A Computational and Experimental Investigation of the Pinacol Coupling and Rearrangement Reactions

Ryan Sullivan

Colby College

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A Computational and Experimental Investigation of the Pinacol Coupling and Rearrangement Reactions

by

Ryan Sullivan

A thesis submitted to the Chemistry Department in partial fulfillment of the requirements for graduation with HONORS IN RESEARCH in Chemistry

Approved:

Bradley P. Henry
Mentor

Reader

Reader

Colby College
Waterville, ME

May, 1996
Ryan Sullivan was born in Hartford, Connecticut to Paul and Mary Sullivan, August 12, 1974. He was raised in nearby West Hartford, and graduated from Hall High School in June, 1992. In the fall of 1992, Ryan matriculated to Colby College where he has spent the past four years. He will graduate, May 26, 1996 and will be heading back to Connecticut with the intent of attending medical school in the fall of 1997.
Acknowledgments

I would like to thank my mentor, Professor Mundy, for giving me the opportunity to work for him. He has been a good friend as well as a great teacher, for which I am truly appreciative. Also, I wish to thank Dr. Tom Poon who has worked with me on this project and whose help has been invaluable. I would like to thank those students who shared the lab with me and who proved to be excellent colleagues. They are Andrew Greenberg, Laura Whittaker and Frank Favaloro.

I would be nowhere without the love and support of my family. Thanks to my father, and my two brothers, Paul and Jeff who have always been there for me. Special thanks goes to my mother who passed away in 1989, she taught me how to live, and I hope that I have made her proud.
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INTRODUCTION:

The coupling of two ketones yields 1,2-diols among other products. These 1,2-diols, known as pinacols, have been studied extensively and show interesting chemistry. For example, when protonated, pinacols undergo rearrangement to form spiranone products. This pinacol rearrangement thus provides a simple entry into spiranes, a general class of compounds including natural products having a number of interesting structural variations. There are other ways to synthesize these types of molecules, however rearrangement appears to be the best for certain spiranes, especially the spirovetivanes, acoranes and axisonitrile. Pinacol rearrangement is a useful way to do this if the rearrangement process can be controlled or predicted. This project has evolved into a reassessment of the pinacol coupling and rearrangement reactions.

The initial goal of this project was to analyze yields of pinacol products under different reaction conditions. There is consensus that the pinacol coupling reaction generates statistical yields of pinacol products. A general scheme of the coupling reaction of two cycloalkanones is shown below:

\[
\begin{align*}
\text{Figure 1. Asymmetric pinacol coupling} & \\
\text{Previous coupling work performed on various cycloalkanone systems by Ramanujan Srinivasa has been the basis for this coupling study. Srinivasa found non-statistical yields for all the systems he worked on. These included the coupling of cyclopentanone with cyclohexanone (5,6 system), cyclohexanone with cycloheptanone (6,7 system), and cycloheptanone with cyclopentanone (5,7 system).}^2
\end{align*}
\]

Our work has involved extensive work with the 5,6 system (Fig.2) and some exciting chemistry has been observed.
The coupling of two different cycloalkanones can yield three pinacol products. The initial goals of the pinacol coupling project were to couple cyclopentanone and cyclohexanone using various pinacol coupling procedures, observe the ratios of product, and determine whether or not the 5-6 pinacol system showed a statistical product distribution. As the project has evolved, computations have been performed on all three systems and have been compared to experimental yields in an attempt to determine whether product yields can be predicted computationally.

The rearrangement study was two-fold, consisting of a computational phase and followed by a series of experimental rearrangement procedures. The rearrangement of the asymmetrical pinacol can proceed along two paths to form two different ketone products. The initial goal of the calculations was to optimize the geometries of the various reactant, intermediates, transition states, and products, and then to perform single point energy calculations. These were done to provide reaction coordinates for each pathway and to determine whether the reaction is controlled by thermodynamics or kinetics. The ultimate goal was to be able to predict the direction the reaction will run depending upon kinetic vs. thermodynamic factors. The pathways for the rearrangement of cyclopentylcyclohexane-1,1'-diol proceed as follows:
Figure 3. Stepwise mechanism of the pinacol rearrangement of cyclopentylcyclohexane-1,1'-diol.

The question "can we control or predict which way the rearrangement will go?" has been investigated using this model system. Along with the computations, numerous experiments were performed on cyclopentylcyclohexane-1,1'-diol to answer this question. Rearrangement reactions using p-toluenesulfonic acid, tosyl chloride, and H2SO4 have been done, along with analysis of previous reactions carried out by Srinivasa.3

Recent articles have suggested that the pinacol rearrangement reaction could proceed along a different mechanism.4 This concerted mechanism, shown below, is dependent upon the migration of an R group which produces an interesting transition structure. The rearrangement of cyclopentylcyclohexane-1,1'-diol was investigated along both pathways, the stepwise and concerted mechanisms, in order to gain a more thorough understanding of the pinacol rearrangement. The concerted mechanism is shown below along with the stepwise transition:

Figure 4. Concerted (left) vs. stepwise mechanism transition states4
The concerted method was previously considered for molecules whose carbonium ions were not shown to be stable when *ab initio* calculations were performed on them. The concerted pathway is analyzed here as another possible route for rearrangement. The initial hypothesis is that the concerted transition states will be very difficult to stabilize due to the extensive ring structures of the molecules used in this study.

This project has become an extensive study of the pinacol methodology, which involves not only a mechanistic question but also extends into synthesis. Below is an example of the possible synthetic application of the rearrangement of a cyclopentylcyclohexane-1,1'-diol to form, in this case, the simplest member of the acorane natural product family.

![Figure 5. Possible synthesis of an acorane via pinacol rearrangement](image)

If a procedure for prediction of pinacol rearrangement can be devised, then easier and quicker synthetic pathways can be developed for various natural products. This study combines experimental and computational techniques to carry out the investigation.
RESULTS AND DISCUSSION:

PINACOL COUPLING

The pinacol coupling portion of the project was separated into two parts, experimental and computational. The experimental section included the preparation of a cyclohexanone-cyclopentanone stock solution, the individual coupling of cyclohexanone and cyclopentanone to determine GC/MS peaks for two of the pinacol coupling products, the coupling of the stock solution using different reagents, and the analysis of the yield data. The relative yields of the coupling performed here as well as those listed by Srinivasa were then compared to ab initio calculations performed using the Spartan computer package.

A stock solution was prepared, but not before the bottles of cyclohexanone and cyclopentanone were analyzed. This was done to make sure that the stock was pure. Each ketone was analyzed by GC/MS and the FT-IR systems. The IR spectra were compared to literature and each matched up well. The GC/MS spectra showed one peak for each, and a library search was used for confirmation. Indeed, each reagent, as expected, was shown to be pure.

Before coupling of the stock solution could be performed, symmetrical couplings of cyclohexanone and cyclopentanone had to be carried out so that GC retention times and GC/MS spectra could be mapped out for the asymmetric coupling. Symmetrical couplings will only yield one pinacol product. If the symmetric couples of the reactants are done, then the products of these reactants will show characteristic chromatogram, and the retention times of two of the three products will be known. By process of elimination, the asymmetric coupling product will then be known when it is analyzed later.

The spectra from these symmetrical coupling runs are shown in the appendix. In the case of the cyclopentanone coupling, the chromatogram shows a single peak with retention time at 10.17 minutes. The mass spectrum was analyzed and showed a large peak at 85 which is an expected peak, half of the weight of the desired symmetric molecule, identifying it as the 5-5 pinacol. Similar results were seen in the coupling of cyclohexanone. The spectrum showed a single peak at 16.20 min. The mass spectrum showed a
half-weight peak of 99, indicating that the molecule was the desired 6-6 pinacol.

At this time, the stock solution was coupled using the Al/HgCl method and the GC/MS spectrum was analyzed. Three large peaks were seen with retention times of 10.1, 13.2, and 16.2 min. The peaks at 10.1 and 16.2 were shown by their mass spectra to be the symmetrical pinacols, 5-5 and 6-6 respectively. The peak at 13.2 showed mass spectrum fragmentation at 166, 148, 99, and 85 which are all consistent with the mixed pinacol (166-loss of water; 148-loss two waters; 99 and 85 half fragments). The coupling was then carried out using the TiCl4 and SmI2 methods and their spectra were analyzed. The TiCl4 method showed a chromatograph the same as the Al/HgCl method did. The SmI2 method didn't show any peaks and it was thought that the reaction did not work. Other coupling reactions performed in the lab using SmI2 (not described here) were also unsuccessful.

The relative yields from the successful coupling reactions were obtained by integrating the spectra and by comparing areas for each pinacol peak. The data are provided in the table below.

<table>
<thead>
<tr>
<th>Method</th>
<th>5-5 pinacol</th>
<th>5-6 pinacol</th>
<th>6-6 pinacol</th>
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</thead>
<tbody>
<tr>
<td>Al/HgCl (run1)</td>
<td>21</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>Al/HgCl (run2)</td>
<td>22</td>
<td>54</td>
<td>24</td>
</tr>
<tr>
<td>TiCl4</td>
<td>23</td>
<td>53</td>
<td>24</td>
</tr>
</tbody>
</table>

The data suggest that the asymmetric coupling of the cyclohexanone-cyclopentanone stock mixture exhibits statistical yields, meaning the 1:2:1 ratio of symmetrical: asymmetrical: symmetrical. For the 5-6 coupling, Srinivasa observed the yield to be 16:59:25. This is consistent with the numbers compiled in table 1. However, his data for the 5-7 (cyclopentanone-cycloheptanone) and 6-7 (cyclohexanone-cycloheptanone) systems show non-statistical yields. The next step in this study is to determine why some systems show statistical yields and some do not, and more importantly, whether these yields can be predicted.

The computational analysis of pinacol coupling was an investigation of how well the products of the reactions can be predicted using molecular orbital calculations. The systems examined were the coupling of: 1.
cyclohexanone-cyclopentanone; 2. cycloheptanone-cyclopentanone; 3.
cycloheptanone-cyclohexanone. The coupling data of Srinivasa was used for
each system and system 1 was also analyzed with the data collected from the
reactions described previously.

These calculations were performed in order to determine which
molecule in each asymmetric coupling would be the most favorable product
and to predict the order and relative yield of products. The mechanism for
the pinacol coupling reaction involves the formation of radical anion species
and the complexation of these species to the coupling reagent. These
complexed species then couple with other complexed species in an energy
dependent manner. Frontier molecular orbital (FMO) theory states that the
lower the HOMO-LUMO gap, the more favorable the reaction. In the figure
below, M represents a metal surface.

Figure 6. Mechanistic diagram of pinacol coupling (5-5 symmetric)

The calculated values for the HOMO and LUMO of each radical anion
(gas phase without metal) were then matched up with the HOMO's and
LUMO's of the other radical anions and HOMO-LUMO gaps were determined.
For example (shown in Fig. 7), the HOMO of the cyclopentanone radical
anion was subtracted from the LUMO of the radical anion of cyclohexanone
to determine the energy gap to form cyclopentylcyclohexane-1,1'-diol.
However, the LUMO of the cyclopentanone radical could also react with the
HOMO of the cyclohexanone radical and form the same product. The lowest
energy difference of the two was then used for addition analysis.

Figure 7. Example of HOMO-LUMO gap calculation
Srinivasa's asymmetrical data is shown below in Table 2. The product ratio is represented by all the products of the reaction including all alkene products and all pinacol products. The pinacol product relative ratios are provided in Table 3. Represented in Table 4 are the HOMO-LUMO gaps for each coupling series. A graph was then created for each system by plotting experimental (pinacol) yield vs. the calculated HOMO-LUMO gaps.

Table 2. Data from pinacol coupling series performed by Srinivasa

<table>
<thead>
<tr>
<th>m</th>
<th>n</th>
<th>A_{mm}</th>
<th>A_{nn}</th>
<th>P_{mn}</th>
<th>P_{nm}</th>
<th>P_{nn}</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>10.2</td>
<td>4.1</td>
<td>11.4</td>
<td>42.0</td>
<td>18.2</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>8.0</td>
<td>16.7</td>
<td>27.8</td>
<td>33.9</td>
<td>10.8</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>1.8</td>
<td>4.8</td>
<td>28.7</td>
<td>48.8</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Table 3. Pinacol coupling data converted into relative % yield

<table>
<thead>
<tr>
<th>m</th>
<th>n</th>
<th>m-m</th>
<th>m-n</th>
<th>n-n</th>
<th>m-m</th>
<th>m-n</th>
<th>n-n</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>11.4</td>
<td>42.0</td>
<td>18.2</td>
<td>15.9</td>
<td>58.7</td>
<td>25.4</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>27.8</td>
<td>33.9</td>
<td>10.8</td>
<td>38.3</td>
<td>46.8</td>
<td>14.9</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>28.7</td>
<td>48.8</td>
<td>8.7</td>
<td>33.3</td>
<td>56.6</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Table 4. Calculated HOMO-LUMO gaps (ab initio 6-31G*)

<table>
<thead>
<tr>
<th>m</th>
<th>n</th>
<th>series</th>
<th>Δ in Energy (HOMO-LUMO gap)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>H_mL_m</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>1</td>
<td>0.36465</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.36465</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>1</td>
<td>0.36465</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.36465</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>1</td>
<td>0.39042</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.39042</td>
</tr>
</tbody>
</table>

8
Figure 8. Plots of % yield of pinacol products vs. calculated HOMO-LUMO gap
A great deal of information can be gathered by examining the three graphs. First, it is important to look at the R values for the curve fit. The 5-6 system shows a very poor value of 0.245, while values of 0.998 and 0.959 are seen for the 5-7 and 6-7 ring systems, respectively. It is difficult to say that the calculations are not a good tool for analyzing these systems because it does an excellent job of characterizing the latter two systems. On the assumption, then, that the calculations are valid, it becomes imperative to analyze the 5-6 ring system with greater focus. With this said, the next step was to apply the data collected from the coupling reactions performed here (Table 1.) to the graphical model (Fig. 9).

5-6 coupling using TiCl₄ method

![](5-6_coupling_Ticl4.png)

5-6 coupling using Al/HgCl method

![](5-6_coupling_AlHgCl.png)

Figure 9. Plot of % yield of pinacol products vs. calculated HOMO-LUMO gap
The plots using the data collected from the Al/HgCl and TiCl4 do not show a much better correlation with the computational data. The R values are 0.315 and 0.425, respectively, for the Al/HgCl and TiCl4. This is not very revealing as to what is causing the discrepancies seen in the 5-6 system. It is clear that more research into this system is necessary, however circumstances surrounding this study pushed the focus of the project toward pinacol rearrangement. Perhaps free energy calculations or other variations of the computational work here can lead to a resolution of the intriguing question, "why is the 5-6 system different?".

PINACOL REARRANGEMENT

The rearrangement portion of this project was separated into two parts. The first included the calculations performed on the various species of the stepwise and concerted mechanisms in an attempt to characterize the mechanism for the rearrangement of the 5-6 pinacol. The second included the coupling of a large amount of the cyclopentanone/cyclohexanone stock solution, the subsequent separation and purification of cyclopentylcyclohexane-1,1'-diol, and the various rearrangement reactions run on that molecule. The rearrangement reactions were then described graphically using data derived from the Spartan calculations.

According to the stepwise mechanism, the pinacol rearrangement of cyclopentylcyclohexane-1,1'-diol can proceed along two pathways. Figure 11 shows molecules which were analyzed using semi-empirical AM1 geometry optimizations. Molecule A is the 5-6 mixed pinacol which can be rearranged into either E or E' depending upon thermodynamic versus kinetic factors. The pathway includes the protonation of one of the hydroxyl groups (B or B'), the subsequent loss of H2O and formation of a tertiary carbocation (C or C'), and the migration of a carbon-carbon bond to form a larger ring structure and another tertiary carbocation (D or D'). The deprotonation of the hydroxyl group leads to the formation of the spiranone product (E or E'). Each intermediate was built, optimized and its energy was calculated. Also, the transition state between C/C' and D/D', characterized by bond migration, was built and run using the transition structure feature of the AM1 calculation.

The concerted mechanism was looked at by building the required transition states (Fig. 4) and carrying out calculations in the same manner as done for the stepwise transition states. The concerted mechanism has been
Figure 10. Molecules upon which Spartan calculations were performed
documented as including the same protonation of the pinacol (B or B'), but then the reaction proceeds by a transition state that incorporates the loss of water and the migration of the carbon-carbon bond in one step yielding D or D'. The general concerted transition state is diagrammed in Figure 4. For the 5-6 pinacol rearrangement, the transition was looked at for both pathways with R₂ and R₁ equal to the expanding ring and R₃ and R₄ representative of the ring with the carbocation.

For the stepwise mechanism the results of the energy calculations are characterized below (Table 5). The concerted transition state energies could not be calculated because the computer regularly ran out of cycles. The calculations are generated by optimizing the geometries and calculating the heat of the formation for each geometry variation. The computer usually runs a maximum of 300 cycles (different geometries) until the heat of formation approaches an asymptotic value. This value is then the energy of the optimized geometry. For the concerted transition states, 2000 cycles were run on the molecules and no final energy value was calculated. Also, the geometries of these structures "blew apart". For instance, the H₂O and carbon bond was about 21 Å, over ten times the length it should have been. This computational series supports the stepwise mechanism.

With the stepwise mechanism established as the working mechanism, it is important to investigate the query, "Can pinacol rearrangement be predicted using computational techniques?". The data below are useful in generating an answer.

| Table 5. Calculated AM1 heats of formation for the 5-6 pinacol rearrangement |
|---------------------------------|---------------------------------|
| Path 1  | ΔHₖ (kcal/mol) | Path 2  | ΔHₖ (kcal/mol) |
| A       | -140.436       | A       | -140.436       |
| B       | 30.029         | B'      | 29.620         |
| C       | 101.519        | C'      | 100.688        |
| Cₜₛ     | 122.007        | C'ₜₛ   | 122.003        |
| D       | 61.988         | D'      | 87.443         |
| E       | -76.620        | E'      | -81.232        |

In determining controlling features of the reaction, it is imperative to analyze the heats of formations of the two possible products. It is shown above that E' is more stable then E by 4.612 kcal/mol. This number would suggest that
under thermodynamic conditions (time and high temp.), E' would be the predominate product. The next step of this project was to compare the computational data to experimental results.

The first rearrangement reaction was run to determine the effect of tosylating one of the -OH groups. This was carried out by adding 1 equivalent of toluenesulfonyl chloride with the idea that one and only one alcohol group would be tosylated. The result of which group is tosylated would shed some light as to which -OH group is more thermodynamically stable. Below is a look at the possible products.

![Possible tosylated molecules](image)

If this were to occur, rearrangement should only move in one direction to yield either:

![Rearrangement products after tosylation](image)

Unfortunately, no rearrangement was seen under these conditions. The GC/MS spectrum showed one peak consistent with the starting material.

Pinacol rearrangement reactions were also run under acidic conditions using either sulfuric acid or p-toluenesulfonic acid. The sulfuric acid rearrangement yielded a product ratio of 60:40 (E:E'). This ratio was taken from the integrated peaks of the GC/MS spectrum, 12.43 and 12.60. These were determined to be the rearranged products by analysis of the mass spectrum of each. Each spiranone product has a molecular weight of 166, and
the spectra showed this peak as well as the dehydration peak of 148. The two spiрананones were distinguished by comparing a previously synthesized sample of the 6-6 spiрананone (E') which, when analyzed on the GC/MS gave a peak at 12.6 with a very similar mass spectrum to that of the H2SO4 peak at 12.60.

The 60:40 ratio found from this first reaction is contrary to calculations, which showed that molecule E' was more thermodynamically stable. This experiment suggests that the rearrangement reaction can be controlled by kinetics factors such as the relative short reaction time (90 min) and the temperature of the vessel (bathed in dry ice and isopropanol).

The p-toluenesulfonic acid rearrangement showed results suggestive of thermodynamic conditions. The reaction was run at room temperature for over 24 hours. A GC/MS spectrum was taken and showed only one product, molecule E'. This is a powerful example of a thermodynamically driven reaction.

If thermodynamic vs. kinetic factors are important then the ratio of products should shift as the reaction proceeds. Numerous experiments were run using p-toluenesulfonic acid and some interesting data was obtained. One of the reactions yield the following data:

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>E (GC peak at 12.45)</th>
<th>E' (GC peak at 12.60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:01</td>
<td>0.35</td>
<td>0.65</td>
</tr>
<tr>
<td>9:26</td>
<td>0.34</td>
<td>0.66</td>
</tr>
<tr>
<td>9:49</td>
<td>0.33</td>
<td>0.67</td>
</tr>
<tr>
<td>10:14</td>
<td>0.31</td>
<td>0.69</td>
</tr>
<tr>
<td>10:39</td>
<td>0.32</td>
<td>0.68</td>
</tr>
<tr>
<td>11:36</td>
<td>0.38</td>
<td>0.62</td>
</tr>
<tr>
<td>1:12</td>
<td>0.32</td>
<td>0.68</td>
</tr>
<tr>
<td>reflux 1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:03</td>
<td>0.28</td>
<td>0.72</td>
</tr>
<tr>
<td>48 hours</td>
<td>0.24</td>
<td>0.76</td>
</tr>
</tbody>
</table>

This reaction was run and samples were taken out at the listed times and analyzed on the GC/MS. The areas of the peaks were calculated and the established rearrangement peaks at 12.45 and 12.60 were compared to each other to give the data in the table. After the first seven samples were taken, it
was clear the reaction was proceeding, albeit very slowly. Thus, the reaction was given a push and was refluxed for an hour. The relative percentages jumped from 32:68 to 28:72. After two days of stirring, the ratio was shown to be 24:76.

Three additional tosic acid reactions were performed in an attempt to understand the early stages of the reaction. The procedures are listed in the experimental section. However, access to the GC/MS was not always possible, and in an attempt to store the aliquots from various times of the reaction, the samples decomposed and gave unreadable GC spectra. After a few failed runs, the 5-6 pinacol product that was sparse from the beginning ran out and with time as a factor, production of more pinacol was unfeasible. This early reaction certainly holds important information regarding the control of the reaction and this area should be investigated further.

After all the rearrangement reactions were performed, they were then analyzed computationally in the gas phase and corrected for the sulfuric acid, and p-toluenesulfonic acid conditions. Reaction coordinates were developed using the previously performed gas phase calculations of the rearrangement mechanism. In addition, calculations under the same conditions as the above molecules were performed on sulfuric acid (G) and p-toluenesulfonic acid (F) and their conjugate bases (G- and F- respectively). Also, the rearrangement mechanism involves the loss of water and so the water molecule was also geometrically optimized and an energy calculation was performed (H). To build the profiles of each system, the heats of formation of the appropriate molecules were added and/or subtracted. The three reaction diagrams are shown on the following three pages. It is important to note that the peak values are guesses, but those transition state energies have not been included into the profile. Also, the three diagrams are on the same energy scale but may involve a different range of energies.

The analysis of each leads to a couple of conclusions. Mainly that thermodynamically, the 6-6 spiranone is more favored. Also, the last intermediate is more stable for the 5-7 spiranone (D) than for the 6-6 spiranone (D'). This suggests that an intermediate molecule between D and E' may exist that shifts the equilibrium from E to E'. Srinivasa discusses the possibility of such a secondary rearrangement and proposes the following mechanism.
This mechanism makes intuitive sense in that the second molecule is essentially D, and it then undergoes a second bond migration occurs in the next step and ends up forming E'. When D* was built in Spartan and the energy was calculated using the same techniques as before, the heat of formation was 105.419 kcal/mol, which is higher than any of the other molecules in the secondary mechanism. This suggests that the molecule could not act as the intermediate as it was proposed. Srinivasa showed otherwise in the rearrangement of trans-perhydrobenzocycloheptane-10,11-diol (the diol form of D*). In this reaction, the conditions were concentrated H2SO4 at 0° C, and the result was the formation of spiranones at 76:24 (E:E'). This reaction may take place in a different mechanism.

Certainly some intermediate is necessary for the formation of the thermodynamically favored spiranone. If that molecule is indeed that suggested by Srinivasa, then better calculations may be needed for the molecule to fit its designation. The calculations were performed at a low level of theory and conformation searches were not run before calculations. Higher levels of theory are necessary to fully substantiate the general conclusion that pinacol rearrangement can indeed be predicted by computational analysis and may also be controlled by reaction environment.
Reaction Profile: Gas Phase, Uncorrected

\[ \text{C} \quad 101.519 \quad \text{D'} \quad 87.443 \]
\[ \text{D} \quad 61.998 \quad \text{B'} \quad 29.620 \]
\[ \text{E} \quad -76.690 \quad \text{E}’ \quad -81.323 \]
\[ \text{A} \quad -140.436 \]
Reaction Profile: Gas Phase, Corrected ($\text{H}_2\text{SO}_4$)

\[ C + G \cdot H \rightarrow C' + G \cdot + H \]

\[ D + G^- + H \rightarrow -231.130 \]

\[ A + G^- \rightarrow -203.859 \]

\[ B' + G^- \rightarrow -204.268 \]

\[ C' + G^- + H \rightarrow -192.44 \]

\[ D' + G^- + H \rightarrow -205.685 \]

\[ E + G + H \rightarrow -274.261 \]

\[ A + G \rightarrow -278.767 \]

\[ E' + G + H \rightarrow -278.803 \]
Reaction Profile: Gas Phase, Corrected (TsOH)

\[
\begin{align*}
E + F + H & \rightarrow -286.299 \\
C + F^- + H & \rightarrow -163.271 \\
B + F^- & \rightarrow -175.521 \\
D + F^- + H & \rightarrow -202.792 \\
A' + F & \rightarrow -290.535 \\
C' + F^- + H & \rightarrow -164.102 \\
B' + F^- & \rightarrow -175.930 \\
D' + F^- + H & \rightarrow -177.347 \\
E' + F + H & \rightarrow -290.571
\end{align*}
\]
EXPERIMENTAL:

PINACOL COUPLING

Preparation of a cyclohexanone/cyclopentanone stock solution

One mole of cyclohexanone (MW=98.145 g/mol; 103.637 ml) was added to one mole of cyclopentanone (MW=84.118 g/mol; 88.452 ml) to give the stock solution. Both the cyclohexanone and cyclopentanone were tested for purity using the GC/MS and a library search of each spectrum. Also IR spectra were compared to literature spectra. After tested for purity, a fourth of a mole of each (24.53 g cyclohexanone and 21.03 g cyclopentanone) was placed into a 50 ml Erlenmeyer flask and mixed thoroughly. A plastic syringe cap was placed over the flask. This allowed for the drawing of the mixture by syringe for the duration of the experiments.

Symmetric coupling of cyclohexanone and cyclopentanone

Al/HgCl

The symmetrical coupling reactions were run using an aluminum/mercuric chloride reagent. This method called for 0.45 g of Al and 0.24 g HgCl to be added into a round bottom flask with 10 ml of benzene. This mixture was then stirred at reflux for thirty minutes. At this time, 1.05 ml of cycloalkanone was then added, and the resulting slurry was refluxed overnight. The next day, the reaction was quenched with 1 ml of water, and refluxed an additional twenty five minutes after the addition of another ml water and 15 ml of ether. The reaction material was then filtered in a round bottom flask and removed by rotary evaporation. The result was the formation of yellowish-orange crystals. These crystals were then analyzed using the GC/MS, FFLOWT setting. FFLOWT parameters were as follows: injB T= 150; detB T= 150; T range= 65-150; rate= 5deg/min. A Supelco 2-4026 (15m x 0.25mm) column was used for all GC-MS analysis.

Asymmetric coupling of the cyclohexanone/cyclopentanone stock solution

The asymmetric coupling portion of this study was performed using three different coupling reagents. The first was the aluminum/mercuric chloride (Al/HgCl) method described above. The second was a titanium tetrachloride (TiCl4) method and the third used samarium iodide (SmI2).
Since integrated peak area is proportional to concentration, and the proportionality constant was assumed to be the same for all pinacol products, product yields were calculated and compared to determine if a statistical relationship could be seen.

**Al/HgCl Method**

The first asymmetrical coupling was run using the aluminum/mercuric chloride method and two reaction flasks were set up. Flask 1 contained 0.242g HgCl, 0.453g Al, and about 10 ml of benzene and flask 2 had virtually identical contents (0.243, 0.453, and 10). Each was refluxed for twenty five minutes, and then 1g of stock solution was injected into each flask, and the reaction ran overnight at reflux. The reaction was quenched with 1 ml of water and refluxed for five minutes. Then another ml of water and 15 ml of ether were added to the flask and reflux went on for twenty five more minutes. The mixture was rotovapped and orange crystals formed. The crystals from each flask were collected and labeled. A small amount of product was added to CH₂Cl₂ and was run through the GC/MS using the FFLOWT method.

**TiCl₄ Method**

The reaction flask was charged with magnesium metal (0.590g) and mercuric chloride (0.176g). An argon balloon was positioned on top of the reaction vessel, and the air was flushed out of the flask creating an inert argon atmosphere. Dry tetrahydrofuran (THF), 2 ml, was injected into the flask and the solution was stirred for twenty minutes. The resulting gray supernatant liquid was withdrawn using a syringe with a long needle and the mixture was washed three times with 2 ml portions of fresh THF. THF, 15 ml, was added and the flask was cooled using an isopropyl alcohol, dry-ice bath. TiCl₄, 1.32 ml, was introduced to the mixture dropwise while the solution was continuously stirred, and the solution turned bright yellow. Next, 1 ml of ketone was added and the reaction was stirred continuously for two hours. During this time, the solution turned a dark purple. The reaction was quenched with a saturated aqueous solution of sodium carbonate (1 ml) and stirred for twenty minutes. Ether (5 ml) was added, the solution was stirred briefly, and then filtered. Water was added to the dark purple filtrate and was extracted using ether. The ether layer was removed by rotary evaporation and
a yellow-orange solution was left and crystallized overnight. A small number of crystals were dissolved in CH$_2$Cl$_2$, and the resulting solution was analyzed by GC/MS at the FLOWT method.

Sml$_2$ Method

Sml$_2$ (in THF), 40 ml, was added to a 100 ml three-neck round bottom flask that was under an argon atmosphere, and 0.4 ml of ketone stock solution and 0.4 ml of methanol were added to the reaction flask. The reaction ran for twenty minutes at -78 degrees C (Dry ice in an isopropanol bath). Slowly, the reaction was brought to room temperature and quenched with NaHCO$_3$ buffer. The organic layer (THF) was separated and the remaining layer containing our product was extracted using ether. Some of the ether was evaporated off, and the remaining solution was analyzed by GC/MS at the FLOWT method.

Calculation of radical anions HOMO and LUMOs

The three molecules below were built using Spartan, and semi-empirical conformational searches were run on the radical anions of cyclopentanone, cyclohexanone, and cycloheptanone (shown below).

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Figure 14. Radical anion species
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The geometries of the lowest energy conformer were then optimized at the semi-empirical level (AM1: charge=-1, multiplicity=2). Ab initio molecular orbital calculations were performed on the resulting geometries. The level of theory was UHF (unrestricted Hartree-Fock) which is used for doublet and triplet molecules and two basis sets were performed, first 3-21G*, then 6-31G*. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were determined from the molecular orbital calculations based on the number of electrons in each molecule.
Computational analysis of the Pinacol Rearrangement mechanism

All calculations performed on rearrangement species were semi-empirical AM1 geometry optimizations, charge dependent on the molecule, multiplicity set at one. For reactant, intermediate, and product molecules, geometry optimizations were performed followed by single point energy calculations of the resulting structures. The transition structures were computationally analyzed using the transition structure feature at the AM1 level. The stepwise transition structures were build using pentavalent carbons and the bonds that could be formed between the pentavalent carbons were not, but were constrained to 1.8 Å (6-6 transition shown in Fig. 7). The transition structures for the concerted mechanism were also computed using the transition structure feature at the AM1 level.

Figure 15. Transition state built using Spartan, showing the pentavalent carbons

Pinacol coupling of the stock solution

Using the same TiCl4 coupling technique described earlier, 10 ml of ketone stock solution was coupled. The three necked 500 ml round bottom flask was charged with 5.905 g of Ms (s) and 1.768 g of HgCl (s). Dry THF, 20 ml, was injected and stirred for 20 minutes. The flask was then washed three times with 20 ml portions of dry THF; then about 300 ml of THF was added to the reaction vessel. The reaction flask was then cooled in a NaCl, ice and water bath to about -10° C. 10 ml of TiCl4 was added dropwise, then 10 ml of ketone stock solution was injected. The reaction was stirred for two hours at 0° C. Quenching of the reaction took place with the addition of 10 ml of NaCO3 and 20 minutes of stirring. Ether was added to the flask, and following brief stirring, the contents were filtered. Water was added to the filtered
solution and the product was extracted with ether. The product solution was rotary evaporated to yield a dense, yellow-orange solution.

**Cyclopentylcyclohexane-1,1-diol separation using column chromatography**

Silica gel (63-200 mesh) was used for the stationary phase and a petroleum ether (then hexanes) and ether mixture was used as the eluent. The procedure followed was from Srinivasa's separation in his doctoral thesis (p. 91). Since only the mixed pinacol product was desired, the separation's first two phases, addition of petroleum ether (100%) and addition of pet. ether/ether (80:20), were completed "quick and dirty" to separate the starting ketones and the three alkene products. The eluent was switched to a pet. ether/ether (50:50) mixture when the drops from the column stopped showing UV activity on a thin layered chromatography (TLC) plate, thus indicating that no more alkene products were left. The next step was to carefully and orderly fill numbered test tubes with the drops. This process was carried out until over a hundred tubes were filled.

The contents of the test tubes were then analyzed using TLC. Every other test tube was spotted on a plate, and a hexanes (in place of pet. ether which ran out)/ether mixture (50:50) was used as the solvent. After the solvent had traveled the length of the plate, the plate was removed from the bottle and sprayed with a vanillin spray produced in the lab. The plate was then heated with a hair dryer and the individual molecules could be distinguished from each other because of different R\textsubscript{f} values.

The contents of test tube 47 were analyzed using the GC/MS and the molecule was determined to be the mixed pinacol product. The test tubes that showed only this molecule on the TLC plates, tubes 31-62, were combined and the solvent was removed by rotary evaporation. Crystals were formed and weighed, and a total of 0.29 g of pure product was collected.

**Rearrangement Study**

A number of reactions were run on the mixed pinacol pure product to gather information about the rearrangement of pinacols. Three distinct rearrangement procedures were performed. The first was a toluenesulfonyl
chloride method, the second a H$_2$SO$_4$ protocol, and the third a series of reactions run using the reagent, p-toluenesulfonic acid.

**Tosylchloride Method**

In this reaction, one equivalent of pinacol (0.0451 g) and one equivalent of toluenesulfonyl chloride (0.0468 g) were added to 2 ml of pyridine in a 10 ml round bottom flask. The resulting mixture was heated at reflux for about 90 minutes. Water was added to the product which was then extracted with CH$_2$Cl$_2$. A GC/MS spectrum, using a new FFLOWT method (all same except T=50-150 instead of 65-150), was then taken to analyze the product.

**H$_2$SO$_4$ Method**

One ml of H$_2$SO$_4$ was added to just a few pinacol crystals and placed into a 10 ml flask. This was stirred in an ice bath for about 90 minutes. The reaction was quenched with ice water and KOH to neutralize the acid. The product was extracted with CH$_2$Cl$_2$. Some of the CH$_2$Cl$_2$ was evaporated leaving a small amount of product solution left. The remaining solution was analyzed using the new FFLOWT method on the GC/MS.

**p-Toluensulfonic acid Method**

The first reaction was run using 0.25 g of pinacol and 0.20 g of p-toluenesulfonic acid. The crystals were placed into a 10 ml round bottom flask with 5 ml of CH$_2$Cl$_2$. The reaction was commenced at 8:50 AM and samples were collected on the hour until 2:50. The reaction was allowed to run overnight and GC/MS measurements were taken the next morning. The mixture turned from a yellowish transparent color to a deep purple overnight.

The second reaction was performed using 0.024 g of pinacol and 0.012 g of p-toluenesulfonic acid in 5 ml of CH$_2$Cl$_2$. This reaction was again run at room temperature and the reactants were combined at 8:38. Samples were taken at regular intervals, and were directly run through the GC/MS. Samples were taken at 9:01, 9:26, 9:49, 10:14, 10:39, 11:36 AM, 1:12 PM. The reaction was then heated to reflux at 1:57 and a spectrum was taken at 3:03. In the hour of reflux, the solution turned from a cream soda color to a deep purple. The reaction was allowed to run overnight and a spectrum was taken.
The third reaction was run in an ice bath and aliquots were taken every 3-4 minutes for 40 minutes. Similar reactant proportions were used as the earlier runs (0.030 g of pinacol, 0.020 g tosic acid, in 5 ml CH₂Cl₂. The temperature of the reaction solution was 2°. GC/MS scans were performed on every aliquot immediately after sampling. This necessitated a new, quicker method for sampling.

The fourth and fifth reactions were run under similar conditions. In the fourth, 0.032 g of pinacol and 0.027 g of tosic acid were added to 5 ml of CH₂Cl₂. These reactions were run at room temperature and aliquots were taken every 3-4 minutes and were quenched with a couple drops of saturated sodium bicarbonate solution. These aliquots were then stored until they could be analyzed on the GC/MS.
CONCLUSIONS:

This project was developed from previous reports concerned with the pinacol coupling and rearrangement methodologies. It is hoped that the results and conclusions of this study may provide someone in the future a chance to gain a more complete view of this material.

Analysis of the pinacol coupling reaction shows that the yields of the pinacol products are not statistical for the asymmetric cycloalkanone systems. Also, the yields of the 5-7 and 6-7 systems plotted versus *ab initio* gas phase calculations of HOMO-LUMO gaps showed r values at or near 1.00. This correlation is excellent and offers an example of how product yields may be predicted computationally. As exciting as this is, the 5-6 system did not match up well, experimentally vs. computationally, and further work is needed to gain a better understanding of this system.

The AM1 gas phase calculations used on pinacol rearrangement mechanistic species proved to be very useful. First, they substantiated that the stepwise mechanism was occurring rather than the concerted mechanism in the rearrangement of cyclopentylcyclohexane-1,1'-diol. Also, the calculations were used to plot reaction diagrams of the various conditions. These show that, in the gas phase, the 6-6 spiroketone is lower in energy than the 5-7 spiroketone. This is consistent with experimental data which indicate that the 6-6 product is favored when the reactions are stirred for a long time at room temperature. The 5-7 product is only favored when the reaction is short (30 min.) and performed at low temperature (0°C). These results indicate that a thermodynamic vs. kinetic effect is occurring in this system. Furthermore, calculations appear to be adept at predicting the most thermodynamically stable molecule.

Additional computational experiments need to be run on this system, including observation of the effects of polar and non-polar solvents and the upgrading of the calculations to the *ab initio* level. Also, other systems need to be studied before predictions can be made concerning natural product synthesis, but according to the data so far, computations look like an effective way to analyze these systems.
REFERENCES:

APPENDIX:

A. FT-IR spectrum of cyclopentanone
B. GC-MS spectrum of cyclopentanone (parameters under Misc Info)
C. FT-IR spectrum of cyclohexanone
D. GC-MS spectrum of cyclohexanone (parameters under Misc Info)
E. GC-MS spectrum of symmetric coupling of cyclopentanone (FFLOWT)
F. GC-MS spectrum of symmetric coupling of cyclohexanone (FFLOWT)
G. GC-MS spectrum of asymmetric coupling, Al/HgCl method (FFLOWT)
H. GC-MS spectrum of asymmetric coupling, TiCl₄ method (FFLOWT)
I. GC-MS spectrum of asymmetric coupling, TiCl₄ method (new FFLOWT, T=50-150 rather then 65-150); shows new retention times.
J. GC-MS of cyclopentylcyclohexane-1,1'-diol, confirming 5-6 pinacol retention times (new FFLOWT).
K. GC-MS of pure 6-6 spiroketone, showing retention time of one of the rearranged products, 12.66 minutes (new FFLOWT).
L. GC-MS of products from H₂SO₄ rearrangement, spiroketones at 12.45 minutes and 12.60 minutes, MS at 12.45 (new FFLOWT).
M. GC-MS of products from H₂SO₄ rearrangement, spiroketones at 12.45 minutes and 12.60 minutes, MS at 12.60 (new FFLOWT).
N. GC-MS of products from TsOH rearrangement, spiroketones at 12.45 minutes and 12.60, MS at 12.45 (new FFLOWT).
O. GC-MS of products from TsOH rearrangement, spiroketones at 12.45 minutes and 12.60, MS at 12.60 (new FFLOWT).
File: C:\HPCHEM\1\DATA\CYC50NE.D
Operator: Ryan
Acquired: 14 Sep 95 12:29 pm using AcqMethod FF50SLOW
Instrument: 5970B
Sample Name: cyclopentanone test run
Misc Info: 4min 5deg/min 2min 50-100deg inj 150
Vial Number: 1

Abundance
5e+07
4e+07
3e+07
2e+07
1e+07
0

Time--> 1.00 2.00 3.00 4.00 5.00 6.00 7.00

TIC: CYC50NE.D
File: C:\HPCHEM\1\DATA\FFCY60NE.D
Operator: Frank Favaloro
Acquired: 21 Sep 95 1:24 pm using AcqMethod FF50SLOW
Instrument: 5970B
Sample Name: cyclohexanone
Misc Info: 4min 5deg/min 1min 50-100deg inj200 det280
Vial Number: 1

Abundance

TIC: FFCY60NE.D

Scan 114 (1.837 min): FFCY60NE.D
File: C: \ HPCHEM \ 1 \ DATA \ CYC6PIN.D
Operator: Ryan
Acquired: 3 Oct 95 11:23 am using AcqMethod FFLOWT
Instrument: 5970B
Sample Name: 6/6 pin
Misc Info: injB 150 det.B150 5deg/min 2.00min
Vial Number: 1

Abundance

TIC: CYC6PIN.D

Scan 1355 (16.196 min): CYC6PIN.D

Abundance

m/z -->
Scan 1092 (13.216 min): 56HGA2.D
File: C:\HPCHEM\1\DATA\56PINTI4.D
Operator: Frank
Acquired: 31 Oct 95 12:47 pm using AcqMethod FLOWT
Instrument: 5970B
Sample Name: 5/6pin using TiCl4
Misc Info: FLOWT
Vial Number: 1

Abundance
500000
400000
300000
200000
100000

Time--> 2.00 4.00 6.00 8.00 10.00 12.00 14.00 16.00 18.00 20.00
File: C:\HPCHEM\1\DATA\RS66AR.D
Operator: rs
Acquired: 16 Feb 96 3:22 pm using AcqMethod FLOWT
Instrument: 5970B
Sample Name: 6/6 rearrangement product again
Misc Info: fflowt
Vial Number: 1

Abundance

TIC: RS66AR.D
12166

Scan 1064 (12.657 min): RS66AR.D

m/z -->
0 50 100 150 200 250 300 350 400 450 500 550
215 251 287 315 343 404 446 473 498 536

Abundance

Scan 1064 (12.657 min): RS66AR.D
File: C:\HPCHEM\1\DATA\RSPINH.D
Operator: rs
Acquired: 23 Jan 96 11:13 am using AcqMethod FFLOWT
Instrument: 5970B
Sample Name: pin rearr. from H2SO4
Misc Info: fflowt
Vial Number: 1

Abundance

TIC: RSPINH.D

Scan 1042 (12.429 min): RSPINH.D
File: C:\HPCHEM\1\DATA\RSPINH.D
Operator: rs
Acquired: 23 Jan 96 11:13 am using AcqMethod FFLOWT
Instrument: 5970B
Sample Name: pin rearr. from H2SO4
Misc Info: fflowt
Vial Number: 1

Abundance

TIC: RSPINH.D

Time-->
0  5.00  10.00  15.00  20.00

Abundance

Scan 1057 (12.600 min): RSPINH.D

m/z-->
0  20  40  60  80  100  120  140  160  180  200

21  28  41  55  67  81  98  122  137  148  166  177  192

20000  15000  10000  5000  1000  500  100  50  10  5  1

File Operator Acquired Instrument Sample Name Misc Info Vial Number
File: C:\HPCHEM\1\DATA\TOSACID.D
Operator: rs
Acquired: 25 Jan 96 11:56 am using AcqMethod FLOWT
Instrument: 5970B
Sample Name: tos.acid 9:50
Misc Info: fflowt
Vial Number: 1

Abundance

Scan 1042 (12.443 min): TOSACID.D
File: C:\HECM\1\DATA\TOSACID.D
Operator: rs
Acquired: 25 Jan 96 11:56 am using AcqMethod FFLOWT
Instrument: 5970B
Sample Name: tos.acid 9:50
Misc Info: fflowt
Vial Number: 1

Abundance

TIC: TOSACID.D

Scan 1056 (12.603 min): TOSACID.D