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Theoretical and experimental studies of reactive organic molecules

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**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

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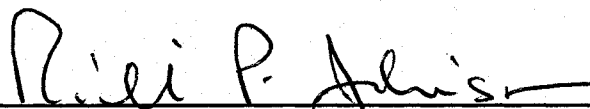
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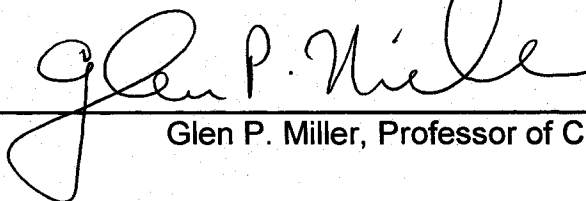
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8/18/06

Date

DEDICATION

To my parents,

Michael Konrad and Peggie Menzies

To my sister,

Rebekka Konrad

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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.

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ABSTRACT

THEORETICAL AND EXPERIMENTAL STUDIES OF REACTIVE ORGANIC MOLECULES

by

Kaleen 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_8 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

chemistry was unable to yield 1-cycloalkenyl-1a,9b-dihydro-1H-cyclopropa[1]phenanthrene as a precursor to C₅H₆ and C₆H₈ vinylcarbenes. A base-catalyzed isomerization of the vinylidene precursor, 1-cyclobutylidene-1a,9b-dihydro-1H-cyclopropa[1]phenanthrene, was unsuccessful in the preparation of this target. Gilman chemistry yielded traces of the C₆H₈ vinylcarbene precursor. Additionally, Simmons-Smith chemistry with 1,1-dibromo-1a,9b-dihydro-1H-cyclopropa[1]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.

¹⁸O-labeling studies supported the existence of tetroxolanes. ¹⁸O-labeled *t*-butyl cyclohexanone, acetophenone and benzophenone were prepared by exchange with H₂¹⁸O. 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.¹ 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.

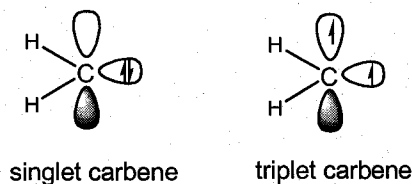
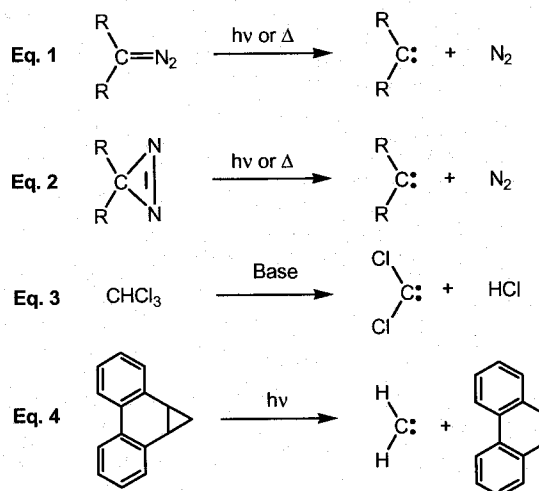


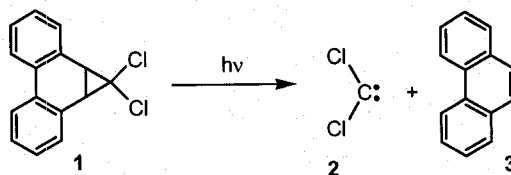
Figure 1: Singlet vs. Triplet Carbenes

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**).² Griffin utilized photochemical cyclo-eliminations to produce carbenes from cyclopropane derivatives.³ This involved a [3→2+1] cycloelimination, now generally known as the Griffin fragmentation (**Eq. 4**).



Scheme 1: Carbene Formation by Thermal and Photochemical Activation

In 1965, Richardson and coworkers reported the photochemical generation of singlet methylene from a cyclopropanated phenanthrene.⁴ 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**).⁵ Kirchoff later showed that upon photolysis of **1**, dichlorocarbene (**2**) and phenanthrene (**3**) were generated. (Scheme 2).⁶ Collaborative studies with Chateaneuf revealed for the first time the absolute kinetics of the reactivity of dichlorocarbene with several alkenes.⁷

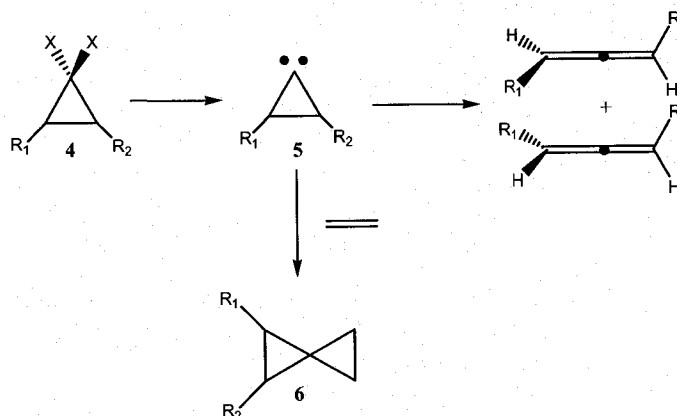


Scheme 2: Generation of Dichlorocarbene

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.⁶ Abbot continued this work by forming and trapping various alkyl carbenes, including benzylchlorocarbene, vinylcarbene and vinylidene.⁸ 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.⁹ Lewis's work included studies of benzylchlorocarbene and the synthesis and photolysis of novel vinylidene carbene precursors.¹⁰

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.¹¹ Allenes contain two consecutive double bonds where the central carbon atom is sp-hybridized.¹² 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**).¹³



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 spirocyclopentanes (**6**) in low yields. The cyclopropylidene intermediate (**5**) can open easily to the allene because of its low energy barriers¹⁴; therefore, only low yields of the spirocyclopentanes (**6**) have been obtained.

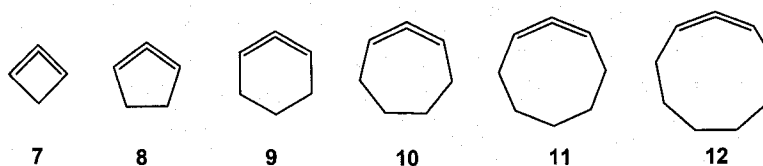


Figure 2: Cyclic Allene Series

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**).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.¹⁵ Nevertheless, the unsubstituted 1,2-cyclopentadiene (**8**) remains unknown. The synthesis and properties of the cyclic allene series has been extensively reviewed elsewhere.^{17,19,20} 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**).²¹

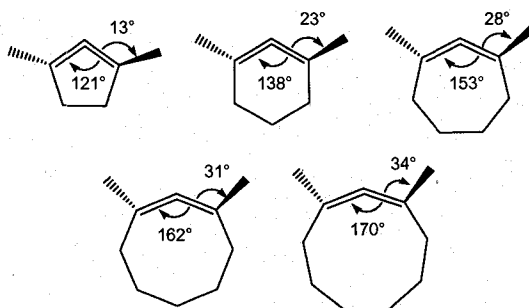


Figure 3: MNDO Torsional and Bending Angles for Cyclic Allenes

Carbene Rearrangements on the C₅H₆ and C₆H₈ 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**).

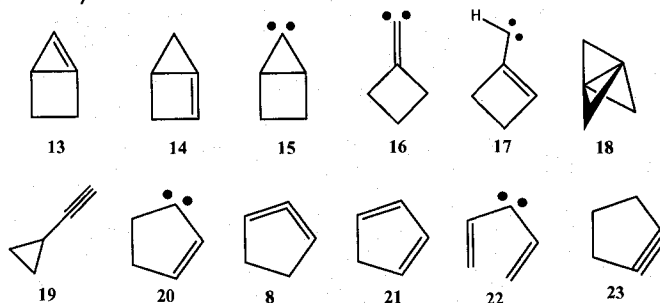


Figure 4: Species on the C₅H₆ Energy Surface

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.²² The enthalpies of formation of **13** and bicyclo[3.1.0]hex-1,5-ene (**24**), its C₆H₈ homologue, were also studied.²³ In general, these cyclopropene adducts can be generated at ambient temperature by base induced eliminations, but readily dimerize.²⁴ The ring strain of **14** and its C₆H₈ homologue **25** was determined using homodesmotic reactions and compared to the corresponding phosphorus heterocycles.²⁵ 5-Carbenabicyclo[2.1.0]pentane (**15**) was included in a homodesmotic reaction designed to compare the aromatic nature of carbenes in tricyclic systems.²⁶ The interconversion of cyclobutylidenecarbene (**16**) and cyclopentyne (**23**) has been explored.²⁷ This same carbene has been suggested as intermediate in the pyrolysis of a Meldrum's acid derivative.²⁸ The predicted NMR spectra were reported for **16** and cyclopenten-3-ylidene (**20**) using Density Functional Theory (DFT).²⁹ 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.³⁰ Chemical Abstracts present no reports of 1-cyclobutenylcarbene (**17**) although 2-cyclobutenylcarbene has been theoretically studied for its intramolecular cycloadditions.³¹ The kinetics of the thermal rearrangement of [1.1.1]propellane (**18**) were investigated by pyrolysis experiments along with DFT calculations.³² Cyclopropylacetylene (**19**) has been widely studied and can be prepared by treatment of 5-chloro-1-pentyne

with BuLi in cyclohexane.³³ Theoretical studies of **19** include ring strain estimates³⁴ and ¹³C NMR predictions.³⁵ 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 *ab initio* CASSCF, as well as DFT methods.³⁶ In conjunction with the pyrolysis of **21**, the heats of formation and relative stabilities of closed and open shell C₅H₆ hydrocarbons were examined with MINDO/3 theory.³⁷ This includes the only report on **22**. Cyclopentyne (**23**) has received more attention than most species in this series. Detailed *ab initio* studies of its electronic structure have been published.³⁸ More recently, [2+2] cycloadditions of **23** have been studied by various computational methods.³⁹

The C₆H₈ surface has been even more extensively explored (**Figure 5**). Many reports including these species were mentioned above as they also included the corresponding C₅H₆ homologues and will not be further discussed here.

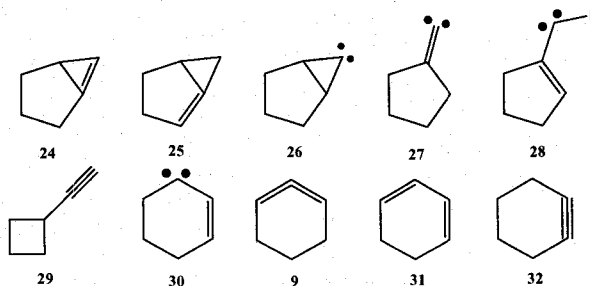


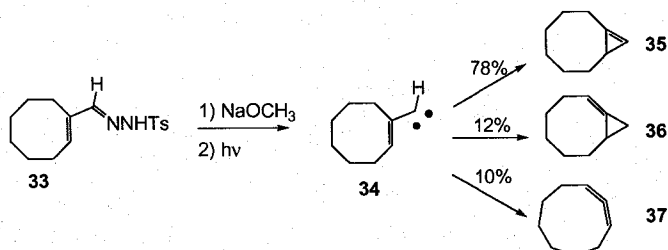
Figure 5: Species on the C₆H₈ Energy Surface

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.⁴⁰ The

cyclopropylidencarbene **26** is a well known intermediate in the Doering-Moore-Skattebol method with a low barrier for ring opening to **9**.¹⁴ Cyclopentylidencarbene (**27**) readily ring expands to form cyclohexyne (**32**).^{28,41,42} Both **27** and **28** have been suggested as intermediates in the thermal fragmentation of cyclopentylidencarbene-Meldrum's acid (See **Scheme 10** below). Cyclobutylacetylene (**29**) has been prepared by thermal extrusion of Ph₃PO from a oxobutylidetriphenylphosphorane.⁴³ Its Raman and IR spectra have been reported, along with the conformational stability using *ab initio* calculations.⁴⁴ 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.⁴⁵ 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 cyclopentylidencarbene (**27**), where it can be trapped with a suitable reagent.⁴¹ Shevlin examined the thermal reactions of cyclohexyne (**32**) at elevated temperatures experimentally and using *ab initio* calculations with MP2 theory.⁴² The singlet and triplet electronic states have also been examined with *ab initio* methods⁴⁶ and, more recently, the conformational surface was investigated.⁴⁷

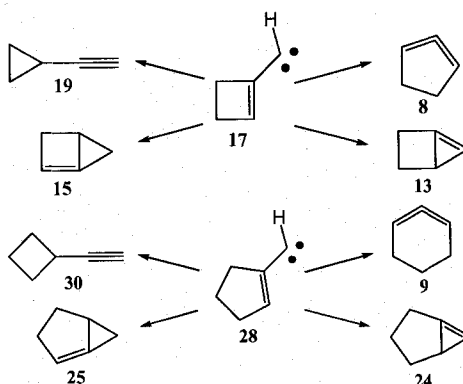
These studies encompass a wide variety of chemistry on the C_5H_6 and C_6H_8 potential energy surfaces. A complete investigation of their interconversions, either theoretically or experimentally has yet to be reported.

Experimental studies of larger carbenes homologues may provide a model for these C_5H_6 and C_6H_8 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

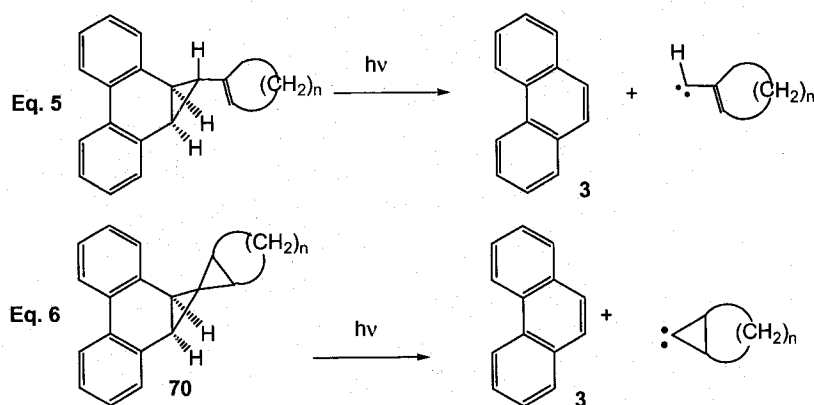
If similar chemistry is observed for the smaller ring systems, this might generate highly strained products including cyclic allenes (**8-9**), cyclopropenes (**13, 24**), and methylene cyclopropanes (**15, 25**). Another fragmentation, not shown in **Scheme 4**, might give acetylenes (**19, 30**) (**Scheme 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 C_5H_6 and C_6H_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_5H_6 and C_6H_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

Computational Methods

For each stationary point investigated, initial geometry optimizations were performed using Spartan '04⁵⁰ 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 03⁵¹ 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 C₅H₆ (**17**) and C₆H₈ (**28**) cycloalkenylcarbenes.

The C₅H₆ 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.

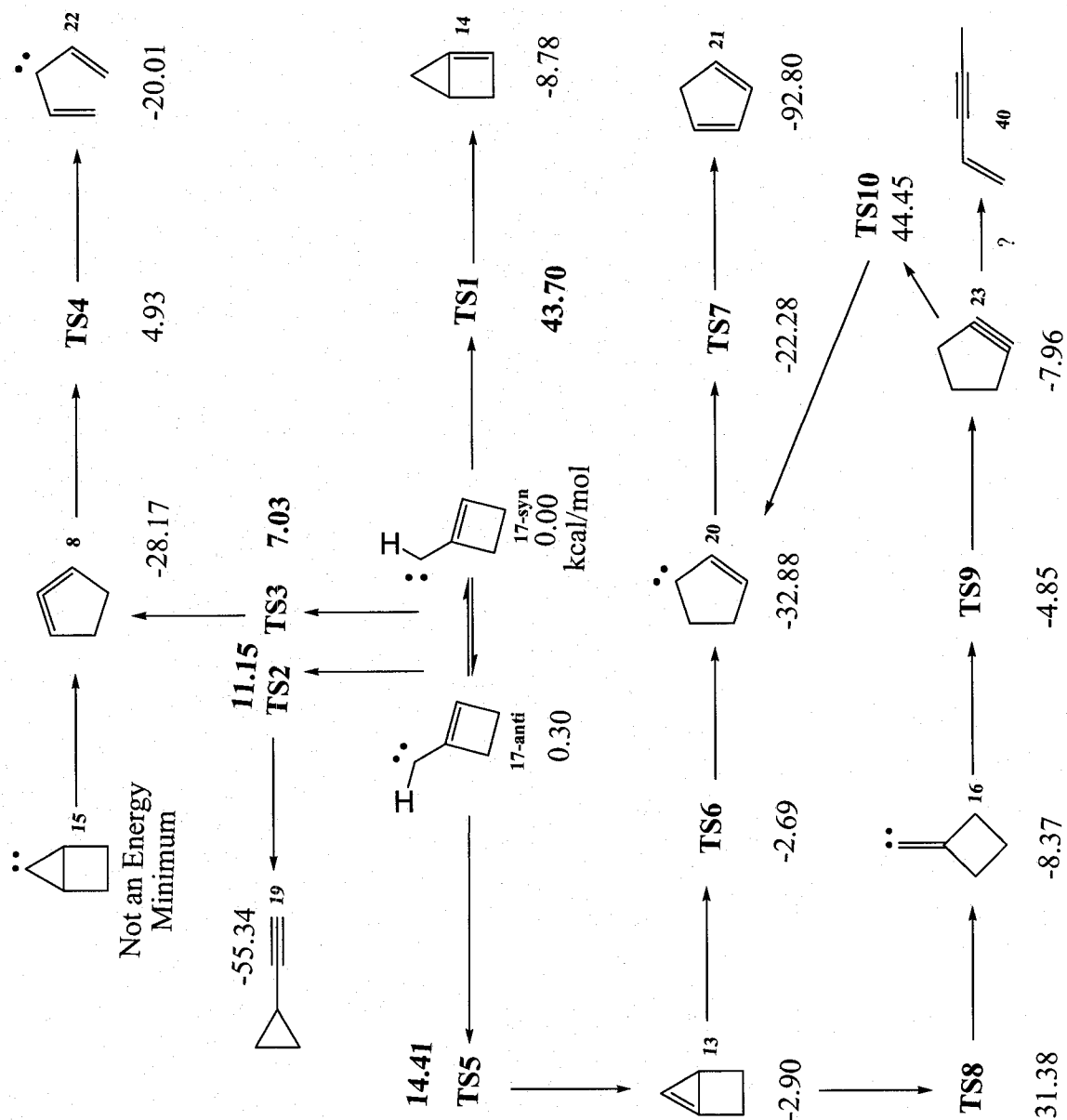
1,2-cyclopentadiene (**8**)

1,2-cyclopentadiene (**8**) is calculated to have C₂ 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 a 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**.



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

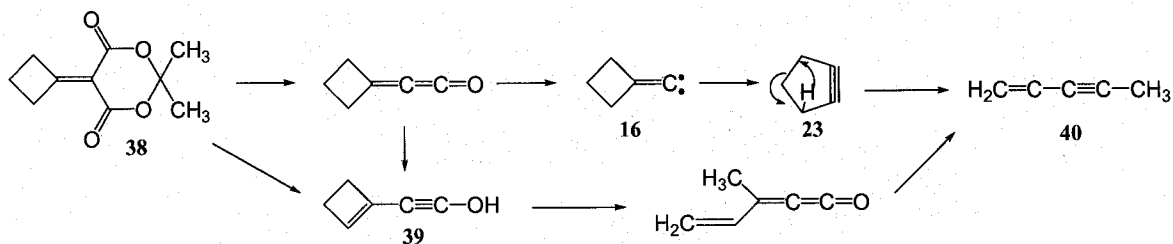
Cyclopenten-3-ylidene (20) and 1,3-cyclopentadiene (21)

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

Cyclopentyne (**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 cyclopentyne-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.

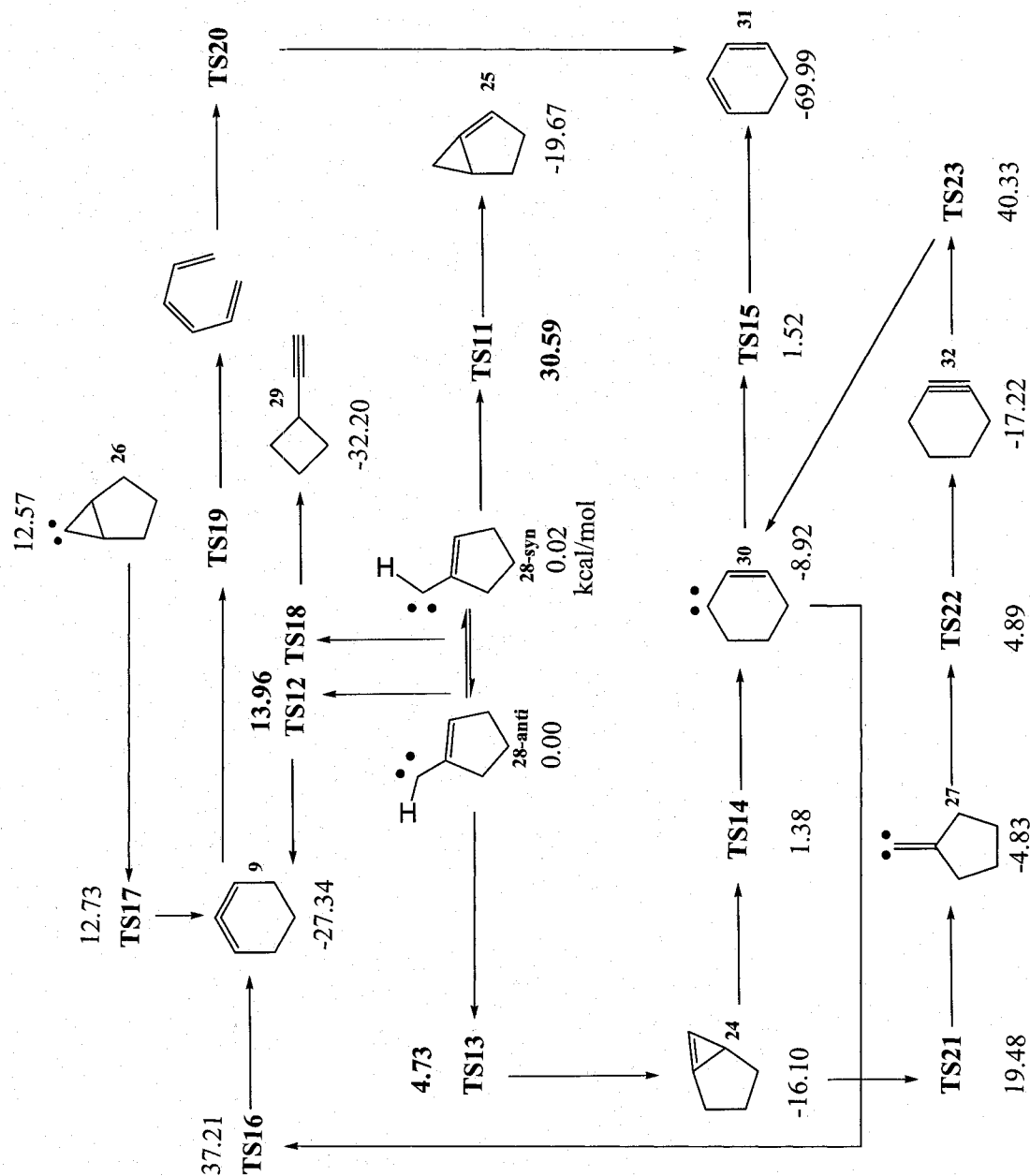
1,2-Cyclohexadiene (**9**)

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 C_6H_8

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 cyclohexenyldiene, the corresponding 1,3-cyclohexadiene was obtained.⁴⁵

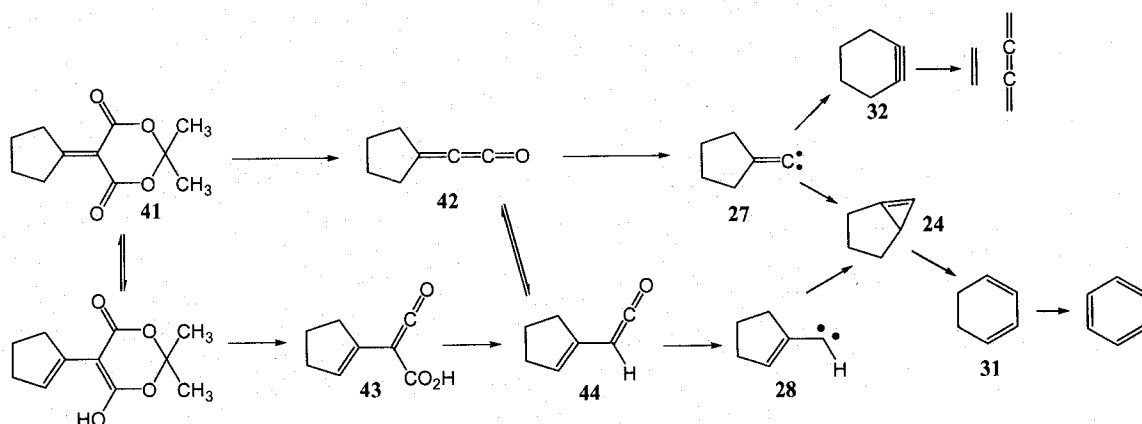
Cyclopentylidenecarbene (**27**) and cyclohexyne (**32**)

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.⁴² 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.

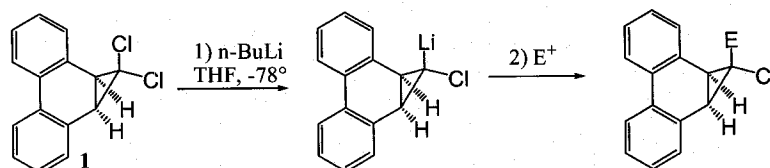
In review, mapping of this potential energy surface suggests that cyclopentenylcarbene (**28**) is energetically favored to form cyclopropene adduct **24** with further rearrangement to 1,3-cyclohexadiene (**31**) via carbene **30**. This result is supported by Wentrup⁵³ and Shevlin's⁴² experiments. The same rearrangement energetics were not observed for cyclobutenylcarbene (**17**); however, this result is consistent with Stierman and Johnson's result⁴⁸, 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

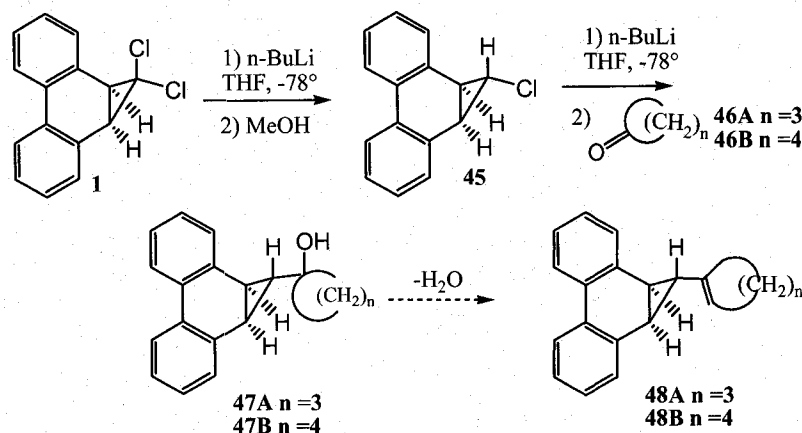
Dehydration Approach

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

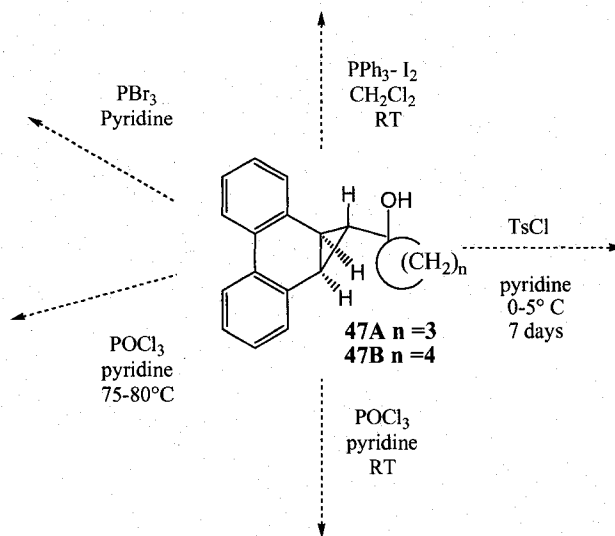
Kirchhoff showed that quenching with methanol resulted in protonation.⁶ While Hernandez and Lewis found quenching with a ketone yields an alcohol.^{9,10} A combination of this chemistry is the basis for our proposed route, shown in **Scheme 12**. The final step involves dehydration, which should be a novel approach to the desired cycloalkenylcarbene precursors (**47 A-B**).



Scheme 12: Dehydration Approach

Following a procedure by Kirchhoff⁶, 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

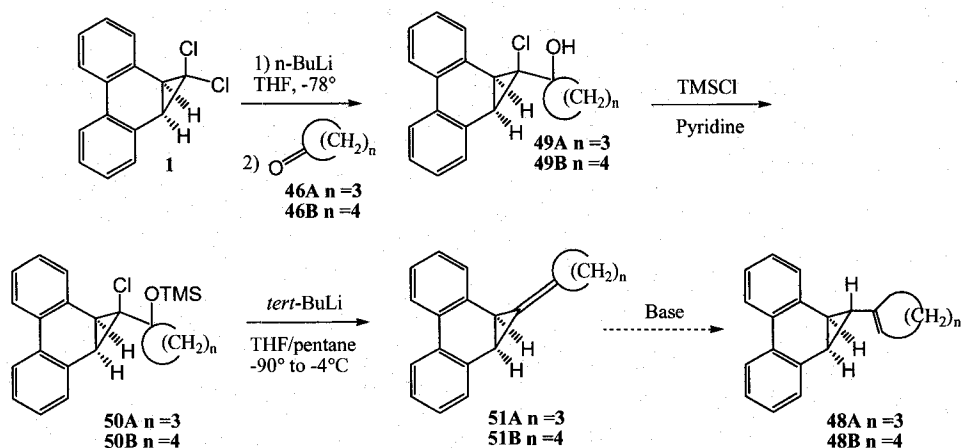
Initially, dehydration attempts were run using cyclobutanol **47A**. Multiple attempts were made to prepare **47A** by treatment with PBr_3 in pyridine⁵⁴; these proved to be unsuccessful and decomposition of the substrate was seen. $\text{PPh}_3\text{-I}_2$ was reported as an efficient and mild reagent for the dehydration of tertiary alcohols⁵⁵; however, reaction of it with **47A** 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 develop 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.⁵⁶ 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.⁵⁷ 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**).⁹ 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 TMSCl in pyridine furnishes the TMS-ether **50** and, in the last step, *tert*-butyllithium induces 1,2-elimination of TMSOLi to yield **51**.



Scheme 14: Base-Catalyzed Isomerization Approach

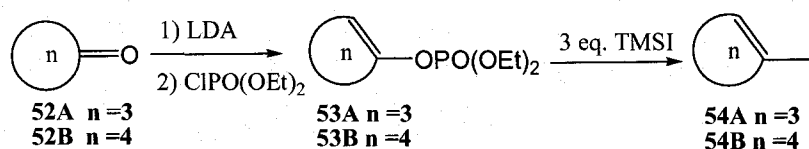
B3LYP/6-31G* computations suggest that isomerization to the desired cycloalkenyl precursors should be favored because the cyclobutenylcarbene precursor (**48A**) is downhill 7.7 kcal/mol and cyclopentenylcarbene precursor (**48B**) is downhill 10.1 kcal/mol. Treatment of **51** with base should catalyze 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.⁵⁶ In fact, Jones and Ruck found that treatment of **1** with a Gilman reagent, yielded a coupled product.⁵⁸

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**).⁵⁹

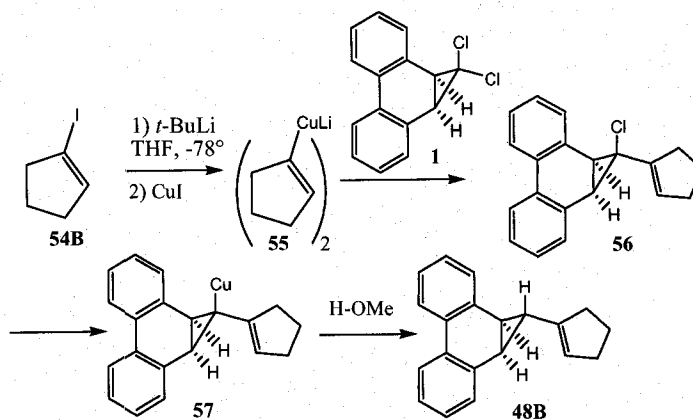


Scheme 15: Synthesis of Vinyl Iodides from Ketones

Lewis had previously attempted the synthesis of cyclopentenyl iodide (**54A**) via the hydrazone.¹⁰ This method was found to yield an abundance of side products such as the gem-iodide which were difficult to remove.⁶⁰ In contrast, this new route claims to produce minimal side products.

Following Weimer and Lee's route, cyclopentanone (**52B**) was treated sequentially with LDA⁶¹ 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. This

vinyl iodide (**54B**) was treated sequentially with *t*-BuLi⁶² and CuI⁶³ 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 CH₃OH 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 ¹H NMR spectrum.

This prompted a brief ^1H NMR computational investigation of the predicted vinyl ^1H 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 ^1H 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 1: Predicted Vinyl ^1H Shifts for Cyclopentenyl Halides

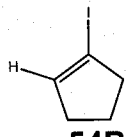
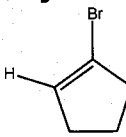
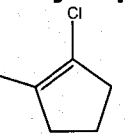
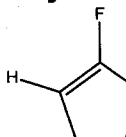
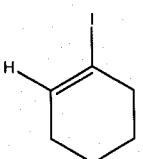
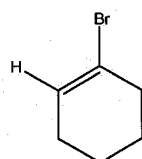
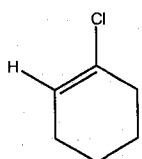
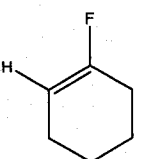
Vinyl ^1H Shift	 54B	 58	 59	 60
HF/3-21G*	5.97	5.75	5.59	4.72
B3LYP/ 3-21G*	5.49	5.27	5.90	4.28
MP2/3-21G*	6.20	5.80	5.83	4.96
Literature	6.02 ⁵⁹	5.74 ⁶⁴	5.55 ⁴	4.8 - 4.9 ⁶⁵

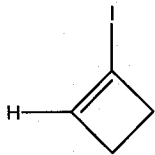
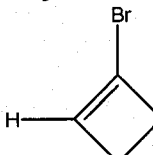
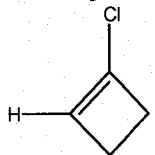
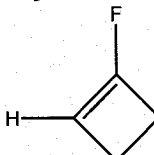
Table 2: Predicted Vinyl ^1H Shifts for Cyclohexenyl Halides

Vinyl ^1H Shift	 61	 62	 63	 64
HF/3-21G*	6.06	5.90	5.72	4.91
Literature	6.30 - 6.36 ⁶⁶	5.83 - 6.08 ⁶⁷	5.77 - 5.82 ⁶⁸	5.07 ⁶⁹

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 ¹H 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 ¹H 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 3: Predicted Vinyl ¹H Shifts for Cyclobutenyl Halides

Vinyl ¹ H Shift	 54A	 65	 66	 67
HF/3-21G*	6.61	6.25	5.99	4.72
Literature	Unreported	6.05 ¹⁹	5.82 ⁷⁰	4.67 – 4.74 ⁷⁰

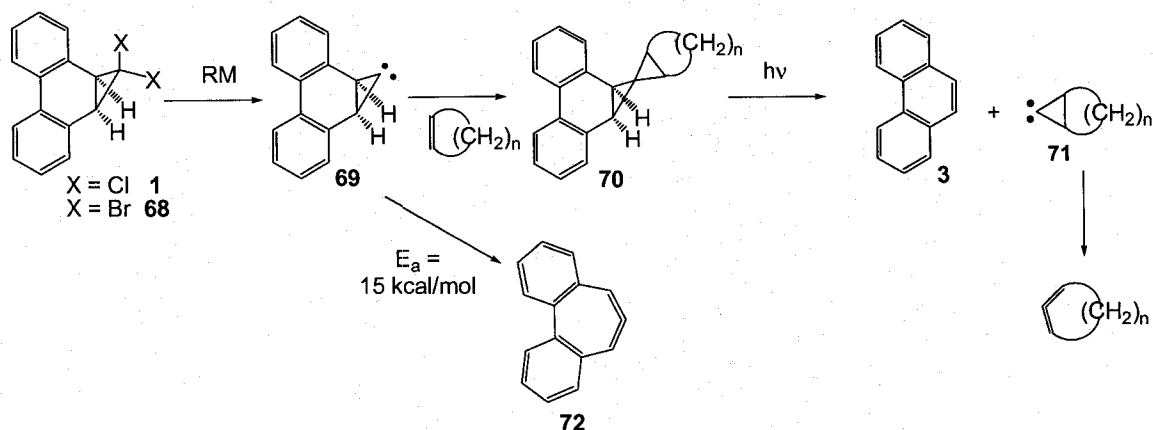
Following Weimer and Lee's route⁵⁹, cyclobutanone (**52A**) was treated sequentially with LDA and diethyl phosphonate to yield the vinyl phosphonate (**53A**) in 90% yield as a light yellow liquid. This was further treated with 3 eq. of TMSI. Inspection of the ¹H NMR spectrum showed that there was a signal at 6.51 ppm, which is within 0.3 ppm of the predicted vinyl ¹H shift. The ¹H 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

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 ^1H 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.

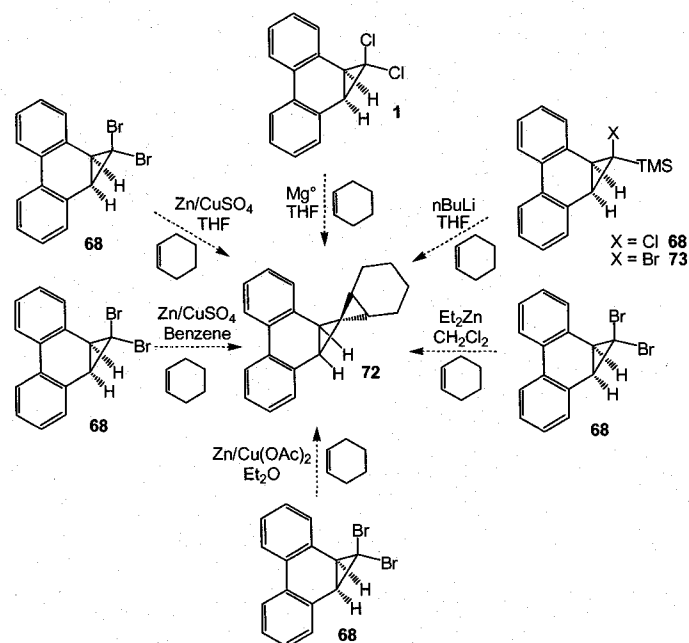


Scheme 17: Proposed Generation of Cyclopropylidenes

In some previous attempts, Hernandez⁹ and Kirchoff⁶ 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.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 material¹⁰ (**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^0 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.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. ^1H and ^{13}C NMR along with mp data⁷¹ helped to characterize **68**.



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.⁵⁶ 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.⁷² The carbenoid formation is generally more effective with gem-diiodo 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.⁷³ 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)₂.⁷² 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.⁷⁴ 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 ¹H, ¹³C 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_5H_6 and C_6H_8 potential energy surfaces. The predicted rearrangements and energetics for the interconversion of various C_5H_6 and C_6H_8 isomers are generally in good agreement with reported experimental results. On the C_5H_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_6H_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.⁷⁵ The idea of molecular strain was first introduced well over one hundred years ago by Adolf von Baeyer.⁷⁶ 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.⁷⁷ 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 homodesmotic 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.⁷⁸ With careful definition, isodesmotic reactions should give accurate predictions of specific types of functional group strain while homodesmotic 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.⁷⁹ 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.⁸⁰ Otherwise, only crude estimates have been reported for cyclic allenes.⁸¹ A 1985 MNDO study by our own group reported the bending angles and out-of-plane angles for the allene series.²¹ (see **Figure 3**) Kamigata used *ab initio* MO calculations to study the strain energy of cyclic bisallenenes with seven- to ten-membered rings.⁸² 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* calculations⁸³; 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 π bond between the two central carbons. The series of cyclic butatrienes has received less attention (**Figure 6**).

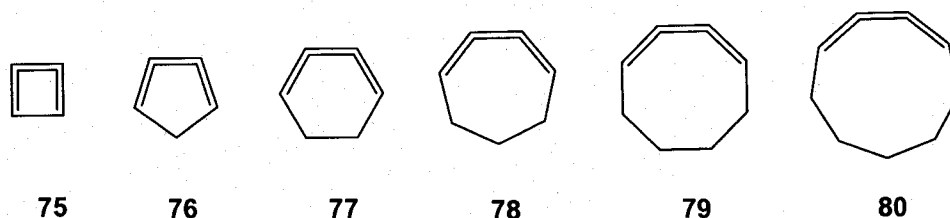


Figure 6: Cyclic Butatriene Series

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

(Figure 7).²¹ However there have been several other computational studies on cyclic butatrienes.^{47,86}

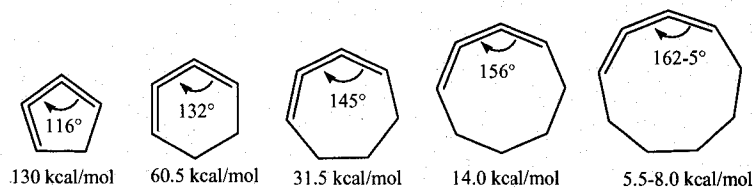


Figure 7: MNDO Bending Angles and Strain Energies for Cyclic Butatrienes

Accurate predictions for strain in the cyclic butatriene series are desirable. Daoust had used MP4SDTQ/6-31G**/MP2(FC)/6-31G* calculations⁸³; once again, better levels of theory may provide more reliable predictions.

Statement of Goals

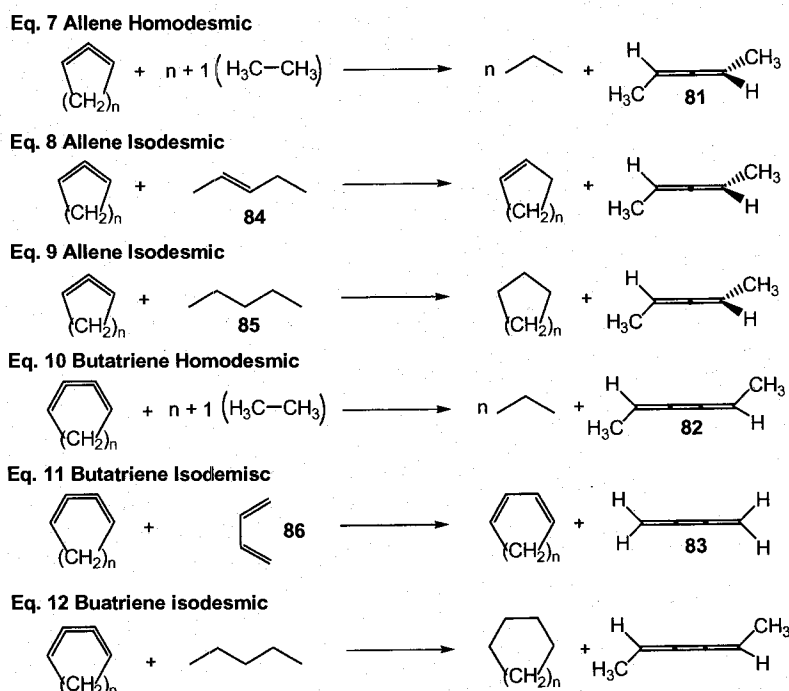
This project is focused on the computational investigations of strain estimates for the cyclic allenes and cyclic butatriene series which will include the four- to nine-membered rings. The isodesmic and homodesmic schemes developed by Daoust will be utilized but with DFT energetics.

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.⁵⁰ Further geometry optimization was carried out with Gaussian 03⁵¹ 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 is 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.



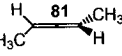















Another approach we developed, referred to as “fragment strain”, provides estimates for allene and butatriene strain. We isolate the allene or butatriene fragment from the ring by simply deleting the other atoms; the remaining C₃H₄ or C₄H₄ moiety is subjected to a single point DFT calculation. A similar 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 4: Homodesmic Reaction Energies for Cyclic Allenes

		ΔH_R	
		B3LYP/ 6-311+G**	MP4/ 6-31G**// MP2/ 6-31G*
Eq. 13	 + 2H ₃ C-CH ₃ →  + 	-89.87	-99.2
Eq. 14	 + 3H ₃ C-CH ₃ → 2  + 	-55.29	-60.6
Eq. 15	 + 4H ₃ C-CH ₃ → 3  + 	-32.05	-32.1
Eq. 16	 + 5H ₃ C-CH ₃ → 4  + 	-20.49	
Eq. 17	 + 6H ₃ C-CH ₃ → 5  + 	-11.91	
Eq. 18	 + 7H ₃ C-CH ₃ → 6  + 	-10.95	

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 be 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

		ΔH_R		B3LYP/ 6-311+G**	MP4/6-31G** MP2/6-31G*
Eq. 19				-61.49	-66.1
Eq. 20				-66.74	
Eq. 21				-51.09	-54.0
Eq. 22				-50.18	
Eq. 23				-31.58	-32.6
Eq. 24				-31.81	
Eq. 25				-14.26	
Eq. 26				-13.48	
Eq. 27				-1.80	
Eq. 28				-0.31	
Eq. 29				0.88	
Eq. 30				4.52	

Table 6: Fragment Strain Energies for Cyclic Allenes


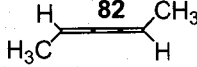










Structure	Fragment Strain (kcal/mol)
8	62.8
9	33.2
10	14.9
11	5.0
12	1.7

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, ΔH_R , increases dramatically as the ring size decreases. Our DFT results are in good agreement with Daoust's MP2 predictions.

Table 7: Homodesmic Reaction Energies for Cyclic Butatrienes

		ΔH_R	
		B3LYP/ 6-311+G**	MP4/ 6-31G** MP2/ 6-31G*
Eq. 31	 + H ₃ C-CH ₃ →  + 82 -187.68		
Eq. 32	 + 2 H ₃ C-CH ₃ →  + 82 -84.42 -79.0		
Eq. 33	 + 3 H ₃ C-CH ₃ → 2  + 82 -51.75 -49.4		
Eq. 34	 + 4 H ₃ C-CH ₃ → 3  + 82 -32.07		
Eq. 35	 + 5 H ₃ C-CH ₃ → 4  + 82 -29.67		
Eq. 36	 + 6 H ₃ C-CH ₃ → 5  + 82 -14.80		

Isodesmic reactions predict the in-plane π 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

		ΔH_R	
		B3LYP/ 6-311+G**	MP4/ 6-31G**// MP2/ 6-31G*
Eq. 37		-114.78	
Eq. 38		-164.50	
Eq. 39		-79.23	-74.0
Eq. 40		-79.26	
Eq. 41		-47.76	-46.8
Eq. 42		-51.40	
Eq. 43		-26.31	
Eq. 44		-25.00	
Eq. 45		-20.54	
Eq. 46		-17.83	
Eq. 47		-0.51	
Eq. 48		0.73	

Table 9: Fragment Strain Energies for Cyclic Butatrienes

Structure	Fragment Strain (kcal/mol)
77	50.3
78	26.9
79	16.4
80	4.8

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 intermediates⁹; 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 be 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 solution¹³ 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-Cyclononatriene⁴² (**80**) is the only isolable compound in this butatriene series with a predicted strain value of 15 kcal/mol.

CHAPTER III

NEW CHEMISTRY OF OZONE: THE TETROXOLANE CONNECTION

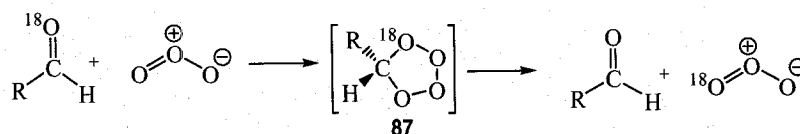
Introduction

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.⁸⁹ Alkene ozonolysis has been largely studied for its role in the atmosphere and organic synthesis.^{90,91} Known chemical routes to ozone are unexpectedly sparse. In atmospheric chemistry, ozone is produced by photolysis of O_2 and NO_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.⁵⁶

Recent reports suggest that ozone may be generated as part of the human immune system.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.⁹⁴ Keinan and coworkers speculated that inflammation in asthma may also involve ozone formation by white blood cells.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 biogenesis 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.^{95,96} They reported that reaction of ¹⁸O 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.

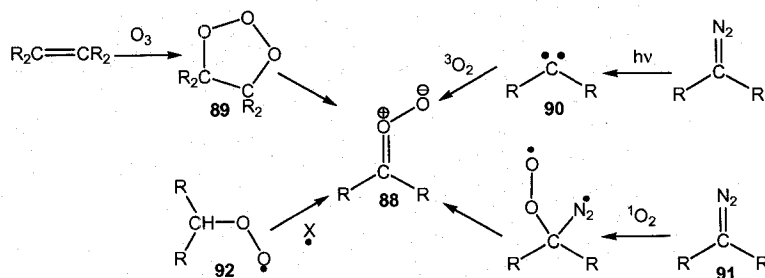


Scheme 20: ¹⁸O Label Exchange of Isobutyraldehyde and Ozone

Tetroxolanes have received surprisingly little attention; although their sulfur analog, tetrathiolanes, have been isolated and examined by x-ray crystallography.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.⁹⁷ A related study examined the lowest energy isomers of the oxygen-rich carbonyl series, CO_n (n = 3-8).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.⁹⁹ Tetroxanes (or tetraoxanes), have been shown to exhibit anti-malarial activity and are easily prepared by the dimerization of carbonyl oxides.^{100,101}

Carbonyl oxides (**88**) are another oxygenated species which have received a great deal of attention.¹⁰² They are known to have diradical character but often are written in a zwitterionic form¹⁰³ (**Scheme 21**). Carbonyl oxides (**88**) or “Criegee intermediates” are key intermediates in the ozonolysis of alkenes.⁹¹ 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 $^3\text{O}_2$ or by the oxidation of a diazo compound (**91**) with $^1\text{O}_2$; these reactions have been utilized in low-temperature matrices.¹⁰⁴ 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.¹⁰⁵



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 ^{18}O chemistry by including several ketones and aldehydes.

Computational Methods

For each of the stationary points investigated, geometry optimizations were performed using Gaussian 03⁵¹ 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 model¹⁰⁶ combines the design of the CBS-Q energy calculation¹⁰⁷ with B3LYP DFT optimized geometries and frequencies. This method requires the following calculations:

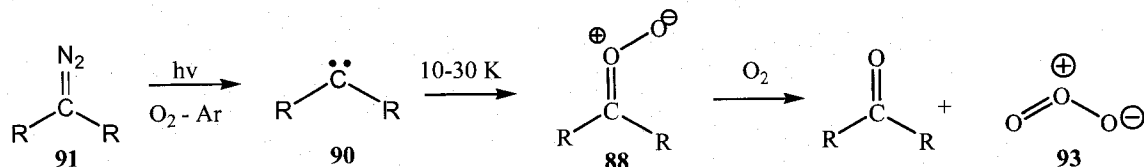
- (i) B3LYP/6-311+g(d,p) geometry optimization and frequencies
- (ii) CCSD(T)/6-31+G(d') energy
- (iii) MP4(SDQ)/CBSB4 energy
- (iv) MP2/CBSB3 energy and CBS extrapolation

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.¹⁰⁸ 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 04⁵⁰ at B3LYP/6-31G* level of theory. All energies are reported in kcal/mol.

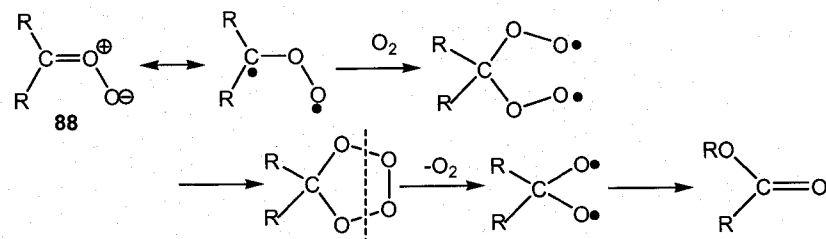
Computational Results and Discussion

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 chemistry¹⁰⁹ but the tetroxolane intermediate is also possible (**Scheme 22**).



Scheme 22: Carbonyl Oxide Formation in a Matrix

Sawaki reported on the mechanism of ester formation where he proposed that the addition of O₂ to a carbonyl oxide may generate a tetroxolane. This can eliminate O₂ to afford a biradical and then the ester (**Scheme 23**).¹¹⁰

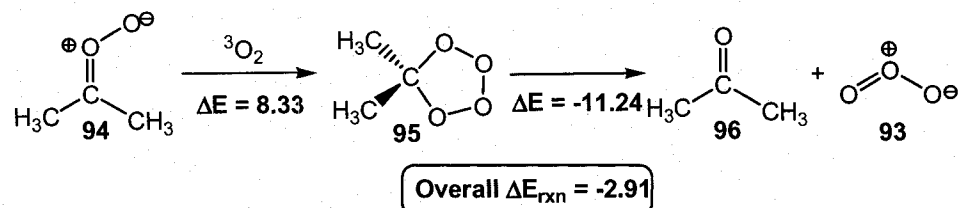


Scheme 23: Mechanism of Ester Formation from Carbonyl Oxide

This mechanism was consistent with ¹⁸O-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 ΔE_{rxn} of -2.9 kcal/mol (**Scheme 24**). This result prompted us to undertake a complete study of the reaction pathway.

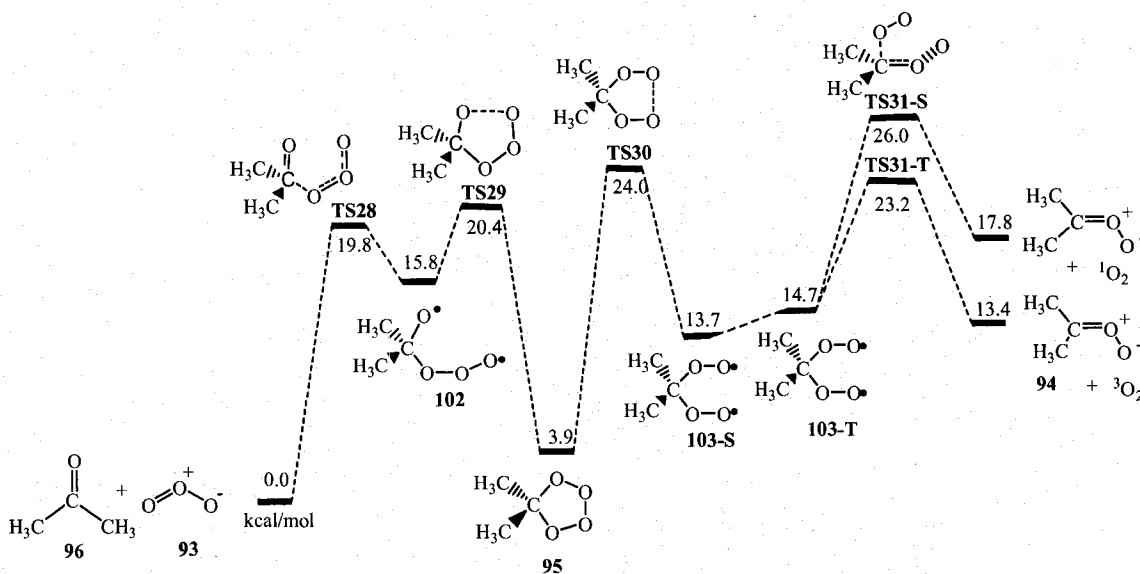


Scheme 24: B3LYP/6-31G* Predicted Energetics for Ozone Formation

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.¹¹² As an alternative, CBS-QB3 methods¹⁰⁶ might afford more accurate predictions for these species and transition states, with little penalty in computational speed.¹¹² It has been suggested that this method may overcompensate for the effects of spin contamination in open-shell species.¹¹³ Recent studies also suggested that CBS-QB3 methods may provide greater accuracy than single-point CCSD(T) calculations.^{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 10: Comparison of Formaldehyde + Ozone Surface Energetics

Structure	B3LYP/ 6-311+G(d,p)	CCSD(T)// 6-311+G(d,p)	CBS-QB3
97 + 93	0.0	0.0	0.0
TS24	11.1	19.0	21.8
98	2.8	9.6	9.2
TS25	15.2	22.5	14.3
99	7.6	8.6	3.5
TS26	11.1	24.0	20.0
100-S	1.5	7.6	12.5
100-T	1.3	8.0	10.9
TS27-T	11.7	25.6	24.2
101 + ³O₂	6.7	14.5	16.4

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 be 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 3O_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

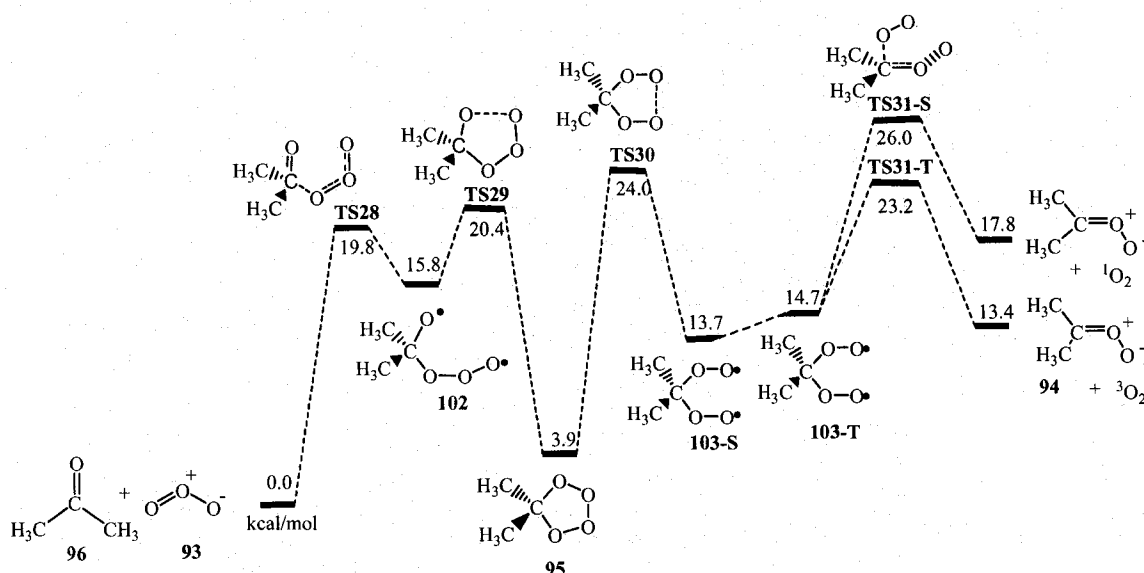
We next explored the same pathways for acetone (**96**) with ozone (**93**). Once again, CBS-QB3 methods are suggested to provide the most accurate depiction of this surface. A comparison to DFT methods is provided in **Table 11**. CCSD(T) methods were not used as they were found to be too computationally demanding for this surface. However, BH&HLYP was employed for comparison. This functional has been shown to provide accurate barrier heights¹¹⁵ while paralleling those predicted by CBS-QB3 methods.¹¹⁶

Table 11: Comparison of Acetone + Ozone Surface Energetics

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

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 ~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.

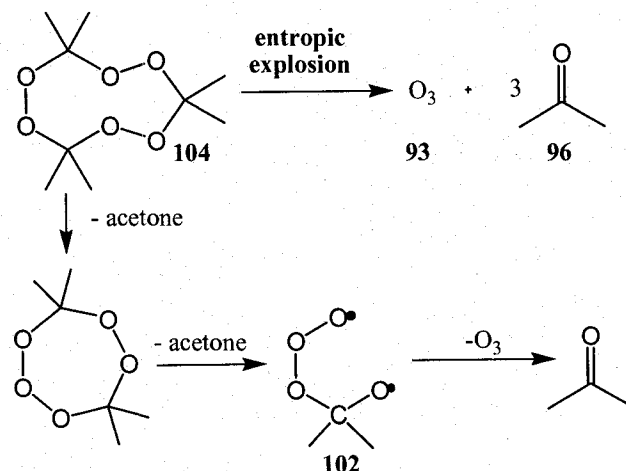


Scheme 26: CBS-QB3 Energetics of Acetone + Ozone

The reaction of acetone carbonyl oxide (**94**) and $^1\text{O}_2$ was also investigated. Addition of $^1\text{O}_2$ to **94** was found to be higher in energy than the triplet route, as expected. However, CBS-QB3 methods predict $^1\text{O}_2$ 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

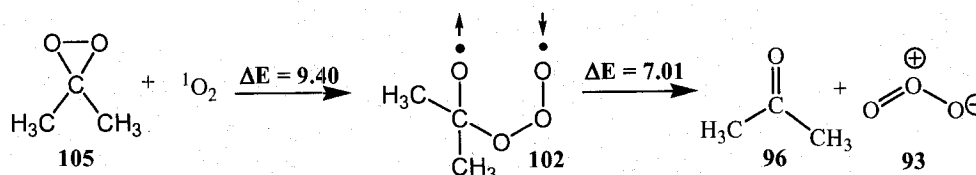


Scheme 27: Decomposition of TATP

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**).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.¹¹⁹ We found that addition

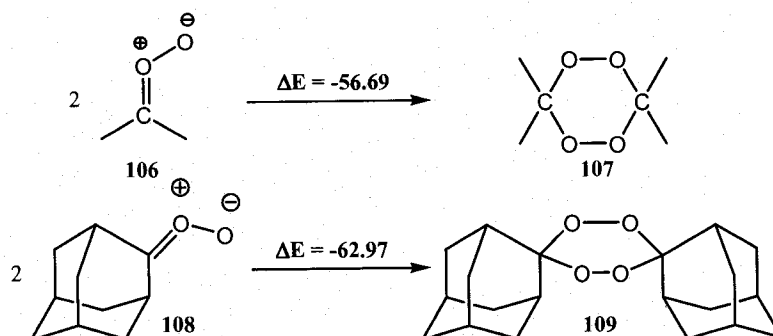
of singlet O_2 to **105** is not predicted to be a likely route to ozone because of its endothermic energetics (**Scheme 28**).



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.



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

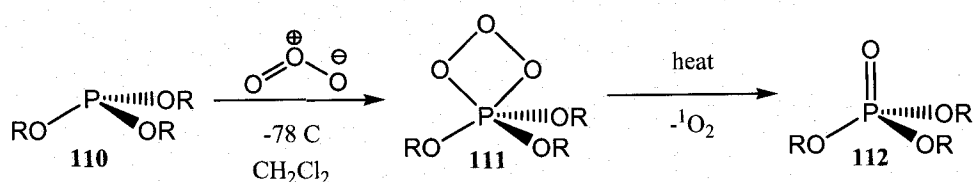
Heteroatom Chemistry

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.

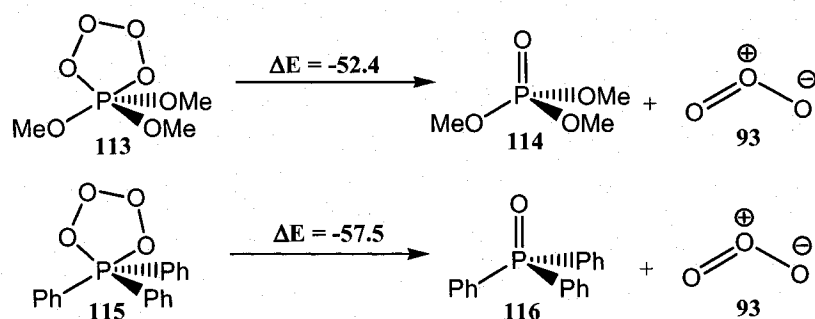
We have used computations to explore possible candidate structures.

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

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**).

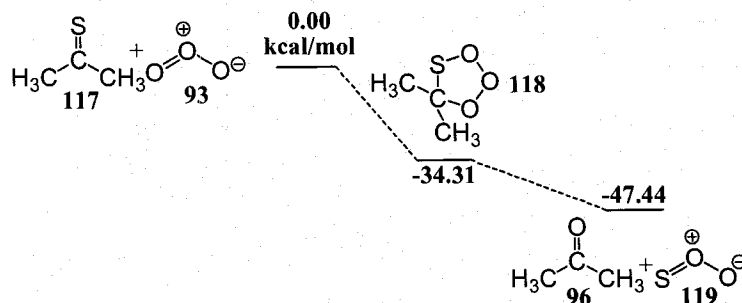


Scheme 31 B3LYP/6-31G* Energetics for Decomposition of a Phosphotetroxolane

Sulfur chemistry may provide a route to a tetroxolane intermediate:

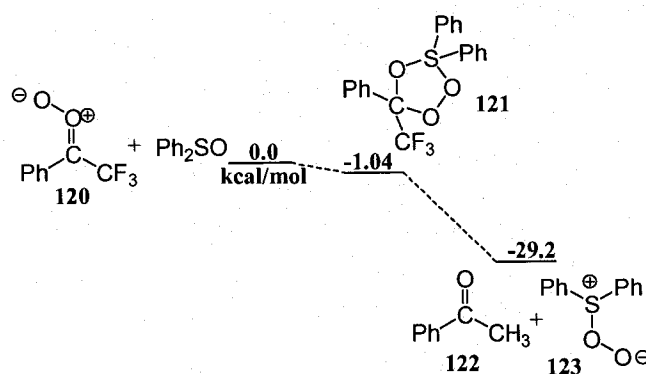
Zwanenburg and Carlsen reported that unhindered thioketones (**117**) react with

O₃ to give rise to the corresponding ketone (**96**), perhaps through a thiatetroxolane intermediate (**118**) (**Scheme 32**).^{121,122} Our calculations support the observed formation of thiozone (**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

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



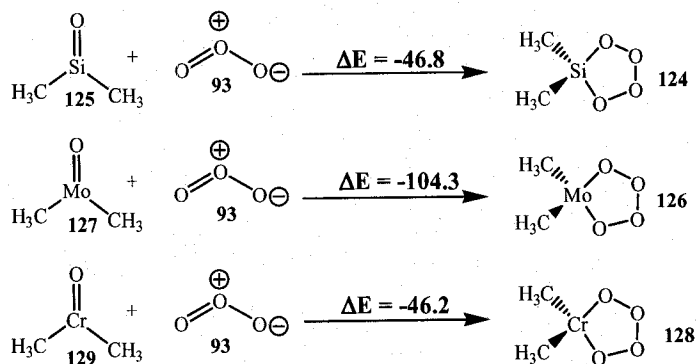
Scheme 33: B3LYP/6-31G* Energetics for Sulfurane Intermediate

The work of Zwanenburg¹²², Carlsen¹²¹ and Sawaki¹²³ 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 O₃ were investigated. The tetroxolane type intermediates were not found as energy minima on this surface because they easily dissociate to O₂ and either NO₂ or SO₂. 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.



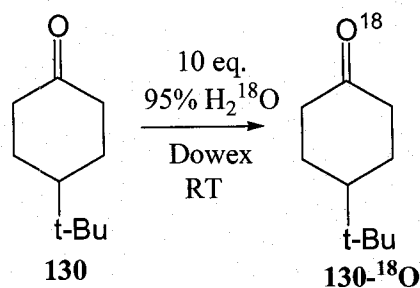
Scheme 34: B3LYP/6-31G* Energetics of Metal Oxides

Experimental Results and Discussion

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 ¹⁸O 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 ¹⁸O label was easily accomplished by reaction of *t*-butyl cyclohexanone (**130**) with 10 eq. 95% H₂¹⁸O 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.



Scheme 35: ¹⁸O Labeling of t-Butyl Cyclohexanone

We wanted to determine the best spectroscopic method for analyzing the ¹⁸O content in our compounds. Klopman chose GC-MS analysis but there are also reports of following aldehyde and ketone ¹⁸O labeling reactions by IR¹²⁴ and ¹³C NMR spectroscopy.¹²⁵ IR spectroscopy with ¹⁸O labeled ketone **130** was not able to give quantitative results, but 2 overlapping carbonyl stretches could be seen. ¹³C NMR spectroscopy gave rise to 2 carbonyl C shifts at 212.59 (¹⁶O=C) and 212.54 (¹⁸O=C) ppm but it was difficult to quantify the %¹⁸O since they were poorly resolved. GC-MS analysis provided the best quantitative results typically showing 62-74% ¹⁸O. 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 %¹⁸O was calculated. An error analysis study using the HP GC/MS showed reproducibility of ±1.3% ¹⁸O 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.

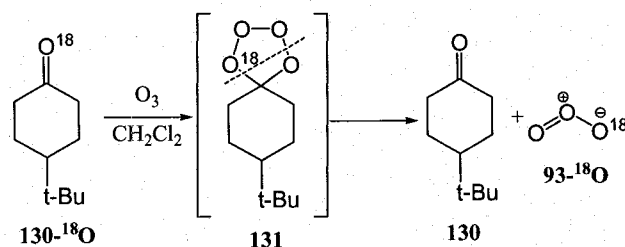
This chemistry is new to our group and the experimental conditions needed to be carefully determined. As previously stated, we did not expect to observe an instantaneous exchange. This is unlike Klopman's results where he reported a 22% loss of label at -78°C after 1 min. Our experiments were carried 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 CH_2Cl_2 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 .¹²⁶ 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.^{122,126} 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 CH_2Cl_2 at -78°C , warmed to 0°C and then immediately treated with a labeled ketone in CH_2Cl_2 , 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 %¹⁸O, 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**).

$$\% \text{ Loss Label} = \left(1 - \frac{\%^{18}\text{O at } t = x}{\%^{18}\text{O at } t = 0} \right) * 100 \quad (\text{Eq. 49})$$

With the methodology worked out, we began to study the exchange reaction with ozone (**93**). A solution of ¹⁸O *t*-butyl cyclohexanone (**130-¹⁸O**) was added to the saturated ozone solution and the reaction monitored by GC-MS by repeatedly injecting the solution over a 1½ 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 CH₂Cl₂.¹²²



Scheme 36: Label Exchange with *t*-Butyl Cyclohexanone

Approximately one minute passed between mixing and injection of a one- μ L sample into the GC mass spectrometer. Initially there is little label loss, however, after 1922 seconds the % ¹⁸O 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 (**130-¹⁸O**) and ozone (**93**), which helps to provide evidence for the tetroxolane intermediate (**131**).

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

Time (sec)	% ¹⁸ O	% Label Loss
0	69.2	-
60	65.9	4.8
1922	23.1	66.0
3482	20.8	70.0
5042	21.9	68.3

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-¹⁸O (**130-¹⁸O**) was freshly prepared and subjected to an error analysis study. This showed that the Thermo GC/MS results were reproducible within $\pm 2.0\%$ ¹⁸O. Upon repeating the ozone exchange experiment, significant label loss was once again observed (**Table 13**). The %¹⁸O label progressively dropped; however, not as quickly as seen in the previous results.

Table 13: Label Exchange of ^{18}O *t*-Butyl Cyclohexanone (130- ^{18}O) + Ozone (93), Monitored by Thermo GC/MS

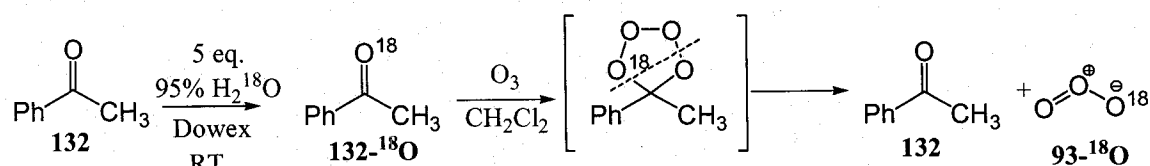
Time (sec)	% ^{18}O	% Label Loss
0	58.1	-
60	52.9	8.9
1290	39.0	32.9
2780	35.0	39.7
4202	32.7	43.7

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 O_2 is also assumed to present in solution, since the ozonizer does not achieve 100% conversion. In order to verify that it is indeed O_3 and not O_2 reacting in solution, we developed another control experiment. The exchange experiment was run by treating the *t*-butyl cyclohexanone- ^{18}O (**130- ^{18}O**) with an oxygen solution. This was prepared under identical conditions as the O_3 solution but instead, the O_2 line was directly bubbled into dry solvent. Analysis of this reaction by GC/MS showed no change in % ^{18}O , within experimental error, and shows that O_3 is the active oxygen species.

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



Scheme 37: ^{18}O Labeling and Exchange Experiment with Acetophenone

This sample was stored in the refrigerator under N_2 , 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.

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

Time (sec)	% ^{18}O	% Label Loss
0	56.7	-
60	51.4	9
1371	50.4	11
2815	48.6	14
4282	42.6	25

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 15: Competition Experiment of ^{18}O *t*-Butyl Cyclohexanone (130- ^{18}O) and ^{18}O Acetophenone (132- ^{18}O)

Time (sec)	<i>t</i> -bu cyclohexanone		acetophenone	
	% ^{18}O	% Label Loss	% ^{18}O	% Label Loss
0	60.0	-	41.2	-
60	52.3	12.8	40.4	1.9
1462	49.1	18.2	39.8	3.4
2202	45.6	24.0	39.5	4.1
3509	45.7	24.0	36.9	10.4

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_2Cl_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

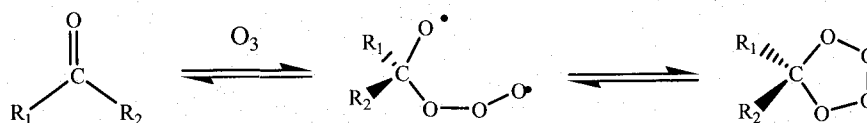
hours only 12.6% ^{18}O was observed and even after 24 hours there was no further change. Water is not miscible with CH_2Cl_2 and the reaction was vigorously stirred to ensure proper mixing of these layers. The solvent was changed to THF to increase the solubility. However, after 6 hours the carbonyl 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 16: Label Exchange of ^{18}O -Benzophenone ($133\text{-}^{18}\text{O}$) + Ozone (93)

Time (sec)	% ^{18}O	% Label Loss
0	44.5	-
60	41.9	6
1327	39.8	11
2757	38.3	14
4318	34.6	22

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**).

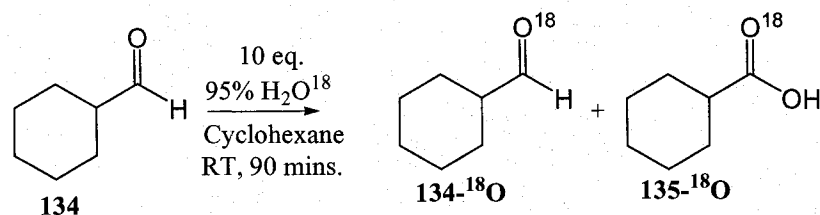


Scheme 38: Proposed Mechanism for Ozone Exchange with Ketone

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^{nd} order kinetics.

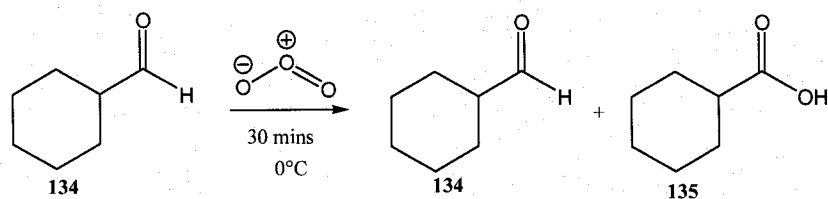
Aldehyde Chemistry

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**).



Scheme 39: ^{18}O Labeling of Cyclohexanecarbaldehyde

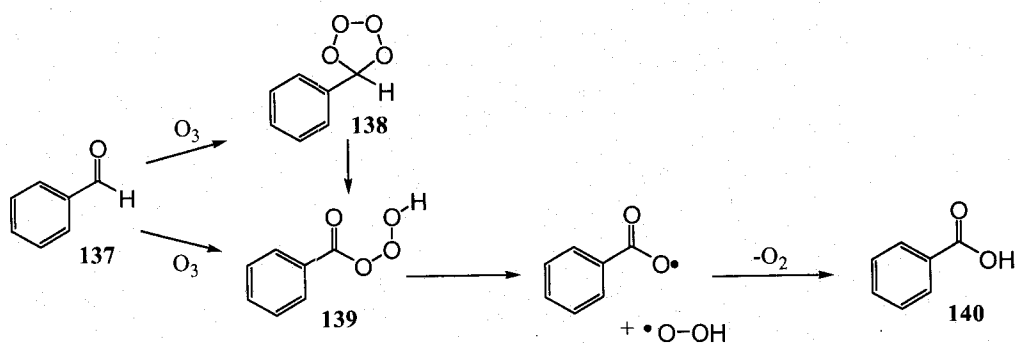
This unanticipated result was supported by both ^{13}C NMR spectroscopy and GC-MS which indicated a 23 to 3 ratio of carboxylic acid to aldehyde. Both species contained a label, $^{135}\text{-}^{18}\text{O}$ was 59.4% labeled while $^{134}\text{-}^{18}\text{O}$ was only 34.3% labeled. Oxidation of an 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 $\text{O}_3\text{-O}_2$ 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

Aldehyde oxidation was not observed by Klopman.^{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**).^{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**).¹²⁷



Scheme 41: Reported Mechanism for Aldehyde Oxidation

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 σ values supported these proposed mechanisms. Huisgen speculated that the formation of tetroxolanes are not energetically favored.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 ¹⁸O label will exchange upon reaction of a ketone with ozone. Control experiments showed that O₃, not O₂, 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 ¹⁸O₂ can exchange with carbonyl oxides. This will require preparation of stable carbonyl oxides.¹²⁹

CHAPTER IV

EXPERIMENTAL

General Experimental

Instrumentation

^1H 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 $(\text{CH}_3)_4\text{Si}$ 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 $1\mu\text{L}$ 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 O_2 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 intelligent 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 (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2). 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 (CDCl_3), benzene-d₆ (C_6D_6), and acetone-d₆ ($\text{C}_3\text{D}_6\text{O}$).

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.⁹ 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 $\frac{1}{2}$ 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 (MgSO_4), 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 (CDCl_3) 8.03-8.05 (d, 2H), 7.30-7.41 (m, 6H), 2.96 (d, 2H), 3.74 (t, 1H). ^{13}C NMR (500 MHz) δ ppm (CDCl_3) 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 (MgSO_4), filtered and concentrated. Radial chromatography (50% methylene chloride in hexane) afforded a yellow solid (115 mg, 77.2%). ^1H NMR (400 MHz) δ ppm (CDCl_3) 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). ^{13}C 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. ¹H NMR (400 MHz) δ ppm (CDCl₃) 5.26 (m, 1H, vinyl), 4.15-4.19 (q, 4H), 2.46 (m, 2H), 2.34 (m, 2H), 1.93 (q, 2H), 1.34-1.38 (m, 6H). ¹³C NMR (400 MHz) δ ppm (CDCl₃) 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). ¹H NMR (400 MHz) δ ppm (CDCl₃) 6.03 (s, 1H, vinyl), 2.50 (m, 2H), 2.02 (m, 2H), 1.80 (m, 2H). ¹³C NMR (400 MHz) δ ppm (CDCl₃) 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°C⁷¹). ¹H NMR (400

MHz) δ ppm (CDCl₃) 8.01-7.98 (d, 2H), 7.50-7.31 (m, 12H), 3.50 (s, 2H). ¹³C NMR (400 MHz) δ ppm (CDCl₃) 131.42, 131.13, 129.71, 128.44, 128.31, 123.24, 37.58, 31.07.

Preparation of zinc/copper couple with CuSO₄⁷²

A finely powdered mixture of CuSO₄·5H₂O and Zn dust (1:10 molar ratio) were stirred magnetically under N₂. 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 CuSO₄

The round bottom flask was fitted with a condenser, addition funnel and N₂ inlet and purged with N₂ for 15 minutes. 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) 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 NaHCO₃ (1 x 5 mL), dried (MgSO₄), 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°C⁷¹). ¹H NMR (400 MHz) δ ppm

(CDCl₃) 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). ¹³C NMR (400 MHz) δ ppm (CDCl₃) 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)₂⁷⁴

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-ylidene (72) by Zn/Cu couple with CuOAc₂

The round bottom flask was fit with a condenser, addition funnel and N₂ inlet and purged with N₂ 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 CH₂Cl₂ (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 (MgSO_4), 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 Et_2Zn

In a 50-mL three-necked round bottom flask equipped with a stir bar, addition funnel, condenser and N_2 inlet, dry CH_2Cl_2 (3 mL) and cyclohexene (50 mg, filtered through silica) were added and the system was purged with N_2 . 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 CH_2Cl_2 (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 CH_2Cl_2 (10 mL) and quenched with saturated NaHCO_3 (3 mL). The organic layer was separated, washed with saturated NH_4Cl (2 x 5 mL), dried (MgSO_4), 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 (CDCl_3) 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% H_2^{18}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 ($^{16}\text{O}=\text{C}$), 212.54 ($^{18}\text{O}=\text{C}$), 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% H_2^{18}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.

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: t_R 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 (**130-¹⁸O**)

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 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 ¹⁸O-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% H₂¹⁸O (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% ¹⁸O. The solution was dried (MgSO₄), 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, ¹⁶O parent ion), (121.95, 102, ¹⁸O parent ion).

Ozone reaction with acetophenone (132)

Acetophenone (10 mg) was dissolved in CH_2Cl_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_2Cl_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 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 CH_2Cl_2 (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 CH_2Cl_2 (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.

O_3 reaction with *t*-butyl cyclohexanone ($^{130}\text{-}^{18}\text{O}$) and acetophenone ($^{132}\text{-}^{18}\text{O}$)

^{18}O *t*-butyl cyclohexanone (10 mg, 0.66 mmol) and ^{18}O -acetophenone (8 mg, 0.66 mmol) were dissolved in dry CH_2Cl_2 (5 mL), cooled to 0°C in an ice bath and injected in the GC-MS for analysis as a standard. Dry CH_2Cl_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 ^{18}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}O parent ion), (156.29, 25.0, ^{18}O parent ion); $t = 60$ sec (154.16, 16.4, ^{16}O), (156.18, 18.0, ^{18}O); $t = 1462$ sec, (154.15, 15.0, ^{16}O), (156.19, 14.5, ^{18}O); $t = 2202$ sec, (154.15, 15.5, ^{16}O), (156.21, 13.0, ^{18}O); $t = 3509$ sec (154.12, 14.5, ^{16}O), (156.17, 12.3, ^{18}O). Acetophenone t_{R} 4.5-4.7 min; $t = 0$ sec, (m/z, abundance): (120.14, 43.5, ^{16}O parent ion), (122.07, 30.5, ^{18}O parent ion); $t = 60$ sec, (119.98, 54.5, ^{16}O); (121.97, 37.0, ^{18}O); $t = 1462$ min, (119.97, 49.5, ^{16}O); (121.96, 33.0, ^{18}O); $t = 1462$ min, (119.98, 49.0, ^{16}O), (121.96, 32.0, ^{18}O); $t = 3509$ sec, (119.88, 89.0, ^{16}O), (121.90, 52.0, ^{18}O).

Synthesis of ^{18}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% H_2^{18}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}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_2Cl_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_2Cl_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_2Cl_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_2Cl_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 ($^{16}\text{O}=\text{C}$), 205.04 ($^{18}\text{O}=\text{C}$), 49.98, 26.05, 25.09; cyclohexanecarboxylic acid 182.81 ($^{16}\text{O}=\text{C}$) 182.79 ($^{18}\text{O}=\text{C}$), 43.10, 28.90, 25.83, 25.46.

Control ozone reaction with cyclohexanone carbaldehyde (134)

Dry CH_2Cl_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_2Cl_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 CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_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 . Freshly distilled isobutyraldehyde (10 mg) was dissolved in dry CH_2Cl_2 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. ^{13}C NMR (500 MHz) δ ppm (CDCl_3) 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.

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APPENDICES

APPENDIX A: Computational Data

Chapter I

Structure	B3LYP/ 6-311G+(d,p)	E + ZPVE	Free Energy
C ₅ carbene syn (17-syn)	-194.004185	-193.916235	-193.943691
C ₅ carbene anti (17-anti)	-194.004262	-193.916721	-193.944318
C ₅ methylene cyclopropane insertion (TS1)	-193.931339	-193.846595	-193.873471
C ₅ methylene cyclopropane (14)	-194.022361	-193.932036	-193.958939
1,2-shift to 1,2- cyclopentadiene (TS3)	-193.993012	-193.905031	-193.932264
1,2-cyclopentadiene (8)	-194.050440	-193.96112	-193.987625
divinylcarbene closure (TS4)	-194.012301	-193.924097	-193.950953
divinylcarbene (22)	-193.036113	-193.948122	-193.976425
C ₅ carbene rearr to acetylene (TS2)	-193.984890	-193.898464	-193.925795
cyclopropylacetylene (19)	-194.094829	-194.004420	-193.032059
C ₅ cyclopropene closure (TS5)	-193.980217	-193.893267	-193.920177
C ₅ cyclopropene (13)	-194.010603	-193.920853	-193.947753
C ₅ cyclopropene open to carbene (TS6)	-193.009513	-193.920520	-193.947191

cyclopentenylidene (20)	-194.058457	-193.968627	-193.996219
1,2 shift to 1,3-cyclopentadiene (TS7)	-194.038813	-193.951747	-193.978344
1,3-cyclopentadiene (21)	-194.156236	-194.064117	-194.090716
C ₅ cyclopropene opening to vinylidene (TS8)	-193.9520769	-193.866223	-193.893014
cyclobutylidene (16)	-194.0194562	-193.929572	-193.957843
cyclopentyne rear (TS9)	-194.013834	-193.923959	-193.952446
C ₅ 1,2-H migration to carbene (TS10)	-193.9308893	-193.845400	-193.872132
C ₆ carbene syn (28-syn)	-233.368936	-233.250487	-233.279397
C ₆ carbene anti (28-anti)	-233.368664	-233.250522	-233.279494
C ₆ cyclopropane insertion (TS11)	-233.316782	-233.201769	-233.229882
C ₆ methylene cyclopropane (25)	-233.402153	-233.281849	-233.309949
1,2-shift to 1,2-cyclohexadiene A (TS12)	-233.3458318	-233.228273	-233.256629
1,2-cyclohexadiene (9)	-233.414504	-233.294095	-233.322810
1,3,5-hexatriene	-233.464719	-233.346354	-233.375978

Ring Closure (TS19)	-233.363406	-233.246916	-233.274559
Cyclobutylacetylene (29)	-233.4214987	-233.301835	-233.331149
C ₆ cyclopropene closure (TS13)	-233.3604849	-233.242984	-233.271782
C ₆ cyclopropene (24)	-233.396621	-233.276173	-233.304627
C ₆ cyclopropene open to carbene (TS14)	-233.3670223	-233.248326	-233.276490
Cyclohexenylidene (30)	-233.384018	-233.264744	-233.293223
1,2-shift to 1,2-cyclohexadiene B (TS16)	-233.305167	-233.191218	-233.220207
1,2 shift to 1,3-cyclohexadiene (TS15)	-233.364680	-233.248091	-233.276318
1,3-cyclohexadiene (31)	-233.483877	-233.362064	-233.389644
C ₆ cyclopropene opening to vinylidene (TS20)	-233.3357144	-233.219473	-233.248324
cyclopentylidene (27)	-233.3781816	-233.258223	-233.288020
cyclohexyne rear (TS21)	-233.362224	-233.242734	-233.271480
cyclohexyne (32)	-233.399012	-233.277966	-233.305851
C ₆ 1,2-H migration to carbene (TS22)	-233.3015034	-233.186245	-233.214929

Chapter II

Structure	B3LYP/ 6-311G+(d,p)	ZPVE	E + ZPVE
cyclobutene	-156.017281	0.086020	-155.931261
cyclopentene	-195.381944	0.116189	-195.265755
cyclohexene	-234.713220	0.145561	-234.567659
cycloheptene	-272.028757	0.174324	-273.854433
<i>cis</i> -cyclooctene	-313.347559	0.203359	-313.144201
(<i>Z</i>)-cyclononene	-352.691959	0.231776	-352.437419
1,2-cyclobutadiene (7)	-154.669005	0.058958	-154.610047
1,2-cyclopentadiene (8)	-194.050440	0.089328	-193.961112
1,2-cyclohexadiene (9)	-233.414051	0.120409	-233.294095
1,2-cycloheptadiene (10)	-272.758127	0.149731	-272.608481
1,2-cyclooctadiene (11)	-312.096720	0.178623	-311.918097
1,2-cyclononadiene (12)	-351.422981	0.207384	-351.215597
cyclobutatriene* (75)	-153.274221	0.035151	-153.239070

cyclopentatriene (76)	-192.765584	0.066015	-192.699569
cyclohexatriene (77)	-232.143887	0.096210	-232.047677
cycloheptatriene (78)	-271.500597	0.125677	-271.374920
cyclooctatriene (79)	-310.829250	0.154564	-310.674686
cyclononatriene (80)	-350.177887	0.183535	-349.994352
1,3-cyclobutadiene	-154.7211603	0.060893	-154.660268
1,3-cyclopentadiene	-194.156236	0.092119	-194.064117
1,3-cyclohexadiene	-233.4838769	0.121814	-233.362063
1,3-cycloheptadiene	-272.8059512	0.150823	-272.655128
<i>cis</i> -1,3-cyclooctadiene	-312.1253129	0.179605	-311.945708
<i>cis</i> -1,3-cyclononadiene	-351.4413051	0.207859	-351.233446
cyclobutane	-157.257205	0.110251	-157.146954
cyclopentane	-196.611661	0.140042	-196.471619
cyclohexane	-235.9448331	0.169497	-235.775336

cycloheptane	-275.2585949	0.198089	-275.060506
cyclooctane	314.5761069	0.227259	-314.348848
cyclononane	-353.8948124	0.255876	-353.638936
1,3-dimethylallene (81)	-195.351437	0.111905	-195.239531
propane	-119.180826	0.102894	-119.078189
ethane	-79.856542	0.074310	-79.782232
2-trans-pentene (84)	-196.598671	0.135909	-196.462762
<i>trans</i> -2,3,4- hexatriene (82)	-233.4370224	0.116643	-233.320379
1,3-butadiene (86)	-156.0408103	0.084757	-155.956054
butatriene (83)	-154.777635	0.059864	-154.717771
n-pentane (85)	-197.8298083	0.159731	-197.670077
n-hexane	-237.1541295	0.188031	-236.966098
<i>cis</i> -2,3,4-hexatriene	-233.4369871	0.116637	-233.320350

* transition state

Chapter III

Structure	B3LYP/ 6-311+G(d,p) + ZPVE	CCSD(T)// 6-311+G(d,p)	CBS-QB3 Energy	BH&HLYP/ 6-311+G(d,p) +ZPVE
ozone (95)	-225.473327	-225.001281	-225.186935	-225.328017
formaldehyde (97)	-114.515263	-114.266529	-114.341304	-
acetone (96)	-193.135142	-	-192.815054	-193.009222
triplet oxygen (³ O ₂)	-150.366696	-150.044813	-150.162251	-150.289500
singlet oxygen (¹ O ₂)	-150.350294	-150.029213	-150.153137	-150.270183
carbonyl oxide (101)	-189.611347	-189.199939	-189.339824	-
carbonyl oxide (94)	-268.237134	-	-267.818430	-268.062458
³ O ₂ addition (TS27-T)	-339.970590	-339.227044	-339.489718	-
³ O ₂ addition (TS31-T)	-418.589539	-	-417.964980	-418.331815
¹ O ₂ addition (TS27-S)	-339.945277	-	-	-
¹ O ₂ addition (TS31-S)	-418.580799	-	-417.960546	-418.319773
triplet biradical (100-T)	-339.986553	-339.255090	-339.510927	-
triplet biradical (103-T)	-418.598546	-	-417.982437	-418.358959

singlet biradical (100-S)	-339.986208	-339.255726	-339.508246	-
singlet biradical (103-S)	-418.598164	-	-417.980113	-418.358801
TS26	339.961260	-339.229590	-339.496307	-
TS30	-418.576591	-	-417.963662	-418.320218
tetroxolane (99)	-339.976507	-339.254165	-339.522632	-
tetroxolane (95)	-418.590552	-	-417.995797	-418.337913
TS25	-339.964413	-339.231987	-339.501161	-
TS29	-418.574043	-	-417.969527	-418.316981
singlet diradical (98)	-339.992974	-339.252517	-339.513516	-
singlet diradical (102)	-418.597158	-	-417.523311	-418.349961
TS24	-339.970876	-339.237581	-339.493568	-
TS28	-418.582486	-	-417.970470	-
Concerted TS (97+94)	-	-339.239094	-	-

APPENDIX B: Spectra

