The Anodic Oxidation of Diphenylacetaldehyde in the Presence of Alcohols

by

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Abstract

The aerobic and electrochemical oxidations of diphenylacetaldehyde (1) were investigated. It was demonstrated that 1 undergoes autoxidation with molecular oxygen to produce benzophenone (2). The anodic oxidation of 1 was carried out in the presence of a structural variety of alcohols. The major product of these reactions was the corresponding benzhydryl alkyl ether. Through deuterium-labeling studies it was demonstrated that ether formation was occurring through two competing mechanistic pathways. Using NMR integration analysis and mass spectroscopic ion counts of the deuterium-labeled products it was determined that at least 60%, and probably 80-90%, of the benzhydryl alkyl ether products were formed by oxidation of the enol of 1; the remaining product was formed by direct α-cleavage of the formyl group followed by nucleophilic attack by the alcohol. In the enolic oxidative pathway, α-alkoxydiphenylacetaldehydes were characterized as stable intermediates. Alternate silver ion-promoted syntheses of α-alkoxyaldehydes often resulted in atropisomeric products. Similar effects were also observed in benzhydryl-α-d phenethyl ether. Further research on the stereochemical properties of α-alkoxyaldehydes and benzhydryl alkyl ethers is ongoing.
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Introduction

Anodic electrochemistry is a useful and often underutilized method in organic synthesis\(^1\). It allows for the addition of increased functionality to a molecule and for the close study of reaction mechanisms under mild conditions\(^2\). In addition, chemical oxidations and reductions often utilize harmful reagents or result in toxic byproducts that are environmental hazards\(^3\). In many cases, the use of electrochemistry to affect chemical transformations circumvents this issue. Instead of potentially toxic reduced byproducts, the electrochemical oxidation processes are driven towards the formation of molecular hydrogen. Anodic oxidation also allows for fine-tuning of the reaction conditions either through the control of the anode potential or through the magnitude of the current passed through the reaction. The research and results presented here are a practical demonstration of the power and versatility of synthetic organic electrochemistry.

The primary focus of this research is the anodic oxidation of diphenylacetaldehyde (1) in the presence of various nucleophiles. Specifically, we wanted to investigate the mechanistic pathway(s) by which this reaction occurs. Our interest in this topic has its origins in previous work conducted in the Fry lab on the electrochemical dimerization of benzyl radicals\(^4\). Porter \textit{et al.} demonstrated that the electrochemical reduction of \(\alpha\)-substituted benzyl bromides produces radicals that couple to dimers as opposed to undergoing further reduction to anions.
Scheme 1: Dimerization of α-substituted benzyl bromide radicals

The cathodic reduction of substituted benzhydryl bromide 3c yielded results which were of particular interest. The radical coupling reaction produced three stereochemically related dimers 4, 5, and 6 in relative ratios of 72:19:9.

Scheme 2: Electrochemical reduction of α-trimethylsilylbenzyl bromide (3c)

Other groups had demonstrated that the electrochemical oxidation of benzyl silanes produces benzyl carbocations that are then trapped by nucleophiles in the electrolysis medium. It was therefore postulated that 1,2-disilanes like 4 might act as synthons for 1,2-dications. The electrochemical oxidation of 4 resulted in 65:35 mixture of 1,2-dimethoxy-1,2-diphenylethane (7) and diphenylacetaldehyde dimethylacetal (8). The formation of these products is believed to proceed through a common cationic
intermediate (9). Cation 9 can suffer nucleophilic attack by methanol to give 7. Alternatively, 9 can rearrange via phenyl-group migration to 10, which then undergoes nucleophilic attack by methanol to afford 7.

![Diagram](attachment:image.png)

**Scheme 3:** Electrochemical oxidation of a 1,2-disilanes to afford 1,2-dimethoxy-1,2-dimethylethane (7) and diphenylacetaldehyde dimethylacetal (8).

It was postulated that stabilization of cation 9 could inhibit the 1,2-phenyl shift rearrangement and yield a higher ratio of products similar to 7. The anodic oxidation of the \( p,p' \)-dimethoxy derivative of 3c yielded only the product analogous to 7. The corresponding acetal product was not observed. Apparently, the \( p \)-methoxy group stabilizes the cation sufficiently that it does not rearrange. It was therefore
postulated that the replacement of the methoxy with an electron-withdrawing group would destabilize 9 and lead to an increased proportion of the 1,2-aryl shift products analogous to 8.

However, the synthesis of 3c bearing electron withdrawing groups by reductive silylation of the corresponding stilbene (as was done for the stilbene compounds bearing electron-donating groups) proved unsuccessful\(^5\). It was decided to take another approach to the production of electronegatively substituted cation 9 analogs; it was reasoned that the anodic oxidation of the corresponding stilbene (11) would produce a radical cation (12) which would suffer nucleophilic attack. This would afford a radical species (13) which could be oxidized further to give an electronegatively substituted form of 9 (Scheme 4).

**Scheme 4:** Electrochemical synthesis of cation 9 analogs bearing electron withdrawing groups from the corresponding stilbenes \(^7\).  

Although the initial intent of anodically oxidizing stilbenes bearing *para* electron-withdrawing groups had been to study the driving force of the 1,2-aryl shift in analogs of 9, it was found that the oxidation of compounds like 11 in aqueous
acetonitrile gave interesting results worthy of separate study. Instead of following the reaction pathways outlined in Schemes 3 and 4 above, the electrochemical oxidation of electronegatively substituted stilbenes in aqueous acetonitrile yields two equivalents of benzaldehydes in good yield\textsuperscript{9}.

\[
\begin{align*}
\text{ArC=CHAr} & \quad \text{[O]} \quad 99:1 \text{CH}_3\text{CN}:\text{H}_2\text{O} \quad \text{Bu}_4\text{NBF}_4 \\
& \quad \text{ArCH-CHAr} \quad \text{OH} \quad \text{[O]} \quad 99:1 \text{CH}_3\text{CN}:\text{H}_2\text{O} \quad \text{Bu}_4\text{NBF}_4 \\
& \quad \text{2 ArCH=O}
\end{align*}
\]

A four electron oxidation process for the oxidation of stilbenes to benzaldehydes was proposed based on mechanistic studies carried out by Wu, Davis, and Halas in the Fry lab\textsuperscript{7-9}. It was determined that the reaction proceeds through the diol analog of 7 formed from nucleophilic attack by water on electrogenerated carbocations. The diol then cleaves to give two equivalents of benzaldehydes.
Based on these results, it was decided to expand the study to the oxidation of 1,1-diphenylethylenes (14) to determine if this reaction proceeded by a similar mechanistic pathway to that shown in Scheme 5\textsuperscript{10}. If so, the corresponding diol 15 would be produced, and then benzophenone (2) would be observed as a reaction product. Matt Sagotsky of the Fry group demonstrated that the anodic oxidation of 14 yields 2 or the substituted analog (Scheme 6). Of interest however is that analysis of the reaction at various stages by gas chromatograph/mass spectroscopy (GC/MS) indicated the presence of 1, although only in small quantities. This presented the possibility that the formation of 2 was occurring through two different pathways,
either through diol cleavage (Path A), as postulated for stilbenes, or since cation 16 could result in the enol of 1 (1a), oxidation might occur via the enol (Path B).

\[
\begin{align*}
\text{Path A:} & \quad \begin{array}{c}
\text{Ar} \quad \text{CH}_2 \\
\text{Ar} \\
\text{Ar}
\end{array} \\
\text{14} \\
\xrightarrow{[O]} \\
\begin{array}{c}
\text{Ar} \quad \text{OH}\quad \text{H} \\
\text{Ar} \\
\text{Ar}
\end{array} \\
\text{16} \\
\xrightarrow{\text{H}_2\text{O}, -\text{H}^+} \\
\begin{array}{c}
\text{Ar} \quad \text{OH}\quad \text{H} \\
\text{Ar} \\
\text{Ar}
\end{array} \\
\text{1a} \\
\xrightarrow{[O]} \\
\begin{array}{c}
\text{Ar} \quad \text{CH} \\
\text{Ar}
\end{array} \\
\text{1}
\end{align*}
\]

\[
\begin{align*}
\text{Path B:} & \quad \begin{array}{c}
\text{Ar} \quad \text{OH}\quad \text{H} \\
\text{Ar} \\
\text{Ar}
\end{array} \\
\text{16} \\
\xrightarrow{\text{?}, -\text{H}^+} \\
\begin{array}{c}
\text{Ar} \quad \text{OH}\quad \text{H} \\
\text{Ar} \\
\text{Ar}
\end{array} \\
\text{1a} \\
\xrightarrow{[O]} \\
\begin{array}{c}
\text{Ar} \quad \text{CH} \\
\text{Ar}
\end{array} \\
\text{1}
\end{align*}
\]

Scheme 6: Electrochemical oxidation of 1,1-diphenylethylenes (14) to produce benzophenones (2)

The appearance of 1 in the electrochemical oxidation pathway of 14 was unexpected, and the mechanism of its conversion to 2 was not understood. The apparent loss of a carbon atom in the reaction was particularly perplexing. It could be hypothesized that the unusual carbon-carbon bond cleavage observed in the oxidation of 1 to 2 was facilitated by the presence of the two geminal phenyl groups. We also considered the question of whether the oxygen in 2 was the carbonyl oxygen already present in the compound or whether it originated from another source. However, the chemical literature on the oxidation of 1, and of aldehydes in general, is sparse. Most literature on the subject investigates the anodic oxidation of aldehydes to carboxylic acids or esters\textsuperscript{11}. As such, the mechanism of the oxidation of 1 to 2 is the beginning of the line of inquiry presented here. Based on Sagotsky’s work on the anodic oxidation of 11 and 14, it was decided to study the oxidation of 1 itself in the presence of water.
Results

A. Two Pathways of Diphenylacetaldehyde (1) Oxidation

Controlled Potential Electrolysis of Diphenylacetaldehyde (1) in the Presence of Water. The initial experiments involving the electrochemical oxidation of diphenylacetaldehyde (1) were designed to determine the mechanistic pathway by which 1 is converted to benzophenone (2). The anodic oxidations were carried out in an electrolyte solution consisting of 0.1 M tetrabutylammonium tetrafluoroborate (Bu₄NBF₄) in acetonitrile. The reference electrode was 0.1 M silver nitrate (AgNO₃) in acetonitrile, and both the anode and cathode were constructed by weaving platinum wire through a 4 cm² piece of carbon cloth. By recording the background current passed by the electrolyte solution alone and comparing it with the current passed with 1 in solution it was determined that 1.7 V was the ideal potential at which to conduct the controlled potential electrolysis experiments. At this potential the reaction solution containing 1 was able to conduct 50-55 mA, while the background current was sufficiently low so as to not be concerned with oxidation of the electrolyte.

The first controlled potential electrolysis experiments demonstrated that 1 was converted to 2 through a stable, previously unobserved intermediate. This confirmed the hypothesis that it was possible for the oxidation of 1 to result in 2. This had been previously hypothesized by Matt Sagotsky and the Fry group when 1 appeared in small quantities in the anodic oxidation of 1,1-diphenylethylene (14)¹⁰. Based on the mass spectrum and the potential pathways of conversion it was hypothesized that the intermediate is α-hydroxydiphenylacetaldehyde (17), formed from nucleophilic
attack by water on a cationic intermediate generated when a π-bonding electron is removed from 1a (the enol form of 1). It should be noted that in early experiments the electrolyte solution was not stored over molecular sieves. The experiments were often performed open to the atmosphere and no additional effort was made to keep reagents or glassware dry. It is likely that the main source of water in the constant potential electrolysis reactions was the electrolyte solution (both acetonitrile and Bu₄NBF₄ are hygroscopic).

The experimental mass spectroscopic fragmentation pattern of the intermediate corresponded well with reported data for 17. Any attempt to isolate the intermediate however was unsuccessful. As shown in Figure 1 on page 12 all three compounds–1, 2, and 17–were present simultaneously in the electrolysis reaction solution. Unfortunately, all three compounds display similar Rf values on a TLC plate in a wide range of eluents, making separation by chromatography difficult. In order to affect separation it was decided to attempt converting the carbonyl groups to their 2,4-dinitrophenylhydrazine (2,4-DNP) analogs. Carbonyl compounds react readily with 2,4-DNP to form the corresponding derivative. As a result, these compounds have a significantly increased molecular weight and are often solids instead of liquids or oils. Additionally, the 2,4-DNP derivatives are usually bright yellow, orange, or red. This allows for separation by chromatography and characterization of a complex mixture which otherwise may not have been possible. However, the 2,4-DNP reagent is prepared in concentrated phosphoric acid solution and 17 decomposed under the highly acidic conditions.
Therefore, it was decided to conclusively characterize the identity of the intermediate by other means. If the intermediate in the anodic oxidation of 1 in the presence of water was in fact 17, then the analogous α-alkoxydiphenylacetaldehyde would be formed should water be replaced with an alcohol. Alcohols containing several carbon atoms were chosen in order to affect gas chromatographic separability. These experiments are discussed in detail later on, but of importance here is the fact that these experiments served to bolster the conclusion that the intermediate is in fact 17.

A $^1$H NMR spectrum of the product of an electrolysis reaction carried to completion verified that 2 is the final product of the oxidative electrolysis. Figure 1 below shows the progression as monitored by GC/MS of the electrolysis of 1 in the presence of water. The mass spectra of 1, 17, and 2 are shown in Figure 2. The mass spectrum of 1 in Figure 2a displays a small parent ion of $m/z$ 196 and a large fragment of $m/z$ 167 corresponding to loss of the carbonyl group via α-cleavage ([M-CHO]$^+$). Mass spectroscopic α-cleavage is ubiquitous for aldehydes and widely reported. In Figure 2b the parent peak $m/z$ 212 of 17 is not observed. Of interest, however, is the fragment $m/z$ 183 which is indicative of protonated benzophenone generated by loss of the aldehyde carbonyl group through α-cleavage. The mass spectrum of 2 (Figure 2c) shows a parent peak of $m/z$ 182 and a large fragment $m/z$ 105 from loss of a phenyl group. Also, the retention time of 11.0 minutes of electrochemically-derived 2 is the same as the retention time displayed for authentic 2. The fragment weighing $m/z$ 105 also appears in the spectrum of 17 and would
easily have been generated from loss of the hydroxyl proton and a phenyl group from the protonated benzophenone.

**Figure 1**: Gas chromatograms showing the progression of the constant potential electrolysis of diphenylacetaldehyde (1) in the presence of water
Figure 2: Mass spectra of a) diphenylacetaldehyde (1); b) α-hydroxydiphenylacetaldehyde (17); c) benzophenone (2)
In order to fully characterize the intermediate, alternate chemical syntheses of
17 were attempted by several different oxidative methods. Following a procedure
introduced by Albright and Goldman, 2,2-diphenyl-2-hydroxyethanol (18) was stirred
in the presence of DMSO and acetic anhydride for five days (lit. 18-24 hours)\(^\text{15}\). Diol
18 was obtained from a double Grignard reaction of ethyl glycolate and phenyl
magnesium bromide\(^\text{10}\). The progress of the oxidation of 18 was monitored by GC/MS.
After five days of stirring, the starting alcohol remained the major component in
solution. Gas chromatographic analysis indicated that some 17 had formed, and a
small amount of 2 was also present. However, due to the long reaction time required,
it was decided to carry out the synthesis of authentic 17 by a Swern oxidation of 18\(^\text{16}\).
The diol was reacted with oxalyl chloride and DMSO in methylene chloride at -60°C.
Triethylamine was used as an organic base. The reaction did not proceed; \(^1\)H NMR of
the product showed only starting material. Finally, the synthesis of 17 was attempted
by oxidizing 18 using pyridinium chlorochromate (PCC)\(^\text{17}\). A GC/MS analysis of the
product revealed that most of the starting material had been over-oxidized to 2, with 1
and other unidentified byproducts also present.

Further literature research on 17 revealed that it is dimeric under atmospheric
conditions and as such could not be isolated in its monomeric form for complete
characterization\(^\text{18}\). However, the GC/MS data combined with the results of the
electrochemical experiments performed in the presence of other nucleophiles served
to conclusively support the contention that 17 is the intermediate in the anodic
conversion of 1 to 2.
**Aerobic Oxidation of Diphenylacetaldehyde (1).** It was observed that older bottles of 1 often developed a white solid on the bottom of the container, which GC/MS showed to be 2. The autoxidation of 1 with molecular oxygen has been previously documented\(^\text{19}\). It was therefore possible that the oxidation of 1 to 2 observed in the controlled potential electrolysis experiments could have occurred by both chemical and electrochemical pathways simultaneously, and therefore the reaction with molecular oxygen could not be discounted. A series of experiments were carried out in order to test the extent to which autoxidation of 1 occurs.

A solution of 200 µL 1 in 15 mL acetonitrile was stirred in an open round bottom flask for three days. A comparison of the baseline and final GC/MS results shows that approximately 21% of 1 was converted to 2 in that time, indicating that the aerobic oxidation reaction is significant.

![Scheme 7: Aerobic oxidation of diphenylacetaldehyde (1) to benzophenone (2)](image)

To further explore the reaction of 1 with air, a controlled potential electrolysis experiment was performed with air bubbled through the reaction medium. The air was bubbled through a canister containing dry acetonitrile over molecular sieves and introduced into the flask via a needle. Upon starting the experiment, the reaction immediately started passing approximately 200 mA of current, as compared with 50-
55 mA typical of the controlled potential electrolyses without additional air. This is attributed to better stirring of the reaction medium due to agitation by the air. The conversion to 2 occurred much more quickly upon the addition of air with relatively little formation of 17. In previous controlled potential electrolysis experiments it was observed that a significant amount of 17 accumulated in solution before any 2 formed. However, in the experiments in which air was bubbled through the reaction, formation of 2 occurred immediately. In some instances a relative increase in the amount of 2 was noted within five minutes of beginning the experiment.

In order to fully test the reaction of 1 with molecular oxygen, a sample of 1 in acetonitrile was stirred in the presence of 18O-doubly labeled molecular oxygen for two weeks. In that time, it was possible to observe the formation of a white solid (2) in the solution.

Scheme 8: Aerobic oxidation of diphenylacetaldehyde (1) to 18O-labeled-benzophenone (2)

Analysis by GC/MS of the reaction medium demonstrated that 50% of 1 had been oxidized to 2 over the reaction time of two weeks. Of greater significance however is that the 2 present in solution showed incorporation of 18O. An 18O-labeled parent peak of m/z 184, as well as a peak of m/z 107 corresponding to a benzoyl group ([PhCO]+), were observed in the mass spectrum. This evidence conclusively verifies that 1
undergoes chemical oxidation by a reaction with molecular oxygen. The presence of ion fragments of 2 that did not show $^{18}$O-incorporation suggest that the sample of 1 used may have already undergone aerobic oxidation to 2. Also, the reaction was carried out under slight vacuum, and so atmospheric oxygen may have leaked into the system during the time it was standing.

**Figure 3:** Mass spectrum demonstrating incorporation of $^{18}$O into benzophenone (2) formed as a result of oxidation of diphenylacetaldehyde (1) by molecular oxygen

In order to ensure that the formation of 2 in the anodic oxidations of 1 was not due partially or exclusively to the reaction with molecular oxygen, the electrolysis of 1 was performed under nitrogen. The inert gas was bubbled through dry acetonitrile and introduced into the reaction via a needle. In these experiments, 17 built up in solution before significant formation of 2 was observed. This confirmed that 2 can indeed be formed via anodic oxidation of 1 and not solely as a result of autoxidation.
In order to minimize aerobic oxidation of 1, this practice of carrying out the electrolyses under inert gas was followed in all subsequent experiments.

**Controlled Potential Electrolysis of Diphenylacetaldehyde (1) in the Presence of $^{18}$O-Labeled Water.** It was postulated that 17 was formed from nucleophilic attack by water on an electrogenerated carbocation in the electrolysis of 1. Therefore, the oxygen in 2 would have originated from the water and not from the carbonyl oxygen originally present in 1. In order to test this hypothesis, the controlled potential electrolysis of 1 was carried out in presence of $^{18}$O-labeled water (3% by volume). The experiment was performed using both 3% and 97% $^{18}$O-labeled water. The experiment in which 3% $^{18}$O-labeled water was used suggested incorporation of the heavy oxygen into both 17 and 2 but the results were not conclusive. However, the experiment in which 97% $^{18}$O labeled water was used clearly indicated the electrochemical incorporation of $^{18}$O into both 17 and 2. The incorporated $^{18}$O was visible in the mass spectroscopic ion fragments, in particular $m/z$ 184 of 2 and $m/z$ 185 of 17 (Figure 4).

![Scheme 9: Anodic oxidation of diphenylacetaldehyde (1) in the presence of $^{18}$O-labeled water](image)

**Scheme 9:** Anodic oxidation of diphenylacetaldehyde (1) in the presence of $^{18}$O-labeled water
Figure 4: Mass spectra showing incorporation of $^{18}$O into benzophenone (2, top) and $\alpha$-hydroxydiphenylacetaldehyde (17, bottom) from the electrolysis of diphenylacetaldehyde (1) carried out in the presence of 97% $^{18}$O-labeled water.

To control for possible atmospheric oxygen exchange as the source of the $^{18}$O in 2, a solution containing 2 and $^{18}$O-labeled water in acetonitrile was prepared and stirred overnight. GC/MS analysis showed no incorporation of $^{18}$O into 2.
The results of the experiments involving the reactivity of 1 in the presence of water and molecular oxygen demonstrate that the conversion of 1 into 2 can occur through two competing mechanistic pathways: a chemical reaction with molecular oxygen and an electrochemical reaction in which 17 is generated an intermediate (Scheme 9). As such, care was taken in all later electrochemical experiments to remove all air from the reaction solutions in order to eliminate the possibility of side reactions of 1 with molecular oxygen.

**B. Electrochemical Oxidation of Diphenylacetaldehyde (1) in the Presence of Various Alcohols.**

As discussed above, 1, benzo phenone (2), and α-hydroxydiphenylacetaldehyde (17) are not separable by column chromatography. Based on the research indicating that 1 is converted to 2 through 17 (Scheme 9), it was hypothesized that the electrochemical oxidation of 1 in the presence of alcohols would produce the corresponding α-alkoxyaldehydes by analogous nucleophilic attack. By using a large alcohol, the increased molecular mass would improve separability and allow for characterization of reaction intermediates and products. It was predicted that the α-alkoxyaldehyde would not be oxidized further to 2 as this would involve breakage of a carbon-oxygen bond (as opposed to an oxygen-hydrogen bond). However, the electrochemical oxidation of 1 in the presence of a variety of alcohols proved to be more complex than anticipated. It was necessary to study the mechanism and scope of these reactions in greater detail. As a result, the main objective of this research became the investigation, proposal, and verification of the general mechanistic pathway(s) of the electrolysis of 1 in the presence of a structural variety of alcohols.
**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Cyclohexanol.** Prior to the constant current electrolysis of 1 in the presence of cyclohexanol discussed below at length, several similar controlled potential experiments were performed using different alcohols as nucleophiles. These controlled potential electrolysies produced the same results as the constant current experiments. The decision was made to switch from controlled potential to constant current in hopes of shortening the reaction times required. Additionally, constant current electrolyses are simpler and easier experiments to carry out.

The constant current electrolysis of 1 in the presence of cyclohexanol was the oxidative electrolysis in the presence of an alternate nucleophile studied in the greatest detail. These electrolysis experiments were performed at 25 mA using equimolar quantities of 1 and cyclohexanol in 0.1 M tetrabutylammonium tetrafluoroborate (Bu₄NBF₄) in acetonitrile. The progress of the reactions was monitored every hour by gas chromatography/mass spectroscopy GC/MS (Figure 5). At 180 minutes of reaction time a significant amount of an intermediate compound (A) with a GC retention time (rt) of 17.2 minutes had formed. By 330 minutes, GC analysis indicated that there was more A in the reaction solution than 1. At 480 minutes A had been converted to a compound B whose retention time is approximately 16.5 minutes. The electrolysis was continued to 980 minutes, at which time no 1 remained, and the major product was a third compound C, which displayed a retention time of 15.0 minutes. A small amount of benzhydrol (19) and 2 were present in solution, as well as some unreacted A and B.
**Figure 5:** Gas chromatograms showing the progression of the anodic oxidation of diphenylacetaldehyde (1) in the presence of cyclohexanol as a function of time.
It should be noted that in the middle of the reaction the sequential conversions of $A \rightarrow B \rightarrow C$ are all occurring simultaneously in solution. Additionally, as can be seen in Figure 5, the starting material is not completely consumed before the formation of $C$ begins. (This will become more significant in the Discussion section on the reaction mechanism.) The small peak with a retention time of approximately twelve minutes observed in the gas chromatogram at 480 minutes is 17. Despite efforts to keep reagents, solvents, and glassware dry, a small amount of water contamination was observed in each electrolysis performed. This is likely a result of the long reaction times required, the brief exposure to air required to extract samples for GC/MS analysis, and the difficulty of drying the hygroscopic electrolyte.

It is believed that $A$ is diphenylacetaldehyde cyclohexyl hemiacetal (20) that results from two subsequent nucleophilic attacks by cyclohexanol on electrogogenerated carbocations. A detailed mechanism for the formation of 20 will be presented in the Discussion section.

![Proposed structure of diphenylacetaldehyde cyclohexyl hemiacetal (20)](image)

**Figure 6:** Proposed structure of diphenylacetaldehyde cyclohexyl hemiacetal (20)

The mass spectrum of 20 (Figure 7) did not provide any further insight into its structure. No obvious parent peak is visible, and the heaviest ion of consequence in the spectrum is a fragment of $m/z$ 189 ($m/z$ 207 results from column bleed-off). The
base peak in the spectrum is \( m/z \) 107. Both of these fragments are of low enough molecular weight to have originated from any number of fragmentation processes.

![Mass spectrum](image_url)

**Figure 7:** Mass spectrum of C, proposed to be diphenylacetaldehyde cyclohexyl hemiacetal (20)

It was not possible to isolate and fully characterize 20. It was however demonstrated that the conversion of 20 to B occurs chemically as opposed to electrochemically. This was discovered by performing another constant current electrolysis under identical conditions and turning the current off once a significant amount of A had formed (as determined by monitoring by GC/MS). The reaction solution was allowed to stir overnight under nitrogen, after which a GC/MS experiment showed that the majority of 20 had disappeared and the quantity of B in solution had significantly increased. This suggested that 20 and B were in an equilibrium favoring B (Scheme 10). Additionally, attempts to isolate 20 by working up an electrolysis reaction when 20 and 1 were the only compounds present in
significant quantities were unsuccessful. The chromatography and extraction necessary to remove 20 from the electrolyte medium resulted in the isolation of B. As discussed in great detail below, B was later identified to be α-cyclohexyloxydiphenylacetaldehyde (21). The fact that 20 converts to 21 chemically as opposed to electrochemically is consistent with the proposed structure for 20.

**Scheme 10:** Equilibrium of diphenylacetaldehyde cyclohexyl hemiacetal (20) and α-cyclohexyloxydiphenylacetaldehyde (21)
Figure 8: Gas chromatograms illustrating the chemical conversion of diphenylacetaldehyde cyclohexyl hemiacetal (20) to B. The top shows the electrolysis at 420 minutes, after which the current was turned off. The bottom shows the same reaction after stirring overnight under nitrogen.

Due to the number of byproducts and partial decomposition during chromatography it was often difficult or impossible to obtain pure samples for clean NMR spectra necessary to identify and fully characterize the other electrolysis
products B and C. Therefore as further proof of structures, the proposed electrolysis products were synthesized by alternate chemical (as opposed to electrochemical) methods. These products were characterized by NMR and GC/MS and compared to the data available for the electrolysis products. Most compound identifications were made by comparing GC/MS data (retention time and mass fragmentation patterns), but NMR analysis was also used whenever possible.

The mass spectrum of B (Figure 21) does not contain a peak for a parent ion. The heaviest ion in the spectrum is m/z 265. Based on comparison with the reaction of 1 in the presence of water in which 17 is produced as an intermediate, the m/z 265 peak would correspond to loss of the formyl group from α-cyclohexyloxydiphenylacetaldehyde (21). As mentioned earlier on page 11 this type of α-cleavage of the formyl group is very common for aldehydes. The largest ion fragment in the spectrum is m/z 183, which is generated from proton abstraction by the oxygen followed by loss of the cyclohexyl ring from the m/z 265 fragment. The fragmentation pattern shown in Figure 10 is consistent with what is expected for 21.

![Structure of α-cyclohexyloxydiphenylacetaldehyde (21)](image)}

Figure 9: Structure of α-cyclohexyloxydiphenylacetaldehyde (21)
Figure 10: Mass spectrum of $\alpha$-cyclohexyloxydiphenylacetaldehyde (21)

Because of its instability, it was not possible to obtain a pure sample of 21 by electrolytic methods for characterization. Therefore, it was decided to obtain the authentic material by another synthetic route. As demonstrated by Fry and Migron, the synthesis of $\alpha$-alkoxyaldehydes can be accomplished by silver ion-mediated nucleophilic substitutions of $\alpha$-bromoaldehydes\textsuperscript{20}. Treatment of $\alpha$-bromodiphenylacetaldehyde\textsuperscript{21} (22) with one equivalent of cyclohexanol in the presence of an excess of silver tetrafluoroborate (AgBF$_4$) afforded 21.
**Scheme 11:** Silver ion-mediated synthesis of $\alpha$-cyclohexyloxydiphenylacetaldehyde (21)

In addition to having the same retention time, the mass spectra of the electrolysis and authentic products are identical. As with the electrolysis product, a parent peak $m/z$ 294 is not observed in the mass spectrum, and the heaviest ion is $m/z$ 265 corresponding to loss of the formyl group. This $\alpha$-alkoxyaldehyde was a previously unreported compound. Therefore, the predicted molecular formula was confirmed by accurate mass analysis using electrospray ionization/atmospheric-pressure chemical ionization (ESI/ACPI)\textsuperscript{22}. The positive identification of 21 as the electrolysis product was confirmed by comparison of the $^1$H NMR spectra of the electrolysis product and the authentic sample (**Figure 11** on page 31).

Regrettably, it was not possible to obtain a completely pure sample of 21 for further spectral analysis. The synthesis of 21, as well as the synthesis of $\alpha$-phenethyloxydiphenylacetaldehyde (23) discussed below, produced a significant number of byproducts. In particular, a large amount of an impurity X was produced in both reactions, as well as in the silver-mediated ether syntheses discussed later. In the $^1$H NMR spectra of these compounds, X results in two large multiplets (resembling solvent peaks) at 1.62 ppm and 3.41 ppm. Due to the intensity with which it appears in the $^1$H NMR spectra it was believed that X was of low molecular weight. This
hypothesis was corroborated by the fact that the impurity was not visible by GC/MS analysis, even with the solvent delay removed. All reagents and solvents were analyzed by $^1$H NMR to check for impurities, but the source of impurity X was not elucidated until very recently. It was discovered that THF polymerizes in the presence of a strong acid to yield poly(tetramethylene ether) glycol (PTMEG)$^{23}$. In the $\alpha$-alkoxyaldehyde syntheses the polymerization of THF was promoted by the fluoroboric acid that was formed as a byproduct. The polymer is reported to be a very viscous oil, which is exactly the nature of the crude $\alpha$-alkoxyaldehyde products obtained in the silver ion-mediated syntheses. The PTMEG does not appear on a TLC plate, but it was determined that it was possible to remove by column chromatography.

Unfortunately, it was observed that the $\alpha$-alkoxyaldehydes are acid sensitive and will often decompose on silica gel. Therefore, it was necessary to push the $\alpha$-alkoxyaldehydes through the chromatography columns quickly, so complete separation and purification could not be achieved. Attempting to achieve separation through a slow, drop-wise chromatography column resulted in decomposition of the material. Furthermore, following attempted chromatography, isolated yields by weight were low, usually in the range of 20-30%. Spectral analysis of old samples of $\alpha$-alkoxyaldehydes from both electrolyses and alternate synthetic methods showed decomposition of the material. The instability of $\alpha$-alkoxyaldehydes is not unprecedented. McGill reports $\alpha$-alkoxyaldehydes to be frustratingly unstable and difficult to work with$^{24}$. As such, $^1$H NMR spectra of the synthesized $\alpha$-
alkoxyaldehydes contain a large number of impurity peaks, but also do show signals in the predicted regions for these compounds.

The $^1$H NMR spectra of 21 from both electrochemical and alternate syntheses are shown below (Figure 11). The spectrum from authentic material is displayed first. The distinctive signals in both spectra are identical. The aldehyde proton is observed at 9.80 ppm. A number of other small aldehyde peaks in the spectrum of the authentic material are also visible. The small peak at the base of the large aldehyde signal is attributed to unreacted $\alpha$-bromodiphenylacetaldehyde (22). The interpretation of the other aldehyde signals is discussed later on. In the spectrum of the electrolysis product (bottom spectrum) one of the extra aldehyde peaks is the result of unreacted 1; the other is an unidentified impurity. The other distinctive signal in both spectra is the multiplet at 3.42 ppm, which is attributed to the methine proton on the cyclohexyl ring. In the spectrum of the authentic material (top), the aldehyde signal integrates to approximately half of the methine proton, even though both of the signals correspond to one proton. The are two explanations for this phenomenon: 1) PTMEG appears at 3.41 ppm, and therefore if it was not completely removed on the chromatography column it would overlap with the methine signal and increase the apparent integration value; and 2) the aldehyde proton relaxes more slowly than the methine proton due to its lack of nearby magnetic nuclei. This would cause the integration of the aldehyde proton to be decreased compared to that of the methine proton. The multiplet at 3.61 ppm is due to unreacted cyclohexanol in the electrolysis. The quartet centered at 3.80 ppm is the result of diethyl ether that was not removed in vacuo.
Figure 11: $^1$H NMR spectra of $\alpha$-cyclohexyloxydiphenylacetaldehyde (21). The top spectrum shows the authentic material; the bottom spectrum is of the product isolated from a constant current electrolysis.
Despite the difficulties of working with 21 and other similar compounds, it is believed that the comparison of GC/MS data from the electrolysis and synthetic experiments, the accurate mass analysis, and the $^1$H NMR spectra serve to conclusively identify 21 as the intermediate in the constant current electrolysis of 1 in the presence of cyclohexanol.

The mass spectrum of C (Figure 13) shows a weak parent ion of $m/z$ 266. In considering possible structure for C it was realized that a molecular mass of 266 could be obtained by the addition of a proton to the $m/z$ 265 fragment observed in the mass spectrum of 21 (Figure 10 on page 27). The mass spectrum of C also displays a very strong $m/z$ 167 which is indicative of a [Ph$_2$CH]$^+$ fragment. Therefore, it was proposed that C was benzhydryl cyclohexyl ether (13). The $^1$H NMR of the isolated electrolysis product corroborated this hypothesis. The distinctive benzhydryl proton is observed at 5.63 ppm. The cyclohexyl methine proton appears at 3.37 ppm. All other protons (aryl and cyclohexyl) appear at the expected chemical shifts with the correct relative integrations.

Figure 12: Structure of benzhydryl cyclohexyl ether (24)
Figure 13: Mass spectrum of benzhydryl cyclohexyl ether (24)

An authentic sample of 24 was synthesized in a similar manner as 21\textsuperscript{20}. The same chemistry principles of silver ion-mediated nucleophilic attack were applied. Ether 24 was obtained by treating benzhydryl chloride with one equivalent of cyclohexanol in the presence of an excess of silver tetrafluoroborate (AgBF\textsubscript{4}).

Scheme 12: Synthesis of benzhydryl cyclohexyl ether (24)
The electrolysis product and the authentic compound displayed the same retention time of 15.0 min in the GC analysis; additionally, their mass spectra were identical. This characterization was verified by $^1$H NMR comparison of the authentic sample to the electrolysis product. The experimental spectral data obtained for 24 correspond well with reported data for the compound$^{26}$.

Finally, as proof that 21 is converted to ether 24 in the constant current electrolysis, an authentic sample of 21 was electrochemically oxidized under the same conditions as the electrolysis of 1 carried out in the presence of cyclohexanol. Compound 21 rapidly and cleanly converted to 24.

The overall electrochemical reaction pathway for the anodic oxidation of 1 in the presence of cyclohexanol is therefore as follows:

**Scheme 13:** Electrochemical conversion of diphenylacetaldehyde (1) to benzhydryl cyclohexyl ether (24)

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of 2-Phenylethanol.** This constant current electrolysis of 1 was performed in the presence of an equimolar quantity of 2-phenylethanol in 0.1 M Bu$_4$NBF$_4$ in acetonitrile. The reaction was carried out at 25 mA and was monitored periodically by GC/MS. The reaction required 25 hours to reach completion. This electrolysis followed a reaction pathway similar to that of the oxidation of 1 in the presence of cyclohexanol, with one significant difference: the corresponding hemiacetal was not observed. The first
product to form was $\alpha$-phenethyloxydiphenylacetaldehyde (23), which was the major product at 720 minutes of reaction time (Figure 14). Compound 23 was then converted to benzhydryl phenethyl ether (25) by cleavage of the formyl group. The reaction was allowed to continue until all of 23 had been converted to 25 and most of 1 had been consumed. Due to the presence of some water in solution as a result of long reaction times and the difficulty of drying the electrolyte, small amounts of $\alpha$-hydroxydiphenylacetaldehyde (17) and benzophenone (2) (with retention times of 10.8 minutes and 11.8 minutes, respectively) were present in solution and are visible in the gas chromatogram. As with the electrolysis using cyclohexanol, 25 appeared in solution before all of 1 and 23 had been consumed.
Figure 14: Gas chromatograms of the anodic oxidation of diphenylacetaldehyde (1) in the presence of 2-phenylethanol as a function of time
The products of this constant current electrolysis were identified and characterized by comparison with authentic samples in the same manner as was used for 21 and 24. Both 23 and 25 were synthesized by the same procedures used for the cyclohexyl products. Treatment of 22 with an equimolar amount of 2-phenylethanol in the presence of an excess of silver tetrafluoroborate (AgBF₄) afforded 23.

Scheme 14: Synthesis of α-phenethyloxydiphenylacetaldehyde (23)

The GC retention time and mass spectroscopic fragmentation pattern of authentic 23 clearly indicated that 23 is the first product to appear in the constant current electrolysis. The heaviest ion observed is $m/z$ 287 corresponding to the loss of the carbonyl group; as with 21 the parent ion ($m/z$ 316) is not observed in the spectrum. Compound 23 was a previously unreported compound. The molecular formula was confirmed by exact mass analysis (ESI/APCI).
Figure 15: Mass spectrum showing fragmentation of $\alpha$-phenethyloxydiphenylacetaldehyde (23)

Purification of 23 presented the same difficulties as with 21, as discussed above. The $^1$H NMR spectra for both the authentic (top) and electrolysis (bottom) products are shown below (Figure 16 on page 40). The spectrum of the synthetic product, however, shows two aldehyde singlets at 9.72 ppm and 9.99 ppm and two sets of two methylene triplets, even though GC/MS shows only a single peak. Analysis of the crude sample by TLC shows that no unreacted 2-phenylethanol remained in the product. An explanation for this phenomenon is provided below, but of importance here is that the distinctive signals in the spectrum of 23 isolated from the electrolysis match peaks in the authentic material. The aldehyde proton appears at 9.72 ppm, and the two methylene triplets are visible at 2.96 ppm and 3.50 ppm. Both methylene triplets integrate to slightly more than two protons. As with the
cyclohexanol, this is attributed to a longer relaxation time for the aldehyde proton due to a lack of nearby magnetic nuclei\textsuperscript{25}. In the electrolysis spectrum, a number of other triplets are also visible in this region. TLC analysis of the isolated electrolysis product shows there was no residual 2-phenylethanol. It is likely the latter signals are the result of decomposition of 23 on the chromatography column.
Figure 16: $^1$H NMR spectra of $\alpha$-phenethyloxydiphenylacetaldehyde (23). The top spectrum shows the authentic material; the bottom spectrum is of the product isolated from a constant current electrolysis.
Benzhydryl phenethyl ether (25) was synthesized by reacting 1 with an equimolar quantity of 2-phenylethanol in the presence of an excess of silver tetrafluoroborate.

\[
\begin{align*}
\text{Ph} & \quad \text{Cl} \quad \text{Ph} \\
+ \quad \text{Ph} & \quad \text{CH}_2 \text{CH} \quad \text{OH} \quad \text{AgBF}_4 \quad \text{THF} \\
\rightarrow \quad \text{Ph} & \quad \text{O} \quad \text{Ph} \quad \text{CH} \quad \text{CH}_2 \text{CH} \quad \text{OH} \\
\text{25}
\end{align*}
\]

Scheme 15: Synthesis of benzhydryl phenethyl ether (25)

Comparison of the electrolysis and synthetic product gas chromatograms and mass spectra confirmed that 25 was the electrolysis product. A \(^1\)H NMR spectrum obtained from the electrolysis of 1,1-diphenylacetone in the presence of 2-phenylethanol performed by Boris Sheludko in the Fry lab showed good correspondence with the synthetic product\(^{27}\). The spectra of 25 from both the electrolysis experiments and the alternate synthesis of the authentic material were compared with the reported literature and found to be in agreement\(^{28}\).

Therefore, the overall mechanistic pathway for the anodic oxidation of 1 in the presence of 2-phenylethanol is as follows:

\[
\begin{align*}
\text{Ph} & \quad \text{CH} \quad \text{CH}_2 \text{CH} \quad \text{OH} \quad \text{[O]} \quad \text{Ph} & \quad \text{O} \quad \text{Ph} \quad \text{CH} \quad \text{CH}_2 \text{CH} \quad \text{OH} \\
\text{1} & \quad \text{2-phenylethanol} \quad 0.1 \text{ M Bu}_4 \text{NBF}_4/\text{CH}_3\text{CN} \quad \text{23} \quad \text{25}
\end{align*}
\]

Scheme 16: Electrochemical conversion of diphenylacetaldehyde (1) to benzhydryl phenethyl ether (25)
**Atropisomers.** While the silver ion-mediated alternative syntheses of the \( \alpha \)-alkoxyaldehydes proved invaluable in identifying the constant current electrolysis products, the compounds themselves presented an unexpected and complex issue. The synthesis of authentic \( \alpha \)-cyclohexyloxydiphenylacetaldehyde (21) and \( \alpha \)-phenethyloxydiphenylacetaldehyde (23) sometimes resulted in the appearance of two large aldehyde peaks in the \(^1\)H NMR spectrum. Other distinguishing signals, such as the methylene triplets of 23 (see Figure 16, page 40), were duplicated as well. This phenomenon is believed to be the result of atropisomeric products formed in the synthesis of the \( \alpha \)-alkoxyaldehydes. Atropisomers are stereoisomers that are the result of restricted rotation about a single bond due to high steric hindrance\(^{29}\). The atropisomers are distinguishable in the \(^1\)H NMR spectrum but appear as one peak in a gas chromatogram. Both 21 and 23 come off the gas chromatography column as single peaks at approximately 225˚C. This would be the case if the two atropisomers interconvert at high temperature.

This phenomenon is particularly noticeable in the \(^1\)H NMR of 23 (Figure 17). The spectrum displays two aldehyde peaks and two sets of two methylene triplets. TLC analysis confirmed that the extra set of triplets was not due to unreacted 2-phenylethanol. In the lower spectrum of Figure 17 there are multiplets at 3.41 ppm and 3.75 ppm. The signal at 3.41 ppm is due to polymerized THF\(^{23}\). The signal at 3.75 ppm is the result of THF (solvent) that was not completely removed.
Figure 17: $^1$H NMR spectra showing atropisomers of α-phenethyloxydiphenylacetaldehyde (23), with a close view of the region displaying duplicated methylene triplets.
A COSY experiment verified that there were two distinct sets of four coupled methylene protons present in the sample. COSY showed that the outer signals represented one set of coupled protons and the inner signals represented another set.

![COSY spectrum](RLM_1130_crude_cosy.fid.esp)

**Figure 18:** COSY of α-phenethoxydiphenylacetaldehyde (23) showing the distinct methylene signals resulting from atropisomerism.

The synthesis of 21 also yielded atropisomers. The $^1$H NMR spectrum shows aldehyde peaks of nearly equal size at 9.79 and 9.98 ppm. Unfortunately, the signal for the distinct methine proton on the cyclohexyl ring is obscured beneath the poly(tetramethylene ether) glycol (PTMEG) signal at 3.41 ppm. Any attempt to completely remove the PTMEG by chromatography resulted in the decomposition or
interconversion of one of the atropisomers. The atropisomer corresponding to the signal at 9.79 ppm was shown to be more stable, as column chromatography yielded only that stereoisomer.

**Figure 19**: $^1$H NMR spectra showing atropisomers of $\alpha$-cyclohexyloxydiphenylacetaldehyde (21)

Attempts were made the study the kinetics of interconversion between the two atropisomers. This entailed heating a sample of 23 and recording the $^1$H NMR spectrum over a range of temperatures (room temperature to 120°C). The integration ratios of the two aldehyde peaks changed during heating. This indicates that at sufficiently high temperatures the isomers equilibrate. However, the instrumentation available at Wesleyan did not allow for the sample to be heated to a high enough
temperature to observe coalescence of the two aldehyde peaks. Additionally, the sample started to decompose at higher temperatures. As such, the interconversion of the atropisomers was not studied in detail. However, our interest in the subject remains, and it will be investigated further when possible.

Although not rigorously studied, it was generally observed that the amount of time for which the reaction is allowed to stir affects whether both atropisomers are formed. In the syntheses of 21 which were allowed to stir for a longer period of time (usually overnight), only one of the atropisomers was observed in the $^1$H NMR spectrum. Due to the acidic nature of the reaction solution (HBF$_4$ is produced as a byproduct) it is likely that the alkoxy group can be protonated, allowing the isomers to equilibrate. If sufficient reaction time is allowed, the thermodynamic product (more stable atropisomer) would predominate.

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Methanol.** The constant current electrolysis of 1 was performed in the presence of an equimolar amount of methanol. The reaction was carried out at 25 mA and proceeded as expected based on the results of previous experiments carried out in the presence of cyclohexanol and 2-phenylethanol. The corresponding hemiacetal was not observed. Monitoring by GC/MS showed the formation of $\alpha$-methyloxydiphenylacetaldehyde (26) which was then converted to benzhydryl methyl ether (27). All mass spectra displayed the expected fragmentation patterns. A parent peak of m/z 226 was not observed in the mass spectrum of 26 (Figure 20 on page 48); the heaviest fragment m/z 197 corresponded to the ion obtained by carbonyl group cleavage. Furthermore, the synthesis of 26 was carried out by treating $\alpha$-
bromodiphenylacetaldehyde (22) with methanol in the presence of excess silver tetrafluoroborate. Unexpectedly, however, the synthesis produced nearly equal amounts of 26 and benzophenone (2).

Scheme 17: Synthesis of α-methoxydiphenylacetaldehyde (26). Approximately half the reaction product was benzophenone (2).

Despite the presence of 2, ¹H NMR confirmed that 26 was present in the authentic product mixture. Analysis by GC/MS of authentic 26 identified it as the intermediate in the electrolysis. The synthesis of 26 was attempted again using HPLC grade methanol to exclude the possibility that wet methanol had contributed to the formation of 2. The second synthesis gave the same results. It was hypothesized that when methanol is used as a nucleophile the mild oxidizing nature of silver (I) is sufficient to oxidize 26 to 2. Although a pure sample of 26 could not be obtained, the distinct methoxy and aldehyde protons were observed at 3.22 and 9.81 ppm, respectively. Due to the difficulty in obtaining a pure sample, additional spectra for characterization were not acquired. It should be noted that PTMEG was evident in the ¹H NMR of the synthetic 26. Based on the ¹H NMR and GC/MS data it was concluded that 26 was produced in the constant current electrolysis experiment.
Figure 20: Mass spectrum of α-methyloxydiphenylacetaldehyde (26)
Figure 21: $^1$H NMR spectrum of synthetic $\alpha$-methoxydiphenylacetaldehyde (26)
Benzhydryl methyl ether (27) was successfully synthesized by reacting benzhydryl chloride with methanol in the presence of silver tetrafluoroborate. The reaction gave the expected ether in nearly quantitative yield by weight. The $^1$H NMR spectrum does display PTMEG at 3.41 ppm and 1.62 ppm. The mass spectroscopic data of the authentic product also agreed with the electrolysis spectra. As with the other benzhydryl alkyl ethers, the mass spectrum of 27 did contain a parent peak of $m/z$ 198. Fragments observed in the mass spectra of 24 and 25 ($m/z$ 167 and 105) were present in the mass spectrum of 27. A sample of 27 without the impurity was obtained from an alternate electrolysis performed by Boris Sheludko$^{27}$. The $^1$H NMR data from the constant current electrolysis product gave excellent correspondence with the authentic product. Furthermore the spectra from both the electrolysis and synthetic experiments were in excellent agreement with the reported spectral data for 27$^{30}$.

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of 3-Ethyl-3-pentanol.** The constant current electrolysis of 1 was carried out in the presence of an equimolar quantity of 3-ethyl-3-pentanol (triethylcarbinol) at 25 mA. The progress of the reaction was monitored by GC/MS and was allowed to proceed for 29 hours, at which time a mixture of compounds was present in solution, one of which was believed to be the benzhydryl triethylcarbinyl ether (28). In general, this electrolysis did not proceed as cleanly as the other constant current electrolysis experiments and resulted in more byproducts. Most notably, the expected α-alkoxyaldehyde, α-triethylcarbinyl diphenylacetaldehyde (29), produced from nucleophilic attack by triethylcarbinol, was not observed in the GC/MS analysis.
Flash chromatography of the electrolysis product yielded two major fractions: one contained the compound believed to be 28 and an unknown, D; the second fraction contained a mixture of 1, benzhydrol (19), and α-hydroxydiphenylacetaldehyde (17). Attempts to synthesize authentic samples of 28 for characterization and comparison to the electrolysis product were unsuccessful. Treating benzhydryl chloride with triethylcarbinol in the presence of silver tetrafluoroborate (as described for the other alcohols) did not yield 28; only unreacted benzhydryl chloride and 3-ethyl-3-pentanol were recovered. The synthesis of 28 by a Williamson ether synthesis route was also attempted using stronger nucleophiles (NaH and n-BuLi). Both reactions were heated to reflux for several days, but neither method yielded 28. Again, only starting materials were isolated upon workup.

Scheme 18: Attempted syntheses of benzhydryl triethylcarbinyl ether (28)
Attempts to synthesize the ether by solvomercuration-demercuration of 3-ethyl-2-pentene with mercuric trifluoroacetate (Hg(CF\(_3\)COO)\(_2\)) in the presence of 19 were also unsuccessful\(^{27,31}\). Brown et al. reported high yields in the synthesis of unhindered ethers by this synthetic method but indicated that yields were low when \(t\)-butyl alcohol was used as the nucleophilic reagent\(^{31d}\).

**Scheme 19:** Attempted synthesis of benzhydryl triethylcarbinyl ether(28): Solvomercuration-demercuration of 3-ethyl-2-pentene in the presence of benzhydrol (19)

The fragmentation pattern observed in the GC/MS analysis of the product indicated that the synthesis resulted in constitutional isomers of 28. In the solvomercuration-demercuration synthesis of sterically hindered ethers the formation of the anti-Markovnikov product has been reported\(^{31d}\). It is believed the combined steric bulk of the alkyl and aryl groups prevented the formation of the desired product. However, 28 was successfully isolated from an anodic oxidation of 1,1-diphenylacetone carried out in the presence of triethylcarbinol performed by Boris Sheludko\(^{27}\). Comparison of the GC/MS data and \(^1\)H NMR data of the chromatographed sample containing two compounds confirmed that 28 was one of the compounds present, along with D. The mass spectrum of 28 does not display a parent ion of \(m/z\) 282. The largest ion fragment is \(m/z\) 253 corresponding to loss of an
ethyl group from 28. As with the other ethers, ions of \( m/z \) 183 ([Ph\(_2\)C=OH]\(^+\)) and \( m/z \) 105 ([PhCO]\(^+\)) are also observed. Compound D has yet to be identified but is currently under investigation. It displays a shorter GC retention time of 12.6 minutes. The heaviest ion in the mass spectrum is a weak \( m/z \) 254; it is not known if this fragment is a parent ion. The base peak in the spectrum is \( m/z \) 167, which is typically indicative of a [Ph\(_2\)CH]\(^+\) fragment. However, the structure of the unknown compound cannot be elucidated from this information.
Figure 22: Mass spectra of benzhydryl triethylcarbinyl ether (28, top) and unknown D (bottom)
A $^1$H NMR overlay of authentic 28 and the electrolytic mixture clearly shows 28 to be present in the mixture (Figure 23). The $^1$H NMR of D indicates that it is likely an aldehyde as evidenced by the signal at approximately 9.7 ppm. A close view of this signal shows it to be split into a doublet with a small coupling constant of 1.76 Hz. A small coupling constant is often noted with aldehydes\textsuperscript{32}. The only other distinguishing signal for D in the $^1$H NMR spectrum of the mixture is a multiplet at 3.3 ppm. Integration of these two peaks indicates that the aldehyde signal corresponds to half as many protons as the multiplet. The $^1$H NMR spectrum of authentic 28\textsuperscript{27} (Figure 24) contains the expected alkyl triplet and quartet at 0.72 ppm and 1.52 ppm, respectively. The benzhydryl proton appears at 5.52 ppm, and each of the three chemically distinct aromatic protons display separate signals that it was possible to cleanly integrate.

Benzhydryl triethylcarbinyl ether was a previously unidentified compound and was further characterized by $^{13}$C NMR, HSQC, and ESI/APCI\textsuperscript{22}. The $^{13}$C and HSQC spectra are consistent with the proposed structure and connectivity for 28. The $^{13}$C NMR spectrum is shown below (Figure 25). Carbon atom assignments were made based on connectivity displayed in the HSQC spectrum. The alkyl, benzhydryl, and bound aromatic carbons are identified. The assignments of the remaining aromatic carbons were ambiguous and so were not explicitly identified.
Figure 23: $^1$H NMR overlay showing a mixture of products from the constant current electrolysis of diphenylacetaldehyde (1) in the presence of triethylcarbinol (top) and pure benzhydryl triethylcarbinyl ether (28, bottom)
Figure 24: $^1$H NMR spectrum of benzhydryl triethylcarbinyl ether (28)\textsuperscript{27}
Figure 25: $^{13}$C NMR spectrum of benzhydryl triethylcarbinyl ether (28)
C. Mechanistic Studies

The electrochemical experiments described above provided a great deal of insight into the potential mechanistic pathways through which the anodic conversion of diphenylacetaldehyde (1) to various benzhydryl ethers occurred. However, the source of the benzhydryl proton in the ether product remained unclear. Additionally, evidence gathered by Boris Sheludko in Fry lab suggested that there might be two mechanisms of ether formation occurring simultaneously: 1) direct oxidative cleavage of the C-C bond of 1 followed by further oxidation and hydrogen abstraction, and (2) oxidative cleavage of the α-alkoxyaldehyde.

Scheme 20: Two electrochemical pathways by which diphenylacetaldehyde (1) is converted to benzhydryl alkyl ethers

A series of mechanistic studies were performed with the goal of elucidating the pathway(s) by which the conversions observed in this work occur.
**Acid-Mediated Enol Formation.** The constant current electrolysis experiments often exhibited an induction period before product was observed. In some experiments four or five hours of reaction time was required before any product was evident (as determined by GC/MS). It is believed that this long period of time before any electrolysis product appeared was due to the slow rate of enolization of 1 to its enol 1a. As discussed previously, the active species in the anodic oxidation of 1 is presumed to be 1a. It is known that 1 has a higher enol content relative to that of other aldehydes. To test the hypothesis that the oxidation of 1 proceeds through 1a, p-toluenesulfonic acid monohydrate (PTSA) was added to a constant current electrolysis of 1 in order to facilitate enol formation. It was speculated that the acid would increase the rate of the enol transformation and hence the rate of the electrolysis reaction. The electrolysis experiment was initially carried out with equimolar quantities of 1, cyclohexanol, and PTSA. In the time in which the reaction solution was being degassed under nitrogen before beginning the electrolysis, the solution had already turned pale yellow in color. Analysis by GC/MS revealed a previously unseen compound with a parent peak of m/z 278. Upon starting the electrolysis, no induction period was observed, and α-cyclohexyloxydiphenylacetaldehyde (21) formed much more quickly than in experiments performed without acid. At 270 minutes the reaction showed nearly complete conversion of 1 to 21. This can be compared with Figure 5 on page 21 in which 21 (B) was the major product at 480 minutes with a significant amount of 1 still unreacted. Formation of diphenylacetaldehyde cyclohexyl hemiacetal (20) was not observed in the electrolysis experiments in which PTSA was utilized.
Based on the mass spectroscopic results, the compound formed upon adding acid to the electrolysis medium was hypothesized to be diphenylacetaldehyde cyclohexyl enol ether (30) in equilibrium with 1 and cyclohexanol. As the electrochemical oxidation of 1 proceeded through 1a, the equilibrium of 1 and 30 was driven back towards 1, and 30 was depleted as the constant current electrolysis progressed.

![Scheme 21: Equilibrium of 1/1a, cyclohexanol, and diphenylacetaldehyde cyclohexyl enol ether (30)](image)

This experiment was repeated with a catalytic amount (five mole percent) of PTSA. The same color change was observed and a baseline GC/MS analysis showed the same compound with a parent peak of $m/z$ 278. The reaction was monitored by GC/MS every hour. At five hours, the majority of 1 had been converted to 21. The reaction required a further six hours (eleven total) to reach completion.

The identity of 30 was verified by alternate synthesis which was carried out by heating to reflux 1 and two molar equivalents of cyclohexanol in the presence of catalytic PTSA in benzene. When only one molar equivalent of cyclohexanol was used, the reaction did not go to completion. (The need for an excess of nucleophile in similar syntheses is not unprecedented. The syntheses of aldehyde enamines often require a large excess of amine for the reaction to go to completion\(^{34}\).) A Dean-Stark
trap was used to remove water from the solution medium and drive the reaction equilibrium towards 30. The product was purified by column chromatography and isolated in 45% overall yield. The proposed identity of the product was confirmed by GC/MS and \(^1\)H NMR. As 30 was a previously unreported compound, \(^{13}\)C NMR and HSQC spectra and accurate mass by ESI/APCI were also acquired. All experimental spectral data supported the proposed structure of 30. Assignments of distinctive carbon atoms in the \(^{13}\)C spectrum (Figure 27 on page 64) were made by examining the connectivity displayed in the HSQC spectrum (Figure 28 on page 65). As predicted the quaternary aromatic carbons do not appear in the HSQC spectrum.
Figure 26: $^1$H NMR of diphenylacetaldehyde cyclohexyl enol ether (30)
**Figure 27:** $^{13}$C NMR spectrum of diphenylacetaldehyde cyclohexyl enol ether (30)
Figure 28: HSQC spectrum of diphenylacetaldehyde cyclohexyl enol ether (30)

Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Two Molar Equivalents of Cyclohexanol. It was postulated that should the relative amount of cyclohexanol in the constant current electrolysis solution be increased, the observed concentration of diphenylacetaldehyde cyclohexyl hemiacetal (20) would be greater relative to when only molar equivalent of alcohol was used. No formation of
20 was observed, however. Hourly GC/MS analysis of the electrolysis solution showed small, but fairly constant amounts, of 30. This suggests that 30 was produced at its equilibrium concentration and was then rapidly consumed as \( \alpha \)-cyclohexyloxydiphenylacetaldehyde (21) was formed. The reaction proceeded as predicted from 21 to benzhydryl cyclohexyl ether (24).

**Attempted Synthesis of \( \alpha \)-Methyldiphenylacetaldehyde (31).** We had hoped to investigate the role of the alkoxy group in the anodic oxidation of \( \alpha \)-alkoxyaldehydes. Of particular interest was the question of whether the reaction requires an alkoxy group at the \textit{alpha}-position. We wondered whether the reaction would yield the same ether products if the \( \alpha \)-alkoxy group were replaced with an aliphatic group, i.e. aldehydes of type \textbf{b} below.

![Chemical Structure](https://example.com/structure.png)

\textbf{a}, \( R_1 \)=alkoxy; \( R_2 \)=H  
\textbf{b}, \( R_1 \)=alkyl; \( R_2 \)=H  
\textbf{c}, \( R_1 \)=alkyl; \( R_2 \)=alkyl

The synthesis of \( \alpha \)-methyldiphenylacetaldehyde (31) was attempted. A two-step synthetic route was followed, in which \( E-\alpha \)-methylstilbene (32) was oxidized to \( E-\alpha \)-methylstilbene oxide (33) using \( m \)-chloroperbenzoic acid (MCPBA) in aqueous NaHCO$_3$ solution$^{35}$. The reaction proceeded smoothly and yielded 33 as a pale orange viscous liquid in 99.4% crude yield by weight. Due to the acid-sensitive nature of epoxides, the crude product was used directly in the next phase of the synthesis with
the intention to purify the final product. The rearrangement of 33 to 31 was attempted using an indium chloride-promoted reaction\textsuperscript{36}.

Scheme 22: Synthesis of $\alpha$-methyldiphenylacetaldehyde (31)

Ranu and Jana reported the successful synthesis of 31 by this two-step process in high overall yield\textsuperscript{36}. Despite this, the isolation of pure 31 was unsuccessful. The reaction did not proceed cleanly and produced a large number of byproducts. Comparison of the experimental $^1$H NMR with the reported values indicated that 31 was present in the product. However, the product decomposed on a silica gel chromatography column and no 31 was recovered. Due to the apparent instability of the $\alpha$-alkylaldehyde, it was decided to forego the electrochemical investigation of 31 and pursue other methods of mechanistic study since Sheludko’s work had shown that the alkoxy group is unnecessary for the anodic decarbonylation process\textsuperscript{27}.

The Use of Deuterated Material in Mechanism Determination. Boris Sheludko carried out the anodic oxidation of 1,1-diphenylacetone (34) 100% deuterated at the methine carbon and dideuterated at the methyl group (34-$d_3$) in the presence of 2-phenylethanol\textsuperscript{27}.
He demonstrated that only some of the ether product retained deuterium at the benzhydryl position, thus proving that electrochemical ether formation from 34 can occur by two competing mechanistic pathways. Ether formation could occur through the enol of 34 or by direct $\alpha$-cleavage of the carbonyl group. It was believed that the same was true for 1.

**Scheme 23:** Two electrochemical pathways to benzhydryl alkyl ether formation from diphenylacetaldehyde (1)

In the electrolyses of 1 significant amounts of $\alpha$-alkoxyaldehyde accumulated in solution before formation of the corresponding benzhydryl alkyl ether was observed.
(except in the case of triethylcarbinol as a nucleophile). This suggests that the
electrochemical conversion of 1 to benzhydryl alkyl ethers occurs through the enolic
route shown in Scheme 23 above. Based on Sheludko’s research, however, we
decided to test if, and the extent to which, the conversion of 1 to the ether occurs by
direct α-cleavage.

The replacement of the benzhydryl proton of 1 with deuterium (to give 1-\textit{d})
would allow for analysis of the percent deuterium in the constant current electrolysis
product. If the electrolysis of 1-\textit{d} proceeded exclusively via the enol (α-
alloxyaldehyde pathway) then deuterium would not be retained in the product. If,
however, the reaction proceeded by direct α-cleavage of the carbonyl group, the ether
product would remain deuterated (Scheme 25 on page 70). The deuteration of 1 was
carried out by stirring 1 in acetonitrile in the presence of an excess of D\textsubscript{2}O and
D\textsubscript{2}SO\textsubscript{4}. After working up the deuteration reaction three times 1-\textit{d} was isolated in 78%
yield and was shown to be 90% deuterated as determined by comparison of the
aldehyde and benzhydryl signal integration values. Any attempt to further deuterate 1
resulted in decomposition and the formation of byproducts.

\begin{equation}
\begin{array}{c}
\text{Scheme 24: Synthesis of diphenylacetaldehyde-}d (1-\textit{d})
\end{array}
\end{equation}
Scheme 25: a) Electrochemical enolic conversion of diphenylacetaldehyde-$d$ (1-$d$) to benzhydryl alkyl ether; b) electrochemical cleavage conversion of 1-$d$ to benzhydryl alkyl ether, showing retained deuterium

In order to avoid complications with diphenylacetaldehyde cyclohexyl hemiacetal (20), the constant current electrolysis of 1-$d$ was carried out in the presence of 2-phenylethanol. The reaction did not proceed cleanly as it did with the undeuterated starting material; a significant number of byproducts not seen during electrolyses of undeuterated material were formed. The reaction was allowed to proceed for 18 hours, at which time GC/MS analysis indicated that 25 was the major product. However, a great number of cleavage byproducts were also visible in the GC/MS analysis. A $^1$H NMR of the electrolysis product showed a large amount of unreacted 2-phenylethanol. The $^1$H NMR spectrum of the product does not contain an aldehyde peak from unreacted 1, and the cause of the unreacted 2-phenylethanol is unknown. A $^1$H NMR overlay of the electrolytic ether product and authentic 25 did however show that 25 was produced in the electrolysis reaction.
Figure 30: $^1$H NMR overlay showing the electrolysis product (bottom) and the authentic benzhydryl phenethyl ether (25, top)

A small peak for the benzhydryl proton of 25 is visible at 5.42 ppm. A close view of the ether methylene triplets at 2.94 ppm and 3.65 ppm show doubling that appears to be two triplets slightly offset by approximately 4 parts per billion ($\delta$ 1.76 Hz) (Figure 31). As no other peaks in the spectrum are duplicated, it was speculated at this point that the doubling was the result of long-range deuterium effects causing a slight chemical shift in the deuterated ether relative to the protio ether$^{37}$. 
Figure 31: Close views of the methylene triplets displaying doubling in the benzhydryl phenethyl ether (25) produced in the constant current electrolysis of diphenylacetaldehyde-\(d\) (1-\(d\)).

A rough estimate of the relative integrations of the overlapped triplets was calculated by integrating separately each of the peaks of the signal at 3.65 ppm (top spectrum in Figure 31). For all three sets of peaks, the integration value for the taller signal is approximately twice as large as the integration of the shorter peak. A precise
relative value could not be obtained due to the inaccurate nature of the calculations, but it was estimated that the benzhydryl singlet at 5.42 ppm integrates to approximately 60% of the value of the larger methylene triplet centered at 3.65 ppm, suggesting that there is both deuterated and undeuterated ether present. This supports the contention that the electrochemical oxidation of 1 in the presence of alcohols occurs through two competing pathways: the undeuterated ether is produced when the reaction proceeds via the enolic (\(\alpha\)-alkoxyaldehyde) route; the deuterated ether is formed when the reaction proceeds via direct cleavage of the formyl group (Figure 25 on page 70).

Mass spectroscopic analysis of the relative ion counts was also used to estimate the percentage of deuterated material present in the electrolysis product. This was accomplished by comparing ion intensities of the mixed protio and deutero electrolysis product. Corrections for the percentage of the ion intensity due to M+1 fragments were taken into account. This was done by comparing the relative ion intensities of the parent (\(m/z\) 288) and M+1 (\(m/z\) 289) peaks in a sample of authentic 25. The M+1 peak was calculated to be approximately 20% the size of the parent ion in the authentic material. The mass spectrum of the ether product from the electrolysis of 1-\(d\) is shown below (Figure 32). The parent peak for protio benzhydryl phenethyl ether of \(m/z\) 288 is visible. The \(m/z\) 289 peak is attributed mostly to benzhydryl-\(\alpha\)-\(d\) phenethyl ether (25-\(d\)), with a small contribution from the M+1 ion from the protio product. The small \(m/z\) 290 signal is the M+1 peak for 25-\(d\).
Figure 32: Mass spectrum of electrolysis product from the reaction of diphenylacetaldehyde-\textit{d} (1-\textit{d}) in the presence of 2-phenylethanol

The adjusted ratios of the relative ion counts indicate that approximately 65% of the ether was formed through the enolic pathway, in relatively good agreement with the NMR estimate.

As a further exploration of the mechanism of anodic oxidation of 1 in the presence of alcohols, the constant current electrolysis of 1 (undeuterated) was repeated in deuterated acetonitrile. In this instance any ether that formed through the enol would be expected to contain deuterium it abstracted from the solvent (25-\textit{d}). The cleavage product would be the protio ether (25).
Scheme 26: a) Electrochemical enolic conversion of diphenylacetaldehyde (1) to benzhydryl alkyl ether in acetonitrile-$d_3$, showing abstracted deuterium; b) electrochemical cleavage conversion of 1 to benzhydryl alkyl ether

The deuterated solvent appeared to cause significant isotope effects, discussed further below. As with the oxidative electrolysis of 1-$d$, the reaction resulted in a large number of byproducts. The GC/MS data indicated the presence of deuterated ether in the product, but an accurate percentage could not be calculated. As with the anodic oxidation of 1-$d$ described above, the fragmentation pattern showed signals of $m/z$ 289 and $m/z$ 290 corresponding to the deuterated ether and its M+1 peak, respectively. The $^1$H NMR spectrum of the ether product shows a large amount of unreacted 2-phenylethanol and other byproducts. The methylene triplet and benzhydryl singlet at 3.65 ppm and 5.42 ppm, respectively, are visible; the other methylene triplet at 2.94 ppm is obscured beneath an impurity. Relative to the triplet at 3.65 ppm, the benzhydryl proton integrates to approximately 60% of one proton.

For the electrolysis experiments with both 1-$d$ and acetonitrile-$d_3$, deuterium isotope effects must be considered. It is known that a deuterium in the alpha-position
of a ketone or aldehyde slows the rate of enolization\textsuperscript{38}. This effect can be significant, and it has even been shown that a deuterium in the alpha-position can suppress unwanted enolization during the alkylation of ketones\textsuperscript{39}. Most of the measurements for the extent of the isotope effect on enolization were performed on ketones, which generally have simpler enolization processes than aldehydes\textsuperscript{40}. Comparison to the available data for aldehydes however suggests that for both classes of compounds $k_{H}^{enol}/k_{D}^{enol}$ is generally in the range of 2-6, depending on conditions. Therefore, the deuterium isotope effect slows the rate of enolization of 1-$d$ compared to 1, but not the rate of $\alpha$-cleavage, and so the amount of observed deuterated ether overestimates the amount of product produced by direct cleavage. If the ratios of protio to deutero ether are adjusted to account for the slower rate of enolization of 1-$d$ (taking the initial measurement of product obtained through the enol to be 60%) then approximately 80-94% of the electrolysis product is formed by the enolic route. It is also known that deuterated water can slow the rate enolization by approximately half to two thirds\textsuperscript{38a,41}. A correction for the rate of enolization in deuterated acetonitrile could not be found, but it is likely that the rate of enolization was slowed in the electrolysis and the reaction was influenced towards direct $\alpha$-cleavage. As such, more of the $\alpha$-cleavage product (in this case the protio ether, see Scheme 25 on page 70) is formed than would be under normal conditions. Accounting for this, it is likely that at least 80% of the product is formed through the enolic route. This agrees well with the calculations from the anodic oxidation of 1-$d$. The significant accumulation of $\alpha$-alkoxyaldehydes before the appearance of benzhydryl alkyl ethers bolsters this
contention and demonstrates that the α-alkoxyaldehydes are the primary source of the benzhydryl ether products (See Discussion).

Additionally, the anodic oxidation of 1 in acetonitrile-$d_3$ verified that solvent is the source of the benzhydryl proton in the ether products formed via the enolic pathway.

**Synthesis of Benzhydryl-$d$ Phenethyl Ether (25-$d$) and Investigation of Possible Long-Range Isotope Effects on NMR Spectra.** The possibility of long-range deuterium effects shown in Figure 31 on page 72 is not unprecedented$^{37}$. We decided to test for the possible operation of such effects in this system by synthesizing an authentic sample of benzhydryl-$\alpha$-$d$ phenethyl ether (25-$d$).

Benzhydryl-$\alpha$-$d$ phenethyl ether was obtained from a simple, multi-step synthetic route. Benzophenone (2) was treated with lithium aluminum deuteride (LiAlD$_4$) in THF overnight to afford benzhydrol-$\alpha$-$d$ (19-$d$). Following two recrystallizations in heptane, white needle crystals were obtained in 81% yield. $^1$H NMR and GC/MS confirmed 19-$d$ was acquired and showed complete deuteration of the benzhydryl proton. Compound 19-$d$ was treated with an excess of thionyl chloride in dichloromethane$^{42}$. The reaction was stirred for two hours at room temperature and the solvent removed *in vacuo* to produce pure benzhydryl-$d$ chloride (35-$d$) in 97% yield. Deuterated chloride 35-$d$ was then treated with an equimolar amount of 2-phenylethanol in the presence of an excess of silver tetrafluoroborate (AgBF$_4$). This afforded 25-$d$ in 66% yield.
Scheme 27: Synthesis of benzhydryl-\textit{d} phenethyl ether (25\textit{d})

The $^1$H NMR spectra of 25\textit{d} verified the complete deuteration of the benzhydryl proton. Unexpectedly however, six triplets were observed in the spectrum (Figure 33). The triplets display approximately 10:5:1.5 integration ratios. A small amount of polymerized THF$^{23}$ in the sample is visible at 1.65 and 3.41 ppm. A COSY experiment of the sample indicated the presence of three coupled pairs of protons (see Figure 34 on page 80). The gas chromatogram of the sample showed there was only one compound and TLC indicated that no unreacted 2-phenylethanol was present.
Figure 33: $^1$H NMR spectrum of benzhydryl-$\alpha$-$d$ phenethyl ether (25-$d$, top) with a close view showing the three sets of methylene triplet peaks (bottom)
Figure 34: COSY analysis of benzhydryl-α-d phenethyl ether (25-d).

The addition of authentic protio 25 to the NMR sample did not produce the doubling effect of the signals observed in the electrolysis product. The only observed consequence was a relative increase of the size of the largest triplets at 2.95 and 3.65 ppm and the appearance of the benzhydryl proton. Thus the doubling of the spectrum seen in Figure 31 on page 72 is not due to a deuterium effect on the $^1$H NMR spectrum. The reason for the three sets of triplets for ether 25-d is not clear at this time, but may be related to the atropisomerism believed to be observed with the α-alkoxyaldehydes. This is under continuing investigation.
Discussion

A. Enol Content of Diphenylacetaldehyde (1)

Before the mechanisms of the oxidation of 1 can be discussed, it is necessary to consider its enol content. A $^1$H NMR spectrum of authentic 1 in CDCl$_3$ shows no indication that the enol (1a) is present in appreciable concentrations. However, the keto-enol equilibrium constant of 1 is known to be unusually large compared to most other aldehydes and ketones.$^{33a}$ Kresge et al. reported the keto-enol equilibrium constant of 1 in aqueous solution at 25°C to be $K_E=0.104$ (pK$_a=0.98$), as compared with $K_E=5.9 \times 10^{-7}$ (pK$_a=6.23$) for acetaldehyde under the same conditions. Data gathered by Rochlin and Rappoport support the conclusion that the keto-enol equilibrium constant of 1 is large compared to other simple carbonyls.$^{33b}$ Rochlin and Rappoport reported that in DMSO-d$_6$ over the temperature range 294K to 364 K 1a was always present in excess of 1. At 294 K 83.5% was in the enol form ($K_{enol}=5.06$); at 364 K the percent enol had decreased to 54.8% ($K_{enol}=1.21$). Rochlin and Rappoport attribute their higher equilibrium constants in comparison to Kresge’s value to stabilization of the enol through hydrogen bonding of its hydroxyl group to the DMSO-d$_6$. They argue that DMSO is a much stronger hydrogen-bond acceptor.

![Scheme 28: Structures of diphenylacetaldehyde (1) and its enol (1a)](image)
than water, based on Kamlet-Taft hydrogen-bond accepting parameters\textsuperscript{43}. In either solvent, however, it was demonstrated that the enol content of 1 is large compared to that of other simple aldehydes and ketones.

The high keto-enol equilibrium constant is attributed to phenyl-group stabilization through conjugation with the enolic double bond\textsuperscript{33}. Kresge \textit{et al.} pointed out however that the substituent effect stabilization by the phenyl group is 3.6 kcal/mol. This is less than the value of 4.9 kcal/mol expected based on Hine’s parameters, which are a measure of the relative double-bond stabilizing abilities of substituents\textsuperscript{44}. Kresge argued that the discrepancy is likely the result of steric crowding preventing a completely coplanar alignment of the phenyl groups with the enolic double bond. This analysis is consistent with the results presented by Rochlin and Rappoport in which they demonstrated that conjugation achieved through coplanarity affords greater enol stabilization than bulky β-aryl substituents\textsuperscript{33b}. Density functional computations (B3LYP/6-31G(d)) performed by Dr. Fry show the dihedral angle between the two phenyl groups in 1 is 30°. It is known that \textit{p-p} orbital overlap goes approximately as the square of the cosine of the dihedral angle between the orbital\textsuperscript{45}. For 1, therefore, \(\cos^2(30°)=0.75\). Despite the twist of the two phenyl rings, there is still sufficient overlap of aromatic and enolic \textit{p}-orbitals (75\%) to obtain resonance stabilization of 1\textit{a}.

All these data support the contention that the amount of enol present in solution is significant enough to allow for anodic oxidation of 1 to proceed through 1\textit{a}.
B. Reaction of Diphenylacetaldehyde (1) with Molecular Oxygen and its Anodic Oxidation in the Presence of Water

The experiments in which 1 was reacted with $^{18}$O-labeled water (via anodic oxidation) and $^{18,18}$O$_2$ (via autoxidation) clearly demonstrated that the conversion of 1 to 2 can occur by two mechanistic pathways, as shown in Scheme 29 below.

Scheme 29: a) Anodic oxidation of diphenylacetaldehyde (1) in the presence of $^{18}$O-labeled water; b) Aerobic oxidation of 1 by doubly-labeled molecular oxygen

The oxidation of 1 by molecular oxygen has been previously documented, but the mechanism has not been studied in detail.$^{19}$ We believe that the reaction occurs by the addition of oxygen across the double bond of the enol form of diphenylacetaldehyde (1a) (Scheme 30). It is possible that this addition occurs by the stepwise formation of the two carbon-oxygen bonds to form a dioxetane species (36). Species like 36 are known to decompose via a retro[2+2] process as shown in Scheme 30$^{16}$. 

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Scheme 30: Autoxidation of diphenylacetaldehyde (1) by reaction by molecular oxygen

Based on the data gathered from the controlled potential experiments performed on 1 in the presence of air, inert gas, and/or H$_2^{18}$O (see pp. 8-19 and on the results found for cyclohexanol), a mechanistic pathway for the electrochemical conversion of 1 to 2 is proposed (Scheme 31 on page 85). The anodic oxidation of 1 begins with removing a π-bonding electron from 1a to give a radical cation 37 which is stabilized by the two phenyl groups. Species 37 is then attacked by water (or another nucleophile), yielding a radical species 38 from which another electron is removed to give a new cation (39). Species 39 is postulated to undergo nucleophilic attack to produce a tri-hydroxy intermediate (40) which then rapidly loses water to give α-hydroxydiphenylacetaldehyde (17). As discussed earlier, 17 is the long-lived intermediate that is observed in the GC/MS analysis of the electrolysis of 1 in the presence of water. Finally, anodic oxidation of 17 yields benzophenone (2) and other unidentified byproducts. This proposed mechanism is consistent with the data.
gathered from the electrochemical experiments in the presence of $^{18}\text{O}$-labeled water which demonstrated that the oxygen in 2 originates from water and not from the original carbonyl group.

Scheme 31: Proposed mechanistic pathway for the anodic oxidation of 1 in the presence of water
There is strong theoretical evidence that after a $\pi$-bonding electron is removed from 1a, water will attack the terminal carbon, as shown in Scheme 31 for species 37 above. Density functional theory (DFT) B3LYP/6-31G(d) computations performed by Dr. Fry indicate that the charge on the cation radical of 1a (37) is highly localized on the terminal carbon. Mulliken atomic charge computations obtained from the DFT computation indicate that the charge is distributed such that there is approximately six times as much charge located on the terminal carbon than on the central carbon bearing the phenyl groups. When the Mulliken charges are calculated with the hydrogen atoms summed into the heavy atoms, the computation shows the charge on the terminal carbon to be approximately fourteen times as large as the charge on the other (central) enolic carbon.

Figure 35: Ball and stick representations of diphenylacetaldehyde enol cation radical (37) demonstrating the charge distribution as determined from density functional theory B3LYP/6-31G(d) computations. The dark blue regions are highly positive; teal regions are less positive.

The terminal carbocation is believed to carry most of the charge as a result of resonance stabilization obtained due to the powerful cation-stabilizing nature of oxygen.
Scheme 32: Resonance stabilization of diphenylacetaldehyde enol cation radical (37)

The mechanism for the anodic oxidation of 1 to 2 shown in Scheme 31 on page 85 is consistent with the calculated charge distribution data presented above.

C. Mechanism of Anodic Oxidation of Diphenylacetaldehyde (1) in the Presence of Alcohols

Mechanism Determination. The data from the constant current electrolysis and mechanistic studies showed that the anodic oxidation of 1 in the presence of a variety of alcohols to the corresponding benzhydryl ether occurs through two competing mechanistic pathways. In particular both the anodic oxidation of deuterated diphenylacetaldehyde (1-\textit{d}) (see pp. 67-74) and 1 in acetonitrile-\textit{d}_3 (see pp. 74-77) showed incorporation of deuterium. Although it was not possible to obtain exact ratios from the deuterium experiments, the \textit{^1}H NMR and mass spectroscopic ion count data generally showed that the majority, at least 60\%, but probably a much higher percentage, of the oxidation of 1 to benzhydryl ethers occurred through the enolic route (Path B, See Scheme 33 below). The proposed mechanisms for both the enolic and direct \textit{\alpha}-cleavage (Path B) pathways are shown below in Scheme 33.
Scheme 33: Electrochemical conversion of diphenylacetaldehyde (1) to benzhydryl alkyl ethers via Path A (direct α-cleavage) and Path B (anodic oxidation of diphenylacetaldehyde enol, 1a)
It has been reported that there are deuterium isotope effects on the rate of enolization \( k_{H^{\text{enol}}}^{\text{enol}} / k_{D^{\text{enol}}}^{\text{enol}} \) in the range of 2-6 for ketones and aldehydes of similar structure to 1. That is, the deuterium isotope effect slows the rate of enolization of 1. Most of the research on deuterium isotope effects on the rate of enolization has been carried out for ketones. The data available for aldehydes is less substantial. This has been attributed to the fact that the enolization processes of aldehydes are more susceptible to oxidation or hydration. An exact value for \( k_{H^{\text{enol}}}^{\text{enol}} / k_{D^{\text{enol}}}^{\text{enol}} \) for 1 could not be found. However, based on the data available the deuterium isotope effect on the rate of enolization is similar for simple ketones and aldehydes.

Since the deuterium isotope effect slows the rate of enolization of 1-d but does not inhibit direct \( \alpha \)-cleavage, the apparent amount of the deuterated product exaggerates the percentage produced by cleavage. The slower rate of enolization also helps to account for the large number of byproducts in the deuterium experiments as compared to the oxidations of 1 carried out under standard conditions. With the slower rate of enolization, 1 can undergo any number of cleavage reactions which are not typically observed. Deuterated water has also been shown to slow the rate of enolization of acetone. Assuming a similar effect for 1 in acetonitrile-\( d_3 \), the experimental data again exaggerate the amount of the product formed by \( \alpha \)-cleavage.

As mentioned above, it was not possible to obtain accurate ratios of the deuterated to undeuterated ether due the number of cleavage byproducts produced in the electrolyses as a result of slowed enolization of 1.

Path B shown in Scheme 33 above presents the question of whether the alkoxy group of the \( \alpha \)-alkoxyaldehyde is required for decarbonylation. We had hoped
to investigate this issue by carrying out the anodic oxidation of $\alpha$-
methyldiphenylacetaldehyde (31), but 31 was unstable and could not be isolated for
use. However, Boris Sheludko demonstrated that the oxidation of 1-alkyl-1,1-
diphenylacetone (34) in the presence of 2-phenylethanol afforded benzhydryl
phenethyl ether (25), thus proving that the alkoxy group is not needed for
decarbonylation of the $\alpha$-alkoxyaldehydes$^{37}$.

The electrochemical oxidation of 1 and other ketones to benzhydryl methyl
ether (27) has been previously reported$^{47}$. However, those reactions were performed
under different conditions at controlled potential (as opposed to constant current) in a
divided cell. Under these conditions 27 was oxidized further to benzophenone (2),
whereas 27 is stable under the experimental conditions described in this work. In
addition, it was reported that in some of the electrolyses sodium bicarbonate was
added to the reaction medium to scavenge protons and prevent acid catalyzed
reactions$^{47a}$. This is of particular significance since we showed that the formation of
diphenylacetaldehyde enol (1a) from 1 can be catalyzed by acid. By adding a proton
scavenger to the reaction, Miller et al. inhibited enol formation, and so it is not
surprising that their data support the predominance of cleavage products. However,
they did concede that other pathways, including the oxidation of enols, could lead to
eventual cleavage of the benzylic carbon-carbon bond. Our data (see pp. 67-77)
suggest that in the absence of a proton scavenger at least 60%, and more likely 80-
90%, of the anodic oxidation of 1 in the presence alcohols proceeded via the enolic
($\alpha$-alkoxyaldehyde) pathway.
**Hemiacetal Stability.** Acyclic hemiacetals are notoriously unstable compounds and often cannot be isolated. The fact that an intermediate proposed to be diphenylacetaldehyde cyclohexyl hemiacetal (20) is observed in the constant current electrolysis of 1 in the presence of cyclohexanol but not in the presence of the other alcohols is still under investigation. It is possible that hemiacetals are also formed in the presence of other alcohols but are less stable and rapidly convert to the corresponding α-alkoxyaldehyde through loss of an alcohol (see Scheme 10 on page 24). It is also likely that the hemiacetals do not survive the workup necessary for GC/MS analysis. The stability of 20 was unexpected, but not unprecedented. In particular, McGill reports the formation of stable hemiacetals from α-alkoxyaldehydes in 2-10% aqueous acetonitrile solutions. The hemiacetals synthesized by McGill were sufficiently stable to characterize by 1H, 13C, and COSY NMR analysis. It was also reported that the stability of the hemiacetals was unique to the acetonitrile/water solvent system. There are also a number of other precedents for stable hemiacetals or dimeric derivatives when the alpha carbon bears one or more electron-withdrawing groups. It is unknown at present whether the apparent stability of 20 is true for all secondary alcohols or whether it is specific to cyclohexanol. Future investigation of the anodic oxidation of 1 should certainly involve the use of other secondary alcohols.

**Induction Period.** The mechanisms proposed in Path A and Path B in Scheme 33 on page 88 above are two-electron and four-electron processes, respectively. All the constant current electrolyses in the presence of alcohols were carried out at 25 mA with 225 mmol 1 as starting material. Using a value of 96,500 Coulombs/mole for
Faraday’s constant, it was calculated that the four-electron oxidation (Path B) which our data indicate dominate the reaction, should require just over 9.5 hours to reach completion in ideal conditions.

\[
2.25 \times 10^{-3} \text{ mol } 1 \times \frac{4 \text{ mol } e^-}{\text{ mol } 1} \times \frac{96,500 \text{ C}}{\text{ mol}} = 870 \text{ C}
\]

\[
\frac{870 \text{ C}}{0.025 \text{ C/s}} = 34,800 \text{ s} = 9.7 \text{ hrs}
\]

**Scheme 34**: Sample calculation of predicted reaction time for a four-electron oxidation at 25 mA under ideal conditions

It is expected that some of the current will be absorbed by the solvent, and so a reaction time of 10.5-11 hours would not be considered unreasonable. However, as shown in Figures 5 and 14 (on pages 21 and 36, respectively) in the Results section above, the reaction times required to achieve complete conversion to the benzhydryl alkyl ethers were much longer. This has been attributed to several factors. The electrolyses usually exhibit an induction period in which no product is observed for several hours. In some experiments this induction period was as long as five hours. It was postulated that despite the relatively high keto-enol equilibrium constant for 1, there simply was not enough enol of 1 (1a) present to drive the reaction forward at a noticeable rate. When product began to appear, the rate of the reaction increased. The formation of both α-alkoxyaldehyde and benzhydryl alkyl ether produce protons, and so the reaction should be autocatalytic, since as the electrolysis proceeds the enol formation is catalyzed by the acid produced in the electrolysis. Furthermore, it is believed that tetrabutylammonium tetrafluoroborate (Bu4NBF4) consumes more of the current than previously anticipated. The crude product obtained from working up an
electrolysis reaction, regardless of nucleophile, was always dark brown oil. It was possible to remove the electrolyte and the colored components of the reaction product by filtering the mixture through silica gel using diethyl ether as eluent. The dark brown compounds remained at the top of the chromatography column, suggesting a high degree of polarity. Therefore, it is believed that the dark color of the electrolysis solutions is the result of oxidized electrolyte. Due to the consumption of current by the electrolyte, it was necessary to carry out the electrolyses for a period of time longer than calculated in order for the reactions to reach completion.

**Diphenylacetaldehyde Cyclohexyl Enol Ether (30).** As discussed on the results of facilitating the formation of diphenylacetaldehyde enol (1a) with acid, stirring 1 in the presence of cyclohexanol with catalytic p-toluenesulfonic acid monohydrate (PTSA) affords an equilibrium with 30.

![Scheme 35](image)

**Scheme 35:** Equilibrium of diphenylacetaldehyde (1) with diphenylacetaldehyde cyclohexyl enol ether (30)

It was possible to isolate 30 for characterization by forcing the reaction to completion. This was accomplished by heating a solution of 1, cyclohexanol, and catalytic PTSA in benzene to reflux and removing the water produced with a Dean-Stark trap. It is believed that 30 is formed through a mechanistic pathway analogous to acetal
formation, as shown below.

Scheme 36: Proposed mechanism for the formation of diphenylacetaldehyde cyclohexyl enol ether (30)

**Atropisomers.** The formation of atropisomers in the silver-promoted syntheses of α-alkoxyaldehydes appears to have a general negative correlation with the length of time for which the reactions are allowed to stir. That is, the amount of atropisomerism decreases with long stirring time. This relationship was not studied rigorously but warrants future investigation. The formation of atropisomers, however, is consistent with the mechanism for nucleophilic attack on α-bromoketones as proposed by Fry and Migron. They argued that since tertiary α-bromoketones react readily while primary α-bromoketones give no reaction, it is likely that the silver ion-assisted reaction proceeds through formation of a carbocation (S_N1) instead of via S_N2 attack. Fry and Migron also argued that due to the difficulty of forming a carbocation adjacent to a carbonyl group the reaction likely involves stabilization by the carbonyl oxygen and probably participation of the carbonyl group in the ionization.
Scheme 37: Stabilization of carbocation intermediate by neighboring group participation in the silver ion-mediated synthesis of α-alkoxyaldehydes\textsuperscript{20}

The observed atropisomerism is also consistent with the formation of a strong acid (HBF\textsubscript{4}) in the silver-ion mediated α-alkoxyaldehyde syntheses.

Scheme 38: Silver ion-mediated synthesis of α-alkoxyaldehydes in which fluoroboric acid (HBF\textsubscript{4}) is a byproduct

Due to the presence of a strong acid in solution it is conceivable that the alkoxy group could be reprotonated and dissociate from the aldehyde, reforming the carbocation. If sufficient reaction time were allowed the more stable atropisomer (thermodynamic product) would predominate. This explains why atropisomerism of the products is not always observed – longer reaction times allow for equilibration by acid. When the fluoroboric acid was neutralized after only fifteen minutes, however, a mixture of thermodynamic and kinetic products was isolated. The decomposition of one of the α-cyclohexyloxydiphenylacetaldehyde (21) and
α-phenethylxydiphenylacetaldehyde (23) atropisomers on the silica gel chromatography column is further evidence of the acid-mediated interconversion of the stereoisomers. Each purification process yielded only one atropisomer.

Variable temperature $^1$H NMR experiments on a sample of 23 displaying atropisomerism indicated that the two rotamers interconvert at high temperatures. Above 100°C the two aldehyde peaks appeared slightly broadened and the relative ratios of the integration values had changed. Prior to heating, the aldehyde signals showed at 10:4 integration ratio; at 120°C the ratio was approximately 10:2. At this temperature the sample started to decompose, but these data suggest that at high enough temperatures the atropisomers freely interconvert. This is consistent with the gas chromatograms of 21 and 23, both of which contain a single peak at 225°C, the temperature at which 21 and 23 are detected coming off the column.

The suggestion that atropisomerism might be possible for a compound as simple as an α-alkoxydiphenylacetaldehyde may be questioned. However, there are in fact a number of precedents for restricted rotation in substituted diphenylmethanes and triarylmethanes where two of the rings are equivalent$^{50}$. Even where the two rings are unsubstituted as in the present case, the two rings are non-equivalent: typically the plane of one ring is almost perpendicular to that of the other;$^{51}$ the structure is chiral because of the non-equivalence of the two rings. Rotation of both rings, though fast, involves simultaneous correlated motion of both rings because of steric hindrance to rotation of a single ring past the other. This correlated motion, which Mislow has described as a “two-flip” mechanism,$^{52}$ is undoubtedly rapid in 1$^{50b,c}$. Addition of the bulky cyclohexyloxy group at the alpha position to form 21 should create much more
steric hindrance to rotation, raising the barrier to rotation. This was tested in this work by constructing a model of 21 and rotating the formyl group in increments between 0 and 360°, carrying out a series of single point density functional B3LYP/6-31G(d) computations at each point to construct a diagram representing the energy of the system as a function of the O-O dihedral angle (Figure 36). Rotation was carried out from 0 to 360 degrees instead of 0 to 180 degrees because of the non-equivalence of the two rings; the two-ring flip converts the compound into its enantiomer but preserves the non-equivalence of the two rings.

Figure 36: Energy of α-cyclohexyloxydiphenylacetaldehyde (21) as a function of O-O dihedral angle as determined from B3LYP/6-31G(d) computations

Figure 36 shows minima at dihedral angles of 60° and 220°; the two corresponding structures are shown below. The difference in energy between the two minima is 1.0 kcal.
Haller and Schneider found two conformations of 1 differing by 0.25 kcal$^{32}$. The barrier to interconversion of the two conformations of 21 coming out of the computations is unrealistically high because the geometry of the remainder of the molecule wasn’t allowed to change during the formyl group rotation. In the future, the computations should be repeated allowing the geometry to relax at each dihedral angle. Since the single point computations in Figure 36 required several hours for each point, this will be a long computation but should provide a more realistic picture of the barrier to rotation.

The appearance of three distinct sets of two coupled triplet signals in the $^1\text{H}$ NMR of benzhydryl-$\alpha$-d phenethyl ether (25-d) is particularly perplexing (Figure 33 on page 79, bottom). According to GC/MS and TLC analysis there was only one compound in the reaction sample. A number of possible causes of this phenomenon have been considered but are still under investigation. One possibility is that we are observing a similar atropisomeric effect. Unlike the alkoxy group however, deuterium is not large enough to restrict rotation about a bond due to steric hindrance$^{29}$. It is also possible that the silver ion-promoted synthesis was not allowed to stir long enough to
permit equilibration by acid. Further spectral studies including $^{13}$C, HSQC, and variable temperature NMR are currently being pursued to determine the source of the three sets of triplets.

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Triethylcarbinol.** The mechanistic pathway for the anodic oxidation of 1 in the presence of triethylcarbinol is the least understood. Analysis of the reaction mixture and isolation of products was hindered by the significant number of byproducts that result from the anodic oxidation. It is believed, as well, that the bulky nature of the alcohol with the three ethyl groups inhibits the mechanistic pathway observed for the other constant current electrolyses and opens up the reaction to numerous other cleavage pathways. No $\alpha$-triethylcarbinyloxydiphenylacetaldehyde (29) was observed in the constant current electrolysis of 1 in the presence of triethylcarbinol. This is not to say that it is not possible that the anodic oxidation of 1 did not proceed through 1a; given the high keto-enol equilibrium constant of 1, it is likely that the anodic oxidation did proceed via an enolic route. It is postulated that the bulky alkyl groups prevented nucleophilic attack on radical cation species 37 produced adjacent to the phenyl groups (See Scheme 33 on page 88), and so the reaction proceeded via another (and as yet unknown) pathway. It was also considered that 29 did form but was quite unstable due to severe steric strain and was rapidly converted to benzhydryl triethylcarbinyl ether (28) or the other unknown (D) produced in the reaction. In addition to identifying D and the pathway of its formation, future experiments should explore the anodic oxidation of 1 in the presence of other sterically hindered nucleophiles.
D. Applications and Future Directions

As discussed above, the keto-enol equilibrium constant for diphenylacetaldehyde (1) is unusually large as compared to other simple aldehydes\(^{33}\). This has been attributed to the stabilization of the enol through conjugation of the double bond with the two phenyl groups. It has been a concern that the germinal diphenyl functionality is necessary for the electrochemistry presented here, particularly the formation of \(\alpha\)-alkoxydiphenylacetaldehydes. If other aldehydes do not have sufficient enol content to drive the anodic oxidation through the enolic pathway, the applications for synthesis are limited. Therefore, future research will explore the anodic oxidation of carbonyl compounds bearing other groups in the \(\alpha\)-position. The discovery that acid catalyzed enol formation rapidly accelerates the formation of \(\alpha\)-alkoxyaldehydes with no induction period suggests that it may be possible to apply the chemistry presented here to carbonyl compounds of low enol content lacking the germinal diphenyl moiety by adding acid to the medium. The electrolysis of diphenylacetaldehyde-\(d\) (1-\(d\)) should also be carried out in the presence of catalytic acid. This experiment would show whether all of the ether products are formed through the \(\alpha\)-alkoxyaldehydes under acidic conditions.

Future research will also include carrying out the electrochemical oxidation of 1 in the presence of a wide range of other nucleophiles. This includes other alcohols, amines, and even nucleophilic alkenes, enol ethers, or ketene acetals. By exploiting the electrogenerated carbocations, this chemistry offers significant synthetic opportunities, including the possibility of carbon-carbon bond formation.

The stereochemical characteristics of the \(\alpha\)-alkoxyaldehydes and the
benzhydryl alkyl ethers are currently being explored. In particular, the appearance of three sets of three triplets in the $^1\text{H}$ NMR spectrum of benzhydryl-$\alpha$-d phenethyl ether (25-d) (Figure 33 on page 79) raises some interesting stereochemical questions. The literature on diarylmethanes demonstrates that the two phenyl groups are generally non-equivalent, despite presumed free rotation about the benzhydryl carbon bond$^{50-51}$. Instead, they exhibit correlated (simultaneous) rotation of both phenyl rings. Thus the carbon bearing the two phenyl rings is a chiral center even in substituted benzhydrols and their ethers. This research is still in the very early stages, however, and will be reported in later publications.
Experimental

A. General

Instrumentation and Materials. Gas chromatography/mass spectrometry (GC/MS) experiments were performed on an Agilent Technologies 6890 Network GC system with a 5797 Network mass selective detector. The same GC method was used for all GC/MS acquisitions. The initial oven temperature of 75°C was held for two minutes. The oven temperature was then increased at a rate of 10°C/min to 225°C, where it was held for five minutes. Finally, the oven temperature was increased again at 20°C/min to 280°C and was held at this temperature for five minutes. This second increase in temperature had the sole purpose of removing any remaining high boiling point materials from the GC column. This method resulted in a total run time of 29.75 minutes. All NMR spectra (\(^1\)H, \(^{13}\)C, COSY, and HSQC) were acquired at Wesleyan University on Varian Mercury 300 MHz or Varian UNITYplus 400 MHz NMR instrument. Chemical shifts are given relative to an internal TMS standard. All accurate mass experiments were performed by the High Resolution Mass Spectroscopy Facility at the University of California, Riverside on an Aglient ACTOF spectrometer\(^{22}\).

It was often difficult to cleanly extract the final product from the electrolysis reaction mixture for characterization. Therefore, a number of alternate chemical (as opposed to electrochemical) syntheses were completed in order to produce authentic samples of the electrolysis products for characterization and analysis. The synthesized samples were identified and characterized by GC/MS retention time and fragmentation patterns, \(^1\)H NMR and \(^{13}\)C NMR. In the instances in which a
previously unknown compound was synthesized an HSQC spectrum was also acquired. All solvents were stored over molecular sieves (3A, 8-12 mesh) for at least 24 hours prior to use. Unless otherwise noted, all reagents were purchased from commercial sources. The doubly-labeled oxygen gas was purchased from Icon Isotopes (Summit, New Jersey, USA).

**Typical Controlled Potential Electrolysis.** The following standard setup was used in most controlled potential electrolysis experiments: a 50 mL 3-neck round bottom flask equipped with a magnetic stir bar was used as the reaction vessel. Platinum wire was woven through carbon cloth to create the electrodes (both the anode and the cathode were approximately 2 cm x 2 cm). The reference electrode consisted of 0.1 M AgNO₃ in CH₃CN. The electrolyte solution was 0.1 M tetrabutylammonium tetrafluoroborate (Bu₄BF₄) in CH₃CN. Stock electrolyte solutions were prepared as necessary and stored over molecular sieves. Typically, constant potential electrolysis experiments were using 0.20 mL (1.1x10⁻³ mol) I in 15 mL electrolyte solution (0.075 M) (see Figure 38). All controlled potential experiments were performed at 1.7 V.
Typical Constant Current Electrolysis. A standard constant current electrolysis experimental setup: A 50 mL 3-neck round bottom flask with a magnetic stir bar was used as a reaction vessel. Platinum wire was woven through carbon cloth to create both the anode (3 cm x 3 cm) and the cathode (2 cm x 2 cm). The electrolyte solution consisted of 0.1 M Bu₄BF₄ in CH₃CN. Stock electrolyte solutions were prepared as necessary and stored over molecular sieves (3A, 8-12 mesh). Unless stated otherwise, the constant current electrolysis experiments typically used 34 mL electrolyte solution and were 0.075 M in each regent. All constant current electrolysis experiments were performed at 25 mA. The reactions were performed under nitrogen gas in order to minimize the reaction of 1 with atmospheric oxygen. All three necks of the reaction vessel were stoppered with rubber septa through which the electrode wires and nitrogen needle were threaded. The reaction mediums were degassed with nitrogen for 20 minutes prior to starting the electrolysis experiments. The constant current electrolysis reactions were monitored by GC/MS by extracting 0.1 mL samples of the
electrolysis reaction mixture. A mini-workup to prepare the sample for GC/MS analysis was performed in a test tube by adding approximately 0.5 mL of hexanes and 0.5 mL deionized water to the extracted sample. The mixture was agitated, and the electrolysis sample for GC/MS analysis was siphoned off the top organic layer.

A standard workup procedure was followed for all constant current electrolysis experiments. The electrolyte solution was removed under reduced pressure to yield an oil which still contained the electrolyte, tetrabutylammonium tetrafluoroborate ($\text{Bu}_4\text{NBF}_4$). The oil was filtered quickly through a short column of silica gel using diethyl ether as eluent; $\text{Bu}_4\text{NBF}_4$ is slightly soluble in diethyl ether, but remained on the chromatography column. The solvent was then removed \textit{in vacuo} to yield the crude electrolysis product. Further purification was done as necessary.

\begin{center}
\includegraphics[width=0.5\textwidth]{figure39.png}
\end{center}

\textbf{Figure 39:} A typical setup for a constant current electrolysis experiment
B. Oxidations of Diphenylacetaldehyde (1) by Electrochemical and Aerobic Methods

Controlled Potential Electrolysis of Diphenylacetaldehyde (1) under Nitrogen in the Presence of Water. The controlled potential electrolysis of 1 produced α-hydroxydiphenylacetaldehyde (17) as an intermediate, before continuing to benzophenone (2). All three compounds including starting material were present in the reaction solution simultaneously but could not be separated by chromatography. The reaction required 600 minutes (10 hours) to reach completion. Conversion of the carbonyl compounds to their 2,4-dinitrophenylhydrazine (2,4-DNP) derivatives was attempted in order to increase the molecular weight of the compounds and thereby improve separability. The synthesis of the 2,4-DNP derivatives proved unsuccessful as 17 decomposed under the highly acidic conditions. The positive identification of 17 was made by GC/MS analysis and subsequent comparison to the mass spectral fragmentations of α-alkoxyaldehydes formed when the water was replaced with alcohols. GC: rt =10.8 min (2), 11.2 min (1), 11.9 min (17); MS: m/z (2) 182 ([M]+), 105, 77; (1) 196 ([M]+), 167, 152; (17): 183 ([M-CHO]+), 105, 77.

Controlled Potential Electrolysis of Diphenylacetaldehyde (1) with Air Bubbled Through. The reaction flask was equipped with a bubbler containing dry acetonitrile over molecular sieves (3A, 8-12 mesh). Air was passed through a bubbler and into the reaction flask. Formation of 2 was observed within five minutes of beginning the controlled potential experiment. At 45 minutes a significant amount of 2 was present as compared with other controlled potential electrolysis experiments performed.
without air bubbled through. The electrochemical oxidation of 1 in the presence of water still occurred, but to a lesser extent than observed in other electrolyses as evidenced by the small amount of 17 present in solution. GC: rt = 10.8 min (2), 11.2 min (1), 11.9 min (17); MS: m/z (2) 182 ([M]+), 105, 77; (1) 196 ([M]+), 167, 152; (17) 183 ([M-CHO]+), 105, 77.

Controlled Potential Electrolysis of Diphenylacetaldehyde (1) in the presence of 18O-Labeled Water. Due to the expense of H218O, this constant potential experiment was scaled down as compared to the typical procedure described above. A 25 mL 3-neck round bottom flask was used as the reaction flask. The reaction medium consisted of 0.13 mL 1 and 0.3 mL 97% H218O in 10 mL 0.1 Bu4NBF4 in CH3CN. The constant potential electrolysis proceeded for 360 minutes, at which point incorporation of the 18O was observed in both 17 and 2. Mass spectrometric analysis indicated the presence of both the 18O-labeled and unlabeled products. GC: rt = 11.0 min (2), 11.5 min (1), 12.0 min (17) MS: m/z (2) 184 ([18O M]+), 182 ([M]+), 107, 105, 77, 51; (17) 185 ([18O M-CHO]+), 183 ([M-CHO]+), 107, 105, 77, 51.

Reaction of Diphenylacetaldehyde (1) with 18,18O2. This reaction was carried to conclusively determine that 1 reacts with molecular oxygen to produce 2. The reaction was performed using 200 µL (1.13x10⁻³ mol) 1 in 15 mL dry CH3CN in a 50 mL two-neck round bottom flask. One neck of the reaction flask was connected via rubber tubing to a bulb with a break-seal containing the 18O2; the other neck was connected to a vacuum line. The solution was frozen in liquid nitrogen, after which the atmosphere above the solution was pumped off. As the reaction solution thawed,
bubbles of dissolved oxygen escaping the solution were observed. Once completely thawed, the reaction was once again frozen in liquid nitrogen and the atmosphere pumped off. This freeze-thaw cycle was completed a total of three times to ensure that no oxygen remained in the flask. After the third freeze-thaw cycle, the system was maintained under vacuum. The break-seal was broken using a metal weight. The solution was allowed to stir under the $^{18}$O$_2$ for two weeks, at which time a sample was extracted and analyzed via GC/MS. The GC analysis showed that approximately 51% of 1 had been converted to 2. Incorporation of $^{18}$O was evident from the cation fragments. The mass spectrum also showed that unlabeled 2 had formed. Since the reaction was carried out in a slight vacuum, atmospheric O$_2$ could have leaked into the system during the reaction time of two weeks. GC: rt =10.7 min (2), 11.2 min (1); MS: m/z (2) 184 ([$^{18}$O M]$^+$), 182 ([M]$^+$), 107, 105, 77; (1) 196 ([M]$^+$), 167, 165.

C. Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Alcohols and the Associated Syntheses

Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Cyclohexanol. This constant current electrolysis was carried out using equimolar quantities ($2.55 \times 10^{-3}$ mol) of 1 (0.45 mL) and cyclohexanol (0.27 mL) in 34 mL electrolyte solution. The reaction was monitored periodically by GC/MS. Sequential conversion of 1$\rightarrow$ diphenylacetaldehyde cyclohexyl hemiacetal (20)$\rightarrow$$\alpha$-cyclohexyloxydiphenylacetaldehyde (21)$\rightarrow$ benzhydryl cyclohexyl ether (24) as shown in Figure 5 on page 22. Hemiacetal 20 could not be independently characterized as the workup procedure necessary to isolate it yielded only 21.
Compounds 21 and 24 were identified and characterized by GC/MS analysis and comparison to authentic samples obtained from alternate syntheses as described below\textsuperscript{20,26,53}. The electrolysis reaction required 960 minutes (16 hours) to reach completion. GC: rt = 15.0 min (24), 16.5 min (21), 17.2 min (20); MS m/z (24) 266 ([M]\textsuperscript{+}), 167, 152; (21) 265 ([M–CHO]\textsuperscript{+}), 183, 165, 105, 77; (20) 189, 107, 107, 79, 77.

\textbf{α-Bromodiphenylacetaldehyde (22).} This synthesis was performed several times on a relatively large scale. A typical reaction procedure is described. A 250 mL 3-neck round bottom flask was equipped with a dropping funnel and a reflux condenser, with the third neck stoppered. The reaction was performed in 60 mL CH\textsubscript{2}Cl\textsubscript{2} plus an additional 10 mL CH\textsubscript{2}Cl\textsubscript{2} into which the Br\textsubscript{2} was dissolved. The reaction was performed with equimolar quantities (1.45x10\textsuperscript{-2} mol) of 1 (2.58 mL) and Br\textsubscript{2} (0.74 mL). Compound 1 was added directly to the round bottom flask while the Br\textsubscript{2} was dissolved into the extra 10 mL CH\textsubscript{2}Cl\textsubscript{2}. After the dropwise addition of 10 mole percent (1 mL Br\textsubscript{2}/CH\textsubscript{2}Cl\textsubscript{2} solution), the reaction was stirred until the orange color faded to yellow. The reaction was then placed in an ice bath and the remaining Br\textsubscript{2} solution added dropwise over the course of approximately 10 minutes. The reaction was then stirred for 90 minutes. The reaction solution was washed with 20 mL 0.1 M sodium bisulfite to neutralize any excess Br\textsubscript{2} and HBr. The reaction was washed with 50 mL deionized H\textsubscript{2}O and extracted into CH\textsubscript{2}Cl\textsubscript{2}. The organic layers were combined and dried over Na\textsubscript{2}SO\textsubscript{4}, after which the solvent was removed \textit{in vacuo}. Upon the addition of a seed crystal the entire product solidified into 3.64 g of pale yellow/orange crystals in 92% yield. The crude product was shown by \textsuperscript{1}H NMR to be
clean and was used without further purification. The experimental $^1$H NMR corresponded well with reported data$^{21}$. m.p. = 49-51°C; $^1$H NMR (CH$_3$CN, 400 MHz): δ 7.35 (m, 4 H), 7.41 (m, 6 H), 9.80 (s, 1 H).

**α-Cyclohexyloxydiphenylacetaldehyde (21):** This α-alkoxyaldehyde was synthesized in order to confirm that this compound is the second intermediate (B) in the constant current electrolysis of 1 in the presence of cyclohexanol. The synthesis of (21) was performed several times. A typical synthetic procedure is described. The reagents were added in the following order to a 50 mL round bottom flask containing 15 mL dry THF and a magnetic stir bar: 0.94 g (3.4x10$^{-3}$ mol) α-bromodiphenylacetaldehyde (22), 0.36 mL (3.4x10$^{-3}$ mol) cyclohexanol, and 1.34 g (6.9x10$^{-3}$ mol) AgBF$_4$. Upon adding the AgBF$_4$ a pale yellow precipitate (AgBr) fell out of solution. The reaction was stirred for one hour and then neutralized with 15 mL saturated NaHCO$_3$ solution. The solution was filtered under vacuum through filter agent Celite 521 to remove the precipitate. The filtrate was washed with 15 mL deionized H$_2$O and extracted in 3x15 mL hexanes. The organic fractions were combined and dried over Na$_2$SO$_4$. The hexanes were removed *in vacuo* to provide a pale yellow very viscous oil in 95% crude yield by weight. Analysis of the crude material by $^1$H NMR showed the majority of the crude product to be polymerized THF$^{23}$. The sample was quickly filtered through a short silica gel column (5% ethyl acetate in hexanes) to yield 0.22 g of a pale yellow oil in 22% overall yield. $^1$H NMR analysis indicated there were still impurities present, but the compound was possible to identify based on the signals in the spectrum. GC: rt = 16.41 min; MS: $m/z$ 265 ([M-CHO]$^+$), 183, 165, 105, 77; Exact Mass (ESI/APCI)$^{22}$: Calc’d $m/z$ for C$_{20}$H$_{22}$O$_2$: 225.1512; Found: 225.1513.
294.3866, Found: C_{22}H_{32}O_2, 295.1693 (MH^+). $^1$H NMR (400 MHz, CDCl_3): δ 1.21 (m, 6 H), 1.53 (m, 2 H), 1.67 (m, 2 H), 3.42 (m, 1 H), 7.32-7.53 (m, 10 H), 9.80 (s, 1 H).

**Benzhydryl Cyclohexyl Ether (24).** This synthesis was carried out in order to conclusively identify and characterize the final (third) product (C) of the constant current electrolysis of I in the presence of cyclohexanol. A 50 mL round bottom flask was used as the reaction vessel. The reagents were added to the 15 mL dry THF in the following order: 0.736 g (3.8x10^-3 mol, slight excess) AgBF_4, 0.36 mL (3.4x10^-3 mol) cyclohexanol, and 0.67 mL (3.4x10^-3 mol) benzhydryl chloride. Upon adding the benzhydryl chloride a pale yellow precipitate (AgBr) immediately formed. The reaction was stirred for one hour at room temperature and then filtered through filter agent Celite 521 to remove the precipitate. The filtrate was washed with 15 mL deionized H_2O and extracted in 3x15 mL diethyl ether. The organic layers were combined and dried over Na_2SO_4, after which the solvent was removed in vacuo. The crude product was purified by column chromatography (2% ethyl acetate in hexanes) to give 0.26 g of a very pale yellow oil in 29% overall yield. The experimental spectral results corresponded well with the reported data for 24^26. GC: rt = 14.933 min; MS: m/z 266 ([M]^+), 168, 167, 152; $^1$H NMR (300 MHz, CD_3CN): δ 1.23-1.51 (m, 6 H), 1.74 (m, 2 H), 1.94 (m, 2 H), 3.37 (m, 1 H), 5.63, (s, 1 H), 7.24-7.42 (m, 10 H); $^{13}$C (75 MHz, CDCl_3): δ 24.72, 26.58, 33.11, 75.72, 80.54, 127.74, 129.25, 144.69.
**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of 2-Phenylethanol.** This constant current electrolysis was conducted using equimolar quantities (2.55x10^{-3} mol) of 1 (0.452 mL) and 2-phenylethanol (0.311 mL) in 34 mL electrolyte solution. The reaction was monitored periodically by GC/MS, which showed sequential conversion of 1→α-phenethyloxydiphenylacetaldehyde (23)→benzhydryl phenethyl ether (25) (See Figure 14 on Page 36). The constant current electrolysis required 25 hours to reach completion. Compounds 23 and 25 were conclusively identified and characterized by alternate syntheses (see below).

GC: rt = 17.2 min (25); 18.7 min (23); MS: m/z (25) 288 ([M]^+), 183, 167, 152; (23) 287 ([M–CHO]^+), 165, 105, 77.

**α-Phenethyloxydiphenylacetaldehyde (23).** This α-alkoxyaldehyde was synthesized to confirm that this compound is the intermediate in the constant current electrolysis of 1 in the presence of 2-phenylethanol. A 25 mL round bottom flask was used as the reaction vessel. The reagents were added in the following order to 10 mL dry THF solvent: 1.04 g (5.3x10^{-3} mol, approx. 2x excess) AgBF₄, 0.70 g (2.5x10^{-3} mol) α-bromodiphenylacetaldehyde (22), and 0.30 mL (2.5x10^{-3} mol) 2-phenylethanol. Upon the addition of 22 a yellow precipitate (AgBr) immediately crashed out of solution. The reaction was stirred for 1 hour at room temperature, and then the solution was filtered under suction through filter agent Celite 521 to remove the solids. The filtrate was washed with 20 mL deionized H₂O and extracted into 3x10 mL hexanes. The organic layers were combined and dried over Na₂SO₄. The solvent was removed in vacuo to yield a very viscous pale yellow oil. Analysis of the crude product showed it to mainly be polymerized THF²⁻. The crude material was
filtered through a silica gel column (5% ethyl acetate in hexanes) to yield 0.29 g of pale yellow oil in 37% yield. Impurities were still present in the \(^1\)H NMR spectrum, but the predicted product signals were observed. GC: rt = 18.639 min; MS: \(m/z\) 287 ([M-CHO]+), 165, 105, 77; Exact Mass (ESI/APCI): Calc’d \(m/z\) for C\(_{22}\)H\(_{20}\)O\(_2\): 316.3922, Found: C\(_{22}\)H\(_{21}\)O\(_2\), 317.1523 (MH\(^+\)). \(^1\)H NMR (CDCl\(_3\), 400 MHz): 2.96 (t, \(^3\)J = 7.03 Hz, 2 H), 3.50 (t, \(^3\)J = 7.03 Hz, 2 H), 7.20-7.36 (m, 5 H), 7.47-7.51 (m, 2 H), 7.58-7.62 (m 2 H), 7.82 (m, 1 H), 9.72 (s, 1 H).

**Benzhydryl Phenethyl Ether (25).** This synthesis was carried out in order to conclusively identify and characterize the final product in the constant current electrolysis of 1 in the presence of 2-phenylethanol. A 50 mL round bottom flask was used as the reaction vessel. The reagents were added to 15 mL dry THF in the following order: 1.12 g (5.8x10\(^{-3}\) mol, slight excess) AgBF\(_4\), 0.42 mL (3.5x10\(^{-3}\) mol) 2-phenylethanol, and 0.62 mL (3.5x10\(^{-3}\) mol) benzhydryl chloride. A white precipitate (AgCl) crashed out of solution upon the addition of benzhydryl chloride. The reaction was stirred at room temperature for one hour and was then filtered through Filter Agent Celite 521 to remove the precipitate. The filtrate was washed with 15 mL deionized H\(_2\)O and extracted in 3x10 mL diethyl ether. The organic layers were combined and dried over Na\(_2\)SO\(_4\), after which the solvent was removed \textit{in vacuo}. The crude material was purified by column chromatography (5% ethyl acetate in hexanes) to give 0.47 g of a clear colorless oil in 47% overall yield. Spectral analysis agreed well with reported data\(^2\). GC: rt = 17.050 min; MS: \(m/z\) 288 ([M]+), 183, 167, 152; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.94 (2 H, t, \(^3\)J = 6.0 Hz), 3.65 (2 H, t,
\( J^\varphi = 6.0 \text{ Hz} \), 5.33 (1 H, s), 7.18-7.40 (15 H, m); \( ^{13}\text{C} (75 \text{ MHz, CD}_3\text{CN}) \): \( \delta \) 36.97, 70.48, 84.04, 127.01, 127.56, 128.24, 129.17, 129.29, 129.94, 143.89.

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Methanol.** This constant current electrolysis experiment was performed using equimolar quantities (2.6x10\(^{-3}\) mol) of 1 (0.45 mL) and methanol (0.10 mL) in 34 mL electrolyte solution. The reaction proceeded as expected: analysis by GC/MS showed sequential conversion of 1 → \( \alpha \)-methyloxydiphenylacetaldehyde (26) → benzhydryl methyl ether (27). The constant current electrolysis experiment required 38 hours to reach completion. The positive identification and characterization of 26 and 27 was accomplished by alternate syntheses of authentic material (see below). GC: rt = 10.0 min (27), 11.9 min (26); MS: \( m/z \) (27) 198 ([M\(^{+}\)], 167, 165, 121, 105, 77; (26) 197 ([M-CHO]\(^{+}\)], 165, 105, 77.

**\( \alpha \)-Methyloxydiphenylacetaldehyde (26).** The synthesis of 26 was carried in order to positively characterize and identify the compound produced in the constant current electrolysis of 1 in the presence of methanol. A 25 mL round bottom flask equipped with a magnetic stir bar was used as the reaction vessel. The reagents were added to the solvent in the following order: 0.87 g (4.5x10\(^{-3}\) mol, approx. 2x excess), 0.07 mL (2.0x10\(^{-3}\) mol) methanol, and 0.61 mL (2.2x10\(^{-3}\) mol) \( \alpha \)-bromodiphenylacetaldehyde (22). Upon adding 22 a pale yellow precipitate (AgBr) formed. The reaction was stirred overnight at room temperature. The solution was then neutralized with 10 mL saturated aqueous NaHCO\(_3\) solution, washed with 20 mL deionized water, and extracted with 3x20 mL diethyl ether. The combined organic layers were dried over
Na₂SO₄, after which the solvent was removed under reduced pressure to yield 0.46 g of a clear yellow liquid in 92% crude yield. GC/MS analysis indicated that the desired aldehyde, 26, was obtained; however, approximately 50% of the product (by integration of the gas chromatogram) was composed of 2. It was believed that this was due to water in the methanol. The synthesis was repeated using a new bottle of HPLC grade methanol. The second attempt yielded the same results. It is possible that the mild oxidizing nature of silver (I) in AgBF₄ was sufficient to oxidize 26 to 2. Separation of 26 and 2 by chromatography was not possible. However, ¹H NMR analysis of the reaction product showed the signals predicted for 26. The combined GC/MS and NMR data served to conclusively identify 26 as the product of the electrolysis of 1 in the presence of methanol. GC/MS: 11.9 min; MS m/z 197 ([M-CHO]+), 165, 105, 77; ¹H NMR (400 MHz, CDCl₃) δ 3.21 (s, 3 H), [7.38, 7.46-7.49, 7.57-7.60, 7.80] (m, 10 H), 9.80 (s, 1 H).

**Benzhydryl Methyl Ether (27).** This synthesis was performed in order to conclusively identify and characterize the final product in the constant current electrolysis of 1 in the presence of methanol. A 25 mL round bottom flask was used as the reaction vessel with 10 mL dry THF as solvent. The reagents were added to the reaction flask following order: 0.98 g (5.0x10⁻³ mol, 2x excess) AgBF₄, 0.10 mL (2.5x10⁻³ mol) methanol, and 0.45 mL (2.5x10⁻³ mol) benzhydryl chloride. A white/pale yellow precipitate (AgCl) crashed out of solution immediately upon the addition of the benzhydryl chloride. The reaction was stirred overnight and then neutralized with 15 mL saturated aqueous NaHCO₃ solution. The reaction was then filtered through filter agent Celite 521 to remove the precipitate. The collected filtrate
was washed with 15 mL deionized H$_2$O and extracted with 3x15 mL diethyl ether. The organic layers were combined and dried over Na$_2$SO$_4$. The diethyl ether was removed under reduced pressure to afford 0.47 g of a clear pale yellow oil in 96% crude yield. Spectral analysis of the crude material showed a small amount of polymerized THF at 1.62 ppm and 3.41 ppm$^{23}$. However, the impurity signals did not overlap with the product peaks, and the product was otherwise pure. Therefore, no further purification was attempted. The experimental spectral data corresponding well with reported data$^{30}$. GC: rt = 9.965 min; MS: $m/z$ 198 ([M]$^+$), 167, 165, 152, 121, 105, 77; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.30 (s, 3 H), 5.17 (s, 1 H), 7.16-7.28 (m, 10 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 57.14, 85.56, 127.03, 127.56, 128.51, 142.20.

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of 3-Ethyl-3-pentanol.** This constant current electrolysis experiment was performed using equimolar quantities (2.6x10$^{-3}$ mol) 1 (0.452 mL) and 3-ethyl-3-pentanol (0.36 mL) in 34 mL electrolyte solution. The constant current electrolysis was monitored periodically by GC/MS. Analysis by GC of the reaction solutions indicated a mixture of compounds was present but showed no evidence of the corresponding $\alpha$-alkoxyaldehyde, 29. The electrolysis was allowed to proceed for 29 hours. The reaction solution was chromatographed (silica gel column, 5% ethyl acetate in hexanes) to yield two fractions. The first fraction contained what was later identified to be benzhydryl triethylcarbinyl ether (28) and an as yet unidentified unknown, D. Compound 28 and D could not be separated by column chromatography. The second fraction contained a mixture of 1, benzhydrol (19), and $\alpha$-hydroxydiphenylacetaldehyde (17). Boris Sheludko was able to isolate and
characterize 28 from the constant current electrolysis of 1,1-diphenylacetone in the presence of 3-ethyl-3-pentanol\textsuperscript{27}. Comparison of the \textsuperscript{1}H NMR of the electrolysis product with the \textsuperscript{1}H NMR from Sheludko’s work showed that 28 was in fact produced in the electrolysis of 1 with 3-ethyl-3-pentanol. Mass spectrometric analysis supported this conclusion. Based on the \textsuperscript{1}H NMR of the electrolysis product it was determined that D is an aldehyde but its exact structure is still under investigation.

**Acid-Mediated Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Cyclohexanol.** This constant current electrolysis experiment was carried out using equimolar quantities (1.1x10\textsuperscript{-3} mol) 1 (0.20 mL), cyclohexanol (0.12 mL) and p-toluenesulfonic acid monohydrate (0.22 g) in 15 mL electrolyte solution. The reaction solution became pale yellow after five minutes of stirring while degassing under nitrogen. A baseline GC/MS analysis showed the appearance of a previously unobserved compound, later identified as diphenylacetaldehyde cyclohexyl enol ether (30) by alternate synthesis of the authentic material. Once turning the current on, the reaction proceeded much more quickly (and cleanly) than without the acid. No diphenylacetaldehyde cyclohexyl hemiacetal (20) was observed; GC/MS analysis showed direct formation of 21 without the usual induction period observed in the absence of acid. At 30 minutes a significant amount of 21 had formed. Compare this with **Figure 5** on page 21 in which it is shown that 480 minutes of reaction time was
required for \textbf{21} (compound B) to accumulate in the electrolysis medium. At 180 minutes nearly all of the starting material had been converted to \textbf{21}. From this point the constant current electrolysis proceeded at the normal rate from \textbf{21} to benzhydryl cyclohexyl ether (\textbf{24}). GC: rt=15.0 min (\textbf{24}), 16.3 min (\textbf{21}), 16.9 min (\textbf{30}); MS: \textit{m/z} (\textbf{24}) 266 ([M]+), 168, 167, 105, 77; (\textbf{21}) 265 ([M-CHO]+), 183, 165, 105, 77; (\textbf{30}) 278 ([M]+), 196, 167, 165.

\textbf{Diphenylacetaldehyde cyclohexyl enol ether (30).} The synthesis of \textbf{30} was achieved by utilizing a Dean-Stark trap to remove the water produced in the reaction and drive the equilibrium towards \textbf{30}. Benzene was used as a solvent, since a high-boiling solvent that forms an azeotrope with water was required. A 25 mL round bottom flask was used as the reaction vessel with 15 mL benzene as solvent. The reaction was carried out by reacting 0.68 mL (3.83x10^{-3} mol) \textbf{1} in the presence of two molar equivalents of cyclohexanol (0.81 mL, 7.67x10^{-3} mol) and approximately five molar percent (0.0431g, 2.27x10^{-4} mol) \textit{p}-toluenesulfonic acid monohydrate (PTSA). The reaction was heated to reflux (90-95°C) overnight. The red/orange solution was extracted in saturated NaHCO$_3$ solution and hexanes. The collected organics were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The reaction yielded 1.26 g of a clear red/orange oil in 87% crude yield. Because it was unknown how acid sensitive \textbf{30} is and whether it would be stable on a silica gel column, only 1.0 g of the sample was purified by chromatography. The product was chromatographed using 4:10 (v/v) dichloromethane:hexanes as the eluent. Following purification 0.46 g of a clear pale yellow oil was obtained to give a 46% yield. GC: rt =16.80 min; MS: \textit{m/z} 278 ([M]+), 196, 167, 165; Exact Mass (ESI/APCI)$^{22}$: Calc’d
$m/z$ for $C_{20}H_{22}O$: 278.39, Found: $C_{20}H_{22}O$, 278.1665 (MH$^+$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.29-1.38 (m, 3 H), 1.52-1.62 (m, 3 H), 1.76-1.83 (m, 2 H), 1.94-1.98 (m, 2 H), 3.81-3.88 (m, 1 H), 6.58 (s, 1 H), 7.20-7.34 (m, 8 H), 7.46-7.49 (m, 2 H); $^{13}$C (75 MHz, CDCl$_3$): 23.75, 25.60, 32.52, 81.10, 126.25, 126.34, 127.89, 128.31, 128.69, 129.92, 144.52.

**Acid-Catalyzed Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Cyclohexanol.** Since the previous experiment used a full equivalent of acid, this constant current electrolysis experiment was performed to determine if catalytic quantities of an acid are sufficient to increase the rate the enolization of 1 or if an equimolar amount necessary. In this experiment equimolar quantities ($1.1 \times 10^{-3}$ mol) 1 (0.20 mL) and cyclohexanol (0.13 mL) were used with five molar percent PTSA ($5.7 \times 10^{-4}$ mol, 0.011 g) in 15 mL electrolyte solution. A 25 mL 3-neck round bottom flask was used as the reaction vessel. The reaction solution became pale yellow after stirring for five minutes under nitrogen. A baseline GC/MS analysis indicated the formation of 30. The reaction was monitored every hour. At five hours nearly all of the starting material had been converted to 21 with no induction period observed. In the absence of acid, a minimum of eight hours (480 minutes) of reaction time is need to achieve significant conversion of 1 to 21 (See **Figure 5** on page 21). Six additional hours were required to achieve complete conversion to 24. GC: rt=15.0 min (24), 16.3 min (21), 16.9 min (30); MS: $m/z$ (24) 266 ([M$^+$]), 168, 167, 105, 77; (21) 265 ([M-CHO]$^+$), 183, 165, 105, 77; (30) 278 ([M$^+$]), 196, 167, 165.
**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of Two Molar Equivalents of Cyclohexanol.** This constant current electrolysis experiment was carried out using 0.45 mL (2.55x10^{-3} mol) 1 in the presence of 0.54 mL (5.1x10^{-4} mol) cyclohexanol in 34 mL electrolyte solution. The experiment was performed to determine if the higher alcohol concentration would promote formation of diphenylacetaldehyde dicyclohexyl acetal (41) instead of stopping at diphenylacetaldehyde cyclohexyl hemiacetal (20). However, neither 20 nor 41 was observed. Hourly analysis of the electrolysis solution by GC/MS indicated the presence of 30 in small amounts. The electrolysis reaction proceed sequentially from 1→21→24 as with other anodic oxidations of 1 in which 30 was present; 20 was not observed. The reaction was not clean, however. The reaction produced many more byproducts than usual, apparently promoted by the addition of an extra equivalent. The GC/MS data for 24, 21, and 30 were the same as was observed in other electrolyses and alternate syntheses.

**Diphenylacetaldehyde-\textit{d} (1-\textit{d}).** The deuterated form of 1 was synthesized by stirring 0.90 mL (1.0 g, 5.10x10^{-3} mol) 1 in the presence of twenty molar excess D\textsubscript{2}O (1.845 mL) and approximately 1% by volume D\textsubscript{2}SO\textsubscript{4} (0.22 mL) in 20 mL dry CH\textsubscript{3}CN. The solution was degassed under nitrogen for fifteen minutes and then sealed and stirred. Every 24-48 hours the reaction was washed with saturated aqueous NaHCO\textsubscript{3} solution and extracted three times with CH\textsubscript{2}Cl\textsubscript{2}. To minimize exchange of the deuterium with water, the sample was poured into a separatory funnel already containing methylene chloride and the saturated NaHCO\textsubscript{3} solution. The organic layers were combined and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed \textit{in vacuo}. \textsuperscript{1}H NMR analysis was used to
determine if all of the 1 had been deuterated. If a peak corresponding to the benzhydryl proton was still visible in the $^1$H NMR spectrum, the partially deuterated 1 was stirred in the presence of fresh D$_2$O and D$_2$SO$_4$. It was observed that 1 started to decompose after three workups and previously unseen byproducts appeared in the $^1$H NMR spectrum. Furthermore, despite replacing the D$_2$O and D$_2$SO$_4$ three times, it was not possible to deuterate more than 90% of the sample. It is not yet understood why 1 could not be fully deuterated as it was possible to fully deuterate the benzhydryl proton of 1,1-diphenylacetone by the same experimental method$^{27}$. In all experiments and calculations in which 1-$d$ was used it was necessary to account for the 10% undertreated material. $^1$H NMR (CD$_3$CN, 400 mHz): δ 4.89 (s, 0.1 H, 0.9 D), 7.22-7.38 (m, 10 H), 9.95 (s, 1 H).

**Constant Current Electrolysis of Diphenylacetaldehyde-$d$ (1-$d$) in the Presence of 2-Phenylethanol.** The constant current electrolysis of 1-$d$ was carried out in the presence of an equimolar quantity of 2-phenylethanol. Due to the limited quantity of 1-$d$ available, this electrolysis was performed on a smaller scale that most: 0.22 g 1-$d$ was anodically oxidized in the presence of 0.14 g 2-phenylethanol in 15 mL electrolyte solution. The reaction was monitored periodically by GC/MS and was carried out for 1080 min (18 hours), at which time the majority of 1-$d$ had been oxidized to benzhydryl phenethyl ether (25). Significantly more byproducts that usually form in this type of experiment were present. It is believed that the slower rate of enolization of 1 to 1a caused by deuterium isotope effects$^{38a}$ allows for other cleavage reaction pathways that are not observed under normal conditions. Analysis by GC/MS of the ether product in this electrolysis experiment showed mostly the
protio form of 25 but indicated some of the deuterium had been incorporated. An accurate percentage could not be calculated, but rough calculations based on relative ion counts suggest that 80-90% of the product was of the protio form. The $^1$H NMR spectrum showed a benzhydryl peak at 5.33 ppm that integrates to less than one proton compared to the two methylene triplets at 2.94 ppm and 3.65 ppm. Due to the number of byproducts overlapping with the methylene peaks an exact ratio could not be calculated, but the rough integrations indicate that approximately 80% of the product was the protio ether, in good agreement with the GC/MS data (See pp. 67-77). GC: rt=17.1 min; MS: m/z 289 ([M-d]$$^+$$), 288 ([M]$$^+$$), 168, 167, 165. $^1$H NMR: see detailed analysis on pp. 70-77 and 89.

**Constant Current Electrolysis of Diphenylacetaldehyde (1) in the Presence of 2-Phenylethanol in Acetonitrile-$d_3$.** The constant current electrolysis of 1 in the presence of 2-phenylethanol was carried using CD$_3$CN as the electrolyte solvent. The reaction was performed using equimolar quantities (2.6x10$^{-3}$ mol) 1 (0.46 g) and 2-phenylethanol (0.29 mL) in 34 mL of 0.1 M Bu$_4$NBF$_4$ in CD$_3$CN. This reaction exhibited a very long induction period, approximately 17 hours. The first product to appear was $\alpha$-phenethyloxydiphenylacetaldehyde (23). The reaction was carried out for 49.5 hours total, at which time benzhydryl phenethyl ether (25) was the major product in solution. However, a significant number of byproducts were also present. As with the electrolysis of 1-$d$, this is believed to be due to the slower rate of enolization caused by deuterium isotope effects. The GC/MS analysis of the ether product indicated the incorporation of deuterium, but an exact percentage could not
be calculated (see pp. 75-77). Due to the large number of byproducts in the $^1$H NMR, no accurate relative integrations could be obtained. GC: rt=17.1 min; MS: $m/z$ 289 ([M-$d^1$]$^+$), 288 ([M]$^+$), 168, 167, 165.

**E-α-Methylstilbene Oxide (33).** The synthesis of 33 was performed in aqueous NaHCO$_3$ solution under mild conditions on a relatively large scale$^{35}$. A 250 mL round bottom flask was used as the reaction vessel. The reaction was carried out by stirring 1.85 g (9.5x10$^{-3}$ mol) E-α-methylstilbene to 80 mL 0.3 M NaHCO$_3$ solution at 0°C. The reaction was stirred for ten minutes, at which time 2.79 g (1.62x10$^{-2}$ mol, 1.7 molar equiv.) $m$-chloroperbenzoic acid (MCPBA) was added. The reaction was removed from the ice bath and stirred at room temperature overnight. All reagents are insoluble in water and so initially the reaction was cloudy. After stirring overnight the reaction was nearly clear with a clumpy white precipitate on the bottom. It is hypothesized that the reaction proceeds in water with the reagents associating due to their hydrophobic nature. The product was extracted in 3x50 mL diethyl ether. The organic layer was washed with 40 mL of a cooled 10% NaOH solution followed by 40 mL brine. The organics were combined and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to yield 1.99 g of a pale orange viscous liquid (99.4% crude yield). Analysis by $^1$H NMR indicated a few minor impurities (unreacted E-α-methyl-stilbene, alkyl impurities) but comparison with the literature indicated that the desired product was obtained in good yield$^{54}$. However, it was decided to not purify the sample by column chromatography on silica gel due to the potentially acid sensitive nature of 33. It was intended to use the crude product as a regent in the synthesis of α-methylidiphenylacetaldehyde (31) and purify the final
H NMR (CHCl$_3$, 400 mHz): $\delta$ 1.50 (s, 3 H), 4.00 (s, 1 H), 7.31-7.37 (m, 2 H), 7.39-7.44 (m, 6 H), 7.47-7.50 (m, 2 H).

**α-Methyldiphenylacetaldehyde (31) – Attempted.** The E-$\alpha$-methylstilbene oxide (33) (described above) was used as a starting material in this synthesis. The procedure followed was adapted from that described by Ranu and Jana$^{36}$. A suspension of 0.48 g (2.14x10$^{-3}$ mol) InCl$_3$ in 5 mL THF was stirred under nitrogen for 20 minutes, after which a solution of 0.75 g (3.6x10$^{-3}$ mol) 33 in 3 mL THF was injected. The reaction was heated to reflux (approximately 70°C) overnight, after which the solution had turned from cloudy and gray (due to the suspended InCl$_3$) to clear and pale yellow. TLC analysis indicated disappearance of 33. The reaction was neutralized with saturated NaHCO$_3$ solution and extracted three times with diethyl ether. The combined organic layers were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The reaction yielded 0.72 g of a dark orange oil in 96.3% crude yield. Analysis by $^1$H NMR and comparison with the literature indicated 31 was present, albeit with a significant amount of impurity$^{36}$. Purification by column chromatography was attempted (gradient of pure hexanes to 70:30 dichloromethane:hexanes as eluent), but the product proved to be unstable on the column and was not recovered. $^1$H NMR (400 MHz, CDCl$_3$, crude): 1.78 (s, 3 H), 7.18-7.39 (m, 10 H), 9.91 (s, 1 H).

**Benzhydrol-$\alpha$-$d$ (19-$d$).** Deuterated benzhydrol was synthesized to be used as a starting material in the synthesis of deuterated benzhydryl phenethyl ether (25-$d$). A solution of 1.01 g (5.53x10$^{-3}$ mol) 2 in 25 mL dry THF was added to a 100 mL 3-neck
round bottom flask equipped with a reflux condenser and a dropping funnel. A suspension of 0.125 g (2.98x10^{-3} mol) LiAlD₄ in 10 mL THF was added dropwise to the stirred solution. The reaction was allowed to stir overnight, after which the solution had become pale yellow. The reaction was chilled in an ice bath and the excess LiAlD₄ neutralized with approximately 5 mL 1% HCl solution. The reaction was extracted in CH₂Cl₂ and H₂O. The combined organic layers were dried over Na₂SO₄, and the solvent was removed in vacuo to yield 1.1 g of a yellow solid in over 100% crude yield by weight. The product was recrystallized twice in heptane to give 0.83 g of white needle crystals in 81% overall yield. ¹H NMR confirmed the purity of the product and the deuteration of the benzhydryl proton. m.p. = 63-65˚C; ¹H NMR (400 MHz, CDCl₃): δ 2.18 (s, 1 H), 7.25-7.29 (m, 2 H), 7.32-7.40 (m, 8 H).

**Deuterated benzhydryl chloride (35-d):** Deuterated benzhydryl chloride was synthesized from 19-d for use as a starting material in the synthesis of benzhydryl-α-d phenethyl ether (25-d)⁴². To 5 mL CH₂Cl₂ was added 0.20 g (1.1x10^{-3} mol) 19-d. While stirring, 0.10 mL (1.37x10^{-3} mol) thionyl chloride was added dropwise. The reaction was stirred for two hours at room temperature. The solvent and residual thionyl chloride were removed in vacuo to give 0.21 g (1.05x10^{-3} mol) 35-d in 96% yield. ¹H NMR and GC/MS analysis confirmed the identity and purity of the product. GC: rt=10.7 min; MS: m/z 203 ([M⁺]^+), 168, 153, 77. ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.39 (m, 6 H), 7.43-7.46 (m, 4 H).

**Benzhydryl-α-d Phenethyl Ether (25-d).** The synthesis of 25-d was carried out by stirring 0.98 mmol of 35-d (0.20 mL) and 2-phenylethanol (0.11 mL) in the presence
of 1.5 molar equivalents of AgBF₄ (0.29 g). Upon addition of the alcohol a white/pale yellow solid (AgCl) precipitated out of solution immediately, as with the other ether syntheses. The reaction was stirred for one hour and then quenched with saturated NaHCO₃ solution. The solution was filtered through filter agent Celite 521 to remove the particulates. The filtrate was washed with water and extracted into CH₂Cl₂. The combined organic layers were dried over Na₂SO₄. The solvent was removed in vacuo to afford 0.26 g of a yellow oil in 96% yield. Analysis by GC/MS confirmed the desired deuterated product was isolated. ¹H NMR and COSY analysis showed three sets of two coupled methylene triplets, the cause and meaning of which are still under investigation (See Figure 33 on page 79 and associated results). GC: rt = 17.0 min. MS: m/z 289 ([M]⁺), 168 ([M–CH₂CH₂Ph]⁺); ¹H NMR: (400 MHz, CDCl₃) δ 2.81 (t, $J=6.84$ Hz), 2.90 (t, $J=6.84$ Hz), 3.00 (t, $J=6.84$ Hz), 3.70 (t, $J=6.84$ Hz), 3.89 (t, $J=6.84$ Hz), 3.97 (t, $J=6.84$ Hz), 7.24-7.35 (m, 15 H).
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