Student Handout: pH-Controlled Oxidation of an Aromatic Ketone

This experiment examines the reaction of an aromatic ketone, 4'-methoxyacetophenone, with bleach under both basic and acidic conditions (Scheme 1). You will see that the product of the oxidation can be controlled by the pH of the reaction mixture; that is, different products are formed when the reaction occurs under acidic or basic conditions.

A key point to keep in mind as you perform the reactions is that bleach is an aqueous 6% by mass solution of an oxidizing agent, sodium hypochlorite. Sodium hypochlorite is the active ingredient of bleach that makes it a powerful cleaner, stain remover, and disinfectant. There are two equilibria that are important for understanding the species present in a solution of bleach (Scheme 2). The first equation illustrates that the hypochlorite ion is in equilibrium with its conjugate acid, hypochlorous acid. The equilibrium constant for this reaction is determined by the pH of the solution. The second equation demonstrates that hypochlorite and chloride ion, which is also present in the solution, are in equilibrium with molecular chlorine. A small amount of Cl₂ is present in the solution regardless of its pH. Even though it is present in only low concentrations, chlorine (or a related species) is often the active oxidizing agent in reactions involving bleach. Therefore, bleach is a relatively safe source of the powerful but hazardous reagent molecular chlorine.

![Scheme 1. Reactions of 4'-methoxyacetophenone with bleach in the presence of base and acid.](image1)

![Scheme 2. Equilibria involving hypochlorite that affect the major species present in bleach.](image2)

One main focus of this lab lies in identifying the products of these two reactions. About half of your lab section will perform the experiment under acidic conditions, and the other half will perform the reaction under basic conditions. You will collect data to characterize (identify) your product. In addition, you will be provided additional spectral data that will be helpful in identifying the products.

These two reactions involve two issues of selectivity that often occur in organic synthesis: chemoselectivity and regioselectivity. Chemoselectivity refers to the fact that different functional groups often react differently under the same reaction conditions. For example, the aromatic ring of methyl ketone group (Figure 1) will react differently than the methyl ketone in the same molecule. Regioselectivity refers to the fact that the same functional group in different positions of a molecule may react differently. For example, there are two types of unsubstituted aromatic positions in 4'-methoxyacetophenone (Figure 1). There are two positions closer (ortho) to the carbonyl, and there are two positions closer (ortho) the ether group. These two sites may react differently to the same reagent even though they are the same functional group.

![Figure 1. Illustrations to help explain the concepts of chemoselectivity and regioselectivity](image3)
Several physical organic methods (spectroscopies and spectrometries) are tools that help us elucidate the structures of organic compounds. IR spectroscopy indicates the functional groups that are present in a molecule. \(^1\)H and \(^13\)C NMR spectroscopies provide information about functional groups as well as information about the symmetry, number, and connectivity of those functional groups in the organic structure. Mass spectrometry provides insight into the molar mass of the molecule and may indicate the presence of particular atoms (nitrogen, chlorine, bromine, and iodine) in the structure; sometimes the fragmentation patterns provide additional information.

When you are solving for the structure of an unknown that is the product of a reaction (as you will do for this experiment), a helpful place to start is to analyze the spectral data for the substrate. Assigning the spectra of the substrate will correlate the signals in the spectra with its functional groups and structure. For example, assigning the \(^1\)H NMR spectrum of 4'-methoxyacetophenone will let you know the chemical shift of each methyl group's protons. Comparing the spectra of the unknown products with the spectra of the substrate will help you identify differences in the functional groups of the molecules. Remember that solving for an unknown organic molecule using several types of spectral data is like working a giant jigsaw puzzle; it is a trial and error process that requires patience and perseverance.

The other main focus of this lab is to illustrate the ideas of green chemistry. Organic chemistry is essential for preparing many of the products in our everyday lives and is used in the production of products as varied as commodity plastics and many medicines. For example, the cholesterol-lowering drug atorvastatin (Figure 2) is a completely synthetic pharmaceutical agent sold under the brand name Lipitor\textsuperscript{®}. In addition, two research groups recently have developed more efficient processes for making the anti-flu drug oseltamivir (Tamiflu\textsuperscript{®}) (Figure 2). However, there have been drawbacks to the widespread use of organic synthesis to prepare commercial products. Improper disposal of effluents have polluted the environment. Inefficient processes have wasted valuable resources. Petrochemicals serve as starting materials for many processes, but they are being consumed ever more rapidly as fuels.

Clearly the current situation cannot continue forever. Some leaders in chemical research are advocating the research, development, and application of sustainable processes. They recognize that while organic synthesis is essential to the Western standard of living, it can be implemented more wisely. These leaders advocate using green chemistry to produce our materials. There are twelve goals of green chemistry, listed below, which suggest significant improvements to existing practices.\textsuperscript{2} The goals illustrated in this experiment are in bold.

1. **Prevention of waste**
2. Atom economy
3. **Less hazardous chemical syntheses**
4. Designing safer chemicals
5. **Safer solvents**
6. Energy efficiency
7. Renewable feedstocks
8. Fewer derivatives
9. Catalysis
10. Design for degradation
11. Real-time analysis for pollution prevention
12. **Inherently safer chemistry for accident prevention**

In this experiment, bleach is used as the oxidizing agent instead of the more hazardous chlorine gas or heavy metals. Water and water-soluble acetic acid are used as the solvents for the reaction instead of a toxic organic solvent. No organic solvent is used to work up or purify the product. It should be noted
that these reactions encompass only a few green chemistry principles and might be made greener.

Your report for the lab will focus on two aspects of the experiment. The first aspect is the identification of each reaction product from the physical data. It is important to identify each product correctly, but it is even more important to explain why the data support your conclusions. The second aspect that should be addressed in your report is to assess the "greenness" of this experiment. Identify the procedures and reagents that were green and those that were not.

**Procedure:**

Cautions: Wear gloves while manipulating the reagents for this experiment. Wear safety glasses or goggles to protect your eyes. 4'-Methoxyacetophenone is harmful if swallowed and irritating to the skin. Sodium hypochlorite is corrosive. Glacial acetic acid is a dehydrating agent and an irritant and is corrosive. Avoid contact of skin and eyes with sodium thiosulfate solution. The solid products are irritants; a by-product is harmful and relatively volatile. Perform both experiments in a fume hood. Dispose of wastes in the appropriate containers.

**Under basic conditions**

This experiment should be carried out in a fume hood. In a 25 mL round bottom flask containing a small stir bar sequentially add 4'-methoxyacetophenone (0.15 g, freshly ground in a mortar and pestle) and household bleach (nominally 6.0% sodium hypochlorite, 6.0 mL). Add a Vigreux column to the top of the flask. Stir the mixture rapidly (at the highest setting of consistent stirring) and heat it to 70-75°C using a heating mantle for 30 min.

Allow the mixture to cool at room temperature for 15 minutes. Remove the stir bar from the flask. While you swirl the flask, add sodium thiosulfate solution (10%, 2 mL) to quench the excess hypochlorite, and then add hydrochloric acid (3M, 2 mL) to lower the pH. Tare a filter paper and use vacuum filtration to collect the resulting solid on a Buchner funnel. Wash the solid with water. Discard the filtrate appropriately. Dry your solid in a 60°C oven for 1 h. Determine the experimental yield for the reaction. Collect the mp and 1H NMR spectrum of your sample.

**Under acidic conditions**

This experiment should be carried out in a fume hood. In a 25 mL round bottom flask containing a small stir bar (tared), sequentially add 4'-methoxyacetophenone (0.15 g, freshly ground in a mortar and pestle), glacial acetic acid (1.0 mL), and household bleach (nominally 6.0% sodium hypochlorite, 2.0 mL); the bleach should be added dropwise. Stir the mixture rapidly at room temperature for 30 min.

Add water (5 mL) to the mixture. Tare a filter paper and use vacuum filtration to collect the solid on a Buchner funnel. Wash the solid with water. After you have removed the Buchner funnel from the filter flask, quench the excess hypochlorite in the filtrate by slowly adding sodium thiosulfate solution (10%, 2 mL); discard the solution appropriately. Dry your solid in a 60°C oven for 1 h. Determine the experimental yield for the reaction. Collect the mp and 1H NMR spectrum of your sample.

**For both experiments**

Use 1H and 13C NMR, IR, and mass spectra to help you determine the structure of each product. After you have determined the structure of both products, determine the percent yield of each product.

**Postlab Questions:**

1. Write the reaction equation for acid-base equilibrium between hypochlorous acid and hypochlorite ion.
2. How will the above equilibrium be affected under low pH? Under high pH?
3. Why was the 4’-methoxyacetophenone ground in a mortar and pestle before it was used in the experiments?
4. Why must both reaction mixtures be stirred vigorously to obtain uniform reaction?
5. What is the purpose of the thiosulfate additions? Write a chemical equation to show the process.
6. After you determine the structures of the two products in this experiment, predict the major product of each of the following reactions.

References: