about 1300 Hz (2.8 ppm).

For each acid the $K_a^H/K_a^D$ values, defined in equation 1-12, were determined from changes in NMR chemical shifts as the sample was deprotonated. These changes in chemical shifts, observed from spectra of the three samples, were analyzed as a three-point plot according to equation 1-14, and $K_a^H/K_a^D$ was determined for each acid at eight or nine temperature points between -2 and 70 °C. Figure 1-10 is an example of such a three-point plot.

![Figure 1-10](image)

**Figure 1-10.** Linearized three-point plot (eq. 1-14) for formic acid isotopologues at 22.9 °C.
Two of the points on these three-point plots are at the origin whereas the third is a pair of non-zero values calculated from the chemical shifts obtained from the experimental half neutralized sample. Because two of the three points are necessarily at the origin the values of the correlation coefficient, r, for all plots are exactly equal to 1. Table 1-10 lists $K_a^H/K_a^D$ values at different temperatures for all acids studied, along with the errors in $K_a^H/K_a^D$, which are discussed below in more detail. The isotope effect for acetic-$d_2$ acid is double that for acetic-$d_1$ acid at all temperatures. Table 1-11 shows that the $K_a^H/K_a^D$ values obtained from our three-point plots and interpolated to 18 °C agree at the 95% confidence level with those previously reported.10

Table 1-10. Temperature dependence of $K_a^H/K_a^D$ for formic acid, acetic acid, and difluorophenol isotopologues.

<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>$K_a^H/K_a^D$ Formic-$d$</th>
<th>$K_a^H/K_a^D$ Acetic-$d_1$</th>
<th>$K_a^H/K_a^D$ Acetic-$d_2$</th>
<th>$K_a^H/K_a^D$ DFP-$d_3$</th>
<th>$K_a^H/K_a^D$ DFP-$d_3$ (65%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.3</td>
<td>1.0766</td>
<td>1.01177</td>
<td>1.02353</td>
<td>1.0489</td>
<td>1.0495</td>
</tr>
<tr>
<td>4.2</td>
<td>1.0754</td>
<td>1.01148</td>
<td>1.02250</td>
<td>1.0471</td>
<td>1.0481</td>
</tr>
<tr>
<td>13.6</td>
<td>1.0726</td>
<td>1.01110</td>
<td>1.02189</td>
<td>1.0458</td>
<td>1.0459</td>
</tr>
<tr>
<td>22.9</td>
<td>1.0701</td>
<td>1.01078</td>
<td>1.02098</td>
<td>1.0439</td>
<td>1.0436</td>
</tr>
<tr>
<td>32.2</td>
<td>1.0679</td>
<td>1.01023</td>
<td>1.02043</td>
<td>1.0428</td>
<td>1.0419</td>
</tr>
<tr>
<td>41.6</td>
<td>1.0672</td>
<td>1.00998</td>
<td>1.01968</td>
<td>1.0412</td>
<td>1.0417</td>
</tr>
<tr>
<td>50.9</td>
<td>1.0647</td>
<td>1.00925</td>
<td>1.01847</td>
<td>1.0403</td>
<td>1.0392</td>
</tr>
<tr>
<td>60.3</td>
<td>1.0621</td>
<td>1.00905</td>
<td>1.01796</td>
<td>1.0392</td>
<td>1.0376</td>
</tr>
<tr>
<td>69.6</td>
<td>1.0615</td>
<td></td>
<td></td>
<td>1.0365</td>
<td>1.0387</td>
</tr>
</tbody>
</table>

$a \pm 0.0005. \ b \pm 0.0001. \ c \pm 0.0002. \ d \pm 0.0005. \ e \pm 0.0008.$
Table 1-11. $K_a^H/K_a^D$ values at 18 °C.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$K_a^H/K_a^D$</th>
<th>±</th>
<th>$K_a^H/K_a^D$</th>
<th>±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-$d$</td>
<td>1.0743</td>
<td>0.0014</td>
<td>1.0715</td>
<td>0.0005</td>
</tr>
<tr>
<td>Acetic-$d_1$</td>
<td>-</td>
<td>-</td>
<td>1.01084</td>
<td>0.0001</td>
</tr>
<tr>
<td>Acetic-$d_2$</td>
<td>1.025</td>
<td>0.003</td>
<td>1.02144</td>
<td>0.0002</td>
</tr>
<tr>
<td>DFP-$d_3$</td>
<td>1.0442</td>
<td>0.0005</td>
<td>1.0450</td>
<td>0.0005</td>
</tr>
<tr>
<td>DFP-$d_3$ (65%)</td>
<td>-</td>
<td>-</td>
<td>1.0451</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

$a$ Values determined previously.\(^{10}\)

Temperature Dependence of the Isotope Effects

$K_a^H/K_a^D$ values as determined by the above method and as tabulated in Table 1-10 were found to be temperature dependent. Figure 1-11 shows the $K_a^H/K_a^D$ values determined for each compound between -2 and 70 °C plotted vs. inverse temperature.

![Graph showing temperature dependence of isotope effects](image)

**Figure 1-11.** $K_a^H/K_a^D$ versus 1000/T in Kelvin for: (♦) formic acid isotopologues, (×) 3,5-difluorophenol isotopologues, (■) acetic and acetic-$d_2$ isotopologues, (▲) acetic and acetic-$d_1$ isotopologues.
Additionally, plotting the natural logarithm of $K_a^H/K_a^D$ vs. reciprocal temperature gives the van’t Hoff plots, eq. 1-17, which have a slope of $-\Delta H^°/R$ and an intercept of $\Delta S^°/R$. Figures 1-12, 1-13, 1-14, 1-15, and 1-16 are the van’t Hoff plots of all of the compounds studied. The slopes, standard errors of the slope, intercepts, standard errors of the intercepts, and correlation coefficients found from these plots are listed in Table 1-12. The correlation coefficients found from these plots are all $>0.99$, except for the 65% sample, which was designed to test how the accuracy of the results depends on exact neutralization.

Figure 1-12. Variable-temperature data for the relative acidities of formic acid and formic-$d$ acid.
Figure 1-13. Variable-temperature data for the relative acidities of acetic acid and acetic-$d_1$ acid.

Figure 1-14. Variable-temperature data for the relative acidities of acetic acid and acetic-$d_2$ acid.
Figure 1-15. Variable-temperature data for the relative acidities of 3,5-difluorophenol and 3,5-difluorophenol-2,4,6- $d_3$.

Figure 1-16. Variable-temperature data for the relative acidities of 3,5-difluorophenol (65%) and 3,5-difluorophenol-2,4,6- $d_3$, from the 65%-neutralized sample.
Table 1-12. Slope, standard error of the slope, intercept, standard error of the intercept, and correlation coefficient found from the van’t Hoff plots of all samples.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Slope</th>
<th>±</th>
<th>Intercept</th>
<th>±</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-(d)</td>
<td>0.0189</td>
<td>0.0006</td>
<td>0.0043</td>
<td>0.002</td>
<td>0.99622</td>
</tr>
<tr>
<td>Acetic-(d_1)</td>
<td>0.00397</td>
<td>0.00021</td>
<td>-0.0028</td>
<td>0.0007</td>
<td>0.99194</td>
</tr>
<tr>
<td>Acetic-(d_2)</td>
<td>0.00764</td>
<td>0.00032</td>
<td>-0.0050</td>
<td>0.0011</td>
<td>0.99488</td>
</tr>
<tr>
<td>DFP-(d_3)</td>
<td>0.0141</td>
<td>0.0006</td>
<td>-0.0043</td>
<td>0.002</td>
<td>0.99353</td>
</tr>
<tr>
<td>DFP-(d_3) (65%)</td>
<td>0.0147</td>
<td>0.0010</td>
<td>-0.0063</td>
<td>0.003</td>
<td>0.98285</td>
</tr>
</tbody>
</table>

\(^a\)Correlation Coefficient.

**Linearity of the van’t Hoff Plots**

The good linearity in the van’t Hoff plots, as seen in Figures 1-12, 1-13, 1-14, 1-15, and 1-16, shows that the values of \(\Delta H^\circ\) (eq. 1-6), obtained from the slopes of these plots according to eq. 1-17, do not vary with temperature. The variation of enthalpy with temperature can be described by equation 1-26\(^{37}\), where \(C^\circ_p\) is the heat capacity at constant pressure. In our case a temperature dependence of \(\Delta H^\circ\) would be caused by a contribution from \(\Delta C^\circ_p\), eq. 1-27, where the term \(\Delta C^\circ_p(H)\) is given by eq. 1-28 and \(\Delta C^\circ_p(D)\) by a similar equation. According to these equations, \(\Delta H^\circ\) would be temperature dependent if \(\Delta C^\circ_p\) for the deprotonation of the deutero isotopologue was different from the value of \(\Delta C^\circ_p\) for the deprotonation of the protio isotopologue. But as mentioned earlier, the lack of curvature in the slopes of our van’t Hoff plots indicates that \(\Delta H^\circ\) is constant over the temperature range studied and that there is no significant contribution from \(\Delta C^\circ_p\).

\[
\left(\frac{\partial H^\circ}{\partial T}\right)_p = C^\circ_p
\]  

1-26
In addition to the good linearity of the van’t Hoff plots, further evidence supporting that there is no significant contribution from $\Delta \Delta C_p^\circ$ in our experiments is presented below. We would expect translational, rotational, and electronic contributions to $\Delta \Delta C_p^\circ$ to be insignificant.$^{38}$ However, since thermal excitation of bond vibrations to higher energy levels can contribute to heat capacity for the dissociation of these acids, a vibrational contribution to heat capacity, $C_{\text{vib}}^\circ$, is possible and could lead to a temperature dependence of $\Delta \Delta H^\circ$. This possibility is examined in more detail below.

The magnitude of the vibrational contributions, to heat capacity due to the excitation of vibrational modes of the acids and their anions, would depend on the extent of excitation of the vibrational modes of each species ([H$_o$], [D$_o$], [H$_-$] and [D$_-$]), at each temperature, as given by equation 1-29.$^{39}$ Equation 1-29 relates temperature ($T$) and vibrational frequency ($\nu$) to the population of first excited state ($N_1$) relative to the population of the ground state ($N_0$), where $h$ and $k_B$ are Planck’s constant and the Boltzmann constant. According to equation 1-29, if thermal excitation of bond vibrations were to occur, it would be the greatest for the species with the lowest vibrational frequencies. The extent of excitation would also increase with temperature. For formic acid isotopologues the extent of excitation would be the greatest for the deprotonated deutero isotopologue ($\nu = 2122 \text{ cm}^{-1}$) followed by the deutero acid ($\nu = 2220 \text{ cm}^{-1}$), then followed by the deprotonated protio isotopologue ($\nu$
= 2825 cm\(^{-1}\)), and lastly the least amount of thermal excitation would occur for the protio acid \((v = 2943 \text{ cm}^{-1})\).\(^{12}\) Therefore, the contribution to \(C\text{\_vib}^0\) by the anion would be greater than that of its respective acid and also the contribution of the deutero acid and anion would be greater than that of the protio. If the extent of excitation in the temperature range of these studies is sufficient for excitation and if there is a difference between \(\Delta C\text{\_vib(H)}^0\) and \(\Delta C\text{\_vib(D)}^0\), the value of \(\Delta \Delta C\text{\_vib}^0\) \((\Delta \Delta C\text{\_vib}^0 = \Delta C\text{\_vib(H)}^0 - \Delta C\text{\_vib(D)}^0)\) would not be zero and would lead to a temperature dependence of \(\Delta \Delta H^0\).

The change in the vibrational heat capacity for the protio isotopologue, \(\Delta C\text{\_vib(H)}^0\), is defined as: \(\Delta C\text{\_vib(H)} = \Delta C\text{\_vib(H)}^0 - \Delta C\text{\_vib(Ho)}^0\) and similarly for \(\Delta C\text{\_vib(D)}^0\). The possibility of this type of contribution for our acids and an estimate for formic acid, which has the largest C-H frequency decrease upon deprotonation, is presented below.

\[
\frac{N_1}{N_0} = e^{-\frac{hv}{k_B T}} \tag{1-29}
\]

It is very difficult to pinpoint which isotope sensitive vibrations are responsible for the IEs of these acids (other than formic), and therefore difficult to say whether or not thermal excitation of low frequency vibrations contributes to the IEs.\(^{10}\) Calculations have shown, however, that for formic and acetic acids the high frequency C-H stretching vibration accounts for over half of the calculated IE, but did not give insight into which vibrations contributed to the IE in 3,5-difluorophenol.\(^{10}\) While a vibrational contribution to \(\Delta \Delta C_p^0\) from the excitation of low frequency isotope sensitive vibrations is unlikely for the compounds in our study, a contribution to the kinetic isotope effect from a \(\text{NH}_2\) wagging mode with the frequency of 289 cm\(^{-1}\) was
previously seen in the rate of rotation about the amide bond of formamide.\textsuperscript{40} Therefore, to explore hypothetically the effect of a non-zero $\Delta \Delta C_{\text{vib}}^\circ$ on our experimental results, the vibrational contribution to $\Delta \Delta H^\circ$, $\Delta \Delta H_{\text{vib}}^\circ$, was estimated from experimental formic acid frequencies\textsuperscript{12} both at -3 and 70 °C (270 and 343 °K). Even though it doesn't have low-frequency vibrations, formic acid was used for this estimate because its C-H frequency is especially sensitive to deprotonation (the C-H frequency is lowered the most upon deprotonation) and of all the acids studied here it has the largest IE.

First, the contribution to the total enthalpy from thermally excited vibrations, $H_{\text{vib}}^\circ$, was obtained from equation 1-30\textsuperscript{41}, where the vibrational temperature, $\theta_{\text{vib}}$, is given by equation 1-31\textsuperscript{41}, where $N$, $v$, $h$, and $k_B$ are Avogadro's number, the vibrational frequency, Planck's constant, and the Boltzmann constant. In our case, as will be shown later on in the Results, $E_{\text{vib}}^\circ$ in equation 1-30 is equal to $H_{\text{vib}}^\circ$. The first term in eq. 1-30, which represents the zero-point energy, can be ignored for the purpose of evaluating the contribution of thermal excitation, and the value of $H_{\text{vib}}^\circ$ can be obtained from the second term, which represents thermal excitation. The values of $\Delta H_{\text{vib}}^\circ$\textsuperscript{(H)} and $\Delta H_{\text{vib}}^\circ$\textsuperscript{(D)} were then obtained at 270 and 343 °K from equation 1-32 and the corresponding equation for the deuterated isotopologue. The values of $\Delta \Delta H_{\text{vib}}^\circ$ were obtained at 270 and 343 °K from equation 1-33.

$$E_{\text{vib}}^\circ = H_{\text{vib}}^\circ = NK_B \sum_{j=1}^{\alpha} \left( \frac{\theta_{\text{vib},j}}{2} + \frac{\theta_{\text{vib},j} e^{-\theta_{\text{vib},j}/T}}{(1 - e^{-\theta_{\text{vib},j}/T})} \right)$$  1-30
\[ \theta_{\text{vib}, j} = \frac{h \nu_j}{k_B} \]  

\[ \Delta H_{\text{vib}(H)}^\circ = H_{\text{vib}(H^-)}^\circ - H_{\text{vib}(H^\circ)}^\circ \]  

\[ \Delta \Delta H_{\text{vib}}^\circ = \Delta H_{\text{vib}(H)}^\circ - \Delta H_{\text{vib}(D)}^\circ \]

Table 1-13 lists the frequencies of the vibrations, the vibrational temperature (\(\theta_{\text{vib}}\)), \(H_{\text{vib}}^\circ\) for each frequency at 270 and 343 °K, \(\Delta H_{\text{vib}}^\circ\) for H and D both at 270 and 343 °K, and also \(\Delta \Delta H_{\text{vib}}^\circ\) at 270 and 343 °K. The data in Table 1-13 show that thermal excitation of these formic acid frequencies does not significantly contribute to \(\Delta \Delta H_{\text{vib}}^\circ\) at either 270 or 343 °K. This is because the values of \(\Delta \Delta H_{\text{vib}}^\circ\) at 270°K and \(\Delta \Delta H_{\text{vib}}^\circ\) at 343°K are -0.0278 and -0.2356 cal/mol, respectively, which (as will be presented later in the Results section and also in Table 1-15) is about half of the smallest error, 0.4 cal/mol, that we report for \(\Delta \Delta H^\circ\). These calculations justify the linearity of the van’t Hoff plot and indicate that for the reactions studied a vibrational contribution to \(\Delta \Delta H^\circ\), and therefore a contribution from \(\Delta \Delta C_{\text{vib}}^\circ\) is not significant.
Table 1-13. Contribution from experimental frequency vibrations to the vibrational heat capacity.

<table>
<thead>
<tr>
<th>v (cm(^{-1}))</th>
<th>H(_o)</th>
<th>H.</th>
<th>D(_o)</th>
<th>D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2943</td>
<td>2825</td>
<td>2220</td>
<td>2122</td>
<td></td>
</tr>
<tr>
<td>(\theta_v) (°K)</td>
<td>4225</td>
<td>4056</td>
<td>3187</td>
<td>3046</td>
</tr>
<tr>
<td>(H_{vib}^\circ) at 270°K (cal/mol)</td>
<td>0.0013</td>
<td>0.0024</td>
<td>0.0473</td>
<td>0.0761</td>
</tr>
<tr>
<td>(H_{vib}^\circ) at 343°K (cal/mol)</td>
<td>0.0375</td>
<td>0.0590</td>
<td>0.5835</td>
<td>0.8406</td>
</tr>
</tbody>
</table>

\(\Delta H_{vib}^\circ(H)\) at 270°K (cal/mol) 0.0011
\(\Delta H_{vib}^\circ(D)\) at 270°K (cal/mol) 0.0288
\(\Delta H_{vib}^\circ(H)\) at 343°K (cal/mol) 0.0215
\(\Delta H_{vib}^\circ(D)\) at 343°K (cal/mol) 0.2571
\(\Delta \Delta H_{vib}^\circ\) at 270°K (cal/mol) -0.0278
\(\Delta \Delta H_{vib}^\circ\) at 343°K (cal/mol) -0.2356

**Error Analysis of \(K_a^H/K_a^D\)**

The random error in \(K\), \(\sigma_K\), at each temperature could not be obtained from the ‘titration’ plots, which have only three points, with two of those points at the origin. Instead the error in \(K\) was obtained from the standard deviation of \(y\) in the van't Hoff plot using propagation of uncertainty. The standard error of \(y\) obtained from the van't Hoff plot is the error in \(\ln(K_a^H/K_a^D)\), \(\sigma_{\ln K}\). In this case, where \(K = e^{\ln K}\), the error in \(K\) is given by equation 1-34. These errors in \(K\) are indicated in Table 1-10.

\[
\sigma_K = K \times \sigma_{\ln K} \tag{1-34}
\]

One contributing factor to the error in \(K\) is the deviation of the non-zero point from its value at optimum neutralization. As defined earlier, when the non-zero point
is at its optimum neutralization value, it extends the farthest in the x and y directions on the plot of \((\delta_{D, -} \cdot \delta_{D, -})(\delta_{H, -} \cdot \delta_{H, -})\) versus \((\delta_{H, -} \cdot \delta_{H, -})(\delta_{D, -} \cdot \delta_{D, -})\), and the error in the slope, \(K\), is minimal. Any deviation from optimum neutralization leads to a larger error in \(K\) but not to a systematic error, because the three-point fit is valid for any three points.

This error can be evaluated from equation 1-35, which is a general equation relating the error in the slope (\(\sigma\)) to the distribution of the points on the x-axis and the standard deviation of y (\(\sigma_y\)) for those points. The value of \(\sigma_y\) could not be obtained by performing a linear regression analysis on the three-point plot. Instead, it could be obtained from equation 1-36. The values of \(x_{i, \text{exp}}\), in equation 1-36 are the value of the x-coordinate of the experimental non-zero point (\(x_{\text{exp}}\), eq. 1-37) and also the x-coordinates of the two points at the origin (which are zero). The value of \(\sigma_K\) can be obtained from eq. 1-34.

\[
\sigma = \frac{\sigma_y}{\sqrt{\sum (x_i - \bar{x})^2}} \quad 1-35
\]

\[
\sigma_K = \frac{\sigma_y}{\sqrt{\sum (x_{i, \text{exp}} - \bar{x}_{\text{exp}})^2}} \quad 1-36
\]

\[
x_{\text{exp}} = (\delta_{Do} - \delta_{D})(\delta_{H} - \delta_{H-}) \quad 1-37
\]

The errors in \(K\), when the non-zero point is at the half neutralization (\(x_{\text{half}}\), eq 1-38), optimum neutralization (\(x_{\text{opt}}\), eq 1-39), and experimental neutralization (\(x_{\text{exp}}\), eq
position, can be determined by substituting the appropriate values for \( x \) into eq. 1-35. If the values 0, \( x_{\text{half}} \) or \( x_{\text{opt.}} \), and 0 are used in place of \( x \) in eq. 1-35, the hypothetical errors in the slopes of the half neutralization (\( \sigma_{\text{half}} \)) and optimum neutralization (\( \sigma_{\text{opt.}} \)) samples are obtained, respectively. The chemical shifts needed to evaluate eqs. 1-37, 1-38, and 1-39 can be found in Tables 1-1 and 1-2. The error in \( K \) of the experimental half neutralization sample is equal to the observed error \( \sigma_K \), evaluated from eq 1-34. To compare the differences among \( \sigma_{\text{exp}} \), \( \sigma_{\text{half}} \), and \( \sigma_{\text{opt.}} \), errors are multiplied by \( 10^4 \) and reported to more decimal places. The three values can then be compared to determine how much error is introduced as a result of the deviation of the experimental sample from optimum neutralization.

\[
x_{\text{half}} = (\delta_{D_0} - \delta_{D_{\text{half}}})(\delta_{H_{\text{half}}} - \delta_{H_-})
\]

\[
x_{\text{opt.}} = (\delta_{D_0} - \delta_{D_{\text{opt.}}})(\delta_{H_{\text{opt.}}} - \delta_{H_-})
\]

Table 1-14 lists the values of the errors in \( K \) when the non-zero point is at experimental half neutralization, at the calculated half neutralization, and at optimum neutralization. As can be seen, deviation of the experimental neutralization from its optimum does not lead to a significant increase in the error. Even for the DFP-\textit{d}_3 (65\%) sample, which deviates about 15\% from optimum neutralization, the difference between \( 10^4 \sigma_{\text{exp}} \) and \( 10^4 \sigma_{\text{opt.}} \) is less than 0.5\%. Additional evidence showing that this random error does not contribute appreciably is that the experimental value of \( K \) for the DFP-\textit{d}_3 (65\%) sample, 1.0436 ± 0.0008, agrees with that for the DFP-\textit{d}_3 sample, 1.0439 ± 0.0005. The data in Table 1-14 also show that the \( 10^4 \sigma_{\text{exp}} \) is even smaller.
than $10^4 \sigma_{\text{opt.}}$ in all cases except for the acetic acid-$d_1$ and DFP-$d_3$ (65%) samples. This is most likely due to errors in the experimental chemical shifts, $\delta_{\text{D,exp}}$ and $\delta_{\text{H,exp}}$, used to obtain $x_{\text{exp}}$. We don’t expect this error to affect our analysis and in fact this suggests that the uncertainty in chemical shift is larger than the uncertainty due to deviation of the non-zero point from the optimum position on the $x$ axis. Neither of these uncertainties has a significant impact on our determination of the IE. In view of this, we conclude that the inability to adjust the experimental neutralization of these samples to their optimum is not a concern, and therefore no effort was exerted to achieve this.

**Table 1-14.** Values of $K$, experimental error in $K$ obtained from the van’t Hoff plot, and errors in $K$ obtained from the three-point plot when the non-zero point is at its experimental, half, and optimum neutralization values at 22.9 °C.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$K$</th>
<th>$\sigma_K$</th>
<th>$10^4 \sigma_{\text{exp}}$</th>
<th>$10^4 \sigma_{\text{half}}$</th>
<th>$10^4 \sigma_{\text{opt.}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-$d_1$</td>
<td>1.0701</td>
<td>0.0005</td>
<td>5.093</td>
<td>5.097</td>
<td>5.096</td>
</tr>
<tr>
<td>Acetic-$d_1$</td>
<td>1.01078</td>
<td>0.0001</td>
<td>1.3697</td>
<td>1.3694</td>
<td>1.3694</td>
</tr>
<tr>
<td>Acetic-$d_2$</td>
<td>1.02098</td>
<td>0.0002</td>
<td>2.1190</td>
<td>2.1192</td>
<td>2.1192</td>
</tr>
<tr>
<td>DFP-$d_3$</td>
<td>1.0439</td>
<td>0.0005</td>
<td>4.8495</td>
<td>4.8519</td>
<td>4.8518</td>
</tr>
<tr>
<td>DFP-$d_3$ (65%)</td>
<td>1.0436</td>
<td>0.0008</td>
<td>8.3158</td>
<td>8.2619</td>
<td>8.2618</td>
</tr>
</tbody>
</table>

**Enthalpy and Entropy Contributions to the Isotope Effect**

From the temperature dependence of $K_a^H/K_a^D$, the enthalpy and entropy contributions to the IE were then evaluated for each of the acids. These enthalpy and entropy contributions were found from a van’t Hoff plot of the natural logarithm of
$K_a^{H}/K_a^{D}$ vs. reciprocal temperature, which gives a slope of $-\Delta H^o/R$ and an intercept of $\Delta S^o/R$, eq. 1-17. The slopes, standard errors of the slope, intercepts, standard errors of the intercepts, and correlation coefficients found from these plots are listed in Table 1-12.

The isotope effects at 22.9 °C for the compounds studied, along with the enthalpy and entropy contributions to each (obtained from the temperature dependence of the isotope effect) are presented in Table 1-15. All enthalpy contributions are negative, corresponding to a secondary deuterium IE that decreases the acidity. The enthalpy and entropy contributions for acetic:acetic-$d_2$ acid are properly double those for acetic:acetic-$d_1$ acid. The results in Table 1-15 also show that in the formic acid sample, the contribution from entropy is not statistically different from zero at the 95% confidence level. Due to the limited number of measurements, the 95% confidence interval for $\Delta S^o$ for the formic acid sample was calculated using the Student’s $t$ distribution, with 7 degrees of freedom. For the others $\Delta S^o$ is negative. The values of $\Delta pK$ per D and $\Delta H^o$ per D were also calculated and can be found in Table 1-16. The $\Delta pK$ per D and $\Delta H^o$ per D for acetic:acetic-$d_1$ acid are the same as those for acetic:acetic-$d_2$ acid.
Table 1-15. Secondary deuterium isotope effects on acidities along with ΔΔH° and ΔΔS° contributions.

<table>
<thead>
<tr>
<th></th>
<th>$K_a^H/K_a^D$ (22.9 °C)</th>
<th>ΔΔH° (cal/mole)</th>
<th>ΔΔS° (cal/(mole*K))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-$d$</td>
<td>1.0701 ± 0.0005</td>
<td>-37.5 ± 1.2</td>
<td>0.009 ± 0.004</td>
</tr>
<tr>
<td>Acetic-$d_1$</td>
<td>1.01078 ± 0.0001</td>
<td>-7.9 ± 0.4</td>
<td>-0.006 ± 0.001</td>
</tr>
<tr>
<td>Acetic-$d_2$</td>
<td>1.02098 ± 0.0002</td>
<td>-15.2 ± 0.6</td>
<td>-0.010 ± 0.002</td>
</tr>
<tr>
<td>DFP-$d_3$</td>
<td>1.0439 ± 0.0005</td>
<td>-27.9 ± 1.2</td>
<td>-0.009 ± 0.004</td>
</tr>
<tr>
<td>DFP-$d_3$ (65%)</td>
<td>1.0436 ± 0.0008</td>
<td>-29.2 ± 2.1</td>
<td>-0.013 ± 0.007</td>
</tr>
</tbody>
</table>

Table 1-16. Secondary deuterium isotope effects on acidities at 22.9 °C.

<table>
<thead>
<tr>
<th></th>
<th>p$K_a^D$ - p$K_a^H$</th>
<th>ΔpK per D</th>
<th>ΔΔH° per D (cal/mole)</th>
<th>n$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic-$d$</td>
<td>0.0294 ± 0.0002</td>
<td>0.0294 ± 0.0002</td>
<td>-37.5 ± 1.2</td>
<td>2</td>
</tr>
<tr>
<td>Acetic-$d_1$</td>
<td>0.00466 ± 0.00004</td>
<td>0.00466 ± 0.00004</td>
<td>-7.9 ± 0.4</td>
<td>3</td>
</tr>
<tr>
<td>Acetic-$d_2$</td>
<td>0.00902 ± 0.00009</td>
<td>0.00451 ± 0.000045</td>
<td>-7.6 ± 0.3</td>
<td>3</td>
</tr>
<tr>
<td>DFP-$d_3$</td>
<td>0.0187 ± 0.0002</td>
<td>0.0062 ± 0.0001</td>
<td>-9.3 ± 0.4$^b$</td>
<td>3,5</td>
</tr>
<tr>
<td>DFP-$d_3$ (65%)</td>
<td>0.0185 ± 0.0003</td>
<td>0.0062 ± 0.0001</td>
<td>-9.7 ± 0.7$^b$</td>
<td>3,5</td>
</tr>
</tbody>
</table>

$^a$ Number of bonds between D and O. $^b$ with the simplifying assumption that all three D contribute equally.
Discussion

Isotope Effects on the Acidity

The data in Table 1-15 show that there are deuterium IEs on the acidities of formic acid, acetic acid, and 3,5 difluorophenol. For all of the compounds studied and at all temperatures, the values of $K_a^H/K_a^D$ are greater than one, meaning that the acid dissociation constant for the deutero compound is smaller (less favorable) than that of the protio. This agrees with the results of many previous studies on the isotope effects of these acids.

Distance Dependence of Isotope Effects

A decrease of the IE with distance from the OH is observed in formic and acetic acids. Table 1-16 lists values of $pK_D - pK_H$, $\Delta pK$ per D and $\Delta H^\circ$ per D. They are sequenced in order of increasing $n$, the number of bonds between the deuterium and the oxygen. The value of $\Delta pK$ per D decreases from 0.0294 for $n = 2$ to 0.00466 or 0.00451 for $n = 3$. The absolute value of $\Delta H^\circ$ per D also decreases from 37.5 to 7.9 or 7.6 cal/mole as the deuterium is moved from two to three bonds away from the OH group. The decrease of the IE with distance from $n=2$ in formic acid to $n=3$ in acetic-$d_1$ and acetic-$d_2$ acids had suggested an inductive contribution since an inductive effect decreases with distance. In fact, the fall-off of the IE with distance by a factor of 2.8 between acetic and pivalic acids was previously\textsuperscript{18} used as evidence of an inductive contribution to the IE. This decrease, however, is shown here to be
entirely due to enthalpy, and not due to an inductive effect as suggested earlier.\textsuperscript{9,18} For the 3,5-difluorophenol sample, where $n =$ both 3 and 5, the value of $\Delta pK$ per D was found to be 0.0062 (with the simplifying assumption that all three D contribute equally) and the absolute value of $\Delta \Delta H^\circ$ per D was found to be 9.3 cal/mole.

**Nonadditivity of Isotope Effects on the Acidity of Acetic Acid**

The data in Tables 1-15 and 1-16 seem to indicate an additive relationship for deuterium substitution in acetic-$d_1$ and acetic-$d_2$ acids. The IE ($pK_a^D - pK_a^H$) observed for acetic-$d_2$ is double that for acetic-$d_1$, and the $\Delta \Delta H^\circ$ value of acetic-$d_2$, -15.2 ± 0.6 cal/mole, is also double that of acetic-$d_1$, -7.9 ± 0.4 cal/mole. This seems to support a contribution from an inductive effect, which would be additive and proportional to the number of deuteriums. On the other hand, we would expect that the IEs of successive deuteriums would, in principle, be nonadditive if the IE is of vibrational origin.\textsuperscript{43,11} The nonadditivity, however, would be very small. Even in trimethylamine the nonadditivity was found to be near 1 cal/mol\textsuperscript{43} where $\Delta \Delta G^\circ$ per D is around 30 cal/mol. In our case, where $\Delta \Delta G^\circ$ per D is less than 8 cal/mol, the effect can be estimated to be $<<$1 cal/mol and too small to be reliably detected.
Origin of the Isotope Effects

Electron Delocalization

The deuterium IE on acidities can be attributed to changes in vibrational frequencies on deprotonation, which may be caused by \( n-\sigma^* \) delocalization. This was previously found to explain the secondary IEs in alcohols,\(^4\) amines,\(^1\) and formic acid.\(^1\)\(^0\) For example, in the formate anion, the delocalization of the oxygen lone pair that is antiperiplanar to the \( \sigma_{\text{C-H}}^* \) orbital (as shown in 3 of Figure 1-5) should lead to the reduction of C-H frequency and the lengthening of the C-H bond upon deprotonation. Indeed, IR experimental data shows that the C-H stretching frequency decreases from 2943 cm\(^{-1}\) in formic acid to 2825 cm\(^{-1}\) in the formate anion. Similarly, the C-D stretching frequency in formic-d acid, 2274 cm\(^{-1}\), decreases to 1876 cm\(^{-1}\) in formate-d anion.\(^1\)\(^2\) Furthermore, computations\(^1\)\(^0\) show that the C-H bond distance increases from 1.097 Å in formic acid to 1.138 Å in the formate anion.

For acetic acid, this interpretation has also been supported by computations showing that upon deprotonation \( n-\sigma^* \) delocalization of the oxygen lone pair into the antibonding \( \sigma_{\text{CC}}^* \) orbital (4, Figure 1-5) results in an increase of the C-C bond distance,\(^1\)\(^0\) and a decrease in its frequency and zero-point energy. However, the three C-H bond distances were also found to increase, and the greatest increase was found to be for the C-H bond in the molecular plane. The increase in acetic acid C-H bond lengths upon deprotonation cannot be explained by \( n-\sigma^* \) delocalization. For phenol, computations\(^1\)\(^0\) revealed that upon deprotonation all 5 hydrogens gain electron density and the frequencies and zero-point energies decrease for all five C-D bonds, even
though σ-delocalization can explain an increase in electron density on the H and a decrease in zero-point energy of the bond only at the meta-positions (5, Figure 1-5). The increase of electron density on the ortho and para hydrogens and the decrease of the ortho and para C-D frequencies and ZPEs upon deprotonation cannot be explained by negative hyperconjugation.

Our measurements of the IEs for 3,5-difluorophenol, presented in Tables 1-15 and 1-16, show that $K_a^H/K_a^D$ is $1.0439 \pm 0.0005$ and the $\Delta pK$ per D is $0.0062 \pm 0.0001$ assuming that all three deuteriums contribute equally. Our findings for 3,5-difluorophenol show that an IE was observed even though no deuterium was at the meta positions, whereas, as shown in 5 of Figure 1-5, σ delocalization can account for changes in vibrational frequencies only at the meta position, not the ortho or para. Our findings for 3,5-difluorophenol support the previously reported,10 mentioned above, which suggest that $n$-σ* delocalization cannot entirely explain changes in vibrational frequencies on deprotonation and thereby account for the IE in phenol.

**Enthalpic Contribution**

As can be seen from the data in Table 1-15, these isotope effects appear in the enthalpy, as had been observed before.11 An enthalpic contribution to the IE is expected if the IEs have an origin in zero-point energies. The explanation for a vibrational origin of these IEs is based on changes in bond vibrations due to isotopic substitution. The C-H or C-D bonds of the deprotonated acids and phenol are weaker
than those in the corresponding protonated acids and phenol. As a result the C-H and C-D bonds of the deprotonated acids have lower frequencies, lower zero-point energies, and a smaller separation between H and D zero-point energies (Figure 1-2) than those same bonds in the protonated acids. Figure 1-2 shows that the C-H bond has the smaller energy difference for deprotonation and a more favorable energy of reaction. Likewise, the enthalpy difference for deprotonation of the protio isotopologue is smaller than that of the deutero, and the protio isotopologue has a more favorable enthalpy of reaction.

All $\Delta \Delta \text{H}^\circ$ values in Table 1-15 are negative. A negative $\Delta \Delta \text{H}^\circ$, eq. 1-6, indicates that, as suggested above, the enthalpy difference for deprotonation of the protio isotopologue is smaller than that of the deutero. As a result, the protio isotopologues have a more favorable enthalpy of reaction. Likewise, the deutero isotopologues have a less favorable enthalpy of reaction. The negative $\Delta \Delta \text{H}^\circ$ is therefore consistent with the observation that deuteration decreases acidity and with the observed values of $K_a^\text{H}/K_a^D$, which are greater than one.

**Entropic Contribution**

An inductive contribution to the isotope effect on the acidities of carboxylic acids and phenols, which would be manifested in entropy, must be due to electrostatic interactions between carboxylate or phenoxide anions and dipole moments of C-H or C-D bonds (to be consistent with the Born-Oppenheimer Approximation). According
to this reasoning, an inductive contribution would arise because the smaller dipole moment of the C-D bond would have less of a stabilizing effect on the negative charge of the deprotonated acid than the larger C-H dipole moment. The negative charge on the deutero anions would therefore be greater than the negative charge on the protio anions. In order to stabilize their greater negative charge, the deutero anions would require more solvent organization than the protio, which would lead to a less favorable (more negative) entropy of deprotonation for the deutero isotopologues. For example, as discussed in the Introduction, the entropy for the deprotonation of acetic acid is more negative than the entropy for the deprotonation of formic acid because the electron donating methyl group leads to a larger negative charge on acetate anion, which necessitates more solvent organization around the acetate anion than the formate.

The key result, which can be seen from the data in Table 1-15, is that these isotope effects lie entirely in the enthalpy and that there is no contribution from entropy. For formic acid and 3,5-difluorophenol the contributions from entropy, 0.009 ± 0.004 cal/(mole*K) and -0.009 ± 0.004 cal/(mole*K), respectively, are not statistically different from zero at the 95% confidence level, according to Student's t test.\textsuperscript{42} For the others the values seem to be statistically significant but we cannot accept them with full confidence because their values for ΔΔS° are negative. As mentioned above, an inductive contribution to the isotope effect would require a positive, not negative ΔΔS°. This is because an inductive effect from an electrostatic interaction between the anion and the dipole moment of the C-H or C-D bond would
lead to a more negative entropy of deprotonation for the deuterio acid and a positive $\Delta S^\circ$, eq. 1-7. Consequently, it is difficult to accept the negative $\Delta S^\circ$ as real because a negative $\Delta S^\circ$ would mean that the entropy contribution from deuteration increases acidity, and there is no explanation for this.
Conclusion

Deuterium substitution decreases the acidity of all four acids studied in these experiments.

Additionally, the IE found for acetic-\(d_2\) acid is double that found for acetic-\(d\) acid. This would suggest that the IE increases with increasing deuterium substitution, in a way that would be expected for an inductive effect, which is additive and proportional to the number of deuteriums. Only a non-additive increase in the IE per deuterium is consistent with a vibrational origin. Unfortunately, the nonadditivity effect is estimated to be too small to be reliably detected.

Our experimental results also show that the positional dependence of the IEs cannot be clearly attributed to \(n-\sigma^*\) delocalization. Delocalization could account for an IE in phenol only when the deuterium substitution occurs at the meta position. An IE, however, is still observed for substitution at the ortho and para carbons. This suggests that the changes in vibrational frequencies upon deprotonation may not solely be due to negative hyperconjugation.

For formic acid and 3,5-difluorophenol, variable temperature experiments show that the IE lies entirely in enthalpy, not entropy. Also as explained earlier, the small value reported as the contribution from entropy for the acetic acid samples might seem to be statistically significant, but it is negative, and inconsistent with any inductive contribution. All these findings confirm that there is no inductive
contribution to the IE on the acidity of carboxylic acids and phenols, and that the origin of the IE is entirely vibrational.

In summary, our findings show that the IEs on the acidities of the carboxylic acids and phenol studied originate in changes in vibrational frequencies and zero-point energies upon deprotonation. An inductive contribution due to electrostatic interactions between carboxylate or phenoxide anions and the C-H or C-D bond dipoles (where the differences in dipole moment arise from the anharmonicities of C-H and C-D bond vibrations), which would be manifested in entropy, was not found.

The material in Chapter 1, in part, has been published in Angewandte Chemie, 2011, Perrin, C. L.; Flach, A., Wiley-VCH, 2011.
References


Derivation of equation 1-24:

\[
\delta_H = \frac{\delta_{H^-}[H^-] + \delta_{H^+}[H^+]}{[H^-] + [H^+]}
\]

\[
\delta_{H^-}[H^-] + \delta_{H^+}[H^+] = \delta_{H^-}[H^-] + \delta_{H^+}[H^+]
\]

\[
\delta_{H^-}[H^-] - \delta_{H^+}[H^-] = \delta_{H^-}[H^-] - \delta_{H^+}[H^-]
\]

\[
[H^-](\delta_{H^-} - \delta_{H^-}) = [H^+](\delta_{H^+} - \delta_{H^+})
\]

\[
\frac{[H^-]}{[H^-]} = \frac{\delta_{H^-} - \delta_{H^-}}{\delta_{H^+} - \delta_{H^-}}
\]


36 The equation and calibration instructions can be found in the Bruker Instruments, Inc. VT-Calibration Manual.


39 Chang, R. Physical Chemistry for the Chemical and Biological Sciences; University Science Books: Sausalito, CA, 2000; p 60.


CHAPTER TWO

Kinetic and Mechanistic Studies of Reactions of Malonic Anhydrides
Abstract

The rate constants for the thermal decomposition of malonic, methylmalonic and dimethylmalonic anhydrides were measured at various temperatures using NMR spectroscopy. Additionally, the activation parameters, $\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ were evaluated from the temperature dependence of the rate constants. Methylmalonic anhydride was found to have the highest rate of decomposition and the lowest Gibbs free energy of activation. Dimethylmalonic anhydride was found to have the lowest rate of decomposition and the highest Gibbs free energy of activation.

Based on the results of our kinetic studies, we conclude that the mechanism for the thermal decomposition of malonic anhydrides is the concerted $[2s+2a]$ cycloreversion, which proceeds via a twisted Möbius transition state to form ketene and carbon dioxide. The concerted cycloreversion mechanism is supported by the characteristically low enthalpies of activation and the large negative entropies of activation found for all three anhydrides. The rates of decomposition were found to be influenced by steric and electronic factors, both of which are manifested in the enthalpy of activation. Dimethylmalonic anhydride, which has the highest steric barrier to the formation of its transition state due to its bulky methyl groups, was found to have the highest activation enthalpy. Methylmalonic anhydride (which must overcome the same steric barrier to reach its transition state as malonic anhydride and a lower steric barrier than dimethylmalonic anhydride) appeared to have the lowest enthalpy of activation due to the stabilization by its electron-donating methyl group of the sp$^2$ carbons forming in the transition state. Our results show that the dominant
influence on the rates of decomposition of malonic anhydrides is due to steric factors and that there is also a minor contribution from electronic factors.

The reactions of methylmalonic anhydride with various hindered bases were also monitored by NMR spectroscopy. Our experimental data undoubtedly show that the reaction of malonic anhydrides with base leads to the deprotonation of the anhydride. Several possible mechanisms for the deprotonation are proposed. The rate constants for the deprotonation of methylmalonic anhydride with the various hindered bases were measured and the relative acidity of the methylmalonic anhydride was estimated.
INTRODUCTION

Malonic Anhydride

Malonic and dimethylmalonic anhydrides were first synthesized by Perrin and Arrhenius\(^1\) after many attempts by others.\(^2\) The seemingly most elementary synthetic route to these compounds, dehydration by heating the corresponding dicarboxylic acid, which could be used to synthesize glutaric and succinic anhydrides,\(^3\) fails to give malonic anhydride.\(^1\) The challenge of this synthesis was in creating the highly strained 4-membered ring. Thus, the great success of the Perrin and Arrhenius synthesis was in starting with a compound having an already formed 4-membered ring and then converting it to the anhydride.

The reaction scheme of the Perrin and Arrhenius synthesis of malonic anhydride can be found in Figure 2-1. Ozonolysis of a diketene at \(-78^\circ C\) produces the molozonide, which opens to produce the malonic anhydride and the corresponding carbonyl oxide. Perrin and Arrhenius also conclude that the formation of malonic anhydride and carbonyl oxide is more likely than the formation of anhydride oxide and \(R_2CO\) because ozonolysis of dihydropyran was found to produce formate ester (the carbonyl group forms on the olefinic carbon which has more electron withdrawing groups) and aldehyde oxide (the zwitterion forms on the olefinic carbon which has more electron donating groups).\(^1,4\)
Figure 2-1. Perrin and Arrhenius synthesis of malonic anhydride by ozonolysis of diketene.

The carbonyl oxide can then undergo various reactions, which are shown in Figure 2-2. One possibility is that the carbonyl oxide forms dimers and trimers, as shown in pathway a. The carbonyl oxide can also form a second type of dimer shown in pathway b, which then decomposes to form O₂ and the corresponding aldehyde or ketone. Pathways a and b in Figure 2-2 are most likely to occur, and the formation of peroxide dimers and trimers and formaldehyde or acetone were all observed in the previous synthesis. The reaction of formaldehyde peroxide with malonic anhydride to form the ozonide, pathway c, usually occurs only with aldehydes, and is unlikely to occur with malonic anhydride.
Figure 2-2. Possible reaction pathways of formaldehyde peroxide: a) the formation of dimers and trimers b) decomposition into formaldehyde and oxygen c) reaction with malonic anhydride to form an ozonide.

The synthesis of malonic anhydride was an important contribution to the field of synthetic organic chemistry because this anhydride, which had been a classic unknown compound for many years, can be easily converted to a variety of monoester and monoamide derivatives\(^6\) commonly used in the synthesis of pharmaceuticals, natural products, and other biologically active compounds.\(^7\) One especially significant use for this synthesis is the ability to convert malonic anhydrides to Meldrum's acid,\(^8\) which itself is another widely useful reagent in organic synthesis.\(^9\)
The ability to synthesize monoester and monoamide derivatives and Meldrum's acid from malonic anhydrides is valuable because many of these compounds are expensive and otherwise difficult to prepare.\(^6\) This route is a straightforward one-pot synthesis, does not necessitate isolation of the anhydrides and affords excellent yields ranging from 70 to nearly 100 %. According to the procedure, an excess of the appropriate derivatizing agent (such as an alcohol or an amine, or a Lewis acid to prepare Meldrum's acid) is simply added to the cold reaction flask immediately after ozonolysis and the mixture is warmed to room temperature.\(^6\),\(^8\) In addition, the synthetic route used by Perrin and Arrhenius for the synthesis of malonic anhydride can also be utilized to synthesize variously substituted malonic anhydrides, such as methylmalonic or dimethylmalonic anhydride, and then obtain derivatives thereof.\(^6\)

The downside to this procedure is the generation of aldehyde and ketone peroxides, which are potentially explosive, and make it rather difficult to carry out this reaction on an industrial scale. However, this problem can be avoided\(^8\) by the addition of certain aldehydes, such as acetaldehyde, formaldehyde, or propionaldehyde, that react with the peroxides to form an ozonide, which can then be decomposed (to the corresponding aldehydes or ketones) with reducing agents such as trimethyl phosphite or dimethyl sulfide.\(^5\) The generation of aldehyde and ketone peroxides can also be prevented using \(N\)-methylmorpholine \(N\)-oxide, whose addition to the sample prior to the ozonolysis has been found to trap the short-lived carbonyl oxide intermediates.\(^10\)

One other interesting result of the synthesis of malonic anhydride is its IR (Infrared) and Raman spectra.\(^11\) Because of the elusiveness of malonic anhydride, in
addition to NMR, IR and Raman spectra were obtained for a more conclusive structure verification. Initially, an erroneous report claimed that for malonic anhydride, the symmetric and asymmetric carbonyl IR stretching frequencies are at 1980 and 1900 cm\(^{-1}\), respectively.\(^2\) Later a more accurate estimate,\(^11\) based on the linear extrapolation of the C=O stretching frequencies of glutaric and succinic anhydrides, was made and the symmetric and asymmetric C=O stretching frequencies were projected to be 1940 and 1830 cm\(^{-1}\), respectively. Nevertheless, the IR spectra of authentic malonic and dimethylmalonic anhydrides, prepared by ozonolysis, show only the asymmetric C=O stretch around 1820 cm\(^{-1}\). The symmetric stretch, on the other hand, was judged to be too weak to be seen in the IR spectrum. The lack of intensity stems from the fact that the carbonyl groups of the malonic anhydride are opposed and therefore their symmetric stretch does not lead to a large change in the overall dipole moment. Similarly, a lack of the symmetric C=O stretch is observed for tetramethyl-1,3-cyclobutanedione, where the opposing C=O groups also lead to a cancellation of the overall dipole moment for the symmetric stretching vibration of the carbonyls.\(^11\) Although absent in the IR, the higher frequency symmetric C=O stretch of dimethylmalonic anhydride was observed in the Raman spectrum at 1947 cm\(^{-1}\). This is a champion among organic C=O frequencies. The complementary IR and Raman spectra not only showed excellent proof of structure of malonic and dimethylmalonic anhydrides, but also provided an example of a remarkably high frequency carbonyl stretching vibration. The only other compound reported with such a high frequency carbonyl vibration is \(\beta,\beta\)-bis(trifluoromethyl)-\(\beta\)-propiolactone, whose carbonyl stretching frequencies are claimed to be at 1890 and 1949 cm\(^{-1}\).\(^12\) However these
unusual stretching frequencies have not been confirmed. The carbonyl stretching frequency of a similar compound, 4-phenyl-4-(trifluoromethyl)oxetan-2-one, was reported\textsuperscript{13} to be at 1850 cm\textsuperscript{-1}, which is much lower than the 1949 cm\textsuperscript{-1} reported for \(\beta,\beta\text{-bis(trifluoromethyl)}\text{-}\beta\text{-propiolactone.}\)

**Decomposition of Malonic Anhydrides via [2+2] Cycloreversion**

If not converted to monoester and monoamide derivatives, both malonic and dimethylmalonic anhydrides decompose upon warming to carbon dioxide and a ketene.\textsuperscript{1} This would strongly suggest that the mechanism of decomposition is a [2+2] cycloreversion, which is the reverse of a [2+2] cycloaddition reaction.

Both of these reactions, the thermal [2+2] cycloreversion and cycloaddition, are widely used in synthetic organic chemistry. Examples include the synthesis of substituted olefins (with retention of configuration),\textsuperscript{14,15} natural products,\textsuperscript{16} antibiotics,\textsuperscript{17} and fused bicyclic cyclobutane derivatives.\textsuperscript{18}

Despite its usefulness, many aspects of this mechanism are still unclear. While working with the malonic anhydrides Perrin and Arrhenius made some very interesting observations. First they noticed that the rate of this particular decomposition is quite remarkable, as both malonic and dimethylmalonic anhydrides were found to decompose at room temperature. Thermal decomposition via [2+2] cycloreversion at room temperature is truly unusual and a much lower temperature than the temperatures reported for other cycloreversions, which are in excess of 100
Additionally, Perrin and Arrhenius found that malonic anhydride decomposes faster than dimethylmalonic anhydride.\textsuperscript{1} Yet the electron-donating methyl groups of dimethylmalonic anhydride should help to stabilize the sp\textsuperscript{2} carbons forming in the transition state, but if this were the dominant effect, a faster reaction would be seen for dimethylmalonic anhydride. Alternatively, steric effects could be the dominant influence on the reaction rate, because the bulky methyl groups of dimethylmalonic anhydride hinder the formation of the transition state and therefore diminish the reaction rate. We hope that our kinetic and mechanistic studies of the decomposition of malonic anhydrides, which will be described in more detail below, will provide insight into how ketene substituents affect \([2+2]\) cycloreversion and cycloaddition reactions. Our findings can be applied to both because according to the principle of microscopic reversibility “the pathway for conversion of the product back to the reactant is the exact microscopic reverse of the forward pathway.”\textsuperscript{20} Since cycloreversion reactions are simply reverse cycloadditions, insights gained into cycloreversion reactions also apply to cycloadditions.

\textbf{Cycloaddition and Cycloreversion Reactions}

A cycloaddition is “a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity.”\textsuperscript{19} One example of a cycloaddition reaction is the Diels-Alder reaction between a diene and alkene, Figure 2-3a.\textsuperscript{20} These reactions involve the breaking of \(\pi\) bonds in the reactants and the formation of \(\sigma\)
bonds in the product. Therefore, cycloaddition reactions are named according to the number of \( \pi \) electrons of the reactant molecules participating in the reaction. For example the Diels-Alder and ketene dimerization reactions in Figure 2-3a and 2-3b are named [2+4] and [2+2] cycloadditions, respectively. Furthermore, cycloaddition reactions are concerted, with the breaking of the \( \pi \) bonds and formation of the \( \sigma \) bonds happening simultaneously, and proceeding through a transition state that has a cyclic array of electrons. If all of the new bonds are formed and all of the old bonds are broken to the same extent in the transition state, then the cycloaddition is said to be synchronous. Most cycloaddition reactions, however, are asynchronous, which means that their bond formation and bond breaking have not progressed to the same extent at the transition state.

![Cycloaddition Reactions](image)

**Figure 2-3.** Examples of cycloaddition reactions. a) Diels-Alder  b) Ketene dimerization.
One other key aspect of cycloaddition reactions is the geometry of interaction between the reactants, which is the factor determining whether the cycloaddition is favorable (allowed) or unfavorable (forbidden). The approach of an individual reactant is known as suprafacial when its interaction involves only one face of the π-system and antarafacial when its interaction involves opposite faces of the π-system. The three different possible approaches, for a [2+2] cycloaddition, are illustrated in Figure 2-4. The suprafacial approach is denoted with the subscript ‘s’ and the antarafacial with the subscript ‘a’. For example the notation [2s+2a] conveys that the approach of one molecule is suprafacial and that the approach of the other is antarafacial.

![Figure 2-4. The types of atomic orbital interactions in cycloaddition reactions. a) suprafacial-suprafacial b) antarafacial-suprafacial c) antarafacial-antarafacial.](image)

There are three models that relate these geometric arrangements of reactants (more specifically the geometry of interaction of their orbitals) to the favorability of the reaction. These three models provide mechanistic insight into these reactions and are fundamental to understanding cycloaddition reactions.
The most renowned of these models was developed by Woodward and Hoffmann\textsuperscript{21} who developed a method for determining the allowed topology of interaction between the reactants by looking for conservation of orbital symmetry during the reaction. The key aspect of this model lies in the assumption that the symmetry of the molecular orbitals of the reactants must be the same as the symmetry of the molecular orbitals of the product. Woodward and Hoffmann performed their analysis with the help of orbital correlation diagrams, which are made by drawing the molecular orbitals of the reactants and then the product for the various modes of orbital interactions (either suprafacial-suprafacial, antarafacial-suprafacial, or antarafacial-antarafacial). Only the orbitals that are involved in the reaction are drawn. The others, for example the $\sigma_{CH}$ bonds in Figure 2-3a, can be omitted from this analysis because, while they undergo changes in hybridization, their number, approximate energies, and symmetry do not change during the reaction.\textsuperscript{21} Once all of the orbitals involved in the reaction are drawn, symmetry designations are then assigned to each orbital with respect to a minimum number of symmetry elements that are necessary to distinguish between allowed or forbidden pathways. Because orbital symmetry must be maintained during the reaction, these diagrams can be used to correlate whether the product resulting from each topology of interaction is favorable, or in other words that the activation barrier along reaction path predicted for a particular topology of interaction is low (the predicted pathway will not require the reactant/s to cross the energy gap to get to the product/s).
The second model, frontier molecular orbital theory, was proposed by Fukui.\textsuperscript{22} Unlike the Woodward-Hoffmann model which looks at all of the orbitals involved in the cycloaddition (or cycloreversion) reaction, this model focuses only on the interactions between the HOMO (Highest Occupied Molecular Orbital) and the LUMO (Lowest Occupied Molecular Orbital). If the geometry of interaction between the reactants is such that mixing between the HOMO and LUMO orbitals leads to a bonding interaction then the reaction is allowed. If not, then the reaction is forbidden.

The last model that can be used to gain insight into cycloaddition reactions is aromatic transition state theory.\textsuperscript{20,23} This approach focuses on the geometry of the transition states of these reactions. If the interaction between the reactants leads to a transition state having the more conventional Hückel topology of atomic orbitals, Figure 2-5, the reaction will be allowed if the cyclic array of electrons in the transition state is made up of 4\(n+2\) electrons. It is allowed because this transition state is stabilized by aromaticity. If the Hückel transition state involves 4\(n\) electrons, the reaction will be forbidden because an antiaromatic transition state is unfavorable. On the other hand, the interaction between the reactants could also lead to a transition state having Möbius topology, Figure 2-5, in which the \(p\) orbitals are twisted in such a way that the arrangement of the \(\pi\) system is similar to that of a Möbius strip. In this arrangement one set (or an odd number of sets) of two adjacent \(p\) atomic orbitals will have an antibonding relationship with each other, regardless of how the phases of the atomic orbitals are chosen. For transition states with Möbius topology a cyclic array made up of 4\(n\) electrons is favorable because this topology avoids antiaromaticity;
however, if the Möbius transition state involves $4n+2$ electrons, the reaction will be forbidden. Transition states with Möbius topology having $4n$ electrons can be said to be Möbius aromatic, although this is an extension of the original meaning.

![Hückel topology](image1.png) ![Möbius topology](image2.png)

**Figure 2-5.** Hückel and Möbius transition state topologies. In the diagram of Möbius topology, a dashed line lies between the two atomic $p$ orbitals that have an antibonding relationship.

All three of these models are complementary and each describes cycloaddition reactions from a different perspective. However the third model, which focuses on the geometry of the transition states, may provide the most insight into the mechanism of decomposition of malonic anhydrides and will solely be used to interpret the results of this work.
Stereoselectivity and Substituent Effects of Cycloreversions and Cycloaddition Reactions Involving Ketenes

As described above, malonic anhydride decomposes to form ketene and carbon dioxide via the [2+2] cycloversion mechanism. According to the Woodward and Hoffman model a [2+2] thermal cyclic reaction is allowed only if one of the reactants is oriented relative to the other in an antarafacial manner. According to aromatic transition state theory this transition state would have a twisted Möbius topology in order to avoid antiaromaticity. Figure 2-6 shows the antarafacial-suprafacial atomic orbital interaction of a ketene with an alkene. An example of a Möbius transition state, in the case of a [2a+2a] cycloaddition reaction between a ketene and an alkene, is shown in Figure 2-7.

![Ketene (antarafacial) and Alkene (suprafacial)](image)

**Figure 2-6.** The antarafacial (ketene) and suprafacial (alkene) atomic orbital interaction between a ketene and an alkene.
One important feature of cycloaddition reactions in general, but also of cycloaddition reactions involving ketenes, is stereoselectivity. Cycloaddition reactions always favor the pathway which minimizes strain in the transition state, even over those leading to more stable products.\textsuperscript{20,25} For example, reactions involving an asymmetrically substituted ketene with an alkene are preferred when the approach of the ketene is orthogonal to the alkene, and with the larger substituent on the ketene pointing away from the alkene and also with both ketene substituents approaching the less hindered side of the alkene, Figure 2-7.\textsuperscript{25} The result of this approach is that, in the product, the larger substituent on the ketene is \textit{cis} to the larger substituents on the alkene, Figure 2-7. Similarly, the cycloaddition of ethyl ketene with cyclopentadiene leads to the product having the ethyl group in the \textit{endo} position.\textsuperscript{20}

In most cases the stereochemistry on the alkene is maintained. For example the [2+2] cycloaddition of dimethylketene with \textit{cis}-2-butene results in only the product whose methyl groups on carbons 3 and 4 are \textit{cis}, Figure 2-8a.\textsuperscript{26} Likewise, the [2+2] cycloreversions of \textit{cis} and \textit{trans} 2,3-dimethylcyclobutanones also proceed with retention of stereochemistry of the alkene, Figure 2-8b.
A second feature of the [2+2] cycloaddition mechanism, which is also the focus of this work, is substituent effects. A [2+2] cycloaddition reaction involving ketene is driven by the interaction of the electron-rich alkene and the electrophilic ketene. Electron-withdrawing substituents on the ketene accelerate the reaction by lowering the energy of the LUMO of the ketene even further, allowing for a better interaction with the HOMO of the alkene. Accordingly, it has been observed that the cycloaddition rate of alkenes is higher with dichloroketenes than with
dimethylketenes.\textsuperscript{27,25} The substituents on the alkene also affect the rate of the reaction. For example, in the [2+2] thermolysis of β-lactones, electron-donating substituents on the C-4 carbon, Figure 2-9, were found to increase the reaction rate and lower the activation energy for the decomposition.\textsuperscript{28} The authors concluded that the increase in rate is due to the ability of the electron-donating substituents to stabilize the partial positive charge developing on the C-4 carbon in the transition state (the partial positive charge develops because the reaction is asynchronous). In contrast, electron-donating substituents on the C-3 carbon were not found to affect the activation energy of [2+2] thermal decomposition of the β-lactones.\textsuperscript{28}

![Proposed zwitterionic transition state for the decarboxylation of β-lactones](image)

**Figure 2-9.** Proposed\textsuperscript{28} zwitterionic transition state for the decarboxylation of β-lactones. Although not drawn as such, this is an asynchronous transition state.

When considering the impact of electronic substituent effects on the decomposition of malonic anhydrides, it is certainly reasonable to suggest that the electron-donating methyl groups of dimethylmalonic anhydride enhance the reaction rate (when compared to malonic anhydride) by stabilizing the sp\textsuperscript{2} carbons forming in the transition state. However, Perrin and Arrhenius found that dimethylmalonic anhydride decomposes more slowly than malonic anhydride.\textsuperscript{1} This result strongly
suggests that sterics, not electronics, are the dominant influence on the rate of decomposition of malonic anhydrides. This is because the bulky methyl groups are expected to hinder, and therefore slow down, the formation of the twisted Möbius transition state for dimethylmalonic anhydride (when compared to malonic anhydride). Such a steric substituent effect was seen in the [2+2] cycloaddition reactions of alkylphenylketenes with cis and trans ethyl propenyl ethers. Reaction rates were found to be lower for cycloadditions where bulky groups hindered the formation of the transition states. With the substituent R being CH₃, Figure 2-10, the partial rate constant for the cycloaddition occurring with the orientation of reactants 1, 985 L*mol⁻¹*sec⁻¹, is higher than that for orientation 3, 61 L*mol⁻¹*sec⁻¹. In orientation 3, the trans substituents of ethyl propenyl ether hinder the formation of the Möbius transition state more than those of cis-ethyl propenyl ether in orientation 1 (for comparison, see Figure 2-7 for a minimally strained transition state structure). The rate was also found to decrease as the size of the substituent on the ketene increased. For example, when the size of substituent, R, was increased from methyl to ethyl, for orientation 1, the partial rate constant for the cycloaddition decreased from 985 to 77 L*mol⁻¹*sec⁻¹. Likewise for orientation 3, a decrease in the partial rate constant was observed with an increase in the bulkiness of the substituent. Unfortunately, for orientations 2 and 4, the observed decrease in the partial rate constants with increased substituent size could not be explained by steric factors. This is because in orientations 2 and 4 the substituent, R, points away from the ketenophile and is in a position where it does not hinder the formation of the transition state. The authors conclude that electronic factors must be responsible and that an increase in the
electron-donating ability of R leads to a more stable ketene that is less reactive. For example, for orientation 2, when the size of substituent R was increased from methyl to (the more electron-donating) t-butyl, the partial rate constant for the cycloaddition decreased from 130 to 5.1 L*mol$^{-1}$*sec$^{-1}$.

![Chemical structures](image)

**Figure 2-10.** Possible modes of interaction between alkylphenylketenes and ethyl propenyl ethers.

A great deal of kinetic experiments have already been done in an effort to learn about electronic and steric effects on cycloreversion and cycloaddition reactions.$^{26,25,14,30}$ However, not many address the extent to which these substituent effects influence the reaction rate. For example, although malonic anhydrides have already been shown$^1$ to decompose via [2+2] cycloreversion with steric effects most likely being the dominant influence on the reaction rate, it is still unclear to what extent electronic factors contribute. In our study, the rates of decomposition and the activation parameters of three variously substituted malonic anhydrides: malonic (MA, 5), methylmalonic (MMA, 6), and dimethylmalonic (DMA, 7), Figure 2-11, were obtained in an effort to gain some insight into this puzzle.
Research Proposal

The values of the activation parameters: the Gibbs free energy ($\Delta G^\ddagger$), enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) of activation, equation 2-1, obtained from our experiments should provide some information about the reaction mechanism and the structure of the transition state. The Gibbs free energy of activation is the difference between the energy of the transition state and the ground state energy of the reactant (or reactants). The two components of the Gibbs free energy of activation, the enthalpy and entropy of activation, provide information about the changes in bonding and the changes in the order of the system, respectively, that occur when the reactant is transformed into the transition state.

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$  

2-1
Enthalpy of Activation

Determining the enthalpy of activation for the decomposition of the three malonic anhydrides, Figure 2-11, may provide additional, more conclusive, evidence supporting the previously reported\textsuperscript{1} [2+2] cycloreversion mechanism, and additionally may provide insight into the extent to which the steric bulk and the electron-donating ability of the methyl substituents influence the reaction rate.

Additional evidence, supporting the previously proposed\textsuperscript{1} [2+2] cycloreversion as the mechanism of decomposition of malonic anhydrides, could be obtained from these experiments if the enthalpy of activation is found to be low, as expected for a concerted mechanism. Typically, reactions proceeding via concerted mechanisms are expected to have low activation energies because during a concerted reaction the energy lost due to bonds that have been partially broken as the reactant is transformed into the transition state, is compensated for by the simultaneous partial formation of new bonds. For example the enthalpy of activation for the [4+2] cycloreversion of dicyclopentadiene is 27.5 $\pm$ 1 kcal/mol.\textsuperscript{32} During this reaction, while two $\sigma_{\text{C-C}}$ bonds (81 kcal/mol\textsuperscript{33}) and one $\pi_{\text{C=C}}$ bond (64 kcal/mol\textsuperscript{33}) are being broken, three new $\pi_{\text{C=C}}$ bonds are simultaneously being formed. The loss of energy due to the partial breaking of the $\sigma_{\text{C-C}}$ and $\pi_{\text{C=C}}$ bonds in the transition state is compensated by the simultaneous partial formation of the new $\pi_{\text{C=C}}$ bonds, resulting in the low activation enthalpy. Other examples of low activation enthalpy values for [2+2] cycloreversions include those determined for the decomposition of bicyclo[3.2.0]hept-2-en-6-one, 36.7
kcal/mol, and the cycloreversion of diketene, 48.31 kcal/mol. However, the activation enthalpies for the cycloreversions of MA, MMA, and DMA may be even lower than those given above. Although unusual, much lower activation enthalpies for the decomposition of the malonic anhydrides would not be surprising because, in their previous experiments, Perrin and Arrhenius found that both malonic and dimethylmalonic anhydrides decompose at temperatures much lower than those reported for other [2+2] cycloreversions. One explanation for why the activation enthalpies for the cycloreversions of MA, MMA, and DMA, could be lower than those (for example) of bicyclo[3.2.0]hept-2-en-6-one, diketene or dicyclopentadiene is because the decomposition of the anhydrides produces CO$_2$, which is more stable than the cycloreversion products of the other three reactions (which are: two ketenes for the cycloreversion of diketene, two cyclopentadienes for the cycloreversion of dicyclopentadiene, and ketene and cyclopentadiene for the cycloreversion of bicyclo[3.2.0]hept-2-en-6-one). In other words, the decomposition of the malonic anhydrides leads to the formation of the C=O bond of CO$_2$, whose bond dissociation energy (192 kcal/mol$^{34}$) is much higher than the bond dissociation energies of typical C=C (145 kcal/mol$^{66}$) or C=O (173 kcal/mol$^{66}$) bonds.

Additionally, the activation enthalpies for the cycloreversions of MA, MMA, and DMA should be lower than those expected for reactions proceeding via stepwise mechanisms. For comparison, the calculated$^{35}$ and experimental$^{36}$ activation enthalpies for the stepwise thermal decomposition of cyclobutane, which proceeds via the tetramethylene biradical intermediate, are 62.7 kcal/mol and 61.1 kcal/mol,
respectively (the latter determined from $E_a = \Delta H^\ddagger + RT$,\textsuperscript{37} where $E_a = 62.5$ kcal/mol and $T = 440$ °C). The activation enthalpy of this stepwise process is higher than that of the concerted process because the rate-determining step of the stepwise process involves only the homolytic cleavage of a $\sigma_{C-C}$ bond, with no bond formation to compensate for the energy lost as a result of the bond breaking.

In addition to providing further evidence to support the [2+2] cycloreversion mechanism, the activation enthalpy values for the decomposition of the parent and dimethylmalonic anhydrides should also provide information about the influence of electronic and steric effects on the reaction rate. For example, if electronic factors are the dominant influence on the reaction rate, the electron-donating methyl groups of dimethylmalonic anhydride would stabilize the formation of the transition state more than the hydrogens of the parent anhydride would, and the enthalpy of activation of dimethylmalonic anhydride would be lower than that of the parent. On the other hand, if steric effects are the dominant influence on the reaction rate, then the bulky methyl groups of dimethylmalonic anhydride would hinder the formation of the transition state and the activation enthalpy of the parent anhydride would be lower than that of the dimethyl. Although previous experiments\textsuperscript{1} have already shown that the rate of decomposition of dimethylmalonic anhydride is lower than that of the parent, suggesting that steric effects are the dominant influence, obtaining activation enthalpy values will substantiate this observation more explicitly.

It would also be beneficial to obtain activation enthalpy values and rate
constants for the decomposition of methylmalonic anhydride, which would provide information about the extent to which electronic effects influence the reaction rate. For example, if steric effects are the dominant factor influencing the decomposition, then methylmalonic anhydride will have the same activation enthalpy as the parent anhydride. This is because methylmalonic anhydride will twist (in only one direction) so that the methyl group does not sterically hinder the formation of the transition state, Figure 2-12, and therefore the methylmalonic anhydride will have the same activation barrier to overcome as the parent anhydride (and hence the same activation enthalpy). In this case the rate of decomposition of methylmalonic anhydride will be lower than that of the parent since methylmalonic anhydride can twist in the preferred direction only half of the time. On the other hand, if there is also a significant contribution from electronic factors, the activation enthalpy of methylmalonic anhydride will be lower than that of the parent. Given that the contribution to the enthalpy of activation from steric strain will be the same for both methylmalonic and the parent anhydride, stabilization of the sp² carbons forming in the transition state by the electron-donating methyl group will result in a lower activation enthalpy of methylmalonic anhydride relative to that of the parent.
Figure 2-12. Number of possible rotations to reach the transition state for a) the parent anhydride and b) methylmalonic anhydride.

A study by Strausz and DoMinh\textsuperscript{38} shows that steric effects influencing the reactivity of ethoxyketene with variously substituted olefins are manifested in the enthalpy of activation. At 100 °C the rate constants of the [2+2] cycloaddition of ethoxyketene with \textit{cis}-2-butene and \textit{trans}-2-butene (relative to that of 2,3-dimethyl-2-butene) are 25.0 and 1.7, respectively. The difference between their activation
energies, $E_{a(\text{trans})} - E_{a(\text{cis})}$, was found to be 0.26 kcal/mol. (Since $E_a = \Delta H^\ddagger + RT$, the value of $E_{a(\text{trans})} - E_{a(\text{cis})}$ is equal to that of $\Delta H^\ddagger_{(\text{trans})} - \Delta H^\ddagger_{(\text{cis})}$.) Electronic effects (in this case the ability of methyl substituents to stabilize the double bond of each olefin) should not have a significant impact on the cycloaddition reaction of cis-2-butene and trans-2-butene with ethoxyketene. The reason for this is that cis-2-butene and trans-2-butene both have one methyl group stabilizing each end of the double bond, and they differ only in the orientation (not the electron-donating ability) of the substituents on the double bond, which in this case are the methyl groups. The decrease in the reactivity of trans-2-butene relative to cis-2-butene is therefore due to steric effects, or more specifically it is due to the trans-methyl group hindering the formation of the transition state of trans-2-butene (See Figure 2-7 for an example of a transition state with minimal strain). This steric strain manifests itself in the enthalpy of activation, and thus the enthalpy of activation is higher for the trans isomer than the cis.

![Figure 2-13](image)

**Figure 2-13.** Examples of the exo and endo modes of interaction between a ketene and an alkene.

In another study, Moyano and co-workers\textsuperscript{39} used theoretical values of
activation enthalpies of [2+2] cycloadditions of ketenes and olefins to show that both electronic and steric effects influence their reaction rates. The activation enthalpies for reaction of ketene, chloroketene, and dichloroketene with ethene, which are 39.8, 33.7, and 33.1 kcal/mol, agree with previous observations\textsuperscript{25} that electronegative ketene substituents increase the reactivity of ketenes with olefins. Additionally, the ability of calculations to compare the enthalpies of activation of exo and endo (the endo is theoretical) approach, Figure 2-13, of chloroketene to the olefin, makes it possible to assess the magnitude of the steric strain that results when a chlorine atom of dichloroketene approaches the ethene (relative to ketene). The steric strain of the exo approach of chloroketene and ethene should be similar to that for ketene and ethene because the chlorine in the exo position does not greatly increase the steric strain of the transition state (See Figure 2-7 for an example of a transition state with minimal strain). Comparison of the calculated enthalpies of activation of the exo vs. the endo approach of chloroketene and ethene allows for the determination of the sterics separately from the electronic effects, because in both cases the ketene (and olefin) substituents are the same. The value obtained (from the calculations of the exo and endo approach of chloroketene) for the steric component of the activation enthalpy of dichloroketene with ethene (relative to that of ketene and ethene) is 3.4 kcal/mol. In agreement with expectations, the steric strain calculated in this way for other ketene substituents increases with the size of the substituent, from 3.4 kcal/mol for a Cl group to 3.8 kcal/mol for a CH\textsubscript{3} group, and finally to 5.7 kcal/mol for a phenyl group (all relative to that of H). Knowing the magnitude of the steric component on the activation enthalpy of the reaction of dichloroketene and ethene, the electronic
component, $\Delta H^\ddagger_{\text{electronic}}$, could also be evaluated from equation 2-2, where $\Delta H^\ddagger_{\text{ketene}}$, $\Delta H^\ddagger_{\text{dichloroketene}}$ and $\Delta H^\ddagger_{\text{steric}}$ are the activation enthalpy for the cycloaddition of ketene with ethene (39.8 kcal/mol), dichloroketene with ethene (33.1 kcal/mol), and the strain component of the activation enthalpy for the cycloaddition of dichloroketene with ethene (3.4 kcal/mol), respectively. The value of the electronic component of the activation enthalpy for the cycloaddition of dichloroketene with ethene is -10.1 kcal/mol. (This also works out to be -5.05 kcal/mol for each Cl group, so that $\Delta H^\ddagger$ for chloroketene with ethene should be: 39.8 – 5.05 = 34.75 kcal/mol. This agrees reasonably well with the value of 33.7 kcal/mol calculated independently for the cycloaddition of chloroketene with ethene.)

$$\Delta H^\ddagger_{\text{electronic}} = \Delta H^\ddagger_{\text{dichloroketene}} - \Delta H^\ddagger_{\text{ketene}} - \Delta H^\ddagger_{\text{steric}} \tag{2-2}$$

Moyano and co-workers also report activation enthalpy values for the [2+2] cycloaddition of methylketene with ethene (37.5 kcal/mol) to be more favorable than those of ketene with ethene (39.8 kcal/mol), but the activation enthalpy of the reaction of dimethylketene and ethene was not determined. In this case, because of the exo approach of methylketene, the steric contribution to $\Delta H^\ddagger$ should be minimal. The difference in the activation enthalpy values found for the cycloaddition with ketene and the cycloaddition with methylketene, therefore, has to be due to electronic effects. Unfortunately, finding an explanation for this difference in activation enthalpies, in terms of only electronic effects, is difficult. The problem lies in the fact that the electron-donating methyl substituent provides a greater stabilization of methylketene
relative to ketene, and should result in a less favorable, not more favorable, activation enthalpy for the cycloaddition of methylketene (relative to that of ketene). The enthalpy of activation for the [2+2] cycloreversions of 2-methylcyclobutanone into methylketene and ethene (70.1 kcal/mol) was also found to be more favorable than the value of $\Delta H^\ddagger$ for the cycloreversion of cyclobutanone into ketene and ethene (75.1 kcal/mol). These values suggest that electronic effects, the stabilization of the sp$^2$ carbons forming in the transition state, accelerate the cycloreversion of cyclobutanones. Moyano and co-workers did not comment on the relative activation enthalpies of the cycloaddition and cycloreversion of methylketene relative to that of ketene. They did state that despite the fact that “a clear understanding of substituent effects in the [cycloaddition/cycloreversion] reaction would be very important,” the electronic and steric effects on the cycloaddition and cycloreversion reactions of methyl and dimethylketenes are not fully understood. Moyano and co-workers emphasized the need for further research into the effects of substituents on these reactions saying that “the precise role of the ketene substituents (i.e., if they accelerate the cycloaddition either by energetic or entropic factors…) is not fully understood”.

**Entropy of Activation**

The entropy of activation is a measure of order in terms of the gain or loss of translational, rotational, and vibrational degrees of freedom and also solvation (the gain or loss of the order of solvent molecules). The entropy of activation values for
cycloreversion reactions are expected to be negative because the twisted transition state is more ordered than the reactant. For some cycloreversions, the entropy of activation values may also be near zero because the loss of degrees of freedom due to a highly ordered transition state may be balanced by a gain in the degrees of freedom due to the bond breaking that occurs when the reactant is transformed into the transition state. Examples of activation entropy values for thermal cycloreversions include: -16.2 ± 2.7 cal/(K*mol)$^{32}$ for the cycloreversion of dicyclopentadiene, 6.3 cal/(K*mol)$^{41}$ for the cycloreversion of cyclobutanone, and -0.3 cal/(K*mol)$^{67}$ for the cycloreversion of bicyclo[3.2.0]hept-2-en-6-one.$^{42}$

In addition to the change in degrees of freedom, entropy can also be related to symmetry and the number of ways that the reactant can be rotated to reach the transition state. Accordingly, the activation entropy values expected for the malonic anhydrides would depend not only on the amount of strain present in the transition state vs. the increased ability of the broken bonds to move in the transition state, but also on the number of paths that the anhydride could take to reach the transition state. The entropy of activation for the parent malonic anhydride would be more positive than that of methylmalonic anhydride because the parent anhydride can be rotated in two different ways to reach the transition state, whereas because of its bulky methyl group methylmalonic anhydride can rotate in only one way to reach the transition state, Figure 2-12. This symmetry contribution should make the activation entropy of the parent anhydride more favorable than that of the methylmalonic anhydride by $R\ln2$. 

Base Catalyzed Decomposition of Methylmalonic Anhydride

Another interesting puzzle concerning the reactivity of malonic anhydride is the acidity of its hydrogen and the mechanism of its reaction with base. The deprotonation of malonic or methylmalonic anhydride could proceed via either a stepwise mechanism, Figure 2-14, a concerted pericyclic ring opening, Figure 2-15, (both of which involve the deprotonation of MA to form the intermediate 8) or result in the polymerization of the anhydride as shown in Figure 2-16. The resonance forms of intermediate 8 are shown in Figure 2-14b. It should be noted that the two forms with the positive charge on the oxygen are antiaromatic and thus do not contribute much. Reactivity similar to that proposed in Figures 2-14 and 2-15 has also been observed for β-lactones and β-lactams. Because of the many potential synthetic uses for malonic anhydrides (discussed above) and the wide range of synthetic applications that already exist for β-lactones and β-lactams, including the synthesis of substituted allenes, amino acids, polymers and antibiotics, it would be very valuable to learn more about this mechanism. Furthermore, finding an additional example of a reaction proceeding via an intermediate having antiaromatic character with a barrier low enough to proceed at room temperature would be interesting from a mechanistic standpoint.

The mechanisms proposed for the deprotonation of malonic anhydrides in Figures 2-14 and 2-15 are not less reasonable than the polymerization mechanism, despite the fact that they proceed via structure 8, because the antiaromatic resonance
forms do not contribute much and four-membered unsaturated heterocyclic transition states and intermediates with antiaromatic character, similar to that of 8 in Figures 2-14 and 2-15 have been reported for nitrogen-heterocycles,\textsuperscript{48} phosphorous-heterocycles,\textsuperscript{49} and oxygen-heterocycles.\textsuperscript{50} Monitoring the reaction of malonic (or methylmalonic) anhydride with a hindered base by NMR should be a straightforward way to distinguish between the polymerization mechanism (whose product would not be visible in the NMR spectrum) and the mechanisms presented in Figures 2-14 and 2-15. In an attempt to distinguish further between the mechanisms in Figures 2-14 and 2-15 (the products of both are ketene and CO\textsubscript{2}), it is possible to rationalize that because 8 is an anion, in chloroform, the step-wise mechanism (Figure 2-14) would be favored over the concerted (Figure 2-15). In this work we would like to determine if the base catalyzed deprotonation (possible mechanisms proposed in Figures 2-14 and 2-15) proceeding via the intermediate 8 occurs at a reasonable rate at room temperature and if it is more favorable than the polymerization, Figure 2-16. If the deprotonation is favorable, it would also be interesting to estimate the acidity of the malonic anhydride hydrogen. The calculated\textsuperscript{51} pKa values of malonic and methylmalonic anhydride are 7.33 ± 0.20 and 8.61 ± 0.20.
Figure 2-14. a) Stepwise, base catalyzed decomposition of methylmalonic anhydride.
b) Resonance forms of compound 8, the last two are anti-aromatic and don’t contribute much.
Figure 2-15. Concerted, base catalyzed decomposition of methylmalonic anhydride.
Figure 2.16. Polymerization of methylmalonic anhydride.
Kinetic Measurements

To obtain the values of the enthalpies and entropies of activation for the three anhydrides, the reaction rates and rate constants for each must first be determined. The decomposition of the anhydrides is described by equation 2-3, where A is the anhydride, K the ketene, and C carbon dioxide.\textsuperscript{20}

\[
A \rightarrow K + C
\]  
2-3

The rate of decomposition of the anhydride, the rate of formation of ketene, and the rate of formation of carbon dioxide can be expressed as first order rate laws according to equations 2-4, 2-5, and 2-6, respectively.\textsuperscript{52} In these equations [A] is the concentration of the anhydride, [K] the concentration of ketene, and [C] the concentration of carbon dioxide. The proportionality constant, \( k \), relates the rates of these reactions to the concentration of [A].\textsuperscript{20}

\[
-\frac{d[A]}{dt} = k[A]  
\]  
2-4

\[
\frac{d[K]}{dt} = k[A]  
\]  
2-5

\[
\frac{d[C]}{dt} = k[A]  
\]  
2-6

The concentrations of these species as a function of time could be obtained by integrating the differential rate equations above. For example, the integrated first order rate law for the decomposition of anhydride is given by equation 2-7 and in its logarithmic form by equation 2-8. The term \([A]_0\) represents the concentration of
anhydride at time zero. According to equation 2-8, the value of $-k$ can be obtained from the slope of a plot of $\ln([A]/[A]_0)$ versus time, or, because $[A]_0$ does not change throughout the run, from the slope of $\ln[A]$ versus time. $^52$

$$[A] = [A]_0 e^{-kt} \quad 2-7$$

$$\ln[A] = \ln[A]_0 - kt \quad 2-8$$

However, determining $k$ from the slope of $\ln[A]$ versus time is not ideal for several reasons. $^53$ The first problem lies in obtaining accurate values of $[A]$ throughout the run. When spectroscopic methods, in our case NMR, are used to monitor the reaction, changes in $[A]$ can be found by integrating the area under its peak (relative to the area of the standard) because signal intensity is proportional to concentration. Systematic error can be introduced if there are smaller peaks or noise hidden underneath the peak of interest. Extraneous peaks will lead to an increased peak area, and therefore an inaccurate determination of the concentration. In the case of the anhydride, as the reaction progresses, the anhydride decomposes and its signal decreases. Extraneous signals would affect the measurement of $[A]$ to a greater and greater extent as the reaction progresses and therefore result in an error in $k$ determined from the slope of $\ln[A]$ versus time. The second problem with this type of analysis is that an increasing error is introduced when logarithms of smaller and smaller values are taken. $^53$ Thus the relative error in the calculated value of $\ln[A]$ increases as the concentration of anhydride decreases. Lastly, the plot of $\ln[A]$ versus time may appear to be linear even when the reaction does not follow first order kinetics. $^53$ In our case knowing absolutely that the kinetics are first order is essential because it guarantees that, in addition to the thermal cycloreversion, the malonic
anhydride is not undergoing decomposition via a second order pathway. Sufficient
evidence that a reaction is first order can be obtained from the logarithmic analysis
only if the reaction is monitored for at least two half-lives. The half-life, $t_{1/2}$, for a first
order reaction is given by equation 2-9.\(^{53}\)

$$
t_{1/2} = -\frac{\ln\left(\frac{\frac{1}{2}[A]_t}{[A]_0}\right)}{k} = \frac{\ln 2}{k}
$$

The value of $k$ can also be obtained, more reliably, by using non-linear
regression analysis to fit the experimental data to equation 2-10.\(^{53}\) The terms $[A]_t$ and
$[A]_\infty$ in equation 2-10 represent the concentration of anhydride at any given time, $t$, and the concentration of anhydride at time infinity, respectively. The term $[A]_\infty$ serves
to correct the calculated value of $[A]_t$ for any extraneous signals hidden under the
anhydride peak. Non-linear regression analysis is a more reliable method of
determining $k$ than the plot of $\ln[A]$ versus time for two reasons. The first is because
it accounts for extraneous signals hidden under the anhydride peak. The second is that
it allows for a more dependable verification that the reaction is first order from the
quality of the fit of the experimental data to the first order rate law.

$$
[A]_t = \left(\left([A]_0 - [A]_\infty\right)e^{-kt}\right) + [A]_\infty
$$

2-10

The thermodynamic parameters of activation $\Delta H^\ddagger$ and $\Delta S^\ddagger$ could then be
determined from the temperature dependence of $k$ according to the Eyring equation,
eq 2-11, where $R$, $k_B$, and $h$ are the gas, Boltzmann, and Planck’s constants. Equation
2-11 states that a plot of the natural logarithm of $k/T$ versus reciprocal temperature
gives a slope of $-\Delta H^\ddagger/R$ and an intercept of $\ln(k_B/h) + \Delta S^\ddagger/R$. 
Base Catalyzed Decomposition Experiments

To determine whether the deprotonation of malonic anhydrides proceeds via the polymerization mechanism, Figure 2-16, or via either the step-wise or mechanisms in Figures 2-14 and 2-15, the reaction of MMA with hindered bases 4-dimethylaminopyridine (DMAP), N,N-diisopropylethylamine (DIEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 2,6-lutidine (LUT), and 4-cyanopyridine (CP) was monitored by NMR, for each base individually. The structures of the bases and the pK\textsubscript{a} values of their conjugate acids can be found in Table 2-1. MMA was used for these studies because its methyl group may allow us to observe the intermediate, 8 (Figures 2-14 and 2-15), if it is stable enough (long lived enough) to be observed by NMR. Also hindered bases were used to make the polymerization mechanism less likely.

It is possible to distinguish between the polymerization mechanism, Figure 2-16, and one of the mechanisms going via intermediate 8, Figures 2-14 and 2-15, by comparing the amount of ketene generated during the reaction with base to the amount of ketene generated, during the same time and at the same temperature, by the thermal decomposition (without added base). One possible outcome is that the amount of ketene generated during the reaction with added base will be less than the amount generated by the thermal mechanism alone. This would be a strong indication that the

\[
k = \left(\frac{k_B T}{h}\right) e^{\frac{-\Delta H^*_R}{RT} + \frac{-\Delta S^*_R}{R}}
\]

2-11
addition of base leads to the polymerization of the malonic anhydride, which results in the formation of polymer not ketene. The formation of a non-crystalline solid in the reaction vessel (in this case an NMR tube) would also support the polymerization mechanism. A second possible outcome is that the amount of ketene generated will be greater than the amount expected from the thermal mechanism alone. This would suggest that the reaction with base leads to the deprotonation of malonic anhydride, via intermediate 8, to produce ketene as shown in Figures 2-14 and 2-15. According to the mechanisms shown in Figures 2-14 and 2-15 the deprotonation is expected to be catalytic in nature, whereby 20% base can catalyze the decomposition of the entire amount of anhydride.

![Chemical Diagram]

**Figure 2-17.** The thermal and base catalyzed decomposition of MMA.
If it is found that the addition of base leads to the deprotonation of malonic anhydride, followed by decomposition to ketene + CO₂, assuming that the base catalyzed polymerization does not occur simultaneously, then the rate constant for the base catalyzed decomposition, $k_{BCD}$, could be obtained from eqs. 2-12 and 2-13, where $t$, $[K]_{BCD}$, $[A]_{base}$, $[A]_0$, and $k$ are the time in seconds, the concentration of ketene (generated by the base catalyzed decomposition only) at time $t$, the concentration of anhydride at time $t$ (generated during the reaction with added base), the initial concentration of anhydride, and the rate constant for the thermal decomposition of the anhydride in sec⁻¹, respectively (this is also shown in Figure 2-17). It should be noted that in previous studies, ketene was found to hydrolyze over time¹ and so its concentration at time $t$ may not accurately represent the amount of ketene generated. Accordingly, equation 2-13, which uses the concentration of anhydride at time $t$ (generated during the reaction with added base) instead of the concentration of ketene at time $t$, affords a more accurate value of $k_{BCD}$ than eq. 2-12.

\[
[K]_{BCD} = \frac{k_{BCD} [A]_0}{k_{BCD} + k} \left[1 - e^{-(k_{BCD} + k)t}\right] \quad 2-12
\]

\[
[A]_{base} = [A]_0 e^{-(k_{BCD} + k)t} \quad 2-13
\]
Table 2-1. The names, abbreviations, and structures of the bases used for the base catalyzed decomposition studies, along with the pKa values of their conjugate acids.

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Structure</th>
<th>pKa&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
<td>DBU</td>
<td><img src="Image" alt="Structure" /></td>
<td>13.28 ± 0.20</td>
</tr>
<tr>
<td>N,N-diisopropylethylamine</td>
<td>DIEA</td>
<td><img src="Image" alt="Structure" /></td>
<td>10.98 ± 0.28</td>
</tr>
<tr>
<td>4-dimethylaminopyridine</td>
<td>DMAP</td>
<td><img src="Image" alt="Structure" /></td>
<td>9.52 ± 0.10</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>LUT</td>
<td><img src="Image" alt="Structure" /></td>
<td>6.67 ± 0.10</td>
</tr>
<tr>
<td>4-cyanopyridine</td>
<td>CP</td>
<td><img src="Image" alt="Structure" /></td>
<td>1.92 ± 0.10</td>
</tr>
</tbody>
</table>

<sup>a</sup> The calculated pKa values for the protonated bases at 25°C.²⁸
Summary

In summary, the goal of this work is to gain insight into the [2+2] cycloreversion mechanism by performing kinetic measurements on the decomposition of malonic, methylmalonic, and dimethylmalonic anhydrides, Figure 2-11. These anhydrides 5, 6, and 7 can be synthesized using the Perrin and Arrhenius synthetic procedure. The rates of decomposition of these malonic anhydrides will be monitored by NMR spectroscopy and the activation parameters determined according to eq. 2-11. If sterics are the dominant influence on the reaction rate, the enthalpy of activation of dimethylmalonic anhydride should be higher than that of the parent malonic anhydride. On the other hand, if electronics are the major influence, then the enthalpy of activation of dimethylmalonic anhydride should be lower than that of the parent. The enthalpy of activation of methylmalonic anhydride should provide information about the extent to which electronic effects influence the rate of decomposition. The entropy of activation, which is a reflection of the number of ways that the reactant can be rotated to reach the transition state, is predicted to be more favorable for the parent malonic anhydride than that for methylmalonic anhydride by the amount Rln2.

Finally, the decomposition of methylmalonic anhydride with various sterically hindered bases will be monitored in an effort to determine whether this decomposition results in the polymerization of the anhydride or leads to ketene and CO$_2$ via one of the pathways with the intermediate 8, Figures 2-14 and 2-15. The experiments with base will also help to establish the relative acidity of malonic anhydride.
Experimental

Materials

Malonic, methylmalonic, and dimethylmalonic anhydrides were produced by ozonolysis of diketene (9, Figure 2-18), 4-ethylidene-3-methyl-2-oxetanone (10, Figure 2-18), and 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (11, Figure 2-18), respectively.1 Diketene was purchased from Aldrich and purified by distillation. The distilled diketene was found to be pure by NMR, and the spectral data can be found under ‘Characterization of Products’. The dimethylmalonic and monomethylmalonic anhydride precursors, 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone and 4-ethylidene-3-methyl-2-oxetanone, were synthesized as reported in literature.54,55,56 All other reagents were obtained from commercial suppliers and used as received.

Figure 2-18. The precursors to malonic anhydride (diketene, 9), methylmalonic anhydride (methylketene dimer, 10), and dimethylmalonic anhydride (3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone, 11).
Synthesis of 4-(Z)-ethylidene-3-methyl-2-oxetanone

The methylketene dimer (10, Figure 2-18) synthesis was adapted from a previously reported procedure. A two-neck flask was fitted with a dropping funnel and a reflux condenser. The dropping funnel and reflux condenser were both fitted with rubber septa and a balloon. The system was placed under a nitrogen atmosphere. Anhydrous ethyl ether (200 mL) and propionyl chloride (17 mL, 0.19 moles) were added through the condenser via syringe under stirring. Triethylamine (28 mL, 0.20 moles) was then added dropwise to the flask from the dropping funnel and the mixture was allowed to reflux. The rate of addition was adjusted to maintain reflux. After the triethylamine addition, heat was applied to maintain reflux for one hour. The reaction mixture was stirred for one additional hour and then allowed to stand overnight at room temperature.

The cream-colored triethylamine hydrochloride precipitate was filtered off, and the ether was evaporated from the filtrate under reduced pressure to give the crude product. The crude product was distilled under reduced pressure, then further purified by Kugelrohr distillation, giving product (10, Figure 2-18), a colorless oil. The $^1$H NMR (500 MHz, CDCl$_3$) product peaks were at 1.40 ppm (d, $J = 7.5$ Hz, CH$_3$), 1.68 ppm (dd, $J = 7.0$, 1.5 Hz, CH$_3$), 3.96 ppm (qp, $J = 7.5$, 1.5, 1.5 Hz, H), 4.73 ppm (qd, $J = 7.0$, 1.5 Hz, H), (lit. $^5$ 1.41 ppm (d, $J = 7.6$, CH$_3$), 1.68 ppm (dd, $J = 7.0$, 1.4, CH$_3$), 3.99 ppm (qd, $J = 7.6$, 1.4, H), 4.76 ppm (qd, $J = 7.0$, 1.4, H). The peak at 3.96 ppm is split into a quartet as a result of coupling with the methyl group at 1.41 ppm ($^3$J = 7.5 Hz). It is further split by coupling with the vinyl H at 4.73 ppm ($^4$J = 1.5 Hz) and the
methyl at 1.68 ppm (\(^J = 1.5\) Hz), resulting in a quartet of pentets where the outermost lines are too weak to see (so that it looks like a quartet of triplets). The splitting pattern which we report for the peak at 3.96 ppm is different from that of the literature reference, where the splitting pattern of the corresponding peak at 3.99 ppm is reported\(^56\) as a quartet of doublets. Presumably that is a typo because every J value should appear twice. The \(^1\text{H}\) NMR also showed a small amount of propionic anhydride impurity at 2.4 ppm (q, CH\(_2\)), 1.15 ppm (t, CH\(_3\)), (lit.\(^57\) \(\delta\) 2.50, and 1.19), which did not interfere with the kinetics.

The stereochemistry of the methylketene dimer had been confirmed to be 4-(Z)-ethylidene-3-methyl-2-oxetanone,\(^58\) by comparison of its experimental dipole moment to the calculated dipole moments for both isomers and also from the comparison of proton NMR chemical shifts of its alpha and vinyl hydrogens to those of 8-oxo-9-oxabicyclo[5.2.0]nonene-1.

**Synthesis of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid \(\beta\)-lactone**

The dimethylketene dimer (11, Figure 2-18) was prepared according to the previously reported procedure.\(^{55}\) Tetramethyl-1,3-cyclobutanedione (2.53 g, 18.0 mmoles) in a 3-neck flask equipped with a reflux condenser and thermometer was heated at 115-120°C until the material melted and turned dark brown. Aluminum chloride, which was purchased as anhydrous and newly opened (0.05 g, 0.4 mmoles), was then added under stirring. The temperature rose to 160°C and the mixture began to reflux. This temperature was maintained, to continue reflux for 30 min. The
reaction mixture was then distilled under reduced pressure through a Vigreux column, giving the crude product (11, Figure 2-18). This mixture was further purified by fractional distillation under atmospheric pressure giving product (11, Figure 2-18), which was found to be pure by NMR. The $^1$H NMR (400 MHz, CDCl$_3$) peaks were at 1.45 ppm (s, CH$_3$), 1.61 ppm (s, CH$_3$), and 1.66 ppm (s, CH$_3$) (lit.$^{59}$ δ 1.45, 1.62, and 1.67).

**Preparation of Samples for Thermal Decomposition Experiments**

Three stock solutions, one for each ketene dimer (diketene, methylketene dimer, and dimethylketene dimer), were prepared. The diketene and dimethylketene stock solutions were stored at -2 °C under nitrogen and the methylketene stock solution was stored at -20 °C under nitrogen. Aliquots of these stock solutions were then used to prepare the samples used for the ozonolysis of the ketene dimers and the subsequent kinetic experiments.

The diketene stock solution was prepared to be 0.3 M diketene and 0.03 M cyclopentane as the internal reference standard in chloroform-$d$ (CDCl$_3$). The methylketene dimer stock solution was prepared to be 0.03 M methylketene dimer in CDCl$_3$ (the internal reference standard, acetonitrile, was not added to the stock solution, but to each individual sample prior to the ozonolysis – as described below). The dimethylketene dimer stock solution was prepared to be 0.1 M dimethylketene dimer and 0.2 M acetonitrile (ACN) as the internal reference standard in CDCl$_3$.

Each sample was prepared the day of the experiment by adding the desired ketene dimer stock solution, internal reference standard (if not already present in the
stock solution), CDCl$_3$, and propionaldehyde (for the diketene and methylketene dimer samples) into an NMR tube. The total volume of sample prepared for ozonolysis was 200 µL (to minimize the amount of sample splashing out of the NMR tube during ozonolysis). Propionaldehyde (PIA) was used to scavenge the peroxides formed during the ozonolysis. Earlier attempts to scavenge the dissolved peroxides in the parent malonic anhydride with 1 – 2 equivalents of acetone or cyclohexanone failed, and in both cases did not lead to the formation of the expected ozonide. The exact composition of every sample, as diluted by additional CDCl$_3$, is listed in Table 2-2. In addition to these, a ‘dual run’ sample was prepared. It was composed of 0.1 M methylketene dimer, 0.05 M dimethylketene dimer, 0.2 M PIA, and 0.1 M ACN in 200 µL total volume in CDCl$_3$. The dual run sample was prepared using a different distillation fraction of methylketene dimer, one containing more of the propionic anhydride impurity. This was done to test whether the propionic anhydride interferes with the kinetic experiments. As will be shown later in ‘Results’, this impurity was not found to interfere.

**Table 2-2.** Composition of diketene, methylketene dimer, and dimethylketene dimer samples prior to ozonolysis, in 200 µL total volume in CDCl$_3$.

<table>
<thead>
<tr>
<th>Sample</th>
<th>[Ketene Dimer] (M)</th>
<th>PIA (M)</th>
<th>Cyclopentane (M)</th>
<th>ACN (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>diketene</td>
<td>0.2</td>
<td>1</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>methylketene dimer</td>
<td>0.02</td>
<td>0.1</td>
<td>-</td>
<td>0.02</td>
</tr>
<tr>
<td>dimethylketene dimer</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Preparation of Samples for Base Catalyzed Decomposition Experiments

The samples for the base catalyzed decomposition experiments were prepared on the day of the experiment and were composed of 0.1 M methylketene dimer and either 0.05 or 0.1 M acetonitrile as the internal reference standard in 200 µL total volume in CDCl$_3$ as the solvent. After ozonolysis was performed (the details of the ozonolysis procedure is described in the section below), the samples were frozen and 20 mole % of base was added along with additional CDCl$_3$ so that the total sample volume was between 600-700 µL. The bases used were 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N,N-diisopropylethylamine (DIEA), 4-dimethylaminopyridine (DMAP), 2,6-lutidine (LUT), and 4-cyanopyridine (CP). All bases were determined to be pure by NMR and used without further purification. The DBU, DIEA, DMAP, and LUT were flushed with nitrogen gas and stored in a dessicator.

Ozonolysis

Once the given sample was in the NMR tube, it was placed in a dry ice/acetone cooling bath, and ozonolysis using an OREC Model 03V5-O ozone generator (Ozone Research and Equipment Corp.) was performed at -65 °C. The temperature of the cooling bath was monitored with a thermometer and was maintained by adding additional dry ice as needed. Ozone gas was bubbled through the NMR tube until the solution turned light blue, at which point oxygen gas was bubbled through to remove excess ozone from the sample. After ozonolysis, additional CDCl$_3$ (which was also chilled in the dry ice/acetone-cooling bath at -60 °C) was added into the NMR tube so that the total sample volume was between 600-700 µL. The NMR tube was capped,
but not parafilmed. Next, more dry ice was added to the cooling bath and the sample was frozen in an effort to prevent decomposition during transfer into the probe of the magnet.

After ozonolysis of the diketene sample, the peroxide solids, which were generated during the reaction, needed to be filtered off. The peroxide solids of the MA sample were found to interfere with the measurement of the rate of decomposition of the anhydride, and reproducible rates were found only after the peroxides were filtered off. The peroxides could have affected either the actual rate of decomposition of the anhydride by reacting with the anhydride or could have affected the apparent rate of its decomposition, which would happen if a peroxide peak was at the same chemical shift as the anhydride and was disappearing spontaneously. The malonic anhydride peak appears to be a clean, base-line separated singlet at 4.1 ppm, but it may be that a peroxide peak which is disappearing is hidden underneath. The peroxide peaks (due to the dissolved peroxides) in the 5.0 – 6.0 region do not change over the course of the reaction. The reaction of malonic anhydride with formaldehyde peroxide would be expected to produce an ozonide, Figure 2-19, which was not observed in the NMR spectrum. The NMR spectrum of this ozonide would exhibit the characteristic AB splitting pattern (due to the 2 sets of diastereotopic hydrogens), around 4.0 – 4.5 ppm for one set and 5.0 – 6.0 ppm for the other.
Figure 2-19. Ozonide product expected from the reaction of malonic anhydride with formaldehyde peroxide.

The filtering of the peroxide solids was done by quickly pouring the sample through a pre-cooled (using dry ice) 1 mL Corning Inc. plastic micropipette tip (blue) equipped with a piece of cotton to serve as the filter. The liquid was pushed through the filter using nitrogen gas. The peroxide solids of the methylketene dimer and dimethylketene dimer samples were found not to interfere with the kinetics, because the results of a kinetic run performed on each of the samples after filtering away the peroxides agreed with the results of runs where the samples were not filtered. The peroxides of the methylketene dimer and dimethylketene dimer samples were therefore not filtered away. Also, the dissolved peroxide dimers and trimers present in the monomethyl and dimethyl anhydride samples were found not to interfere because addition of the peroxide scavenging agent, PIA, did not affect the rate of decomposition in those two samples.

Even though water is not miscible with chloroform, the possibility of trace water reacting with our malonic anhydrides was tested by adding 2 equivalents of ethanol to a sample of malonic anhydride kept at -65 °C, immediately inserting it into the NMR probe cooled to -10 °C, and monitoring the subsequent reaction. As
expected, the result of adding ethanol was rapid decomposition of anhydride and the immediate formation of $^1$H NMR peaks at 1.31 ppm (t, 3H), 3.43 ppm (s, 2H) and 4.24 ppm (q, 2H), which are assigned to 3-ethoxy-3-oxopropanoic acid (monoethyl malonate, lit. $^6$ δ 1.3, 3.5, and 4.2), along with other decomposition products at 2.1 ppm (s) and 4.11 ppm (q), which may be due to ethyl acetate (lit. $^6$ δ 1.26, 2.04, and 4.11) if the peak at 1.26 ppm is hidden underneath the ethanol CH$_3$ signal (the two peaks present were too small to be accurately integrated). Since the formation of malonic acid was not observed in any of our anhydride spectra, we conclude that reaction of residual water with our anhydrides does not affect our kinetic experiments.

**NMR Kinetics**

All $^1$H NMR spectra were acquired on a JEOL 500 MHz ECA spectrometer. The NMR parameters used to acquire the kinetic data for the malonic (MA), methylmalonic (MMA), and dimethylmalonic (DMA) anhydride samples, including the excitation pulse (pw), $T_1$ values for the anhydrides and standards at -50 and 20 °C, repetition time ($T_R$), acquisition time ($T_a$), tip angle ($\alpha_T$), number of scans, and number of points, are listed in Table 2-3. The NMR parameters for the experiments with base were the same as those for the thermal decomposition experiments of MMA.
Table 2-3. NMR parameters used for kinetic studies of the three anhydrides, including the excitation pulse (\(pw\)), \(T_1\), repetition time (\(T_R\)), acquisition time (\(T_a\)), tip angle (\(\alpha_T\)), number of scans (\(N_{\text{scans}}\)), and number of points (\(N_{\text{points}}\)).

<table>
<thead>
<tr>
<th>Sample</th>
<th>(pw) ((\mu)s)</th>
<th>(T_1^a) (sec)</th>
<th>(T_1^b) (sec)</th>
<th>(T_R) (sec)</th>
<th>(T_a) (sec)</th>
<th>(\alpha_T)</th>
<th>(N_{\text{scans}})</th>
<th>(N_{\text{points}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>13.5</td>
<td>1.59</td>
<td>-</td>
<td>9.74</td>
<td>8.74</td>
<td>68</td>
<td>2</td>
<td>65,536</td>
</tr>
<tr>
<td>MMA</td>
<td>10.5</td>
<td>1.36</td>
<td>-</td>
<td>6.37</td>
<td>4.37</td>
<td>68</td>
<td>4</td>
<td>32,768</td>
</tr>
<tr>
<td>DMA</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>30.0</td>
<td>8.74</td>
<td>90</td>
<td>1</td>
<td>65,536</td>
</tr>
<tr>
<td>MMA + DMA</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>6.37</td>
<td>4.37</td>
<td>68</td>
<td>4</td>
<td>32,768</td>
</tr>
<tr>
<td>Cyclopentane</td>
<td>-</td>
<td>2.97</td>
<td>5.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACN</td>
<td>-</td>
<td>1.45</td>
<td>3.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(a\) at -50 ºC.  \(b\) at 20 ºC.  \(c\) This was the minimum interval between kinetic points used for DMA.

The time reported for each time-point is the time at the beginning of the first acquisition. A more accurate time would be the average of the midpoints of all of the acquisitions for that time-point. The average of the midpoints of all of the acquisitions for the time-points could be obtained by adding \(1.5T_R + 0.5T_a\) to the time of the beginning of the first acquisition for the experiments with 4 scans, \(0.5(T_R + T_a)\) to the time of the beginning of the first acquisition for the experiments with 2 scans, and \(0.5T_a\) to the time of the beginning of the first acquisition for the experiments with 1 scan.

The error in the rate constant that results from using the time at the beginning of the first acquisition as opposed to the time of the average of the midpoints of all of the acquisitions used for that time-point is found to be negligible by the following analysis. (For a detailed procedure of how the rate constants were determined, please see the end of this section.)
Correcting the time (of each time-point) does not affect the logarithmic rate constant because increasing the time (at each time-point) by the same amount does not change the slope of the plot of \(\ln[\text{anhydride}]_{\text{rel}}\) vs. time, eq 2-8 (please see the introduction and end of the experimental section for a discussion of eq. 2-8).

Correcting the time (of each time-point) does affect the nonlinear regression rate constant, which is determined by fitting the normalized experimental intensities of the anhydride peaks (the intensity is proportional to the concentration of anhydride) at each time-point to a value calculated according to eq. 2-10 (please see the introduction and end of the experimental section for a discussion of eq. 2-10). The intensity at each time-point can be calculated using either the time at the beginning of the first acquisition (to give the intensity of the anhydride signal at the start of each time-point) or using the time which is the average of the midpoints of all of the acquisitions for that time-point (to give the intensity at the midpoint of each time-point) as the value of \(t\) in eq. 2-10. Performing the nonlinear regression fit using the intensity of the anhydride signal at the start of each time-point (as was done in our case) or using the intensity of the anhydride signal at the midpoint, can easily be shown to lead to a 0.005 % error in the rate constant (for the longest \(T_R\) and the fastest \(k\); for the decomposition of MMA at 15.6 °C). An error of 0.005 % is negligible.

Saturation-recovery experiments were used to determine the \(T_1\) relaxation times for MA and MMA and the internal reference standards at -50 °C. Because of the thermal decomposition of the anhydrides, their \(T_1\) relaxation times could not be determined at higher temperatures, but the \(T_1\) relaxation times were determined for the
internal reference standards at 20 °C. Since the $T_1$ relaxation times of the reference standards are longer than those of the anhydrides at -50 °C, it was assumed that they are also longer than those of the anhydrides at 20 °C. Therefore, using the $T_1$ relaxation times of the reference standards near 20 °C, the pulse sequence for each anhydride was set up to allow for complete relaxation between pulses, which usually requires 5 $T_1$. To accommodate more scans in a shorter time period while still allowing for complete relaxation of the sample, the pulse sequences were adjusted to reduce the repetition time by reducing the tip angle. The desired tip angles were found using the Ernst equation\(^{60}\), equation 2-14, where $\alpha_T$, $T_R$, and $T_1$ are the tip angle, the repetition time, and the $T_1$ relaxation time, respectively. The tip angle for the MA and MMA samples was reduced to 68°. Our values of $T_R$, which can be found in Table 2-3, were longer than the repetition times required by the Ernst equation for experiments using a 68° tip angle. The $T_1$ relaxation times were not measured for DMA because only one scan was used to acquire the spectrum. For the DMA samples the minimum interval between time points was 30 sec, which is sufficient for complete relaxation. For the dual MMA + DMA run, to ensure complete relaxation of both anhydrides, the relaxation time determined for MMA was used, along with the shorter 8 $\mu$s pulse width determined for DMA.

$$\cos \alpha_T = e^{(-T_R/T_1)} \tag{2-14}$$

The free-induction decays were zero-filled (4x) to increase digital resolution, and line broadening of 0.2 Hz was applied. Malonic anhydride chemical shifts and intensities were referenced to internal cyclopentane ($\delta 1.51$)\(^{61}\). Monomethyl and
dimethylmalonic anhydride chemical shifts and intensities were referenced to internal acetonitrile ($\delta$ 2.10)\textsuperscript{62}. The spectra were processed using JEOL Delta and iNMR\textsuperscript{63} software. The integration region was chosen for each run on a case by case basis. First, all of the spectra from an individual kinetics experiment were overlaid in the NMR processing software so that all of the peaks from the same run could be integrated over the same region. Once the spectra were overlaid, an appropriate integration region was chosen for each peak, and the integrations were performed. It is also possible to use peak heights to monitor the anhydride decomposition, but integrations are easier because they do not require that very good shimming of the magnet be maintained throughout the decomposition.

First order rate constants were obtained at temperatures between 0 °C and 25 °C for MA, between -10 °C and 15 °C for MMA, and between 5 °C and 30 °C for DMA, at 5 °C intervals. The base catalyzed deprotonation experiments were performed at 15 °C. A few experiments with base were also performed at -40 and -30 °C, but those resulted only in the polymerization of the anhydride. Prior to the experiment, the temperature of the probe was set in the Delta software. The probe was first set to -50 °C and 15-20 min was allowed for cooling and temperature calibration. Once the sample was inserted into the magnet, one spectrum was taken at -50 °C and then the temperature was set to the desired value. Once the desired temperature was set, the samples were allowed to sit inside the probe for 5 minutes to allow for temperature equilibration, and then the kinetic experiment began. This 5-minute equilibration period was skipped for the base-catalyzed deprotonation samples (including one sample without added base, which was run for comparison) and the
acquisition of spectra for the base-catalyzed deprotonation samples began 1.0 – 1.75 minutes after insertion of the sample into the magnet. For the thermal decomposition samples, the extent of decomposition during this 5-minute equilibration time (at the highest temperature used to obtain the kinetic data) for MA (25.9 °C), MMA (15.6 °C), and DMA (31.4 °C) was found to be 42, 35, and 30 %, respectively. This initial decomposition does lead to a reduction in accuracy, but as will be seen from the rate constants and their errors presented in the Results section, this loss of accuracy is not large enough to prevent the accurate measurement of these rate constants.

For the thermal decomposition samples, time intervals between spectra at each temperature were adjusted so that a minimum of 15 spectra were acquired per run, and so that the reaction was monitored for more than one half-life. Also, one decomposition reaction for each anhydride was monitored until completion (more than 10 half-lives) to determine whether any residual peaks were obscured by the anhydride signal. Small peaks were found under the DMA signal. These peaks were assumed to be due to peroxides whose signals are also found in that region. As will be discussed in ‘data analysis’, these hidden peaks could result in an erroneous value of the logarithmic rate constant, but performing the nonlinear fit will eliminate this error.

For the base catalyzed decomposition samples, the time interval between spectra was 30 seconds, for all samples. In an effort to acquire spectra a minute after insertion into the magnet, the first few spectra were not shimmed, but shims saved for a similar samples were loaded prior to the acquisitions. Shimming was performed after the first 2-4 spectra and the acquisition of spectra every 30 seconds was resumed until the anhydride signal was no longer visible.
The temperature inside the NMR probe was measured twice for each run, once before the run and once after, using a 4% methanol in methanol-\(d_4\) standard.\(^{64}\) The probe temperature could be determined with the 4% methanol sample from eq. 2-15 or 2-16 (depending on the temperature) by recording \(\Delta\), the chemical shift difference between the methanol OH and CH\(_3\) groups.\(^{64}\) The difference between the temperature recorded before the run and the one recorded after was considered to be the variation in temperature during the run. This variation was found to be less than 1 °C for all of the runs.

\[
230 - 270^\circ K : T = (3.92 - \Delta)/0.008
\]

\[
270 - 300^\circ K : T = (4.109 - \Delta)/0.008708
\]

Characterization of Products

**Malonic Anhydride:** Ozonolysis of diketene (9, Figure 2-18) \(^1\)H NMR (500 MHz, CDCl\(_3\)) 4.9 ppm (dt, 1H, \(J = 4.2, 2.0\) Hz), 4.5 ppm (dt, 1H, \(J = 4.2, 1.5\) Hz), and 3.9 ppm (dd, 2H, \(J = 2.0, 1.5\) Hz) (lit.\(^5\) \(\delta 4.88, 4.50\) and 3.91) produced malonic anhydride (5, Figure 2-11) \(^1\)H NMR 4.1 ppm (s, 2H) (lit.\(^1\) \(\delta 4.1\)) and peroxides 5.0-6.0 ppm (lit.\(^1\) \(\delta 5.0-6.0\)). Disappearance of the malonic anhydride was monitored by normalizing the peak area of the anhydride signal to that of cyclopentane, the internal reference. Upon
decomposition of malonic anhydride the formation of ketene was observed at 2.3 ppm (s, 2H).

**Monomethylmalonic Anhydride:** Ozonolysis of 4-ethylidene-3-methyl-2-oxetanone (10, Figure 2-18) $^1$H NMR (500 MHz, CDCl$_3$) 1.40 ppm (d, J = 7.5 Hz, CH$_3$), 1.68 ppm (dd, J = 7.0, 1.5 Hz, CH$_3$), 3.96 ppm (qt, J = 7.5, 1.5, 1.5 Hz, H), 4.73 ppm (qd, J = 7.0, 1.5 Hz, H), (lit.$^a$ δ 1.41, 1.68, 3.99, and 4.76) produced methylmalonic anhydride (6, Figure 2-11) $^1$H NMR 4.30 ppm (q, 1H, J = 8.0 Hz) and 1.65 ppm (d, 3H, J = 8.0 Hz) and peroxides 1.0-2.0 and 5.0-6.0 ppm. Disappearance of the anhydride was monitored by normalizing the 4.30 ppm peak area of the anhydride to that of acetonitrile, the internal reference. Formation of methylketene was observed at 2.72 ppm (q, 1H, J = 7.3 Hz) and 1.69 ppm (d, 3H, J = 7.3 Hz).

**Dimethylmalonic anhydride:** Ozonolysis of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (11, Figure 2-18) $^1$H NMR (400 MHz, CDCl$_3$) 1.45 ppm (s, CH$_3$), 1.61 ppm (s, CH$_3$), and 1.66 ppm (s, CH$_3$) (lit.$^a$ δ 1.45, 1.62, and 1.67) produced dimethylmalonic anhydride (7, Figure 2-11) $^1$H NMR (500 MHz, CDCl$_3$) 1.63 ppm (s, CH$_3$) (lit.$^1$ δ 1.55) and acetone peroxides 1.0-2.0 ppm. Disappearance of the anhydride was monitored by normalizing the peak area of the anhydride to that of acetonitrile, the internal reference. Formation of dimethylketene was observed at 1.69 ppm (s, CH$_3$).
The formation of the ketene was not quantitative for any of the three samples. All three ketenes were found to apparently undergo hydrolysis or possibly polymerization during the course of the kinetic experiment. Ketene hydrolysis was previously reported for ketene and dimethylketene. Peaks found in our NMR spectra, which can be assigned to ketene (H_2CCO) hydrolysis products, were at 2.1 ppm, corresponding to acetic acid (lit. \( \delta \) 11.43 and 2.1 – the OH peak may have been too small or too broad to be observed in our sample), and at 2.2 ppm, corresponding to acetic anhydride (lit. \( \delta \) 2.2). NMR peaks which correspond to dimethylketene hydrolysis products were at 2.7 ppm (m, 1H/2H) and 1.02 ppm (d, 6H/12H), corresponding to either isobutyric acid (lit. \( \delta \) 11.88, 2.58, 1.2 – the OH peak may have been too small or too broad to observe in our sample) or isobutyric anhydride (lit. \( \delta \) 2.66, 1.24). NMR peaks attributable to the formation of propionic acid (lit. \( \delta \) 11.73, 2.38, 1.16) or propionic anhydride (lit. \( \delta \) 2.50, and 1.19) due to the hydrolysis of monomethylketene were not observed. Those peaks may have been obscured by the PIA peaks at 1.1 and 2.5 ppm. The peak area of propionic anhydride, which was present as an impurity from the synthesis of 4-ethylidene-3-methyl-2-oxetanone (10, Figure 2-18), did not appear to change over the course of the reaction.

**Base catalyzed decomposition of methylmalonic anhydride:** For all of the samples with added base the \(^1\)H NMR chemical shifts of methylmalonic anhydride were 4.3 ppm (q, 1H, \( J = 8.0 \) Hz) and 1.65 ppm (d, 3H, \( J = 8.0 \) Hz). Disappearance of the anhydride resulted in the formation of methylketene, whose peaks appeared at 3.6 ppm (q, 1H, \( J = 7.3 \) Hz) and 1.58 ppm (d, 3H, \( J = 7.3 \) Hz). Additionally, formation of
acetic acid was observed at 2.2 ppm (s - the OH peak may have been too small or too
broad to observe in our sample), and very small amounts of acetic anhydride at 2.3
ppm (s, CH₃) and propionic acid (or anhydride) at 2.5 ppm (q, CH₂) and 1.2 ppm (t,
CH₃). The 1.2 ppm propionic acid/anhydride triplet partially overlapped with the
peroxide peaks in the 1.0 – 2.0 ppm region. The presence of acetic acid and acetic
anhydride was verified by adding a small amount of first acetic acid, then acetic
anhydride into the NMR tube at the end of the reaction and observing an increase in
intensity of the corresponding peaks. Disappearance of the methylmalonic anhydride
was monitored by normalizing the 4.3 ppm peak area of the anhydride to that of
acetonitrile, the internal reference. Formation of methylketene was monitored by
normalizing the peak area of the quartet observed at 2.72 ppm in the experiment
without base, and 3.6 ppm in the experiments with base to that of acetonitrile. For the
experiments with DBU, the methylketene quartet at 3.6 ppm overlapped with another
peak and only one of the small outer peaks of the quartet was baseline separated. For
this sample the peak area of the ketene was found by integrating the baseline-separated
outer peak, and calculating the total area of the quartet knowing that the ratios of the
peaks should be 1:3:3:1.

Data Analysis

Thermal Decomposition

The concentration of anhydride relative to the concentration of the standard,
[anhydride]₀, at each time point was obtained by dividing the integrated peak area of
the anhydride by the integrated peak area of the standard. The first order rate constant
was then obtained by two methods. First, \( k \) was obtained from the slope of the plot of \( \ln[\text{anhydride}]_{\text{rel}} \) vs. time, eq 2-8. Second, \( k \) was obtained using non-linear regression analysis to fit the data to eq. 2-10. The terms \( k \), \( t \), \( [A]_r \), \( [A]_0 \), and \( [A]_\infty \), in equations 2-8 and eq 2-10 represent the rate constant, time, the relative concentration of anhydride at each time point, the relative concentration of anhydride at time zero, and the relative concentration of anhydride at time infinity, respectively. The term \( [A]_\infty \) serves to account for any extraneous signals hidden under the anhydride peak, which might be seen at the end of the reaction when the anhydride has fully decomposed. Non-linear regression analysis was performed to eliminate systematic error from integrating extraneous peaks hidden under the anhydride peak and also to avoid systematic error potentially caused by the increase in error when logarithms of smaller and smaller values are taken as the concentration of anhydride decreases.

The non-linear regression analysis was performed by using an iterative method, the Solver routine in an Excel spreadsheet, to vary the values of \( k \), \( [A]_\infty \), and \( [A]_0 \), eq. 2-17, to find \( [A]_t \) \(_{\text{calc}} \) at all time points so that the value of ss, eq. 2-18, was minimal. The terms \( [A]_t \) \(_{\text{exp}} \), and \( [A]_t \) \(_{\text{calc}} \) are the experimental and calculated relative anhydride concentrations at any given time point. The initial guesses for \( [A]_0 \), and \( [A]_\infty \) used in the iterative calculation were their experimental values, and the initial guess for \( k \) was the value obtained from the logarithmic plot of eq 2-8. The rate constant determined from the logarithmic plot will be referred to as \( k_{\text{Lin}} \), and the one determined using non-linear regression analysis as \( k_{\text{NL}} \).

\[
[A]_{\text{calc}} = \left( ([A]_0 - [A]_\infty e^{-kt}) + [A]_\infty \right)
\] 2-17
\[ ss = \sum (A_{\text{exp}} - A_{\text{calc}})^2 \]

For each anhydride \( \Delta H^\ddagger \) and \( \Delta S^\ddagger \), as well as the standard errors in these quantities, were then obtained from a plot of \( \ln(k_{\text{Lin}}/T) \) or \( \ln(k_{\text{NL}}/T) \) versus \( 1/T \), eq. 2-11.

**Base Catalyzed Decomposition**

The values of \( k_{\text{BCD}} \) were determined from, eq. 2-13, using the value of \( k \) that was extrapolated form the NLR MMA Eyring plot for the appropriate temperature. The term \([A]_0\), in eq. 2-13, is the relative concentration of anhydride at the first time-point of the base-catalyzed deprotonation experiment and term and \([A]_{\text{base}}\) is the amount of anhydride left at time \( t \) after decomposition due to both the thermal and the base catalyzed mechanisms, respectively. The values of \([A]_0\) and \([A]_{\text{base}}\) are obtained from each NMR spectrum by dividing the integrated peak area of the anhydride by the integrated peak area of the acetonitrile standard.

The percent of ketene produced in the reactions with base, \( \%\text{ketene}_{\text{base}} \), relative to the amount of ketene generated only from the thermal decomposition (without added base) was obtained from equation 2-19. It should be noted that the relative concentrations of ketene discussed below were obtained by dividing the integrated peak area of the ketene by the integrated peak area of the acetonitrile standard. In equation 2-19, \([K]_{\text{base}}\) is the relative concentration of ketene formed (in the experiments with added base) and \([K]_{\text{thermal, calc}}\) is the relative concentration of ketene expected from thermal decomposition to give exclusively ketene (at the same
temperature and during the same time period). The values of $[K]_{\text{base}}$ and $[K]_{\text{thermal,calc}}$ were found from equations 2-20 and 2-21, respectively. In equation 2-20, $[K]_0$ is the relative concentration of ketene at the first time-point and $[K]_t$ is the relative concentration of ketene at a particular time, $t$. The relative concentration of ketene that is expected exclusively from the thermal decomposition, $[K]_{\text{thermal,calc}}$, (this value does NOT include the amount of ketene generated by the deprotonation of the malonic anhydride) was obtained from equation 2-21 from the known amount of anhydride present in the beginning of the reaction with base and the calculated amount of anhydride that should be left at time $t$, if the anhydride was undergoing thermal decomposition only. In eq. 2-21, $[A]_0$ is the relative concentration of anhydride at the first time-point of each base-catalyzed deprotonation run and the value of $[A]_t$ is obtained from equation 2-10 using the known time, $t$ (duration of the run), the value of $[A]_\infty$ (0.0001) found from the nonlinear regression fit for the thermal MMA kinetics experiment at 15.6 °C, the value of $k$ for the thermal decomposition that was extrapolated from the NLR MMA Eyring plot for each temperature, and the value of $[A]_0$ (the relative concentration of anhydride at the first time-point) that is obtained from each individual base-catalyzed deprotonation run. As can be seen from eq. 2-21, the value of $[A]_0 - [A]_t$ is equal to the amount of anhydride that underwent thermal decomposition, $[A]_{\text{thermal}}$, during the time, $t$. Since each molecule of anhydride that undergoes thermal decomposition produces one molecule of ketene, the amount of anhydride that underwent thermal decomposition is equal to the amount of ketene that should be generated by the thermal decomposition, $[K]_{\text{thermal,calc}}$. It should be noted that due to hydrolysis of ketene, the concentration of ketene obtained by integrating
the area of the ketene peak in the NMR spectrum would be smaller than the concentration of ketene calculated from concentrations of anhydride. For example, in an experiment without added base, the relative concentration of ketene determined from the integrated area of the ketene peak, \([K]_{\text{thermal, exp}}\), would be smaller than the value of \([K]_{\text{thermal, calc}}\), calculated from concentrations of anhydride using eq. 2-21. The ratio of \([K]_{\text{thermal, exp}}\) to \([K]_{\text{thermal, calc}}\) multiplied by 100 (or \% ketene\textsubscript{thermal, exp} in eq. 2-22), where both values of \([K]_{\text{thermal, exp}}\) and \([K]_{\text{thermal, calc}}\) were obtained from data of the same run without added base, is 73 \%, and is listed in Table 2-13 of the Results. This means that 73 \% of the ketene generated by the thermal decomposition of malonic anhydride has not undergone hydrolysis (during a period of time that is comparable to that of the base-catalyzed deprotonation experiments).

\[
%\text{ketene}_{\text{base}} = \frac{[K]_{\text{base}}}{[K]_{\text{thermal, calc}}} \times 100 \quad 2-19
\]

\[
[K]_{\text{base}} = [K]_t - [K]_0 \quad 2-20
\]

\[
[K]_{\text{thermal, calc}} = [A]_0 - [A]_t = [A]_{\text{thermal}} \quad 2-21
\]

\[
%\text{ketene}_{\text{thermal, exp}} = \frac{[K]_{\text{thermal, exp}}}{[K]_{\text{thermal, calc}}} \times 100 \quad 2-22
\]
Results

Rate constants for the decomposition of malonic anhydrides

The first-order rate constants at each temperature determined from the logarithmic plots, eq. 2-8, and from nonlinear regression analysis, eq. 2-10, for the decomposition of all three anhydrides can be found in Tables 2-4, 2-5, and 2-6. The values listed in Tables 2-4 – 2-6 (and also Tables 2-7 – 2-13) were rounded off to the correct number of significant figures, but the insignificant figures of those values were used in the calculations.

Table 2-4. Values of $k_{Lin}$, standard error and relative standard deviation of $k_{Lin}$, correlation coefficient determined from the logarithmic plot, along with the values of $k_{NL}$ and $(A/x/A_0)*100$ for MA at various temperatures.

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>$10^4k_{Lin}$ (sec$^{-1}$)</th>
<th>$10^4\sigma_{Lin}$</th>
<th>% $\sigma_{Lin}$</th>
<th>$r$</th>
<th>$10^4k_{NL}$ (sec$^{-1}$)</th>
<th>$(A/x/A_0)100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.9</td>
<td>18.1</td>
<td>0.2</td>
<td>1.1</td>
<td>0.9990</td>
<td>18</td>
<td>0.007</td>
</tr>
<tr>
<td>20.7</td>
<td>10.1</td>
<td>0.1</td>
<td>1.4</td>
<td>0.9976</td>
<td>10.2</td>
<td>0.017</td>
</tr>
<tr>
<td>20.5</td>
<td>9.3</td>
<td>0.2</td>
<td>2.0</td>
<td>0.9939</td>
<td>9.3</td>
<td>0.022</td>
</tr>
<tr>
<td>15.7</td>
<td>6.7</td>
<td>0.08</td>
<td>1.1</td>
<td>0.9979</td>
<td>6.76</td>
<td>0.001</td>
</tr>
<tr>
<td>10.7</td>
<td>4.49</td>
<td>0.05</td>
<td>1.2</td>
<td>0.9975</td>
<td>4.42</td>
<td>-0.102</td>
</tr>
<tr>
<td>5.8</td>
<td>2.79</td>
<td>0.05</td>
<td>1.9</td>
<td>0.9960</td>
<td>2.85</td>
<td>0.067</td>
</tr>
<tr>
<td>0.8</td>
<td>1.73</td>
<td>0.01</td>
<td>0.8</td>
<td>0.9988</td>
<td>1.73</td>
<td>0.008</td>
</tr>
<tr>
<td>0.8</td>
<td>1.63</td>
<td>0.02</td>
<td>1.1</td>
<td>0.9978</td>
<td>1.61</td>
<td>0.018</td>
</tr>
</tbody>
</table>
Table 2-5. Values of $k_{Lin}$, standard error and relative standard deviation of $k_{Lin}$, correlation coefficient determined from the logarithmic plot, along with the values of $k_{NL}$ and $(A_x/A_0)*100$ for MMA at various temperatures.

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>$10^4k_{Lin}$ (sec$^{-1}$)</th>
<th>$10^4\sigma_{Lin}$</th>
<th>% $\sigma_{Lin}$</th>
<th>r</th>
<th>$10^4k_{NL}$ (sec$^{-1}$)</th>
<th>$(A_x/A_0)100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.6</td>
<td>14.08</td>
<td>0.07</td>
<td>0.5</td>
<td>0.997</td>
<td>14.15</td>
<td>0.005</td>
</tr>
<tr>
<td>10.6</td>
<td>8.34</td>
<td>0.03</td>
<td>0.3</td>
<td>0.9999</td>
<td>8.21</td>
<td>0.003</td>
</tr>
<tr>
<td>10.6</td>
<td>7.39</td>
<td>0.08</td>
<td>1.1</td>
<td>0.9985</td>
<td>7.36</td>
<td>0.001</td>
</tr>
<tr>
<td>10.6</td>
<td>7.36</td>
<td>0.15</td>
<td>2.0</td>
<td>0.9947</td>
<td>7.22</td>
<td>0.001</td>
</tr>
<tr>
<td>10.7</td>
<td>8.32</td>
<td>0.03</td>
<td>0.4</td>
<td>0.9998</td>
<td>8.37</td>
<td>0.003</td>
</tr>
<tr>
<td>10.7</td>
<td>8.04</td>
<td>0.05</td>
<td>0.7</td>
<td>0.9997</td>
<td>7.73</td>
<td>0.003</td>
</tr>
<tr>
<td>10.7</td>
<td>7.14</td>
<td>0.08</td>
<td>1.2</td>
<td>0.9985</td>
<td>7.21</td>
<td>0.007</td>
</tr>
<tr>
<td>5.7</td>
<td>5.24</td>
<td>0.04</td>
<td>0.8</td>
<td>0.9993</td>
<td>5.18</td>
<td>0.002</td>
</tr>
<tr>
<td>0.8</td>
<td>3.51</td>
<td>0.03</td>
<td>0.9</td>
<td>0.9988</td>
<td>3.45</td>
<td>0.003</td>
</tr>
<tr>
<td>-3.8</td>
<td>2.29</td>
<td>0.04</td>
<td>1.6</td>
<td>0.9960</td>
<td>2.29</td>
<td>0.001</td>
</tr>
<tr>
<td>-9.1</td>
<td>1.43</td>
<td>0.01</td>
<td>0.9</td>
<td>0.9988</td>
<td>1.43</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 2-6. Values of $k_{Lin}$, standard error and relative standard deviation of $k_{Lin}$, correlation coefficient determined from the logarithmic plot, along with the values of $k_{NL}$ and $(A_x/A_0)*100$ for DMA at various temperatures.

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>$10^4k_{Lin}$ (sec$^{-1}$)</th>
<th>$10^4\sigma_{Lin}$</th>
<th>% $\sigma_{Lin}$</th>
<th>r</th>
<th>$10^4k_{NL}$ (sec$^{-1}$)</th>
<th>$(A_x/A_0)100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.4</td>
<td>11.15</td>
<td>0.04</td>
<td>0.4</td>
<td>0.9999</td>
<td>12.33</td>
<td>5.7</td>
</tr>
<tr>
<td>26.0</td>
<td>7.11</td>
<td>0.04</td>
<td>0.5</td>
<td>0.9998</td>
<td>7.86</td>
<td>3.8</td>
</tr>
<tr>
<td>20.9</td>
<td>4.54</td>
<td>0.01</td>
<td>0.3</td>
<td>0.9999</td>
<td>4.89</td>
<td>2.9</td>
</tr>
<tr>
<td>15.6</td>
<td>2.614</td>
<td>0.008</td>
<td>0.3</td>
<td>0.9999</td>
<td>2.78</td>
<td>3.2</td>
</tr>
<tr>
<td>15.6</td>
<td>2.671</td>
<td>0.009</td>
<td>0.3</td>
<td>0.9999</td>
<td>2.797</td>
<td>2.7</td>
</tr>
<tr>
<td>15.6</td>
<td>2.621</td>
<td>0.014</td>
<td>0.5</td>
<td>0.9998</td>
<td>2.981</td>
<td>7.0</td>
</tr>
<tr>
<td>10.6</td>
<td>1.476</td>
<td>0.014</td>
<td>0.9</td>
<td>0.9992</td>
<td>1.697</td>
<td>6.8</td>
</tr>
<tr>
<td>5.6</td>
<td>0.891</td>
<td>0.006</td>
<td>0.6</td>
<td>0.9994</td>
<td>1.036</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Tables 2-4, 2-5, and 2-6 also list the error in $k_{\text{Lin}}$ ($\sigma_{\text{Lin}}$), determined from the standard error of the slope of the logarithmic plots, the relative standard deviation of $k_{\text{Lin}}$ ($\% \sigma_{\text{Lin}}$), the correlation coefficient ($r$), and the percent infinity absorbance not due to anhydride ($\left(\frac{A_\infty}{A_0}\right)\times 100$, determined from the nonlinear regression analysis). For all three anhydrides, the values of $k_{\text{NL}}$ are more reliable because, as explained earlier, they account for infinity absorbance and errors in the logarithmic plots at smaller values of $[\text{anhydride}]_{\text{rel}}$. The error in $k$ will be discussed and a comparison of $k_{\text{Lin}}$ and $k_{\text{NL}}$ will be made below.

As seen from the data in Tables 2-4, 2-5, and 2-6, all three anhydrides were found to decompose at room temperature. This had been observed before for malonic and dimethylmalonic anhydrides. At similar temperatures the rate constant for the decomposition is the highest for methylmalonic anhydride and lowest for dimethylmalonic anhydride. The values of $\left(\frac{A_\infty}{A_0}\right)\times 100$ for MA and MMA are close to zero. The average value of $\left(\frac{A_\infty}{A_0}\right)\times 100$ calculated for DMA is 4.8. This agrees well with the experimental data, where no infinity signal was observed for MA and MMA, but small residual peaks were seen in the spectrum of DMA. As seen from the values in Tables 2-4, 2-5, and 2-6, although the value of $\left(\frac{A_\infty}{A_0}\right)\times 100$ for the DMA sample is larger than that for MA and MMA, the error, $\% \sigma_{\text{Lin}}$, for the DMA sample is not higher than for MA or MMA.
Determination of the Activation Parameters

The parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ of activation were determined from the Eyring plot, eq. 2-11, of the natural logarithm of $k/T$ versus reciprocal temperature, which has a slope of $-\Delta H^\ddagger/R$ and an intercept of $\ln(k_B/h) + \Delta S^\ddagger/R$, where $R$, $k_B$, and $h$ are the gas, Boltzmann, and Planck’s constants. Figures 2-20, 2-21, 2-22, 2-23, 2-24 and 2-25 are the Eyring plots for each anhydride. There are two plots for each anhydride: one plotted using the logarithmic rate constant ($k_{\text{Lin}}$), and the other using the NLR rate constant ($k_{\text{NL}}$). Both sets of rate constants could not be plotted on the same plot because the points overlap too closely. The slopes, standard errors of the slope, intercepts, standard errors of the intercepts, correlation coefficients, and standard error of the y ($\sigma_y$) found from these plots are listed in Table 2-7. The correlation coefficients found from these plots are all > 0.99. Since the Eyring plots are adequately linear, there is no evidence that $\Delta H^\ddagger$ is temperature-dependent or that there is any detectable $\Delta C_P^\ddagger$. The values of the enthalpy, $\Delta H^\ddagger$, and entropy, $\Delta S^\ddagger$, of activation along with their errors, which will be discussed below, are listed in Table 2-8.
Figure 2-20. MA Eyring plot, using the logarithmic rate constants.

Figure 2-21. MA Eyring plot, using the NLR rate constants.
Figure 2-22. MMA Eyring plot, using the logarithmic rate constants.

Figure 2-23. MMA Eyring plot, using the NLR rate constants.
Figure 2-24. DMA Eyring plot, using the logarithmic rate constants.

Figure 2-25. DMA Eyring plot, using the NLR rate constants.
Table 2-7. The slopes, standard errors of the slope, intercepts, standard errors of the intercepts, correlation coefficients, and standard error of the y for the Eyring plots in Figures 2-20 – 2-25.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>Slope</th>
<th>±</th>
<th>Intercept</th>
<th>±</th>
<th>r</th>
<th>σy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA (Lin)</td>
<td>-7.1</td>
<td>0.2</td>
<td>11.7</td>
<td>0.8</td>
<td>0.9972</td>
<td>0.068</td>
</tr>
<tr>
<td>MA (NL)</td>
<td>-7.1</td>
<td>0.2</td>
<td>11.7</td>
<td>0.8</td>
<td>0.9972</td>
<td>0.068</td>
</tr>
<tr>
<td>MMA (Lin)</td>
<td>-6.4</td>
<td>0.3</td>
<td>9.7</td>
<td>0.9</td>
<td>0.9928</td>
<td>0.081</td>
</tr>
<tr>
<td>MMA (NL)</td>
<td>-6.4</td>
<td>0.3</td>
<td>9.6</td>
<td>1.0</td>
<td>0.9922</td>
<td>0.083</td>
</tr>
<tr>
<td>DMA (Lin)</td>
<td>-8.1</td>
<td>0.1</td>
<td>14.2</td>
<td>0.5</td>
<td>0.9991</td>
<td>0.037</td>
</tr>
<tr>
<td>DMA (NL)</td>
<td>-8.0</td>
<td>0.1</td>
<td>13.8</td>
<td>0.4</td>
<td>0.9994</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Table 2-8. The enthalpy and entropy of activation values along with their errors found from Figures 2-20 – 2-25.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>$\Delta H^\ddagger$ (kcal/mol)</th>
<th>±</th>
<th>$\Delta S^\ddagger$ cal/(mole*K)</th>
<th>±</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA (Linear)</td>
<td>14.2</td>
<td>0.4</td>
<td>-24.0</td>
<td>1.5</td>
</tr>
<tr>
<td>MA (NL)</td>
<td>14.2</td>
<td>0.4</td>
<td>-23.9</td>
<td>1.5</td>
</tr>
<tr>
<td>MMA (Linear)</td>
<td>12.7</td>
<td>0.5</td>
<td>-27.9</td>
<td>1.8</td>
</tr>
<tr>
<td>MMA (NL)</td>
<td>12.6</td>
<td>0.5</td>
<td>-28.1</td>
<td>1.9</td>
</tr>
<tr>
<td>DMA (Linear)</td>
<td>16.2</td>
<td>0.3</td>
<td>-18.9</td>
<td>1.0</td>
</tr>
<tr>
<td>DMA (NL)</td>
<td>15.9</td>
<td>0.2</td>
<td>-19.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Error Analysis

Error in the Rate Constant and Temperature Effects

The errors in the first-order rate constants were determined by three different methods. The first was to determine the error in the rate constants from the error in the slope of each logarithmic plot of ln[anhydride]_rel versus time. These errors, $\sigma_{Lin}$, are listed in Tables 2-4, 2-5, 2-6. The average values of $10^4k_{Lin}$ and $10^4\sigma_{Lin}$ (obtained by averaging $\sigma_{Lin}$ for each anhydride over all temperatures) for MA, MMA, and DMA are $6.85 \pm 0.09$, $6.65 \pm 0.06$, and $4.14 \pm 0.02$ sec$^{-1}$, respectively. The second method was to determine the errors in the first-order rate constants from the standard deviation of the $y$, $\sigma_y$, in the Eyring plots, using propagation of uncertainty. The relationship between the standard deviation of $y$ of the Eyring plot and the error in $k$, $\sigma_k$, is given by equation 2-23, where $\sigma_y$ is equal to $\sigma_{lnk}$ because we assume that there is no error in temperature. To distinguish the error in $k$ found according to eq. 2-23 from the other error values of $k$ that we describe, we call the error in $k$ determined from the standard deviation of $y$ of the Eyring plot, $\sigma_{k(Eyr)}$ (so that in eq. 2-23, $\sigma_k = \sigma_{k(Eyr)}$). The errors, $\sigma_{k(Eyr)}$, can be converted to percent standard deviations, as shown by equation 2-24, simply by multiplying the values of $\sigma_y$ (Table 2-7) by 100. Accordingly, the values of $\% \sigma_{k(Eyr)}$, for the logarithmic rate constants are 6.8, 8.1, and 3.7 % for MA, MMA, and DMA, respectively. The values of $\% \sigma_{k(N,Eyr)}$ for the NLR rate constants are 6.8, 8.3, and 2.8 % for MA, MMA, and DMA, respectively. The values of $\% \sigma_{k(Eyr)}$ and $\sigma_{k(Eyr)}$, which were determined from the Eyring plots, are larger than the average values of $\sigma_{Lin}$ and $\%\sigma_{Lin}$, given above.
\[ \sigma_y = \sigma_{\ln k} = \frac{\partial \ln k}{\partial k} \cdot \sigma_k = \frac{1}{k} \cdot \sigma_k = \frac{1}{k} \cdot \sigma_{k(Eyr)} \]  \hspace{1cm} 2-23

\[ \%\sigma_{k(Eyr)} = \frac{\sigma_{k(Eyr)}}{k} \cdot 100 = \frac{k \cdot \sigma_y}{k} \cdot 100 = \sigma_y \cdot 100 \]  \hspace{1cm} 2-24

The third method to determine the error in the rate constants is from the variation in rate constant in experiments repeated at the same temperature. These errors, \( \sigma_{k(Rep)} \), can be seen in Tables 2-4 – 2-6 and also in the Eyring plots in Figures 2-20 – 2-25. Their values have also been listed in Table 2-9, which contains the temperature at which the repeated runs were performed, the average linear rate constant for all runs at that particular temperature, the standard deviation in \( k_{Lin} \) determined from repeated runs at that same temperature, relative standard deviation \( \%\sigma_{k(Lin)} \), the average NLR rate constant for all runs at that particular temperature, the standard deviation in \( k_{NL} \) determined from repeated runs at that same temperature, and relative standard deviation \( \%\sigma_{k(NL)} \). The values of \( \%\sigma_{k(Rep)} \) (5.1, 7.3, and 3.9 % for MA, MMA, and DMA, respectively) are comparable to the values of \( \%\sigma_{k(N,Eyr)} \) (6.8, 8.3, and 2.8 % for MA, MMA, and DMA, respectively). Likewise, the values of \( \%\sigma_{k(L,Rep)} \) (4.1, 7.6, and 1.2 % for MA, MMA, and DMA, respectively) are comparable to the values of \( \%\sigma_{k(L,Eyr)} \) (6.8, 8.1, and 3.7 % for MA, MMA, and DMA, respectively). However, the values of \( \%\sigma_{k(Eyr)} \) are more reliable than the values of \( \%\sigma_{k(Rep)} \) because they are determined using more data points. Both of the values of \( \%\sigma_{k(Eyr)} \) and \( \%\sigma_{k(Rep)} \) are larger than \( \%\sigma_{Lin} \).
Table 2-9. The average linear and NLR rate constant for MA, MMA, and DMA for repeated runs at the same temperature along with the variation in the rate constant determined from the repeated experiments.

<table>
<thead>
<tr>
<th>anhydride</th>
<th>T (°C)</th>
<th>$&lt;10^4 k_{Lin}&gt;$ (sec$^{-1}$)</th>
<th>$10^4 \sigma_k$ (sec$^{-1}$)</th>
<th>$&lt;10^4 k_{NL}&gt;$ (sec$^{-1}$)</th>
<th>$10^4 \sigma_k$ (sec$^{-1}$)</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>0.8</td>
<td>1.68</td>
<td>0.07</td>
<td>4.1</td>
<td>1.67</td>
<td>0.09</td>
<td>5.1</td>
</tr>
<tr>
<td>MMA</td>
<td>10.6</td>
<td>7.7</td>
<td>0.6</td>
<td>7.3</td>
<td>7.6</td>
<td>0.5</td>
<td>7.1</td>
</tr>
<tr>
<td>MMA</td>
<td>10.7</td>
<td>7.8</td>
<td>0.6</td>
<td>7.9</td>
<td>7.8</td>
<td>0.6</td>
<td>7.5</td>
</tr>
<tr>
<td>DMA</td>
<td>15.6</td>
<td>2.64</td>
<td>0.03</td>
<td>1.2</td>
<td>2.85</td>
<td>0.11</td>
<td>3.9</td>
</tr>
</tbody>
</table>

As stated in the previous paragraph, a comparison of $\% \sigma_k(\text{Eyr})$ and $\% \sigma_{Lin}$ shows that the variation in $k$ during one experiment is not as large as the variation in $k$ in experiments at different temperatures. The errors determined from the logarithmic plot would include error due to the variation in temperature during a single experiment, while errors determined from the Eyring plots would include errors due to variation in temperature for the entire temperature range over which the data points were acquired. The relative standard deviation of $k$ due to uncertainty in temperature, $\% \sigma_k(\text{Temp})$, could be estimated using equation 2-25. This equation gives only a very good approximation of $\% \sigma_k(\text{Temp})$ because it ignores the contribution from $k_B T/h$, equation 2-11. The estimates of $\% \sigma_k(\text{Temp})$ found using equation 2-25 can be found in Table 2-10, which also lists the values of $\Delta H^\ddagger$ for each anhydride, the average temperature over which the kinetic measurements were made, and the uncertainty in the temperature as determined using the methanol thermometer, $\Delta T$. The uncertainty
in the probe temperature determined using the 4% methanol thermometer was assumed to 0.8 °K, which was the error previously reported for a 100% MeOH thermometer. The estimated values of % \( \sigma_{k(\text{Temp})} \) found in Table 2-10 are comparable to the experimental errors, % \( \sigma_{k(\text{Eyr})} \), suggesting that uncertainties in our temperature measurements could explain the errors in the rate constants.

\[
\%\sigma_{k(\text{Temp})} = \frac{\Delta k}{k} \times 100 = \frac{\Delta H^*}{RT} \times \frac{\Delta T}{T} \times 100
\]

Table 2-10. The value of \( \Delta H^\ddagger \) (in kcal/mole) for each anhydride, the average temperature over which the kinetic measurements were made in °C, the uncertainty in the temperature determined using the methanol thermometer, and the relative standard deviation of \( k \) due to uncertainty in temperature.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>( \Delta H^\ddagger ) kcal/mole</th>
<th>(&lt;T&gt; ) (°C)</th>
<th>( \Delta T ) (°K)</th>
<th>% ( \sigma_{k(\text{Temp})} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>14.2</td>
<td>12.5</td>
<td>0.8</td>
<td>7.0</td>
</tr>
<tr>
<td>MMA</td>
<td>12.6</td>
<td>2.5</td>
<td>0.8</td>
<td>6.7</td>
</tr>
<tr>
<td>DMA</td>
<td>15.9</td>
<td>17.5</td>
<td>0.8</td>
<td>7.6</td>
</tr>
</tbody>
</table>

The values of \( \Delta H^\ddagger \) and \( \Delta S^\ddagger \) (each determined from logarithmic and NLR rate constants) along with their errors are listed in Table 2-8. The errors in the values of \( \Delta H^\ddagger \) and \( \Delta S^\ddagger \) of activation were determined from the errors in the slope and the intercept of the Eyring plot, respectively. The enthalpy of activation is the smallest for MMA and the largest for DMA. The entropy of activation for DMA is significantly less negative than for MMA and MA, and that for MMA is more negative than for MA, but perhaps not significantly so.
Other Error Analysis

Table 2-11 lists the values of \( k_{\text{Lin}} \), \( \sigma_{k(L,Eyr)} \), \( k_{\text{NL}} \) and \( \sigma_{k(N,Eyr)} \) found from a dual run of MMA and DMA at 15.8 °C and also those values extrapolated from the MMA and DMA linear and NLR Eyring plots at that temperature. The extrapolated values were found using the temperature value of 15.77 °C, which was the exact readout of the methanol temperature thermometer. As can be seen from the data in Table 2-11, rate constants determined from a dual run containing MMA and DMA agree, at the 95 % confidence level, with the values extrapolated from individual MMA and DMA experiments (whose results can be found in Tables 2-5 and 2-6, respectively). Additionally, the dual run served to test whether the peroxide solids affect the rate of decomposition of DMA. The results of the dual run, where the peroxides were filtered off, were compared to the results obtained when the DMA peroxides were not filtered off (those extrapolated from the values in Table 2-6). The agreement between the dual-run and extrapolated rate constants shows that the peroxide solids have no effect on the rate of decomposition of DMA.

Finally, a dual run was made with a stock solution using a different distillation fraction of methylketene dimer, containing a greater amount of the propionic anhydride impurity (produced during the synthesis of the methylketene dimer). Again, the agreement between the dual-run and the extrapolated rate constants shows that propionic anhydride does not affect the rate of decomposition of MMA (or DMA).
Table 2-11. Values of $k_{Lin}$, $\alpha_{k(L,Eyr)}$, $k_{NL}$ and $\alpha_{k(N,Eyr)}$ found from the dual run of MMA and DMA along with the corresponding values (of $k_{Lin}$, $\alpha_{k(L,Eyr)}$, $k_{NL}$ and $\alpha_{k(N,Eyr)}$) extrapolated from the MMA and DMA linear and NLR Eyring plots at 15.8 °C.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>$10^4k_{Lin}$ (sec$^{-1}$)</th>
<th>$10^4\alpha_{k(L,Eyr)}$</th>
<th>$10^4k_{NL}$ (sec$^{-1}$)</th>
<th>$10^4\alpha_{k(N,Eyr)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMA $^a$</td>
<td>13.3</td>
<td>1.1</td>
<td>13.4</td>
<td>1.0</td>
</tr>
<tr>
<td>MMA $^b$</td>
<td>12.2</td>
<td>1.0</td>
<td>12.4</td>
<td>0.9</td>
</tr>
<tr>
<td>DMA $^a$</td>
<td>2.41</td>
<td>0.09</td>
<td>2.84</td>
<td>0.08</td>
</tr>
<tr>
<td>DMA $^b$</td>
<td>2.62</td>
<td>0.10</td>
<td>2.91</td>
<td>0.08</td>
</tr>
</tbody>
</table>

$^a$ Values obtained from dual experiment. $^b$ Values extrapolated from Linear and NLR MMA and DMA data above. (MMA: Table 2-5 and Figures 2-22 and 2-23; DMA Table 2-6 and Figures 2-24 and 2-25)

The peroxide solids were also not filtered off of the MMA samples, whose data is shown in Table 2-5, with the exception of the samples used to test the effect of filtering the peroxide solids as described here. To test the effect of peroxide solids on the rate of decomposition of MMA, the rate constant of an unfiltered sample was compared to the rate constants of samples whose peroxides were filtered off. The data obtained from these experiments are shown in Table 2-12, which lists the values of $k_{Lin}$, $\alpha_{k(L,Eyr)}$, $k_{NL}$ and $\alpha_{k(N,Eyr)}$ found from the decomposition of MMA at the same temperature, three samples at 10.6 °C and three at 10.7 °C, with one being unfiltered. These data are also presented in Table 2-5 and used to create the Eyring plots in Figures 2-22 and 2-23; however, Table 2-12 lists the values of $\alpha_{k(L,Eyr)}$ and $\alpha_{k(N,Eyr)}$, which makes comparison of these values easier. The rate constant of the unfiltered sample agrees, at the 95 % confidence level, with the rate constants of the filtered samples, showing that the peroxide solids have no effect on the rate of decomposition of MMA.
Table 2-12. Values of $k_{\text{Lin}}$, $\sigma_{k(L,Eyr)}$, $k_{\text{NL}}$ and $\sigma_{k(N,Eyr)}$ found from MMA runs at the same temperature, performed to test the effect of peroxide solids on the rate of decomposition of MMA.

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>$10^4 k_{\text{Lin}}$ (sec$^{-1}$)</th>
<th>$10^4 \sigma_{k(L,Eyr)}$</th>
<th>$10^4 k_{\text{NL}}$ (sec$^{-1}$)</th>
<th>$10^4 \sigma_{k(N,Eyr)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.6</td>
<td>8.3</td>
<td>0.7</td>
<td>8.2</td>
<td>0.7</td>
</tr>
<tr>
<td>10.6</td>
<td>7.4</td>
<td>0.6</td>
<td>7.4</td>
<td>0.6</td>
</tr>
<tr>
<td>10.6</td>
<td>7.4</td>
<td>0.6</td>
<td>7.2</td>
<td>0.6</td>
</tr>
<tr>
<td>10.7$^a$</td>
<td>8.3</td>
<td>0.7</td>
<td>8.4</td>
<td>0.7</td>
</tr>
<tr>
<td>10.7</td>
<td>8.0</td>
<td>0.6</td>
<td>7.7</td>
<td>0.6</td>
</tr>
<tr>
<td>10.7</td>
<td>7.1</td>
<td>0.6</td>
<td>7.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

$^a$ Values obtained from sample where the peroxide solids were not filtered.

Lastly, the decomposition of MMA was monitored without added PIA, to test the effect of the dissolved peroxides on its rate of decomposition. The conditions for this experiment were the same as those for the base catalyzed deprotonation experiments, meaning that there was no 5 minute equilibration period after the temperature was set to 15 °C, and that the collection of spectra began 1.5 minutes after the sample was inserted into the magnet. The probe was pre-cooled to 15 °C prior to the insertion of the sample. Additionally, because in this case the desired temperature of 15 °C was so close to ambient temperature, which varies between 17 – 20 °C, a wait time of 1.5 minutes was sufficient for temperature equilibration. This was independently tested with a methanol thermometer, which showed that the temperature after 1.5 min of setting the temperature (to 15 °C) was 15.75 °C, and after 5.5 min was 15.96 °C. The value of $10^4 k_{\text{Lin}}$ (15.9 °C) for the sample without added PIA was found
to be 14.39 sec\(^{-1}\), while the value of \(10^4k_{\text{Lin}} (15.6 \, ^\circ\text{C}, \text{Table 2-5})\) for the sample with PIA was found to be 14.08 sec\(^{-1}\). Even with the temperature difference, the relative standard deviation for these two rate constants is 1.5 %. The relative standard deviation for the NLR rate constants of these two samples, 14.50 sec\(^{-1}\) (15.9 \, ^\circ\text{C}, \text{no PIA added}) and 14.15 sec\(^{-1}\) (15.6 \, ^\circ\text{C}, \text{with PIA, Table 2-5}), was found to be 1.7 %. Also, the value of \((A_x/A_0)*100\) obtained from the NLR analysis of the data for the MMA kinetic experiment without added PIA was found to be 0.001, which agrees with the values of \((A_x/A_0)*100\) found in Table 2-5, which were found for the samples with PIA added. These results suggest that the dissolved peroxides do not significantly affect the rate of the decomposition of MMA.

**Base Catalyzed Decomposition of Methylmalonic Anhydride**

The rate constants for the base catalyzed decomposition of MMA, eq. 2-13, found for the experiments with DMAP, DIEA, DBU, and LUT are listed in Table 2-13 along with the temperature at which each experiment was performed and the values of % ketene\(_{\text{base}}\) (which will be discussed in the next paragraph). The rate constant for the base catalyzed decomposition of MMA with the base CP is not \(k_{\text{BCD}}\) (eq. 2-13, Figure 2-17) because this decomposition does not lead to ketene (this will be discussed in the next paragraph). The rate constant for the base catalyzed decomposition of MMA with CP is defined here as \(k_D (\ln([A]_{\text{base}}/[A_0]) = -t(k_D + k)\), where \(t\), \([A]_{\text{base}}\), \([A]_0\), and \(k\) are the time in seconds, the concentration of anhydride at time \(t\) (generated during the reaction with added base), the initial concentration of anhydride, and the rate constant.
for the thermal decomposition of the anhydride in sec^{-1}, respectively.) The rate constant for the base catalyzed decomposition of MMA listed in Table 2-13 for the experiment with CP is therefore $10^4 k_D$ not $10^4 k_{BCD}$.

As can be seen from Table 2-13, the rate constants for the base catalyzed decomposition are about 10 times larger than the value of $k$ found from the thermal decomposition experiment. The experiment with DIEA was performed in duplicate, which allowed us to determine that the error in $k_{BCD}$ is 9%. The increased rate of decomposition of MMA in the presence of base supports our proposed mechanism for base-catalyzed deprotonation via intermediate 8 (Figures 2-14 and 2-15). Our control experiment ruling out the polymerization mechanism will be discussed in the following paragraph.

Table 2-13. The rate constants and values of % ketene_{base} obtained for the base catalyzed decomposition experiments and one run without added base at temperatures near 16 °C.

<table>
<thead>
<tr>
<th>Sample</th>
<th>T (°C)</th>
<th>$10^4 k_{BCD}$ (sec^{-1})</th>
<th>% Ketene_{base}</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMA, no base added</td>
<td>15.9</td>
<td>14^{a}</td>
<td>73^{b}</td>
</tr>
<tr>
<td>MMA + DMAP</td>
<td>16.0</td>
<td>148</td>
<td>267</td>
</tr>
<tr>
<td>MMA + DIEA</td>
<td>16.0</td>
<td>126</td>
<td>100</td>
</tr>
<tr>
<td>MMA + DIEA</td>
<td>15.9</td>
<td>111</td>
<td>116</td>
</tr>
<tr>
<td>MMA + DBU</td>
<td>16.0</td>
<td>154</td>
<td>168</td>
</tr>
<tr>
<td>MMA + LUT</td>
<td>16.3</td>
<td>89</td>
<td>101</td>
</tr>
<tr>
<td>MMA + CP</td>
<td>16.3</td>
<td>79^{c}</td>
<td>4</td>
</tr>
</tbody>
</table>

^{a}Value of $k$ (not $k_{BCD}$, sec^{-1}). ^{b}Obtained from eq. 2-22, as explained in the experimental section.

^{c}As described above, this is the value of $k_D$ not $k_{BCD}$. 
To exclude the polymerization mechanism, the values of $\% \text{ketene}_{\text{base}}$, eq. 2-19, were obtained from the experiments where 20 mole percent of base was added to a sample of methylmalonic anhydride. The values of $\% \text{ketene}_{\text{base}}$ for each experiment are listed in Table 2-13. The $\% \text{ketene}_{\text{base}}$ values for the experiments with DMAP, DIEA, DBU, and LUT are all greater than 73 %, which shows that the amount of ketene generated during the experiments with added base is greater than the amount expected from the thermal decomposition alone and therefore that the addition of base leads to the deprotonation of malonic anhydride via a mechanism which leads to the production of ketene. As was described in the Experimental section, the amount of ketene expected from the thermal decomposition alone, as determined from eq. 2-22, is 73 % and is lower than 100 % because some of the ketene is hydrolyzed over time (this value is also listed in Table 2-13). The $\% \text{ketene}_{\text{base}}$ value for the experiment with CP is much less than the yield of ketene in the experiment without added base. Based on the values obtained for the duplicate runs with DIEA the error in $\% \text{ketene}_{\text{base}}$ is 11 %.
Discussion

Kinetics of Decomposition of Malonic Anhydride

Our results confirm the previous observation\(^1\) that MA decomposes faster than DMA, and additionally show that MMA decomposes faster than both MA and DMA. This can be seen from the data in Tables 2-4 – 2-6, which show that at similar temperatures the rate constant for the thermal decomposition of MMA is the highest of the three anhydrides studied and that of DMA is the lowest. This trend is demonstrated more explicitly by using the rate constants for the thermal decomposition of the three anhydrides extrapolated from their respective NLR Eyring plots (Figures 2-21, 2-23, and 2-25). At 15.0 °C, the extrapolated values of \(10^4k\) for MA, MMA, and DMA are 6.4 ±0.4 sec\(^{-1}\), 11.3 ±0.9 sec\(^{-1}\), and 2.7 ±0.1 sec\(^{-1}\), respectively. An unusual feature, that should be noted, is that these rates are not linear with the number of methyl groups.

The values of \(\Delta G^\ddagger\) at 15.0 °C, for MA, MMA, and DMA that were determined according to eq. 2-26 (using the values of \(k\) that were extrapolated from their respective NLR Eyring plots, Figures 2-21, 2-23, and 2-25) are 21.05 ± 0.04 kcal/mol, 20.72 ± 0.05 kcal/mol, and 21.54 ± 0.02 kcal/mol, respectively. These confirm that MMA has the lowest value of \(\Delta G^\ddagger\) and that DMA has the highest value of \(\Delta G^\ddagger\).

\[
k = \left(\frac{k_B T}{h}\right) e^{\frac{-\Delta G^\ddagger}{RT}}
\] 2-26
The Enthalpy of Activation for the Decomposition of Malonic Anhydrides

As can be seen from the values of $\Delta H^\ddagger$ in Table 2-8 the enthalpy of activation increases from 12.6±0.5 and 14.2±0.4 kcal/mol for the thermal decomposition of MMA and MA, respectively, to 15.9±0.2 kcal/mol for the thermal decomposition of DMA. These values provide strong evidence supporting the claim that the decomposition of these malonic anhydrides occurs via the [2+2] cycloreversion pathway because they agree with the low activation enthalpy values expected for a concerted mechanism. According to the IUPAC Glossary of Terms used in Physical Organic Chemistry\textsuperscript{19} two or more “primitive changes,” such as the formation or the breaking of bonds, “are said to be concerted (or to constitute a concerted process) if they occur within the same elementary reaction,” where an elementary reaction is defined as “a reaction for which no reaction intermediates have been detected or need to be postulated in order to describe the chemical reaction on a molecular scale.”\textsuperscript{19}

The activation enthalpy of a concerted process is characteristically low because when the bond breaking and forming happen simultaneously, the energy gain due to bond formation compensates for the energy loss due to bond breaking. For example, the enthalpy of activation for the [4+2] cycloreversion of dicyclopentadiene is 27.5 ± 1 kcal/mol.\textsuperscript{32} The transition state structure of this reaction is made up of two partially broken $\sigma_{\text{C-C}}$ bonds, one partially broken $\pi_{\text{C=C}}$ bond and three partially formed $\pi_{\text{C=C}}$ bonds. The energy cost of breaking the two $\sigma_{\text{C-C}}$ bonds (the typical bond energy of a C-C bond is 81 kcal/mol)\textsuperscript{33} and the one $\pi_{\text{C=C}}$ bond (the typical bond energy of a C=C
bond is 64 kcal/mol) \(^{33}\) is compensated for by the simultaneous formation of the three new \(\pi_{C=C}\) bonds. Examples of activation enthalpy values determined for other [2+2] cycloreversion reactions include that of bicyclo[3.2.0]hept-2-en-6-one, 36.7 kcal/mol \(^{67}\) and also that for the cycloreversion of diketene, 48.31 kcal/mol. \(^{68}\) The activation enthalpy values determined for MA, MMA and DMA were found to be even lower than those reported for bicyclo[3.2.0]hept-2-en-6-one, diketene, and others. \(^{67,41,28}\) The unusually low activation enthalpies for the cycloreversions of MA, MMA, and DMA are due to the stability of the products, especially the CO\(_2\), whose production involves the formation of an exceptionally strong C=O bond with a bond dissociation energy (192 kcal/mol) \(^{34}\) that is much higher than the bond dissociation energies of typical C=C (145 kcal/mol) \(^{66}\) or C=O (173 kcal/mol) \(^{66}\) bonds.

For comparison with a stepwise process, the calculated \(^{35}\) and experimental \(^{36}\) activation enthalpies for the thermal decomposition of cyclobutene, a reaction that proceeds through the tetramethylene biradical intermediate, are 62.7 kcal/mol and 61.1 kcal/mol, respectively (the latter determined from \(E_a = \Delta H^\ddagger + RT\), \(^{69}\) where \(E_a = 62.5\) kcal/mol and \(T = 440\) °C). The activation enthalpy of this stepwise process is much higher than that of the concerted process because the rate-determining step of the stepwise process involves only the homolytic cleavage of a \(\sigma_{C-C}\) bond, with no bond formation to compensate for the energy lost as a result of the bond breaking.

Two factors that can contribute to the enthalpy of activation and thus the relative rates of decomposition of the malonic anhydrides are the steric bulk and the \(\sigma - \pi\) electron-donating ability of the methyl substituents. For cycloaddition and
cycloreversion reactions, where pathways minimizing steric strain in the transition state are favored, steric factors should increase activation enthalpies and decrease rates for reactants with bulky substituents which hinder the formation of the twisted transition state (see Figure 2-7 for a minimally strained transition state structure). If steric factors are the dominant influence on the decomposition of malonic anhydrides, then DMA should have a lower rate of decomposition and higher activation enthalpy than MA. The second factor, which is the $\sigma - \pi$ electron-donating ability of alkyl substituents, decreases the relative electrophilicity of ketenes, which would decrease their reactivity in cycloaddition reactions. Electron-donating methyl substituents increase the rates of cycloreversions by increasing the stability of the $sp^2$ carbons forming in the transition states. If electronic effects are the dominant influence on the decomposition rate of malonic anhydrides, then DMA, whose electron-donating methyl substituents stabilize the transition state, should have a higher rate of decomposition and lower activation enthalpy than MA.

For example, the effect of steric factors on the [2+2] cycloaddition of an alkene with an asymmetrically substituted ketene is evident from the favored geometry of interaction between them, which is when the larger ketene substituent points away from the alkene and when the bulky substituents on the alkene point away from the substituents on the ketene, Figure 2-7. This approach minimizes the steric interaction of the substituents in the transition state and is preferred over other approaches. The results of a study comparing the rates of [2+2] cycloaddition reactions between ethoxyketene and variously substituted olefins show that the activation enthalpy
increases and the rate decreases when substituents create steric strain in the transition state. At 100 °C the rate constants of the [2+2] cycloaddition of ethoxyketene with cis-2-butene and trans-2-butene (relative to that of 2,3-dimethyl-2-butene) are 25.0 and 1.7, respectively. The difference between their activation energies, $E_a(\text{trans}) - E_a(\text{cis})$, was found to be 0.26 kcal, with the larger activation energy for the alkene whose substituents lead to the more sterically strained transition state. The effect of bulky substituents on cycloaddition reaction rates can also be demonstrated by the results of studies of the [2+2] cycloaddition reactions of alkylphenylketenes to cis and trans ethyl propenyl ethers,\textsuperscript{29} Figure 2-10. For example, the partial rate constant of the cycloaddition for orientation 1 (R=CH$_3$, Figure 2-10), 985 L*mol$^{-1}$*sec$^{-1}$, is higher than that for orientation 3, 61 L*mol$^{-1}$*sec$^{-1}$. Furthermore, the rate of the cycloaddition for orientations 1 and 3 was found to decrease as the size of the substituent on the ketene increased. The rate of the cycloaddition for orientations 2 and 4 was also found to decrease with increasing size of the ketene substituent. For example, for orientation 2, when the size of the substituent, R, was increased from methyl to $t$-butyl, the partial rate constant for the cycloaddition decreased from 130 to 5.1 L*mol$^{-1}$*sec$^{-1}$. The decrease in the partial rate constants (observed for orientations 2 and 4) could not be explained by steric factors because the substituent, R, was pointing away from the ketenophile, but could be explained because an increased stabilization due to an increased electron-donating ability of larger alkyl substituents leads to a reduction in ketene reactivity. The authors, therefore, suggested that electronic factors must also contribute.
The results of our kinetic experiments show that DMA has a higher value of $\Delta H^\ddagger$ than both MA and MMA, supporting the proposal that bulky substituents hinder the formation of the DMA twisted transition state and that steric effects are the dominant influence on the rate of decomposition of DMA, relative to MA and MMA. The values of $\Delta H^\ddagger$ of MA and MMA are not significantly different at the 95% confidence interval, but at the 68% confidence interval the value of $\Delta H^\ddagger$ of MMA is smaller than that of MA. A smaller $\Delta H^\ddagger$ for MMA is consistent with an acceleration due to electronic stabilization of the $sp^2$ carbons forming in the transition state. If the activation enthalpy for the decomposition of MMA were due only to sterics, it would be expected that the value of $\Delta H^\ddagger$ of MMA would be the same as that of MA, because the bulky methyl group of MMA would always rotate in a way to minimize steric strain in the transition state, as shown in Figures 2-7 and 2-12. In addition, the rate of decomposition of MMA would be half that of MA, because MMA would rotate in the favorable direction only 50% of the time. Another possibility is that in addition to steric factors, electronic factors also contribute to the activation enthalpy of the anhydrides. If both electronics and sterics contribute to the value of $\Delta H^\ddagger$ of MMA, then the value of $\Delta H^\ddagger$ of MMA would be expected to be less than that of MA. This is because the MMA methyl group would not only twist to avoid steric strain in the transition state, but would also lead to a stabilization of the $sp^2$ carbons forming in the transition state, lowering the activation barrier of MMA relative to that of MA. Depending on the extent to which the activation barrier is lowered for MMA relative to MA, the reduction in the activation barrier could also lead to a higher rate of decomposition for MMA, even though only half of the rotations are favorable. As
discussed earlier we did find that the rate for the decomposition of MMA is higher than the rate for the decomposition of MA. In addition, as can be seen from the data in Table 2-8, the value of $\Delta H^\ddagger$ determined for MMA is indeed lower than the value of $\Delta H^\ddagger$ determined for MA, at the 68% confidence interval. These findings suggest that both steric and electronic effects influence the rates of decomposition of the malonic anhydrides.

Using the enthalpy data in Table 2-8, we can estimate the amount that one methyl group stabilizes (due to electronics) and destabilizes (due to steric) the transition state of this cycloreversion. First, we can calculate the decrease in activation enthalpy due to the electronic stabilization of the transition state by one methyl group from the values of $\Delta H^\ddagger$ of MMA and MA. As mentioned above the steric effects would be the same for MA and MMA and therefore the lower activation enthalpy of MMA ($\Delta H^\ddagger_{\text{MA}} - \Delta H^\ddagger_{\text{MMA}}$) must be due to the stabilization of the MMA transition state by its electron donating methyl group. The amount of this stabilization, which is the electronic stabilization of the transition state by one methyl group is $1.6 \pm 0.6$ kcal/mol. Next, using this estimate the increase in $\Delta H^\ddagger$ due to the steric destabilization of the transition state by one methyl could be found. This estimate can be made knowing that the activation enthalpy of MA, $\Delta H^\ddagger_{\text{MA}}$, should be equal to the activation enthalpy of DMA, $\Delta H^\ddagger_{\text{DMA}}$, plus the enthalpy due to the electronic stabilization of the DMA transition state by two methyl groups, $2(1.6 \pm 0.6)$ kcal/mol, minus the enthalpy due to the steric destabilization of the DMA transition state by one methyl group, $\Delta H^\ddagger_{\text{S}}$ ($\Delta H^\ddagger_{\text{MA}} = \Delta H^\ddagger_{\text{DMA}} + 2(1.6 \pm 0.6) - \Delta H^\ddagger_{\text{S}} = 4.9 \pm 0.9$)
kcal/mol). The amount of this destabilization, which is the steric destabilization of the transition state by one methyl group is 4.9 ± 0.9 kcal/mol.

These estimates are plotted on an energy diagram in Figure 2-26, which shows the relative activation enthalpies of MA, MMA, and DMA along with estimates for the steric destabilization and electronic stabilization by one methyl group. The symbol TS represents transition state and GS represents the ground state. The hypothetical TS for DMA (19.1 kcal/mol) represents the energy of the hypothetical DMA transition state without electronic stabilization by the two methyl groups. Also it should be noted that the transition states for the three anhydrides are shown at different points along the reaction coordinate only for clarity. As can be seen from Figure 2-26 and from the above estimates, the steric destabilization due to one methyl (4.9 ± 0.9 kcal/mol) is larger than the electronic stabilization due to one methyl group (1.6 ± 0.6 kcal/mol). The plot also shows that the activation enthalpies for the thermal decomposition of these anhydrides are not linear with the number of methyl groups.
Figure 2-26. Energy diagram of the relative activation enthalpies of MA, MMA, and DMA.

The Entropy of Activation for Decomposition of Malonic Anhydrides

The values of $\Delta S^\ddagger$, which can also be found in Table 2-8, show that the entropy of activation found for the decomposition of DMA, $-19.8\pm0.8$ cal/(K*mol), is less negative than the entropy of activation found for the decomposition of MMA, $-28.1\pm1.9$ cal/(K*mol). The value of $\Delta S^\ddagger$ of MA, $-23.9\pm1.5$ cal/(K*mol), seems to be less negative than that of MMA and more negative than that of DMA, but due to experimental error the value of $\Delta S^\ddagger$ of MA is different from that of MMA or DMA at a 68% confidence level but not at a 95% confidence level. The large negative values of $\Delta S^\ddagger$ found for MA, MMA, and DMA are consistent with values expected for
cycloversion reactions, which proceed via highly ordered (therefore entropically unfavorable) transition states, even though they show a positive $\Delta S^\circ$, owing to the conversion of one molecule to two. For example, a positive $\Delta S^\circ$ value of 24.10 cal/(K*mole)\(^{68}\) was calculated for the cycloversion of diketene. Examples of activation entropy values for thermal cycloversions include: $-16.2 \pm 2.7$ cal/(K*mol)\(^{32}\) for the cycloversion of dicyclopentadiene, 6.3 cal/(K*mol)\(^{41}\) for the cycloversion of cyclobutanone, and $-0.3$ cal/(K*mol)\(^{67}\) for the cycloversion of bicyclo[3.2.0]hept-2-en-6-one.\(^{42}\) The activation entropy values found for MA, MMA, and DMA are more negative than those found for the cycloversions of cyclobutanone and bicyclo[3.2.0]hept-2-en-6-one. This signifies that relative to the respective reactant (either bicyclo[3.2.0]hept-2-en-6-one, cyclobutanone, or the malonic anhydrides) the transition states of the malonic anhydrides are the most rigid. The cycloversion of dicyclopentadiene does not proceed through a Möbius transition state, but its activation entropy is comparable to those found for the malonic anhydrides. For the cycloversion of dicyclopentadiene, loss of degrees of freedom in the transition state is due to loss of flexibility and the necessity to align its orbitals for the cycloversion.

Another factor contributing to the entropy of activation for the decomposition of malonic anhydrides is the number of ways that the reactant can be rotated to reach the transition state. The parent anhydride should have a more favorable entropy of activation than MMA, because MA can be rotated in two different ways to reach the transition state, whereas MMA can rotate in only one way because of its bulky methyl
group, Figure 2-12. This should lead to a more favorable $\Delta S^\ddagger$ for the parent than for the methylmalonic anhydride. The entropy of activation of the parent should be more favorable by $R \ln 2 \text{cal/(K mol)}$. The entropy of activation for MMA, $-28.1 \pm 1.9 \text{cal/(K mol)}$, is more negative than that for MA, $-23.9 \pm 1.5 \text{cal/(K mol)}$, and the difference between them, $4.2 \pm 2.4 \text{cal/(K mol)}$, is consistent with the estimate that the entropy of activation of the parent anhydride will be more favorable than that of methylmalonic anhydride by $R \ln 2 \text{cal/(K mol)}$.

**Base Catalyzed Decomposition of Methylmalonic Anhydride**

The values of $10^4 k_{BCD}$ for the decomposition of MMA with the bases DMAP, DIEA, DBU, and LUT are 148, 119, 154, and 89 sec$^{-1}$, respectively at temperatures near 16 °C (Table 2-13). The error in $k_{BCD}$, determined from duplicate runs with DIEA, was found to be 9%. The values of $10^4 k_{BCD}$ are about 10 times larger than the value of $10^4 k$, which is 14 sec$^{-1}$ at 15.9 °C (Table 2-13). The increase in rate of decomposition of MMA found upon the addition of base provides strong evidence supporting our proposed mechanism for base-catalyzed deprotonation via intermediate 8 (Figures 2-14 and 2-15).

Reaction of MMA with DMAP, DIEA, DBU, and LUT does not lead to the polymerization of the anhydride as shown in Figure I-16. This can be seen from the values of % ketene$\_\text{base}$ in Table 2-13 (267, 108, 168, and 101 % for DMAP, DIEA, DBU, and LUT, respectively), which are all greater than 73 %, the amount of ketene
generated exclusively from the thermal decomposition. These values of \% ketene\textsubscript{base} show undoubtedly that the reaction of MMA with base leads to the production of ketene, which is proposed by the mechanisms in Figures 2-14 and 2-15, but not the mechanism in Figure I-16, which results in the production of polymer, not ketene.

From these experiments the relative pK\textsubscript{a} of MMA was estimated to be lower than that of the lutidinium ion (6.67\textsuperscript{51}) and higher than that of the 4-cyanopyridinium ion (1.92\textsuperscript{51}). Our experimentally determined relative pK\textsubscript{a} of MMA is also lower than the value of 8.61 ± 0.20, which was calculated using ACD/Labs Software\textsuperscript{51}. Our experimentally determined, relatively low, pK\textsubscript{a} of methylmalonic anhydride is consistent with the proposal that the reaction of malonic anhydride with base results in the deprotonation of malonic anhydride, as shown by the mechanisms in Figures 2-14 and 2-15.
Conclusion

The rate constants and activation parameters for the thermal decomposition of MA, MMA and DMA were reliably obtained. MA was found to decompose at a higher rate and with a lower value of $\Delta G^\ddagger$ than DMA. Additionally, MMA was found to decompose at an even higher rate and with a lower value of $\Delta G^\ddagger$ than both MA and DMA.

The enthalpy of activation values were obtained to provide additional evidence supporting the previously proposed $[2+2]$ cycloreversion mechanism for the decomposition of malonic anhydride, and also to determine the extent to which electronic and steric factors influence the rate of decomposition. Our experimentally determined activation enthalpy values were found to be low, as expected for a concerted $[2+2]$ cycloreversion mechanism, but they were much lower than other activation enthalpies reported for $[2+2]$ cycloreversions, due to the formation of the especially stable C=O bond of the CO$_2$ product. The activation enthalpy found for the cycloreversion of DMA is larger than those found for MA and MMA. Also, the activation enthalpy for the cycloreversion of MA is larger than that found for MMA, at the 68% confidence interval. From the differences, in the activation enthalpies of MA, MMA, and DMA, the electronic and steric contributions to $\Delta H^\ddagger$ were determined. Our estimates show that the contribution of steric effects (the hindrance to the formation of the transition state by one methyl group) is larger than the contribution of electronic effects (the stabilization of the sp$^2$ carbons forming in the transition state by one electron donating methyl group). This would indicate that steric factors are the
dominant influence on the rate of decomposition of malonic anhydrides, but electronic factors also contribute.

The entropies of activation for all three anhydrides were found to be large and negative, which is consistent with the values expected for highly ordered and rigid transition states of Möbius topology, such as those predicted for \([2_s+2_a]\) cycloreversions. The entropy of activation found for the decomposition of DMA is less negative than the entropy of activation found for the decomposition of MMA. The entropy of activation found for MA is less negative than that of MMA and more negative than that of DMA, at the 68% confidence interval. Because the parent anhydride can rotate in two different ways to reach the transition state, it was found (as expected) that MA has a more favorable entropy of activation relative to that of MMA by \(R \ln 2 \text{ cal/(K*mol)}\).

Finally, the reactions of MMA with various hindered bases were found to proceed via deprotonation of the anhydride. This was evident from the rate constants for the base catalyzed deprotonation of MMA, which were found to be about 10 times larger than the rate constants for the thermal decomposition of MMA. The polymerization mechanism was ruled out because the reaction of MMA with base was found to produce more ketene than would be expected from the thermal decomposition alone, which established that the reaction of MMA with base leads to the production of ketene. Our experimental findings support that malonic anhydrides undergo deprotonation with base to produce ketene, according to the mechanisms proposed in Figures 2-14 and 2-15, and not polymerization (which does not lead to the
production of ketene). The relative pKa of MMA was estimated to be lower than that of the lutidinium ion and higher than that of the 4-cyanopyridinium ion. Our estimate is lower than the pKa calculated for MMA using ACD/Labs Software.
References


33 The generalized bond energies of a C-C and a C=C bond are 81 and 145 kcal/mol, respectively. The cost of breaking the C=C \( \pi \) bond would then be \( 145 - 81 = 64 \) kcal/mol. The generalized bond energies can be found in the text: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanism*. Springer: New York, NY, 2007, p 258.


The values of $\Delta S^\dagger$ for cyclobutanone and bicyclo[3.2.0]hept-2-en-6-one were determined from the reported logA values using the equation: $A = (ek_B T/h)e^{\Delta S^\dagger/RT}$, $T = 25 \degree C$. Frey, H. M.; Walsh, R. *Chem. Rev.* **1969**, *69*, 103 – 124.


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63 More information about iNMR can be found on www.inmr.net


CHAPTER THREE

Developing an ITC Method to Measure Heats of Proton Transfer
Abstract:

Preliminary work has been done towards developing a new isothermal titration calorimetry method to measure the enthalpies of proton transfer between isopropylamine and various large ring cycloalkylamines (in the range of $n = 14 – 21$, where $n$ is the number of carbons in the cycloalkylamine ring). The calorimetric method would enable us to dissect the relative basicities of these amines into enthalpic and entropic components. The enthalpic and entropic components to the relative basicities of cycloalkylamines and isopropylamine ought to clarify whether conformational effects or hindrance to the solvation of the cycloalkylammonium ions by additional carbons are responsible for the previously observed,¹ unexpectedly low, basicities of large ring cycloalkylamines. The successes, challenges, and future goals of this work are discussed.
INTRODUCTION

Basicity of Cycloalkylamines and Ring Strain

Cycloalkanes and their derivatives are abundant in natural products,\textsuperscript{2} fuels,\textsuperscript{3} and they are used in chemical synthesis\textsuperscript{4} and in kinetic and structural studies.\textsuperscript{5} Because of their utility, cycloalkanes have been extensively studied in hopes of learning more about their reactivity and structural properties.\textsuperscript{6}

In particular, one unique feature of cycloalkanes that has often been studied is their ring strain. Ring strain, in cycloalkanes and similar cyclic compounds, is caused by the unusual bond angles, torsional angles, and steric factors that these compounds have because they are tied into a ring. The strain energy and types of strain in cycloalkanes vary with ring size. For small rings ($n =$ 3 and 4, where $n$ is the number of carbons making up the ring) and cyclopentane the majority of the strain is due to compressed bond angles and torsional strain. Cyclohexane, which has one of the common rings ($n =$ 5, 6, 7), is unique in that it is strain free and is found predominantly in its chair configuration, which allows for tetrahedral bond angles and no eclipsed hydrogens to avoid torsional strain. The majority of the strain in medium rings ($n =$8-12) and cycloheptane is due to expanded bond angles,\textsuperscript{1} torsional strain, and transannular interactions. Finally, large rings ($n =$13-17) have torsional and transannular strain, but are free of angle strain.\textsuperscript{7}

The contribution of angle strain to the total ring strain, separate from torsional strain and transannular interactions, has been previously studied Perrin.\textsuperscript{1} In these
studies Perrin, Fabian, and Rivero\textsuperscript{1} were able to determine the extent of angle strain in rings of various sizes from the measured (by NMR titration\textsuperscript{16}) relative basicities of various cycloalkylamines (the studies included cycloalkylamines of various sizes, \( n = 3\)-12, 15-16, and 21, 2-butylamine, 2-pentylamine, and 3-hexylamine, along with exo- and endo- 2-norbornylamines). Acid-base behavior can be used to study bond angle strain because the effective electronegativity of a carbon and its acidity are related to its hybridization. A carbon in a small, strained ring re-hybridizes (from the \( sp^3\) hybridization in the unstrained system) to give more \( p\) character to the bonds forming the ring and more \( s\) character to the bonds with the other attached atoms. For example, the ring carbons of cyclopropylamine hybridize to allow for a CCC interorbital angle of 104° as opposed to 60°. As \( s\) character increases, the carbon becomes more electronegative toward the attached atoms, and in the case of cycloalkylamines is better able to withdraw electron density from the attached nitrogen, reducing its basicity. Lower \( pK_a\) values, relative to cyclohexylamine, indicate that the CCC bond angles in the ring are compressed, while higher \( pK_a\) values indicate that the bond angles are larger than tetrahedral.

The results of these studies\textsuperscript{1} confirmed\textsuperscript{8} that angle strain in small ring cycloalkylamines is due to the compression of the ring CCC angles, and showed for the first time that angle strain in cycloheptylamine and medium ring cycloalkylamines is due to a slight expansion of the ring CCC angles. Figure 3-1 shows a plot of the basicities of the various cycloalkylamines and exo-2-norbornylamine, which were determined by the Perrin Lab\textsuperscript{1} in D\textsubscript{2}O, CD\textsubscript{3}OD/D\textsubscript{2}O, DMSO-\( d_6\), and CD\textsubscript{2}Cl\textsubscript{2}, relative
to isopropylamine, versus ring size. The plot in Figure 3-1 shows that
cyclopropylamine and cyclobutylamine are very much less basic than
cyclohexylamine and, therefore, that their ring CCC bond angles are unmistakably
more compressed than those of cyclohexylamine. This plot (Figure 3-1) also shows
the medium ring cycloalkylamines (n = 7-11) are more basic than cyclohexylamine
and, therefore, that their ring CCC bond angles are larger than those of
cyclohexylamine.

**Figure 3-1.** Relative pKₘₐₚ for cycloalkylamines (n = 3-12, 15-16, 21) and exo-2-
norbornylamine (exo) in D₂O, CD₃OD/D₂O, DMSO-d₆, and CD₂Cl₂ vs. ring size.¹
Exo-2-norbornylamine was arbitrarily assigned a ring size of 4.5.
It was also found, however, that the basicities of large-ring cycloalkylamines ($n > 12$) converge toward a limit that is below that of cyclohexylamine, suggesting (contrary to fact) that their bond angles are smaller than tetrahedral. Given that these rings are strain-free, this lowered basicity must be due to some other factor, which is the subject of this work.

Finally, the basicities of exo- and endo- 2-norbornylamines were also examined in this study. Because the CCC bond angle of 2-norbornylamine is 102.7°, its $pK_a$ should be between that of cyclobutylamine and cyclopentylamine. Indeed, Perrin et al. found this to be true and at 25 °C in D$_2$O the $pK_a$s of exo- and endo- 2-norbornylamine, cyclobutylamine and cyclopentylamine (relative to that of isopropylamine) are -0.179 ± 0.002, -0.228 ± 0.002, -0.607 ± 0.004, and -0.011 ± 0.002, respectively. As can be seen from Figure 3-1, which shows exo-2-norbornylamine only, this trend was also observed in the other solvents tested, which include 3:1 CD$_3$OD/D$_2$O, DMSO-d$_6$, and CD$_2$Cl$_2$.

**Research Proposal**

As discussed above, previous work done by the Perrin lab shows that large ring cycloalkylamines are less basic than cyclohexylamine, but the origin of this decreased basicity in unclear. The focus of this study is to get a better understanding of what factors influence the basicities of large ring cycloalkylamines. This insight can also be applied to cycloalkanes and their derivatives, which would have broad
implications for many different areas of research. Our goal is to develop an isothermal titration calorimetry method to measure the heats of protonation of various cycloalkylamines relative to that of isopropylamine, and then use their relative basicities, measured by NMR titration, to evaluate the entropy contributions. As discussed in detail below, these thermodynamic parameters should clarify the origin of the lower basicities of large-ring amines.

Breaking down relative basicities into entropic and enthalpic contributions has been used in the past to explain the anomalous order of amine basicity in solution. In gas phase the basicity of amines increases with the number of alkyl substituents, which stabilize the positive charge of the ammonium ion. The order of decreasing amine basicity in the gas phase is \((\text{CH}_3)_3\text{N} > (\text{CH}_3)_2\text{NH} > (\text{CH}_3)\text{NH}_2 > \text{NH}_3\). In solution, the role of the alkyl substituents is more complex. On one hand the electron donating alkyl substituents increase the basicity of the amine, but at the same time they hinder the solvation of the ammonium ion, which leads to a decrease in basicity. (The order of decreasing amine basicity in solution is \((\text{CH}_3)_2\text{NH} > (\text{CH}_3)\text{NH}_2 > \text{CH}_3\text{N} > \text{NH}_3\).) An in-depth explanation for these differences in basicities (between gas phase and solution) was provided by the measured enthalpic and entropic contributions to the basicities of these amines and also the enthalpies and entropies of solvation of each neutral amine and ammonium ion.

In the gas phase, the dominant contribution to the amine basicities, which is manifested in enthalpy, is the ability of the alkyl substituents to stabilize the ammonium ion. The gas phase enthalpies of ionization (relative to \(\text{NH}_4^+\)) of
(CH₃)NH⁺⁺, (CH₃)₂NH²⁺, and (CH₃)₃NH⁺ are 9.3, 15.4, and 19.6 kcal/mol, respectively.⁹

In solution, enthalpy and entropy factors were both found to contribute. It was found that the enthalpic effect increasing the basicity of the more substituted amines was almost entirely canceled by the opposing enthalpy of solvation of the more substituted ammonium ions. Also the enthalpy of solvation of the neutral amines was found to decrease with alkyl substitution and was found to lead to a decrease in basicity with an increased number of alkyl groups. The overall enthalpies of ionization in solution (relative to NH₄⁺) of (CH₃)NH⁺⁺, (CH₃)₂NH²⁺, and (CH₃)₃NH⁺ are 0.70, -0.45, and -3.67 kcal/mol, respectively.⁹ The enthalpic contribution to the basicity of amines in solution was found to lead to a decrease in the basicity of the two more substituted amines. The entropic contribution, however, was found to have the opposite effect. The overall entropies of ionization, the values of TΔS° at 25 °C, in solution (relative to NH₄⁺) of (CH₃)NH⁺⁺, (CH₃)₂NH²⁺, and (CH₃)₃NH⁺ are -1.22, -2.54, and -4.42 kcal/mol, respectively.⁹ The dominant contributing factor to the entropy term is the entropy of solvation of the free amines, which decreases with increased alkyl substitution. The entropy of solvation of the ammonium ions was found to be constant with alkyl substitution.

In addition to the classic example above, there are many other examples where thermodynamics have been used to study basicity.¹⁰,¹¹ None of these studies, however, explored the basicities of large ring cycloalkylamines. The Perrin lab was the first to investigate this topic¹ and they have presented very strong evidence and
intriguing questions that warrant a further investigation into the origin of the unexpectedly lower basicities of large ring cycloalkylamines. For example, one interesting result from their study was that obtained for the exo-2-norbornylamine. As described earlier, in agreement with their respective CCC bond angles, the pK of exo-2-norbornylamine was found to be between that of cyclobutylamine and cyclopentylamine at 25 °C in D$_2$O, 3:1 CD$_3$OD/D$_2$O, DMSO-d$_6$, and CD$_2$Cl$_2$. The enthalpic and entropic contributions to the relative pK of cyclopentylamine and exo-2-norbornylamine were then determined in DMSO-d$_6$, CD$_3$OD/D$_2$O, and D$_2$O. The general equations giving the enthalpic, $\Delta\Delta H^\circ$, and entropic, $\Delta\Delta S^\circ$, contributions to the relative basicities of any two amines are eq. 3-1 and eq. 3-2, respectively. The subscripts $B_1$H$^+$ and $B_2$H$^+$, in eqs. 3-1 and 3-2, represent the conjugate acids and the subscripts on $B_1$ and $B_2$ represent the conjugate bases of the two amines.

\[
\Delta\Delta H^\circ = (H^\circ_{B2H^+} - H^\circ_{B2}) - (H^\circ_{B1H^+} - H^\circ_{B1}) \quad 3-1
\]

\[
\Delta\Delta S^\circ = (S^\circ_{B2H^+} - S^\circ_{B2}) - (S^\circ_{B1H^+} - S^\circ_{B1}) \quad 3-2
\]

The values of $\Delta\Delta H^\circ$ and $\Delta\Delta S^\circ$ could be evaluated from the temperature dependence of the relative basicities of as follows. First, the relationship between the relative basicities of the two bases, $K_a^{B1}/K_a^{B2}$, and $\Delta\Delta G^\circ$ is given by eq. 3-3, where R is the gas constant and T is the temperature. The value of $\Delta\Delta G^\circ$ indicates how favorable the protonation of $B_1$ is relative to $B_2$, $\Delta\Delta G^\circ = (G^\circ_{B2H^+} - G^\circ_{B2}) - (G^\circ_{B1H^+} - G^\circ_{B1})$. A negative value of $\Delta\Delta G^\circ$ would mean that the protonation of $B_2$ is more favorable than the protonation of $B_1$, or in other words that $B_2$ is more basic than $B_1$. 
Equation 3-4 relates $\Delta \Delta G^\circ$ to $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$. Next, according to equation 3-5 (which can be derived from eqs. 3-3 and 3-4), a plot of $\ln K$ versus inverse temperature will give a slope equal to $-\Delta \Delta H^\circ/R$ and an intercept equal to $\Delta \Delta S^\circ/R$.

$$\Delta \Delta G^\circ = -RT \ln \frac{K_{aB1}}{K_{aB2}}$$

$$\Delta \Delta H^\circ = \Delta \Delta S^\circ$$

$$\ln \frac{K_{aB1}}{K_{aB2}} = \frac{\Delta \Delta H^\circ}{RT} + \frac{\Delta \Delta S^\circ}{R}$$

The values listed in Table 3-1 are the enthalpic and entropic contributions to the relative basicities of cyclopentylamine and exo-2-norbornylamine determined in DMSO-$d_6$, CD$_3$OD/D$_2$O, and D$_2$O using the general procedure described above. Surprisingly, it was found that the dominant contribution is due to entropy not enthalpy, especially in the protic solvents.

**Table 3-1.** The enthalpic and entropic contributions to the relative basicities of cyclopentylamine and exo-2-norbornylamine in various solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>enthalpic contribution kcal/mol</th>
<th>entropic contribution kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO-$d_6$</td>
<td>-0.21 ± 0.02</td>
<td>0.41 ± 0.07</td>
</tr>
<tr>
<td>CD$_3$OD/D$_2$O</td>
<td>0.02 ± 0.03</td>
<td>0.81 ± 0.09</td>
</tr>
<tr>
<td>D$_2$O</td>
<td>0.01 ± 0.08</td>
<td>0.73 ± 0.28</td>
</tr>
</tbody>
</table>
A dominant entropic contribution is surprising because a reduced basicity due to compression of the CCC bond angle (and an increased electron withdrawing ability of the ring carbons) ought to be manifested in enthalpy. This could be seen from the enthalpic and entropic contributions to the relative basicities of cyclopropylamine and cyclohexylamine, which are $-2.66 \pm 0.08$ and $-0.54^{12}$ kcal/mol, respectively. An entropic contribution could be explained by restricted internal rotations of exo-2-norbornylammonium. Previously a less favorable entropy of protonation was observed for 2,6-di-tert-butylpyridine than for less sterically hindered pyridines. It was determined that as water solvated the ammonium ion through hydrogen bonding, it hindered the rotation of the two tert-butyl groups and two of the methyl groups on the tert-butyl groups of the 2,6-di-tert-butylpyridine. In addition, it was found that the water itself was not able to move freely around the hydrogen bond because of steric hindrance by the two tert-butyl groups. It is possible, as suggested by the large entropic contribution, that loss of rotational freedom is a contributing factor to the basicity of exo-2-norbornylammine.

The decreased basicities of the large ring cycloalkylamines, as shown in Figure 3-1, cannot be due to angle strain because the bond angles of large rings are tetrahedral. Another explanation is that this decrease in basicity is of entropic origin, arising because solvation of the large ring ammonium ion constrains the ring, and in doing so, reduces the number of conformations available to the protonated amine when compared to the number of conformations available to the neutral amine. This conformational explanation, however, was not found to be consistent with the
enthalpic and entropic contributions to relative pK\textsubscript{a}s determined\textsuperscript{1} for the large ring cycloalkylamine, cyclohexadecylamine (n = 16), relative to that of cyclohexylamine. In CD\textsubscript{3}OD/D\textsubscript{2}O enthalpic and entropic contributions to the relative pK\textsubscript{a}s of cyclohexadecylamine and cyclohexylamine were found to be -0.26 ± 0.06 kcal/mol and 0.17 ± 0.18 cal/mol*K, respectively. In DMSO-\textit{d}_6 the enthalpic and entropic contributions were found to be -0.12 ± 0.06 kcal/mol and 0.35 ± 0.21 cal/mol*K, respectively. As can be seen for the above enthalpic and entropic contributions in CD\textsubscript{3}OD/D\textsubscript{2}O (where the effect of solvation should be most pronounced) the entropic contribution is not significantly different from zero. An entropic contribution was found in DMSO-\textit{d}_6, but along with a contribution from enthalpy.

The authors then suggested that since the decreased basicity is due neither to compressed CCC bond angles nor to a conformation effect, then it must be due to the hindrance to solvation of the ammonium ion by the additional carbons of the large rings. In support they point out that in aliphatic amines (in solution), basicity decreases as the number of CH\textsubscript{2} groups increases. The basicities (ΔpK\textsubscript{a}s relative to isopropylamine) of 2-butylamine, 3-pentylamine, and 3-hexylamine were measured in this study\textsuperscript{1} and found to be -0.068 ± 0.001, -0.143 ± 0.001, and -0.112 ± 0.003, respectively. Decreased basicity of amines with increasing hydrocarbon chain length and branching was also found by others.\textsuperscript{11}

In support of an explanation based on solvation, the authors\textsuperscript{1} point out that they found variation of the pK\textsubscript{a}s with solvent. For example, the differences between the pK\textsubscript{a}s of cyclohexadecylamine (n = 16), cycluncosylamine (n = 21) and that of
cyclohexylamine in CD$_3$OD/D$_2$O are 0.208 ± 0.004 and 0.138 ± 0.004, respectively. However, these differences in $pK_a$s are less pronounced in the less polar solvent, CD$_2$Cl$_2$, where the role of solvation is less important, 0.104 ± 0.009 ($n = 16$ and 6) and 0.079 ± 0.007 ($n = 21$ and 6). Furthermore, the difference in the $pK_a$s of endo-2-norbornylamine (-0.228 ± 0.002, D$_2$O) and exo-2-norbornylamine (-0.179 ± 0.002, D$_2$O) differ by 0.049 ± 0.003. Endo-2-norbornylamine is less basic than exo-2-norbornylamine because solvation of its ammonium ion (which is in the endo position) is more difficult than that of exo, whose ammonium ion is tethered away from the ring and therefore more accessible to the solvent.

Finally, the trends observed in how $pK_a$ varies with solvent for all of the amines studied also gave some insight into the impact of solvation on basicity. One notable trend, which can be seen from Figure 3-1 and more clearly in Figure 3-2, is that the relative $pK_a$s of the small ring cycloalkylamines are more sensitive to ring size in DMSO-$d_6$ than in CD$_3$OD/D$_2$O. On the other hand, the relative $pK_a$s of the larger ring cycloalkylamines, with the exception of cyclouncosylamine, are equal in both solvents.
Figure 3-2. Relative $pK_a$s for cycloalkylamines ($n = 3-21$) in DMSO-$d_6$ and CD$_3$OD/D$_2$O vs. ring size.$^1$

Another trend, which can be seen from Figure 3-1 and more clearly in Figure 3-3, is that the relative $pK_a$s of small and medium ring cycloalkylamines are slightly higher in DMSO-$d_6$ than in the less polar CD$_2$Cl$_2$, but for the most part the relative $pK_a$s are parallel in both solvents. The relative $pK_a$s of the large ring cycloalkylamines are much higher in the less polar solvent, CD$_2$Cl$_2$, than in DMSO-$d_6$. In fact, a closer look reveals that in CD$_2$Cl$_2$, the large ring cycloalkylamines are not very much less basic than cyclohexylamine, as opposed to in the more polar DMSO-$d_6$ (and CD$_3$OD/D$_2$O) where the large ring cycloalkylamines are substantially less basic than cyclohexylamine.
This suggests that solvation does have a significant effect on the basicities of large ring cycloalkylamines and may explain why the basicities of the large ring cycloalkylamines appear to converge toward a value that is lower than the basicity of cyclohexylamine. One possibility would be that in DMSO-$d_6$, the ammonium ion of cyclohexylamine is better solvated than the ammonium ion of the large ring cycloalkylamines, which have additional CH$_2$ groups hindering its solvation. In agreement with what is observed in Figure 3-3, the hindrance to solvation of the ammonium ion would lead to a reduced basicity of the large ring cycloalkylamines (relative to cyclohexylamine) in polar solvents such as DMSO-$d_6$, CD$_3$OD/D$_2$O, or
D$_2$O more so than in the less polar CD$_2$Cl$_2$, where solvation plays a less important role.

The goal of this project is to determine the enthalpic ($\Delta\Delta H^\circ$, eq 3-1) and entropic ($\Delta\Delta S^\circ$, eq 3-2) contributions to the basicities of large ring cycloalkylamines (relative to isopropylamine, although any small aliphatic primary amine or cyclohexylamine could be used) in an effort to gain insight into the origin of their unexpectedly low basicities. The relative basicities of cyclohexylamine and cyclohexadecylamine were found in the previous study,$^1$ but with a large uncertainty. We hope to minimize the experimental error and expand the study to include cycloalkylamines (in the range of $n = 14 - 21$). An enthalpic contribution would suggest that the decrease in basicity originates in the hindrance to solvation of the cycloalkylammonium ions. An entropic contribution, which was not found to be dominant previously, would suggest that the decreased basicity is due to conformational restriction of the large ring cycloalkylammonium ions.

**Isothermal Titration Calorimetry**

The isothermal titration calorimetry (ITC) method, which is currently being developed by our lab, would make it possible to precisely obtain the values of the thermodynamic parameters, $\Delta\Delta H^\circ$ and $\Delta\Delta S^\circ$, associated with the relative basicities of the large ring cycloalkylamines and isopropylamine. The method, which is described in detail in the experimental section, involves titrating a mixture of the conjugate acid
and base of one amine into a mixture of the conjugate acid and base of another. The solutions are prepared to ensure that proton transfer occurs between the two amines during the titration, as shown in equation 3-6. In equation 3-6, the terms B₁H⁺, B₁⁻, B₂H⁺, and B₂ represent the conjugate acid of the less basic amine, conjugate base of the less basic amine, the conjugate acid of the more basic amine, and conjugate base of the more basic amine.

\[ \text{B}_1\text{H}^+ + \text{B}_2 \leftrightarrow \text{B}_2\text{H}^+ + \text{B}_1 \]  

During the titration the amount of heat generated by proton transfer during each injection, q, is measured by the calorimeter. The values of q can then be used to find \( \Delta \Delta H^\circ \) for each injection according to eq. 3-7, where moles\(_{H^+}\) is the known amount of moles of proton transferred between the two amines. The determination of moles\(_{H^+}\) is described in detail in the Experimental section.

\[ \Delta \Delta H^\circ = \frac{q}{\text{moles}_{H^+}} \]  

Finally, \( \Delta \Delta S^\circ \) can be obtained according to equation 3-8 from the value of \( \Delta \Delta G^\circ \) for the protonation of B₁ is relative to B₂, which can be found from equation 3-9. The terms R and T in equation 3-9 are the gas constant and temperature, respectively. The equilibrium constant, K, in eq. 3-9 describes the exchange in eq. 3-6. The value of K can be determined by NMR titration or from the ratio of the acidity constants of the two amines according to equation 3-10, where \( K_{a}^{B_1} \) and \( K_{a}^{B_2} \) are the acidity constants of B₁H⁺ and B₂H⁺, respectively. In the experiments with
cycloalkylamines, where $B_1$ would represent the large ring cycloalkylamine and $B_2$ would represent isopropylamine, the values of $\Delta \Delta G^\circ$ should be negative.

\[
\Delta \Delta G^\circ = \Delta \Delta H^\circ - T \Delta \Delta S^\circ
\]

\[
\Delta G^\circ = (G_{B2H^+}^\circ - G_{B2}^\circ) - (G_{B1H^+}^\circ - G_{B1}^\circ) = -RT \ln K
\]

\[
K = \frac{K_{aB1}^{B^1}}{K_{aB2}^{B^2}} = \frac{[B_2 \cdot H^+][B_1]}{[B_1][B_2 \cdot H^+]}
\]

Method development and testing were done using Tris(hydroxymethyl)aminomethane (Tris), imidazole, 2-methylimidazole (Me-I), 2aminopyridine (2AP), cyclohexylamine (6), and cyclooctylamine (8). These amines were used for the method development stage, instead of the cycloalkylamines, because they are readily available and have larger differences in basicity than the cycloalkylamines. Proton transfer reactions of amines having larger differences in basicity would generate more heat (providing that their differences in basicity are enthalpic in origin) than those with smaller differences in basicity and should make the initial measurements and method development easier.
Experimental

Preparation of Solutions

All solvents, amines, and other reagents were purchased from commercial suppliers and used as received, unless otherwise specified. The water used to prepare all samples was purified by a Barnstead NanoPure Water Purification System. Tris(hydroxymethyl)aminomethane, imidazole, methylamine (40 wt. % solution in water) and sucrose were used as purchased without further purification. 2-Methylimidazole and 2-aminopyridine were purified by recrystallization. Cyclohexylamine was redistilled before using. Cyclooctylamine was synthesized as previously reported, by reductive amination of cyclooctanone using ammonium acetate and NaBH₃CN.

Preparation of ITC Samples

All ITC samples were prepared using volumetric flasks, calibrated glass pipettes, and a Sartorius R2000D analytical balance. In all cases, except when solubility was an issue, the ITC samples were prepared from stock solutions. These stock solutions were made by adding the desired amine to a volumetric flask, dissolving it in water, and then filling the flask to volume with additional water. Solid amines were weighted out on the analytical balance. The volumes of those that were liquid were measured using calibrated glass pipettes. The volumes of the liquids measured using the calibrated glass pipettes could be converted to grams from their
known densities and then from grams to moles from their known molar masses. These stock solutions were then used to prepare ITC sample solutions of concentrations varying between 1.00 and 50.0 mM as described below.

Two sample solutions were prepared for each run, one to be added into the calorimeter vessel and the other into the syringe. The goal was to measure the heat of proton transfer from one amine to another, eq. 3-6, by titrating a mixture of the conjugate acid (B₁H⁺) and base (B₁) of one amine into a mixture of the conjugate acid (B₂H⁺) and base (B₂) of another. The samples were prepared so that for the more basic amine, B₂, the concentration of its conjugate base exceeded that of its conjugate acid, [B₂] > [B₂⋅H⁺], and also so that for the less basic amine, B₁, the concentration of its conjugate acid exceeded that of its conjugate base, [B₁⋅H⁺] > [B₁]. Furthermore, the solutions were prepared so that the ionic strength of the solution remained constant during the run, [B₁⋅H⁺] = [B₂⋅H⁺], to avoid the unwanted heat from the dilution of ions.

The methylamine and sucrose solutions were prepared by adding the appropriate amounts of both methylamine and methylamine hydrochloride or just sucrose, respectively, to a volumetric flask and dissolving them in water. Once the compounds were dissolved, the flask was filled to volume with water. The TRIS, imidazole, 2-methylimidazole, cyclohexylamine, and cyclooctylamine solutions were prepared by first dissolving the desired amine in water inside a volumetric flask. Then the flask containing this amine and water solution was put on ice for about 15 minutes. For each pair of amines the desired amount (as needed to achieve [B₁⋅H⁺] = [B₂⋅H⁺]),
[B₁•H⁺] > [B₁], [B₂] > [B₂•H⁺]) of cold, standardized HCl was then added slowly into each flask using a calibrated glass pipette. If the solutions were not chilled, a white vapor (possibly HCl gas or amine hydrochloride and water vapor) could be seen coming out of the flask when the HCl was added. After the HCl was added, the flasks were returned to room temperature and brought up to volume with water. Cyclooctylamine and cyclohexylamine solutions were wrapped in aluminum foil and kept in a dark cabinet. The solutions were degassed under house vacuum for 5-10 min., no more than 24 hours before the experiment was performed.

Instrumentation

ITC data were obtained using a MicroCal VP-ITC Calorimeter. The calorimeter has a sample cell, a reference cell, and a syringe whose working volumes are exactly 1459.5 µL, approximately 14 mL, and approximately 250 µL, respectively. The sample cell and syringe were filled with the desired samples and the reference cell with NanoPure water, which was degassed once a week. While setting up each experiment, all of the necessary precautions were taken to avoid air or air bubbles in the syringe and cell. These precautions are described in detail in the MicroCal VP-ITC Calorimeter users' manual.

Once the syringe, sample, and reference cells are filled, the temperature of the calorimeter needs to be set and equilibrated so that there is no temperature difference between them. The amount of power needed to maintain this equilibrium is monitored
exactly. At the start of the experiment, when the solution is injected into the vessel from the syringe, the amount of heat needed to maintain the sample cell at the set temperature changes depending on whether the reaction is exothermic or endothermic. For an exothermic reaction, when heat is evolved and less power is needed to maintain the temperature of the sample cell, the thermograph (the graph of the power needed to maintain the temperature of the sample cell, in µcal/sec, versus time) will show peaks in the negative direction. When these peaks are integrated, the amount of heat generated by the reaction, in µcal, is obtained.

Unless otherwise specified, the following instrument settings were used for these experiments: 10 injections, 30.00 °C cell temp, 180 sec. initial delay, 307 rpm. stir rate, 10 µL injection volume, 7 sec. injection duration, 240 sec. spacing between injections, and 1 sec. filter period. The reference power was varied between 5 and 30 µcal/sec, depending on the amount of heat generated during the reaction. These settings were determined to be optimum for the current study. All titrations were performed in duplicate or triplicate. Microcal VPViewer 2000 Software was used to control the operation of the instrument and both Origin and Microsoft Excel were used post-run for data analysis. It should be noted that because of premature leakage of the sample in the syringe into the vessel before the first injection, the heat obtained from the first injection was not used in the data analysis.
Calculations

Heats of Proton Transfer

The method used to calculate the enthalpy of proton transfer from the ITC data is described below.

For the purpose of this write-up we arbitrarily assign the less basic amine, B\textsubscript{1}, as the one in the vessel and the more basic amine, B\textsubscript{2}, as the one in the syringe. (The experiment can also be performed with the more basic amine in the vessel and the less basic amine in the syringe. However the samples have to be prepared so that \([B\textsubscript{1}H^+] = [B\textsubscript{2}H^+], [B\textsubscript{2}] > [B\textsubscript{1}H^+], \) and \([B\textsubscript{1}H^+] > [B\textsubscript{1}]\). If the injection volume remained the same in both cases, a smaller number of moles of proton would be transferred when the less concentrated base (B\textsubscript{1}) as opposed to the more concentrated base (B\textsubscript{2}) was in the syringe.) The total concentration of amine B\textsubscript{1} inside the sample cell, \([B\textsubscript{1}]\text{total}\), is given by eq. 3-11, and the total concentration of amine B\textsubscript{2} inside the syringe, \([B\textsubscript{2}]\text{total}\), is given by eq. 3-12.

\[
[B\textsubscript{1}]\text{total} = [B\textsubscript{1}] + [B\textsubscript{1}H^+] \quad 3-11
\]

\[
[B\textsubscript{2}]\text{total} = [B\textsubscript{2}] + [B\textsubscript{2}H^+] \quad 3-12
\]

The initial values of \([B\textsubscript{1}]\text{total}\) and \([B\textsubscript{2}]\text{total}\) before the start of the titration, \([B\textsubscript{1}]\text{total,0}\) and \([B\textsubscript{2}]\text{total,0}\), can be calculated from the amount of amine used to prepare each sample as described in the ‘Preparation of ITC Samples’ section. Once the titration begins,
the values of \([B_1]_{\text{total}} \) and \([B_2]_{\text{total}} \) inside the vessel after each injection, \([B_1]_{\text{total},i} \) and \([B_2]_{\text{total},i} \), can be determined from the procedure below. Ultimately the values of \([B_1]_{\text{total},i} \) and \([B_2]_{\text{total},i} \) can be used to calculate the concentrations of \([B_1], [B_1\cdot H^+]\), \([B_2], [B_2\cdot H^+]\) and the number of moles of proton transferred for each injection.

Before proceeding with the description of our calculation of \([B_1]_{\text{total},i} \) and \([B_2]_{\text{total},i} \), we would like to describe one factor that needs to be accounted for in our calculations to ensure an accurate determination of \([B_1]_{\text{total},i} \) and \([B_2]_{\text{total},i} \), and therefore the number of moles of proton transferred for each injection. This factor is the overflow of solution from the reaction vessel that occurs with each injection. The volume of this overflow is equal to the volume of sample injected into the vessel from the syringe. Since the overflow solution is pushed out through the top of the vessel as the new solution is injected from the syringe near the very bottom of the vessel, it is assumed that the overflow does not participate in the proton transfer reaction. The alternative, which is that complete equilibration between the two bases is achieved before the overflow is discarded, is considered in the Results section and determined to be less reliable than the treatment presented below.

We treat the overflow as follows. For a run where amine \(B_1\) is in the reaction vessel, the concentration of \(B_1\) after each injection during the titration is given by equation 3-13, where \([B_1]_{\text{total},i} \) is the concentration of \(B_1\) in the sample cell after the injection and \([B_1]_{\text{total},i-1} \) is the concentration of \(B_1\) in the sample cell before the injection and the ensuing overflow dilution. Also, \(V_{\text{cell}} \) and \(V_{\text{inject}} \) are the working volume of the sample cell and the injection volume, respectively, which are known.
exactly and are listed in the ‘Instrumentation’ section. The concentration of $B_2$ inside the vessel after the first injection, $[B_2]_{\text{total,1}}$, is given by equation 3-14.

$$[B_1]_{\text{total,i}} = \frac{[B_1]_{\text{total,i-1}}(V_{\text{cell}} - V_{\text{inject}})}{V_{\text{cell}}}$$  \hspace{1cm} 3-13

$$[B_2]_{\text{total,1}} = \frac{[B_2]_{\text{total}} V_{\text{inject}}}{V_{\text{cell}}}$$  \hspace{1cm} 3-14

After the first injection, the reaction vessel contains sample $B_1$ and the newly injected sample $B_2$. Accordingly, overflow from the subsequent injections will contain both of these samples and the concentration of $B_2$ inside the reaction vessel also needs to be corrected for overflow dilution. This can be done using similar logic as above. The concentration of amine $B_2$ inside the vessel for any subsequent injection, $[B_2]_{\text{total,i}}$, is given by equation 3-15, where $[B_2]_{\text{total,i-1}}$ is the concentration of $B_2$ in the sample cell before the most recent injection $i$. The value of $[B_2]_{\text{total,i}}$ includes the newly injected amine $B_2$ (the first term in eq. 3-15) plus the concentration of the amine $B_2$ already present in the reaction vessel corrected for overflow after the most recent injection (the second term in eq. 3-15).

$$[B_2]_{\text{total,i}} = \frac{[B_2]_{\text{total}} V_{\text{inject}}}{V_{\text{cell}}} + \frac{[B_2]_{\text{total,i-1}}(V_{\text{cell}} - V_{\text{inject}})}{V_{\text{cell}}}$$  \hspace{1cm} 3-15

Next from the values of $[B_1]_{\text{total,i}}$ and $[B_2]_{\text{total,i}}$, which were determined as described above, the concentrations of $B_1$, $B_1\cdot H^+$, $B_2$, and $B_2\cdot H^+$ in the reaction vessel for any point during the titration, $[B_1]_i$, $[B_1\cdot H^+]_i$, $[B_2]_i$, and $[B_2\cdot H^+]_i$, could be obtained. For our study, this was done by first defining each of these concentrations in terms of
the variables \( x \) (the concentration of \( B_1 \cdot H^+ \) in the vessel) and \( I \) (the total ionic strength inside the vessel, eq. 3-16), as shown in equations 3-17, 3-18, 3-19, and 3-20 (where the subscript ‘\( i \)’ indicates a given point during the titration). Next, equations 3-17, 3-18, 3-19, and 3-20 were substituted into equation 3-21, which relates the concentrations of all of the species in solution to the ratio of acidity constants, \( K_{B1} \) and \( K_{B2} \), and the overall equilibrium constant, \( K \), for the proton transfer reaction described by eq. 3-6. The resulting equation was then simplified to give equation 3-22. The variable \( x \) can now be solved for using the quadratic equation. Once the value of \( x \) is known, the values of \([B_2 \cdot H^+], [B_1], \) and \([B_2] \) can also be determined at all points during the titration from equations 3-18, 3-19, and 3-20, respectively.

\[
I = [B_1 H^+]_i + [B_2 H^+]_i \quad 3-16
\]

\[
[B_1 H^+]_i = x_i \quad 3-17
\]

\[
[B_2 H^+]_i = I - x_i \quad 3-18
\]

\[
[B_1]_i = [B_1]_{total,i} - x_i \quad 3-19
\]

\[
[B_2]_i = [B_2]_{total,i} - ([I] - x_i) \quad 3-20
\]

\[
K = \frac{[B_2 \cdot H^+][B_1]}{[B_2][B_1 H^+]} = \frac{K_{B1}}{K_{B2}} \quad 3-21
\]

\[
0 = (K - 1)x_i^2 + (K \times [B_2]_{total,i} - K \times I + [B_1]_{total,i})x_i - (I \times [B_1]_{total,i}) \quad 3-22
\]

The input values of \( K \) and \( I \) needed to solve equation 3-18, 3-20, and 3-22 can all be easily obtained. First, the ratio of the acid dissociation constants, \( K \), can either
be determined experimentally\textsuperscript{16} or found from literature values of the acid dissociation constants of the individual amines. Next, the value of I can be found from the amount of HCl added to a given sample, as described in the ‘Preparation of ITC Samples’ section. The value of I remains constant throughout the titration, so the value of I will always be equal to the concentration of the protonated amine inside the reaction vessel before the start of the titration.

Finally from above determined concentrations of $B_1$, $B_1\cdot H^+$, $B_2$, and $B_2\cdot H^+$ present in the vessel after each injection, the moles of proton transferred can be found. We chose to find the moles of proton transferred, moles\textsubscript{$H^+$ transfer}, for each injection using the values of $[B_1]_i$, eq. 3-23, where the moles of proton transferred are equivalent to the moles of $B_1$ formed, moles\textsubscript{$B_1$ formed} (or the moles of $B_1\cdot H^+$ that were deprotonated). According to eq. 3-23, the moles of proton transferred are equal to moles $B_1$ in the vessel after the injection ($[B_1]_i\cdot V_{cell}$) minus moles $B_1$ in the vessel before the injection corrected for the overflow ($[B_1]_{i-1}(V_{cell} – V_{inject})$). It is important to correct the moles $B_1$ in the vessel before the injection for overflow because, as explained above we are assuming that the overflow solution gets pushed out of the vessel before it participates in the proton transfer reaction. Therefore, for the number of moles of $B_1$ present in the vessel before the injection we use the number of moles of $B_1$ that does not get pushed out of the vessel during the injection. Without this correction the calculated value of moles\textsubscript{$H^+$ transfer} would be too small.

$$moles_{H^+\text{ transfer}} = moles_{B_1 \text{ formed}} = [B_1]_i\cdot V_{cell} - [B_1]_{i-1}(V_{cell} – V_{inject})$$ \textcopyright{} 3-23
Finally the heat of proton transfer for each injection, $\Delta \Delta H^0$, is given by equation 3-24, where $q$ is the amount of heat generated per each injection, which is measured by the calorimeter.

$$\Delta \Delta H^0 = \frac{q}{\text{moles}_{B_i \text{ formed}}} \quad 3-24$$

**Heats of Dilution**

The heats of proton transfer measured for every injection should be corrected for the heat of dilution\textsuperscript{17} using equation 3-25, where $q_d$, $q$, $M_{s}$, $M_{v}$, moles$_{s}$, and moles$_{v}$ are the heat of dilution, the amount of heat generated per each injection, the change in the molarity of the solution in the syringe, the change in the molarity of the solution in the vessel, moles injected from the syringe, and moles in the vessel corrected for dilution, respectively. Equation 3-25 was adopted from the one previously reported by Gucker et al., $q_d = \Delta H / \Delta m$\textsuperscript{17} to account for the dilution of the solution in the vessel by the solution injected from the syringe and also the dilution of the solution injected from the syringe into the vessel by the solution in the vessel. The experiments measuring the heats of dilution of sucrose were performed with a 0.1 – 0.2 $m$ sucrose solution in the vessel and degassed NanoPure water in the syringe. The experiments measuring the heats of dilution of TRIS were performed with a 0.15 – 1.4 M TRIS solution in the vessel and 0.15 – 2.4 M TRIS solution in the syringe.

$$q_d = \frac{q}{(\Delta M_s \cdot \text{moles}_s) + (\Delta M_v \cdot \text{moles}_v)} \quad 3-25$$
Results:

Heats of Dilution

The heat of dilution was first measured for sucrose samples to test the reliability of our method. Tables 3-2 and 3-3 list the raw heats of dilution and the values of $\Delta H/\Delta m$ (equation 3-25, but the concentration is molal instead of molar) for the dilution of 0.1, 0.14, 0.2 m sucrose solutions with water. The successive heats decrease because with each injection of water the amount of sucrose in the vessel decreases. While a decrease in the concentration of sucrose leads to a decrease in $\Delta m$ with each injection, it (the decrease in the concentration sucrose due to dilution and overflow) also leads to a decrease in $\Delta H^\circ$ with each injection, which outweighs the decrease in $\Delta m$ and leads to an overall decrease in the successive heats of dilution. The average of those ten runs, $141.7 \pm 3.4 \text{ cal/(mol} \cdot \text{molal)}$, agrees with the value obtained from data previously reported, $140 \pm 3 \text{ cal/(mol} \cdot \text{molal)}$. It should be noted that the calculated values listed in Table 3-3 and also Tables 3-6 – 3-14 were rounded off to the correct number of significant figures, but the insignificant figures of those values were used in the calculations.
Table 3-2. Raw heats of dilution, in µcal, for 0.1, 0.14, 0.2 m sucrose solutions.

<table>
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<tr>
<th>Injection No.</th>
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<th>0.1 m ii</th>
<th>0.1 m iii</th>
<th>0.1 m iv</th>
<th>0.1 m v</th>
<th>0.14 m</th>
<th>0.2 m</th>
<th>0.2 m ii</th>
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Table 3-3. Heats of dilution, in cal/(mol·molal), for 0.1, 0.14, 0.2 m sucrose solutions. Also the average and standard deviation values, σ for each run.

<table>
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<tr>
<th>Injection No.</th>
<th>0.1 m</th>
<th>0.1 m ii</th>
<th>0.1 m iii</th>
<th>0.1 m iv</th>
<th>0.14 m</th>
<th>0.14 m ii</th>
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<th>0.2 m ii</th>
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</table>

Average: 136.5 138.9 145.7 145.7 143.7 142.5 139.1 141.9

σ: 2.4 5.1 2.4 1.3 1.7 0.7 0.7
The heat of dilution of Tris was also measured. Tables 3-4 and 3-5 list the raw heats of dilution of these samples with concentrations of Tris ranging from 0.15 – 2.5 M and concentrations of Tris•H⁺ ranging from 0.3 – 1.2 M, the same in both vessel and syringe. Some measurements were taken so that the more concentrated solution is in the syringe and the less concentrated solution is in the vessel and some were taken with these solutions reversed. The average value of $q_d$, eq. 3-25 (this time using molar), for these ten samples was found to be $15.2 \pm 2.4 \text{ cal/(mol·M)}$. 
Table 3-4. Raw heats of dilution, in µcal, for 0.15 - 1.1 M Tris solutions.

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<tr>
<th>[Tris] Syringe</th>
<th>0.96</th>
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<th>0.15</th>
<th>1.08</th>
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<td>1.08</td>
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<td>0.3</td>
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Table 3-5. Raw heats of dilution, in µcal, for 0.3 - 2.5 M Tris solutions.

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<th>1.4</th>
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<th>1.5</th>
<th>2.4</th>
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<td>[Tris] Vessel</td>
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<td>0.3</td>
<td>0.25</td>
<td>0.6</td>
</tr>
<tr>
<td>[Tris H+]</td>
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<td>-292.49719</td>
</tr>
<tr>
<td>19</td>
<td>-142.28423</td>
<td>-155.63639</td>
<td>-69.94440</td>
<td>-141.54999</td>
<td>-291.30521</td>
</tr>
<tr>
<td>20</td>
<td>-141.33333</td>
<td>-154.43657</td>
<td>-69.90609</td>
<td>-140.88620</td>
<td>-289.74545</td>
</tr>
<tr>
<td>21</td>
<td>-140.27740</td>
<td>-150.20561</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>-136.20127</td>
<td>-147.88765</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>-130.71148</td>
<td>-146.28203</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-130.77627</td>
<td>-143.42518</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>-129.97698</td>
<td>-141.05525</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Enthalpies of Proton Transfer

The enthalpies of proton transfer obtained at varying concentrations of amines and ionic strengths, for all compounds studied, can be found in Tables 3-6, 3-7, 3-8, 3-9, 3-10, 3-11, 3-12, and 3-13. Each enthalpy of proton transfer reported in Tables 3-6 – 3-13, ΔH°, was obtained by averaging nine values of ΔΔH°, found for nine consecutive injections for a particular run. The enthalpies of proton transfer for each
injection were determined (using the experimentally determined heats of proton transfer) as described in the ‘Calculations’ portion of the ‘Experimental’ section. The errors in $\Delta \Delta H^\circ_9$ listed in Tables 3-6 – 3-13 are the standard deviations of the nine values of $\Delta \Delta H^\circ$.

To evaluate whether there is any systematic relationship between the $\Delta \Delta H^\circ$ for each injection during a run and injection number, the tables also list the slope obtained from the plot of $\Delta \Delta H^\circ$ for each injection during a run versus injection number, the error in that slope, and the $F$ statistic associated with the slope, $F$. In all cases the values of the degrees of freedom $v_1$ and $v_2$ and the critical level of $F$ at the 95% confidence level are 1, 7, and 5.59 respectively. The $F$-statistic values shows that, for the most part, there is a linear relationship between $\Delta \Delta H^\circ$ for each injection during a run and injection number.

Table 3-6. Values of q, $\Delta \Delta H^\circ_9$, slope of individual $\Delta \Delta H^\circ$ vs. injection number, and $F$ for the proton transfer between tris(hydroxymethyl)aminomethane and imidazole.

<table>
<thead>
<tr>
<th>[Tris] mM</th>
<th>[Imidazole] mM</th>
<th>[I] mM</th>
<th>$\Delta \Delta H^\circ_9$ kcal/mole</th>
<th>±</th>
<th>slope ±</th>
<th>$F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>2.4</td>
<td>4.8</td>
<td>-2.631</td>
<td>0.007</td>
<td>0.0012</td>
<td>0.0008</td>
</tr>
<tr>
<td>7.1</td>
<td>2.4</td>
<td>4.8</td>
<td>-2.612</td>
<td>0.009</td>
<td>0.0022</td>
<td>0.0008</td>
</tr>
<tr>
<td>14.3</td>
<td>2.4</td>
<td>4.8</td>
<td>-2.690</td>
<td>0.010</td>
<td>0.0033</td>
<td>0.0007</td>
</tr>
<tr>
<td>14.3</td>
<td>2.4</td>
<td>4.8</td>
<td>-2.692</td>
<td>0.010</td>
<td>0.0036</td>
<td>0.0003</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
<td>-2.599</td>
<td>0.006</td>
<td>0.0017</td>
<td>0.0004</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
<td>-2.614</td>
<td>0.010</td>
<td>0.0018</td>
<td>0.0012</td>
</tr>
<tr>
<td>6.5</td>
<td>5.5</td>
<td>6</td>
<td>-2.610</td>
<td>0.006</td>
<td>0.0007</td>
<td>0.0008</td>
</tr>
<tr>
<td>2.8</td>
<td>1.8</td>
<td>2.2</td>
<td>-2.578</td>
<td>0.009</td>
<td>0.0006</td>
<td>0.0013</td>
</tr>
<tr>
<td>2.8</td>
<td>1.8</td>
<td>2.2</td>
<td>-2.559</td>
<td>0.005</td>
<td>0.0002</td>
<td>0.0007</td>
</tr>
<tr>
<td>[Me-I] (mM)</td>
<td>[2-AP] (mM)</td>
<td>[I] (mM)</td>
<td>ΔΔH° (kcal/mole)</td>
<td>±</td>
<td>slope (±)</td>
<td>F (kcal/mole)</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------------</td>
<td>---</td>
<td>-----------</td>
<td>--------------</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>20</td>
<td>-1.48</td>
<td>0.01</td>
<td>-0.0047</td>
<td>0.0003</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>10</td>
<td>-1.49</td>
<td>0.01</td>
<td>-0.0047</td>
<td>0.0005</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>5</td>
<td>-1.49</td>
<td>0.02</td>
<td>-0.0054</td>
<td>0.0011</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>2.5</td>
<td>-1.51</td>
<td>0.02</td>
<td>-0.0066</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

**Table 3-8.** Values of q, ΔΔH°, slope of individual ΔΔH° vs. injection number, and F for the proton transfer between methylimidazole and imidazole (i).

<table>
<thead>
<tr>
<th>[Me-I] (mM)</th>
<th>[Imidazole] (mM)</th>
<th>[I] (mM)</th>
<th>ΔΔH° (kcal/mole)</th>
<th>±</th>
<th>slope (±)</th>
<th>F (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>12</td>
<td>24</td>
<td>-1.008</td>
<td>0.009</td>
<td>-0.0026</td>
<td>0.0008</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>12</td>
<td>-1.031</td>
<td>0.002</td>
<td>-0.0008</td>
<td>0.0001</td>
</tr>
<tr>
<td>14.4</td>
<td>3.6</td>
<td>7.2</td>
<td>-1.053</td>
<td>0.004</td>
<td>-0.0010</td>
<td>0.0004</td>
</tr>
<tr>
<td>14.4</td>
<td>3.6</td>
<td>7.2</td>
<td>-1.045</td>
<td>0.028</td>
<td>-0.0006</td>
<td>0.0039</td>
</tr>
<tr>
<td>43.2</td>
<td>7.2</td>
<td>21.6</td>
<td>-1.003</td>
<td>0.003</td>
<td>-0.0012</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 3-9.** Values of q, ΔΔH°, slope of individual ΔΔH° vs. injection number, and F for the proton transfer between methylimidazole and imidazole (ii).
Table 3-10. Values of q, $\Delta \Delta H^o_9$, slope of individual $\Delta \Delta H^o$ vs. injection number, and F for the proton transfer between tris(hydroxymethyl)aminomethane and methylimidazole using the value of K (2.2387) determined from literature.

<table>
<thead>
<tr>
<th>[Tris] [Me-I] [I]</th>
<th>$\Delta \Delta H^o_9$</th>
<th>$\pm$ slope</th>
<th>$\pm$ F</th>
</tr>
</thead>
<tbody>
<tr>
<td>mM</td>
<td>mM</td>
<td>mM</td>
<td>kcal/mole</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>20</td>
<td>-1.37</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>10</td>
<td>-1.37</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>5</td>
<td>-1.33</td>
</tr>
</tbody>
</table>

Table 3-11. Values of q, $\Delta \Delta H^o_9$, slope of individual $\Delta \Delta H^o$ vs. injection number, and F for the proton transfer between tris(hydroxymethyl)aminomethane and methylimidazole using the value of K (1.7770) determined by NMR.

<table>
<thead>
<tr>
<th>[Tris] [Me-I] [I]</th>
<th>$\Delta \Delta H^o_9$</th>
<th>$\pm$ slope</th>
<th>$\pm$ F</th>
</tr>
</thead>
<tbody>
<tr>
<td>mM</td>
<td>mM</td>
<td>mM</td>
<td>kcal/mole</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>20</td>
<td>-1.50</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>10</td>
<td>-1.50</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>5</td>
<td>-1.46</td>
</tr>
</tbody>
</table>

Table 3-12. Values of q, $\Delta \Delta H^o_9$, slope of individual $\Delta \Delta H^o$ vs. injection number, and F for the proton transfer between imidazole and 2-aminopyridine.

<table>
<thead>
<tr>
<th>[Imidazole] [2-AP] [I]</th>
<th>$\Delta \Delta H^o_9$</th>
<th>$\pm$ slope</th>
<th>$\pm$ F</th>
</tr>
</thead>
<tbody>
<tr>
<td>mM</td>
<td>mM</td>
<td>mM</td>
<td>kcal/mole</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>20</td>
<td>-2.1</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>10</td>
<td>-2.1</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>5</td>
<td>-2.1</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>2.5</td>
<td>-2.1</td>
</tr>
</tbody>
</table>
Table 3-13. Values of q, $\Delta H^o_9$, slope of individual $\Delta H^o$ vs. injection number, and F for the proton transfer between cyclooctylamine and cyclohexylamine.

<table>
<thead>
<tr>
<th>[8] mM</th>
<th>[6] mM</th>
<th>[I] mM</th>
<th>$\Delta H^o_9$</th>
<th>±</th>
<th>slope</th>
<th>±</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>5</td>
<td>10</td>
<td>-0.494</td>
<td>0.005</td>
<td>0.0010</td>
<td>0.0005</td>
<td>3.3</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>5</td>
<td>-0.559</td>
<td>0.007</td>
<td>0.0013</td>
<td>0.0008</td>
<td>2.7</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>2.5</td>
<td>-0.67</td>
<td>0.03</td>
<td>0.0076</td>
<td>0.0023</td>
<td>10.4</td>
</tr>
</tbody>
</table>

The $\Delta H^o_9$ values obtained for all concentrations of methylimidazole + 2-aminopyridine, Tris + methylimidazole, or imidazole + 2-aminopyridine agree with each other at the 95% confidence level. The $\Delta H^o_9$ values obtained at various concentration for the samples of Tris + imidazole, methylimidazole + imidazole, or cyclohexylamine + cyclooctylamine differ by more than 2 standard deviations. (It should be noted that for the Tris + imidazole sample, the values of $\Delta H^o_9$ agree for duplicate runs, which have the same concentrations of Tris, imidazole and I.) It is expected, however, that the error between two runs would be larger than the error within a run. As will be presented later in the Discussion section and in Table 3-14, which lists the standard deviations of the $\Delta H^o_9$ values (Tables 3-6 – 3-13) at various concentrations, the differences in the values of $\Delta H^o_9$ for runs of different concentrations may not be large enough to not allow for the accurate determination of the enthalpic and entropic contributions to the relative basicities of the large ring cycloalkylamines and isopropylamine.

For each sample the average values of $\Delta H^o_9$ at all concentrations, $\Delta H^o$, along with the errors in $\Delta H^o$ are listed in Table 3-14. The errors in $\Delta H^o$ listed in
Table 3-14 are the standard deviations of the $\Delta \Delta H^0$ values (Tables 3-6 – 3-13) at various concentrations. The value of $\Delta \Delta H^0$ is the largest for the proton transfer from imidazole·H$^+$ to Tris and smallest for the proton transfer from cyclohexylamine·H$^+$ to cyclooctylamine.

**The Entropy of Proton Transfer**

To determine the entropy of proton transfer, $\Delta \Delta S^0$, the Gibbs free energy of proton transfer, $\Delta \Delta G^0$, was first found from equation 3-9. The entropy of proton transfer was then obtained from the values of $\Delta \Delta G^0$ (determined from eq. 3-9), $\Delta \Delta H^0$ (which was obtained from the calorimetry experiments) and the temperature at which the ITC experiments were performed (30 °C) according to equation 3-8. The values of $K$, $\Delta \Delta G^0$, $\Delta \Delta H^0$, the error in $\Delta \Delta H^0$, and the error in $\Delta \Delta S^0$ are listed in Table 3-14. As mentioned earlier, the values of $\Delta \Delta H^0$ listed in Table 3-14 were obtained by averaging the values of $\Delta \Delta H^0$ (Tables 3-6 – 3-13) obtained for each sample at all concentrations.
Table 3-14. The Gibbs free energy ($\Delta G^\circ$), enthalpy ($\Delta H^\circ$), and entropy ($\Delta S^\circ$), of proton transfer along with errors in $\Delta H^\circ$ and $\Delta S^\circ$.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$K$</th>
<th>$\Delta G^\circ$ kcal/mole</th>
<th>$\Delta H^\circ$ kcal/mole</th>
<th>$\Delta S^\circ$ cal/(K*mole)</th>
<th>$\pm$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tris + Imidazole</td>
<td>14.1254</td>
<td>-1.59</td>
<td>-2.62</td>
<td>0.05</td>
<td>-3.39</td>
</tr>
<tr>
<td>Me-I + 2AP</td>
<td>7.7625</td>
<td>-1.23</td>
<td>-1.49</td>
<td>0.01</td>
<td>-0.86</td>
</tr>
<tr>
<td>Me-I + Imidazole i</td>
<td>6.3096</td>
<td>-1.11</td>
<td>-1.03</td>
<td>0.02</td>
<td>0.27</td>
</tr>
<tr>
<td>Me-I + Imidazole ii</td>
<td>6.3096</td>
<td>-1.11</td>
<td>-1.02</td>
<td>0.01</td>
<td>0.30</td>
</tr>
<tr>
<td>Tris + Me-I (Lit)</td>
<td>2.2387</td>
<td>-0.49</td>
<td>-1.36</td>
<td>0.02</td>
<td>-2.87</td>
</tr>
<tr>
<td>Tris + Me-I (NMR)</td>
<td>1.7770</td>
<td>-0.35</td>
<td>-1.49</td>
<td>0.02</td>
<td>-3.77</td>
</tr>
<tr>
<td>Imidazole + 2AP</td>
<td>1.2302</td>
<td>-0.12</td>
<td>-2.060</td>
<td>0.005</td>
<td>-6.38</td>
</tr>
<tr>
<td>8 + 6</td>
<td>1.7151</td>
<td>-0.32</td>
<td>-0.57</td>
<td>0.09</td>
<td>-0.82</td>
</tr>
</tbody>
</table>

The data in Table 3-14 show that an entropy contribution is found for all proton transfer reactions. The entropic contribution was found to be the most negative for the proton transfer from 2-aminopyridine•H$^+$ to imidazole and positive for the proton transfer from imidazole•H$^+$ to methylimidazole. The entropic contribution was found to be negative for all proton transfer reactions with the exception of the one from imidazole•H$^+$ to methylimidazole.

Error Analysis

As explained in the experimental section, our calculation of $\Delta H^\circ$ involves the assumption that the overflow volume is pushed out of the vessel before it participates
in the proton transfer reaction. Alternatively, it is possible that complete equilibration between the two bases is achieved before the overflow is discarded and that there is proton transfer between the overflow volume and the bulk. In order to determine which of these scenarios best fits our experiments, it is necessary to compare the values of $\Delta \Delta H^\circ$ determined for each injection of a representative run using our analysis (assuming that the overflow does not participate in the proton transfer reaction), $\Delta \Delta H^\circ_i$, with those determined using the alternative analysis (assuming that equilibrium was achieved before the overflow was discarded from the vessel) $\Delta \Delta H^\circ_{i(alt)}$. The values of $\Delta \Delta H^\circ_{i(alt)}$ could be determined as follows. For a run where amine $B_1$ is in the reaction vessel, the total concentration of $B_1$ after each injection during the titration is given by equation 3-26 (instead of eq. 3-13) where $[B_1]_{alt.i}$ is the concentration of $B_1$ in the sample cell after the injection and $[B_1]_{alt.i-1}$ is the concentration of $B_1$ in the sample cell before the injection. (Again, $V_{cell}$ and $V_{inj}$ are the working volume of the sample cell and the injection volume, respectively. Both are listed in the ‘Instrumentation’ section.) The concentration of $B_2$ inside the vessel after the first injection, $[B_2]_{alt.1}$, is given by equation 3-27 (instead of 3-14), where $[B_2]_{total}$ is the total concentration of amine $B_2$ inside the syringe and is given by eq. 3-12. After the first injection the concentration of amine $B_2$ inside the vessel (for any subsequent injection), $[B_2]_{alt.i}$, is given by equation 3-28 (instead of 3-15) where $[B_2]_{alt.i-1}$ is the concentration of $B_2$ in the sample cell before the most recent injection $i$. The value of $[B_2]_{alt.i}$ includes the newly injected amine $B_2$ (the first term in eq. 3-28) plus the concentration of the amine $B_2$ already present in the reaction vessel (the second term in eq. 3-28). The enthalpy of proton transfer per injection could be
calculated according to the procedure described in the ‘Calculations’ portion of the ‘Experimental’ section by using the values of \([B_1]_{\text{alt.i}}\) and \([B_2]_{\text{alt.i}}\) instead of \([B_1]_{\text{total.i}}\) and \([B_2]_{\text{total.i}}\).

\[
[B_1]_{\text{alt.i}} = \frac{[B_1]_{\text{alt.i-1}} V_{\text{cell}}}{V_{\text{cell}} + V_{\text{inject}}} \tag{3-26}
\]

\[
[B_2]_{\text{alt.i}} = \frac{[B_2]_{\text{total}} V_{\text{inject}}}{V_{\text{cell}} + V_{\text{inject}}} \tag{3-27}
\]

\[
[B_2]_{\text{alt.i}} = \frac{[B_2]_{\text{total}} V_{\text{inject}}}{V_{\text{cell}} + V_{\text{inject}}} + \frac{[B_2]_{\text{alt.i-1}} V_{\text{cell}}}{V_{\text{cell}} + V_{\text{inject}}} \tag{3-28}
\]

Table 3-15 lists the values of the individual heats for each injection, \(q_i\), \(\Delta\Delta H^\circ_i\), and \(\Delta\Delta H^\circ_{i(alt)}\) determined for the proton transfer reaction between Tris and methylimidazole, using the NMR determined value of \(K\) (1.7770). Table 3-16 lists the average values of \(\Delta\Delta H^\circ_i\) and \(\Delta\Delta H^\circ_{i(alt)}\), \(\Delta\Delta H^\circ\) (each being the average of the nine \(\Delta\Delta H^\circ\) values shown in Table 3-15), the slopes obtained from the plots of \(\Delta\Delta H^\circ_i\) and \(\Delta\Delta H^\circ_{i(alt)}\) versus injection number, the errors in the slopes, and the F statistic values associated with the slopes, \(F\). As can be seen form Table 3-16, the values of \(\Delta\Delta H^\circ_i\), and \(\Delta\Delta H^\circ_{i(alt)}\) calculated using the two treatments are not significantly different. However, a larger error, slope, and F value were found for \(\Delta\Delta H^\circ_{i(alt)}\), suggesting that a systematic variation may be leading to a decreased constancy of \(\Delta\Delta H^\circ\) when calculated using the alternative approach (which assumes that complete equilibration between the two bases is achieved before the overflow is discarded).
Table 3-15. The individual heats for each injection ($q_i$), $\Delta H^\circ_i$, and $\Delta H^\circ_i(\text{alt})$ for one Tris + methylimidazole run.

<table>
<thead>
<tr>
<th>Injection No.</th>
<th>$q_i$ $\mu$cal</th>
<th>$\Delta H^\circ_i$ kcal/mole</th>
<th>$\Delta H^\circ_i(\text{alt})$ kcal/mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-391.90274</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-393.90084</td>
<td>-1.516</td>
<td>-1.522</td>
</tr>
<tr>
<td>3</td>
<td>-384.40645</td>
<td>-1.512</td>
<td>-1.517</td>
</tr>
<tr>
<td>4</td>
<td>-374.76861</td>
<td>-1.506</td>
<td>-1.511</td>
</tr>
<tr>
<td>5</td>
<td>-366.16660</td>
<td>-1.503</td>
<td>-1.508</td>
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<tr>
<td>6</td>
<td>-357.33358</td>
<td>-1.499</td>
<td>-1.504</td>
</tr>
<tr>
<td>7</td>
<td>-349.36527</td>
<td>-1.498</td>
<td>-1.503</td>
</tr>
<tr>
<td>8</td>
<td>-340.12050</td>
<td>-1.491</td>
<td>-1.495</td>
</tr>
<tr>
<td>9</td>
<td>-332.33110</td>
<td>-1.489</td>
<td>-1.493</td>
</tr>
<tr>
<td>10</td>
<td>-325.00917</td>
<td>-1.489</td>
<td>-1.492</td>
</tr>
</tbody>
</table>

Table 3-16. The values of $\Delta H^\circ_9$ (the average of the nine $\Delta H^\circ_i$, and $\Delta H^\circ_i(\text{alt})$ values in Table 3-15), errors in the values of $\Delta H^\circ_9$, slopes, errors in the slopes, and F values determined for the two treatments of the overflow.

<table>
<thead>
<tr>
<th>$\Delta H^\circ_9$</th>
<th>$\pm$ slope $\pm$ F</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta H^\circ_i$</td>
<td>-1.5005 0.0097 0.0035 0.0002  231</td>
</tr>
<tr>
<td>$\Delta H^\circ_i(\text{alt})$</td>
<td>-1.5050 0.0107 0.0039 0.0002  283</td>
</tr>
</tbody>
</table>
Discussion

Basicities of Large Ring Cycloalkylamines

The goal of this project was to develop a new isothermal titration calorimetry method to accurately measure the heats of proton transfer between large ring cycloalkylamines (in the range of n = 14 - 21) and isopropylamine. This calorimetric method would enable us to determine the enthalpy of proton transfer, or the enthalpic contribution to the relative basicities of the amines, $\Delta \Delta H^o$ (eq. 3-1). The value of $\Delta \Delta H^o$ could then be used along with the free energy, $\Delta \Delta G^o$ (eq. 3-9), to find the entropic contribution, $\Delta \Delta S^o$ (eq. 3-8), to the relative basicities of the large ring cycloalkylamines and isopropylamine. The thermodynamic parameters, $\Delta \Delta H^o$ and $\Delta \Delta S^o$, could clarify the origin of the lower basicities of large-ring amines and provide insight into why the basicities of large ring cycloalkylamines converge toward a limit that is below that of cyclohexylamine. An enthalpic contribution would suggest that the decrease in basicity of the large ring originates in the hindrance to solvation of the cycloalkylammonium ions. An entropic contribution would suggest a conformational origin, which would come about as a result of solvent molecules restricting the conformations of the large ring ammonium ions while accessing the positive charge. The reduced number of possible conformations of the ammonium ions, compared to the neutral amine, would lead to the loss of degrees of freedom upon protonation and would be manifested in entropy.
Progress with the Method Development

The values of $\Delta \Delta G^\circ$, $\Delta \Delta H^\circ$, and $\Delta \Delta S^\circ$ of proton transfer found from our preliminary experiments are listed in Table 3-14. The values of $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$ for the Tris and imidazole run, determined using our method are $-2.62 \pm 0.05$ kcal/mol and $-3.39 \pm 0.15$ cal/K*mol, respectively. For comparison the values of $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$ determined from literature\textsuperscript{18,11} (using the thermodynamic parameters for proton ionization), are $-2.23$ kcal/mol and $-3.7$ cal/K*mol, respectively.

What is evident from the values in Table 3-14 is that our values of $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$ may allow for the determination of the enthalpic and entropic contributions to the relative basicities of large ring cycloalkylamines and isopropylamine with sufficient accuracy. This is especially apparent in the run using cyclooctylamine and cyclohexylamine, which most closely represents the systems that we want to study because the value of $\Delta \Delta G^\circ$ of proton transfer between cyclohexylamine and cyclooctylamine (-0.32 kcal/mol in H$_2$O, at 30 °C) is comparable to (for example) the value of $\Delta \Delta G^\circ$ for the proton transfer between cycloundecylamine ($n = 21$) and isopropylamine (-0.31 kcal/mol in 3:1 CD$_3$OD/D$_2$O, at 30 °C). For the run using cyclooctylamine and cyclohexylamine our errors in $\Delta \Delta H^\circ$ and $\Delta \Delta S^\circ$ are $0.09$ kcal/mol and $0.29$ cal/K*mol ($0.09$ kcal/mol at 30 °C), respectively. Therefore, if the contribution to the relative basicities of cycloundecylamine and isopropylamine is mainly due to entropy or mainly due to enthalpy, then our method will permit the accurate determination of these thermodynamic parameters.
One problem with our method, that still needs to be resolved, is the systematic decrease in $\Delta H^\circ_i$ with injection number. The value of $\Delta H^\circ$ should be the same for the first injection as for the last. This error can be seen from the large and significant slopes, errors in the slopes, and F-statistic values (in Tables 3-6 – 3-13), which have been obtained from the plots of $\Delta H^\circ$ for each injection during a run versus injection number.

To address this we found that using accurate values of $K$ (determined with the NMR titration method\textsuperscript{16}) and pure amines reduced these errors. This can be seen from the values of $\Delta H^\circ$, slopes, and F-statistic obtained from the run with Tris and Me-I, which are listed in Tables 3-10 and 3-11. The values of $\Delta H^\circ$ determined for the proton transfer between Tris and Me-I using the value of $K$ obtained from literature were -1.37 ± 0.02, -1.37 ± 0.02, and -1.33 ± 0.02 kcal/mol for the runs where the concentrations of Tris are 40, 20, and 10 mM, respectively. However when the more accurate value of $K$ (determined by NMR) was used, the values of $\Delta H^\circ$ were determined to be -1.50 ± 0.01, -1.50 ± 0.01, and -1.46 ± 0.02 kcal/mol for the runs where the concentrations of Tris are 40, 20, and 10 mM, respectively. The values of the slopes and F-statistic were reduced on average by 40 and 60%, respectively, for the runs using the more accurate value of $K$.

Heats of Dilution

We were successfully able to measure heats of dilution that were consistent for
measurements of various concentrations. Measurements were taken so that the more concentrated solution was in the syringe and the less concentrated solution was in the vessel and also with these solutions reversed. Our value for the heat of dilution of sucrose with water, $141.7 \pm 3.4 \text{ cal/(mol*}molal\text{)}$, was found to agree for samples of various concentrations and also with the value previously reported, $140 \pm 3 \text{ cal/(mol*}molal\text{)}$.\textsuperscript{17} The value for the heat of dilution of Tris was also successfully measured, but found to be small ($15.2 \pm 2.4 \text{ cal/(mol*M)}$), especially when compared to the values of $\Delta H^\circ$ for the run with Tris and imidazole ($-2.62 \pm 0.05 \text{ kcal/mol}$), where the change in concentration per injection is about $0.05 \text{ mM}$. However, this would be an important correction for the runs where the values of $\Delta H^\circ$ are smaller, for example the $8 + 6$ run, where the value of $\Delta H^\circ$ is $-0.57 \pm 0.09 \text{ kcal/mol}$.

A future goal for this project would be to measure the heats of dilution, especially for cyclooctylamine, cyclohexylamine, isopropylamine, and also the large ring cycloalkylamines to see if correcting for dilution would lead to a constant value of $\Delta H^\circ$, and allow for the determination of $\Delta H^\circ$ with more accuracy.
Conclusion

The goal of this research was to develop an isothermal titration calorimetry method to measure the basicities of various large ring cycloalkylamines relative to isopropylamine. These relative basicities could then be broken down into enthalpy and entropy contributions to clarify the origin of the lower basicities of large ring amines. An enthalpic contribution would suggest that the decreased basicities of large ring cycloalkylamines originate in the hindrance to solvation of the cycloalkylammonium ions whereas an entropic contribution would suggest that a conformational effect is responsible.

To date, a system for sample preparation and a procedure for calculating the enthalpies of proton transfer from the measured heats were established. Enthalpies of proton transfer for a variety of amines were obtained, but the method is still in the development stage. The challenge that still remains to be solved is obtaining $\Delta \Delta H^\circ$ values that do not vary with injection number. In an effort to take on this challenge, a method to measure and calculate the heats of dilution has been successfully developed and used to accurately obtain heats of dilution of tris and sucrose at various concentrations. Future work needs to be done to measure the heats of dilution of large ring cycloalkylamines and cyclopropylamine and use these values to obtain more accurate heats of proton transfer for these compounds.
References


The entropy contribution given is the value of $\Delta S^\circ$ at 25 °C.

The value listed is relative to that of isopropylamine.


