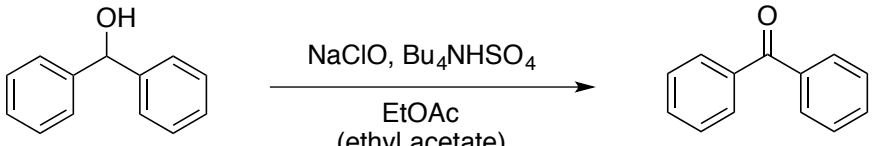
Experiment 3 – Oxidation of Benzhydrol



Benzhydrol **Benzophenone**

Learning Objectives

- Understand phase-transfer catalysis and organic oxidation reactions
- Apply TLC to monitor reaction progress
- Analyze IR spectra to assess purity and success of the reaction
- Assign signals on ^{1}H NMR spectra to the hydrogens in benzhydrol and benzophenone
- Predict sources of error and understand their effects on results

* Please find "How to Prepare for Lab & Assignments" after the procedure in this doc.

Background: Oxidation Reactions and Phase Transfer Catalysis

In this experiment, students will perform a simple oxidation reaction of a secondary, benzylic alcohol with commercial bleach. Recall that Oxidation Is a Loss of electrons while Reduction Is a Gain of electrons (OIL RIG). In order to apply this mnemonic, you need to know the oxidation states of each atom within the compound. Carbon can carry oxidation states ranging from -4 to +4. A few examples are shown in **Figure 1** below.

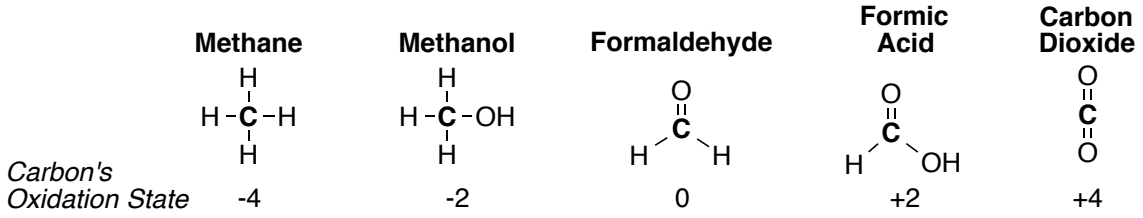


Figure 1. Examples of the oxidation levels of carbon

You may have noticed that all of the compounds in **Figure 1** are neutral and carbon has zero formal charge. The concept of oxidation state and formal charge are similar with one important difference in the calculation: *assuming whether the bonding electrons are shared equally or not*. Both are calculated by taking the difference between the valence electrons from the periodic table and the number of electrons belonging to that atom within the molecule.

The valence electrons of an atom will never change but the electrons 'belonging' to the atom in the molecule will vary depending on lone pairs of electrons and bonds to more or less electronegative atoms.

- **Oxidation states** assign bonding electrons to the more electronegative atom in a bond, except when the two atoms are the same and the bonding electrons are split equally.

- **Formal charge** splits bonding electrons equally between the two atoms.

In summary, the difference in the calculation of oxidation states and formal charge is based on the assignment of bonding electrons. This is how the highlighted carbon in ethanol can have an oxidation state of -1 but a formal charge of zero (**Figure 2**).

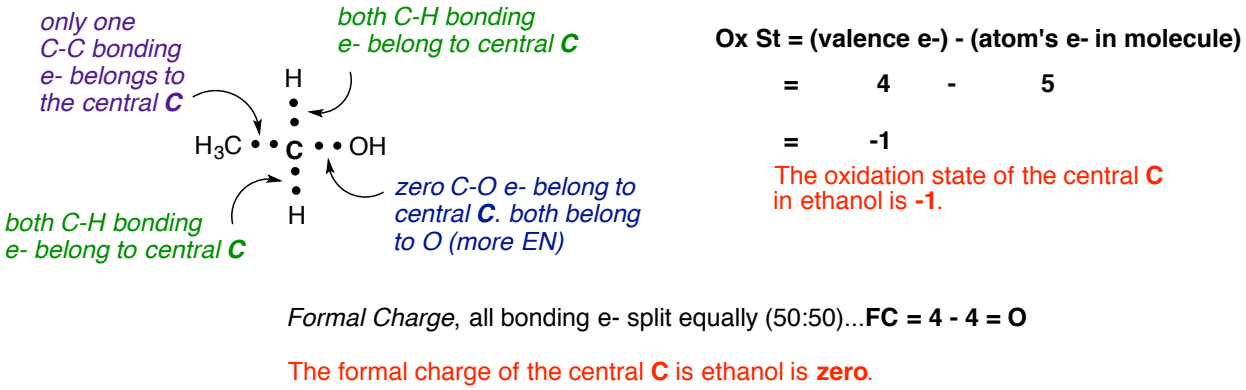


Figure 2. Calculation of oxidation state and formal charge of the central carbon in ethanol

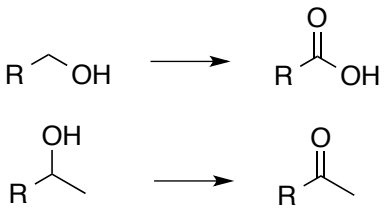
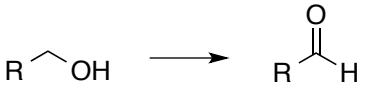
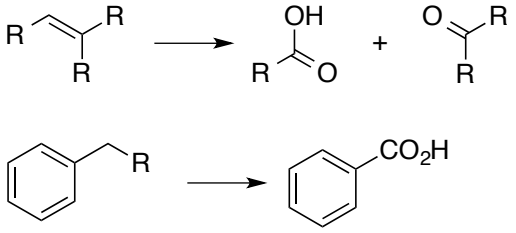
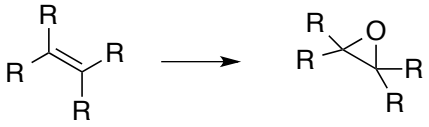
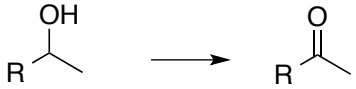
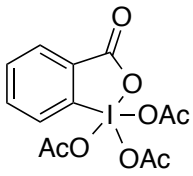
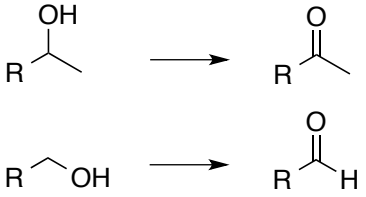
An oxidation reaction is one where an atom loses electrons. In other words, the atom gains a bond to a more electronegative atom (electron hogs!). The examples discussed in this experiment will involve oxygen-containing compounds (alcohols and carbonyl compounds) but there are many other examples of organic oxidation reactions that do not involve oxygen. You should be able to categorize whether the reactions learned in the CHEM 8 series qualify as oxidation or reduction based on the rules outlined above.

Table 1 on the following page highlights common oxidizing agents and their applications. The following issues should be addressed when choosing the appropriate oxidizing agent.

- *Reactivity* – does it react with the starting material? Is it too reactive or not reactive enough for the desired transformation?
- *Selectivity* – will it also react with other functional groups in the molecule?
- *Ease of use* – is it toxic and/or does it require special equipment? How is waste handled?
- *Availability* – is it commercially available or does it need to be made separately? Is it cost-effective?

In this experiment, the oxidation of a secondary alcohol (benzhydrol) is achieved with commercially available bleach. This reagent is inexpensive and easy to handle with typical personal protective equipment (PPE) including goggles and gloves. Most importantly, it works! However, one issue is presented in using bleach: *solubility*. Bleach is an aqueous solution of sodium hypochlorite (NaClO) but many organic compounds, including benzhydrol, are not water-soluble. Thus, a **phase transfer catalyst** (PTC) is employed to facilitate the reaction.

Table 1. Common oxidizing agents and applications

Oxidizing Agent	Main Application(s)	Comments
Jones Reagent: CrO_3, H_2SO_4		CrO_3 is highly toxic and a carcinogen. High waste disposal cost.
Pyridinium chlorochromate (PCC)		Suspected carcinogen, high waste disposal cost.
Potassium Permanganate ($KMnO_4$) with heat		Nonselective – many functional groups are oxidized (alkenes, alkynes, alcohols, etc.)
Peroxyacids (RCO_3H)		Common peroxyacid: *meta*-chloroperoxybenzoic acid (*m*CPBA)
Sodium Hypochlorite (bleach, NaClO)		Cheap and easy!
Dess-Martin Periodinane 		Easy to use but expensive reagent.

The mechanism employed by a PTC is similar to that used in soaps. Soaps contain both non-polar and polar (typically ionic) regions so they can absorb grease and also be washed away with water. Quaternary alkylammonium salts such as tetrabutylammonium hydrogen bisulfate ($Bu_4N^+HSO_4^-$) are common examples of PTCs. For the remainder of this discussion, this salt will be abbreviated by Q^+X^-. These salts are soluble in both water and organic solvents. When NaClO $_{(aq)}$ is mixed with an immiscible organic solvent such as ethyl acetate (EtOAc), little to none of the NaClO enters the organic phase. However, once a small amount of Q^+X^- is added, the salts participate in a dynamic equilibrium where ClO^- pairs with Q^+ and travels into the organic layer (**eq. 1**).

$$Q^+X^- + Na^+ClO^- \rightleftharpoons Q^+ClO^- + Na^+X^- \qquad \textbf{(1)}$$

Some of the hypochlorite (ClO^-) ion, the active oxidizing agent, is paired with the tetrabutylammonium cation Q^+. Because Q^+ is soluble in organic solvents, it can carry the ClO^- ion from the aqueous to the organic phase where the reaction can occur (**Figure 3**). As the ClO^- reacts in the organic phase, the equilibrium shifts to transport more ClO^- from the aqueous phase to reestablish equilibrium. It is important to note that the salts do not instantly transport from one layer to another. *Vigorous stirring is required to facilitate phase transfer.* This continues until the reaction is complete and the solubility issue is resolved! The applications of PTC are widespread to many other types of reactions, not just oxidations.

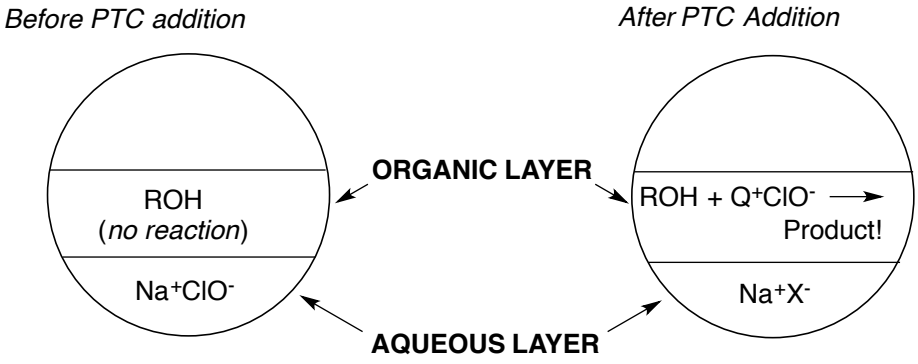


Figure 3. Phase-transfer catalysis (PTC) in an oxidation reaction.

The oxidation of benzhydrol is monitored by TLC to determine reaction progress. The product is isolated via liquid-liquid extraction to remove the aqueous layer and by-products. IR analysis is performed to observe the disappearance of the alcohol O-H stretch and appearance of the conjugated ketone C=O stretch. Proton nuclear magnetic resonance (^{1}H NMR) spectra of benzhydrol and benzophenone are provided for analysis. This valuable analytical tool provides information about the chemical environment of each hydrogen in the molecule. Each hydrogen in benzhydrol and benzophenone will be assigned to a signal on the ^{1}H NMR spectrum.

PROCEDURE

Procedure Diagrams must be complete in your notebook before you can start the lab.

1. Reaction Preparation and Set-up: TLC will be used to monitor reaction progress. Prepare TLC standards and plates before setting up the reaction. Make solutions of the standards (benzhydrol and benzophenone) in small test tubes. This does not require careful measuring, but do be conservative. Dissolve a small amount of the compound (microspatula tip) in ethyl acetate (EtOAc, 1 mL). Obtain three TLC plates, carefully handling by the edges without bending, and gently spot the plate at the origin with a capillary tube (not a melting point capillary). Create one lane for benzhydrol or benzophenone and leave a space for the reaction mixture to be spotted later (2 spots per plate). Be sure to record which lane is which in your notebook. Take note of the solvent in the TLC chambers.

In a 25-mL Erlenmeyer flask equipped with a magnetic stir bar, add 0.37 g (± 0.01 g)* of benzhydrol, 5 mL of commercial bleach (approximately 0.7 M NaClO), 5 mL of ethyl acetate (EtOAc), and 40 mg (± 5 mg)* of tetrabutylammonium hydrogen sulfate (Q^+X^- or $Bu_4N^+HSO_4^-$). Secure the flask to a ring stand, loosely stopper (check for correct size to avoid getting stuck), and *stir vigorously on a stir plate without heat*. Increase the stir speed if two layers are observed.

* It is acceptable to obtain 10 mg more or less benzhydrol and 5 mg more Q^+X^-. Record the exact mass obtained.

2. Monitoring Reaction Progress: After about 10 minutes, stop stirring to allow phase separation and remove a small aliquot of the upper layer of the reaction by touching the tip of a capillary tube to the top of the reaction solvent. Spot the TLC plate with this aliquot using a capillary tube alongside the standards. Run the TLC plate using the chambers provided in the fume hood. *Do not remove the chambers from the fume hood!* Develop the plate with a UV or fluorescence light after evaporating the solvent from the plate in the fume hood.

If starting material is still present in the reaction, continue stirring for another 10 minutes and take another TLC aliquot. A faint spot for benzhydrol may still appear on a visualized plate, even when the reaction is complete. When there is no *dark* spot for benzhydrol in the reaction mixture, you may consider the reaction to be complete. The 10 minutes is counted from the first aliquot (20 min total). By the time you run the first TLC plate, it's probably time to run the second! Continue taking aliquots at 10-minute intervals until the reaction is complete. If the reaction is taking longer than 40 minutes, make a note then proceed to the next step.

3. Reaction Work-Up (FUME HOOD): Transfer the completed reaction mixture to a screw-cap test tube and remove the aqueous layer with a pipet. Wash the organic layer with 3 mL of brine (sat. NaCl) followed by a wash with 2 mL of water – mix, invert, then remove the aqueous layer after each portion of brine or water is added. Dry the organic layer over $MgSO_4$, gravity filter using a pipet with cotton plug, and collect the filtrate in a pre-weighed 25-mL round-bottom flask (RBF). Concentrate using a rota-vap and weigh the product. Pro-tip: the product rarely crystallizes in the rota-vap bath. When the solvent appears to have evaporated, take the flask off the rota-vap and swirl in the ice bath to crystallize. You can still proceed with the product in liquid form.

4. Analysis: Obtain the IR spectrum of your product. Is an OH peak present? The IR of starting material is online and should also be posted in the instrument room. Record the identifying peaks in your notebook. Sketch the final TLC plate into your notebook and calculate the R_f values for each spot. Report your data in table format. Analyze the ^1H NMR spectra of benzhydrol and benzophenone (provided on Canvas) using the table format in the worksheet.

Table 2. Clean-up & Safety

Clean-up	**Safety**
Liquid waste: aqueous layers and contents of rota-vap trap	Ethyl acetate is *flammable*.
Solid waste: $MgSO_4$, pipets, filter pipets, capillary tubes, and TLC plates	Benzophenone, benzhydrol, and Bu_4NHSO_4 are *irritants*.
After analysis, dispose of your product in the liquid waste using a *very small amount* of ethanol from a wash bottle to aid the transfer.	Sodium hypochlorite is an *oxidizer*. It will bleach your clothes so consider your wardrobe for the day!
Wash all glassware and wipe down counters.	Wear gloves & goggles throughout the experiment.
All used pipets & broken glass go in the glass waste box. Please do not throw away glass in the trash as it creates an unexpected occupational hazard for our custodial staff. Thank you for participating in community set up & clean up tasks ☺	

References & Supplemental Reading

Oxidation reactions	Klein 12.10
^{1}H NMR	Klein 15.1-6 or Mohrig Chapter 22.1-22.7
Extraction	Mohrig Chapter 10
TLC	Mohrig Chapter 18

- **Klein**, D. "Organic Chemistry, 3rd Edition";
- **Mohrig**, J. R.; *et. al*. "Techniques in Organic Chemistry, 4th Edition."
- Palleros, D. R. *Experimental Organic Chemistry*, Wiley: New York, **2000**; pp. 255-257.

How to Prepare for Lab + Assignments - Follow Canvas Exp 3 Module…

Before Lab

- Read this PDF – background, procedure, safety, pre-lab and in-lab questions
  - Option: listen to Caitlin read this document in the **8M Exp 3 Podcast**
- Attend and/or watch **lab lecture** – we go over everything you need for your assignments!
- Practice the lab online *via* **Slugs@home platform** - sites.google.com/ucsc.edu/slugshome/home
- Complete the **pre-lab questions** at the end of this doc - incorporated into Canvas quiz ☺
  - **Quiz** due before your enrolled section – check Canvas for due date
- Download the **Exp 3 worksheet** and prepare your **lab notebook**…

Lab Notebook Preparation – *worksheet = template / outline to copy by hand into lab notebook*

- **Purpose:** one-sentence summary of the main lab goals plus the structures of Excedrin components
- **Reagent Table** – add chemical properties; Wikipedia is a reliable source for chemical properties!
- **Procedure with Diagrams** – complete before starting lab; sample on Canvas
  - Use the procedure on the previous pages to create your hand-drawn experimental instructions
    - Simple sketches & labels for all **equipment, chemical names** with **amounts**, & **transfers**
  - Format: Break it up with flow charts, bullet-points, comic strip, and/or whatever works for you!
    - Avoid copying the procedure word-for-word.
    - Make it easy for anyone to follow your procedure without referring to this document.
  - **Slugs@home Exp 3 website** - Equipment & Safety pages; pictures & videos of the whole lab
  - The **class notes** include useful diagrams as well

During Lab

- Check the **safety rules** to dress for lab and arrive a few minutes early to **Thimann Labs**
- **Pre-lab talk:** tips for success and open Q&A
- Show your **lab notebook pages** to your TA
- Perform the experiment with a partner, fill out data & observations in **lab notebook**

After Lab – each partner submits separate, individual assignments

- Upload **Notebook Pages** to Canvas by midnight on lab day – graded on completeness / participation
- Complete & upload the **Lab Report** on GradeScope (GS) – due date on Canvas
  - In-lab questions & experimental methods – see last page of this document

Pre-lab Questions / Quiz

Take the **Exp 3 pre-lab quiz** *before* your enrolled section – see Canvas for due date

- The quiz incorporates the questions below - the questions may be reworded.
- **Be prepared with your responses to the pre-lab questions *before* starting the quiz.**
- There is a 20-minute time limit on the quiz and you get two attempts.
    - Make sure you have enough time to complete the quiz - you can't save and come back later.
    - If you choose to re-take the quiz, your grade will be the highest of the two attempts.

Though we encourage collaboration in this class, this is an individual quiz.

- The responses should be a product of your original work so that you are assessed on *your* understanding of the material.

Sharing your quiz or your responses in any format (screenshots, email, CHEGG, social media, text, carrier pigeon, etc.) is in violation of the UCSC academic integrity policy.

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1. Which **atom is oxidized** in the reaction of benzhydrol with bleach? Draw the **structures** and indicate the **oxidation number** of that atom in the starting material and product (see page 1 of this document for a refresher on oxidation numbers).

2. Predict the **IR spectra of benzhydrol and benzophenone**: identify functional groups, bonds, and expected wavenumber ranges. What are the main **differences** you expect to find between the IR of the starting material and product?

3. Briefly explain how **phase transfer catalysts** work and why one is necessary in this experiment.

4. What are the **advantages of using bleach** as an oxidizing agent? What other **oxidizing agents** could be used to carry out the same transformation (see **table 1**)?

5. What are the **two solvents** used in the oxidation reaction? Will the aqueous layer be on the **top or bottom** in the reaction work-up?

6. Calculate the **mmoles** of each reagent used, identify the **limiting reagent**, and calculate the **theoretical yield** of benzophenone (recall that catalysts cannot be limiting since they are regenerated). Show your work.

LAB REPORT

Canvas > **Experiment 3 Report** for submission details

Upload to GradeScope (GS) after both parts of the lab – see due date on Canvas

- **Select Pages** to correlate your responses to the GS outline ☺

A. In-Lab Questions –Many of these questions are included in the Exp 3 Worksheet (notebook template).

1. Report the mass of benzhydrol used and the theoretical yield of benzophenone. Report the **yield of product (mg and %).** Briefly **discuss** any parts of the procedure that may have caused the yield to be lower than 100%, citing specific steps and transfers.

2. Report the **TLC results** (mobile phase, R_f values, and identification) of TLC analysis in table format and explain how you decided to stop the reaction. Briefly **explain** why the TLC separation of benzhydrol and benzophenone was successful by comparing the polarity of the samples and mobile phase.

3. Report **IR analysis** in table format. **Compare** the IR of the starting material and product. Briefly **explain** which peaks signify reaction completion, including functional group, bond, and stretching frequency. Include a photo of your IR product spectrum.

4. Interpret the **^{1}H NMR spectra of benzhydrol and benzophenone**: re-draw the structures with labeled hydrogens. Create the NMR tables into a word processing document. Answer the following in one sentence: **Which NMR peak(s) best distinguish starting material from product?**

B. Experimental Methods

How to Write the Methods Section:

- Review the 8M Writing Guidelines on Canvas and the **writing section of the Exp 3 worksheet**
  - Use a similar format and writing style to the sample provided in the 8M writing guidelines, incorporating necessary content from the Exp 3 writing worksheet.
- Organize the **key information** into **complete, concise sentences** to allow an experienced synthetic chemist to carry out this experiment.
- Note: the experimental methods section is an *abbreviated* version of the procedure and will omit many procedural details.