The Synthesis of Benzophenone-3,5-Diacid Chloride for the Double Capping of beta-Cyclodextrin

Clyde Wesley Eargle

College of William & Mary - Arts & Sciences

Follow this and additional works at: https://scholarworks.wm.edu/etd

Part of the Organic Chemistry Commons

Recommended Citation


https://dx.doi.org/doi:10.21220/s2-en0f-nh60

This Thesis is brought to you for free and open access by the Theses, Dissertations, & Master Projects at W&M ScholarWorks. It has been accepted for inclusion in Dissertations, Theses, and Masters Projects by an authorized administrator of W&M ScholarWorks. For more information, please contact scholarworks@wm.edu.
The Synthesis of
Benzophenone-3,5-Diacid Chloride
for the Double Capping of β-Cyclodextrin

A Thesis
Presented to
The Faculty of the Chemistry Department
The College of William and Mary in Virginia

In Partial Fulfillment
of the Requirements for the Degree of
Master of Arts

by
C. Wesley Eargle
1997
This thesis is submitted in partial fulfillment of
the requirements for the degree of

Master of Arts

Approved, April 1997

Christopher J. Abelt, Ph.D.

Gary W. Rice, Ph.D.

Robert J. Hinkle, Ph.D.
DEDICATION

This project would have never come as far as it has without the guidance and support of many people, far too many to list on a single page. The author would like to single out three individuals who have, in one way or another, pushed me towards this final goal.

This thesis is dedicated to the memory of my brother, Charles Parham Eargle, Jr., who never got to appreciate the good times that should have been. This thesis is also dedicated to the memory of my grandfather, Clyde Woodward Rutland, for providing the example that I should hope to follow for the rest of my life. This thesis is also dedicated in honor of my best friend, J.P. Northrop, whose constant support and encouragement allowed me to get through the tough times.

Without these people in my life, this thesis would have never come to fruition.
# TABLE OF CONTENTS

DEDICATION .............................................................................................................................iii

ACKNOWLEDGEMENTS ...........................................................................................................v

LIST OF TABLES ......................................................................................................................vi

LIST OF FIGURES ....................................................................................................................vii

ABSTRACT ..................................................................................................................................ix

INTRODUCTION ..........................................................................................................................2

BACKGROUND ..........................................................................................................................6
  - Cyclodextrins ..........................................................................................................................6
  - Inclusion Complexes ..............................................................................................................9
  - Capping ..................................................................................................................................12
  - Photochemistry ....................................................................................................................17
  - Previous Synthetic Pathways ...............................................................................................21

MATERIALS AND METHODS ..................................................................................................24
  - 1-Bromo-3,5-dimethylbenzene .............................................................................................26
  - N,N-Diethylbenzamide .........................................................................................................27
  - 3,5-Dimethylbenzophenone (Lithiation Pathway) ................................................................28
  - 3,5-Dimethylbenzophenone (Grignard Pathway) ................................................................29
  - Benzophenone-3,5-dicarboxylic acid ...............................................................................30
  - Benzophenone-3,5-dicarboxylic acid chloride ....................................................................30
  - $6^A, 6^B, 6^A, 6^B$-(Benzophenone-3,5-diacid)$_2$-$\beta$-cyclodextrin ....................................31

RESULTS AND DISCUSSION ....................................................................................................32

CONCLUSION ............................................................................................................................42

APPENDICES ............................................................................................................................43
  - Appendix I: $^1$H and $^{13}$C NMR Spectra ...........................................................................43
  - Appendix II: Internet NMR Predictions ..............................................................................53
  - Appendix III: PC Model Ball and Stick Structures .............................................................63

REFERENCES ............................................................................................................................65

VITA ..............................................................................................................................................67
ACKNOWLEDGMENTS

The author wishes to express his appreciation to Professor Christopher J. Abelt for his patient guidance and encouragement throughout the investigation and in the preparation of this thesis. The writer also indebted to Professors Gary W. Rice and Robert J. Hinkle for their help in critiquing and offering suggestions for this manuscript, and to Professors W. Gary Hollis and Jonathan Touster for their inspiration and tireless patience during my undergraduate studies.
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Molecular Modeling Data for Benzopinacol Capped β-cyclodextrin</td>
<td>40</td>
</tr>
</tbody>
</table>

vi
<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Structures of $\alpha-), $\beta-) and $\gamma-$cyclodextrins.</td>
<td>6</td>
</tr>
<tr>
<td>2. Dimensions of $\alpha-), $\beta-) and $\gamma-$cyclodextrins.</td>
<td>7</td>
</tr>
<tr>
<td>3. Faces of Cyclodextrins.</td>
<td>8</td>
</tr>
<tr>
<td>4. Hydrophobic Effect</td>
<td>11</td>
</tr>
<tr>
<td>5. Breslow's &quot;Flexible Cap&quot;</td>
<td>13</td>
</tr>
<tr>
<td>6. First True Cyclodextrin Cap</td>
<td>14</td>
</tr>
<tr>
<td>7. Loopers Walk vs Oligomerization</td>
<td>14</td>
</tr>
<tr>
<td>8. AB, AC and AD Caps on $\beta-$Cyclodextrin</td>
<td>15</td>
</tr>
<tr>
<td>9. Tabushi's Regiospecific AB, AC and AD Caps</td>
<td>16</td>
</tr>
<tr>
<td>10. Benzopinacol Formation</td>
<td>19</td>
</tr>
<tr>
<td>11. Three Major Pinacol Products</td>
<td>20</td>
</tr>
<tr>
<td>12. High Intensity Radiation Induced Radical-Radical Reactions</td>
<td>21</td>
</tr>
<tr>
<td>13. Proposed Acetylisophthalic Acid Synthesis</td>
<td>22</td>
</tr>
<tr>
<td>14. Synthesis of 5-Cyano-1,3-Isophthalic Acid</td>
<td>22</td>
</tr>
<tr>
<td>15. Synthesis of Benzophenone-3,5-Dicarboxylic Acid</td>
<td>23</td>
</tr>
<tr>
<td>16. Synthesis of 1-Bromo-3,5-Dimethylbenzophenone</td>
<td>33</td>
</tr>
<tr>
<td>17. Synthesis of N,N-Diethylbenzamide</td>
<td>33</td>
</tr>
<tr>
<td>18. Synthesis of 3,5-Dimethylbenzophenone (Lithiation Pathway)</td>
<td>34</td>
</tr>
<tr>
<td>19. Synthesis of 3,5-Dimethylbenzophenone (Grignard Pathway)</td>
<td>35</td>
</tr>
<tr>
<td>20. Mechanism for the Oxidation of Methyl Groups to the Corresponding Acids</td>
<td>36</td>
</tr>
<tr>
<td>21. Synthesis of Benzophenone-3,5-Dicarboxylic Acid Chloride</td>
<td>38</td>
</tr>
<tr>
<td>22. $^1$H NMR Spectrum of 1-Bromo-3,5-Dimethylbenzene</td>
<td>43</td>
</tr>
<tr>
<td>23. $^{13}$C NMR Spectrum of 1-Bromo-3,5-Dimethylbenzene</td>
<td>44</td>
</tr>
<tr>
<td>24. $^1$H NMR Spectrum of N,N-Diethylbenzamide</td>
<td>45</td>
</tr>
<tr>
<td>25. $^{13}$C NMR Spectrum of N,N-Diethylbenzamide</td>
<td>46</td>
</tr>
<tr>
<td>26. $^1$H NMR Spectrum of 3,5-Dimethylbenzophenone (Lithiation Pathway)</td>
<td>47</td>
</tr>
<tr>
<td>27. $^1$H NMR Spectrum of 3,5-Dimethylbenzophenone (Grignard Pathway)</td>
<td>48</td>
</tr>
<tr>
<td>28. $^{13}$C NMR Spectrum of 3,5-Dimethylbenzophenone (Grignard Pathway)</td>
<td>49</td>
</tr>
<tr>
<td>29. $^1$H NMR Spectrum of Benzophenone-3,5-dicarboxylic acid</td>
<td>50</td>
</tr>
<tr>
<td>30. $^{13}$C NMR Spectrum of Benzophenone-3,5-dicarboxylic acid</td>
<td>51</td>
</tr>
<tr>
<td>31. $^1$H NMR Spectrum of Benzophenone-3,5-dicarboxylic acid chloride</td>
<td>52</td>
</tr>
<tr>
<td>32. Predicted $^1$H NMR Spectrum of 1-Bromo-3,5-dimethylbenzene</td>
<td>53</td>
</tr>
<tr>
<td>33. Predicted $^{13}$C NMR Spectrum of 1-Bromo-3,5-dimethylbenzene</td>
<td>54</td>
</tr>
<tr>
<td>34. Predicted $^1$H NMR Spectrum of N,N-Diethylbenzamide</td>
<td>55</td>
</tr>
<tr>
<td>35. Predicted $^{13}$C NMR Spectrum of N,N-Diethylbenzamide</td>
<td>56</td>
</tr>
<tr>
<td>36. Predicted $^1$H NMR Spectrum of 3,5-Dimethylbenzophenone</td>
<td>57</td>
</tr>
<tr>
<td>37. Predicted $^{13}$C NMR Spectrum of 3,5-Dimethylbenzophenone</td>
<td>58</td>
</tr>
<tr>
<td>38. Predicted $^1$H NMR Spectrum of Benzophenone-3,5-dicarboxylic acid</td>
<td>59</td>
</tr>
<tr>
<td>39. Predicted $^{13}$C NMR Spectrum of Benzophenone-3,5-dicarboxylic acid</td>
<td>60</td>
</tr>
<tr>
<td>40. Predicted $^1$H NMR Spectrum of Benzophenone-3,5-dicarboxylic acid chloride</td>
<td>61</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>41. Predicted $^{13}$C NMR Spectrum of Benzophenone-3,5-dicarboxylic acid chloride</td>
<td>62</td>
</tr>
<tr>
<td>42. Ball and Stick Structure of ABCD3 — Side View</td>
<td>63</td>
</tr>
<tr>
<td>43. Ball and Stick Structure of ABCD3 — Top View</td>
<td>64</td>
</tr>
</tbody>
</table>
ABSTRACT

Several different methods were investigated concerning the synthesis of benzophenone-3,5-diacid chloride and the subsequent double-capping of β-cyclodextrin. The most promising route involved a four step synthesis starting from the recently commercially available 1-bromo-3,5-dimethylbenzene. The next to last step, the chlorination of the carboxylic acid groups in benzophenone-3,5-dicarboxylic acid, was investigated under a number of different reaction conditions.

The chlorination reaction involving oxalyl chloride in methylene chloride proved to be the most promising, and was finally attached to β-cyclodextrin. These products are to be photopinacolized into the first ever “tetracap” for β-cyclodextrin.
SYNTHESIS OF BENZOPHENONE-3,5-DIACID CHLORIDE FOR THE DOUBLE CAPPING OF β-CYCLODEXTRIN
INTRODUCTION

Cyclodextrins, discovered by Villiers in 1891, have a variety of research and industrial applications which has led to the recent explosion into the study of the different and unique properties that these molecules possess. Cyclodextrins are cyclic macromolecules which are composed of different numbers of D-(+)-glucopyranose units connected by α-(1,4)-linkages; this structural arrangement was first published by Freudinger in the 1940s. Cyclodextrins are formed by treating starch with an amylase from Bacillus macerans to form a digest that contains these hollow circular sugars. The three major cyclodextrin products found in this digest have either 6, 7, or 8 units, referred to by their respective Greek prefixes α-, β-, and γ-cyclodextrins. Interest in these cyclodextrins has stemmed from their chemical properties which derive from their structural attributes such as their toroidal shape and hydrophilic faces and hydrophobic cavity.

A major facet in the study of cyclodextrins is their ability to form inclusion complexes. Guest compounds range from polar molecules such as amines, acids and small ions to apolar compounds such as aliphatic and aromatic hydrocarbons. Inclusion complex formation is similar to enzyme-substrate formation, and allows the cyclodextrin to act as a catalyst for various organic reactions through a cage effect. A cage effect increases the probability for both the proper geometry and sufficient energy that are necessary for an organic reaction to occur. Since the size of cyclodextrins is between that of enzymes and most other organic molecules, they can provide valuable insight into the mechanism of enzymatic activity.
Industrial and academic research communities have also investigated other uncommon properties of cyclodextrins. These range from their ability to form stereospecific complexes and the manner in which hydrophobic interactions occur to the dielectric properties of the interior surface which are different from that of the aqueous solution that surrounds the molecule; all of these are characteristics of many enzyme systems. Due to the diversity of these different properties, cyclodextrins have found a niche in the chemical world, and many of the different uses for this macromolecule have been patented in the agricultural, food, cosmetic, and pharmaceutical industries.

Industrial applications of cyclodextrins often utilize the ability to form inclusion complexes. Examples range from the common practice by the agricultural industry of molecular encapsulation of volatile insecticides and herbicides (which allows for the stabilization of potentially dangerous chemicals) to the novel approach of producing a powdered alcoholic beverage via the facility of its inclusion into the cavity of β-cyclodextrin.

The bulk of recent research, however, has occurred within the pharmaceutical industry. This is based on two different enhancements that cyclodextrins provide to the guest drug. First, the host-guest complex provides a stabilizing effect on the drug, which inhibits the effects of oxygen and water on a potentially delicate drug, and prevents decomposition. The second complement is a result of the ability of the slightly water-soluble cyclodextrins to bind nonpolar compounds in their hydrophobic cavity. Such a complex allows the drug to be transported in the body's aqueous medium. Once this cyclodextrin-drug complex reaches the proper site in the body, the drug is released from the host because equilibrium favors the binding between the drug and body to the
binding between the drug and cyclodextrin. It is rare for the drug to become dissociated from the host due to the high site selectivity of modern pharmaceuticals, and the strong hydrophobic interactions which preclude the chance of premature expulsion.

In the quarter of chemical research, derivitized cyclodextrins are being studied by a variety of research groups. Cyclodextrins are fairly stable in basic solutions, while subject to cleavage in highly acidic environments. This detail allows for functional groups to be attached to the cyclodextrin via an alkaline catalyst.

Functional groups can be attached to the cyclodextrin molecule in a variety of ways. The vast majority of these groups are attached to cyclodextrin at the C-6 hydroxyl group of a given glucopyranose residue primarily because steric effects prevent access to the secondary hydroxyl groups. Such a group when attached to one residue is considered a tether; multifunctional groups can bind the same cyclodextrin at two or more residues and are deemed caps. AB capping results when adjacent residues are attached to a given organic molecule; capping two residues that are separated by one sugar subunit is called AC capping, and so forth. Numerous studies of tethers and caps have been published.

The primary reason that cyclodextrin derivitization has been studied is that the ability of cyclodextrins to bind substrates can significantly increase when either capped or tethered. In unsubstituted cyclodextrin, the lack of a “floor” and the accompanying hydrophobic interactions that the derivitization provides can allow a guest to simply flow through the host. This causes nonderivitized cyclodextrins to form less effective inclusion complexes, and therefore make poorer catalysts; this is a significant driving force in investigating caps and tethers for cyclodextrin that maximize hydrophobic interactions as
well as the surface area of the floor in order to provide the ultimate amount of substrate binding potential.

The main focus of this research was to prepare benzophenone-3,5-diacid chloride for the ABA'B' double capping of β-cyclodextrin. It has been shown that two benzophenone molecules, under low intensity radiation, undergo a free-radical coupling reaction in isopropanol to form benzopinacol. It has further been postulated that having a cyclodextrin derivitized with two of these benzophenone caps would result in the first cyclodextrin to be tetrasubstituted by one molecule. Eight different isomers of this pinacolized product exist. After isolation, benzopinacol may prove to be the best cyclodextrin cap known, in terms of substrate binding and general effectiveness.
BACKGROUND

Cyclodextrins:

Cyclodextrins are cyclic oligosaccharides that contain between six and twelve \( \alpha-(1,4) \)-linked glucose units.\(^1\) Alternatively denoted as cycloamyloses, cycloglucans, or Schardinger dextrins, cyclodextrins are commonly referred to by Greek prefixes that correspond to the number of sugar residues that compose that molecule. For example, \( \alpha- \) cyclodextrin contains six glucose molecules, \( \beta- \) cyclodextrin contains seven subunits, \( \gamma- \) cyclodextrin contains eight, and so forth. Cyclodextrins with fewer than six residues have never been isolated, and are believed to be too sterically hindered to exist. Additionally, cyclodextrins with more than nine residues have never been isolated, even though they have been identified as components of the crude digest that arises from the synthesis of cyclodextrins. Fortunately, such large cyclodextrins are considered to be too flexible to be of interest for binding and functionalization studies.

Figure 1: Structures of \( \alpha-, \beta-, \) and \( \gamma- \) cyclodextrins
Cyclodextrins are produced commercially by treating starch with the enzyme amylase from the bacteria *Bacillus macerans*. The crude digest that results contains a variety of different cyclodextrins, primarily $\alpha-$, $\beta-$, and $\gamma-$cyclodextrins. These smaller cyclodextrins may be separated and purified through a variety of methods including different chromatographic means and selective precipitation. Isoamylase has been proven to improve the reaction yield of these more desirable cyclodextrins.

![Diagram of Cyclodextrins Dimensions](image)

**Figure 2: Dimensions of $\alpha-$, $\beta-$, and $\gamma-$cyclodextrins**

Each of the glucopyranose residues exists in a relatively undisturbed chair conformation. This constraint allows for the unique chemical properties of cyclodextrin in that this ordering causes the functional groups of the macromolecule to form discrete hydrophilic and hydrophobic regions. Due to this conformation, all of the primary hydroxyl groups, on C-6, are on the same side of the torus, which is known as the primary face. Similarly, all of the secondary hydroxyl groups, on C-2 and C-3, are on the opposite side of the hollow molecule, called the secondary face. Such an arrangement allows enough surface hydrophilicity to make cyclodextrins water-soluble. Conversely, the inside of the cavity is hydrophobic, due to the C-3 and C-5 hydrogens and the ether-like
oxygens. Therefore, these cavities provide a "microheterogeneous environment" in aqueous solutions by establishing a hydrophobic matrix in an otherwise hydrophilic setting.

Figure 3: Faces of Cyclodextrins

The inherent flexibility of the C-6 hydroxyl groups allows them to rotate and partially block the primary face of the cyclodextrin. This allows the primary face to be somewhat narrow. However, the C-2 and C-3 hydroxyl groups are virtually locked into a constant position due both to the intermolecular hydrogen-bonding and to their direct attachment to the rigid ring which allows the secondary face of cyclodextrin to remain open, and slightly wider than the primary face. In this fashion, cyclodextrin is somewhat "V"-shaped.

The cyclic chain of the glucopyranose residues in cyclodextrin is energetically favored over the corresponding linear form. Empirically, the enthalpy component of its free energy is higher for α-, β-, and γ-cyclodextrins, but the entropy factor compensates. This entropy change is due to the reorientation of the water molecules in
solution around the glucose units once the structure is formed due to their decreased surface area.\(^1\)

\(\beta\) -cyclodextrin has been more widely used in derivitization and complexation studies than any other cyclodextrin. This stems largely from its high rigidity, which is due to the complete hydrogen bonding that occurs between the secondary hydroxyl groups; hydrogen-deuterium exchange reactions confirm that every C-2 and C-3 hydroxyl group is involved in hydrogen bonding. In the smaller \(\alpha\) -cyclodextrin, the amount of conformational strain prohibits such complete hydrogen bonding, and one of the residues is forced to rotate out of alignment with the other five subunits in order to maximize this stabilizing effect which eliminates two such bonds. This deviation from an ideal torus makes \(\alpha\) -cyclodextrin a poor choice for these derivitization and complexation studies. In higher cyclodextrins, the inherent flexibility diminishes the stabilizing effects of the secondary face hydrogen bonding, which similarly renders them useless for these studies. The same rigidity that causes \(\beta\) -cyclodextrin to act as the best agent for derivitization and complexation studies also causes it to be much less soluble in water than other cyclodextrins.\(^7\)

**Inclusion Complexes:**

The single most important feature of cyclodextrins are their ability to act as a host for complexing organic molecules in their cavities. Such guest compounds are known to include various nonpolar molecules such as aliphatic and aromatic hydrocarbons and rare gases, and also a number of highly polar compounds such as acids, amines, and small ions.\(^1\)
Cyclodextrin inclusion complexes are able to form in aqueous solutions because they are energetically favored, both enthalpically and entropically. Several reasons have been proposed to explain this significant enthalpy change. Van der Waals interactions (permanent dipole - induced dipole) and London dispersion forces (induced dipole - induced dipole) exist between the cyclodextrin host and the guest molecule. These appear to play a decisive role in determining how tightly bound a substrate will be to the host. Also, hydrogen bonding between the C-6 hydroxyl groups of the cyclodextrin and similar sites on the guest would favor inclusion enthalpically, although no significant mechanism has been developed to define it as a major energetic driving force behind inclusion complex formation.

The inclusion of a guest molecule into the cavity of the cyclodextrin would also necessitate the ejection of water molecules. Consequently, these water molecules are allowed to rejoin the other water molecules that exist in the solution, and complete a full ensemble of hydrogen bonds that were not available inside the hydrophobic cavity. The release of these higher energy molecules allows nonpolar molecules to order themselves together, and provides the opportunity for water molecules to orient around the nonpolar whole rather than around each individual nonpolar moiety; this reduces the surface to polarity ratio for polar-nonpolar interactions, thus reducing the overall energy. This idea also holds that a higher binding affinity between the host and guest would lead to a more effective displacement of the water from the cavity.8

This water displacement is a significant force in driving complexation reactions in lower order cyclodextrins. Strain in α-cyclodextrin forces one of the residues to rotate out of the plane of the other subunits. X-ray crystallography shows that when an
assortment of different guest molecules were introduced into the cavity of 
$\alpha$-cyclodextrin, the water molecules were displaced, and the skewed residue rejoined the 
orientation of the other subunits. The removal of the angle strain, combined with the 
regained two hydrogen bonds and the entropy effect of the cavity water molecules, favor 
the cyclodextrin complex over that of of free $\alpha$-cyclodextrin. This effect is less dramatic 
in larger cyclodextrins, but still make a contribution towards the overall energetic 
favorability of inclusion complex formation. In fact, this is a significant reason why many 
aromatic and aliphatic hydrocarbons in solution with cyclodextrins prefer to reside in the 
apolar cavity of the macromolecule.

A variety of spectrometric methods can be used to determine whether a substrate 
is actually complexed with the cyclodextrin. Early studies incorporated X-ray 
spectroscopy to determine that a complex actually existed, although more data were 
needed in order to verify that this reaction occurred in solution. Today, NMR is the
primary tool used to confirm the constitution of such complexes. There are other spectrometric techniques that can be employed to analyze the molecular nature of these inclusion complexes, such as circular dichroism, fluorescence, and ultraviolet absorption, but $^1$H NMR still sets the universal standard for proof in modern laboratories for reproducibility. For example, when substituted benzoic acids are added to an $\alpha$-cyclodextrin solution the protons attached to C-3 and C-5, which are oriented towards the interior of cyclodextrin, exhibit a significant upfield shift, which is a deshielding effect that would occur in the presence of a hydrophobic entity. Similarly, but not nearly as pronounced, are the upfield shifts that correspond to the hydrogens bonded to C-1, C-2, and C-4, which are oriented to the outside of the cavity. Therefore, an inclusion complex has been corroborated empirically by $^1$H NMR.

**Capping:**

Considerable attention has been focused on modifying cyclodextrins in order to maximize the binding strength of various inclusion complexes. Capping a cyclodextrin, using a bifunctional reagent, would boost this binding strength by providing additional hydrophobic surface area to the cavity which would more tightly bind a substrate. Capping also helps stabilize the structure of the cyclodextrin. An uncapped cyclodextrin has a disadvantage over a capped cyclodextrin in that both of the ends of the torus are open, which may allow two different means for a guest to dissociate from the host since the additional open end allows another site for substrate attack.

The Nemethy-Shegara theory states that the hydrophobic surface area that is exposed to the solvent is inversely proportional to the hydrophilic binding strength.
Breslow and Emert utilized this theory in hopes that substituting the C-6 hydroxyl groups with other functional groups that would help bind a substrate by favorably orienting these functionalities around the guest within the cavity. They based their assumptions on molecular modeling, and proposed that the alkyl groups of their derivatives would cluster within the void of the host, and form a “flexible cap.”

\[
\begin{align*}
R &= \text{CH}_3 \text{ or } \text{CH}_2\text{CH}_3 \\
X &= \text{Primary Hydroxyl Site of Attachment}
\end{align*}
\]

Figure 5: Breslow’s “Flexible Cap”

1-Adamantanecarboxylic acid was shown to complex with these modified \(\beta\)-cyclodextrins significantly better than that of garden variety \(\beta\)-cyclodextrin, other guests such as \(m\)-nitrophenyl acetate were found to actually form worse complexes than those of a comparable reaction with underivitized \(\beta\)-cyclodextrin. Additional modeling suggested that the flexible capping made the cavity too shallow for the substrates to bind effectively; there were an insufficient number of van der Waals interactions. Also, the flexible capping reduced the overall rigidity of the cyclodextrin due to their inherent ability to freely rotate; this would also reduce the binding ability of the cyclodextrin.

The next year, Tabushi et al. modified Breslow’s work, and reported that a derivitized cyclodextrin had been synthesized using a bifunctional, rigid, highly aromatic molecule. This cap, diphenylmethane-p,p’-disulfonyl chloride, is the first known true cap
for cyclodextrin, and was able to successfully bind both 1-adamantane-carboxylic acid and
$m$-nitrophenyl acetate that had failed with Breslow's flexible cap.\textsuperscript{11}

![Figure 6: First True Cyclodextrin Cap](image)

Tabushi proposed a mechanism for the capping of $\beta$-cyclodextrin, known as the
"looper's walk." A cap, using either a disulfonyl chloride or a diacid chloride as the
functionalities, will react with one of the C-6 primary hydroxyl groups via an
addition-elimination mechanism. The residue that now contains the tether is designated
"A." This tether is free to rotate around each of the available bonds, and the second
functionality is subsequently attacked by one of the other primary hydroxyl groups within

![Figure 7: Loopers Walk vs Oligomerization](image)
the molecule. This residue is labeled according to the number of residues that separate it and A, that is a cap between adjacent residues is an AB cap, and so forth. Intramolecular reactions are rare due to the dilute nature of the solution and the infrequency of proper collisions to allow such reactions. Several factors that influence the types of regioisomers are the flexibility of the cap, the direction of attack, and the distance between functional groups.

Figure 8: AB, AC and AD caps on β-cyclodextrin

The number of regioisomers can be reduced by tailoring the cap to the desired interfunctional group distance. The sp3 carbon in Tabushi's original cap allowed a flexibility that produced a distribution in AC and AD isomers. Regiospecificity can be controlled by adjusting this distance, and Tabushi synthesized three caps to ensure this. These caps, that were fashioned to incorporate the desired distance between functional groups, virtually assured AB, AC and AD capping; they were, respectively, \textit{m}-benzenedisulfonyl chloride, benzophenone-3,3'-disulfonyl chloride, and \textit{E}-stilbene-4,4'-disulfonyl chloride.
Figure 9: Tabushi's Regiospecific AB, AC and AD Caps

Tabushi then took this capping to the next level by designing a tetrasubstituted β-cyclodextrin; polycapping may be achieved with AB and AC caps, but the seven sugar β-cyclodextrin will not allow multiple AD capping due to the mandatory cap crossing that would occur between the rigid attachments. When Tabushi used benzophenone-3,3'-disulfonyl chloride in a 2.6 molar stoichiometric excess to AC-A'C' double cap β-cyclodextrin, the cavity was found to be much more rigid with a significantly more well defined geometry.\textsuperscript{12} Also, $E$-stilbene-4,4'disulfonyl chloride was found to AD-A'D' double cap γ-cyclodextrin with similar cavity enhancements.\textsuperscript{12}

Double capping of β-cyclodextrin with photosensitive groups offers the possibility of further modifications. Such a group would form a true multisite cap that would allow an even more stable and well defined cavity to further increase the binding of a guest to a host.
Photochemistry:

The ultimate goal of this project was to photochemically reduce $\beta$-cyclodextrin doubly capped with a benzophenone derivative to the corresponding benzopinacol in order to produce the first tetracap of a cyclodextrin.

Photochemical reactions occur when a compound absorbs light. This results in excitation when the absorption of this energy changes the electronic configuration of the molecule by boosting a ground state electron into an excited state. However, direct spin inversion is forbidden by the selection rules of quantum mechanics which state that a coupling mechanism is required in order to produce the new minimum energy configuration. Normally, this relaxation occurs through the transfer of heat energy from the excited molecule to the solvent. Intersystem crossing also can occur with this vibrational relaxation through a mechanism that involves the spin inversion of an electron in a half-filled orbital. If this intersystem crossing is significantly faster than the rate of the reaction, the inversion leads to the triplet state configuration, where two electrons have the same spin. This triplet state has a lower energy than the first excited singlet state.

Photosensitization can also produce excited states. For triplet sensitization, intersystem crossing is much faster than the reaction from the singlet state or the heat transfer to solvent. An acceptor molecule reacts with the triplet state of the sensitizer to form the triplet state of the acceptor molecule. Such sensitizers are useful for molecules which undergo slow spin conversion.

Triplet states of carbonyls are stable enough to exist for a time in which a chemical reaction may occur. One of the most common reactions involves the oxygen from the carbonyl group abstracting a proton from either the solvent or another donor in
solution. Such a reaction may be either intramolecular or intermolecular. Hydrogen abstraction from the solvent is often followed by the coupling of the resulting $\alpha$-hydroxy radicals. Cleavage of the C-C bond adjacent to the carbonyl group is another common occurrence.

In addition to this reaction, other reactive excited states exist for more specific types of carbonyls. Among these are the $n\rightarrow\pi^*$ transition for saturated ketones, and the $\pi\rightarrow\pi^*$ for ketones in a $\pi$-system with extensive conjugation. In the $n\rightarrow\pi^*$ state, an electron is transferred from the nonbonding orbital of the oxygen to the $\pi$-antibonding orbital of the carbonyl, which is immediately followed by an intersystem crossing from the initial singlet state to the triplet state. In the $\pi\rightarrow\pi^*$ transition, an electron from the bonding $\pi$ orbital of the oxygen is excited to the antibonding $\pi^*$ orbital.\textsuperscript{16}

In 1900, Ciamician and Silber reported that benzophenone, a nonenolizable highly aromatic ketone, formed benzopinacol when irradiated in ethanol.\textsuperscript{12} After this reaction mechanism was first characterized in 1920 by Cohen,\textsuperscript{17} research on benzophenone chemistry increased dramatically. In the 1940s, Bachmann discovered that the reaction yield of benzopinacol could be maximized by changing the solvent to isopropanol, and irradiating the solution in an inert atmosphere using a low-intensity light source.\textsuperscript{13}

Benzopinacol is formed via the previously described mechanism in which photoexcited triplet benzophenone abstracts a proton in solution. As Bachmann showed, the solvent plays a great role in determining reaction yield in such reactions. In this case, isopropanol, with a small amount of glacial acetic acid in order to boost the amount of
labile protons, allows a nearly quantitative yield with benzopinacol; this is a substantial improvement over Ciamician and Silber’s original ethanol solvent. This is a result of the more stable radical that isopropanol forms upon hydrogen abstraction than a comparable ethanol radical. When a solvent is used that has no readily abstractable protons, such as acetonitrile-water, a benzophenone capped β-cyclodextrin was shown to abstract one of the protons from the C-6 hydroxyl group of one of the nearby glucopyranose residues. The resulting products showed a much lower yield of a coupled benzophenone, along with many other products due to the different pinacol products that arise from the C-6 aldehyde.

Abelt et al. showed that cyclodextrin that was AC capped with benzophenone at the 3 and 3’ positions was subsequently photoreacted in isopropanol to produce intermolecular pinacols. Initially, the benzophenone was excited to its single state via low level radiation. This singlet benzophenone then undergoes intersystem crossing to convert to the triplet state, where the newly formed triplet benzophenone abstracts the acidic
hydrogen from the alcohol, subsequently breaking the carbonyl double bond and creating a carbon-centered radical on the radical the donates hydrogen atom to another, unexcited, benzophenone which provides a more stable radical center through resonance. The two radical centers are now allowed to form a pinacol. HPLC showed that three forms of the photopinacols were formed, endo-endo, exo-exo, and endo-exo. This endo-exo product is the major product formed due to the two modes of attack that are possible, compared to the others that are formed by only one.\textsuperscript{14}

![Diagram of pinacol products]

Figure 11: Three Major Pinacol Products

In addition to these desired pinacols, other products are formed, due to the lack of specificity that is inherent in photochemical reactions. Rubin reports that higher intensity light increases the effects of "light absorbing transients." or LATs.\textsuperscript{18} These act as internal filters and as quenchers of triplet benzophenone. LATs are produced when a ketyl radical couples at either the ortho or para positions of the benhydrol radical. LATs serve to reduce benzopinacol yield because they react with the ketyl radicals to form ground state
benzophenone and the alkyl ketone. Also, any oxygen present in the system serves to quench ketyl radicals as well. Another complication arises when a higher intensity light source is used in that this boosts the levels of reverse hydrogen transfer.

Figure 12: High Intensity Radiation Induced Radical-Radical Reactions

**Previous Synthetic Pathways:**

There is no reported synthesis of benzophenone-3,5-diacid chloride. However, there have been previous, unpublished reports that concern the synthesis of other aromatic carboxylic acid chlorides that showed promise for the double capping of β-cyclodextrin.

In 1993, Sharma reported the attempted synthesis of 5-acetylisophthalic acid. The proposed synthesis, beginning with p-aminoacetophenone, showed promise. This proved to be successful until the 1-(3',5'-dicyanophenyl)-ethanol was found to be
difficult to synthesize. The resulting poor yields forced Sharma to be unable to complete the oxidation and subsequent hydrolysis that were necessary in order to produce the desired final acetylisophthalic acid product.

\[
\begin{align*}
\text{NH}_2 & \quad \xrightarrow{\text{HBr, } \text{H}_2\text{O}} \quad \text{Br} \quad \xrightarrow{\text{H}_2\text{SO}_4, \text{NaNO}_2} \quad \text{Br} \quad \xrightarrow{\text{NaBH}_4, \text{CH}_3\text{OH}} \quad \text{Br} \quad \xrightarrow{\text{CuCN}} \quad \text{H}_2\text{CO}_2\text{H} \\
\text{HO}_2\text{C} & \quad \xrightarrow{\text{H}^+} \quad \text{NC} \quad \xrightarrow{\text{HCr}_2\text{O}_7, \text{acetone}} \quad \text{NC} \\
\end{align*}
\]

Figure 13: Proposed Acetylisophthalic Acid Synthesis

In 1994, Williams reported the attempted synthesis of 3,5-benzophenone diacyl (and disulfonyl) chlorides.\textsuperscript{20} The synthesis of the acids proved problematic, and the bulk of his work was devoted to this enigma. The most successful endeavor that Williams explored involved the replacement of the amino group of dimethyl-5-amino-1,3-isophthalic acid with a cyano group.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \xrightarrow{\text{t-butyl nitrate, } \text{Cu(CN)}_2, \text{CH}_3\text{CN}} \quad \text{CO}_2\text{H} \\
\end{align*}
\]

Figure 13: Synthesis of 5-Cyano-1,3-Isophthalic Acid
In 1995, Cabral reported the synthesis of benzophenone-3,5-dicarboxylic acid. The chlorination and subsequent double-capping of this molecule to cyclodextrin were the principle focus of this project.

Figure 15: Synthesis of Benzophenone-3,5-Dicarboxylic Acid
MATERIALS AND METHODS

Tetrahydrofuran was distilled from sodium metal and benzophenone under nitrogen. Pyridine was distilled from sodium hydride under nitrogen. Commercially available cyclodextrin (Amaizo) was dried under vacuum (0.05 mm Hg, N$_2$ trap) at 100 °C overnight.

$^1$H and $^{13}$C NMR spectra were obtained with a General Electric QE-300 spectrometer and referenced to TMS at 0.0 ppm. Typical deuterated solvents included CDCl$_3$, DMSO-d$_6$ and CDCl$_3$ treated with 2-3 drops of DMSO-d$_6$. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass Spectrometry data were acquired with a Hewlett-Packard 5890 Series II Gas Chromatograph equipped with a HP 5971A Mass Selective Detector under the following conditions:

- **GC Column:** HP-Ultra 1 12 m long, 0.2 mm Column ID crosslinked methyl siloxane column
- **Carrier Gas:** Helium
- **Ionization Current:** 70 eV
- **Injector Temperature:** 230 °C
- **Detector Temperature:** 250 °C
- **Temperature Ramp:** 20 min run; 1.10 min solvent delay
  - Initial Temp: 60 °C for 2.00 min
  - Ramp 1: 11.0 °C/min for 7.40 min to 140 °C
  - Ramp 2: 17.0 °C/min for 6.50 min to 250 °C
  - Maintain 250 °C/min until run completed

Alchemy II from Tripos Associates was used to create molecules that were subsequently imported into PC Model v. 6.0 from Serena Software. Physical molecular modeling calculations were performed with the following parameters: Dipole-Dipole constants were used rather than electrostatic; the dielectric constant was 1.5; MMX calculations were started with full SCF pi calculation with a planar pi system and
unrestricted Hartree-Fock conditions. The multiplicity was set to zero. $^1$H and $^{13}$C NMR predictions were made using Advanced Chemistry Development’s online Java applet, Interactive Lab v. 3 beta, at <http://www.acdlabs.com/activelab/>. These NMR prediction algorithms assume a nonpolar and nonaromatic solvent and a 300.0 MHz system.
1-Bromo-3,5-dimethylbenzene

To a 1000 mL three-neck round bottom flask fitted with a thermometer, addition funnel and reflux condenser was added 21.07 g (0.174 mol) of 2,4-dimethylaniline and 400 mL of deionized water. 48% HBr (36.7 g, 0.455 mol) was added slowly to the solution, and the reaction was heated to 70 °C while stirring for 1.5 hours. 30% H2O2 (18 mL, 0.176 mol) was added dropwise. The heat was subsequently removed, and the exothermic reaction raised the temperature to 85 °C. Upon cooling to 70 °C, the solution was filtered under aspirator vacuum. The remaining solvent was extracted with methylene chloride; this organic layer was rinsed with water, then rinsed with an aqueous solution of Cu(II)Br2 to remove any remaining peroxides. The solvent was removed under reduced pressure. The product was used immediately.

The 1-bromo-3,5-dimethyl-2-aniline was combined with 500 mL of 95% ethanol in a 1000mL three neck round bottom flask fitted with a thermometer, reflux condenser, and an addition funnel. The solution was heated with stirring as concentrated H2SO4 (18 mL) was added dropwise via pipet. A solution of sodium nitrite (30.9 g in 270 mL water) was then added dropwise to the reaction along with a catalytic amount of copper powder. The resulting solution was heated to reflux, and allowed to react for two hours, at which time the above process was repeated in order to maximize yield. The solution was extracted with hexanes, washed with water, and the solvent was removed under reduced pressure via aspirator vacuum. The resulting oil was fractionally distilled, again under aspirator pressure, with the temperature moderated via an oil bath. The fraction recovered between 90 °C and 95 °C
was collected and stored at room temperature. The product was a light-brown clear liquid (10.42 g, 56.3 mmol, 32.3 % yield from 2,4-dimethylaniline).

\[^{1}\text{H} \text{NMR} \delta \text{ (ppm)} 7.20 \text{ (s, 2H)}; 6.98 \text{ (s, 1H)}; 2.35 \text{ (s, 6H)}\]
\[^{13}\text{C} \text{NMR} \delta \text{ (ppm)} 140.8; 129.2; 128.1; 122.4; 21.8\]
GC-MS (retention time) 6.61 min

**N,N-Dimethylbenzamide**

A three-necked 250 mL round bottom flask was equipped with an addition funnel and a CaCl\(_2\) drying tube. Diethylamine (11.45 g, 156.6 mmol) and chloroform (100 mL) were placed in the flask, which was then placed in an ice bath. Benzoyl chloride (10g, 7.12 mmol) was then added dropwise. The reaction was allowed to stir overnight, and was room temperature by morning. The organic layer was separated from the water layer, and this was rinsed with water to remove all traces of diethylamine. The solution was then dried with anhydrous sodium sulfate. After rotary evaporation of the solvent from the solution, the crude product was distilled under vacuum (0.05 mm Hg). The fraction collected between 87 and 91°C was a clear, colorless liquid (7.89 g, 4.48 mmol, 69% yield).

\[^{1}\text{H} \text{NMR} \delta \text{ (ppm)} 7.33 \text{ (t, 2H)}; 7.30 \text{ (d, 2H)}; 7.28 \text{ (t, 1H)}; 3.24 \text{ (q, 4H)}; 1.15 \text{ (t, 6H)}\]
\[^{13}\text{C} \text{NMR} \delta \text{ (ppm)} 170.47; 138.28; 129.26; 128.67; 126.75; 43.3; 39.26; 13.85\]
GC-MS (retention time) 10.85 min
3,5-Dimethylbenzophenone

Distilled tetrahydrofuran (400 mL) and 1-bromo-3,5-dimethylbenzene (12.14 g, 65.6 mmol) were placed in a three-neck, 1000 mL round bottom flask that was equipped with an alcohol (low-temperature) thermometer, addition funnel, and a nitrogen line. A mechanical stirrer was situated above the flask, and a copious amount of plastic film (Parafilm) was wrapped around the neck and stir rod in order to maintain the integrity of the nitrogen atmosphere. The nitrogen flow rate insured a positive pressure that prevented the entry of undesirable oxygen and water into the system. The solution was vigorously stirred under this inert atmosphere, which effectively sparged the system. The flask was then placed in a low form Dewar flask which contained an ethyl ether - liquid nitrogen slurry. \textit{n}-Butyl lithium (45 mL, 1.6 M in hexanes) was slowly added to the system in order to prevent the exothermic lithiation from heating the system above -90 °C. The reaction was allowed to proceed for 45 minutes, whereupon N,N-diethylbenzamide (15.75 g, 89.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature, and was stirred for an additional 45 minutes. In order to quench the excess lithium reagent, a dilute aqueous solution of ammonium chloride followed by a dilute aqueous solution of sodium chloride (each 18 g / 200 mL). The aqueous layer was extracted with several portions of ethyl ether, dried with sodium sulfate, concentrated \textit{in vacuo}, and distilled under vacuum (0.05 mm Hg). The fraction boiling between 122 and 128 °C was recrystallized from ethanol to form a yellow-white solid (6.30 g, 34.0 mmol, 52% yield).

**MP 62-65 °C**

$^1$H NMR $\delta$ (ppm) 7.78 (d, 2H); 7.58 (m, 1H); 7.50 (m, 2H); 7.44 (s, 1H); 7.39
(s, 2H); 2.37 (s, 6H)

GC-MS (retention time) 13.50 min

3.5-Dimethylbenzophenone

A 250 mL round bottom flask, addition funnel, reflux condenser, “duck head” gas line adapter, magnetic stir bar and thermometer were rinsed with acetone and dried with a heat gun. Upon cooling to the touch, the apparatus was assembled, and flushed with nitrogen. Ethyl ether (100 mL), iodine crystals (0.5 g, 3.94 mmol) and fresh magnesium turnings (5.5 g, 226 mmol) were stirred together while refluxing until the brown color disappeared. Commercially available 1-bromo-3,5-dimethylbenzene (Acros) (10 g, 54.0 mmol) in 30 mL dry ether was added dropwise to the mixture. The reaction was allowed to continue under gentle reflux conditions for four hours, whereupon benzonitrile (6.25 g, 60.6 mmol) in 30 mL dry ether was added dropwise to the reaction vessel. After all of the benzonitrile was added, the nitrogen line was replaced by a calcium carbonate drying tube and allowed to reflux overnight. The reaction was then allowed to cool, 75 mL water and 25 mL 95% ethanol were added to the reaction vessel to quench any excess Grignard reagent. The liquid was decanted off of the remaining magnesium into a 1000 mL round bottom flask; the turnings were rinsed several times with a total of 50 mL ethanol to ensure complete product transfer. An additional 100 mL deionized water was added to the products and the mixture was brought to reflux. After an hour, the ether layer was saved, and the aqueous layer was extracted with additional ether. The solvent was removed in
vacuo, and the remaining oil was recrystallized from ethanol to produce a white powder (4.96 g, 23.6 mmol, 43.7% yield).

$^1$H NMR $\delta$ (ppm) 7.86 (d, 2H); 7.67 (m, 1H); 7.56 (m, 2H); 7.46 (s, 1H); 7.31 (s, 2H); 2.45 (s, 6H)

$^{13}$C NMR $\delta$ (ppm) 171.12; 136.30; 134.42; 134.26; 131.94; 130.07; 128.63; 94.84

**Benzophenone-3,5-dicarboxylic acid**

3,5-Dimethylbenzophenone (2.05 g, 9.75 mmol) and 10 mL glacial acetic acid were added to a 100 mL round bottom flask fitted with an addition funnel, thermometer and a reflux condenser, and was brought to reflux. Chromium (VI) oxide (8.00 g, 54.0 mmol) was sonicated with 20 mL acetic acid and 2 mL fuming sulfuric acid, and was added very slowly to the reflux. The reaction was allowed to proceed for seven days, whereupon the product was extracted with methylene chloride. The product was then deprotonated by rinsing the organic layer several times with 1.0 M KOH in a separatory funnel. This aqueous layer was then reacidified with 1.0 M HCl and extracted with methylene chloride. After removing the solvent, a white solid resulted (1.49 g, 5.54 mmol, 56.8% yield).

$^1$H NMR $\delta$ (ppm) 8.07 (d, 2H); 7.79 (m, 1H); 7.58 (m, 2H); 7.44 (m, 3H)

$^{13}$C NMR $\delta$ (ppm) 196.40; 138.32; 138.16; 137.87; 133.80; 131.97; 129.83; 127.89; 21.04

**Benzophenone-3,5-diacid chloride**

A 100 mL round bottom flask was fitted with a reflux condenser, thermometer, calcium carbonate drying tube, and an addition funnel with a rubber cap.
Benzophenone-3,5-dicarboxylic acid (0.30 g, 1.11 mmol) was mixed with 10 mL methylene chloride and catalytic N,N-dimethyl formamide (20 μL) and subsequently brought to reflux. Oxalyl chloride (0.225 g, 1.78 mmol) was added over the course of 30 minutes via a syringe injected through the rubber cap of the addition funnel. The reaction was allowed to proceed for three hours, and the solvent was distilled off under a CaCO₃ drying tube to near dryness and allowed to cool. The product was used immediately. A small sample was taken of this crude wet mixture for NMR confirmation that chlorination had occurred.

¹H NMR δ (ppm) 8.19 (d, 2H); 7.98 (s, 1H); 7.72 (m, 2H); 7.56 (m, 3H)

⁶⁶, ⁶⁸, ⁶⁺, ⁶⁻(Benzophenone-3,5-diacid)-β-cyclodextrin

Vacuum dried β-cyclodextrin (0.51 g, 0.45 mmol) was stirred with freshly distilled pyridine and the crude benzophenone-3,5-diacid chloride product in a 50 mL round bottom flask fitted with a nitrogen line. The reaction was allowed to stir overnight at room temperature, and the pyridine was then distilled off under vacuum (0.05 mm Hg) at 55 °C.
RESULTS AND DISCUSSION

Although the original objective of this research was to synthesize benzophenone-3,5-diacid chloride capped β-cyclodextrin, the vast majority of this work was devoted to the chlorination of the acid groups. The focus of the research then changed in order to discover a way around this obstacle.

The synthetic pathway involved the formation of the desired diacid chloride via the chlorination of the acid groups of benzophenone-3,5-diacid. The synthesis was difficult to characterize due to the instability of the acid chlorides in air. The synthesis of both the diacid and 3,5-dimethylbenzophenone proved to be successful, each producing yields in the 45-55% range. The diacid was prepared from dimethylbenzophenone, which was synthesized either from 1-bromo-3,5-dimethylbenzene and N,N-diethyl benzamide via a lithium exchange reaction or from a Grignard reaction between 1-bromo-3,5-dimethylbenzene and benzonitrile. N,N-Diethylbenzamide and 1-bromo-3,5-dimethylbenzene were originally synthesized; the bromoxylene became commercially available during the course of this project.

Commercially available 2,4-dimethylaniline was brominated with 48% HBr and 30% H₂O₂. These brominating reagents were chosen because they will selectively attack the aromatic ring rather than the methyl groups that bromine alone would. The amino group of the resulting product was removed via a diazotization reaction, giving 1-bromo-3,5-dimethylbenzene in a 32% yield overall. N,N-Diethylbenzamide was successfully prepared with 69% yield via a simple addition-elimination reaction using benzoyl chloride and diethylamine.
Two different approaches were used to synthesize 3,5-dimethylbenzophenone. The first involved an n-butyllithium exchange reaction between the previously mentioned 1-bromo-3,5-dimethylbenzene producing a lithiated xylene intermediate that easily reacted with the N,N-diethylbenzamide to produce the dimethylbenzophenone. Several problems were initially encountered with this reaction. The original n-BuLi had degraded to the point that it was utterly useless, and this was proven by the extremely low yields encountered. An attempt was made to use titration to characterize the activity of the remaining reagent. This titration method involved two separate titrations. The first sought to determine the amount of base present, and used a solution of n-BuLi, water and isopropanol titrated with a potassium hydrogen phthalate standard with phenolphthalein indicator. The second titration was to determine the amount of lithium hydroxide, and used a solution of n-BuLi, ethyl ether, benzyl bromide, water and isopropanol and again
was titrated. This procedure failed to tell exactly how far the n-BuLi reagent had degraded, due to the inherent uncertainty of titrating to a visible indicator endpoint and also due to the practice of drawing off the hexane layer from the volumetric flask and replacing it with water. Subsequent reactions used fresh n-BuLi, and had a much higher yield.

![Chemical reaction](image)

**Figure 18: Synthesis of 3,5-Dimethylbenzophenone (Lithiation)**

The second approach to synthesizing 3,5-dimethylbenzophenone began after 1-bromo-3,5-dimethylbenzene became commercially available. Cabral reported that the "Grignard reagent could not be synthesized," and this was probably due to two factors: the magnesium turnings that were being used were old and oxidized, and her attempt to revive them using HCl rinsings may have failed; also, the distilled bromoxylene was insufficiently pure for a Grignard reagent to form. The bromoxylene reagent was reacted with fresh magnesium turnings that were purchased at the same time, and the reaction produced a moderately lower overall yield than the lithiation pathway; the commercially available bromoxylene produced slightly better yields in the lithiation reaction than did the synthesized reagent.
Chromium (VI) oxide was used in combination with acetic acid and sulfuric acid in order to oxidize the methyl groups into the desired diacid. Cabral found that when a mostly aqueous acidic environment, such as acetic acid, was used to solvate the dimethylbenzophenone the reaction proceeded with a much higher yield than occurred with a strong acid alone, such as sulfuric acid. This oxidation reaction is thought to proceed via a free radical mechanism; the exact character of the reaction is unknown, but is believed to occur through hydrogen atom transfer. This mechanism is the most favored model for this reaction largely due to the fact that Etard characterized a similar oxidizing reagent, chromyl chloride, that proceeds via this process. In this specific case, the hydrogen atom transfer leads to the formation of a free radical. A deprotonated acetic acid group is subsequently added to this site, and then hydrolyzed into the corresponding primary alcohol. This alcohol is then converted into a chromate ester intermediate, which then forms the carboxylic acid.
H-atom transfer

$\text{CrP}_3$,

$\text{Acetic Acid}$

$\text{HC}$.

$\text{Hydrolysis Ionic process } + \text{HO-Cr-OAc (IV) OAc}$

$\text{CH OAc}_2$ + $\text{HO-Cr-OAc (IV)}$

Figure 20: Mechanism for the Oxidation of Methyl Groups to the Corresponding Acids

The primary difficulties with this project involved the attempted conversion of these carboxylic acid groups into the corresponding acid chlorides. The “tried and true” method of using thionyl chloride for this transformation simply did not work as was expected. The original synthesis using this reagent involved using it as a combination solvent and reactant. This surely led to chlorination of the ketone carbonyl, and prevented any viable products from being recovered. Another problem that was encountered was the purity of the thionyl chloride. Great efforts had to be made to exclude any water and air from the system when distilling, and often the colorless distillate frustratingly turned
yellow while being recovered. A different method for purification was sought out, and involved a double distillation — first from quinoline then from boiled linseed oil; linseed oil is commonly found as the primary ingredient in oil based paint. This led to some initial success due to the color changes that were observed in the reaction vessel which indicated that some sort of chemistry was occurring, but whenever the system was exposed to the atmosphere, a black tar resulted. This led us to believe that some sort of different approach was necessary.

Oxalyl chloride was suggested by a colleague as an alternative chlorinating agent. This tends to be a "milder" reagent, which may help prevent ring and carbonyl attacks that may have occurred with the thionyl chloride. Also, it has been reported that excess N,N-dimethylformamide, used as a catalyst in the conversion of acid groups into acid chlorides, actually inhibits chlorination. Finally, an experiment was devised that prevented atmospheric interference, and allowed an in situ reaction with β-cyclodextrin. Upon distilling off the methylene chloride from the reaction, a dilute solution of β-cyclodextrin in pyridine was added to the still moist pot residue that held the crude products. The mixture was allowed to stir at room temperature under a nitrogen atmosphere. Initial NMR data suggested that a reaction did occur between the C6 hydroxyl groups of the cyclodextrin and the benzophenone-3,5-diacid chloride molecule, but this reaction has yet to be fully explored and characterized.
Molecular modeling was used in order to predict the favored stereochemistry of a benzopinacol capped \( \beta \)-cyclodextrin. Several problems were encountered here as well. The X-ray crystallographic file that was the basis for all of the modeling was a real-world situation that was obviously affected by the conditions extant at the time of the sample processing. There was no true C\(_7\) axis of symmetry that one would have expected, and most of the glucopyranose subunits were not aligned in the same plane, which inhibited hydrogen bond formation. This lack of rigidity is evident in the models in that the cap often skewed the molecule greatly after attachment; it is believed that having all fourteen hydrogen bonds present on the secondary face would have prevented this from occurring.

All four stereoisomer caps were modeled on each of the two possible double capping sites on the primary face. Each cap was evaluated as the reaction mechanism predicts — via the loopers walk. A benzophenone diacid moiety was attached at one primary hydroxyl group and then the structure was minimized. The second site of attachment was chosen on an adjacent hydroxyl group, and the structure was again minimized. At this time, the process was repeated with another benzophenone diacid. After the dicapping was complete, the ketone carbonyls were changed into a hydroxide, and the remaining valences were connected. The structure was then reminimized.
Several interesting things occurred during these minimizations. Since there were only three out of a possible fourteen hydrogen bonds present on the secondary face, the cyclodextrin was easily skewed by the minimization of the cap. However, at certain points in the minimization, other hydrogen bonds would appear, and the minimization would restart with this new parameter, causing slightly different end structures each time with the same structure. Also, the “free” phenyl groups on the stereocenters of the caps tended to rotate away from the cavity of the cyclodextrin.

This phenyl group rotation was originally thought to derive from bias that was put into the system at its creation, so new models were created with counter bias. These models were AB and DE caps, since these sites offer the most room in the cavity for movement; also, only the S regioisomer of the cap was used in order to be consistent. Since it has been determined that aromatic compounds energetically favor residing in a cyclodextrin cavity, it follows that this may be a possibility when a reaction occurs. If a cap is inside the cavity rather than outside when the reaction between the diacid chloride and C6 hydroxyl group occurs, then it may tend to stay inside. Also, cyclodextrins have been characterized as catalysts for photochemical reactions as well, so this might be actually favored. It turns out that when two of these caps are placed in the torus and then “pinacolized,” these free phenyl groups attempted to rotate out of the cavity again, this time towards the secondary face. Another model was constructed that had one cap residing inside the cavity with another cap on the outside. Interestingly, the minimization of this model caused two of the glucopyranose subunits that were attached to a cap to rotate 180° in order to accommodate pinacolization.
Another feature of PC Model was attempted as well. Two molecules can be "docked" together to determine the best interaction geometry for the two, but attempts at using the dock feature with anthracene and a capped $\beta$-cyclodextrin simply refused to cooperate, so this investigation was abandoned.

The capped cyclodextrins have been named for their particular sites of attachment and stereochemistry of the cap. ABCD indicates that four contiguous residues have caps; similarly, ABDE has a residue with an unbound C6 hydroxyl between the capped residues. The number suffixes define the stereochemistry of the pinacolized cap. "1" is RR, "2" is RS, "3" is SR, "4" is SS; the first letter in the pair corresponds with the first two letters in the four letter name of the cap attachment sites.

<table>
<thead>
<tr>
<th></th>
<th>Inside 1</th>
<th>Inside 2</th>
<th>ABCD 1</th>
<th>ABCD 2</th>
<th>ABCD 3</th>
<th>ABCD 4</th>
<th>ABDE 1</th>
<th>ABDE 2</th>
<th>ABDE 3</th>
<th>ABDE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMX</td>
<td>182.62</td>
<td>180.32</td>
<td>159.39</td>
<td>168.92</td>
<td>149.73</td>
<td>172.36</td>
<td>208.22</td>
<td>167.56</td>
<td>211.77</td>
<td>211.5</td>
</tr>
<tr>
<td>Str</td>
<td>9.71</td>
<td>8.96</td>
<td>5.98</td>
<td>6.86</td>
<td>5.79</td>
<td>6.63</td>
<td>5.92</td>
<td>6.78</td>
<td>6.1</td>
<td>6.38</td>
</tr>
<tr>
<td>Bnd</td>
<td>52.65</td>
<td>65.19</td>
<td>42.4</td>
<td>41.91</td>
<td>41.78</td>
<td>43.02</td>
<td>103.2</td>
<td>41.56</td>
<td>103.92</td>
<td>104.95</td>
</tr>
<tr>
<td>StrBnd</td>
<td>4.07</td>
<td>3.84</td>
<td>2.49</td>
<td>2.66</td>
<td>2.42</td>
<td>2.53</td>
<td>1.14</td>
<td>2.63</td>
<td>1.21</td>
<td>1.18</td>
</tr>
<tr>
<td>Tor</td>
<td>87.66</td>
<td>83.85</td>
<td>82.66</td>
<td>85.53</td>
<td>78.42</td>
<td>78.7</td>
<td>74.85</td>
<td>81.03</td>
<td>75.37</td>
<td>72.73</td>
</tr>
<tr>
<td>VdW</td>
<td>35.04</td>
<td>22.74</td>
<td>38.4</td>
<td>43.84</td>
<td>32.43</td>
<td>39.63</td>
<td>32.88</td>
<td>46.07</td>
<td>35.31</td>
<td>36.24</td>
</tr>
<tr>
<td>DipMo</td>
<td>22.42</td>
<td>31.95</td>
<td>8.85</td>
<td>8.8</td>
<td>17.34</td>
<td>13.58</td>
<td>18.88</td>
<td>3.73</td>
<td>19.85</td>
<td>20.75</td>
</tr>
<tr>
<td>Hf</td>
<td>608.5</td>
<td>2242.1</td>
<td>-1.9</td>
<td>-1565.6</td>
<td>1250.1</td>
<td>190.0</td>
<td>1304.3</td>
<td>-1607.3</td>
<td>1308.8</td>
<td>1275.9</td>
</tr>
<tr>
<td>SE</td>
<td>11.7</td>
<td>9.4</td>
<td>-11.5</td>
<td>-2</td>
<td>-21.2</td>
<td>-20.3</td>
<td>37.3</td>
<td>-3.4</td>
<td>40.9</td>
<td>40.6</td>
</tr>
</tbody>
</table>

Table 1: Molecular Modeling Data for Benzopinacol Capped $\beta$-cyclodextrin

Table 1 is a verbatim output of the different molecular models that were minimized. The best models are the ABCD3 and the ABDE2. In each of these models, the stereochemistry of the caps, SR and RS respectively, allow the phenyl groups to orient towards the more open area of the primary face of the $\beta$-cyclodextrin. Each of these stereoisomers is significantly favored over their respective enantiomer. Also, the ABCDx set proves to be energetically favored over the ABDE$\text{x}$ group.
Another computer model that was used during the course of this evaluation was NMR prediction. Advanced Chemistry Development, Inc., placed a Java applet on the Internet that allows a user to create a molecule then predict both carbon and proton NMR spectra. These outputs were used to confirm actual NMR spectra obtained during this study since they fairly accurately predict coupling patterns and chemical shift.
CONCLUSION

Although several methods for synthesizing benzophenone-3,5-diacid chloride were attempted, the oxalyl chloride / DMF reaction in methylene chloride showed the greatest amount of success. $^1$H NMR showed that a significant change occurred in the chemical shift that indicates that the acid chloride was synthesized. This method may be further refined in order to produce higher conversions and yields. Having achieved limited success in capping $\beta$-cyclodextrin with this benzophenone molecule, it is conceivable that photopinacolization could be used in order to transform a double cap into a single tetracap.
Figure 22: $^1$H NMR of 1-Bromo-3,5-dimethylbenzene
Figure 23: $^{13}$C NMR of 1-Bromo-3,5-dimethylbenzene
Figure 24: $^1$H NMR of N,N-Diethylbenzamide
Figure 25: $^{13}$C NMR of N,N-Diethylbenzamide
Figure 26: $^1$H NMR of 3,5-Dimethylbenzophenone (Lithiation Pathway)
Figure 27: $^1$H NMR of 3,5-Dimethylbenzophenone (Grignard Pathway)
Figure 28: $^{13}$C NMR of 3,5-Dimethylbenzophenone (Grignard Pathway)
Figure 29: $^1$H NMR of Benzophenone-3,5-dicarboxylic acid
Figure 30: $^{13}$C NMR of Benzophenone-3,5-dicarboxylic acid
Figure 31: $^1$H NMR of Benzophenone-3,5-dicarboxylic acid chloride
APPENDIX II
Internet NMR Predictions

Figure 32: Predicted $^1$H NMR of 1-Bromo-3,5-dimethylbenzene
Figure 33: Predicted $^{13}$C NMR of 1-Bromo-3,5-dimethylbenzene
Figure 34: Predicted $^1$H NMR of N,N-Diethylbenzamide
Figure 35: Predicted $^{13}$C NMR of N,N-Diethylbenzamide
Figure 36: Predicted $^1$H NMR of 3,5-Dimethylbenzophenone
Figure 37: Predicted $^{13}$C NMR of 3,5-Dimethylbenzophenone
Figure 38: Predicted $^1$H NMR of Benzophenone-3,5-dicarboxylic acid
Figure 39: Predicted $^{13}$C NMR of Benzophenone-3,5-dicarboxylic acid
Figure 40: Predicted $^1$H NMR of Benzophenone-3,5-dicarboxylic acid chloride
Figure 41: Predicted $^{13}$C NMR of Benzophenone-3,5-dicarboxylic acid chloride
APPENDIX III
PC Model Ball and Stick Structures

Figure 42: Ball and Stick Structure of ABCD3 — Side View
Figure 43: Ball and Stick Structure of ABCD3 — Top View
REFERENCES

6. Hubbard, B. unpublished data.
10. Abelt, C. J. Molecular modeling using Alchemy II (Tripos Associates) and PCMOL (Serena Software); molecular mechanics using MMX (Serena Software).


20. Williams, D. unpublished data.


VITA

Clyde Wesley Eargle

Born in Florence, South Carolina, 2 October 1973 to Charles and Marie Eargle. Graduated from George Washington High School in June 1991. Received a Bachelor of Science degree in chemistry with a minor in government from the College of William and Mary in August 1995. The author enrolled in the Master of Arts program at the College of William and Mary that same month.