Theoretical and experimental studies of reactive organic molecules

Kleen Marie Konrad

University of New Hampshire, Durham

Follow this and additional works at: https://scholars.unh.edu/thesis

Recommended Citation
https://scholars.unh.edu/thesis/201

This Thesis is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Master's Theses and Capstones by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact nicole.hentz@unh.edu.
Theoretical and experimental studies of reactive organic molecules

Abstract
Chapter I. Density functional theory calculations were used to examine the interconversions of C5H6 and C6H8 isomers. On the C5H6 surface, cyclobutenylcarbene is predicted to rearrange to 1,2-cyclopentadiene. Interconversion of cyclobutylidenecarbene and cyclopentenyne has a small barrier. For the C6H8 surface, cyclopentenyldicarbene is predicted to rearrange to bicyclo[3.1.0]hex-5-ene and further to 1,3-cyclohexadiene. Cyclopentylidenecarbene can easily interconvert with cyclohexyne. These results are in accord with experimental results, to date.

Carbene precursors via a cyclopropanated phenanthrene, 1,1-dihalo-1a,9b-dihydro-1H-cyclopropa[1]phenanthrene, were studied.

Chapter II. Isodesmic and homodesmic equations at B3LYP/6-311+G(d,p) level of theory have been used to estimate strain for the series of cyclic allenes and cyclic butatrienes. A fragment strain approach was also developed and provides more accurate predictions for the larger rings. The strain estimations are in agreement with experimental results for these cumulenes.

Chapter III. We have mapped the energy surface for the ozone + ketone reaction with B3LYP, BH&HLYP, CCSD(T) and CBS-QB3 methods. Oxidation by ozone renders aldehydes unsuitable for examining the tetroxolane hypothesis. (Abstract shortened by UMI.).

Keywords
Chemistry, Organic

This thesis is available at University of New Hampshire Scholars' Repository: https://scholars.unh.edu/thesis/201
THEORETICAL AND EXPERIMENTAL STUDIES
OF REACTIVE ORGANIC MOLECULES

BY

KALEEN MARIE KONRAD
B. S., University of New Hampshire, 2004

THESIS

Submitted to the University of New Hampshire
in Partial fulfillment of
the Requirement for the Degree of

Master of Science
in
Chemistry

September, 2006
This thesis has been examined and approved.

Richard P. Johnson, Professor of Chemistry
Glen P. Miller, Professor of Chemistry
Howard R. Mayne, Professor of Chemistry

8/18/06
Date
DEDICATION

To my parents,
Michael Konrad and Peggie Menzies

To my sister,
Rebekka Konrad
ACKNOWLEDGMENTS

I would like to thank everyone who has continued to support me over the last two years. I would like to thank my research advisor, Dr. Richard P. Johnson for encouraging me to stay for my Masters, along with his guidance and understanding. Also I would also like to thank my committee members, Dr. Glen P. Miller and Dr. Howard R. Mayne. I would like to acknowledge the dedicated professors at the University of New Hampshire. I am grateful for all individuals that have educated, trained or helped me over the years. This includes but it not limited to Cindi Rowher, Peggy Torch, Jane Austin, Kristin McFarlane, Bob Constantine, Kathy Gallagher, the UIC staff and my fellow graduate students. A special thanks to the institution for giving me the opportunity to further my education.

I am very thankful for the support from my family and friends. My Dad: for always encouraging me to do my best. My mother: for her constant open heart and open ear. My sister: for being someone to lean on. Matt: for listening to me when I ramble, always believing and never allowing me to give up. Melissa: for allowing me to expose my inquisitive nature. All of my friends: for listening to me even if you didn’t care or understand. Without all of you, this would not have been possible.
# TABLE OF CONTENTS

DEDICTION ........................................................................................................... iii

ACKNOWLEDGEMENTS ...................................................................................... iv

LIST OF SCHEMES ............................................................................................ viii

LIST OF FIGURES ................................................................................................. x

LIST OF TABLES .................................................................................................. xi

ABSTRACT ............................................................................................................. xii

CHAPTER PAGE

GENERAL INTRODUCTION .................................................................................. 1

I. CARBENE ROUTES TO STRAINED CYCLIC ALLENES ....................... 2
   A. Introduction .................................................................................................... 2
      Carbene Rearrangements on the C₅H₆ and C₆H₈ Potential Surfaces ............. 6
      Statement of Goals ....................................................................................... 11
   B. Computational Methods ............................................................................ 12
   C. Computational Results and Discussion ................................................... 12
      The C₅H₆ Energy Surface ........................................................................... 12
      The C₆H₈ Energy Surface .......................................................................... 17
   D. Experimental Results and Discussion ....................................................... 22
      Synthesis of Vinylcarbene Precursors .................................................... 22
Synthesis towards Cyclopropylidene Precursors ........................................ 31

E. Conclusions .................................................................................................. 35

II. STRAIN ESTIMATES FOR SMALL-RING CYCLIC CUMULENES ............ 37
   a. Introduction ................................................................................................. 37
      Definition of Strain ....................................................................................... 37
      Cyclic Allenes ................................................................................................. 38
      Cyclic Butatrienes ......................................................................................... 39
      Statement of Goals ......................................................................................... 40
   B. Computational Methods ............................................................................. 40
   C. Results and Discussion ............................................................................... 42
      Strain in Cyclic Allenes ................................................................................. 42
      Strain in Cyclic Butatrienes ........................................................................... 45
   D. Conclusions ................................................................................................. 47

III. NEW CHEMISTRY OF OZONE: THE TETROXOLANE CONNECTION ......... 49
   A. Introduction .................................................................................................. 49
      Statement of Goals .......................................................................................... 51
   B. Computational Methods ............................................................................... 52
   C. Computational Results and Discussion ...................................................... 53
      Formaldehyde-Ozone Energetics .................................................................... 54
      Acetone-Ozone Energetics ............................................................................. 58
      Tetroxane Chemistry ...................................................................................... 62
      Heteroatom Chemistry .................................................................................... 62

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
<table>
<thead>
<tr>
<th>Number</th>
<th>Scheme Description</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbene Formation by Thermal and Photochemical Activation</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Generation of Dichlorocarbene</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Doering-Moore-Skattebol Method</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Experimental Rearrangement of Cyclooctenylcarbene</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Rearrangement of Cycloalkenylcarbenes</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>Proposed Generation of Vinyl Carbenes and Cyclopropylidenes</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>B3LYP/6-311+G(d,p)+ZPVE Potential Energy Surface for C₅H₆</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Pyrolysis of Cyclobutylidene Derivative of Meldrum's Acid</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>B3LYP/6-311+G(d,p)+ZPVE Potential Energy Surface for C₆H₈</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>Pyrolysis of Cyclopentylidene Derivative of Meldrum's Acid</td>
<td>21</td>
</tr>
<tr>
<td>11</td>
<td>Lithium Carbenoid Formation</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>Dehydration Approach</td>
<td>23</td>
</tr>
<tr>
<td>13</td>
<td>Attempts at Dehydration of Alcohols</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>Base-Catalyzed Isomerization Approach</td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>Synthesis of Vinyl iodides from Ketones</td>
<td>27</td>
</tr>
<tr>
<td>16</td>
<td>Gilman Coupling Chemistry for Cyclopentenylcarbene Precursor</td>
<td>28</td>
</tr>
<tr>
<td>17</td>
<td>Proposed Generation of Cyclopropylidenes</td>
<td>32</td>
</tr>
<tr>
<td>18</td>
<td>Attempted Spiropentane (72) Formation</td>
<td>33</td>
</tr>
<tr>
<td>19</td>
<td>Isodesmic and Homodesmic Reaction Schemes</td>
<td>41</td>
</tr>
<tr>
<td>20</td>
<td>^18O Label Exchange of Isobutyaldehyde and Ozone</td>
<td>50</td>
</tr>
</tbody>
</table>
**LIST OF FIGURES**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Singlet vs. Triplet Carbenes</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Cyclic Allene Series</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>MNDO Torsional and Bending Angles for Cyclic Allenes</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Species on the C\textsubscript{6}H\textsubscript{6} Energy Surface</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Species on the C\textsubscript{6}H\textsubscript{8} Energy Surface</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Cyclic Butatriene Series</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>MNDO Bending Angles and Strain Energies for Cyclic Butatrienes</td>
<td>40</td>
</tr>
</tbody>
</table>
LIST OF TABLES

<table>
<thead>
<tr>
<th>Number</th>
<th>Table Title</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Predicted Vinyl $^1$H Shifts for Cyclopentenyl Halides</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Predicted Vinyl $^1$H Shifts for Cyclohexenyl Halides</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Predicted Vinyl $^1$H Shifts for Cyclobutenyl Halides</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Homodesmic Reaction Energies for Cyclic Allenes</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Isodesmic Reaction Energies for Cyclic Allenes</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>Fragment Strain Energies for Cyclic Allenes</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>Homodesmic Reaction Energies for Cyclic Butatrienes</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>Isodesmic Reaction Energies for Cyclic Butatrienes</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>Fragment Strain Energies for Cyclic Butatrienes</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>Comparison of Formaldehyde + Ozone Surface Energetics</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>Comparison of Acetone + Ozone Surface Energetics</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>Label Exchange of $^{18}$O $t$-Butyl Cyclohexanone (130-$^{18}$O) + Ozone (93), Monitored by HP GC/MS</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>Label Exchange of $^{18}$O $t$-Butyl Cyclohexanone (130-$^{18}$O) + Ozone (93), Monitored by Thermo GC/MS</td>
<td>71</td>
</tr>
<tr>
<td>14</td>
<td>Label Exchange of $^{18}$O Acetophenone (132-$^{18}$O) + Ozone (93)</td>
<td>73</td>
</tr>
<tr>
<td>15</td>
<td>Competition Experiment of $^{18}$O $t$-Butyl Cyclohexanone (130-$^{18}$O) and $^{18}$O Acetophenone (132-$^{18}$O)</td>
<td>73</td>
</tr>
<tr>
<td>16</td>
<td>Label Exchange of $^{18}$O Benzophenone (132-$^{18}$O) + Ozone (93)</td>
<td>74</td>
</tr>
</tbody>
</table>
ABSTRACT

THEORETICAL AND EXPERIMENTAL STUDIES

OF REACTIVE ORGANIC MOLECULES

by

Kleen Marie Konrad

University of New Hampshire, September, 2006

Chapter I

Density functional theory calculations were used to examine the interconversions of C_5H_6 and C_6H_6 isomers. On the C_5H_6 surface, cyclobutenylcarbene is predicted to rearrange to 1,2-cyclopentadiene. Interconversion of cyclobutylidenecarbene and cyclopentyne has a small barrier. For the C_6H_8 surface, cyclopentenylcarbene is predicted to rearrange to bicyclo[3.1.0]hex-5-ene and further to 1,3-cyclohexadiene. Cyclopentylidenecarbene can easily interconvert with cyclohexyne. These results are in accord with experimental results, to date.

Carbene precursors via a cyclopropanated phenanthrene, 1,1-dihalo-1a,9b-dihydro-1H-cyclopropa[1]phenanthrene, were studied. Dehydration

xii
chemistry was unable to yield 1-cycloalkenyl-1a,9b-dihydro-1H-cyclopropa-
[Ijphenanthrene as a precursor to C\textsubscript{5}H\textsubscript{6} and C\textsubscript{6}H\textsubscript{8} vinylcarbenes. A base-
catalyzed isomerization of the vinylidene precursor, 1-cyclobutylidene-1a,9b-
dihydro-1H-cyclopropa[I]phenanthrene, was unsuccessful in the preparation of
this target. Gilman chemistry yielded traces of the C\textsubscript{6}H\textsubscript{8} vinylcarbene precursor.
Additionally, Simmons-Smith chemistry with 1,1-dibromo-1a,9b-dihydro-1H-
cyclopropa[I]phenanthrene has been unsuccessful for the synthesis of
bicyclo[4.1.0]hept-7-ylidene precursors.

Chapter II

Isodesmic and homodesmic equations at B3LYP/6-311+G(d,p) level of
theory have been used to estimate strain for the series of cyclic allenes and
cyclic butatrienes. A fragment strain approach was also developed and provides
more accurate predictions for the larger rings. For the cyclic allenes series,
predictions for allene strain (kcal/mol) include: 1,2-cyclobutadiene, 65; 1,2-
cyclopentadiene, 51; 1,2-cyclohexadiene, 32; 1,2-cycloheptadiene, 14; 1,2-
cyclooctadiene, 5; and 1,2-cyclononadiene. For the butatriene series,
predictions for butatriene strain include: 1,2,3-cyclobutatriene, >100; 1,2,3-
cyclopentatriene, 80; 1,2,3-cyclohexatriene, 50; 1,2,3-cycloheptatriene, 26; 1,2,3-
cyclooctatriene, 17; and 1,2,3-cyclononatriene, 4. The strain estimations are in
agreement with experimental results for these cumulenes.
Chapter III

Reaction of ozone with carbonyl compounds should yield five-membered ring tetroxolanes. Tetroxolanes should undergo retro-cycloaddition to give ozone plus a carbonyl compound; these are proposed to be a key intermediate along a low energy route to ozone. Carbonyl oxides may provide a route to tetroxolanes and thus ozone. We have mapped the energy surface for the ozone + ketone reaction with B3LYP, BH&HLYP, CCSD(T) and CBS-QB3 methods. Substitution of various elements in the tetroxolane could also play a role in this mechanism.

$^{18}$O-labeling studies supported the existence of tetroxolanes. $^{18}$O-labeled $t$-butyl cyclohexanone, acetophenone and benzophenone were prepared by exchange with $\text{H}_2^{18}\text{O}$. Treatment with ozone in solution resulted in rapid loss of isotopic label, as measured by GC-MS. A competition experiment established relative kinetics for the exchange, which showed the dialkyl-ketone reacted fastest. Oxidation by ozone renders aldehydes unsuitable for examining the tetroxolane hypothesis.
GENERAL INTRODUCTION

This thesis is divided into three separate chapters: 1) Carbene Routes to Strained Cyclic Allenes; 2) Strain Estimates for Small Ring Cyclic Cumulenes; and 3) New Chemistry of Ozone: The Tetroxolane Connection. Due to the diverse nature of the material covered, each chapter is self-contained with its own introduction, results and discussion and conclusion.
CHAPTER I

CARBENE ROUTES TO STRAINED CYCLIC ALLENES

Introduction

Carbenes are neutral, divalent reactive intermediates in which a carbon atom has two covalent bonds to other groups and two non-bonding orbitals containing two electrons between them. The position of non-bonding electrons, either the same or opposite spin, determines whether the carbene is, respectively, of singlet or triplet multiplicity (Figure 1). These reactive species have been a source of great research interest since the late 1800's.

Figure 1: Singlet vs. Triplet Carbenes

There are many ways to generate carbenes. They are most typically formed by loss of a small, stable molecule via thermal or photochemical activation (Scheme 1). Griffin utilized photochemical cyclo-eliminations to produce carbenes from cyclopropane derivatives. This involved a [3→2+1] cycloelimination, now generally known as the Griffin fragmentation (Eq. 4).
In 1965, Richardson and coworkers reported the photochemical generation of singlet methylene from a cyclopropanated phenanthrene. Methylene was initially generated photochemically and added across the 9,10-bond of phenanthrene. Upon photolysis, methylene was re-generated and trapped, while the re-aromatized phenanthrene was formed cleanly. In 1972, Joshi and coworkers published the addition of dichlorocarbene to phenanthrene under phase transfer conditions which produced 7,7-dichlorodibenzo[a,c]-bicyclo[4.1.0]heptane (1). Kirchhoff later showed that upon photolysis of 1, dichlorocarbene (2) and phenanthrene (3) were generated. (Scheme 2). Collaborative studies with Chateaneuf revealed for the first time the absolute kinetics of the reactivity of dichlorocarbene with several alkenes.

Scheme 1: Carbene Formation by Thermal and Photochemical Activation

Scheme 2: Generation of Dichlorocarbene
The same Griffin fragmentation offers routes to many other carbenes. Our group has utilized lithium – halogen exchange reactions of 1, followed by alkylations to form new carbene precursors. Kirchhoff began with the synthesis and trapping of dichlorocarbene and chlorocarbene; while the precursor to dibromocarbene did not yield clean chemistry. Abbot continued this work by forming and trapping various alkyl carbenes, including benzylchlorocarbene, vinylcarbene and vinylidene. Hernandez contributed to this work by photolysis of vinylcarbene precursors and trapping of cyclopropene, along with the synthesis and photolysis of precursors to alkylidenes and cycloalkylidenes. Lewis’s work included studies of benzylchlorocarbene and the synthesis and photolysis of novel vinylidene carbene precursors.

We planned to exploit these carbenes and their rearrangements for the generation and trapping of other highly reactive molecules. One type of species that has continuously been of interest is the series of strained cyclic allenes. Allenes contain two consecutive double bonds where the central carbon atom is sp-hybridized. The parent structure has D_2d symmetry as it favors a linear geometry with orthogonal substituents. Placing an allene moiety in a cyclic system incorporates strain and thus cyclic allenes are more reactive than linear allenes. As the ring size decreases, the strain and reactivity will increase. The first reported attempts to synthesize cyclic allenes date back to the mid-1930’s. One convenient way to synthesize allenes is by the ring opening of substituted
cyclopropylidenes (5); this is known as the Doering-Moore-Skattebol method (Scheme 3).\textsuperscript{13}

\begin{center}
\begin{tikzpicture}
    \node[draw,shape=circle] (a) at (0,0) {4};
    \node[draw,shape=circle] (b) at (1,1) {5};
    \node[draw,shape=circle] (c) at (1,-1) {5};
    \node[draw,shape=circle] (d) at (2,0) {4};
    \node[draw,shape=circle] (e) at (3,0) {5};
    \node[draw,shape=circle] (f) at (4,0) {6};
    \node[draw,shape=circle] (g) at (5,0) {6};

    \draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g) -- (a);
    \draw (b) -- (e);
    \draw (c) -- (f);
    \draw (d) -- (g);
\end{tikzpicture}
\end{center}

\textbf{Scheme 3: Doering-Moore-Skattebol Method}

Treatment of a gem-dihalo cyclopropane (4) with an organolithium, Grignard reagent or sodium metal presents a general method for the synthesis of allenes; however, in the presence of an olefin this sometimes leads to the formation of spiropentanes (6) in low yields. The cyclopropylidene intermediate (5) can open easily to the allene because of its low energy barriers\textsuperscript{14}; therefore, only low yields of the spiropentanes (6) have been obtained.

\begin{center}
\begin{tikzpicture}
    \node[draw,shape=circle] (a) at (0,0) {7};
    \node[draw,shape=circle] (b) at (1,0) {8};
    \node[draw,shape=circle] (c) at (2,0) {9};
    \node[draw,shape=circle] (d) at (3,0) {10};
    \node[draw,shape=circle] (e) at (4,0) {11};
    \node[draw,shape=circle] (f) at (5,0) {12};

    \draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (a);
\end{tikzpicture}
\end{center}

\textbf{Figure 2: Cyclic Allene Series}

There are currently reports for the synthesis of the entire strained cyclic allenes series (7-12) although not for all the parent compounds (Figure 2).\textsuperscript{15-19} 1,2-cyclononadiene (12) is the smallest unsubstituted cyclic allene that has been isolated. The five-membered ring (8) has remained the most elusive of the series.
but in 2002 Balci and coworkers reported the first generation and trapping of a substituted 1,2-cyclopentadiene. Nevertheless, the unsubstituted 1,2-cyclopentadiene (8) remains unknown. The synthesis and properties of the cyclic allene series has been extensively reviewed elsewhere. The only study of the strain in these cyclic allenes was reported by Johnson, Angus and Schmidt in a 1985 MNDO study of the torsional and bending angles (Figure 3).

![Figure 3: MNDO Torsional and Bending Angles for Cyclic Allenes](image)

Carbene Rearrangements on the C₅H₆ and C₆H₆ Potential Surfaces

Carbenes often exist on complex potential energy surfaces connected by myriad intramolecular rearrangements. Many species on the C₅H₆ energy surface have been investigated over the years but no comprehensive study has been described (Figure 4).

![Figure 4: Species on the C₅H₆ Energy Surface](image)
The energies of hydrogenation for a series of alkenes, including, bicyclo[2.1.0]pent-1,2-ene (13), bicyclo[2.1.0]pent-1,5-ene (14) and 1,3-cyclopentadiene (21) were calculated with ab initio methods. The enthalpies of formation of 13 and bicyclo[3.1.0]hex-1,5-ene (24), its C₆H₈ homologue, were also studied. In general, these cyclopropene adducts can be generated at ambient temperature by base induced eliminations, but readily dimerize. The ring strain of 14 and its C₆H₈ homologue 25 was determined using homodesmotic reactions and compared to the corresponding phosphorus heterocycles. 5-Carbenabicyclo[2.1.0]pentane (15) was included in a homodesmotic reaction designed to compare the aromatic nature of carbenes in tricyclic systems. The interconversion of cyclobutylidenecarbene (16) and cyclopentyne (23) has been explored. This same carbene has been suggested as intermediate in the pyrolysis of a Meldrum's acid derivative. The predicted NMR spectra were reported for 16 and cyclopenten-3-ylidene (20) using Density Functional Theory (DFT). The singlet and triplet states of cyclopenten-3-ylidene (20) and its C₆H₈ homologue 30 have been studied computationally using ab initio methods to assess the effect of angle strain on the singlet-triplet gap. Chemical Abstracts present no reports of 1-cyclobutenylcarbene (17) although 2-cyclobutenylcarbene has been theoretically studied for its intramolecular cycloadditions. The kinetics of the thermal rearrangement of [1.1.1]propellane (18) were investigated by pyrolysis experiments along with DFT calculations. Cyclopropylacetylene (19) has been widely studied and can be prepared by treatment of 5-chloro-1-pentyne.
with BuLi in cyclohexane. Theoretical studies of 19 include ring strain estimates and $^{13}$C NMR predictions. The chemistry of 1,2-cyclopentadiene (8) was previously discussed in this introduction. Thermal decomposition of 1,3-cyclopentadiene (21) to acetylene plus propyne or allene has been studied using \textit{ab initio} CASSCF, as well as DFT methods. In conjunction with the pyrolysis of 21, the heats of formation and relative stabilities of closed and open shell C$_5$H$_6$ hydrocarbons were examined with MINDO/3 theory. This includes the only report on 22. Cyclopentyne (23) has received more attention than most species in this series. Detailed \textit{ab initio} studies of its electronic structure have been published. More recently, [2+2] cycloadditions of 23 have been studied by various computational methods.

The C$_6$H$_8$ surface has been even more extensively explored (Figure 5). Many reports including these species were mentioned above as they also included the corresponding C$_5$H$_6$ homologues and will not be further discussed here.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Species on the C$_6$H$_8$ Energy Surface}
\end{figure}

Kobrich provided evidence for the existence of a bicyclo[3.1.0]hex-1-ene (25) but was unsuccessful in efforts to trap this species. The
cyclopropylidenecarbene 26 is a well known intermediate in the Doering-Moore-Skattebol method with a low barrier for ring opening to 9. Cyclopentylidenecarbene (27) readily ring expands to form cyclohexyne (32). Both 27 and 28 have been suggested as intermediates in the thermal fragmentation of cyclopentylidenecarbene-Meldrum's acid (See Scheme 10 below). Cyclobutylacetylene (29) has been prepared by thermal extrusion of Ph₃PO from a oxobutylidenetriphenylphosphorane. Its Raman and IR spectra have been reported, along with the conformational stability using ab initio calculations. 1,2-cyclohexadiene (9) has been well studied and can be generated by the Doering-Moore-Skattebol method via 26. Biphenyl substituted carbena-2-cyclohexane (30) has been generated by heating Li salts of the tosylhydrazone in DMSO; this yields the parent ketone and substituted 1,3-cyclohexadiene. 1,3-cyclohexadiene (31) has been extensively explored as well as cyclohexyne (32). Preparation of 32 includes β-elimination of substituted cyclohexenes or ring expansion of cyclopentylidenecarbene (27), where it can be trapped with a suitable reagent. Shevlin examined the thermal reactions of cyclohexyne (32) at elevated temperatures experimentally and using ab initio calculations with MP2 theory. The singlet and triplet electronic states have also been examined with ab initio methods and, more recently, the conformational surface was investigated.
These studies encompass a wide variety of chemistry on the C₅H₆ and C₆H₈ potential energy surfaces. A complete investigation of their interconversions, either theoretically or experimentally has yet to be reported.

Experimental studies of larger carbenes homologues may provide a model for these C₅H₆ and C₆H₈ carbenes surfaces. In 1985, Stierman and Johnson reported the experimental results for the rearrangement of cyclooctenylcarbene (34) (Scheme 4).⁴⁸ Seven and nine-membered rings showed similar behaviors to 33.

Scheme 4: Experimental Rearrangement of Cyclooctenylcarbene

If similar chemistry is observed for the smaller ring systems, this might generate highly strained products including cyclic allenes (8-9), cyclopropanes (13, 24), and methylene cyclopropanes (15, 25). Another fragmentation, not shown in Scheme 4, might give acetylenes (19, 30) (Scheme 5).

Scheme 5: Rearrangement of Cycloalkenylcarbenes
Statement of Goals

This project was focused on the synthesis and continuing development of cyclopropanated phenanthrenes as carbene precursors, in this case as precursors to carbene 17, 28 and cyclopropylidenes. The first fundamental goal was to computationally investigate the potential energy surface for both CsH$_6$ and C$_6$H$_8$ isomers. This was expected to provide insight into their energetics and allow for predictions of the rearranged products. A second goal was to develop a general synthetic route to vinyl carbene precursors (Eq. 5). Specifically, we are interested in C$_5$H$_6$ and C$_6$H$_8$ vinyl carbene precursors. A third goal was the development of a general synthetic methodology that would allow access to cyclic allenes, via cyclopropylidenes (Eq. 6). Finally, in collaboration with Robert S. Sheridan, matrix isolation studies along with IR spectroscopy would be used to provide evidence for these carbenes and their rearrangements.$^{49}$

Scheme 6: Proposed Generation of Vinyl Carbenes and Cyclopropylidenes

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Computational Methods

For each stationary point investigated, initial geometry optimizations were performed using Spartan ’04\(^50\) at the PM3 semiempirical level of theory. B3LYP/6-311+G(d,p) theory was used for optimization of all points on the potential energy surface, followed by vibrational frequency analysis. Gaussian 03\(^51\) was used for all DFT calculations. The energetics below include unscaled zero point vibrational corrections. Selected reactions were followed by intrinsic reaction coordinate calculations in order to characterize the reaction pathway.

Computational Results and Discussion

We first undertook a computational study of the potential energy surface for both C\(_5\)H\(_6\) (17) and C\(_6\)H\(_8\) (28) cycloalkenylcarbenes.

The C\(_5\)H\(_6\) Energy Surface

Scheme 7 summarizes a large assortment of computational results. Many of the species on this surface and their rearrangements will be discussed in detail; analysis begins with the cycloalkenylcarbene (17) since this is our intended experimental goal.

Cyclobutenylcarbene (17)

Both syn and anti isomers should exist for this carbene. The main difference is the H-C-C-C dihedral angle for the carbene arm; 17-syn has an angle of 153° while 17-anti has a -45° angle. These species are essentially isoenergetic, where the syn isomer is 0.30 kcal/mol lower in energy. Rearrangement to methylene cyclopropane (14) by a C-H insertion has a huge
predicted barrier of 43.7 kcal/mol even though the reaction is slightly exothermic. Fragmentation to cyclopropyl acetylene (19) is predicted to have a modest barrier and is downhill by 55.3 kcal/mol. A 1,2-shift to 1,2-cyclopentadiene (8) is the lowest energy intramolecular reaction as it only has a 7.0 kcal/mol energy barrier. These results allow us to conclude that upon the generation of 17, this carbene should undergo rearrangement to 8, unless we have missed some other lower energy process.

1,2-cyclopentadiene (8)

1,2-cyclopentadiene (8) is calculated to have C$_2$ symmetry. This nonplanar distortion is due to the presence of the allenic moiety. This allene is more stable than cyclobutenyl carbene (17) by 28 kcal/mol. Formation of 8 from 17 is likely to be an irreversible process. Further rearrangement of 8 to divinylcarbene (22) has a predicted barrier of 33 kcal/mol. This result suggests that 8 should be observable due to this apparent energy well. In principle, ring opening of the cyclopropylidene (15) will also yield 1,2-cyclopentadiene (8); however, carbene 15 was not found to be an energy minimum and should rearrange spontaneously to 8.

Bicyclo[2.1.0]pent-1,2-ene (13)

This interesting alkene is only 3 kcal/mol more stable than 17 but lies 30 kcal/mol above cyclopenten-3-ylidene (20). A C-H insertion to 13, via TS5, has a barrier of 14 kcal/mol, while ring expansion to 20 only has a barrier of 0.2 kcal/mol. Rearrangement to 16, via TS8 has a huge predicted barrier of 33
kcal/mol. This alkene is predicted to lie in a very shallow minimum. These calculations lead us to conclude that 13 is not likely to be observed but will further rearrange to carbene 20.

![Diagram of molecular structures and energy levels]

Scheme 7: B3LYP/6-311G+(d,p)+ZPVE Potential Energy Surface for C₅H₆

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Cyclopenten-3-ylidene (20) and 1,3-cyclopentadiene (21)

Cyclopenten-3-ylidene (20) has a carbene angle of 103° while 1,3-cyclopentadiene (21) has wider angle of 109°. Carbene 20 is 60 kcal/mol higher in energy than 21. This rearrangement involves a 1,2-H migration to 21 via TS7 with a barrier of 11 kcal/mol. Diene 21 is the most stable species on this surface.

Cyclopenten-3-ylidene (20) can feasibly rearrange in other fashions. Rearrangement to 13 is not likely due to its significant barrier, via TS6, of 30 kcal/mol. Even less probable is a 1,2-H migration to cyclopentyne (23), via TS10 due to its huge barrier of 77 kcal/mol. The lowest energy intramolecular reaction of 20 is rearrangement to 21.

Cyclobutylidene (16) and cyclopentyne (23)

Cyclobutylidene (16) can rearrange through an initial C-H insertion with a barrier of 40 kcal/mol to the cyclopropene adduct (13) and further to 1,3-cyclopentadiene (21). More likely is rearrangement of 16 to cyclopentyne (23), via TS9 with a barrier of only 4 kcal/mol. Baxter and Brown suggested 16 as intermediate in the pyrolysis of cyclobutylidenecarbene derivative of Meldrum's acid (38) which yielded pent-1-en-3-yne (40) (Scheme 8).28 This was postulated to occur by elimination to 16, followed by rearrangement to cyclopentyne (23) and an internal H-migration to afford the hydrocarbon (40). Alternatively, it could occur through an H-migration and ring opening of cyclobutene (39) to yield hydrocarbon 40. The initial mechanistic suggestion agrees with our results; however, we did not computationally study 23 to 40.
Scheme 8: Pyrolysis of Cyclobutylidene Derivative of Meldrum's Acid

Cyclopentene (23) can also rearrange to carbene 20 via TS10 and thence to 1,3-cyclopentadiene (21). However, this process has a very high energy barrier of 52 kcal/mol and interconversion with 16 is more likely. This reaction has been extensively studied by Johnson and Gilbert; our results are in agreement with these reports.27

Potential Energy Surface

In summary, our computations on the C5H6 potential energy surface suggest that cyclobutenyl carbene (17) should undergo rearrangement to 1,2-cyclopentadiene (8) as this process has the lowest barrier. This result encourages our efforts towards the synthesis of this carbene, as generation and trapping of the unsubstituted 1,2-cyclopentadiene (8) has not been previously reported. Upon generation of cyclopenten-3-ylidene (20), this is likely to yield 1,3-cyclopentadiene (21). Our calculations on the cyclopentene-cyclobutylidene carbene surface are consistent with previous studies.
The C₆H₈ Energy Surface

Scheme 9 summarizes a large collection of computational results for the C₆H₈ potential energy surface. Once again, analysis begins with the cycloalkenylcarbene (28).

Cyclopentenylcarbene (28)

Syn and anti cyclopentenylcarbene (28) geometries differ by their dihedral angle H-C-C-C dihedral angle for the carbene arm; 28-syn has a 44° angle while 28-anti has an angle of -145°. These isomers of 28 are essentially isoenergetic. They are less stable than their surrounding intermediates and can lead to a variety of rearrangements. Generation of methylene cyclopropane (25) by a C-H insertion is exothermic but has a large energy barrier of 31 kcal/mol. Rearrangement to 1,2-cyclohexadiene (9) by a 1,2-shift has a modest predicted barrier of 14 kcal/mol. Fragmentation to cyclobutylacetylene is downhill 32 kcal/mol; currently, we have not been able to locate TS18. In this case, the lowest energy intramolecular reaction predicted for carbene 28 is the closure to 24, with a barrier of only 5 kcal/mol.

1,2-Cyclohexadiene (9)

1,2-Cyclohexadiene (9) is distorted along the allene bonds and has near C₂ symmetry. It lies 18 kcal/mol lower in energy than cyclohexenylidene (30), is 27 kcal/mol below than carbene 28, and is more stable than its isomer cyclopropylidene (26) by 40 kcal/mol. It can be formed by ring expansion from 28, via TS12, with a barrier of 14 kcal/mol; however, 28 is predicted to rearrange...
to 24. Rearrangement of 9 to 30, via TS16, requires 64 kcal/mol. From a
different pathway, 1,2-cyclohexadiene (9) is likely to be formed by the ring
opening of cyclopropylidene 26 with a barrier of only 0.2 kcal/mol.14 These
results allow us to conclude that this intermediate is likely to be generated only
from 26. It is calculated to lie in a moderate potential well and direct observation
has been reported. In principle, 9 may undergo retro-ene chemistry to afford 1,3-
cyclohexadiene (31) via 1,3,5-hexatriene. This reaction was not studied here
but, similar chemistry has been previously described by Johnson for 1,2-
cyclononadiene.52

**Bicyclo[3.1.0]hex-5-ene (24)**

Bicyclo[3.1.0]hex-5-ene (24) is more stable than 28 by 16 kcal/mol while
only more stable than 30 by 7 kcal/mol. This bicyclic intermediate is likely to be
generated from 28, via TS13, as it is only has a 5 kcal/mol barrier. Ring opening
to carbene 30, via TS14, exists with a barrier of 17 kcal/mol while rearrangement
to 27, via TS21, has a much larger barrier of 36 kcal/mol. These results suggest
that, if formed, 24 should rearrange to carbene 30.
Scheme 9: B3LYP/6-311+G(d,p)+ZPVE Potential Energy Surface for C₆H₈

Cyclohexen-3-ylidene (30) and 1,3-cyclohexadiene (31)

Cyclohexen-3-ylidene (30) is less stable than its neighboring intermediates. Rearrangement to cyclohexyne (32) via TS23 has a larger barrier.
of 49 kcal/mol. Carbene 30 can rearrange through a 1,2-H shift to either 1,3-cyclohexadiene (31) or 1,2-cyclohexadiene (9); however, TS16 has a barrier of 46 kcal/mol while TS15 only has a 10 kcal/mol barrier. Ring contraction to bicyclic 24 also has a barrier of only 10 kcal/mol. Our results suggest that interconversion of 24 and 30 is likely to be reversible, while 30 to 31 is not. Diene 31 is the global minimum on this surface. In agreement with our results, Freeman showed that upon generation of a biphenyl substituted cyclohexenylidene, the corresponding 1,3-cyclohexadiene was obtained.45

Cyclopentylidenecarbene (27) and cyclohexyne (32)

Cyclopentylidenecarbene (27) is less stable than bicyclo[3.10]hex-5-ene (24) by 11 kcal/mol and cyclohexyne (32) by 12 kcal/mol. Our calculations show that a C-H insertion to 24 has a barrier of 24 kcal/mol. This structure can also undergo ring expansion to 32 with a barrier of 10 kcal/mol. Rearrangement to 32 is the lowest energy intramolecular reaction; however, under high temperature FVP conditions, the bicyclic intermediate may be generated. Cyclohexyne can further rearrange to carbene 30 but this is uphill by 57 kcal/mol. Shevlin showed that a retro Diels-Alder of 32 would yield ethylene and 1,2,3-butatriene42; this was not studied here but will be further discussed below.

Experimental Studies on these Potential Energy Surfaces

An experimental study by Wentrup and coworkers is in accord with our results and connects many of these species (Scheme 10).53 They showed that upon flash vacuum pyrolysis (FVP) of cyclopentylidene-Meldrum’s acid (41) three
ketenes 42, 43, and 44 were observed and 1,3-cyclohexadiene (31) and benzene were obtained. The authors suggested that ketene 44 decarboxylates to cyclopentenylcarbene (28) which further rearranges to 31. This finding is in agreement with our energetics, where formation of 31 from 28 is downhill by 70 kcal/mol. They suggested this passes through intermediates 24 and 30 but did not observe them; this is also in accord with our results. Ketene 42 was believed to isomerize to 44, although another route was suggested where 31 is directly generated from 27. Our computations suggest this rearrangement may be feasible under FVP conditions; however, ring expansion to cyclohexyne (32) has a lower energy barrier.

Scheme 10: Pyrolysis of Cyclopentylidene Derivative of Meldrum’s Acid

Shevlin investigated this pyrolysis further and proposed that a retro Diels-Alder of 32 would yield ethylene and 1,2,3-butatriene. Computationally, he showed that the cleavage of cyclohexyne (32) was higher in energy than rearrangement to 1,3-cyclohexadiene (31). Pyrolysis experiments for 41
suggested that while one path leads to 1,3-cyclohexadiene, another generates ethylene + butatriene; this is also supported by our computations.

In review, mapping of this potential energy surface suggests that cyclopentenylcarbene (28) is energetically favored to form cyclopropene adduct 24 with further rearrangement to 1,3-cyclohexadiene (31) via carbene 30. This result is supported by Wentrup's and Shevlin's experiments. The same rearrangement energetics were not observed for cyclobutenylcarbene (17); however, this result is consistent with Stierman and Johnson's result, where the cyclopropene adduct (24) was formed in the greatest yield. Cyclopentylidene (27) is energetically favored to form cyclohexyne (32), although rearrangement to 1,3-cyclopentadiene (31) via 24 and 30 has been proposed.

**Experimental Results and Discussion**

**Synthesis of Vinylcarbene Precursors**

**Dehydration Approach**

These experimental studies are focused on the synthesis of C₅H₆ and C₆H₈ carbene precursors via cyclopropanated phenanthrenes. We have previously shown reaction of 1 with n-butyllithium generates the carbenoid and electrophilic quenching will yield a substituted cyclopropane (Scheme 11).

![Scheme 11: Lithium Carbenoid Formation](image-url)
Kirchhoff showed that quenching with methanol resulted in protonation. While Hernandez and Lewis found quenching with a ketone yields an alcohol. A combination of this chemistry is the basis for our proposed route, shown in Scheme 12. The final step involves dehydration, which should be a novel approach to the desired cycloalkenylcarbene precursors (47 A-B).

Following a procedure by Kirchhoff, monochloro adduct 45 was prepared by reacting 1 with n-BuLi, followed by quenching with methanol. Adduct 45 was obtained in 89% yield as white crystals and spectral data agreed with Kirchhoff’s results. Reacting this further with n-BuLi, followed by quenching with the appropriate cyclic ketone (46 A-B), generated the alcohol (47). This synthetic strategy was used to successfully prepare the cyclobutanol (47A) and cyclopentanol (47B) adducts. Adduct 47A was purified by radical chromatography (eluted with 1:1, CH₂Cl₂: Hexane) and obtained in 77% yield as a light yellow solid. Adduct 47B was obtained in 88% yield as a light yellow solid also after radial chromatography. Both species were characterized by ¹H and
\[^{13}\]C NMR and then subjected to a variety of dehydration conditions in hopes of producing the carbene precursors **(Scheme 13)**. These alcohols are likely to be very sensitive to acidic conditions; in turn, we explored mild and basic dehydration reactions.

**Scheme 13: Attempts at Dehydration of Alcohols**

Initially, dehydration attempts were run using cyclobutanol \(47\text{A} \)\( \). Multiple attempts were made to prepare \(47\text{A} \) by treatment with \(\text{PBr}_3 \) in pyridine\(^5\); these proved to be unsuccessful and decomposition of the substrate was seen. \(\text{PPh}_3\cdot \text{I}_2 \) was reported as an efficient and mild reagent for the dehydration of tertiary alcohols\(^5\); however, reaction of it with \(47\text{A} \) at RT for 20 hours also did not yield the desired product. Cyclobutane rings are known to be fragile and highly reactive due to their associated strain. In addition, cyclobutanone is an expensive reagent therefore, we wanted to developed our synthetic route with a less expensive and strained system.
The cyclopentanol adduct (47B) is considered to be a less strained; therefore, 47B was subjected to dehydration chemistry. Converting the alcohol to a tosylate should make it more susceptible to elimination; however, reacting 47B with tosyl chloride in pyridine for 1 week at 0°C did not yield the desired tosylate. Phosphorus-oxychloride (POCl₃) is often able to induce dehydration of tertiary alcohols even at 0°C. Reaction of 47B with POCl₃ in anhydrous pyridine was monitored by TLC; but, after 2 hours at RT no new spots had developed. Stirring for an additional 2 hours at 40°C gave rise to a complex product mixture, as seen by NMR. There was a small ¹H signal between 5-6 ppm, which was speculated to be the vinyl proton in the desired product (48B). A procedure in the literature reported the preparation of model compounds, cyclopropyl-substituted cycloalkenes by treatment with POCl₃ in anhydrous pyridine at 80°C for 1 hour. Treating 48B with these reported conditions, once again produced only possible traces of product. Multiple dehydration attempts were unsuccessful and a new approach was employed.

Base-Catalyzed Isomerization Approach

Isomerization of vinylidene carbene precursors may provide a route to our desired cycloalkenyl carbene precursors. Hernandez previously developed a synthetic route to vinylidene precursors (51A-B) (Scheme 14). This begins by lithium-halogen exchange between 1 and n-butyllithium to form the carbenoid. Quenching with the appropriate cyclic ketone (46) yields chlorhydrin 49.
Treatment of this alcohol with TMSCI in pyridine furnishes the TMS-ether 50 and, in the last step, tert-butyl lithium induces 1,2-elimination of TMSOLi to yield 51.

B3LYP/6-31G* computations suggest that isomerization to the desired cycloalkenyl precursors should be favored because the cyclobutenylcarbene precursor (48A) is downhill 7.7 kcal/mol and cyclopentenylcarbene precursor (48B) is downhill 10.1 kcal/mol. Treatment of 51 with base should catalyze isomerization to the cycloalkenyl-carbene precursors 48A and 48B. Upon reacting 51B with KOBu-t in DMSO for 1 hour at 50°C, a variety of 1H signals were seen by NMR but no signals indicating product formation. This result suggests decomposition of the substrate. Mild bases may yield the desired chemistry and should be further investigated in the future.

**Vinyl Halide Coupling Approach**

A Gilman reagent could prove to be useful in preparing our carbene precursors. They have been shown to be synthetically useful since they undergo organometallic coupling reactions with alkyl halides which make it possible to
prepare larger molecules from smaller pieces. In fact, Jones and Ruck found that treatment of 1 with a Gilman reagent, yielded a coupled product.

In order to utilize this approach, we needed to develop a synthesis to cyclopentenyl iodide, which will then be used to prepare the Gilman reagent. Weimer and Lee recently reported the synthesis of vinyl iodides (54) from ketones (52) via vinyl phosphates (53) (Scheme 15).

Lewis had previously attempted the synthesis of cyclopentenyl iodide (54A) via the hydrazone. This method was found to yield an abundance of side products such as the gem-iodide which where difficult to remove. In contrast, this new route claims to produce minimal side products.

Following Weimer and Lee’s route, cyclopentanone (52B) was treated sequentially with LDA and diethyl phosphonate to yield the vinyl phosphonate (53B) in a 77% yield as a light yellow liquid. Reacting 53B with 3 eq. of TMSI, followed by flash chromatography on silica or florisil with pentane elution produced cyclopentenyl iodide (54B) in a 43% crude yield. There were minor contaminants in the sample and attempts to purify by flash chromatography and vacuum distillation were unsuccessful. IR spectroscopy helped to confirm the identity of the desired product, which was used without further purification.
vinyl iodide (54B) was treated sequentially with t-BuLi\(^6\) and CuI\(^6\) to generate Gilman reagent 55 (Scheme 16).

Scheme 16: Gilman Coupling Chemistry for Cyclopentenylcarbene Precursor

Reaction of 1 with the Gilman reagent (55) should generate the coupled product (56). It is known that quenching the coupling reaction with R-X will allow for the addition of R through a cuprate intermediate (57).\(^{58,63}\) Therefore, our reaction was quenched with CH\(_3\)OH in hopes of producing the protonated target precursor (48B). Upon inspection of the NMR spectrum, a small signal appeared at ~5.5 ppm which was believed to be the vinyl proton. Radial chromatography failed to yield the desired product. Further purification of 54B may be necessary in order to effectively generate the coupled product.

Weimer and Lee did not report the preparation of 1-iodocyclobutene (54A)\(^{59}\), which is needed for our synthesis. We speculated this is due to the high cost of the starting material, cyclobutanone. There are no reports in the literature of cyclobutenyl iodide (54A) and therefore we were unsure of its \(^1\)H NMR spectrum.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
This prompted a brief $^1$H NMR computational investigation of the predicted vinyl $^1$H shifts, expected to be the most distinct signal within the molecule. In order to find a method that would provide the most accurate predictions, we began by comparing the predicted vinyl $^1$H shifts to the literature for cyclopentenyl halides (54B, 58-60) with various methods (Table 1). Basis sets above 3-21G* were not used because they are not parameterized for iodine in Spartan '04.

<table>
<thead>
<tr>
<th>Table 1: Predicted Vinyl $^1$H Shifts for Cyclopentenyl Halides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinyl $^1$H Shift</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>HF/3-21G*</td>
</tr>
<tr>
<td>B3LYP/3-21G*</td>
</tr>
<tr>
<td>MP2/3-21G*</td>
</tr>
<tr>
<td>Literature</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Predicted Vinyl $^1$H Shifts for Cyclohexenyl Halides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinyl $^1$H Shift</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>HF/3-21G*</td>
</tr>
<tr>
<td>Literature</td>
</tr>
</tbody>
</table>

This study showed that HF/3-21G* provided predictions within 0.20 ppm of the reported literature values. Surprisingly, other methods afforded less accurate
predictions. We also looked at the predictions for the cyclohexenyl halides (61-64) at HF/3-21G* and they were found to be within 0.3 ppm of the reported literature values (Table 2). This preliminary study allowed us to investigate cyclobutenyl halides (Table 3); where the predicted vinyl $^1$H shifts for cyclobutenyl bromide (65), chloride (66) and fluoride (67) were all within the 0.3 ppm of literature values. Our calculations predicted that cyclobutenyl iodide (38A) will have a vinyl $^1$H shift at 6.61 +/- 0.30 ppm. This provides us with a predicted chemical shift and will help in the characterization of the next synthetic step.

<table>
<thead>
<tr>
<th>Vinyl $^1$H Shift</th>
<th>54A</th>
<th>65</th>
<th>66</th>
<th>67</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF/3-21G*</td>
<td>6.61</td>
<td>6.25</td>
<td>5.99</td>
<td>4.72</td>
</tr>
<tr>
<td>Literature</td>
<td>Unreported</td>
<td>6.05 $^{19}$</td>
<td>5.82 $^{70}$</td>
<td>4.67 - 4.74 $^{70}$</td>
</tr>
</tbody>
</table>

Following Weimer and Lee's route$^{59}$, cyclobutanone (52A) was treated sequentially with LDA and diethyl phosphonate to yield the vinyl phosphonate (53A) in 90% yield as a light yellow liquid. This was further treated with 3 eq. of TMSI. Inspection of the $^1$H NMR spectrum showed that there was a signal at 6.51 ppm, which is within 0.3 ppm of the predicted vinyl $^1$H shift. The $^1$H NMR suggests that the cyclobutenyl iodide (54A) was formed, along with several side products. Attempts to purify the iodoalkene by flash chromatography on silica or

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
florisil, with pentane as the eluent, were unsuccessful. This likely led to
decomposition of the substrate. Reaction time was shortened to reduce side
products but \(^1\)H NMR analysis still showed a variety of undesired signals.
Reducing the temperature to 0° C gave the same results. Following a suggestion
of Weimer and Lee, we increased the TMSI to 4 eq. in hopes of further reducing
the formation of side products, but this was also unsuccessful. Our sample of
cyclobutenyl iodide (38A) was too impure for continuation with the coupling
chemistry.

In summary, alcohol dehydration, base-catalyzed isomerization and
Gilman chemistry all failed to yield our desired cycloalkenylcarbene precursors.

**Synthesis towards Cyclopropylidene Precursors**

We have also sought to develop a general method for the synthesis of
cyclopropylidenes based on cyclopropanated phenanthrene photolysis (Scheme
17). Calculations showed the barrier to ring opening of cyclopropylidene 69 to
the substituted 1,2-cycloheptadiene (72) is ~15 kcal/mol; this could allow for
addition to an olefin to form the desired substituted spiropentanes (70).
Photolysis of this product would lead to the generation of the substituted
cyclopropylidene (71), which might allow for us to study kinetics of the ring
opening or properties of the cyclic allenes.
Scheme 17: Proposed Generation of Cyclopropylidenes

In some previous attempts, Hernandez\textsuperscript{9} and Kirchhoff\textsuperscript{6} treated the gem-dihalo cyclopropane (1) with an organolithium reagent under a variety of reaction conditions but did not obtain the expected spiro product. Hernandez also found the reaction of 68 with lithium wire to be unsuccessful.\textsuperscript{9} Lewis attempted to prepare 73 by reaction of chloro-TMS adduct with n-BuLi, in the presence of cyclohexene; this reaction yielded monochloro adduct and starting material\textsuperscript{10} (Scheme 18). No evidence of the ring opened allene (72) was found, which offered promise for our approach.

We treated the gem-dichloro cyclopropane (1) with Mg\textsuperscript+ in THF and cyclohexene but only obtained mono-chloro adduct (45). These results suggest that the C-Cl bond is too strong to cleave and the cyclopropylidene is not likely to be formed. Therefore we decided to attempt further chemistry using the gem-dibromo adduct (68) because the C-Br bond is weaker by 14 kcal/mol.\textsuperscript{56} This was prepared by dibromo carbene addition to phenanthrene under phase transfer (PT) conditions. Mechanical stirring for 5 days with 50% NaOH and
benzyltrimethylammonium chloride, as the PT catalyst, yielded a light brown solid in 60% yield. $^1$H and $^{13}$C NMR along with mp data helped to characterize.

Scheme 18: Attempted Spiropentane (72) Formation

Organozinc chemistry offered a variety of potential routes to 72 and related structures. In the Simmons-Smith approach, dihalomethanes are treated with active zinc to generate a zinc carbenoid. Addition of an olefin yields a substituted cyclopropane. Utilizing a zinc carbenoid instead of a free carbene, might favor alkene addition over ring opening to the cyclic allene. Substituted zinc carbenoids have been effective at generating 1,2,3-substituted cyclopropanes but there are only a few reports of 1,2,3,4-substituted cyclopropanes formed by this method. The carbenoid formation is generally more effective with gem-dilodo cyclopropanes; however, dibromides and even activated dichlorides have been successful.
Various active Zn species were used with the goal of developing a general method. Angus developed a preparation for a highly reactive Zn/Cu couple.\(^7\) Utilizing his Zn/Cu couple in the Simmons-Smith reaction led to monobromo adduct (73) and no remaining starting material, as seen by NMR spectroscopy. This suggests that the active Zn is inserting into the C-Br bond to form the zinc carbenoid and upon aqueous work-up, the monobromo product (73) is formed. Therefore, the olefin is not reacting with the carbenoid. Cyclohexene was used as co-solvent without major effect. NMR analysis showed traces of a potential product but, chromatography failed to isolate this product. The reaction was initially run in THF at room temperature but it was also refluxed in a higher boiling solvent, benzene, in order to help further drive the reaction also without success. A more traditional preparation of a Zn/Cu couple was used involving Zn and Cu(OAc)\(_2\).\(^7\) Unfortunately this active zinc species was found to be less effective, as primarily starting material was obtained, along with monobromo adduct (73) and the same unknown alkylated product.

In a final attempt, diethyl zinc was used directly.\(^7\) Refluxing overnight yielded starting material, monobromo adduct (73) and a new unidentified product (74). In this case, this product was isolated by chromatography and analyzed by \(^1\)H, \(^13\)C and 2D NMR along with MALDI-TOF MS. COSY NMR did suggest that this unidentified alkylated product (74) was a mixture of two stereoisomers. Unfortunately even with all of this data, the structure could not be determined. Although the data are not conclusive, it does suggest that the cyclopropylidene
ring opened to yield 1,2-cycloheptadiene (72) which would quickly react with other molecules in solution, including itself. Based on our present data, diethyl zinc appears to be too harsh a reagent while Zn/Cu couples are not effective enough.

**Conclusions**

We have presented the results of a comprehensive study of the C$_5$H$_6$ and C$_6$H$_8$ potential energy surfaces. The predicted rearrangements and energetics for the interconversion of various C$_5$H$_6$ and C$_6$H$_8$ isomers are generally in good agreement with reported experimental results. On the C$_5$H$_6$ surface, cyclobutenylcarbene (17) is predicted to rearrange to 1,2-cyclopentadiene (8). Cyclobutylidenecarbene (16) should be involved in the interconversion to cyclopentyne (23). For the C$_6$H$_8$ surface, cyclopentenylcarbene (28) should rearrange to bicyclo[3.1.0]hex-5-ene (24) and further to 1,3-cyclohexadiene (31). Cyclopentylidenecarbene (27) is likely to interconvert with cyclohexyne (32). At high temperature, 27 should yield 1,3-cyclohexadiene (31) via 24.

Our synthetic efforts towards the vinylcarbene precursors (48A-B) have so far been unsuccessful. Dehydration attempts of precursor alcohols have failed. Base-catalyzed isomerization of the vinylidene precursors (51A-B) has so far been ineffective. However, computations suggest this is a favorable process and other bases can be investigated. The synthesis of cyclopentenyl iodide (54B) was successful, but the preceding coupling chemistry yielded only traces of
desired product (48B). Even if this chemistry could be optimized, unfortunately the synthesis towards cyclobutenyl iodide (54A) was found to be difficult.

Synthetic attempts towards cyclopropylidene precursors (72) were also unsuccessful. Zinc carbenoids were successfully formed by treatment with Zn/Cu couples; however, the olefin was not able to effectively add to yield the carbene precursor. Diethyl zinc was found to be too harsh a reagent and was believed to induce ring opening of the cyclopropylidene (69).

These syntheses remain important goals, but both clearly require different synthetic approaches. If further synthetic attempts can yield the desired carbene precursors 48 A-B and 72, they will be subjected to photolysis, matrix isolation studies and trapping experiments.
CHAPTER II

STRAIN ESTIMATES FOR SMALL-RING CYCLIC CUMULENES

Introduction

Definition of Strain

Strain can be defined as destabilization due to deviation from an ideal bonding geometry. The idea of molecular strain was first introduced well over one hundred years ago by Adolf von Baeyer. He proposed the idea that smaller rings are strained because of the deviation of bond angles from the preferred tetrahedral geometry of carbon. Ring strain, or Baeyer strain, represents only a portion of the total strain in molecules.

Strain energy may arise from distortions in bond angles, bond lengths, torsional angles and non-bonded interactions. Each of these components contributes to strain, which then affects the nature and chemical reactivity of that molecule. Strain energy can be determined by comparison of a strained molecule to an unstrained reference compound. Computational methods are now used extensively in order to predict the strain energy and hence stability of compounds before their synthesis is attempted. Hehre and Pople first proposed the use of isodesmic reactions to estimate strain from enthalpy of formation data. This is a hypothetical scheme which more generally utilizes ab initio derived energies to estimate strain. Isodesmic reactions are defined as a
scheme in which the number of each type of bond, i.e. single, double or triple, is retained on either side of a balanced molecular equation. Trachtman and George later extended this idea to homodesmic reactions, a more strictly defined subset which required that the number of carbon atoms in each hybridization state must be equal in the products and reactants. With careful definition, isodesmic reactions should give accurate predictions of specific types of functional group strain while homodesmic reactions afford predictions of total strain.

Cyclic Allenes

Cyclic allenes are the smallest structures in the cumulene series and have been previously described in Chapter 1. The first crude strain estimates for cyclic allenes were reported by Gasteiger and Dammer for five- to eight-membered rings. The authors estimate strain energies of 30, 20, 15, and 10 kcal/mol for 1,2-cyclopentadiene to 1,2-cyclooctadiene. Bachrach reported the ring strain energy for 1,2-cyclohexadiene to be 29.56 kcal/mol by using a group equivalent approach. Otherwise, only crude estimates have been reported for cyclic allenes. A 1985 MNDO study by our own group reported the bending angles and out-of-plane angles for the allene series. (see Figure 3) Kamigata used ab initio MO calculations to study the strain energy of cyclic bisallen es with seven- to ten-membered rings. The maximum strain energy in an allene may be roughly equated to the energy required for allene π bond rotation, coupled with energy derived from bending of the normally linear allene. Better estimates
of the total strain and allene strain energy in these compounds are needed and require sophisticated *ab initio* methods. In her UNH M.S. thesis, Daoust reported estimates based on MP4SDTQ/6-31G*/MP2(FC)/6-31G* calculations\(^8\); with advancement in computational methods, better predictions should be available.

**Cyclic Butatrienes**

Cyclic butatrienes are the next compounds in the cumulene series. Butatrienes are linear and planar, with \(D_{2h}\) symmetry. The two central carbons are sp hybridized; strain in the butatrienes usually is generated from bending the in-plane \(\pi\) bond between the two central carbons. The series of cyclic butatrienes has received less attention (Figure 6).

![Cyclic Butatriene Series](image)

**Figure 6: Cyclic Butatriene Series**

Six- to nine-membered cyclic butatrienes have been generated, but only 1,2,3-cyclononatriene (80) proved to be isolable.\(^{16}\) As with the cyclic allene series, the five-membered ring (76) has remained elusive. However, 5-thia and 5-aza derivatives have been successfully prepared.\(^{84}\) 1,2,3-cyclobutatriene (75) has been reported by Mabry to be a transition state rather than an energy minimum.\(^{85}\) The only description of the strain in this series is a MNDO study by Angus and Johnson where they reported the bending angles and strain energies

39

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
However there have been several other computational studies on cyclic butatrienes.\textsuperscript{47,86}

![Figure 7: MNDO Bending Angles and Strain Energies for Cyclic Butatrienes](image)

Accurate predictions for strain in the cyclic butatriene series are desirable. Daoust had used MP4SDTQ/6-31G*//MP2(FC)/6-31G* calculations\textsuperscript{83}; once again, better levels of theory may provide more reliable predictions.

**Statement of Goals**

This project is focused on the computational investigations of strain estimates for the cyclic allenes and cyclic butatriene series which will include the four- to nine-membered rings. The isodesmic and homodesmic schemes developed by Daoust will be utilized but with DFT energetics.

**Computational Methods**

For each of the cyclic allenes and cyclic butatrienes investigated, initial geometry optimization at the semi-empirical level were performed using the Spartan 04 modeling program.\textsuperscript{50} Further geometry optimization was carried out with Gaussian 03 \textsuperscript{51} using B3LYP/6-311+G(d,p), density functional methods followed by vibrational frequency analysis. Strain energies below include unscaled zero point vibrational corrections; corrections are near unity for the
chosen DFT method. For the more strained compounds, care was taken to test the stability of the wavefunction as some degree of diradical character is likely.

The isodesmic and homodesmic expressions used to evaluate the strain can be seen below in **Scheme 19**. Equations 7, 8, 10, and 11 were previously developed by Daoust, while equations 9 and 12 are newly written reactions.

**Scheme 19: Isodesmic and Homodesmic Reaction Schemes**

In both homodesmic reactions (**Eq. 7** and **Eq. 10**), strain in the cumulene is referenced to the corresponding unstrained acyclic structure. These reactions will provide estimates for the total strain in the cyclic cumulenes and, as written, will be a negative value since strain in being relieved. The isodesmic reactions (**Eqs. 8, 9, 11 and 12**) are used to predict the strain in the cumulene functionality. In each of these reactions, the strained cumulenes are referenced to the corresponding unstrained cyclic structure.
Another approach we developed, referred to as "fragment strain", provides estimates for allene and butatriene strain. We isolate the allene or butatriene fragment from the ring by simply deleting the other atoms; the remaining C₃H₄ or C₄H₄ moiety is subjected to a single point DFT calculation. A similar approach has been previously used.⁸⁷

**Results and Discussion**

**Strain in Cyclic Allenes**

Daoust initially investigated the total strain in 1,2-cyclobutadiene (7), 1,2-cyclopentadiene (8) and 1,2-cyclohexadiene (9) using homodesmic reactions.⁸³ The larger cyclic allenes were considered to be too computationally demanding for MP4SDTQ/6-31G*/MP2(FC)/6-31G* theory. However, now the entire series can be evaluated with DFT methods. Our homodesmic results for the allene series are reported in Table 4. As expected the total strain decreases as the ring size is increased. When comparing our DFT results to Daoust's MP2 results, good correlation is seen.

<table>
<thead>
<tr>
<th>Table 4: Homodesmic Reaction Energies for Cyclic Allenes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ΔHₑ</strong></td>
</tr>
<tr>
<td>Eq. 13</td>
</tr>
<tr>
<td>Eq. 14</td>
</tr>
<tr>
<td>Eq. 15</td>
</tr>
<tr>
<td>Eq. 16</td>
</tr>
<tr>
<td>Eq. 17</td>
</tr>
<tr>
<td>Eq. 18</td>
</tr>
</tbody>
</table>

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Allene strain was evaluated using two isodesmic reactions. These results can be seen in Table 5. When comparing our results to Daoust’s MP2 predictions (Eqs. 19, 21, 23, 25, 27 and 29), good correlation is seen. The other isodesmic reaction (Eqs. 20, 22, 24, 26, 28 and 30), where the strained allene is referenced to an unstrained cycloalkane, was developed to help ensure we were calculating accurate strain estimations. The values from both reactions correlate well with each other. For example, the allene strain in 1,2-cyclohexadiene (9) is 31.58 and 31.81 kcal/mol for Eqs. 23 and 24, respectively. The fragment strain estimate is also in good agreement with these methods (Table 6). When comparing this to the results from the homodesmic scheme, it can been seen that the strain in 1,2-cyclohexadiene (9) arises solely from the allene moiety as all reactions predict ~32 kcal/mol. This is consistent with the fact that six membered rings are essentially unstrained and therefore the allene moiety will provide the only strain in this system. These results help to validate our methodology as they are also similar to Bachrach’s earlier predictions.80

Comparison of the various estimates shows that the cumulene strain is largely accountable for the total strain. For 1,2-cyclobutadiene (7), the total strain (89.87 kcal/mol) is largely derived from the cumulene strain (61-67 kcal/mol) and typical four-membered ring strain (27 kcal/mol). For, 1,2-cyclopentadiene (8) allene strain (50-51 kcal/mol) contributed the most to the total strain (55.29 kcal/mol).
For the larger cyclic allenes the isodesmic schemes appear to be less reliable. With the nine-membered ring (Eqs. 29 and 30), isodesmic predictions even change sign. Seemingly, the allene strain is minor in comparison to the ring strain. Fragment strain estimates help address this issue because ring strain is not included.

**Table 5: Isodesmic Reaction Energies for Cyclic Allenes**

<table>
<thead>
<tr>
<th>Structure</th>
<th>$\Delta H_R$ (kcal/mol)</th>
<th>B3LYP/6-31G**</th>
<th>MP4/6-31G**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eq. 19</td>
<td>-61.49</td>
<td>-66.1</td>
<td></td>
</tr>
<tr>
<td>Eq. 20</td>
<td>-54.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 21</td>
<td>-32.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 22</td>
<td>-50.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 23</td>
<td>-31.58</td>
<td>-32.6</td>
<td></td>
</tr>
<tr>
<td>Eq. 24</td>
<td>-51.09</td>
<td>-54.0</td>
<td></td>
</tr>
<tr>
<td>Eq. 25</td>
<td>-14.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 26</td>
<td>-13.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 27</td>
<td>-1.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 28</td>
<td>-0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 29</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eq. 30</td>
<td>4.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6: Fragment Strain Energies for Cyclic Allenes**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Fragment Strain (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>62.8</td>
</tr>
<tr>
<td>9</td>
<td>33.2</td>
</tr>
<tr>
<td>10</td>
<td>14.9</td>
</tr>
<tr>
<td>11</td>
<td>5.0</td>
</tr>
<tr>
<td>12</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Strain in Cyclic Butatrienes

Daoust only evaluated the strain in 1,2,3-cyclopentatriene (76) and 1,2,3-cyclohexatriene (77) as the larger rings were once again considered to be too computationally demanding.\(^{83}\) We were able to evaluate the entire series of four-to nine-membered rings. DFT geometries were optimized by Dr. Iain D. Mackie. 1,2,3-cyclobutatriene (74) was included in the study for completeness. However, the structure is not an energy minimum and has one imaginary mode at this level of theory.\(^{88}\)

Results for the homodesmic reactions can be seen in Table 7. As expected, the total strain, \(\Delta H_R\), increases dramatically as the ring size decreases. Our DFT results are in good agreement with Daoust's MP2 predictions.

<table>
<thead>
<tr>
<th>Eq.</th>
<th>Reaction</th>
<th>(\Delta H_R)</th>
<th>B3LYP/6-31+G**</th>
<th>MP2/6-31G**</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>(\text{H}_3\text{C}-\text{CH}_3)</td>
<td>-187.68</td>
<td>-84.42</td>
<td>-79.0</td>
</tr>
<tr>
<td>32</td>
<td>(2\text{H}_3\text{C}-\text{CH}_3)</td>
<td>-51.75</td>
<td>-49.4</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>(3\text{H}_3\text{C}-\text{CH}_3)</td>
<td>-32.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>(4\text{H}_3\text{C}-\text{CH}_3)</td>
<td>-29.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>(5\text{H}_3\text{C}-\text{CH}_3)</td>
<td>-14.80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Isodesmic reactions predict the in-plane \(\pi\) bond strain with results summarized in Table 8. Once again, in order to show that our scheme was
providing accurate predictions, another approach (Eq. 38, 40, 42, 44, 46 and 48) was developed in which the cyclic butatriene is referenced to an unstrained cyclic alkane. The results for both isodesmic schemes are generally in good agreement. An exception is seen with 1,2-cyclobutatriene (75); presumably due to the antiaromaticity of 1,3-cyclobutadiene.

Table 8: Isodesmic Reaction Energies for Cyclic Butatrienes

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ΔH_R</th>
<th>B3LYP/MP4/6-31G**//6-311+G**</th>
<th>MP2/6-31G*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eq. 37</td>
<td></td>
<td>-114.78</td>
<td></td>
</tr>
<tr>
<td>Eq. 38</td>
<td></td>
<td>-164.50</td>
<td></td>
</tr>
<tr>
<td>Eq. 39</td>
<td></td>
<td>-79.23</td>
<td>-74.0</td>
</tr>
<tr>
<td>Eq. 40</td>
<td></td>
<td>-79.26</td>
<td></td>
</tr>
<tr>
<td>Eq. 41</td>
<td></td>
<td>-47.76</td>
<td>-46.8</td>
</tr>
<tr>
<td>Eq. 42</td>
<td></td>
<td>-51.40</td>
<td></td>
</tr>
<tr>
<td>Eq. 43</td>
<td></td>
<td>-26.31</td>
<td></td>
</tr>
<tr>
<td>Eq. 44</td>
<td></td>
<td>-25.00</td>
<td></td>
</tr>
<tr>
<td>Eq. 45</td>
<td></td>
<td>-20.54</td>
<td></td>
</tr>
<tr>
<td>Eq. 46</td>
<td></td>
<td>-17.83</td>
<td></td>
</tr>
<tr>
<td>Eq. 47</td>
<td></td>
<td>-0.51</td>
<td></td>
</tr>
<tr>
<td>Eq. 48</td>
<td></td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>
Table 9: Fragment Strain Energies for Cyclic Butatrienes

<table>
<thead>
<tr>
<th>Structure</th>
<th>Fragment Strain (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>50.3</td>
</tr>
<tr>
<td>78</td>
<td>26.9</td>
</tr>
<tr>
<td>79</td>
<td>16.4</td>
</tr>
<tr>
<td>80</td>
<td>4.8</td>
</tr>
</tbody>
</table>

As expected, strain in the cyclic cumulenes decreases rapidly as the ring size increases. The total strain of 1,2,3-cyclopentatriene (76) (84.42 kcal/mol) is a composite of the cumulene strain (79 kcal/mol) and ring strain typical for a five-membered ring. For the six-membered ring (77), the total strain (51.7 kcal/mol) arises almost solely from the butatriene moiety (48-51 kcal/mol). The butatriene strain (25-26 kcal/mol) in 1,2,3-cycloheptatriene (78) has a large contribution to the total strain (32.1 kcal/mol) where ring strain plays a minor role. For eight-(79) and nine-membered (80) rings, cumulene strain is small compared to the other ring contributions. Fragment strain estimates probably provide more accurate predictions.

Conclusions

The strain in the cyclic allene and butatriene series was investigated using isodesmic and homodesmic reaction schemes. Strain predictions for 1,2-cyclohexadiene (9) were useful in evaluating our methodology since the six-membered ring is essentially unstrained.

These strain predictions correlate well with experimental results. 1,2-cyclobutadiene (7) is estimated to have a total strain of 90 kcal/mol and is suggested as a reactive intermediate.46 For the five-membered ring, substituted
1,2-cyclopentadiene (8) has been trapped,\(^8\) even with a strain of 50 kcal/mol. The six- (9) and seven-membered (10) cyclic allenes have also been trapped as reactive intermediates\(^9\); this is expected for strain predictions of 32 and 14 kcal/mol, respectively. 1,2-Cyclooctadiene (11) readily dimerizes at room temperature in spite of its minimal predicted strain of 5 kcal/mol. We have shown this ring size is isolable with a single tert-butyl group.\(^{52}\) It is easy to see why 1,2-cyclononadiene (12) is the first isolable compound in the allene series; it has a minimal predicted strain of 2 kcal/mol.

1,2,3-cyclobutatriene (75) stands out as a highly strained species, with an estimated strain energy of 180 kcal/mol, and is suggested to only exist as a transition state. 1,2,3-cyclopentatriene (76) remains unknown; this is in accord with a total strain of 84 kcal/mol. The six-membered ring (77) has been trapped as a reactive intermediate. It is noteworthy that 77 and 1,2-cyclopentadiene (8) can prepared both with a strain of approximately 50 kcal/mol. The seven-membered (78) cyclic butatriene has a predicted total strain of 32 kcal/mol.\(^{42}\) It is easily generated and trapped. This is comparable to the strain 1,2-cyclohexadiene (9). 1,2,3-Cyclooctatriene (79) has been trapped in solution\(^{13}\) and has a predicted strain of 30 kcal/mol. Interestingly its homologue, 1,2-cyclooctadiene (11), with a strain of only 5 kcal/mol is not isolable. 1,2,3-Cyclononatriene\(^{42}\) (80) is the only isolable compound in this butatriene series with a predicted strain value of 15 kcal/mol.
NEW CHEMISTRY OF OZONE: THE TETROXOLANE CONNECTION

Introduction

Ozone is well known in atmospheric chemistry. Stratospheric ozone shields the earth’s surface from ultraviolet light while tropospheric ozone is a cause of hazardous pollution.\textsuperscript{8,9} Alkene ozonolysis has been largely studied for its role in the atmosphere and organic synthesis.\textsuperscript{90,91} Known chemical routes to ozone are unexpectedly sparse. In atmospheric chemistry, ozone is produced by photolysis of O\textsubscript{2} and NO\textsubscript{2} in the stratosphere and troposphere, respectively. In the laboratory, ozone is usually prepared by passing a stream of oxygen through a high-voltage electrical discharge.\textsuperscript{56}

Recent reports suggest that ozone may be generated as part of the human immune system.\textsuperscript{92-94} Low levels of biogenerated ozone might be involved in inflammatory diseases such as arteriosclerosis or asthma. Recent studies by Wentworth and coworkers found evidence that ozone is produced by white blood cells during inflammatory processes as part of the body’s defense against pathogens.\textsuperscript{94} Keinan and coworkers speculated that inflammation in asthma may also involve ozone formation by white blood cells.\textsuperscript{92} In support of this theory, they found that inhalation of electron-rich olefins, natural ozone scavengers, provided significant improvement for asthmatic symptoms in sensitized rats.
Singlet oxygen has been suggested as a precursor in the biogeneration of ozone but the actual mechanism remains unknown.

In 1975, Klopman and Andreozzi provided indirect evidence for a new route to ozone while investigating the mechanism of ozonolysis.\textsuperscript{95,96} They reported that reaction of $^{18}$O labeled isobutyraldehyde with ozone resulted in facile exchange of the isotopic label (Scheme 20). The authors suggested an intermediate tetroxolane (87) and utilized semi empirical MO calculations to support this hypothesis.

\textbf{Scheme 20: $^{18}$O Label Exchange of Isobutyraldehyde and Ozone}

Tetroxolanes have received surprisingly little attention; although their sulfur analog, tetrathiolanes, have been isolated and examined by x-ray crystallography.\textsuperscript{81} One study of tetroxolanes investigated their conformational and energetic properties with Hartree-Fock (HF) calculations and suggested that tetroxolane will exist in a puckered conformation.\textsuperscript{97} A related study examined the lowest energy isomers of the oxygen-rich carboxide series, \( \text{CO}_n \) (\( n = 3-8 \)).\textsuperscript{98}

Other highly oxygenated species are well known in the literature; many of these cyclic systems are found in alkene ozonolysis. Dioxiranes are commonly used as synthetic reagents for epoxide formation.\textsuperscript{99} Tetroxanes (or tetraoxanes), have been shown to exhibit anti-malarial activity and are easily prepared by the dimerization of carbonyl oxides.\textsuperscript{100,101}
Carbonyl oxides (88) are another oxygenated species which have received a great deal of attention. They are known to have diradical character but often are written in a zwitterionic form (Scheme 21). Carbonyl oxides (88) or "Criegee intermediates" are key intermediates in the ozonolysis of alkenes. In this process, they are formed by decomposition of the primary ozonide (89). Carbonyl oxides (88) can also be generated by the reaction of triplet carbenes (90) with $^3$O$_2$ or by the oxidation of a diazo compound (91) with $^1$O$_2$; these reactions have been utilized in low-temperature matrices. More recently, it has been shown that hydrogen-abstraction from peroxyalkyl radicals (92) yields carbonyl oxides (88) as a major product; this is likely to be important route since these radicals are common atmospheric species.

Scheme 21: Generation of Carbonyl Oxides

Statement of Goals

The goal of this project was to investigate pathways to ozone via tetroxolane intermediates. The biological connection remains speculative but these routes may play a role in atmospheric chemistry. One fundamental goal was to provide evidence for the existence of tetroxolanes. This was done by
computationally studying ozone’s connection to tetroxolanes. We have also carried out experiments to further develop Klopman’s $^{16}$O chemistry by including several ketones and aldehydes.

**Computational Methods**

For each of the stationary points investigated, geometry optimizations were performed using Gaussian 03\textsuperscript{51} with density functional methods. B3LYP/6-311+G(d,p) was used for geometry optimization of all points followed by vibrational frequency analysis. Select reactions were also studied with BH&HLYP functional. The energetics below include unscaled zero point vibrational corrections. Each transition state has only one imaginary frequency and select reactions were followed by calculation of intrinsic reaction coordinates in order to fully characterize the reaction surface. Singlet diradical species were treated with an open shell wave function. The geometry and vibrational frequencies of some species were then recomputed with CCSD(T) and/or CBS-QB3 methods.

The CBS-QB3 model\textsuperscript{106} combines the design of the CBS-Q energy calculation\textsuperscript{107} with B3LYP DFT optimized geometries and frequencies. This method requires the following calculations:

- (i) B3LYP/6-311+g(d,p) geometry optimization and frequencies
- (ii) CCSD(T)/6-31+G(d') energy
- (iii) MP4(SDQ)/CBSB4 energy
- (iv) MP2/CBSB3 energy and CBS extrapolation
All calculations were performed with Gaussian 03. The closed shell species were calculated using CBS-QB3/6-311+g(d,p) coding. The singlet diradical species in this study were treated with an open shell wavefunction for the geometry optimization and single-point energy calculations. This was accomplished by running steps i-iv for the CBS-QB3 procedure in sequence. The complete basis set (CBS) extrapolation energies were calculated using formulas provided by Houk. These formulas were validated by comparing the results to the CBS extrapolation calculated by Gaussian for various closed shell species.

Select reactions, as stated throughout, were studied using Spartan 04 at B3LYP/6-31G* level of theory. All energies are reported in kcal/mol.

**Computational Results and Discussion**

We infer from Klopman’s study that other routes to tetroxolanes should yield ozone (93) by ring cleavage. One potential route may involve the reaction of carbonyl oxides with oxygen to form a tetroxolane intermediate. There is some literature to support this. Low-temperature matrix reaction of cyclopentadienone oxide (88) with O₂ generated a ketone and O₃ (93). This result was attributed to oxygen atom chemistry but the tetroxolane intermediate is also possible (Scheme 22).

![Scheme 22: Carbonyl Oxide Formation in a Matrix](image)
Sawaki reported on the mechanism of ester formation where he proposed that the addition of \( \text{O}_2 \) to a carbonyl oxide may generate a tetroxolane. This can eliminate \( \text{O}_2 \) to afford a biradical and then the ester (Scheme 23).\(^{110}\)

\[
\text{Scheme 23: Mechanism of Ester Formation from Carbonyl Oxide}
\]

This mechanism was consistent with \(^{18}\text{O}\)-tracer studies but, later this mechanism was ruled out and further studies suggested a radical chain mechanism.\(^{111}\) Sawaki's initial mechanism is closely related to our proposed mechanism which instead involves the tetroxolane cleaving to a ketone and ozone.

Our preliminary B3LYP/6-31G* calculations showed the energetic feasibility of this route with an overall \( \Delta E_{\text{rxn}} \) of -2.9 kcal/mol (Scheme 24). This result prompted us to undertake a complete study of the reaction pathway.

\[
\text{Scheme 24: B3LYP/6-31G* Predicted Energetics for Ozone Formation}
\]

**Formaldehyde-Ozone Energetics**

For simplicity, we began by investigating the reaction of formaldehyde (97) with ozone (93), as well as connection to the carbonyl oxide. Scheme 25 shows
structures for the relevant intermediates, transition states, and the tetroxolane (99). Reaction energetics are referenced to ozone since we are interested in how the tetroxolane and other species can lead to its generation. We began by locating a concerted transition state for the cycloaddition of formaldehyde (97) and ozone (93) but the DFT wavefunction failed a “stability” test, which means that it has open-shell diradical character. This suggested a radical mechanism and we were able to find a stepwise radical process for this cycloaddition.

Scheme 25: CBS-QB3 Energetics of Formaldehyde + Ozone

Formation of the C-O bond via TS24 generates the diradical (98) and subsequent formation of the O-O bond via TS25 produces the tetroxolane intermediate (99). This intermediate may also be formed by reaction of the carbonyl oxide (101) with triplet oxygen. This will initially lead to formation of the triplet diradical (100-T) via TS27-T. Spin conversion of 100-T to the singlet diradical (100-S) is
expected to be nearly isoenergetic. Finally, formation of the O-O bond via TS3 leads to closure of the tetroxolane (99).

Methodology becomes a critical issue in these calculations. There are some suggestions that the popular B3LYP DFT method may not accurately describe highly oxygenated species.\textsuperscript{112} As an alternative, CBS-QB3 methods\textsuperscript{106} might afford more accurate predictions for these species and transition states, with little penalty in computational speed.\textsuperscript{112} It has been suggested that this method may overcompensate for the effects of spin contamination in open-shell species.\textsuperscript{113} Recent studies also suggested that CBS-QB3 methods may provide greater accuracy than single-point CCSD(T) calculations.\textsuperscript{14,112,114} Based on these studies, CBS-QB3 calculations are suggested to provide the most accurate predictions; although, the best methodology for describing highly oxygenated species is yet to be determined. Comparison of the three methods is made below in Table 10.

<table>
<thead>
<tr>
<th>Structure</th>
<th>B3LYP/6-311+G(d,p)</th>
<th>CCSD(T)/6-311+G(d,p)</th>
<th>CBS-QB3</th>
</tr>
</thead>
<tbody>
<tr>
<td>97 + 93</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TS24</td>
<td>11.1</td>
<td>19.0</td>
<td>21.8</td>
</tr>
<tr>
<td>98</td>
<td>2.8</td>
<td>9.6</td>
<td>9.2</td>
</tr>
<tr>
<td>TS25</td>
<td>15.2</td>
<td>22.5</td>
<td>14.3</td>
</tr>
<tr>
<td>99</td>
<td>7.6</td>
<td>8.6</td>
<td>3.5</td>
</tr>
<tr>
<td>TS26</td>
<td>11.1</td>
<td>24.0</td>
<td>20.0</td>
</tr>
<tr>
<td>100-S</td>
<td>1.5</td>
<td>7.6</td>
<td>12.5</td>
</tr>
<tr>
<td>100-T</td>
<td>1.3</td>
<td>8.0</td>
<td>10.9</td>
</tr>
<tr>
<td>TS27-T</td>
<td>11.7</td>
<td>25.6</td>
<td>24.2</td>
</tr>
<tr>
<td>101 + $^3$O$_2$</td>
<td>6.7</td>
<td>14.5</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Table 10: Comparison of Formaldehyde + Ozone Surface Energetics

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
In general, all levels of theory suggest a process with relatively low, yet finite barriers; however, all show a marked variation in predicted barriers. B3LYP predicts all barriers to be substantially lower than the other methods. CSSD(T) and CBS-QB3 methods are found to be closer in agreement. Several transition states have similar energetics. Values for energy minima vary; for example, both 99 is \(~6\) kcal/mol lower with CBS-QB3 methods. Diradical 100-T and 100-S have a slightly more noticeable energy difference with CBS-QB3 methods, while they were nearly isoenergetic with the other methods. For all levels of theory, the tetroxolane intermediate (99) was found to have C\(_2\) symmetry, as reported by Cremer.\(^97\) The depth of the energy minimum for 99 suggests that it should have a significant lifetime and may observable in a low-temperature matrix.

Our results support the hypothesis that tetroxolanes should lead to the formation of ozone (93) plus formaldehyde (97) via a slightly exothermic process. The relatively low energy barriers also support a reversible process, as seen by Klopman.\(^95,96\) This process should not occur over a period of seconds but, rather minutes or hours since the barriers to reaction are significant. The reaction of carbonyl oxide (101) plus \(^3\)O\(_2\) was found to have reasonably low barriers although they are generally the highest barriers on the surface. These reactants should lead to the formation of tetroxolane (99) and once formed, decompose to ozone (93) plus formaldehyde (97).
Acetone-Ozone Energetics

We next explored the same pathways for acetone (96) with ozone (93). Once again, CBS-QB3 methods are suggested to provide the most accurate depiction of this surface. A comparison to DFT methods is provided in Table 11. CCSD(T) methods were not used as they were found to be too computationally demanding for this surface. However, BH&HLYP was employed for comparison. This functional has been shown to provide accurate barrier heights while paralleling those predicted by CBS-QB3 methods.

Table 11: Comparison of Acetone + Ozone Surface Energetics

<table>
<thead>
<tr>
<th>Structure</th>
<th>B3LYP/6311+G(d,p)</th>
<th>CBS-QB3</th>
<th>BH&amp;HLYP/6311+G(d,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96 + 93</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TS28</td>
<td>16.1</td>
<td>19.8</td>
<td>-</td>
</tr>
<tr>
<td>102</td>
<td>7.0</td>
<td>15.8</td>
<td>-8.0</td>
</tr>
<tr>
<td>TS29</td>
<td>21.5</td>
<td>20.4</td>
<td>12.7</td>
</tr>
<tr>
<td>95</td>
<td>11.2</td>
<td>3.9</td>
<td>-0.4</td>
</tr>
<tr>
<td>TS30</td>
<td>19.9</td>
<td>24.0</td>
<td>10.7</td>
</tr>
<tr>
<td>103-S</td>
<td>6.5</td>
<td>13.7</td>
<td>-13.5</td>
</tr>
<tr>
<td>103-T</td>
<td>6.2</td>
<td>14.7</td>
<td>-13.6</td>
</tr>
<tr>
<td>TS31-T</td>
<td>11.9</td>
<td>23.2</td>
<td>3.4</td>
</tr>
<tr>
<td>94 + 3O2</td>
<td>2.7</td>
<td>13.4</td>
<td>-9.2</td>
</tr>
<tr>
<td>TS31-S</td>
<td>17.6</td>
<td>26.0</td>
<td>-</td>
</tr>
<tr>
<td>94 + 1O2</td>
<td>11.9</td>
<td>17.8</td>
<td>-</td>
</tr>
</tbody>
</table>

There are many notable differences when comparing these results (Scheme 26). As previously seen, addition of ozone to the carbonyl group is endothermic with B3LYP and CBS-QB3 methods; however, BH&HLYP predictions are exothermic by 8 kcal/mol. We have been unable to locate TS28 using the BH&HLYP functional. Energetics for diradical 102 vary by 24 kcal/mol;
this significant difference is presumably due to the effect of spin contamination. TS29 is 10-16 kcal/mol higher in energy than 95 where this tetroxolane sits in a deep energy well. This result further suggests this intermediate may be observable. As with the formaldehyde surface, there is a modest barrier for addition of $^3\text{O}_2$ to 94; all methods predict $\sim$10 kcal/mol. This is a slightly endothermic process to yield 103-T with B3LYP and CBS-QB3 methods while BH&HLYP predicts a slightly exothermic process. All methods suggest diradical 103-T and 103-S are close to isoenergetic. Similar to diradical 102, the energetics for 103-T and 103-S vary by almost 30 kcal/mol. Once again, this is may be due to spin contamination. Ring closure of 103-S has a substantial barrier, which is consistent with the previous computations on formaldehyde. B3LYP and BH&HLYP predict ring closure to be endothermic by 5-10 kcal/mol, while CBS-QB3 methods suggest an exothermic reaction.

\[ \text{Scheme 26: CBS-QB3 Energetics of Acetone + Ozone} \]
The reaction of acetone carbonyl oxide (94) and $^{1}$O$_2$ was also investigated. Addition of $^{1}$O$_2$ to 94 was found to be higher in energy than the triplet route, as expected. However, CBS-QB3 methods predict $^{1}$O$_2$ to be 20 kcal/mol too low. When considering the DFT results, it is important to note that singlet oxygen is known to be inaccurately described with DFT methods. This is because of its peculiar symmetry and electronic structure which leads to a singlet/triplet difference that is 10 kcal/mol too low.

We utilized multiple levels of theory in hopes of accurately describing this surface. Clearly, these methods are not in agreement with each other. In general, these results do suggest that this reaction may occur with 15-25 kcal/mol barriers; however the most accurate method can still be debated. Undoubtedly, the best methodology for describing high oxygenated species is yet to be determined.

Our proposed mechanism can be linked to a recent study on the decomposition of triacetone triperoxide (TATP).$^{117}$ TATP (104) is one of the most dangerous explosives known because it is extremely sensitive to impact, temperature change and friction. This easily prepared explosive has been used by suicide bombers in Israel and London and also by Richard Reid, also known as the “shoe bomber”.$^{118}$
A recent study employed B3LYP calculations to study the explosive nature of TATP; previous experimental studies have found acetone to be a byproduct (Scheme 27).\textsuperscript{117} Ozone was not identified, but also seems a likely product. Computations predict an “entropy burst” as a result of the formation of one ozone and three acetone molecules. Along a complex scheme, this reaction was suggested to involve the intermediacy of a 1,5-diradical (102) which dissociates to yield ozone (93) and a final acetone molecule (96). This intermediate is precisely the diradical we predicted would dissociate in the same fashion. As suggested in this study, this 1,5-diradical (102) originating from an independent pathway, is also a likely route to ozone. A tetroxolane intermediate was not considered in the TATP mechanism but may possibly play a minor role. Dimethyl carbonyl oxide (94) and dioxirane (105) were considered as possible intermediates.

Carbonyl oxides can close photochemically to their cyclic form, the dioxirane (105) which is a surprisingly stable species.\textsuperscript{119} We found that addition

---

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
of singlet $O_2$ to 105 is not predicted to be a likely route to ozone because of its endothermic energetics (Scheme 28).

\[ \Delta E = 9.40 \]

\[ \Delta E = 7.01 \]

Scheme 28: B3LYP/6-311+G(d,p) Energetics for Addition of $^1O_2$ to Dioxirane

**Tetroxane Chemistry**

Tetroxanes or carbonyl oxide dimers have recently attracted considerable attention because of their impressive antimalarial activity.\(^{100}\) These odd structures are easily prepared and we questioned whether they could be cleaved to yield two carbonyl oxides.\(^{101}\) If this cleavage were feasible, it could pose a route to the generation of ozone (Scheme 29). However, our computations show that the dimerization process is highly exothermic and the tetroxanes (107, 109) are unlikely to revert to carbonyl oxides (106, 108), even with bulky substituents.

\[ \Delta E = -56.69 \]

\[ \Delta E = -62.97 \]

Scheme 29: B3LYP/6-311+G(d,p) Energetics for Carbonyl Oxide Dimerization

**Heteroatom Chemistry**

The biological ozone connection remains exploratory but we felt that this chemistry could be the basis for an enzymatic process, perhaps through
substituting the carbon for a heteroatom or metal. Any element with favorable energetics to form a tetroxolane ring may undergo retro cycloaddition to yield ozone.

We have used computations to explore possible candidate structures. The reaction of ozone with triaryl and trialkyl phosphites (110) has been reported; they generate a phosphite ozonide complex (111) which yields the corresponding phosphate (112) and singlet oxygen (Scheme 30).120

![Scheme 30: Formation of a Phosphite Ozonide Complex](image)

Applying similar chemistry to our key intermediate, shows that the decomposition of a phosphotetroxolane (113, 115) will be highly exothermic. This process should yield ozone; although, it may not be a likely route to this tetroxolane intermediate (Scheme 31).

![Scheme 31 B3LYP/6-31G* Energetics for Decomposition of a Phosphotetroxolane](image)

Sulfur chemistry may provide a route to a tetroxolane intermediate:

Zwanenburg and Carlsen reported that unhindered thioketones (117) react with...
$O_3$ to give rise to the corresponding ketone (96), perhaps through a thiatetroxolane intermediate (118) (Scheme 32).\textsuperscript{121,122} Our calculations support the observed formation of thiazone (119) and the intermediate thiatetroxolane (118). This interesting potential surface bears more careful exploration.

![Scheme 32: B3LYP/6-311+G(d,p) Energetics for the Thiatetroxolane Intermediate](image)

In a related report, Sawaki found that trifluoroacetophenone oxide (120) reacted electrophilically with sulfoxide affording a sulfide (123) as the major product (Scheme 33).\textsuperscript{123} An $^{18}$O-tracer study suggested that it passes through a cyclic sulfurane intermediate (121). Our calculations support the observed formation of the ketone and sulfurane intermediate.

![Scheme 33: B3LYP/6-31G* Energetics for Sulfurane Intermediate](image)
The work of Zwanenburg\textsuperscript{122}, Carlsen\textsuperscript{121} and Sawaki\textsuperscript{123} does not lead to the formation of tetroxolane or ozone but rather sulfur containing species. However the mechanisms include similar intermediates to tetroxolanes and help to show precedent for our proposed mechanism.

Reactions of sulfoxides and nitroxides with O\textsubscript{3} were investigated. The tetroxolane type intermediates were not found as energy minima on this surface because they easily dissociate to O\textsubscript{2} and either NO\textsubscript{2} or SO\textsubscript{2}. Therefore, these species do not provide a likely pathway to a tetroxolane type intermediate or ozone.

**Metal Chemistry**

It would be especially significant to find metals that would help promote this chemistry as they may be able to play a role in the biogeneration of ozone. Si, Mo, and Cr were studied because they are known to readily form oxides. Preliminary results suggest that various metal oxides may react with ozone to form tetroxolane type intermediates (124, 126, 128) (Scheme 34). Continuation of this investigation is necessary as more biologically relevant metals may also have favorable energetics.
Our computations support the existence of tetroxolane intermediates. They also suggest this process should not occur instantaneously at low temperature because barriers are in the 15-25 kcal/mol range. We began by repeating Klopman's $^{18}O$ labeling experiment. This included investigating a variety of carbonyl species in order to develop a general methodology.

**Ketone Chemistry**

We began by examining the reaction of ketones with ozone. Our first substrate was $t$-butyl cyclohexanone (130), a crystalline compound that can be obtained pure and is easily identifiable by spectroscopy. Addition of the $^{18}O$ label was easily accomplished by reaction of $t$-butyl cyclohexanone (130) with 10 eq. 95% $H_2^{18}O$ and Dowex, an acidic resin catalyst, in either cyclohexane or dichloromethane (Scheme 35). Both solvents were found to promote significant label exchange, but their efficiency was not directly compared.
We wanted to determine the best spectroscopic method for analyzing the $^{18}$O content in our compounds. Klopman chose GC-MS analysis but there are also reports of following aldehyde and ketone $^{18}$O labeling reactions by IR$^{124}$ and $^{13}$C NMR spectroscopy.$^{125}$ IR spectroscopy with $^{18}$O labeled ketone 130 was not able to give quantitative results, but 2 overlapping carbonyl stretches could be seen. $^{13}$C NMR spectroscopy gave rise to 2 carbonyl C shifts at 212.59 ($^{16}$O=C) and 212.54 ($^{18}$O=C) ppm but it was difficult to quantify the $^{18}$O since they were poorly resolved. GC-MS analysis provided the best quantitative results typically showing 62-74% $^{18}$O. This analysis was done using an HP G1800C GCD Series II GC/MS. From the relative heights of the parent peaks, in this case 154 and 156, the $^{18}$O was calculated. An error analysis study using the HP GC/MS showed reproducibility of ±1.3% $^{18}$O label, when the same labeled sample was repeatedly injected. In order to verify that the label percentage is independent of the experimental conditions, the GC-MS method was altered by increasing the oven temperature to 70° and 100°C and the results were identical within experimental error.
This chemistry is new to our group and the experimental conditions needed to be carefully determined. As previously stated, we did not expect to observe an instantaneous exchange. This is unlike Klopman's results where he reported a 22% loss of label at -78°C after 1 min. Our experiments were carried out at 0°C which should allow the reaction to occur at a reasonable rate where kinetics might be studied.

Ozone was prepared by passing a stream of oxygen through a high-voltage electrical discharge and then bubbled into dry solvent to yield a saturated solution. Initially, the ozone solution was prepared at 0°C in CH₂Cl₂ until a light blue coloration was seen, which took over 30 minutes. However, literature reports of saturated ozone solutions more typically describe preparation at -78°C. Preparing the ozone solution at -78°C with a dry ice/acetone bath afforded a cloudy bright blue solution within 5-10 minutes. Clearly, the decrease in temperature increased ozone solubility. According to Rubin and Zwanenburg, a blue saturated ozone solution in dichloromethane at -78°C contains 0.04 mol/L. Upon warming the saturated ozone solution to 0°C, a blue-gray cloudy coloration remained. The concentration of ketone was based on Klopman's experiments and was typically kept below 1 mmol. As a general procedure, the saturated ozone solution was prepared in CH₂Cl₂ at -78°C, warmed to 0°C and then immediately treated with a labeled ketone in CH₂Cl₂, also cooled to 0°C. Care was taken to ensure all reactions remained dry by using oven-dried glassware and dry solvents. The reactions were maintained at
0°C with an ice bath while being monitored. In addition to calculating the %\(^{18}\)O, Klopman utilized % loss of label which helps to show the progression of the reaction and allows us to compare results of other reactions. The % loss of label is defined below, where x is the reaction time (Eq. 49).

\[
\% \text{ Loss Label} = \left( 1 - \frac{\%^{18}\text{O at } t = x}{\%^{18}\text{O at } t = 0} \right) \times 100
\]  

(Eq. 49)

With the methodology worked out, we began to study the exchange reaction with ozone (93). A solution of \(^{18}\)O t-butyl cyclohexanone (130-\(^{18}\)O) was added to the saturated ozone solution and the reaction monitored by GC-MS by repeatedly injecting the solution over a 1\(\frac{1}{2}\) hr period (Scheme 36). After the ketone addition occurs, we observed that the blue-gray cloudy coloration immediately begins to fade, eventually yielding a clear solution. This observation is also consistent with Zwanenburg’s experiment, where decolorization was seen when a saturated ozone solution was mixed with thiobenzophenone in CH\(_2\)Cl\(_2\).\(^{122}\)

![Scheme 36: Label Exchange with t-Butyl Cyclohexanone](image)

Approximately one minute passed between mixing and injection of a one-\(\mu\)L sample into the GC mass spectrometer. Initially there is little label loss, however, after 1922 seconds the % \(^{18}\)O quickly drops and then levels off. The % label loss at 5042 seconds is within experimental error (Table 12). Each GC/MS
run took just under 20 minutes (or 1200 seconds) and before injecting the next sample the instrument needs to recalibrate itself. Thus, our present method limits the frequency of analyses. These results clearly indicate that label exchange is occurring between \( t \)-butyl cyclohexanone (130\(^{18}\text{O}\)) and ozone (93), which helps to provide evidence for the tetroxolane intermediate (131).

Table 12: Label Exchange of \(^{18}\text{O} \ t\)-Butyl Cyclohexanone (130\(^{18}\text{O}\)) + Ozone (93), Monitored by HP GC/MS

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>% (^{18}\text{O})</th>
<th>% Label Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>69.2</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>65.9</td>
<td>4.8</td>
</tr>
<tr>
<td>1922</td>
<td>23.1</td>
<td>66.0</td>
</tr>
<tr>
<td>3482</td>
<td>20.8</td>
<td>70.0</td>
</tr>
<tr>
<td>5042</td>
<td>21.9</td>
<td>68.3</td>
</tr>
</tbody>
</table>

We wanted to show that these results are reproducible and repeated the experiment with identical conditions except on a Thermo Trace GC Ultra Polaris Q GC/MS. \( t \)-Butyl cyclohexanone-\(^{18}\text{O}\) (130\(^{18}\text{O}\)) was freshly prepared and subjected to an error analysis study. This showed that the Thermo GC/MS results were reproducible within \( \pm 2.0\% \^{18}\text{O}\). Upon repeating the ozone exchange experiment, significant label loss was once again observed (Table 13). The \%\(^{18}\text{O}\) label progressively dropped; however, not as quickly as seen in the previous results.
Table 13: Label Exchange of $^{18}$O t-Butyl Cyclohexanone (130-18O) + Ozone (93), Monitored by Thermo GC/MS

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>% $^{18}$O</th>
<th>% Label Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>58.1</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>52.9</td>
<td>8.9</td>
</tr>
<tr>
<td>1290</td>
<td>39.0</td>
<td>32.9</td>
</tr>
<tr>
<td>2780</td>
<td>35.0</td>
<td>39.7</td>
</tr>
<tr>
<td>4202</td>
<td>32.7</td>
<td>43.7</td>
</tr>
</tbody>
</table>

In this second experiment, the observed rate of $^{18}$O label loss was significantly lower; reasons for this difference are unclear. Based on Henry's law, providing the temperature is being maintained, ozone should remain dissolved in solution. One possibility for incomplete conversion is that something in solution is catalyzing the decomposition of ozone. Nonetheless, based on these results the role of ozone and its concentration over time are not fully understood and further studies are necessary. The time in between samples is not identical for both instruments although each sample was injected as quickly as possible. The HP GC/MS took longer to recalibrate than the Thermo GC/MS. Ultimately, our experimental results reproducibly show that label loss is not a fast process but it occurs over a matter of hours. This is in qualitative agreement with our computations.

Several control experiments were carried out. Initially, a control experiment was run by reacting unlabelled t-butyl cyclohexanone (130) with ozone (93). After 30 minutes, the reaction mixture was concentrated at 0°C, the reaction temperature, and NMR analysis of the product showed only pure ketone was present. This demonstrates that no other chemistry was occurring and the
label exchange is caused by another species present in our reaction. Ozone is proposed to be this active species but O₂ is also assumed to present in solution, since the ozonizer does not achieve 100% conversion. In order to verify that it is indeed O₃ and not O₂ reacting in solution, we developed another control experiment. The exchange experiment was run by treating the t-butyl cyclohexanone-¹⁸O (130-¹⁸O) with an oxygen solution. This was prepared under identical conditions as the O₃ solution but instead, the O₂ line was directly bubbled into dry solvent. Analysis of this reaction by GC/MS showed no change in %¹⁸O, within experimental error, and shows that O₃ is the active oxygen species.

In order to test the generality of this reaction, we studied other ketones. Addition of an ¹⁸O label to acetophenone (132) was found to be facile; after 5 hours the carbonyl contained 69.4% ¹⁸O (Scheme 37).

![Scheme 37: ¹⁸O Labeling and Exchange Experiment with Acetophenone](image)

This sample was stored in the refrigerator under N₂, however loss of some label was observed over a period of days probably by exchange with water. The ozone exchange reaction showed a steady decrease in % label over a 70 minute period (Table 14). Again, this exchange is not happening fast but, appears to occur at a slower rate.
In order to determine relative kinetics of these two ketones, we developed a competition experiment where a saturated ozone solution was treated with equimolar amounts of $t$-butyl cyclohexanone-$^{18}$O and acetophenone-$^{18}$O. Monitoring the reaction by GC/MS yielded the following results (Table 15).

**Table 14: Label Exchange of $^{18}$O Acetophenone (132-$^{18}$O) + Ozone (93)**

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>$^{18}$O</th>
<th>% Label Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56.7</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>51.4</td>
<td>9</td>
</tr>
<tr>
<td>1371</td>
<td>50.4</td>
<td>11</td>
</tr>
<tr>
<td>2815</td>
<td>48.6</td>
<td>14</td>
</tr>
<tr>
<td>4282</td>
<td>42.6</td>
<td>25</td>
</tr>
</tbody>
</table>

These results demonstrate $t$-butyl cyclohexanone (130) is losing its label at a faster rate. Presumably acetophenone (132) exchanges slower because of the effect of the aromatic ring, which reduces the reactivity of the carbonyl carbon.

The chemistry of benzophenone (133), a final ketone, was explored. Unfortunately, the addition of an $^{18}$O label was found to be very difficult. The reaction was initially performed in CH$_2$Cl$_2$ with 10 eq. of 95% H$^{18}$O$_2$ and Dowex, as an acid catalyst. The reaction was periodically analyzed by GC/MS but after 8
hours only 12.6% $^{18}$O was observed and even after 24 hours there was no further change. Water is not miscible with CH$_2$Cl$_2$ and the reaction was vigorously stirred to ensure proper mixing of these layers. The solvent was changed to THF to increase the solubility. However, after 6 hours the carbonyl contained only 12.6% $^{18}$O. Even running this reaction in a microwave (MW) for 5 minutes at 75°C, afforded only 20.0% $^{18}$O. This is still an unacceptably slow rate. In a last attempt, switching to a homogenous catalyst, p-TsOH, while running at 100°C for 30 minutes in THF under MW irradiation afforded 90% $^{18}$O. Clearly, further exchange experiments might be best carried out under microwave reaction conditions.

The labeled sample was stored under N$_2$ at 0°C but after one week significant label loss to 44.5% was seen. This is still a sufficient amount of label to perform our experiments. After 4318 seconds, ~72 minutes, the GC mass spectrum showed 34.6% $^{18}$O of the ketone, indicating that it had lost 22% of its original label. The rate of exchange is slightly slower than acetophenone but both see a gradual decrease in $^{18}$O. No direct competition experiments were carried out.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>%$^{18}$O</th>
<th>% Label Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>44.5</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>41.9</td>
<td>6</td>
</tr>
<tr>
<td>1327</td>
<td>39.8</td>
<td>11</td>
</tr>
<tr>
<td>2757</td>
<td>38.3</td>
<td>14</td>
</tr>
<tr>
<td>4318</td>
<td>34.6</td>
<td>22</td>
</tr>
</tbody>
</table>
These results must be viewed as preliminary but clearly demonstrate the expected exchange of $^{18}$O label upon reaction of ketone with O$_3$. Control experiments showed that no other reaction was occurring and O$_3$, not O$_2$, caused loss of label. Our results support the following relative rates of reaction for ketones: $R_1 = R_2 = \text{alkyl} > R_1 = \text{alkyl}, R_2 = \text{aryl} > R_1 = R_2 = \text{aryl}$ (Scheme 38).

Scheme 38: Proposed Mechanism for Ozone Exchange with Ketone

At this point, we can only speculate that relative rates may be determined by the first step in this process, in which ozone adds to the ketone. The data obtained is not likely to yield reliable kinetic information as the conditions were not rigorously defined. More rigorous kinetic experiments will be useful in evaluating these reactions where our proposed mechanism should follow reversible mixed 2$^{\text{nd}}$ order kinetics.

Aldehyde Chemistry

We next examined the reaction of aldehydes with ozone. Our first substrate was cyclohexanecarbaldehyde (134), a substance less volatile and more easily identifiable by spectroscopic analysis than isobutyraldehyde. Addition of an $^{18}$O label to the aldehyde (134) was expected to be facile; however, we observed that the aldehyde was primarily oxidized to the carboxylic (Scheme 39).
This unanticipated result was supported by both $^{13}$C NMR spectroscopy and GC-MS which indicated a 23 to 3 ratio of carboxylic acid to aldehyde. Both species contained a label, 135-$^{18}$O was 59.4% labeled while 134-$^{18}$O was only 34.3% labeled. Oxidation of an aldehyde by O$_2$ to a carboxylic acid is well known to occur by a radical mechanism. This is likely to have occurred because the system was not purged of air, allowing O$_2$ to act as an oxidant. If the reaction system was run under N$_2$, it should be possible to obtain the labeled aldehyde as the major product. But this result also leads us to question the ozone experiment, will the O$_3$-O$_2$ mixture also cause oxidation to occur? A control experiment was able to quickly answer this question. Reacting unlabeled cyclohexanecarbaldehyde (134) with ozone (93) did indeed generate a mixture of the aldehyde (134) and carboxylic acid (135) in a 2 to 5 ratio, as seen by $^{13}$C NMR (Scheme 40).

Scheme 40: Control Experiment for Cyclohexanecarbaldehyde

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Aldehyde oxidation was not observed by Klopman.\textsuperscript{95,96} One notable difference between his original experiment and ours was the temperature, where his was run at -78°C. Running the control experiment with 134 at -78°C generated the same results. Another difference was that Klopman used isobutyraldehyde (136).\textsuperscript{95,96} Reactions were run with 136 at both 0° and -78°C; these experiments also showed oxidation to the carboxylic acid. As a final difference, Klopman used a hydrocarbon solvent. Repeating the experiment using hexanes, instead of dichloromethane, at -78°C afforded the same results. Klopman analyzed his reaction by GC-MS solely and it is likely that the polar nature of 136 caused it not to pass through the GC column. We also investigated similar chemistry with benzaldehyde (137). Again, experiments at 0°C showed significant oxidation.

Our experiments thus show that oxidation is the dominant reaction when aldehydes are reacted with ozone. Precedent for these results was reported by Erickson who studied the mechanism of ozonation reactions of aldehydes, work published prior to Klopman’s findings (Scheme 41).\textsuperscript{127}

\begin{center}
\textbf{Scheme 41: Reported Mechanism for Aldehyde Oxidation}
\end{center}

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
This study found that aldehydes react with ozone by an electrophilic mechanism. It was suggested that the initial attack of ozone on an aldehyde (137) involves either a direct insertion of ozone into the C-H bond to form 139 or by formation of a tetroxolane intermediate (138) which can then rearrange to 139. Intermediate 139 will then fragment to the carboxylic acid (140). Deuterium isotope effects and Hammett $\sigma$ values supported these proposed mechanisms. Huisgen speculated that the formation of tetroxolanes are not energetically favored.\textsuperscript{128}

In summary, oxidation by oxygen and ozone renders aldehydes unsuitable for examining the tetroxolane hypothesis. Although Erickson suggested that this oxidation may involve a tetroxolane intermediate, these studies did not provide evidence for or against the existence of tetroxolanes.

**Conclusions**

Our calculations lead us to conclude that ozone (93) can add to a carbonyl compound with a modest barrier via a stepwise mechanism. The intermediate tetroxolanes lie in a relatively deep energy well and may be observable in a cryogenic matrix or solution. Tetroxolanes may be formed by addition of oxygen to carbonyl oxides and thus fragment to produce ozone. We evaluated this surface with several levels of theory but the best method is still unclear. This process could play a minor role in atmospheric chemistry; while the biological connection is still speculative. We explored other elements that could be active in both atmospheric or biological chemistry; their predicted energetics support the formation of tetroxolane type intermediates. We are now aware of several
literature connections$^{95, 96, 121, 122, 127}$ that help support our proposed mechanism and the existence of tetroxolanes.

Our calculations support the experiments of Klopman and Andreozzi$^{95, 96}$; it is easy to understand how isotopically labeled oxygen will scramble by the symmetry of this process. Our results, although preliminary, demonstrate that $^{18}$O label will exchange upon reaction of a ketone with ozone. Control experiments showed that O$_3$, not O$_2$, caused loss of label and no other reaction was occurring. Competition experiments established relative kinetics for the exchange, which showed that simple dialkyl ketones reacted fastest. Oxidation renders aldehydes unsuitable and prevents the appropriate monitoring of the reaction. These results provide evidence for the tetroxolane intermediate and show that it may lead to generation of ozone. Beyond this, it is necessary to demonstrate that $^{18}$O$_2$ can exchange with carbonyl oxides. This will require preparation of stable carbonyl oxides.$^{129}$
CHAPTER IV

EXPERIMENTAL

General Experimental

Instrumentation

$^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer or a Varian INOVA 500 MHz NMR spectrometer with an inverse probe. All spectra were measured in CDCl$_3$ as a solvent and (CH$_3$)$_4$Si as an internal standard. Chemical shifts are reported in parts per million (ppm) relative to the internal standard. All spectral data compared favorably to those described earlier.$^{6,9,10,59,71}$

IR spectra were recorded a Thermo Nicolet Avatar 380 FT-IR spectrophotometer.

GC-MS spectra were recorded on either of two instruments: a) HP G1800C GCD Series II Gas chromatograph with mass ionization spectrophotometer; or b) Thermo Trace GC Ultra Polaris Q. The following method was used unless otherwise noted. The injection chamber temperature was 280°C, the oven was 50°C and the detection chamber was 250°C. The flow rate was 3.88 mL/min and all injections were splitless and 1μL in volume. The column in both instruments was 30.0m in length and 0.25m in diameter with a maximum temperature of 350°C.
Ozone was produced by an OREC Ozone System V Series instrument. The ozone solutions were prepared by bubbling ozone through dry solvent at -78°C in a dry ice/acetone bath, until a persistent blue color developed, typically taking 10 minutes. The instrument was set at 1 L/min of compressed O₂ with 50V.

Molecular Modeling was performed using Gaussian '03 and Spartan '04 on a Dell Computer.

Microwave reactions were performed in the CEM Discover. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure is controlled by CEM's intellivent system. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All reactions were performed using a stirring option by a rotating magnetic plate below the vessel and a Teflon-coated magnetic stir bar in the vessel.

Solvents
The following solvents were freshly obtained from the automatic still: diethyl ether (Et₂O), tetrahydrofuran (THF), dichloromethane (CH₂Cl₂). Cyclohexane, pentane, hexane and methanol were purchased from Fischer Scientific and used without further purification. All deuterated solvents for NMR analysis were purchased from Cambridge Isotope Laboratories and stored over 4 Å molecular sieves: chloroform-d (CDCl₃), benzene-d₆ (C₆D₆), and acetone-d₆ (C₃D₆O).
Reagents
All reagents were purchased from the following companies: Fisher Scientific (Acros), Alfa Aesar, Aldrich or Lancaster.

Chromatography and Adsorbents
Florisil: 100-200 mesh Fischer Scientific florisil was used as obtained.

Thin Layer Chromatography (TLC) was completed using Whatman polyester plates coated with 250 μm layer silica gel doped with phosphor. Visualization was accomplished with an ultraviolet light.

Chromatotron, Model 7924T, was use for preparative separations on silica gel.

Glassware
All glassware was oven-dried prior to use.

Chapter I Experimental
Synthesis of monochloro adduct (45)
The procedure of Susana Hernandez was followed. Dichloro adduct (1) (0.517 g, 1.98 mmol) in dry THF (15 ml) was added to a 50-mL three-necked round-bottom flask outfitted with a magnetic stir bar and nitrogen line. The flask was cooled to -78°C in a dry ice/acetone bath. n-Butyllithium (0.8 mL of a 2.5 M solution in Hexanes, 2.0 mmol) was added dropwise by syringe, producing a green color. After ½ hr of stirring at -78°C, 0.7 mL of methanol was added to the flask by syringe, turning the solution yellow. The reaction was stirred at -78°C for 2 hr and then gradually warmed to room temperature. After stirring overnight,
the yellow solution was washed with brine (2 x 4 mL), dried with magnesium sulfate (MgSO₄), filtered and concentrated to afford a tan solid. Purification by radial chromatography (50% methylene chloride in hexanes) afforded white crystals (400 mg, 89.2%). mp 133-136°C. The ¹H NMR spectrum of the endo chloro adduct matched that reported in Susana Hernandez's dissertation. ¹H NMR (500 MHz) δ ppm (CDCl₃) 8.03-8.05 (d, 2H), 7.30-7.41 (m, 6H), 2.96 (d, 2H), 3.74 (t, 1H). ¹³C NMR (500 MHz) δ ppm (CDCl₃) 132.21, 130.65, 129.55, 127.94, 127.46, 122.85, 29.05, 25.08.

**Synthesis of cyclobutanol adduct (47A)**

A solution of monochloro adduct (45) (130 mg, 0.57 mmol) in dry THF (5 mL) was added to a 50-mL round-bottom flask outfitted with a magnetic stir bar, septum and nitrogen line. The flask was cooled to -78°C in a dry ice/acetone bath, where n-butyllithium (0.3 mL of a 2.5 M solution in Hexanes, 0.75 mmol) was added dropwise by syringe. After 1 hr of stirring at -78°C, cyclobutanone (0.07 mL, 0.97 mmol) was added dropwise by syringe, and the solution was gradually warmed to room temperature. After stirring overnight, brine (5 mL) was injected into the flask. The organic layer was separated and washed with brine (2 x 5 mL), dried (MgSO₄), filtered and concentrated. Radial chromatography (50% methylene chloride in hexane) afforded a yellow solid (115 mg, 77.2%). ¹H NMR (400 MHz) δ ppm (CDCl₃) 8.05-8.03 (d, 2H), 7.42-7.31 (m, 6H), 3.76-3.72 (d, 2H), 2.96, 2.34 (t, 1H), 2.26-2.34 (m), 1.96-2.18 (m), 1.74-1.88 (m). ¹³C NMR
(400 MHz) δ ppm (CDCl₃) 132.20, 130.64, 127.93, 127.45, 122.98, 122.84, 35.02, 33.01, 29.04, 28.98, 28.00, 25.83, 25.83, 25.07.

**Synthesis of cyclopentanol adduct (47B)**

A solution of monochloro adduct (1) (150 mg, 0.66 mmol) in dry THF (5 ml) was added to a 50-mL round-bottom flask outfitted with a magnetic stir bar, septum and nitrogen line. The flask was cooled to -78°C in a dry ice/acetone bath, where n-butyllithium (0.4 mL of a 2.5 M solution in Hexanes, 1.0 mmol) was added dropwise by syringe. After 1 hr of stirring at -78°C, cyclopentanone (0.04 mL, 1.12 mmol) was added dropwise by syringe, and then gradually warmed to room temperature. After stirring overnight, brine (5 mL) was injected into the flask. The organic layer was separated and washed with brine (2 x 5 mL), dried (MgSO₄), filtered and concentrated. Radial chromatography (50% methylene chloride in hexane) afforded a light yellow solid (150 mg, 88%). mp 140-142°C

**1H NMR (400 MHz) δ ppm (CDCl₃) 8.03-8.05 (d, 2H), 7.30-7.42 (m, 6H), 3.72-3.75 (t, 1H), 2.96-2.98 (d, 2H), 2.79 (1H, m), 2.53 (m, 1H), 2.30 (m, 2H), 1.95-1.70 (m, 4H). **

**13C NMR (500 MHz) δ ppm (CDCl₃) 132.02, 130.45, 129.37, 127.73, 127.25, 122.65, 39.84, 38.39, 34.34, 33.28, 32.60, 28.85, 23.40, 23.26.**

**Synthesis of cyclopentenyl phosphate (53B)**

LDA was prepared *in situ* from diisopropylamine (4.3 mL, 30.5 mmol) and n-BuLi (12.2 mL, 2.5 M solution, 30.5 mmol) in dry THF (20 mL) at -78°C. After stirring for 1 h, cyclopentanone (2.4 mL, 27.7 mmol) in dry THF (15 mL) was added dropwise by addition funnel. After an additional 45 minutes, diethyl
chlorophosphate (4.4 mL, 30.5 mmol) was added dropwise by addition funnel. The mixture was allowed to warm to 0° C over 1 hr. The organic layer was separated and washed with saturated NH₄Cl (2 x 5 mL), dried (MgSO₄) and concentrated to afford a light yellow liquid (4.72 g, 77%). White crystals precipitated out of solution over time but were not isolated. 

\[ \text{H}^1 \text{NMR (400 MHz)} \delta \text{ ppm (CDCl}_3\text{) } 5.26 \text{ (m, 1H, vinyl)}, 4.15-4.19 \text{ (q, 4H), 2.46 (m, 2H), 2.34 (m, 2H), 1.93 (q, 2H), 1.34-1.38 (m, 6H).} \]

\[ \text{C}^{13} \text{NMR (400 MHz)} \delta \text{ ppm (CDCl}_3\text{) 150.29, 109.39, 64.45, 31.71, 31.66, 28.58, 21.04, 16.28, 16.22.} \]

**Synthesis of 1-iodocyclopentene (54B)**

To a solution of cyclopentenyl phosphate (1 g, 4.52 mmol) in anhydrous CH₂Cl₂ (10 mL), TMSI (1.8 g, 13.6 mmol) was added via syringe. After stirring for 10 min at room temperature, the reaction mixture was quenched with a saturated NaHCO₃/Na₂SO₃ solution. The organic layer was separated and the aqueous layer was extracted twice with CH₂Cl₂. The combined organic extracts were dried (MgSO₄), filtered and concentrated. The vinyl iodide was purified by flash chromatography using n-pentane as an eluent to yield a pink liquid (383 mg, 43% yield). 

\[ \text{H}^1 \text{NMR (400 MHz)} \delta \text{ ppm (CDCl}_3\text{) 6.03 (s, 1H, vinyl), 2.50 (m, 2H), 2.02 (m, 2H), 1.80 (m, 2H).} \]

\[ \text{C}^{13} \text{NMR (400 MHz)} \delta \text{ ppm (CDCl}_3\text{) 138.91, 55.47, 42.43, 32.72, 22.59.} \]

**Synthesis of cyclobutenyl phosphate (54A)**

LDA was prepared in situ from diisopropylamine (4.3 mL, 30.5 mmol) and n-BuLi (12.2 mL, 2.5 M solution in Hexanes, 30.5 mmol) in dry THF (20 mL) at
-78°C. After stirring for 1 hr, cyclobutanone (2.2 mL, 27.7 mmol) in dry THF (20 mL) was added dropwise by addition funnel. After an additional 45 minutes, diethyl chlorophosphate (4.4 mL, 30.5 mmol) was added dropwise by addition funnel. The mixture was allowed to warm to 0°C over 1 hr. The organic layer was separated and washed with saturated NH₄Cl (2 x 5 mL), dried (MgSO₄) and concentrated to afford a light yellow liquid (5.24 g, 90%). ¹H NMR (500 MHz) δ ppm (CDCl₃) 5.05 (s, 1H, vinyl), 4.20 (m, 4H), 2.76 (2H, m), 2.12 (m, 2H), 1.37 (t, 6H, methyl). ¹³C NMR (400 MHz) δ ppm (CDCl₃) 109.81, 64.45, 64.40, 33.03, 32.98, 20.48, 16.07, 16.02. IR (KBr) 2923 cm⁻¹, 2847, 1713, 1605, 1437, 1166, 1033, 940, 907, 783, 734, 498, 427.

Synthesis of dibromo adduct 68

Phenanthrene (3.6g, 20.0 mmol) and benzyltrimethylammonium chloride (1.86g, 0.01 mmol) were introduced into a 100-mL, three-necked, round bottom flask, fitted with a mechanical stirrer, condenser and addition funnel. Bromoform (17.5 mL, 200 mmol) was added and vigorous stirring was begun. An aqueous sodium hydroxide solution (50%, 8 mL) was added dropwise through the addition funnel over 30 minutes. The reaction mixture was stirred at room temperature for 5 days. The brown emulsion was poured into water (10 mL) in a separatory funnel and extracted with chloroform (4 x 20 mL). (Note emulsion formation upon vigorous shaking) The combined organic layers were dried (MgSO₄) filtered and concentrated to yield a light brown solid. Recrystallization in hexanes yielded white crystals (4.2 g, 60%). mp 122-124°C (lit. 125-126°C). ¹H NMR (400
MHz) $\delta$ ppm (CDCl$ _3$) 8.01-7.98 (d, 2H), 7.50-7.31 (m, 12H), 3.50 (s, 2H). $^{13}$C NMR (400 MHz) $\delta$ ppm (CDCl$ _3$) 131.42, 131.13, 129.71, 128.44, 128.31, 123.24, 37.58, 31.07.

Preparation of zinc/copper couple with CuSO$_4$

A finely powered mixture of CuSO$_4$·5H$_2$O and Zn dust (1:10 molar ratio) were stirred magnetically under N$_2$. Dry DMF was added quickly by syringe until the surface was just covered. An exothermic reaction ensued and the mixture immediately became black. After, cooling the mixture was diluted with dry ether and used directly in the Simmons-Smith type reaction.

Attempt to prepare Bicyclo[4.1.0]hept-7-ylidene (72) by Zn/Cu couple with CuSO$_4$

The round bottom flask was fitted with a condenser, addition funnel and N$_2$ inlet and purged with N$_2$ for 15 minutes. Cyclohexene (1 mL), previously filtered through silica, was added dropwise to the mixture via the addition funnel. The dibromro adduct (68) (200 mg, 0.57 mmol) in dry THF (5 mL) was added dropwise to the solution over 30 minutes. The mixture was stirred at room temperature overnight. The reaction was quenched with brine (2 mL) and the solids were filtered off. The organic layer was separated, washed with brine and saturated NaHCO$_3$ (1 x 5 mL), dried (MgSO$_4$), filtered and concentrated. Starting material and endo-monobromo adduct (73) (31 mg, 20% yield) were obtained. NMR analysis indicated an unknown alkylated product. Radial chromatography (25% methylene chloride in hexanes) afforded endo-monobromo product (73) as a white solid, mp 103-104°C (lit mp 104-105°C$^{17}$). $^1$H NMR (400 MHz) $\delta$ ppm
(CDCl$_3$) 8.05-8.03 (d, 2H), 7.40-7.29 (m, 12H), 3.74 (t, J = 8 Hz, 1H) 2.98 (d, J = 8 Hz, 2H). $^{13}$C NMR (400 MHz) δ ppm (CDCl$_3$) 234.64, 131.97, 130.92, 130.52, 127.93, 127.49, 122.87, 24.65, 20.46.

**Preparation of zinc/copper couple with Cu(OAc)$_2$**

In a 50-mL three-necked round bottom flask equipped with a stir bar, cupric acetate monohydrate (0.11 g, 0.55 mmol) was dissolved upon heating in 5 mL of glacial acetic acid. Zinc powder (1.1 g, 17.2 mmol) was added to this stirred solution, and after 60 seconds, the green coloration disappeared and a metallic dark red coloration appeared. The stirring was stopped and the supernatant liquid was decanted and replaced with 5 mL of glacial acetic acid. The suspension was stirred once again and the supernatant liquid was decanted and then replaced with 5 mL of dry ether. The couple was washed in this fashion 3 times with 5 mL portions of dry ether. Finally, the couple was covered with 7 mL of dry ether and used directly in the Simmons-Smith reaction.

**Attempt to prepare Bicyclo[4.1.0]hept-7-yllidene (72) by Zn/Cu couple with CuOAc$_2$**

The round bottom flask was fit with a condenser, addition funnel and N$_2$ inlet and purged with N$_2$ for 15 minutes. A few drops of the dibromo adduct (68) in dry ether were added. Cyclohexene (1 mL), previously filtered through silica, was added dropwise to the mixture via the addition funnel. The dibromo adduct (68) (200 mg, 0.57 mmol) dissolved in dry ether (9 mL) and dry CH$_2$Cl$_2$ (0.5 mL, to increase solubility) was added dropwise to the solution over 30 minutes. The mixture was stirred and heated at a gentle reflux overnight. After cooling to room
temperature, deionized water (2 mL) was added dropwise. The solids were filtered off and remaining solution was washed with 10% aqueous HCl and deionized water (x 3). The solution was dried (MgSO₄), filtered and concentrated. Starting material and mono bromo adduct (73) were obtained in a 2:3 ratio along with an unknown alkylated product.

Attempt to prepare Bicyclo[4.1.0]hept-7-ylidene (72) with Et₂Zn

In a 50-mL three-necked round bottom flask equipped with a stir bar, addition funnel, condenser and N₂ inlet, dry CH₂Cl₂ (3 mL) and cyclohexene (50 mg, filtered through silica) were added and the system was purged with N₂. Diethylzinc (1.4 mmol of a 1.0 M solution in hexanes) was added by syringe. Dibromo adduct (68) (349 mg, 1.0 mmol) in dry CH₂Cl₂ (4.5 mL) was added dropwise over 30 minutes. The mixture was stirred at room temperature for 2 hours, followed by reflux overnight. The solution was cooled and diluted with CH₂Cl₂ (10 mL) and quenched with saturated NaHCO₃ (3 mL). The organic layer was separated, washed with saturated NH₄Cl (2 x 5 mL), dried (MgSO₄), filtered and concentrated. Radial chromatography (10% methylene chloride in hexanes) afforded starting material, monobromo adduct (74) and an unidentified tan solid.

¹H NMR (400 MHz) δ ppm (CDCl₃) 7.74-7.20 (m), 6.98-9.86 (d, 10H), 3.70 (t, 5H), 2.87 (t, 2H), 2.25 (septet, 1H), 2.07 (septet, 2H), 1.46 (septet, 8H), 1.29 (septet, 13H), 0.99 (t, 12H), 0.76 (t, 23H). m/z (MALDI-TOF) 378.86.
Chapter III Experimental

Synthesis of $^{18}$O t-butyl cyclohexanone in cyclohexane (130)

A solution of t-butyl cyclohexanone (100 mg, 0.65 mmol) in cyclohexane (2 mL) was prepared in a 4 mL conical vial equipped with a stir bar. 95% $\text{H}_2^{18}\text{O}$ (131 mg, 6.48 mmol) was added to a solution along with ~10 mg of Dowex. The mixture stirred vigorously at RT for 35 minutes. The organic layer was decanted and concentrated to yield a white solid in quantitative yield. A trace amount was dissolved in spectrophotometric grade cyclohexane (1 mL) and injected into the HP GC-MS indicating 74.0% $^{18}$O. $t_R$ 10.16 min, (m/z, abundance) (154.00, 368, $^{16}$O parent ion), (156.10, 1049, $^{18}$O parent ion). $^{13}$C NMR (500 MHz) δ ppm (CDCl$_3$) 212.59 ($^{16}$O=C), 212.54 ($^{18}$O=C), 46.73, 41.33, 32.49, 27.63. IR (neat) 2951.60 cm$^{-1}$, 1702.88, 1429.43, 1358.34, 1220.28, 1164.22, 941.20.

Synthesis of $^{18}$O t-butyl cyclohexanone in dichloromethane (130)

A solution of t-butyl cyclohexanone (100 mg, 0.65 mmol) in dry dichloromethane (2 mL) was prepared in a 4-mL conical vial equipped with a stir bar. 95% $\text{H}_2^{18}\text{O}$ (131 mg, 6.5 mmol) was added to a solution along with ~ 10 mg of Dowex. The mixture was stirred vigorously at RT for 2 hrs. The organic layer was decanted and concentrated to yield a white solid in quantitative yield. A trace amount was dissolved in dry dichloromethane (1 mL) and injected into the Thermo GC-MS indicating 58.1% $^{18}$O. $t_R$ 6.00-6.15 min, (m/z, abundance) (153.95, 19.5, $^{16}$O parent ion), (156.02, 27.0 $^{18}$O parent ion). $^{13}$C NMR and IR spectra were identical to the above product.

90

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Ozone reaction with t-butyl cyclohexanone (130-18O)

t-Butyl cyclohexanone (10 mg) was dissolved in dry CH2Cl2 (3 mL) in a vial and cooled to 0°C in an ice bath. It was then injected in the GC-MS for analysis as a standard. Dry CH2Cl2 (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a persistent blue color developed. The ozone solution was warmed to 0°C and the t-butyl cyclohexanone solution was added. The reaction was monitored at 0°C by both the HP and Thermo GC-MS, individually. HP GC/MS: t = 0 sec, (m/z, abundance): (154.05, 510, 16O parent ion), (156.10, 1148, 18O parent ion); t = 60 sec, (154.05, 505, 16O); (156.10, 977, 18O parent ion); t = 1922 sec, (154.05, 399, 16O); (156.10, 120, 18O); t = 3482 sec, (154.05, 1352, 16O), (156.10, 356, 18O); t = 5042 sec, (154.05, 1897, 16O), (156.10, 531, 18O).
Thermo GC/MS: tR 6.00-6.15 min; t = 0 sec, (m/z, abundance): (153.95, 19.5, 16O parent ion), (156.02, 27.0, 18O parent ion); t = 60 sec, (154.04, 11.6, 16O); (156.09, 13.5, 18O parent ion); t = 1290 sec, (153.98, 17.5, 16O); (156.11, 11.0, 18O); t = 2780 sec, (153.92, 22.2, 16O), (156.09, 12.0, 18O); t = 4202 sec, (153.96, 19.5, 16O), (156.09, 9.5, 18O).

Control ozone reaction with t-butyl cyclohexanone (130-18O)

t-Butyl cyclohexanone (10 mg) was dissolved in dry CH2Cl2 (3 mL) in a vial and cooled to 0°C in an ice bath. Dry CH2Cl2 (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a persistent blue color developed. The ozone solution was warmed to 0°C. The unlabeled t-butyl
cyclohexanone solution was added to the saturated ozone solution and stirred for 30 minutes at 0°C. The solution was concentrated on a rotary evaporator at 0°C and analyzed by NMR spectroscopy. Spectral properties were unchanged.

**Control oxygen reaction with t-butyl cyclohexanone (130-^{18}O)**

T-Butyl cyclohexanone (10 mg) was dissolved in dry CH$_2$Cl$_2$ (3 mL) in a vial and cooled to 0°C in an ice bath. It was then injected in the GC-MS for analysis as a standard. Dry CH$_2$Cl$_2$ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with oxygen for 10 minutes. The ozone solution was warmed to 0°C. The unlabeled t-butyl cyclohexanone solution was added to the saturated oxygen solution and the reaction was monitored for ~ 60 minutes at 0°C by use of the Thermo GC-MS. Spectral properties of each sample were unchanged.

**Synthesis of $^{18}$O-acetophenone (132)**

A solution of acetophenone (100 mg, 0.83 mmol) in dry dichloromethane (1 mL) was prepared in a 4 mL conical vial equipped with a stir bar. 95% H$_2^{18}$O (80 mg, 4.77 mmol) was added to a solution along with ~10 mg of Dowex. The mixture stirred vigorously at RT for 3 hours. A drop of the solution was removed, diluted with dry dichloromethane and injected into the Thermo GC-MS for analysis indicating 69.9% $^{18}$O. The solution was dried (MgSO$_4$), filtered through a glass wool plug and concentrated to yield a light yellow liquid in a quantitative yield. $t_R$ 4.52 min; (m/z, abundance) (119.95, 44, $^{16}$O parent ion), (121.95, 102, $^{18}$O parent ion).
Ozone reaction with acetophenone (132)

Acetophenone (10 mg) was dissolved CH₂Cl₂ (5 mL) in a vial and cooled to 0°C in an ice bath. This sample was injected in the GC-MS for analysis as a standard. Dry CH₂Cl₂ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a persistent blue color developed. The ozone solution was warmed to 0°C and the acetophenone solution was added. The reaction was monitored at 0°C by use of the Thermo GC-MS. \( t_R \) 4.58 min; \( t = 0 \) sec, (m/z, abundance): (120.18, 27.8 $^{16}$O parent ion), (122.13, 37.0, $^{18}$O parent ion); \( t = 60 \) min, (120.03, 37.2, $^{16}$O); (122.01, 41.0, $^{18}$O); \( t = 1371 \) sec, (120.03, 38.0, $^{16}$O); (122.01, 39.0, $^{18}$O); \( t = 2815 \) sec, (120.05, 41.2, $^{16}$O), (122.04, 39.0, $^{18}$O); \( t = 4282 \) sec, (119.97, 47.5, $^{16}$O), (121.96, 35.0, $^{18}$O).

Control ozone reaction with acetophenone (132)

Dry CH₂Cl₂ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. Acetophenone (10 mg) was dissolved in dry CH₂Cl₂ (3 mL) in a vial. The ozone solution was warmed to 0°C. The unlabeled acetophenone solution was added and stirred for 30 minutes at 0°C. The solution was concentrated on a rotary evaporator at 0°C. Spectral data showed no change.

O₃ reaction with t-butyl cyclohexanone (130-$^{18}$O) and acetophenone (132-$^{18}$O)

$^{18}$O t-butyl cyclohexanone (10 mg, 0.66 mmol) and $^{18}$O-acetophenone (8 mg, 0.66 mmol) were dissolved in dry CH₂Cl₂ (5 mL), cooled to 0°C in an ice bath and injected in the GC-MS for analysis as a standard. Dry CH₂Cl₂ (10 mL) was
cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a persistent blue color developed. The ozone solution was warmed to 0°C and the \(^{18}\text{O}\) ketone solution was added. The reaction was monitored at 0°C by use of the Thermo GC-MS. \(t\)-butyl cyclohexanone \(t_R\) 6.1-6.2 min; \(t = 0\) seconds, (m/z, abundance): (154.25, 43.5, \(^{16}\text{O}\) parent ion), (156.29, 25.0, \(^{18}\text{O}\) parent ion); \(t = 60\) sec (154.16, 16.4, \(^{16}\text{O}\)), (156.18, 18.0, \(^{18}\text{O}\)); \(t = 1462\) sec, (154.15, 15.0, \(^{16}\text{O}\)), (156.19, 14.5, \(^{18}\text{O}\)); \(t = 2202\) sec, (154.15, 15.5, \(^{16}\text{O}\)), (156.21, 13.0, \(^{18}\text{O}\)); \(t = 3509\) sec (154.12, 14.5, \(^{16}\text{O}\)), (156.17, 12.3, \(^{18}\text{O}\)). Acetophenone \(t_R\) 4.5-4.7 min; \(t = 0\) sec, (m/z, abundance): (120.14, 43.5, \(^{16}\text{O}\) parent ion), (122.07, 30.5, \(^{18}\text{O}\) parent ion); \(t = 60\) sec, (119.98, 54.5, \(^{16}\text{O}\)), (121.97, 37.0, \(^{18}\text{O}\)); \(t = 1462\) min, (119.97, 49.5, \(^{16}\text{O}\)), (121.96, 33.0, \(^{18}\text{O}\)); \(t = 1462\) min, (119.98, 49.0, \(^{16}\text{O}\)), (121.96, 32.0, \(^{18}\text{O}\)); \(t = 3509\) sec, (119.88, 89.0, \(^{16}\text{O}\)), (121.90, 52.0, \(^{18}\text{O}\)).

**Synthesis of \(^{18}\text{O}\) labeled benzophenone (133)**

Reaction with Dowex at room temperature failed to yield labeled benzophenone. A solution of benzophenone (50 mg, 0.27 mmol) in dry THF (4 mL) was prepared in a 10-mL microwave vial equipped with a stir bar. 95\% \(\text{H}_{2}\)\(^{18}\text{O}\) (0.05 mL, 2.74 mmol) was added to a solution along with ~10 mg of \(p\)-TsOH. The vial was appropriately capped and placed in the microwave cavity. The reaction was run at 100°C with a hold time of 30 minutes. After cooling, a 1 mL sample was removed, diluted to 5 mL with dry THF and analyzed using the Thermo GC/MS indicating 90.1\% \(^{18}\text{O}\). The sample was combined with the original mixture, neutralized with NaOMe, dried with MgSO\(_4\), filtered through a glass wool plug.
and concentrated to yield a white solid in quantitative yield. GC-MS: $t_R$ 9.69 min, (m/z, abundance) (182.31, 11.0, $^{16}$O parent ion), (184.26, 100.0, $^{18}$O parent ion).

**Ozone reaction with benzophenone (133)**

Benzophenone (12 mg) was dissolved CH$_2$Cl$_2$ (5 mL) in a vial and cooled to 0°C in an ice bath. This sample was injected in the GC-MS for analysis as a standard. Dry CH$_2$Cl$_2$ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a persistent blue color developed. The ozone solution was warmed to 0°C and the benzophenone solution was added. The reaction was monitored at 0°C by use of the Thermo GC-MS. $t_R$ 9.62 min; $t = 0$ sec, (m/z, abundance): (182.23, 95.5 $^{16}$O parent ion), (184.15, 77.5, $^{18}$O parent ion); $t = 60$ sec, (182.14, 100.0, $^{16}$O); (184.11, 72.0, $^{18}$O); $t = 1327$ sec, (182.12, 100.0, $^{16}$O); (184.15, 66.0, $^{18}$O); $t = 2757$ sec, (182.08, 100.0, $^{16}$O), (184.16, 62.0, $^{18}$O); $t = 4318$ sec, (182.09, 100.0, $^{16}$O), (184.09, 53.0, $^{18}$O).

**Control ozone reaction with benzophenone (133)**

Dry CH$_2$Cl$_2$ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. Benzophenone (12 mg) was dissolved in dry CH$_2$Cl$_2$ (5 mL) in a vial. The ozone solution was warmed to 0°C. The unlabeled benzophenone solution was added and stirred for 30 minutes at 0°C. The solution was concentrated on a rotary evaporator at 0°C. Spectral properties were unchanged.
Attempted synthesis of $^{18}$O labeled cyclohexanone carbaldehyde (134)

A solution of cyclohexane carbaldehyde (100 mg, 0.89 mmol) in cyclohexane (2 mL) was prepared in a 4 mL conical vial equipped with a stir bar. 95% H$_2^{18}$O (140 mg, 6.94 mmol) was added to a solution along with ~10 mg of Dowex. The mixture stirred vigorously at RT for 90 minutes. The organic layer was decanted, dissolved in spectrophotometric grade cyclohexane and injected into the HP GC-MS. Analysis of the product showed both labeled cyclohexane carboxylic acid (34.3% $^{18}$O) and labeled cyclohexane carbaldehyde (59.4% $^{18}$O) in 23 to 1 a ratio.

GC-MS (m/z, abundance) cyclohexane-carbaldehyde: $t_R$ 4.94 min, (112.00, 300, $^{16}$O parent ion), (114.04, 157, $^{18}$O parent ion); cyclohexanecarboxylic acid: $t_R$ 7.90 min, (m/z, abundance) (128.05, 1427, $^{16}$O parent ion), (130.05, 2087, $^{18}$O parent ion). $^{13}$C NMR (500 MHz) cyclohexanecarbaldehyde 205.14 ($^{16}$O=C), 205.04 ($^{18}$O=C), 49.98, 26.05, 25.09; cyclohexanecarboxylic acid 182.81 ($^{16}$O=C) 182.79 ($^{18}$O=C), 43.10, 28.90, 25.83, 25.46.

Control ozone reaction with cyclohexanone carbaldehyde (134)

Dry CH$_2$Cl$_2$ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. The solution was warmed to 0°C. Cyclohexanone carbaldehyde (10 mg) was dissolved in dry CH$_2$Cl$_2$ (3 mL) in a vial and cooled to 0°C in an ice bath. The unlabeled cyclohexanone carbaldehyde solution was added to the saturated ozone solution and stirred for 30 minutes at 0°C. The solution was concentrated on a rotary evaporator at 0°C.
NMR analysis of the product showed cyclohexanecarboxylic acid and cyclohexane carbaldehyde in a 5 to 2 ratio. Spectral properties were unchanged.

**Control ozone reaction with cyclohexanone carbaldehyde (134) at -78°C**

Dry CH₂Cl₂ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. Cyclohexanone carbaldehyde (10 mg) was dissolved in dry CH₂Cl₂ (3 mL) in a vial and cooled to -78°C. The unlabeled cyclohexanone carbaldehyde solution was added to the saturated ozone solution and stirred for 30 minutes at -78°C. The solution was concentrated on a rotary evaporator at -78°C for 15 minutes to remove excess ozone and then warmed to 0°C to remove the remaining solvent. NMR analysis of the product showed cyclohexane carboxylic acid and cyclohexane carbaldehyde in 1.2 to 1 a ratio.

**Control ozone reaction with isobutyraldehyde (136)**

Dry CH₂Cl₂ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. The solution was warmed to 0°C. Freshly distilled isobutyraldehyde (10 mg) was dissolved in dry CH₂Cl₂ or hexanes (3 mL) in a vial and cooled to 0°C in an ice bath. The unlabeled isobutyraldehyde solution was added to the saturated ozone solution and stirred for 30 minutes at 0°C. The solution was concentrated on a rotary evaporator at 0°C. NMR analysis of the product showed aldehyde and carboxylic acid formation in a 1 to 2 ratio. ¹³C NMR (500 MHz) δ ppm (CDCl₃) isobutyraldehyde: 204.86, 41.07, 15.48; isobutyric acid: 184.00, 34.06, 18.79.
Control ozone reaction with isobutyraldehyde (136) at -78°C

Dry CH₂Cl₂ (10 mL) was cooled to -78°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. Freshly distilled isobutyraldehyde (10 mg) was dissolved in dry CH₂Cl₂ or hexanes (3 mL) in a vial and cooled to -78°C in an ice bath. The unlabeled isobutyraldehyde solution was added to the saturated ozone solution and stirred for 30 minutes at -78°C. The solution was concentrated on a rotary evaporator at -78°C for 15 minutes to remove excess ozone and then warmed to 0°C to remove the remaining solvent. NMR analysis of the product showed aldehyde and carboxylic acid formation in a 1 to 2 ratio.

Control ozone reaction with benzaldehyde (137)

Dry CH₂Cl₂ (10 mL) was cooled to 0°C in a dry ice/acetone bath and then saturated with ozone until a blue color developed. The solution was warmed to 0°C. Freshly distilled benzaldehyde (10 mg) was dissolved in dry CH₂Cl₂ (3 mL) in a vial and cooled to 0°C. The unlabeled benzaldehyde solution was added to the saturated ozone solution and stirred for 30 minutes at 0°C. The solution was concentrated on a rotary evaporator at 0°C. NMR analysis of the product showed aldehyde and carboxylic acid formation in a 5.7 to 1 ratio. § ¹³C NMR (500 MHz) δ ppm (CDCl₃) benzaldehyde: 192.28, 136.47, 136.43, 129.68, 128.98; benzoic acid: 172.77, 133.83, 130.28, 129.44, 128.49.
LIST OF REFERENCES


(17) Balci, M.; Taskeneligil, Y. *Advances in Strained and Interesting Organic Molecules* 2000, 8, 43.


(34) Khoury, P. R.; Goddard, J. D.; Tam, W. Tetrahedron 2004, 60, 8103.


(118) Naughton, P. In www.timesonline.co.uk/article/0,,22989-1695442,00.html; TimesOnline, July 15, 2005.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
APPENDIX A: Computational Data
### Chapter I

<table>
<thead>
<tr>
<th>Structure</th>
<th>B3LYP/6-311G+(d,p)</th>
<th>E + ZPVE</th>
<th>Free Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₅ carbene syn (17-syn)</td>
<td>-194.004185</td>
<td>-193.916235</td>
<td>-193.943691</td>
</tr>
<tr>
<td>C₅ carbene anti (17-anti)</td>
<td>-194.004262</td>
<td>-193.916721</td>
<td>-193.944318</td>
</tr>
<tr>
<td>C₅ methylene cyclopropane insertion (TS1)</td>
<td>-193.931339</td>
<td>-193.846595</td>
<td>-193.873471</td>
</tr>
<tr>
<td>C₅ methylene cyclopropane (14)</td>
<td>-194.022361</td>
<td>-193.932036</td>
<td>-193.958939</td>
</tr>
<tr>
<td>1,2-shift to 1,2-cyclopentadiene (TS3)</td>
<td>-193.993012</td>
<td>-193.905031</td>
<td>-193.932264</td>
</tr>
<tr>
<td>1,2-cyclopentadiene (8)</td>
<td>-194.050440</td>
<td>-193.96112</td>
<td>-193.987625</td>
</tr>
<tr>
<td>divinylcarbene closure (TS4)</td>
<td>-194.012301</td>
<td>-193.924097</td>
<td>-193.950953</td>
</tr>
<tr>
<td>divinylcarbene (22)</td>
<td>-193.036113</td>
<td>-193.948122</td>
<td>-193.976425</td>
</tr>
<tr>
<td>C₅ carbene rearr to acetylene (TS2)</td>
<td>-193.984890</td>
<td>-193.898464</td>
<td>-193.925795</td>
</tr>
<tr>
<td>cyclopropylacetylene (19)</td>
<td>-194.094829</td>
<td>-194.004420</td>
<td>-193.032059</td>
</tr>
<tr>
<td>C₅ cyclopropene closure (TS5)</td>
<td>-193.980217</td>
<td>-193.893267</td>
<td>-193.920177</td>
</tr>
<tr>
<td>C₅ cyclopropene (13)</td>
<td>-194.010603</td>
<td>-193.920853</td>
<td>-193.947753</td>
</tr>
<tr>
<td>C₅ cyclopropene open to carbene (TS6)</td>
<td>-193.009513</td>
<td>-193.920520</td>
<td>-193.947191</td>
</tr>
</tbody>
</table>

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
<table>
<thead>
<tr>
<th>Reaction Description</th>
<th>Energy 1</th>
<th>Energy 2</th>
<th>Energy 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclopentenylidene (20)</td>
<td>-194.058457</td>
<td>-193.968627</td>
<td>-193.996219</td>
</tr>
<tr>
<td>1,2 shift to 1,3-cyclopentadiene (TS7)</td>
<td>-194.038813</td>
<td>-193.951747</td>
<td>-193.978344</td>
</tr>
<tr>
<td>1,3-cyclopentadiene (21)</td>
<td>-194.156236</td>
<td>-194.064117</td>
<td>-194.090716</td>
</tr>
<tr>
<td>C₅ cyclopropene opening to vinylidene (TS8)</td>
<td>-193.9520769</td>
<td>-193.866223</td>
<td>-193.893014</td>
</tr>
<tr>
<td>cyclobutylidene (16)</td>
<td>-194.0194562</td>
<td>-193.929572</td>
<td>-193.957843</td>
</tr>
<tr>
<td>cyclopentyne rear (TS9)</td>
<td>-194.013834</td>
<td>-193.923959</td>
<td>-193.952446</td>
</tr>
<tr>
<td>C₆ 1,2-H migration to carbene (TS10)</td>
<td>-193.9308893</td>
<td>-193.845400</td>
<td>-193.872132</td>
</tr>
<tr>
<td>C₆ carbene syn (28-syn)</td>
<td>-233.368936</td>
<td>-233.250487</td>
<td>-233.279397</td>
</tr>
<tr>
<td>C₆ carbene anti (28-anti)</td>
<td>-233.368664</td>
<td>-233.250522</td>
<td>-233.279494</td>
</tr>
<tr>
<td>C₆ cyclopropane insertion (TS11)</td>
<td>-233.316782</td>
<td>-233.201769</td>
<td>-233.229882</td>
</tr>
<tr>
<td>C₆ methylene cyclopropane (25)</td>
<td>-233.402153</td>
<td>-233.281849</td>
<td>-233.309949</td>
</tr>
<tr>
<td>1,2-shift to 1,2-cyclohexadiene A (TS12)</td>
<td>-233.3458318</td>
<td>-233.228273</td>
<td>-233.256629</td>
</tr>
<tr>
<td>1,2-cyclohexadiene (9)</td>
<td>-233.414504</td>
<td>-233.294095</td>
<td>-233.322810</td>
</tr>
<tr>
<td>1,3,5-hexatriene</td>
<td>-233.464719</td>
<td>-233.346354</td>
<td>-233.375978</td>
</tr>
<tr>
<td>Reaction Description</td>
<td>Energy 1</td>
<td>Energy 2</td>
<td>Energy 3</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Ring Closure (TS19)</td>
<td>-233.363406</td>
<td>-233.246916</td>
<td>-233.274559</td>
</tr>
<tr>
<td>Cyclobutylacetylene (29)</td>
<td>-233.4214987</td>
<td>-233.301835</td>
<td>-233.331149</td>
</tr>
<tr>
<td>C$_6$ cyclopropene closure (TS13)</td>
<td>-233.3604849</td>
<td>-233.242984</td>
<td>-233.271782</td>
</tr>
<tr>
<td>C$_6$ cyclopropene (24)</td>
<td>-233.396621</td>
<td>-233.276173</td>
<td>-233.304627</td>
</tr>
<tr>
<td>C$_6$ cyclopropene open to carbene (TS14)</td>
<td>-233.3670223</td>
<td>-233.248326</td>
<td>-233.276490</td>
</tr>
<tr>
<td>Cyclohexenyldiene (30)</td>
<td>-233.384018</td>
<td>-233.264744</td>
<td>-233.293223</td>
</tr>
<tr>
<td>1,2-shift to 1,2-cyclohexadiene B (TS16)</td>
<td>-233.305167</td>
<td>-233.191218</td>
<td>-233.220207</td>
</tr>
<tr>
<td>1,2 shift to 1,3-cyclohexadiene (TS15)</td>
<td>-233.364680</td>
<td>-233.248091</td>
<td>-233.276318</td>
</tr>
<tr>
<td>1,3-cyclohexadiene (31)</td>
<td>-233.483877</td>
<td>-233.362064</td>
<td>-233.389644</td>
</tr>
<tr>
<td>C$_6$ cyclopropene opening to vinylidene (TS20)</td>
<td>-233.3357144</td>
<td>-233.219473</td>
<td>-233.248324</td>
</tr>
<tr>
<td>Cyclopentylidene (27)</td>
<td>-233.3781816</td>
<td>-233.258223</td>
<td>-233.288020</td>
</tr>
<tr>
<td>Cyclohexyne rear (TS21)</td>
<td>-233.362224</td>
<td>-233.242734</td>
<td>-233.271480</td>
</tr>
<tr>
<td>Cyclohexyne (32)</td>
<td>-233.399012</td>
<td>-233.277966</td>
<td>-233.305851</td>
</tr>
<tr>
<td>C$_6$ 1,2-H migration to carbene (TS22)</td>
<td>-233.3015034</td>
<td>-233.186245</td>
<td>-233.214929</td>
</tr>
</tbody>
</table>
## Chapter II

<table>
<thead>
<tr>
<th>Structure</th>
<th>B3LYP/6-311G+(d,p)</th>
<th>ZPVE</th>
<th>E + ZPVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclobutene</td>
<td>-156.017281</td>
<td>0.086020</td>
<td>-155.931261</td>
</tr>
<tr>
<td>cyclopentene</td>
<td>-195.381944</td>
<td>0.116189</td>
<td>-195.265755</td>
</tr>
<tr>
<td>cyclohexene</td>
<td>-234.713220</td>
<td>0.145561</td>
<td>-234.567659</td>
</tr>
<tr>
<td>cycloheptene</td>
<td>-272.028757</td>
<td>0.174324</td>
<td>-273.854433</td>
</tr>
<tr>
<td>cis-cyclooctene</td>
<td>-313.347559</td>
<td>0.203359</td>
<td>-313.144201</td>
</tr>
<tr>
<td>(Z)-cyclononene</td>
<td>-352.691959</td>
<td>0.231776</td>
<td>-352.437419</td>
</tr>
<tr>
<td>1,2-cyclobutadiene</td>
<td>-154.669005</td>
<td>0.058958</td>
<td>-154.610047</td>
</tr>
<tr>
<td>1,2-cyclopentadiene</td>
<td>-194.050440</td>
<td>0.089328</td>
<td>-193.961112</td>
</tr>
<tr>
<td>1,2-cyclohexadiene</td>
<td>-233.414051</td>
<td>0.120409</td>
<td>-233.294095</td>
</tr>
<tr>
<td>1,2-cycloheptadiene</td>
<td>-272.758127</td>
<td>0.149731</td>
<td>-272.608481</td>
</tr>
<tr>
<td>1,2-cyclooctadiene</td>
<td>-312.096720</td>
<td>0.178623</td>
<td>-311.918097</td>
</tr>
<tr>
<td>1,2-cyclononadiene</td>
<td>-351.422981</td>
<td>0.207384</td>
<td>-351.215597</td>
</tr>
<tr>
<td>cyclobutatriene* (75)</td>
<td>-153.274221</td>
<td>0.035151</td>
<td>-153.239070</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>cyclopentatriene (76)</td>
<td>-192.765584</td>
<td>0.066015</td>
<td>-192.699569</td>
</tr>
<tr>
<td>cyclohexatriene (77)</td>
<td>-232.143887</td>
<td>0.096210</td>
<td>-232.047677</td>
</tr>
<tr>
<td>cycloheptatriene (78)</td>
<td>-271.500597</td>
<td>0.125677</td>
<td>-271.374920</td>
</tr>
<tr>
<td>cyclooctatriene (79)</td>
<td>-310.829250</td>
<td>0.154564</td>
<td>-310.674686</td>
</tr>
<tr>
<td>cyclononatriene (80)</td>
<td>-350.177887</td>
<td>0.183535</td>
<td>-349.994352</td>
</tr>
<tr>
<td>1,3-cyclobutadiene</td>
<td>-154.7211603</td>
<td>0.060893</td>
<td>-154.660268</td>
</tr>
<tr>
<td>1,3-cyclopentadiene</td>
<td>-194.156236</td>
<td>0.092119</td>
<td>-194.064117</td>
</tr>
<tr>
<td>1,3-cyclohexadiene</td>
<td>-233.4838769</td>
<td>0.121814</td>
<td>-233.362063</td>
</tr>
<tr>
<td>1,3-cycloheptadiene</td>
<td>-272.8059512</td>
<td>0.150823</td>
<td>-272.655128</td>
</tr>
<tr>
<td>cis-1,3-cyclooctadiene</td>
<td>-312.1253129</td>
<td>0.179605</td>
<td>-311.945708</td>
</tr>
<tr>
<td>cis-1,3-cyclononadiene</td>
<td>-351.4413051</td>
<td>0.207859</td>
<td>-351.233446</td>
</tr>
<tr>
<td>cyclobutane</td>
<td>-157.257205</td>
<td>0.110251</td>
<td>-157.146954</td>
</tr>
<tr>
<td>cyclopentane</td>
<td>-196.611661</td>
<td>0.140042</td>
<td>-196.471619</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>-235.9448331</td>
<td>0.169497</td>
<td>-235.775336</td>
</tr>
<tr>
<td>Substance</td>
<td>Energy 1</td>
<td>Energy 2</td>
<td>Energy 3</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>cycloheptane</td>
<td>-275.258</td>
<td>0.198</td>
<td>-275.060</td>
</tr>
<tr>
<td>cyclooctane</td>
<td>314.576</td>
<td>0.227</td>
<td>-314.349</td>
</tr>
<tr>
<td>cyclononane</td>
<td>-353.895</td>
<td>0.256</td>
<td>-353.639</td>
</tr>
<tr>
<td>1,3-dimethylallene (81)</td>
<td>-195.351</td>
<td>0.112</td>
<td>-195.239</td>
</tr>
<tr>
<td>propane</td>
<td>-119.181</td>
<td>0.103</td>
<td>-119.078</td>
</tr>
<tr>
<td>ethane</td>
<td>-79.857</td>
<td>0.074</td>
<td>-79.782</td>
</tr>
<tr>
<td>2-trans-pentene (84)</td>
<td>-196.599</td>
<td>0.136</td>
<td>-196.463</td>
</tr>
<tr>
<td>trans-2,3,4-hexatriene (82)</td>
<td>-233.437</td>
<td>0.117</td>
<td>-233.320</td>
</tr>
<tr>
<td>1,3-butadiene (86)</td>
<td>-156.041</td>
<td>0.085</td>
<td>-155.956</td>
</tr>
<tr>
<td>butatriene (83)</td>
<td>-154.778</td>
<td>0.059</td>
<td>-154.718</td>
</tr>
<tr>
<td>n-pentane (85)</td>
<td>-197.829</td>
<td>0.159</td>
<td>-197.671</td>
</tr>
<tr>
<td>n-hexane</td>
<td>-237.155</td>
<td>0.188</td>
<td>-236.966</td>
</tr>
<tr>
<td>cis-2,3,4-hexatriene</td>
<td>-233.437</td>
<td>0.117</td>
<td>-233.320</td>
</tr>
</tbody>
</table>

* transition state
# Chapter III

<table>
<thead>
<tr>
<th>Structure</th>
<th>B3LYP/6-311+G(d,p) + ZPVE</th>
<th>CCSD(T)/6-311+G(d,p)</th>
<th>CBS-QB3 Energy</th>
<th>BH&amp;HLYP/6-311+G(d,p) + ZPVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ozone (95)</td>
<td>-225.473327</td>
<td>-225.001281</td>
<td>-225.186935</td>
<td>-225.328017</td>
</tr>
<tr>
<td>formaldehyde (97)</td>
<td>-114.515263</td>
<td>-114.266529</td>
<td>-114.341304</td>
<td>-</td>
</tr>
<tr>
<td>acetone (96)</td>
<td>-193.135142</td>
<td>-</td>
<td>-192.815054</td>
<td>-193.009222</td>
</tr>
<tr>
<td>triplet oxygen ((^3)O(_2))</td>
<td>-150.366696</td>
<td>-150.044813</td>
<td>-150.162251</td>
<td>-150.289500</td>
</tr>
<tr>
<td>singlet oxygen ((^1)O(_2))</td>
<td>-150.350294</td>
<td>-150.029213</td>
<td>-150.153137</td>
<td>-150.270183</td>
</tr>
<tr>
<td>carbonyl oxide (101)</td>
<td>-189.611347</td>
<td>-189.199939</td>
<td>-189.339824</td>
<td>-</td>
</tr>
<tr>
<td>carbonyl oxide (94)</td>
<td>-268.237134</td>
<td>-</td>
<td>-267.818430</td>
<td>-268.062458</td>
</tr>
<tr>
<td>(^3)O(_2) addition (TS27-T)</td>
<td>-339.970590</td>
<td>-339.227044</td>
<td>-339.489718</td>
<td>-</td>
</tr>
<tr>
<td>(^3)O(_2) addition (TS31-T)</td>
<td>-418.589539</td>
<td>-</td>
<td>-417.964980</td>
<td>-418.331815</td>
</tr>
<tr>
<td>(^1)O(_2) addition (TS27-S)</td>
<td>-339.945277</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(^1)O(_2) addition (TS31-S)</td>
<td>-418.580799</td>
<td>-</td>
<td>-417.960546</td>
<td>-418.319773</td>
</tr>
<tr>
<td>triplet biradical (100-T)</td>
<td>-339.986553</td>
<td>-339.255090</td>
<td>-339.510927</td>
<td>-</td>
</tr>
<tr>
<td>triplet biradical (103-T)</td>
<td>-418.598546</td>
<td>-</td>
<td>-417.982437</td>
<td>-418.358959</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>singlet biradical</td>
<td>-339.986208</td>
<td>-339.255726</td>
<td>-339.508246</td>
<td></td>
</tr>
<tr>
<td>(100-S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>singlet biradical</td>
<td>-418.598164</td>
<td>-</td>
<td>-417.980113</td>
<td>-418.358801</td>
</tr>
<tr>
<td>(103-S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS26</td>
<td>339.961260</td>
<td>-339.229590</td>
<td>-339.496307</td>
<td></td>
</tr>
<tr>
<td>TS30</td>
<td>-418.576591</td>
<td>-</td>
<td>-417.963662</td>
<td>-418.320218</td>
</tr>
<tr>
<td>tetroxolane (99)</td>
<td>-339.976507</td>
<td>-339.254165</td>
<td>-339.522632</td>
<td></td>
</tr>
<tr>
<td>tetroxolane (95)</td>
<td>-418.590552</td>
<td>-</td>
<td>-417.995797</td>
<td>-418.337913</td>
</tr>
<tr>
<td>TS25</td>
<td>-339.964413</td>
<td>-339.231987</td>
<td>-339.501161</td>
<td></td>
</tr>
<tr>
<td>TS29</td>
<td>-418.574043</td>
<td>-</td>
<td>-417.969527</td>
<td>-418.316981</td>
</tr>
<tr>
<td>singlet diradical</td>
<td>-339.992974</td>
<td>-339.252517</td>
<td>-339.513516</td>
<td></td>
</tr>
<tr>
<td>(98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>singlet diradical</td>
<td>-418.597158</td>
<td>-</td>
<td>-417.523311</td>
<td>-418.349961</td>
</tr>
<tr>
<td>(102)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS24</td>
<td>-339.970876</td>
<td>-339.237581</td>
<td>-339.493568</td>
<td></td>
</tr>
<tr>
<td>TS28</td>
<td>-418.582486</td>
<td>-</td>
<td>-417.970470</td>
<td></td>
</tr>
<tr>
<td>Concerted TS</td>
<td></td>
<td></td>
<td>-339.239094</td>
<td></td>
</tr>
<tr>
<td>(97+94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX B: Spectra