Properties and Reactions of Organic Compounds

# 19 EXPERIMENT 19

Reactivities of Some Alkyl Halides

S_N1/S_N2 reactions
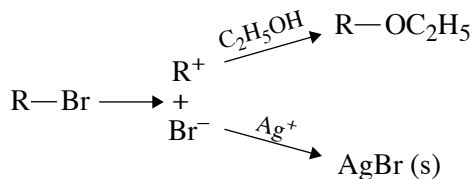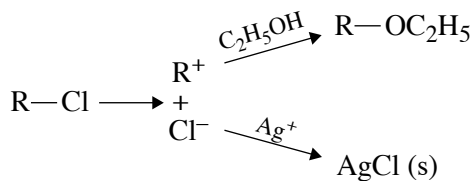
Relative rates

Reactivities

The reactivities of alkyl halides in nucleophilic substitution reactions depend on two important factors: reaction conditions and substrate structure. The reactivities of several substrate types will be examined under both S_N1 and S_N2 reaction conditions in this experiment.

Sodium Iodide or Potassium Iodide in Acetone

A reagent composed of sodium iodide or potassium iodide dissolved in acetone is useful in classifying alkyl halides according to their reactivity in an S_N2 reaction. Iodide ion is an excellent nucleophile, and acetone is a nonpolar solvent. The tendency to form a precipitate increases the completeness of the reaction. Sodium iodide and potassium iodide are soluble in acetone, but the corresponding bromides and chlorides are not soluble. Consequently, as bromide ion or chloride ion is produced, the ion is precipitated from the solution. According to LeChâtelier's Principle, the precipitation of a product from the reaction solution drives the equilibrium toward the right; such is the case in the reaction described here:

$$R—Cl + Na^+I^- \longrightarrow RI + NaCl\ (s)$$
$$R—Br + Na^+I^- \longrightarrow RI + NaBr\ (s)$$
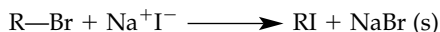
Silver Nitrate in Ethanol

A reagent composed of silver nitrate dissolved in ethanol is useful in classifying alkyl halides according to their reactivity in an S_N1 reaction. Nitrate ion is a poor nucleophile, and ethanol is a moderately powerful ionizing solvent. The silver ion, because of its ability to coordinate the leaving halide ion to form a silver halide precipitate, greatly assists the ionization of the alkyl halide. Again, a precipitate as one of the reaction products also enhances the reaction.

$$R—Cl \longrightarrow \begin{matrix} R^+ \\ + \\ Cl^- \end{matrix} \quad \begin{matrix} \xrightarrow{C_2H_5OH} R—OC_2H_5 \\ \\ \xrightarrow{Ag^+} AgCl\ (s) \end{matrix}$$

$$R—Br \longrightarrow \begin{matrix} R^+ \\ + \\ Br^- \end{matrix} \quad \begin{matrix} \xrightarrow{C_2H_5OH} R—OC_2H_5 \\ \\ \xrightarrow{Ag^+} AgBr\ (s) \end{matrix}$$

REQUIRED READING

Before beginning this experiment, review the chapters dealing with nucleophilic substitution in your lecture textbook.

SPECIAL INSTRUCTIONS

Some compounds used in this experiment, particularly crotyl chloride and benzyl chloride, are powerful lachrymators. **Lachrymators** cause eye irritation and the formation of tears.

CAUTION

Because some of these compounds are lachrymators, perform these tests in a hood. Be careful to dispose of the test solutions in a waste container marked for halogenated organic waste. After testing, rinse the test tubes with acetone and pour the contents into the same waste container.

SUGGESTED WASTE DISPOSAL

Dispose of all the halide wastes into the container marked for halogenated waste. Any acetone washings should also be placed in the same container.

NOTES TO THE INSTRUCTOR

Each of the halides should be checked with NaI/acetone and $AgNO_3$/ethanol to test for their purity before the class performs this experiment. If molecular modeling software is available, you may wish to assign the exercises included at the end of this experiment.

An alternative approach[1] for conducting this experiment is to restrict the list of test compounds to the following five substrates: 1-chlorobutane, 1-bromobutane, 2-chlorobutane, 2-bromobutane, and 2-chloro-2-methylpropane (*tert*-butyl chloride). If conducted in this way, one can simplify the experiment by eliminating the allylic, benzylic, and halocycloalkanes. This experiment can best be used if assigned *before* the S_N1 and S_N2 reactions have been discussed in lecture! An excellent and meaningful guided-inquiry experience can then be achieved by having students submit their results to a campus discussion board, such as BlackBoard, prior to any discussion of the results by the instructor. Once the class results have been posted ON BLACKBOARD, have the students study the class data to look for patterns. Encourage the class to try to "discover" how the reactivities in the sodium iodide/acetone and silver nitrate/ethanol depend on the substrate structure and the leaving group.

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[1]This approach was suggested and utilized successfully by Professor Emily Borda, Department of Chemistry, Western Washington University, Bellingham, WA 98225. The authors wish to thank Professor Borda for her excellent contribution.

PROCEDURE

Part A. Sodium Iodide in Acetone

The Experiment.   Label a series of ten clean and dry test tubes (10 × 75 mm test tubes may be used) from 1 to 10. In each test tube, place 2 mL of a 15% NaI-in-acetone solution. Now add 4 drops of one of the following halides to the appropriate test tube: (1) 2-chlorobutane, (2) 2-bromobutane, (3) 1-chlorobutane, (4) 1-bromobutane, (5) 2-chloro-2-methylpropane (*t*-butyl chloride), (6) crotyl chloride $CH_3CH=CHCH_2Cl$ (see Special Instructions), (7) benzyl chloride (α-chlorotoluene) (see Special Instructions), (8) bromobenzene, (9) bromocyclohexane, and (10) bromocyclopentane. Make certain you return the dropper to the proper container to avoid cross-contaminating these halides.

Reaction at Room Temperature.   After adding the halide, shake the test tube[1] well to ensure adequate mixing of the alkyl halide and the solvent. Record the times needed for any precipitate or cloudiness to form.

Reaction at Elevated Temperature.   After about 5 minutes, place any test tubes that do not contain a precipitate in a 50°C water bath. Be careful not to allow the temperature of the water bath to exceed 50°C, because the acetone will evaporate or boil out of the test tube. After about 1 minute of heating, cool the test tubes to room temperature and note whether a reaction has occurred. Record the results.

Observations.   Generally, reactive halides give a precipitate within 3 minutes at room temperature, moderately reactive halides give a precipitate when heated, and unreactive halides do not give a precipitate, even after being heated. Ignore any color changes.

Report.   Record your results in tabular form in your notebook. Explain why each compound has the reactivity you observed. Explain the reactivities in terms of structure. Compare relative reactivities for compounds of similar structure.

Part B. Silver Nitrate in Ethanol

The Experiment.   Label a series of ten clean and dry test tubes from 1 to 10, as described in the previous section. Add 2 mL of a 1% ethanolic silver nitrate solution to each test tube. Now add 4 drops of the appropriate halide to each test tube, using the same numbering scheme indicated for the sodium iodide test. To avoid cross-contaminating these halides, return the dropper to the proper container.

Reaction at Room Temperature.   After adding the halide, shake the test tube well to ensure adequate mixing of the alkyl halide and the solvent. After thoroughly mixing the samples, record the times needed for any precipitate or cloudiness to form. Record your results as dense precipitate, cloudiness, or no precipitate/cloudiness.

Reaction at Elevated Temperature.   After about 5 minutes, place any test tubes that do not contain a precipitate or cloudiness in a hot water bath at about 100°C. After about 1 minute of heating, cool the test tubes to room temperature and note whether a reaction has occurred. Record your results as dense precipitate, cloudiness, or no precipitate/cloudiness.

Observations.   Reactive halides give a precipitate (or cloudiness) within 3 minutes at room temperature, moderately reactive halides give a precipitate (or cloudiness) when heated, and unreactive halides do not give a precipitate, even after being heated. Ignore any color changes.

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[1]Do not use your thumb or a stopper. Instead, hold the top of the test tube between the thumb and index finger of one hand and "flick" the bottom of the test tube using the index finger of your other hand.

Report.   Record your results in tabular form in your notebook. Explain why each compound has the reactivity that you observed. Explain the reactivities in terms of structure. Compare relative reactivities for compounds of similar structure.

MOLEULAR MODELING (OPTIONAL)

Many points developed in this experiment can be confirmed through the use of molecular modeling. The following experiments were developed with PC Spartan. It should be possible to use other software, but the instructor may have to make some modifications.

S_N1 Reactivities

Part One.   The rate of an S_N1 reaction is related to the energy of the carbocation intermediate that is formed in the rate-determining ionization step of the reaction. It is expected that the activation energy required to form an intermediate is close to the energy of the intermediate. When two intermediates are compared, the activation energy leading to the intermediate of lower energy is expected to be lower than the activation energy leading to the intermediate of higher energy. The easier it is to form the carbocation, the faster the reaction will proceed. An AM1 semiempirical method for determining the approximate energies of carbocation intermediates is described in Experiment 18B. Complete the computational exercises in Experiment 18B, and compare the calculated results to the experimental results you obtained in this experiment. Do the experimental results parallel the calculated results?

Part Two.   Using the density–elpot surface plot described in Experiment 18D, it is possible to compare the amount of charge delocalization in various carbocations through a visualization of the ions. Complete Experiment 18D, and determine whether the charge distributions (delocalization) are what you would expect for the series of carbocations studied.

Part Three.   The benzyl (and allyl) halides are a special case; they have resonance. To see how the charge is delocalized in the benzyl carbocation, request two plots: the electrostatic potential mapped onto a density surface and the LUMO mapped onto a density surface. Submit these for calculation at the AM1 semiempirical level. On a piece of paper, draw the resonance-contributing structures for the benzyl cation. Do the computational results agree with the conclusions you draw from your resonance hybrid?

Part Four.   Repeat the calculation outlined in Part Three for the benzyl cation; however, in this calculation, turn the CH_2 group so that its hydrogens are perpendicular to the plane of the benzene ring. Compare your results to those obtained in Part Three.

S_N2 Reactivities

The problem in the S_N2 reaction is not an electric one, but rather a steric problem. Using the AM1 semiempirical method, request a LUMO surface and a density surface for each substrate. The simplest way to visualize the steric problem is to plot

the LUMO inside a density surface mapped as a net or a transparent surface. Now imagine having to attack the back lobe of the LUMO. Compare bromomethane, 2-bromo-2-methylpropane (*tert*-butyl bromide), and 1-bromo-2,2-dimethylpropane (neopentyl bromide). Is there any electron density (atoms) in the way of the nucleophile? Request and calculate another surface, mapping the LUMO onto the density surface. What are your conclusions? Can you find the "hot spot" where the nucleophile will attack? Is there any steric hindrance?

QUESTIONS

1. In the tests with sodium iodide in acetone and silver nitrate in ethanol, why should 2-bromobutane react faster than 2-chlorobutane?

2. Why is benzyl chloride reactive in both tests, whereas bromobenzene is unreactive?

3. When benzyl chloride is treated with sodium iodide in acetone, it reacts much faster than 1-chlorobutane, even though both compounds are primary alkyl chlorides. Explain this rate difference.

4. 2-Chlorobutane reacts much more slowly than 2-chloro-2-methylpropane in the silver nitrate test. Explain this difference in reactivity.

5. Bromocyclopentane is more reactive than bromocyclohexane when heated with sodium iodide in acetone. Explain this difference in reactivity.

6. How do you expect the following series of compounds to compare in behavior in the two tests?

$$CH_3—CH{=}CH—CH_2—Br \qquad CH_3—\underset{\underset{Br}{|}}{C}{=}CH—CH_3 \qquad CH_3—CH_2—CH_2—CH_2—Br$$
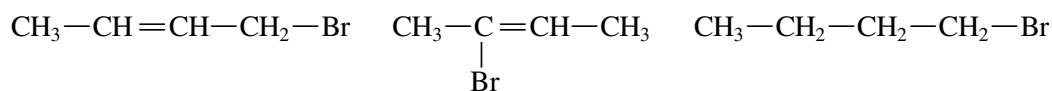
20   E X P E R I M E N T   2 0

Nucleophilic Substitution Reactions: Competing Nucleophiles

*Nucleophilic substitution*

Heating under reflux

Extraction
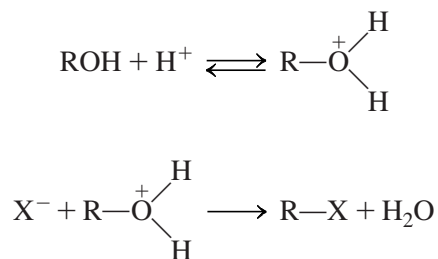
Gas chromatography

NMR spectroscopy

In this experiment, you will compare the relative nucleophilicities of chloride ions and bromide ions toward each of the following alcohols: 1-butanol (*n*-butyl alcohol), 2-butanol (*sec*-butyl alcohol), and 2-methyl-2-propanol (*t*-butyl alcohol). The two nucleophiles will be present at the same time in each reaction, in equimolar concentrations, and they will be competing for substrate. A protic solvent is used in these reactions.

In general, alcohols do not react readily in simple nucleophilic displacement reactions. If they are attacked by nucleophiles directly, hydroxide ion, a strong base, must be displaced. Such a displacement is not energetically favorable and cannot occur to any reasonable extent:

$$X^- \;+\; ROH \;\xrightarrow{\;\;//\;\;}\; R{-}X \;+\; OH^-$$
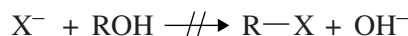
To avoid this problem, you must carry out nucleophilic displacement reactions on alcohols in acidic media. In a rapid initial step, the alcohol is protonated; then water, a stable molecule, is displaced. This displacement is energetically favorable, and the reaction proceeds in high yield:

$$ROH + H^+ \rightleftharpoons R{-}\overset{+}{O}\!\!\begin{array}{c} H \\ \diagdown \\ H \end{array}$$

$$X^- + R{-}\overset{+}{O}\!\!\begin{array}{c} H \\ \diagup \\[-2pt] \diagdown \\ H \end{array} \longrightarrow R{-}X + H_2O$$

Once the alcohol is protonated, it reacts by either the S_N1 or the S_N2 mechanism, depending on the structure of the alkyl group of the alcohol. For a brief review of these mechanisms, consult the chapters on nucleophilic substitution in your lecture textbook.

You will analyze the products of the three reactions in this experiment by a variety of techniques to determine the relative amounts of alkyl chloride and alkyl bromide formed in each reaction. That is, using equimolar concentrations of chloride ions and bromide ions reacting with 1-butanol, 2-butanol, and 2-methyl-2-propanol, you will determine which ion is the better nucleophile. In addition, you will determine for

which of the three substrates (reactions) this difference is important and whether an S_N1 or S_N2 mechanism predominates in each case.

REQUIRED READING

Review: Techniques 1 through 6

          *Technique 7   Reaction Methods, Sections 7.2, 7.4, and 7.8

          *Technique 12   Extractions, Separations, and Drying Agents

                          Sections 12.7, 12.9, and 12.11

          Technique 22   Gas Chromatography

          Technique 26   Nuclear Magnetic Resonance Spectroscopy

Before beginning this experiment, review the appropriate chapters on nucleophilic substitution in your lecture textbook.

SPECIAL INSTRUCTIONS

Each student will carry out the reaction with 2-methyl-2-propanol. Your instructor will also assign you either 1-butanol or 2-butanol. By sharing your results with other students, you will be able to collect data for all three alcohols. You should begin this experiment with Experiment 20A. During the lengthy reflux period, you will be instructed to on go on to Experiment 20B. When you have prepared the product of that experiment, you will return to complete Experiment 20A. To analyze the results of both experiments, your instructor will assign specific analysis procedures in Experiment 20C that the class will accomplish.

The solvent−nucleophile medium contains a high concentration of sulfuric acid. Sulfuric acid is corrosive; be careful when handling it.

In each experiment, the longer your product remains in contact with water or aqueous sodium bicarbonate, the greater the risk that your product will decompose, leading to errors in your analytical results. Before coming to class, prepare so that you know exactly what you are supposed to do during the purification stage of the experiment.

SUGGESTED WASTE DISPOSAL

When you have finished the three experiments and all the analyses have been completed, discard any remaining alkyl halide mixture in the organic waste container marked for the disposal of halogenated substances. All aqueous solutions produced in this experiment should be disposed of in the container for aqueous waste.

NOTES TO THE INSTRUCTOR

The solvent−nucleophile medium must be prepared in advance for the entire class. Use the following procedure to prepare the medium.

This procedure will provide enough solvent−nucleophile medium for about 10 students (assuming no spillage or other types of waste). Place 100 g of ice in a 500-mL Erlenmeyer flask and carefully add 76 mL concentrated sulfuric acid. Carefully weigh 19.0 g ammonium chloride and 35.0 g ammonium bromide into a

beaker. Crush any lumps of the reagents to powder and then, using a powder funnel, transfer the halides to an Erlenmeyer flask. Carefully add the sulfuric acid mixture to the ammonium salts a little at a time. Swirl the mixture vigorously to dissolve the salts. It will probably be necessary to heat the mixture on a steam bath or a hot plate to achieve total solution. Keep a thermometer in the mixture and make sure that the temperature does not exceed 45°C. If necessary, you may add as much as 10 mL of water at this stage. Do not worry if a few small granules do not dissolve. When a solution has been achieved, pour it into a container that can be kept warm until all students have taken their portions. The temperature of the mixture must be maintained at about 45°C to prevent precipitation of the salts. Be careful that the solution temperature does not exceed 45°C, however. Place a 10-mL or 20-mL calibrated pipet fitted with a pipet pump in the mixture. The pipet should always be left in the mixture to keep it warm.

Be certain that the *tert*-butyl alcohol has been melted before the beginning of the laboratory period.

The gas chromatograph should be prepared as follows: column temperature, 100°C; injection and detector temperature, 130°C; carrier gas flow rate, 50 mL/min. The recommended column is 8 feet long, with a stationary phase such as Carbowax 20M. If you wish to analyze the products from the reaction of *tert*-butyl alcohol (Experiment 20B) by gas chromatography, be sure that the *tert*-butyl halides do not undergo decomposition under the conditions set for the gas chromatograph. *tert*-Butyl bromide is susceptible to elimination.

Unless the samples are analyzed by gas chromatography immediately after preparing them, it is essential that they be stored in leak-proof vials. The relative percentages of the products will change if any loss of sample occurs. We have found GC-MS vials to be ideal for this purpose.

20A   **E X P E R I M E N T   2 0 A**

Competitive Nucleophiles with 1-Butanol or 2-Butanol


P R O C E D U R E

Apparatus. Assemble an apparatus for reflux using a 25-mL round-bottom flask, a reflux condenser, and a trap, as shown in the figure. Use a heating mantle as the heat source. The beaker of water will trap the hydrogen chloride and hydrogen bromide gases produced during the reaction. Do not place the round-bottom flask into the heating mantle until the reaction mixture has been added to the flask. Several Pasteur pipets and two centrifuge tubes with Teflon-lined caps should also be assembled for use.

C A U T I O N

The solvent−nucleophile medium contains a high concentration of sulfuric acid. This liquid will cause severe burns if it touches your skin.
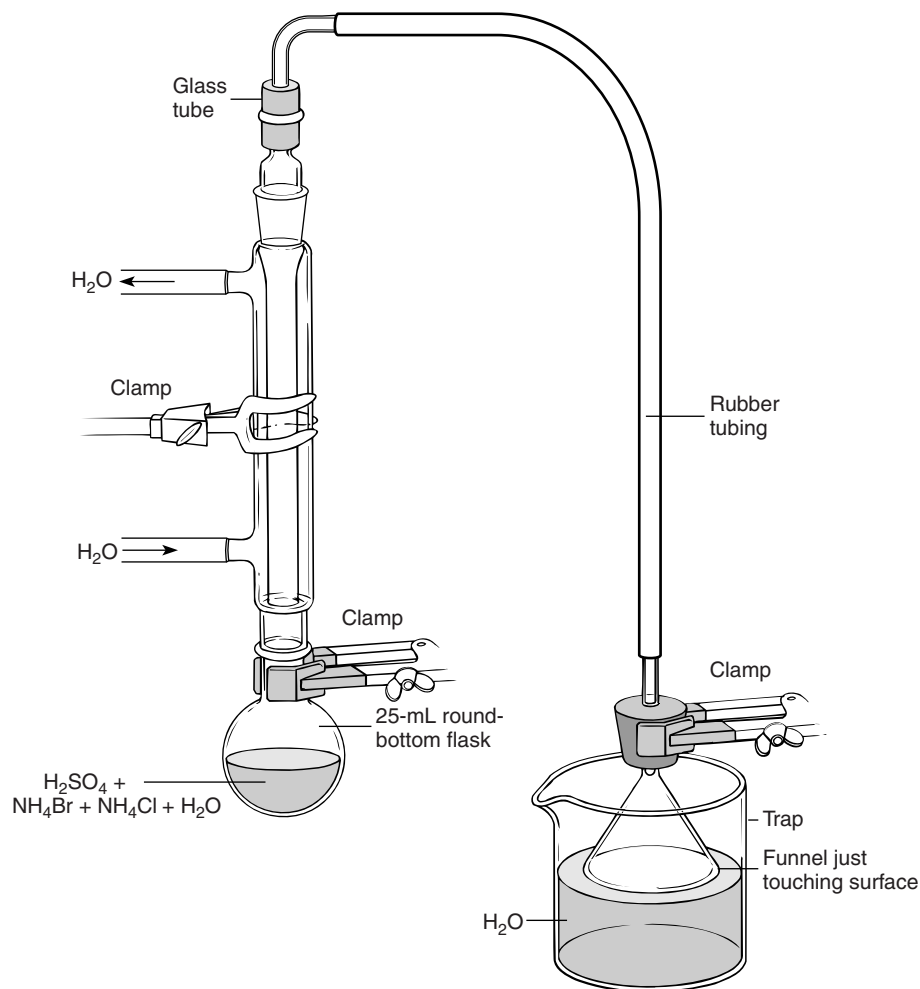
Apparatus for reflux.

Preparation of Reagents. If a calibrated pipet fitted with a pipet pump is provided, you may adjust the pipet to 10 mL and deliver the solvent−nucleophile medium directly into your 25-mL round-bottom flask (temporarily placed in a beaker for stability). Alternatively, you may use a warm 10-mL graduated cylinder to obtain 10.0 mL of the solvent−nucleophile medium. The graduated cylinder must be warm in order to prevent precipitation of the salts. Heat it by running hot water over the outside of the cylinder or by putting it in the oven for a few minutes. Immediately pour the mixture into the round-bottom flask. With either method, a small portion of the salts in the flask may precipitate as the solution cools. Do not worry about this; the salts will redissolve during the reaction. Now place the round-bottom flask in the heating mantle and attach the condenser as shown in the figure.

Reflux. Using the following procedure, add 0.75 mL of 1-butanol (*n*-butyl alcohol) or 0.75 mL of 2-butanol (*sec*-butyl alcohol), depending on which alcohol you were assigned, to the solvent−nucleophile mixture contained in the reflux apparatus. Dispense the alcohol from the automatic pipet or dispensing pump into a test tube. Remove the condenser

and, with a Pasteur pipet, dispense the alcohol directly into the round-bottom flask. Also add an inert boiling stone.[1] Replace the condenser and start circulating the cooling water. Lower the reflux apparatus so that the round-bottom flask is in the heating mantle. Adjust the heat from the heating mantle so that this mixture maintains a *gentle* boiling action. Be very careful to adjust the reflux ring, if one is visible, so that it remains in the lower fourth of the condenser. Violent boiling will cause loss of product. Continue heating the reaction mixture containing 1-butanol for 75 minutes. Heat the mixture containing 2-butanol for 60 minutes. During this heating period, go on to Experiment 20B and complete as much of it as possible before returning to this procedure.

Purification. When the period of reflux has been completed, discontinue heating, lift the apparatus out of the heating mantle, and allow the reaction mixture to cool. Do not remove the condenser until the flask is cool. Be careful not to shake the hot solution as you lift it from the heating mantle, or a violent boiling and bubbling action will result; this could allow material to be lost out the top of the condenser. After the mixture has cooled for about 5 minutes, immerse the round-bottom flask (with condenser attached) in a beaker of cold tap water (no ice) and wait for this mixture to cool down to room temperature.

An organic layer should be present at the top of the reaction mixture. Add 1.0 mL of pentane to the mixture and *gently* swirl the flask. The purpose of the pentane is to increase the volume of the organic layer so that the following operations are easier to accomplish. Using a Pasteur pipet, transfer most (about 7 mL) of the bottom (aqueous) layer to another container. Be careful that all of the top organic layer remains in the boiling flask. Transfer the remaining aqueous layer and the organic layer to a centrifuge tube with screw cap, taking care to leave behind any solids that may have precipitated. Allow the phases to separate and remove the bottom (aqueous) layer using a Pasteur pipet.

NOTE: For the following sequence of steps, be certain to be well prepared. If you find that you are taking longer than 5 minutes to complete the entire extraction sequence, you probably have affected your results adversely!

Add 1.5 mL of water to the tube and *gently* shake this mixture. Allow the layers to separate and remove the aqueous layer, which is still on the bottom. Extract the organic layer with 1.5 mL of saturated sodium bicarbonate solution and remove the bottom aqueous layer.

Drying. Using a clean dry Pasteur pipet, transfer the remaining organic layer into a small test tube (10 × 75 mm) and dry over anhydrous granular sodium sulfate (see Technique 12, Section 12.9). Transfer the dry halide solution with a clean, dry Pasteur pipet to a small, dry leak-proof vial, taking care not to transfer any solid.[2] *Be sure the cap is screwed on tightly*. Do not store the liquid in a container with a cork or a rubber stopper, because these will absorb the halides. This sample can now be analyzed by as many of the methods in Experiment 21C as your instructor indicates. If possible, analyze the sample on the same day.

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[1]Do not use calcium carbonate−based stones or Boileezers because they will partially dissolve in the highly acidic reaction mixture.
[2]We have found GC-MS vials ideal for this purpose.

20B   EXPERIMENT 20B

Competitive Nucleophiles with 2-Methyl-2-Propanol

PROCEDURE

Place 6.0 mL of the solvent–nucleophile medium into a 15-mL centrifuge tube, using the same procedure described in the "Preparation of Reagents" section at the beginning of Experiment 20A. Place the centrifuge tube in cold tap water and wait until a few crystals of ammonium halide salts just begin to appear. Using an automatic pipet or dispensing pump, transfer 1.0 mL of 2-methly-2-propanol (*tert*-butly alcohol, mp 25°C) to the 15-mL centrifuge tube. Replace the cap and make sure that it doesn't leak.

> **CAUTION**
>
> **The solvent−nucleophile mixture contains concentrated sulfuric acid.**

Shake the tube vigorously, venting occasionally, for 5 minutes (use gloves). Any solids that were originally present in the centrifuge tube should dissolve during this period. After shaking, allow the layer of alkyl halides to separate (10−15 minutes at most). A fairly distinct top layer containing the products should have formed by this time.

> **CAUTION**
>
> ***tert*-Butyl halides are volatile and should not be left in an open container any longer than necessary.**

Slowly remove most of the bottom aqueous layer with a Pasteur pipet and transfer it to a beaker. After waiting 10−15 seconds, remove the remaining lower layer in the centrifuge tube, including a small amount of the upper organic layer to be certain that the organic layer is not contaminated by any water.

NOTE: For the following purification sequence, be certain to be well prepared. If you find that you are taking longer than 5 minutes to complete the entire sequence, you probably have affected your results adversely!

Using a dry Pasteur pipet, transfer the remainder of the alkyl halide layer into a small test tube (10 × 75 mm) containing about 0.05 g of solid sodium bicarbonate. As soon as the

bubbling stops and a clear liquid is obtained, transfer it with a Pasteur pipet into a small, dry leak-proof vial, taking care not to transfer any solid.[3] *Be sure the cap is screwed on tightly.* Do not store the liquid in a container with a cork or a rubber stopper, because these will absorb the halides. This sample can now be analyzed by as many of the methods in Experiment 20C as your instructor indicates. If possible, analyze the sample on the same day. When you have finished this procedure, return to Experiment 20A.

20C   E X P E R I M E N T   2 0 C

Analysis

P R O C E D U R E

The ratio of 1-chlorobutane to 1-bromobutane, 2-chlorobutane to 2-bromobutane, or *tert*-butyl chloride to *tert*-butyl bromide must be determined. At your instructor's option, you may do this by one of three methods: gas chromatography, refractive index, or NMR spectroscopy. The products obtained from the reactions of 1-butanol and 2-butanol, however, cannot be analyzed by the refractive index method (they contain pentane). The products obtained from the reaction of *tert*-butyl alcohol may be difficult to analyze by gas chromatography because the *tert*-butyl halides sometimes undergo elimination in the gas chromatograph.[4]

Gas Chromatography[5]

The instructor or a laboratory assistant may either make the sample injections or allow you to make them. In the latter case, your instructor will give you adequate instruction beforehand. A reasonable sample size is 2.5 µL. Inject the sample into the gas chromatograph and record the gas chromatogram. The alkyl chloride, because of its greater volatility, has a shorter retention time than the alkyl bromide.

Once the gas chromatogram has been obtained, determine the relative areas of the two peaks (see Technique 22, Section 22.12). If the gas chromatograph has an integrator, it will report the areas. Triangulation is the preferred method of determining areas if an integrator is not available. Record the percentages of alkyl chloride and alkyl bromide in the reaction mixture.

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[3]See foot note #2.

[4]*Note to the Instructor:* If pure samples of each product are available, check the assumption here that the gas chromatograph responds equally to each substance. Response factors (relative sensitivities) are easily determined by injecting an equimolar mixture of products and comparing the peak areas.

[5]*Note to the Instructor:* To obtain reasonable results for the gas chromatographic analysis of the *tert*-butyl halides, it may be necessary to supply the students with response factor correction (see Technique 22, Section 22.13).

$$\% \text{ }n\text{-BuCl} = \frac{4.5}{4.5 + 24} \times 100 = 16\%$$

$$\% \text{ }n\text{-BuBr} = \frac{24}{4.5 + 24} \times 100 = 84\%$$
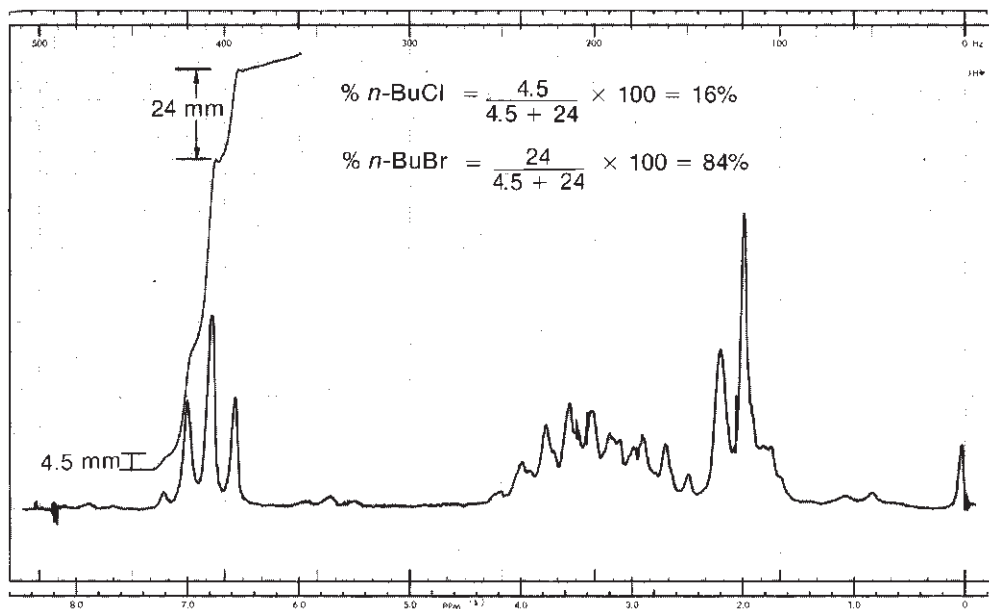
A 60-MHz NMR spectrum of 1-chlorobutane and 1-bromobutane, sweep width 250 Hz (no pentane in sample).

$$\% \text{ }t\text{-BuCl} = \frac{49}{49 + 60} \times 100 = 45\%$$

$$\% \text{ }t\text{-BuBr} = \frac{60}{49 + 60} \times 100 = 55\%$$
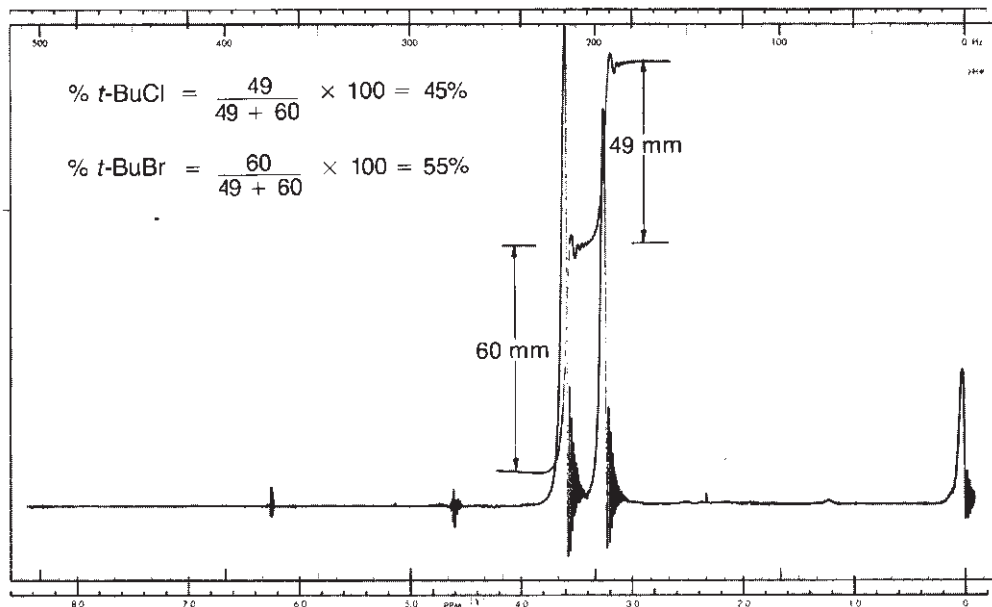
A 60-MHz spectrum of *tert*-butyl chloride and *tert*-butyl bromide, sweep width 250 Hz.

Nuclear Magnetic Resonance Spectroscopy

The instructor or a laboratory assistant will record the NMR spectrum of the reaction mixture.[6] Submit a sample vial containing the mixture for this spectral determination. The spectrum will also contain integration of the important peaks (see Technique 21, Nuclear Magnetic Resonance Spectroscopy).

If the substrate alcohol was 1-butanol, the resulting halide and pentane mixture will give rise to a complicated spectrum. Each alkyl halide will show a downfield triplet caused by the CH_2 group nearest the halogen. This triplet will appear farther downfield for the alkyl chloride than for the alkyl bromide. In a 60-MHz spectrum, these triplets will overlap, but one branch of each triplet will be available for comparison. Compare the integral of the *downfield* branch of the triplet for 1-chlorobutane with the *upfield* branch of the triplet for 1-bromobutane. The upper spectrum on the previous page provides an example. The relative heights of these integrals correspond to the relative amounts of each halide in the mixture.

If the substrate alcohol was 2-methyl-2-propanol, the resulting halide mixture will show two peaks in the NMR spectrum. Each halide will show a singlet because all the CH_3 groups are equivalent and are not coupled. In the reaction mixture, the upfield peak is due to *tert*-butyl chloride, and the downfield peak is caused by *tert*-butyl bromide. Compare the integrals of these peaks. The NMR spectrum of the *tert*-butyl chloride and bromide mixture shown here provides an example. The relative heights of these integrals correspond to the relative amounts of each halide in the mixture.

REPORT

Record the percentages of alkyl chloride and alkyl bromide in the reaction mixture for each of the three alcohols. You need to share your data from the reaction with 1-butanol or 2-butanol with other students in order to do this. The report must include the percentages of each alkyl halide determined by each method used in this experiment for the two alcohols you studied. On the basis of product distribution, develop an argument for which mechanism (S_N1 or S_N2) predominated for each of the three alcohols studied. The report should also include a discussion of which is the better nucleophile, chloride ion or bromide ion, based on the experimental results. All gas chromatograms and spectra should be attached to the report.

Q U E S T I O N S

1. Draw complete mechanisms that explain the resultant product distributions observed for the reactions of *tert*-butyl alcohol and 1-butanol under the reaction conditions of this experiment.

2. Which is the better nucleophile in a protic solvent, chloride ion or bromide ion? Try to explain this in terms of the nature of the chloride ion and the bromide ion.

3. What is the principal organic by-product for each of these reactions?

4. A student left some alkyl halides (RCl and RBr) in an open container for several minutes. What happened to the composition of the halide mixture during that time? Assume that some liquid remains in the container.

---

[6]It is difficult to determine the ratio of 2-chlorobutane to 2-bromobutane using nuclear magnetic resonance. This method requires at least a 90-MHz instrument. At 300 MHz, all downfield peaks are fully resolved.

5. What would happen if all the solids in the nucleophile medium were not dissolved? How might this affect the outcome of the experiment?

6. What might have been the product ratios observed in this experiment if an aprotic solvent such as dimethyl sulfoxide had been used instead of water?

7. Explain the order of elution you observed while performing the gas chromatography for this experiment. What property of the product molecules seems to be the most important in determining relative retention times?

8. When you calculate the percentage composition of the product mixture, exactly what kind of "percentage" (i.e., volume percent, weight percent, mole percent) are you dealing with?

9. When a pure sample of *tert*-butyl bromide is analyzed by gas chromatography, two components are usually observed. One of them is *tert*-butyl bromide, and the other one is a decomposition product. As the temperature of the injector is increased, the amount of the decomposition product increases and the amount of *tert*-butyl bromide decreases.

(a) What is the structure of the decomposition product?

(b) Why does the amount of the decomposition increase with increasing temperature?

(c) Why does *tert*-butyl bromide decompose much more easily than *tert*-butyl chloride?

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21 **EXPERIMENT 21**

Synthesis of n-*Butyl Bromide and* t-*Pentyl Chloride*

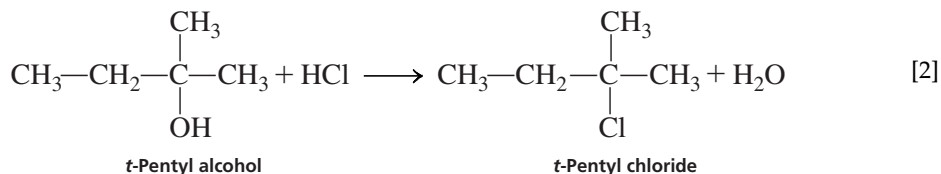*Synthesis of alkyl halides*

Extraction

Simple distillation

The synthesis of two alkyl halides from alcohols is the basis for these experiments. In the first experiment, a primary alkyl halide *n*-butyl bromide is prepared as shown in equation 1.

$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OH + NaBr + H_2SO_4 \longrightarrow$
    n-Butyl alcohol

$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Br + NaHSO_4 + H_2O$ [1]
    n-Butyl bromide
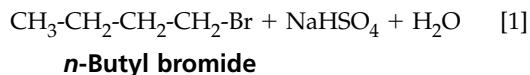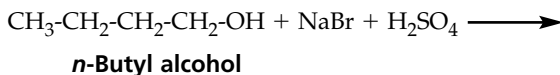
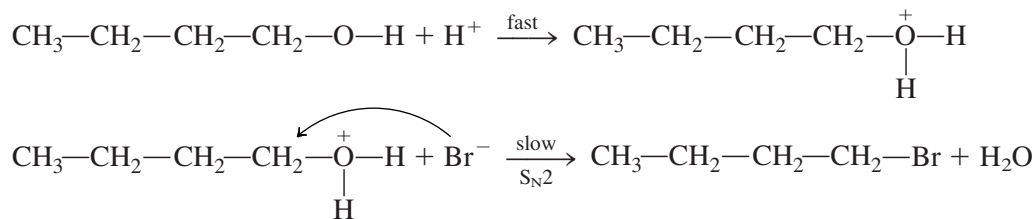In the second experiment, a tertiary alkyl halide *t*-pentyl chloride is prepared as shown in equation 2.

$$CH_3-CH_2-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 + HCl \longrightarrow CH_3-CH_2-\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 + H_2O \qquad [2]$$

**   *t*-Pentyl alcohol   *t*-Pentyl chloride**

These reactions provide an interesting contrast in mechanisms. The *n*-butyl bromide synthesis proceeds by an S_N2 mechanism, while *t*-pentyl chloride is prepared by an S_N1 reaction.

n-BUTYL BROMIDE

The primary alkyl halide *n*-butyl bromide can be prepared easily by allowing *n*-butyl alcohol to react with sodium bromide and sulfuric acid by equation 1. The sodium bromide reacts with sulfuric acid to produce hydrobromic acid.

$$2\ NaBr + H_2SO_4 \longrightarrow 2\ HBr + Na_2SO_4$$
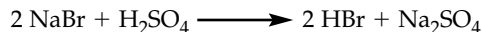
Excess sulfuric acid serves to shift the equilibrium and thus to speed the reaction by producing a higher concentration of hydrobromic acid. The sulfuric acid also protonates the hydroxyl group of *n*-butyl alcohol so that water is displaced rather than the hydroxide ion OH^-. The acid also protonates the water as it is produced in the reaction and deactivates it as a nucleophile. Deactivation of water keeps the alkyl halide from being converted back to the alcohol by nucleophilic attack of water. The reaction of the primary substrate proceeds via an S_N2 mechanism.

$$CH_3-CH_2-CH_2-CH_2-O-H + H^+ \xrightarrow{\text{fast}} CH_3-CH_2-CH_2-CH_2-\overset{+}{\underset{\underset{H}{|}}{O}}-H$$

$$CH_3-CH_2-CH_2-CH_2-\overset{+}{\underset{\underset{H}{|}}{O}}-H + Br^- \xrightarrow[S_N2]{\text{slow}} CH_3-CH_2-CH_2-CH_2-Br + H_2O$$

During the isolation of the *n*-butyl bromide, the crude product is washed with sulfuric acid, water, and sodium bicarbonate to remove any remaining acid or *n*-butyl alcohol.

t-PENTYL CHLORIDE

The tertiary alkyl halide can be prepared by allowing *t*-pentyl alcohol to react with concentrated hydrochloric acid according to equation 2. The reaction is accomplished simply by shaking the two reagents in a separatory funnel. As the reaction proceeds, the insoluble alkyl halide product forms an upper phase. The reaction of the tertiary substrate occurs via an S_N1 mechanism.

$$CH_3-CH_2-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 + H^+ \xrightarrow{\text{fast}} CH_3-CH_2-\underset{\underset{\underset{HH}{}}{\overset{|}{O^+}}}{\overset{\overset{CH_3}{|}}{C}}-CH_3$$

$$CH_3-CH_2-\underset{\underset{\underset{HH}{}}{\overset{|}{O^+}}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 \xrightarrow{\text{slow}} CH_3-CH_2-\underset{+}{\overset{\overset{CH_3}{|}}{C}}-CH_3 + H_2O$$

$$CH_3-CH_2-\underset{+}{\overset{\overset{CH_3}{|}}{C}}-CH_3 + Cl^- \xrightarrow{\text{fast}} CH_3-CH_2-\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3$$
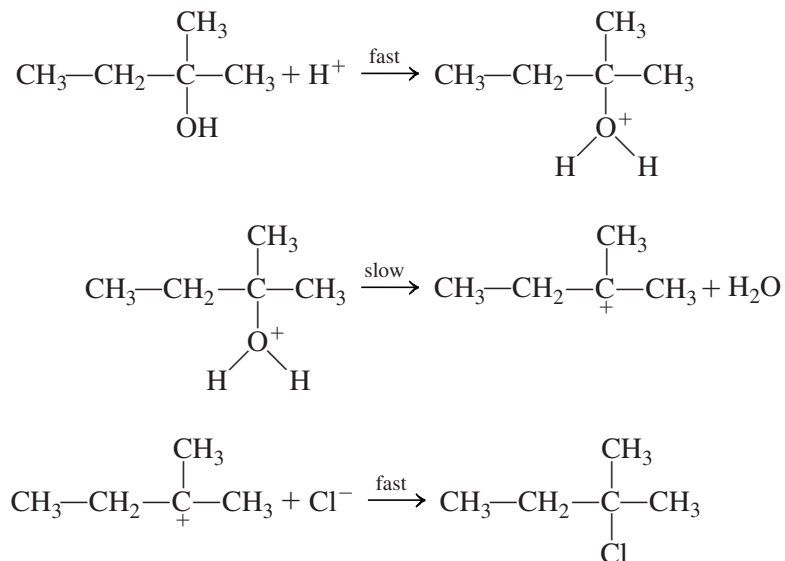
A small amount of alkene, 2-methyl-2-butene, is produced as a by-product in this reaction. If sulfuric acid had been used as it was for *n*-butyl bromide, a much larger amount of this alkene would have been produced.

REQUIRED READING

Review: Techniques 5, 6, 7, 12, and 14

SPECIAL INSTRUCTIONS

> **CAUTION**
>
> **Take special care with concentrated sulfuric acid; it causes severe burns.**

As your instructor indicates, perform either the *n*-butyl bromide or the *t*-pentyl chloride procedure, or both.

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous solutions produced in this experiment in the container marked for the disposal of aqueous waste. If your instructor asks you to dispose of your alkyl halide product, dispose of it in the container marked for the disposal of alkyl halides. Note that your instructor may have specific instructions for the disposal of wastes that differ from the instructions given here.

E X P E R I M E N T   2 1 A

n-*Butyl Bromide*

P R O C E D U R E

Preparation of n-Butyl Bromide. Place 17.0 g of sodium bromide in a 100-mL round-bottom flask and add 17 mL of water and 10.0 mL of *n*-butyl alcohol (1-butanol, *MW* = 74.1, *d* = 0.81 g/mL). Cool the mixture in an ice bath and slowly add 14 mL of concentrated sulfuric acid with continuous swirling in the ice bath. Add several boiling stones to the mixture and assemble the reflux apparatus and trap shown in the figure. The trap absorbs the hydrogen bromide gas evolved during the reaction period. Heat the mixture to a gentle boil for 60–75 minutes.

   Extraction. Remove the heat source and allow the apparatus to cool until you can disconnect the round-bottom flask without burning your fingers.

NOTE: Do not allow the reaction mixture to cool to room temperature. Complete the operations in this paragraph as quickly as possible. Otherwise, salts may precipitate, making this procedure more difficult to perform.

Disconnect the round-bottom flask and carefully pour the reaction mixture into a 125-mL separatory funnel. The *n*-butyl bromide layer should be on top. If the reaction is not yet complete, the remaining *n*-butyl alcohol will sometimes form a *second organic layer* on top of the *n*-butyl bromide layer. Treat both organic layers as if they were one. Drain the lower aqueous layer from the funnel.

   The organic and aqueous layers should separate as described in the following instructions. However, to make sure that you do not discard the wrong layer, it would be a good idea to add a drop of water to any aqueous layer you plan to discard. If a drop of water dissolves in the liquid, you can be confident that it is an aqueous layer. Add 14 mL of 9 M H_2SO_4 to the separatory funnel and shake the mixture (see Technique 12, Section 12.4). Allow the layers to separate. Because any remaining *n*-butyl alcohol is extracted by the H_2SO_4 solution, there should now be only one organic layer. The organic layer should be the top layer. Drain and discard the lower aqueous layer.

   Add 14 mL H_2O to the separatory funnel. Stopper the funnel and shake it, venting occasionally. Allow the layers to separate. Drain the lower layer, which contains *n*-butyl bromide (*d* = 1.27 g/mL), into a small beaker. Discard the aqueous layer after making certain the correct layer has been saved. Return the alkyl halide to the funnel. Add 14 mL of saturated aqueous sodium bicarbonate, a little at a time, while swirling. Stopper the funnel and shake it for 1 minute, venting frequently to relieve any pressure that is produced. Drain the lower alkyl halide layer into a dry Erlenmeyer flask. Add 1.0 g of anhydrous calcium chloride to dry the solution (see Technique 12, Section 12.9). Stopper the flask and swirl the contents until the liquid is *clear*. The drying process can be accelerated by gently warming the mixture on a steam bath.
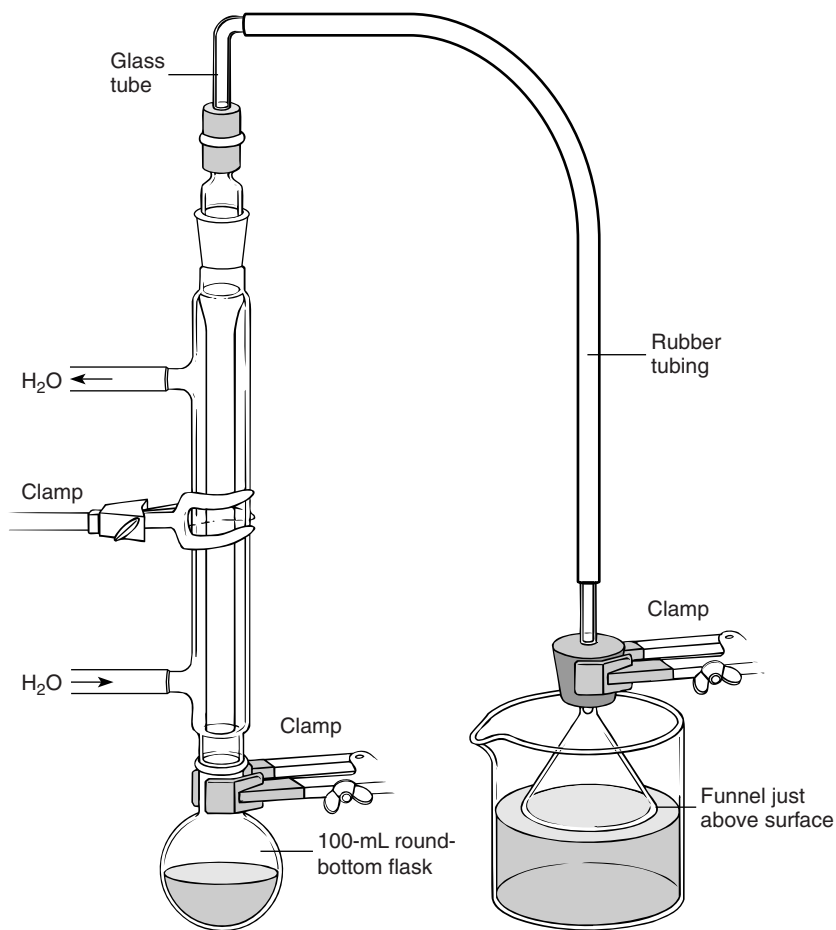
Apparatus for preparing *n*-butyl bromide.

Distillation. Transfer the clear liquid to a *dry* 25-mL round-bottom flask using a Pasteur pipet. Add a boiling stone and distill the crude *n*-butyl bromide in a *dry* apparatus (see Technique 14, Section 14.1, Figure 14.1). Collect the material that boils between 94° and 102°C. While distilling, pay close attention as the liquid distills to determine the range where most of the liquid distills. This will be the value that you should report for the boiling point of 1-bromobutane in your report. Weigh the product and calculate the percentage yield. Determine the infrared spectrum of the product using salt plates (see Technique 25, Section 25.2). You to determine a boiling point using the microscale boiling point method (see Technique 13, Section 13.3). Submit the remainder of the sample in a properly labeled vial, along with the infrared spectrum, when you submit your report to the instructor.

Frequency (cm⁻¹)
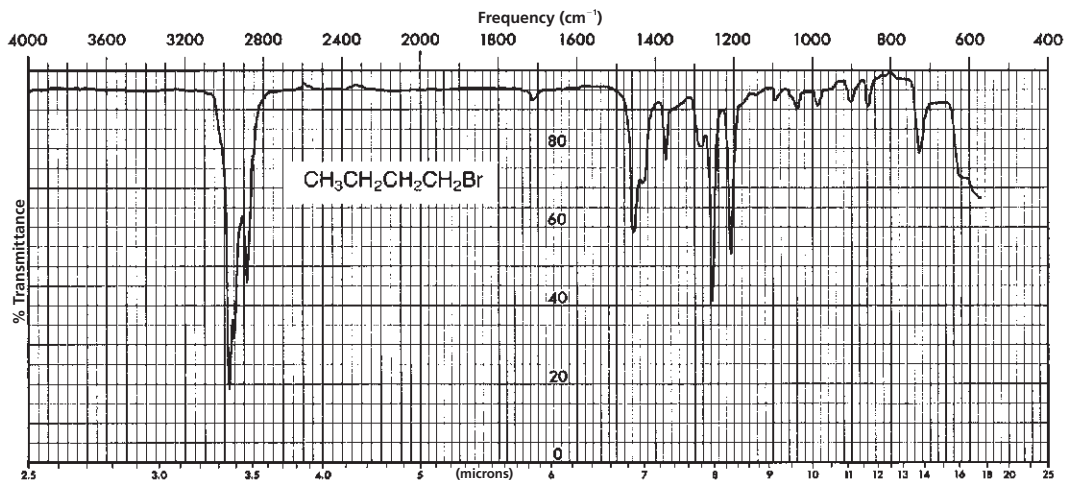
Infrared spectrum of n-butyl bromide (neat).

21B   EXPERIMENT 21B

t-*Pentyl Chloride*

PROCEDURE

Preparation of *t*-Pentyl Chloride. In a 125-mL separatory funnel, place 10.0 mL of *t*-pentyl alcohol (2-methyl-2-butanol, $MW = 88.2$, $d = 0.805$ g/mL) and 25 mL of concentrated hydrochloric acid ($d = 1.18$ g/mL). Do not stopper the funnel. Gently swirl the mixture in the separatory funnel for about 1 minute. After this period of swirling, stopper the separatory funnel and carefully invert it. Without shaking the separatory funnel, immediately open the stopcock to release the pressure. Close the stopcock, shake the funnel several times, and again release the pressure through the stopcock (see Technique 12, Section 12.4). Shake the funnel for 2−3 minutes, with occasional venting. Allow the mixture to stand in the separatory funnel until the two layers have completely separated. The *t*-pentyl chloride ($d = 0.865$ g/mL) should be the top layer, but be sure to verify this by adding a few drops of water. The water should dissolve in the lower (aqueous) layer. Drain and discard the lower layer.

Extraction. The operations in this paragraph should be done as rapidly as possible because the *t*-pentyl chloride is unstable in water and sodium bicarbonate solution. It is easily hydrolyzed back to the alcohol. In each of the following steps, the organic layer should be on top; however, you should add a few drops of water to make sure. Wash (swirl and shake) the organic layer with 10 mL of water. Separate the layers and discard the aqueous phase after making certain that the proper layer has been saved. Add a 10-mL portion of 5% aqueous sodium bicarbonate to the separatory funnel. Gently swirl the funnel (unstoppered) until the contents are thoroughly mixed. Stopper the funnel and carefully invert it.

Release the excess pressure through the stopcock. Gently shake the separatory funnel, with frequent release of pressure. Following this, vigorously shake the funnel, again with release of pressure, for about 1 minute. Allow the layers to separate and drain the lower aqueous layer. Wash (swirl and shake) the organic layer with one 10-mL portion of water and again drain the lower aqueous layer.

Transfer the organic layer to a small, dry Erlenmeyer flask by pouring it from the top of the separatory funnel. Dry the crude *t*-pentyl chloride over 1.0 g of anhydrous calcium chloride until it is clear (see Technique 12, Section 12.9). Swirl the alkyl halide with the drying agent to aid the drying.

Distillation. Transfer the clear liquid to a dry 25-mL round-bottom flask using a Pasteur pipet. Add a boiling stone and distill the crude *t*-pentyl chloride in a dry apparatus (see Technique 14, Section 14.1, Figure 14.1). Collect the pure *t*-pentyl chloride in a receiver cooled in ice. Collect the material that boils between 78°C and 84°C.
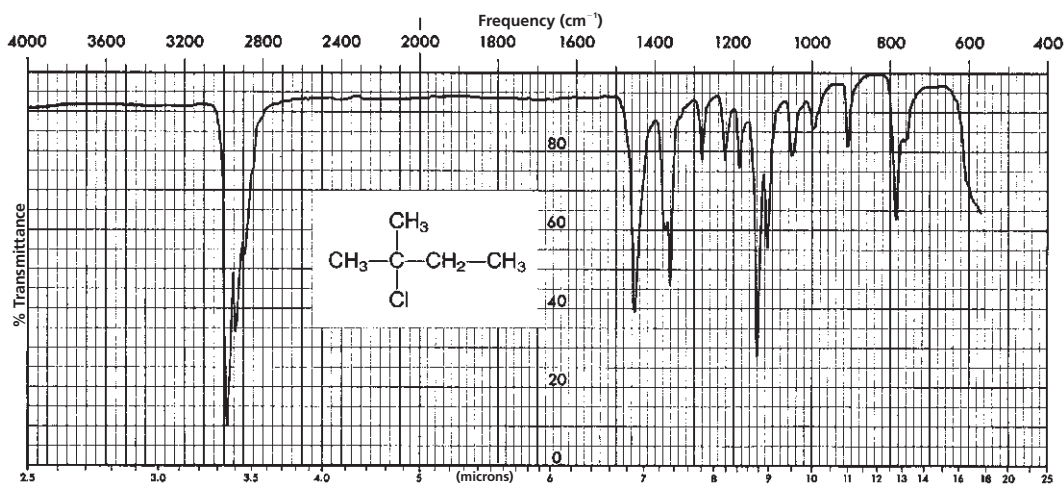
Infrared spectrum of *t*-pentyl chloride (neat).

While distilling, pay close attention as the liquid distills to determine the range where most of the liquid distills. This will be the value that you should record as the boiling point for *t*-pentyl chloride in your report. Weigh the product and calculate the percentage yield. Determine the infrared spectrum of the product using salt plates (see Technique 25, Section 25.2). Your instructor may ask to determine a boiling point using the microscale boiling point method (see Technique 13, Section 13.3). Submit the remainder of the sample in a properly labeled vial, along with the infrared spectrum, when you submit your report to the instructor.

QUESTIONS

n-Butyl Bromide

1. What are the formulas of the salts that may precipitate when the reaction mixture is cooled?

2. Why does the alkyl halide layer switch from the top layer to the bottom layer at the point where water is used to extract the organic layer?

3. An ether and an alkene are formed as by-products in this reaction. Draw the structures of these by-products and give mechanisms for their formation.

4. Aqueous sodium bicarbonate was used to wash the crude *n*-butyl bromide.

   a. What was the purpose of this wash? Give equations.

   b. Why would it be undesirable to wash the crude halide with aqueous sodium hydroxide?

5. Look up the density of *n*-butyl chloride (1-chlorobutane). Assume that this alkyl halide was prepared instead of the bromide. Decide whether the alkyl chloride would appear as the upper or lower phase at each stage of the separation procedure: after the reflux, after the addition of water, and after the addition of sodium bicarbonate.

6. Why must the alkyl halide product be dried carefully with anhydrous calcium chloride before the distillation? (*Hint:* See Technique 15, Section 15.8.)

t-Pentyl Chloride

1. Aqueous sodium bicarbonate was used to wash the crude *t*-pentyl chloride.

   a. What was the purpose of this wash? Give equations.

   b. Why would it be undesirable to wash the crude halide with aqueous sodium hydroxide?

2. Some 2-methyl-2-butene may be produced in the reaction as a by-product. Give a mechanism for its production.

3. How is unreacted *t*-pentyl alcohol removed in this experiment? Look up the solubility of the alcohol and the alkyl halide in water.

4. Why must the alkyl halide product be dried carefully with anhydrous calcium chloride before the distillation? (*Hint:* See Technique 15, Section 15.8.)

5. Will *t*-pentyl chloride (2-chloro-2-methylbutane) float on the surface of water? Look up its density in a handbook.

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22   E X P E R I M E N T   2 2

4-Methylcyclohexene

Preparation of an alkene

Dehydration of an alcohol

Distillation

Bromine and permanganate tests for unsaturation

$$\text{4-Methylcyclohexanol} \xrightarrow[\Delta]{H_3PO_4/H_2SO_4} \text{4-Methylcyclohexene} + H_2O$$
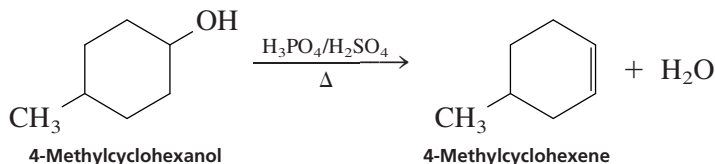
Alcohol dehydration is an acid-catalyzed reaction performed by strong, concentrated mineral acids such as sulfuric and phosphoric acids. The acid protonates the alcoholic hydroxyl group, permitting it to dissociate as water. Loss of a proton from the intermediate (elimination) brings about an alkene. Because sulfuric acid often causes extensive charring in this reaction, phosphoric acid, which is comparatively

free of this problem, is a better choice. In order to make the reaction proceed faster, however, you will also use a minimal amount of sulfuric acid.

The equilibrium that attends this reaction will be shifted in favor of the product by distilling it from the reaction mixture as it is formed. The 4-methylcyclohexene (bp 101−102°C) will codistill with the water that is also formed. By continuously removing the products, you can obtain a high yield of 4-methylcyclohexene. Because the starting material, 4-methylcyclohexanol, also has a somewhat low boiling point (bp 171−173°C), the distillation must be done carefully so that the alcohol does not also distill.

Unavoidably, a small amount of phosphoric acid codistills with the product. It is removed by washing the distillate mixture with a saturated sodium chloride solution. This step also partially removes the water from the 4-methylcyclohexene layer; the drying process will be completed by allowing the product to stand over anhydrous sodium sulfate.

Compounds containing double bonds react with a bromine solution (red) to decolorize it. Similarly, they react with a solution of potassium permanganate (purple) to discharge its color and produce a brown precipitate (MnO_2). These reactions are often used as qualitative tests to determine the presence of a double bond in an organic molecule (see Experiment 55C). Both tests will be performed on the 4-methylcyclohexene formed in this experiment.
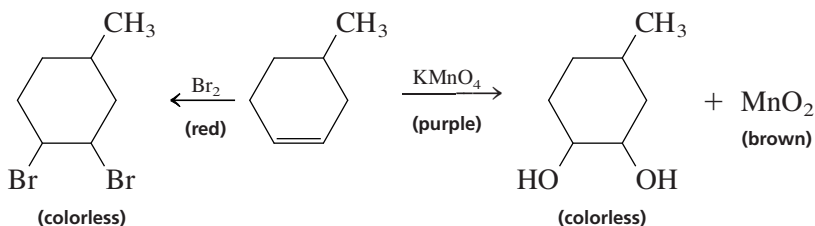
REQUIRED READING

Review: Techniques 5 and 6

          *Technique 12   Extractions, Separations, and Drying Agents,
          Sections 12.7, 12.8, and 12.9

New: *Technique 14   Simple Distillation

If performing the optional infrared spectroscopy, also read

          Technique 25   Infrared Spectroscopy

SPECIAL INSTRUCTIONS

Phosphoric and sulfuric acids are very corrosive. Do not allow either acid to touch your skin.

SUGGESTED WASTE DISPOSAL

Dispose of aqueous wastes by pouring them into the container designated for aqueous wastes. Residues that remain after the first distillation may also be placed in the aqueous waste container. Discard the solutions that remain after the bromine test for

unsaturation in an organic waste container designated for the disposal of *halogenated* wastes. The solutions that remain after the potassium permanganate test should be discarded into a waste container specifically marked for the disposal of potassium permanganate waste.

PROCEDURE

Apparatus Assembly. Place 7.5 mL of 4-methylcyclohexanol (*MW* = 114.2) in a tared 50-mL round-bottom flask and reweigh the flask to determine an accurate weight for the alcohol. Add 2.0 mL of 85% phosphoric acid and 30 drops (0.40 mL) of concentrated sulfuric acid to the flask. Mix the liquids thoroughly using a glass stirring rod and add a boiling stone. Assemble a distillation apparatus as shown in Technique 14, Figure 14.1 (omit the condenser), using a 25-mL flask as a receiver. Immerse the receiving flask in an ice-water bath to minimize the possibility that 4-methylcyclohexene vapors will escape into the laboratory.

Dehydration. Start circulating the cooling water in the condenser and heat the mixture with a heating mantle until the product begins to distill and collect in the receiver. The heating should be regulated so that the distillation requires about 30 minutes. Too rapid distillation leads to incomplete reaction and isolation of the starting material, 4-methylcyclohexanol. Continue the distillation until no more liquid is collected. The distillate contains 4-methylcyclohexene as well as water.

Isolation and Drying of the Product. Transfer the distillate to a centrifuge tube with the aid of 1 or 2 mL of saturated sodium chloride solution. Allow the layers to separate and remove the bottom aqueous layer with a Pasteur pipet (discard it). Using a dry Pasteur pipet, transfer the organic layer remaining in the centrifuge tube to an Erlenmeyer flask containing a small amount of granular anhydrous sodium sulfate. Place a stopper in the flask and set it aside for 10 − 15 minutes to remove the last traces of water. During this time, wash and dry the distillation apparatus, using small amounts of acetone and an air stream to aid the drying process.
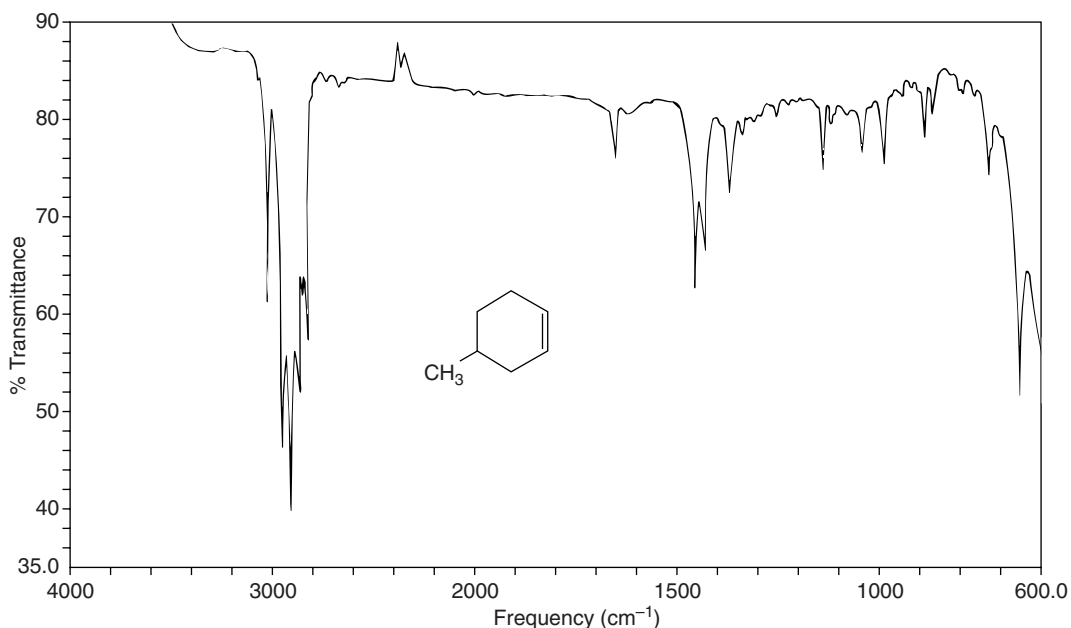
Infrared spectrum of 4-methylcyclohexene (neat).

Distillation. Transfer as much of the dried liquid as possible to the clean, dry 50-mL round-bottom flask, being careful to leave as much of the solid drying agent behind as possible. Add a boiling stone to the flask and assemble the distillation apparatus as before, using a *preweighed* 25-mL receiving flask. Because 4-methylcyclohexene is so volatile, you will recover more product if you cool the receiver in an ice-water bath. Using a heating mantle, distill the 4-methylcyclohexene, collecting the material that boils over the range 100°C−105°C. Record your observed boiling-point range in your notebook. There will be little or no forerun, and very little liquid will remain in the distilling flask at the end of the distillation. Reweigh the receiving flask to determine how much 4-methylcyclohexene you prepared. Calculate the percentage yield of 4-methylcyclohexene (*MW* = 96.2).

Spectroscopy. If your instructor requests it, obtain the infrared spectrum of 4-methylcyclohexene (see Technique 25, Section 25.2, or 25.3). Because 4-methylcyclohexene is so volatile, you must work quickly to obtain a good spectrum using sodium chloride plates. Compare the spectrum with the one shown in this experiment. After performing the following tests, submit your sample, along with the report, to the instructor.[1]

UNSATURATION TESTS

Place 4−5 drops of 4-methylcyclohexanol in each of two small test tubes. In each of another pair of small test tubes, place 4−5 drops of the 4-methylcyclohexene you prepared. Do not confuse the test tubes. Take one test tube from each group and add a solution of bromine in carbon tetrachloride or methylene chloride, drop by drop, to the contents of the test tube until the red color is no longer discharged. Record the result in each case, including the number of drops required. Test the remaining two test tubes in a similar fashion with a solution of potassium permanganate. Because aqueous potassium permanganate is not miscible with organic compounds, you will have to add about 0.3 mL of 1,2-dimethoxyethane to each test tube before making the test. Record your results and explain them.

QUESTIONS

1. Outline a mechanism for the dehydration of 4-methylcyclohexanol catalyzed by phosphoric acid.

2. What major alkene product is produced by the dehydration of the following alcohols?

   a. Cyclohexanol

   b. 1-Methylcyclohexanol

   c. 2-Methylcyclohexanol

   d. 2,2-Dimethylcyclohexanol

   e. 1,2-Cyclohexanediol (*Hint:* Consider keto-enol tautomerism.)

---

[1]The product of the distillation may also be analyzed by gas chromatography. We have found that when using gas chromatography−mass spectrometry to analyze the products of this reaction, it is possible to observe the presence of isomeric methylcyclohexenes. These isomers arise from rearrangement reactions that occur during the dehydration.

3. Compare and interpret the infrared spectra of 4-methylcyclohexene and 4-methylcyclohexanol.

4. Identify the C — H out-of-plane bending vibrations in the infrared spectrum of 4-methylcyclohexene. What structural information can be obtained from these bands?

5. In this experiment, $1-2$ mL of saturated sodium chloride is used to transfer the crude product after the initial distillation. Why is saturated sodium chloride, rather than pure water, used for this procedure?
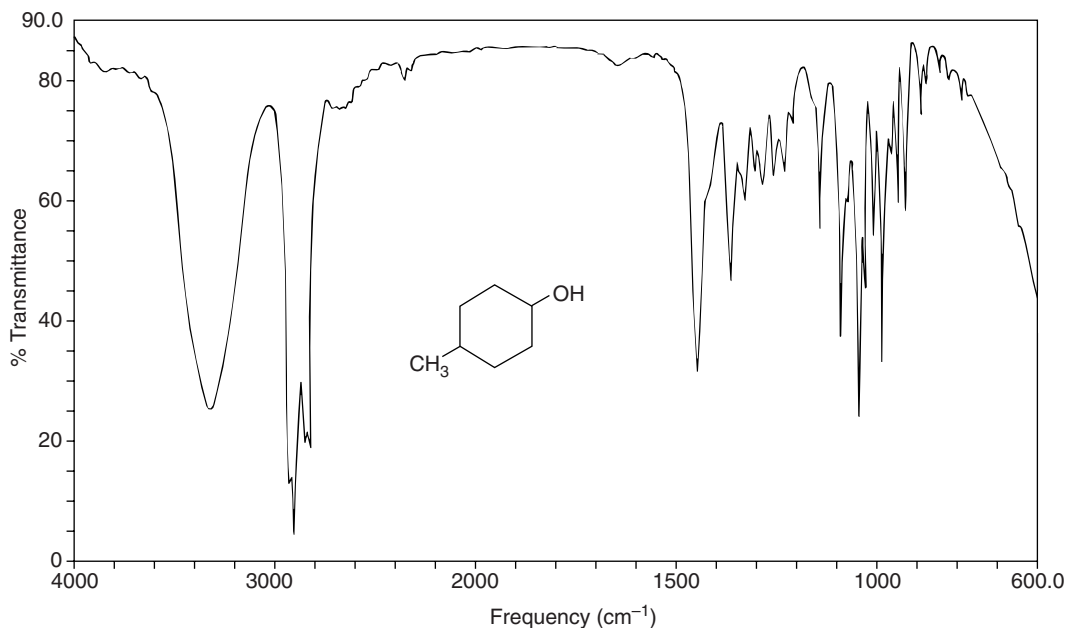
Infrared spectrum of 4-methylcyclohexanol (neat).

ESSAY

Fats and Oils

In the normal human diet, about 25% to 50% of the caloric intake consists of fats and oils. These substances are the most concentrated form of food energy in our diet. When metabolized, fats produce about 9.5 kcal of energy per gram. Carbohydrates and proteins produce less than half this amount. For this reason, animals tend to build up fat deposits as a reserve source of energy. They do this, of course, only when their food intake exceeds their energy requirements. In times of starvation, the body metabolizes these stored fats. Even so, some fats are required by animals for bodily insulation and as a protective sheath around some vital organs.

The constitution of fats and oils was first investigated by the French chemist Chevreul from 1810 to 1820. He found that when fats and oils were hydrolyzed, they gave rise to several "fatty acids" and the trihydroxylic alcohol glycerol. Thus, fats and oils are **esters** of glycerol, called **glycerides** or **acylglycerols**. Because glycerol has three hydroxyl groups, it is possible to have mono-, di-, and

triglycerides. Fats and oils are predominantly triglycerides (triacylglycerols), constituted as follows:

3 Fatty acids + glycerol   =   A triglyceride
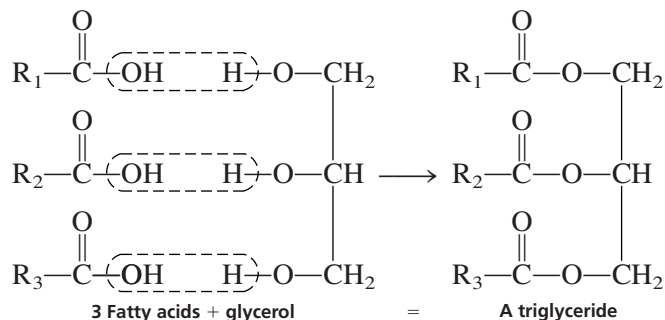
TABLE 1 Common Fatty Acids

C_{12} Acids	Lauric	$CH_3(CH_2)_{10}COOH$
C_{14} Acids	Myristic	$CH_3(CH_2)_{12}COOH$
C_{16} Acids	Palmitic	$CH_3(CH_2)_{14}COOH$
	Palmitoleic	$CH_3(CH_2)_5CH{=}CH{-}CH_2(CH_2)_6COOH$
C_{18} Acids	Stearic	$CH_3(CH_2)_{16}COOH$
	Oleic	$CH_3(CH_2)_7CH{=}CH{-}CH_2(CH_2)_6COOH$
	Linoleic	$CH_3(CH_2)_4(CH{=}CH{-}CH_2)2(CH_2)_6COOH$
	Linolenic	$CH_3CH_2(CH{=}CH{-}CH_2)_3(CH_2)_6COOH$
	Ricinoleic	$CH_3(CH_2)_5CH(OH)CH_2CH{=}CH(CH_2)_7COOH$

Thus, most fats and oils are esters of glycerol, and their differences result from the differences in the fatty acids with which glycerol may be combined. The most common fatty acids have 12, 14, 16, or 18 carbons, although acids with both lesser and greater numbers of carbons are found in several fats and oils. These common fatty acids are listed in Table 1 along with their structures. As you can see, these acids are both saturated and unsaturated. The saturated acids tend to be solids, whereas the unsaturated acids are usually liquids. This circumstance also extends to fats and oils. Fats are made up of fatty acids that are most saturated, whereas oils are primarily composed of fatty acid portions that have greater numbers of double bonds. In other words, unsaturation lowers the melting point. Fats (solids) are usually obtained from animal sources, whereas oils (liquids) are commonly obtained from vegetable sources. Therefore, vegetable oils usually have a higher degree of unsaturation.

About 20 to 30 fatty acids are found in fats and oils, and it is not uncommon for a given fat or oil to be composed of as many as 10 to 12 (or more) fatty acids. Typically, these fatty acids are randomly distributed among the triglyceride molecules, and the chemist cannot identify anything more than an average composition for a given fat or oil. The average fatty acid composition of some selected fats and oils is given in Table 2. As indicated, all the values in the table may vary in percentage, depending, for instance, on the locale in which the plant was grown or on the particular diet on which the animal subsisted. Thus, perhaps there is a basis for the claims that corn-fed hogs or cattle taste better than animals maintained on other diets.

Vegetable fats and oils are usually found in fruits and seeds and are recovered by three principal methods. In the first method, **cold pressing,** the appropriate part of the dried plant is pressed in a hydraulic press to squeeze out the oil. The second

TABLE 2 Average Fatty Acid Composition (by Percentage) of Selected Fats and Oils

	C10 C8 C6 C4	C12 Lauric	C14 Myristic	C16 Palmitic	C18 Stearic	C20 C22 C24	C16 Palmitoleic	C18 Oleic	C18 Ricinoleic	C18 Linoleic (2)	C18 Linolenic (3)	C18 Eleostearic (3)	C20 C22 C24 Unsaturated
	Saturated Fatty Acids (No Double Bonds)						Unsaturated (1 Double Bond)			Unsaturated (>1 Double Bond)			
Animal fats													
Tallow			2–3	24–32	14–32		1–3	35–48		2–4			
Butter	7–10	2–3	7–9	23–26	10–13		5	30–40		4–5			2
Lard			1–2	28–30	12–18		1–3	41–48		6–7			2
Animal oils													
Neat's foot				17–18	2–3			74–77					
Whale			4–5	11–18	2–4		13–18	33–38					17–31
Sardine			6–8	10–16	1–2		6–15	↓		24–30		↑	12–19
Vegetable oils													
Corn			0–2	7–11	3–4		0–2	43–49		34–42			
Olive			0–1	5–15	1–4		0–1	69–84		4–12			
Peanut				6–9	2–6	3–10	0–1	50–70		13–26			
Soybean			0–1	6–10	2–6			21–29		50–59	4–8		
Safflower			0–1	6–10	1–4			8–18		70–80	2–4		
Castor bean				0–1				0–9	80–92	3–7			
Cottonseed			0–2	19–24	1–2		0–2	23–33		40–48			
Linseed				4–7	2–5			9–38		3–43	25–58		
Coconut	10–22	45–51	17–20	4–10	1–5			2–10		0–2			
Palm			1–3	34–43	3–6			38–40		5–11			
Tung				←— 2–6 —→				4–16		0–1		74–91	

method is **hot pressing**, which is the same as the first method but done at a higher temperature. Of the two methods, cold pressing usually gives a better grade of product (more bland); the hot pressing method gives a higher yield, but with more undesirable constituents (stronger odor and flavor). The third method is **solvent extraction**. Solvent extraction gives the highest recovery of all and can now be regulated to give bland, high-grade food oils.

Animal fats are usually recovered by **rendering**, which involves cooking the fat out of the tissue by heating it to a high temperature. An alternative method involves placing the fatty tissue in boiling water. The fat floats to the surface and is easily recovered. The most common animal fats, lard (from hogs) and tallow (from cattle), can be prepared in either way.

Many triglyceride fats and oils are used for cooking. We use them to fry meats and other foods and to make sandwich spreads. Almost all commercial cooking fats and oils, except lard, are prepared from vegetable sources. Vegetable oils are liquids at room temperature. If the double bonds in a vegetable oil are hydrogenated, the resultant product becomes solid. In making commercial cooking fats (Crisco, Spry, Fluffo, etc.), manufacturers hydrogenate a liquid vegetable oil until the desired degree of consistency is achieved. This makes a product that still has a high degree of unsaturation (double bonds) left. The same technique is used for margarine. "Polyunsaturated" oleomargarine is produced by the partial hydrogenation of oils from corn, cottonseed, peanut, and soybean sources. The final product has a yellow dye (β-carotene) added to make it look like butter; milk, about 15% by volume, is mixed into it to form the final emulsion. Vitamins A and D are also commonly added. Because the final product is tasteless (try Crisco), salt, acetoin, and biacetyl are often added. The latter two additives mimic the characteristic flavor of butter.

Acetoin   **Biacetyl**
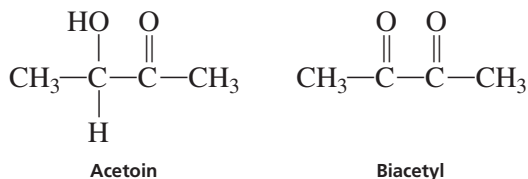
Many producers of margarine claim it to be more beneficial to health because it is "high in polyunsaturates." Animal fats are low in unsaturated fatty acid content and are generally excluded from the diets of people who have high cholesterol levels. Such people have difficulty in metabolizing saturated fats correctly and should avoid them because they encourage cholesterol deposits to form in the arteries. This ultimately leads to high blood pressure and heart trouble. People who pay close attention to their intake of fats tend to avoid consuming large quantities of saturated fats, knowing that eating these fats increases the risk of heart disease. Diet-conscious people try to limit their fat consumption to unsaturated fats, and they make use of the current mandatory food labeling to obtain information on the fat content of the food they eat.

Unfortunately, not all of the unsaturated fats appear to be equally safe. When we eat partially hydrogenated fats, we increase our consumption of **trans-fatty acids**. These acids, which are isomers of the naturally occurring *cis*-fatty acids, have been implicated in a variety of conditions, including heart disease, cancer, and diabetes. The strongest evidence that *trans*-fatty acids may be harmful comes in studies of the incidence of coronary heart disease. Ingestion of *trans*-fatty acids appears to increase blood cholesterol levels, in particular the ratio of low-density lipoproteins (LDL, or "bad" cholesterol) to high-density lipoproteins (HDL, or

"good" cholesterol). The *trans*-fatty acids appear to exhibit harmful effects on the heart that are similar to those shown by saturated fatty acids.

The *trans*-fatty acids do not occur naturally to any significant extent. Rather, they are formed during the partial hydrogenation of vegetable oils to make margarine and solid forms of shortening. For a small percentage of *cis*-fatty acids subjected to hydrogenation, only one hydrogen atom is added to the carbon chain. This process forms an intermediate free radical, which is able to rotate its conformation by 180 degrees before it releases the extra hydrogen atom back to the reaction medium. The result is an isomerization of the double bond.
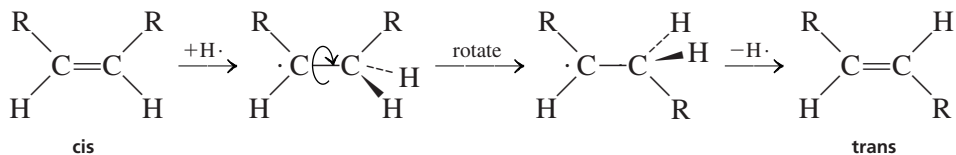
Concern over the health and nutrition of the public, particularly over the average fat intake of most Americans, has prompted food chemists and technologists to develop a variety of **fat replacers.** The objective has been to discover substances that have the taste and mouth-feel of a real fat, but do not have deleterious effects on the cardiovascular system. One product that has recently appeared in certain snack foods is **olestra** (marketed under the trade name **Olean,** by the Procter and Gamble Company). Olestra is not an acylglycerol; rather, it is composed of a

Olestra
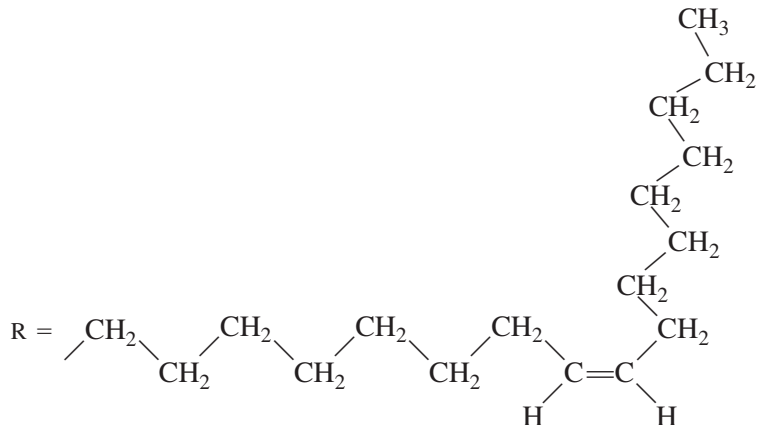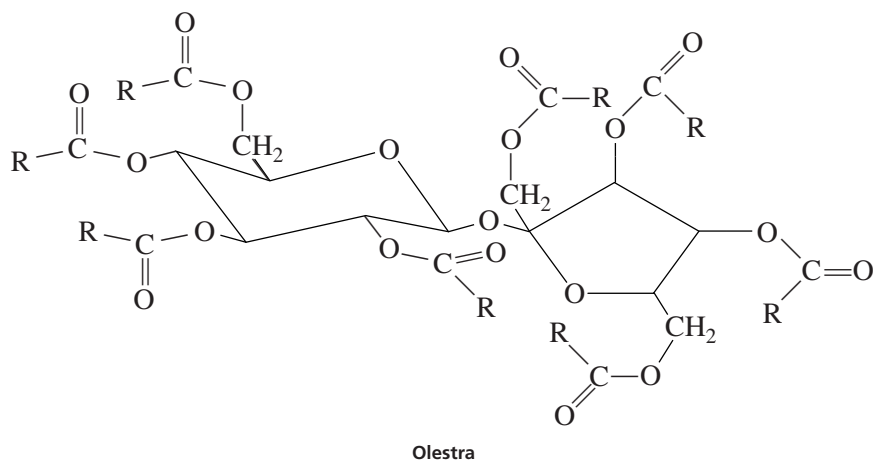
molecule of **sucrose** that has been substituted by long-chain fatty acid residues. It is a **polyester,** and the body's enzyme systems are not capable of attacking it and catalyzing its breakdown into smaller molecules.

Because the body's enzyme systems are unable to break this molecule down, it does not contain any usable dietary calories. Furthermore, it is heat stable, which makes it ideal for frying and other cooking. Unfortunately, for some individuals there may be harmful or unpleasant side effects. The use of olestra has been reported to deplete certain fat-soluble vitamins, particularly Vitamins A, D, E, and K. For this reason, products prepared with olestra have these vitamins added to offset this effect. Also, some people have reported diarrhea and abdominal cramps.

Is the development of fat replacers such as olestra part of the wave of the future? As the average American's appetite for snack foods continues to grow and as health problems arising from obesity also increase, the demand for satisfying foods that are less fattening will always be strong. In the long run, however, it would probably be better if we all learned to curtail our appetite for fatty foods and, instead, tried to increase our intake of fruits, vegetables, and other healthful foods. At the same time, a change from a sedentary lifestyle to one that includes regular exercise would also be much more beneficial to our health.

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Methyl Stearate from Methyl Oleate

Catalytic hydrogenation

Filtration (Pasteur pipet)

Recrystallization

Unsaturation tests

In this experiment, you will convert the liquid methyl oleate, an "unsaturated" fatty acid ester, to solid methyl stearate, a "saturated" fatty acid ester, by catalytic hydrogenation.

$$CH_3(CH_2)_7-CH{=}CH-(CH_2)_7-\overset{\overset{\textstyle O}{\|}}{C}-O-CH_3 \xrightarrow[\text{H}_2]{\text{Pd/C}}$$

Methyl oleate
(methyl *cis*-9-octadecenoate)

$$CH_3(CH_2)_7-\underset{\overset{|}{H}}{CH}-\underset{\overset{|}{H}}{CH}-(CH_2)_7-\overset{\overset{\textstyle O}{\|}}{C}-O-CH_3$$

Methyl stearate
(methyl octadecanoate)
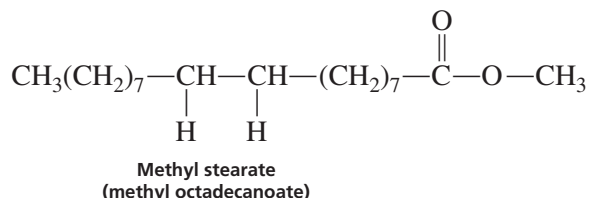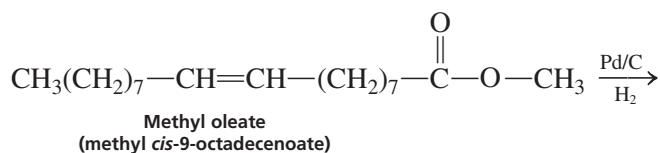
By commercial methods similar to those described in this experiment, the unsaturated fatty acids of vegetable oils are converted to margarine (see the essay "Fats and Oils"). However, rather than using the mixture of triglycerides that would be present in a cooking oil such as Mazola (corn oil), we use as a model the pure chemical methyl oleate.

For this procedure, a chemist would usually use a cylinder of hydrogen gas. Because many students will be following the procedure simultaneously, however, we use the simpler expedient of causing zinc metal to react with dilute sulfuric acid:

$$Zn + H_2SO_4 \xrightarrow{\text{H}_2\text{O}} H_2(g) + ZnSO_4$$
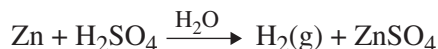
The hydrogen so generated will be passed into a solution containing methyl oleate and the palladium on carbon catalyst (10% Pd/C).

R E Q U I R E D   R E A D I N G

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Review: Techniques 5, 6, and 8

New: *Technique 8   Filtration, Sections 8.3–8.5

         *Technique 9   Physical Constants of Solids: The Melting Point

         Essay   Fats and Oils

You should also read those sections in your lecture textbook that deal with catalytic hydrogenation. If the instructor indicates that you should perform the optional unsaturation tests on your starting material and product, read the descriptions of the Br_2/CH_2Cl_2 test at the end of this experiment and in the introduction to Experiment 22.

SPECIAL INSTRUCTIONS

Because this experiment calls for generating hydrogen gas, no flames will be allowed in the laboratory.

CAUTION

No flames will be allowed.

Because a buildup of hydrogen is possible within the apparatus, it is especially important to remember to wear your safety goggles; you can thus protect yourself against the possibility of minor "explosions" from joints popping open, from fires, or from any glassware accidentally cracking under pressure.

CAUTION

Wear safety goggles.

When you operate the hydrogen generator, be sure to add sulfuric acid at a rate that does not cause hydrogen gas to evolve too rapidly. The hydrogen pressure in the flask should not rise much above atmospheric pressure; neither should the hydrogen evolution be allowed to stop. If this happens, your reaction mixture may be "sucked back" into your hydrogen generator.

SUGGESTED WASTE DISPOSAL

Carefully dilute the sulfuric acid (from the hydrogen generator) with water and place it in a container provided for this purpose. Place any leftover zinc in the solids container designated for unreacted zinc. After centrifugation, transfer the Pd/C catalyst to a specially designated container for later recycling. After collecting the methyl stearate by filtration, place the methanol filtrate in the nonhalogenated organic waste. Discard the solutions that remain after the bromine test for unsaturation into a waste container designed for the disposal of halogenated organic solvents. Note that your instructor may establish a different method of collecting wastes in this experiment.

NOTES TO THE INSTRUCTOR

Use methyl oleate that is 100% (or nearly 100%) pure. Avoid the practical grades, which may be only 70–80% of methyl oleate. We use Aldrich Chemical Co., No. 31,111-1. A commercial cooking oil could be substituted for methyl oleate in this experiment, but the results would not be as clear-cut.

Instructors may decide to substitute a less pyrophoric form of palladium catalyst for this experiment. GFS Chemical, 800 Mckinley Ave, Columbus, OH 43222, (614) 224-2689 sells "Royer Palladium Catalyst Powder/Beads, 3% Pd on polyethyleneimine/SiO_2," which the manufacturers claim is less pyrophoric than the standard palladium on carbon catalyst. Use of this alternative catalyst has not been checked, but it seems like a reasonable choice. We thank Professor Matt Koutroulis of Rio Hondo College in Whittier, California for the suggestion.

PROCEDURE

Apparatus. Assemble the hydrogenation apparatus as illustrated in the figure shown below. The apparatus consists of basically three parts:

1. Hydrogen generator
2. Reaction flask
3. Mineral oil bubbler trap

The **hydrogen generator** is a 20 × 150 mm sidearm test tube, fitted with a No. 3 rubber stopper. The **reaction flask** is a 50-mL round-bottom flask with a Claisen head attached. The hydrogen enters the reaction flask through a bubbler tube (ebulliator) attached to the top of the Claisen head by using the thermometer adapter. A small magnetic stirring bar is placed in the round-bottom flask, and the bubbler tube is adjusted to be just high enough to avoid contact but to allow hydrogen to bubble *through* the solution. A second thermometer adapter, fitted with a short piece of glass tubing, allows connection to the mineral oil bubbler. (No. 2 one-hole rubber stoppers could be substituted for the thermometer adapters if your joint size is ᚁ19/22.) A 150-mL beaker, filled with water and placed on a stirring hot plate, provides the heating bath. The **mineral oil bubbler**, a 20 × 150 mm sidearm test tube, has two functions. First, it allows you to keep a pressure of hydrogen within the system that is slightly above atmospheric. Second, it prevents back-diffusion of air into the system. The functions of the other two units are self-explanatory.

So that hydrogen leakage is prevented, the tubing used to connect the various subunits of the apparatus should be either relatively new rubber tubing, without cracks or breaks, or Tygon tubing. The tubing can be checked for cracks or breaks simply by stretching and bending it before use. It should be of such size that it will fit onto all connections tightly. Similarly, if any rubber stoppers are used, they should be fitted with a size of glass tubing that fits firmly through the holes in their centers. If the seal is tight, it will not be easy to slide the glass tubing up and down in the hole.

Preparing for the Reaction. Fill the bubbler trap (second sidearm test tube) about one-fourth full with mineral oil. The end of the glass tube should be submerged below the surface of the oil.

To charge the hydrogen generator, weigh out about 3 g of mossy zinc and place it in the sidearm test tube. Seal the large opening at its top using a rubber stopper. Obtain about 10 mL of 6 *M* sulfuric acid and place it in a small Erlenmeyer flask or beaker, but do not add it yet.

Weigh a 10-mL graduated cylinder and record its weight. Place 2.5 mL of methyl oleate into it. Reweigh the cylinder in order to obtain the exact amount of methyl oleate used. Detach the 50-mL round-bottom flask, place it in a small beaker to keep it upright, and transfer the methyl oleate. Do not clean the graduated cylinder. Instead, pour two consecutive 8 mL portions of methanol solvent (16 mL total) into the cylinder to rinse it and pour each of them into the reaction flask. Also remember to place a magnetic stirring bar into the flask. Using smooth weighing paper, weigh about 0.050 g (50 mg) of 10% Pd/C. Carefully place about one-third of the catalyst into the flask and gently swirl the liquid until the solid catalyst
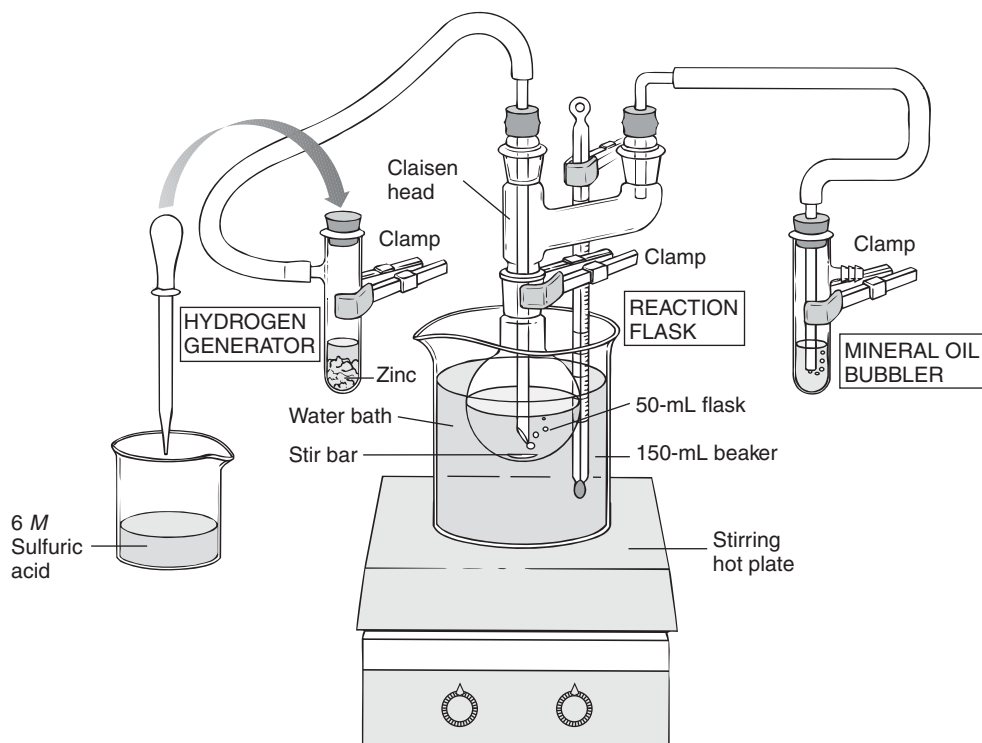
Hydrogenation apparatus for Experiment 26.

has sunk into the liquid. Repeat this with the rest of the catalyst, adding one-third of the original amount each time.

C A U T I O N

Be careful when adding the catalyst; sometimes it will cause a flame. Do not hold onto the flask; it should be in a small beaker on the lab bench. Have a watch glass handy to cover the opening and smother the flame should this occur.

Running the Reaction. Complete the assembly of the apparatus, making sure that all the seals are gas tight. Place the round-bottom flask in a warm water bath maintained at 40°C. This will help to keep the product dissolved in the solution throughout the course of the reaction. If the temperature rises above 40°C, you will lose a significant amount of the methanol solvent (bp 65°C). If this occurs, do not hesitate to add more methanol to the reaction flask through the sidearm of the Claisen head. Begin stirring the reaction mixture with the magnetic stirring bar. Avoid stirring too fast or a vortex will form, leaving the bubbler tube out of the solution. Start the evolution of hydrogen by removing the rubber stopper and adding a portion of the 6 *M* sulfuric acid solution (about 6 mL) to the hydrogen generator (use a small disposable Pasteur pipet). Replace the rubber stopper. A good rate of bubbling in the reaction flask is about three to four bubbles a second. Continue the evolution of hydrogen for at least 60 minutes. If necessary, open the generator, *empty it*, and refresh the zinc and sulfuric acid. (Keep in mind that the acid is used up as hydrogen is produced and becomes more dilute as the zinc reacts. As the acid solution becomes more dilute, the rate of hydrogen evolution will slow down.)

Stopping the Reaction. After the reaction is complete, stop the reaction by disconnecting the generator from the reaction flask. Decant the acid in the sidearm test tube into a designated waste container, being careful not to transfer any zinc metal. Rinse the zinc in the test tube several times with water and then place any unreacted zinc in a waste container provided for this purpose.

Keep the temperature of the reaction mixture at about 40°C until you perform the centrifugation; otherwise, the methyl stearate may crystallize and interfere with removal of the catalyst. There should not be any white solid (product) in the round-bottom flask. If there is a white solid, add more methanol and stir until the solid dissolves.

Removal of the Catalyst. Pour the reaction mixture into a centrifuge tube. Place the centrifuge tube into the water bath at 40°C until just before you are ready to centrifuge the mixture. (If the solution won't fit in a single centrifuge tube, divide it between two tubes and place them opposite each other in the centrifuge.) Centrifuge the mixture for several minutes. After centrifugation, the black catalyst should be at the bottom of the tube. If some of the catalyst is still suspended in the liquid, heat the mixture to 40°C and centrifuge the mixture again. Carefully pour (or remove with a Pasteur pipet) the supernatant liquid (leaving the black catalyst in the centrifuge tube) into a small beaker and cool to room temperature.

Crystallization and Isolation of Product. Place the beaker in an ice bath to induce crystallization. If crystals do not form or if only a few crystals form, you may need to reduce the volume of solvent. Do this by heating the beaker in a water bath and directing a slow stream of air into the beaker, using a Pasteur pipet for a nozzle (see Technique 7, Figure 7.18A). If crystals begin to form while you are evaporating the solvent, remove the beaker from the water bath. If crystals do not form, reduce the volume of the solvent by about one-third. Allow the solution to cool and then place it in an ice bath.

Collect the crystals by vacuum filtration, using a small Büchner funnel (see Technique 8, Section 8.3). Save both the crystals and the filtrate for the tests below. After the crystals are dry, weigh them and determine their melting point (literature, 39°C). Calculate the percentage yield. Submit your remaining sample to your instructor in a properly labeled container along with your report.

Optional: Unsaturation Tests. Using a solution of bromine in methylene chloride, test for the number of drops of this solution decolorized by

1. About 0.1 mL of methyl oleate dissolved in a small amount of methylene chloride

2. A small spatulaful of your methyl stearate product dissolved in a small amount of methylene chloride

3. About 0.1 mL of the filtrate that you saved as previously directed

Use small test tubes and Pasteur pipets to make these tests. Include the results of the tests and your conclusions in your report.

QUESTIONS

1. Using the information in the essay on fats and oils, draw the structure of the triacylglycerol (triglyceride) formed from oleic acid, linoleic acid, and stearic acid. Give a balanced equation and show how much hydrogen would be needed to reduce the triacylglycerol completely; show the product.

2. A 0.150-g sample of a pure compound subjected to catalytic hydrogenation takes up 25.0 mL of H_2 at 25°C and 1 atm pressure. Calculate the molecular weight of the compound, assuming that it has only one double bond.

3. A compound with the formula C_5H_6 takes up 2 moles of H_2 on catalytic hydrogenation. Give one possible structure that would fit the information given.

4. A compound of formula C_6H_{10} takes up 1 mole of H_2 on reduction. Give one possible structure that would fit the information.

5. How would this experiment differ in outcome if you used a commercial cooking oil instead of methyl oleate?

ESSAY

Petroleum and Fossil Fuels

Crude petroleum is a liquid that consists of hydrocarbons, as well as some related sulfur, oxygen, and nitrogen compounds. Other elements, including metals, may be present in trace amounts. Crude oil is formed by the decay of marine animal and plant organisms that lived millions of years ago. Over many millions of years, under the influence of temperature, pressure, catalysts, radioactivity, and bacteria, the decayed matter was converted into what we now know as crude oil. The Crude oil is trapped in pools beneath the ground by various geological formations.

Most crude oils have a specific gravity between 0.78 and 1.00 g/mL. As a liquid, crude oil may be as thick and black as melted tar or as thin as colorless as water. Its characteristics depend on the particular oil field from which it comes. Pennsylvania crude oils are high in straight-chain alkane compounds (called **paraffins** in the petroleum industry); those crude oils are therefore useful in the manufacture of lubricating oils. Oil fields in California and Texas produce crude oil with a higher percentage of cycloalkanes (called **naphthenes** by the petroleum industry). Some Middle East fields produce crude oil containing up to 90% cyclic hydrocarbons. Petroleum contains molecules in which the number of carbons ranges from 1 to 60.

When petroleum is refined to convert it into a variety of usable products, it is initially subjected to a fractional distillation. Table 1 lists the various fractions obtained from fractional distillation. Each of these fractions has its own particular uses. Each fraction may be subjected to further purification, depending on the desired application.

TABLE 1 Fractions Obtained from the Distillation of Crude Oil

Petroleum Fraction	Composition	Commercial Use
Natural gas	C_1 to C_4	Fuel for heating
Gasoilne	C_5 to C_{10}	Motor fuel
Kerosene	C_{11} to C_{12}	Jet fuel and heating
Light gas oil	C_{13} to C_{17}	Furnaces, diesel engines
Heavy gas oil	C_{18} to C_{25}	Motor oil, paraffin wax, petroleum jelly
Residuum	C_{26} to C_{60}	Asphalt residual oils, waxes

The gasoline fraction obtained directly from the distillation of crude oil is called **straight-run gasoline**. An average barrel of crude oil will yield about 19% straight-run gasoline. This yield presents two immediate problems. First, there is not enough gasoline contained in crude oil to satisfy current needs for fuel to power automobile engines. Second, the straight-run gasoline obtained from crude oil is a poor fuel for modern engines. It must be "refined" at a chemical refinery.

The initial problem of the small quantity of gasoline available from crude oil can be solved by **cracking** and **polymerization**. Cracking is a refinery process by which large hydrocarbon molecules are broken down into smaller molecules. Heat and pressure are required for cracking, and a catalyst must be used. Silica–alumina and silica–magnesia are among the most effective cracking catalysts. A mixture of saturated and unsaturated hydrocarbons is produced in the cracking process. If gaseous hydrogen is also present during the cracking, only saturated hydrocarbons are produced. The hydrocarbon mixtures produced by these cracking processes tend to have a fairly high proportion of branched-chain isomers. These branched isomers improve the quality of the fuel.

$$\text{C}_{16}\text{H}_{34} + \text{H}_2 \xrightarrow[\text{heat}]{\text{catalyst}} 2\,\text{C}_8\text{H}_{18} \quad \text{Cracking}$$
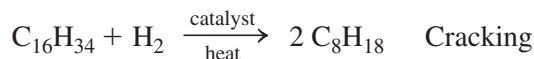
In the polymerization process, also carried out at a refinery, small molecules of alkenes are caused to react with one another to form larger molecules, which are also alkenes.

2-Methylpropene
(isobutylene)   2,4,4-Trimethyl-2-pentene   Polymerization
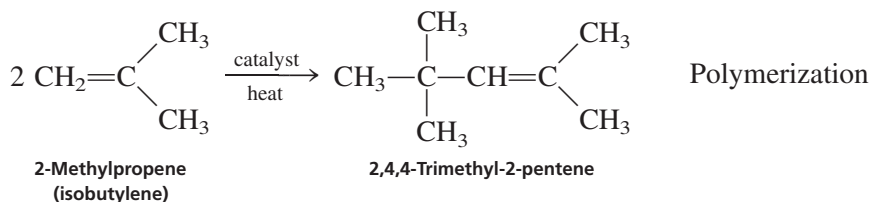
The newly formed alkenes may be hydrogenated to form alkanes. The reaction sequence shown here is a very common and important one in petroleum refining because the product, 2,2,4-trimethylpentane (or "isooctane"), forms the basis for determining the quality of gasoline. By these refining methods, the percentage of gasoline that can be obtained from a barrel of crude oil may rise to as much as 45% or 50%.

2,2,4-Trimethylpentane
(isooctane)
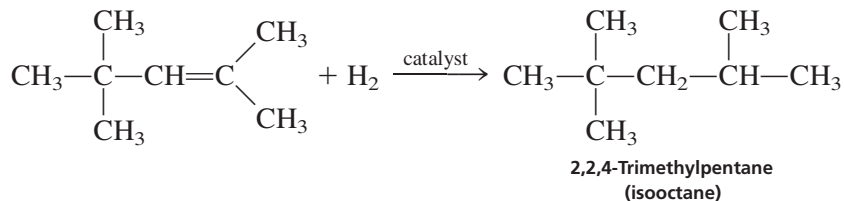
The internal combustion engine, as it is found in most automobiles, operates in four cycles or **strokes**. They are illustrated in the figure. The power stroke is of greatest interest from the chemical point of view because combustion occurs during this stroke.
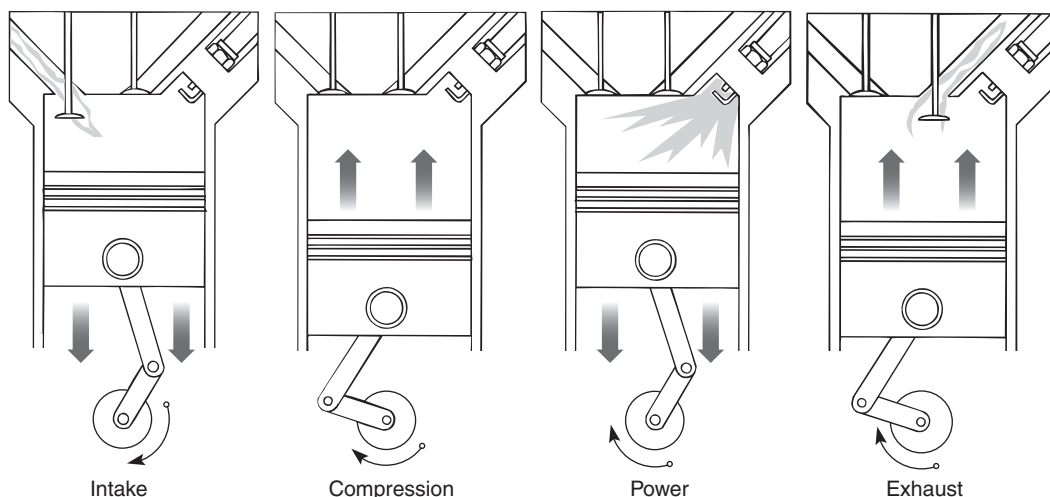
Operation of a four-cycle engine.

When the air–fuel mixture is ignited, it does not explode. Rather, it burns at a controlled, uniform rate. The gases closest to the spark are ignited first; then they in turn ignite the molecules farther from the spark; and so on. The combustion proceeds in a wave of flame or a **flame front**, which starts at the spark plug and proceeds uniformly outward from that point until all the gases in the cylinder have been ignited. Because a certain time is required for this burning, the initial spark is timed to ignite just before the piston has reached the top of its travel. In this way, the piston will be at the very top of its travel at the precise instant that the flame front and the increased pressure that accompanies it reach the piston. The result is a smoothly applied force to the piston, driving it downward.

If heat and compression should cause some of the air–fuel mixture to ignite before the flame front has reached it or to burn faster than expected, the timing of the combustion sequence is disturbed. The flame front arrives at the piston before the piston has reached the very top of its travel. When the combustion is not perfectly coordinated with the motion of the piston, we observe **knocking**, or **detonation** (sometimes called "pinging"). The transfer of power to the piston under these conditions is much less effective than in normal combustion. The wasted energy is merely transferred to the engine block in the form of additional heat. The opposing forces that occur in knocking may eventually damage the engine.

The tendency of a fuel to knock is a function of the structures of the molecules composing the fuel. Normal hydrocarbons, those with straight carbon chains, have a greater tendency to lead to knocking than do alkanes with highly branched chains. A fuel can be classified according to its antiknock characteristics. The most important rating system is the octane rating of gasoline. In this method of classification, the antiknock properties of a fuel are compared in a test engine with the antiknock properties of a standard mixture of heptane and 2,2,4-trimethylpentane. This latter compound is called "isooctane," hence the name *octane rating*. A fuel that has the same antiknock properties as a given mixture of heptane and isooctane has an octane rating numerically equal to the percentage of isooctane in that reference mixture. Today's 87-octane unleaded gasoline is a mixture of compounds that have, taken together, the same antiknock characteristics as a test fuel composed of 13% heptane and 87% isooctane. Other substances besides hydrocarbons may also have high resistance to knocking. Table 2 presents a list of organic compounds with their octane ratings.

TABLE 2 Octane Ratings of Organic Compounds

Compound	Octane Number	Compound	Octane Number
Octane	−19	1-Butene	97
Heptane	0	2,2,4-Trimethylpentane	100
Hexane	25	Cyclopentane	101
Pentane	62	Ethanol	105
Cyclohexane	83	Benzene	106
1-Pentene	91	Methanol	106
2-Hexene	93	Methyl *tert*-butyl ether	116
Butane	94	*m*-Xylene	118
Propane	97	Toluene	120

Note: The octane values in this table are determined by the **research method**.

Several chemical refining processes are used to improve the octane rating of gasoline and to increase the percentage of gasoline that can be obtained from petroleum. Some of these reactions, collectively known as **reforming**, are dehydrogenation, dealkylation, cyclization, and isomerization. The products of these reactions, sometimes referred to as **reformates**, contain many branched alkanes and aromatic compounds. Several examples of reforming reactions are:

$$CH_3(CH_2)_6CH_3 \xrightarrow{\text{catalyst}} CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-\underset{\overset{CH_3}{|}}{CH}-CH_3 \qquad \textbf{Reforming}$$

$$CH_3(CH_2)_5CH_3 \xrightarrow{\text{catalyst}} \qquad \textbf{Reforming}$$

$$CH_3-CH_2-CH_2-CH_2-CH_3 \xrightarrow{\text{AlBr}_3} CH_3-\underset{\overset{CH_3}{|}}{CH}-CH_2-CH_3 \qquad \textbf{Reforming}$$
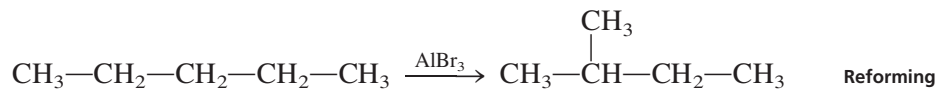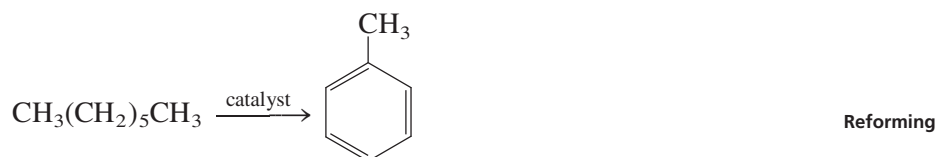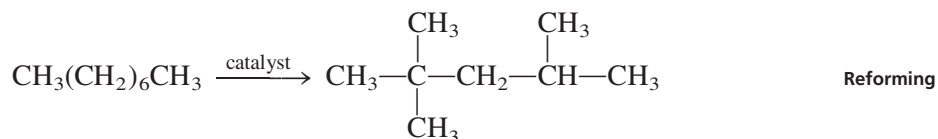
Other chemical reactions, referred to as **alkylation**, can also be used to increase the octane rating. Alkylation involves the catalytic addition of an alkane to alkene, such as 2-methylpropane to propene or butane. The products of these reactions are sometimes referred to as **alkylates**. Another refining process, called **hydrocracking** (cracking in the presence of hydrogen gas), also produces hydrocarbons that reduce knocking.

None of these processes converts all the normal hydrocarbons into branched-chain isomers; consequently, additives are also put into gasoline to improve the octane rating of the fuel. Before 1996, the most common additive used to reduce knocking has been **tetraethyllead**. Gasoline that contains tetraethyllead is called **leaded** gasoline, whereas gasoline produced without tetraethyllead is sometimes called **unleaded** gasoline. Because of concern over the possible health hazard associated with emission of lead into the atmosphere and Environmental Protection Agency began in 1973 to limit the amount of tetraethyllead in gasoline. In 1996, the Clean Air

Act completely banned the sale of leaded gasoline for use in all on-road vehicles. Many other countries have followed with similar bans; however, some countries in Eastern Europe, the Middle East, and Africa continue to use leaded gasoline.

$$CH_3-CH_2-\underset{\underset{CH_2-CH_3}{|}}{\overset{\overset{CH_2-CH_3}{|}}{Pb}}-CH_2-CH_3$$
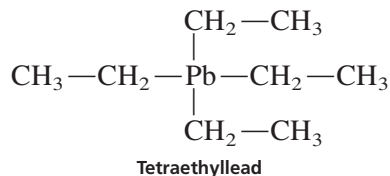
Tetraethyllead

To replace tetraethyllead, oil companies have developed other additives and strategies that will improve the octane rating of gasoline without producing harmful emissions. One approach is to increase quantities of hydrocarbons that have very high antiknock properties themselves. Typical are the aromatic hydrocarbons, including benzene, toluene, and xylene. Such compounds are natural components of most crude petroleum, and additional aromatic compounds can be added to gasoline to improve the quality. Increasing the proportion of aromatic hydrocarbons brings with it certain hazards, however. These substances are toxic, and benezene is considered a serious carcinogenic hazard. The risk that illness will be contracted by workers in refineries, and especially by persons who work in service stations, is increased. A safer approach is to increase the amount of alkylates.

Benzene   **Toluene**   **Xylene**
                                          (1,3-dimethylbenzene)
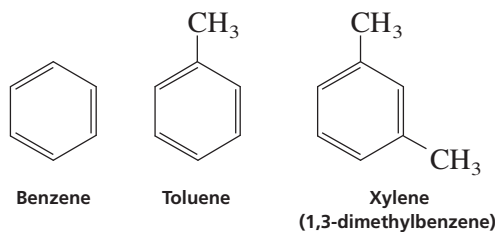
Research has also been directed toward development of nonhydrocarbon compounds that can improve the quality of unleaded gasoline. To this end, compounds such as methyl *tert*-butyl ether (MTBE), ethanol, and other **oxygenates** (oxygen-containing compounds) are added to improve the octane rating of fuels. Ethanol is attractive because it is formed by fermentation of living material, a renewable resource (see essays "Biofuels" and "Ethanol and Fermentation Chemistry" that precedes Experiment 16). Ethanol not only would improve the antiknock properties of gasolines, but also would potentially help the country to reduce its dependence on imported petroleum. Substituting ethanol for hydrocarbons in petroleum would have the effect of increasing the "yield" of fuel produced from a barrel of crude oil. As in many stories that are too good to be true, it is not clear that the energy needed to produce the ethanol by fermentation and distillation is significantly smaller than the amount of energy that is produced when the ethanol is burned in an engine!

$$CH_3-O-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 \qquad CH_3-CH_2-OH$$

Methyl *tert*-butyl ether   **Ethanol**
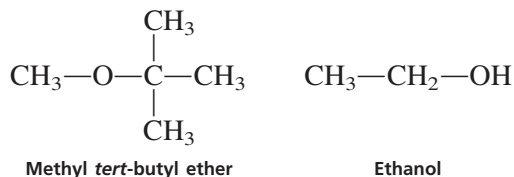
In an effort to improve air quality in urban areas, the Clean Air Act of 1990 mandated the addition of oxygen-containing compounds in many urban areas during the winter (November to February). These compounds are expected to reduce carbon monoxide emissions produced when the gasoline burns in cold engines by helping to oxidize carbon monoxide to carbon dioxide. They also help to reduce the amount of ozone created by emission products reacting in sunlight; and they increase the octane rating. Refineries add "oxygenates," such as ethanol or methyl *tert*-butyl ether, to the gasoline sold in the carbon monoxide−containment areas. By law, gasoline must contain at least 2.7% oxygen by weight, and the areas must use it for a minimum of the four winter months. In 1995, the Clean Air Act also required that **reformulated gasoline** (RFG) be sold year round in sites with the worst ground-level ozone concentrations. RFG must contain a minimum of 2% oxygen by weight.

Although methyl *tert*-butyl ether is still used in some states, the use of ethanol is much more common. There are several reasons for the preference for ethanol. First, ethanol is cheaper than MTBE because of special tax breaks and subsidies that have been granted to producers of ethanol formed by fermentation. Second, there has been much concern that MTBE may cause health problems, and there have been some widely publicized occurrences of groundwater contamination by MTBE. Furthermore, people notice the odor of gasoline more easily when MTBE is present in the fuel. Because of these concerns, the use of MTBE was outlawed by California in January 2004, and many other states have issued similar or partial bans. It is possible that a complete ban on MTBE in the United States will follow. Therefore, ethanol has become the preferred oxygenate for gasoline. However, there are disadvantages with the use of ethanol, too. There is some evidence that because ethanol is more volatile than MTBE, it may increase the emission of chemicals such as volatile organic compounds (VOCs) that contribute to smog. This is a concern especially during the warmer months. In addition, studies have suggested that fuel with ethanol increases the formation of atmospheric acetaldehyde. Because acetaldehyde is a precursor to peroxyacetyl nitrate, it is possible that *increased* air pollution results from use of ethanol as an oxygenate. Other oxygenates such as ethyl *tert*-butyl ether and methanol are also being considered.

The number of grams of air required for the complete combustion of one mole of gasoline (assuming the formula C_8H_{18}) is 1.735 grams. This gives rise to a theoretical air−fuel ratio of 15.1:1 for complete combustion. For several reasons, however, it is neither easy nor advisable to supply each cylinder with a theoretically correct air−fuel mixture. The power and performance of an engine improve with a slightly richer mixture (lower air−fuel ratio). Maximum power is obtained from an engine when the air−fuel ratio is near 12.5:1, and maximum economy is obtained when the air−fuel ratio is near 16:1. Under conditions of idling or full load (that is, acceleration), the air−fuel ratio is lower than what would be theoretically correct. As a result, complete combustion does not take place in an internal combustion engine, and carbon monoxide (CO) is produced in the exhaust gases. Other types of nonideal combustion behavior give rise to the presence of unburned hydrocarbons in the exhaust. The high combustion temperatures cause the nitrogen and oxygen of the air to react, forming a variety of nitrogen oxides in the exhaust. Each of these materials contributes to air pollution. Under the influence of sunlight, which has enough energy to break covalent bonds, these materials may react with each other and with air to produce **smog**, which contributes to many health problems. Smog consists of **ozone**, which deteriorates rubber and damages plant life; **particulate matter**, which produces haze; **oxides of nitrogen**, which produce a brownish color in the atmosphere; and a variety of eye irritants, such as **peroxyacetyl nitrate**

(PAN). Sulfur compounds in the gasoline may lead to the production of noxious sulfur-containing gases in the exhaust.

$$CH_3-\overset{\overset{\textstyle O}{\|}}{C}-O-O-NO_2$$

Peroxyacetyl nitrate
(PAN)
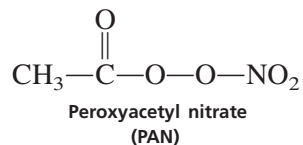
Efforts to reverse the trend of deteriorating air quality caused by automotive exhaust have taken many forms. The advent of catalytic converters, which are mufflerlike devices containing catalysts that can convert carbon monoxide, unburned hydrocarbons, and nitrogen oxides into harmless gases, has resulted from such efforts. Some success in reducing exhaust emissions has been attained by modifying the design of combustion chambers of internal combustion engines. Additionally, the use of computerized control of ignition systems has achieved positive results.

It should be obvious from this discussion that there are many factors considered in the formulation of gasoline. The gasoline produced today consist of several hundred compounds! There is substantial variation in the actual composition, depending on the local climate and regional environmental regulations. The approximate composition is 15% C_4-C_8 staright-chain alkanes, 25% C_4-C_{10} branched alkanes, 10% cycloalkanes, less than 25% aromatic compounds, and 10% straight-chain and cyclic alkenes.

Although much has been accomplished in terms of making it safer to use gasoline, there is another looming problem having to do with the supply of petroleum. The amount of petroleum and other fossil fuels in the world is finite. In 1956, Marion King Hubbert, a Shell Oil geophysicist, predicted that the U.S. production of oil would reach a peak around 1970, and from then on the amount extracted would decline significantly. Although most people ignored his warning, it did peak at 9 million barrels per day in 1970 and has been declining ever since, with about 6 million barrels per day being produced in 2004. Many experts have used similar methods of analysis to make predictions about when the world's supply of oil will peak; and although there is much variations in the actual year predicted, most experts agree that the peak has already occurred. Because the demand for petroleum continues to increase every year, it is clear that declining petroleum production will have a dramatic effect on how we live. Not only is petroleum the main source of fuel used for transportation but it also provides the raw materials for a wide variety of other products, including plastics, drugs, and pesticides. Although it is possible that the decrease in production of petroleum may be partially offset by more dependence on natural gas and coal, the amount of these fossil fuels is also finite, and it seems inevitable that major adjustments will need to be made as the availability of fossil fuels declines.

Many developments in recent years have addressed some of the emission problems associated with burning gasoline and the need to stretch the supply of fossil fuels. These developments involve changes in the design of automobile engines and in the use of different fuels.

Some of the success in reducing exhaust emission has been attained by modifying the design of combustion chambers of internal combustion engines. Additionally, the use of computerized control of ignition systems has helped to reduce the level of pollutants emitted. Another strategy that could be implemented without any technological changes would be to increase fuel standard requirements, thus improving the average miles per gallon. Because this would result in less gasoline consumption, there would also be less emission of pollutants.

Diesel engines have been used in automobiles for more than 20 years. These engines require a different fraction of crude oil (see Table 1 at the beginning of this essay) than gasoline, and they have been improved significantly since the initial highly polluting diesel vehicles. The diesel engine has the advantage of producing only small quantities of carbon monoxide and unburned hydrocarbons. It does, however, produce significant amounts of nitrogen oxides, soot (containing polynuclear aromatic hydrocarbons), and odor-causing compounds. Presently, the emission standards for diesel automobiles are more lenient than for those burning gasoline. More stringent standards were scheduled to be implemented in 2006 and 2009. Diesel automobiles yield higher fuel mileage than gasoline engines of a similar size; however, more oil must be refined in order to produce diesel fuel compared to gasoline. In the United States, about 3% of all new automobiles have diesel engines, whereas in Europe, about 40% of the new automobiles sold are diesel. Biodiesel, which is a chemically altered vegetable oil that can even be produced in one's, garage using discarded cooking oil, can also be used in today's diesel engines and results in fewer harmful pollutants compared to regular diesel fuel. However, the mileage is slightly less, and it would not be possible to produce enough of this fuel for more than a small percentage of the cars on the road today.

Another possible fuel is methanol, which is produced from natural gas, coal, or biomass. Studies indicate that the amount of principal pollutants in automobiles is lowered when methanol is used instead of gasoline, but methanol is more corrosive and extensive engine modifications must be made. Other fuels that show promise are hydrogen, methane (natural gas), and propane; however, storage and delivery of these fuels, which are gases at room temperature, are more difficult and other significant technical problems also must be solved.

It is now clear that the most significant problem related to the combustion of fossil fuels is likely global warming, due to the increasing concentration of carbon dioxide in the atmosphere. Most of the radiant energy from the sun passes through the earth's atmosphere and reaches the earth, where much of this energy is converted into heat. Most of this heat in the form of infrared radiation is radiated away from the earth. Carbon dioxide and other atmospheric compounds, such as, water and methane can absorb this infrared radiation. When this heat energy is released by these molecules, it radiates in all directions—including back toward the earth. The retention of some of this heat is referred to as the **greenhouse effect**. The greenhouse effect is extremely valuable in terms of keeping the temperature of the earth in a range where life can exist. However, the temperature of the earth has been increasing during the past century, likely because of the increase in the amount of carbon dioxide in the atmosphere. Most of this additional carbon dioxide is produced by the combustion of fossil fuels. There is much concern that if the temperature of the earth continues to increase, the implication for life on the earth could be devastating. The sea levels might rise high enough to force millions of people living in coastal areas to migrate, and the negative effect on farming and fresh water sources could have a serious impact on people in all parts of the world.

Hybrid-electric automobiles have become an attractive alternative to the standard automobile in the United States. Hybrid cars combine a small fuel-efficient combustion engine with an electric motor and battery. The electric motor can assist the gas engine when more power is needed, and the battery is recharged while the car is slowing down or coasting. This results in greater fuel efficiency, as well as a drastic reduction in the amount of carbon dioxide released and smog-forming pollutants. Even greater fuel efficiency is possible with diesel hybrid cars that are now being developed. In the past few years, there has been increasing interest in the development of electric

plug-in cars that run off a large storage battery. These batteries can be charged at night when the overall electrical demand on the grid is low, and the cars can be driven about 30−120 miles on a charge, depending on the type of battery. If the electricity were generated by a renewable energy source such as solar, wind, or geothermal, then the contribution to the greenhouse effect by driving electric cars would be minimal.

Another recent promising development is the use of fuel cells that can produce electrical energy from hydrogen. This electrical energy is then used by an electric motor to propel the automobile. Although there are many proponents of hydrogen fuel cells who believe that this technology can play a major role in reducing our dependency on fossil fuels, significant technological challenges must first be overcome. The task of developing a hydrogen energy infrastructure would also be costly. Furthermore, most of the hydrogen now produced comes from natural gas or coal, and this process also requires energy.

It should be clear that the use of fossil fuels, poses many challenges and opportunities. How we utilize fossil fuels will in the next few decades, and chemistry will play a significant role change.

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Gas-Chromatographic Analysis of Gasolines

Gasoline

Gas chromatography

In this experiment, you will analyze samples of gasoline by gas chromatography. From your analysis, you should learn something about the composition of these fuels. Although all gasolines are compounded from the same basic hydrocarbon components, each company blends these components in different proportions to obtain a gasoline with properties similar to those of competing brands.

Sometimes the composition of the gasoline may vary, depending on the composition of the crude petroleum from which the gasoline was derived. Frequently, refineries vary the composition of gasoline in response to differences in climate, seasonal changes, or environmental concerns. In the winter or in cold climates, the relative proportion of butane and pentane isomers is increased to improve the volatility of the fuel. This increased volatility permits easier starting. In the summer or in warm climates, the relative proportion of these volatile hydrocarbons is reduced. The decreased volatility reduces the possibility of forming a vapor lock. Occasionally, differences in composition can be detected by examining the gas chromatograms of a particular gasoline over several months. In this experiment, we will not try to detect such small differences.

There are different octane rating requirements for "regular" and "premium" gasolines. You may be able to observe differences in the composition of these two types of fuels. You should pay particular attention to increases in the proportions of those hydrocarbons that raise octane ratings in the premium fuels.

In some areas of the country, manufacturers are required from November to February to control the amounts of carbon monoxide produced when the gasoline burns. To do this, they add oxygenates, such as ethanol or methyl *tert*-butyl ether (MTBE), to the gasoline. You should try to observe the presence of these oxygenates, which may be observed in gasolines produced in carbon monoxide-containment areas. Because MTBE has been banned or partially banned in most states (see previous essay), it is unlikely that you will observe MTBE.

The class will analyze samples of regular unleaded and premium unleaded gasolines. If available, the class will analyze oxygenated fuels. If different brands are analyzed, equivalent grades from the different companies should be compared.

Discount service stations usually buy their gasoline from one of the large petroleum-refining companies. If you analyze gasoline from a discount service station, you may find it interesting to compare that gasoline with an equivalent grade from a major supplier, noting particularly the similarities.

R E Q U I R E D   R E A D I N G

New:	Technique 22	Gas Chromatography
	Essay	Petroleum and Fossil Fuels

SPECIAL INSTRUCTIONS

Your instructor may want each student in the class to obtain a sample of gasoline from a service station. The instructor will compile a list of the different gasoline companies represented in the nearby area. Each student will then be assigned to collect a sample from a different company. You should collect the gasoline sample in a labeled screw-cap jar. An easy way to collect a gasoline sample for this experiment is to drain the excess gasoline from the nozzle and hose into the jar after the gasoline tank of a car has been filled. The collection of gasoline in this manner must be done *immediately after* the gas pump has been used. If not, the volatile components of the gasoline may evaporate, thus changing the composition of the gasoline. Only a small sample (a few *milli*liters) is required because the gas-chromatographic analysis requires no more than a few *micro*liters (μL) of material. Be certain to close the cap of the sample jar tightly to prevent the selective evaporation of the most volatile components. The label on the jar should list the brand of gasoline and the grade (unleaded regular, unleaded premium, oxygenated unleaded, etc.). Alternatively, your instructor may supply samples for you.

> **CAUTION**
>
> **Gasoline contains many highly volatile and flammable components. Do not breathe the vapors, and do not use open flames near gasoline.**

This experiment may be assigned along with another short one because it requires only a few minutes of each student's time to carry out the actual gas chromatography. For this experiment to be conducted as efficiently as possible, you may be asked to schedule an appointment for using the gas chromatograph.

SUGGESTED WASTE DISPOSAL

Dispose of all gasoline samples in the container designated for nonhalogenated wastes.

NOTES TO THE INSTRUCTOR

You need to adjust your gas chromatograph to the proper conditions for the analysis. We recommend that you prepare and analyze the reference mixture listed in the Procedure section. Most chromatographs will be able to separate this mixture cleanly with the possible exception of the xylenes. One possible set of conditions for a Gow-Mac model 69-350 chromatograph is the following; column temperature, 110−115°C; injection port temperature, 110–115°C; carrier gas flow rate, 40–50 mL/min; column length, approximately 12 ft. The column should be packed with a nonpolar stationary phase similar to silicone oil (SE-30) on Chromosorb W or with some other stationary phase that separates components principally according to boiling point.

The chromatograms shown in this experiment were obtained on a Hewlett Packard model 5890 gas chromatograph. A 30-meter, DB 5 capillary column (0.32 mm, with 0.25 micron film) was used. A temperature program was run starting at 5°C

and ramping to 105°C. Each run took about 8 minutes. A flame-ionization detector was used. The conditions are given in the Instructor's Manual. Superior separations are obtained using capillary columns, which are recommended. Even better results are obtained with longer columns.

PROCEDURE

Reference Mixture. First, analyze a standard mixture that includes pentane, hexane (or hexanes), benzene, heptane, toluene, and xylenes (a mixture of *meta*, *para*, and *ortho* isomers). Inject a 0.5-μL sample or an alternative sample size as indicated by your instructor into the gas chromatograph. Measure the retention time of each component in the reference mixture on your chromatogram (see Technique 22, Section 22.7). The previously listed compounds elute in the order given (pentane first and xylenes last). Compare your chromatogram to the one posted near the gas chromatograph or the one reproduced in this experiment.

Your instructor or a laboratory assistant may prefer to perform the sample injections. The special microliter syringes used in the experiment are delicate and expensive. If you are performing the injections yourself, be sure to obtain instruction beforehand.

Oxygenated Fuel Reference Mixture. Oxygenated compounds are added to gasolines in carbon monoxide-containment areas during November through February. Currently, ethanol is used most commonly. It is much less likely that methyl *tert*-butyl ether will be found. Your instructor may have available a reference mixture that includes all the previously listed compounds and either ethanol or methyl *tert*-butyl ether. Again, you need to inject a sample of this mixture and analyze the chromatogram to obtain the retention times for each component in this mixture.

Gasoline Samples. Inject a sample of a regular unleaded, premium unleaded, or oxygenated gasoline into the gas chromatograph and wait for the gas chromatogram to be recorded. Compare the chromatogram to the reference mixture. Determine the retention times for the major components and identify as many of the components as possible. For comparison, gas chromatograms of a premium unleaded gasoline and the reference mixture are shown below. On the list of the major components in gasolines, notice that the oxygenate methyl *tert*-butyl ether appears in the C_6 region. Does your oxygenated fuel show this component? See if you can notice a difference between regular and premium unleaded gasolines.

Analysis. Be certain to compare carefully the retention times of the components in each fuel sample with the standards in the reference mixture. Retention times of compounds vary with the conditions under which they are determined. It is best to analyze the reference mixture and each of the gasoline samples in succession to reduce the variations in retention times that may occur over time. Compare the gas chromatograms with those of students who have analyzed gasolines from other dealers.

Report. The report to the instructor should include the actual gas chromatograms, as well as an identification of as many of the components in each chromatogram as possible.

Major components in gasolines*

C_4 Compounds	Isobutane
	Butane
C_5 Compounds	Isopentane
	Pentane
C_6 Compounds and	2,3-Dimethylbutane
oxygenates	2-Methylpentane
	3-Methylpentane
	Hexane
	Methyl *tert*-butyl ether (oxygenate)
C_7 Compounds and	2,4-Dimethylpentane
aromatics (benzene)	Benzene (C_6H_6)
	2-Methylhexane
	3-Methylhexane
	Heptane
C_8 Compounds and	2,2,4-Trimethylpentane (isooctane)
aromatics (toluene,	2,5-Dimethylhexane
ethylbenzene, and xylenes)	2,4-Dimethylhexane
	2,3,4-Trimethylpentane
	2,3-Dimethylhexane
	Toluene (C_7H_8)
	Ethylbenzene (C_8H_{10})
	m-, *p*-, *o*-Xylenes (C_8H_{10})
C_9 Aromatic compounds	1-Ethyl-3-methylbenzene
	1,3,5-Trimethylbenzene
	1,2,4-Trimethylbenzene
	1,2,3-Trimethylbenzene

*Approximate order of elution.
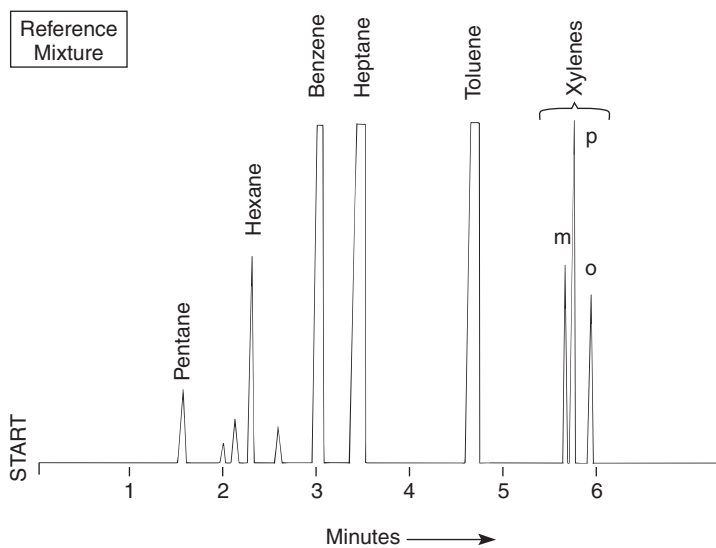
Gas chromatogram of the reference mixture.
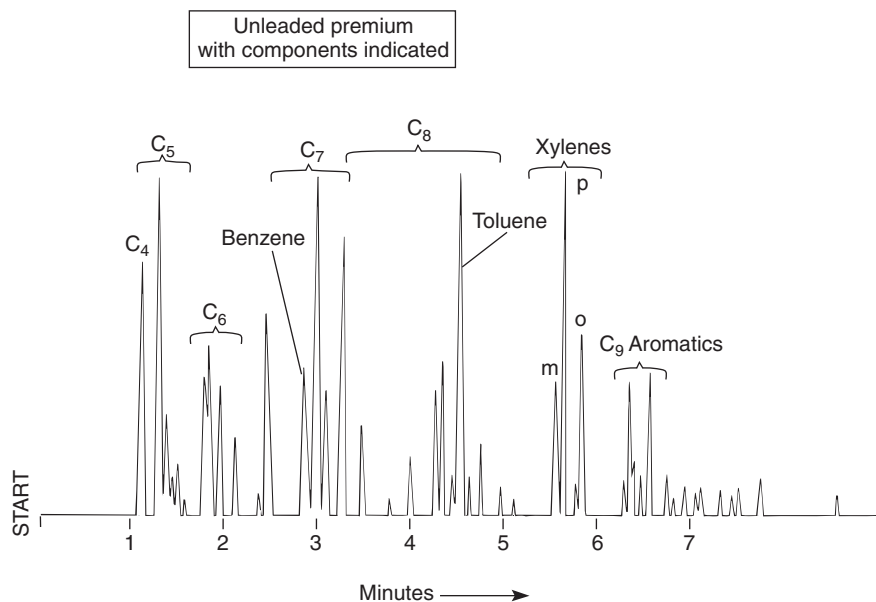
Gas chromatogram of a premium unleaded gasoline.

QUESTIONS

1. If you had a mixture of benzene, toluene, and *m*-xylene, what would be the expected order of retention times? Explain.

2. If you were a forensic chemist working for the police department and the fire marshal brought you a sample of gasoline found at the scene of an arson attempt, could you identify the service station at which the arsonist purchased the gasoline? Explain.

3. How could you use infrared spectroscopy to detect the presence of ethanol in an oxygenated fuel?

ESSAY

Biofuels

In recent years there has been an increasing interest in **biofuels,** fuels that are produced from biological materials such as corn or vegetable oil. These sources of biofuels are considered to be renewable because they can be produced in relatively short time. On the other hand, **fossil fuels** are formed by the slow decay of marine animal and plant organisms that lived millions of years ago. Fossil fuels, which include petroleum, natural gas, and coal, are considered to be nonrenewable.

The increased emphasis on biofuels is due primarily to the increasing cost and demand for liquid fuels such as gasoline and diesel, and our desire to be less dependent on foreign oil. In addition to increased demand, the higher cost of petroleum may be related to the peak oil theory, discussed in the essay on petroleum and fossil fuels. According to this theory, the amount of petroleum in the earth is finite;

and at some point, the total amount of petroleum produced each year will begin to decrease. Many experts believe that we have either already reached the peak in oil production, or we will reach it within a few years.

In addition to biofuels, the use of many other types of alternative energy sources has been increasing in recent years. Alternative energy sources such as solar, wind, and geothermal are used primarily to produce electricity, and they cannot replace liquid fuels such as gasoline and diesel. As long as we continue to depend on automobiles and other vehicles with the current engine technology, we will need to produce more liquid fuels. Because of this, the demand to produce more biofuels is very great. In this essay, we will focus on the biofuels ethanol and biodiesel.

Ethanol

The knowledge of how to produce ethanol from grains has been around for many centuries (see the essay "Ethanol and Fermentation Chemistry" that precedes Experiment 16). Until recently, most of the ethanol produced by fermentation was used mainly in alcoholic beverages. In 1978, Congress passed the National Energy Act, which encouraged the use of fuels such as Gasohol, a blend of gasoline with at least 10% ethanol produced from renewable resources. Ethanol can be produced by the fermentation of sugars such as sucrose, which is found in sugar cane or beets. In this country, it is more common to use corn kernels as the feedstock to produce Ethanol. Corn contains starch, a polymer of glucose that must first be broken down into glucose units. This is usually accomplished by adding a mixture of enzymes that catalyze the hydrolysis of starch into glucose. Other enzymes are then added to promote the fermentation of glucose into ethanol:

$$C_6H_{12}O_6 \xrightarrow{\text{Enzymes}} 2CH_3CH_2OH + 2CO_2$$

Glucose   **Ethanol**
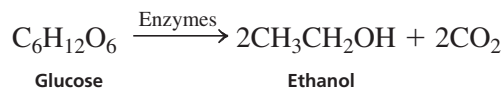
After fermentation, fractional distillation is used to separate the Ethanol from the fermentation mixture. In Experiment 26, you will produce and isolate ethanol from frozen corn kernels.

The use of corn to produce ethanol as a biofuels has been strongly encouraged in the United States. Government subsidies have resulted in a higher production of corn in the Midwest, and many new ethanol refineries have also been built. However, it is now clear that use of Ethanol as a biofuel has some significant drawbacks. First, as more corn is planted and used for fuel production, less corn and other crops are available as a source of food. This has led to food shortages and higher prices, which is especially hard on people who are already struggling to get enough food. Second, it now appears that the total amount of energy expended to grow corn and to produce ethanol is almost as much as the amount of energy released by burning the ethanol. Third, recent studies have indicated that growing corn to produce ethanol for use as a fuel results in the production of more greenhouse gases than the use of similar amounts of fossil fuels. Therefore, the use of corn ethanol may actually increase global warming compared to fossil fuels. In spite of these drawbacks, given that so much investment in corn ethanol has already been made, it is still likely that corn will continue to be a source of ethanol in this country for some time to come.

One alternative to corn ethanol is **cellulosic ethanol**. Sources of cellulose that can be used to produce ethanol include fast-growing grasses such as switchgrass, agricultural waste such as corn stalks, and waste wood from the milling of lumber.

Like starch, cellulose is a polymer of glucose, but the structure is slightly different than starch and it is much more difficult to break down. Cellulose can be broken down by acid or base treatment at high temperature and by hydrolysis reactions with enzymes. Once the cellulose is broken down into glucose, it can be fermented to produce ethanol, just like with corn starch. Cellulosic ethanol addresses some of the drawbacks for corn ethanol mentioned in the previous paragraph. Many of the sources of cellulosic ethanol can be grown on non-arable land that would not normally be used to produce food. It also appears that the overall energy production is more favorable than corn ethanol. Finally, the contribution to greenhouse gases is not so great. However, because of the difficulty of breaking down cellulose, there is not yet a commercial plant in operation that produces cellulosic ethanol.

Evaluating biofuels in terms of contribution to global warming is difficult to do. Initially, it was believed that all biofuels produced less greenhouse gases than fossil fuels. This is because carbon dioxide is absorbed by the plants as they grow, which helps to offset the carbon dioxide that is released when the biofuels is burned. However, recent studies suggest that the situation is more complicated. In order to grow the crops required to make biofuels and to replace the food crops that are now used to make biofuels, it is often necessary to destroy forestland. Forests are much more effective than farmland at absorbing carbon dioxide from the air. When the loss of forests is also factored in, it appears that ethanol production from corn or even other sources such as switchgrass may contribute more to the greenhouse effect than burning fossil fuels.

Another option for producing ethanol exists that may have advantages over both of the methods described above. This newer option involves the conversion of carbon-containing matter into **syngas**. Almost any material that contains carbon, such as municipal waste, old tires, or agricultural waste, can be used. The feedstock is gasified into a mixture of carbon monoxide and hydrogen, which is known as syngas. Syngas can then be catalytically converted into ethanol. This process is much more efficient energetically than the methods described above and its also created less greenhouse gases, especially when the feedstock is some kind of waste material. Furthermore, these feedstocks do not compete with food crops.

Biodiesel

Another biofuel that is widely used in the United States is **biodiesel.** Biodiesel is produced from fats or oils in a based-catalyzed transesterification reaction:

Fat or oil   Methanol   Biodiesel   Glycerol
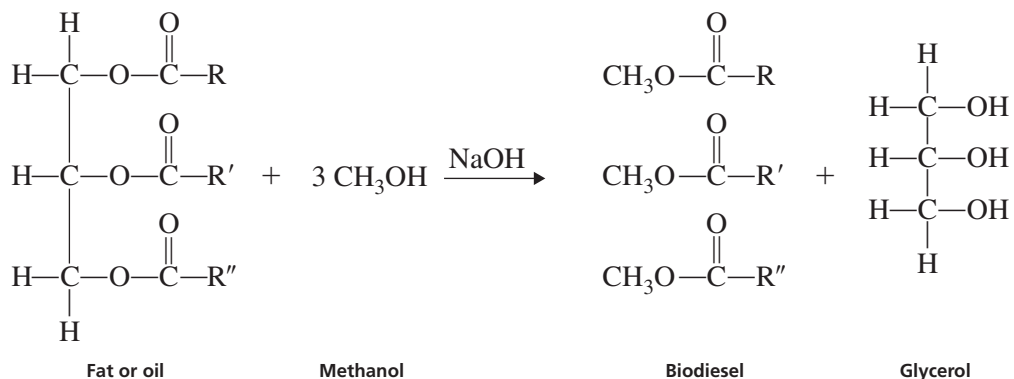
Because the R groups may have different numbers of carbons and double bonds, biodiesel is a mixture of different molecules, all of which are methyl esters of fatty acids. Most of the R groups have between 12–18 carbons arranged in straight chains. Any kind of vegetable oil can be used to make biodiesel, but the most common ones used are the oils from soybean, canola, and palm. In Experiment 25, biodiesel is made from coconut oil and other vegetable oils.

Biodiesel has similar properties to the diesel fuel that is produced from petroleum, and it can be burned in any vehicle with a diesel engine or in furnaces that burn diesel fuel. It should be noted that vegetable oil can also be burned as a fuel, but because the viscosity of vegetable oil is somewhat greater than diesel fuel, engines must be modified in order to burn vegetable oil.

How does biodiesel compare with ethanol? Like corn ethanol, growing the vegetables required to produce the oil feedstock results in diverting farmland from growing food to producing fuels. In fact, this is more of a problem with biodiesel because more land is required to produce an equivalent amount of fuel compared to corn ethanol. The net energy produced by biodiesel is greater than for corn ethanol, but less than for cellulosic ethanol. Finally, it appears that the production of biodiesel, like ethanol, produces more greenhouse gases than fossil fuels, again because forested land must be destroyed in order to grow the vegetables required to produce biodiesel.

Some alternative approaches for making biodiesel exist that could address some of these issues. Algae can produce oils that can be used to make biodiesel. Algae can be grown in ponds or even waste water and does not require the use of farmland. The algae oil can be converted into biodiesel in the same way that vegetable oil is converted. Recently, a different chemical method for making biodiesel from vegetable oil has been developed. This method utilizes a sulfated zirconia catalyst that is placed in a column, similar to column chromatography. As the mixture of oil and alcohol is passed through the column at high temperature and pressure, biodiesel is produced and elutes from the bottom of the column. The process is much more efficient than the current methods used to produce biodiesel. An interesting side story related to this process is that the original idea for this method was based on the work that a student completed for his undergraduate research project in chemistry!

Because of the importance of liquid fuels in this country, fuels other than ethanol and biodiesel are also being researched. There is also considerable interest in the use of plug-in electrical cars that would not require any liquid fuels. If the electrical energy used to charge the batteries in electric cars comes from renewable sources of electricity such as wind, solar, or geothermal, then the need for liquid fuels could be greatly decreased.

In 2007, the United States consumed a combined total of about 7.5 billion gallons of ethanol and biodiesel. By comparison, about 140 billion gallons of gasoline and 40 billion gallons of diesel fuel were consumed. Therefore, biofuels presently represent a small percentage of our total fuel consumption. Recently, Congress passed a bill requiring 36 billion gallons of biofuel to be produced yearly by 2022. Even if this goal is met, it is likely that we will still primarily rely on both fossil fuels and biofuel for the foreseeable future.

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25   EXPERIMENT 25

Biodiesel[1]

In this experiment, you will prepare biodiesel from a vegetable oil in a base-catalyzed transesterification reaction:

| Fat or oil | Methyl alcohol | Biodiesel | Glycerol |
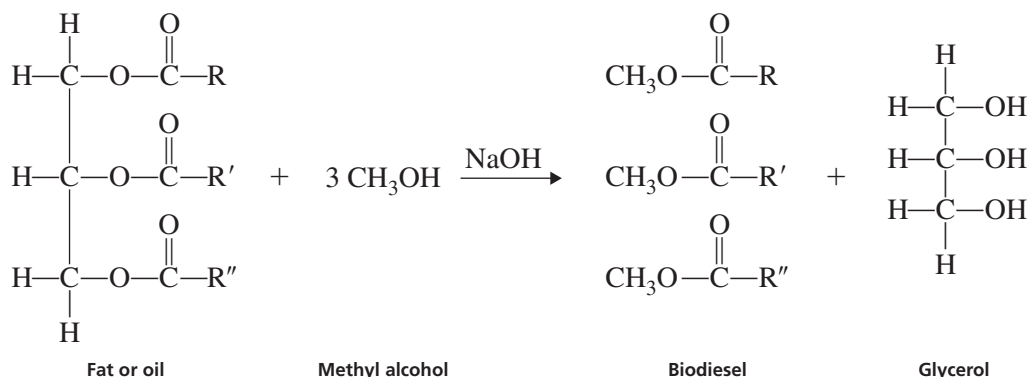
The first step in the mechanism for this synthesis is an acid-base reaction between sodium hydroxide and methyl alcohol:

$$NaOH \ + \ CH_3OH \longrightarrow Na^+ \ OCH_3^- \ + \ H_2O$$
Sodium methoxide
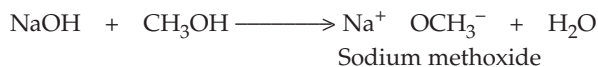
Methoxide ion is a strong nucleophile that now attacks the three carbonyl groups in the vegetable oil molecule. In the last step, glycerol and biodiesel are produced.

[1]This experiment is based on a similar experiment developed by John Thompson, Lane Community College, Eugene, Oregon. It is posted on Greener Educational Materials (GEMs), an interactive database on green chemistry that is found on the University of Oregon green chemistry website (http://greenchem.uoregon.edu/).

Because the R groups may have different numbers of carbons and they may be saturated (no double bonds) or may have one or two double bonds, biodiesel is a mixture of different molecules—all of which are methyl esters of fatty acids that made up the original vegetable oil. Most of the R groups have between 10–18 carbons that are arranged in straight chains.

When the reaction is complete, the mixture is cooled and then centrifuged in order to separate the layers more completely. Since some unreacted methyl alcohol will be dissolved in the biodiesel layer, this layer is heated in an open container to remove all the methyl alcohol. The remaining liquid should be pure biodiesel.

When biodiesel is burned as a fuel, the following reaction occurs:

$$CH_3O\text{-}C\text{-}(CH_2)_{15}CH_3 + 26\ O_2 \longrightarrow 18\ CO_2 + 18\ H_2O_{15} + energy$$

with O double-bonded (‖) to the carbon.

One possible
biodiesel molecule
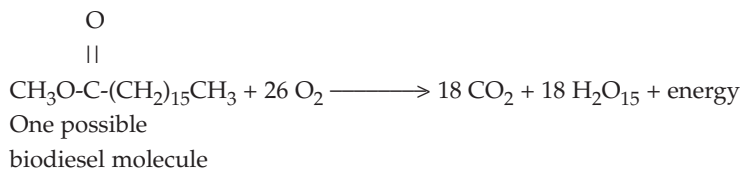
Burning biodiesel will produce a specific amount of energy, which can be measured using a bomb calorimeter. By combusting a specific weight of your biodiesel and measuring the temperature increase of the calorimeter, you can calculate the heat of combustion of biodiesel.

In Experiment 25A, coconut oil is converted into biodiesel, and other oils are converted into biodiesel in Experiment 25B. In Experiment 25C, the biodiesel is analyzed by infrared spectroscopy, NMR spectroscopy, and gas chromatography-mass spectrometry (GC-MS). The heat of combustion of biodiesel can also be determined in Experiment 25C.

REQUIRED READING

New: Technique 22   Gas Chromatography, Section 22.13

Technique 25   Infrared Spectroscopy

Technique 26   Nuclear Magnetic Resonance Spectroscopy

Essays: Biofuels

Fats and Oils

SUGGESTED WASTE DISPOSAL

Discard the glycerol layer and leftover biodiesel into the container for the disposal of nonhalogenated organic waste.

NOTES TO THE INSTRUCTOR

We have found this experiment to be a good way to introduce infrared spectroscopy, NMR spectroscopy, and GC-MS. It is helpful to place the bottle containing the coconut oil into a beaker of warm water to keep the oil in the liquid state.

25A	**E X P E R I M E N T 2 5 A**

Biodiesel from Coconut Oil

P R O C E D U R E

Prepare a warm water bath in 250-mL beaker. Use about 50 mL of water and heat the water to 55-60°C on a hot plate. (Do not let the temperature exceed 60° during the reaction on a hot plate period.) Weigh a 25-mL round-bottom flask. Add 10 mL of coconut oil to the flask and reweigh to get the weight of the oil. (Note: The coconut oil must be heated slightly in order to convert it to a liquid that can be measured in a graduated cylinder. It may also be advisable to warm the graduated cylinder.) Transfer 2.0 mL of sodium hydroxide dissolved in methyl alcohol solution to the flask.[2] (Note: Swirl the sodium hydroxide mixture before taking the 2-mL portion to make sure that the mixture is homogenous.) Place a magnetic stir bar in the round-bottom flask and attach the flask to a water condenser. (You do not need to run water through the water-condenser.) Clamp the condenser so that the round-bottom flask is close to the bottom of the beaker. Turn on the magnetic stirrer to the highest level possible (this may not be the highest setting on the stirrer if the stir bar does not spin smoothly at high speeds). Stir for 30 minutes.

Transfer all of the liquid in the flask to a 15-mL plastic centrifuge tube with a cap and let it set for about 15 minutes. The mixture should separate into two layers: the larger top layer is biodiesel and the lower layer is mainly glycerol. To separate the layers more completely, place the tube in a centrifuge and spin for about 5 minutes (don't forget to counterbalance the centrifuge). If the layers have not separated completely after centrifugation, continue to centrifuge for another 5–10 minutes at a higher speed.

Using a Pasteur pipet, carefully remove the top layer of biodiesel and transfer this layer to a preweighed 50-mL beaker. You should leave behind a little of the biodiesel layer to make sure you don't contaminate it with the bottom layer.

Place the beaker on a hot plate and insert a thermometer into the biodiesel, holding the thermometer in place with a clamp. Heat the biodiesel to about 70°C for 15–20 minutes to remove all the methyl alcohol. When the biodiesel has cooled to room temperature, weigh the beaker and liquid and calculate the weight of biodiesel produced. Record the appearance of the biodiesel.

To analyze your biodiesel, proceed to Experiment 25C.

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[2]Note to instructor: Dry sodium hydroxide pellets overnight in an oven at 100°C. After grinding the dried sodium hydroxide with a mortar and pestle, add 0.875 g of this to an Erlenmeyer flask containing 50 mL of highly pure methanol. Place a magnetic stir bar in the flask and stir until all of the sodium hydroxide has dissolved. The mixture will be slightly cloudy.

25B   EXPERIMENT 25B

Biodiesel from Other Oils

Follow the procedure in Experiment 25A (Biodiesel from Coconut Oil), except use a different oil than coconut. Any of the oils listed at the bottom of Table 2 in the essay "Fats and Oils" than precedes Experiment 23 can be used. It will not be necessary to heat the oil when measuring out the 10 mL of oil, as all of these oils are liquids at room temperature.

To analyze your biodiesel, proceed to Experiment 25C.

25C   EXPERIMENT 25C

Analysis of Biodiesel

Spectroscopy.   Obtain an infrared spectrum using salt plates (see Technique 25, Section 25.2). Determine the proton NMR spectrum using 3–4 drops of your biodiesel in 0.7 mL of deuterated chloroform. Since biodiesel consists of a mixture of different molecules, it is not helpful to perform an integration of the area under the peaks. Compare the NMR spectrum of biodiesel to the spectrum of vegetable oil shown here. Finally, analyze your sample using gas chromatography-mass spectrometry (GC-MS). Your instructor will provide you with instructions on how to do this.

Calorimetry (optional).   Determine the heat of combustion (in kjoules/gram) of your biodiesel. Your instructor will provide instructions on how to use the bomb calorimeter and how to perform the calculations.

REPORT

Calculate the percent yield of biodiesel. This is difficult to do in the normal way based on moles because the vegetable oil and biodiesel molecules have variable composition. Therefore, you can base this calculation on the weight of oil used and the weight of biodiesel produced.

Analyze the infrared spectrum by identifying the principal absorption bands. Look for peaks in the spectrum that may indicate possible contamination from methanol, glycerol, or free fatty acids. Indicate any impurities found in your biodiesel bases on the infrared spectrum.

Analyze the NMR spectrum by comparing it to the NMR spectrum of vegetable oil with some of the signals labeled that is shown below. Look for evidence in the NMR spectrum for contamination by methanol, free fatty acids, or the original vegetable oil. Indicate any impurities found based on the NMR spectrum.

The library search contained in the software for the GC-MS instrument will give you a list of components detected in your sample, as well as the retention time and relative area (percentage) for each component. The results will also list possible substances that the computer has tried to match against the mass spectrum of each component. This list—often called a "hit list"—will include the name of each possible compound, its Chemical Abstracts Registry number (CAS number), and a "quality" ("confidence") measure expressed as a percentage. The "quality" parameter estimates how closely the mass spectrum of the substance on the "hit list" fits the observed spectrum of that component in the gas chromatogram. The components that you identify from the GC-MS will be the methyl esters of the fatty acids that were initially part of the vegetable oil molecule. From the GC-MS data, you can determine the fatty acid composition (by percentages) in the original vegetable oil. Make a table of the main fatty acid components and the relative percentages. Compare this with the fatty acid composition given for this oil in Table 2 in the essay "Fats and Oils" that precedes Experiment 23. Is the fatty acid composition the same, and how do the relative percentages compare?

NMR spectrum of vegetable oil.
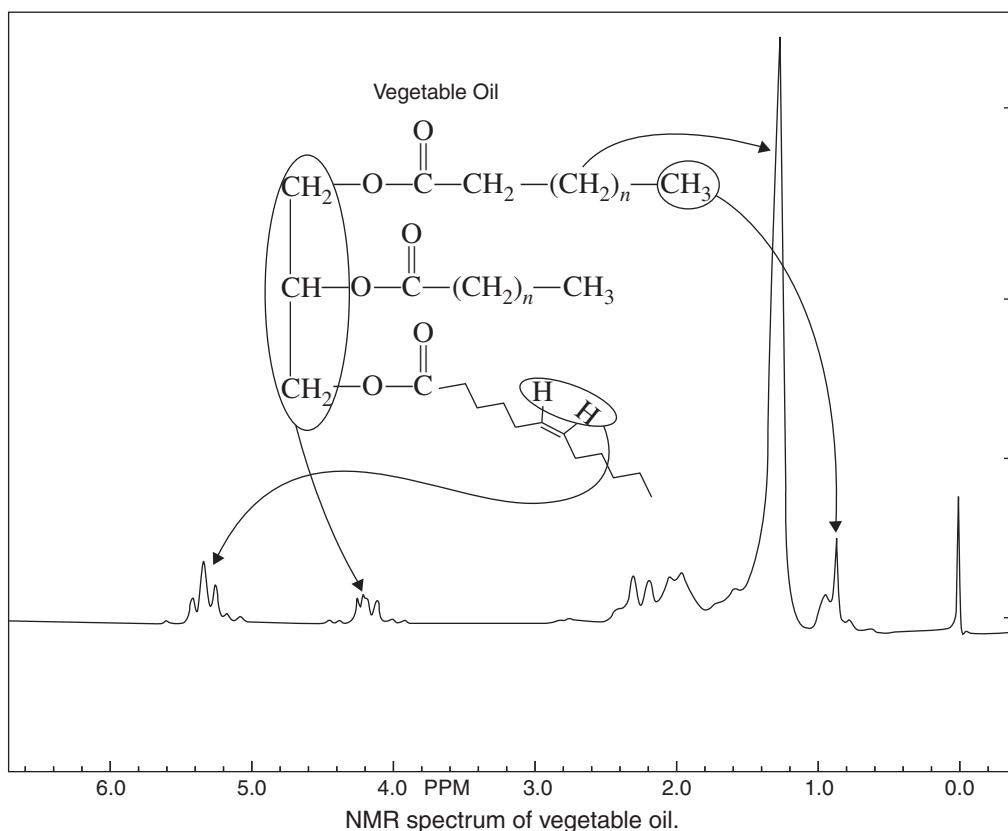
If you performed the experiment with the bomb calorimeter, list the data and calculate the heat of combustion for biodiesel in kj/g. The heat of combustion for heptane, a component of gasoline, is 45 kj/g. How do they compare? If you also determined the heat of combustion of ethanol in Experiment 26 (Ethanol from Corn), you should compare the heats of combustion for biodiesel and ethanol.

QUESTIONS

1. Write a complete reaction mechanism for this based-catalyzed transesterification reaction. Rather than starting with a complete oil molecule, give the mechanism for the reaction between the following ester and methanol in the presence of NaOH.

$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3 + CH_3OH \xrightarrow{\text{NaOH}} CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 + CH_3CH_2OH$$
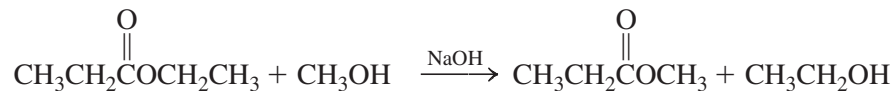
2. If you calculated the heat of combustion of biodiesel and ethanol using bomb calorimeter, answer the following questions:
    a. Compare the heat of combustion of biodiesel with heptane. Why does heptane have a larger heat of combustion? The heat of combustion of heptane is 45 kj/g. (*Hint:* In answering this question, it may be helpful to compare the molecular formulas of biodiesel and heptane).
    b. If you also determined the heat of combustion of ethanol, compare the heats of combustion of biodiesel and ethanol. Why does biodiesel have a larger heat of combustion than ethanol?

3. One argument for using biodiesel rather than gasoline is that the net amount of carbon dioxide released into the atmosphere from combusting biodiesel is sometimes claimed to be zero (or near zero). How can this argument be made, given that the combustion of biodiesel also releases carbon dioxide?

4. When the reaction for making biodiesel occurs, two layers are formed: biodiesel and glycerol. In which layer will most of each of the following substances be found? If a substance will be found to a large extent in both layers, you should indicate this.

$$CH_3OH \quad OCH_3^- \quad H_2O \quad Na^+ \quad OH^-$$

26   EXPERIMENT 26

Ethanol from Corn

Most of the ethanol that is used as a biofuel in this country is produced from corn. In this experiment, you will make ethanol from frozen corn kernels using a process similar to the method used in industry. The first step is to break down the corn starch into glucose molecules. This is accomplished with two enzymes, amylase and amyloglucosidase. Starch does not dissolve in water at lower temperatures, and it cannot be hydrolyzed by these enzymes unless it is dissolved. To dissolve the starch, it must be heated in water to 100°C. This causes the internal hydrogen bonds in starch to be broken, allowing water to be absorbed by the starch. When the mixture is cooled, starch remains in solution.

Starch is a polymer of D-glucose comprised of two different components, amylose and amylopectin. Amylose is a linear polymer of D-glucose connected by α (1→4) linkages. Amylopectin is a branched polymer of D-glucose with α (1→4) linkages, as in amylose, and α (1→6) linkages at the branches.
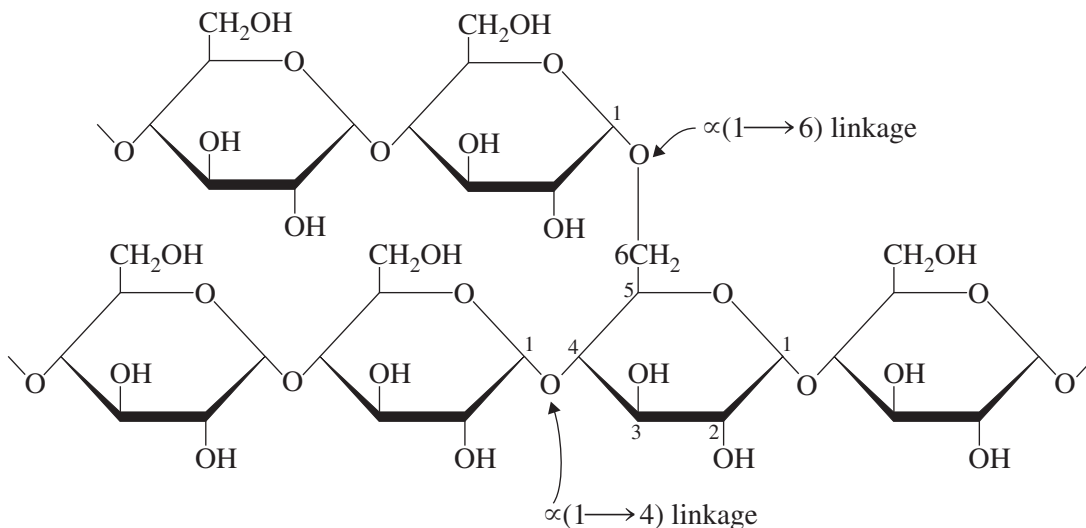
Amylase randomly hydrolyzes the α (1 $\longrightarrow$ 4) bonds to produce smaller fragments of starch. Amyloglucosidase can attack both 1 $\longrightarrow$ 4 and 1 $\longrightarrow$ 6 linkages, and it breaks off single glucose units on the end of the polymer. Over time, the combination of the two enzymes will completely break down starch into glucose.

Yeast, which is also added to the mixture, provides the enzymes that catalyze the fermentation of glucose into ethanol and carbon dioxide:

$$C_6H_{12}O_6 \longrightarrow 2\ CH_3CH_2OH + 2\ CO_2$$

When the fermentation is complete, the mixture is filtered to remove most of the solid residue. Using fractional distillation, ethanol is isolated from the mixture. It is necessary to add anti-foam agent to prevent excessive frothing during the distillation. Ethanol and water form an azeotropic mixture consisting of 95% ethanol and 5% water by weight, which is the most concentrated ethanol that can be obtained from fractional distillation of dilute ethanol–water mixtures.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	Technique 8	Filtration, Sections 8.3 and 8.4
	Technique 13	Physical Constants of Liquids, Part A. Boiling Points and Thermometer Correction
New:	Technique 13	Physical Constants of Liquids, Part B. Density
	*Technique 15	Fractional Distillation, Azeotropes
	Essays	Ethanol and Fermentation Chemistry Biofuels

SPECIAL INSTRUCTIONS

Start the fermentation at least one week before the period in which the ethanol will be isolated.

SUGGESTED WASTE DISPOSAL

Discard all aqueous solutions in the waste container marked for the disposal of aqueous waste.

NOTES TO THE INSTRUCTOR

During the fermentation period, it may be necessary to use an external heat source to maintain a temperature of 30–35°C. Place a lamp in the hood to act as a heat source. During the distillation, it is best to use a mercury thermometer in the distilling head so that the temperature can be monitored more accurately. Alternatively, the temperature can be monitored with a Vernier LabPro interface with a laptop computer and stainless-steel temperature probe. If you use the Vernier LabPro interface, you will need to give students instructions on how to use this.

PROCEDURE

Grind 150 g of corn (frozen corn that has been thawed) for several minutes in a mortar and pestle. Transfer the corn to a 500-mL Erlenmeyer flask and add 150 mL of water. The water can also be used to rinse the mortar so that all of the corn is transferred. Boil the mixture gently for 15 minutes, adding more water if the mixture becomes too dry. After letting the mixture cool until the temperature is about 55°C, add 50 mL of water, 15 mL of amylase solution,[1] and 15 mL of calcium acetate solution[2]. Mix thoroughly and let it stand for 10 minutes. Add 55 mL of buffer solution,[3] 15 mL of amyloglucosidase solution,[4] and 1.0 g of dried baker's yeast. Mix thoroughly and weigh the flask. Cover the flask opening with Saran wrap or other plastic wrap, using a rubber band to hold the plastic wrap firmly in place. Alternatively, you may set up the fermentation apparatus shown in Experiment 16. Allow the mixture to stand at about 30–35°C until fermentation is complete, as indicated by the cessation of gas evolution. Usually 4–7 days is required.

When fermentation is complete, weigh the flask and compare this to the weight before fermentation. The difference in weight corresponds to the amount of carbon dioxide produced during the fermentation. Pour this mixture through a 9-inch square of 4–5 layers of cheesecloth into a 250-mL beaker. Most of the corn residue should be caught by the cheesecloth. After most of the liquid has drained out of the cheesecloth, carefully squeeze the cheesecloth with your hands so that the remaining liquid is recovered. Some solid will remain, but this should not interfere with the distillation step.

Fractional Distillation.   Add 3 mL of antifoam emulsion[5] to the filtered liquid to prevent frothing during the distillation. Assemble the apparatus shown in Technique 15, Figure 15.2 using a 500-mL round-bottom flask as the distilling flask. It is helpful to use a three-neck flask so that the temperature of the liquid in the distilling flask can be monitored with a thermometer that is held in place with a thermometer adapter. Place the bulb of the thermometer below the surface of the liquid in the flask. Plug the third neck with a glass stopper. It is best to use a

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[1]Amylase solution: Mix 3 mL of stock solution (Bacterial amylase from Carolina Biological) with 97 mL water.
[2]Calcium acetate solution: Dissolve 0.5 g of calcium acetate in 100 mL water.
[3]Buffer solution: 3.75 g glacial acetic acid and 3.125 g sodium acetate in 250 mL water.
[4]Amyloglucosidase solution: Mix 3 mL of stock solution (amyloglucosidase from Carolina Biological) with 97 mL water.
[5]Make a 1/10 dilution of Antifoam B silicon emulsion (from JT Baker) in water.

mercury thermometer in the distilling head so that the distillation temperature can be monitored more accurately (see Technique 13, Section 13.4). The bulb of the thermometer must be placed below the sidearm, or it will not read the temperature correctly. If you use a temperature probe with the Vernier LabPro interface, the bottom of the temperature probe must be placed below the sidearm (see Technique 13, Section 13.5). Insulate the distilling head by covering it with a layer of cotton held in place with aluminum foil. Use a pre weighed 25-mL round-bottom flask as the receiving flask and a heating mantle for the heat source. Pack the fractionating column (condenser with the larger inner diameter) uniformly with 2 g of stainless-steel sponge (see Apparatus section in Experiment 6).

CAUTION

You should wear heavy cotton gloves when handling the stainless-steel sponge. The edges are very sharp and can easily cut into the skin.

It is important to distill the liquid **slowly** through the fractionating column to get the best possible separation. This can be done by carefully following these instructions: Distillation will begin when the temperature of the liquid in the distilling flask is about 85–90°C. When the liquid begins boiling, it is best to turn the heat down immediately and then gradually raise it so that the heat setting required to maintain boiling is at the lowest possible setting. If you are using a temperature probe with the Vernier LabPro interface, you will need to hit the "Start Collecting" button on the screen and the temperature will be monitored by the computer. As ethanol moves up the distillation column, it will not wet the stainless-steel sponge and you will not be able to see the ethanol. After all of the ethanol has begun moving up the column, water will begin to enter the column. Since water will wet the stainless-steel sponge, you will be able to see the water gradually moving up the column. To get a good separation, you should control the temperature in the distilling flask so that it takes about 10–15 minutes for the water to move up the column. Once ethanol reaches the top of the column, the temperature in the distillation head will increase to about 78°C and then rise gradually until the ethanol fraction is distilled. Collect the fraction boiling between 78 and 84°C, and discard the residue in the distillation flask. You should collect about 2–4 mL of distillate. The distillation should then be interrupted by removing the apparatus from the heat source.

Analysis of Distillate. Determine the total weight of the distillate. Determine the approximate density of the distillate using the method given in the Analysis of Distillation section in Experiment 16. Using the table in Experiment 16, determine the percentage composition by weight of the ethanol in your distillate from the density of your sample. The extent of purification of the ethanol is limited because ethanol and water form a constant-boiling mixture, an azeotrope, with a composition of 95% ethanol and 5% water. Submit the ethanol to the instructor in a labeled vial.

Calorimetry (optional). Determine the heat of combustion (in kjoules/gram) of your biodiesel. Your instructor will provide instructions on how to use the bomb calorimeter and how to perform the calculations.

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Maslowsky, E. Ethanol from Corn: One Route to Gasohol. *J. Chem. Educ.* **1983,** *60,* 752.

QUESTIONS

1. Using the weight of carbon dioxide that was produced during the fermentation, calculate the weight of ethanol that should have been produced (see the balanced equation given earlier in the introduction to this overall experiment on). Based on this weight, calculate the percent recovery of ethanol that you obtained from the fractional distillation. To do this calculation, you will also need the weight of the distillate and the percentage composition of ethanol by weight that you determined from the density determination.

2. If you also determined the heat of combustion of biodiesel in Experiment 25 (Biodiesel), you should compare the heats of combustion for biodiesel and ethanol. Why does biodiesel have a larger heat of combustion than ethanol?

ESSAY

Green Chemistry

The economic prosperity of the United States demands that it continue to have a robust chemical industry. In this age of environmental consciousness, however, we can no longer afford to allow the type of industry that has been characteristic of past practices to continue operating as it always has. There is a real need to develop an environmentally benign, or "green," technology. Chemists must not only create new products, but also design the chemical syntheses in a way that carefully considers their environmental ramifications.

Beginning with the first Earth Day celebration in 1970, scientists and the general public began to understand that the earth is a closed system in which the consumption of resources and indiscriminate disposal of waste materials are certain to bring about profound and long-lasting effects on the worldwide environment. Over the past decade, interest has begun to grow in an initiative known as *green chemistry*.

Green Chemistry may be defined as the invention, design, and application of chemical products and processes to reduce or eliminate the use and generation of hazardous substances. Practitioners of green chemistry strive to protect the environment by cleaning up toxic waste sites and by inventing new chemical methods that do not pollute and that minimize the consumption of energy and natural resources. Guidelines for developing green chemistry technologies are summarized in the "Twelve Principles of Green Chemistry" shown in the table.

THE TWELVE PRINCIPLES OF GREEN CHEMISTRY

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary whenever possible and innocuous when used.

6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Unnecessary privatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Chemical products should be designed so that at end of their function they do not persist in the environment and do break down into innocuous degradation products.

11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control before the formation of hazardous substances.

12. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Source: P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice.* New York: Oxford University Press, 1998. Reprinted by permission of the publisher.

The green chemistry program was begun shortly after the passage of the Pollution Prevention Act of 1990 and is the central focus of the Environmental Prevention Agency's Design for the Environment Program. As a stimulus for research in the area of reducing the impact of chemical industry on the environment, the Presidential Green Chemistry Challenge Award was begun in 1995. The theme of the Green Chemistry Challenge is "Chemistry is not the problem; it's the solution." Since 1995, award winners have been responsible for the elimination of more than 460 million pounds of hazardous chemicals and have saved more than 440 million gallons of water and 26 million barrels of oil.

Winners of the Green Chemistry Challenge Award have developed foam fire retardants that do not use halons (compounds containing fluorine, chlorine, or bromine), cleaning agents that do not use tetrachloroethylene, methods that facilitate the recycling of polyethylene terephthalate soft-drink bottles, a method of synthesizing ibuprofen that minimizes the use of solvents and the generation of wastes, and a formulation that promotes the efficient release of ammonia from urea-based fertilizers. This latter contribution allows a more environmentally friendly means of applying fertilizers without the need for tilling or disturbing (and losing) precious topsoil.

Green syntheses of the future will require making choices about reactants, solvents, and reaction conditions that are designed to reduce resource consumption and waste production. We need to think about performing a synthesis in a way that will not consume excessive amounts of resources (and thus use less energy and be more economical), that will not produce excessive amounts of toxic or harmful by-products, and that will require milder reaction conditions.

The application of green-chemistry principles in an organic synthesis begins with the selection of the starting materials, called **feedstock**. Most organic compounds used as feedstock are derived from petroleum, a nonrenewable resource (see essay "Petroleum and Fossil Fuels" that preceeds Experiment 24). A green approach is to replace these petrochemicals with chemicals derived from biological sources such as trees, corn, or soybeans. Not only is this approach more sustainable, but the refining of organic compounds from these plant-derived materials, sometimes called **biomass**, is also less polluting than the refining process for petrochemicals. Many pharmaceuticals, plastics, agricultural chemicals, and even transportation fuels can

now be produced from chemicals derived from biomass. A good example of this is adipic acid, an organic chemical widely used in the production of nylon and lubricants. Adipic acid can be produced from benzene, a toxic petrochemical, or from glucose, which is found in plant sources.

Industrial processes are being designed that are based on the concept of **atom economy**. Atom economy means that close attention is paid to the design of chemical reactions so that all or most of the atoms that are starting materials in the process are converted into molecules of the desired product rather than into wasted by-products. Atom economy in the industrial world is the equivalent of ensuring that a chemical reaction proceeds with a high percentage yield in a classroom laboratory experiment.

The atom economy for a reaction can be calculated using the following equation:

$$\text{Percent atom economy} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weights of all rectants}} \times 100\%$$

For example, consider the reaction for the synthesis of aspirin (Experiment 8, "Acetylsalicylic Acid"):

Salicylic acid
MW 138.1   **Acetic anhydride**   **Acetylsalicylic acid**   **Acetic acid**
                    MW 102.1   **MW 180.2**
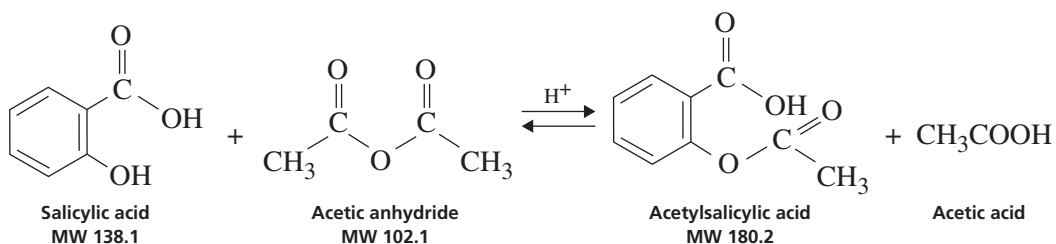
$$\text{Percent atom economy} = \frac{180.2}{138.1 + 102.1} \times 100\% = 75.0\%$$

This calculation assumes the complete conversion of reactants into product and 100% recovery of the product, which is not possible. Furthermore, the calculation does not take into account that often an excess of one reactant is used to drive the reaction to completion. In this reaction, acetic anhydride is used in large excess to ensure the production of more acetylsalicylic acid. Nonetheless, the atom economy calculation is a good way to compare different possible pathways to a given product.

To illustrate the benefits of atom economy, consider the synthesis of ibuprofen, mentioned earlier, that won the Presidential Green Chemistry Challenge Award in 1997. In the former process, developed in the 1960s, only 40% of the reactant atoms were incorporated into the desired ibuprofen product; the remaining 60% of the reactant atoms found their way into unwanted by-products or wastes that required disposal. The new method requires fewer reaction steps and recovers 77% of the reactant atoms in the desired product. This "green" process eliminates millions of pounds of waste chemical by-products every year, and it reduces by millions of pounds the amount of reactants needed to prepare this widely used analgesic.

Another green chemistry approach is to select safer reagents that are used to carry out the synthesis of a given organic compound. In one example of this, milder or less toxic oxidizing reagents may be selected to carry out a conversion that is normally done in a less green way. For example, sodium hypochlorite (bleach) can be used in some oxidation reactions instead of the highly toxic dichromate/sulfuric acid mixture. In some reactions, it is possible to use biological reagents, such as

enzymes, to carry out a transformation. Another approach in green chemistry is to use a reagent that can promote the formation of a given product in less time and with greater yield. Finally, some reagents, especially catalysts, can be recovered at the end of the reaction period and recycled for use again in the same conversion.

Many solvents used in traditional organic syntheses are highly toxic. The green chemistry approach to the selection of solvents has resulted in several strategies. One method that has been developed is to use supercritical carbon dioxide as a solvent. Supercritical carbon dioxide is formed under conditions of high pressure in which the gas and liquid phases of carbon dioxide combine to a single-phase compressible fluid that becomes an environmentally benign solvent (temperature 31°C; pressure 7280 kpa, or 72 atmospheres). Supercritical CO_2 has remarkable properties. It behaves as a material whose properties are intermediate between those of a solid and those of a liquid. The properties can be controlled by manipulating temperature and pressure. Supercritical CO_2 is environmentally benign because of its low toxicity and easy recyclability. Carbon dioxide is not added to the atmosphere; rather, it is removed from the atmosphere for use in chemical processes. It is used as a medium to carry out a large number of reactions that would otherwise have many negative environmental consequences. It is even possible to perform stereoselective synthesis in supercritical CO_2.

Some reactions can be carried out in ordinary water, the most green solvent possible. Recently, there has been much success in using near-critical water at higher temperatures where water behaves more like an organic solvent. Two of the award winners of the 2004 Green Chemistry Award, Charles Eckert and Charles Liotta, have advanced our understanding of supercritical CO_2 and near-critical water as solvents. One example of their work takes advantage of the dissociation of water that takes place under near-critical conditions, leading to a high concentration of hydronium and hydroxide ions. These ions can serve as self-neutralizing catalysts, and they can replace catalysts that must normally be added to the reaction mixture. Eckert and Liotta were able to run Friedel-Crafts reactions (Experiment 60, "Friedel-Crafts Acylation") in near-critical water without the need for the acid catalyst $AICI_3$, which is normally used in large amounts in these reactions.

Research has also focused on **ionic liquids**, salts that are liquid at room temperature and do not evaporate. Ionic liquids are excellent solvents for many materials, and they can be recycled. An example of an ionic liquid is
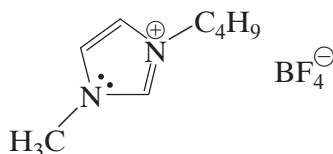
Even though many of the ionic liquids are expensive, their high initial cost is mitigated because, through recycling, they are not consumed or discarded. In addition, product recovery is often easier than with traditional solvents. In the past five years, many new ionic liquids have been developed with a broad range of properties. By selecting the appropriate ionic liquid, it is now possible to carry out many types of organic reactions in these solvents. In some reactions, a well-designed ionic solvent can lead to better yields under milder conditions than is possible with traditional solvents. Recently, researchers have developed ionic liquids made from artificial "sweeteners" that are nontoxic and extend even further the concept of green chemistry.

It is possible in some organic syntheses to completely eliminate the need for any solvent! Some reactions that are traditionally carried out in solvents can be carried out either in the solid or gas phases without the presence of any solvent.

Another approach to making organic chemistry greener involves the way in which a reaction is carried out, rather than in the selection of starting material, reagents, or solvents. Microwave technology (see Technique 7, Section 7) can be used in some reactions to provide the heat energy required to make the transformation go to completion. With microwave technology, reactions can take place with less toxic reagents, in a shorter time, and with fewer side reactions—all goals of green chemistry. Microwave technology has also been used to create supercritical water that behaves more like an organic solvent and could replace more toxic solvents in carrying out organic reactions.

Another green approach involving technology is the use of solid-phase extraction (SPE) columns (see Technique 12, Section 12.14). Using SPE columns, extractions such as removing caffeine from tea can be carried out more quickly and with less toxic solvents. In other applications, SPE columns can be used to carry out the synthesis of organic compounds more efficiently with less use of toxic reagents.

Industry has discovered that environmental stewardship makes good economic sense, and there is a renewed interest in cleaning up manufacturing processes and products. In spite of the continuing adversarial nature of relations between industry and environmentalists, companies are discovering that preventing pollution in the first place, using less energy, and developing atom-economic methods makes as much sense as spending less money on raw materials or capturing a greater share of the market for their product. Although U.S. chemical industries are by no means near their stated goal of reducing the emission of toxic substances to zero or near-zero levels, significant progress is being made.

The teaching of the principles of green chemistry is beginning to find its way into the classroom. In this textbook, we have attempted to improve the green qualities of some of the experiments and have added several green experiments. The following table lists the experiments in this textbook that have a significant green component, along with the primary aspect of the experiment that makes it green.

Experiment	Green Aspect
Exp. 24, "Gas Chromatographic Analysis of Gasolines"	Discussion of pollution-controlling additives
Exp. 25, "Biodiesel"	Transportation fuel using recycled materials
Exp. 26, "Ethanol from Corn"	Transportation fuel made from renewable resources
Exp. 27, "Chiral Reduction of Ethyl Acetoacetate"	Biological reagent, baker's yeast
Exp. 28, "Nitration of Aromatic Compounds Using a Recyclable Catalyst"	Use of a recyclable catalyst to increase reaction efficiency
Exp. 29, "Reduction of Ketones Using Carrot Extract"	Biological reagent
Exp. 30, "An Oxidation-Reduction Scheme: Borneol, Camphor, Isoborneol"	Less-toxic oxidizing agents
Exp. 34, "Aqueous-Based Organozinc Reactions"	Water used as the solvent
Exp. 35, "Sonogashira Coupling of Iodoaromatic Compounds with Alkynes"	Use of a recyclable catalyst to increase reaction efficiency

Experiment	Green Aspect
Exp. 36, "Grubb's-Catalyzed Matathesis of Eugenol with *cis*-1,4-Butenediol"	Use of a recyclable catalyst to increase reaction efficiency
Exp. 38, "A Green Enantioselective Aldol Condensation Reaction"	Use of less-toxic reagents
Exp. 40, "Preparation of Triarylpyridines"	Solvent-less reaction
Exp. 41, "1,4-Dipheny1-1,3-butadiene"	Solvent-less reaction
Exp. 48, "Synthesis of a New Polymer Using Grubb's Catalyst"	Use of a recyclable catalyst to increase reaction efficiency
Exp. 50, "Diels-Alder Reaction with Anthracene-9-methanol"	Water used as the solvent
Exp. 64, "Green Epoxidation of Chalcones"	Use of a less-toxic reagents
Exp. 65, "Cyclopropanation of Chalcones"	Use of a less-toxic reagents

In addition, Experiment 55 (Identification of Unknowns) offers a "green" alternative procedure. This procedure avoids the use of toxic chemicals for classification tests and substitutes the use of spectroscopy, which does not require any chemical reagents (except a small amount of organic solvent).

Certainly, enormous challenges remain. Generations of new scientists must be taught that it is important to consider the environmental impact of any new methods that are introduced. Industry and business leaders must learn to appreciate that adopting an atom-economic approach to the development of chemical processes makes good long-term economic sense and is a responsible means of conducting business. Political leaders must also develop an understanding of what the benefits of a green technology can be and why it is responsible to encourage such initiatives.

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Chiral Reduction of Ethyl Acetoacetate; Optical Purity Determination

Green chemistry

Stereochemistry

Reduction with yeast

Use of a separatory funnel

Chiral gas chromatography

Polarimetry

Optical purity (enantiomeric excess) determination

Nuclear magnetic resonance (optional)

Chiral chemical shift reagents (optional)

The experiment described in Experiment 27A uses common baker's yeast as a chiral reducing medium to transform an achiral starting material, ethyl acetoacetate, into a chiral product. When a single stereoisomer is formed in a chemical reaction from an achiral starting material, the process is said to be **enantiospecific**. In other words, one stereoisomer (enantiomer) is formed in preference to its mirror image. In the present experiment, the ethyl (S)-3-hydroxybutanoate stereoisomer is formed preferentially. In actual fact, however, some of the (R)-enantiomer is also formed in the reaction. The reaction, therefore, is described as an **enantioselective** process because the reaction does not produce one stereoisomer exclusively. Chiral gas chromatography and polarimetry will be employed to determine the percentages of each of the enantiomers. Generally, the chiral reduction produces less than 8% of the ethyl (R)-3-hydroxybutanoate.

Ethyl acetoacetate   **Ethyl (S)-3-hydroxybutanoate**
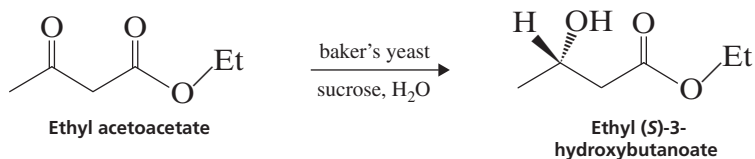
In contrast, when ethyl acetoacetate is reduced with sodium borohydride in methanol, the reaction yields a 50-50 mixture of the (R) and (S)-stereoisomers. A racemic mixture is formed because the reaction is not being conducted in a chiral medium.
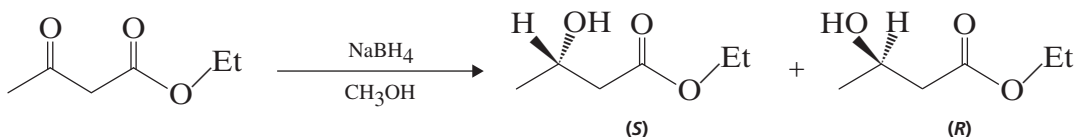
                                          (S)   **(R)**

In Experiment 27B (optional), you may use nuclear magnetic resonance spectroscopy to determine the relative amounts of (*R*) and (*S*) enantiomers produced in the chiral reduction of ethyl acetoacetate. This part of the experiment requires the use of a chiral shift reagent.

27A   E X P E R I M E N T   2 7 A

Chiral Reduction of Ethyl Acetoacetate

R E Q U I R E D   R E A D I N G

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for techniques marked
with an asterisk.

Review: *Technique 8   Filtration, Sections 8.3 and 8.4

*Technique 12   Extractions, Separations, and Drying Agents,
Sections 12.4 and 12.10

Techniques 22 and 25

Techniques 26 and 27 (optional)

New: Technique 23   Polarimetry

Essay   Green Chemistry

S P E C I A L   I N S T R U C T I O N S

Day 1 of the experiment involves setting up the reaction. Another experiment can be conducted concurrently with this experiment. Part of this first laboratory period is used to mix the yeast, sucrose, and ethyl acetoacetate in a 500-mL Erlenmeyer flask. The mixture is stirred during part of that first period. The mixture is then covered and stored until the next period. The reduction requires at least 2 days.

Day 2 of the experiment is used to isolate the chiral ethyl 3-hydroxybutanoate. After this has been isolated, each student's product is analyzed by chiral gas chromatography and polarimetry to determine the percentages of each of the enantiomers. As an optional experiment (Experiment 27B), the products can also be analyzed by NMR using a chiral shift reagent to determine the percentages of each of the enantiomers present in the ethyl 3-hydroxybutanoate produced in the chiral reduction.

S U G G E S T E D   W A S T E   D I S P O S A L

The Celite, residual yeast, and cheesecloth from the reduction can be disposed of in the trash. The aqueous solutions and emulsion left from the extraction with methylene chloride should be placed in the aqueous waste container. Methylene chloride waste should be poured into the waste container designated for halogenated waste.

NOTES TO THE INSTRUCTOR

It is strongly advised that rotary evaporators be made available for this experiment. Approximately 90 mL of methylene chloride is used for each student. The experiment will be more "green" if the solvent can be recovered. The instructor will need to make available to each student a large Büchner funnel (10 cm), 500-mL filter flask, 500-mL Erlenmeyer flask, 1.5- or 2-inch magnetic stir bar, and a 500-mL separatory funnel. It is advised that packaged dry yeast be used. We suggest Fleischmann's Rapid Rise (baker's) Yeast, which contains 7 g of yeast per package. Purchase packages of 100% cotton cheesecloth that consists of three layers (do not separate the layers from each other). Cut the three-ply cheesecloth into 4 × 8 inch strips to be folded into 4 × 4 inch sections for the Büchner funnel. In some cases, the yeast does not grow substantially during the first half hour. It is best to discard the mixture and start the reaction again if it appears that the yeast is not growing. In most cases, the temperature may not have been controlled carefully. It is recommended that the flasks containing the reaction mixture be stored in an area where the temperature is maintained at about 25°C, if possible. The optimal reduction period is four days. A small amount of unreduced ethyl acetoacetate remains after a 2-day reduction (less that 1%), and a 4-day reduction yields no remaining ethyl acetoacetate. The expected yield of chiral hydroxyester should be around 65%, consisting of 92–94% ethyl (*S*)-3-hydroxybutanoate.

PROCEDURE

Yeast Reduction. To a 500-mL Erlenmeyer flask, add 150 mL of deionized (DI) water and a 1.5- or 2-inch stir bar. Warm the water to about 35–40°C using a hot plate set on low. Add 7 g of sucrose and 7 g of Fleischmann's Rapid Rise (dry baker's) Yeast to the flask. Swirl the contents of the flask in order to distribute the yeast into the aqueous solution; otherwise it will remain at the top of the solution. Stir the mixture for 15 minutes while maintaining the temperature at 35°C. During this time, the yeast will become activated and will grow substantially. Add 3.0 g of ethyl acetoacetate and 8 mL of hexane to the yeast mixture. Stir the mixture with a magnetic stirrer for 1.5 hours. Because the mixture may become thick, check periodically to see whether the mixture is being stirred. The reaction is somewhat exothermic, so you may not need to heat the mixture. Nevertheless, you should monitor the temperature to make sure that it remains near 30°C. Adjust the temperature to 30°C if the temperature falls below this value.

Label the Erlenmeyer flask with your name and ask your instructor to store the flask. Cover the top of the flask loosely with aluminum foil so that carbon dioxide can be expelled during the reduction. The mixture will stand, without stirring, until the next laboratory period (2–4 days). At some point during the laboratory period, obtain the infrared spectrum of ethyl acetoacetate for the purpose of comparison to the reduced product.

> ### CAUTION
>
> **Do not breathe the Celite power.**

Isolation of the Alcohol Product. Obtain a 500-mL separatory funnel, a large Büchner (10 cm) funnel, and a 500-mL filter flask from your instructor. To the yeast solution, add 5 g of Celite and stir the mixture magnetically for 1 minute (see Technique 8, Section 8.4). Allow the solid to settle as much as possible (at least 5 minutes). Set up a vacuum-filtration apparatus using the large Büchner funnel (see Technique 8, Section 8.3). Wet one piece of filter paper with water and place it into the funnel. Obtain a 4 × 8 inch strip of cheesecloth and fold it over

to make a 4 × 4 inch square. Wet it with water and place it on top of the filter paper so that it completely covers the filter paper and is partly up the side of the Büchner funnel. You are now ready to filter your solution. Turn on the vacuum source (aspirator or the house vacuum). Decant the clear supernatant liquid slowly into the Büchner funnel. If you do this slowly, you may avoid plugging the filter paper with small particles. Once the supernatant liquid has been poured into the funnel, add the Celite slurry to the Büchner funnel. Rinse the flask with 20 mL of water and pour the remaining Celite–yeast mixture into the Büchner funnel. Discard the Celite, yeast, and cheesecloth waste into the trash. The Celite helps to trap the very tiny yeast particles. Some of the yeast and Celite will pass through the filter into the filter flask. This is unavoidable.

Add 20 g of sodium chloride to the filtrate in the filter flask and swirl the flask gently until the sodium chloride dissolves. If an emulsion forms, you may be swirling the flask too vigorously. Pour the filtrate into a 500-mL separatory funnel. Add 30 mL of methylene chloride to the funnel and stopper the funnel (see Technique 12, Section 12.4). In order to avoid a difficult emulsion, do not shake the separatory funnel; instead, slowly invert the funnel and bring it back to the upright position. Repeat this motion over a period of 5 minutes. Vent the funnel occasionally to relieve pressure. Drain the lower methylene chloride layer from the separatory funnel into a 250-mL Erlenmeyer flask, leaving behind a small amount of emulsion and the aqueous layer in the separatory funnel. Add another 30-mL portion of methylene chloride to the separatory funnel and repeat the extraction procedure. Drain the lower methylene chloride layer into the same Erlenmeyer flask holding the first methylene chloride extract. Repeat the extraction process a third time with a 30-mL portion of methylene chloride. Discard the emulsion and aqueous layer remaining in the separatory funnel into a suitable aqueous waste container.

Dry the three combined methylene chloride extracts over about 1 g of anhydrous granular sodium sulfate for at least 5 minutes. Occasionally, swirl the contents of the flask to help dry the solution. Decant the liquid into a 250-mL beaker and evaporate the solvent using an air or nitrogen stream until the volume of liquid remains constant (approximately 1–2 mL). (Alternatively, a rotary evaporator or distillation may be used to remove the methylene chloride from the product).[1] Often the remaining liquid contains some water. To remove the water, add 10 mL of methylene chloride to dissolve the product and add 0.5 g of anhydrous granular sodium sulfate to the solution. Decant the methylene chloride solution away from the drying agent into a preweighed 50-mL beaker. Evaporate the solvent using an air or nitrogen stream until the volume of liquid remains constant. Tile liquid contains the ethyl (*S*)-3-hydroxybutanoate that has been produced by chiral reduction of ethyl acetoacetate. A small amount of ethyl acetoacetate may remain unreduced in the sample. Reweigh the beaker to determine the weight of the product. Calculate the percentage yield of product.

Infrared Spectroscopy. Determine the spectrum of your isolated product. The infrared spectrum provides the best direct evidence for the reduction of ethyl acetoacetate. Look for presence of a hydroxyl group (about 3440 cm^{-1}) that was produced in the reduction of the carbonyl group. Compare the spectrum of the product, ethyl 3-hydroxybutanoate, to the starting material, ethyl acetoacetate. What differences do you notice in the two spectra? Label the two spectra with peak assignments and include them with your laboratory report.

Chiral Gas Chromatography. Chiral gas chromatography will provide a direct measure of amounts of each stereoisomer present in your chiral ethyl 3-hydroxybutanoate sample. A Varian CP-3800 equipped with an Alltech Cyclosil B capillary column (30 m, 0.25-mm ID, 0.25 μm) provides an excellent separation of (*R*) and (*S*)-enantiomers. Set the FID detector

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[1]Pour the dry methylene chloride extracts into a round-bottom flask and remove the solvent with a rotary evaporator or by distillation. After removing the solvent, add 10 mL of fresh methylene chloride and 0.5 g of anhydrous granular sodium sulfate to the round-bottom flask. Decant the solution away from the drying agent into a preweighed beaker as indicated in the procedure.

at 270°C and the injector temperature at 250°C, with a 50:1 split ratio. Set the column oven temperature at 90°C and hold at that temperature for 20 minutes. The helium flow rate is 1 mL/min. The compounds elute in the following order: ethyl (S)-3-hydroxybutanoate (14.3 min) and the (R)-enantiomer (15.0 min). Any remaining ethyl acetoacetate present in the sample will produce a peak with a retention time of 14.1 minutes. Your observed retention times may vary from those given here, but the order of elution will be the same. Calculate the percentages of each of the enantiomers from the chiral gas chromatography results. Usually, about 92–94% of the (S)-enantiomer is obtained from the reduction.

Polarimetry. Fill a 0.5-dm polarimeter cell with your chiral hydroxyester (about 2 mL required). You may need to combine your product with material obtained by one other student in order to have enough material to fill the cell. Determine the observed optical rotation for the chiral material. Your instructor will show you how to use the polarimeter. Calculate the specific rotation for your sample using the equation provided in Technique 23. The concentration value, c, in the equation is 1.02 g/mL. Using the published value for the *specific* rotation of ethyl (S)-(+)-3-hydroxybutanoate of $[\alpha_D^{25}] = +43.5°$, calculate the optical purity (enantiomeric excess) for your sample (see Technique 23, Section 23.5). Report the observed rotation, the calculated specific rotation, the optical purity (enantiomeric excess), and the percentages of each of the enantiomers to the instructor. How do the percentages of each of the enantiomers calculated from the polarimeter measurement compare to the values obtained from chiral gas chromatography?[2]

Proton and Carbon NMR Spectroscopy (Optional). At the option of the instructor, you may obtain the proton spectrum (shown in Figures 1 and 2 and interpreted in Experiment 27B) and the carbon NMR spectra of the product. The carbon NMR spectrum shows peaks at 14.3, 22.6, 43.1, 60.7, 64.3, and 172.7 ppm.

27B EXPERIMENT 27B (OPTIONAL)

NMR Determination of the Optical Purity of Ethyl (S)-3-Hydroxybutanoate

In Experiment 27A, the yeast reduction of ethyl acetoacetate forms a product that is predominantly the (S)-enantiomer of ethyl 3-hydroxybutanoate. In this part of the experiment, we will use NMR to determine the percentages of each of the enantiomers in the product. The 300 MHz proton NMR spectrum of racemic ethyl 3-hydroxybutanoate is shown in Figure 1. The expansions of the individual patterns from Figure 1 are shown in Figure 2. The methyl protons (H_a) appear as a doublet at 1.23 ppm, and the methyl protons (H_b) appear as a triplet at 1.28 ppm. The methylene protons (H_c and H_d) are diastereotopic (nonequivalent) and appear at 2.40 and 2.49 ppm (each a doublet of doublets). The hydroxyl group appears at about 3.1 ppm. The quartet at 4.17 ppm results from the methylene protons (H_e) split by the protons (H_b). The methane proton (H_f) is buried under the quartet at about 4.2 ppm.

---

[2]The percentages calculated from polarimetry may vary considerably from those obtained by chiral gas chromatography. Often the samples contain some solvent and other impurities that reduce the observed optical rotation value. The solvent and impurities do not influence the more accurate percentages obtained directly by chiral gas chromatography.

$$CH_3\text{-}\underset{H_a}{\underset{|}{C}}H\text{-}\underset{H_c}{C}H_2\text{-}\overset{O}{\overset{||}{C}}\text{-}O\text{-}\underset{H_e}{C}H_2\text{-}\underset{H_b}{C}H_3$$

$$\underset{H_a}{}\ \underset{H_f}{OH}\ \ \underset{H_c}{}\ \ \underset{H_d}{}\ \ \underset{H_e}{}\ \underset{H_b}{}$$
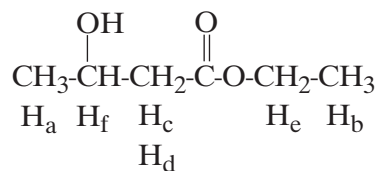
Although the normal proton NMR spectrum for the racemic ethyl 3-hydroxybutanoate is not expected to be any different from the proton NMR spectra of each of the enantiomers in an **achiral environment**, the introduction of a chiral shift reagent creates a **chiral environment**. This chiral environment allows the two enantiomers to be distinguished from each other. A general discussion of nonchiral chemical shift reagents is found in Technique 26, Section 26.15. These reagents spread out the resonances of the compound with which they are used, increasing by the largest amount the chemical shifts of the protons that are nearest the center of the metal complex. Because the spectra of both enantiomers are identical under these conditions, the usual chemical shift reagent would not help our analysis. However, if we use a chemical shift reagent that is itself chiral, we can distinguish the two enantiomers by their NMR spectra. The two enantiomers, which are each chiral, will interact differently with the chiral shift reagent. The complexes formed from the (*R*), and (*S*)-enantiomers and with the chiral shift reagent will be diastereomers. Diastereomers usually have different physical properties, and the NMR spectra are no exception. The two complexes will be formed with slightly differing geometries. Although the effect may be small, it is large enough to see differences in the NMR spectra of the two enantiomers.

The chiral shift reagent used in this experiment is *tris*-[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium (III), or Eu(hfc)$_3$. In this complex, the europium is in a chiral environment because it is complexed to camphor, which is a chiral molecule. Eu(hfc)$_3$ has the structure shown below the NMR spectrum provided.
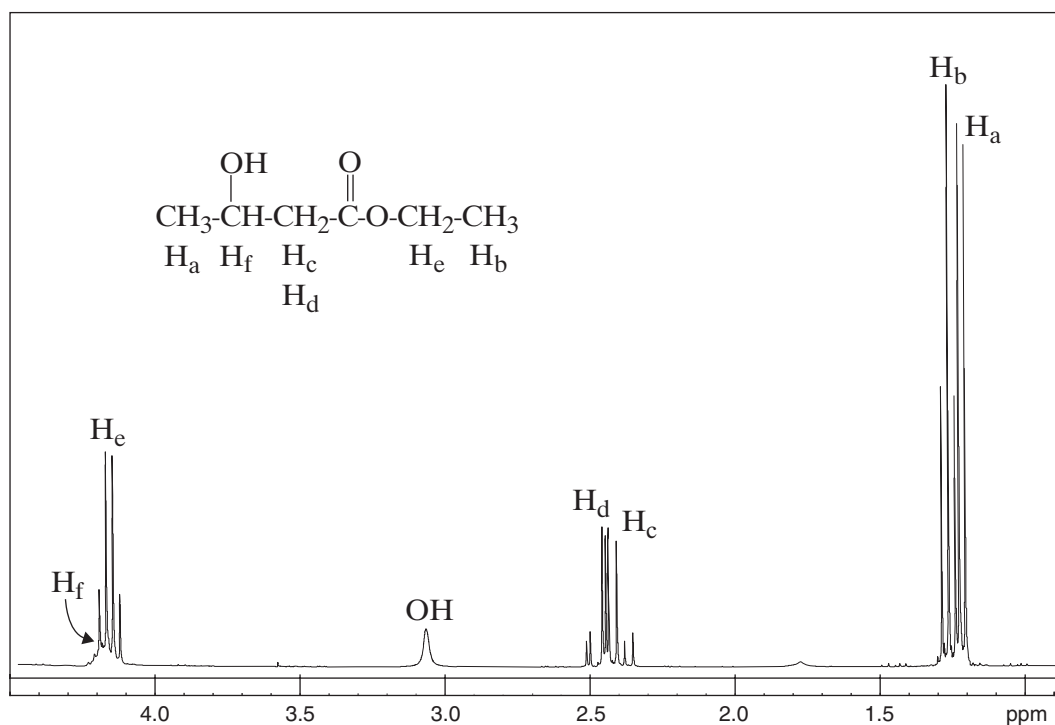
Figure 1. NMR spectrum (300 MHz) of racemic ethyl 3-hydroxybutanoate with no chiral shift reagent present.
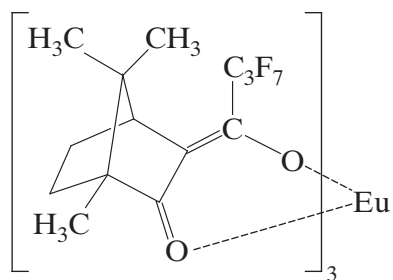
REQUIRED READING

New: Technique 26   Nuclear Magnetic Resonance Spectroscopy,
Section 26.15

SPECIAL INSTRUCTIONS

This experiment requires the use of a high-field NMR spectrometer in order to obtain sufficient separation of peaks for the two enantiomers. The chiral shift reagent does cause some peak broadening, so care should be taken not to add too much of this reagent to the chiral ethyl 3-hydroxybutanoate sample. A 0.035-g sample of the chiral material and 8–11 mg of chiral shift reagent should be sufficient to give good results.
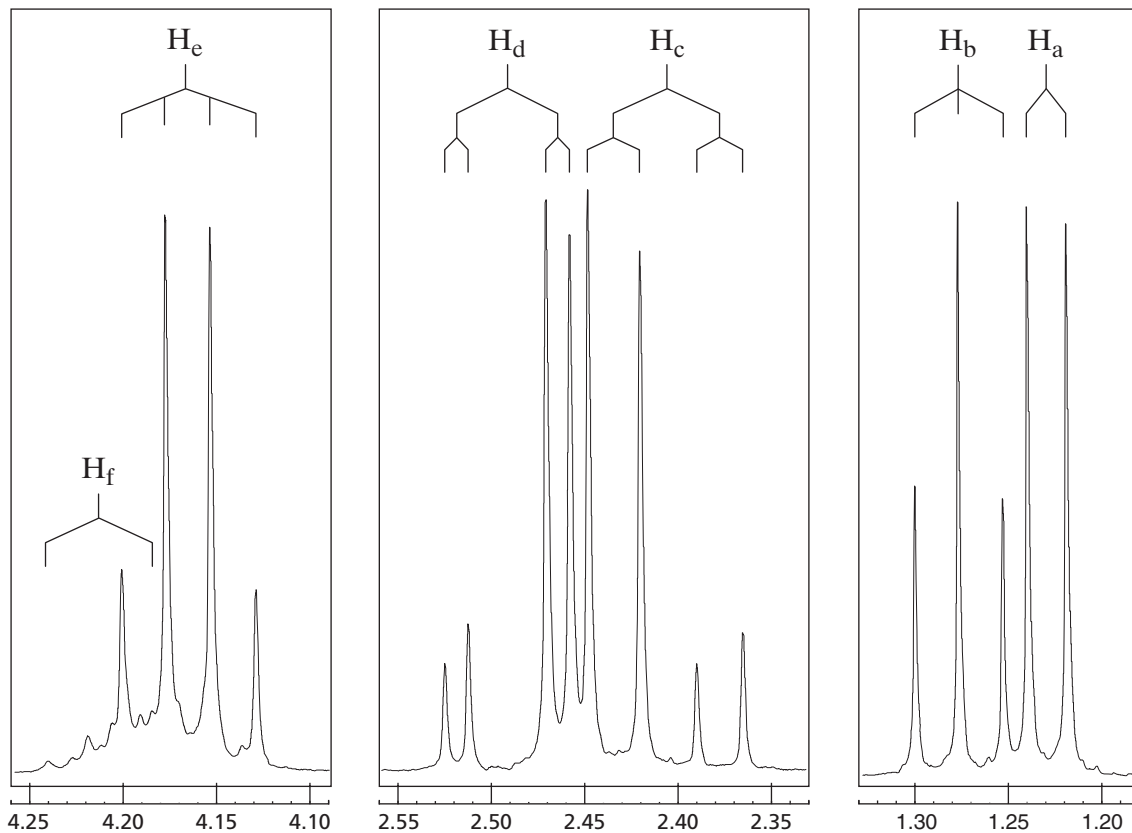
Figure 2. Expansions of the NMR spectrum of racemic ethyl 3-hydroxybutanoate.

SUGGESTED WASTE DISPOSAL

Discard the remaining solution from your NMR tube into the container designated for the disposal of halogenated organic waste.

PROCEDURE

Using a Pasteur pipet to aid the transfer, weigh 0.035 g of chiral ethyl 3-hydroxybutanoate from Experiment 27A directly into an NMR tube. Weigh 8–11 mg of *tris* [3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium(III) chiral shift reagent on a piece of weighing paper and add the chiral shift reagent to the chiral hydroxyester in the NMR tube. Take care to avoid chipping the fragile NMR tube while adding the shift reagent with a microspatula. Add $CDCl_3$ solvent to the NMR tube until the level reaches 50 mm. Cap the tube and invert it to mix the sample. Allow the NMR sample to stand for a minimum of about 5–8 minutes before determining the NMR spectrum. Record in your notebook the exact weights of sample and chiral shift reagent that you used.

Determine the NMR spectrum of the sample. The peaks of interest are the methyl protons, H_a (doublet) and H_b (triplet). Notice in Figure 3 that the doublet and triplet peaks for the two methyl groups in the **_racemic_** ethyl 3-hydroxybutanoate are doubled. The downfield doublet (1.412 and 1.391 ppm) and triplet (1.322, 1.298, and 1.274 ppm) peaks are assigned to the (*S*)-enantiomer. The upfield doublet (1.405 and 1.384 ppm) and triplet (1.316, 1.293, and 1.269 ppm) peaks are assigned to the (*R*)-enantiomer. Your expansion of this area of the NMR spectrum should also show a doubling of the peaks as in Figure 3, but the upfield doublet for the (*R*)-enantiomer will be smaller. The same will be true for the (*R*)-enantiomer in the triplet pattern. By integration, determine the percentages of the (*S*)- and (*R*)-enantiomers in the chiral ethyl 3-hydroxybutanoate from Experiment 27A. Although the positions of the peaks may vary somewhat from those shown in Figure 3, you should still find that the doublet and triplet for the (*S*)-enantiomer will always be downfield relative to the (*R*)-enantiomer.

The assignments for the (*S*)- and (*R*)-enantiomers shown in Figure 3 were determined by obtaining the NMR spectrum of pure samples of each enantiomer in the presence of the chiral shift reagent (Figures 4 and 5). You may have noticed that the doublet has moved further downfield relative to the triplet (compare Figures 2 and 3). The reason for this is that the complexation of the chiral shift reagent occurs at the hydroxyl group. Because the methyl group (H_a) is closer to the europium atom, it is expected that that group will be shifted further downfield relative to the other methyl group (H_b).
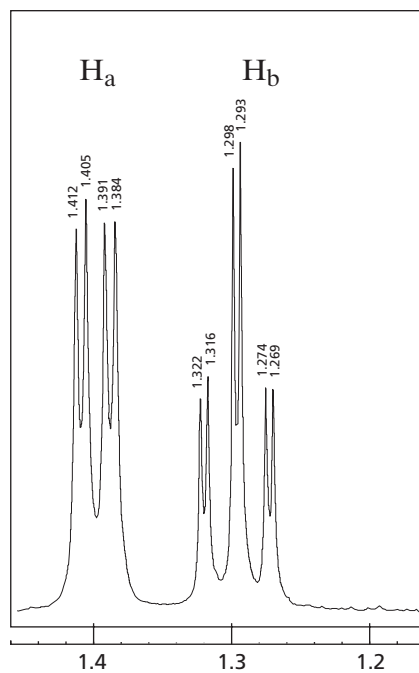
Figure 3. NMR spectrum (300 MHz) of racemic ethyl 3-hydroxybutanoate, with chiral shift reagent added.
Note: H$_a$ for the (*S*)-enantiomer = 1.412, 1.391; H$_b$ for the (*S*)-enantiomer = 1.322, 1.298, 1.274; H$_a$ for the (*R*)-enantiomer = 1.405, 1.384; H$_b$ for the (*R*)-enantiomer = 1.316, 1.293, 1.269.
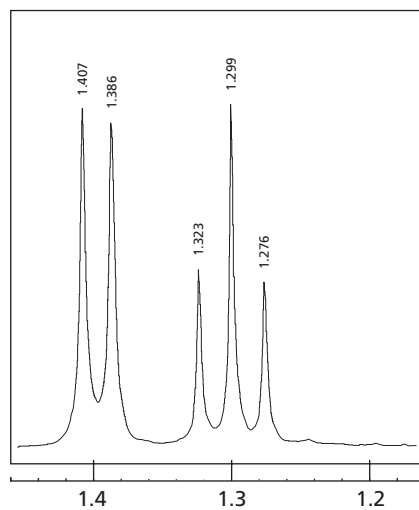
Figure 4. NMR spectrum (300 MHz) of ethyl (S)-3-hydroxybutnoate, with chiral shift reagent added.
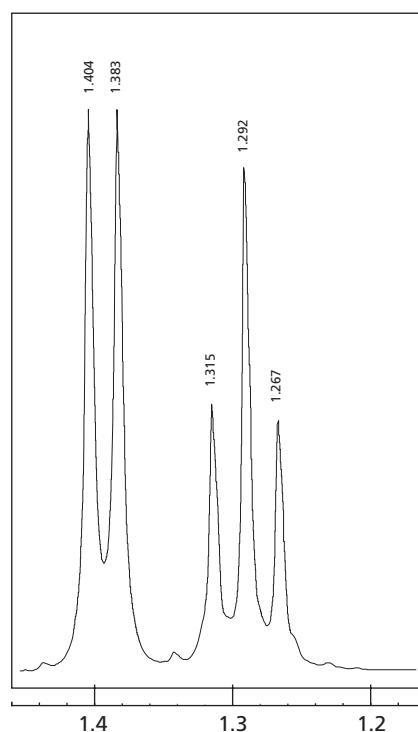
Figure 5. NMR spectrum (300 MHz) of ethyl (R)-3-hydroxybutanoate, with chiral shift reagent added.

REFERENCES

Cui, J-N.; Ema, T.; Sakai, T.; Utaka, M. Control of Enantioselectivity in the Baker's Yeast Asymmetric Reduction of Chlorodiketones to Chloro (S)-Hydroxyketones. *Tetrahedron: Asymmetry* **1998,** *9,* 2681–2691.

Naoshima, Y.; Maeda, J.; Munakata, Y. Control of the Enantioselectivity of Bioreduction with Immobilized Bakers' Yeast in a Hexane Solvent System. *J. Chem. Soc. Perkin Trans. 1* **1992,** 659–660.

Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. Yeast Reduction of Ethyl Acetoacetate: (*S*)-(+)-Ethyl 3-Hydryoxybutanoate. *Org. Synth.* **1984,** *63,* 1–9.

QUESTIONS

1. Would you expect to see a difference in retention times for the ethyl (*S*)-3-hydroxybutanoate and the (*R*)-enantiomer on gas chromatography columns described in Technique 22?

2. What is the biological reducing agent that gives rise to the formation of chiral ethyl 3-hydroxybutanoate? You may need to look in a reference book to find an answer to this question.

3. Explain the NMR patterns for protons H_c and H_d shown in Figure 2. (*Hints:* These protons are nonequivalent because of their location adjacent to a stereocenter. The ^2J coupling constants for protons attached to an sp^3 carbon are very large—in this case, 16.5 Hz. The ^3J coupling constants are not equal. Draw a sawhorse projection for the molecule. Can you see why the ^3J coupling constants might be different?)

Nitration of Aromatic Compounds Using a Recyclable Catalyst

Green chemistry

Nitration

Atom-economic reaction

Recyclable catalyst

Rotary evaporator (optional)

Mass spectrometry

Gas chromatography

Chemists in academia and industry are attempting to make chemical reactions more environmentally friendly (see the essay "Green Chemistry"). One way to accomplish this is to use exact (stoichiometric) amounts of starting reagents so that no excess material need be thrown away, thus contributing to a higher atom economy. Another aspect of Green Chemistry is that chemists should use catalysts. These materials have the advantage of allowing reactions to occur under milder conditions, and catalysts can also be reused. Thus, Green Chemistry helps keep the environment clean while producing useful products.

In the present experiment, we employ a Lewis acid, ytterbium (III) trifluoromethanesulfonate, as a catalyst for the nitration of a series of aromatic substrates with nitric acid. This catalyst will be recycled (recovered) and reused.

$$R \!-\!\!\!\left\langle \text{benzene ring} \right\rangle \xrightarrow[\text{Yb(OSO}_2\text{CF}_3)_3]{\text{HNO}_3} R \!-\!\!\!\left\langle \text{benzene ring} \right\rangle\!\!-\!\text{NO}_2$$
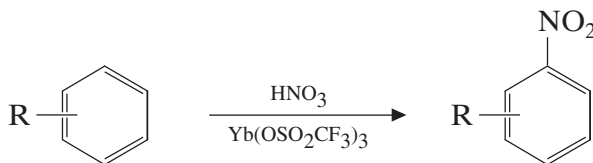
The solvent used in this reaction, 1,2-dichloroethane, is not environmentally friendly, but the solvent can be recovered using a rotary evaporator.

A proposed mechanism for this reaction involves the following three steps to generate the nitronium ion.[1] The trifluoromethanesulfonate (triflate) ions act as spectators. The ytterbium cation is believed to be hydrated by the water present in the aqueous nitric acid solution. Nitric acid binds strongly to the hydrated ytterbium cation, as shown in equation 1. A proton is generated, as shown in equation 2, by the strong polarizing effect of the metal. Nitronium ion is then formed by the process shown in equation 3. Although the nitronium ion may serve as the active electrophilic species, it is more likely that a nitronium carrier, such as the intermediate formed in equation 2, may serve as the electrophile. In any case, the reaction yields a nitrated aromatic compound.

---

[1]C. Braddock, "Novel Recyclable Catalysts for Atom Economic Aromatic Nitration." *Green Chemistry, 3* (2001): G26−G32.

$$Yb(H_2O)_x^{3+} + H\text{-}O\text{-}\overset{+}{N}\overset{O}{\underset{O^-}{}} \longrightarrow H\text{-}O\text{-}\overset{+}{N}\overset{O}{\underset{O_-}{}}\cdots Yb(H_2O)_y^{3+} \quad \textbf{(1)}$$

Nitric acid

$$H\text{-}O\text{-}\overset{+}{N}\overset{O}{\underset{O_-}{}}\cdots Yb(H_2O)_y^{3+} \longrightarrow O{=}\overset{+}{N}\overset{O^-}{\underset{O_-}{}}\cdots Yb(H_2O)_y^{3+} + H^+ \quad \textbf{(2)}$$

$$H^+ + HNO_3 \longrightarrow NO_2^+ + H_2O \quad \textbf{(3)}$$

Nitronium ion
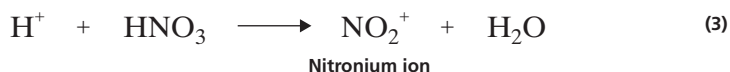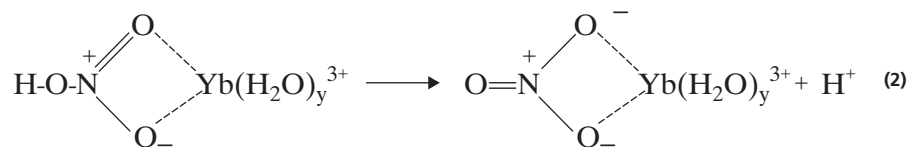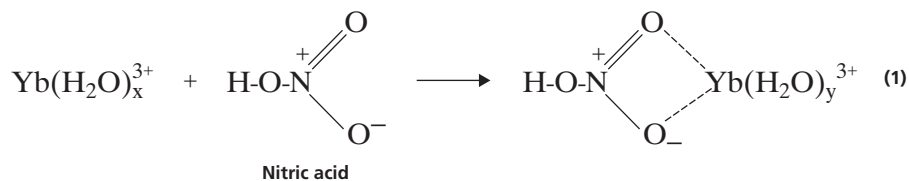
In this experiment, you will nitrate an aromatic substrate and analyze the composition of the mixture obtained by gas chromatography-mass spectrometry (GC-MS). In some cases, starting material will also be present in the mixture. You should be able to explain, mechanistically, why the observed products are obtained from the reaction.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:

	*Technique 7	Reaction Methods, Sections 7.2 and 7.10
	Technique 7	Section 7.11 (optional)
	*Technique 12	Extractions, Separations, and Drying Agents, Sections 12.4 and 12.9
	Technique 22	Gas Chromatography
New:	Essay	Green Chemistry
	Technique 28	Mass Spectrometry

SPECIAL INSTRUCTIONS

Some of the nitrated products may be toxic. All work should be conducted in a fume hood. Wear protective gloves to avoid skin contact with the nitrated products.

SUGGESTED WASTE DISPOSAL

The aqueous layer contains the catalyst, ytterbium triflate. Do not discard it. Instead, recycle the catalyst for future use by evaporating water on a hot plate. Transfer the colorless solid to a storage container or submit it to the instructor. If the material is highly colored, ask your instructor for advice. If the solvent, 1,2-dichloroethane, has been recovered using a rotary evaporator, pour it into a container so that it can be recycled.

N O T E S   T O   T H E   I N S T R U C T O R

It is suggested that each pair of students select a different substrate from the list provided. In most cases, the reaction will not go to completion, and, as expected will provide isomeric products. For example, toluene yields the expected *ortho* and *para* products, but a small amount of *meta* product is also formed. The products are analyzed by GC-MS. This experiment provides an excellent opportunity to discuss mass spectrometry because most of the compounds yield abundant molecular ions. The products are identified by searching the National Institute of Standards and Technology (NIST) database. Although it is best to search the database to identify the compounds, the experiment can also be conducted with gas chromatography. If this is done, one can usually assume that the nitro compounds will emerge in the following order: *ortho, meta,* and *para.* Adequate separations can be achieved on a GC-MS instrument using a J & W DB-5MS or Varian CP-Sil 5CB capillary column (30 m, 0.25-mm ID, 0.25 μm). Set the injector temperature at 260°C. The column oven conditions are the following: start at 60°C (hold for 1 min), increase to 280°C at 20°C/min (12 min), and then hold at 280°C (4.5 min). Each run takes about 17 minutes. The helium flow rate is 1 mL/min. The mass range is set for 40 to 400 m/e.

P R O C E D U R E

Select one of the following aromatic substrates:

Toluene	Biphenyl
Butylbenzene	4-Methylbiphenyl
Isopropylbenzene	Diphenylmethane
tert-Butylbenzene	Phenylacetic acid
ortho-Xylene	Fluorobenzene
meta-Xylene	Iodobenzene
para-Xylene	Naphthalene
Anisole	Fluorene
1,2-Dimethoxybenzene (Veratrole)	Acetanilide
1,3-Dimethoxybenzene	Phenol
1,4-Dimethoxybenzene	α-Naphthol
4-Methoxytoluene	β-Naphthol

Place 0.375 g ytterbium (III) trifluoromethanesulfonate hydrate catalyst (ytterbium triflate) into a 25-mL round-bottom flask. Add 10 mL of 1,2-dichloroetheane solvent followed by 0.400 mL of concentrated nitric acid (automatic pipet). Add two boiling stones to the flask. To this solution, weigh out and add approximately 6 millimoles of the aromatic substrate. Connect the round-bottom flask to a reflux condenser and clamp it into place on a ring stand. Use a very slow flow of water through the condenser. With a hot plate, heat the mixture to reflux for 1 hour.

After refluxing the mixture for 1 hour, allow the mixture to cool to room temperature and add 8 mL of water. Transfer the mixture into a separatory funnel. Shake the mixture gently

and allow the two phases to separate. Drain the organic layer (bottom layer) into a 25-mL Erlenmeyer flask. Dry the organic layer with a small scoop of anhydrous magnesium sulfate (about 0.5 g). If a rotary evaporator is available, transfer the organic layer to a preweighed 50-mL round-bottom flask for removal of solvent. The apparatus allows the possibility of recovering most of the 1,2-dichloroethane. When the solvent has been removed, remove the flask and weigh it.

Alternatively, the solvent may be removed by using the apparatus shown in Technique 7, Figure 7.17C. Transfer the dried organic layer to a preweighed 125-mL filter flask. Add a melting-point capillary tube to the flask (open end down) and then cork the top. The melting-point capillary tube helps speed the evaporation process. Connect the sidearm of the filter flask to the house vacuum system or aspirator, using a trap cooled in ice. There will be a cooling effect while the evaporation takes place, so you will need to heat the flask gently (lowest setting on a hot plate). Most of your solvent should be evaporated in less than 1 hour, under vacuum and with gentle heating. Weigh the filter flask.

The aqueous layer remaining in the separatory funnel contains the ytterbium catalyst. Pour the aqueous layer from the top of the separatory funnel into a preweighed 50-mL Erlenmeyer flask. Completely evaporate the water on a hot plate. Weigh the flask to determine how much catalyst you were able to recover. Place the catalyst in a container that holds the recycled catalyst that will be reused in other classes.

Unless instructed otherwise, prepare a sample for analysis by GC–MS by dissolving 2 drops of the mixture of nitrated aromatic compounds in about 1 mL of methylene chloride. These samples will be run using automation software on the GC–MS system.

When your sample has been run, you will have an opportunity to search the NIST mass spectral library to determine the structures of the product(s) of the nitration. Determine the structures of the product(s) and the percentages of each component. There will likely be starting material left in the reaction mixture. It would be of interest to see how your product ratios compare to the values obtained from the literature (see References).

REFERENCES

Braddock, C. Novel Recyclable Catalysts for Atom Economic Aromatic Nitration. *Green Chem.* **2001,** *3,* G26–G32.

Schofield, K. *Aromatic Nitration;* Cambridge University Press: London, 1980.

Waller, F. J.; Barrett, G. M.; Braddock, D. C.; Ramprasad, D. Lanthanide (III) Triflates as Recyclable Catalysts for Atom Economic Aromatic Nitration. *Chem. Comm.* **1997,** 613–614.

QUESTIONS

1. Interpret the mass spectrum of the compounds formed in the nitration of your aromatic substrate.
2. Draw a mechanism that explains how the nitro-substituted aromatic products observed in your reaction were formed.

Reduction of Ketones Using Carrots as Biological Reducing Agents

Green chemistry

Use of a biological reducing agent

Reduction of a ketone to an alcohol

A very common reaction in organic chemistry is the reduction of a ketone to a secondary alcohol.

$$
\underset{\underset{CH_3 \quad\quad R}{}}{\overset{O}{\underset{\|}{C}}} \quad \xrightarrow[\text{agent}]{\text{reducing}} \quad \underset{\underset{CH_3 \quad\quad R}{}}{\overset{OH}{\underset{|}{CH}}}
$$
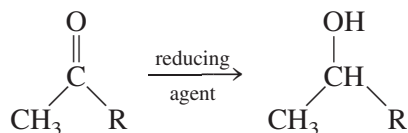
The most widely-used reducing agents include lithium aluminum hydride, sodium borohydride (see Experiment 31), and catalytic hydrogenation. The reaction takes place in an organic solvent, such as diethyl ether or methanol.

Biological reducing agents can also be used to bring about the reduction of a ketone to a secondary alcohol. The reduction of the carbonyl group of ethyl aceto-acetate (Experiment 27) is carried out using baker's yeast as a reducing medium. In this experiment, grated carrot is used to bring about a similar reaction. This type of reaction is an example of a Green Chemistry application, because water is the only solvent and the principal reagent is a common garden vegetable.

In each of these biological reduction experiments, an organic molecule is used by the biological system as the actual reducing agent. This reducing agent is **nico-tinamide adenine dinucleotide** (**NADH**). NADH acts as a *cofactor*; its chemical properties are expressed in coordination with an enzyme, which regulates the process.

**Nicotinamide Adenine Dinucleotide
(NADH)**
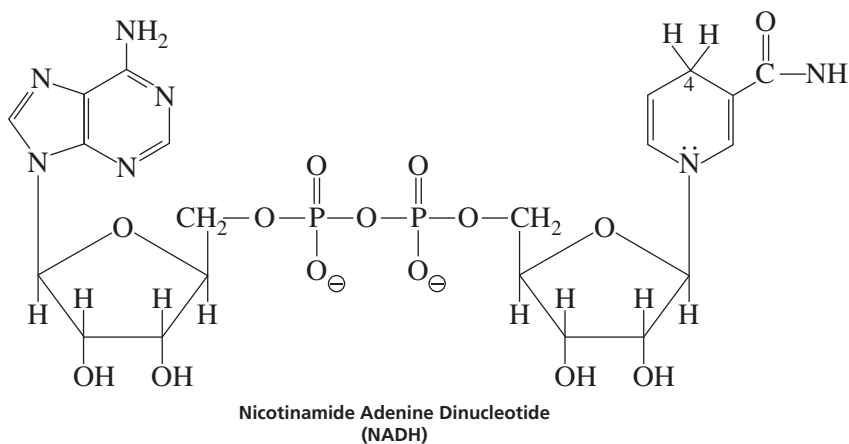
While the structure of NADH may seem overly complex, it is only necessary to focus on the nicotinamide ring—specifically on the hydrogen atoms attached to C4.

This is the actual reactive site of the NADH molecule; the rest of the structure is important for enzyme-substrate binding, water solubility, ease of transport through cell walls, etc.

In the biological reduction of a ketone, one of the hydrogens at C4 of the nicotinamide ring is transferred *with* its pair of electrons, in the form of a hydride, to the carbonyl carbon of the ketone. Note that the hydride is acting as a *nucleophile* as it attacks the carbonyl carbon.

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-R \xrightarrow{\ H^+\ } CH_3-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-R$$

NADH   **NAD⁺**
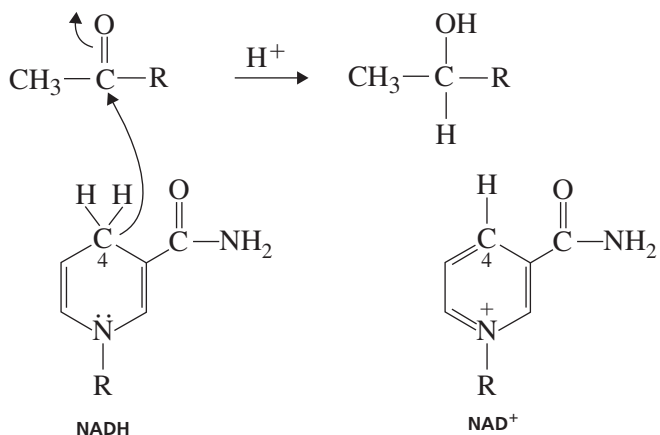
In the process of reducing the ketone, NADH is oxidized to NAD^+. This reaction is energetically favorable, because the aromatic property of the pyridine ring is restored—a gain in *resonance energy*.

In this experiment, the biological source of NADH will be a common garden carrot. The reaction is:

$$\text{carrot pieces} \atop H_2O \atop \text{room temperature}$$

Benzofuran-2-yl methyl ketone   **1-Benzofuran-2-yl ethanol**
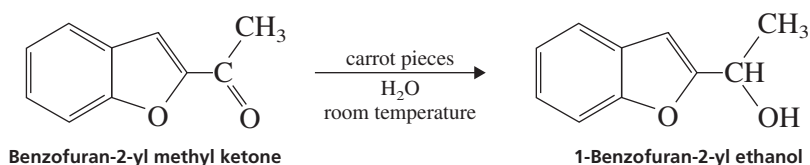
The results of the reduction will be analyzed by infrared spectroscopy. While we might expect this reduction to be stereoselective, the scale of the reaction used here does not permit an optical purity analysis by polarimetry.

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: Essay   Green Chemistry

         *Technique 8   Filtration

         *Technique 12   Extractions, Separations, and Drying Agents

         Technique 25   Infrared Spectroscopy

SPECIAL INSTRUCTIONS

This experiment must be allowed to stand aside for a period of at least 24 hours. Another experiment can be conveniently co-scheduled with this one.

SUGGESTED WASTE DISPOSAL

The carrot residue may be safely disposed of in the trash. Diethyl ether solvent can be recovered after the evaporation step if a rotary evaporator is available.

PROCEDURE

Grate one fresh carrot to obtain approximately 25 g of grated carrot. Wash this carrot material with distilled water. Weigh the grated carrot in a 150-mL Erlenmeyer flask, and add 75 mL of distilled water and a magnetic stirring bar. Add 50 mg of benzofuran-2-yl methyl ketone to the flask, stopper it with a cork, and clamp it in position above a magnetic stirrer. Allow the mixture to stir for at least 24 hours. Be sure to clamp the flask so that there is some space between the bottom of the flask and top of the magnetic stirrer. This is to avoid any heating from the stirrer motor, which may stop the reaction.

After the stirring has been stopped, filter the reaction mixture through a layer of cheesecloth to remove the larger chunks of carrot. Remove the remaining carrot residue by vacuum filtration using a Hirsch funnel (see Technique 8, Section 8.3).

Extract the filtrate three times with 10-mL portions of diethyl ether. Dry the ether extract over anhydrous magnesium sulfate. Transfer the dried solution into a clean flask, and remove the ether solvent by evaporation (if a rotary evaporator is available, it is best to use it).

Determine the infrared spectrum of the product as a neat liquid (see Technique 25, Section 25.2). You should be able to observe the extent of the reduction by noting the disappearance of the carbonyl stretching peak at about 1700 cm^{-1} and the appearance of a strong O-H stretching peak at about 3450 cm^{-1}. Be sure to submit your spectra with your laboratory report.

REFERENCE

Ravia, S.; Gamenara, D.; Schapiro, V.; Bellomo, A.; Adum, J.; Seoane, G.; Gonzalez, D. Enantioselective Reduction by Crude Plant Parts: Reduction of Benzofuran-2-yl Methyl Ketone with Carrot (*Daucus carota*) Bits. *J. Chem. Educ.* **2006,** *83,* 1049–1051.

30   **EXPERIMENT 30**

Resolution of (±)-α-Phenylethylamine and Determination of Optical Purity

Resolution of enantiomers

Use of a separatory funnel

Polarimetry

Chiral gas chromatography

NMR spectroscopy

Chiral resolving agent

Diastereomeric methyl groups

Although recemic (±)-α-phenylethylamine is readily available from commercial sources, the pure enantiomers are more difficult to obtain. In this experiment, you will isolate one of the enantiomers, the levorotatory one, in a high state of optical purity (large enantiomeric excess). A **resolution**, or separation, of enantiomers will be performed, using (+)-tartaric acid as the resolving agent.

Resolution of Enantiomers

The resolving agent to be used is (+)-tartaric acid, which forms diastereomic salts with racemic α-phenylethylamine. The important reactions for this experiment follow.
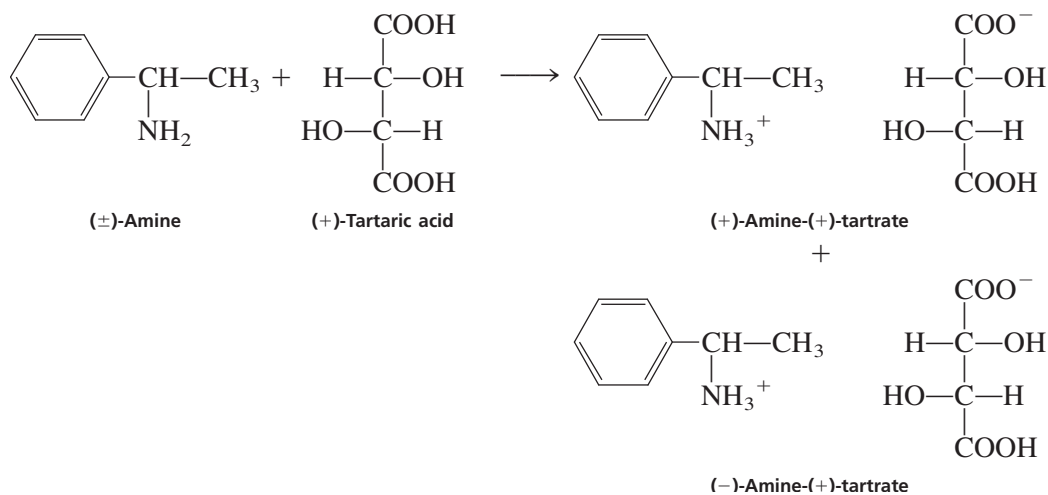
Optically pure (+)-tartaric acid is abundant in nature. It is frequently obtained as a by-product of winemaking. The separation depends on the fact that diastereomers usually have different physical and chemical properties. The (–)-amine-(+)-tartrate salt has a lower solubility than its diastereomeric counterpart, the (+)-amine-(+)-tartrate salt. With some care, the (–)-amine-(+)-tartrate salt can be induced to crystallize, leaving (+)-amine-(+)-tartrate in solution. The crystals are removed by filtration and purified. The (–)-amine can be obtained from the crystals by treating them with base. This breaks apart the salt by removing the proton, and it regenerates the free, unprotonated (–)-amine.

A polarimeter will be used to measure the observed rotation, α, of the resolved amine sample. From this value, you will calculate the specific rotation $[\alpha]_D$ and the optical purity (enantiomeric excess) of the amine. You will then calculate the percentages of each of the enantiomers present in the resolved sample. The (S)-α-phenylethylamine predominates in the sample. An optional chiral gas chromatographic method may be used to directly determine the percentages of each of the enantiomers in the sample.

NMR Determination of Optical Purity

An alternate means of determining the optical purity of the sample makes use of NMR spectroscopy (see Experiment 30B). A group attached to a stereogenic (chiral) carbon normally has the same chemical shift whether that carbon has either an *R* or *S* configuration. However, that group can be made diastereomeric in the NMR

spectrum (have different chemical shifts) when the recemic parent compound is treated with an optically pure chiral resolving agent to produce diastereomers. In this case, the group is no longer found in two enantiomers but, rather, in two different diastereomers, and its chemical shift will be different in each environment.
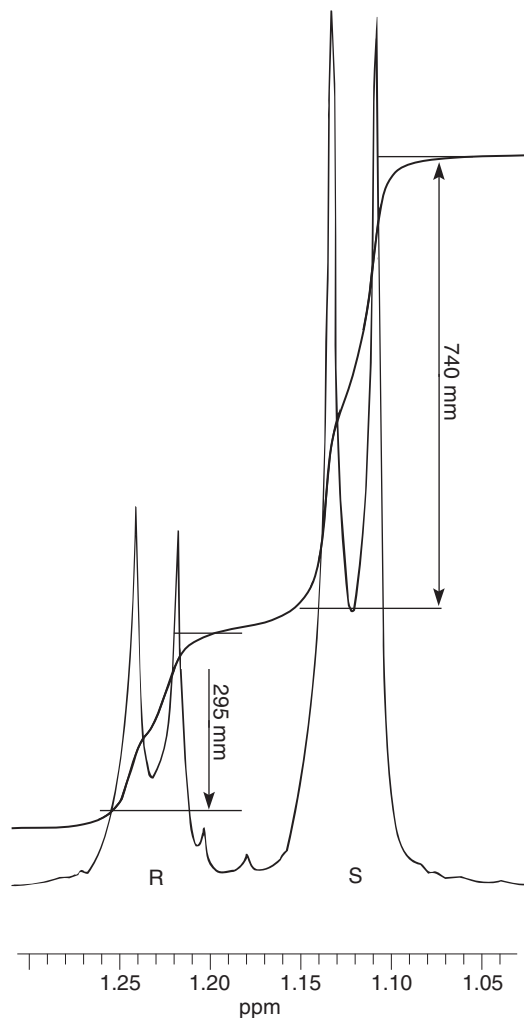
300-MHz Spectrum of a 50:50 mixture of resolved and unresolved α-phenylethylamine in CDCl₃. The chiral resolving agent (S)-(+)-O-acetylmandelic acid was added.

In this experiment, the partly resolved amine (containing both *R* and *S* enantiomers) is mixed with optically pure (*S*)-(+)-O-acetylmandelic acid in an NMR tube containing CDCl₃. Two diastereomers are formed:

$$\underset{\textbf{α-Phenylethylamine}}{\overset{(R/S)}{CH_3-\underset{\underset{Ph}{|}}{CH}-NH_2}} + \underset{\textbf{(S)-(+)-O-Acetylmandelicacid}}{\overset{(S)}{Ph-\underset{\underset{OAc}{|}}{CH}-COOH}} \longrightarrow$$

$$\left[\overset{(R)}{CH_3-\underset{\underset{Ph}{|}}{CH}-NH_3^+} + \overset{(S)}{Ph-\underset{\underset{OAc}{|}}{CH}-COO^-} \right]$$

$$+$$

$$\left[CH_3-\underset{\underset{\underset{(S)}{Ph}}{|}}{CH}-NH_3^+ + Ph-\underset{\underset{\underset{(S)}{OAc}}{|}}{CH}-COO^- \right]$$
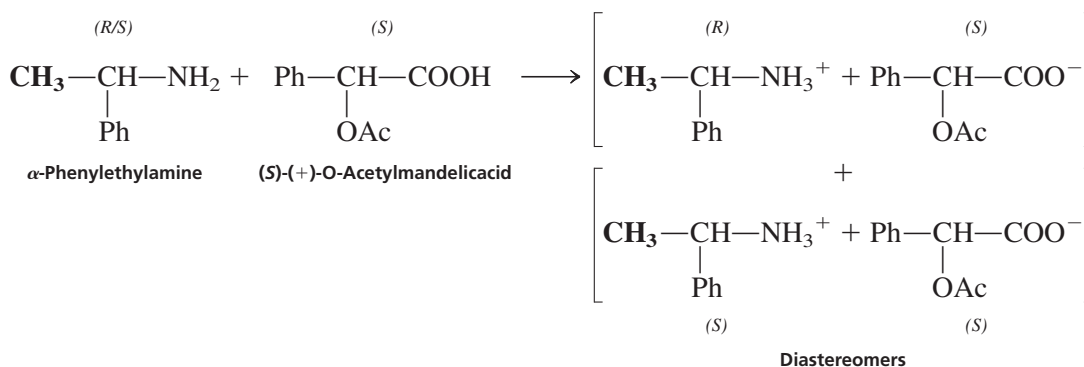
Diastereomers

The methyl groups in the amine portions of the two diastereomeric salts are attached to a stereocenter, (S) in one case and (R) in the other. As a result, the methyl groups themselves become diastereomeric, and they have different chemical shifts. In this case, the (R) isomer is downfield, and the (S) isomer is upfield. These methyl groups appear at approximately (varies) 1.1 and 1.2 ppm, respectively, in the proton NMR spectrum of the mixture. Because the methyl groups are adjacent to a methine (CH) group, they appear as doublets. These doublets may be integrated in order to determine the percentage of the (R) and (S) amines in the resolved α-phenylethylamine. In the example, the NMR spectrum was determined with a mixture made by dissolving equal quantities (50:50 mixture) of the original unresolved (±)-α-phenylethylamine and a student's resolved product, which contained predominantly (S)-(+)-α-phenylethylamine.

30A   E X P E R I M E N T   3 0 A

Resolution of (±)-α-Phenylethylamine

In this procedure, you will resolve racemic (±)-a-phenylethylamine, using (+)-tartaric acid as the resolving agent.

R E Q U I R E D   R E A D I N G

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: *Technique 8   Section 8.3

 *Technique 12   Sections 12.4, 12.8, 12.9

 Technique 23

 Technique 22   (optional)

SPECIAL INSTRUCTIONS

α-Phenylethylamine readily reacts with carbon dioxide in the air to form a white solid, the *N*-carboxyl amine derivative. Every effort should be taken to avoid prolonged exposure of the amine to air. Be sure to close the bottle tightly after you have measured the rotation of your amine and be sure to place your sample quickly into the flask where you will perform the resolution. This flask should also be stoppered. Use a cork stopper because a rubber stopper will dissolve somewhat and discolor your solution. The crystalline salt will not react with carbon dioxide until you decompose it to recover the resolved amine. Then, you must be careful once again.

The observed rotation for a sample isolated by a single student may be only a few degrees, which limits the precision of the optical purity determination. Better results can be obtained if four students combine their resolved amine products for the polarimetric analysis. If you have allowed your amine to have excessive exposure to air, the polarimetry solution may be cloudy. This will make it difficult to obtain an accurate determination of the optical rotation.

SUGGESTED WASTE DISPOSAL

Place the mother liquor solution from the crystallization, which contains (+)-α-phenylethylamine, (+)-tartaric acid, and methanol, in the special container provided for this purpose. Aqueous extracts will contain tartaric acid, dilute base, and water; they should be placed in the container designated for aqueous wastes. When you are finished with polarimetry, depending on the wishes of your instructor, you should either place your resolved (*S*)-(–)-α-phenylethylamine in a special container marked for this purpose or you should submit it to your instructor in a suitably labeled container that includes the names of those people who have combined their samples.

PROCEDURE

NOTE TO THE INSTRUCTOR

This experiment is designed for students to work individually, but to combine their products with three other students for polarimetry.

Preparations Place 7.8 g of L-(+)-tartaric acid and 125 mL of methanol in a 250-mL Erlenmeyer flask. Heat this mixture on a hot plate until the solution is nearly boiling. Slowly add 6.25 g of racemic α-phenylethylamine (α-methylbenzylamine) to this hot solution.

CAUTION

At this step, the mixture is likely to froth and boil over.

Crystallization Stopper the flask and let it stand overnight. The crystals that form should be prismatic. If needles form, they are not optically pure enough to give a complete resolution of the enantiomers; *prisms must form*. Needles should be dissolved (by careful heating)

and cooled slowly to crystallize once again. When you recrystallize, you can "seed" the mixture with a prismatic crystal, if one is available. If it appears that you have prisms but that they are overgrown (covered) with needles. The mixture may be heated until *most* of the solid has dissolved. The needle crystals dissolve easily, and usually a small amount of the prismatic crystals remains to seed the solution. After dissolving the needles, allow the solution to cool slowly and form prismatic crystals from the seeds.

Workup Filter the crystals, using Büchner funnel (see Technique 8, Section 8.3, and Figure 8.5), and rinse them with a few portions of cold methanol. Partially dissolve the crystalline amine-tartrate salt in 25 mL of water, add 4 mL of 50% sodium hydroxide, and extract this mixture with three 10-mL portions of methylene chloride using a separatory funnel (see Technique 12, Section 12.4). Combine the organic layers from each extraction in a stoppered flask and dry them over about 1 g of anhydrous sodium sulfate for about 10 minutes.

Two different methods should be considered for removing the solvent. Ask your instructor which method you should use. **Method 1** involves using a rotary evaporator to remove the solvent. If you are employing this method, preweigh a 100-mL round bottom flask, and decant the methylene chloride solution containing the amine into the flask. Ask your instructor to demonstrate the use of the rotary evaporator. A liquid remains after the solvent has been removed. You may need to increase the temperature of the water bath to ensure that all of the solvent has been removed. About 2 or 3 mL of the liquid amine should remain. Proceed to the Yield Calculation and Storage section below.

If your instructor asks you to use **method 2**, proceed as follows. While the solution is drying over anhydrous sodium sulfate, preweigh a clean, dry 50-mL Erlenmeyer flask. Decant the dried solution into the flask and evaporate the methylene chloride on a hot plate (about 60°C) in a hood. A stream of nitrogen or air should be directed into the flask to increase the rate of evaporation. When the volume of liquid reaches about 2 or 3 mL total, you should carefully insert a hose attached to the house vacuum or aspirator system to remove any remaining methylene chloride. The hose should be inserted into the neck of the flask. Note that the desired product is a **liquid**. Some solid amine carbonate may start to form on the sides of the flask during the course of the evaporation. This undesired solid is more likely to form if you prolong the heating operation. You will want to take care to avoid the formation of this white solid if at all possible. If you do obtain a cloudy solution or solids are present, transfer the material to a centrifuge tube and centrifuge the sample. Then remove the clear liquid for the polarimetry part of this experiment.

Yield Calculation and Storage Stopper the flask and weigh it to determine the yield. Also calculate the percentage yield of the (S)-(−)-amine based on the amount of the racemic amine you started with.

Polarimetry Combine your product with the products obtained by three other students. If anyone's product is highly colored or if a large amount of solid is present, do not use it. If the amine is a little cloudy or if there is just a small amount of solid present, transfer the sample to a small centrifuge tube (microcentrifuge tubes work well here) and centrifuge the sample for about 5 minutes. Remove the *clear* liquid with a Pasteur pipet to avoid drawing up any solid into the pipet and fill a preweighed 10 mL volumetric flask. You will not get good results with the polarimeter if the amine is cloudy or if there are suspended solids present in your amine, so be careful to avoid transferring any solid.

Weigh the flask to determine the weight of amine and calculate the density (concentration) in grams per milliliter. You should obtain a value of about 0.94 g/mL. This should give you a sufficient amount of material to proceed with the polarimetry measurements that follow without diluting your sample. If, however, your combined products do not amount to more than 10 mL of the amine, you may have to dilute your sample with methanol (check with your instructor).

If you have less than 10 mL of product, weigh the flask to determine the amount of the amine present. Then fill the volumetric flask to the mark with absolute methanol and mix the solution thoroughly by inverting 10 times. The concentration of your solution in grams per milliliter is easily calculated.

Transfer the solution to a 0.5-dm polarimeter tube and determine its observed rotation. Your instructor will show you how to use the polarimeter. Report the values of the observed rotation, specific rotation, and optical purity (enantiomeric excess) to the instructor. The published value for the specific rotation is $[\alpha]_D^{22} = -40.3°$. Calculate the percentage of *each* of the enantiomers in the sample (see Technique 23, Section 23.5), and include the figures in your report.

Due to the presence of some methylene chloride in the sample of the chiral amine, you may obtain low rotation values from polarimetry. Because of this, your calculated value of the optical purity (enantiomeric excess) and percentages of the enantiomers will be in error. The percentages of the enantiomers obtained from the optional chiral gas chromatography experiment below should provide more accurate percentages of each of the stereoisomers.

Chiral Gas Chromatography (Optional) Chiral gas chromatography will provide a direct measure of the amounts of each stereoisomer present in your resolved α-phenylethylamine sample. A Varian CP-3800 equipped with a J & P (Agilent) Cyclosil B capillary column (30 m, 0.25-mm ID, 0.25 μm) provides an excellent separation of (*R*) and (*S*)-enantiomers.

Set the FID detector at 270°C and the injector temperature at 250°C. The initial split ratio should be set at 150:1 and then changed to 10:1 after 1.5 minutes. Set the oven temperature at 100°C and hold at that temperature for 25 minutes. The helium flow rate is 1 mL/min. The compounds elute in the following order: (*R*)-α-phenylethylamine (17.5 min) and (*S*)-enantiomer (18.1 min). Your observed retention times may vary from those given here, but the order of elution will be the same. Because the peaks overlap slightly. You may not observe a distinct peak for the (*R*)-enantiomer. Instead, you may observe a shoulder for the (*R*)-enantiomer peak on the side of the large peak for the (*S*)-enantiomer. If you are able to see the (*R*)-enantiomer, integrate the area under the peaks to obtain the percentages of each of the enantiomers in your sample and compare your results to those obtained with the polarimeter. It should be noted that the resolution process used in this experiment is highly selective for the (*S*)-enantiomer. That is the good news; the bad news is that you may have such a pure (*S*)-α-phenylethylamine sample that you will not be able to obtain percentages from the analysis on the chiral column.

30B   E X P E R I M E N T   3 0 B

Determination of Optical Purity Using NMR and a Chiral Resolving Agent

In this procedure, you will use NMR spectroscopy with the chiral resolving agent (S)-(+)-O-acetylmandelic acid to determine the optical purity of the (S)-(–)-α-phenylethylamine you isolated in Experiment 30A.

REQUIRED READING

New: Technique 26   Nuclear Magnetic Resonance Spectroscopy

SPECIAL INSTRUCTIONS

Be sure to use a clean Pasteur pipet whenever you remove $CDCl_3$ from its supply bottle. Avoid contaminating the stock of NMR solvent. Also be sure to fill and empty the pipet several times before attempting to remove the solvent from the bottle. If you bypass this equilibration technique, the volatile solvent may squirt out of the pipet before you can transfer it successfully to another container.

SUGGESTED WASTE DISPOSAL

When you dispose of your NMR sample, which contains $CDCl_3$, place it in the container designated for halogenated wastes.

PROCEDURE

Using a small test tube, weigh approximately 0.05 mmole (0.006 g, *MW* = 121) of your resolved amine by adding it from a Pasteur pipet. Cork the test tube to protect it from atmospheric carbon dioxide. Carbon dioxide reacts with the amine to form an amine carbonate (white solid). Using a weighing paper, weigh approximately 0.06 mmole (0.012 g, *MW* = 194) of (*S*)-(+)-O-acetylmandelic acid and add it to the amine in the test tube. Using a clean Pasteur pipet, add about 0.25 mL of $CDCl_3$ to dissolve everything. If the solid does not completely dissolve, you can mix the solution by drawing it several times into your Pasteur pipet and redelivering it back into the test tube. When everything is dissolved, transfer the mixture to an NMR tube using a Pasteur pipet. Using a clean Pasteur pipet, add enough $CDCl_3$ to bring the total height of the solution in the NMR tube to 50 mm.

Determine the proton NMR spectrum, preferably at 300 MHz, using a method that expands and integrates the peaks of interest. Using the integrals, calculate the percentages of the *R* and *S* isomers in the sample and its optical purity.[1] Compare your results from this NMR determination to those you obtained by polarimetry (Experiment 40A).

---

[1]*Note to the Instructor:* In some cases, the resolution is so successful that it is very difficult to detect the doublet arising from the (*R*)-(+)-α-phenylethylamine + (*S*)-(+)-O-acetylmandelic acid diastereomer. If this occurs, it is useful to have the students add a single drop of *racemic* α-phenylethylamine to the NMR tube and redetermine the spectrum. In this way, both diastereomers can be clearly seen.

REFERENCES

Ault, A. Resolution of D, L-α-Phenylethylamine. *J. Chem. Educ.* **1965,** *42,* 269.

Jacobus, J.; Raban, M. An NMR Determination of Optical Purity. *J. Chem. Educ.* **1969,** *46,* 351.

Parker, D.; Taylor, R. J. Direct ^{1}H NMR Assay of the Enantiomeric Composition of Amines and β-Amino Alcohols Using O-Acetyl Mandelic Acid as a Chiral Solvating Agent. *Tetrahedron* **1987,** *43* (22), 5451.

QUESTIONS

1. Using a reference textbook, find examples of reagents used in performing chemical resolutions of acidic, basic, and neutral racemic compounds.

2. Propose methods of resolving each of the following racemic compounds.

   a.

   $$CH_3-CH-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$
   $$|$$
   $$Br$$

   b.
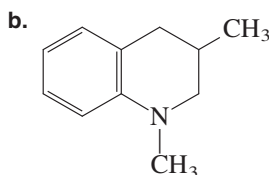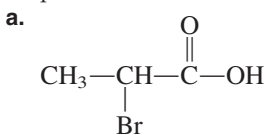
3. Explain how you would proceed to isolate (*R*)-(+)-α-phenylethylamine from the *mother liquor* that remained after you crystallized (*S*)-(−)-α-phenylethylamine.

4. What is the white solid that forms when α-phenylethylamine comes in contact with carbon dioxide? Write an equation for its formulation.

5. Which method, polarimetry or NMR spectroscopy, gives the more accurate results in this experiment? Explain.

6. Draw the three-dimensional structure of (*S*)-(−)-α-phenylethylamine.

7. Draw the three-dimensional structure of the diastereomer formed when (*S*)-(−)-α-phenylethylamine is reacted with (*S*)-(+)-O-acetylmandelic acid.

EXPERIMENT 31

An Oxidation–Reduction Scheme: Borneol, Camphor, Isoborneol

Green chemistry

Sodium hypochlorite (bleach) oxidation

Monitoring reactions by thin-layer chromatography (TLC)

Sodium borohydride reduction

Sublimation (optional)

Stereochemistry

Gas chromatography

Spectroscopy (infrared, proton NMR, carbon-13 NMR)

Computational chemistry (optional)
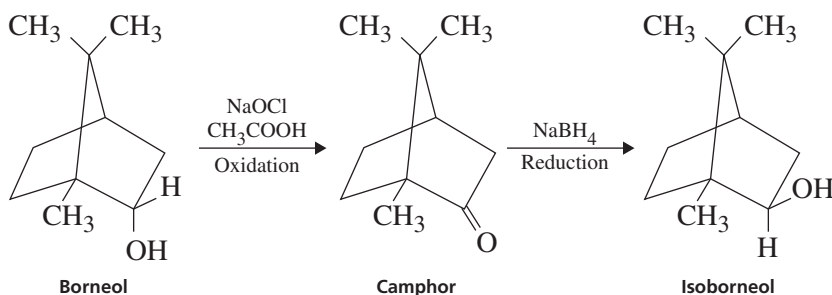
This experiment will illustrate the use of a "green" oxidizing agent, sodium hypochlorite (bleach) in acetic acid, for converting a secondary alcohol (borneol) to a ketone (camphor). This reaction will be followed by TLC to monitor the progress of the oxidation. The camphor is then reduced by sodium borohydride to give the *isomeric* alcohol, isoborneol. The spectra of borneol, camphor, and isoborneol will be compared to detect structural differences and to determine the extent to which the final step produces an alcohol isomeric with the starting material, borneol.

OXIDATION OF BORNEOL WITH HYPOCHLORITE

Sodium hypochlorite, bleach, can be used to oxidize secondary alcohols to ketones. Because this reaction occurs more rapidly in an acidic environment, it is likely that the actual oxidizing agent is hypochlorous acid, HOCl. This acid is generated by the reaction between sodium hypochlorite and acetic acid.

$$NaOCl \ + \ CH_3COOH \longrightarrow HOCl \ + \ CH_3COONa$$

Although the mechanism is not fully understood, there is evidence that an alkyl hypochlorite intermediate is produced, which then gives the product via an E2 elimination:
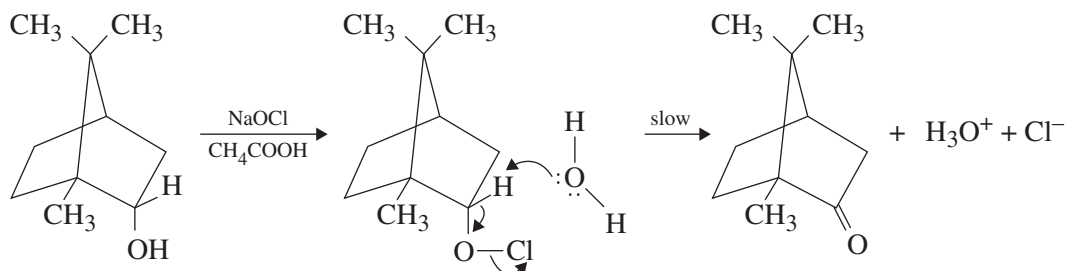
REDUCTION OF CAMPHOR WITH SODIUM BOROHYDRIDE

Metal hydrides (sources of H:⁻) of the Group III elements, such as lithium aluminum hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$, are widely used in reducing carbonyl groups. Lithium aluminum hydride, for example, reduces many compounds containing carbonyl groups such as aldehydes, ketones, carboxylic acids, esters, or amides, whereas sodium borohydride reduces only aldehydes and ketones. The reduced reactivity of borohydride allows it to be used even in alcohol and water solvents, whereas lithium aluminum hydride reacts violently with these solvents to produce hydrogen gas and thus must be used in nonhydroxylic solvents. In the present experiment, sodium borohydride is used because it is easily handled, and the results of reductions using either of the two reagents are essentially the same. The same care required for lithium aluminum hydride in keeping it away from water need not be taken for sodium borohydride.

The mechanism of action of sodium borohydride in reducing a ketone is as follows:

(1)
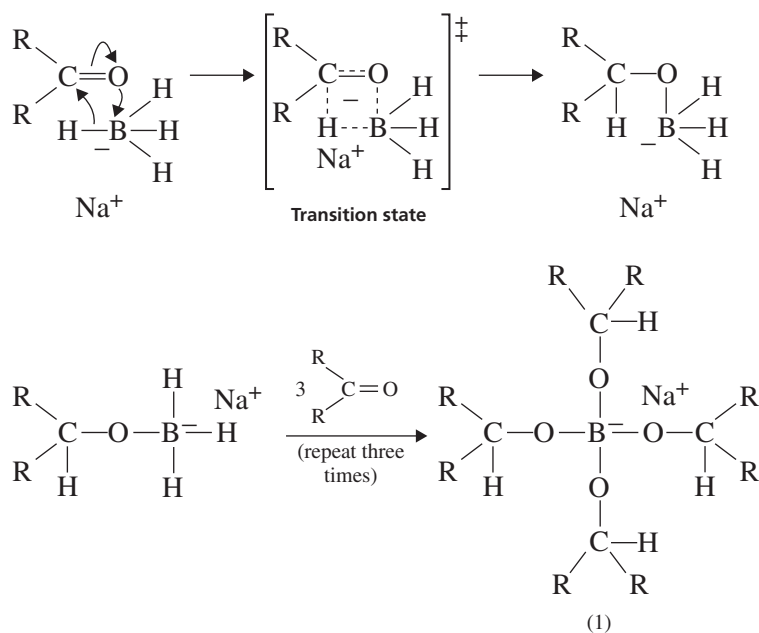
Note in this mechanism that all four hydrogen atoms are available as hydrides (H:⁻), and thus one mole of borohydride can reduce four moles of ketones. All of the steps are irreversible. Usually, excess borohydride is used because there is uncertainty regarding its purity and because some of it reacts with the solvent.

Once the final tetraalkoxyboron compound (1) is produced, it can be decomposed (along with excess borohydride) at elevated temperatures as shown:

$$(R_2CH-O)_4B^-Na^+ + 4\ R'OH \longrightarrow 4\ R_2CHOH + (R'O)_4B^-Na^+$$
$$\text{(1)}$$

The stereochemistry of the reduction is very interesting. The hydride can approach the camphor molecule more easily from the bottom side (**endo** approach) than from the top side (**exo** approach). If attack occurs at the top, a large steric repulsion is created by one of the two **geminal** methyl groups. Geminal methyl groups are groups that are attached to the same carbon. Attack at the bottom avoids this steric interaction.
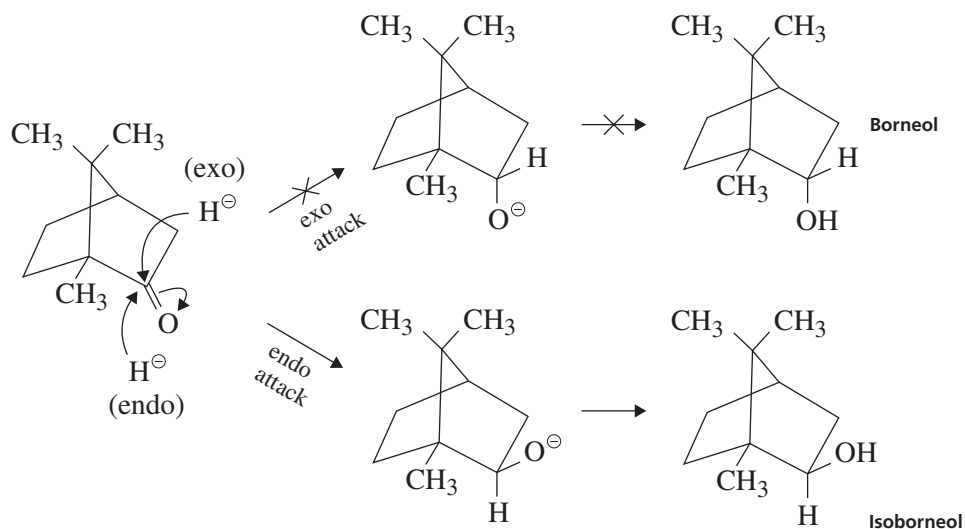
It is expected, therefore, that **isoborneol**, alcohol produced from the attack at the *least*-hindered position, will *predominate but will not be the exclusive product* in the final reaction mixture. The percentage composition of the mixture can be determined by spectroscopy.

It is interesting to note that when the methyl groups are removed (as in 2-norbornanone), the top side (**exo** approach) is favored, and the opposite stereochemical result is obtained. Again, the reaction does not give exclusively one product.
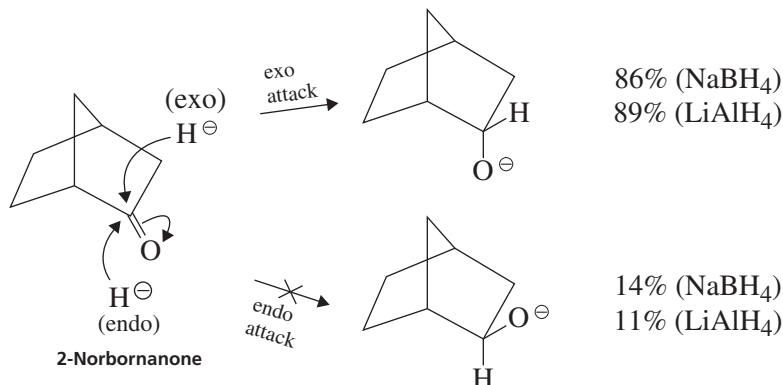
Bicyclic systems such as camphor and 2-norbornanone react predictably according to steric influences. This effect has been termed **steric approach control**. In the reduction of simple acyclic and monocyclic ketones, however, the reaction seems to be influenced primarily by thermodynamic factors. This effect has been termed **product development control**; In the reduction of 4-*t*-butylcyclohexanone, the thermodynamically more stable product, is produced by product development control.
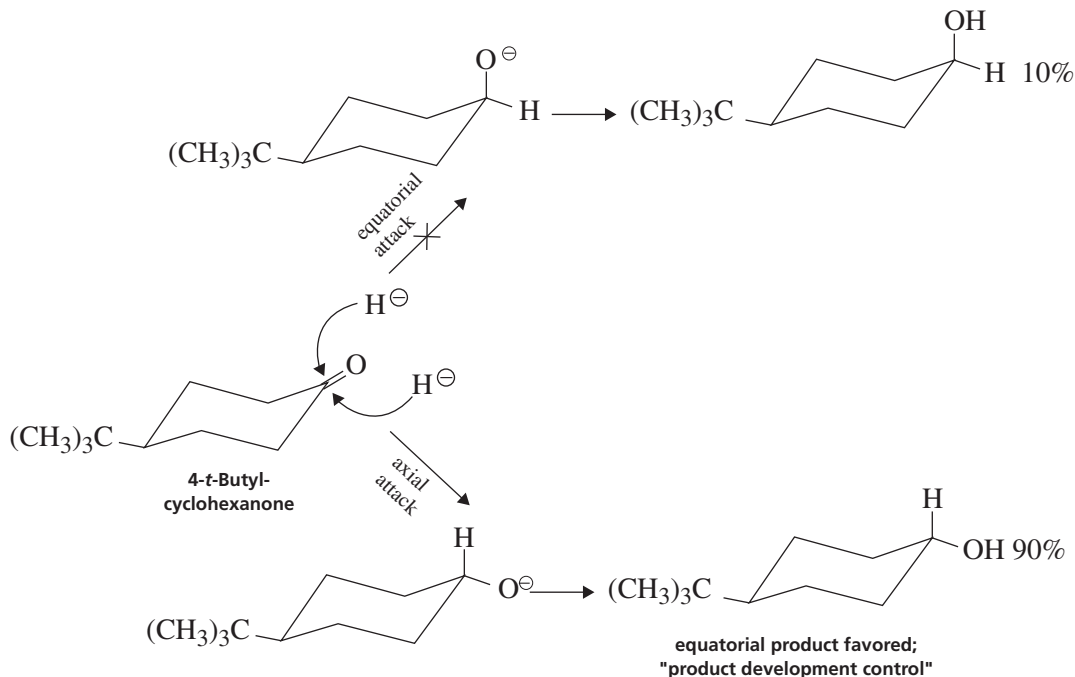
4-*t*-Butyl-cyclohexanone

equatorial attack

axial attack

**equatorial product favored;
"product development control"**

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: Technique 6   Heating and Cooling Methods, Sections 6.1–6.3

*Technique 7   Reaction Methods, Sections 7.1–7.4 and 7.10

*Technique 8   Filtration, Section 8.3

Technique 9   Physical Constants of Solids: The Melting Point,
Sections 9.7 and 9.8

*Technique 12   Extractions, Separations, and Drying Agents
Section 12.4

Techniques 20, 22, 25, 26, and 27

New: *Technique 17   Sublimation (optional)

Essay   Green Chemistry

Essay and Experiment 18   Computational Chemistry (optional)

SPECIAL INSTRUCTIONS

The reactants and products are all highly volatile and must be stored in tightly closed containers. The reaction should be carried out in a well-ventilated room or under a hood because a small amount of chlorine gas will be emitted from the reaction mixture.

SUGGESTED WASTE DISPOSAL

The aqueous solutions obtained from the extraction steps should be placed in the aqueous waste container. Any leftover methanol may be placed in the nonhalogenated organic waste container. Methylene chloride may be placed in the halogenated waste container.

NOTES TO THE INSTRUCTOR

We use commercial 6% sodium hypochlorite solution (VWR Scientific Products, No. VW3248-1) for this reaction because it more reliably oxidizes borneol to camphor. Even with this solution, however, some students may not completely oxidize the borneol. It is advisable to follow the progress of the reaction by TLC. If some borneol remains after the normal reaction period, additional sodium hypochlorite should be added. Some students will obtain a liquid product. In this case, it is likely that the borneol has not been completely oxidized. If the infrared spectrum shows the presence of borneol (OH stretch), then it is advisable to use a commercial source of camphor for Part B. An optional procedure is provided for students to sublime their camphor. It is recommended that students use one of the two microscale sublimators shown in Technique 17, Figures 17.2A and B.

The sodium borohydride should be checked to see whether it is active. Place a small amount of powdered material in some methanol, and heat it gently. The solution should bubble vigorously if the hydride is active.

Percentages of borneol and isoborneol can be determined by gas chromatography. Any gas chromatograph should be suitable for this determination. For example, a Gow-Mac 69-930 instrument with an 8-ft column of 10% Carbowax 20M, at 180°C and with a 40 mL/min helium flow rate, will give a suitable separation. The compounds elute in the following order: camphor (8 min), isoborneol (10 min), and borneol (11 min). A Varian CP-3800 with autosampler equipped with a J & W DB-5 or Varian CP-Sil 5CB capillary column (30 m, 0.25-mm ID, 0.25 *μm)* also provides a good separation. Set the injector temperature at 250°C. The column oven conditions are the following: start at 75°C (hold for 10 min), increase to 200°C at 35°C min, and then hold at 200°C (1 min). Each run takes about 15 minutes. The helium flow rate is 1 mL/min. The compounds elute in the following order: camphor (12.9 min), isoborneol (13.1 min), and borneol (13.2 min). An optional procedure is provided that involves computational chemistry.

PROCEDURE

Part A. Oxidation of Borneol to Camphor

Assemble the Apparatus. To a 50-mL round-bottom flask, add 1.0 g of racemic borneol, 3 mL of acetone, and 0.8 mL of acetic acid. After adding a magnetic stir bar to the flask, attach a water condenser and place the round-bottom flask in a warm water bath at 50°C, as shown in Technique 6, Figure 6.4. The apparatus should be set up in a good fume hood or in a well-ventilated room because of the potential for evolution of chlorine gas. It is important that the temperature of the water bath remain near 50°C during the entire reaction period. Stir the mixture until the borneol is dissolved. If it does not dissolve, add about 1 mL of acetone.

Addition of Sodium Hypochlorite. Measure out 18 mL of 6% sodium hypochlorite solution in a graduated cylinder.[1] Add dropwise 1.5 mL of the hypochlorite solution every 4 minutes through the top of the water-cooled condenser. The addition will take 48 minutes to complete. Continue to stir and heat the mixture during the 48-minute period. Following the addition, heat and stir the mixture for an additional 15 minutes. Allow the reaction mixture to cool to room temperature. Remove the condenser.

Monitoring the Oxidation with Thin-Layer Chromatography (TLC). The reaction progress can be monitored by TLC (see Technique 20, Section 20.10 and Figure 20.7). Remove about 1 mL of reaction mixture with a Pasteur pipet, and place it into a centrifuge tube. Add about 1 mL of methylene chloride, cap the tube, and shake the tube for a few minutes. Remove the lower, methylene chloride layer with a Pasteur pipet in such a way to avoid drawing up any of the aqueous layer. Place the methylene chloride extract into a dry test tube.

Prepare a 30 × 70 mm silica gel TLC plate (Whatman Silica Gel plate with aluminum backing, No. 4420-222) that will be spotted with three solutions using micropipets (see Technique 20, Section 20.4). Borneol (2% in methylene chloride) is spotted in lane 1, camphor (2% in methylene chloride) in lane 2, and the reaction mixture dissolved in methylene chloride in lane 3. Spot each solution 5 or 6 times, each time spotting it on top of the previous spot (allow the previous spot to dry before applying the next one). Prepare a developing chamber from a 4-oz wide-mouth, screw-cap jar (as described in Technique 20, Section 20.5) using methylene chloride as the solvent. Put the plate into the developing chamber. When the solvent front has traveled about 5 cm, remove the plate, evaporate the solvent, and place the plate into another jar that contains a few crystals of iodine (see Technique 20, Section 20.7). Heat the jar on a hot plate. The iodine vapors will visualize the spots. Camphor will have a larger R_f value than borneol. Unfortunately, camphor and borneol do not give intense spots with iodine, but you should be able to see them. The relative amounts of borneol and camphor can be determined by the relative intensity of the spots on the plates. The reaction will be judged to be complete if the borneol spot in lane 3 is not visible. If some borneol remains, as determined by the TLC method, reattach the water condenser, reheat the reaction mixture in the round-bottom flask, and then add 3 mL more of the sodium hypochlorite solution dropwise to the reaction mixture over a 15-minute period. Check the mixture again using the previous procedure and a new TLC plate. Ideally, borneol should not be visible on the plate, and camphor should be visible.

Extraction of Camphor. When the reaction is complete, allow the mixture to cool to room temperature. Remove the water condenser and transfer the mixture to a separatory funnel using 10 mL of methylene chloride to aid the transfer. Shake the separatory funnel in the usual manner (see Technique 12, Section 12.4). Drain the lower organic layer from the funnel. Extract the aqueous layer remaining in the separatory funnel with another 10-mL portion of methylene chloride. Combine the two organic layers. Extract the combined methylene chloride layers with 6 mL of saturated sodium bicarbonate solution, being careful to vent the funnel frequently to release carbon dioxide gas formed from reaction with acetic acid. Drain the lower organic layer, and discard the aqueous layer. Return the organic layer to the separatory funnel, and extract it with 6 mL of 5% sodium bisulfite solution. Drain the lower organic layer and discard the aqueous layer. Return the organic layer to the separatory funnel, and extract it with 6 mL of water. Drain the organic layer into a dry Erlenmeyer flask, and add about 2 g of granular anhydrous sodium sulfate to dry the solution. Swirl gently until any cloudiness in the solution is removed. If all of the sodium sulfate clumps together when the mixture is stirred with a spatula, add some additional drying agent. Cork the flask, and allow the solution to dry for about 15 minutes.

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[1] We use commercial 6% sodium hypochlorite solution (VWR Scientific Products, No. VW3248-1).

Isolation of Product. Transfer the dried methylene chloride extracts to a preweighed 50-mL Erlenmeyer flask. Evaporate the solvent in the hood with a gentle stream of dry air or nitrogen gas while heating the Erlenmeyer flask in a water bath at 40–50°C (see Figure 7.17A). When all of the liquid has evaporated and a solid has appeared, remove the flask from the heat source. If the crystals appear wet with solvent, apply a vacuum for a few minutes to remove any residual solvent.

Analysis of Camphor. Weigh the flask to determine the weight of your product, and calculate the percentage yield. If your instructor requests it, determine the melting point of your product. The melting point of pure camphor is 174°C, but it is likely that the melting point obtained will be lower than this value because impurities drastically affect the melting behavior of camphor (see Question 4). Your instructor may ask you to purify the camphor by sublimation. If that is the case, it is advisable to obtain the melting point after sublimation.

Infrared Spectrum. Before proceeding to Part B, you should verify that the oxidation was successful. This can be done by determining the infrared spectrum of the camphor product. The spectrum is best obtained employing the dry film method (see Technique 25, Section 25.4). By examing the infrared peaks, determine if the borneol (an alcohol OH stretch) is absent, or nearly absent, and if the borneol has been oxidized to camphor (a ketone C $=$ O stretch). For comparison, an infrared spectrum of camphor is shown below. If your oxidation was not totally successful, consult your instructor for your options. The camphor is reduced in Part B to isoborneol. Store the camphor in a tightly stoppered flask.

Optional Exercise: Sublimation. If your instructor requests it, purify your camphor by vacuum sublimation using an aspirator or house vacuum system and the procedure and apparatus shown in Technique 17, Sections 17.5 and 17.6. A microburner is a convenient heating source for the sublimation, but great care must be taken to avoid fires. You must be certain that no one is using ether near your desk. Check with your instructor for clearance. You should sublime your camphor in portions. Scrape the purified material from the cold finger onto a preweighed smooth piece of paper with a spatula, reweigh the paper, and determine the amount of material recovered from the sublimation. Calculate a percentage yield of purified camphor, based on the original amount of borneol that you used. Determine the melting point of your purified camphor. The infrared spectrum of the purified camphor may be determined as well.

Part B. Reduction of Camphor to Isoborneol

Reductions. The camphor obtained in Part A should not contain borneol. If it does, show your infrared spectrum to your instructor and ask for advice. If the amount of camphor obtained in Part A, or after the sublimation if you did this, is less than 0.25 g, obtain some camphor from the supply shelf to supplement your yield. If the amount is more than 0.25 g, scale up the reagents appropriately from the following amounts. Add 1.5 mL of methanol to the camphor contained in a 50-mL flask. Stir with a glass stirring rod until the camphor has dissolved. In portions, cautiously and intermittently add 0.25 g of sodium borohydride to the solution with a spatula. When all of the borohydride is added, boil the contents of the flask on a warm hot plate (low setting) for 2 minutes.

Isolation and Analysis of Product. Allow the reaction mixture to cool for several minutes, and carefully add 10 mL of ice water. Collect the white solid by filtering it on a Hirsch funnel and, by using suction, allow the solid to dry for a few minutes. Transfer the solid to a dry Erlenmeyer flask. Add about 10 mL of methylene chloride to dissolve the product. Once the product has dissolved (add more solvent, if necessary), add about 0.5 g of granular anhydrous sodium sulfate to dry the solution. When dry, the solution should not be cloudy. If the solution is still cloudy, add some more granular anhydrous sodium sulfate. Transfer the solution from the drying agent into a preweighed dry flask. Evaporate the solvent in a hood, as described previously.

Determine the weight of the product, and calculate the percentage yield. If your instructor requests it, determine the melting point; pure isoborneol melts at 212°C. Determine the infrared spectrum of the product by the dry film method used previously with camphor. Compare the spectrum with the infrared spectra for borneol and isoborneol shown in the figures.

Part C. Percentages of Isoborneol and Borneol Obtained from the Reduction of Camphor

NMR Determination. The percentage of each of the isomeric alcohols in the borohydride mixture can be determined from the NMR spectrum (see Technique 26, Section 26.1) The NMR spectra of the alcohols are shown. The hydrogen atom on the carbon atom bearing the hydroxyl group appears at 4.0 ppm for borneol and 3.6 ppm for isoborneol. To obtain the product ratio, integrate these peaks (using an expanded presentation) in the NMR spectrum of the sample obtained from borohydride reduction. In the spectrum shown on page 265, the isoborneol–borneol ratio of 6:1 was obtained. The percentages obtained are 85% isoborneol and 15% borneol.

Gas Chromatography. The isomer ratio and percentages can also be obtained by gas chromatography. Your instructor will provide instructions for preparing your sample. A Gow-Mac 69-360 instrument fitted with an 8-ft column of 10% Carbowax 20M, in an oven set at 180°C, and with a 40 mL/min helium flow rate will completely separate isoborneol and borneol from each other. In addition, any residual camphor can be observed. The retention times for camphor, isoborneol, and borneol are 8, 10, and 11 minutes, respectively. Other instrument conditions are provided in the Notes to the Instructor.
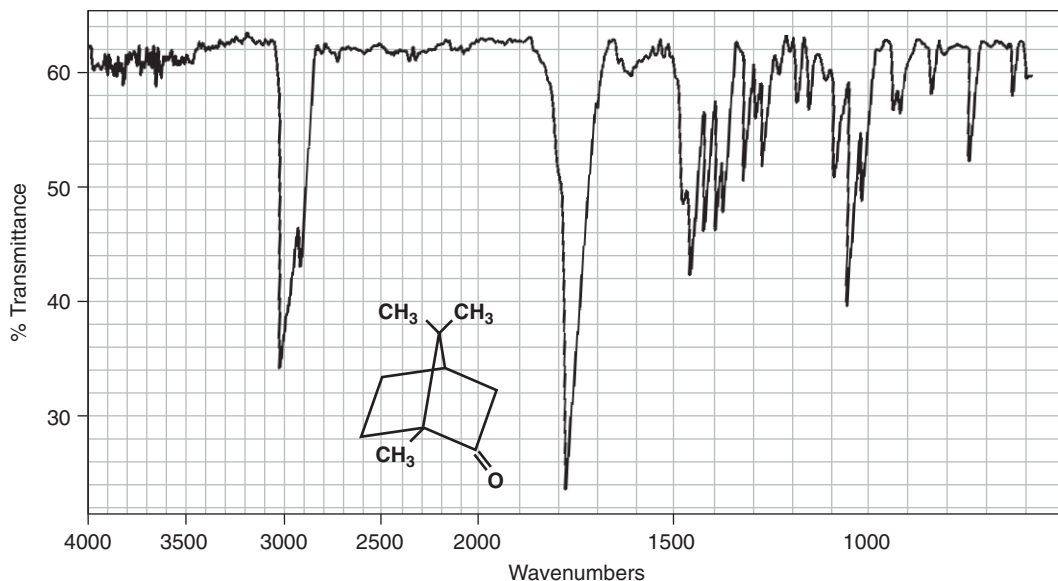
Infrared spectrum of camphor (KBr pellet).
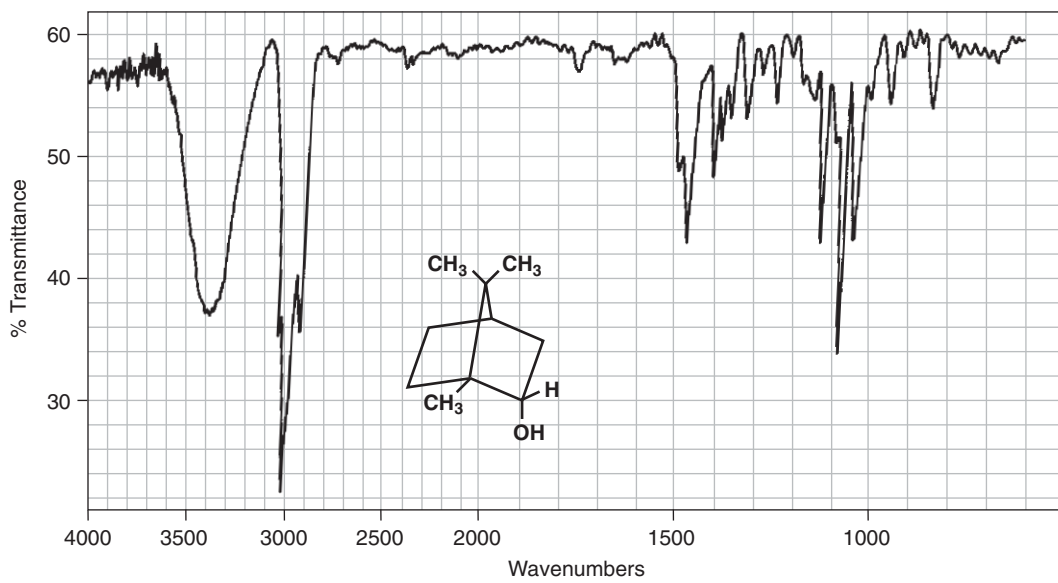
Infrared spectrum of borneol (KBr pellet).
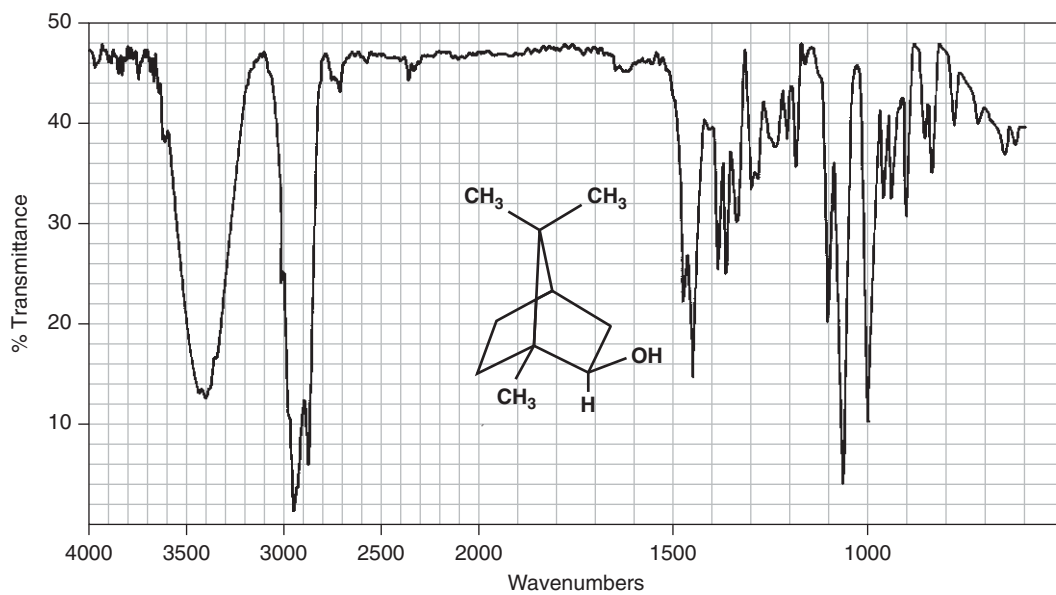
Infrared spectrum of isoborneol (KBr pellet).
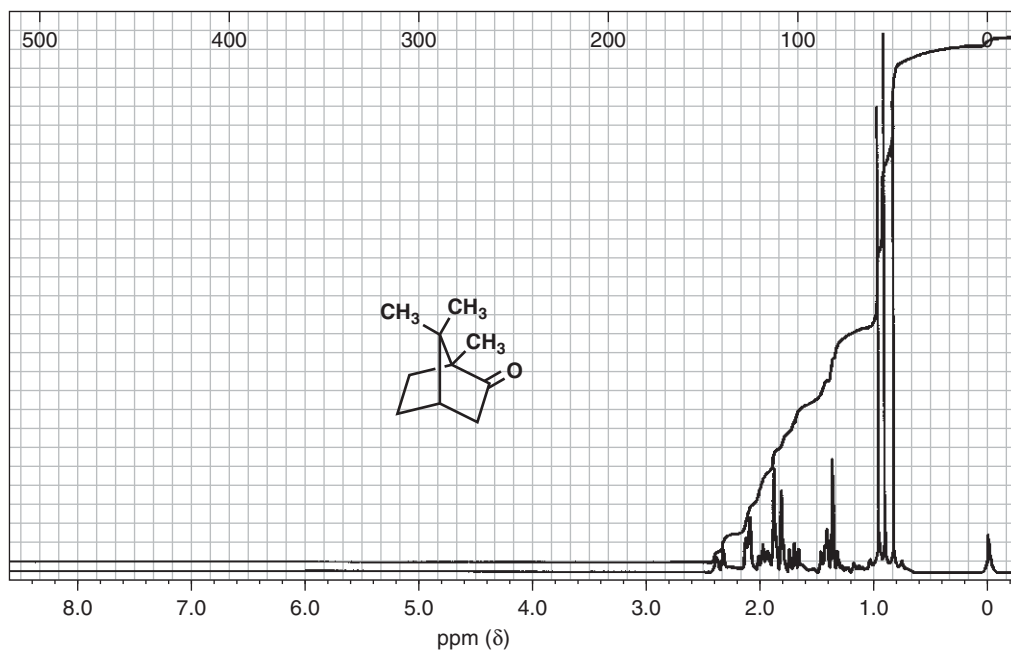
300-MHz NMR spectrum of camphor, CDCl$_3$.
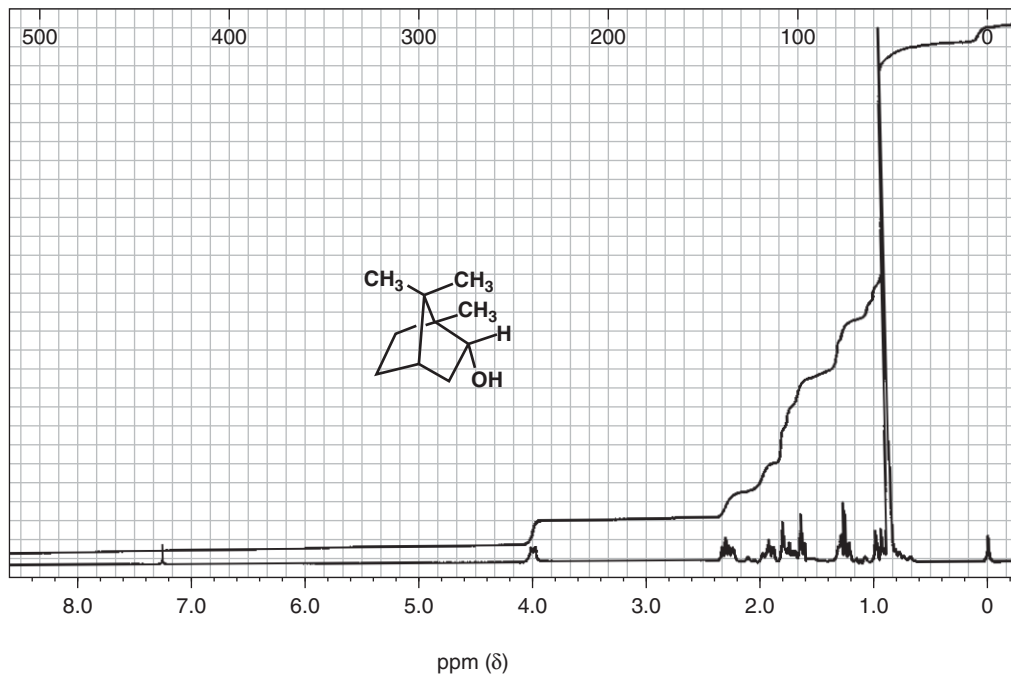
300-MHz NMR spectrum of borneol, CDCl$_3$.

ppm (δ)

300-MHz spectrum of isoborneol, CDCl₃.

a = 9.1 ppm q
b = 19.0 q
c = 19.6 q
d = 26.9 t
e = 29.8 t
f = 43.1 t
g = 43.1 d
h = 46.6 s
i = 57.4 s
j = 218.4 (not shown)

Carbon-13 spectrum of camphor, CDCl₃.

Carbon-13 spectrum of borneol, CDCl₃.

Carbon-13 spectrum of isoborneol, CDCl₃. (Small peaks at 9, 19, 30, and 43 are due to impurities.)
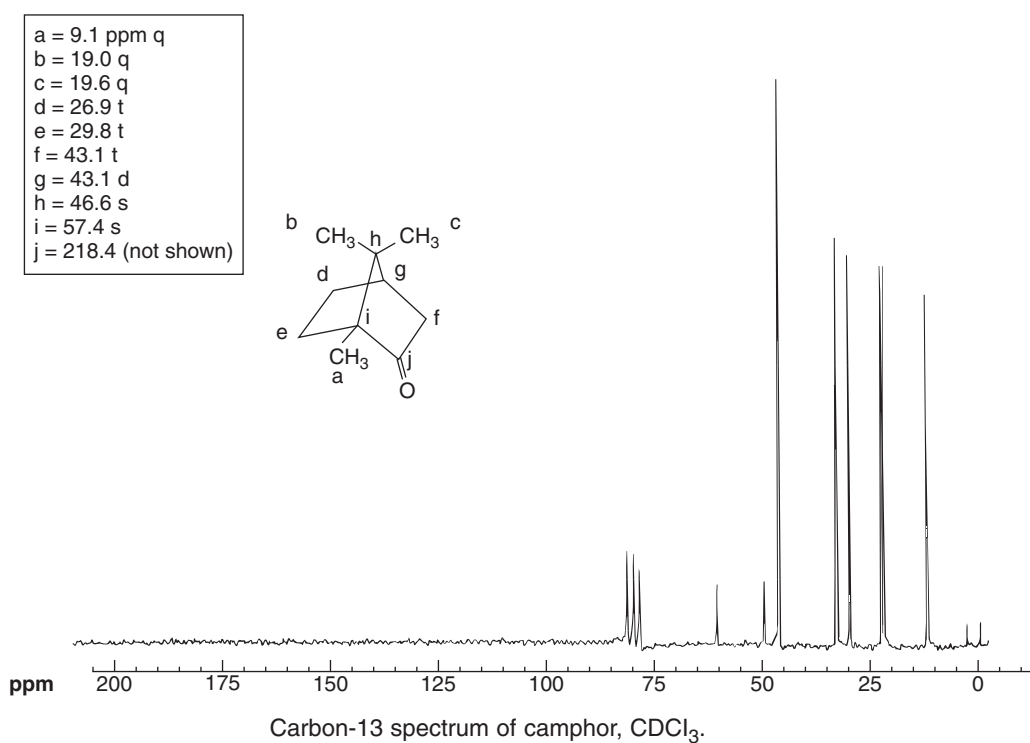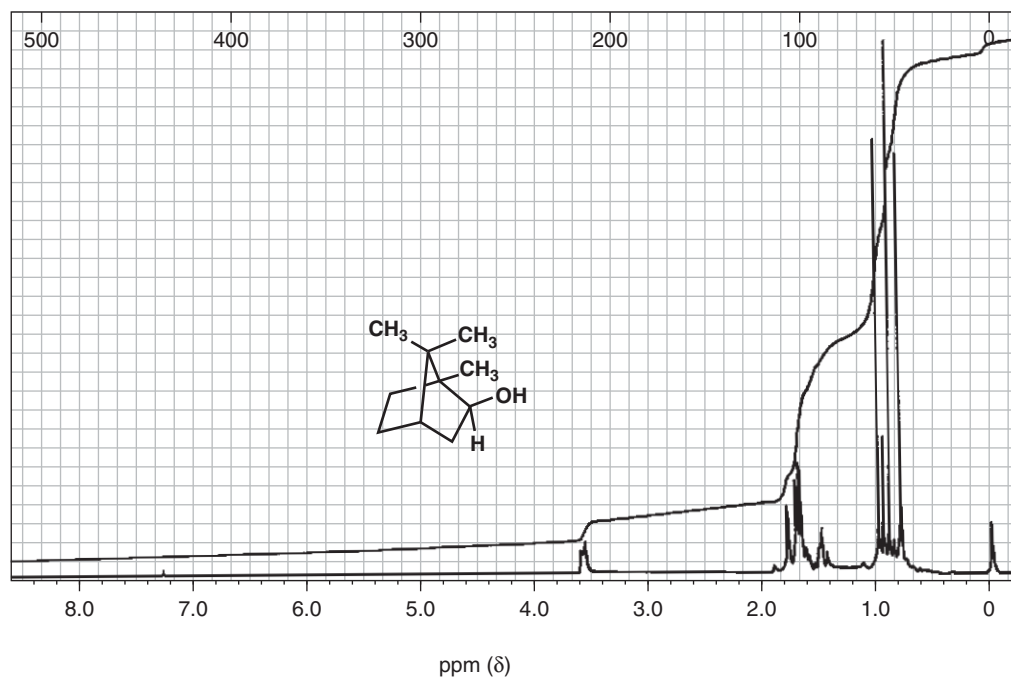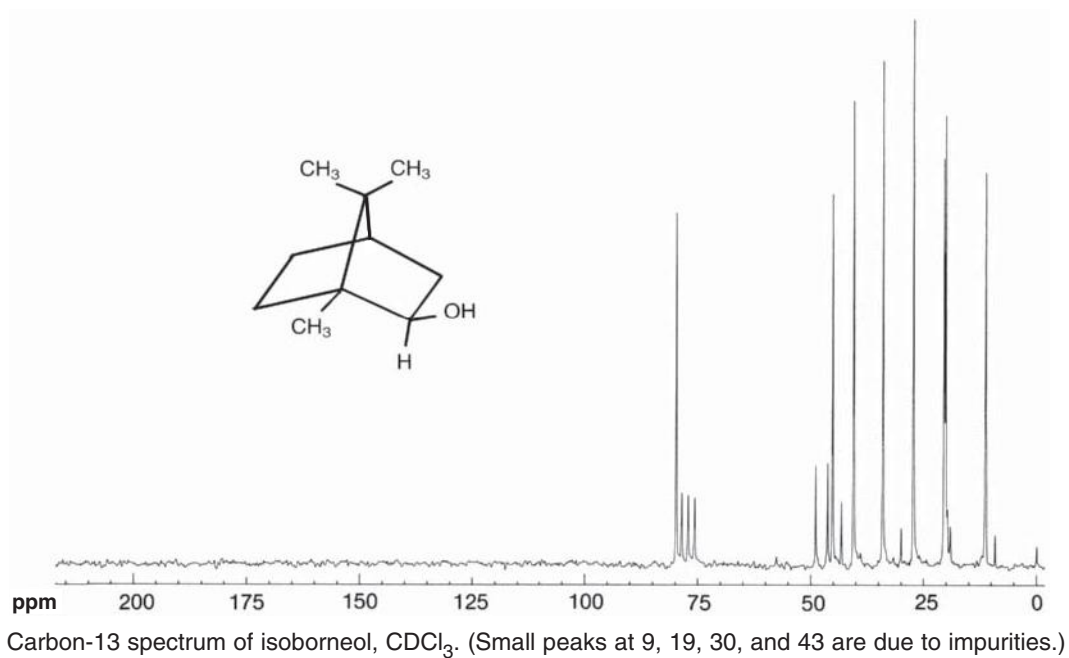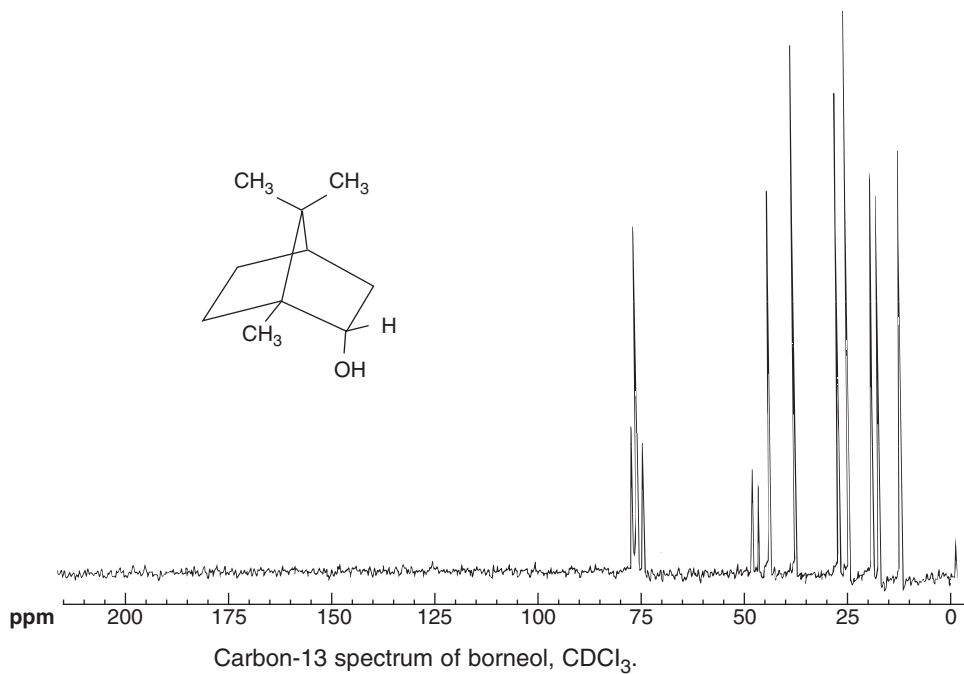
Molecular Modeling (Optional)

In this exercise, we will seek to understand the experimental results obtained in the borohydride reduction of camphor and compare them to the results for the simpler norbornanone system (no methyl groups). Because the hydride ion is an electron donor, it must place its electrons into an empty substrate orbital to form a new bond. The most logical orbital for this action is the LUMO (lowest unoccupied molecular orbital). Accordingly, the focus of our calculations will be the shape and location of the LUMO.

Part A.

Build a model of norbornanone, and submit it to an AM1-level calculation of its energy using a geometry optimization. Also request that density and LUMO surfaces be calculated, along with a density–LUMO surface (a mapping of the LUMO onto the density surface).
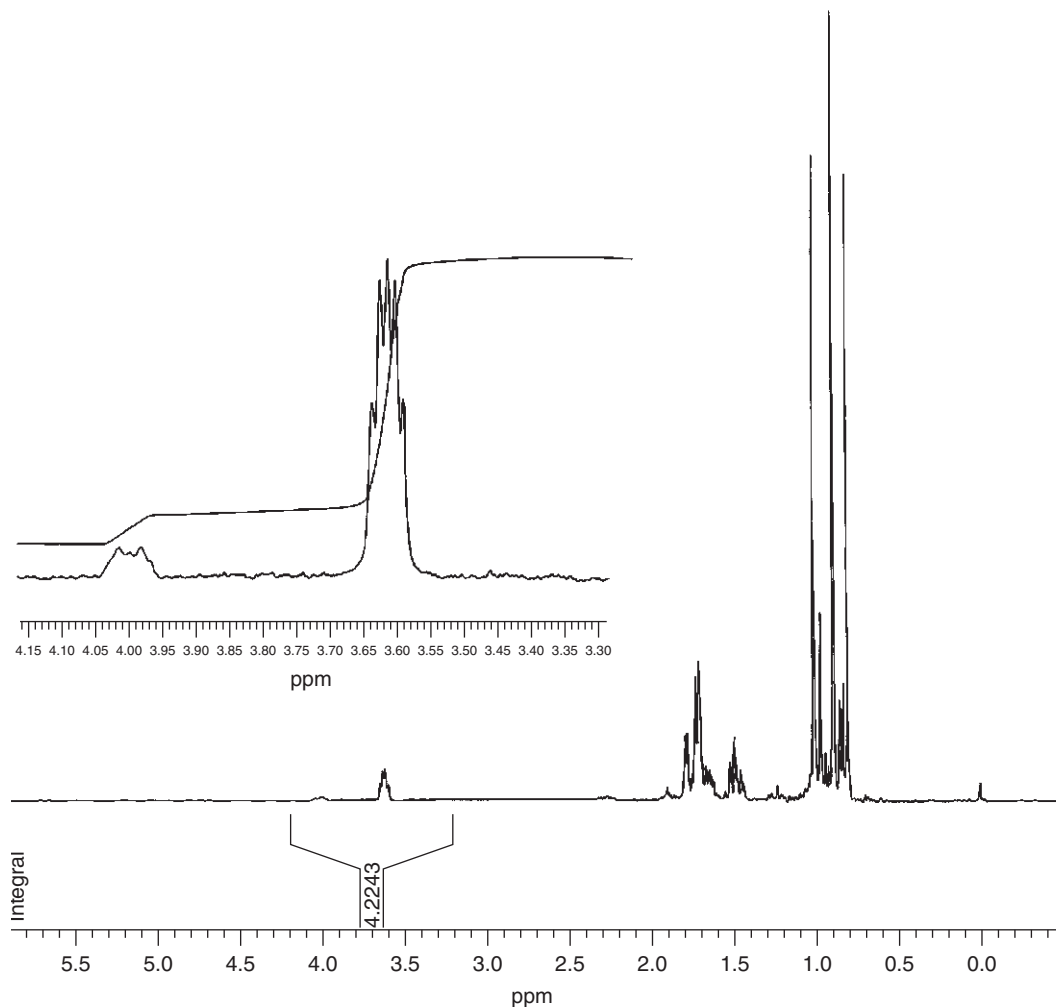
300-MHz proton-NMR spectrum of borohydride reduction product, CDCl$_3$. *Inset:* Expansion of the 3.5–4.1 ppm region.

When the calculation is complete, display the LUMO on the norbornanone skeleton. Where is the size of the LUMO (its density) largest? Which atom is this? This is the expected site of addition. Now map a density surface onto the same norbornanone surface. When you consider the approach of the borohydride ion, which face is less hindered? Is an *exo* or *endo* approach favored? An easier way to decide is to view the density–LUMO surface. On this surface, the intersection of the LUMO with the density surface is color-coded. The spot where the access to the LUMO is easiest (the location of its largest value) will be coded blue. Is this spot on the *endo* or on the *exo* face? Do your modeling results agree with the observed reaction percentages (see Part C completed earlier)?

Part B.

Follow the same instructions given earlier for norbornanone using camphor—that is, calculate and view density, LUMO, and density–LUMO surfaces.

Do you reach the same conclusions as for norbornanone? Are there new stereochemical considerations? Do your conclusions agree with the experimental results (the borneol/isoborneol ratio) you obtained in this experiment? In your report, discuss your modeling results and how they relate to your experimental results.

REFERENCES

Brown, H. C.; Muzzio, J. Rates of Reaction of Sodium Borohydride with Bicyclic Ketones. *J. Am. Chem. Soc.* **1966,** *88,* 2811.

Dauben, W. G.; Fonken, G. J.; Noyce, D. S. Stereochemistry of Hydride Reductions. *J. Am. Chem. Soc.* **1956,** *78,* 2579.

Markgraf, J. H. Stereochemical Correlations in the Camphor Series. *J. Chem. Educ.* **1967,** *44,* 36.

QUESTIONS

1. Interpret the major absorption bands in the infrared spectra of camphor, borneol, and isoborneol.

2. Explain why the *gem*-dimethyl groups appear as separate peaks in the proton-NMR spectrum of isoborneol, although they almost overlap in borneol.

3. A sample of isoborneol prepared by reduction of camphor was analyzed by infrared spectroscopy and showed a band at 1750 cm^{-1}. This result was unexpected. Why?

4. The observed melting point of camphor is often low. Look up the molal freezing point–depression constant K for camphor, and calculate the expected depression of the melting point of a quantity of camphor that contains 0.5 molal impurity. (*Hint:* Look in a general chemistry book under "freezing-point depression" or "colligative properties of solutions.")

5. Why was the methylene chloride layer washed with sodium bicarbonate in the procedure for preparing camphor?

6. Why was the methylene chloride layer washed with sodium bisulfite in the procedure for preparing camphor?

7. The peak assignments are shown on the carbon-13 NMR spectrum of camphor. Using these assignments as a guide, assign as many peaks as possible in the carbon-13 spectra of borneol and isoborneol.

32   EXPERIMENT 32

Multistep Reaction Sequences: The Conversion of Benzaldehyde to Benzilic Acid

Green chemistry

Multistep reactions

Thiamine-catalyzed reaction

Oxidation with nitric acid

Rearrangement

Crystallization

Computational chemistry (optional)

This experiment demonstrates multistep synthesis of benzilic acid, starting from benzaldehyde. In Experiment 32A, benzaldehyde is converted to benzoin using a thiamine-catalyzed reaction. This part of the experiment demonstrates how a "green" reagent can be utilized in organic chemistry. In Experiment 32B, nitric acid oxidizes benzoin to benzil. Finally, in Experiment 32C, benzil is rearranged to benzilic acid. The scheme below shows the reactions.

REQUIRED READING

Sign in at www.cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	Technique 6	Heating and Cooling Methods, Sections 6.1–6.3
	*Technique 7	Reaction Methods, Sections 7.1–7.4
	*Technique 8	Filtration, Section 8.3
	Technique 9	Physical Constants of Solids: The Melting Point, Sections 9.7 and 9.8
	*Technique 11	Crystallization: Purification of Solids, Section 11.3
	*Technique 12	Extractions, Separations, and Drying Agents, Section 12.4
	Technique 25	Infrared Spectroscopy, Section 25.4
New:	Essay and Experiment 18	Computational Chemistry (Optional)

NOTES TO THE INSTRUCTOR

Although this experiment is intended to illustrate a multistep synthesis to the students, each part may be done separately, or two out of the three reactions can be linked together. The sections on Special Instructions and Waste Disposal are included in each part of this experiment. You may also create another multistep synthesis by linking together benzoin (Experiment 32A) and benzil (Experiment 32B).
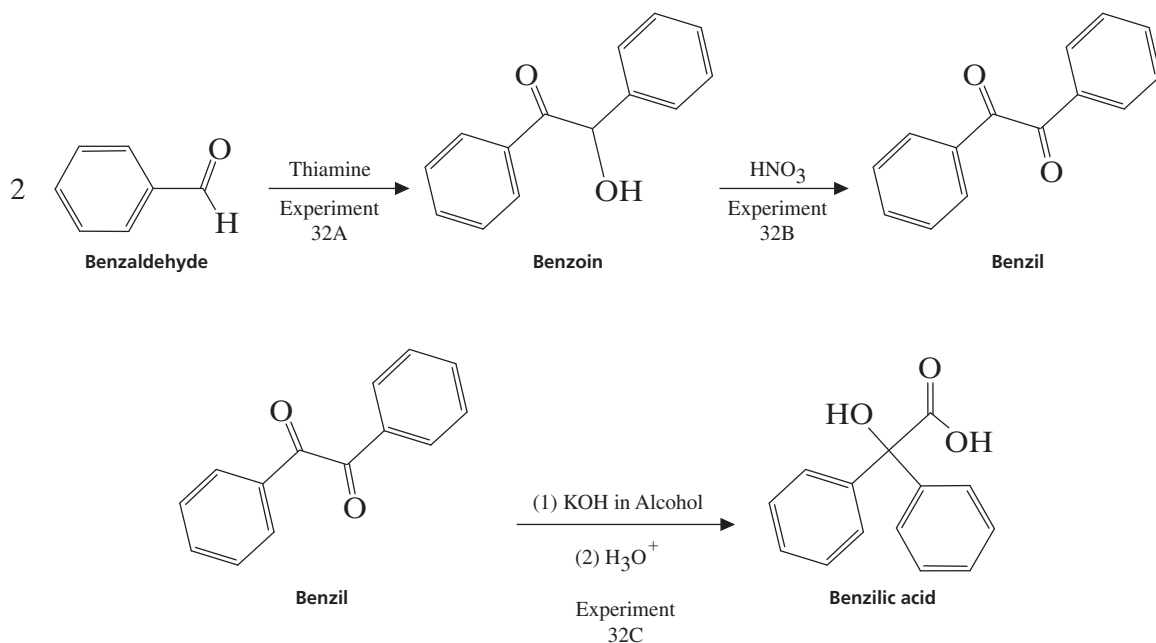
Preparation of Benzoin by Thiamine Catalysis

In this experiment, two molecules of benzaldehyde will be converted to benzoin using the catalyst thiamine hydrochloride. This reaction is known as a benzoin condensation reaction.
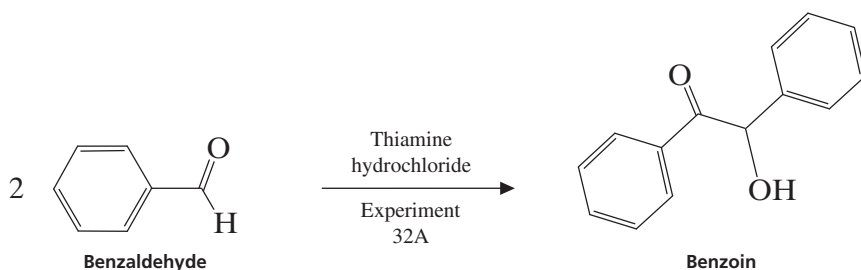
Thiamine hydrochloride is structurally similar to thiamine pyrophosphate (TPP). TPP is a coenzyme universally present in all living systems. It catalyzes several biochemical reactions in natural systems. It was originally discovered as a required nutritional factor (vitamin) in humans because of its link with the disease beriberi. **Beriberi** is a disease of the peripheral nervous system caused by a deficiency of Vitamin B_1 in the diet. Symptoms include pain and paralysis of the extremities, emaciation, and swelling of the body. The disease is most common in Asia.

Thiamine pyrophosphate   **Thiamine hydrochloride**
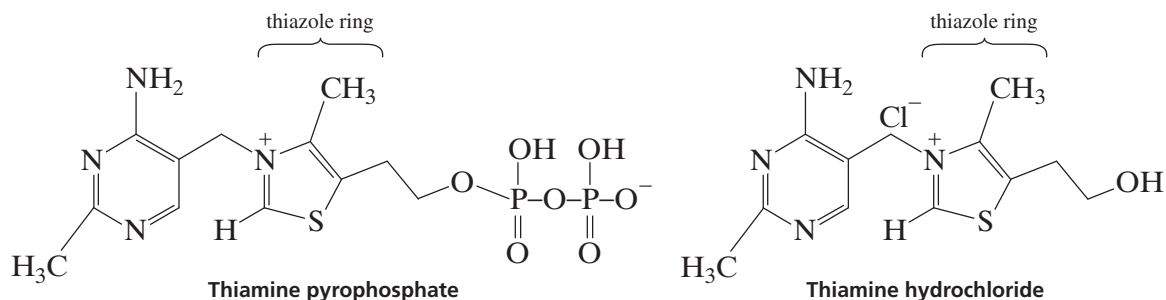
Thiamine binds to an enzyme before the enzyme is activated. The enzyme also binds to the substrate (a large protein). Without the coenzyme thiamine, no chemical reaction would occur. The coenzyme is the *chemical reagent.* The protein molecule (the enzyme) helps and mediates the reaction by controlling stereochemical, energetic, and entropic factors, but it is nonessential to the overall course of reactions that it catalyzes. A special name, vitamins, is given to coenzymes that are essential to the nutrition of the organism.

The most important part of the entire thiamine molecule is the central ring, the thiazole ring, which contains nitrogen and sulfur. This ring constitutes the *reagent* portion of the coenzyme. Experiments with the model compound 3,4-dimethylthiazolium bromide have explained how thiamine-catalyzed reactions work. It was found that this model thiazolium compound rapidly exchanged the C-2 proton for deuterium in D_2O solution. At a pD of 7 (no pH here), this proton was completely exchanged in seconds!

This indicates that the C-2 proton is more acidic than one would have expected. It is apparently easily removed because the conjugate base is a highly stabilized **ylide.** An **ylide** is a compound or intermediate with positive and negative formal charges on adjacent atoms.

3,4-Dimethylthiazolium   **Ylide**
bromide
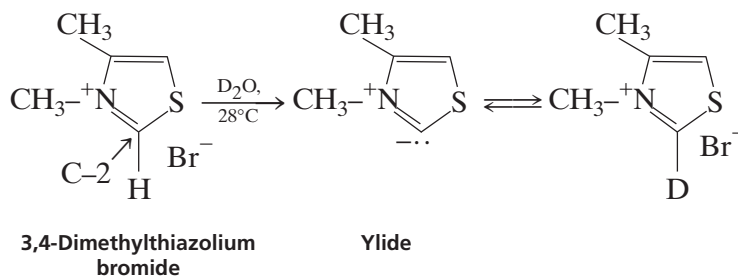
The sulfur atom plays an important role in stabilizing this ylide. This was shown by comparing the rate of exchange of 1,3-dimethyl-imidazolium ion with the rate for the thiazolium compound shown in the previous equation. The dinitrogen compound exchanged its C-2 proton more slowly than the sulfur-containing ion. Sulfur, being in the third row of the periodic chart, has *d* orbitals available for bonding to adjacent atoms. Thus, it has fewer geometrical restrictions than carbon and nitrogen atoms do and can form carbon–sulfur multiple bonds in situations in which carbon and nitrogen normally would not.
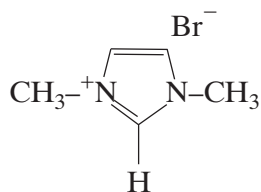
**1,3-Dimethylimidazolium
bromide**

In Experiment 32A, we will utilize thiamine hydrochloride rather than thiamine pyrophosphate (TPP) to catalyze the benzoin condensation. The mechanism is shown below. For simplicity, only the thiazole ring is shown.
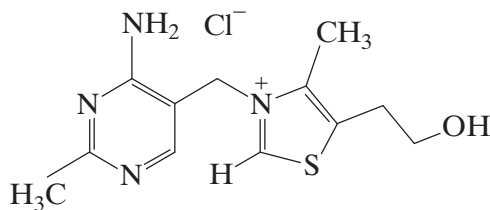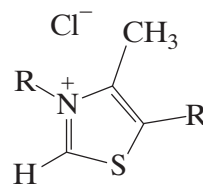
Thiamine hydrochloride   **Thiazole ring in thiamine hydrochloride**

The mechanism involves the removal of the proton at C-2 from the thiazole ring with a weak base to give the ylide (step 1). The ylide acts as a nucleophile that adds to the carbonyl group of benzaldehyde forming an intermediate (step 2). A proton is removed to yield a new intermediate with a double bond (step 3). Notice that the nitrogen atom helps to increase the acidity of that proton. This intermediate can now react with a second benzaldehyde molecule to yield a new intermediate (step 4). A base removes a proton to produce benzoin and also regenerates the ylide (step 5). The ylide re-enters the mechanism to form more benzoin by the condensation of two more molecules of benzaldehyde.
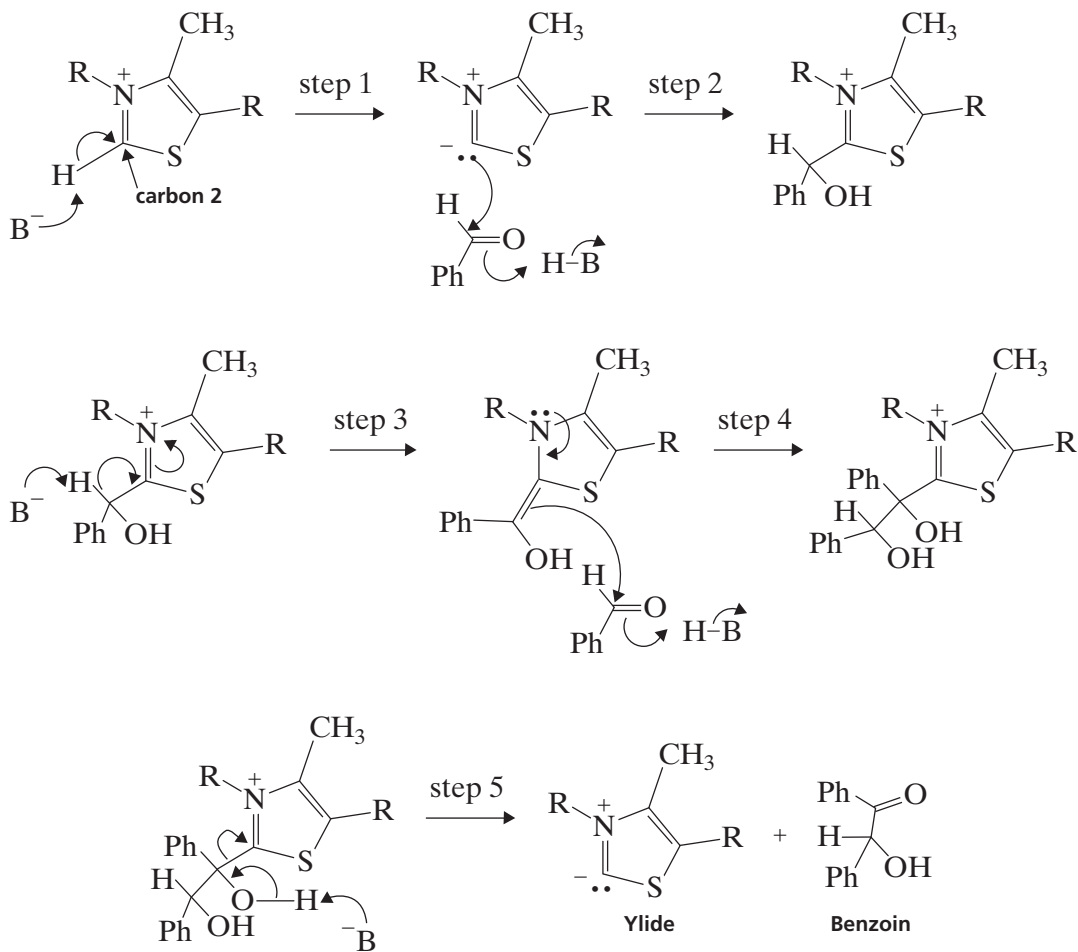
SPECIAL INSTRUCTIONS

This experiment may be conducted concurrently with another experiment. It involves a few minutes at the beginning of a laboratory period for mixing reagents. The remaining portion of the period may be used for another experiment.

SUGGESTED WASTE DISPOSAL

Pour all of the aqueous solutions produced in this experiment into a waste container designated for aqueous waste. The ethanolic mixtures obtained from the crystallization of crude benzoin should be poured into a waste container designated for nonhalogenated waste.

NOTES TO THE INSTRUCTOR

It is essential that the benzaldehyde used in this experiment be *pure*. Benzaldehyde is easily oxidized in air to benzoic acid. Even when benzaldehyde *appears* free of benzoic acid by infrared spectroscopy, you should check the purity of your

benzaldehyde and thiamine by following the instructions given in the first paragraph of the Procedure ("Reaction Mixture"). When the benzaldehyde is pure, the solution will be nearly filled with solid benzoin after 2 days (you may need to scratch the inside of the flask to induce crystallization). If no solid appears, or very little appears, then there is a problem with the purity of the benzaldehyde. If possible, use a newly opened bottle that has been purchased recently. *However, it is essential that you check both the old and new benzaldehyde before doing the laboratory experiment.*

We have found that the following procedure does an adequate job of purifying benzaldehyde. The procedure does not require distillation of benzaldehyde. Shake the benzaldehyde in a separatory funnel with an equal volume of 5% aqueous sodium carbonate solution. Shake gently and occasionally open the stopcock of the funnel to vent carbon dioxide gas. An emulsion forms that may take 2–3 hours to separate. It is helpful to stir the mixture occasionally during this period to help break the emulsion. Remove the lower sodium carbonate layer, including any remaining emulsion. Add about ¼ volume of water to the benzaldehyde, and shake the mixture gently to avoid an emulsion. Remove the cloudy *lower* organic layer, and dry the benzaldehyde with calcium chloride until the next day. Any remaining cloudiness should be removed by gravity filtration through fluted filter paper. The resulting *clear,* purified benzaldehyde should be suitable for this experiment without vacuum distillation. *You must check the purified benzaldehyde to see if it is suitable for the experiment by following the instructions in the first paragraph of the Procedure.*

It is advisable to use a fresh bottle of thiamine hydrochloride, which should be stored in the refrigerator. Fresh thiamine does not seem to be as important as pure benzaldehyde for success in this experiment.

PROCEDURE

Reaction Mixture. Add 1.5 g thiamine hydrochloride to a 50-mL Erlenmeyer flask. Dissolve the solid in 2 mL of water by swirling the flask. Add 15 mL of 95% ethanol and swirl the solution until it is homogeneous. To this solution, add 4.5 mL of an aqueous sodium hydroxide solution, and swirl the flask until the bright yellow color fades to a pale yellow color.[1] Carefully measure 4.5 mL of pure benzaldehyde (density = 1.04 g/mL), and add it to the flask. Swirl the contents of the flask until they are homogeneous. Stopper the flask and allow it to stand in a dark place for at least 2 days.

Isolation of Crude Benzoin. If crystals have not formed after 2 days, initiate crystallization by scratching the inside of the flask with a glass stirring rod. Allow about 5 minutes for the crystals of benzoin to form fully. Place the flask, with crystals, into an ice bath for 5–10 minutes.

If for some reason the product separates as an oil, it may be helpful to scratch the flask with a glass rod or seed the mixture by allowing a small amount of solution to dry on the end of a glass rod and then placing this into the mixture. Cool the mixture in an ice bath before filtering.

Break up the crystalline mass with a spatula, swirl the flask rapidly, and quickly transfer the benzoin to a Büchner funnel under vacuum (see Technique 8, Section 8.3 and Figure 8.5). Wash the crystals with two 5-mL portions of ice-cold water. Allow the benzoin to dry in the

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[1]Dissolve 40g of NaOH in 500 mL water.

Büchner funnel by drawing air through the crystals for about 5 minutes. Transfer the benzoin to a watch glass, and allow it to dry in air until the next laboratory period. The product may also be dried in a few minutes in an oven set at about 100°C.

Yield Calculation and Melting-Point Determination. Weigh the benzoin and calculate the percentage yield based on the amount of benzaldehyde used initially. Determine the melting point (pure benzoin melts between 134°C and 135°C). Because crude benzoin normally melts between 129°C and 132°C, the benzoin should be crystallized before the conversion to benzil (Experiment 32B).

Crystallization of Benzoin. Purify the crude benzoin by crystallization from hot 95% ethanol (use 8 mL of alcohol/g of crude benzoin) using an Erlenmeyer flask for the crystallization (see Technique 11, Section 11.3; omit step 2 shown in Figure 11.4). After the crystals have cooled in an ice bath, collect them on a Büchner funnel. The product may be dried in a few minutes in an oven set at about 100°C. Determine the melting point of the purified benzoin. If you are not scheduled to perform Experiment 32B, submit the sample of benzoin, along with your report, to the instructor.

Spectroscopy. Determine the infrared spectrum of the benzoin by the dry film method (see Technique 25, Section 25.4). A spectrum is shown here for comparison.

QUESTIONS

1. The infrared spectrum of benzoin and benzaldehyde are given in this experiment. Interpret the principal peaks in the spectra.
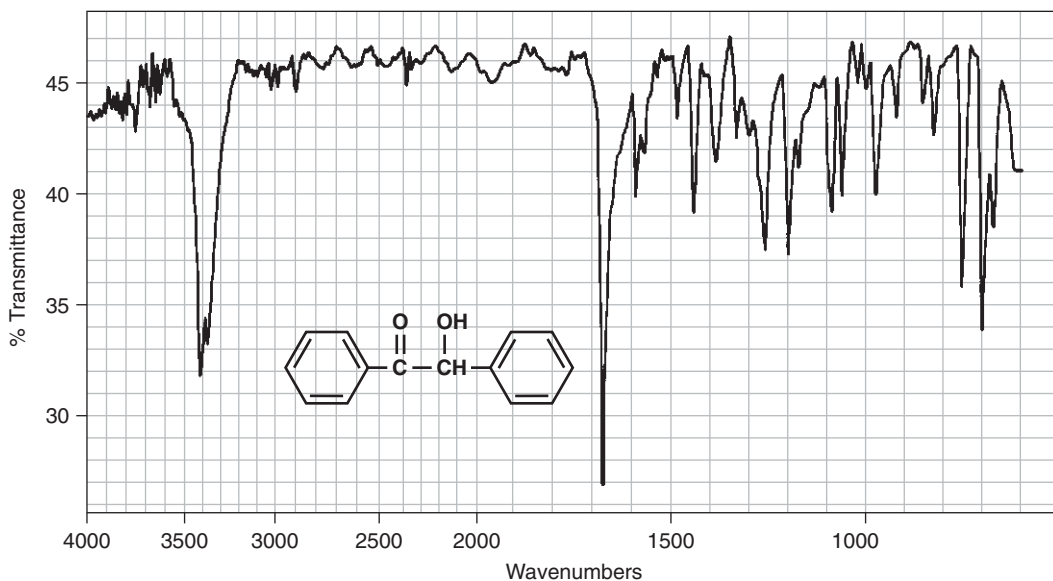
Infrared spectrum of benzoin, KBr.
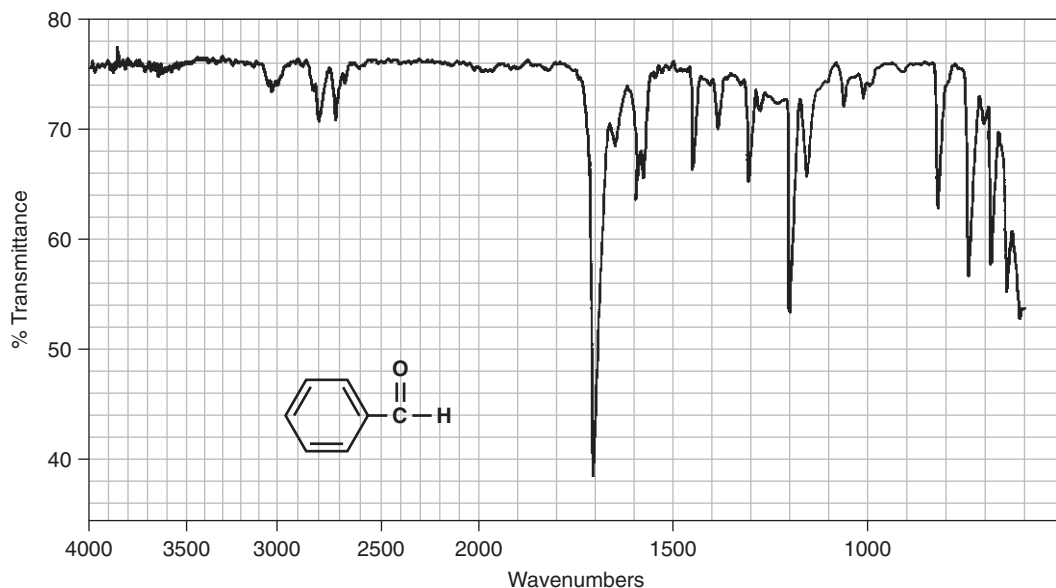
Infrared spectrum of benzaldehyde (neat).

2. How do you think the appropriate enzyme would have affected the reaction (degree of completion, yield, stereochemistry)?

3. What modifications of conditions would be appropriate if the enzyme were to be used?

4. Draw a mechanism for the cyanide-catalyzed conversion of benzaldehyde to benzoin. The intermediate, shown in brackets, is thought to be involved in the mechanism.

Benzaldehyde   **Benzoin**
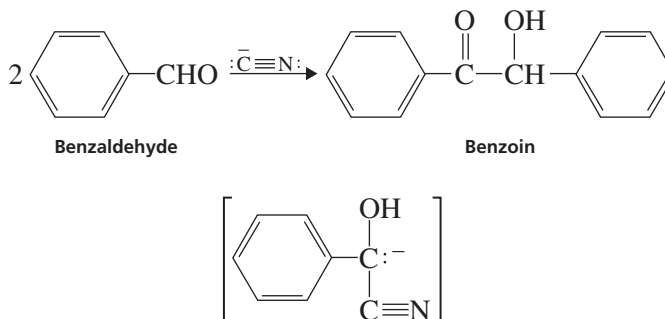
32B   EXPERIMENT 32B

Preparation of Benzil

In this experiment, benzil is prepared by the oxidation of an α-hydroxyketone, benzoin. This experiment uses the benzoin prepared in Experiment 32A and is the second step in the multistep synthesis. This oxidation can be done easily with mild oxidizing agents such as Fehling's solution (alkaline cupric tartrate complex) or

copper sulfate in pyridine. In this experiment, the oxidation is performed with nitric acid.

Benzoin → HNO₃ (Experiment 32B) → Benzil
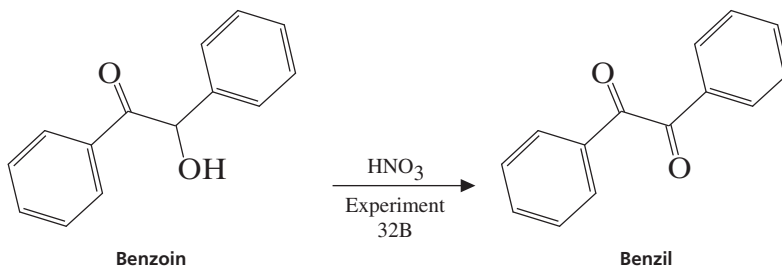
SPECIAL INSTRUCTIONS

Nitric acid should be dispensed with in a good hood to avoid the choking odor of this substance. The vapors will irritate your eyes. Avoid contact with your skin. During the reaction, considerable amounts of noxious nitrogen oxide gases are evolved. Be sure to run the reaction in a good fume hood.

SUGGESTED WASTE DISPOSAL

The aqueous nitric acid wastes should be poured into a container designated for nitric acid wastes. Do not put them into the aqueous waste container. The ethanolic wastes from the crystallization should be poured into the nonhalogenated waste container.

PROCEDURE

Reaction Mixture. Place 2.5 g of benzoin (Experiment 32A) into a 25-mL round-bottom flask, and add 12 mL of concentrated nitric acid. Add a magnetic stirring bar and attach a water condenser. In a hood, set up the apparatus for heating in a hot water bath, as shown in Technique 6, Figure 6.4). Heat the mixture in a hot water bath at about 70°C for 1 hour, with stirring. Avoid heating the mixture above this temperature to reduce the possibility of forming a by-product.[1] During the 1-hour heating period, nitrogen oxide gases (red) will be evolved. If it appears that gases are still being evolved after 1 hour, continue heating for another 15 minutes but then discontinue heating at that time.

Isolation of Crude Benzil. Pour the reaction mixture into 40 mL of cool water, and stir the mixture vigorously until the oil crystallizes completely as a yellow solid. Scratching or seeding will be necessary to induce crystallization. Vacuum filter the crude benzil on a Büchner funnel, and wash it well with cold water to remove the nitric acid. Allow the solid to dry thoroughly by drawing air through the filter. Weigh the crude benzil, and calculate the percentage yield of the crude benzil.

Crystallization of Product. Purify the solid by dissolving it in hot 95% ethanol in an Erlenmeyer flask (about 5 mL per 0.5 g of product), using a hot plate as the heating source. Be careful not to melt the solid on the hot plate. You can avoid melting the benzil by occasionally lifting the flask

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[1]At higher temperatures, some 4-nitrobenzil will be formed along with benzil.

from the hot plate and swirling the contents of the flask. You want the solid to dissolve in the hot solvent rather than melt. You will obtain better crystals if you add a little extra solvent after the solid dissolves completely. Remove the flask from the hot plate, and allow the solution to cool slowly. As the solution cools, seed it with a solid product that forms on a spatula after the spatula is dipped into the solution. The solution may become supersaturated unless this is done, and crystallization will occur too rapidly. Yellow crystals are formed. Cool the mixture in an ice bath to complete the crystallization. Collect the product on a Büchner funnel, under vacuum. Rinse the flask with small amounts (about 3 mL total) of ice-cold 95% ethanol to complete the transfer of product to the Büchner funnel. Continue drawing air through the crystals on the Büchner funnel by suction for about 5 minutes. Then remove the crystals and air-dry them.

Yield Calculation and Melting-Point Determination. Weigh the dry benzil, and calculate the percentage yield. Determine the melting point. The melting point of pure benzil is 95°C. Submit the benzil to the instructor unless it is to be used to prepare benzilic acid (Experiment 32C). Obtain the infrared spectrum of benzil using the dry film method. Compare the spectrum to the one shown. Also compare the spectrum with that of benzoin shown in Experiment 32A. What differences do you notice?
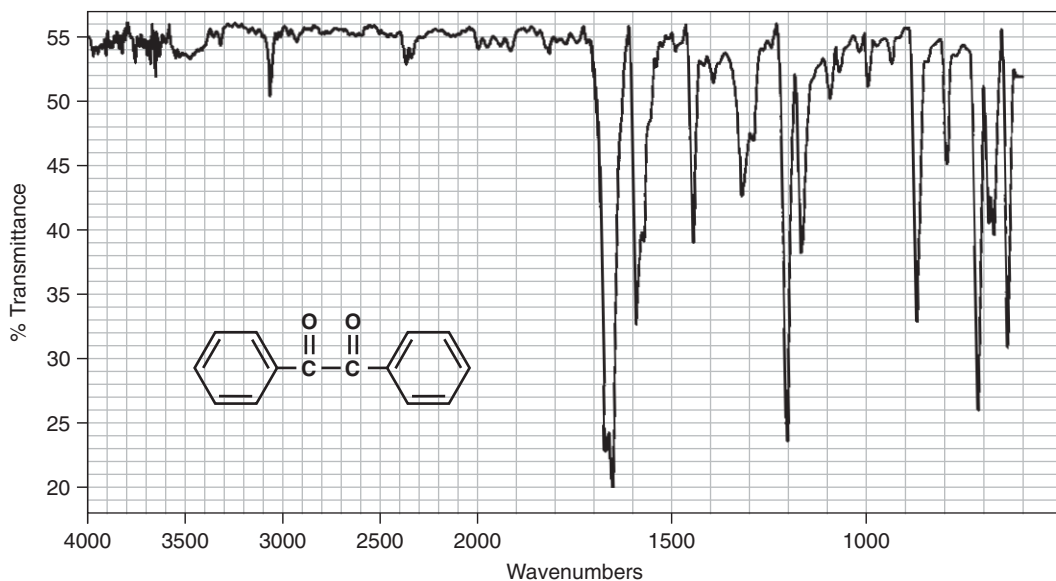
Infrared spectrum of benzil, KBr.

E X P E R I M E N T   3 2 C

Preparation of Benzilic Acid

In this experiment, benzilic acid will be prepared by causing the rearrangement of the α-diketone benzil. Preparation of benzil is described in Experiment 32B. The rearrangement of benzil proceeds in the following way:
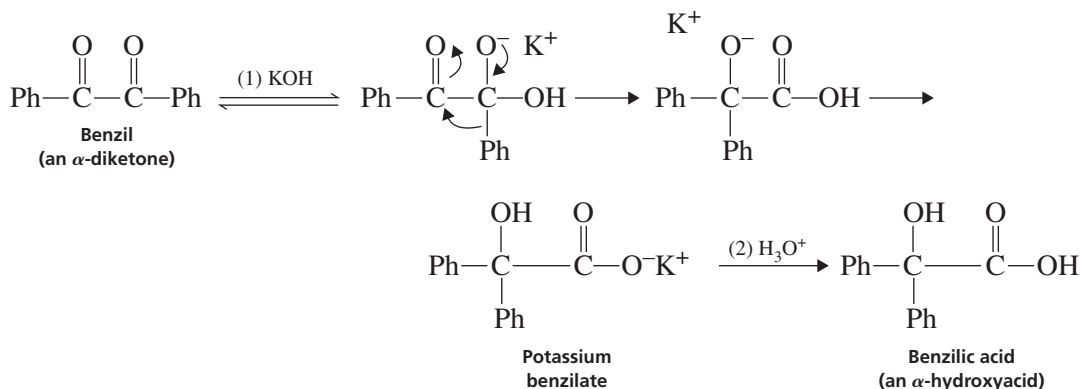
The driving force for the reaction is provided by the formation of a stable carboxylate salt (potassium benzilate). Once this salt is produced, acidification yields benzilic acid. The reaction can generally be used to convert aromatic α-diketones to aromatic α-hydroxyacids. Other compounds, however, also will undergo a benzilic acid-type of rearrangement (see questions).

SPECIAL INSTRUCTIONS

This experiment works best with pure benzil. The benzil prepared in Experiment 32B is usually of sufficient purity after it has been crystallized.

SUGGESTED WASTE DISPOSAL

Pour all of the aqueous filtrates into the waste bottle designated for aqueous waste. Ethanolic filtrates should be put in the nonhalogenated organic waste bottle.

PROCEDURE

Running the Reaction. Add 2.00 g benzil and 6 mL 95% ethanol to a 25-mL round-bottom flask. Place a boiling stone in the flask, and attach a reflux condenser. Be sure to use a thin film of stopcock grease when attaching the reflux condenser to the flask. Heat the mixture with a heating mantle or hot plate until the benzil has dissolved (see Technique 6, Figure 6.2). Using a Pasteur pipet, add dropwise 5 mL of an aqueous potassium hydroxide solution downward through the reflux condenser into the flask.[1] Gently boil the mixture with occasional swirling of the contents of the flask. Heat the mixture at reflux for 15 minutes. The mixture will be blue-black in color. As the reaction proceeds, the color will turn to brown, and the solid should dissolve completely. Solid potassium benzilate may form during the reaction period. At the end of the heating period, remove the assembly from the heating device, and allow it to cool for a few minutes.

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[1]The aqueous potassium hydroxide solution should be prepared for the class by dissolving 55.0 g of potassium hydroxide in 120 mL of water. This will provide enough solution for 20 students, assuming little solution is wasted.

Crystallization of Potassium Benzilate. Detach the reflux condenser when the apparatus is cool enough to handle. Transfer the reaction mixture, which may contain some solid, with a Pasteur pipet into a small beaker. Allow the mixture to cool to room temperature, and then cool in an ice-water bath for about 15 minutes until crystallization is complete. It may be necessary to scratch the inside of the beaker with a glass stirring rod to induce crystallization. Crystallization is complete when virtually the entire mixture has solidified. Collect the crystals on a Büchner funnel by vacuum filtration, and wash the crystals thoroughly with three 4-mL portions of ice-cold 95% ethanol. The solvent should remove most of the color from the crystals.

Transfer the solid, which is mainly potassium benzilate, to a 100-mL Erlenmeyer flask containing 60 mL of hot (70°C) water. Stir the mixture until all the solid has dissolved or until it appears that the remaining solid will not dissolve. Any remaining solid will likely form a fine suspension. *If solid does remain in the flask,* gravity-filter the hot solution through fast fluted filter paper until the filtrate is clear (see Technique 8, Section 8.1). *If no solid remains in the flask,* the gravity filtration step may be omitted. In either case, proceed to the next step.

Formation of Benzilic Acid. With swirling of the flask, slowly add dropwise 1.3 mL of concentrated hydrochloric acid to the warm solution of potassium benzilate. As the solution becomes acidic, solid benzilic acid will begin to precipitate. Keep adding the hydrochloric acid until the solid stays permanently, and then start monitoring the pH. The ideal pH should be about 2; if it is higher than this, add more acid and check the pH again. Allow the mixture to cool to room temperature, and then complete the cooling in an ice bath. Collect the benzilic acid by vacuum filtration, using a Büchner funnel. Wash the crystals with two 30-mL portions of ice-cold water to remove potassium chloride salt that sometimes coprecipitates with benzilic acid during the neutralization with hydrochloric acid. Remove the wash water by drawing air through the filter. Dry the product thoroughly by allowing it to stand until the next laboratory period.

Melting Point and Crystallization of Benzilic Acid. Weigh the dry benzilic acid, and determine the percentage yield. Determine the melting point of the dry product. Pure benzilic acid melts at 150°C. If necessary, crystallize the product using minimum amount of hot water needed to dissolve the solid (see Technique 11, Section 11.3 and Figure 11.4). If some impurities remain undissolved, gravity filter the hot mixture through fast fluted filter paper (see Technique 8, Section 8.1). It will be necessary to keep the mixture hot during this gravity-filtration step. Cool the solution and induce crystallization (see Technique 11, Section 11.8), if necessary, when the mixture has reached room temperature. Allow the mixture to stand at room temperature until crystallization is complete (about 15 minutes). Cool the mixture in an ice bath, and collect the crystals by vacuum filtration on a Büchner funnel. Determine the melting point of the crystallized product after it is thoroughly dry.

If your instructor requests it, determine the infrared spectrum of the benzilic acid in potassium bromide (see Technique 25, Section 25.5). Calculate the percentage yield. Submit the sample to your laboratory instructor in a labeled vial.
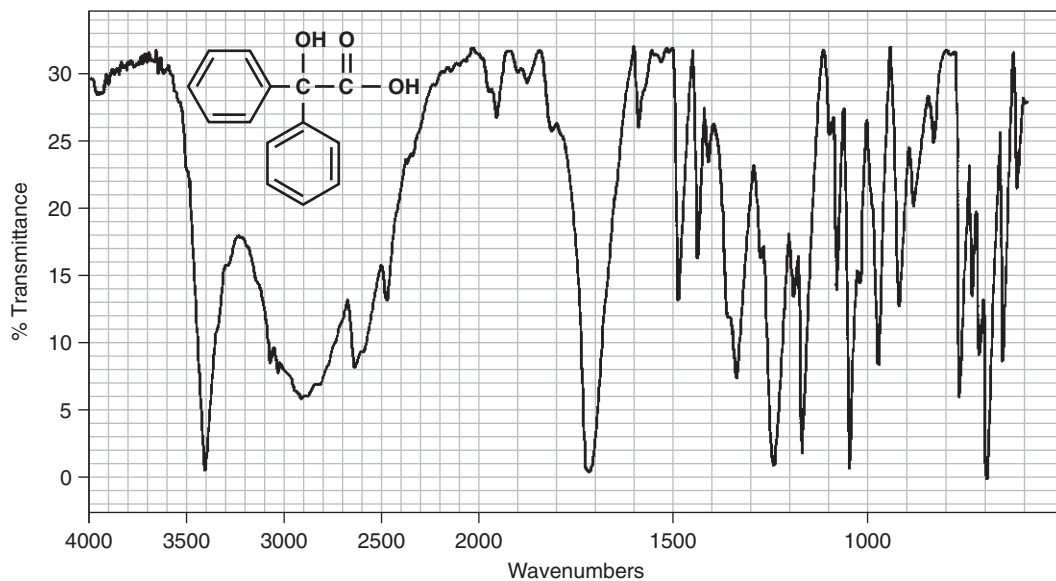
Infrared spectrum of benzilic acid, KBr.

QUESTIONS

1. Show how to prepare the following compounds, starting from the appropriate aldehyde.

(a)   (b)
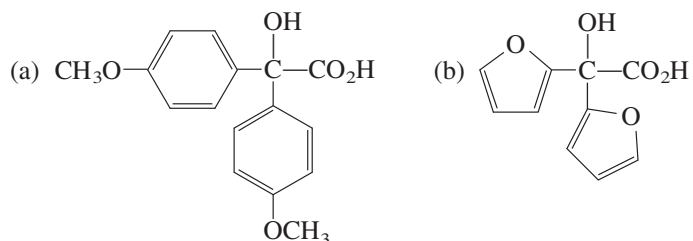
2. Give the mechanisms for the following transformations:

(a)

$$\text{(1) KOH, alcohol} \quad \text{(2) H}^+$$

(b)

$$\text{(1) KOH, H}_2\text{O} \quad \text{(2) H}^+$$

Citric acid

(c)

$$\text{Ph—C—C—Ph} \xrightarrow[\text{CH}_3\text{OH}]{^-\text{OCH}_3} \text{Ph—C—COCH}_3$$
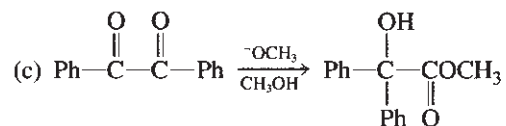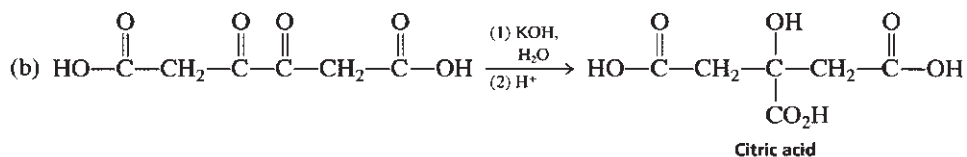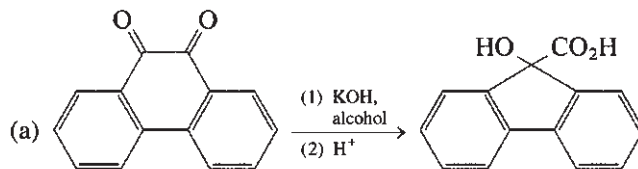
3. Interpret the infrared spectrum of benzilic acid.

E X P E R I M E N T   3 3

Triphenylmethanol and Benzoic Acid

Grignard reaction

Extraction

Crystallization

In this experiment, you will prepare a Grignard reagent or organomagnesium reagent. The reagent is phenylmagnesium bromide.

Bromobenzene   **Phenylmagnesium bromide**
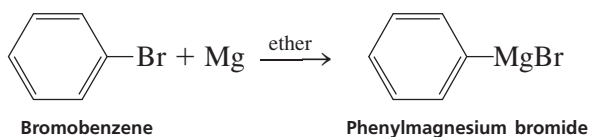
This reagent will be converted to a tertiary alcohol or a carboxylic acid, depending on the experiment selected.

EXPERIMENT 33A

Benzophenone

Triphenylmethanol

EXPERIMENT 33B

Benzoic acid
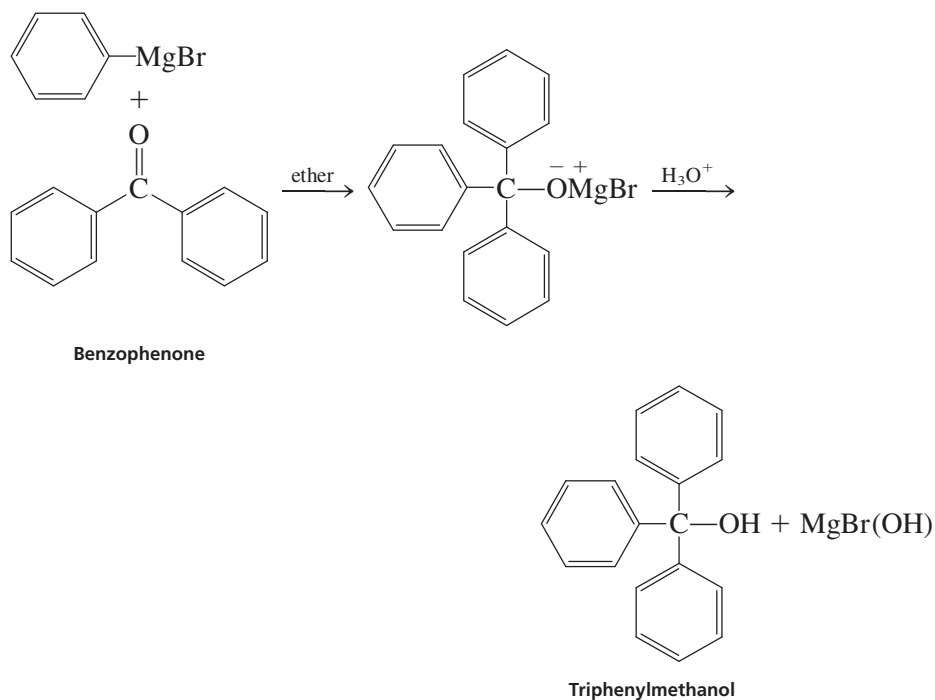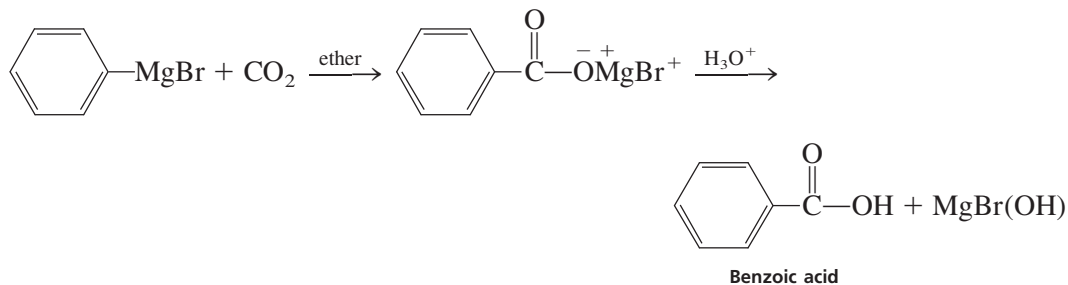
The alkyl portion of the Grignard reagent behaves as if it had the characteristics of a **carbanion**. We may write the structure of the reagent as a partially ionic compound:

$$\overset{\delta-}{R} \cdots \overset{\delta+}{MgX}$$
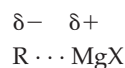
This partially bonded carbanion is a Lewis base. It reacts with strong acids, as you would expect, to give an alkane.

$$\overset{\delta-}{R} \cdots \overset{\delta+}{MgX} + HX \longrightarrow R—H + MgX_2$$

Any compound with a suitably acidic hydrogen will donate a proton to destroy the reagent. Water, alcohols, terminal acetylenes, phenols, and carboxylic acids are all acidic enough to bring about this reaction.

The Grignard reagent also functions as a good nucleophile in nucleophilic addition reactions of the carbonyl group. The carbonyl group has an electrophilic character at its carbon atom (due to resonance), and a good nucleophile seeks out this center for addition.
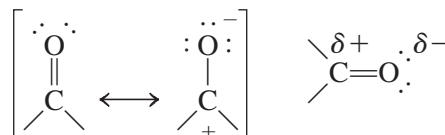
The magnesium salts produced form a complex with the addition product, an alkoxide salt. In the second step of the reaction, these must be hydrolyzed (protonated) by addition of dilute aqueous acid.

Step 1   **Step 2**
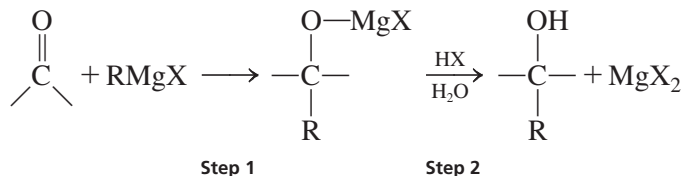
The Grignard reaction is used synthetically to prepare secondary alcohols from aldehydes and tertiary alcohols from ketones. The Grignard reagent will react with esters twice to give tertiary alcohols. Synthetically, it can also be allowed to react with carbon dioxide to give carboxylic acids and with oxygen to give hydroperoxides.

$$RMgX + O=C=O \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-OMgX \xrightarrow[H_2O]{HX} R-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

Carboxylic acid

$$RMgX + O_2 \longrightarrow ROOMgX \xrightarrow[H_2O]{HX} ROOH$$

Hydroperoxide
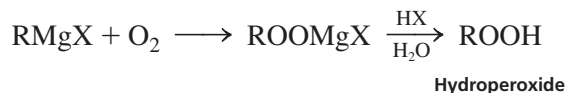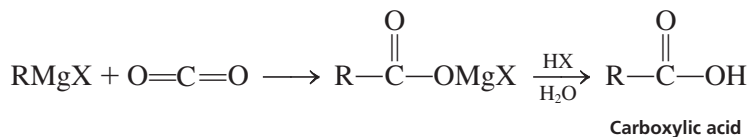
Because the Grignard reagent reacts with water, carbon dioxide, and oxygen, it must be protected from air and moisture when it is used. The apparatus in which the reaction is to be conducted must be scrupulously dry (recall that 18 mL of H_2O is 1 mole), and the solvent must be free of water or anhydrous. During the reaction, the flask must be protected by a calcium chloride drying tube. Oxygen should also be excluded. In practice, this can be done by allowing the solvent ether to reflux. This blanket of solvent vapor keeps air from the surface of the reaction mixture.

In the experiment described here, the principal impurity is **biphenyl**, which is formed by a heat- or light-catalyzed coupling reaction of the Grignard reagent and unreacted bromobenzene. A high reaction temperature favors the formation of this product. Biphenyl is highly soluble in petroleum ether, and it is easily separated from triphenylmethanol. Biphenyl can be separated from benzoic acid by extraction.
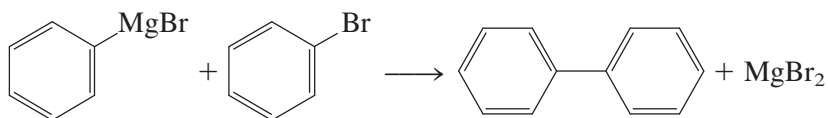
REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: *Technique 8   Filtration, Section 8.3

*Technique 11   Crystallization: Purification of Solids, Section 11.3

*Technique 12   Extractions, Separations, and Drying Agents, Sections 12.4, 12.5, 12.8, and 12.10

Technique 25   Infrared Spectroscopy, Section 25.5

SPECIAL INSTRUCTIONS

This experiment must be conducted in one laboratory period, either to the point after which benzophenone is added (Experiment 33A) or to the point after which the Grignard reagent is poured over dry ice (Experiment 33B). The Grignard reagent cannot be stored; you must react it before stopping. This experiment uses diethyl ether, which is extremely flammable. Be certain that no open flames are in your vicinity when you are using ether.

During this experiment, you will need to use *anhydrous* diethyl ether, which is usually contained in metal cans with a screw cap. You are instructed in the experiment to transfer a small portion of this solvent to a stoppered Erlenmeyer flask. Be certain to minimize exposure to atmospheric water during this transfer. Always recap the ether container after use. Do not use solvent-grade ether, because it may contain some water.

All students will prepare the same Grignard reagent, phenylmagnesium bromide. If your instructor requests it, you should then proceed to either Experiment 33A (triphenylmethanol) or Experiment 33B (benzoic acid) when your reagent is ready.

SUGGESTED WASTE DISPOSAL

All aqueous solutions should be placed in a container designated for aqueous waste. Be sure to decant these solutions away from any magnesium chips before placing them in the waste container. The unreacted magnesium chips that you separate should be placed in a solid waste container designated for that purpose. Place all ether solutions in the container for nonhalogenated liquid wastes. Likewise, the mother liquor from the crystallization, using isopropyl alcohol (Experiment 33A), should also be placed in the container for nonhalogenated liquid wastes.

NOTES TO THE INSTRUCTOR

Whenever possible, you should require that your class wash and dry the necessary glassware *the period before this experiment is scheduled.* It is not a good idea to use glassware that has been washed earlier in the same period, even if it has been dried in the oven. When drying, be certain that no Teflon stopcocks, plastic stoppers, or plastic clips are placed in the oven.

PROCEDURE
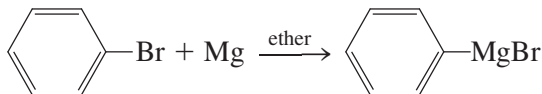
PREPARATION OF THE GRIGNARD REAGENT: PHENYLMAGNESIUM BROMIDE

Glassware.   The following glassware is used:

100-mL round-bottom flask	Claisen head
125-mL separatory funnel	water-jacketed condenser
$CaCl_2$ drying tubes (2)	50-mL Erlenmeyer flasks (2)
10-mL graduated cylinder	

Preparation of Glassware. If necessary, dry all the pieces of *glassware* (no plastic parts), given in the list, in an oven at 110°C for at least 30 minutes. This step can be omitted if your glassware is clean and has been unused in your drawer for at least two to three days. Otherwise, all glassware used in your Grignard reaction must be scrupulously dried. Surprisingly, large amounts of water adhere to the walls of glassware, even when it is apparently dry. Glassware washed and dried the same day, if it is to be used, can still cause problems in starting a Grignard reaction.

Apparatus. Add a clean, dry stirring bar to the 100-mL round-bottom flask, and assemble the apparatus as shown in the figure. Place drying tubes (filled with fresh calcium chloride) on both the separatory funnel and on the top of the condenser. A stirring hot plate will

be used to stir and heat the reaction.[1] Make sure that the apparatus can be moved up and down easily on the ring stand. Movement up and down relative to the hot plate will be used to control the amount of heat applied to the reaction.

C A U T I O N

Do not place any plasticware, plastic connectors, or Teflon stoppers in the oven, as they may melt, burn, or soften. Check with your instructor if in doubt.
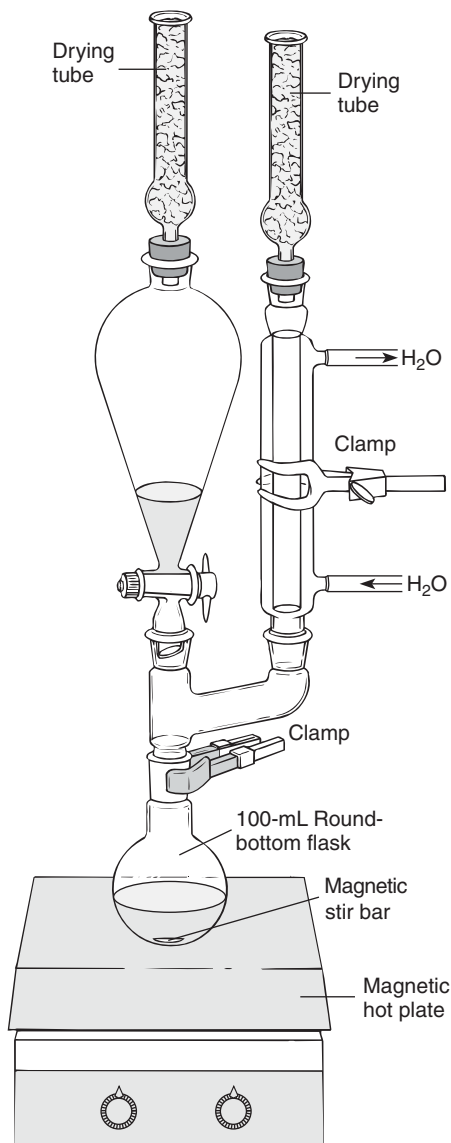
Apparatus for Grignard reactions.

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[1]A steam bath or steam cone may be used, but you will probably have to forgo any stirring and use a boiling stone instead of a spin bar. A heating mantle could be used to heat the reaction. With a heating mantle, it is probably best to clamp the apparatus securely and to support the heating mantle under the reaction flask with wooden blocks that can be added or removed. When the blocks are removed, the heating mantle can be lowered away from the flask.

Formation of the Grignard Reagent. Using smooth paper or a small beaker, weigh about 0.5 g of magnesium turnings (*AW* = 24.3) and place them in the 100-mL round-bottom flask. Using a preweighed 10-mL graduated cylinder, measure approximately 2.1 mL of bromobenzene (*MW* = 157.0), and reweigh the cylinder to determine the exact mass of the bromobenzene. Transfer the bromobenzene to a stoppered 50-mL Erlenmeyer flask. Without cleaning the graduated cylinder, measure a 10-mL portion of anhydrous ether and transfer it to the same 50-mL Erlenmeyer flask containing the bromobenzene. Mix the solution (swirl) and then, using a dry, disposable Pasteur pipet, transfer about half of it into the round-bottom flask containing the magnesium turnings. Add the remainder of the solution to the 125-mL separatory funnel. Then add an additional 7.0 mL of anhydrous ether to the bromobenzene solution in the separatory funnel. At this point, make sure all joints are sealed and that the drying tubes are in place.

Position the apparatus just above the hot plate, and stir the mixture *gently* to avoid throwing the magnesium out of the solution and onto the side of the flask. You should begin to notice the evolution of bubbles from the surface of the metal, which signals that the reaction is starting. It will probably be necessary to heat the mixture, using your hot plate, to start the reaction. The hot plate should be adjusted to its lowest setting. Because ether has a low boiling point (35°C), it should be sufficient to heat the reaction by placing the round-bottom flask just above the hot plate. Once the ether is boiling, check to see if the bubbling action continues after the apparatus is lifted above the hot plate. If the reaction continues to bubble without heating, the magnesium is reacting. You may have to repeat the heating several times to successfully start the reaction. After you have made several attempts at heating, the reaction should start, but if you are still experiencing difficulty, proceed to the next paragraph.

Optional Steps. You may need to employ one or more of the following procedures if heating fails to start the reaction. If you are experiencing difficulty, remove the separatory funnel. Place a long, *dry*, glass stirring rod into the flask, and gently twist the stirring rod to crush the magnesium against the glass surface. *Be careful not to poke a hole in the bottom of the flask; do this gently!* Reattach the separatory funnel and heat the mixture again. Repeat the crushing procedure several times, if necessary, to start the reaction. If the crushing procedure fails to start the reaction, then add one small crystal of iodine to the flask. Again, heat the mixture *gently.* The most drastic action, other than starting the experiment over again, is to prepare a small sample of the Grignard reagent *externally* in a test tube. When this external reaction starts, add it to the main reaction mixture. This "booster shot" will react with any water that is present in the mixture and allow the reaction to get started.

Completing the Grignard Preparation. When the reaction has started, you should observe the formation of a brownish-gray, cloudy solution. Add the remaining solution of bromobenzene slowly over a period of 5 minutes at a rate that keeps the solution boiling gently. If the boiling stops, add more bromobenzene. It may be necessary to heat the mixture occasionally with the hot plate during the addition. If the reaction becomes too vigorous, slow the addition of the bromobenzene solution, and raise the apparatus higher above the hot plate. Ideally, the mixture will boil without the application of external heat. *It is important that you heat the mixture if the reflux slows or stops.* As the reaction proceeds, you should observe the gradual disintegration of the magnesium metal. When all the bromobenzene has been added, place an additional 1.0 mL of *anhydrous* ether in the separatory funnel to rinse it and add it to the reaction mixture. Remove the separatory funnel after making this addition, and replace it with a stopper. Heat the solution under gentle reflux until most of the remaining magnesium dissolves (don't worry about a few small pieces). This should require about 15 minutes. Note the level of the solution in the flask. You should add additional anhydrous ether to replace any that is lost during the reflux period. During this reflux period, you can prepare any solution needed for Experiment 33A or Experiment 33B. When the reflux is complete, allow the mixture to cool to room temperature. As your instructor designates, go on to either Experiment 33A or Experiment 33B.

33A   **E X P E R I M E N T   3 3 A**

Triphenylmethanol

Adduct
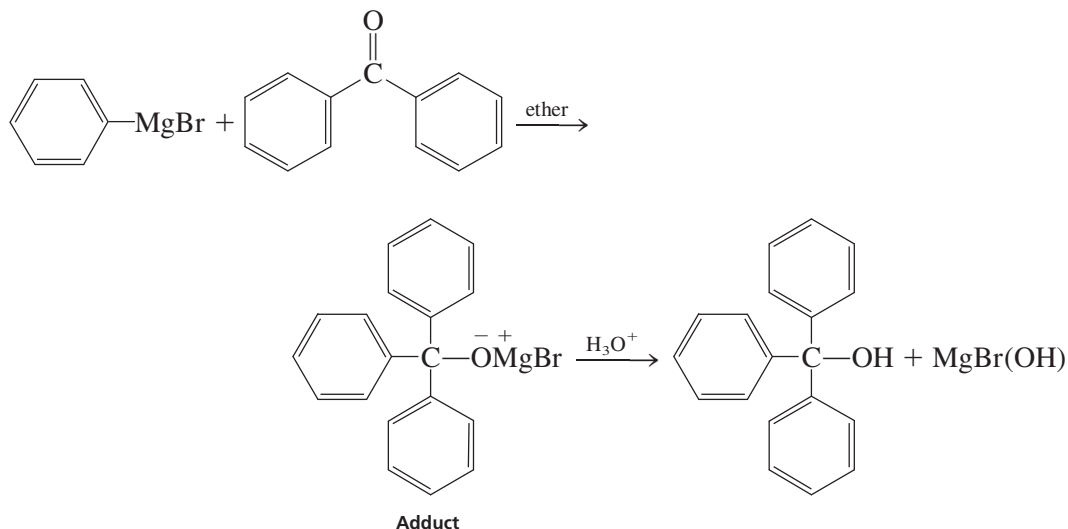
P R O C E D U R E

Addition of Benzophenone. While the phenylmagnesium bromide solution is being heated and stirred under reflux, make a solution of 2.4 g benzophenone in 9.0 mL of *anhydrous* ether in a 50-mL Erlenmeyer flask. Stopper the flask until the reflux period is over. Once the Grignard reagent is cooled to room temperature, reattach the separatory funnel and transfer the benzophenone solution into it. Add this solution as rapidly as possible to the stirred Grignard reagent but at such a rate that the solution does not reflux too vigorously. Rinse the Erlenmeyer flask that contained the benzophenone solution with about 5.0 mL of anhydrous ether, and add it to the mixture. Once the addition has been completed, allow the mixture to cool to room temperature. The solution should turn to a rose color and then gradually solidifies as the adduct is formed. When magnetic stirring is no longer effective, stir the mixture with a spatula. Remove the reaction flask from the apparatus and stopper it. Occasionally, stir the contents of the flask. The adduct should be fully formed after about 15 minutes. You may stop here.

Hydrolysis. Add enough 6 *M* hydrochloric acid (*dropwise at first*) to neutralize the reaction mixture (approximately 7.0 mL). Enough acid has been added when the lower aqueous layer turns blue litmus paper red. The acid converts the adduct to triphenylmethanol and inorganic compounds (MgX_2). Eventually, you should obtain two distinct phases: the upper ether layer will contain triphenylmethanol; the lower aqueous hydrochloric acid layer will contain the inorganic compounds. Use a spatula to break up the solid during the addition of hydrochloric acid. Swirl the flask occasionally to assure thorough mixing. Because the neutralization procedure evolves heat, some ether will be lost due to evaporation. You should add enough ether to maintain a 5- to 10-mL volume in the upper organic phase. Make sure that you have two distinct liquid phases before proceeding to separate the layers. More ether or hydrochloric acid may be added, if necessary, to dissolve any remaining solid.[2]

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[2]In some cases, it may be necessary to add additional water instead of more hydrochloric acid.

If some material stubbornly remains undissolved or if there are three layers, transfer all the liquids to a 250-mL Erlenmeyer flask. Add more ether and more hydrochloric acid to the flask, and swirl it to mix the contents. Continue adding small portions of ether and hydrochloric acid to the flask and swirl it until everything dissolves. At this point, you should have two clear layers.

Separation and Drying. Transfer your mixture to a 125-mL separatory funnel, but avoid transferring the spin bar (or boiling stone). Shake and vent the mixture and then allow the layers to separate. If any unreacted magnesium metal is present, you will observe bubbles of hydrogen being formed. You may remove the aqueous layer even though the magnesium is still producing hydrogen. Drain off the lower aqueous phase, and place it in a beaker for storage. Next, *save the upper ether layer* in an Erlenmeyer flask; it contains the triphenyl-methanol product. Reextract the saved aqueous phase with 5.0 mL of ether. Remove the lower aqueous phase and discard it. Combine the remaining ether phase with the first ether extract. Transfer the combined ether layers to a dry Erlenmeyer flask, and add about 1.0 g of granular anhydrous sodium sulfate to dry the solution. Add more drying agent if necessary.

Evaporation. Decant the dried ether solution from the drying agent into a small Erlen-meyer flask, and rinse the drying agent with more diethyl ether. Evaporate the ether solvent in a hood by heating the flask in a warm water bath. Evaporation will occur more quickly if a stream of nitrogen or air is directed into the flask. You should be left with a mixture that varies from a brown oil to a colored solid mixed with an oil. This crude mixture contains the desired triphenylmethanol and the by-product biphenyl. Most of the biphenyl can be removed by adding about 10 mL of petroleum ether (bp 30–60°C). Petroleum ether is a mixture of hydro-carbons that easily dissolves the hydrocarbon biphenyl and leaves behind the alcohol triph-enylmethanol. Do not confuse this solvent with diethyl ether ("ether"). Heat the mixture slightly, stir it, and then cool the mixture to room temperature. Collect the triphenylmethanol by vacuum filtration on a small Büchner funnel, and rinse it with small portions of petroleum ether (see Technique 8, Section 8.3 and Figure 8.5). Air-dry the solid, weigh it, and calculate the percentage yield of the crude triphenylmethanol ($MW = 260.3$).

Crystallization. Crystallize all of your product from hot isopropyl alcohol, and collect the crystals using a Büchner funnel (see Technique 11, Section 11.3 and Figure 11.4). Step 2 in Figure 11.4 (removal of insoluble impurities) should not be required in this crystallization. Set the crystals aside to air-dry. Report the melting point of the purified triphenylmethanol (litera-ture value, 162°C) and the recovered yield in grams. Submit the sample to the instructor.
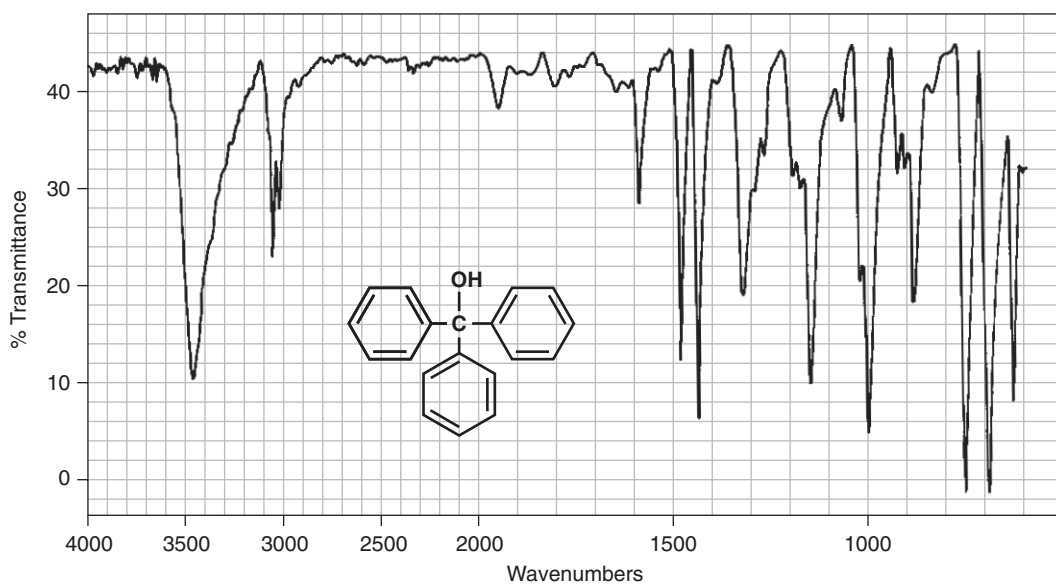
Infrared spectrum of triphenylmethanol, KBr.

Spectroscopy. If your instructor requests it, determine the infrared spectrum of the puri-fied material in a KBr pellet (see Technique 25, Section 25.5). Your instructor may assign cer-tain tests on the product you prepared. These tests are described in the Instructor's Manual.

33B   EXPERIMENT 33B

Benzoic Acid

The reaction: phenylmagnesium bromide (PhMgBr) $+ CO_2 \xrightarrow{\text{ether}}$ intermediate benzoate magnesium salt $\xrightarrow{H_3O^+}$ Benzoic acid $+ MgBr(OH)$

Benzoic acid
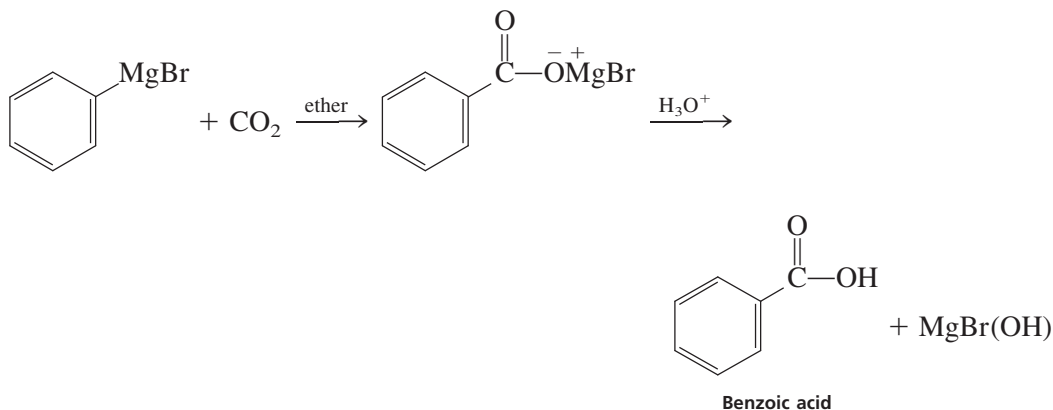
PROCEDURE

Addition of Dry Ice. When the phenylmagnesium bromide solution has cooled to room tem-perature, pour it as quickly as possible onto 10 g of crushed dry ice contained in a 250-mL beaker. The dry ice should be weighed as quickly as possible to avoid contact with atmos-pheric moisture. It need not be weighed precisely. Rinse the flask, in which the phenylmag-nesium bromide was prepared, with 2 mL of anhydrous ether and add it to the beaker.

> **CAUTION**
>
> **Exercise caution in handling dry ice. Contact with the skin can cause severe frostbite. Always use gloves or tongs. The dry ice is best crushed by wrapping large pieces in a clean, dry towel and striking them with a hammer or a wooden block. It should be used as soon as possible after crushing it to avoid contact with atmospheric water.**

Cover the reaction mixture with a watch glass, and allow it to stand until the excess dry ice has completely sublimed. The Grignard addition compound will appear as a viscous, glassy mass.

Hydrolysis. Hydrolyze the Grignard adduct by slowly adding approximately 8 mL of 6 *M* hydrochloric acid to the beaker and stirring the mixture with a glass rod or spatula. Any remaining magnesium chips will react with the acid to evolve hydrogen. At this point, you should have two distinct liquid phases in the beaker. If you have solid present (other than magnesium), try adding a little more ether. If the solid is insoluble in ether, try adding a little

more 6 *M* hydrochloric acid solution or water. Benzoic acid is soluble in ether, and inorganic compounds (MgX$_2$) are soluble in the aqueous acid solution. Transfer the liquid phases to an Erlenmeyer flask, leaving behind any residual magnesium. Add more ether to the beaker to rinse it, and add this additional ether to the Erlenmeyer flask. You may stop here. Stopper the flask with a cork, and continue with the experiment during the next laboratory period.

Isolation of the Product. If you stored your product and the ether layer evaporated, add several milliliters of ether. If the solids do not dissolve on stirring or if no water layer is apparent, try adding some water. Transfer your mixture to a 125-mL separatory funnel. If some material remains undissolved or if there are three layers, add more ether and hydrochloric acid to the separatory funnel, stopper it, shake it, and allow the layers to separate. Continue adding small portions of ether and hydrochloric acid to the separatory funnel, and shake it until everything dissolves. After the layers have separated, remove the lower aqueous layer. The aqueous phase contains inorganic salts and may be discarded. The ether layer contains the product benzoic acid and the by-product biphenyl. Add 5.0 mL of 5% sodium hydroxide solution, restopper the funnel, and shake it. Allow the layers to separate, *remove the lower aqueous layer, and save this layer in a beaker.* This extraction removes benzoic acid from the ether layer by converting it to the water-soluble sodium benzoate. The by-product biphenyl stays in the ether layer along with some remaining benzoic acid. Again, shake the remaining ether phase in the separatory funnel with a second 5.0-mL portion of 5% sodium hydroxide, and transfer the lower aqueous layer into the beaker with the first extract. Repeat the extraction process with a third portion (5.0 mL) of 5% sodium hydroxide, and save the aqueous layer as before. Discard the ether layer, which contains the biphenyl impurity, into the waste container designated for nonhalogenated organic wastes.

Heat the combined basic extracts while stirring on a hot plate (100°C–120°C) for about 5 minutes to remove any ether that may be dissolved in this aqueous phase. Ether is soluble in water to the extent of 7%. During this heating period, you may observe slight bubbling, but the volume of liquid *will not* decrease substantially. Unless the ether is removed before the benzoic acid is precipitated, the product may appear as a waxy solid instead of crystals.
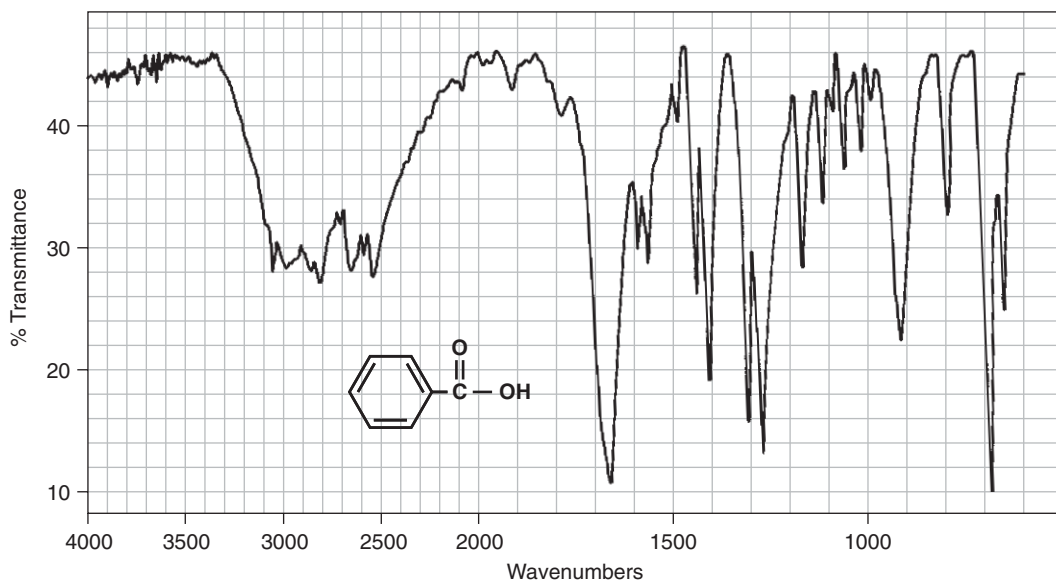
Infrared spectrum of benzoic acid, KBr.

Cool the alkaline solution, and precipitate the benzoic acid by adding 10.0 mL of 6.0 *M* hydrochloric acid while stirring. Cool the mixture in an ice bath. Collect the solid by vacuum filtration on a Büchner funnel (see Technique 8, Section 8.3 and Figure 8.5). The transfer may be aided and the solid washed with several small portions of cold water. Allow the crystals to dry thoroughly at room temperature at least overnight. Weigh the solid, and calculate the percentage yield of benzoic acid (*MW* = 122.1).

Crystallization. Crystallize your product from hot water, using a Büchner funnel to collect the product by vacuum filtration (see Technique 11, Section 11.3 and Figure 11.4). Step 2 in Figure 11.4 (removal of insoluble impurities) should not be required in this crystallization. Set the crystals aside to air-dry at room temperature before determining the melting point of the purified benzoic acid (literature value, 122°C) and the recovered yield in grams.[3] Submit your product to your instructor in a properly labeled vial.

Spectroscopy. If your instructor requests it, determine the infrared spectrum of the purified material in a KBr pellet (see Technique 25, Section 25.5). Your instructor may assign certain tests on the product you prepared. These tests are described in the Instructor's Manual.

QUESTIONS

1. Benzene is often produced as a side product during Grignard reactions using phenylmagnesium bromide. How can its formation be explained? Give a balanced equation for its formation.

2. Write a balanced equation for the reaction of benzoic acid with hydroxide ion. Why is it necessary to extract the ether layer with sodium hydroxide?

3. Interpret the principal peaks in the infrared spectrum of either triphenylmethanol or benzoic acid, depending on the procedure used in this experiment.

4. Outline a separation scheme for isolating either triphenylmethanol or benzoic acid from the reaction mixture, depending on the procedure used in this experiment.

5. Provide methods for preparing the following compounds by the Grignard method:

(a) $CH_3CH_2CHCH_2CH_3$
           |
          OH

(c) $CH_3CH_2CH_2CH_2CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH$

(b) $CH_3CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-CH_2CH_3$

(d) a phenyl group attached to $-\overset{\overset{\displaystyle OH}{|}}{CH}-CH_2CH_3$

---
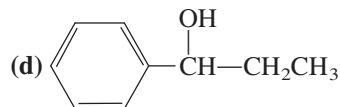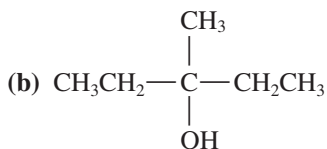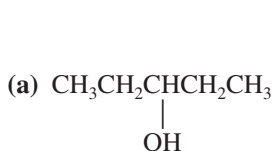
[3]If necessary, the crystals may be dried in a low temperature (ca. 50°C) oven for a short period of time. Be warned that benzoic acid sublimes, and heating it for a long time at elevated temperatures could result in loss of your product.

34   E X P E R I M E N T 3 4

Aqueous-Based Organozinc Reactions

Organometallic reactions

Green chemistry

Extractions

Use of a separatory funnel

Gas chromatography

Spectroscopy

One of the most important categories of reactions in organic synthesis is the class of reactions that result in the formation of a carbon-carbon bond. Among these, one of the best-known reactions is the Grignard reaction, where an organomagnesium reagent is formed from an alkyl halide and then allowed to react with a variety of substances to form new molecules. The nucleophilic nature of the organomagnesium reagent is used in the formation of new carbon-carbon bonds. The equation shown below illustrates this type of synthesis. The Grignard reaction is introduced in Experiment 33.

$$R\!-\!Br \;+\; Mg \;\xrightarrow{\;ether\;}\; R\!-\!MgBr$$

$$R\!-\!MgBr \;+\; \underset{R'}{\overset{O}{\underset{\displaystyle C}{\|}}}\!\!R'' \;\longrightarrow\; \underset{R}{\overset{\;:\!\overset{\ominus}{O}\!:\;\overset{\oplus}{MgBr}}{R'\!-\!\underset{|}{\overset{|}{C}}\!-\!R''}}$$

$$\underset{R}{\overset{\;:\!\overset{\ominus}{O}\!:\;\overset{\oplus}{MgBr}}{R'\!-\!\underset{|}{\overset{|}{C}}\!-\!R''}} \;+\; H_2O \;\xrightarrow{\;H^+\;}\; \underset{R}{\overset{:\overset{..}{O}\!-\!H}{R'\!-\!\underset{|}{\overset{|}{C}}\!-\!R''}} \;+\; MgBr(OH)$$
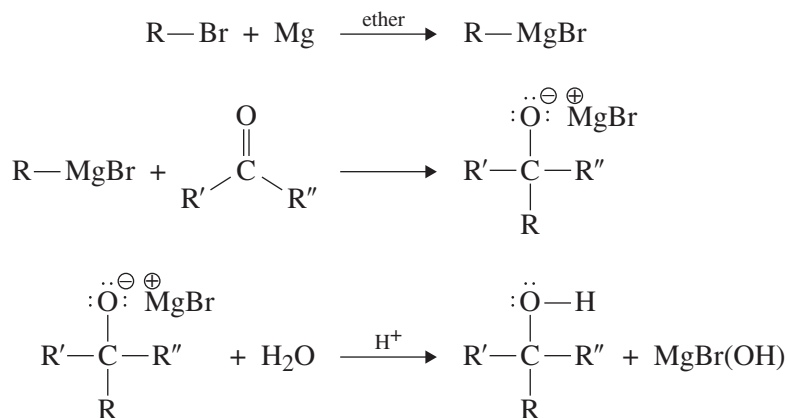
Because the organomagnesium reagent reacts with water, carbon dioxide, and oxygen, it must be protected from air and moisture when it is used. The apparatus in which the reaction is to be conducted must be scrupulously dry, and the solvent must be completely anhydrous. In addition, diethyl ether is required as a solvent; without the presence of an ether, the organomagnesium reagent will not form.

This experiment presents a variation on the basic idea of a Grignard synthesis but one that does not use magnesium and that can be conducted in a mixed organic-aqueous solution. The reaction presented in this experiment is a variation on the Barbier-Grignard reaction, where zinc is used as the metal. A small amount of an ether, in this case tetrahydrofuran (THF), is still required for this reaction, but the principal component of the solvent system is water. By eliminating much of the organic solvent, this method can be used to illustrate some of the principles of "Green Chemistry," in which reactions are conducted under conditions that are less harmful to the environment than traditional chemical methods.

$$R\!\!-\!\!Br + Zn \xrightarrow{\text{ether}} R\!\!-\!\!ZnBr$$

$$R\!\!-\!\!ZnBr + \underset{R'}{\overset{\displaystyle O}{\underset{\displaystyle \big\|}{C}}}\!\!\!-\!\!R'' \longrightarrow R'\!\!-\!\!\underset{R}{\overset{:\overset{\ominus}{O}:\ \overset{\oplus}{ZnBr}}{\underset{\displaystyle |}{\overset{\displaystyle |}{C}}}}\!\!-\!\!R''$$

$$R'\!\!-\!\!\underset{R}{\overset{:\overset{\ominus}{O}:\ \overset{\oplus}{ZnBr}}{\underset{\displaystyle |}{\overset{\displaystyle |}{C}}}}\!\!-\!\!R'' + H_2O \xrightarrow{H^+} R'\!\!-\!\!\underset{R}{\overset{:\overset{..}{O}\!\!-\!\!H}{\underset{\displaystyle |}{\overset{\displaystyle |}{C}}}}\!\!-\!\!R'' + ZnBr(OH)$$
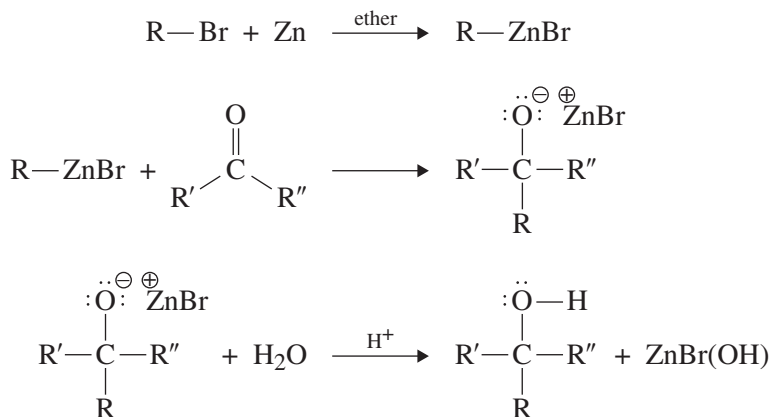
Although this organozinc method of synthesis is very similar to the Grignard reaction, there are also some interesting differences. The organozinc reagent is much more selective than the organomagnesium reagent, and rearrangements of the alkyl group attached to the metal are also possible. Whereas the formation of Grignard reagents from allylic halides is notoriously difficult, the formation of organozinc reagents seems to require that one begin with an allylic halide. A comparison of the structure of the products of this reaction with the structure of the starting alkyl halide can reveal some of this interesting chemistry.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: *Technique 8   Section 8.3

Technique 7   Section 7.10

*Technique 12 Sections 12.5, 12.8, 12.9, 12.11

Technique 22

Technique 25   Sections 25.2, 25.4

Technique 26   Section 26.1

Technique 27   Section 27.1

SPECIAL INSTRUCTIONS

This reaction involves the use of allyl bromide, a substance that is volatile and may also be a **lachrymator**. Be certain to dispense this material under the hood. Do not attempt to weigh this substance; determine the approximate volume of allyl bromide needed using the specific gravity provided in this experiment, and dispense the allyl bromide by volume using a calibrated pipet. Students should work in pairs for this experiment.

SUGGESTED WASTE DISPOSAL

All aqueous solutions should be placed in a waste container designated for the disposal of aqueous wastes.

PROCEDURE

Activated zinc

Carefully weigh 1.31 g (0.02 moles) of zinc powder, and add it to a small (10-mL) Erlenmeyer flask or beaker. Add 1 mL of 5% aqueous hydrochloric acid, and allow the mixture to stand for 1 to 2 minutes. There will be a noticeable evolution of hydrogen gas during this time. At the end of this period, pour the entire mixture into a Hirsch funnel, and isolate the zinc by vacuum filtration. Rinse the zinc with 1 mL of water, followed by 1 mL of ethanol and 1 mL of diethyl ether. The zinc should be ready to use for the procedure, as described below.

Preparation and Reaction of the Organozinc Reagent

Add 10 mL of saturated aqueous ammonium chloride solution to a 25-mL round-bottom flask. Add 1.31 g zinc powder (0.02 moles) and a stirring bar to the flask. Attach an air condenser to the flask and begin continuous stirring while adding the remaining reagents. Carefully weigh 0.86 g (0.01 moles) of the 3-pentanone. Add the ketone and 1.6 mL of tetrahydrofuran to a test tube, and add this solution dropwise to the zinc/NH_4Cl solution. The rate of addition should be about one drop per second. Note that this addition can be made by dropping the solution carefully down the opening in the air condenser; use a Pasteur pipet to add the solution. Allow the solution to stir for 10 to 15 minutes, giving time for the carbonyl compound to form a complex with the zinc. Add 2.4 g (0.02 moles—use the specific gravity 1.398 g/mL to estimate the volume required) of allyl bromide (3-bromopropene) to the stirring solution. *Be sure to dispense this reagent in the hood!* The rate of addition should be about one drop per second. Add the halide carefully by dropping it down the opening in the air condenser. Allow the reaction mixture to stir for 1 hour.

Set up a vacuum filtration apparatus with a Hirsch funnel. Decant the liquid from the reaction mixture through the Hirsch funnel. Rinse the round-bottom flask with approximately 1 mL of diethyl ether, and pour the liquid into the Hirsch funnel. Using a second 1-mL portion of diethyl ether, rinse the solid that has collected in the Hirsch funnel. Discard the solid. Prepare a filter-tip pipet, and transfer the liquid that was collected in the vacuum filtration into a separatory funnel. Use 1 mL of diethyl ether to rinse the inside of the filter flask, and use the filter-tip pipet to transfer this liquid to the separatory funnel. Shake the separatory funnel gently to extract the organic material from the aqueous layer to the ether layer. Drain the lower (aqueous) layer into a 50-mL Erlenmeyer flask. *Do not discard this aqueous layer.* Collect the upper (organic) layer from the separatory funnel into a 25-mL Erlenmeyer flask (remember to collect the upper layer by pouring it from the top of the separatory funnel). Replace the aqueous layer in the separatory funnel, and wash it with a 2-mL portion of ether. Separate the layers, save the aqueous layer in the same 50-mL Erlenmeyer flask as before, and combine the ether layer with the ether solution collected in the previous extraction. Repeat this extraction process of the aqueous phase one more time using a fresh 2-mL portion of ether. Dry the combined ether extracts with 3–4 microspatulafuls of anhydrous sodium sulfate (see Technique 12, Section 12.9). Stopper the Erlenmeyer flask with a cork, and allow it to stand for at least 15 minutes (or overnight).

Use a filter-tip pipet to transfer the dried liquid to a clean, preweighed Erlenmeyer flask. Use a small amount of ether to rinse the inside of the original flask, and add this ether to the dried liquid. Evaporate the ether with a rotary evaporator or under a gentle stream of air. When the ether has evaporated completely, reweigh the flask to determine the yield of the product. If it should be necessary to store your final product, use Parafilm® to seal the container.

Prepare a sample of your final product for analysis by gas chromatography. Determine the infrared spectrum and both proton and ^{13}C NMR spectrum of your product. Use these spectra to determine the structure of your product. In your laboratory report, include an interpretation of each spectrum, identifying the principal absorption bands and demonstrating how the spectrum corresponds to the structure of your compound. Submit your sample in a labeled vial with your laboratory report.

QUESTIONS

1. Write *balanced* chemical equations for the formation of a substance that you prepared in this experiment.

2. Outline a series of chemical equations to show how your product could have been prepared using a Grignard reaction. Be sure to show the structures of all starting materials and intermediates.

3. Draw the structure of the product that would have been formed if benzaldehyde had been used in place of 3-pentanone in this experiment.

4. When benzaldehyde is used as the carbonyl compound in this experiment, the CH_2 peak in the proton-NMR spectrum appears as *two* separate, complex resonances. Explain why this is observed.

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35   EXPERIMENT 35

Sonogashira Coupling of Iodosubstituted Aromatic Compounds with Alkynes using a Palladium Catalyst

Green chemistry

Organometallic chemistry

Palladium-catalyzed reaction

In this experiment, we will conduct some modern organic chemistry using a palladium catalyst. It is a rare opportunity for students in undergraduate laboratories to experience this powerful chemistry. We will react the iodosubstituted aromatic compounds, shown below, with 1-pentyne, 1-hexyne, or 1-heptyne in the presence of the catalysts, palladium acetate and cuprous iodide, to yield 4-substituted-1-pentynyl, 4-substituted-1-hexynyl, or 4-substituted-1-heptynylaromatic compounds. This reaction is called the Sonogashira coupling reaction.[1] The reaction will be carried out in refluxing 95% ethanol as the solvent. In addition, piperazine will be employed both as a base and as a hydride donor.
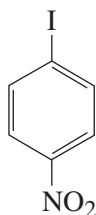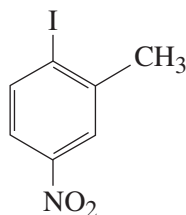
1-iodo-4-nitrobenzene   2-iodo-5-nitrotoluene   4-iodoacetophenone   ethyl 4-iodobenzoate
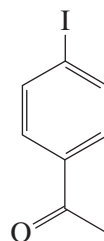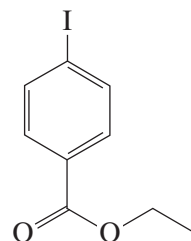
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[1]a) Takahashi, S., Kuroyama, Y., Sonogashira, K., Hagihara, N. *Synthesis*, **1980**, 627–630.
b) Thorand, S., and Krause, N. *J. Org. Chem.*, **1998**, *63*, 8551–8553.

BACKGROUND

Palladium-catalyzed reactions can be used to connect the terminal end of an alkyne and aromatic iodide, as shown in the reaction below.[2] They are useful in industry and are widely employed in the academic arena. The experiment presented here was adapted from an article by Goodwin, Hurst, and Ross.[3] The mechanism shown is for the coupling of 1-iodo-4-nitrobenzene with 1-pentyne. Small amounts of a dimer obtained from the coupling of the 1-alkynes are also formed in these reactions. It is likely that the dimers result from the formation of the copper intermediate (step 3 of the mechanism). Thus, reactions involving 1-pentyne yield some 4,6-decadiyne.

$$R = -CH_2-CH_2-CH_3 \quad \text{Pentyne}$$

$$R = -CH_2-CH_2-CH_2-CH_3 \quad \text{Hexyne}$$

$$R = -CH_2-CH_2-CH_2-CH_2-CH_3 \quad \text{Heptyne}$$
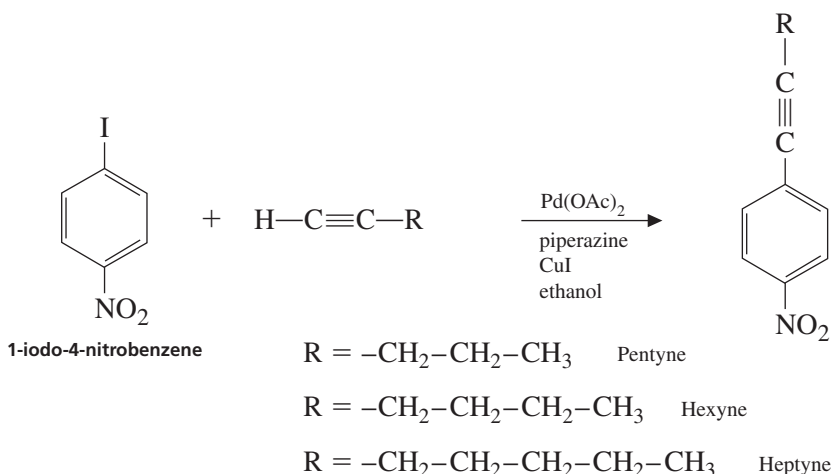
The mechanism is thought to proceed in five steps, as shown below.

Step 1: Transfer of hydride from piperazine to palladium
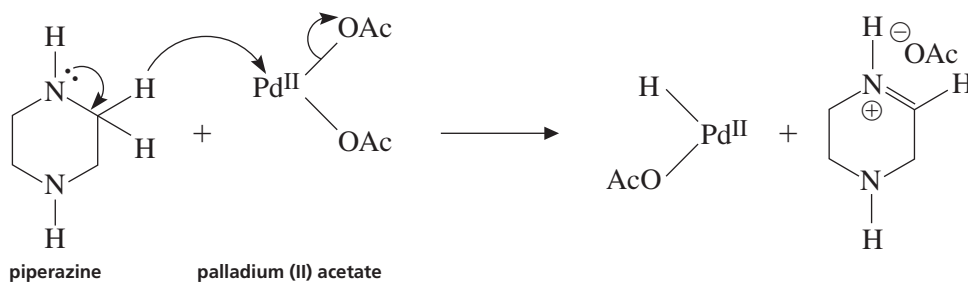
[2]Brisbois, R. G., Batterman, W. G., and Kragerud, S. R. *J. Chem. Ed.* **1997**, *74*, 832–833.
[3]Goodwin, T. E., Hurst, E. M., and Ross, A. S. *J. Chem. Ed.* **1999,** *76*, 74–75. Experiment developed by Brogan, H., Engles, C., Hanson, H., Phillips, S., Rumberger, S., and Lampman, G. M., Western Washington University, Bellingham, WA.

Step 2: Reduction of Pd(II) to Pd^0 by removal of HOAc with piperazine
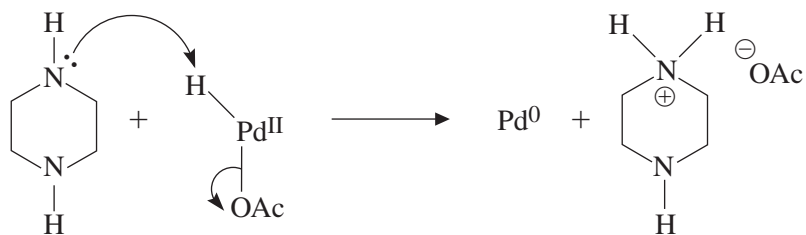
The Pd^0 is probably complexed with piperazine ligands (L).
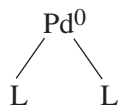
Step 3: Preparation of cuprate
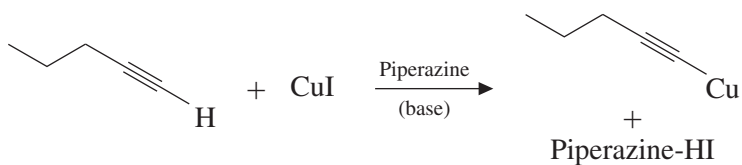
Step 4: Oxidative addition
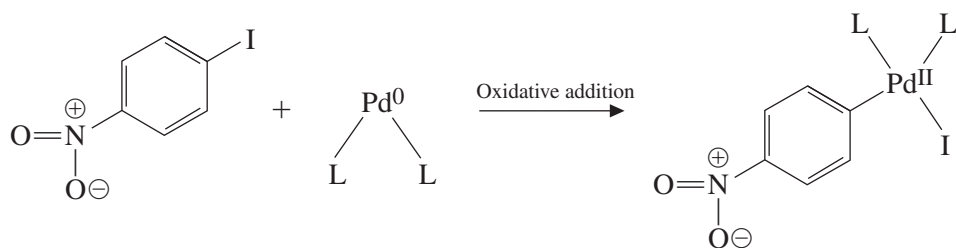
Step 5: Coupling of cuprate to the palladium complex
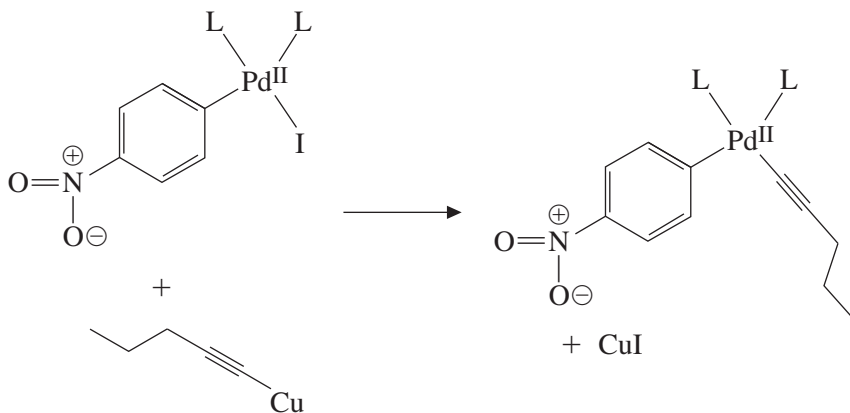
Step 6: Reductive elimination forms the product and regenerates Pd^0
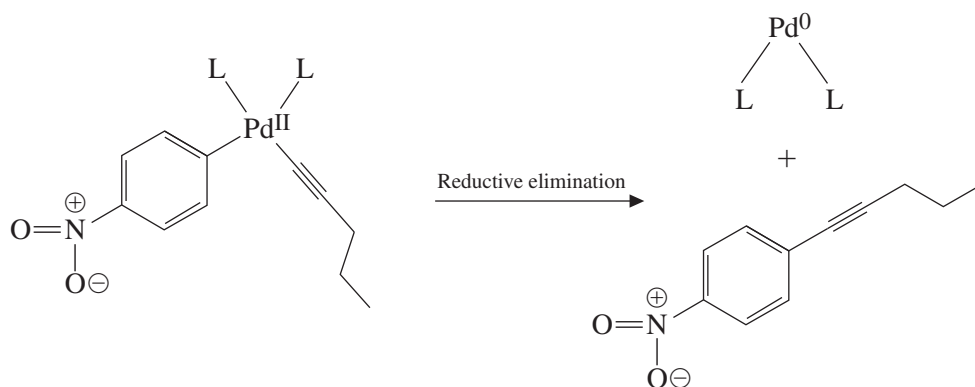
REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: Techniques 5, 6, *7, *12, *19, 25, and 26

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes in the container for aqueous waste. Place the organic waste in the nonhalogenated organic waste container. Place the halogenated waste in the appropriate waste container.

NOTES TO THE INSTRUCTOR

It is suggested that students work in pairs for this experiment.

The Sonogashira reaction works best when electron withdrawing functional groups are attached to the aromatic ring. Thus, the four compounds shown above work well employing a 30-minute reaction period. These compounds contain nitro, acetyl, and carboethoxy functional groups, along with the iodo group. When electron-releasing groups, such as methoxy are attached to the ring, the reaction is much slower and requires much longer reaction times. We have found success with the less reactive compounds employing microwave technology. If your laboratory includes a commercial microwave reactor, such as the CEM Explorer, you can achieve excellent success with 4-iodoanisole (1-iodo-4-methoxybenzene) using the optional procedure.

PROCEDURE

Preparation of the Reaction Mixture. Add 0.200 mmol of one of the four iodo substrates shown on page 294 to a 25-mL round-bottom flask. Use a 4-place analytical balance for weighing the substrates and all of the materials listed next. Now add 55 mg of piperazine and a clean magnetic stir bar to the flask. Add 1.25 ml of 95% ethanol to the flask to dissolve the

materials. Now add 16.5 mg of palladium (II) acetate and 10 mg of copper (I) iodide to the flask. Finally, use an automatic pipet to dispense 70 μL of 1-pentyne, 1-hexyne, or 1-heptyne, depending on which alkyne you were assigned, to the round-bottom flask. Attach a water-cooled condenser to the flask. Heat the contents at reflux for 30 minutes on a hot plate, with stirring.

After the solution has been refluxed for 30 minutes, allow the mixture to cool for a few minutes. Remove the flask and remove the ethanol on a rotary evaporator.[4] When using the rotary evaporator, be sure to spin the flask rapidly and don't heat the water in the water bath. There may be a tendency for the sample to "bump." When it appears that the ethanol has been removed, attach the flask to a vacuum pump for at least 3 minutes to remove the remaining ethanol and any dimer formed in the reaction. When the ethanol has been successfully removed, add 1 mL of methylene chloride to the flask followed by 0.2 g of silica gel. Swirl the flask to ensure that most of the liquid is adsorbed onto the silica gel. Put the flask back onto the rotary evaporator and remove the methylene chloride. Your product is now adsorbed, onto the silica, yielding a dry, free-flowing solid. Use a spatula to break up the silica containing your product. Pour the solid onto a piece of paper and keep it handy until you have made up the column.

Column Chromatography. Prepare a silica gel column for chromatography using a 10-mL Pyrex disposable cleanup/drying column (Corning #214210 available from Fisher #05-722-13; the column is about 30 cm long and 1 cm in diameter). Push some cotton down into the bottom using a glass rod, but don't pack the cotton too tightly. The cotton must be tight enough to keep the silica gel from leaking out of the bottom of the column, but not too tight to reduce the flow of solvent. Add silica gel[5] until it is about 5 cm from the top of the column.

Now, a funnel will be constructed out of a disposable plastic Pasteur pipet in order to add the sample to the top of the chromatography column. To make the funnel, first cut off the top of a 1-mL plastic pipet and also remove most of the tip to make a small funnel (your instructor will demonstrate this). Pour the silica sample containing your adsorbed product from the weighing paper into the top of the silica gel column using your funnel. The solid now resides at the top of your chromatography column. Obtain 10 mL of hexanes and 20 mL of CH_2Cl_2. First pass the 10 mL of hexane through the column, in portions, to wet the silica, and collect the eluent in a preweighed 100-mL round-bottom flask (obtain the flask from your instructor, and use a 4-place balance). Then pass the CH_2Cl_2 solvent through the column in portions while collecting the eluent into the same 100-mL flask. The column removes the palladium catalyst, which remains as a black substance at the top of the chromatography column.

Isolation of the Product. After all of the elutants have been collected in the round-bottom flask, attach the flask to the rotary evaporator and remove the solvent, under vacuum. (Be careful that the solvent doesn't bump up into the trap!) After removing the hexanes and CH_2Cl_2, attach the flask to a vacuum pump[6] for about 3 minutes to ensure that all of the solvent and dimer[7] have been removed from the product. Remove the flask and weigh it on the 4-place balance to determine the amount of product obtained. Calculate the percentage yield.

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[4]An alternative procedure for removing the ethanol solvent is to blow air on the sample. Allow at least 10 to 15 minutes at 50°C for removal of the ethanol.
[5]Fisher Chromatographic Silica Gel, 60-200 mesh, #S818-1, Davisil® Grade 62, type 150A°.
[6]The vacuum pump is required to remove all traces of hexane and methylene chloride. In the NMR spectrum, these peaks appear at 0.9 ppm (triplet) and 1.3 ppm (multiplet). Any remaining CH_2Cl_2 appears at about 5.3 ppm (singlet).
[7]The vacuum pump helps remove any dimer present in the sample. Be sure to use a good quality vacuum pump to remove the dimer from the product.

Analysis of the Product. Determine the NMR spectrum of the sample remaining in the 100-mL flask in CDCl$_3$. Add a few drops of CDCl$_3$ directly to the flask. Transfer the solution to the NMR tube with a Pasteur pipet. Put more drops of CDCl$_3$ into the flask, and transfer this to the NMR tube. Repeat until you are fairly certain that you have transferred most of your product to the NMR tube. Finally, if necessary, add enough CDCl$_3$ to bring the total height to about 50 mm. Run the NMR spectrum and interpret the patterns. Four reference spectra are shown in Figures 1, 2, 3, and 4. Figure 1 shows the spectrum for the product obtained from 1-iodo-4-nitrobenzene and 1-hexyne. Notice that the spectrum shows a triplet at 0.96 ppm, a sextet at 1.50 ppm, a quintet at 1.60 ppm, another triplet at 2.45 ppm, and 2 doublets—one at 7.50 ppm and one at 8.15 ppm. A trace of 5,7-dodecadiyne is observed at about 0.9, 1.4, and 2.2 ppm in the NMR spectrum. Be on the alert for a sharp singlet that may appear near 7.25 ppm for chloroform (CHCl$_3$) present in the CDCl$_3$ solvent. Other NMR spectra are shown in Figures 2, 3, and 4. Compare your results to those shown in the figures when making the assignments for your sample.

The plan is to run the proton NMR, and then use your sample to obtain the infrared spectrum. Pour the contents of the NMR tube into a small test tube. Transfer a small amount of the CDCl$_3$ solution to a salt plate using a Pasteur pipet, blow on the plate to evaporate the solvent, and then determine the infrared spectrum. Make sure that the CDCl$_3$ has evaporated before determining the infrared spectrum. The infrared spectrum for the product obtained from 1-iodo-2-methyl-4-nitrobenzene and 1-hexyne is shown in Figure 5 for comparison. A sharp peak at about 2227 cm^{-1} is observed for the triple bond, as well as two sharp peaks at 1518 and 1343 cm^{-1} for the NO$_2$ group. Assign peaks for your compound.
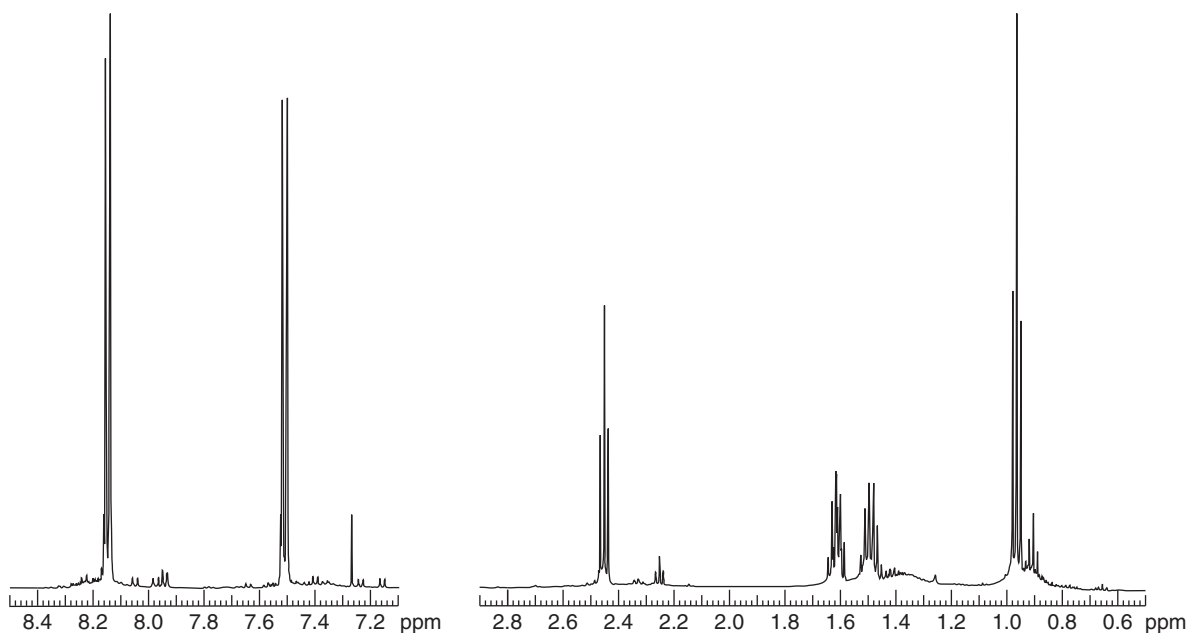
Figure 1. 500 MHz NMR spectrum of the product of 1-iodo-4-nitrobenzene and 1-hexyne. A trace of a dimer, 5,7-dodecadiyne, formed from 1-hexyne is observed at about 0.9 ppm (3H), 1.4 ppm (4H), and 2.2 ppm (2H) in the NMR spectrum. Traces of other impurities are also found in the spectrum. CHCl$_3$ appears at about 7.25 ppm.
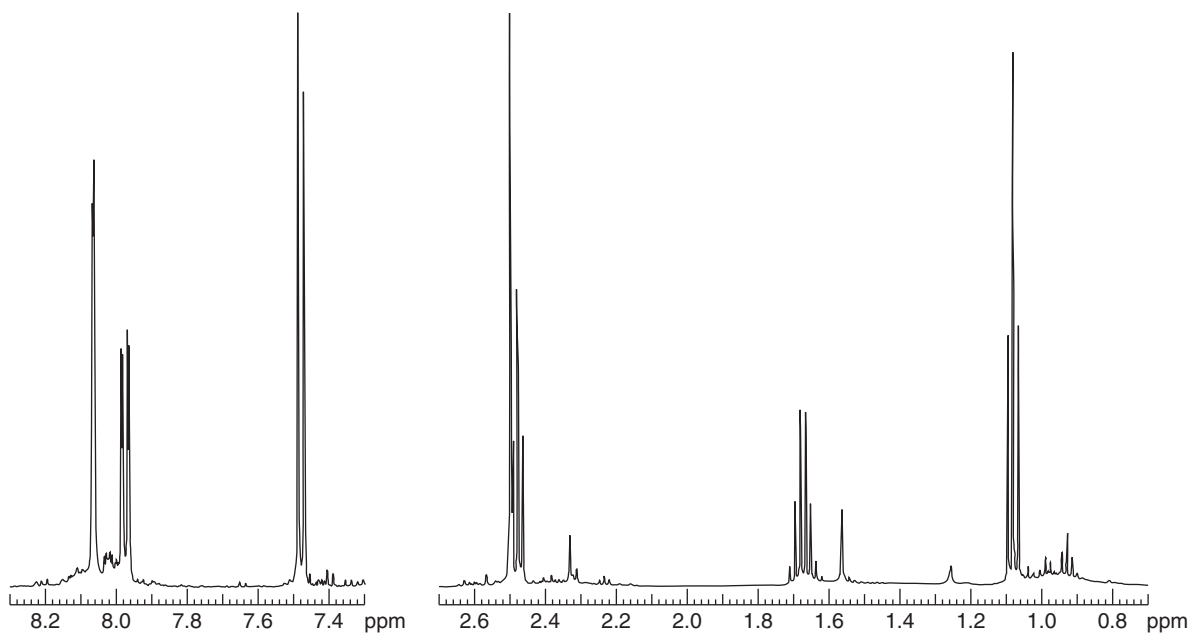
Figure 2. 500 MHz NMR spectrum of 1-iodo-2-methyl-4-nitrobenzene and 1-pentyne. Notice that the singlet for the methyl group partially overlaps with the triplet at 2.5 ppm.
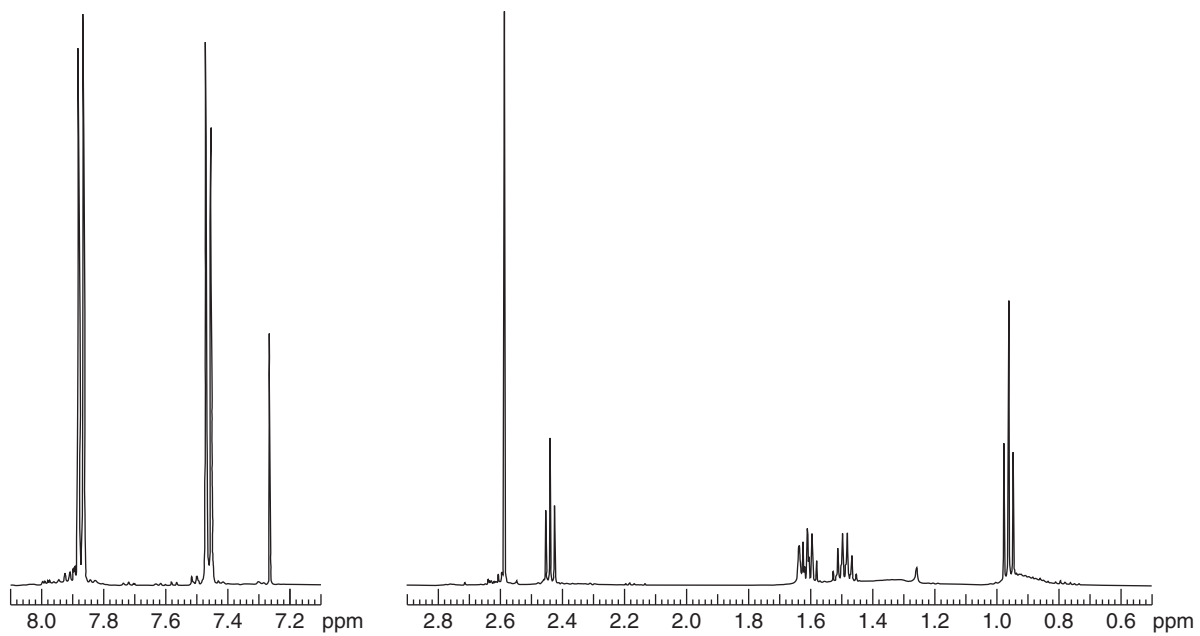
Figure 3. 500 MHz NMR spectrum of 4-iodoacetophenone and 1-hexyne. $CHCl_3$ appears at about 7.25 ppm.
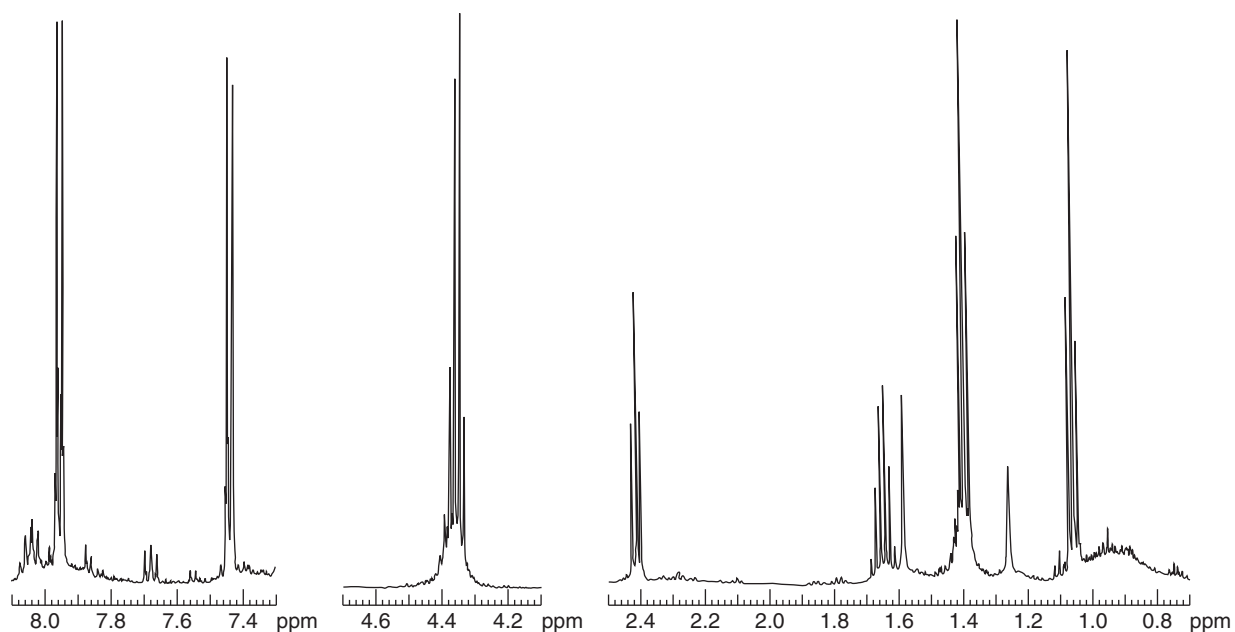
Figure 4. 500 MHz NMR spectrum of ethyl 4-iodobenzoate and 1-pentyne. The –CH$_2$- in the ethyl group appears as a quarter at 4.4 ppm, while the CH$_3$ group in the ethyl group appears as a triplet at 1.4 ppm. The triplet at 1.05 ppm, sextet at 1.65 ppm, and triplet at 2.40 ppm are assigned to the –CH$_2$-CH$_2$-CH$_3$ chain. The pair of doublets at 7.45 and 7.95 ppm are assigned to the *para*-disubstituted benzene ring. Impurity peaks appear at 0.95 (broad) ppm, 1.25 ppm, and 1.60 ppm and along with some miscellaneous small impurities appearing in the aromatic ring region.
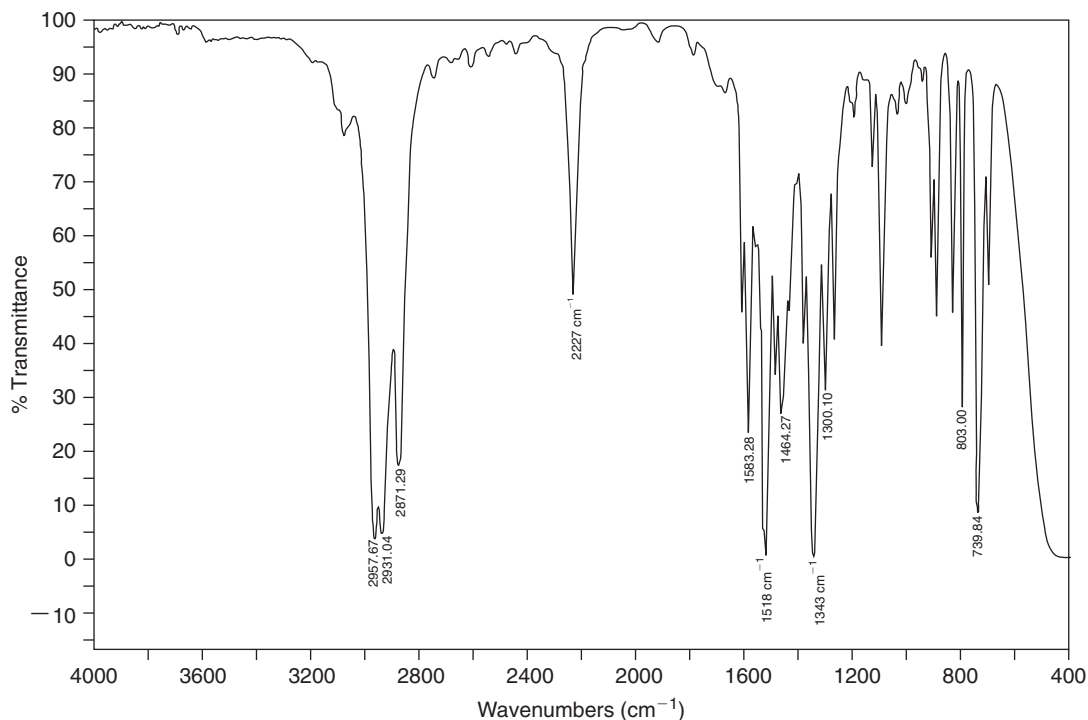
Figure 5. Infrared spectrum of the product of 1-iodo-2-methyl-4-nitrobenzene and 1-hexyne. The sharp peak at 2227 cm^{-1} is assigned to the triple bond in 1-hexyny1–2-methyl-4-nitrobenzene, and the two sharp peaks at 1518 and 1343 cm^{-1} are assigned to the nitro group.

OPTIONAL PROCEDURE USING MICROWAVE TECHNOLOGY[8]

Reaction.[9] Add 0.0573 g (0.24 mmol) of 4-iodoanisole, 0.0120 g of palladium black powder, 0.1460 g of 40% potassium fluoride on alumina (Aldrich Chemical Co. #316385), 0.0317 g triphenylphosphine, 0.0410 g of cuprous iodide, 1 mL of 95% ethanol, and 70 μL of 1-pentyne to a standard microwave tube (12 mL). Add a stir bar recommended by the manufacturers of the microwave reactor. Cap the microwave tube securely with one of the caps supplied by the manufacturer of the microwave unit.

Microwave Instrument Conditions. Using the software supplied by the manufacturer, set the instrument to run at 100°C for 30 min with stirring on high.

Workup Procedure. Following the 30 min reaction period and cooling period, add another 1 mL portion of 95% ethanol and vacuum filter the mixture (see Technique 8, Figure 8.5) through a Hirsch funnel with filter paper to remove all of the solids present in the reaction tube. Aid the transfer process by using about 3 mL of 95% ethanol.

Purification Procedure. Using a 1-mL pipet, transfer the liquid contents in the filter flask to a preweighed 25-mL round-bottom flask. Remove the ethanol, under vacuum, with a rotary evaporator. When it appears that the ethanol has been removed on the rotary evaporator, remove the flask and attach the flask to a good vacuum pump source to remove the remaining ethanol and any dimer (4,6-decadiyne) that may have formed in the reaction from the 1-pentyne. Continue pumping on the flask for at least 3 minutes. Release the vacuum, remove the flask, and reweigh the flask to determine the amount of product obtained. Calculate the theoretical yield for the reaction.

NMR Spectroscopy. Add about 0.7 mL of $CDCl_3$ to the sample in the flask. In most cases, you will find a small amount of undesired solid present that does not dissolve in the $CDCl_3$. Prepare a filtering pipet (see Technique 8, Section 8.1C), draw up the $CDCl_3$ solution with a Pasteur pipet, and add it to the filtering pipet. Collect the solution in a small test tube. This filtering process should remove all or most of the solid, which can be discarded with the filtering pipet. Draw up the filtrate with a Pasteur pipet, and add it to the NMR tube. Add additional $CDCl_3$ solvent to the NMR tube until the liquid level reaches 50 mm. Determine the ^{1}H NMR spectrum and interpret the spectrum. This procedure can be applied to other electron-releasing or unreactive compounds such as iodobenzene, 4-iodotoluene, 1-bromo-2-iodobenzene, and 1-bromo-3-iodobenzene. An interesting result is obtained with methyl 2-iodobenzoate in which the methyl ester is converted to the ethyl ester by a transesterification reaction in ethanol during the course of the Sonogashira coupling reaction.

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[8]Microwave apparatus: CEM Explorer, CEM Corp, 3100 Smith Farm Road, Mathews, NC 28106-0200.
[9]Kabalka, G. W., Wang, L., Namboodiri, V., and Pagni, R. M. "Rapid microwave-enhanced, solventless Sonogashira coupling reaction on alumina," *Tetrahedron Letters,* **2000**, *41,* 5151–5154.

QUESTIONS

1. Draw the structure of the product expected in the following Sonogashira reactions:
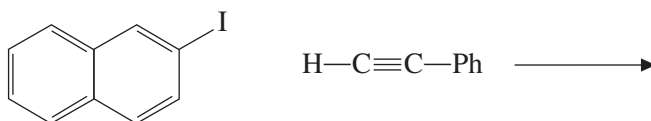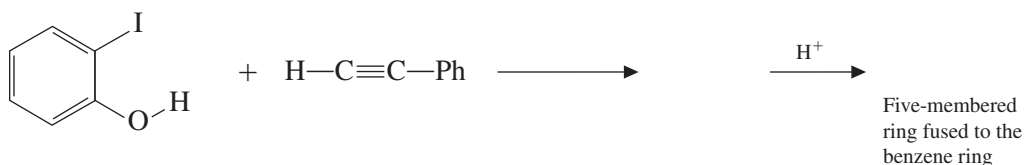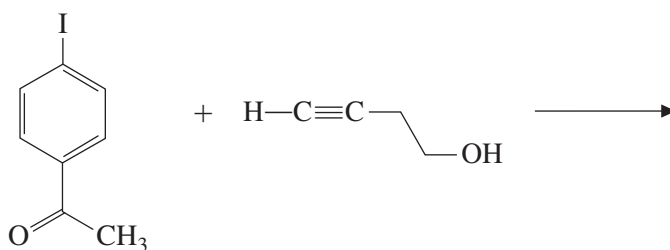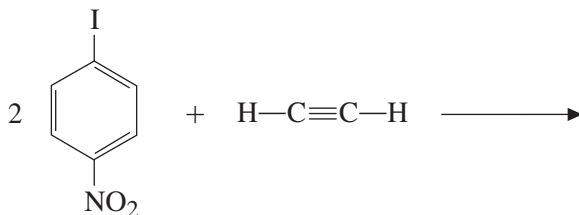
2. Draw the structures of the intermediates and product of the following reaction.
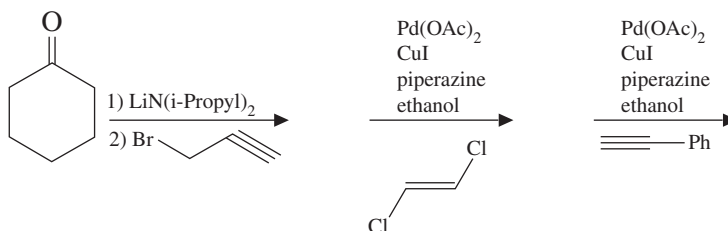
3. A small amount of 4,6-decadiyne is formed in reactions involving 1-pentyne. At what point in the mechanism does this compound form?

4. Draw a mechanism for the formation of your product.

Grubbs-Catalyzed Metathesis of Eugenol with 1,4-Butenediol to Prepare a Natural Product

Green chemistry

Organometallic chemistry

Ruthenium-catalyzed reactions

Grubbs' catalyst is useful in organometallic chemistry due to its relative stability in air and its tolerance of a variety of solvents. Grubbs' catalyst is a ruthenium-based organometallic catalyst used in cross-coupling metathesis, ring-opening metathesis, ring-closing metathesis, and ring-opening metathesis polymerization (ROMP). The four processes are shown below. The dotted line indicates how one can visualize the metathesis process. The development of metathesis reaction in organic synthesis led to the award of the Nobel Prize in Chemistry in 2005 to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock.
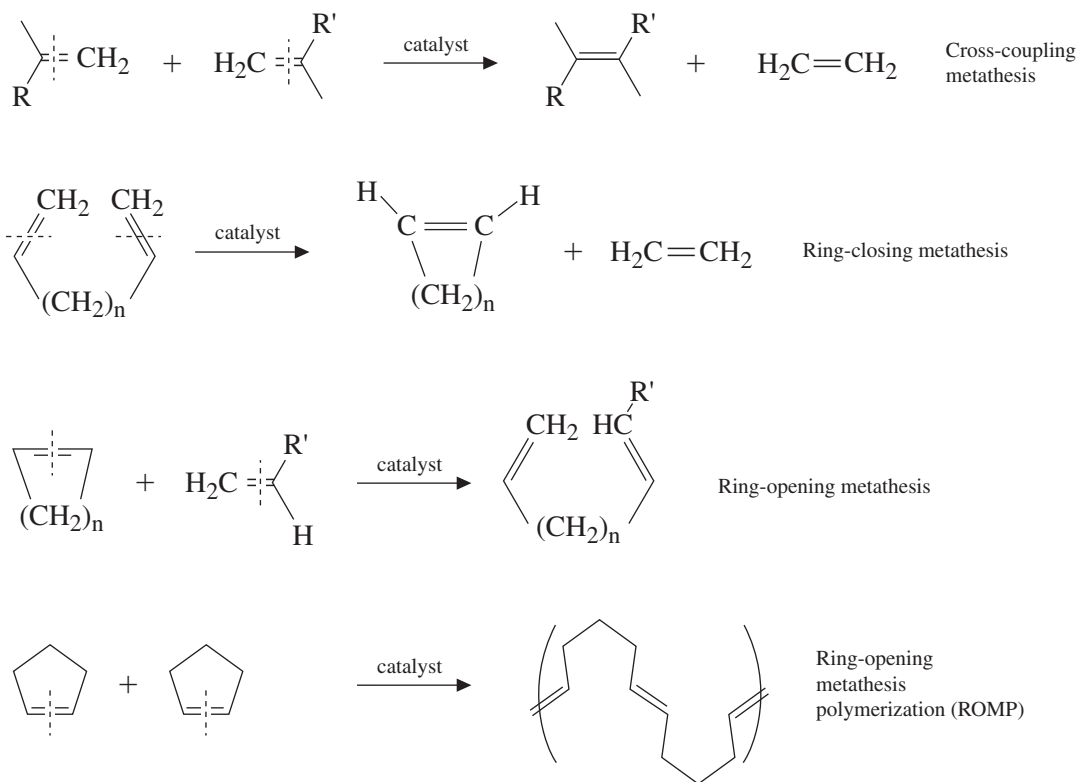
The Grubbs' catalyst that we will use in this experiment is called Grubbs' 2nd Generation catalyst. The IUPAC name is so complicated that researchers don't

give the compound a formal IUPAC name! This catalyst has a higher activity than Grubbs' Generation 1 catalyst that will be used in Experiment 48 for the ROMP polymerization experiment. The mechanism for the cross-metathesis reaction is shown on the next page. The current experiment illustrates a very important reaction widely used in research and industry. It is called olefin cross-metathesis.
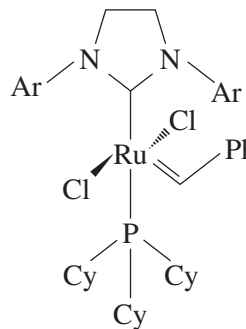
Cy = cyclohexyl
Ph = phenyl
Ar = 2,4,6-trimethylphenyl

Grubbs' Generation 2

In this experiment, Grubb's catalyst will be used in the cross-metathesis of eugenol with *cis*-1,4-butendiol[1] to form a natural product known for its medicinal qualities. The product of the reaction, (*E*)-4-(4-hydroxy-3-methoxyphenyl)-2-buten-1-ol, was first isolated from the roots of a South Asian plant, *Zingiber cassumunar*, and is known for its anti-inflammatory and antioxidant properties. You will recognize the pleasant fragrance of eugenol, which is isolated from cloves(see Experiment 13). The reactions are shown below. Natural products such as eugenol are very valuable for making medicinals. The mechanism is shown on the next page.

| Eugenol | *cis*-1,4-butenediol | (E)-4-(4-hydroxy-3-methoxyphenyl)-2-buten-1-ol | 2-propen-l-ol |
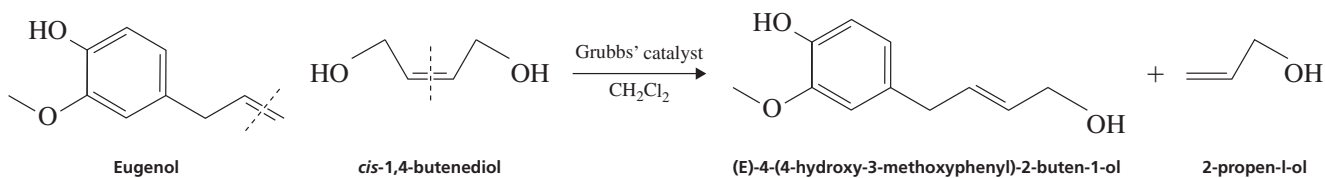
[1]Taber, D. F. and Frankowski, K. J. "Grubbs Cross Metathesis of Eugenol with *cis*-1,4-butene-1, 4-diol to Make a Natural Product," *Journal of Chemical Education*, **2006**, *83*, 283–284. Experiment developed by Conrardy, D. and Lampman, G. M., Western Washington University, Bellingham, WA.
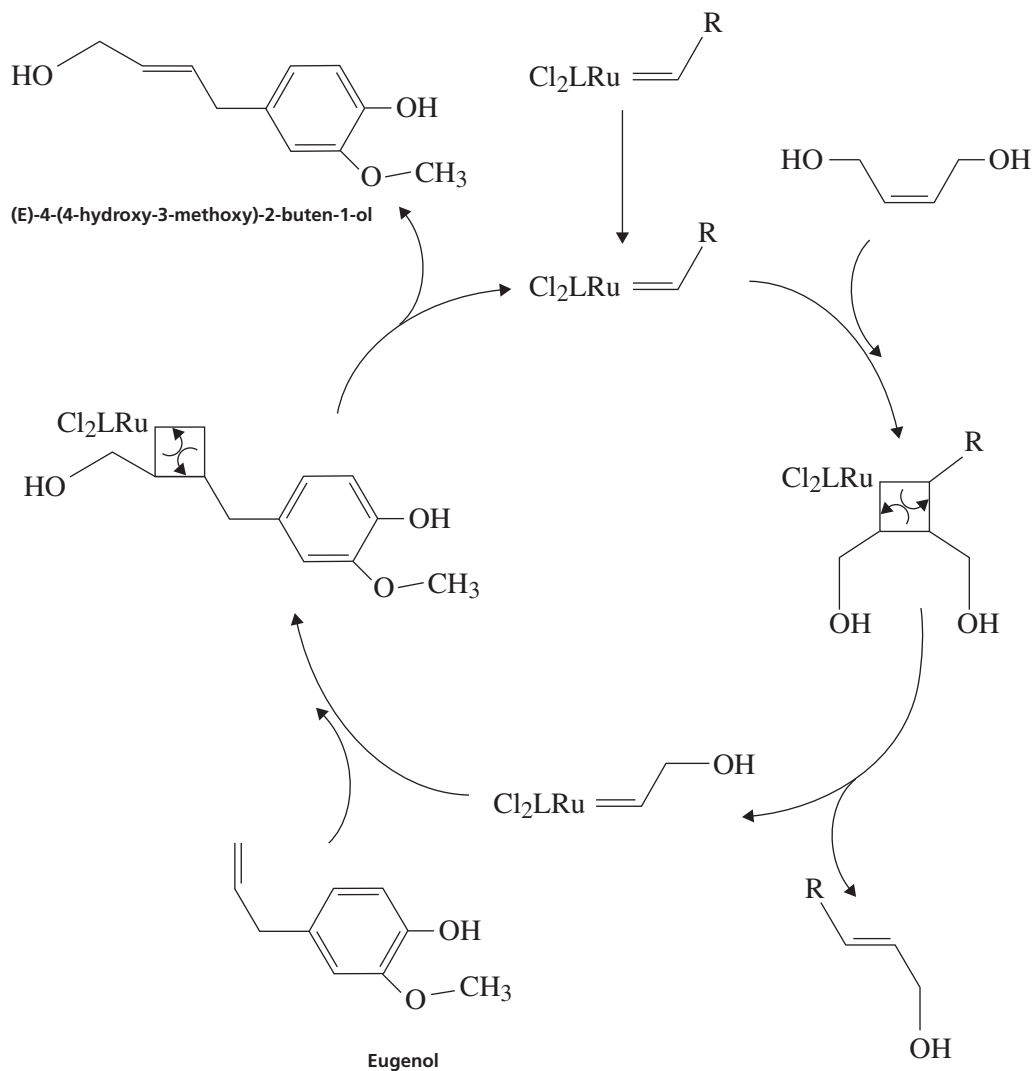
(E)-4-(4-hydroxy-3-methoxy)-2-buten-1-ol

Eugenol

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: Techniques 5, 6, *7, *12, *19, 26

SPECIAL INSTRUCTIONS

The Grubbs' catalyst is expensive and is air-sensitive. Take care when using it to
avoid waste.

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes in the container for aqueous waste. Place the organic waste in the nonhalogenated organic waste container. Place the halogenated waste in the appropriate container.

NOTES TO THE INSTRUCTOR

It is suggested that students work in pairs for this experiment.

PROCEDURE

Preparation of the Reaction Mixture. Transfer the liquid, eugenol, dropwise to a 50-mL round-bottom flask using a Pasteur pipet until 0.135 g of eugenol has been obtained. Weigh this material on a 4-place analytical balance. Tare the balance and add 0.490 g of cis-1,4-butenediol directly to the same round-bottom flask.

Add 6 mL of methylene chloride to the round-bottom flask. Quickly weigh out 0.022 g of Grubb's 2nd generation catalyst on a piece of weighing paper, using the analytical balance. Weigh the catalyst quickly and add it to the round-bottom flask. The catalyst is sensitive to air and is also very expensive! Work quickly, and remember that it is not important to get an exact amount of the catalyst. Add another 1 mL of methylene chloride and a small stir bar to the mixture in the round-bottomed flask.

Tightly stopper the flask with a plastic cap to prevent evaporation of the solvent. Stir the mixture with a magnetic stirrer at a medium rate so as to avoid splashing. If you are using a stirrer/hot plate unit, make sure that the heat is turned off. This reaction proceeds at room temperature. Stir the mixture for at least 1 hour. Cover the cap with Parafilm to reduce the chance of evaporation of the solvent. Allow the mixture to stand at room temperature in your locker, with the stopper securely attached, until the next laboratory period. Allow at least 24 hours. Longer reaction times are also acceptable.

Isolation of the Product. Remove the solvent from the reaction mixture with a rotary evaporator, under vacuum. Continue the evaporation process until a thick, brownish liquid is formed in the bottom of the flask. Remove the flask and add about 1 mL of methylene chloride and about 0.2 g of silica gel.[2] Swirl the flask so as much of the liquid as possible is absorbed in the silica. Then reattach the round-bottom flask to a rotary evaporator and evaporate for another minute or two, under vacuum, to ensure that all of the solvent has been removed. A free-flowing solid material will result with the product adsorbed in the silica. Pour the dry solid onto a piece of weighing paper and cover the sample with an inverted beaker.

Column Chromatography. Prepare a silica gel column for chromatography using a 10-mL Pyrex disposable cleanup/drying column (Corning #214210 available from Fisher #05-722-13; the column is about 30 cm long and 1 cm in diameter). Push some cotton down into the bottom using your thermometer. Do not force the cotton too firmly into the tip of the column. It must be tight enough to keep the silica gel from leaking out of the bottom of

the column, but not too tight to reduce the flow of solvent. Add enough chromatographic-grade silica gel[2] to prepare a 15-cm column.

Make a funnel out of a disposable plastic Pasteur pipet in order to add the sample to the top of the chromatography column. To make the funnel, first cut off the top of a 1-mL plastic pipet and also remove most of the tip to make a small funnel (your instructor should demonstrate this). Pour the silica sample containing your adsorbed product from the weighing paper into the top of the silica gel column through the funnel. The solid now resides at the top of the chromatography column.

Add, in portions, 10 mL of petroleum ether (30 to 60°C grade) through the column. Be sure to keep a small amount of liquid at the top of the column at all times to avoid the column drying out. Allow the petroleum ether to flow through the column to wet the silica and begin the elution process. Collect the eluent in an Erlenmeyer flask. Once the petroleum ether has passed through the column, slowly add 30-mL portions of methylene chloride to the column. Allow the column to elute by gravity; do not push the liquid through the column under pressure with a rubber bulb. You are *not likely to see* a distinct band moving down the column; rather, due to dispersion, the colored material spreads out in the column, making it hard to observe the movement of the colored product. The material passing through the column has been variously described as a "trail" of pale light green or a light mint green color or, in some cases, as a grayish/yellow material moving down the column. Because of its pale color, it is often hard to see the material moving down the column. Often the colored material will move below a dark band (you do not want the dark band). Continue to collect the eluent in the Erlenmeyer flask until the colored product reaches the tip of the chromatography column. When the colored product begins to elute, switch from the Erlenmeyer flask to a 50-mL round-bottom flask. You may want to start collecting the eluent early because you may not actually see the colored material dripping out of the tip because the color is so indistinct. If necessary, you may require more methylene chloride to remove the colored product. The liquid in the Erlenmeyer flask is mostly colorless starting material (eugenol), which elutes before the product. The desired product should collect in the round-bottomed flask. After all of the colored product has eluted from the column, remove the solvent in the 50-mL round-bottom flask on the rotary evaporator, under vacuum.

Isolation and Analysis of the Product. When all of the solvent has been removed, a yellowish-brown solid should be left in the flask; this is the crude product. Add 6 mL of hexane and 1 mL of diethyl ether (not petroleum ether) to the flask and swirl to ensure that all of the product has come into contact with the mixture of solvents. You may need to scrape the bottom of the flask with a spatula to remove the product that is stuck to the bottom. Transfer the product to a Hirsch funnel, under vacuum, to isolate the purified solid product. Use hexane to remove the remaining product from the flask. Continue to draw air through the Hirsch funnel until the product is completely dry. Discard the filtrate. The product should be a solid that ranges in color from yellow to brownish, or perhaps gold or even grayish. Obtain the melting point of the product. Typically, you should expect the melting point to range from 91 to 94°C, but report the actual melting point you obtain. Determine the ^{1}H NMR spectrum in $CDCl_3$. For comparison, the NMR spectrum of the product of the reaction, (*E*)-4-(4-hydroxy-3-methoxyphenyl)-2-buten-1-ol, on the next page. The full NMR spectrum is drawn in the lower trace with expansions of individual peaks shown as insets above the

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[2]Fisher Chromatographic Silica Gel, 60-200 mesh, #S818-1, Davisil® Grade 62, type 150Å.

full spectrum. The peaks have been labelled on the NMR spectrum to correspond to the structure also shown on the next page.
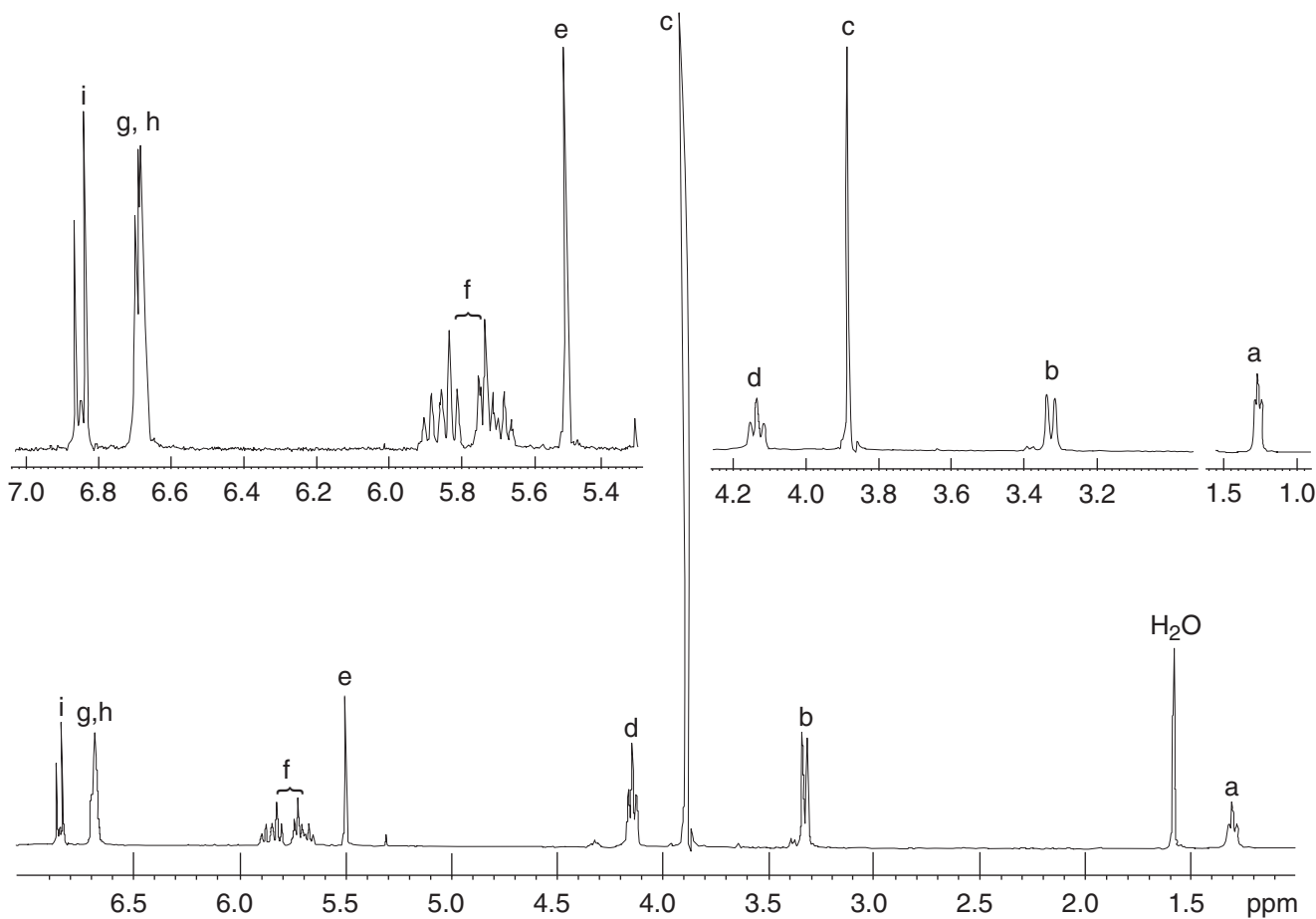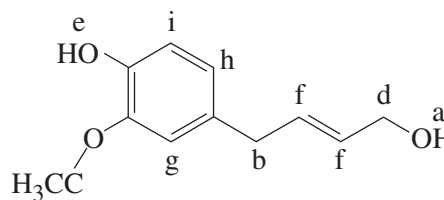
The NMR spectrum of (b1-4-(4-hydro 3-methoxyphenyl)-2-buten-1-ol. 500 MHz in CDCl$_3$. The inset peaks Shows expansions for the protons in the methathesis product. The label correspond to the structure shown on above. A peak for water appears at 1.6 ppm.

QUESTIONS

1. Column chromatography is used in this experiment to separate the compounds in the mixture from each other. Suggest the order you would expect the following to elute from the column. Use 1 for the first and 4 for the last.

   unreacted eugenol

   unreacted 1,4-butenediol

   ruthenium metal by-products

   your metathesized product.

2. Draw a mechanism for the following ring-closing metathesis reaction.
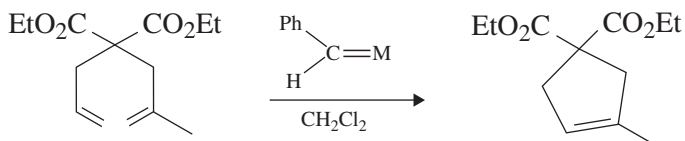
3. Ring-closing metathesis reactions (RCM) have found wide use in forming large ring compounds. Draw the structures of the expected products of the following RCM reactions. See the lab procedure for the general example of RCM.
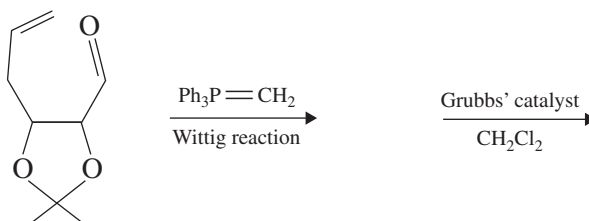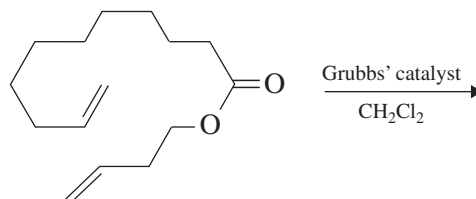
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Taber, D. F. and Frankowski, K. J. "Grubbs Cross Metathesis of Eugenol with *cis*-1,4-butene-1, 4-diol to Make a Natural Product," *Journal of Chemical Education,* 2006, *83,* 283–284.

Trnka, T. M. and Grubbs, R. H. "Development of L2X2Ru=CHR Olefin Metathesis Catalysts: An Organometallic Success Story," *Accounts of Chemical Research,* 2001, *34,* 18–29.

37   E X P E R I M E N T   3 7

The Aldol Condensation Reaction: Preparation of Benzalacetophenones (Chalcones)

Aldol condensation

Crystallization

Molecular Modeling (Optional)

Benzaldehyde reacts with a ketone in the presence of base to give α, β-unsaturated ketones. This reaction is an example of a crossed aldol condensation where the intermediate dehydrates to produce the resonance-stabilized unsaturated ketone.

$$C_6H_5-\overset{H}{\underset{O}{C}} + CH_3-\overset{O}{\overset{\|}{C}}-R \xrightarrow{OH^-} C_6H_5-\overset{H}{\underset{OH}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-R \xrightarrow{-H_2O} \overset{H}{\underset{C_6H_5}{C}}=\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-R$$

Intermediate
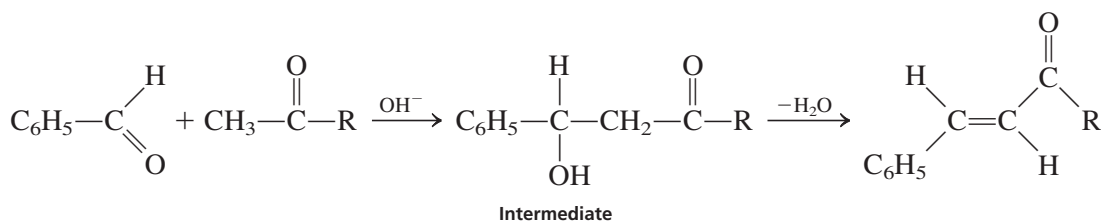
Crossed aldol condensations of this type proceed in high yield since benzaldehyde cannot react with itself by an aldol condensation reaction because it has no α-hydrogen. Likewise, ketones do not react easily with themselves in aqueous base. Therefore, the only possibility is for a ketone to react with benzaldehyde.

In this experiment, procedures are given for the preparation of benzalacetophenones (chalcones). You should choose one of the substituted benzaldehydes and react it with the ketone, acetophenone. All the products are solids that can be recrystallized easily.

Benzalacetophenones (chalcones) are prepared by the reaction of a substituted benzaldehyde with acetophenone in aqueous base. Piperonaldehyde, *p*-anisaldehyde, and 3-nitrobenzaldehyde are used.

A benzaldehyde   **Acetophenone**   **A benzalacetophenone**
(*trans*)

Piperonaldehyde   ***p*-Anisaldehyde**   **3-Nitrobenzaldehyde**
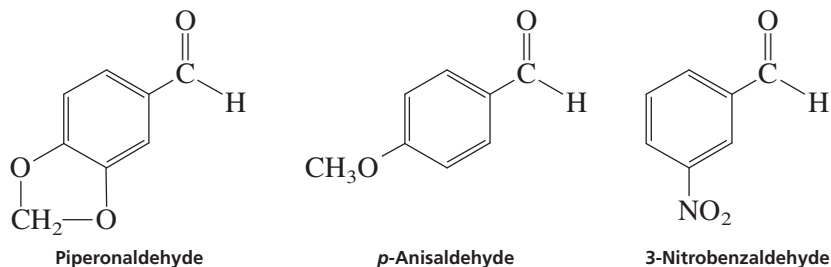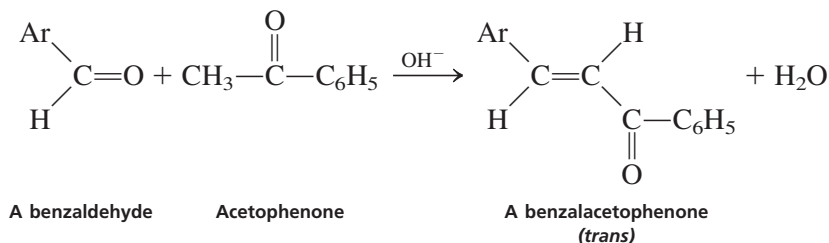
An optional molecular modeling exercise is provided in this experiment. We will examine the reactivity of the enolate ion of a ketone to see which atom, oxygen, or carbon, is more nucleophilic. The molecular modeling part of this experiment will help you to rationalize the results of this experiment. It would be helpful to look at Experiment 18E in addition to the material given in this experiment.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: *Technique 8   Filtration, Section 8.3

*Technique 11   Crystallization: Purification of Solids, Section 11.3

Experiment 2   Crystallization

New: Essay and Experiment 18   Computational Chemistry (Optional)

SPECIAL INSTRUCTIONS

Before beginning this experiment, you should select one of the substituted benzaldehydes. Alternatively, your instructor may assign a particular compound to you.

SUGGESTED WASTE DISPOSAL

All filtrates should be poured into a waste container designated for nonhalogenated organic waste.

PROCEDURE

Running the Reaction. Choose one of three aldehydes for this experiment: piperonaldehyde (solid), 3-nitrobenzaldehyde (solid), or *p*-anisaldehyde (liquid). Place 0.75 g of piperonaldehyde (3,4-methylenedioxybenzaldehyde, *MW* = 150.1) or 0.75 g of 3-nitrobenzaldehyde

(*MW* = 151.1) into a 50-mL Erlenmeyer flask. Alternatively, transfer 0.65 mL of *p*-anisaldehyde (4-methoxybenzaldehyde, *MW* = 136.2) to a *tared* 50-mL Erlenmeyer flask and reweigh the flask to determine the weight of material transferred.

Add 0.60 mL of acetophenone (*MW* = 120.2, *d* = 1.03 g/mL) and 4.0 mL of 95% ethanol to the flask containing your choice of aldehyde. Swirl the flask to mix the reagents and dissolve any solids present. It may be necessary to warm the mixture on a steam bath or hot plate to dissolve the solids. If this is necessary, then the solution should be cooled to room temperature before proceeding with the next step.

Add 0.5 mL of sodium hydroxide solution to the benzaldehyde/acetophenone mixture.[1] Add a magnetic stir bar and stir the mixture. Before the mixture solidifies, you may observe some cloudiness. *Wait until the cloudiness has been replaced with an obvious precipitate settling out to the bottom of the flask before proceeding to the next paragraph.* Continue stirring until solid forms (approximately 3 to 5 minutes).[2] Scratching the inside of the flask with your microspatula or glass stirring rod may help to crystallize the chalcone.

Isolation of the Crude Product. Add 10 mL of ice water to the flask *after a solid has formed, as indicated in the previous paragraph.* Stir the solid in the mixture with a spatula to break up the solid mass. Transfer the mixture to a small beaker with 5 mL of ice water. Stir the precipitate to break it up and then collect the solid on a Hirsch or Büchner funnel, under vacuum. Wash the product with cold water. Allow the solid to air-dry for about 30 minutes. Weigh the solid and determine the percentage yield.

Crystallization of the Chalcone. You will need to use the crystallization procedure introduced in Experiment 2 (Part A. Macroscale Crystallization) to crystallize the chalcone. Once the crystals have been allowed to dry thoroughly, weigh the solid, determine the percentage yield, and determine the melting point. Crystallize all or part of the chalcone as follows:

3,4-methylenedioxychalcone (from piperonaldehyde). Crystallize all of the sample from hot 95% ethanol. Use about 12.5 mL of ethanol per gram of solid. The literature melting point is 122°C.

4-methoxychalcone (from *p*-anisaldehyde). Crystallize all of the sample from hot 95% ethanol. Use about 4 mL of ethanol per gram of solid. Scratch the flask to induce crystallization while cooling. The literature melting point is 74°C.

3-nitrochalcone (from 3-nitrobenzaldehyde). Crystallize a 0.50-g sample from about 20 mL of hot methanol. Scratch the flask gently to induce crystallization while cooling. The literature melting point is 146°C.

Laboratory Report. Determine the melting point of your purified product. At the option of the instructor, obtain the proton and/or carbon-13 NMR spectrum. Include a balanced equation for the reaction in your report. Submit the crude and purified samples to the instructor in labeled vials.

Molecular Modeling (Optional)

In this exercise, we will examine the enolate ion of acetone and determine which atom, oxygen, or carbon, is the more nucleophilic site. Two resonance structures can be drawn for the enolate ion of acetone, one with the negative charge on oxygen, structure A, and one with the negative charge on carbon, structure B.

---

[1]This reagent should be prepared in advance by the instructor in the ratio of 6.0 g of sodium hydroxide to 10 mL of water.
[2]In some cases, the chalcone may not precipitate. If this is the case, stopper the flask and allow it to stand until the next laboratory period. It is sometimes helpful to add an additional portion of base. Usually the chalcone will precipitate during that time.

$$\underset{A}{H_2C=\overset{\overset{\displaystyle :\ddot{O}:^-}{|}}{C}-CH_3} \longleftrightarrow \underset{B}{H_2\ddot{\overline{C}}-\overset{\overset{\displaystyle \cdot\ddot{O}\cdot}{||}}{C}-CH_3}$$

The enolate ion is an **ambident nucleophile**—a nucleophile that has two possible nucleophilic sites. Resonance theory indicates that structure A should be the major contributing structure because the negative charge is better accommodated by oxygen, a more electronegative atom than carbon. However, the reactive site of this ion is carbon, not oxygen. Aldol condensations, brominations, and alkylations take place at carbon, not oxygen. In frontier molecular orbital terms (see the essay "Computational Chemistry" that procedes Experiment 18), the enolate ion is an electron pair donor, and we would expect the pair of electrons donated to be those in the highest occupied molecular orbital, the HOMO.

In the structure-building editor of your modeling program, build structure A. Be sure to delete an unfilled valence from oxygen and to place a –1 charge on the molecule. Request a geometry optimization at the AM1 semiempirical level. Also request the HOMO surface and maps of the HOMO and the electrostatic potential onto the electron-density surface. Submit your selections for computation. Plot the HOMO on the screen. Where are the biggest lobes of the HOMO, on carbon or on oxygen? Now map the HOMO onto the electron-density surface. The "hot spot," the place where the HOMO has the highest density at the point where it intersects the surface, will be bright blue. What do you conclude from this mapping? Finally, map the electrostatic potential onto the electron density. This shows the electron distribution in the molecule. Where is the overall electron density highest, on oxygen or on carbon?

Finally, build structure B and calculate the same surfaces as requested for structure A. Do you obtain the same surfaces as for structure A, or are they different? What do you conclude? Include your results, along with your conclusions, in your report on this experiment.

QUESTIONS

1. Give a mechanism for the preparation of the appropriate benzalacetophenone using the aldehyde that you selected in this experiment.

2. Draw the structure of the *cis* and *trans* isomers of the compound that you prepared. Why did you obtain the *trans* isomer?

3. Using proton NMR, how could you experimentally determine that you have the *trans* isomer rather than the *cis* one? (*Hint:* Consider the use of coupling constants for the vinyl hydrogens.)

4. Provide the starting materials needed to prepare the following compounds:

(a) $\underset{\qquad\qquad\quad\underset{\displaystyle CH_3}{|}}{CH_3CH_2CH=C-\overset{\overset{\displaystyle O}{||}}{C}-H}$

(b) $\underset{CH_3}{\overset{CH_3}{>}}C=CH\overset{\overset{\displaystyle \ }{\underset{\displaystyle \underset{O}{||}}{C}}}{}-CH_3$

(c)

$$\underset{CH_3}{\overset{Ph}{}}\!\!\!C=CH-\overset{\overset{\displaystyle O}{\|}}{C}-Ph$$

(d) CH_3O-⟨benzene ring⟩$-CH=CH-\overset{\overset{\displaystyle O}{\|}}{C}-CH=CH-$⟨benzene ring⟩$-OCH_3$

(e) O_2N-⟨benzene ring⟩$-CH=CH-\overset{\overset{\displaystyle O}{\|}}{C}-$⟨benzene ring⟩$-Br$

(f) $Cl-$⟨benzene ring⟩$-CH=CH-\overset{\overset{\displaystyle O}{\|}}{C}-$⟨benzene ring with NO_2⟩
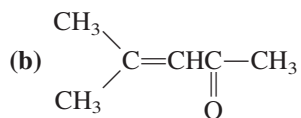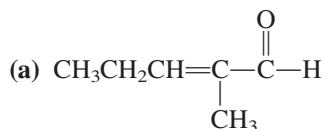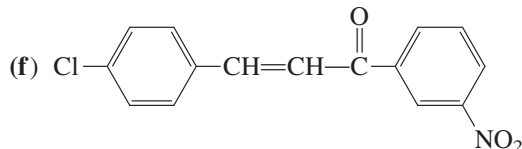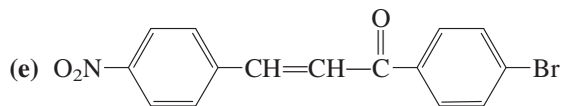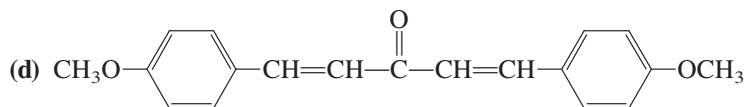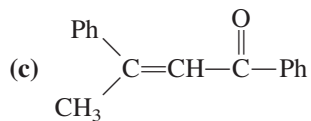
5. Prepare the following compounds starting from benzaldehyde and the appropriate ketone. Provide reactions for preparing the ketones starting from aromatic hydrocarbon compounds (see Experiment 59).

⟨benzene ring⟩$-CH=CH-\underset{\underset{\displaystyle O}{\|}}{C}-$⟨benzene ring⟩$-CH_2CH_3$ ⟨benzene ring⟩$-CH=\underset{\underset{\displaystyle CH_3}{|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-$⟨benzene ring with CH_3 and CH_3⟩
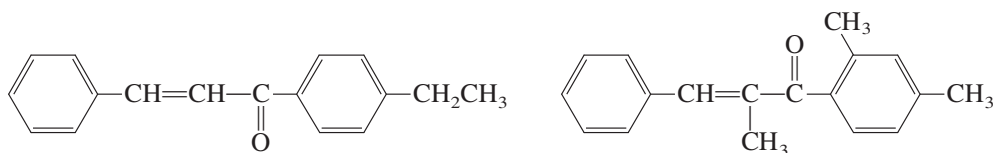
A Green Enantioselective Aldol Condensation Reaction

Green chemistry

Proline-catalyzed asymmetric induction

The aldol condensation is a fundamental reaction in chemistry and biology. In its most common form, a ketone reacts with an aldehyde to form a 3-hydroxy ketone (sometimes referred to as a *β*-hydroxy ketone). A new C-C bond is formed in the reaction, and a new stereocenter is formed at the position of the hydroxyl group. The most common catalyst used in aldol condensation reactions is sodium hydroxide. Under these conditions, a racemic mixture is formed when acetone is allowed to react with an aldehyde. In the example shown, acetone is reacted with isobutyraldehyde.
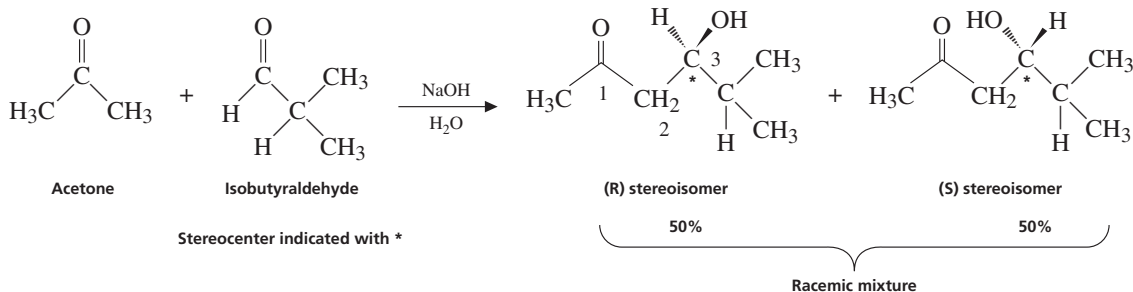
The dream of every organic chemist is to avoid creating a recemic mixture and instead obtain a single stereoisomer! This type of reaction is often referred to as an enantioselective reaction, in which one stereoisomer is primarily created in the reaction. In order to do this, one needs to start with a chiral catalyst, in this case L-proline, a naturally occurring amino acid. Biological reactions form one stereoisomer because the enzymes in natural systems are themselves chiral. In effect, we are trying to mimic the process that occurs in natural systems. L-proline mimics the class I aldolase enzymes in natural systems.[1,2]
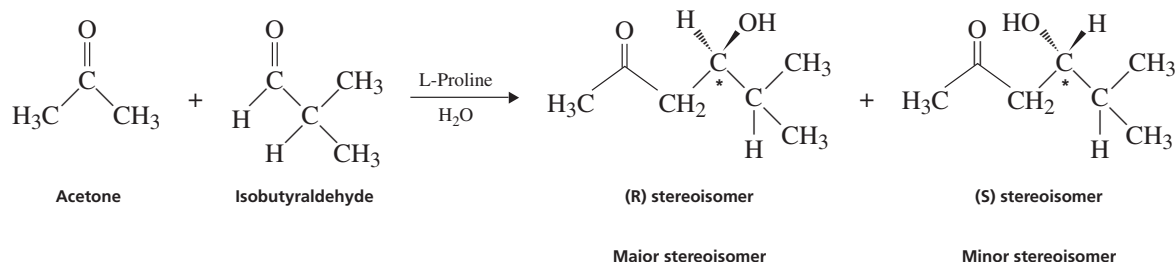
This experiment demonstrates an important concept that has wide use in the pharmaceutical industry, where formation of single enantiomers is critical. In many cases, one enantiomer elicits the correct biological response, while the other enantiomer may have harmful effects.

Often the product from the aldol condensation reaction undergoes further reaction by eliminating the elements of water. This is especially common when a substituted acetophenone reacts with substituted benzaldehyde. Two experiments are included in this book to demonstrate this pathway (see Experiment 37 and 63). In these types of experiments, the intermediate β-hydroxyketone loses water to form a conjugated ketone. The driving force for this reaction is the formation of the highly resonance-stabilized ketone. The compounds formed in this reaction are given the trivial name of chalcone or the IUPAC name of 1,3-diphenyl–2-propen-1-one. The chalcone that is formed loses the stereocenters and becomes achiral (non-chiral). We should expect that in certain reactions, the aldol product will give rise to some elimination by-product. Fortunately, elimination is not a major pathway for the reaction of acetone with isobutyraldehyde.

[1]Bennett, G. D. "A Green Enantioselective Aldol Condensation for the Undergraduate Organic Laboratory," *Journal of Chemical Education,* 2006, *83,* 1871–1872. Experiment developed by Bowen, G. and Lampman, G. M., Western Washington University, Bellingham, WA.
[2]List, B., Lerner, R. A., and Barbas III, C. F. "Proline-Catalyzed Direct Asymmetric Aldol Reactions," *Journal of the American Chemical Society,* 2000, *122,* 2395–2396.
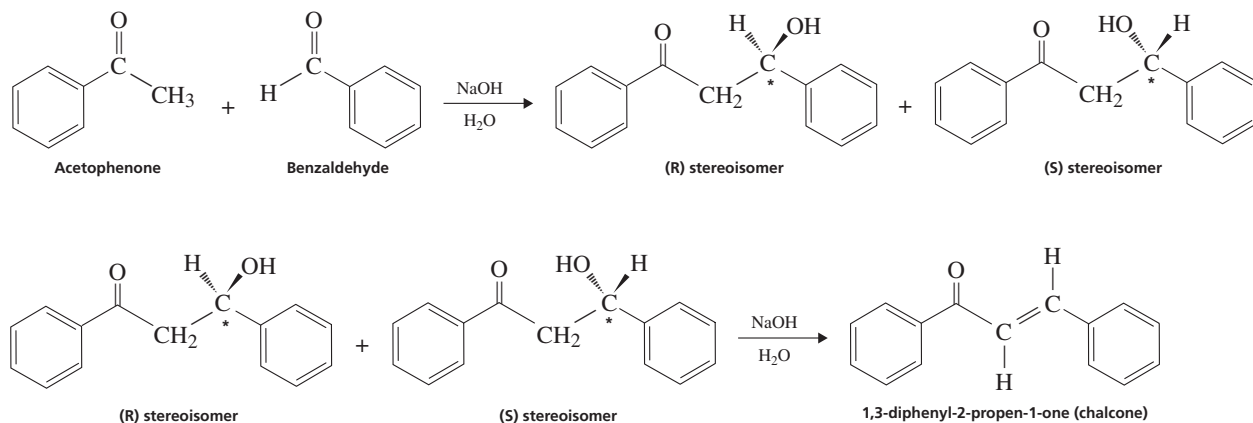
The relative amounts of the aldol condensation product and the elimination (dehydration) products can be determined by NMR. We will employ a polarimeter to determine the degree of stereospecificity for the reaction of acetone with isobutyraldehyde to give the aldol adduct. In order to determine the enantiomeric excess (ee), we need the specific rotation value for one of the pure enantiomers, in this case the *(R)* enantiomer. Unfortunately, it is sometimes difficult to find the specific rotation values for other reactions in the chemical literature.[3] Other methods must be employed in research laboratories to determine the enantioselectivity of the aldol condensation products. Methods that are often used in research are chiral gas chromatography and chiral HPLC.

The mechanism for the *L*-proline-catalyzed aldol condensation reaction is shown in Scheme 1. Steps 3A and 3B show the two possible chair structures for the transition states leading to the *(R)* and *(S)* products. Notice that the isopropyl group is in an axial position in 3A, while this group is attached to an equatorial position in 3B. We should, therefore, expect that the lower energy barrier should proceed through 3B and yield the *(R)* adduct as the major aldol condensation product.

REQUIRED READING

W

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: Techniques 5, 6, *7, *8, *12, 25, and 26
New: Technique 23

SPECIAL INSTRUCTIONS

Isobutyraldehyde is an irritant, and some of the products can cause an allergic response. It is advised that you wear gloves for this experiment.

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[3]Ramachandran, P. V., Xu, Wei-chu, and Brown, H. C. "Contrasting Steric Effects of the Ketones and Aldehydes in the Reactions of the Diisopinocampheyl Enolborinates of Methyl Ketones with Aldehydes." *Tetrahedron Letters*, 1996, *37*, 4911–4914.

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes in the container for aqueous waste. Place the organic waste in the nonhalogenated organic waste container.

NOTES TO THE INSTRUCTOR

Although this experiment is labeled as a Green experiment, acetone is used in a large excess—making the experiment rather poor in terms of atom economy, even though the addition reaction itself has a high degree of atom economy. The excess is required to avoid unfavorable side reactions. The use of *L*-proline, a natural amino acid, in catalytic amounts helps to make this experiment "green." Since the reaction proceeds slowly, it would be difficult to apply this reaction in an industrial setting. Diethyl ether is used as a solvent for extraction, avoiding the use of methylene chloride.

Other substrates may be used in this experiment. Examples include the reaction of acetone with pivaldehyde (2,2-dimethylpropanal) and the reaction of acetone with acetophenone. In the latter case, a significant amount of elimination is observed. The NMR easily reveals when elimination is an important side reaction. NMR itself cannot be used to determine the relative amounts of the enantiomers, but it is the best way of analyzing the amount of elimination that occurs in these reactions. For example, you can expect about 3% to 6% elimination (dehydration) in the acetone/isobutyraldehyde or acetone/pivaldehyde reactions. The acetone/benzaldehyde reaction gives more than 60% of the elimination product.

Unfortunately, when the adducts are analyzed by GC-MS, even more of the elimination (dehydration) product forms in the heated inlet of the gas chromatograph. Therefore, it is recommended that the NMR be used to determine the relative amounts of the aldol adduct and dehydration products. The polarimeter is used to determine the ee in the *L*-proline catalyzed reaction.

Using polarimetry, you may find that the class will obtain a value of +34° for the adduct formed by acetone and isobutyraldehyde. This value is compared to the specific rotation for the pure (*S*) enantiomers of 61.7° to give an enantiomeric excess value of 55%. It has been suggested that lower values occur when traces of water are present during the course of the *L*-proline-catalyzed reaction. The acetone/pivaldehyde reaction gives an adduct that has a specific rotation of 56.9° which yields a calculated value of 69% for the enantiomeric excess.[4]

PROCEDURE

Transfer 1.0 mL of isobutyraldehyde to a preweighed 25-mL round-bottom flask using a 1000-μL automatic pipet, and reweigh the flask to determine the precise weight of isobutyraldehyde transferred to the flask. Add 14 mL of acetone and 0.23 g (2 mmoles) of *L*-proline to the flask. Add a magnetic stir bar and insert a glass stopper or plastic cap into the neck of the flask. Stir the mixture for 1 week at room temperature.

[4]Ramachandran, P. V., Xu, Wei-chu, and Brown, H. C. "Contrasting Steric Effects of the Ketones and Aldehydes in the Reactions of the Diisopinocampheyl Enolborinates of Methyl Ketones with Aldehydes," *Tetrahedron Letters,* 1996, *37,* 4911–4914.

Pour the contents of the round-bottom flask into a beaker. Add 20 mL of diethyl ether to the beaker. Add another 5 mL of diethyl ether to rinse out the round-bottomed flask. Some solid may be present that does not dissolve (discard it). Pour 50 mL of saturated aqueous sodium chloride solution into the beaker. Transfer all of the diethyl ether and the saturated salt solution into a separatory funnel, avoiding adding the stir bar to the separatory funnel. Shake the funnel in order to ensure that the product is extracted into the diethyl ether. Drain the lower aqueous layer and discard it. Pour the diethyl ether extract from the top of the separatory funnel into an Erlenmeyer flask and add anhydrous magnesium sulfate to dry the extract. Remove the drying agent by gravity filtration through a fluted filter into a preweighed round-bottom flask. Remove the solvent with a rotary evaporator, under vacuum. Attach the flask to a good vacuum pump to remove any remaining acetone and diethyl ether. Weigh the flask to determine the yield of aldol condensation product and calculate the percentage yield for the reaction.

Add the product to a preweighed 5-mL volumetric flask, and reweigh the flask after the addition. Dissolve the sample in chloroform up to the mark on the volumetric flask. Calculate the density in g/mL for the chloroform solution. Add the chloroform solution to a 0.5-dm polarimeter cell and obtain the optical rotation for the sample. Calculate the specific rotation using the equation shown in Technique 23, Section 23.2. The optically pure (*R*) enantiomer has a reported specific rotation value of +61.7°.[5] The ee is obtained using the equation shown in Technique 23, Section 23.5.[6] Use the ee value to calculate the percentages of the (S) and (R) enantiomers in the mixture (see Technique 23, Section 23.5).

At the option of your instructor, determine the infrared spectrum and the high field (500 MHz) ^{1}H NMR spectrum for your aldol condensation product, *(R)*-4-hydroxy-5-methyl-2-hexanone. Figure 1 shows the ^{1}H NMR spectrum of the product. All of the peaks are assigned to the structure shown, except for the OH group. The stereocenter in the product introduces some very interesting features to the NMR spectrum shown in Figure 1! Of particular interest in the NMR spectrum is the area between 2.50 to 2.65 ppm in the product. This area reveals the presence of the two nonequivalent diastereotopic protons in the methylene group, H_a and H_b, shown in expansion in Figure 1. The peaks in this expansion are labeled with Hz values so that coupling constants can be calculated.

H_a centers on 2.62 ppm and is a doublet of doublets, yielding a coupling constant, $^2J_{ab}$ = 17.5 Hz (1317.38 - 1299.80 Hz). In addition, H_a is coupled to H_c, yielding a value for $^3J_{ac}$ = 2.4 Hz (1302.25 - 1299.80 Hz). The other diastereotopic proton, H_b, centers on about 2.54 ppm and is also a doublet of doublets, with $^2J_{ab}$ = 17.5 Hz (1281.25 - 1263.67 Hz) and $^3J_{bc}$ = 9.7 Hz (1281.25 - 1271.48 Hz). Notice that the diastereotopic protons, H_a and H_b, have identical ^2J values of 17.5 Hz. The ^3J values are different because the dihedral angles are not the same. The dihedral angle for protons H_a and H_c = 60°, whereas the angle for protons H_b and H_c = 180°. To summarize, $^2J_{ab}$ = 17.5 Hz, $^3J_{bc}$ = 9.7 Hz, and $^3J_{ac}$ = 2.4 Hz.

The other area of interest in the ^{1}H NMR spectrum is the pair of doublets, labeled as **f** on the structure and spectrum, that appear at 0.916 and 0.942 ppm in the expansion in Figure 1. It turns out that the two methyl groups are also nonequivalent because of the presence of the stereocenter, and are also diastereotopic. Because of the presence of the stereocenter, the methyl groups appear at different places in the NMR spectrum.

[5] List, B., Lerner, R. A., and Barbas III, C. F. "Proline-Catalyzed Direct Asymmetric Aldol Reactions," *Journal of the American Chemical Society*, 2000, *122*, 2395–2396. These researchers reported an ee as high as 96% for the reaction of isobutyraldehyde and acetone with L-proline.
[6] A typical value of 60% ee may be obtained yielding a mixture of 80% (R) and 20% (S) enantiomers. Other methods were attempted in an effort to obtain the ee: chiral GC column and chiral chemical shift reagents (see Technique 26, Section 26.15), without success. Better results may be achieved by using more concentrated samples and a smaller cell so that higher values of the rotation may be obtained.

We cannot determine the percentages of the two possible enantiomers in the NMR spectrum shown here. It should be strongly stated that both the (R) and the (S) enantiomers will have identical NMR spectra! *Only if the two enantiomers are placed in a chiral environment will they have different NMR spectra!* A polarimeter will show different behavior for the two enantiomers because there is a chiral environment present!
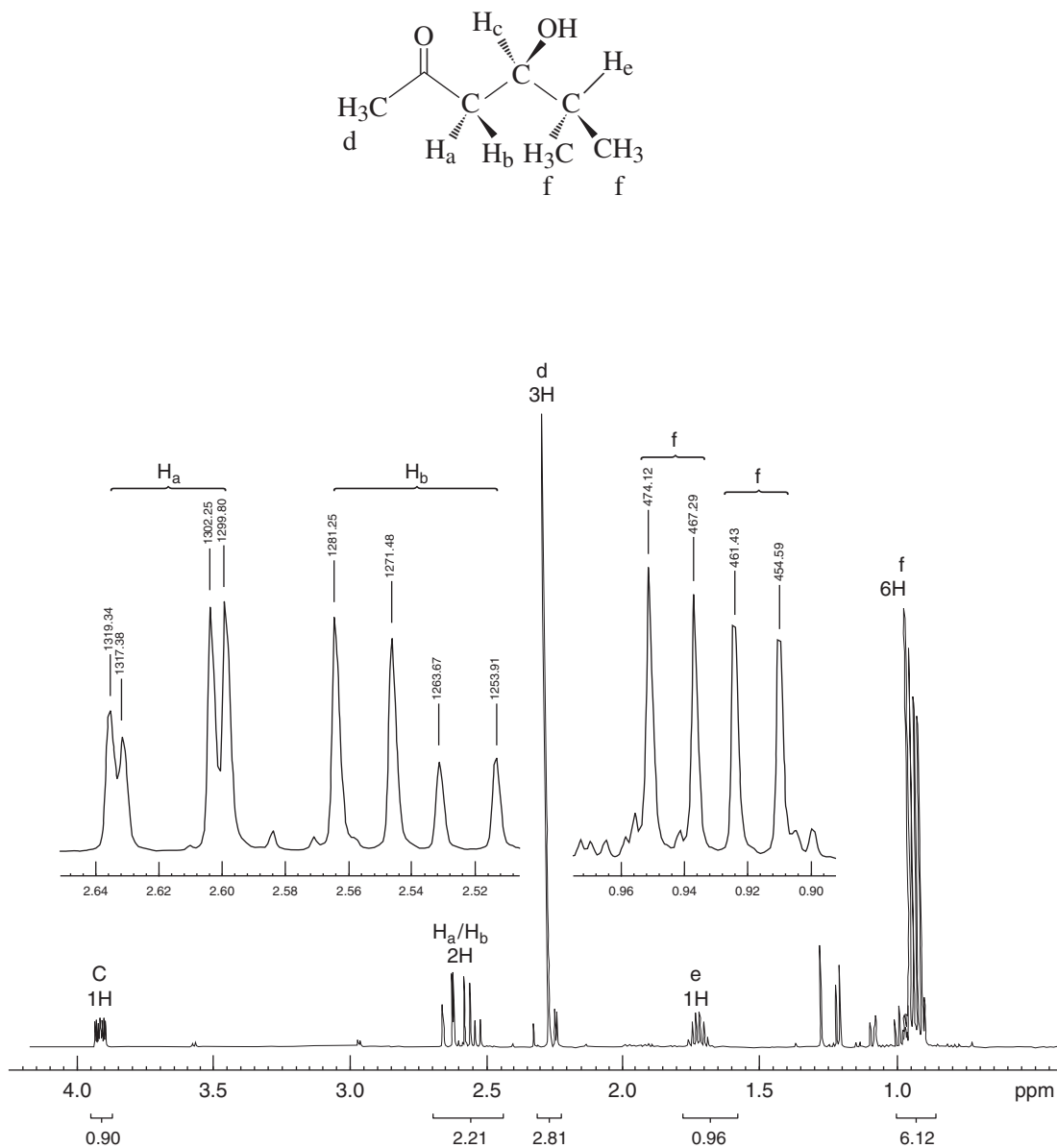

Figure 1. 500MHZ ¹HNMR spectrum of the L-proline-catalyzed aldol condensation of isobutyraldehyde and acetone. The insets show expansions of the diastereotopic methylene group, H_a and H_b, appearing between 2.50 to 2.65 ppm. Also shown as expansions are the two diastereotopic methyl groups, labeled as f on the spectrum. Impurity peaks appear between 0.96 to 1.3ppm.

(1)

(2)

(3A)

(3B)

(4)

(5)
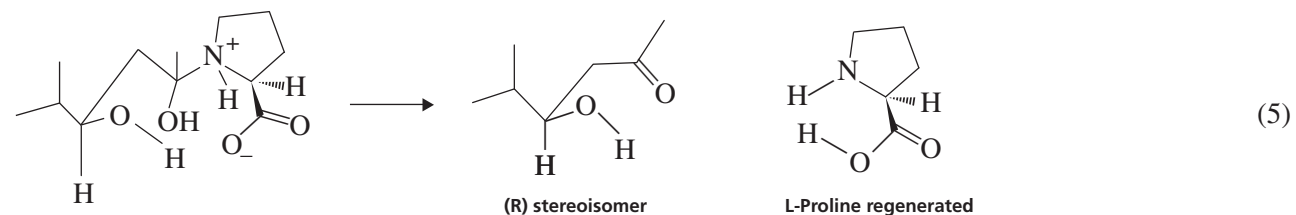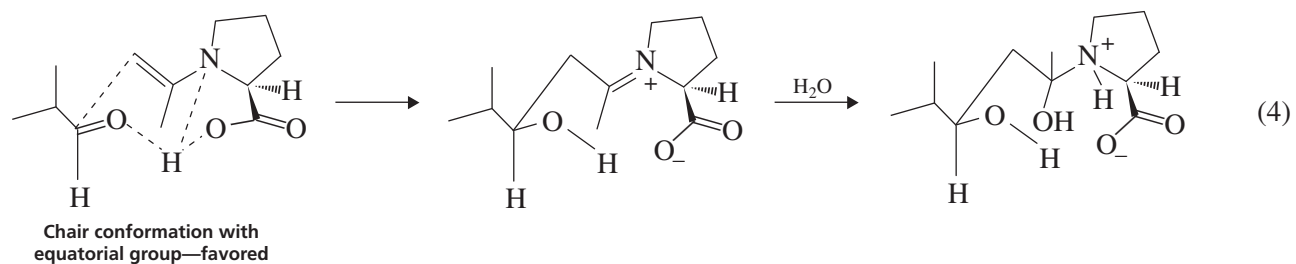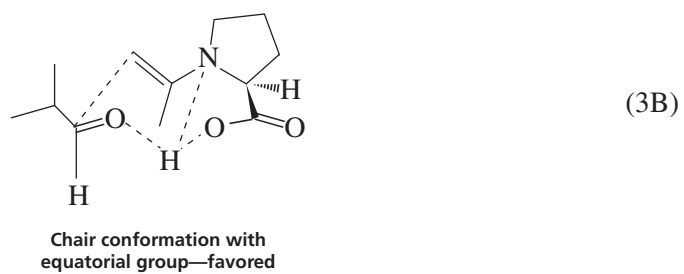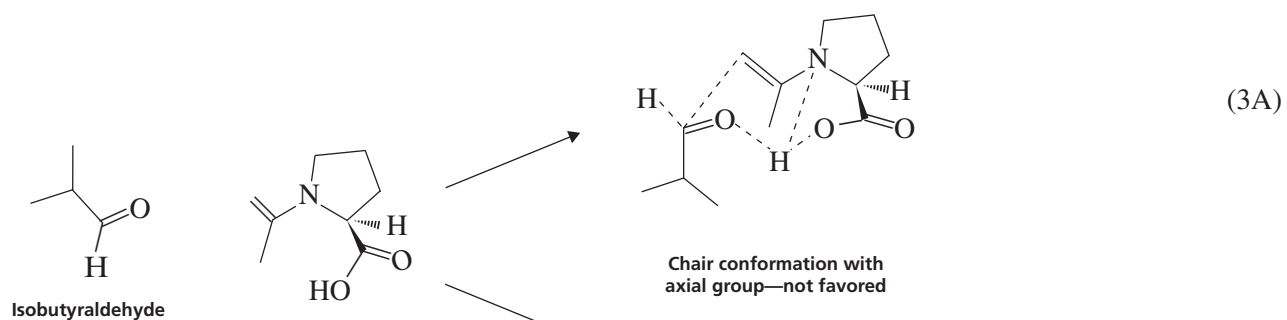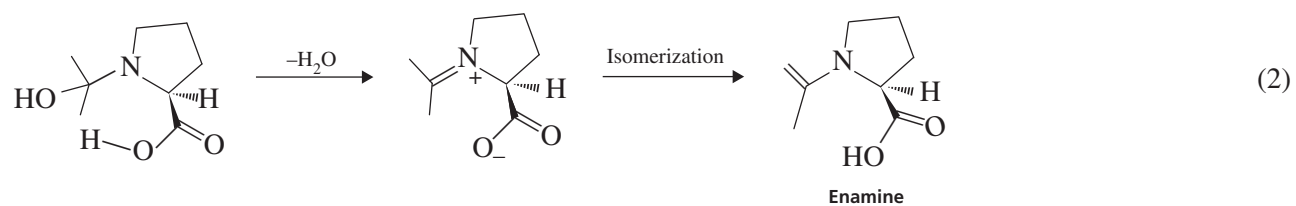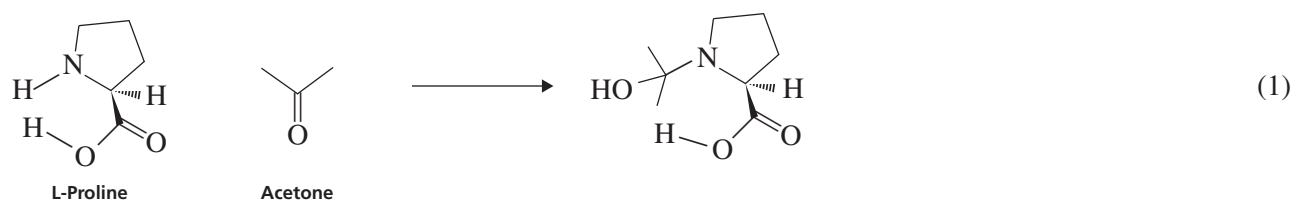
Schem 1. Mechanism of that *L*-proline catalyzed aldol condensation of isobutyraldehyde and acetone.

Preparation of an α, β-Unsaturated Ketone via Michael and Aldol Condensation Reactions

Crystallization

Michael reaction (conjugate addition)

Aldol condensation reaction

This experiment illustrates how two important synthetic reactions can be combined to prepare an α, β-unsaturated ketone, 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone. The first step in this synthesis is a sodium hydroxide–catalyzed conjugate addition of ethyl acetoacetate to *trans*-chalcone (a Michael addition reaction). Sodium hydroxide serves as a source of hydroxide ion to catalyze the reaction.[1] In the reactions that follow, Et and Ph are abbreviations for the phenyl and ethyl groups, respectively.
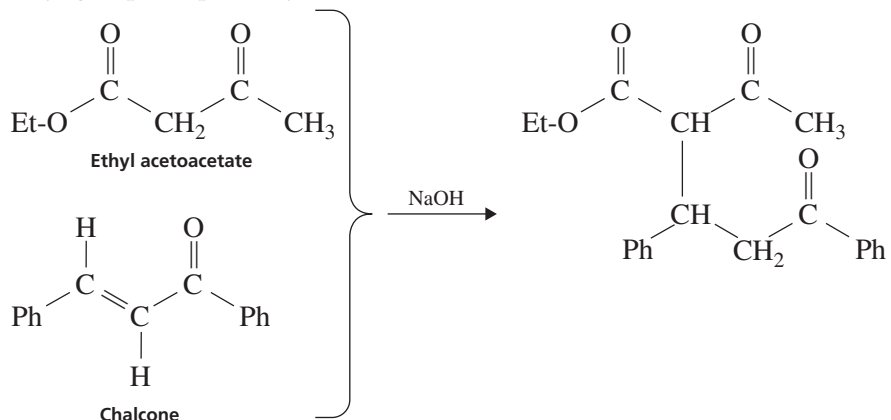
The second step of the synthesis is a base-catalyzed aldol condensation reaction. The methyl group loses a proton in the presence of base, and the resulting methylene carbanion nucleophilically attacks the carbonyl group. A stable six-membered ring is formed. Ethanol supplies a proton to yield the aldol intermediate.
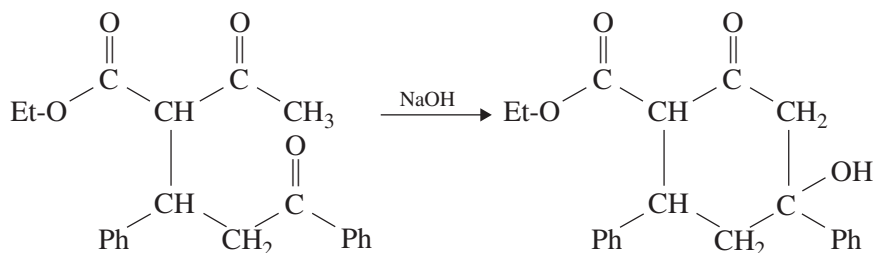
Finally, the aldol intermediate is dehydrated to form the final product, 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone. The α, β-unsaturated ketone that

_____

[1]Barium hydroxide has also been used as a catalyst (see References).

is formed is very stable because of the conjugation of the double bond with both the carbonyl group and a phenyl group.
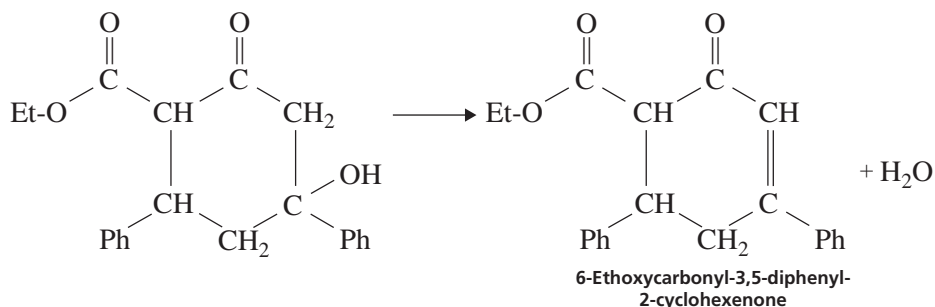
6-Ethoxycarbonyl-3,5-diphenyl-
2-cyclohexenone

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: Techniques *7, *8, *11, and *12

SPECIAL INSTRUCTIONS

The sodium hydroxide catalyst used in this experiment must be kept dry. Be sure to keep the top on the bottle when not in use.

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes containing ethanol in the bottle designated for aqueous wastes. Ethanolic filtrates from the crystallization of the product should be poured into the nonhalogenated organic waste container.

NOTES TO THE INSTRUCTOR

The *trans*-chalcone (Aldrich Chemical Co., No. 13,612-3) should be finely ground for use. The 95% ethanol used in this experiment contains 5% water.

PROCEDURE

Assembling the Apparatus. To a 50-mL round-bottom flask, add 1.2 g of finely ground *trans*-chalcone, 0.75 g of ethyl acetoacetate, and 25 mL of 95% ethanol. Swirl the flask until the solid dissolves and place a boiling stone in the flask. Add 1 pellet (between 0.090 and 0.120 g) of sodium hydroxide. Weigh the pellet quickly before it begins to absorb water. Attach a reflux condenser to the round-bottom flask and heat the mixture to reflux using a hot plate or heating mantle. Once the mixture has been brought to a gentle boil, continue to reflux the mixture for at least 1 hour. During this reflux, the mixture will become very cloudy and solid may begin to precipitate. The mixture may bump during the reflux. If this happens, the solid in the reaction flask will start to "erupt" and throw solid up into the reflux condenser. You will need to reduce the temperature of the hot plate or heating mantle to avoid this problem.

Isolation of the Crude Product. After the end of the reflux period, allow the mixture to cool to room temperature. Add 10 mL of water and scratch the inside of the flask with a glass stirring rod to induce crystallization (an oil may form; scratch vigorously). Place the flask in an ice bath for a minimum of 30 minutes. It is essential to cool the mixture thoroughly in order to completely crystallize the product. Because the product may precipitate slowly, you should also scratch the inside of the flask occasionally over the 30-minute period and cool it in an ice bath.

Vacuum filter the crystals on a Büchner funnel, using 4 mL of ice-cold water to aid in the transfer. Then rinse the round-bottom flask with 3 mL of ice-cold 95% ethanol to complete the transfer of the remaining solid from the flask to the Büchner funnel. Allow the crystals to air-dry overnight. Alternatively, the crystals may be dried for 30 minutes in an oven set at 75 to 80°C. Weigh the dry product. The solid contains some sodium hydroxide and sodium carbonate, which are removed in the next step.

Removal of Catalyst. Place the solid product in a 100-mL beaker. Add 7 mL of reagent-grade acetone and stir the mixture with a spatula.[2] Most of the solid dissolves in acetone, but do not expect all of it to dissolve. Using a Pasteur pipet, remove the liquid and transfer it into one or more glass centrifuge tubes, leaving as much solid as possible behind in the beaker. It is impossible to avoid drawing some solid up into the pipet, so the transferred liquid will contain suspended solids and the solution will be very cloudy. You should not be concerned about the suspended solids in the cloudy acetone extract because the centrifugation step will clear the liquid completely. Centrifuge the acetone extract for approximately 2 to 3 minutes, or until the liquid clears. Using a clean, dry Pasteur pipet, transfer the *clear* acetone extract from the centrifuge tube to a *dry, preweighed* 50-mL Erlenmeyer flask. If the transfer operation is done carefully, you should be able to leave the solid behind in the centrifuge tube. The solids left behind in the beaker and centrifuge tube are inorganic materials related to the sodium hydroxide originally used as the catalyst.

Evaporate the acetone solvent by carefully heating the flask in a hot water bath while directing a light stream of dry air or nitrogen into the flask. Use a *slow* stream of gas to avoid blowing your product out of the flask. When the acetone has evaporated, you may be left with an oily solid in the bottom of the flask. Scratch the oily product with a spatula to induce crystallization. You may need to redirect air or nitrogen into the flask to remove all traces of acetone. Reweigh the flask to determine the yield of this partially purified product.

Crystallization of Product. Crystallize the product using a minimum amount (approximately 9 mL) of boiling 95% ethanol.[3] After all of the solid has dissolved, allow the flask to cool slightly. Scratch the inside of the flask with a glass stirring rod until crystals appear. Allow the flask to sit undisturbed at room temperature for a few minutes. Then place the flask in an ice-water bath for at least 15 minutes.

Collect the crystals by vacuum filtration on a Büchner funnel. Use three 1-mL portions of ice-cold 95% ethanol to aid in the transfer. Allow the crystals to dry until the next laboratory period or dry them for 30 minutes in a 75 to 80°C oven. Weigh the dry 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone and calculate the percentage yield. Determine the melting point of the product (literature value, 111 to 112°C). Submit the sample to the instructor in a labeled vial.

Spectroscopy. At the option of the instructor, obtain the infrared spectrum using the dry-film method (see Technique 25, Section 25.4) or in KBr (see Technique 25, Section 25.5A). You should observe absorbances at 1734 and 1660 cm^{-1} for the ester carbonyl and enone

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[2] You may need to add more acetone than indicated in the procedure because a larger yield of product may have been obtained. About 15 to 20 mL of acetone may be required to dissolve your product. Excess acetone will not affect the results.

[3] The 9 mL of ethanol indicated in the procedure is an approximation. You may need to add *more hot or less hot* 95% ethanol to dissolve the solid. Add boiling ethanol until the solid just dissolves.

groups, respectively. Compare your spectrum to that shown in Figure 1. Your instructor may also want you to determine the ^{1}H and ^{13}C spectra. The spectra. may be run in CDCl$_3$ or DMSO-d_6. The ^{1}H spectrum (500 MHz CDCl$_3$) is shown in Figure 2. Assignments have been made on the spectrum using data from a paper by Delaude, Grandjean, and Noels (see references below.) No attempt has been made to analyze the phenyl resonances, other than to show the integral value (10 H) for the two monosubstituted benzene rings. For reference, the ^{13}C spectrum (75 MHz, CDCl$_3$) shows 17 peaks: 14.1, 36.3, 44.3, 59.8, 61.1, 124.3, 126.4, 127.5, 127.7, 129.0, 129.1, 130.7, 137.9, 141.2, 158.8, 169.5, and 194.3.

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García-Raso, A.; García-Raso, J.; Campaner, B.; Mestres, R.; Sinisterra, J. V. An Improved Procedure for the Michael Reaction of Chalcones. *Synthesis* **1982,** 1037.

García-Raso, A.; García-Raso, J.; Sinisterra, J. V.; Mestres, R. Michael Addition and Aldol Condensation: A Simple Teaching Model for Organic Laboratory. *J. Chem. Educ.* **1986,** *63,* 443.

Delaude, L.; Grandjean, J.; Noels, A. F. The Step-by-Step Robinson Annulation of Chalcone and Ethyl Acetoacetate. *J. Chem. Educ.* **2006,** *83,* 1225–1228 and supplementary materials submitted with this article.

QUESTIONS

1. Why was it possible to separate the product from sodium hydroxide using acetone?
2. The white solid that remains in the centrifuge tube after acetone extraction fizzes when hydrochloric acid is added, suggesting that sodium carbonate is present. How did this substance form? Give a balanced equation for its formation. Also give an equation for the reaction of sodium carbonate with hydrochloric acid.
3. Draw a mechanism for each of the three steps in the preparation of the 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone. You may assume that sodium hydroxide functions as a base and ethanol serves as a proton source.
4. Indicate how you could synthesis *trans*-chalcone. (*Hint:* see Experiment 37).
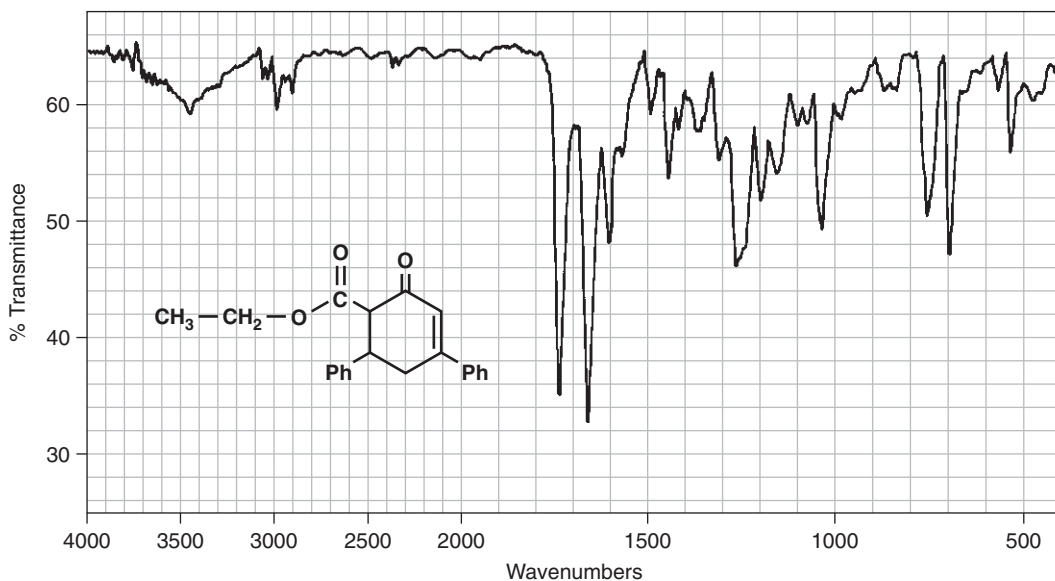
Figure 1. Infrared spectrum of 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone, KBr.
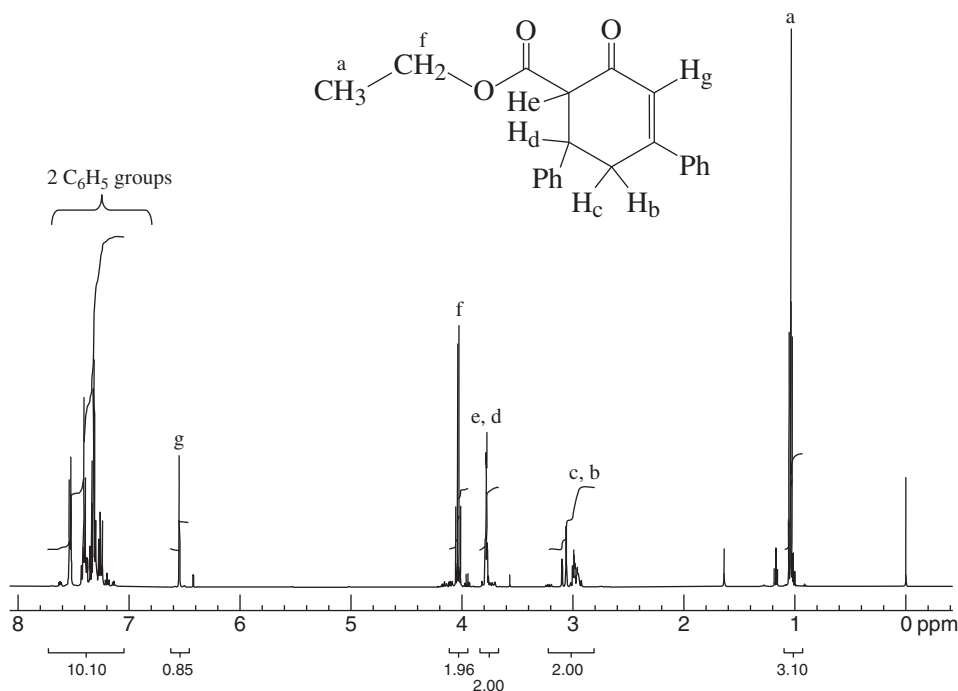
Figure 2. 500 MHz ^{1}H NMR spectrum of 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone, CDCl$_3$. Integral values for each of the patterns is inserted under the peaks to assign the number of protons in each pattern. Protons H$_d$ and H$_e$ overlap at 3.8 ppm in CDCl$_3$, integrating for 2H. In DMSO-d_6, the protons H$_d$ and H$_e$ are totally resolved and appear individually at 3.6 and 4.1 ppm, respectively. The other protons appear at nearly the same values in both solvents. Small impurity peaks appearing in the spectrum can be ignored.

40   EXPERIMENT 40

Preparation of Triphenylpyridine

Green Chemistry

Aldol condensation reaction

Michael addition reaction

Crystallization

Solventless reaction

This experiment is another demonstration of a series of synthetic reactions, specifically aldol condensation followed by Michael addition, which was illustrated in Experiment 39. In this case, however, the method is designed to follow the principles of Green Chemistry. By contrast, the procedure in Experiment 39 includes the use of organic solvents (ethanol and acetone).

This experiment incorporates an aldol condensation reaction, followed by a Michael condensation, to provide a product with an interesting structure. The "green" feature in this experiment is that the entire reaction sequence is conducted without the use of any solvent at all. Avoiding the use of solvents altogether is in accord with Principle 5 of the

Twelve Principles of Green Chemistry (see the essay "Green Chemistry" that precedes Experiment 27): The use of auxiliary substances (solvents, separation agents, etc.) should be avoided whenever possible and innocuous when required.
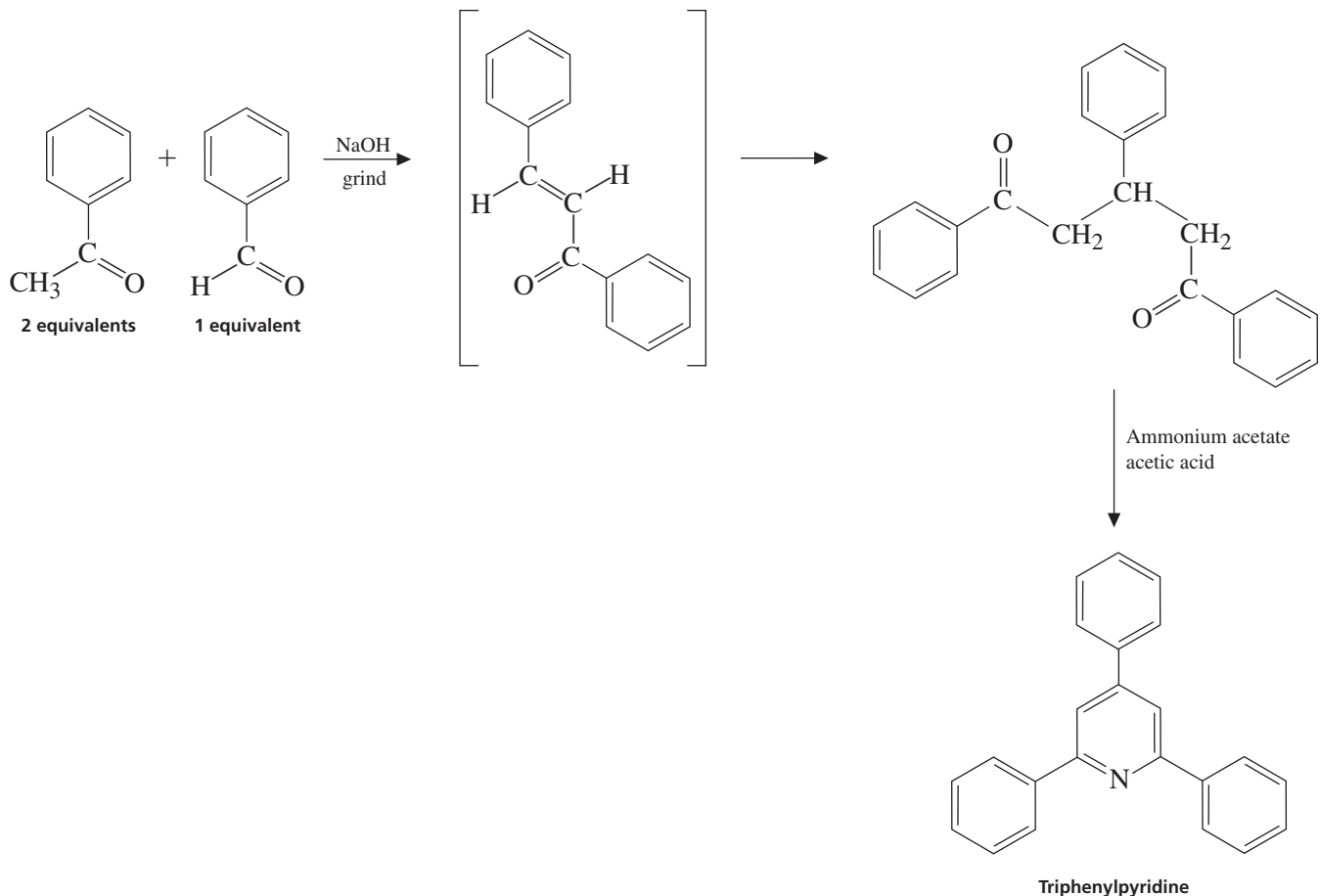
Triphenylpyridine

SUGGESTED WASTE DISPOSAL

All aqueous waste can be disposed of in a waste container designated for non-halogenated aqueous waste. The mortar and pestles should be rinsed with acetone, and this waste should be placed in a container intended for organic waste.

NOTES TO THE INSTRUCTOR

This procedure works best if the sodium hydroxide pellets are fresh. The quality of the product and the ease with which students will be able to grind the reagents in the mortar and pestle will be improved. It is also recommended that students work in pairs for this procedure, in order to share the workload of the lengthy period of grinding.

SAFETY PRECAUTIONS

Sodium hydroxide pellets are corrosive; they should be handled with care. Gloves should be worn during the first part of this reaction.

PROCEDURE

Part 1. Michael-aldol condensation reaction

To a clean dry mortar and pestle, add 1 sodium hydroxide pellet (0.075 to 0.095 g) and grind it to a powder. Add 0.24 g acetophenone and grind the mixture until it is homogeneous. Then add 0.11 g benzaldehyde and continue to grind.

The mixture will go through several stages, through intermediates that resemble a sticky paste, until it becomes a solid. Expect to grind (mix) the mixture for 15 minutes. Grind it thoroughly. If necessary, a metal spatula can be used to scrape the product from the sides of the mortar so the mixture can continue to be ground. Work in pairs in order to share the grinding chore to ensure that the grinding has been thorough and has continued for the full 15 minutes. Also, letting the sample stand for 15 to 20 minutes will give it time to harden. When the mixture becomes too difficult to mix, it will usually harden significantly with time and then it can be broken up and ground. Just give it your best effort for 15 minutes, then let the mixture stand for 20 minutes. The reaction mixture must be ground very well for the full 15 minutes, but it will be messy in the beginning; mix more gently at first until it becomes more solidified or a powder, then start grinding more forcefully.

Part 2. Synthesis of triphenylpyridine

Add 0.15 g of ammonium acetate to a 25-mL round-bottom flask equipped with a stir bar. Measure 10 mL-glacial acetic acid and carefully add it to the round-bottom flask. Stir this mixture for five minutes. Prepare a water-cooled condenser, and after transferring the product from Part 1 to the suspension in the round-bottom flask, connect the condenser to the flask. Heat the mixture to boiling, and allow the mixture to reflux for 2 hours. Cool the reaction mixture to room temperature with the condenser still attached. When the glassware is cool, add 10 mL of water, remove the flask from the condenser, place the flask in a labeled beaker, and place the apparatus in the freezer.

Isolation of Product. After preparing a Hirsch funnel for vacuum filtration, draw 1 or 2 mL of water through the funnel to ensure a proper seal between the filter paper and funnel. Then, vacuum filter the precipitate from the round-bottom flask. Rinse the flask 3 times with 1-mL portions of water and also pass these portions through the vacuum filter. Transfer the product to a 25-mL Erlenmeyer flask and add 10 mL of a 5% solution of sodium bicarbonate. Swirl the mixture for 5 minutes. Transfer the product carefully, because wet filter paper tears very easily. Vacuum filter again, and then rinse the isolated precipitate twice with 1-mL portions of water.

Allow the product to stand under vacuum for 10 minutes to dry it more completely and transfer it to a watch glass to dry. Recrystallize the product from ethyl acetate. Weigh the dry triphenylpyridine and calculate the percentage yield. Determine the melting point of the product (literature value = 137 to 138°C).Determine the proton and ^{13}C NMR spectra of the product and include them and the interpretations in your laboratory report.

REFERENCES

Palleros, D.R. Solvent-Free Synthesis of Chalcones. *J. Chem. Educ.* **2004,** *81,* 1345–1347.

Cave, G.W.V.; Raston, C.L. Efficient Synthesis of Pyridines *via* a Sequential Solventless Aldol Condensation and Michael Addition. *J. Chem. Soc. Perkin Trans. I* **2001,** *24,* 3258–3264.

EXPERIMENT 41

1,4-Diphenyl-1,3-Butadiene

Wittig reaction

Working with sodium ethoxide

Thin-layer chromatography

UV/NMR spectroscopy (optional)

Green Chemistry

The Wittig reaction is often used to form alkenes from carbonyl compounds. In this experiment, the isomeric dienes *cis,trans,* and *trans,trans*-1,4-diphenyl-1,3-butadiene will be formed from cinnamaldehyde and benzyltriphenylphosphonium chloride Wittig reagent. Only the *trans,trans* isomer will be isolated.


trans,trans   cis,trans
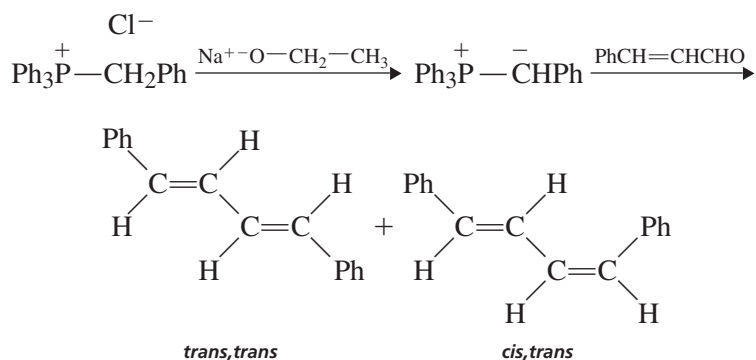
The reaction is carried out in two steps. First, the phosphonium salt is formed by the reaction of triphenylphosphine with benzyl chloride. The reaction is a simple nucleophilic displacement of chloride ion by triphenylphosphine. The salt that is formed is called the "Wittig reagent" or "Wittig salt."

Benzyltriphenylphosphonium chloride
"Wittig salt"
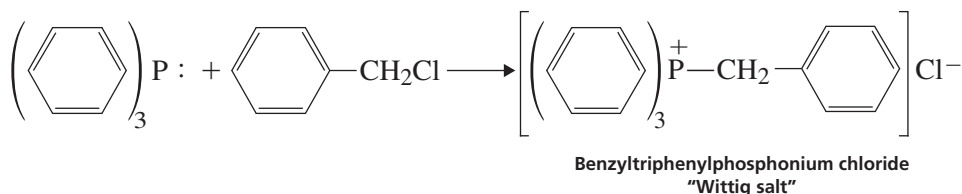
When treated with base, the Wittig salt forms an **ylide**. An ylide is a species having adjacent atoms oppositely charged. The ylide is stabilized due to the ability of phosphorus to accept more than eight electrons in its valence shell. Phosphorus uses its 3d orbitals to form the overlap with the 2p orbital of carbon that is necessary for resonance stabilization. Resonance stabilizes the carbanion.

An ylide
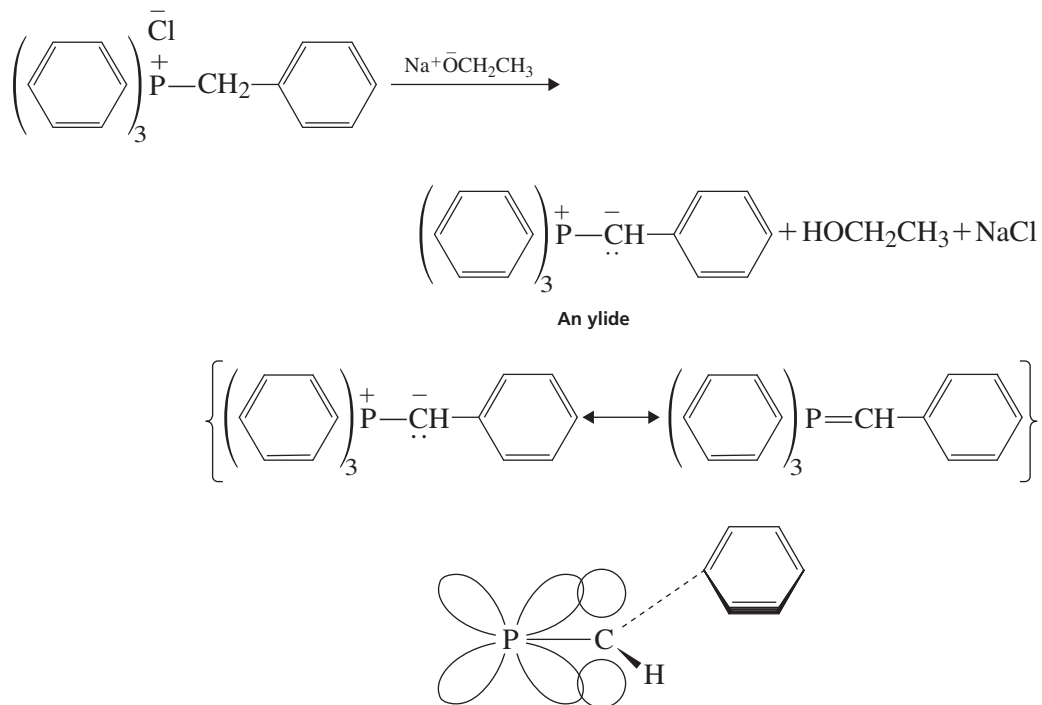
The ylide is a carbanion that acts as a nucleophile, and it adds to the carbonyl group in the first step of the mechanism. Following the initial nucleophilic addition, a remarkable sequence of events occurs, as outlined in the following mechanism:

Triphenylphosphine oxide   **An alkene**
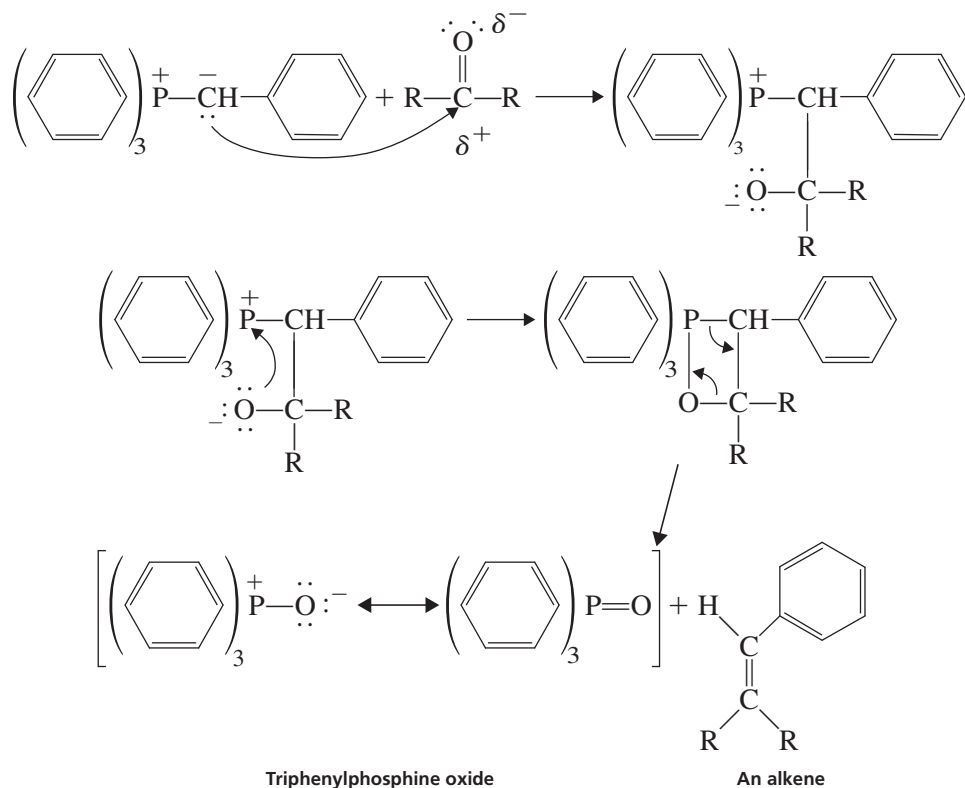
The addition intermediate, formed from the ylide and the carbonyl compound, cyclizes to form a four-membered-ring intermediate. This new intermediate is unstable and fragments into an alkene and triphenylphosphine oxide. Notice that the ring breaks open in a different way than it was formed. The driving force for this ring-opening process is the formation of a very stable substance, triphenylphosphine oxide. A large decrease in potential energy is achieved upon the formation of this thermodynamically stable compound.

In this experiment, cinnamaldehyde is used as the carbonyl compound and yields mainly the *trans,trans*-1,4-diphenyl-1,3-butadiene, which is obtained as a solid. The *cis,trans* isomer is formed in smaller amounts, but it is an oil that is not isolated in this experiment. The *trans,trans* isomer is the more stable isomer and is formed preferentially.

Cinnamaldehyde

trans,trans-1,4-Diphenyl-1,3-butadiene   **Triphenylphosphine oxide**
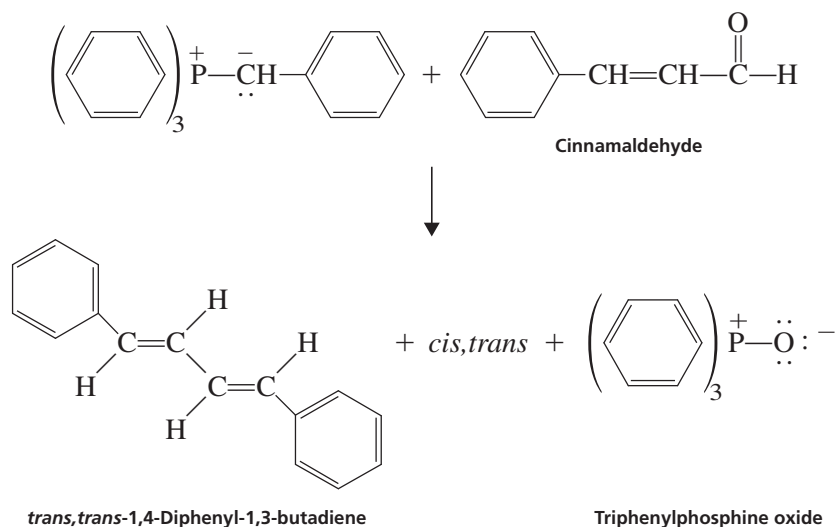
Experiment 41C provides an alternative green chemistry method for preparing 1,4-diphenyl-1,3-butadiene by the Wittig reaction. No solvent is used in this experiment. Instead, the starting materials are ground together with potassium phosphate in a mortar and pestle. This experiment will demonstrate to students a more environmentally friendly method for carrying out a reaction that might be performed on a larger scale in industry.

The reaction will be accomplished by grinding cinnamaldehyde with benzyl-triphenylphosphonium chloride and potassium phosphate (tribasic, K_3PO_4). This is done using a mortar and pestle. TLC will be used to analyze the crystallized *trans, trans*-1,4-diphenyl–1,3-butadiene product, as well as the filtrate from the crystallization procedure that contains both the *cis,trans* and *trans,trans*-1,4-diphenyl-1,3,-butadiene isomers.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: *Technique 8   Filtration, Section 8.3

Technique 20   Thin-Layer Chromatography

SPECIAL INSTRUCTIONS

Your instructor may ask you to prepare 1,4-diphenyl-1,3-butadiene starting with commercially available benzyltriphenylphosphonium chloride. If so, start with Part B of this experiment. The prepared sodium ethoxide solution must be kept tightly stoppered when not in use, as it reacts readily with atmospheric water. *Important:* Fresh cinnamaldehyde should be used in this experiment. Old cinnamaldehyde should be checked by infrared spectroscopy to be certain that it does not contain any cinnamic acid.

If your instructor asks you to prepare benzyltriphenylphosphonium chloride in the first part of this experiment, you can conduct another experiment concurrently during the 1.5-hour reflux period. Triphenylphosphine is rather toxic. Be careful not to inhale the dust. Benzyl chloride is a skin irritant and a lachrymator. It should be handled in the hood with care.

SUGGESTED WASTE DISPOSAL

Place the alcohol, petroleum ether, and xylene wastes into the waste container for nonhalogenated organic solvents. Aqueous mixtures should be poured into the waste bottle designated for aqueous wastes.

PROCEDURE

Part A. Benzyltriphenylphosphonium Chloride (Wittig Salt)

Place 2.2 g of triphenylphosphine (MW = 262.3) into a 100-mL round-bottom flask. In a hood, transfer 1.44 mL of benzyl chloride (MW = 126.6, d = 1.10 g/mL) to the flask and add 8 mL of xylenes (mixture of o-, m-, and p-isomers).

> **CAUTION**
>
> **Benzyl chloride is a lachrymator, a tear-producing substance.**

Add a magnetic stir bar to the flask and attach a water-cooled condenser. Using a heating mantle placed on top of a magnetic stirrer, boil the mixture for at least 1.5 hours. An increased yield may be expected when the mixture is heated for longer periods. The solution will be homogeneous at first, and then the Wittig salt will begin to precipitate. Maintain the stirring during the entire heating period, or bumping may occur. Following the reflux, remove the apparatus from the heating mantle and allow it to cool for a few minutes. Remove the flask and cool it thoroughly in an ice bath for about 5 minutes.

Collect the Wittig salt by vacuum filtration using a Büchner funnel. Use three 4-mL portions of cold petroleum ether (bp 60 to 90°C) to aid the transfer and to wash the crystals free of the xylene solvent. Dry the crystals, weigh them, and calculate the percentage yield of the Wittig salt. At the option of the instructor obtain the proton NMR spectrum of the salt in $CDCl_3$. The methylene group appears as a doublet (J = 14 Hz) at 5.5 ppm because of ^{1}H-^{31}P coupling.

Part B. 1,4-diphenyl-1,3-butadiene

In the following operations, stopper the round-bottom flask whenever possible to avoid contact with moisture from the atmosphere. If you prepared your own benzyltriphenylphosphonium chloride in Part A, you may need to supplement your yield in this part of the experiment.

Preparation of the Ylide. Place 1.92 g of benzyltriphenylphosphonium chloride ($MW =$ 388.9) in a dry, 50-mL round-bottom flask. Add a magnetic stir bar. Transfer 8.0 mL of absolute (anhydrous) ethanol to the flask and stir the mixture to dissolve the phosphonium salt (Wittig salt). Add 3.0 mL of sodium ethoxide solution to the flask using a dry pipet, while stirring continuously.[1] Stopper the flask and stir the mixture for 15 minutes. During this period, the cloudy solution acquires the characteristic yellow color of the ylide.

Reaction of the Ylide with Cinnamaldehyde. Measure 0.60 mL of pure cinnamaldehyde ($MW = 132.2$, $d = 1.11$ g/mL) and place it in a small test tube.[2] To the cinnamaldehyde, add 2.0 mL of absolute ethanol. Stopper the test tube until it is needed. After the 15-minute period, use a Pasteur pipet to mix the cinnamaldehyde with the ethanol and add this solution to the ylide in the round-bottom flask. A color change should be observed as the ylide reacts with the aldehyde and the product precipitates. Stir the mixture for 10 minutes.

Separation of the Isomers of 1,4-Diphenyl-1,3-Butadiene. Cool the flask thoroughly in an ice-water bath for 10 minutes, stir the mixture with a spatula, and transfer the material from the flask to a small Büchner funnel under vacuum. Use two 4-mL portions of ice-cold absolute ethanol to aid the transfer and to rinse the product. Dry the crystalline *trans,trans*-1, 4-diphenyl-1,3-butadiene by drawing air through the solid. The product contains a small amount of sodium chloride that is removed as described in the next paragraph. The cloudy material in the filter flask contains triphenylphosphine oxide, the *cis,trans* isomer, and some *trans,trans* product. Pour the filtrate into a beaker and save it for the thin-layer chromatography experiment described in the next section.

Remove the *trans,trans*-1,4-diphenyl-1,3-butadiene from the filter paper, place the solid in a beaker, and add 12 mL of water. Stir the mixture and filter it on a Büchner funnel, under vacuum, to collect the nearly colorless crystalline *trans,trans* product. Use a minimum of water to aid the transfer. Allow the solid to dry thoroughly.

Analysis of the Filtrate. Use thin-layer chromatography to analyze the filtrate that you saved in the previous section. This mixture must be analyzed as soon as possible so that the *cis,trans* isomer will not be photochemically converted to the *trans,trans* compound. Use a 2 × 8 cm silicagel TLC plate that has a fluorescent indicator (Eastman Chromatogram Sheet, No. 13181). At one position on the TLC plate, spot the filtrate, as is, without dilution. Dissolve a few crystals of the *trans,trans*-1,4- diphenyl-1,3-butadiene in a few drops of acetone and spot it at another position on the plate. Use petroleum ether (bp 60 to 90°C) as a solvent to develop (run) the plate.

Visualize the spots with a UV lamp using both the long- and short-wavelength settings. The order of increasing R_f values is as follows: triphenylphosphine oxide, *trans,trans*-diene, *cis,trans*-diene. It is easy to identify the spot for the *trans,trans* isomer because it fluoresces brilliantly. What conclusion can you make about the contents of the filtrate and the purity of

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[1] This reagent is prepared in advance by the instructor and will serve about 12 students. Carefully dry a 250-mL Erlenmeyer flask and insert a drying tube filled with calcium chloride into a one-hole rubber stopper. Obtain a large piece of sodium, clean it by cutting off the oxidized surface, weigh out a 2.30-g piece, cut it into 20 smaller pieces, and store it under xylene. Using tweezers, remove each piece, wipe off the xylene, and add the sodium slowly over a period of about 30 minutes to 40 mL of absolute (anhydrous) ethanol in the 250-mL Erlenmeyer flask. After the addition of each piece, replace the stopper. The ethanol will warm as the sodium reacts, but do not cool the flask. After the sodium has been added, warm the solution and shake it *gently* until all the sodium reacts. Cool the sodium ethoxide solution to room temperature. This reagent may be prepared in advance of the laboratory period, but it must be stored in a refrigerator between laboratory periods. When it is stored in a refrigerator, it may be kept for about 3 days. Before using this reagent, bring it to room temperature and swirl it gently in order to redissolve any precipitated sodium ethoxide. Keep the flask stoppered between each use.

[2] The cinnamaldehyde must be free of cinnamic acid. Use fresh material and obtain the infrared spectrum to check purity.

the *trans,trans* product? Report the results that you obtain, including R_f values and the appearance of the spots under illumination. Discard the filtrate in the container designated for nonhalogenated waste.

Yield Calculation and Melting-Point Determination. When the *trans,trans*-1,4-diphenyl-1, 3-butadiene is dry, determine the melting point (literature, 152°C). Weigh the solid and determine the percentage yield. If the melting point is below 145°C, recrystallize a portion of the compound from hot 95% ethanol. Redetermine the melting point.

Optional Exercise: Spectroscopy. Obtain the proton NMR spectrum in $CDCl_3$ or the UV spectrum in hexane. For the UV spectrum of the product, dissolve a 10-mg sample in 100 mL of hexane in a volumetric flask. Remove 10 mL of this solution and dilute it to 100 mL in another volumetric flask. This concentration should be adequate for analysis. The *trans, trans* isomer absorbs at 328 nm and possesses fine structure, and the *cis,trans* isomer absorbs at 313 nm and has a smooth curve.[3] See if your spectrum is consistent with these observations. Submit the spectral data with your laboratory report.

Part C. Solventless Preparation of 1,4-Diphenyl-1,3-Butadiene

Reaction. Using an analytical balance, weigh out 309 mg of benzyltriphenylphosphoniurm chloride and 656 mg of potassium phosphate (tribasic, K_3PO_4) and place the solids into a clean and dry 6-cm (inside diameter) porcelain mortar with a pour lip. Using an automatic pipet, measure and add 100 μL of cinnamaldehyde to the mixture in the mortar. Grind the mixture together for a total of 20 minutes. It is much easier to use a pestle that is long enough to grip securely in your hand, thus keeping one's fingers from getting sore or tired. At Ihe beginning of the grinding operation, the mixture will act like putty and have a definite yellow color. Alter a few minutes of grinding, the mixture will start to turn into a thick paste that adheres to the inside of the mortar and the edges of the pestle. Bend the end of a spatula as shown in the figure. This bent spatula is useful for scraping the material off of the inside of the mortar and pestle and directing the mass into the center of the mortar. Repeat the scraping operation after every 1 to 2 minutes of grinding. Include that time in the total of 20 minutes of grinding time.
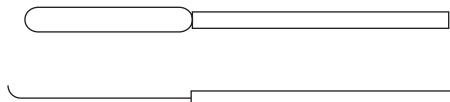
Isolation of Crude 1,4-Diphenyl-1,3-Butadiene. After 20 minutes, add a few milliliters of deionized water to the material in the mortar. Scrape the mortar and pestle a final time to loosen all of the product from the mortar. Pour the mixture into a Hirsch funnel inserted into a filter flask under vacuum. Use a squirt bottle with deionized water to transfer any remaining off-white product into the Hirsch funnel. Discard the filtrate that contains potassium phosphate and some triphenylphosphine oxide. The off-white solid consists mainly of the *trans,trans* isomer, but some of the *cis,trans* isomer will be present as well.

Crystallization. Purify the off-white solid by crystallization from absolute ethanol in a small test tube using the standard technique of adding hot solvent until the solid dissolves. A small amount of impurity might not dissolve. If this is the case, use a Pasteur pipet to *rapidly* remove the hot solution from the impurity and transfer the hot solution to another test tube. Cork the test tube and place it in a warm 25-mL Erlenmeyer flask. Allow the solution to cool slowly. Once the test tube has cooled and crystals have formed, place the test tube in an ice bath for at least 10 minutes to complete the crystallization process. Place 2 mL of absolute ethanol in another test tube and cool the solvent in the ice bath (this solvent will be used to aid the transfer of the product). Loosen the crystals in the test tube with a microspatula and pour the contents of the test tube into a Hirsch funnel under vacuum. Remove the remaining crystals from the test tube using the chilled ethanol and a spatula. Place the colorless crystalline (plates) of *trans,trans* 1,4-diphenyl-1,3-butadiene on the Hirsch funnel for about 5 minutes to completely dry them. Save the filtrate from the crystallization for analysis

by thin-layer chromatography. The *cis,trans*-1,4-diphenyl-1,3-butadiene, which is also formed in the Wittig reaction, is a liquid, and crystallization effectively removes the isomer from the solid *trans,trans* product.

Yield Calculation and Melting Point Determination. Weigh the purified *trans,trans* product and calculate the percentage yield. Determine the melting point of the product (literature, 151°C).

Thin-Layer Chromatography. Following the procedure in Experiment 41B, analyze the filtrate from the crystallization and the purified solid product by thin-layer chromatography. Develop the plate with hexane. This solvent will separate the *cis,trans-diene* from the *trans,trans* isomer. The order of increasing R_f values is as follows: triphenylphosphine oxide, *trans, trans-diene,* and *cis-trans-diene.* Triphenylphosphine oxide is so polar that the R_f value will be nearly zero. After developing the plate in hexane, as indicated in Experiment 41B use the short and long wavelength settings with a UV lamp to visualize the spots. Calculate the R_f values and record them in your notebook.

QUESTIONS

1. There is an additional isomer of 1,4-diphenyl-1,3-butadiene (mp 70°C), which is not present in this experiment. Draw the structure and name it. Why is it not produced in this experiment?

2. Why should the *trans,trans* isomer be the thermodynamically most stable one?

3. A lower yield of phosphonium salt is obtained in refluxing benzene than in xylene. Look up the boiling points for these solvents and explain why the difference in boiling points might influence the yield.

4. Outline a synthesis for *cis* and *trans* stilbene (the 1,2-diphenylethenes) using the Wittig reaction.

5. The sex attractant of the female housefly (*Musca domestica*) is called **muscalure**, and its structure follows. Outline a synthesis of muscalure, using the Wittig reaction. Will your synthesis lead to the required *cis* isomer?

$$CH_3(CH_2)_7 \qquad (CH_2)_{12}CH_3$$
$$C=C$$
$$H \qquad\qquad H$$

Muscalure

---
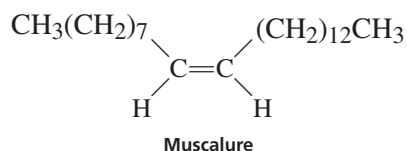
42   EXPERIMENT 42

Relative Reactivities of Several Aromatic Compounds

Aromatic substitution

Relative activating ability of aromatic substituents

Crystallization

When substituted benzenes undergo electrophilic aromatic substitution reactions, both the reactivity and the orientation of the electrophilic attack are affected by the nature of the original group attached to the benzene ring. Substituent groups that

make the ring more reactive than benzene are called **activators**. Such groups are also said to be **ortho, para** directors because the products formed are those in which substitution occurs either ortho or para to the activating group. Various products may be formed depending on whether substitution occurs at the ortho or para position and the number of times substitution occurs on the same molecule. Some groups may activate the benzene ring so strongly that multiple substitution consistently occurs, whereas other groups may be moderate activators, and benzene rings containing such groups may undergo only a single substitution. The purpose of this experiment is to determine the relative activating effects of several substituent groups.

In this experiment, you will study the bromination of acetanilide, aniline, and anisole:
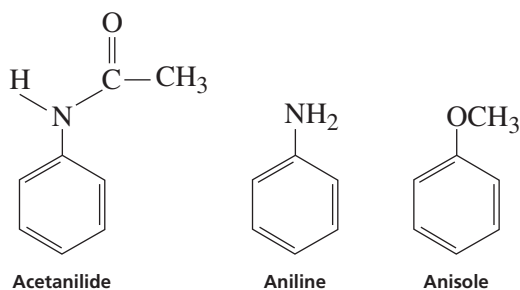
The acetamido group, —$NHCOCH_3$; the amino group,—NH_2; and the methoxy group,—OCH_3; are all activators and ortho, para directors. Each student will carry out the bromination of one of these compounds and determine its melting point. By sharing your data, you will have information on the melting points of the brominated products for acetanilide, aniline, and anisole. Using the table of compounds shown below, you can then rank the three substituents in order of activating strength.

The classic method of brominating an aromatic compound is to use Br_2 and a catalyst such as $FeBr_3$, which acts as a Lewis acid. The first step is the reaction between bromine and the Lewis acid:

$$Br_2 + FeBr_3 \longrightarrow [FeBr_4^- \ Br^+]$$
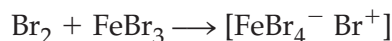
The positive bromine ion then reacts with the benzene ring in an aromatic electrophilic substitution reaction:
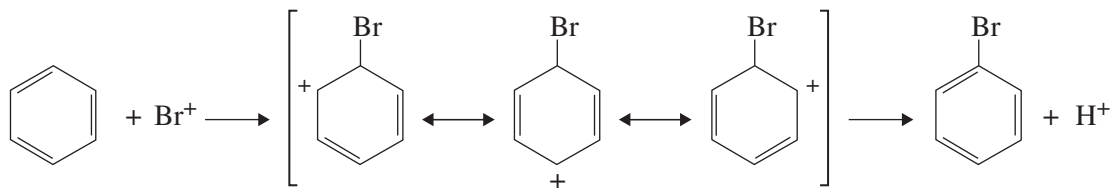
Aromatic compounds that contain activating groups can be brominated without the use of the Lewis acid catalyst, because the π electrons in the benzene ring are more available and polarize the bromine molecule sufficiently to produce the required electrophile Br^+. This is illustrated by the first step in the reaction between anisole and bromine:
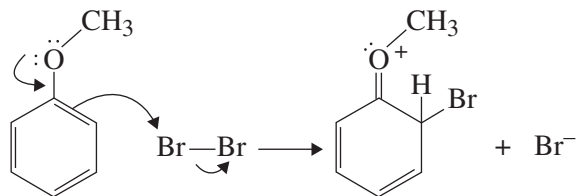
In this experiment, the brominating mixture consists of bromine, hydrobromic acid (HBr), and acetic acid. The presence of bromide ion from the hydrobromic acid helps to solubilize the bromine and increase the concentration of the electrophile.

Melting Points of Relevant Compounds

Compound	Melting Points (°C)
o-Bromoacetanilide	99
p-Bromoacetanilide	168
2,4-Dibromoacetanilide	145
2,6-Dibromoacetanilide	208
2,4,6-Tribromoacetanilide	232
o-Bromoaniline	32
p-Bromoaniline	66
2,4-Dibromoaniline	80
2,6-Dibromoaniline	87
2,4,6-Tribromoaniline	122
o-Bromoanisole	3
p-Bromoanisole	13
2,4-Dibromoanisole	60
2,6-Dibromoanisole	13
2,4,6-Tribromoanisole	87

REQUIRED READING

Review: *Technique 11 Crystallization

You should review the chapters in your lecture textbook that deal with electrophilic aromatic substitution. Pay special attention to halogenation reactions and the effect of activating groups.

SPECIAL INSTRUCTIONS

Bromine is a skin irritant, and its vapors cause severe irritation to the respiratory tract. It will also oxidize many pieces of jewelry. Hydrobromic acid may cause skin or eye irritation. Aniline is highly toxic and a suspected teratogen. All bromoanilines are toxic. This experiment should be carried out in a fume hood or in a well-ventilated laboratory.

Each person will carry out the bromination of only one of the aromatic compounds according to your instructor's directions. The procedures are identical except for the initial compound used and the final recrystallization step.

SUGGESTED WASTE DISPOSAL

Dispose of the filtrate from the Hirsch funnel filtration of the crude product into a container specifically designated for this mixture. Place all other filtrates into the container for halogenated organic solvents.

NOTES TO THE INSTRUCTOR

Prepare the brominating mixture in advance.

PROCEDURE

Running the Reaction. To a tared 25-mL round-bottom flask, add the given amount of one of the following compounds: 0.45 g of acetanilide, 0.30 mL of aniline, or 0.35 mL of anisole. Reweigh the flask to determine the actual weight of the aromatic compound. Add 2.5 mL of glacial acetic acid and a magnetic stir bar to the round-bottom flask. Assemble the apparatus shown in the figure. Pack the drying tube loosely with glass wool. Add about 2.5 mL of 1.0 M sodium bisulfite dropwise to the glass wool until it is moistened, but not soaked. This apparatus will capture any bromine given off during the following reaction. Stir the mixture until the aromatic compound is completely dissolved.

> **CAUTION** ⚠
>
> **The procedure in the next paragraph must be carried out in a fume hood. Unclamp the apparatus shown in the figure and take it to the hood.**

Under the hood, obtain 5.0 mL of the bromine/hydrobromic acid mixture in a 10-mL graduated cylinder.[1] Remove the glass stopper from the Claisen head. Pour the bromine/hydrobromic acid mixture through the Claisen head into the round-bottom flask. Place the stopper on the Claisen head before returning to your lab bench. Clamp the apparatus above the magnetic stirrer and stir the reaction mixture at room temperature for 20 minutes.

---

[1] Note to the instructor: The brominating mixture is prepared by adding 13.0 mL of bromine to 87.0 mL of 48% hydrobromic acid. This will provide enough solution for 20 students, assuming no waste of any type. This solution should be stored in the hood.
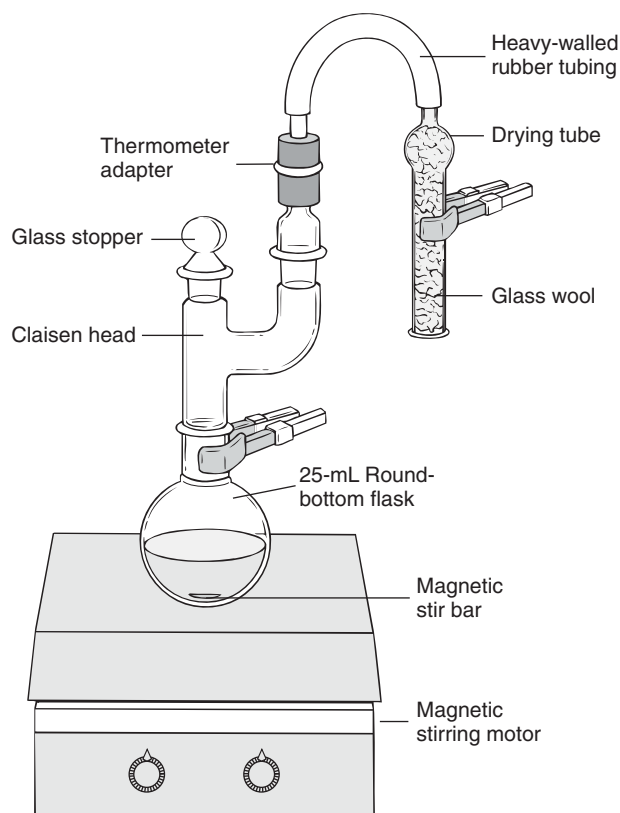
Apparatus for bromination.

CAUTION ⚠️

Be careful not to spill any of the bromine mixture.

Crystallization and Isolation of Product. When the reaction is complete, transfer the mixture to a 125-mL Erlenmeyer flask containing 25 mL of water and 2.5 mL of saturated sodium bisulfite solution. Stir this mixture with a glass stirring rod until the red color of bromine disappears.[2] If an oil has formed, it may be necessary to stir the mixture for several minutes to remove all of the color. Place the Erlenmeyer flask in an ice bath for 10 minutes. If the product does not solidify, scratch the bottom of the flask with a glass stirring rod to induce crystallization. It may take 10 to 15 minutes to induce crystallization of the brominated anisole product.[3] Filter the product on a Hirsch funnel with suction and rinse with several 5-mL portions of cold water. Air-dry the product on the funnel for about 10 minutes with the vacuum on.

Recrystallization and Melting Point of Product. Recrystallize your product from the minimum amount of hot solvent (see Technique 11, Section 11.3, and Figure 11.4). Use 95% ethanol to recrystallize brominated aniline or brominated acetanilide; use hexane to recrystallize the brominated anisole product. Allow the crystals to air-dry and determine the weight and melting point.

---

[2] If the color of bromine is still present, add a few more drops of saturated sodium bisulfite and stir the mixture for a few more minutes. The entire mixture, including liquid and solid (or oil), should be colorless.
[3] If crystals fail to form after 15 minutes, it may be necessary to seed the mixture with a small crystal of product.

Based on the melting point and the preceding table, you should be able to identify your product. Calculate the percentage yield and submit your product, along with your report, to your instructor.

REPORT

By collecting data from other students, you should be able to determine which product was obtained from the bromination of each of the three aromatic compounds. Using this information, arrange the three substituent groups (acetamido, amino, and methoxy) in order of decreasing ability to activate the benzene ring.

REFERENCE

Zaczek, N. M.; Tyszklewicz, R. B. Relative Activating Ability of Various Ortho, Para-Directors. *J. Chem. Educ.* **1986,** *63,* 510.

QUESTIONS

1. Using resonance structures, show why the amino group is activating. Consider an attack by the electrophile E^+ at the *para* position.
2. For the substituent in this experiment that was found to be least activating, explain why bromination took place at the position on the ring indicated by the experimental results.
3. What other experimental techniques (including spectroscopy) might be used to identify the products in this experiment?

43   EXPERIMENT 43

Nitration of Methyl Benzoate

Aromatic substitution

Crystallization

The nitration of methyl benzoate to prepare methyl *m*-nitrobenzoate is an example of an electrophilic aromatic substitution reaction, in which a proton of the aromatic ring is replaced by a nitro group:

Methyl benzoate   **Methyl *m*-nitrobenzoate**
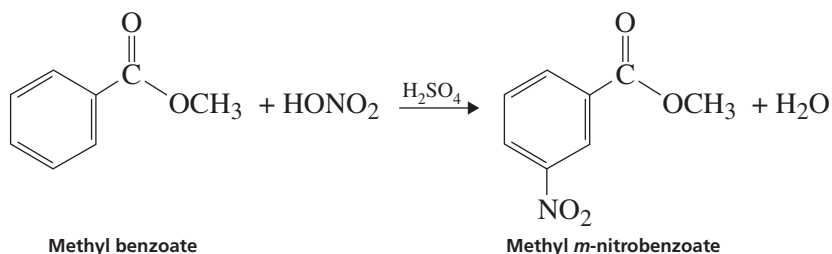
Many such aromatic substitution reactions are known to occur when an aromatic substrate is allowed to react with a suitable electrophilic reagent, and many other groups besides nitro may be introduced into the ring.

You may recall that alkenes (which are electron-rich due to an excess of electrons in the π system) can react with an electrophilic reagent. The intermediate formed is electron-deficient. It reacts with the nucleophile to complete the reaction. The overall sequence is called **electrophilic addition**. Addition of HX to cyclohexene is an example.

Nucleophile

Electrophile

Cyclohexene

Attack of alkene
on electrophile (H⁺)

Carbocation
intermediate
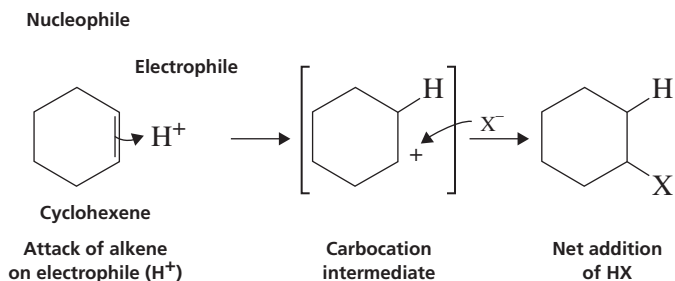
Net addition
of HX

Aromatic compounds are not fundamentally different from cyclohexene. They can also react with electrophiles. However, because of resonance in the ring, the electrons of the π system are generally less available for addition reactions because an addition would mean the loss of the stabilization that resonance provides. In practice, this means that aromatic compounds react only with *powerfully electrophilic reagents*, usually at somewhat elevated temperatures.

Benzene, for example, can be nitrated at 50°C with a mixture of concentrated nitric and sulfuric acids; the electrophile is NO_2^+ (nitronium ion), whose formation is promoted by action of the concentrated sulfuric acid on nitric acid:

Nitric acid
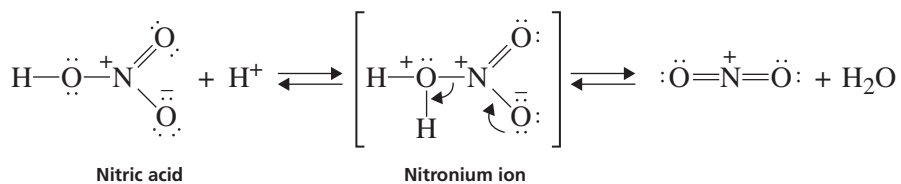
Nitronium ion

The nitronium ion thus formed is sufficiently electrophilic to add to the benzene ring, *temporarily* interrupting ring resonance:
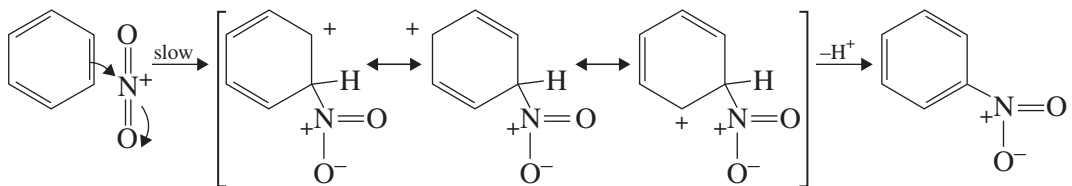
The intermediate first formed is somewhat stabilized by resonance and does not rapidly undergo reaction with a nucleophile; in this behavior, it is different from the unstabilized carbocation formed from cyclohexene plus an electrophile. In fact, aromaticity can be restored to the ring if *elimination* occurs instead. (Recall that elimination is often a reaction of carbocations.) Removal of a proton, probably by HSO_4^-, from the sp³-ring carbon *restores the aromatic system* and yields a net *substitution* wherein a hydrogen has been replaced by a nitro group. Many similar reactions are known, and they are called **electrophilic aromatic substitution reactions**.

The substitution of a nitro group for a ring hydrogen occurs with methyl benzoate in the same way it does with benzene. In principle, one might expect that any hydrogen on the ring could be replaced by a nitro group. However, for reasons beyond our scope here (see your lecture textbook), the carbomethoxy group directs the aromatic substitution preferentially to those positions that are *meta* to it. As a result, methyl *m*-nitrobenzoate is the principal product formed. In addition, one might expect the nitration to occur more than once on the ring. However, both the carbomethoxy group and the nitro group that has just been attached to the ring *deactivate* the ring against further substitution. Consequently, the formation of a methyl dinitrobenzoate product is much less favorable than the formation of the mononitration product.

Although the products described previously are the principal ones formed in the reaction, it is possible to obtain as impurities in the reaction small amounts of the ortho and para isomers of methyl *m*-nitrobenzoate and of the dinitration products. These side products are removed when the desired product is washed with methanol and purified by crystallization.

Water has a retarding effect on the nitration because it interferes with the nitric acid–sulfuric acid equilibria that form the nitronium ions. The smaller the amount of water present, the more active the nitrating mixture. Also, the reactivity of the nitrating mixture can be controlled by varying the amount of sulfuric acid used. This acid must protonate nitric acid, which is a *weak* base, and the larger the amount of acid available, the more numerous the protonated species (and hence NO_2^+) in the solution. Water interferes because it is a stronger base than H_2SO_4 or HNO_3. Temperature is also a factor in determining the extent of nitration. The higher the temperature, the greater will be the amounts of dinitration products formed in the reaction.

Experiment 28 illustrates a Green Chemistry alternative to the nitration of aromatic hydrocarbons. In this version, a recyclable catalyst (ytterbium triflate) is used to generate the nitronium ion. The catalyst is recovered at the end of the experiment.

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review: *Techniques 11   Crystallization: Purification of Solids

Technique 25   Infrared Spectroscopy, Sections 25.4 and 25.5

SPECIAL INSTRUCTIONS

It is important that the temperature of the reaction mixture be maintained at or below 15°C. Nitric acid and sulfuric acid, especially when mixed, are very corrosive substances. Be careful not to get these acids on your skin. If you do get some of these acids on your skin, flush the affected area liberally with water.

SUGGESTED WASTE DISPOSAL

All aqueous solutions should be placed in a container specially designated for aqueous wastes. Place the methanol used to recrystallize the methyl nitrobenzoate in the container designated for nonhalogenated organic waste.

PROCEDURE

In a 100-mL beaker, cool 6 mL of concentrated sulfuric acid to about 0°C and add 3.05 g of methyl benzoate. Using an ice–salt bath (see Technique 6, Section 6.9), cool the mixture to 0°C or below and very slowly add, using a Pasteur pipet, a cool mixture of 2 mL of concentrated sulfuric acid and 2 mL of concentrated nitric acid. During the addition of the acids, stir the mixture continuously and maintain the temperature of the reaction below 15°C. If the mixture rises above this temperature, the formation of by-product increases rapidly, bringing about a decrease in the yield of the desired product.

After you have added all of the acid, warm the mixture to room temperature. After 15 minutes, pour the acid mixture over 25 g of crushed ice in a 150-mL beaker. After the ice has melted, isolate the product by vacuum filtration through a Büchner funnel and wash it with two 12-mL portions of cold water and then with two 5-mL portions of ice-cold methanol. Weigh the product and recrystallize it from an equal weight of methanol (see Technique 11, Section 11.3). The melting point of the recrystallized product should be 78°C. Obtain the infrared spectrum using the dry-film method (see Technique 25, Section 25.4) or as a KBr pellet (see Technique 25, Section 25.5). Compare your infrared spectrum with the one reproduced here. Calculate the percentage yield and submit the product to the instructor in a labeled vial.

Molecular Modeling (Optional)

If you are working alone, complete Part A. If you have a partner, one of you should complete Part A and the other complete Part B. If you work with a partner, you should combine results at the end of the experiment.

Part A. Nitration of Methyl Benzoate

In this exercise, you will try to explain the observed outcome of the nitration of methyl benzoate. The major product of this reaction is methyl *m*-nitrobenzoate, where the nitro group has been added to the *meta* position of the ring. The rate-determining step of this reaction is the attack of the nitronium ion on the benzene ring. Three different benzenium ion intermediates (*ortho, meta,* and *para*) are possible:
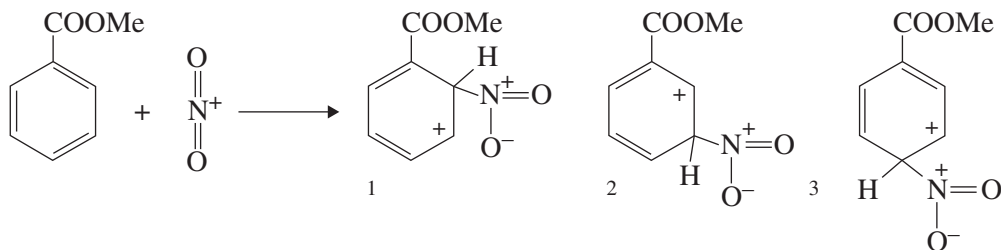
You will calculate the heats of formation for these intermediates to determine which of the three has the lowest energy. Assume that the activation energies are similar to the energies of the intermediates themselves. This is an application of the Hammond Postulate, which states that the activation energy leading to an intermediate of higher energy will be higher than the activation energy leading to an intermediate of lower energy, and vice versa. Although there are prominent exceptions, this postulate is generally true.

Make models of each of the three benzenium ion intermediates (separately) and calculate their heats of formation using an AM1-level calculation with geometry optimization. Don't forget to specify a positive charge when you submit the calculation. What do you conclude?

Now take a piece of paper and draw the resonance structures that are possible for each intermediate. Do not worry about structures involving the nitro group; consider only where the charge in the ring may be delocalized. Also note the polarity of the carbonyl group by placing a $\delta+$ symbol on the carbon and a $\delta-$ symbol on the oxygen. What do you conclude from your resonance analysis?
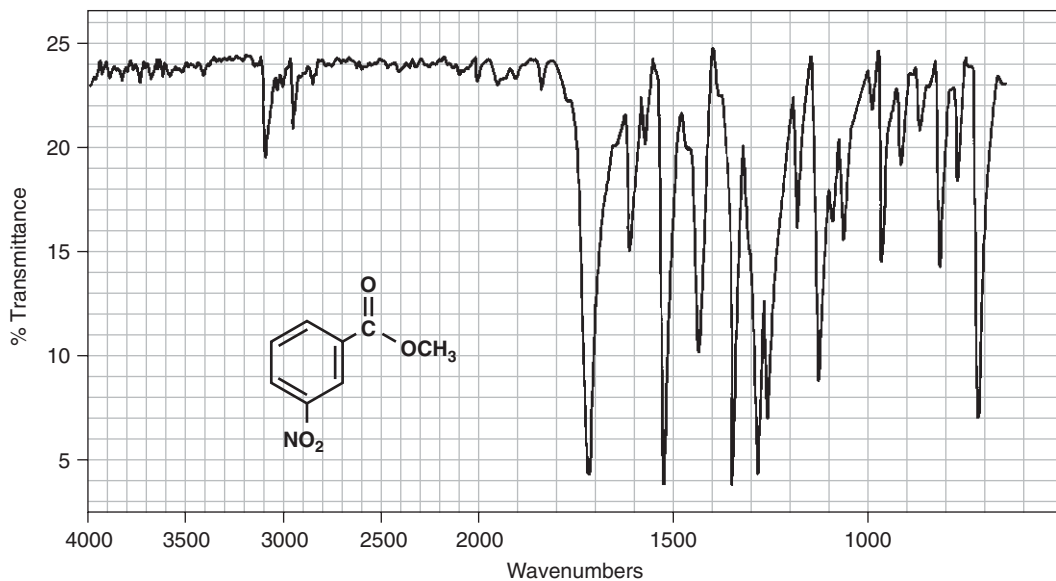
Infrared spectrum of methyl *m*-nitrobenzoate, KBr.

Part B. Nitration of Anisole

For this computation, you will analyze the three benzenium ions formed from anisole (methoxybenzene) and the nitronium ion (see Part A). Calculate the heats of formation using AM1-level calculations with geometry optimization. Don't forget to specify a positive charge. What do you conclude for anisole? How do the results compare to those for methyl benzoate?

Now take a piece of paper and draw the resonance structures that are possible for each intermediate. Do not worry about structures involving the nitro group; consider only where the charge in the ring may be delocalized. Do not forget that the electrons on the oxygen can participate in the resonance. What do you conclude from your resonance analysis?

QUESTIONS

1. Why is methyl *m*-nitrobenzoate formed in this reaction instead of the *ortho* or *para* isomers?

2. Why does the amount of the dinitration increase at high temperatures?

3. Why is it important to add the nitric acid–sulfuric acid mixture slowly over a 15-minute period?

4. Interpret the infrared spectrum of methyl *m*-nitrobenzoate.

5. Indicate the product formed on nitration of each of the following compounds: benzene, toluene, chlorobenzene, and benzoic acid.

Local Anesthetics

Local anesthetics, or "painkillers," are a well-studied class of compounds. Chemists have shown their ability to study the essential features of a naturally occurring drug and to improve on them by substituting totally new, synthetic surrogates. Often such substitutes are superior in desired medical effects and have fewer unwanted side effects or hazards.

The coca shrub (*Erythroxylon coca*) grows wild in Peru, specifically in the Andes Mountains, at elevations of 1,500 to 6,000 ft above sea level. Natives of South America have long chewed these leaves for their stimulant effects. Leaves of the coca shrub have even been found in pre-Inca Peruvian burial urns. Chewing the leaves brings about a definite sense of mental and physical well-being and the power to increase endurance. For chewing, the Indians smear the coca leaves with lime and roll them. The lime, $Ca(OH)_2$, apparently releases the free alkaloid components; it is remarkable that the Indians learned this subtlety long ago by some empirical means. The pure alkaloid responsible for the properties of the coca leaves is **cocaine**.

The amounts of cocaine the Indians consume in this way are extremely small. Without such a crutch of central-nervous-system stimulation, the natives of the Andes would probably find it more difficult to perform the nearly Herculean tasks of their daily lives, such as carrying heavy loads over the rugged mountainous terrain. Unfortunately, overindulgence can lead to mental and physical deterioration and eventually an unpleasant death.

The pure alkaloid in large quantities is a common drug of addiction. Sigmund Freud first made a detailed study of cocaine in 1884. He was particularly impressed by the ability of the drug to stimulate the central nervous system, and he used it as a replacement drug to wean one of his addicted colleagues from morphine. This attempt was successful, but, unhappily, the colleague became the world's first known cocaine addict.

Cocaine

Eucaine
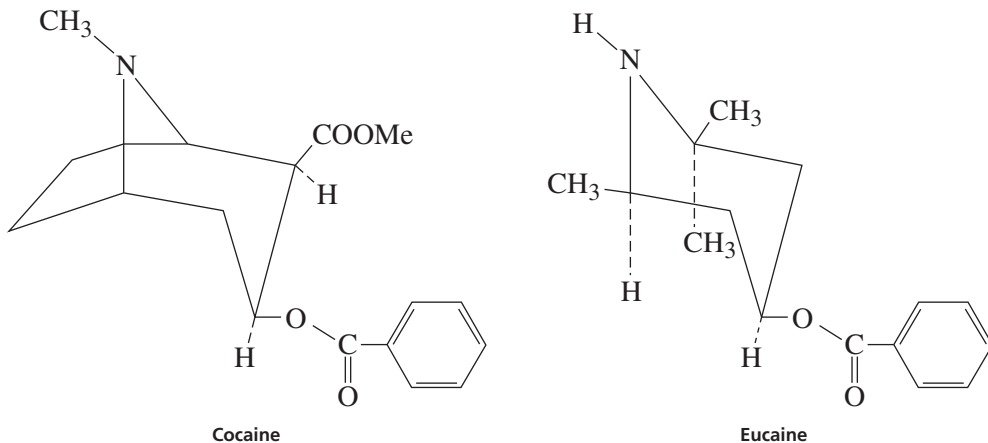
An extract from coca leaves was one of the original ingredients in Coca-Cola. However, early in the present century, government officials, with much legal difficulty, forced the manufacturer to omit coca from its beverage. The company has managed to this day to maintain the *coca* in its trademarked title, even though "Coke" contains none.

Our interest in cocaine lies in its anesthetic properties. The pure alkaloid was isolated in 1862 by Niemann, who noted that it had a bitter taste and produced a queer numbing sensation on the tongue, rendering it almost devoid of sensation. (Oh, those brave, but foolish chemists of yore who used to taste everything!) In 1880, Von Anrep found that the skin was made numb and insensitive to the prick of a pin when cocaine was injected subcutaneously. Freud and his assistant Karl Koller, having failed at attempts to rehabilitate morphine addicts, turned to a study of the anesthetizing properties of cocaine. Eye surgery is made difficult by involuntary reflex movements of the eye in response to even the slightest touch. Koller found that a few drops of a solution of cocaine would overcome this problem. Not only can cocaine serve as a local anesthetic, but it can also be used to produce **mydriasis** (dilation of the pupil). The ability of cocaine to block signal conduction in nerves (particularly of pain) led to its rapid medical use in spite of its dangers. It soon found use as a "local" in both dentistry (1884) and in surgery (1885). In this type of application, it was injected directly into the particular nerves it was intended to deaden.

Soon after the structure of cocaine was established, chemists began to search for a substitute. Cocaine has several drawbacks for wide medical use as an anesthetic. In eye surgery, it also produces mydriasis. It can also become a drug of addiction. Finally, it has a dangerous effect on the central nervous system.

The first totally synthetic substitute was eucaine. It was synthesized by Harries in 1918 and retains many of the essential skeletal features of the cocaine molecule. The development of this new anesthetic partly confirmed the portion of the cocaine structure essential for local anesthetic action. The advantage of eucaine over cocaine is that it does not produce mydriasis and is not habit forming. Unfortunately, it is highly toxic.

A further attempt at simplification led to piperocaine. The molecular portion common to cocaine and eucaine is outlined by dotted lines in the structure shown below. Piperocaine is only a third as toxic as cocaine itself.

The most successful synthetic for many years was the drug procaine, known more commonly by its trade name Novocain (see table). Novocain is only a fourth as toxic as cocaine, giving a better margin of safety in its use. The toxic dose is almost 10 times the effective amount, and it is not a habit-forming drug.

Piperocaine
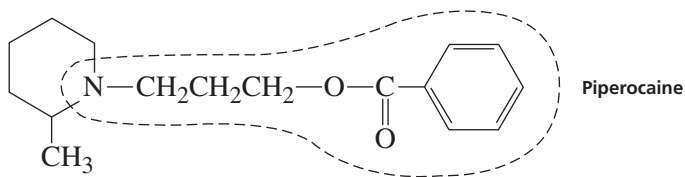
Over the years, hundreds of new local anesthetics have been synthesized and tested. For one reason or another, most have not come into general use. The search for the perfect local anesthetic is still under way. All the drugs found to be active have certain structural features in common. At one end of the molecule is an aromatic ring. At the other is a secondary or tertiary amine. These two essential features are separated by a central chain of atoms usually one to four units long. The aromatic part is usually an ester of an aromatic acid. The ester group is important to the bodily detoxification of these compounds. The first step in deactivating them is a hydrolysis of this ester linkage, a process that occurs in the bloodstream. Compounds that do not have the ester link are both longer lasting in their effects and generally more toxic. An exception is lidocaine, which is an amide. The tertiary amino group is apparently necessary to enhance the solubility of the compounds in the injection solvent. Most of these compounds are used in their hydrochloride salt forms, which can be dissolved in water for injection.

$$-\overset{..}{N}\overset{\displaystyle R}{\underset{\displaystyle R}{{\Large\diagdown}}} \quad + \text{ HCl} \longrightarrow \quad -\overset{\displaystyle R}{\underset{\displaystyle R}{\overset{|}{\underset{|}{N}}}}\overset{\oplus}{-}\text{H} \quad \text{Cl}^{\ominus}$$
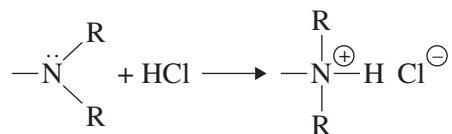
Benzocaine, in contrast, is active as a local anesthetic but is not used for injection. It does not suffuse well into tissue and is not water soluble. It is used primarily in skin preparations, in which it can be included in an ointment or salve for direct application. It is an ingredient of many sunburn-relief preparations.

How these drugs act to stop pain conduction is not well understood. Their main site of action is at the nerve membrane. They seem to compete with calcium at some receptor site, altering the permeability of the membrane and keeping the nerve slightly depolarized electrically.

Aromatic residue	Intermediate chain	Amino group	
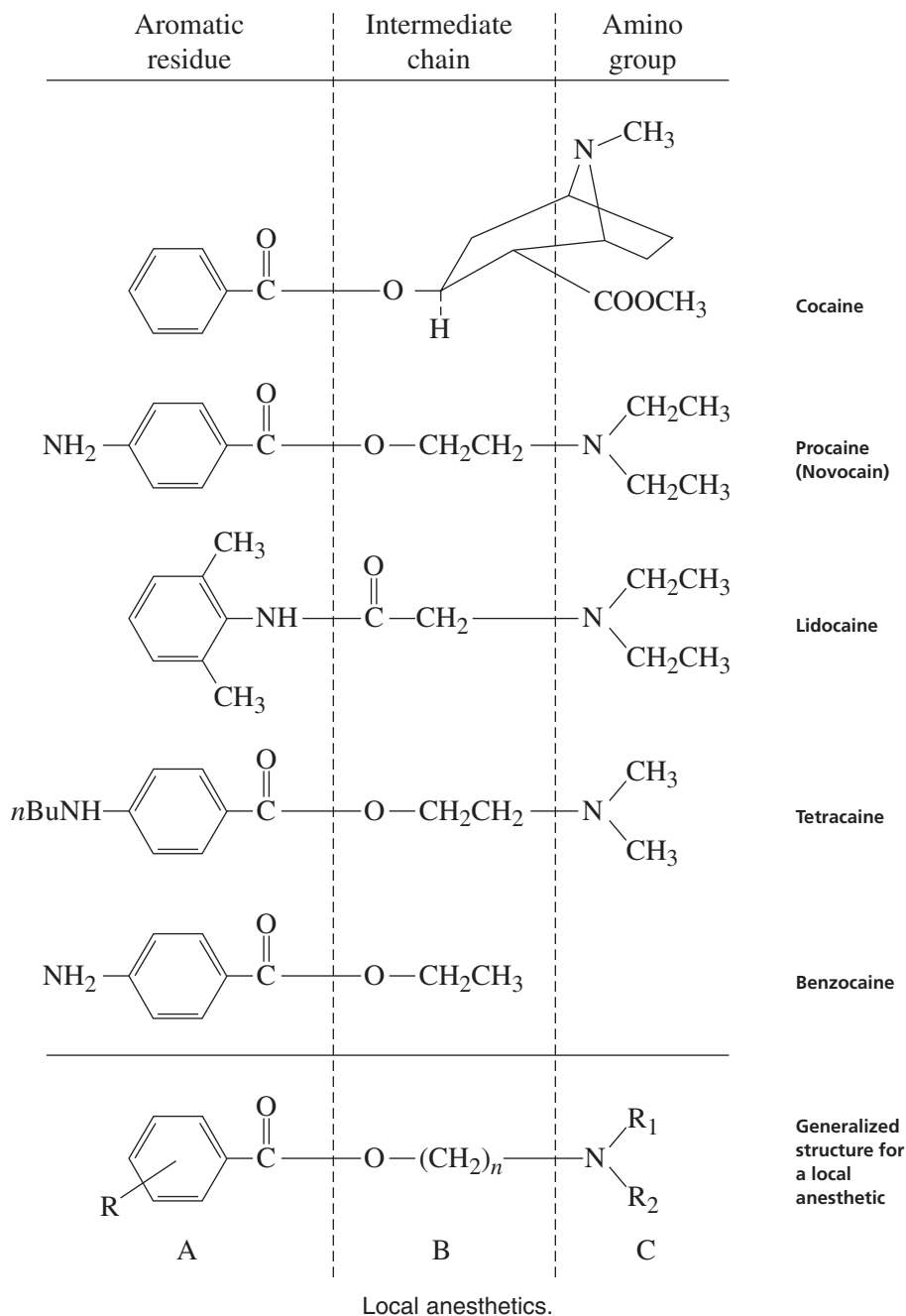
Local anesthetics.

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Taylor, N. *Plant Drugs That Changed the World;* Dodd, Mead: New York, 1965; pp. 14–18.

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44   E X P E R I M E N T   4 4

Benzocaine

Esterification

Crystallization (mixed-solvent method)

In this experiment, a procedure is given for the preparation of a local anesthetic, benzocaine, by the direct esterification of *p*-aminobenzoic acid with ethanol. At the instructor's option, you may test the prepared anesthetic on a frog's leg muscle.
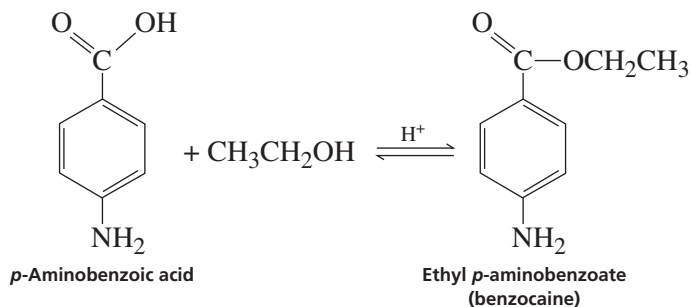
p-**Aminobenzoic acid**   **Ethyl *p*-aminobenzoate (benzocaine)**

R E Q U I R E D   R E A D I N G

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	*Technique 8	Filtration, Section 8.3
	*Technique 11	Crystallization: Purification of Solids, Sections 11.3 and 11.10
New:	Essay	Local Anesthetics

SPECIAL INSTRUCTIONS

Sulfuric acid is very corrosive. Do not allow it to touch your skin. Use a calibrated Pasteur pipet to transfer the liquid.

NOTE TO THE INSTRUCTOR

Benzocaine may be tested for its effect on a frog's leg muscle. See Instructor's Manual for instructions.

SUGGESTED WASTE DISPOSAL

Dispose of all filtrates into the container designated for nonhalogenated organic solvents.

PROCEDURE

Running the Reaction. Place 1.2 g of p-aminobenzoic acid and 12 mL of absolute ethanol in a 100-mL round-bottom flask. Swirl the mixture until the solid dissolves completely. While gently swirling, add dropwise 1.0 mL of concentrated sulfuric acid from a calibrated Pasteur pipet. A large amount of precipitate forms when you add the sulfuric acid, but this solid will slowly dissolve during the reflux that follows. Add boiling stones to the flask, attach a reflux condenser, and heat the mixture at a gentle reflux for 60–75 minutes using a heating mantle. Occasionally, swirl the reaction mixture during this period to help avoid bumping.

Precipitation of Benzocaine. At the end of the reaction time, remove the apparatus from the heating mantle and allow the reaction mixture to cool for several minutes. Using a Pasteur pipet, transfer the contents of the flask to a beaker containing 30 mL of water. When the liquid has cooled to room temperature, add a 10% sodium carbonate solution (about 10 mL needed) dropwise to neutralize the mixture. Stir the contents of the beaker with a stirring rod or spatula. After each addition of the sodium carbonate solution, extensive gas evolution (frothing) will be perceptible until the mixture is nearly neutralized. As the pH increases, a white precipitate of benzocaine is produced. When gas no longer evolves as you add a drop of sodium carbonate, check the pH of the solution and add further portions of sodium carbonate until the pH is about 8.

Collect the benzocaine by vacuum filtration using a Büchner funnel. Use three 10-mL portions of water to aid in the transfer and to wash the product in the funnel. Be sure that the solid is rinsed thoroughly with water so that any sodium sulfate formed during the neutralization will be washed out of your product. After the product has dried overnight, weigh it, calculate the percentage yield, and determine its melting point. The melting point of pure benzocaine is 92°C.

Recrystallization and Characterization of Benzocaine. Although the product should be fairly pure, it may be recrystallized by the mixed-solvent method using methanol and water (see Technique 11, Section 11.10). Place the product in a small Erlenmeyer flask and add hot methanol until the solid dissolves; swirl the mixture to help dissolve the solid. After the solid has dissolved, add hot water dropwise until the mixture turns cloudy or a white precipitate forms. Add a few more drops of hot methanol until the solid or oil redissolves completely.

Allow the solution to cool slowly to room temperature. Scratch the inside of the flask as the contents cool to help crystallize the benzocaine; otherwise, an oil may form. Complete the crystallization by cooling the mixture in an ice bath and collect the crystals by vacuum filtration. Use a minimum amount of ice-cold methanol to aid the transfer of the solid from the flask to the filter. When the benzocaine is thoroughly dry, weigh the purified benzocaine. Again, calculate the percentage yield of benzocaine and determine its melting point.

At the option of the instructor obtain the infrared spectrum using the dry film method (see Technique 25, Section 25.4) or as a KBr pellet (see Technique 25, Section 25.5) and the NMR spectrum in $CDCl_3$ (see Technique 26, Section 26.1).[1] Submit the sample in a labeled vial to the instructor.
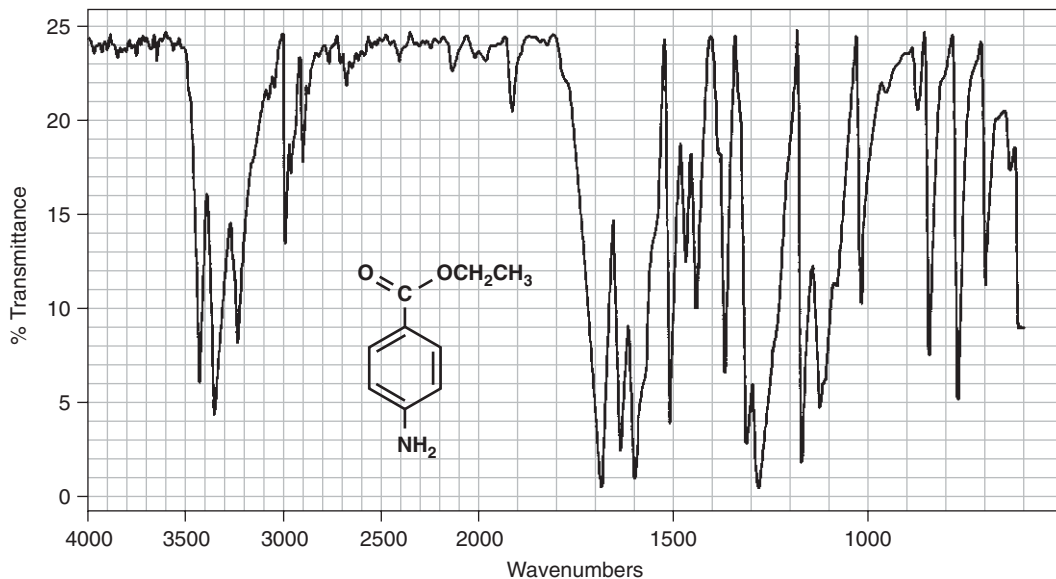
Infrared spectrum of benzocane, KBr.

---

[1]If a 60 MHz NMR spectrometer is used to determine the proton NMR of benzocaine, the amino protons may partially overlap the quartet in the ethyl group. If this is the case, a small amount of deuterated benzene can be added to shift the broad peak for the –NH_2 group away from the quartet: Carpenter, S. B.; R. H. Wallace. A Quick and Easy Simplification of Benzocaine's NMR Spectrum. *J. Chem. Educ.* **2006,** *83* (Apr), 637. A higher-field NMR spectrometer, such as obtained on a 300 MHz instrument, also avoids the overlap problem.
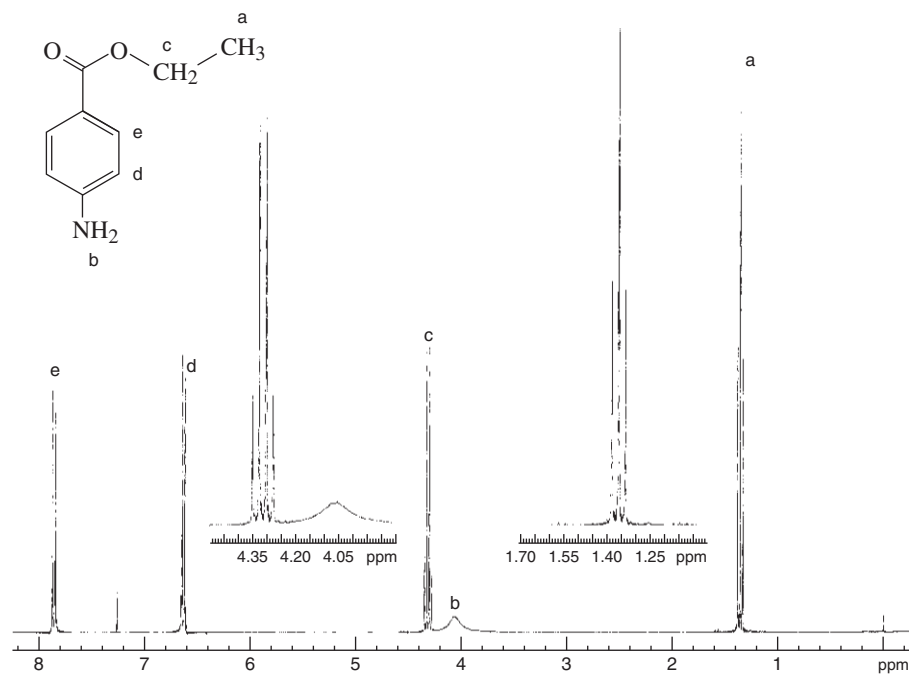
^{1}H NMR spectrum of benzocaine, CDCl$_3$, at 300 mHz. The insets show expansions of the methyl (triplet) and methylene (quartet) groups in the ethyl group.

QUESTIONS

1. Interpret the infrared and NMR spectra of benzocaine.

2. What is the structure of the precipitate that forms after the sulfuric acid has been added?

3. When 10% sodium carbonate solution is added, a gas evolves. What is the gas? Give a balanced equation for this reaction.

4. Explain why benzocaine precipitates during the neutralization.

5. Refer to the structure of procaine in the table in the essay "Local Anesthetics." Using *p*-aminobenzoic acid, give equations showing how procaine and procaine monohydrochloride could be prepared. Which of the two possible amino functional groups in procaine will be protonated first? Defend your choice. (*Hint:* Consider resonance.)

ESSAY

Pheromones: Insect Attractants and Repellents

It is difficult for humans, who are accustomed to heavy reliance on visual and verbal forms of communication, to imagine that some forms of life depend primarily on the release and perception of *odors* to communicate with one another. Among insects, however, this is perhaps the chief form of communication. Many species of insects have developed a virtual "language" based on the exchange of odors. These insects have well-developed scent glands, often of several different types, which have as their sole purpose the synthesis and release of chemical

substances. When these chemical substances, known as **pheromones**, are secreted by insects and detected by other members of the same species, they induce a specific and characteristic response.

TYPES OF PHEROMONES

Releaser pheromones: This type of pheromone produces an immediate behavioral response, but is quickly dissipated. Releaser molecules can attract mates from considerable distances, but the effect is short-lived.

Primer pheromones: Primer pheromones trigger a series of physiological changes in the recipient. In contrast to a releaser pheromone, a primer pheromone has a slower onset and a longer duration.

Recruiting or aggregation pheromones: This type of pheromone can attract individuals of both sexes of the same species.

Recognition pheromones: This type of pheromone allows members of the same species to recognize one another. This type of pheromone serves a similar function to recruiting pheromones.

Alarm pheromones: This type of substance is released when attacked by a predator. It can alert others to escape, or it can cause an aggressive response to members of the same species.

Territorial pheromones: These pheromones mark the boundaries of an organism's territory. In dogs, these pheromones are present in the urine. Dogs can thus mark out their territory.

Trail pheromones: Ants deposit a trail of pheromones as they return to the nest from their source of food. This trail attracts other ants and serves as a guide to the food source. The pheromone must be continually renewed because the low-molecular-weight compounds evaporate rapidly.

Sex pheromones: Sex pheromones indicate the availability of the female for breeding purposes. Male animals also emit pheromones that convey information about their species. No confusion results!

It should be mentioned that there is some overlap of function in pheromones. The pheromones can assume multiple responses even though they may be categorized separately.

SEX ATTRACTANTS

Among the most important types of releaser pheromones are the sex attractants. **Sex attractants** are pheromones secreted by either the female or, less commonly, the male of the species to attract the opposite sex for the purpose of mating. In large concentrations, sex pheromones also induce a physiological response in the recipient (for example, the changes necessary to the mating act) and thus have a primer effect and so are misnamed.

Anyone who has owned a female cat or dog knows that sex pheromones are not limited to insects. Female cats or dogs widely advertise, by odor, their sexual availability when they are "in heat." This type of pheromone is not uncommon to

mammals. Some persons even believe that human pheromones are responsible for attracting certain sensitive males and females to one another. This idea is, of course, responsible for many of the perfumes now widely available. Whether or not the idea is correct cannot yet be established, but there are proven sexual differences in the ability of humans to smell certain substances. For instance, Exaltolide, a synthetic lactone of 14-hydroxytetradecanoic acid, can be perceived only by females or males after they have been injected with an estrogen. Exaltolide is very similar in overall structure to civetone (civet cat) and muskone (musk deer), which are two naturally occurring compounds believed to be mammalian sex pheromones.

Whether or not humans use pheromones as a means of attracting the opposite sex has never been completely established, although it is an active area of research. Humans, like other animals, emit odors from many parts of their bodies. Body odor consists of secretions from several types of skin glands, most of which are concentrated in the underarm region of the body. Do these secretions contain substances that might act as human pheromones?

Research has shown that a mother can correctly identify the odor of her newborn infant or older child by smelling clothing worn previously by the child and can distinguish the clothing from that worn by another child of the same age. Studies conducted over 30 years ago showed that the menstrual cycles of women who are roommates or close friends tend to converge over time. These and other similar investigations suggest that some forms of pheromone-like communication are possible in humans.

Recent studies have clearly identified a specialized structure, called the **vomeronasal organ**, in the nose. This organ appears to respond to a variety of chemical stimuli. In a recent article, researchers at the University of Chicago reported that when they wiped human body-odor secretions from one group of women under the noses of other women, the second group showed changes in their menstrual cycles. The cycles grew either longer or shorter, depending on where the donors were in their own menstrual cycles. The affected women claimed that they did not smell anything except the alcohol on the cotton pads. Alcohol alone had no effect on the women's menstrual cycles. The timing of ovulation for the female test subjects was affected in a similar manner. Although the nature of substances responsible for these effects has not yet been identified, clearly the potential for chemical communication regulating sexual function has been established in humans.

This effect has been described as the McClintock effect, named after the primary investigator, Martha McClintock, at the University of Chicago (see references: McClintock and Stern, 1971 and 1998). The McClintock effect, however, is still not firmly established and more recent studies and reviews of the McClintock research have called into question the result of the study (see references: Yang and Schank, 2006).

One of the first identified insect attractants belongs to the gypsy moth, *Lymantria dispar*. This moth is a common agricultural pest, and it was hoped that the sex attractant that females emit could be used to lure and trap males. Such a method of insect control would be preferable to inundating large areas with insecticides and would be species-specific. Nearly 50 years of work were expended in identifying the chemical substance responsible for the attractant's power. Early in this period, researchers found that an extract from the tail sections of female gypsy moths would attract males, even from a great distance. Experiments with the isolated gypsy moth pheromone demonstrated that the male gypsy moth has an almost unbelievable ability to detect extremely small amounts of the substance. He can detect it in concentrations lower than a few hundred *molecules* per cubic centimeter (about 10^{-19}–10^{-20} g/cc)! When a male moth encounters a small concentration of pheromone, he immediately

heads into the wind and flies upward in search of higher concentrations and the female. In only a mild breeze, a continuously emitting female can activate a space 300 ft high, 700 ft wide, and almost 14,000 ft (nearly 3 miles) long!

In subsequent work, researchers isolated 20 mg of a pure chemical substance from solvent extracts of the two extreme tail segments collected from each of 500,000 female gypsy moths (about 0.1 μg/moth). This emphasizes that pheromones are effective in very minute amounts and that chemists must work with very small amounts to isolate them and prove their structures. It is not unusual to process thousands of insects to get even a minute sample of these substances. Extremely sophisticated analytical and instrumental methods, such as spectroscopy, must be used to determine the structure of a pheromone.

In spite of these techniques, the original researchers assigned an incorrect structure to the gypsy moth pheromone and proposed for it the name **gyplure**. Because of its great promise as a method of insect control, gyplure was soon synthesized. The synthetic material turned out to be totally inactive. After some controversy about why the synthetic material was incapable of luring male gypsy moths (see the References for the complete story), it was finally shown that the proposed structure for the pheromone (that is, the gyplure structure) was incorrect. The actual pheromone was found to be *cis*-7,8-epoxy-2-methyloctadecane, also named (7R,8S)-epoxy-2-methyloctadecane. This material was soon synthesized, found to be active, and given the name **disparlure**. In recent years, disparlure traps have been found to be a convenient and economical method for controlling the gypsy moth.

A similar story of mistaken identity can be related for the structure of the pheromone of the pink bollworm, *Pectinophora gossypiella.* The originally proposed structure was called **propylure**. Synthetic propylure turned out to be inactive. Subsequently, the pheromone was shown to be a mixture of two isomers of 7,11-hexadecadien-1-yl acetate, the *cis,cis* (7Z,11Z) isomer and the *cis,trans* (7Z,11E) isomer. It turned out to be quite easy to synthesize a 1:1 mixture of these two isomers, and the 1:1 mixture was named **gossyplure**. Curiously, adding as little as 10% of either of the other two possible isomers, *trans,cis* (7E,11Z) or *trans,trans* (7E,11E), to the 1:1 mixture greatly diminishes its activity, apparently masking it. Geometric isomerism can be important! The details of the gossyplure story can also be found in the References.

Both these stories have been partly repeated here to point out the difficulties of research on pheromones. The usual method is to propose a structure determined by work on *very tiny* amounts of the natural material. The margin for error is great. Such proposals are usually not considered "proved" until synthetic material is shown to be as biologically effective as the natural pheromone.

OTHER PHEROMONES

The most important example of a primer pheromone is found in honeybees. A bee colony consists of one queen bee, several hundred male drones, and thousands of worker bees, or undeveloped females. It has recently been found that the queen, the only female that has achieved full development and reproductive capacity, secretes a primer pheromone called the **queen substance**. The worker females, while tending the queen bee, continuously ingest quantities of the queen substance. This pheromone, which is a mixture of compounds, prevents the workers from rearing any competitive queens and prevents the development of ovaries in all other females in the hive. The substance is also active as a sex attractant; it attracts drones

to the queen during her "nuptial flight." The major component of the queen substance is shown in the figure.

Honeybees also produce several other important types of pheromones. It has long been known that bees will swarm after an intruder. It has also been known that isopentyl acetate induces a similar behavior in bees. Isopentyl acetate (Experiment 12) is an **alarm pheromone**. When an angry worker bee stings an intruder, she discharges, along with the sting venom, a mixture of pheromones that incites the other bees to swarm on and attack the intruder. Isopentyl acetate is an important component of the alarm pheromone mixture. Alarm pheromones have also been identified in many other insects. In insects less aggressive than bees or ants, the alarm pheromone may take the form of a **repellent**, which induces the insects to go into hiding or leave the immediate vicinity.

Honeybees also release **recruiting** or **trail pheromones**. These pheromones attract others to a source of food. Honeybees secrete recruiting pheromones when they locate flowers in which large amounts of sugar syrup are available. Although the recruiting pheromone is a complex mixture, both geraniol and citral have been identified as components. In a similar fashion, when ants locate a source of food, they drag their tails along the ground on their way back to the nest, continuously secreting a trail pheromone. Other ants follow the trail to the source of food.

In some species of insects, **recognition pheromones** have been identified. In carpenter ants, a caste-specific secretion has been found in the mandibular glands of the males of five different species. These secretions have several functions, one of which is to allow members of the same species to recognize one another. Insects not having the correct recognition odor are immediately attacked and expelled from the nest. In one species of carpenter ant, methyl anthranilate has been shown to be an important component of the recognition pheromone.

We do not yet know all the types of pheromones that any given species of insect may use, but it seems that as few as 10 or 12 pheromones could constitute a "language" that could adequately regulate the entire life cycle of a colony of social insects.

INSECT REPELLENTS

Currently, the most widely used **insect repellent** is the synthetic substance *N, N*-diethyl-*m*-toluamide (see Experiment 45), also called Deet. It is effective against fleas, mosquitoes, chiggers, ticks, deerflies, sandflies, and biting gnats. A specific repellent is known for each of these types of insects, but none has the wide spectrum of activity that this repellent has. Exactly why these substances repel insects is not yet fully understood. The most extensive investigations have been carried out on the mosquito.

Originally, many investigators thought that repellents might simply be compounds that provided unpleasant or distasteful odors to a wide variety of insects. Others thought that they might be alarm pheromones for the species affected, or that they might be the alarm pheromones of a hostile species. Early research with the mosquito indicates that at least for several varieties of mosquitoes, none of these is the correct answer.

Mosquitoes seem to have hairs on their antennae that are receptors enabling them to find a warm-blooded host. These receptors detect the convection currents arising from a warm and moist living animal. When a mosquito encounters a warm and moist convection current, the mosquito moves steadily forward. If it passes out of the current into dry air, it turns until it finds the current again. Eventually, it finds

the host and lands. Repellents cause a mosquito to turn in flight and become confused. Even if it should land, it becomes confused and flies away again.

Researchers have found that the repellent prevents the moisture receptors of the mosquito from responding normally to the raised humidity of the subject. At least two sensors are involved, one responsive to carbon dioxide and the other responsive to water vapor. The carbon dioxide sensor is activated by the repellent, but if exposure to the chemical continues, adaptation occurs, and the sensor returns to its usual low output of signal. The moisture sensor, on the other hand, simply seems to be deadened, or turned off, by the repellent. Therefore, mosquitoes have great difficulty in finding and interpreting a host when they are in an environment saturated with repellent. They fly right through warm and humid convection currents as if the currents did not exist. Only time will tell if other biting insects respond likewise.

Until now, the mechanism of action of insect repellents on molecular targets remained unknown. However, Leslie Vooshall and colleagues at Rockefeller University reported in the March 2008 issue of *Science* that they had identified the molecular targets for the repellent, *N,N*-diethyl-*meta*-toluamide (DEET). They reported that DEET inhibits mosquito and fruit fly olfactory receptors that form a complex with a required olfactory co-receptor, OR83b. In effect, DEET inhibits behavioral attraction by masking the host odor in humans. Now that it is known how DEET affects receptors, new insect repellants may be developed that are safer and more effective, especially for young children.

INSECT SEX ATTRACTANTS
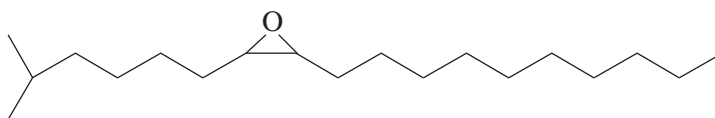
Disparlure
(gypsy moth)

+
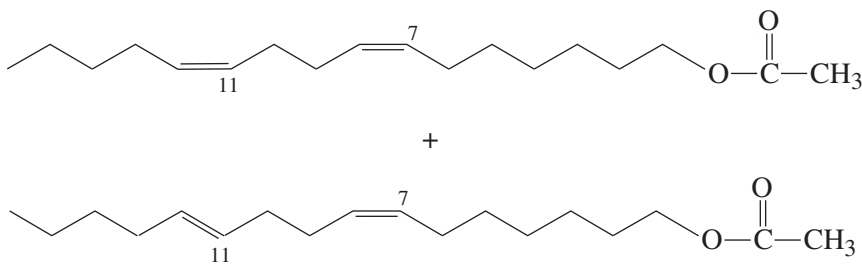
Gossyplure
(pink bollworm)

RECRUITING PHEROMONES   **PRIMER PHEROMONE**
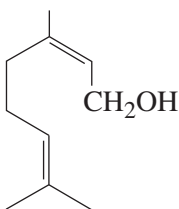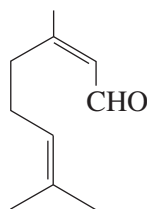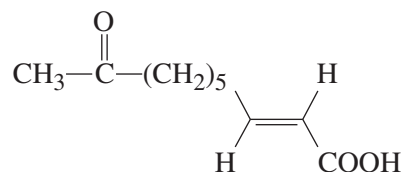
Geraniol   **Citral**   **Queen substance**
(honeybee)   **(honeybee)**   **(honeybee)**

ALARM PHEROMONES

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2CH_2CH\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{}}$$

Isopentyl acetate
(honeybee)

Citral   **Citronellal**
(ant species)

Periplanone B
(American cockroach)

MAMMALIAN PHEROMONES (?)

Exaltolide
(synthetic)

Civetone
(civet cat)

Muskone
(musk deer)
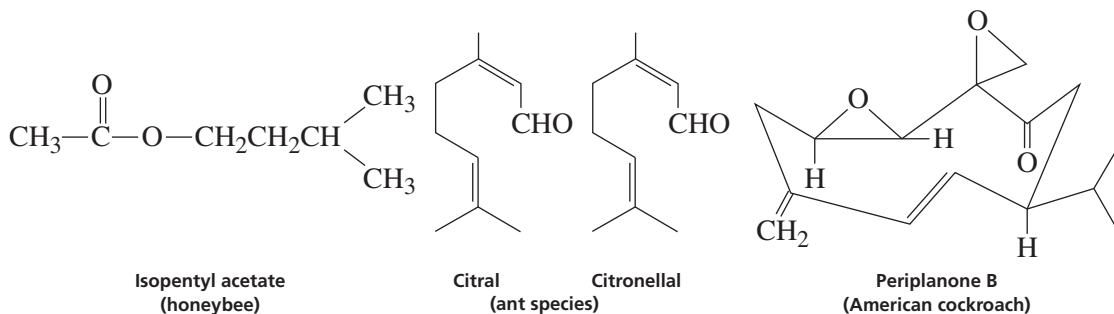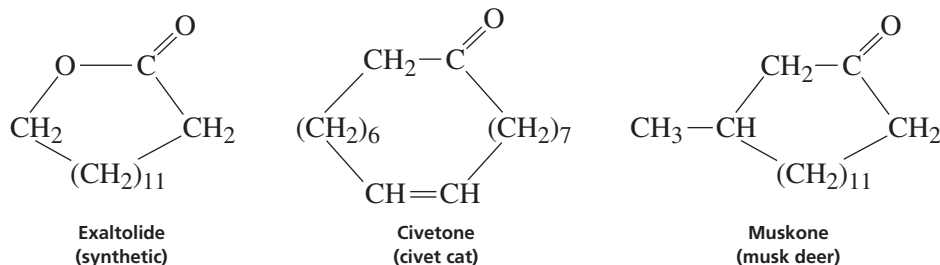
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INTERNET SITES

Wikipedia, http://en.wikipedia.org/wiki/Pheromone. This site describes the various types of pheromones.

Sexual Orientation, in the Brain,

http://www.cbsnews.com/stories/2005/05/09/tech/main694078.shtml

Pherobase, the database of insect pheromones

http://www.pheobase.com/

The Pherobase database is an extensive compilation of behavior-modifying compounds listed in the various pheromone categories: aggregation, alarm, releaser, primer, territorial, trail, sex pheromones, and others. The database contains over 30,000 entries. Jmol images of molecules are shown. The molecules can be projected as either space-filling or wire-frame models. They can be rotated in 3-dimensional space. In addition, the date base includes mass spectral, NMR, and synthesis data for more than 2,500 compounds. This is a fun site!

---

45   E X P E R I M E N T   4 5

N,N-*Diethyl-m-toluamide: The Insect Repellent "OFF"*

Preparation of an amide

Extraction

In this experiment, you will synthesize the active ingredient of the insect repellent "OFF," *N,N*-diethyl-*m*-toluamide. This substance belongs to the class of compounds called **amides**. Amides have the generalized structure

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2$$
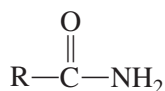
The amide to be prepared in this experiment is a disubstituted amide. That is, two of the hydrogens on the amide—NH_2 group have been replaced with ethyl groups. Amides cannot be prepared directly by mixing a carboxylic acid with an amine. If an acid and an amine are mixed, an acid–base reaction occurs, giving the conjugate base of the acid, which will not react further while in solution:

$$RCOOH + R_2NH \longrightarrow [RCOO^-R_2NH_2^+]$$
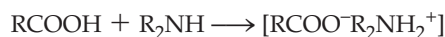
However, if the amine salt is isolated as a crystalline solid and strongly heated, the amide can be prepared:

$$[RCOO^-R_2NH_2^+] \overset{heat}{\longrightarrow} [RCONR_2 + H_2O]$$
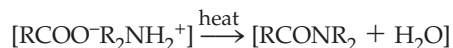
Because of the high temperature required for this reaction, this is not a convenient laboratory method.

Amides are usually prepared via the acid chloride, as in this experiment. In step 1, *m*-toluic acid is converted to its acid chloride derivative using thionyl chloride (SOCl$_2$).

Step 1

m-Toluic acid   Thionyl chloride   Acid chloride

$+ \text{SOCl}_2 \longrightarrow$ $+ \text{SO}_2 + \text{HCl}$
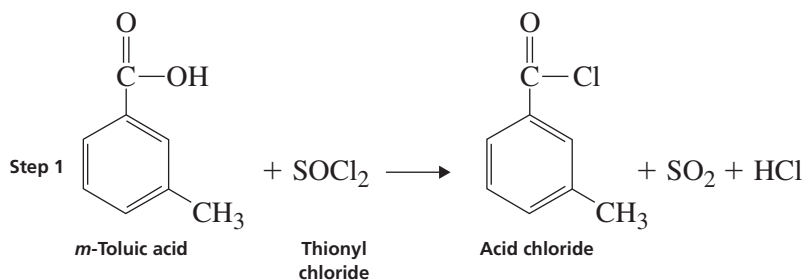
The acid chloride is not isolated or purified, and it is allowed to react directly with diethylamine in step 2. An excess of diethylamine is used in this experiment to react with the hydrogen chloride produced in step 2.
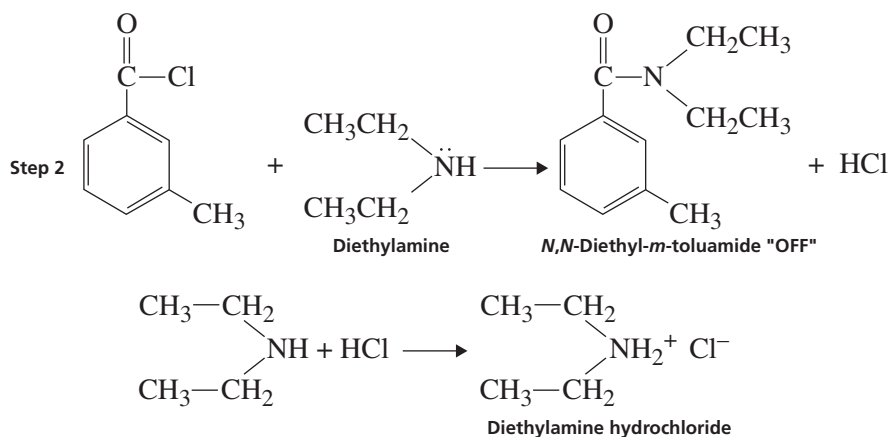
Step 2

Diethylamine   *N,N*-Diethyl-*m*-toluamide "OFF" $+ \text{HCl}$

Diethylamine hydrochloride

REQUIRED READING

Sign in at www .cengage.com to access Pre-Lab Video Exercises for techniques marked with an asterisk.

Review:	Technique 7	Reaction Methods, Sections 7.3 and 7.10
	*Technique 12	Extractions, Separations, and Drying Agents, Sections 12.4, 12.8, 12.9, 12.11
New:	Essay	Pheromones: Insect Attractants and Repellents

SPECIAL INSTRUCTIONS

All equipment used in this experiment should be dry because thionyl chloride reacts with water to liberate HCl and SO$_2$. Likewise, *anhydrous* ether should be used because water reacts with both thionyl chloride and the intermediate acid chloride.

Thionyl chloride is a noxious and corrosive chemical and should be handled with care. If it is spilled on the skin, serious burns will result. Thionyl chloride and diethylamine must be dispensed *in the hood* from bottles that should be kept tightly closed when not in use. Diethylamine is also noxious and corrosive. In addition, it is quite volatile (bp 56°C) and must be cooled in a hood prior to use.

SUGGESTED WASTE DISPOSAL

All aqueous extracts should be poured into the waste bottle designated for aqueous waste.

PROCEDURE

Preparation of the Acid Chloride. Place 1.81 g (0.0133 mol) of m-toluic acid (3-methybenzoic acid, MW = 136.1) into a dry 25-mL round-bottom flask. Add 1 mL of anhydrous diethyl ether to wet the solid (it will not dissolve), and place a stir bar in the flask. In a hood, carefully add 2.0 mL of thionyl chloride (0.0275 mol, density = 1.64 g/mL, MW 118.9) from a plastic Pasteur pipet. Thionyl chloride is a nasty substance, so be careful not to breath in the vapors! Add 5 drops of pyridine. At this point, you should observe a rapid reaction with evolution of gases. ***Lightly stopper the flask.*** The reaction will liberate sulfur dioxide and hydrogen chloride, so make sure that the flask is kept in a well–ventilated hood. Stir the mixture for about 10 minutes. During the course of the reaction period, the solid m-toluic acid will slowly dissolve (react) with the thionyl chloride. Continue stirring until the solid has dissolved.

CAUTION

⚠️

The thionyl chloride is kept in a hood. Do not breathe the vapors of this noxious and corrosive chemical. Use dry equipment when handling this material, as it reacts violently with water. Do not get it on your skin.

Insert a piece of glass tubing through the rubber piece on the thermometer adapter and insert it into the neck of the 25-mL round-bottom flask. Remove the excess thionyl chloride under vacuum using an aspirator (with water trap!) or with the house vacuum system. The best way to remove the excess thionyl chloride is to swirl the flask, rather than using the magnetic stirring unit. Do not heat the mixture. The mixture will show obvious signs on boiling under the vacuum. You should see boiling action around the stir bar, accompanied by a little frothing. Continue to pull a vacuum on the flask until the boiling action ceases or nearly cease. At that point, the volume should have been reduced. It may take about $1/2$ hour to remove the excess thionyl chloride. Swirl the mixture continuously during this time to aid the evaporation process.

Preparation of the Amide. Prepare a solution of diethylamine in aqueous sodium hydroxide solution by adding 4 mL of diethylamine (0.430 mol, density = 0.71 g/mL, MW 73.1) from a plastic disposable Pasteur pipet to 15 mL of 10% aqueous sodium hydroxide solution in a 50-mL Erlenmeyer flask. Cool the mixture to 0°C in an ice-water bath. ***Slowly*** add the acid chloride mixture with a plastic Pasteur pipet to the cooled diethylamine/sodium hydroxide mixture, with swirling of the flask. ***The reaction is violent, and a lot of smoke is observed.*** Add the acid chloride in small portions over about a 5-minute period. Following the addition, swirl the mixture in the flask occasionally over a 10-min period to complete the reaction.

Isolation of the Amide. Pour the mixture into a separatory funnel using portions of 20 mL of diethyl ether to aid the transfer. Add the rest of the diethyl ether and shake the separatory funnel to extract the product from the aqueous mixture. Remove the lower aqueous layer and save it. Pour the ether layer out of the top of the funnel into an Erlenmeyer flask for temporary storage. Return the aqueous layer back into the separatory funnel and extract it with a fresh 20-mL portion of ether. Remove the aqueous layer and discard it. Pour the ether layer from the top of the separatory funnel and into the flask containing the first ether extract.

Return the combined ether layers into the separatory funnel, and shake it with a 20-mL portion of saturated aqueous NaCl solution to do a preliminary drying of the ether layer. Remove the lower aqueous layer and discard it. Pour the ether solution from the top of the separatory funnel into a *dry* Erlenmeyer flask. Dry the ether layer with anhydrous magnesium sulfate. Decant the solution away from the drying agent through a piece of fluted filter paper into a *preweighed* 100-mL round-bottom flask. Remove the ether on a rotary evaporator or remove the ether under vacuum (see Technique 7, Figure 7.7C). Reweigh the flask to determine the yield of the reddish-brown product. Yields are generally reasonable and exceed 80%.

Analysis of the Product. Determine the infrared spectrum of your product. The spectrum can be compared to the one reproduced in Figure 1. You may see a small amount of unreacted diethylamine appearing near 3400 cm^{-1} in your spectrum, which can be ignored.

At the option of the instructor determine the ^{1}H (proton) NMR spectrum of your product. The 500 MHz spectrum determined at 20°C shows an interesting pattern for the ethyl groups attached to a nitrogen Figure 2. The two methylene carbon atoms in the ethyl groups appear as a pair of broad peaks between 3.2 and 3.6 ppm, indicating non-equivalence. Notice that the peaks are broad and do not show up as quartets. Likewise, the two methyl carbon atoms in the ethyl groups appear as a pair of broad peaks between 1.0 and 1.3 ppm and do not show up as triplets. There is restricted rotation in amides resulting from resonance, leading to non-equivalence of the two ethyl groups:
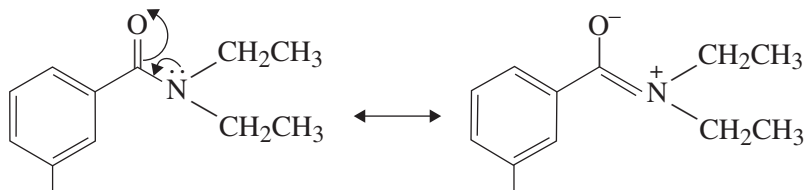
When the temperature is lowered to 0°C, the spectrum shows a pair of quartets and a pair of triplets. See the inset structures in the NMR spectrum (Figure 45.2) for the methylene and methyl groups, respectively.
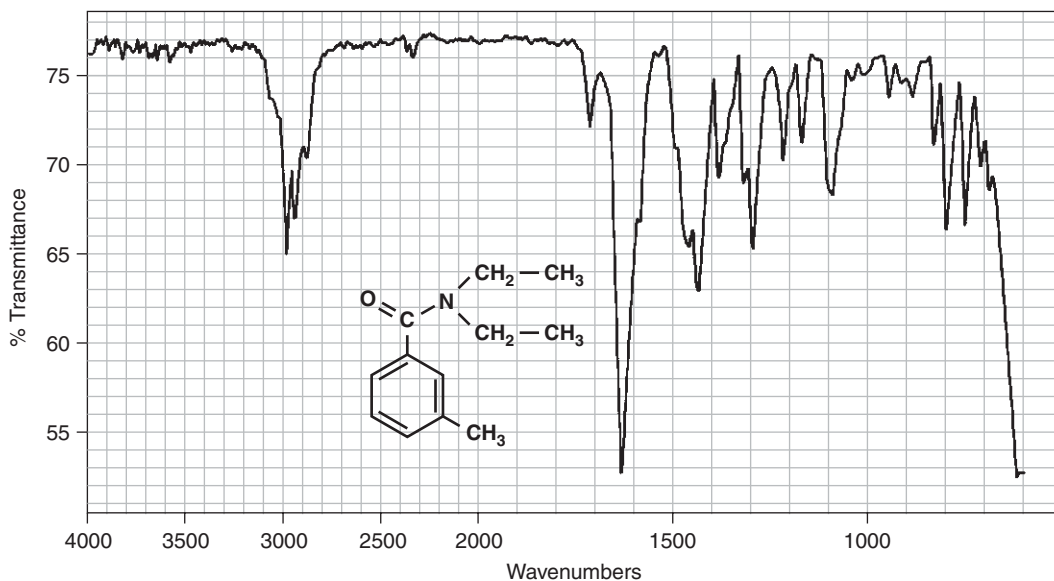
Figure 1. Infrared spectrum of *N,N*-diethyl-*m*-toluamide (neat).
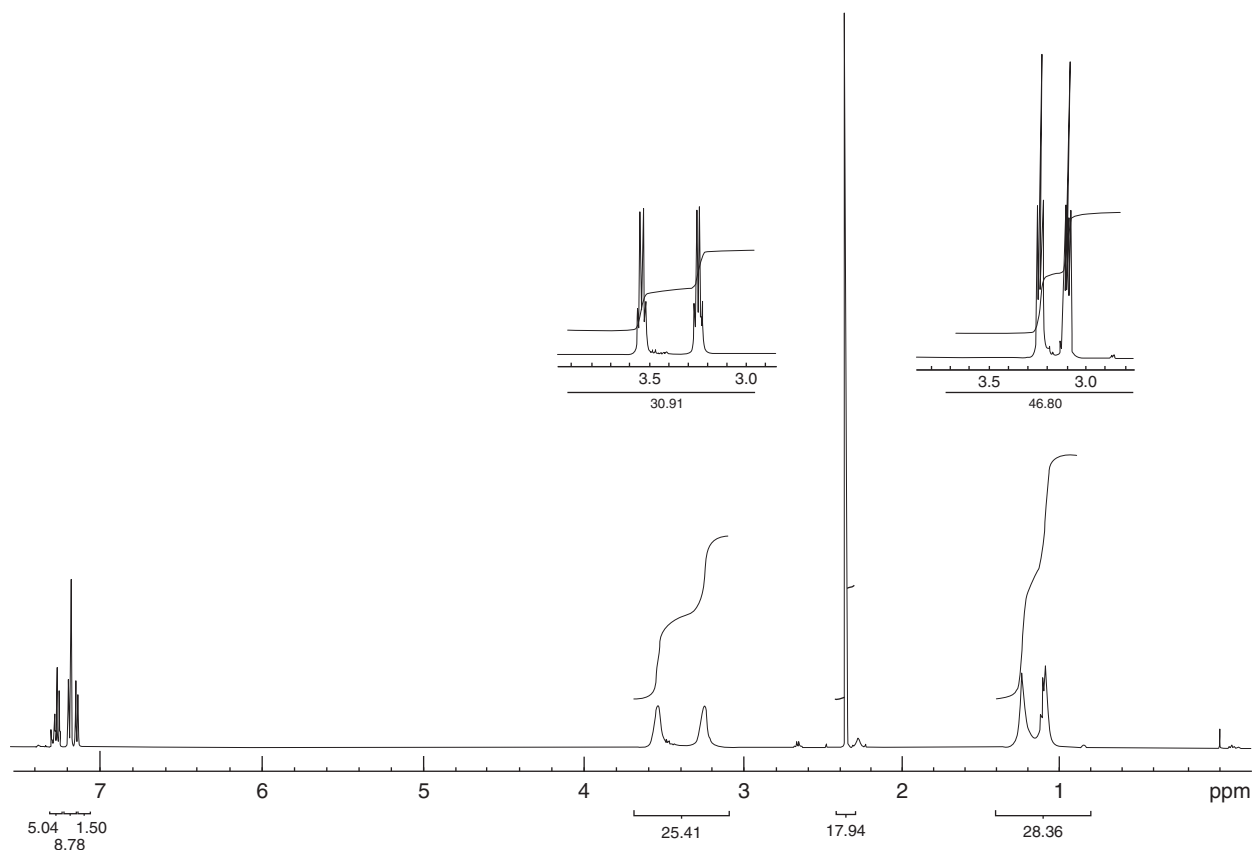
Figure 2. 500 MHz ^{1}H NMR spectrum of *N-N*-diethyl-*m*-toluamide (CDCl$_3$) at 20°C (full spectrum, lower trace) and at 0°C (inset spectrum).

REFERENCE

Knoess, H. P.; Neeland, E. G. A Modified Synthesis of the Insect Repellent DEET. *J. Chem. Educ.* **1998,** *75* (Oct), 1267–78.

QUESTIONS

1. Write an equation that describes the reaction of thionyl chloride with water.

2. What reaction would take place if the acid chloride of *m*-toluic acid were mixed with water?

3. It may be possible that some *m*-toluic acid may remain unreacted or may have formed from the hydrolysis of the acid chloride during the course of the reaction. Explain how the sodium hydroxide mixture removes unreacted carboxylic acid from the mixture. Give an equation with your answer.

4. Write a mechanism for each step in the preparation of *N,N*-diethyl-*m*-toluamide.

5. Interpret each of the principal peaks in the infrared spectrum of *N-N*-diethyl-*m*-toluamide.

Sulfa Drugs

The history of chemotherapy extends as far back as 1909 when Paul Ehrlich first used the term. Although Ehrlich's original definition of chemotherapy was limited, he is recognized as one of the giants of medicinal chemistry. **Chemotherapy** might be defined as "the treatment of disease by chemical reagents." It is preferable that these chemical reagents exhibit a toxicity toward only the pathogenic organism and not toward both the organism and the host. A chemotherapeutic agent is most useful if it does not poison the patient at the same time that it cures the patient's disease!

In 1932, the German dye manufacturing firm I. G. Farbenindustrie patented a new drug, Prontosil. Prontosil is a red azo dye, and it was first prepared for its dye properties. Remarkably, it was discovered that Prontosil showed antibacterial action when it was used to dye wool. This discovery led to studies of Prontosil as a drug capable of inhibiting the growth of bacteria. The following year, Prontosil was successfully used against staphylococcal septicemia, a blood infection. In 1935, Gerhard Domagk published the results of his research, which indicated that Prontosil was capable of curing streptococcal infections in mice and rabbits. Prontosil was shown to be active against a wide variety of bacteria in later work. This important discovery, which paved the way for a tremendous amount of research on the chemotherapy of bacterial infections, earned Domagk the 1939 Nobel Prize in medicine, but an order from Hitler prevented Domagk from accepting the honor.

Prontosil   **Sulfanilamide**
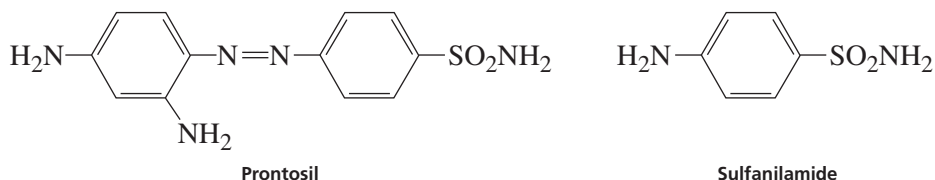
Prontosil is an effective antibacterial substance **in vivo**, that is, when injected into a living animal. Prontosil is not medicinally active when the drug is tested **in vitro**, that is, on a bacterial culture grown in the laboratory. In 1935, the research group at the Pasteur Institute in Paris headed by J. Tréfouël learned that Prontosil is metabolized in animals to **sulfanilamide**. Sulfanilamide had been known since 1908. Experiments with sulfanilamide showed that it had the same action as Prontosil in vivo and that it was also active in vitro, where Prontosil was known to be inactive. It was concluded that the active portion of the Prontosil molecule was the sulfanilamide moiety. This discovery led to an explosion of interest in sulfonamide derivatives. Well over a thousand sulfonamide substances were prepared within a few years of these discoveries.

Sulfadiazine   **Sulfaguanidine**

H_2N — benzene ring — SO_2NH — pyridine (N)

Sulfapyridine

H_2N — benzene ring — SO_2NH — thiazole (N, S)

Sulfathiazole

H_2N — benzene ring — SO_2NH — isoxazole (O, N) with H_3C and CH_3

Sulfisoxazole
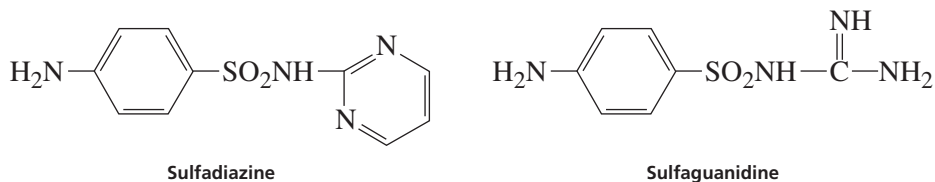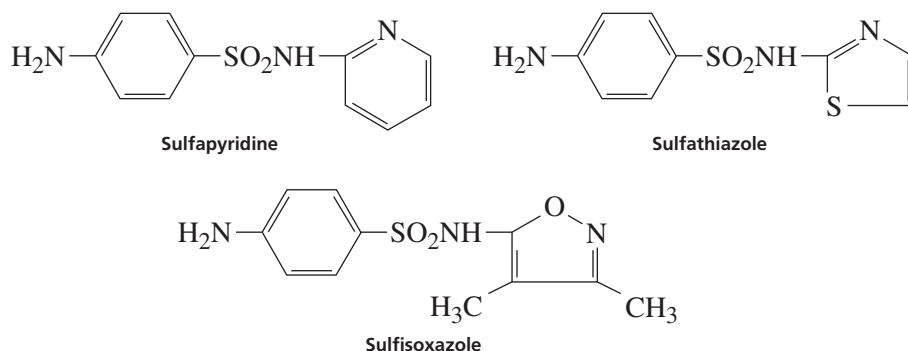
Although many sulfonamide compounds were prepared, only a relative few showed useful antibacterial properties. As the first useful antibacterial drugs, these few medicinally active sulfonamides, or **sulfa drugs**, became the wonder drugs of their day. An antibacterial drug may be either **bacteriostatic** or **bactericidal**. A bacteriostatic drug suppresses the growth of bacteria; a bactericidal drug kills bacteria. Strictly speaking, the sulfa drugs are bacteriostatic. The structures of some of the most common sulfa drugs are shown here. These more complex sulfa drugs have various important applications. Although they do not have the simple structure characteristic of sulfanilamide, they tend to be less toxic than the simpler compound.

Sulfa drugs began to lose their importance as generalized antibacterial agents when production of antibiotics in large quantity began. In 1929, Sir Alexander Fleming made his famous discovery of **penicillin**. In 1941, penicillin was first used successfully to treat humans. Since that time, the study of antibiotics has spread to molecules that bear little or no structural similarity to the sulfonamides. Besides penicillin derivatives, antibiotics that are derivatives of **tetracycline**, including Aureomycin and Terramycin, were also discovered. These newer antibiotics have high activity against bacteria, and they do not usually have the severe unpleasant side effects of many of the sulfa drugs. Nevertheless, the sulfa drugs are still widely used in treating malaria, tuberculosis, leprosy, meningitis, pneumonia, scarlet fever, plague, respiratory infections, and infections of the intestinal and urinary tracts.

Penicillin G

Tetracycline
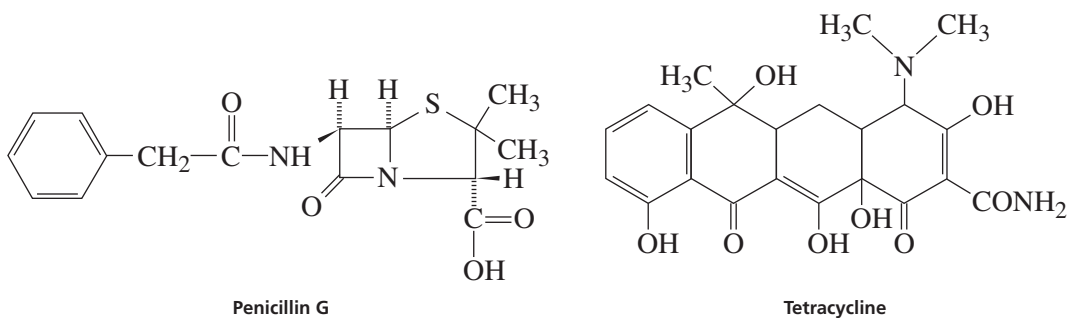
Even though the importance of sulfa drugs has declined, studies of how these materials act provide very interesting insights into how chemotherapeutic substances might behave. In 1940, Woods and Fildes discovered that *p*-aminobenzoic acid (PABA) inhibits the action of sulfanilamide. They concluded that sulfanilamide and PABA, because of their structural similarity, must compete with each other within the organism even though they cannot carry out the same chemical function. Further studies indicated that sulfanilamide does not kill bacteria, but inhibits their

growth. In order to grow, bacteria require an enzyme-catalyzed reaction that uses **folic acid** as a cofactor. Bacteria synthesize folic acid, using PABA as one of the components. When sulfanilamide is introduced into the bacterial cell, it competes with PABA for the active site of the enzyme that carries out the incorporation of PABA into the molecule of folic acid. Because sulfanilamide and PABA compete for an active site due to their structural similarity and because sulfanilamide cannot carry out the chemical transformations characteristic of PABA once it has formed a complex with the enzyme, sulfanilamide is called a **competitive inhibitor** of the enzyme. The enzyme, once it has formed a complex with sulfanilamide, is incapable of catalyzing the reaction required for the synthesis of folic acid. Without folic acid, the bacteria cannot synthesize the nucleic acids required for growth. As a result, bacterial growth is arrested until the body's immune system can respond and kill the bacteria.

One might well ask the question, "Why, when someone takes sulfanilamide as a drug, doesn't it inhibit the growth of *all* cells, bacterial and human alike?" The answer is simple. Animal cells cannot synthesize folic acid. Folic acid must be a part of the diet of animals and is therefore an essential vitamin. Because animal cells receive their fully synthesized folic acid molecules through the diet, only the bacterial cells are affected by the sulfanilamide and only their growth is inhibited.

For most drugs, a detailed picture of their mechanism of action is unavailable. The sulfa drugs, however, provide a rare example from which we can theorize how other therapeutic agents carry out their medicinal activity.

$$H_2N - \underset{\substack{\\ \textbf{\textit{p}-Aminobenzoic acid} \\ \textbf{(PABA)}}}{\bigcirc} - \overset{\overset{O}{\parallel}}{C} - OH$$

PABA residue
(Folic acid)
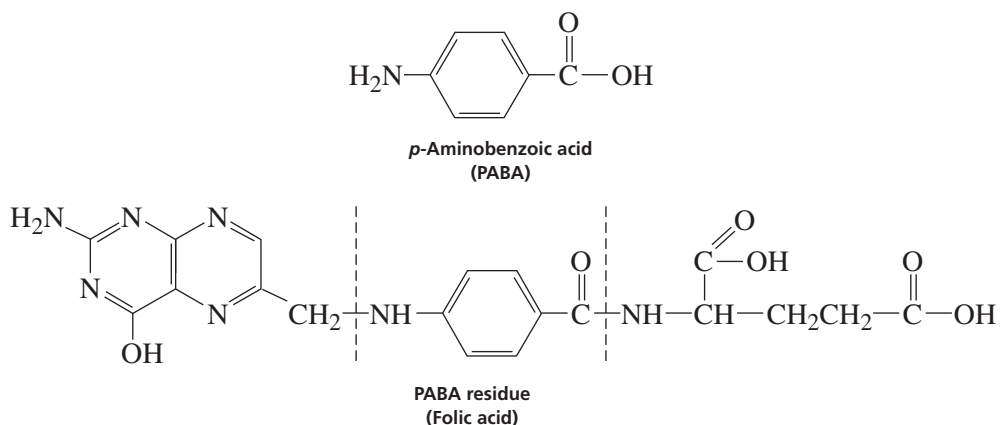
R E F E R E N C E S

Amundsen, L. H. Sulfanilamide and Related Chemotherapeutic Agents. *J. Chem. Educ.* **1942,** *19,* 167.

Evans, R. M. *The Chemistry of Antibiotics Used in Medicine*; Pergamon Press: London, 1965.

Fieser, L. F.; Fieser, M. Chemotherapy. *In Topics in Organic Chemistry*; Reinhold: New York, 1963.

Garrod, L. P.; O'Grady, F. *Antibiotics and Chemotherapy*; E. and S. Livingstone, Ltd.: Edinburgh, 1968.

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Sementsov, A. The Medical Heritage from Dyes. *Chemistry* **1966,** *39* (Nov), 20.

Zahner, H.; Mass, W. K. *Biology of Antibiotics*; Springer-Verlag: Berlin, 1972.

Sulfa Drugs: Preparation of Sulfanilamide

Crystallization

Protecting groups

Testing the action of drugs on bacteria

Preparation of a sulfonamide

Aromatic substitution

In this experiment, you will prepare the sulfa drug sulfanilamide by the following synthetic scheme. The synthesis involves converting acetanilide to the intermediate *p*-acetamidobenzenesulfonyl chloride in step 1. This intermediate is converted to sulfanilamide by way of *p*-acetamidobenzenesulfonamide in step 2.
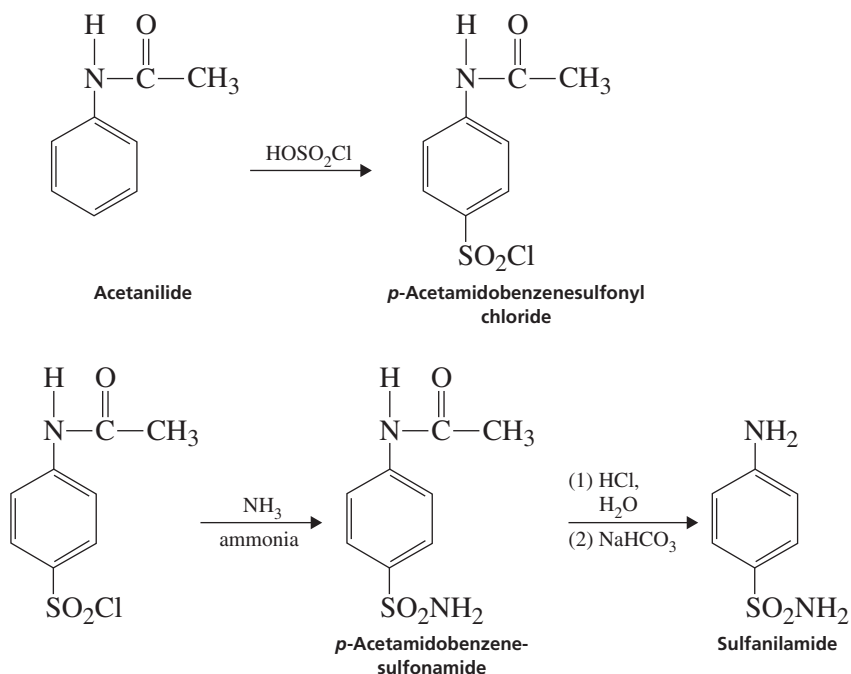
Acetanilide, which can easily be prepared from aniline, is allowed to react with chlorosulfonic acid to yield *p*-acetamidobenzenesulfonyl chloride. The acetamido group directs substitution almost totally to the *para* position. The reaction is an example of an electrophilic aromatic substitution reaction. Two problems would result if aniline itself were used in the reaction. First, the amino group in aniline would be protonated in strong acid to become a *meta* director; and, second, the chlorosulfonic acid would react with the amino group rather than with the ring, to give C_6H_5—$NHSO_3H$. For these reasons, the amino group has been "protected" by acetylation. The acetyl group will be removed in the final step, after it is no longer needed, to regenerate the free amino group present in sulfanilamide.

p-Acetamidobenzenesulfonyl chloride is isolated by adding the reaction mixture to ice water, which decomposes the excess chlorosulfonic acid. This

intermediate is fairly stable in water; nevertheless, it is converted slowly to the corresponding sulfonic acid (Ar — SO_3H). Thus, it should be isolated as soon as possible from the aqueous medium by filtration.

p-Acetamidobenzenesulfonyl chloride → *p*-Acetamidobenzenesulfonic acid + HCl
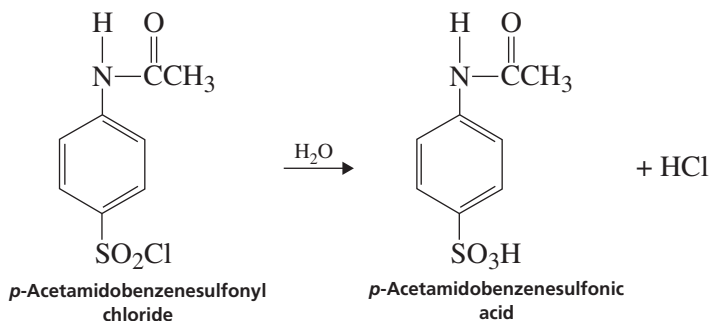
The intermediate sulfonyl chloride is converted to *p*-acetamidobenzenesulfon-amide by a reaction with aqueous ammonia (step 2). Excess ammonia neutralizes the hydrogen chloride produced. The only side reaction is the hydrolysis of the sul-fonyl chloride to *p*-acetamidobenzenesulfonic acid.

The protecting acetyl group is removed by acid-catalyzed hydrolysis to gener-ate the hydrochloride salt of the product, sulfanilamide. Note that of the two amide linkages present, only the carboxylic acid amide (acetamido group) was cleaved, not the sulfonic acid amide (sulfonamide). The salt of the sulfa drug is converted to sulfanilamide when the base, sodium bicarbonate, is added.
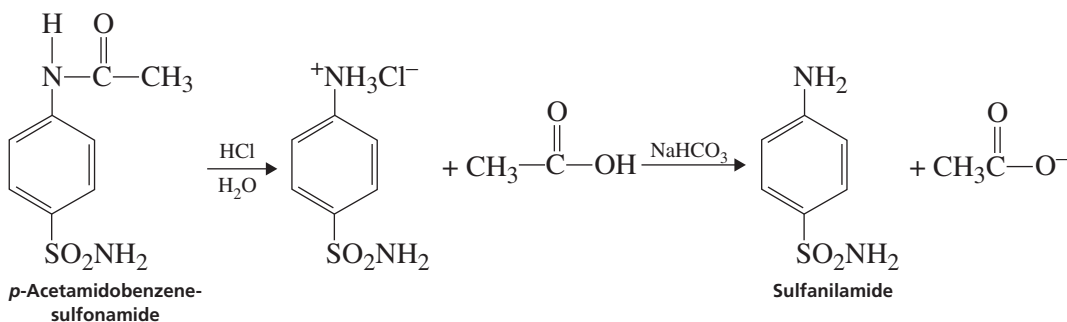
p-Acetamidobenzene-sulfonamide → Sulfanilamide

REQUIRED READING

Review:	*Technique 7	Reaction Methods, Sections 7.2 and 7.8A
	*Technique 8	Filtration, Section 8.3
	*Technique 11	Crystallization: Purification of Solids, Section 11.3
	Technique 25	Infrared Spectroscopy, Sections 25.4 and 25.5
New:	Essay	Sulfa Drugs

SPECIAL INSTRUCTIONS

If possible, all of this experiment should be completed in a fume hood. Otherwise, a hood must be used where indicated in the procedure.

Chlorosulfonic acid must be handled with care because it is a corrosive liquid and reacts violently with water. Be very careful when washing any glassware that has come in contact with chlorosulfonic acid. Even a small amount of the acid will react vigorously with water.

The *p*-acetamidobenzenesulfonyl chloride should be used during the same laboratory period in which it is prepared. It is unstable and will not survive a long storage period. The sulfa drug may be tested on several kinds of bacteria (see Instructor's Manual).

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous filtrates in the container for aqueous waste. Place organic wastes in the nonhalogenated organic waste container. Place the glass wool that has been moistened with 0.1 *M* sodium hydroxide into the container designated for this material.

PROCEDURE

Part A. *p*-Acetamidobenzene-sulfonyl Chloride

The Reaction Apparatus. Assemble the apparatus as shown in the figure. Prepare the sidearm test tube for use as a gas trap by packing the tube loosely with dry glass wool wrapped around the glass tube. Add about 2.5 mL of 0.1 *M* sodium hydroxide dropwise to the glass wool until it is moistened but not soaked. This apparatus will capture any hydrogen chloride that is evolved in the reaction. Attach the Erlenmeyer flask after the acetanilide and chlorosulfonic acid have been added, as directed in the following paragraph.

Reaction of Acetanilide with Chlorosulfonic Acid. Place 1.80 g of acetanilide in the *dry* 50-mL Erlenmeyer flask. Melt the acetanilide (mp 113°C) by heating the flask gently with a flame. Remove the flask from the heat and swirl the heavy oil so that it is deposited uniformly on the lower wall and bottom of the flask. Allow the flask to cool to room temperature and then cool it further in an ice-water bath. Keep the flask in the ice bath until you are instructed to remove it.

> ⚠
> **C A U T I O N**
>
> **Chlorosulfonic acid is an extremely noxious and corrosive chemical and should be handled with care. Use only dry glassware with this reagent. Should the chlorosulfonic acid be spilled on your skin, wash it off immediately with water. Be very careful when washing any glassware that has come in contact with chlorosulfonic acid. Even a small amount of the acid will react vigorously with water and may splatter. Wear safety glasses.**

In a hood, transfer 5.0 mL of chlorosulfonic acid, $ClSO_2OH$ (*MW* = 116.5, *d* = 1.77 g/mL), to the acetanilide in the flask. Attach the trap to the flask at your laboratory bench, remove the flask from the ice bath, and swirl it. Hydrogen chloride gas is evolved vigorously, so be certain that the rubber stopper is securely placed in the neck of the flask. The reaction mixture usually will not have to be cooled. If the reaction becomes too vigorous, however, slight cooling may be necessary. After 10 minutes, the reaction should have subsided and only a small amount of acetanilide should remain. Heat the flask for an additional 10 minutes on the steam bath or in a hot-water bath at 70°C to complete the reaction (continue to use the trap). After this time, remove the trap assembly and cool the flask in an ice bath.
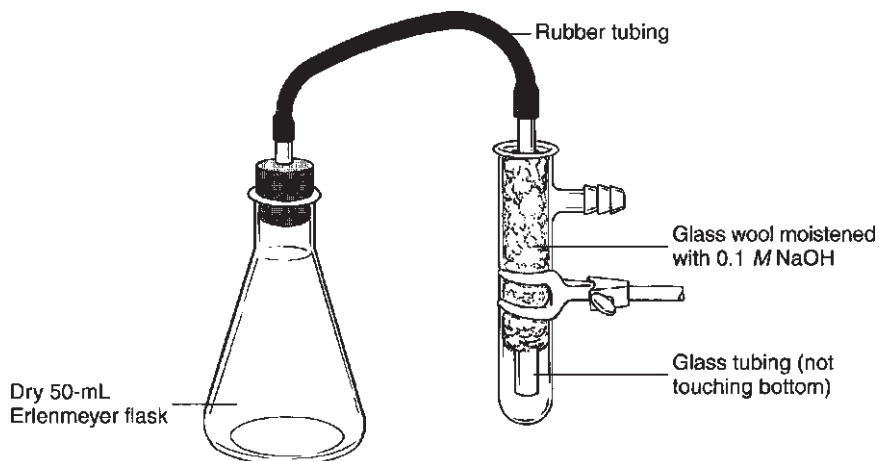
Apparatus for making *p*-acetamidobenzenesulfonyl chloride.

Isolation of *p*-Acetamidobenzenesulfonyl Chloride. The operations described in this paragraph should be conducted as rapidly as possible because the *p*-acetamidobenzenesulfonyl chloride reacts with water. Add 30 g of crushed ice to a 250-mL beaker. In a hood, transfer the cooled reaction mixture slowly (it may splatter somewhat) with a Pasteur pipet onto the ice while stirring the mixture with a glass stirring rod. (The remaining operations in this paragraph may be completed at your laboratory bench.) Rinse the flask with 5 mL of cold water and transfer the contents to the beaker containing the ice. Stir the precipitate to break up the lumps and then filter the *p*-acetamidobenzenesulfonyl chloride on a Büchner funnel (See Technique 8, Section 8.3, and Figure 8.5). Rinse the flask and beaker with two 5-mL portions of ice water. Use the rinse water to wash the crude product on the funnel. Do not stop here. Convert the solid into *p*-acetamidobenzenesulfonamide in the same laboratory period.

Part B. Sulfanilamide

Preparation of *p*-Acetamidobenzenesulfonamide. In a hood, prepare a hot-water bath at 70°C using a 250-mL beaker. Place the crude *p*-acetamidobenzenesulfonyl chloride into a 50-mL Erlenmeyer flask and add 11 mL of dilute ammonium hydroxide solution.[1] Stir the mixture well with a stirring rod to break up the lumps. Heat the mixture in the hot-water bath for 10 minutes, stirring occasionally. Allow the flask to cool to the touch and place it in an ice-water bath for several minutes. The remainder of this experiment may be completed at your laboratory bench. Collect the *p*-acetamidobenzenesulfonamide on a Büchner funnel and rinse the flask and product with about 10 mL of ice water. You may stop here.

Hydrolysis of *p*-Acetamidobenzenesulfonamide. Transfer the solid into a 25-mL round-bottom flask and add 5.3 mL of dilute hydrochloric acid solution and a boiling stone.[2] Attach a reflux condenser to the flask. Using a heating mantle, heat the mixture under reflux until the solid has dissolved (about 10 minutes) and then reflux for an additional 5 minutes. Allow the mixture to cool to room temperature. If a solid (unreacted starting material) appears, bring the mixture to a boil again for several minutes. When the flask has cooled to room temperature, no further solids should appear.

Isolation of Sulfanilamide. With a Pasteur pipet, transfer the solution to a 100-mL beaker. While stirring with a glass rod, cautiously add dropwise a slurry of 5 g of sodium bicarbonate in about 10 mL of water to the mixture in the beaker. Foaming will occur after each addition of the bicarbonate mixture because of carbon dioxide evolution. Allow gas evolution to cease

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[1]Solution prepared by mixing 110 mL of concentrated ammonium hydroxide with 110 mL of water.
[2]Solution prepared by mixing 70 mL of water with 36 mL of concentrated hydrochloric acid.
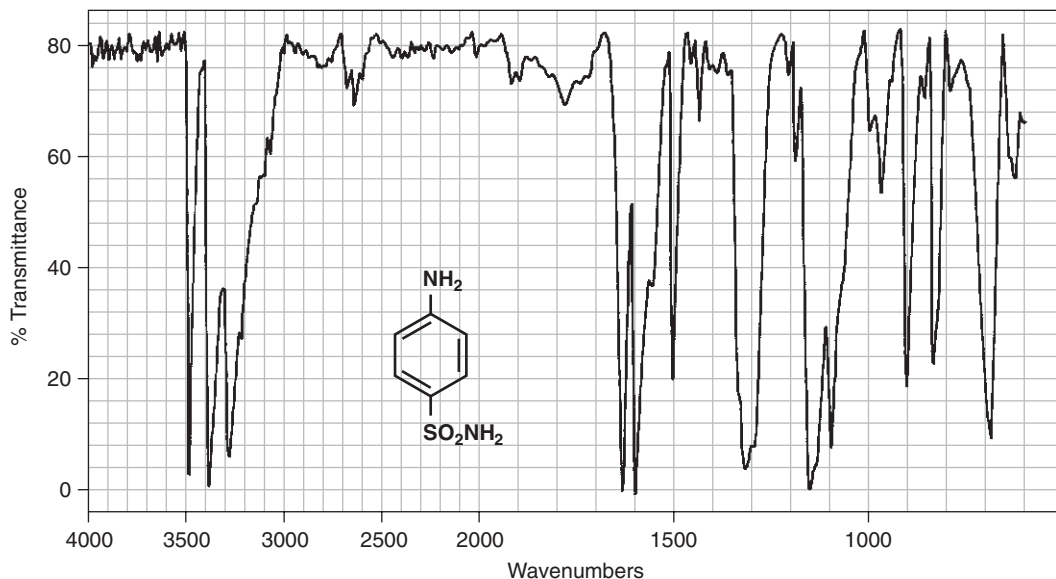
Infrared spectrum of sulfanilamide, KBr.

before making the next addition. Eventually, sulfanilamide will begin to precipitate. At this point, begin to check the pH of the solution. Add the aqueous sodium bicarbonate until the pH of the solution is between 4 and 6. Cool the mixture thoroughly in an ice-water bath. Collect the sulfanilamide on a Büchner funnel and rinse the beaker and solid with about 5 mL of cold water. Allow the solid to air-dry on the Büchner funnel for several minutes using suction.

Crystallization of Sulfanilamide. Weigh the crude product and crystallize it from hot water, using about 10–12 mL water per gram of crude product. Allow the purified product to dry until the next laboratory period.

Yield Calculation, Melting Point, and Infrared Spectrum. Weigh the dry sulfanilamide and calculate the percentage yield ($MW = 172.2$). Determine the melting point (pure sulfanilamide melts at 163–164°C). At the option of the instructor, obtain the infrared spectrum using the dry-film method (See Technique 25, Section 25.4) or as a KBr pellet (see Technique 25, Section 25.5). Compare your infrared spectrum with the one reproduced here. Submit the sulfanilamide to the instructor in a labeled vial or save it for the tests with bacteria (see Instructor's Manual).

QUESTIONS

1. Write an equation showing how excess chlorosulfonic acid is decomposed in water.

2. In the preparation of sulfanilamide, why was aqueous sodium bicarbonate, rather than aqueous sodium hydroxide, used to neutralize the solution in the final step?

3. At first glance, it might seem possible to prepare sulfanilamide from sulfanilic acid by the set of reactions shown here.
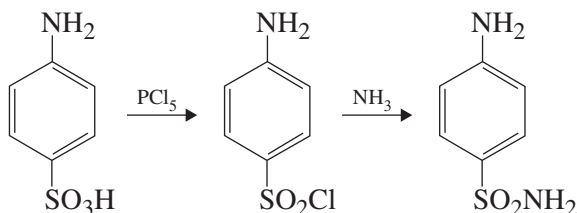
When the reaction is conducted in this way, however, a polymeric product is produced after step 1.

What is the structure of the polymer? Why does *p*-acetamidobenzenesulfonyl chloride not produce a polymer?

ESSAY

Polymers and Plastics

Chemically, plastics are composed of chainlike molecules of high molecular weight called **polymers**. Polymers have been built up from simpler chemicals called **monomers**. The word *poly* is defined as "many," *mono* means "one," and *mer* indicates "units." Thus, many monomers are combined to give a polymer. A different monomer or combination of monomers is used to manufacture each type or family of polymers. There are two broad classes of polymers: addition and condensation. Both types are described here.

Many polymers (plastics) produced in the past were of such low quality that they gained a bad reputation. The plastics industry now produces high-quality materials that are increasingly replacing metals in many applications. They are used in many products such as clothes, toys, furniture, machine components, paints, boats, automobile parts, and even artificial organs. In the automobile industry, metals have been replaced with plastics to help reduce the overall weight of cars and to help reduce corrosion. This reduction in weight helps improve gas mileage. Epoxy resins can even replace metal in engine parts.

CHEMICAL STRUCTURES OF POLYMERS

Basically, a polymer is made up of many repeating molecular units formed by sequential addition of monomer molecules to one another. Many monomer molecules of A, say 1,000 to 1 million, can be linked to form a gigantic polymeric molecule:

Many A ⟶ etc. —A-A-A-A-A—etc.   or $\left(\!A\!\right)_n$
Monomer
molecules
Polymer
molecule
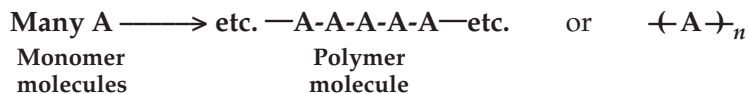
Monomers that are different can also be linked to form a polymer with an alternating structure. This type of polymer is called a **copolymer**.

Many A + many B ⟶ etc. —A-B-A-B-A-B—etc.   or $\left(\!A\text{-}B\!\right)_n$
Monomer
molecules
Polymer
molecule
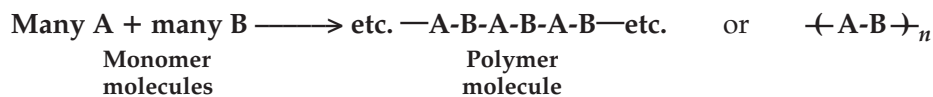
TYPES OF POLYMERS

For convenience, chemists classify polymers in several main groups, depending on the method of synthesis.

1. **Addition polymers** are formed by a reaction in which monomer units simply add to one another to form a long-chain (generally linear or branched) polymer. The monomers usually contain carbon–carbon double bonds. Examples of synthetic addition polymers include polystyrene (Styrofoam), polytetrafluoroethylene (Teflon), polyethylene, polypropylene, polyacrylonitrile (Orlon, Acrilan, Creslan), poly(vinyl chloride) (PVC), and poly(methyl methacrylate) (Lucite, Plexiglas). The process can be represented as follows:
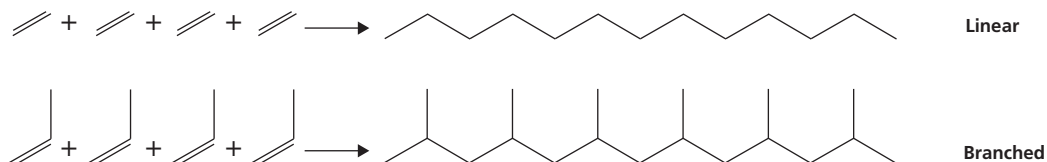
2. **Condensation polymers** are formed by the reaction of bifunctional or polyfunctional molecules, with the elimination of some small molecule (such as water, ammonia, or hydrogen chloride) as a by-product. Familiar examples of synthetic condensation polymers include polyesters (Dacron, Mylar), polyamides (nylon), polyurethanes, and epoxy resin. Natural condensation polymers include polyamino acids (protein), cellulose, and starch. The process can be represented as follows:

3. **Cross-linked polymers** are formed when long chains are linked in one gigantic, three-dimensional structure with tremendous rigidity. Addition and condensation polymers can exist with a cross-linked network, depending on the monomers used in the synthesis. Familiar examples of cross-linked polymers are Bakelite, rubber, and casting (boat) resin. The process can be represented as follows:
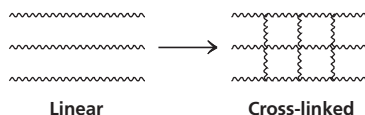
Linear and crossed-linked polymers.

THERMAL CLASSIFICATION OF POLYMERS

Industrialists and technologists often classify polymers as either thermoplastics or thermoset plastics rather than as addition or condensation polymers. This classification takes into account their thermal properties.

1. **Thermal properties of thermoplastics.** Most addition polymers and many condensation polymers can be softened (melted) by heat and re-formed (molded) into other shapes. Industrialists and technologists often refer to these types of

polymers as **thermoplastics**. Weaker, noncovalent bonds (dipole–dipole and London dispersion) are broken during the heating. Technically, thermoplastics are the materials we call plastics. Thermoplastics may be repeatedly melted and recast into new shapes. They may be recycled as long as degradation does not occur during reprocessing.

Some addition polymers, such as poly(vinyl chloride), are difficult to melt and process. Liquids with high boiling points, such as dibutyl phthalate, are added to the polymer to separate the chains from each other. These compounds are called **plasticizers**. In effect, they act as lubricants that neutralize the attractions that exist between chains. As a result, the polymer can be melted at a lower temperature to aid in processing. In addition, the polymer becomes more flexible at room temperature. By varying the amount of plasticizer, poly(vinyl chloride) can range from a very flexible, rubberlike material to a very hard substance.

$$\text{O}$$
$$\overset{\parallel}{\text{C}}\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$$

$$\overset{}{\text{C}}\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$$
$$\overset{\parallel}{\text{O}}$$

**Dibutyl
phthalate**
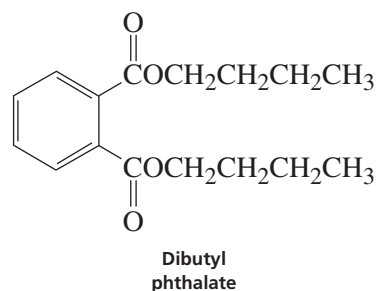
Phthalate plasticizers are volatile compounds of low molecular weight. Part of the new car smell comes from the odor of these materials as they evaporate from the vinyl upholstery. The vapor often condenses on the windshield as an oily film. After some time, the vinyl material may lose enough plasticizer to cause it to crack.

2. **Thermal properties of thermoset plastics.** Industrialists use the term **thermoset** plastics to describe materials that melt initially but on further heating become permanently hardened. Once formed, thermoset materials cannot be softened and remolded without destruction of the polymer, because covalent bonds are broken. Thermoset plastics cannot be recycled. Chemically, thermoset plastics are cross-linked polymers. They are formed when long chains are linked in one gigantic, three-dimensional structure with tremendous rigidity.

Polymers can also be classified in other ways; for example, many varieties of rubber are often referred to as *elastomers*, Dacron is a *fiber*, and poly(vinyl acetate) is an *adhesive*. The addition and condensation classifications are used in this essay.

ADDITION POLYMERS

By volume, most of the polymers prepared in industry are of the addition type. The monomers generally contain a carbon–carbon double bond. The most important example of an addition polymer is the well-known polyethylene, for which the monomer is ethylene. Countless numbers (*n*) of ethylene molecules are linked in long-chain polymeric molecules by breaking the pi bond and creating two new single bonds between the monomer units. The number of recurring units may be large or small, depending on the polymerization conditions.

Many $H_2C=CH_2$ →   etc.—C—C—C—C—etc.   or $\left(-CH_2-CH_2-\right)_n$

**Ethylene
monomer**

**Polyethylene
polymer**
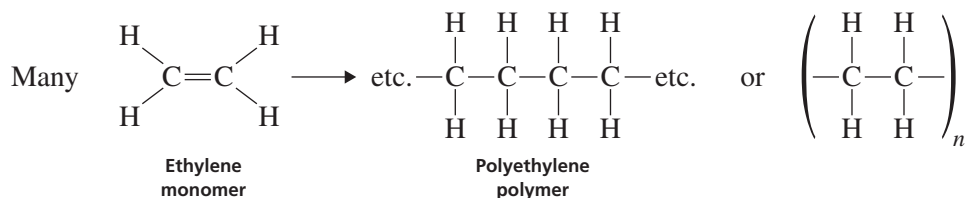
This reaction can be promoted by heat, pressure, and a chemical catalyst. The molecules produced in a typical reaction vary in the number of carbon atoms in their chains. In other words, a mixture of polymers of varying length, rather than a pure compound, is produced.

Polyethylenes with linear structures can pack together easily and are referred to as high-density polyethylenes. They are fairly rigid materials. Low-density polyethylenes consist of branched-chain molecules, with some cross-linking in the chains. They are more flexible than the high-density polyethylenes. The reaction conditions and the catalysts that produce polyethylenes of low and high density are quite different. The monomer, however, is the same in each case.

Another example of an addition polymer is polypropylene. In this case, the monomer is propylene. The polymer that results has a branched methyl on alternate carbon atoms of the chain.

Many   C=C   →   etc.—C—C—C—C—etc.   or $\left(-CH_2-CH(CH_3)-\right)_n$

**Propylene
monomer**

**Polypropylene
polymer**
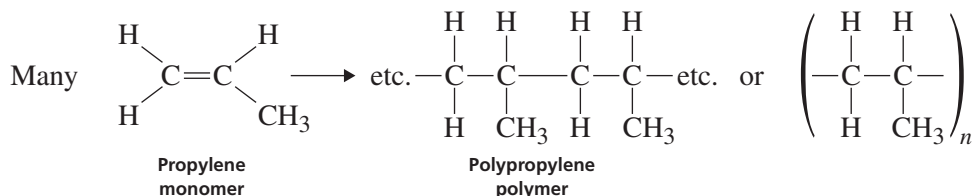
A number of common addition polymers are shown in Table 1. Some of their principal uses are also listed. The last three entries in the table all have a carbon–carbon double bond remaining after the polymer is formed. These bonds activate or participate in a further reaction to form cross-linked polymers called *elastomers*; this term is almost synonymous with *rubber*, because elastomers are materials with common characteristics.

CONDENSATION POLYMERS

Condensation polymers, for which the monomers contain more than one type of functional group, are more complex than addition polymers. In addition, most condensation polymers are copolymers made from more than one type of monomer. Recall that addition polymers, in contrast, are all prepared from substituted ethylene molecules. The single functional group in each case is one or more double bonds, and a single type of monomer is generally used.

Dacron, a polyester, can be prepared by causing a dicarboxylic acid to react with a bifunctional alcohol (a diol):

TABLE 1 Addition Polymers

Example	Monomer(s)	Polymer	Uses
Polyethylene	$CH_2{=}CH_2$	$-CH_2-CH_2-$	Most common and important polymer; bags, insulation for wires, squeeze bottles
Polypropylene	$CH_2{=}CH$ $\quad\quad\ \ CH_3$	$-CH_2-CH-$ $\quad\quad\quad\ \ CH_3$	Fibers, indoor–outdoor carpets, bottles
Polystyrene	$CH_2{=}CH$ (phenyl)	$-CH_2-CH-$ (phenyl)	Styrofoam, inexpensive house-hold goods, inexpensive molded objects
Poly(vinyl chloride) (PVC)	$CH_2{=}CH$ $\quad\quad\ \ Cl$	$-CH_2-CH-$ $\quad\quad\quad\ \ Cl$	Synthetic leather, clear bottles, floor covering, phonogroup records, water pipe
Polytetrafluoroethylene (Teflon)	$CF_2{=}CF_2$	$-CF_2-CF_2-$	Nonstick surfaces, chemically-resistant films
Poly(methyl methacrylate) (Lucite, Plexiglas)	$\quad\quad\ \ CO_2CH_3$ $CH_2{=}C$ $\quad\quad\ \ CH_3$	$\quad\quad\quad\ \ CO_2Cl$ $-CH_2-C-$ $\quad\quad\quad\ \ CH_3$	Unbreakable "glass," latex paints
Polyacrylonitrile (Orlon, Acrilan, Creslan)	$CH_2{=}CH$ $\quad\quad\ \ CN$	$-CH_2-CH-$ $\quad\quad\quad\ \ CN$	Fiber used in sweaters, blankets, carpets
Poly(vinyl acetate) (PVA)	$CH_2{=}CH$ $\quad\quad\ \ OCCH_3$ $\quad\quad\ \ \overset{\|}{O}$	$-CH_2-CH-$ $\quad\quad\quad\ \ OCCH_3$ $\quad\quad\quad\ \ \overset{\|}{O}$	Adhesives, latex paints, chewing gum, textile coatings
Natural rubber	$\quad\quad\quad CH_3$ $CH_2{=}CCH{=}CH_2$	$\quad\quad\quad\quad CH_3$ $-CH_2-C{=}CH-CH_2-$	Polymer cross-linked with sulfur (vulcanization)
Polychloroprene (neoprene rubber)	$\quad\quad\quad Cl$ $CH_2{=}CCH{=}CH_2$	$\quad\quad\quad\quad Cl$ $-CH_2-C{=}CH-CH_2-$	Cross-linked with ZnO; resistant to oil and gasoline
Styrene butadiene rubber (SBR)	$CH_2{=}CH$ (phenyl) $CH_2{=}CHCH{=}CH_2$	$-CH_2CH-CH_2CH{=}CHCH_2-$ (phenyl)	Cross-linked with peroxides; most common rubber; used for tires; 25% styrene, 75% butadiene

$$HO-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-\boxed{OH\ \ H}-OCH_2CH_2OH \longrightarrow$$

Terephthalic acid   **Ethylene glycol**

$$-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_2-O-\ \ + H_2O$$

Dacron
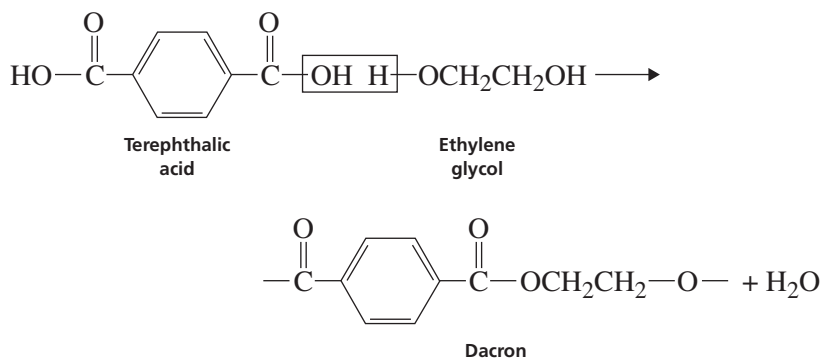
Nylon 6-6, a polyamide, can be prepared by causing a dicarboxylic acid to react with a bifunctional amine.

$$HO-\overset{\overset{\displaystyle O}{\|}}{C}(CH_2)_4\overset{\overset{\displaystyle O}{\|}}{C}-\boxed{OH\ \ H}-\overset{\overset{\displaystyle H}{|}}{N}(CH_2)_6\overset{\overset{\displaystyle H}{|}}{N}H \longrightarrow -\overset{\overset{\displaystyle O}{\|}}{C}(CH_2)_4\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{N}}(CH_2)_6\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{N}}-\ \ + H_2O$$

Adipic acid   **Hexamethylene-diamine**   **Nylon**
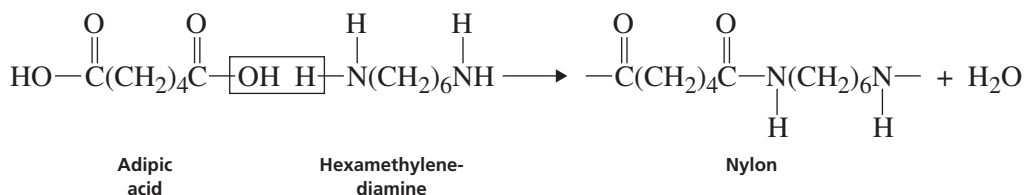
Notice, in each case, that a small molecule, water, is eliminated as a product of the reaction. Several other condensation polymers are listed in Table 2. Linear (or branched) chain polymers, as well as cross-linked polymers, are produced in condensation reactions.

The nylon structure contains the amide linkage at regular intervals:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-$$

This type of linkage is extremely important in nature because of its presence in proteins and polypeptides. Proteins are gigantic polymeric substances made up of monomer units of amino acids. They are linked by the peptide (amide) bond.

Other important natural condensation polymers are starch and cellulose. They are polymeric materials made up of the sugar monomer glucose. Another important natural condensation polymer is the DNA molecule. A DNA molecule is made up of the sugar deoxyribose linked with phosphates to form the backbone of the molecule.

Polycarbonates are another important type of condensation polymer widely used in the marketplace. Since they are a thermoplastic material, they can be easily molded into a number of different products. Polycarbonates have outstanding high-impact resistance, which make them ideal for use as "unbreakable" water bottles and food storage containers. They also have outstanding optical properties, which make them highly desirable for lenses in high-impact eyewear. Since polycarbonates have low scratch-resistance, a hard coating is usually applied to the surface of lenses. Polycarbonates have replaced glass in many applications because of their durability, clarity, breakage resistance, and light weight. Polycarbonates

TABLE 2 Condensation Polymers

Example	Monomers	Polymer	Uses
Polyamides (nylon)	$\overset{O}{\overset{\|}{HOC}}(CH_2)_n\overset{O}{\overset{\|}{COH}}$ $H_2N(CH_2)_nNH_2$	$-\overset{O}{\overset{\|}{C}}(CH_2)_n\overset{O}{\overset{\|}{C}}-NH(CH_2)_nNH-$	Fibers, molded objects
Polyesters (Dacron, Mylar, Fortrel)	$HOC\overset{O}{\|}$—(C$_6$H$_4$)—$\overset{O}{\|}$COH $HO(CH_2)_nOH$	$-C\overset{O}{\|}$—(C$_6$H$_4$)—$\overset{O}{\|}C-O(CH_2)_nO-$	Linear polyesters, fibers, recording tape
Polyesters (Glyptal resin)	phthalic anhydride $HOCH_2CHCH_2OH$, OH	cross-linked structure: $-COCH_2CHCH_2O-$	Cross-linked polyester, paints
Polyesters (casting resin)	$\overset{O}{\overset{\|}{HOC}}CH=CH\overset{O}{\overset{\|}{COH}}$ $HO(CH_2)_nOH$	$-\overset{O}{\overset{\|}{C}}CH=CH\overset{O}{\overset{\|}{C}}-O(CH_2)_nO-$	Cross-linked with styrene and peroxide; fiberglass boat resin
Phenol-formaldehyde resin (Bakelite)	phenol (OH on C$_6$H$_5$) $CH_2{=}O$	$-CH_2$—(aromatic OH ring)—CH_2—(aromatic OH ring)—CH_2- with CH_2 linkages	Mixed with fillers; molded electrical goods, adhesives, laminates, varnishes
Cellulose acetate*	glucose ring: CH_2OH, O, OH, OH CH_3COOH	glucose ring: CH_2OAc, O, OAc, OAc	Photographic film
Silicones	CH_3 $Cl-Si-Cl$ CH_3 H_2O	CH_3 $-O-Si-O-$ CH_3	Water-repellent coatings, temperature-resistant fluids and rubbers (CH_3SiCl_3 cross-links in water)
Polyurethanes	toluene diisocyanate: CH_3, $N{=}C{=}O$, $N{=}C{=}O$ $HO(CH_2)_nOH$	CH_3, $\overset{O}{\overset{\|}{NHC}}-O(CH_2)_nO-$, $NH\overset{O}{\underset{\|}{C}}-O(CH_2)_nO-$	Rigid and flexible foams, fibers

*Cellulose, a polymer of glucose, is used as the monomer.

share some characteristics with the older, more-established material, poly(methyl methacrylate); The structure of this material is shown in Table 1. However, polycarbonates are stronger and more durable than poly(methyl methacrylate), although more expensive, polycarbonates can be identified by looking for the number 7 stamped on the bottoms of containers. Category 7 is the catch-all code for "other" plastics (see Table 3).

The most common type of polycarbonate is made from bisphenol-A (BPA). One way of preparing this plastic involves the reaction of bisphenol-A and phosgene in the presence of sodium hydroxide.

Bisphenol-A   **Phosgene**   **Polycarbonate**
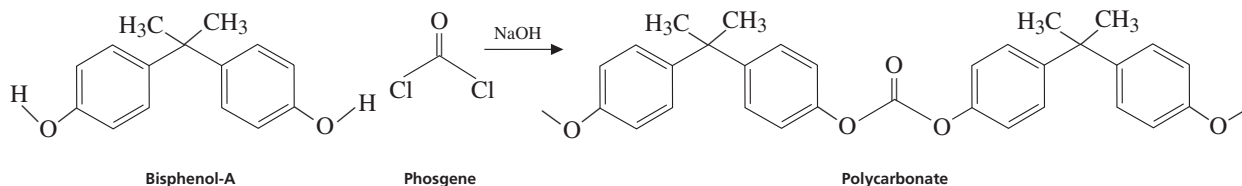
Bisphenol-A is very much in the news today. There is fear that some of this monomer may find its way into food. The major concern is possible contamination from baby bottles made of polycarbonate. The worry is that bisphenol-A may be formed from the break-down of polycarbonate used in baby bottles. If this happens, then bisphenol-A would contaminate infant formula or milk in the bottles and be ingested by babies. In the laboratory setting, bisphenol-A also appears to be released from animal cages made from waste polycarbonate. It appears when water leaches small amounts of it out of the plastic. The study suggests that bisphenol-A may be responsible for enlargement of the reproductive organs of female mice. In the past, these studies have been disputed by the chemical industry which argued that the average dose of bisphenol-A is far too low to be harmful—a finding initially supported by the Federal Drug Administration (FDA).

Recent animal studies have suggested, however, that even small doses of bisphenol-A exposure can cause a number of health risks and may mimic the female hormone estrogen. The study suggests that feminizing effects can develop in fetuses and infants. Studies reported in the *Journal of the American Medical Society* found that higher levels of bisphenol-A in adults were associated with greater incidences of diabetes and cardiovascular problems. In October 2008, the FDA found its original assessment to be flawed. In the meantime most manufactures of water bottles have changed their formulation. On April 18, 2008, Health Canada announced that bisphenol-A is "toxic to human health." Canada is the first country to make this designation. Eastman's Triton® was accepted as a suitable alternative in August 2008 by Health Canada. This material is described as a "copolyester" by the manufacturer. The alcohol components in the Triton polyesters are often mixtures of 2,2,4,4-tetramethylcyclobutane-1,4-diol and 1,4-cyclohexanedimethanol. Often the dicarboxylic acid component is terephthalic acid. Other manufactures may use some 1,3-propanediol in their polyester formulations, along with tetramethylcyclobutanediol.

Tetramethylcyclo-
butanediol   Terephthalic acid   1-4-cyclohexanedimethanol

Polyester
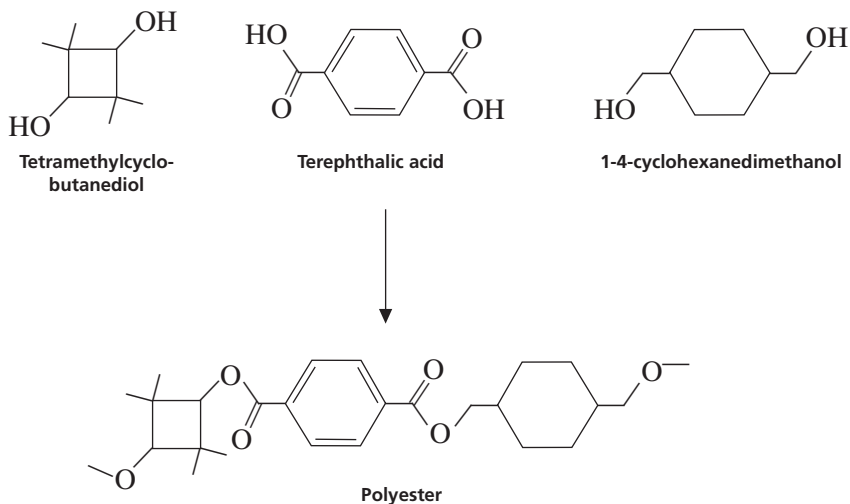
Unfortunately, bisphenol-A (BPA) is also one of the components in the most common type of epoxy resin. BPA-based epoxy resins are often applied to the inside of food and soft-drink cans in order to form a protective coating between the metal can and the food material inside. It turns out that the epoxy resins adhere readily to metal containers, and other potential substitutes do not appear to be as suitable for food-contact purposes. The Food and Drug Administration has not recommended discontinuing the use of BPA–based epoxy, at least at this time.

Ideally, we should either recycle all our wastes or not produce the waste in the first place. Plastic waste consists of about 55% polyethylene and polypropylene, 20% polystyrene, and 11% PVC. All these polymers are thermoplastics and can be recycled. They can be resoftened and remolded into new goods. Unfortunately, thermosetting plastics (crosslinked polymers) cannot be remelted. They decompose on high-temperature heating. Thus, thermosetting plastics should not be used for "disposable" purposes. To recycle plastics effectively, we must sort the materials according to the various types. The plastics industry has introduced a code system consisting of seven categories for the common plastics used in packaging. The code is conveniently stamped on the bottom of the container. Using these codes, consumers can separate the plastics into groups for recycling purposes. These codes are listed in Table 3, together with the most common uses around the home. Notice that the seventh category is a miscellaneous one, called "Other."

It is quite amazing that so few different plastics are used in packaging. The most common ones are polyethylene (low and high density), polypropylene, polystyrene, and poly(ethylene terephthlate). All of these materials can easily be recycled because they are thermoplastics. Incidently, vinyls (polyvinyl chloride) are becoming less common in packaging.

TABLE 3 Code System for Plastic Materials

Code	Polymer	Uses
1 PETE	Poly(ethylene terephthlate) (PET) —O—CH₂—CH₂—O—C⟨⟩C— with carbonyl O's	Soft-drink bottles
2 HDPE	High-density polyethylene —CH₂—CH₂—CH₂—CH₂—	Milk and beverage containers, products in squeeze bottle
3 V	Vinyl/poly(vinyl chloride) (PVC) —CH₂—CH—CH₂—CH— Cl Cl	Some shampoo containers, bottles with cleaning materials in them
4 LDPE	Low-density polyethylene —CH₂—CH₂—CH₂—CH₂— with some branches	Thin plastic bags, some plastic wrap
5 PP	Polypropylene —CH₂—CH—CH₂—CH— CH₃ CH₃	Heavy-duty, microwaveable containers used in kitchens
6 PS	Polystyrene —CH₂—CH—CH₂—CH— (phenyl) (phenyl)	Beverage/foam cups, window in envelopes
7 Other	All other resins, layered multimaterials, containers made of different materials	Some ketchup bottles, snack packs, mixtures where top differs from bottom

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47   E X P E R I M E N T   4 7

Preparation and Properties of Polymers: Polyester, Nylon, and Polystyrene

Condensation polymers

Addition polymers

Cross-linked polymers

Infrared spectroscopy

In this experiment, the syntheses of two polyesters (Experiment 47A), nylon (Experiment 47B), and polystyrene (Experiment 47C) will be described. These polymers represent important commercial plastics. They also represent the main classes of polymers: condensation (linear polyester, nylon), addition (polystyrene), and cross-linked (Glyptal polyester). Infrared spectroscopy is used in Experiment 47D to determine the structure of polymers.

R E Q U I R E D   R E A D I N G

Review:	Technique 25	Infrared Spectroscopy, Section 25B
New:	Essay	Polymers and Plastics

S P E C I A L   I N S T R U C T I O N S

Experiments 47A, 47B, and 47C all involve toxic vapors. Each experiment should be conducted in a well-ventilated hood. The styrene used in Experiment 47C irritates the skin and eyes. Avoid breathing its vapors. Styrene must be dispensed and stored in a hood. Benzoyl peroxide is flammable and may detonate on impact or on heating.

SUGGESTED WASTE DISPOSAL

The test tubes containing the polyester polymers from Experiment 47A should be placed in a box designated for disposal of these samples. The nylon from Experiment 47B should be washed thoroughly with water and placed in a waste container. The liquid wastes from Experiment 47B (nylon) should be poured into a container designated for disposal of these wastes. The polystyrene prepared in Experiment 47C should be placed in the container designated for solid wastes.

47A   EXPERIMENT 47A

Polyesters

Linear and cross-linked polyesters will be prepared in this experiment. Both are examples of condensation polymers. The linear polyester is prepared as follows:
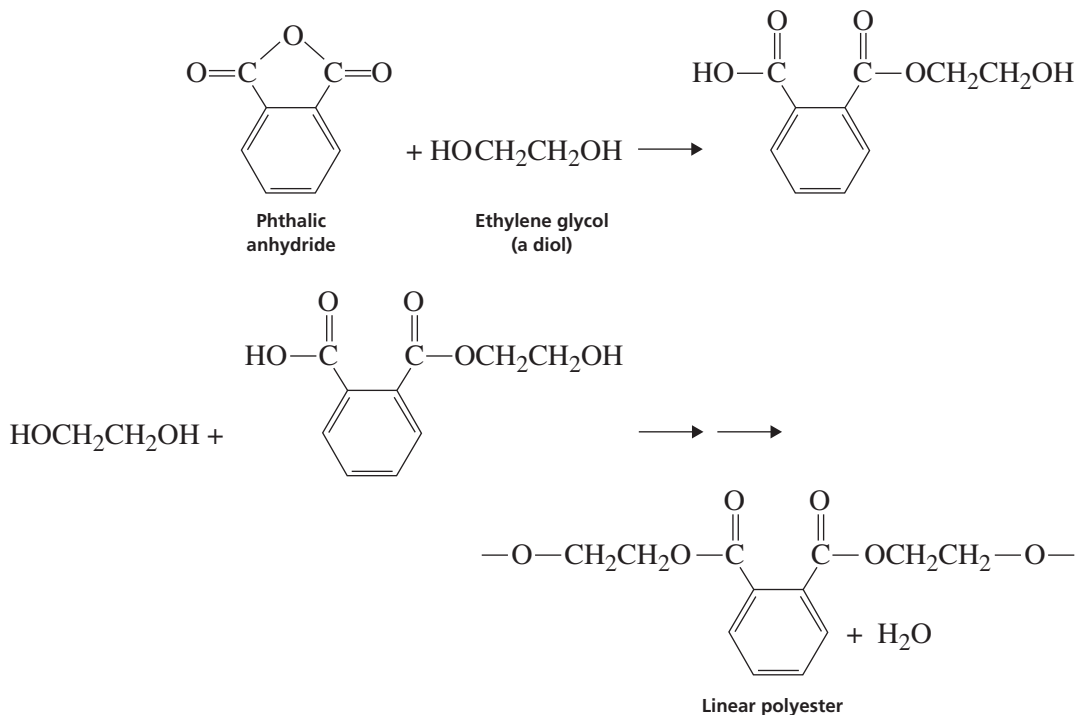
This linear polyester is isomeric with Dacron, which is prepared from terephthalic acid and ethylene glycol (see the preceding essay). Dacron and the linear polyester made in this experiment are both thermoplastics.

If more than two functional groups are present in one of the monomers, the polymer chains can be linked to one another (cross-linked) to form a three-dimensional network. Such structures are usually more rigid than linear structures and are useful in making paints and coatings. They may be classified as thermosetting plastics. The polyester Glyptal is prepared as follows:

Phthalic anhydride

Glycerol (a triol)

Cross-linked polyester (Glyptal resin)
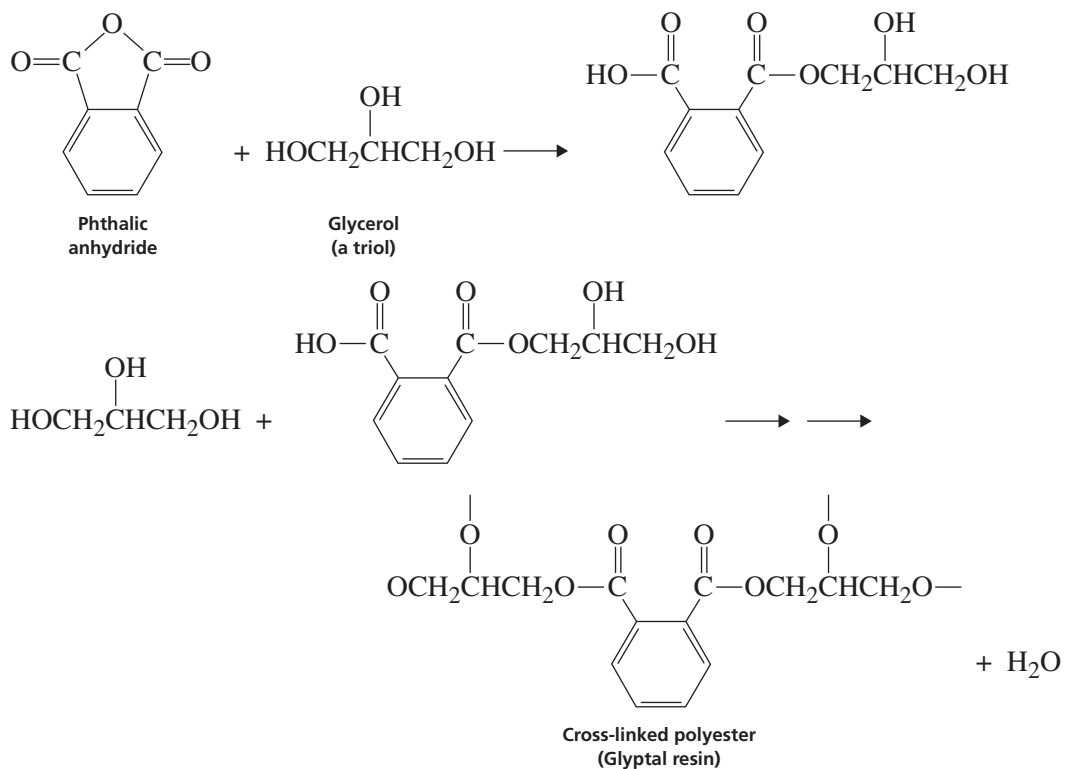
The reaction of phthalic anhydride with a diol (ethylene glycol) is described in the procedure. This linear polyester is compared with the cross-linked polyester (Glyptal) prepared from phthalic anhydride and a triol (glycerol).

PROCEDURE

Place 1 g of phthalic anhydride and 0.05 g of sodium acetate in each of two test tubes. To one tube, add 0.4 mL of ethylene glycol and to the other, add 0.4 mL of glycerol. Clamp both tubes so that they can be heated simultaneously with a flame. Heat the tubes gently until the solutions appear to boil (water is eliminated during the esterification); then continue heating for 5 minutes.

If you are performing the optional infrared analysis of the polymer, immediately save a sample of the polymer formed from ethylene glycol only. After removing a sample for infrared spectroscopy, allow the two test tubes to cool and compare the viscosity and brittleness of the two polymers. The test tubes cannot be cleaned.

Optional Exercise: Infrared Spectroscopy. Lightly coat a watch glass with stopcock grease. Pour some of the *hot* polymer from the tube containing ethylene glycol; use a wooden applicator stick to spread the polymer on the surface to create a thin film of the polymer. Remove the polymer from the watch glass and save it for Experiment 47D.

Polyamide (Nylon)

Reaction of a dicarboxylic acid, or one of its derivatives, with a diamine leads to a linear polyamide through a condensation reaction. Commercially, nylon 6–6 (so called because each monomer has six carbons) is made from adipic acid and hexamethylenediamine. In this experiment, you will use the acid chloride instead of adipic acid. The acid chloride is dissolved in cyclohexane, and this is added *carefully* to hexamethylenediamine dissolved in water. These liquids do not mix, so two layers will form. The polymer can then be drawn out continuously to form a long strand of nylon. Imagine how many molecules have been linked in this long strand! It is a fantastic number.

$$\underset{\textbf{Adipoyl chloride}}{Cl-\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}-Cl} + \underset{\textbf{Hexamethylenediamine}}{H-\overset{\displaystyle H}{\overset{|}{N}}CH_2CH_2CH_2CH_2CH_2CH_2\overset{\displaystyle H}{\overset{|}{N}}-H} \longrightarrow$$

$$\underset{\textbf{Nylon 6-6}}{-\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}-\overset{\displaystyle H}{\overset{|}{N}}CH_2CH_2CH_2CH_2CH_2CH_2\overset{\displaystyle H}{\overset{|}{N}}-}$$

Copper hook

Collapsed film

Diacid chloride in organic solvent

Polyamide film forming at interface

Diamine in water
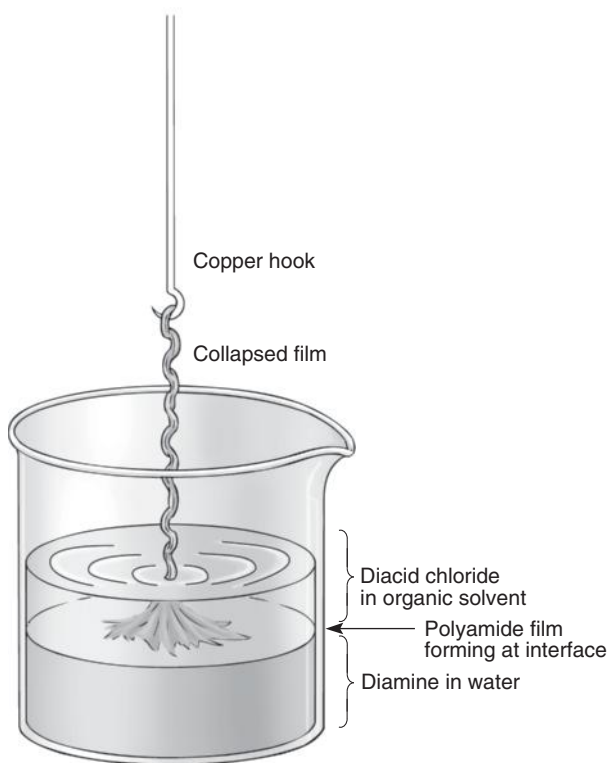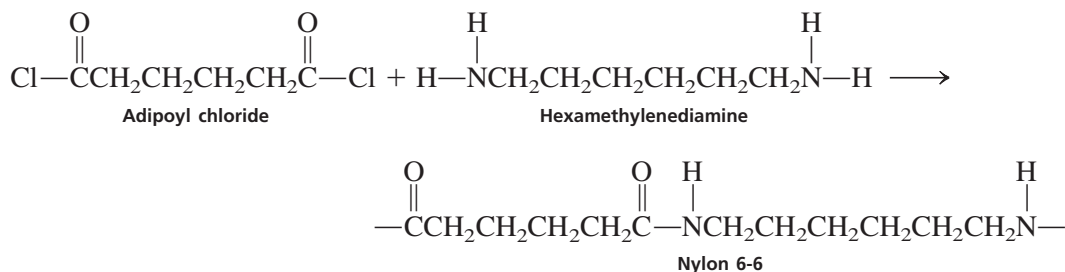
Preparation of nylon.

PROCEDURE

Pour 10 mL of a 5% aqueous solution of hexamethylenediamine (1,6-hexanediamine) into a 50-mL beaker. Add 10 drops of 20% sodium hydroxide solution. Carefully add 10 mL of a 5% solution of adipoyl chloride in cyclohexane to the solution by pouring it down the wall of the slightly tilted beaker. Two layers will form (see figure), and there will be an immediate formation of a polymer film at the liquid–liquid interface. Using a copper-wire hook (a 6-inch piece of wire bent at one end), gently free the walls of the beaker from polymer strings. Then hook the mass at the center and slowly raise the wire so that polyamide forms continuously, producing a rope that can be drawn out for many feet. The strand can be broken by pulling it faster. Rinse the rope several times with water and lay it on a paper towel to dry. With the piece of wire, vigorously stir the remainder of the two-phase system to form additional polymer. Decant the liquid and wash the polymer thoroughly with water. Allow the polymer to dry. Do not discard the nylon in the sink; use a waste container.

47C   EXPERIMENT 47C

Polystyrene

An addition polymer, polystyrene, will be prepared in this experiment. Reaction can be brought about by free-radical, cationic, or anionic catalysts (initiators), the first of these being the most common. In this experiment, polystyrene is prepared by free-radical initiated polymerization.

The reaction is initiated by a free-radical source. The initiator will be benzoyl peroxide, a relatively unstable molecule, which at 80–90°C decomposes with homolytic cleavage of the oxygen–oxygen bond:

Benzoyl peroxide   **Benzoyl radical**
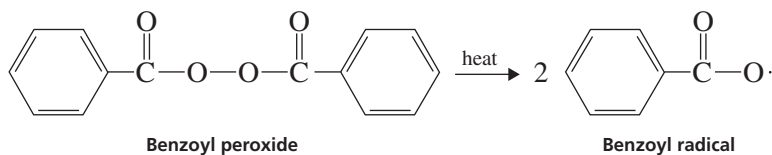
If an unsaturated monomer is present, the radical adds to it, initiating a chain reaction by producing a new free radical. If we let R stand for the initiator radical, the reaction with styrene can be represented as
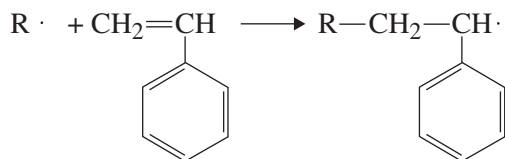
The chain continues to grow:
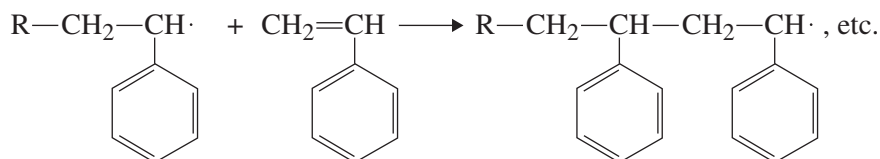
The chain can be terminated by causing two radicals to combine (either both polymer radicals or one polymer radical and one initiator radical) or by causing a hydrogen atom to become abstracted from another molecule.

PROCEDURE

Because it is difficult to clean the glassware, this experiment is best performed by the laboratory instructor. One large batch of polystyrene should be made for the entire class (at least 10 times the amounts given). After the polystyrene is prepared, a small amount will be dispensed to each student. The students will provide their own watch glass for this purpose. Perform the experiment in a hood. Place several thicknesses of newspaper in the hood.

CAUTION

Styrene vapor is very irritating to eyes, mucous membranes, and upper respiratory tract. Do not breathe the vapor and do not get it on your skin. Exposure can cause nausea and headaches. All operations with styrene must be conducted in a hood.

Benzoyl peroxide is flammable and may detonate on impact or on heating (or grinding). It should be weighed on glassine (glazed, not ordinary) paper. Clean all spills with water. Wash the glassine paper with water before discarding it.

Place 12–15 mL of styrene monomer in a 100-mL beaker and add 0.35 g of benzoyl peroxide. Heat the mixture on a hot plate until the mixture turns yellow. When the color disappears and bubbles begin to appear, immediately take the beaker of styrene off the hot plate because the reaction is exothermic (use tongs or an insulated glove). After the reaction subsides, put the beaker of styrene back on the hot plate and continue heating it until the liquid becomes very syrupy. With a stirring rod, draw out a long filament of material from the beaker. If this filament can be cleanly snapped after a few seconds of cooling, the polystyrene is ready to be poured. If the filament does not break, continue heating the mixture and repeat this process until the filament breaks easily.

If you are performing the optional infrared analysis of the polymer, immediately save a sample of the polymer. After removing a sample for infrared spectroscopy, pour the remainder of the syrupy liquid on a watch glass that has been lightly coated with stopcock grease. After being cooled, the polystyrene can be lifted from the glass surface by gently prying with a spatula.

Optional Exercise: Infrared Spectroscopy. Pour a small amount of the *hot* polymer from the beaker onto a warm watch glass (no grease) and spread the polymer with a wooden applicator stick to create a thin film of the polymer. Peel the polymer from the watch glass and save it for Experiment 47D.

Infrared Spectra of Polymer Samples

Infrared spectroscopy is an excellent technique for determining the structure of a polymer. For example, polyethylene and polypropylene have relatively simple spectra because they are saturated hydrocarbons. Polyesters have stretching frequencies associated with the C=O and C—O groups in the polymer chain. Polyamides (nylon) show absorptions that are characteristic for the C=O stretch and and N—H stretch. Polystyrene has characteristic features of a monosubstituted aromatic compound (see Technique 25, Figure 25.12). You may determine the infrared spectra of the linear polyester from Procedure 47A and polystyrene from Experiment 47C in this part of the experiment. Your instructor may ask you to analyze a sample that you bring to the laboratory or one supplied to you.

P R O C E D U R E

Mounting the Samples. Prepare cardboard mounts for your polymer samples. Cut 3 × 5-inch index cards so that they fit into the sample cell holder of your infrared spectrometer. Then cut a 0.5-inch wide × 1-inch high rectangular hole in the center of the cardstock. Attach a polymer sample on the cardboard mount with tape.

Choices of Polymer Samples. If you have completed Experiments 47A and 47C, you can obtain the spectra of your polyester or polystyrene. Alternatively, your instructor may provide you with known or unknown polymer samples for you to analyze.

Your instructor may ask you to bring a polymer sample of your own choice. If possible, these samples should be clear and as thin as possible (similar to the thickness of plastic sandwich wrap). Good choices of plastic materials include windows from envelopes, plastic sandwich wrap, sandwich bags, soft-drink bottles, milk containers, shampoo bottles, candy wrappers, and shrink-wrap. If necessary, the samples can be heated in an oven and stretched to obtain thinner samples. If you are bringing a sample cut from a plastic container, obtain the recycling code from the bottom of the container, if one is given.

Running the Infrared Spectrum. Insert the cardboard mount into the cell holder in the spectrometer so that your polymer sample is centered in the infrared beam of the instrument. Find the thinnest place in your polymer sample. Determine the infrared spectrum of your sample. Because of the thickness of your polymer sample, many absorptions are so strong that you will not be able to see individual bands. To obtain a better spectrum, try moving the sample to a new position in the beam and rerun the spectrum.

Analyzing the Infrared Spectrum. You can use the essay "Polymers and Plastics" and Technique 25 with your spectrum to help determine the structure of the polymer. Most likely, the polymers will consist of plastic materials listed in Table Three of the essay. This table lists the recycling codes for a number of household plastics used in packaging. Submit the infrared spectrum along with the structure of the polymer to your instructor. Do your spectrum and structure agree with the recycling code? Label the spectrum with the important absorption bands consistent with the structure of the polymer.

Using a Polymer Library. If your particular instrument has a polymer library, you can search the library for a match. Do this after you have made a preliminary "educated guess" as to the structure of the polymer. The library search should help confirm the structure you determined.

QUESTIONS

1. Ethylene dichloride ($ClCH_2CH_2Cl$) and sodium polysulfide (Na_2S_4) react to form a chemically resistant rubber, Thiokol A. Draw the structure of the rubber.

2. Draw the structure for the polymer produced from the monomer vinylidene chloride ($CH_2{=}CCl_2$).

3. Draw the structure of the copolymer produced from vinyl acetate and vinyl chloride. This copolymer is employed in some paints, adhesives, and paper coatings.


        Vinyl acetate   **Vinyl chloride**
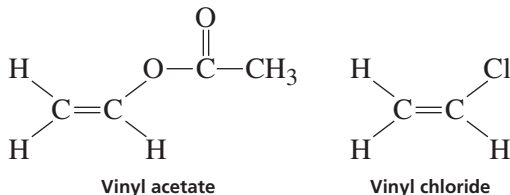
4. Isobutylene, $CH_2{=}C(CH_3)_2$, is used to prepare cold-flow rubber. Draw a structure for the addition polymer formed from this alkene.

5. Kel-F is an addition polymer with the following partial structure. What is the monomer used to prepare it?
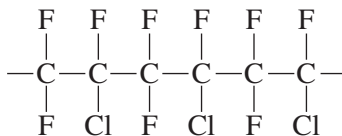
6. Maleic anhydride reacts with ethylene glycol to produce an alkyd resin. Draw the structure of the condensation polymer produced.

        Maleic anhydride
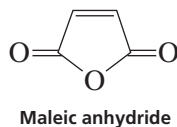
7. Kodel is a condensation polymer made from terephthalic acid and 1,4-cyclohexanedimethanol. Write the structure of the resulting polymer.

   Terephthalic acid   **1,4-Cyclohexanedimethanol**
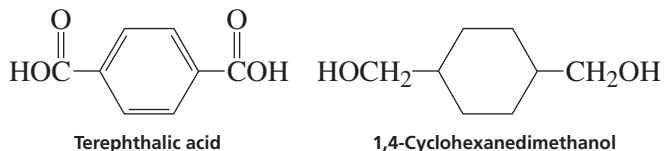
Ring-Opening Metathesis Polymerization (ROMP) using a Grubbs Catalyst: a Three-Step Synthesis of a Polymer

Green chemistry

Ruthenium-catalyzed reactions

Organometallic chemistry

Diels-Alder reaction

Synthesis of a polymer

The goal of this experiment is to prepare a polymer using a modern polymerization reaction pioneered by Robert Grubbs.[1] Grubbs' research group developed a process called Ring-Opening Metathesis Polymerization (ROMP) using well-defined catalysts. The monomers used for this reaction are often bicyclic compounds that contain some ring strain. This experiment is based upon a procedure from the chemical literature.[2] It has been adapted for use in this book.[3]

Experiment 48A. Diels-Alder Reaction of Furan and Maleic Anhydride

The first step in the synthesis of a polymer involves the Diels-Alder reaction in which furan is allowed to react with maleic anhydride. During the first laboratory period, you will mix furan with maleic anhydride in diethyl ether (ether) and allow the reaction to proceed until the next laboratory period. The Diels-Alder adduct crystallizes from the solvent. The adduct has the *exo* stereochemistry as shown (exo stereochemistry has the maleic anhydride on the same side as the oxygen atom from furan). Most Diels-Alder reactions yield products with the *endo* stereochemistry. Consult you lecture textbook for mechanistic details on this important reaction.

furan   maleic anhydride   Diels-Alder adduct   Stereochemistry
                                                              exo product
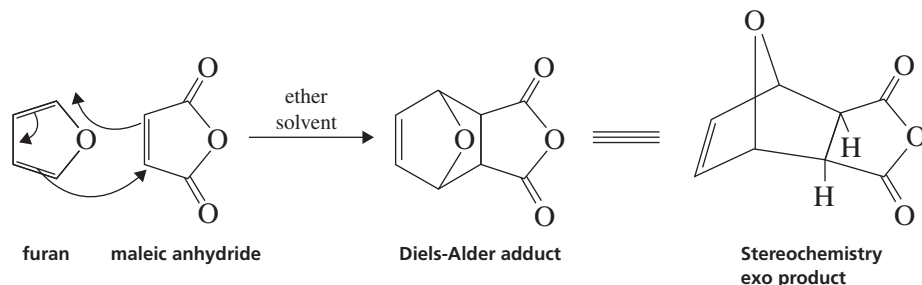
[1] Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* 1995, 34, 2039.
[2] a) France, M. B.; Alty, L. T.; Earl, T. M. *J. Chem. Ed.* **1999**, 76, 659–660.
   b) France, M. B.; Uffelman, E. S. *J. Chem. Ed.* 1999, *76*, 661–665.
[3] Experiment developed by Rumberger, S.; Lampman, G. M. Department of Chemistry, Western Washington University: Bellingham, WA 98225.

Experiment 48B. Ring opening of anhydride in methanol
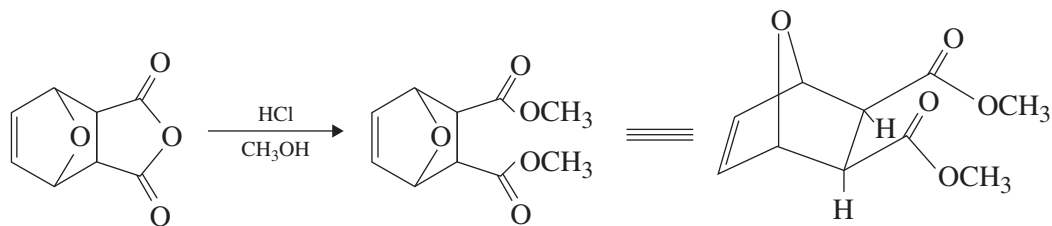
This reaction is an acid-catalyzed conversion of an anhydride in methanol to the dimethyl ester. Hydrochloric acid is used as the acid catalyst. Consult the chapter in your lecture text on reaction of derivatives of carboxylic acids for the mechanism of this reaction.

Experiment 48C. Ring-Opening Metathesis Polymerization (ROMP)

This reaction is one of the four main types of metathesis reactions described previously in Experiment 36. The others are cross-metathesis, ring-closing metathesis, and ring-opening metathesis. The ROMP polymerization reaction has important applications in industry. Polymeric products with excellent properties are prepared by this reaction. The Grubbs' catalyst is one of many catalysts that have been developed.

monomer
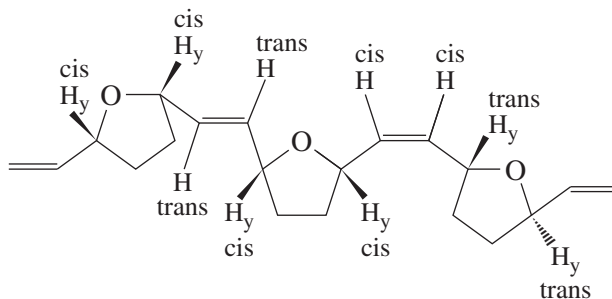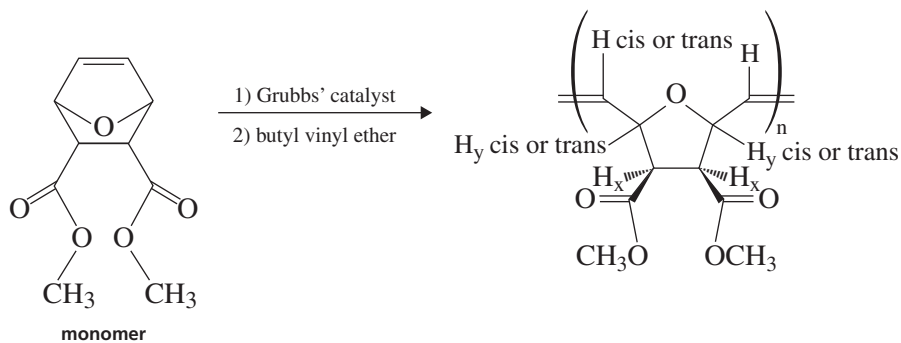
Ester groups have been omitted

Grubbs'
Generation 1
catalyst
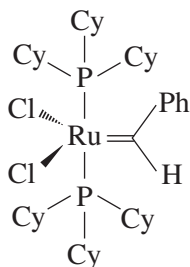
Cy = cyclohexyl

In the following mechanism, the catalyst is abbreviated as:

$$M = C$$
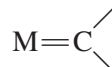
Mechanism of the ROMP polymerization using an organometallic catalyst:

1. Four-membered ring intermediate opens five-membered ring.
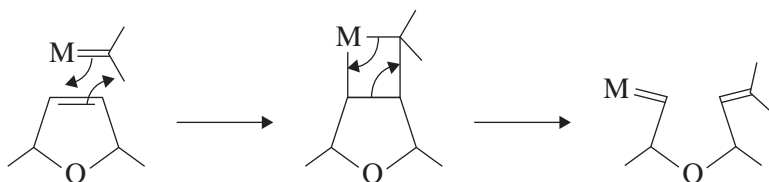
2. The reaction continues reacting with *n* molecules of starting compound. This is called ring-opening metathesis polymerization (ROMP).
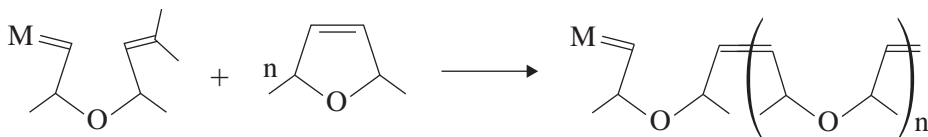
3. Butyl vinyl ether removes the metal from the end of the chain.
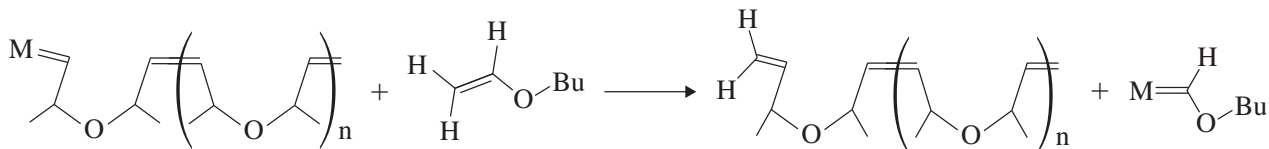
REQUIRED READING

Review: Techniques 6, *7, *8, *11, *19, 25, and 26

New: *Technique 19, Section 19.5, and Technique 21

Experiment 36 for other types of metathesis reactions

Read in your lecture textbook about the Diels-Alder reaction and also about the reactions of derivatives of carboxylic acids.

SPECIAL INSTRUCTIONS

The Grubbs' catalyst is very expensive. Take care when using it to avoid waste.

SUGGESTED WASTE DISPOSAL

Dispose of all aqueous wastes in the container for aqueous waste. Place the organic waste in the nonhalogenated organic waste container. Methylene chloride should be placed in the halogenated waste container.

NOTES TO THE INSTRUCTOR

It is suggested that students work individually to prepare the Diels-Alder adduct (Experiment 48A). For Experiment 48B and 48C, it is suggested that students work in pairs. The suggested schedule is for four laboratory periods: Part A, requires two laboratory periods; Part B, requires one laboratory period, including starting Part C. Part C, the polymer isolation, requires one period. The molecular weight determination in Part C requires a Size-Exclusion (SEC) column inserted into an HPLC instrument. However, if the HPLC instrument is not available, NMR spectroscopy will demonstrate that the polymer has been formed.

The instructor may choose to purchase the Diels-Alder adduct. In that case, start with Experiment 48B, which shortens the experiment by one period.

48A   EXPERIMENT 48A

Diels-Alder Reaction

PROCEDURE[4]

Add 1.2 g of maleic anhydride to a 125-mL Erlenmeyer flask. Using your 10-mL graduate cylinder, measure out 10 mL of anhydrous diethyl ether and add the solvent to the solid. Dissolve the solid by gently heating the mixture to to a boil on a warm hot plate (a few specks will remain undissolved). Allow the mixture to cool to room temperature and then add 1,000 μL of furan to the Erlenmeyer flask using an automatic pipet.

After adding the furan, stopper the flask and wrap Parafilm around the cork and flask to reduce evaporation. Put the flask in your drawer and allow the mixture to stand for 2 full days, or until the next laboratory period. You may choose to conduct some other laboratory work for the remainder of the laboratory period.

The Diels-Alder products should precipitate from the diethyl ether solution upon standing. Break up the solid with a spatula and vacuum filter the mixture to collect the solid. You

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[4] Palmer, D. R. J. *J. Chem. Ed.* **2004**, *81,* 1633–35.

should obtain from 30 to 50% yield of the Diels-Alder product. If necessary, additional product can be obtained by pouring the filtrate into a round-bottom flask, followed by removal of the solvent on a rotary evaporator, or by evaporation of the solvent in a hood. Purify the Diels-Alder adduct by crystallization from ethyl acetate. Refer to Technique 11, Section 11.3 for instructions on crystallizing the solid if you need a review of this procedure. Allow the solid product to dry until the next lab period in an open container in your drawer. When the solid is dry, determine the melting point and obtain the infrared spectrum of the adduct. At the option of your instructor, obtain the ^{1}H (proton) NMR spectrum or, as an alternative, interpret the spectrum shown in Figure 1 as part of your laboratory report.
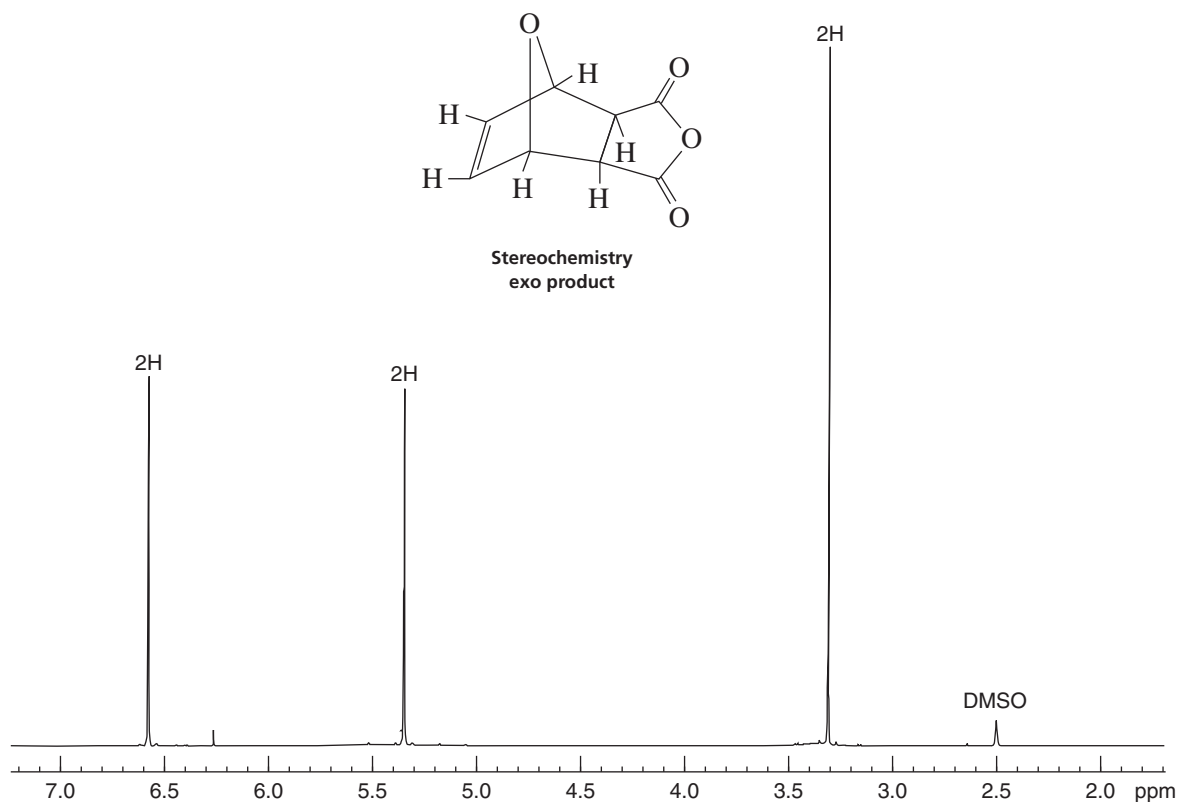
Figure 1. 500 MHz ^{1}H NMR spectrum of the Diels-Adler adduct from Experiment 48A in deuterated DMSO.

<div style="background:#808080">**48B**</div>   **E X P E R I M E N T   4 8 B**

Conversion of the Diels-Alder Adduct to the Diester

Convert some of the Diels-Alder adduct from Experiment 48A to the diester, or use material supplied to you if Experiment 48A was not assigned. This step involves an hour reflux, so start this reaction as soon as possible. *Allow enough time to start Experiment 48C during this laboratory period.*

　　Place 0.50 g of the Diels-Alder adduct in a 25-mL round-bottom flask and add 2 mL of methanol. Using a Pasteur pipet, add 2 drops of concentrated hydrochloric acid to the round-bottom flask. Swirl the reaction mixture for a few minutes. Add

several boiling stones and attach a water-cooled condenser to the flask. Reflux the mixture for 1 hour. During the reflux, the solid will dissolve as it reacts.

After the solution has refluxed for 1 hour, allow the contents of the flask to cool to room temperature; then cool the flask in an ice bath. Scratch the inside of the flask with a glass stirring rod to aid the crystallization process. Place the flask back into an ice bath for further cooling. Make sure that the product has crystallized before filtering the soild.

Set up a vacuum filtration apparatus using a Hirsch or Büchner funnel (see Technique 8, Figure 8.5) and pour the contents of the 25-mL round-bottom flask into the funnel, under vacuum. Be sure to insert a piece of filter paper into the funnel. Use your spatula to remove the solid left in the flask. The transfer process can be aided by using 1 or 2 mL of ice-cold methanol.

Dry the sample in an oven set at 90°C for about 5 or 10 minutes.[5] Weigh the product and calculate the percentage yield. Determine the melting point (the literature value is 120°C but the melting point is often low, as low as 105°C, so don't be too concerned about the melting point.) At the option of your instructor, either determine the NMR spectrum or interpret and label the proton NMR spectrum that is shown in Figure 2 as part of your laboratory report. Be sure to continue on to Experiment 48C during the same laboratory period.
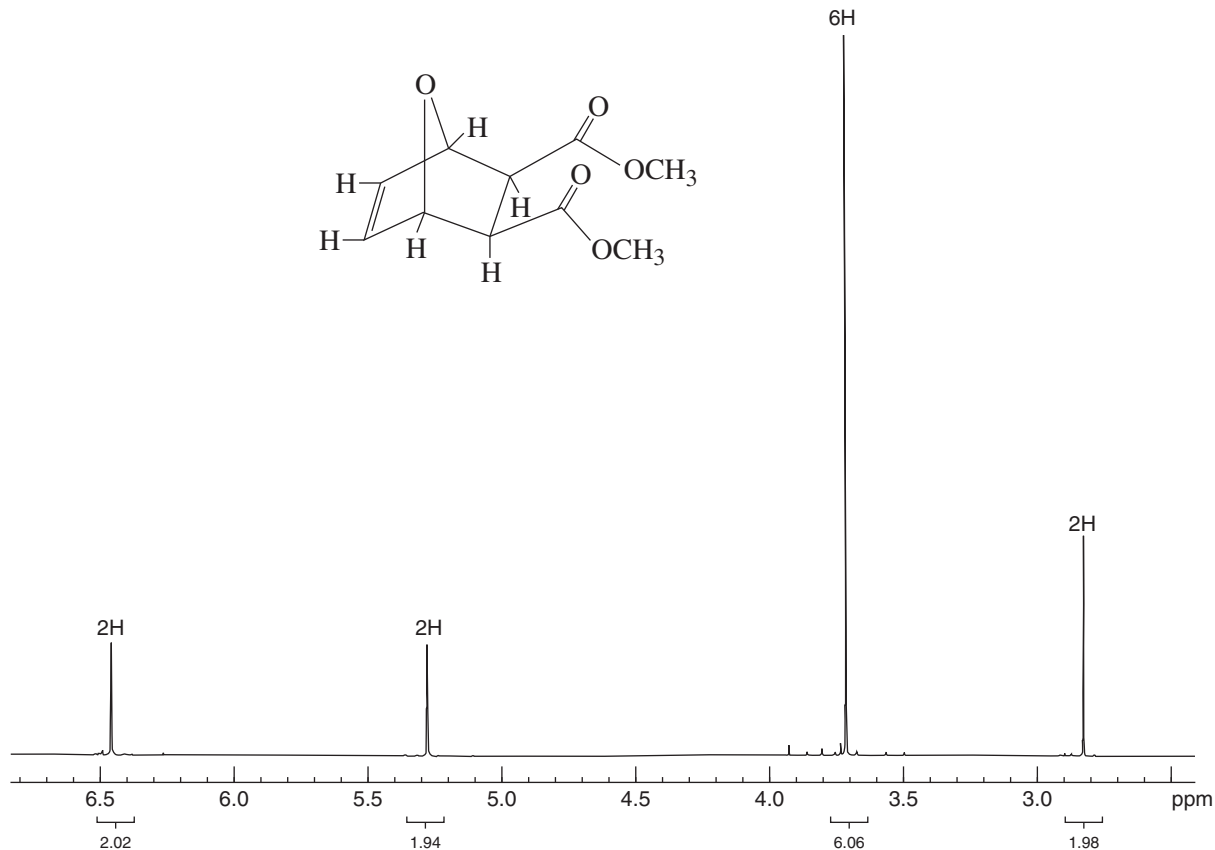
Figure 2. 500 MHz ^{1}H NMR spectrum of the Diester from Experiment 48B.

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[5] The solid may melt in the oven, if that happens, don't worry about that as the material will solidify again when cool!

E X P E R I M E N T   4 8 C

Synthesizing a Polymer by Ring-Opening Metathesis Polymerization (ROMP)

Weigh out 60 mg of the dry diester from Experiment 48B on a piece of paper and add it to a 16 × 100-mm test tube. Weigh out 4–5 mg of "generation one" Grubbs' catalyst and add it to the test tube. For both weighing operations, use a 4-place balance. Save the remaining diester. Have your instructor help you blow some argon or nitrogen gas into the tube to deoxygenate the reaction mixture and then seal the contents of the test tube with a septum cap (provided by instructor). Using a syringe, draw up 1 mL of *anhydrous* CH_2Cl_2 and inject it through the serum cap into the test tube. Cover the septum cap with Parafilm. Place the test tube into a beaker and allow the reaction mixture to sit for at least 2 days (longer is better) in an upright position in your locker.

After the reaction mixture has reacted for two or more days, remove the serum cap. Then use a P200 automatic pipet to add 75 μL of a solution of methylene chloride, butyl vinyl ether, and BHT (butylate hydroxy toluene)[6] to the test tube. Add 1 mL of CH_2Cl_2 to the test tube, then place a *clean* magnetic stir bar into the tube and allow it to stir for 1 hour. Stopper the test tube with a cork.

While the contents of the test tube are stirring, prepare a silica gel column in a Pasteur pipet as follows: place a small amount of cotton into the pipet and tamp it down to the bottom of the column with a wooden stick (do not press too hard!). Using a ruler, make a mark at 1.5 cm and 2.0 cm on the Pasteur pipet using a Sharpie pen, measuring from the exposed end of the cotton. Add silica gel until the level is between these two marks. The exact amount of silica gel that you add is not critical.

After the mixture has stirred for 1 hour, remove it from the magnetic stirrer and dilute the sample with 1 mL of CH_2Cl_2. Use a Pasteur pipet to draw up the contents of the reaction mixture and slowly and carefully add the liquid to the silica column. Collect the elutants in a *preweighed* (analytical 4-place balance) 25-mL round-bottom flask. Elute the polymer with 2 mL of CH_2Cl_2 and collect the eluant in the round-bottom flask. The column removes the cleaved ruthenium metal from the polymer.

Rotary evaporate the solvent the elutants. Alternatively, remove the solvent with a gentle stream of nitrogen or argon gas until all of the CH_2Cl_2 is gone. Remove any remaining solvent using a good quality vacuum pump. Reweigh the flask to determine the weight of the polymer on the 4-place analytical balance. Use this weight for calculating the yield of polymer. Typically, yields range from 40 to 90 mg or 65 to 150%! The yield of polymer should be about the same as the amount of diester you started with (60 mg), but obviously you may obtain a yield that exceeds 100% due to the presence of impurities!

Purify the polymer in the following way: Redissolve the polymer in about 20 drops of CH_2Cl_2. Add 10 ml of methanol to another 25-mL round-bottom flask, put a *clean* magnetic stir bar in the methanol, and place the flask on the magnetic stirrer. Then begin to stir the solution vigorously to create a vortex. Add the

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[6] The solution is prepared by mixing of 8 mL CH_2Cl_2, 1600 μL of butyl vinyl ether (use a P1000 automatic pipet), and 0.4 g of butylated hydroxy toluene (BHT).

polymer solution from the first flask dropwise into the vortex of the methanol in the second flask. A cloudy solution results, with a small (tiny is probably a better description!) amount of polymer adhering to the bottom of the flask and on the stir bar.

Decant the methanol away from the polymer. The polymer adheres to the stir bar and the side of the flask. Dry the contents of the flask by blowing argon or nitrogen onto the polymer for about 2 or 3 minutes to ensure that most of the methanol has evaporated. Remove all of the last traces of methanol by using a vacuum pump for a few minutes. In some cases, almost nothing remains in the flask after decanting the methanol. If this is the case, pour the decanted methanol solution back into the flask and rotary evaporate the methanol solution with a rotary evaporator or use other suitable method (see Technique 7, Figure 7.17); then proceed to the next paragraph. Your instructor will more than likely not be running the NMR spectrum on each sample. If that is the case, interpret the NMR shown in Figure 3 (actually, the spectrum is already interpreted for you). Methanol appears at about 3.5 ppm and methylene chloride appears at about 5.3 ppm.
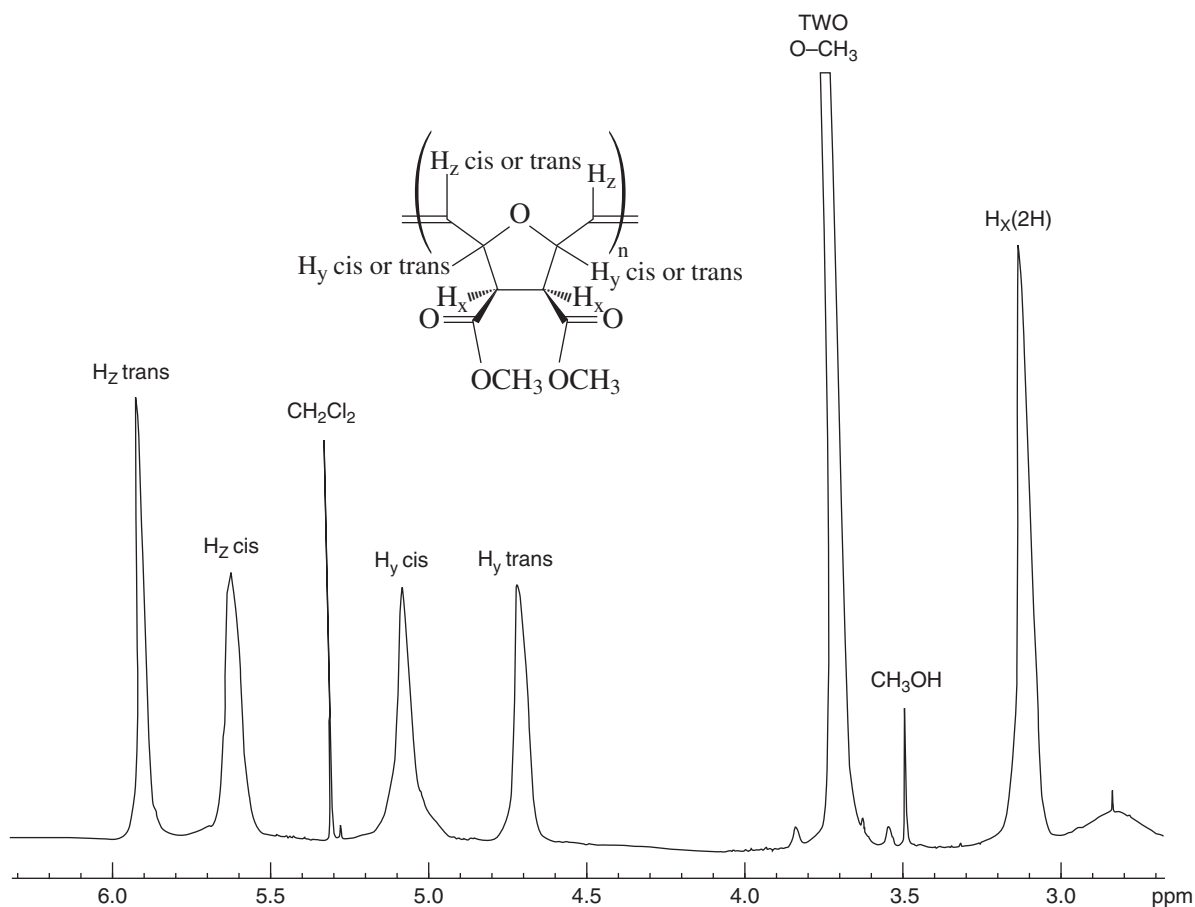
Figure 3. 500 MHZ ^{1}H NMR spectrum of the ROMP polymer formed in Experiment 48C. Assignments are made for each of the peaks. Small amounts of solvents, CH_2Cl_2 and CH_3OH, remain in the sample. The broad peak centering on 2.8 ppm is unassigned.

Dissolve the polymer in the flask in about 10 ml of tetrahydrofuran (THF) and pour it into a suitable container (glass-stoppered bottle or other container supplied by your instructor). Put your names on a label. Store the sample in the freezer compartment in a refrigerator.

A size-exclusion column (gel-permeation column) inserted into an HPLC unit will be used to obtain a chromatogram for each of the polymer samples. With this technique, the largest molecules come off first, followed by the smaller molecules (see Technique 19, Section 19.5 and Technique 21). In order to determine the molecular weight(s) of your polymer sample, you will also be supplied with a reference chromatogram of polystyrene samples of known molecular weights.

A sample data sheet is shown on pages 399 and 400, but your instructor will supply you with new data to plot the log of the molecular weights (MW) for the polystyrene standards vs. the retention volumes (retention times x 1.2 mL/min flow rate) for the polystyrene standards using Excel. The retention times (RT) in minutes will be labeled on the chromatogram. Use Excel to do the calculations for you. Multiply the retention times by the rate of volume flow through the column to give data for column 2 (multiply by 1.2 mL/minute). The log of the molecular weights (MW) of the standards were calculated using Excel in the example and are given in column 3 using the MW values for each of the polystyrene standards shown in column 4. Using Excel, plot the log MW values vs. the retention volumes (retention times x volume flow, 1.2 mL/min) for each of the polystyrene standards. See the attached data sheet shown on page 399 for an example of the plot. Determine the equation for the straight-line.

Your instructor will provide each pair of students with a chromatogram of their ROMP polymer sample. You will probably see one main peak, and possibly a shoulder on the main peak. Using the equation for the straight line, determine the molecular weight(s) of the polymer(s). The low MW peaks shown in the example data are probably assorted non-polymeric materials present in the sample (perhaps unreacted diester and low MW polymers called oligomers). You want to do the calculations for the high MW polymer chains. The molecular weight for your ROMP polymer will vary, but you can expect values ranging from about 8,000 (8K) to 20,000 (20K), sometimes even as high as 41,000 (41K). Yours results from the example shown the data sheet (41K) shown on page 400. Since the calculated values are not that precise, you should round off the molecular weight(s) you obtain.

Submit a post-lab report for each pair of students. Submit the chromatogram for the polystyrene standards, chromatogram of your ROMP polymer sample, and calculated value(s) of MWs you obtained for the various polymer chains. Submit one report/pair, or follow the instructions from your laboratory instructor.

QUESTIONS

1. Draw the structures of the expected ROMP polymers formed from the indicated starting material. The first one is shown as an example:
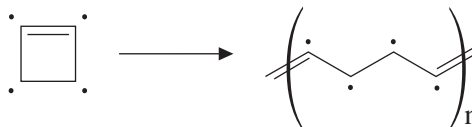
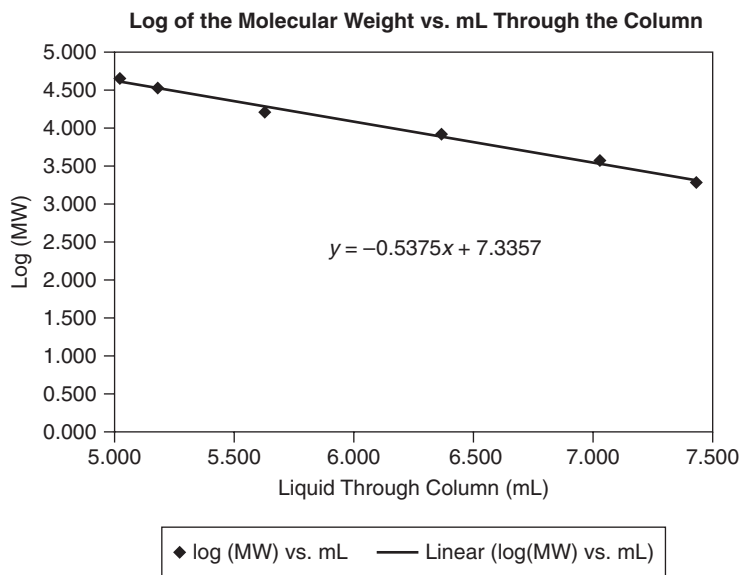The dots indicate the carbon atoms in the monomer and the carbon atoms in the polymer.
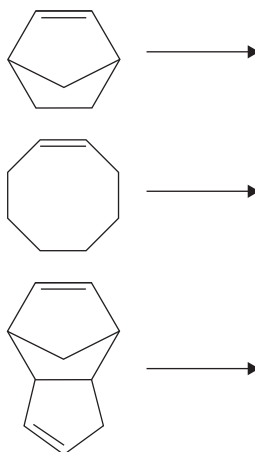
SAMPLE DATE SHEET

Calibration Curve Data

RT	mL	log (MW)	MW
4.183	5.020	4.677	47,500
4.315	5.178	4.544	35,000
4.682	5.618	4.243	17,500
5.299	6.359	3.954	9,000
5.857	7.028	3.602	4,000
6.196	7.435	3.301	2,000

Linear Regression

Log of the Molecular Weight vs. mL Through the Column

$y = -0.5375x + 7.3357$

Liquid Through Column (mL)

◆ log (MW) vs. mL   —— Linear (log(MW) vs. mL)

Polymer Peaks and Corresponding Molecular Weights

RT	mL	log (MW)	MW
4.215	5.058	4.617	41402
8.002	9.602	2.174	149
8.420	10.104	1.905	80
8.806	10.567	1.656	45
9.215	11.058	1.392	25

E S S A Y

Diels–Alder Reaction and Insecticides

Since the 1930s, it has been known that the addition of an unsaturated molecule across a diene system forms a substituted cyclohexene. The original research dealing with this type of reaction was performed by Otto Diels and Kurt Alder in Germany, and the reaction is known today as the **Diels–Alder reaction**. The Diels–Alder reaction is the reaction of a **diene** with a species capable of reacting with the diene, the **dienophile**.

Diene   **Dienophile**
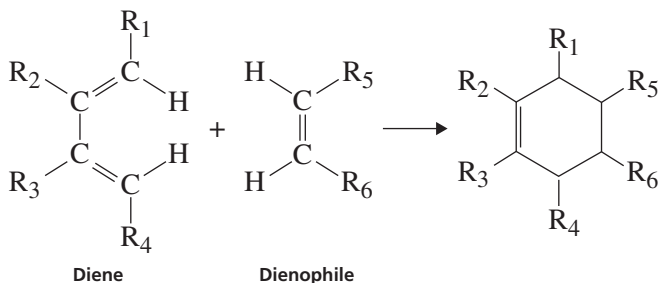
The product of the Diels–Alder reaction is usually a structure that contains a cyclohexene ring system. If the substituents as shown are simply alkyl groups or hydrogen atoms, the reaction proceeds only under extreme conditions of temperature and pressure. With more complex substituents, however, the Diels–Alder reaction may proceed at low temperatures and under mild conditions. The reaction of cyclopentadiene with maleic anhydride (Experiment 49) is an example of a Diels–Alder reaction carried out under reasonably mild conditions.

In the past, a commercially important use of the Diels–Alder reaction involved the use of hexachlorocyclopentadiene as the diene. Depending on the dienophile, a variety of chlorine-containing addition products may be synthesized. Nearly all these products were powerful **insecticides**. Three insecticides synthesized by the Diels-Alder reaction are shown below.

Dieldrin and Aldrin are named after Diels and Alder. These insecticides were once used against the inspect pests of fruits, vegetables, and cotton; against soil insects, termites, and moths; and in the treatment of seeds. Chlordane was used in veterinary medicine against inspect pests of animals, including fleas, ticks, and lice. These insecticides are seldom used today.

Aldrin

Dieldrin

Chlordane
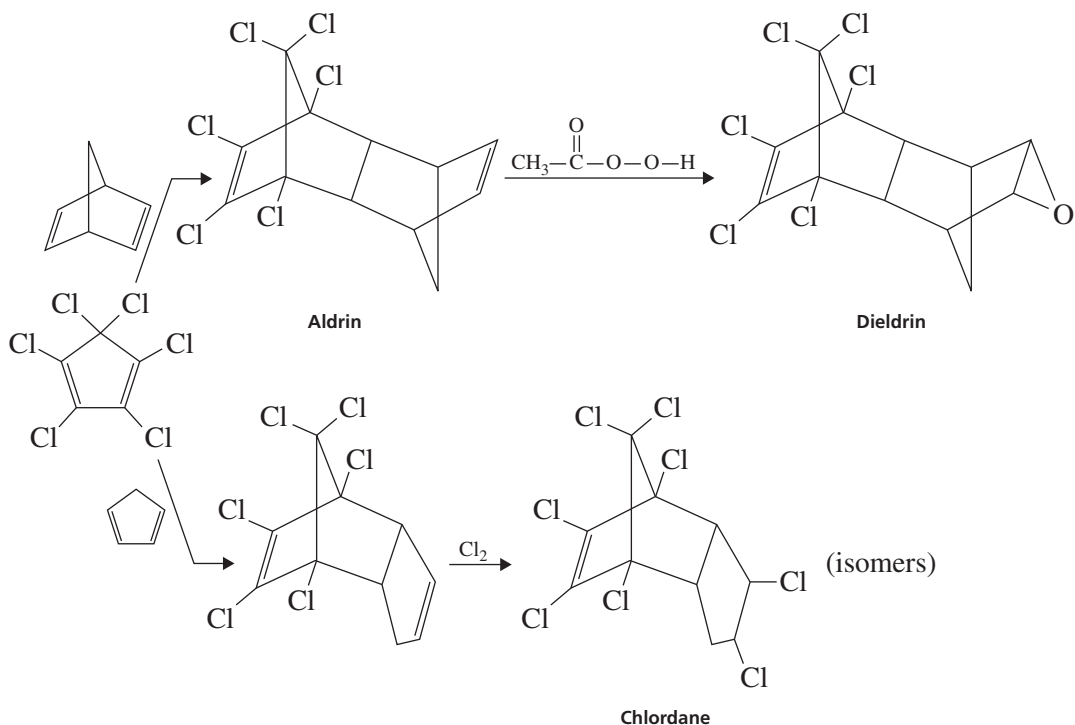
The best known insecticide, DDT, is not prepared by the Diels–Alder reaction, but is nevertheless the best illustration of the difficulties that were experienced when chlorinated insecticides were used indiscriminately. DDT was first synthesized in 1874, and its insecticidal properties were first demonstrated in 1939. It is easily synthesized commercially, with inexpensive reagents.


Chloral   **Chlorobenzene**

DDT
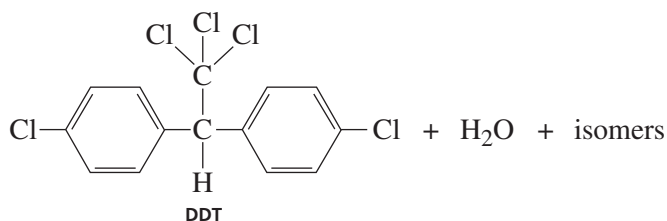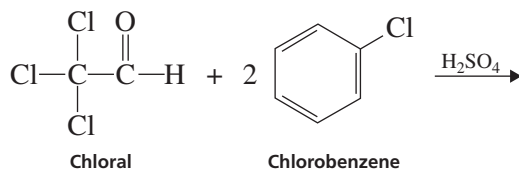
At the time DDT was introduced, it was an important boon to humanity. It was effective in controlling lice, fleas, and malaria-carrying mosquitoes and thus helped control human and animal disease. The use of DDT rapidly spread to the control of hundreds of insects that damage fruit, vegetable, and grain crops.

Pesticides that persist in the environment for a long time after application are called **hard pesticides**. Beginning in the 1960s, some of the harmful effects of such hard pesticides as DDT and the other chlorocarbon materials became known. DDT is a fat-soluble material and is therefore likely to collect in the fat, nerve, and brain

tissues of animals. The concentration of DDT in tissues increases in animals high in the food chain. Thus, birds that eat poisoned insects accumulate large quantities of DDT. Animals that feed on the birds accumulate even more DDT. In birds, at least two undesirable effects of DDT have been recognized. First, birds whose tissues contain large amounts of DDT have been observed to lay eggs having shells too thin to survive until young birds are ready to hatch. Second, large quantities of DDT in the tissues seem to interfere with normal reproductive cycles. The massive destruction of bird populations that sometimes occurred after heavy spraying with DDT became an issue of great concern. The brown pelican and the bald eagle were placed in danger of extinction. The use of chlorocarbon insecticides was identified as the principal reason for the decline in the numbers of these birds.

Because DDT is chemically inert, it persists in the environment without decomposing to harmless materials. It can decompose very slowly, but the decomposition products are every bit as harmful as DDT itself. Consequently, each application of DDT means that still more DDT will pass from species to species—from food source to predator—until it concentrates in the higher animals, possibly endangering their existence. Even humans may be threatened. As a result of evidence of the harmful effects of DDT, the Environmental Protection Agency (EPA) banned general use of DDT in the early 1970s; it may still be used for certain purposes, although permission of the EPA is required. In 1974, the EPA granted permission to use DDT against the tussock moth in the forests of Washington and Oregon.
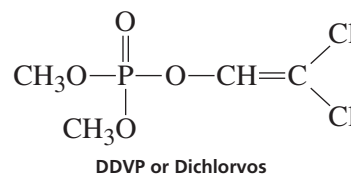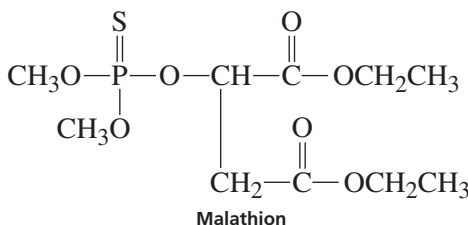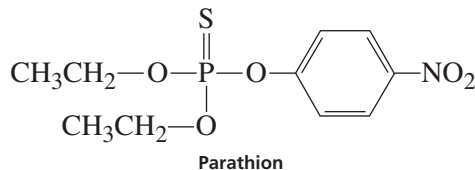
Because the life cycles of insects are short, they can evolve an immunity to insecticides within a short period. As early as 1948, several strains of DDT-resistant insects were identified. Today, the malaria-bearing mosquitoes are almost completely resistant to DDT, an ironic development. Other chlorocarbon insecticides were developed to use as alternatives to DDT against resistant insects. Examples of these chlorocarbon materials include Dieldrin, Aldrin, Chlordane, and the substances whose structures are shown here. Heptachlor and Mirex are prepared using Diels–Alder reactions.

Lindane   **Heptachlor**   **Mirex**
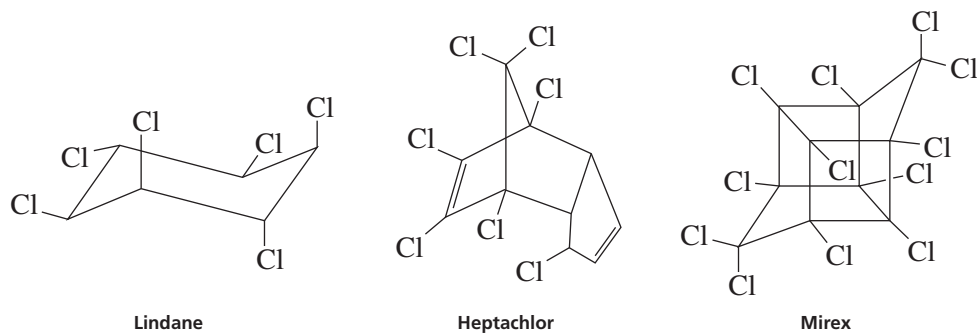
In spite of structural similarity, Chlordane and Heptachlor behave differently than DDT, Dieldrin, and Aldrin. Chlordane, for instance, is short-lived and less toxic to mammals. Nevertheless, all the chlorocarbon insecticides have been the objects of much suspicion. A ban on the use of Dieldrin and Aldrin has also been ordered by the EPA. In addition, strains of insects resistant to Dieldrin, Aldrin, and other materials have been observed. Some insects become addicted to a chlorocarbon insecticide and thrive on it!

The problems associated with chlorocarbon materials have led to the development of "soft" insecticides. These usually are organophosphorus or carbamate derivatives, and they are characterized by a short lifetime before they are decomposed to harmless materials in the environment.

The organic structures of some organophosphorus insecticides are shown here.

$$CH_3CH_2-O-\overset{\overset{\displaystyle S}{\|}}{\underset{\underset{\displaystyle O}{|}}{P}}-O-\text{⬡}-NO_2$$
$$CH_3CH_2-O$$

Parathion

$$CH_3O-\overset{\overset{\displaystyle S}{\|}}{\underset{\underset{\displaystyle O}{|}}{P}}-O-\underset{\underset{\underset{\underset{\displaystyle OCH_2CH_3}{\|}}{\overset{\displaystyle O}{C}}}{|}}{CH}-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_3$$
$$CH_3O \qquad\qquad CH_2$$

Malathion

$$CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{|}}{P}}-O-CH=C\overset{\displaystyle Cl}{\underset{\displaystyle Cl}{}}$$
$$CH_3O$$

DDVP or Dichlorvos

Parathion and Malathion are used widely for agriculture. DDVP is contained in "pest strips," which are used to combat household insect pests. The organophosphorus materials do not persist in the environment, so they are not passed between species up the food chain, as the chlorocarbon compounds are. However, the organophosphorus compounds are highly toxic to humans. Some migrant and other agricultural workers have lost their lives because of accidents involving these materials. Stringent safety precautions must be applied when organophosphorus insecticides are being used.

The carbamate derivatives, including Carbaryl, tend to be less toxic than the organophosphorus compounds. They are also readily degraded to harmless materials. Nevertheless, insects resistant to soft insecticides have also been observed. Furthermore, the organophosphorus and carbamate derivatives destroy many more nontarget pests than the chlorocarbon compounds do. The danger to earthworms, mammals, and birds is very high.

$$CH_3-NH-\overset{\overset{\displaystyle O}{\|}}{C}-O$$

**Carbaryl**
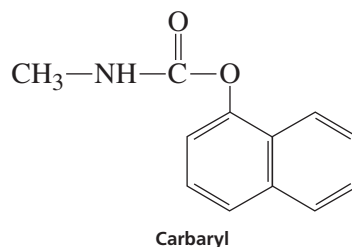
ALTERNATIVES TO INSECTICIDES

Several alternatives to the massive application of insecticides have recently been explored. Insect attractants, including the pheromones (see the essay preceding Experiment 45), have been used in localized traps. Such methods have been effective against the gypsy moth. A "confusion technique," whereby a pheromone is sprayed into the air in such high concentrations that male insects are no longer able to locate females, has been studied. These methods are specific to the target pest and do not cause repercussions in the general environment.

Recent research has focused on using an insect's own biochemical processes to control pests. Experiments with **juvenile hormone** have shown promise. Juvenile

hormone is one of three internal secretions used by insects to regulate growth and metamorphosis from larva to pupa and thence to the adult. At certain stages in the metamorphosis from larva to pupa, juvenile hormone must be secreted; at other stages it must be absent, or the insect will either develop abnormally or fail to mature. Juvenile hormone is important in maintaining the juvenile, or larval, stage of the growing insect. The male cecropia moth, which is the mature form of the silkworm, has been used as a source of juvenile hormone. The structure of the cecropia juvenile hormone is shown below. This material has been found to prevent the maturation of yellow-fever mosquitoes and human body lice. Because insects are not expected to develop a resistance to their own hormones, it is hoped that insects will be unlikely to develop a resistance to juvenile hormone.

Cecropea juvenile hormone　　　　**Paper factor**
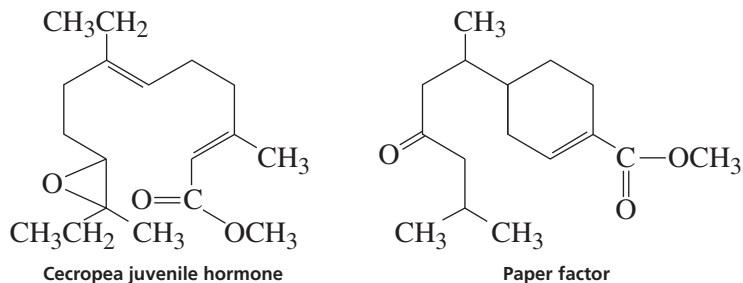
Although it is very difficult to get enough of the natural substance for use in agriculture, synthetic analogues have been prepared, that have been shown to be similar in properties and effectiveness to the natural substance. A substance has been found in the American balsam fir (*Abies balsamea*) known as **paper factor**. Paper factor is active against the linden bug, *Pyrrhocoris apterus,* a European cotton pest. This substance is merely one of thousands of terpenoid materials synthesized by the fir tree. Other terpenoid substances are being investigated as potential juvenile hormone analogues.

Pyrethrin

R = CH_3 or $COOCH_3$
R' = $CH_2CH{=}CHCH{=}CH_2$ or $CH_2CH{=}CHCH_3$
or $CH_2CH{=}CHCH_2CH_3$
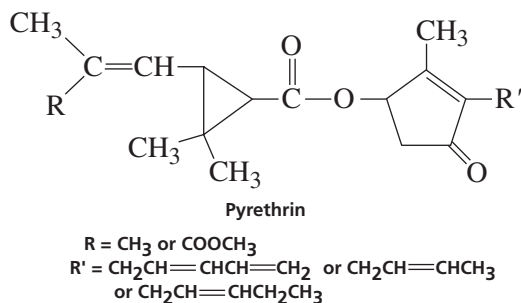
Certain plants are capable of synthesizing substances that protect them against insects. Included among these natural insecticides are the **pyrethrins** and derivatives of **nicotine**.

The search for environmentally suitable means of controlling agricultural pests continues with a great sense of urgency. Insects cause billions of dollars of damage to food crops each year. With food becoming increasingly scarce and with the world's population growing at an exponential rate, preventing such losses to food crops is absolutely essential.

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Peakall, D. B. Pesticides and the Reproduction of Birds. *Sci. Am.* **1970,** *222* (Apr), 72.

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Williams, W. G.; Kennedy, G. G.; Yamamoto, R. T.; Thacker, J. D.; Bordner, J. 2-Tridecanone: A Naturally Occurring Insecticide from the Wild Tomato. *Science* **1980,** *207,* 888.

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49 **EXPERIMENT 49**

The Diels–Alder Reaction of Cyclopentadiene with Maleic Anhydride

Diels–Alder reaction

Fractional distillation

Cyclopentadiene and maleic anhydride react readily in a Diels–Alder reaction to form the adduct, *cis*-norbornene-5,6-*endo*-dicarboxylic anhydride:

Cyclopentadiene Maleic anhydride   *cis*-Norbornene-5,6-*endo*-dicarboxylic anhydride
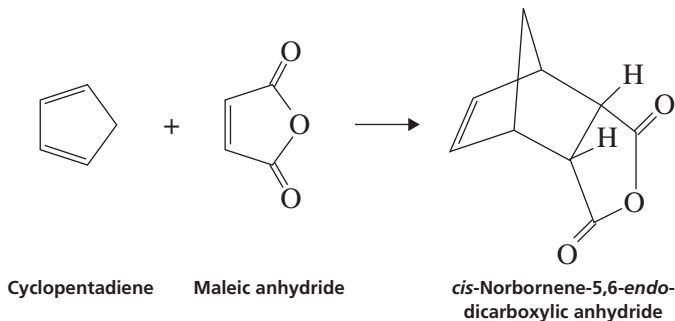
  Because two molecules of cyclopentadiene can also undergo a Diels–Alder reaction to form dicyclopentadiene, it is not possible to store cyclopentadiene in the monomeric form. Therefore, it is necessary to first "crack" dicyclopentadiene to produce cyclopentadiene for use in this experiment. This will be accomplished by heating the dicyclopentadiene to a boil and collecting the cyclopentadiene as it is

formed by fractional distillation. The cyclopentadiene must be kept cold and used fairly soon to keep it from dimerizing.
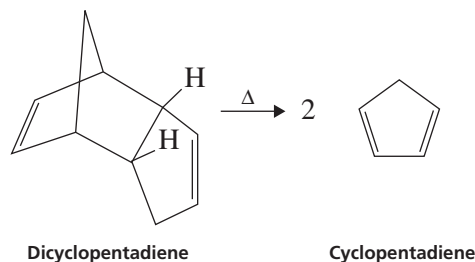
Dicyclopentadiene   **Cyclopentadiene**

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: *Technique 11   Crystallization: Purification of Solids, Section 11.3

*New:*   Essay   Diels–Alder Reaction and Insecticides

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SPECIAL INSTRUCTIONS

The cracking of dicyclopentadiene should be performed by the instructor or laboratory assistant. If a flame is used for this, be sure that there are no leaks in the system, because both cyclopentadiene and the dimer are highly flammable.

SUGGESTED WASTE DISPOSAL

Dispose of the mother liquor from the crystallization in the container designated for nonhalogenated organic solvents.

NOTES TO THE INSTRUCTOR

Working in a hood, assemble a fractional distillation apparatus as shown in the figure. Although the required temperature control can best be obtained with a microburner, using a heating mantle lessens the possibility of a fire occurring. Place several boiling stones and dicyclopentadiene in the distilling flask. The amount of dicyclopentadiene and the size of the distilling flask should be determined by the amount of cyclopentadiene required by your class. The volume of cyclopentadiene recovered will be 50–75% of the initial volume of dicyclopentadiene, depending on the volume distilled and the size of the fractionating column. Control the heat source so that the cyclopentadiene distills at 40–43°C. If the cyclopentadiene is cloudy, dry the liquid over granular anhydrous sodium sulfate. Store the product in a sealed container and keep it cooled in an ice-water bath until all students have taken their portions. It must be used within a few hours to keep it from dimerizing.
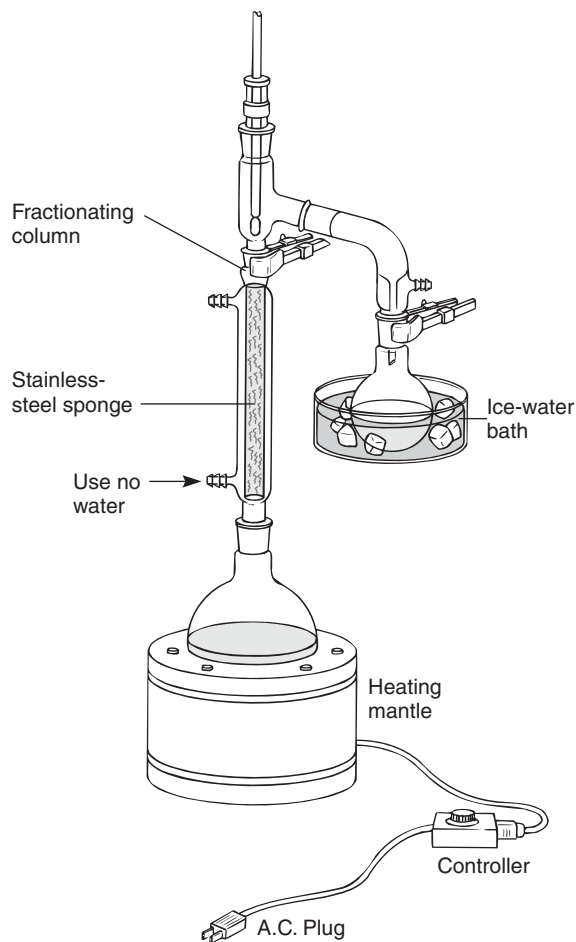
Fractional distillation apparatus for cracking dicyclopentadiene.

PROCEDURE

Preparation of the Adduct. Add 1.00 g of maleic anhydride and 4.0 mL of ethyl acetate to a 25-mL Erlenmeyer flask. Swirl the flask to dissolve the solid (slight heating on a hot plate may be necessary). Add 4.0 mL of ligroin (bp 60–90°C) and swirl the flask to mix the solvents and reactant thoroughly. Add 1.0 mL of cyclopentadiene and mix thoroughly until no visible layers of liquid are present. Because this reaction is exothermic, the temperature of the mixture will likely become high enough to keep the product in solution. However, if a solid does form at this point, it will be necessary to heat the mixture on a hot plate to dissolve any solids present.
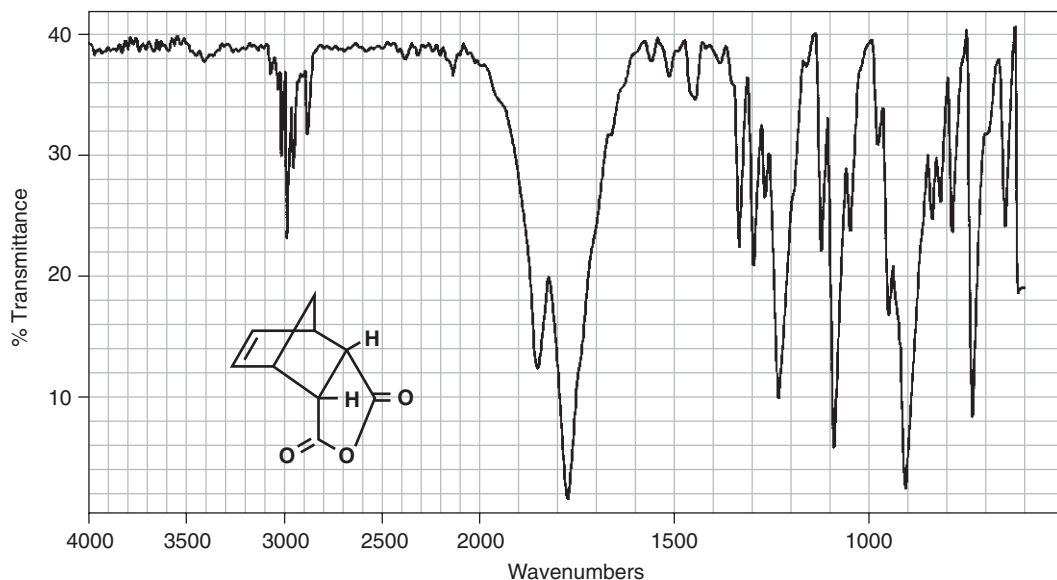
Infrared spectrum of *cis*-norbornene-5,6-*endo*-dicarboxylic anhydride, KBr.

Crystallization of Product. Allow the mixture to cool slowly to room temperature. Better crystal formation can be achieved by seeding the solution before it cools to room temperature. To seed the solution, dip a spatula or glass stirring rod into the solution after it has cooled for about 5 minutes. Allow the solvent to evaporate so that a small amount of solid forms on the surface of the spatula or glass rod. Place the spatula or stirring rod back into the solution for a few seconds to induce crystallization. When crystallization is complete at room temperature, cool the mixture in an ice bath for several minutes.

Isolate the crystals by filtration on a Hirsch funnel or a small Büchner funnel and allow the crystals to air-dry. Determine the weight and the melting point (164°C). At the option of the instructor, obtain the infrared spectrum using the dry-film method (see Technique 25, Section 25.4) or as a KBr pellet (see Technique 25, Section 25.5). Compare your infrared spectrum with the one reproduced here. Calculate the percentage yield and submit the product to the instructor in a labeled vial.

Molecular Modeling (Optional)

In the reaction of cyclopentadiene with maleic anhydride, two products are possible: the *endo* product and the *exo* product.

Calculate the heats of formation for both of these products to determine which is the expected **thermodynamic product** (product of lowest energy). Perform the calculations at the AM1 level with a geometry optimization. The actual product of the Diels–Alder reaction is the *endo* product. Is this the thermodynamic product? Display a space-filling model for each structure. Which one appears most crowded?

endo   *exo*
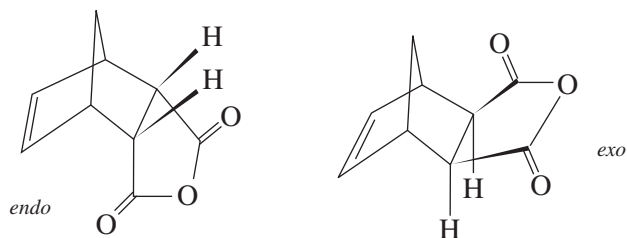
Woodward and Hoffmann have pointed out that the diene is the electron donor and the dienophile, the electron acceptor in this reaction. In accordance with this idea, dienes that have electron-donating groups are more reactive than those without, and dienophiles with electron-withdrawing groups are most reactive. Using the reasoning of frontier molecular orbital theory (see the essay "Computational Chemistry" that precedes Experiment 18), the electrons in the HOMO of the diene will be placed into the LUMO of the dienophile when reaction occurs. Using the AM1 level, calculate the HOMO surface for the diene (cyclopentadiene) and the LUMO surface for the dienophile (maleic anhydride). Display the two simultaneously on the screen in the orientations that will lead to the *endo* and *exo* products.
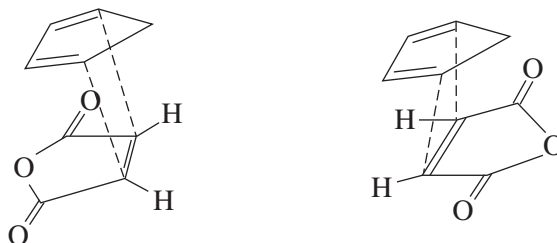
Woodward and Hoffmann suggested that the orientation that leads to the largest degree of constructive overlap between the two orbitals (HOMO and LUMO) is the orientation that would lead to the product. Do you agree?

Depending on the capability of your software, it may be possible to determine the geometry (and energies) of the transition states that lead to each product. Your instructor will have to show you how to do this.

QUESTIONS

1. Draw a structure for the *exo* product formed by cyclopentadiene and maleic anhydride.

2. Because the *exo* form is more stable than the *endo* form, why is the *endo* product formed almost exclusively in this reaction?

3. In addition to the main product, what are two side reactions that could occur in this experiment?

4. The infrared spectrum of the adduct is given in this experiment. Interpret the principal peaks.
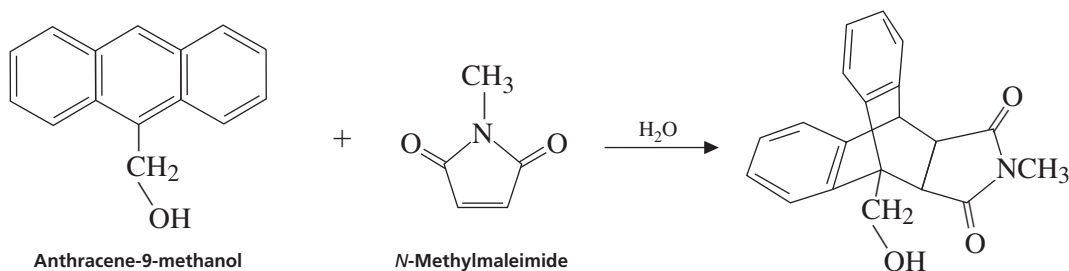
50   EXPERIMENT 50

Diels-Alder Reaction with Anthracene-9 Methanol

Green Chemistry

Diels-Alder reaction

Hydrophobic effect

Spectroscopy

Anthracene-9-methanol   *N*-**Methylmaleimide**

This experiment demonstrates Green Chemistry through the Diels-Alder reaction, which is an important reaction in organic chemistry because it is an important method of ring formation. The "green" components of this experiment include attention to atom economy and waste reduction, but the most important "green" aspect is the use of water as the solvent. Not only is water an environmentally benign solvent, but it also actually improves other aspects of this reaction due to hydrophobic solvent effects.

The *hydrophobic effect* is the property that nonpolar molecules tend to self-associate in the presence of aqueous solution. Two explanations have been advanced to explain why the hydrophobic effect increases the rate of reaction for selected Diels-Alder reactions. The first is that the activated complex is somewhat polar; it is stabilized by hydrogen-bonding, which makes the reaction go faster. The second is that the hydrophobic effect acts to force the two reagents together with a solvation shell and to increase the interaction between them.

SUGGESTED WASTE DISPOSAL

All aqueous waste can be disposed of in a waste container designated for non-halogenated aqueous waste.

SAFETY PRECAUTIONS

N-Methylmaleimide is corrosive and should be handled with care. Gloves should be worn.

PROCEDURE

Reaction. In a 50-mL round-bottom flask equipped with a stir bar, add 0.066 g of anthracene-9-methanol. Using a 25-mL graduated cylinder, add 25 mL of de-ionized water. Note that anthracene-9-methanol is insoluble in water. Add 0.070 g of N-methylmaleimide to the mixture, and fit the flask to a water-cooled condenser. Heat the mixture until it is boiling under reflux, and allow the reaction to continue boiling for 90 minutes while stirring.

Isolation. Remove the heat, and allow the reaction to cool to room temperature (without removing the condenser). Chill the flask in an ice bath for 5 minutes, and collect the precipitate by vacuum filtration using a Hirsch funnel. Allow the solid to dry in the Hirsch funnel, under vacuum, for 15 minutes. Collect crystals on a watch glass, and allow them to dry overnight.

Analysis and Report. Determine the weight of your product, and obtain the melting point range (literature value = 232–235°C). Determine the proton and carbon nuclear magnetic resonance spectra of the product. Include the NMR spectra with your report, along with an interpretation of the peaks and splitting patterns. Be sure to also include your weight percentage recovery calculation. Submit your sample in a properly labeled vial.

REFERENCES

Engberts, J. B. F. N. Diels-Alder Reactions in Water: Enforced Hydrophobic Interaction and Hydrogen Bonding. *Pure Appl. Chem.* **1995,** *67,* 823–28.

Rideout, D. C.; Breslow, R. Hydrophobic Acceleration of Diels-Alder Reactions. *J. Am. Chem. Soc.* **1980,** *102,* 7817–18.

51   EXPERIMENT 51

Photoreduction of Benzophenone and Rearrangement of Benzpinacol to Benzopinacolone
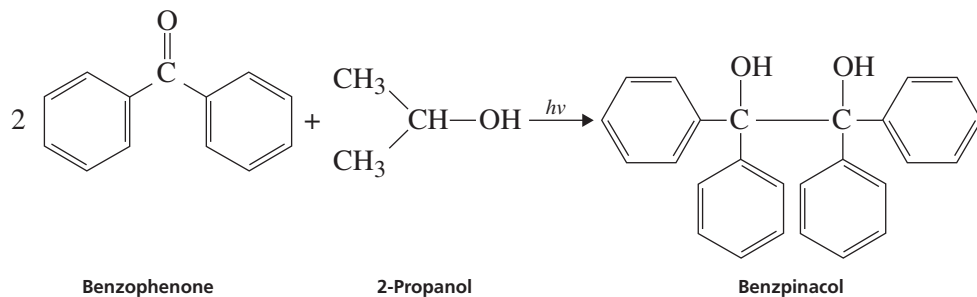
Photochemistry
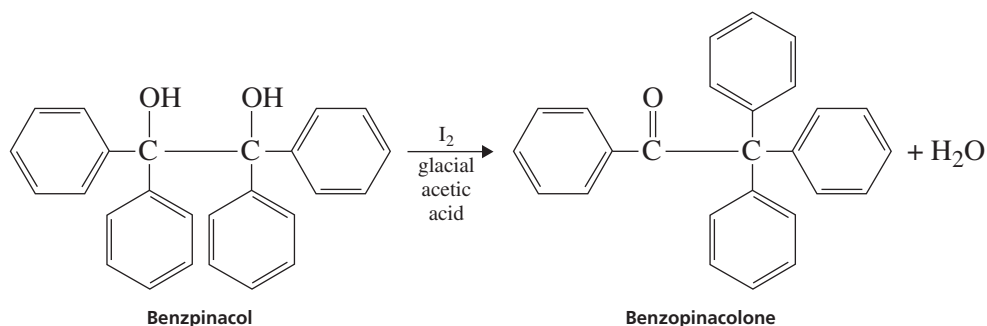
Photoreduction

Energy transfer

Pinacol rearrangement

This experiment consists of two parts. In the first part (Experiment 51A), benzophenone will be subjected to **photoreduction**, a dimerization brought about by exposing a solution of benzophenone in isopropyl alcohol to natural sunlight. The product of this photoreaction is benzpinacol. In the second part (Experiment 51B), benzpinacol will be induced to undergo an acid-catalyzed rearrangement called the **pinacol rearrangement**. The product of the rearrangement is benzopinacolone.

Experiment 51A

Benzophenone   **2-Propanol**   **Benzpinacol**

Experiment 51B

Benzpinacol   **Benzopinacolone**


51A   **E X P E R I M E N T   5 1 A**

Photoreduction of Benzophenone

The photoreduction of benzophenone is one of the oldest and most thoroughly studied photochemical reactions. Early in the history of photochemistry, it was discovered that solutions of benzophenone are unstable in light when certain solvents are used. If benzophenone is dissolved in a "hydrogen-donor" solvent, such as 2-propanol, and exposed to ultraviolet light, hv, an insoluble dimeric product, benzpinacol, will form.

Benzophenone   **2-Propanol**   **Benzpinacol**
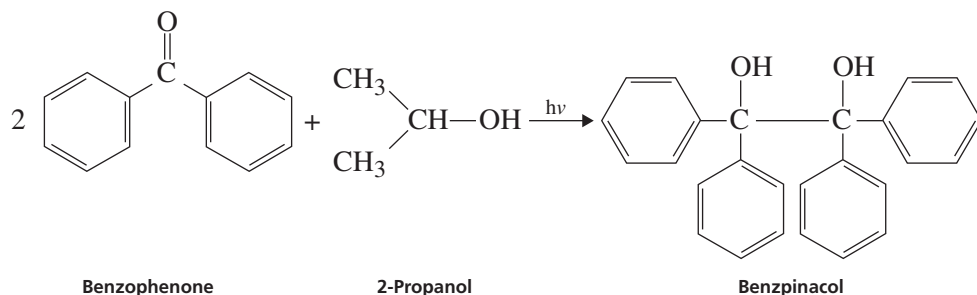
To understand this reaction, let's review some simple photochemistry as it relates to aromatic ketones. In the typical organic molecule, all the electrons are paired in the occupied orbitals. When such a molecule absorbs ultraviolet light of the appropriate wavelength, an electron from one of the occupied orbitals, usually the one of highest energy, is excited to an unoccupied molecular orbital, usually to the one of lowest energy. During this transition, the electron must retain its spin value, because during an electronic transition a change of spin is forbidden by the laws of quantum mechanics. Therefore, just as the two electrons in the highest occupied orbital of the molecule originally had their spins paired (opposite), so they will retain paired spins in the first electronically excited state of the molecule. This is true even though the two electrons will be in *different* orbitals after the transition. This first excited state of a molecule is called a **singlet state** (S_1) because its spin multiplicity (2S + 1) is 1. The original unexcited state of the molecule is also a singlet state because its electrons are paired, and it is called the **ground-state** singlet state (S_0) of the molecule.
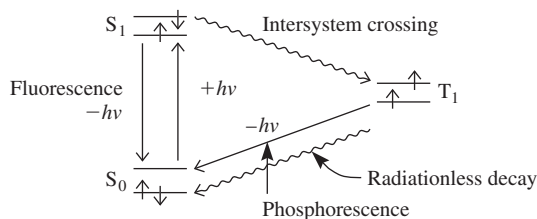

Electronic states of a typical molecule and the possible interconversions. In each state (S_0, S_1, T_1), the lower line represents the highest occupied orbital, and the upper line represents the lowest unoccupied orbital of the unexcited molecule. Straight lines represent processes in which a photon is absorbed or emitted. Wavy lines represent radiationless processes—those that occur without emission or absorption of a photon.

The excited state singlet S_1 may return to the ground state S_0 by reemission of the absorbed photon of energy. This process is called **fluorescence**. Alternatively, the excited electron may undergo a change of spin to give a state of higher multiplicity, the excited **triplet state**, so called because its spin multiplicity (2S + 1) is 3. The conversion from the first excited singlet state to the triplet state is called **intersystem crossing**. Because the triplet state has a higher multiplicity, it inevitably has a lower energy state than the excited singlet state (Hund's Rule). Normally, this change of spin (intersystem crossing) is a process forbidden by quantum mechanics, just as a direct excitation of the ground state (S_0) to the triplet state (T_1) is forbidden. However, in those molecules in which the singlet and triplet states lie close to one another in energy, the two states inevitably have several overlapping vibrational states—that is, states in common—a situation that allows the "forbidden" transition to occur. In many molecules in which S_1 and T_1 have similar energy (ΔE < 10 kcal/mole), intersystem crossing occurs faster than fluorescence, and the molecule is rapidly converted from its excited singlet state to its triplet state. In benzophenone, S_1 undergoes intersystem crossing to T_1 with a rate of $k_{isc} = 10^{10}$ sec^{-1}, meaning that the lifetime of S_1 is only 10^{-10} second. The rate of fluorescence for benzophenone is $k_f = 10^6$ sec^{-1}, meaning that intersystem crossing occurs at a rate that is 10^4 times faster than fluorescence. Thus, the conversion of S_1 to T_1 in benzophenone is essentially a quantitative process. In molecules that have a wide energy gap between S_1 and T_1, this situation would be reversed. As you will see shortly, naphthalene molecule presents a reversed situation.

Because the excited triplet state is lower in energy than the excited singlet state, the molecule cannot easily return to the excited singlet state; nor can it easily return to the ground state by returning the excited electron to its original orbital. Once again, the transition $T_1 \rightarrow S_0$ would require a change of spin for the electron, and this is a forbidden process. The triplet excited state usually has a long lifetime (relative to other excited states) because it generally has nowhere to which it can easily go. Even though the process is forbidden, the triplet T_1 may eventually return to the ground state (S_0) by a process called a **radiationless transition**. In this process, the excess energy of the triplet is lost to the surrounding solution as heat, thereby "relaxing" the triplet back to the ground state (S_0). This process is the study of much current research and is not well understood. In the second process, in which a triplet state may revert to the ground state, **phosphorescence**, the excited triplet emits a photon to dissipate the excess energy and returns directly to the ground state. Although this process is "forbidden," it nevertheless occurs when there is no other open pathway by which the molecule can dissipate its excess energy. In benzophenone, radiationless decay is the faster process, with rate $k_d = 10^5 \ \text{sec}^{-1}$, and phosphorescence, which is not observed, has a lower rate of $k_p = 10^2 \ \text{sec}^{-1}$.

Benzophenone is a ketone. Ketones have *two* possible excited singlet states and, consequently, two excited triplet states as well. This occurs because two relatively low-energy transitions are possible in benzophenone. It is possible to excite one of the π electrons in the carbonyl π bond to the lowest-energy unoccupied orbital, a π* orbital. It is also possible to excite one of the unbonded or *n* electrons on oxygen to the same orbital. The first type of transition is called a π–π* transition, whereas the second is called an *n*–π* transition. In the figure showing the excited energy states of benzophenone and naphthalene, these transitions and the states that result are illustrated pictorially.

Spectroscopic studies show that for benzophenone and most other ketones, the *n*–π* excited states S_1 and T_1 are of lower energy than the π–π* excited states. An energy diagram depicting the excited states of benzophenone (along with one that depicts those of naphthalene) is shown.
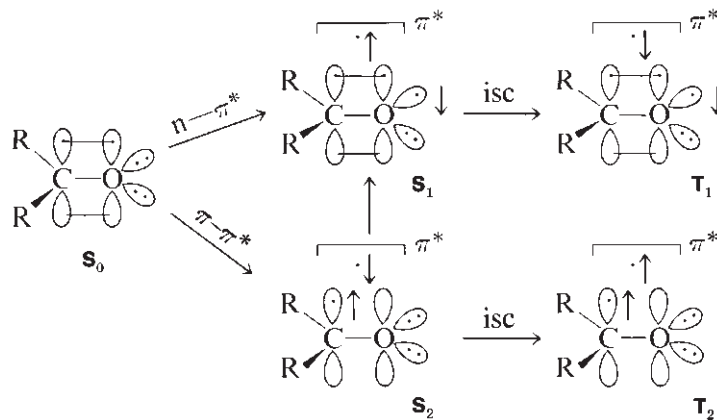

n–π* and π–π* transitions for ketones.

Excited states of benzophenone   **Excited states of naphthalene**
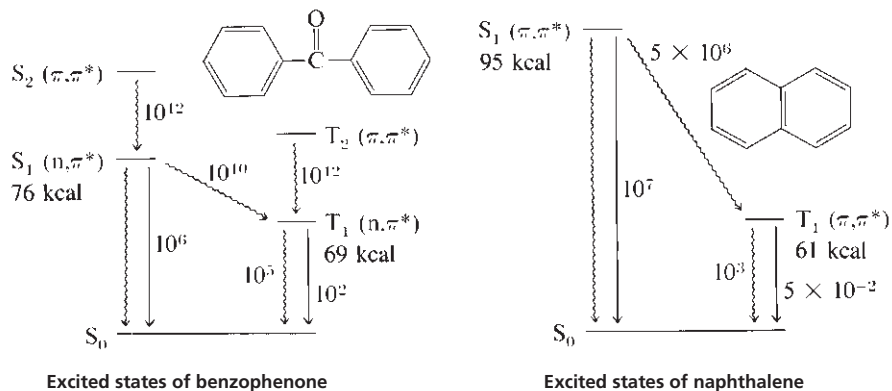
Excited energy states of benzophenone and naphthalene.

It is now known that the photoreduction of benzophenone is a reaction of the $n–\pi^*$ triplet state (T_1) of benzophenone. The $n–\pi^*$ excited states have radical character at the carbonyl oxygen atom because of the unpaired electron in the nonbonding orbital. Thus, the radical-like and energetic T_1 excited-state species can abstract a hydrogen atom from a suitable donor molecule to form the diphenylhydroxymethyl radical. Two of these radicals, once formed, may couple to form benzpinacol. The complete mechanism for photoreduction is outlined in the steps that follow.
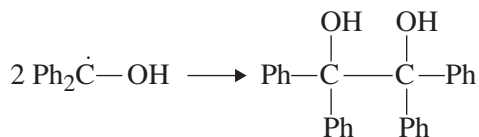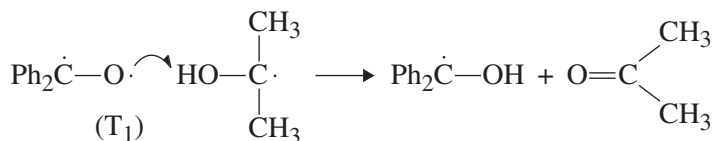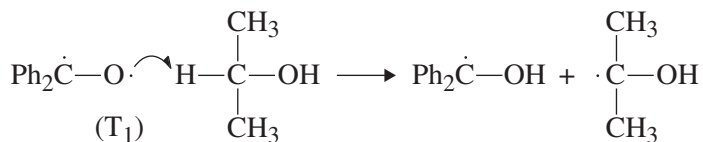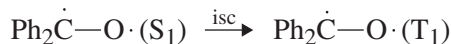
Many photochemical reactions must be carried out in a quartz apparatus because they require ultraviolet radiation of shorter wavelengths (higher energy) than the wavelengths that can pass through Pyrex. Benzophenone, however, requires radiation of approximately 350 nm to become excited to its $n–\pi^*$ singlet state S_1, a wavelength that readily passes through Pyrex. In the figure shown on the next page, the ultraviolet absorption spectra of benzophenone and naphthalene are given. Superimposed on their spectra are two curves, which show the wavelengths that can be transmitted by Pyrex and quartz, respectively. Pyrex will not allow any radiation of wavelengths shorter than approximately 300 nm to pass, whereas quartz allows wavelengths as short as 200 nm to pass. Thus, when benzophenone

is placed in a Pyrex flask, the only electronic transition possible is the $n–\pi^*$ transition, which occurs at 350 nm.

However, even if it were possible to supply benzophenone with radiation of the appropriate wavelength to produce the second excited singlet state of the molecule, this singlet would rapidly convert to the lowest singlet state (S_1). The state S_2 has a lifetime of less than 10^{-12} second. The conversion process $S_2 \rightarrow S_1$ is called an **internal conversion**. Internal conversions are processes of conversion between excited states of the same multiplicity (singlet–singlet or triplet–triplet), and they usually are very rapid. Thus, when an S_2 or T_2 is formed, it readily converts to S_1 or T_1, respectively. As a consequence of their very short lifetimes, very little is known about the properties or the exact energies of S_2 and T_2 of benzophenone.
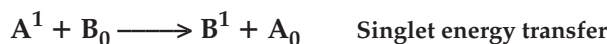
ENERGY TRANSFER

Using a simple **energy-transfer** experiment, one can show that the photoreduction of benzophenone proceeds via the T_1 excited state of benzophenone rather than the S_1 excited state. If naphthalene is added to the reaction, the photoreduction is stopped because the excitation energy of the benzophenone triplet is transferred to naphthalene. The naphthalene is said to have **quenched** the reaction. This occurs in the following way.

When the excited states of molecules have long enough lifetimes, they often can transfer their excitation energy to another molecule. The mechanisms of these transfers are complex and cannot be explained here; however, the essential requirements can be outlined. First, for two molecules to exchange their respective states of excitation, the process must occur with an overall decrease in energy. Second, the spin multiplicity of the total system must not change. These two features can be illustrated by the two most common examples of energy transfer—singlet transfer and triplet transfer. In these two examples, the superscript 1 denotes an excited singlet state, the superscript 3 denotes a triplet state, and the subscript 0 denotes a ground-state molecule. The designations A and B represent different molecules.
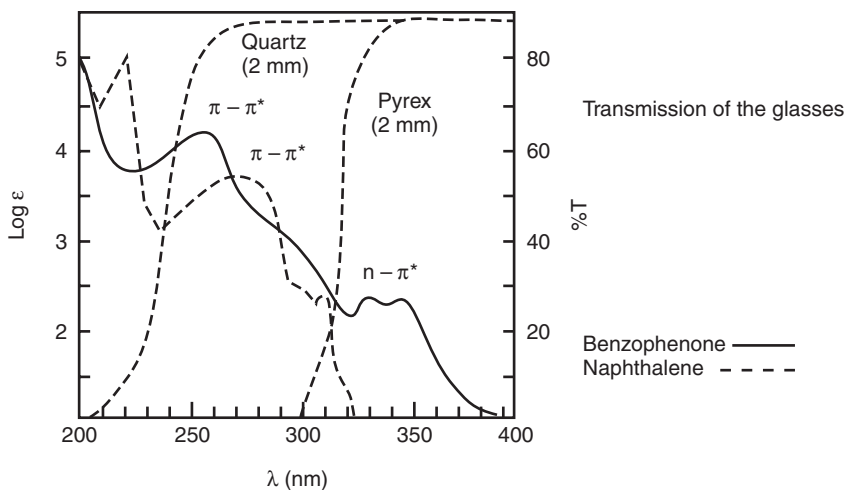
Ultraviolet absorption spectra for benzophenone and naphthalene.

$$A^1 + B_0 \longrightarrow B^1 + A_0 \qquad \text{Singlet energy transfer}$$

$$A^3 + B_0 \longrightarrow B^3 + A_0 \qquad \text{Triplet energy transfer}$$

In singlet energy transfer, excitation energy is transferred from the excited singlet state of A to a ground-state molecule of B, converting B to its excited singlet state and returning A to its ground state. In triplet energy transfer, there is a similar interconversion of excited state and ground state. Singlet energy is transferred through space by a dipole–dipole coupling mechanism, but triplet energy transfer requires the two molecules involved in the transfer to collide. In the usual organic medium, about 10^9 collisions occur per second. Thus, if a triplet state A^3 has a lifetime longer than 10^{-9} second, and if an acceptor molecule B_0, which has a lower triplet energy than that of A^3, is available, energy transfer can be expected. If the triplet A^3 undergoes a reaction (such as photoreduction) at a rate lower than the rate of collisions in the solution, and if an acceptor molecule is added to the solution, the reaction can be *quenched*. The acceptor molecule, which is called a **quencher**, deactivates, or "quenches," the triplet before it has a chance to react. Naphthalene has the ability to quench benzophenone triplets in this way and to stop the photoreduction.

Naphthalene cannot quench the excited-state singlet S_1 of benzophenone because its own singlet has an energy (95 kcal/mol) that is higher than the energy of benzophenone (76 kcal/mol). In addition, the conversion $S_1 \rightarrow T_1$ is very rapid (10^{-10} second) in benzophenone. Thus, naphthalene can intercept only the triplet state of benzophenone. The triplet excitation energy of benzophenone (69 kcal/mol) is transferred to naphthalene ($T_1 = 61$ kcal/mol) in an exothermic collision. Finally, the naphthalene molecule does not absorb light of the wavelengths transmitted by Pyrex (see the ultraviolet absorption spectra given earlier); therefore, benzophenone is not inhibited from absorbing energy when naphthalene is present in solution. Thus, because naphthalene quenches the photoreduction reaction of benzophenone, we can infer that this reaction proceeds via the triplet state T_1 of benzophenone. If naphthalene did not quench the reaction, the singlet state of benzophenone would be indicated as the reactive intermediate. In the following experiment, the photoreduction of benzophenone is attempted both in the presence and in the absence of added naphthalene.

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: *Technique 8 Filtration, Section 8.3

SPECIAL INSTRUCTIONS

This experiment may be performed concurrently with some other experiment. It requires only 15 minutes during the first laboratory period and only about 15 minutes in a subsequent laboratory period about 1 week later (or at the end of the laboratory period if you use a sunlamp).

Using Direct Sunlight. It is important that the reaction mixture be left where it will receive direct sunlight. If it does not, the reaction will be slow and may need more than 1 week for completion. It is also important that the room temperature not be too low, or the benzophenone will precipitate. If you perform this experiment in winter and the laboratory is not heated at night, you must shake the solutions every morning to redissolve the benzophenone. Benzpinacol should not redissolve easily.

Using a Sunlamp. If you wish, you may use a 275-W sunlamp instead of direct sunlight. Place the lamp in a hood that has had its window covered with aluminum foil (shiny side in). The lamp (or lamps) should be mounted in a ceramic socket attached to a ring stand with a three-pronged clamp.

> **CAUTION**
>
> **The purpose of the aluminum foil is to protect the eyes of people in the laboratory. You should not view a sunlamp directly, or damage to the eyes may result. Take all possible viewing precautions.**

Attach samples to a ring stand placed at least 18 inches from the sunlamp. Placing them at this distance will avoid their being heated by the lamp. Heating may cause loss of the solvent. It is a good idea to agitate the samples every 30 minutes. With a sunlamp, the reaction will be complete in 3–4 hours.

SUGGESTED WASTE DISPOSAL

Dispose of the filtrate from the vacuum filtration procedure in the container designated for nonhalogenated organic wastes.

PROCEDURE

Label two 13-mm × 100-mm test tubes near the top of the tubes. The labels should have your name and "No. 1" and "No. 2" written on them. Place 0.50 g of benzophenone in the first tube. Place 0.50 g of benzophenone and 0.05 g of naphthalene in the second tube. Add about 2 mL of 2-propanol (isopropyl alcohol) to each tube, and warm them in a beaker of warm water to dissolve the solids. When the solids have dissolved, add 1 small drop (Pasteur pipet) of glacial acetic acid to each tube and then fill each tube nearly to the top with more 2-propanol. Stopper the tubes tightly with rubber stoppers, shake them well, and place them in a beaker on a windowsill where they will receive direct sunlight.

NOTE: You may be directed by your instructor to use a sunlamp instead of direct sunlight (see Special Instructions).

The reaction requires about 1 week for completion (3 hours with a sunlamp). If the reaction has occurred during this period, the product will have crystallized from the solution. Observe the result in each test tube. Collect the product by vacuum filtration using a small Büchner or Hirsch funnel (see Technique 8, Section 8.3), and allow it to dry. Weigh the product and determine its melting point and percentage yield. At the option of the instructor, obtain the infrared spectrum using the dry film method (see Technique 25, Section 25.4) or in a KBr pellet (see Technique 25, Section 25.5). Submit the product to the instructor in a labeled vial along with the report.

REFERENCE

Vogler, A.; Kunkely, H. Photochemistry and Beer. *J. Chem. Educ.* **1982,** *59,* 25.

EXPERIMENT 51B

Synthesis of *β-Benzopinacolone: The Acid-Catalyzed Rearrangement of Benzpinacol*

The ability of carbocations to rearrange represents an important concept in organic chemistry. In this experiment, the benzpinacol, prepared in Experiment 51A, will rearrange to **benzopinacolone (2,2,2-triphenylacetophenone)** under the influence of iodine in glacial acetic acid.
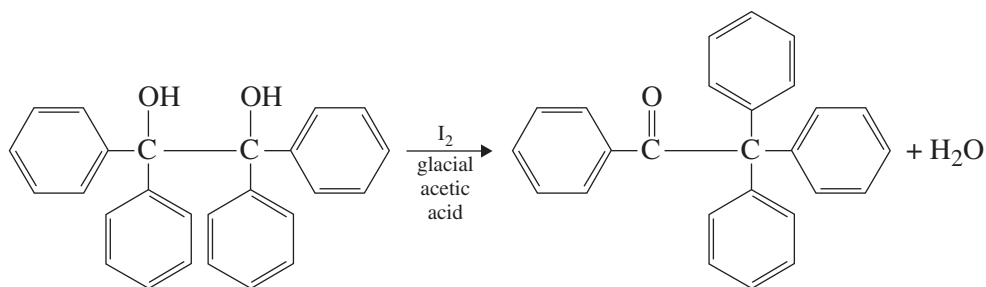
The product is isolated as a crystalline white solid. Benzopinacolone is known to crystallize in two different crystalline forms, each with a different melting point. The **alpha** form has a melting point of 206–207°C, whereas the **beta** form melts at 182°C. The product formed in this experiment is the β-benzopinacolone.

REQUIRED READING

Sign in at www
.cengage.com to access
Pre-Lab Video Exercises
for techniques marked
with an asterisk.

Review: *Technique 7   Reaction Methods, Section 7.2

          *Technique 11   Crystallization: Purification of Solids, Section 11.3

          Technique 25   Infrared Spectroscopy, Part B

          Technique 26   Nuclear Magnetic Resonance Spectroscopy, Part B

Before beginning this experiment, you should read the material dealing with carbocation rearrangements in your lecture textbook.

SPECIAL INSTRUCTIONS

This experiment requires very little time and can be coscheduled with another short experiment.

SUGGESTED WASTE DISPOSAL

All organic residues must be placed in the appropriate container designated for nonhalogenated organic waste.

PROCEDURE

In a 25-mL round-bottom flask, add 5 mL of a 0.015 M solution of iodine dissolved in glacial acetic acid. Add 1 g of benzpinacol and attach a water-cooled condenser. Using a small heating mantle, heat the solution under reflux for 5 minutes. Crystals may begin to appear from the solution during this heating period.

Remove the heat source, and allow the solution to cool slowly. The product will crystallize from the solution as it cools. When the solution has cooled to room temperature, collect the crystals by vacuum filtration using a small Büchner funnel. Rinse the crystals with three 2-mL portions of cold, glacial acetic acid. Allow the crystals to dry in the air overnight. Weigh the dried product, and determine its melting point. Pure β-benzopinacolone melts at 182°C. Obtain the infrared spectrum using the dry-film method (see Technique 25, Section 25.4) or as a KBr pellet (see Technique 25, Section 25.5) and the NMR spectrum in $CDCl_3$ (see Technique 26, Section 26.1).

Calculate the percentage yield. Submit the product to your instructor in a labeled vial, along with your spectra. Interpret your spectra, showing how they are consistent with the rearranged structure of the product.

QUESTIONS

1. Can you think of a way to produce the benzophenone $n-\pi^*$ triplet T_1 *without* having benzophenone pass through its first singlet state? Explain.

2. A reaction similar to the one described here occurs when benzophenone is treated with the metal magnesium (pinacol reduction).

$$2\ Ph_2C{=}O \xrightarrow{\ Mg\ } Ph_2C\underset{|}{\overset{OH}{}}{-}C\underset{|}{\overset{OH}{}}Ph_2$$
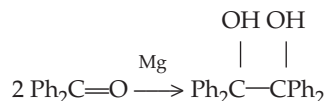
Compare the mechanism of this reaction with the photoreduction mechanism. What are the differences?

3. Which of the following molecules do you expect would be useful in quenching benzophenone photoreduction? Explain.

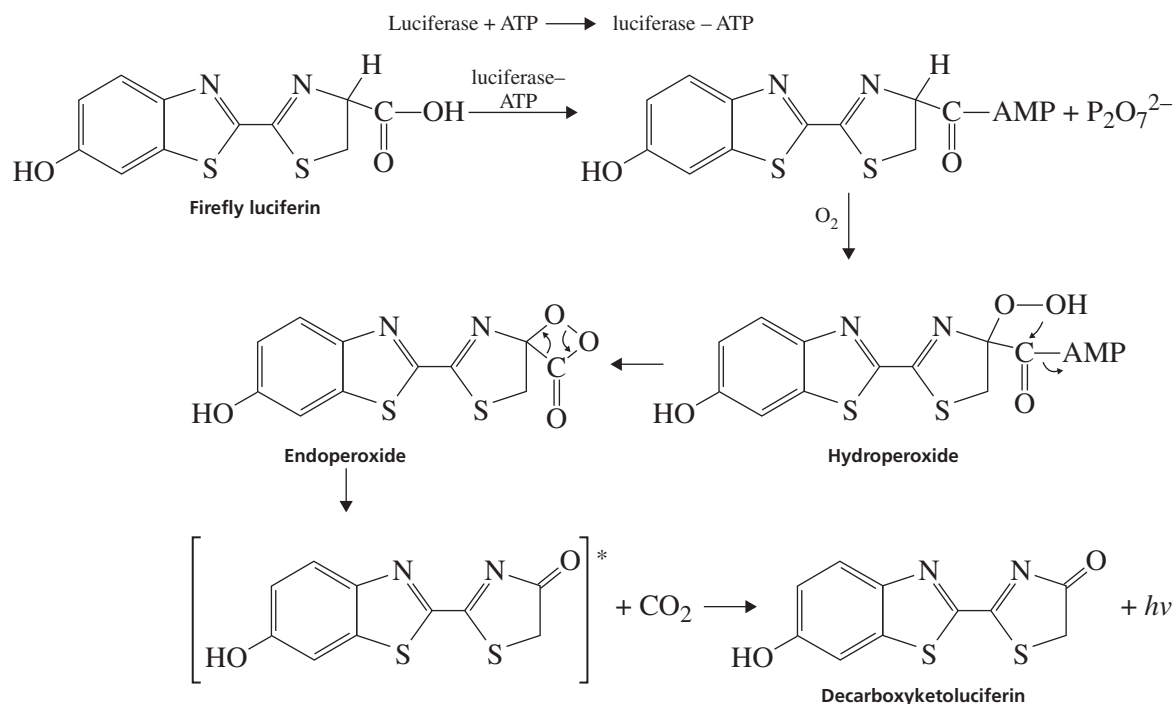|	
Oxygen	(S_1 = 22 kcal/mol)
9,10-Diphenylanthracene	(T_1 = 42 kcal/mol)
trans-1,3-Pentadiene	(T_1 = 59 kcal/mol)
Naphthalene	(T_1 = 61 kcal/mol)
Biphenyl	(T_1 = 66 kcal/mol)
Toluene	(T_1 = 83 kcal/mol)
Benzene	(T_1 = 84 kcal/mol)

Fireflies and Photochemistry

The production of light as a result of a chemical reaction is called **chemiluminescence**. A chemiluminescent reaction generally produces one of the product molecules in an electronically excited state. The excited state emits a photon, and light is produced. If a reaction that produces light is biochemical, occurring in a living organism, the phenomenon is called **bioluminescence**.

The light produced by fireflies and other bioluminescent organisms has fascinated observers for many years. Many different organisms have developed the ability to emit light. They include bacteria, fungi, protozoans, hydras, marine worms, sponges, corals, jellyfish, crustaceans, clams, snails, squids, fish, and insects. Curiously, among the higher forms of life, only fish are included on the list. Amphibians, reptiles, birds, mammals, and the higher plants are excluded. Among the marine species, none is a freshwater organism. The excellent *Scientific American* article by McElroy and Seliger (see References) delineates the natural history, characteristics, and habits of many bioluminescent organisms.

The first significant studies of a bioluminescent organism were performed by the French physiologist Raphael Dubois in 1887. He studied the mollusk *Pholas dactylis,* a bioluminescent clam, indigenous to the Mediterranean Sea. Dubois found that a cold-water extract of the clam was able to emit light for several minutes following the extraction. When the light emission ceased, it could be restored, Dubois found, by a material extracted from the clam by hot water. A hot-water extract of the clam alone did not produce the luminescence. Reasoning carefully, Dubois concluded that there was an enzyme in the cold-water extract that was destroyed in hot water. The luminescent compound, however, could be extracted without destruction in either hot or cold water. He called the luminescent material **luciferin**, and the enzyme that induced it to emit light **luciferase**; both names were derived from *Lucifer,* a Latin name meaning "bearer of light." Today the luminescent materials from all organisms are called *luciferins,* and the associated enzymes are called *luciferases.*

The most extensively studied bioluminescent organism is the firefly. Fireflies are found in many parts of the world and probably represent the most familiar example of bioluminescence. In such areas, on a typical summer evening, fireflies, or "lightning bugs," can frequently be seen to emit flashes of light as they cavort over the lawn or in the garden. It is now universally accepted that the luminescence of fireflies is a mating strategy. The male firefly flies about 2 feet above the ground and emits flashes of light at regular intervals. The female, who remains stationary on the ground, waits a characteristic interval and then flashes a response. In return, the male reorients his direction of flight toward her and flashes a signal once again. The entire cycle is rarely repeated more than 5 to 10 times before the male reaches the female. Fireflies of different species can recognize one another by their flash patterns, which vary in number, rate, and duration among species.

Although the total structure of the luciferase enzyme of the American firefly *Photinus pyralis* is unknown, the structure of luciferin has been established. In spite of a large amount of experimental work, however, the complete nature of the chemical reactions that produce the light is still subject to some controversy. It is possible, nevertheless, to outline the most salient details of the reaction.

Luciferase + ATP $\longrightarrow$ luciferase – ATP

Firefly luciferin

luciferase–
ATP

$\text{C}-\text{AMP} + P_2O_7{}^{2-}$

O$_2$

Endoperoxide

Hydroperoxide

$+ \, CO_2 \longrightarrow$

$+ \, h\nu$

Decarboxyketoluciferin

Besides luciferin and luciferase, other substances—magnesium(II), ATP (adenosine triphosphate), and molecular oxygen—are needed to produce the luminescence. In the postulated first step of the reaction, luciferase complexes with an ATP molecule. In the second step, luciferin binds to luciferase and reacts with the already-bound ATP molecule to become "primed." In this reaction, pyrophosphate ion is expelled, and AMP (adenosine monophosphate) becomes attached to the carboxyl group of luciferin. In the third step, the luciferin–AMP complex is oxidized by molecular oxygen to form a hydroperoxide; this cyclizes with the carboxyl group, expelling AMP and forming the cyclic endoperoxide. This reaction would be difficult if the carboxyl group of luciferin had not been primed with ATP. The endoperoxide is unstable and readily decarboxylates, producing decarboxyketoluciferin in an *electronically excited state*, which is deactivated by the emission of a photon (fluorescence). Thus, it is the cleavage of the four-membered-ring endoperoxide that leads to the electronically excited molecule and hence the bioluminescence.


$\longrightarrow \, 2 \quad \text{O} \, + h\nu$
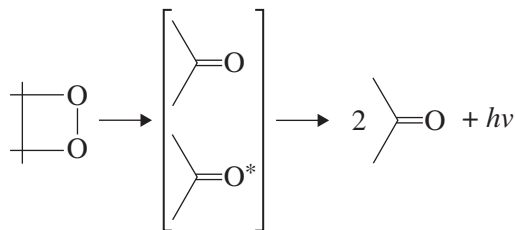
That one of the two carbonyl groups, either that of the decarboxyketoluciferin or that of the carbon dioxide, should be formed in an excited state can be readily predicted from the orbital symmetry conservation principles of Woodward and Hoffmann. This reaction is formally like the decomposition of a cyclobutane ring and yields two ethylene molecules. In analyzing the forward course of that reaction, that is, 2 ethylene $\longrightarrow$ cyclobutane, one can easily show that the reaction, which involves four π electrons, is forbidden for two ground-state ethylenes but allowed

for only one ethylene in the ground state and the other in an excited state. This suggests that, in the reverse process, one of the ethylene molecules should be formed in an excited state. Extending these arguments to the endoperoxide also suggests that one of the two carbonyl groups should be formed in its excited state.

The emitting molecule, decarboxyketoluciferin, has been isolated and synthesized. When it is excited photochemically by photon absorption in basic solution (pH > 7.5–8.0), it fluoresces, giving a fluorescence emission spectrum that is identical to the emission spectrum produced by the interaction of firefly luciferin and firefly luciferase. The emitting form of decarboxyketoluciferin has thus been identified as the **enol dianion**. In neutral or acidic solution, the emission spectrum of decarboxyketoluciferin does not match the emission spectrum of the bioluminescent system.

The exact function of the enzyme firefly luciferase is not yet known, but it is clear that all these reactions occur while luciferin is bound to the enzyme as a substrate. Also, because the enzyme undoubtedly has several basic groups ($-COO^-$, $-NH_2$, and so on), the buffering action of those groups would easily explain why the enol dianion is also the emitting form of decarboxyketoluciferin in the biological system.

Enol dianion
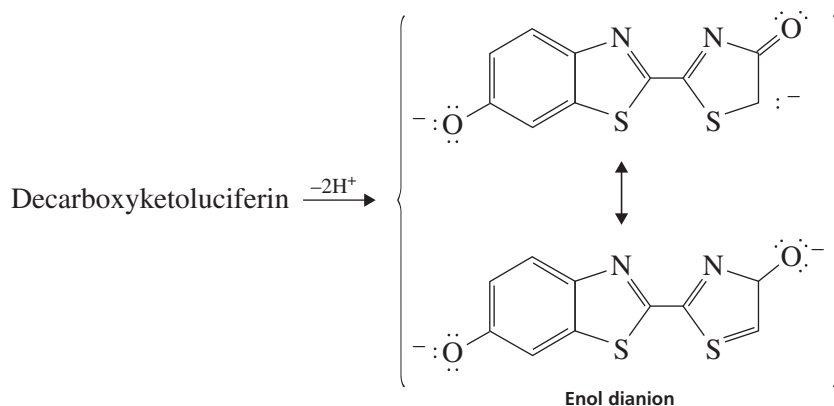
Most chemiluminescent and bioluminescent reactions require oxygen. Likewise, most produce an electronically excited emitting species through the decomposition of a **peroxide** of one sort or another. In the experiment that follows, a **chemiluminescent** reaction that involves the decomposition of a peroxide intermediate is described.

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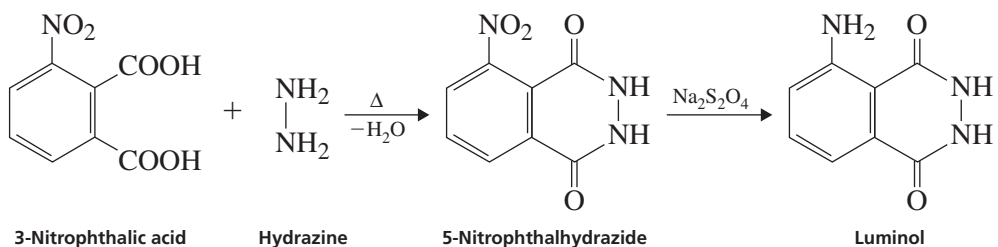
Luminol

Chemiluminescence

Energy transfer
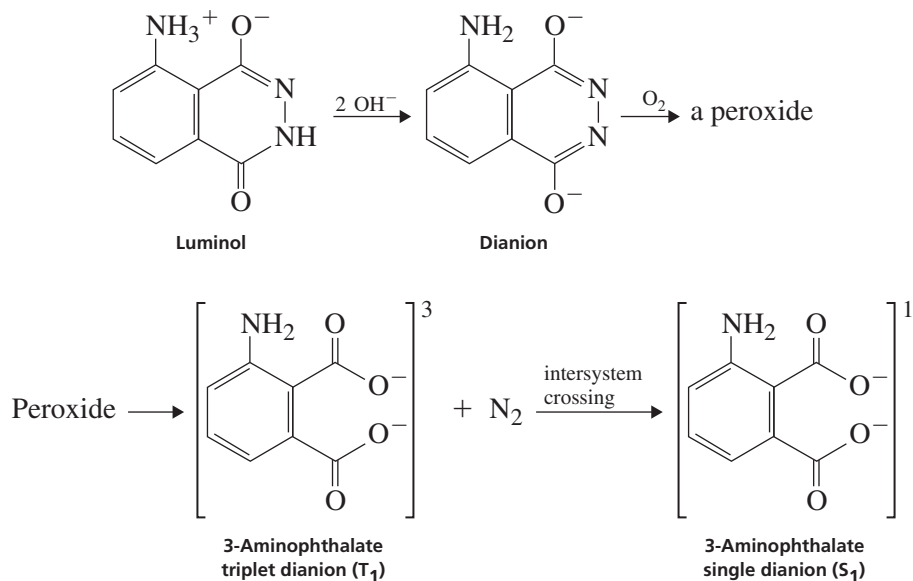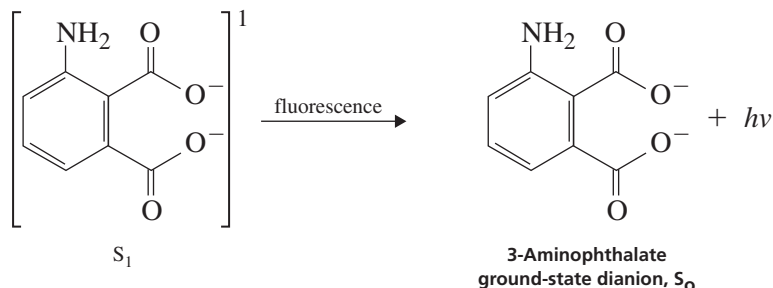
Reduction of a nitro group

Amide formation

In this experiment, the chemiluminescent compound **luminol**, or **5-amino-phthalhydrazide**, will be synthesized from 3-nitrophthalic acid.

3-Nitrophthalic acid   Hydrazine   5-Nitrophthalhydrazide   Luminol

The first step of the synthesis is the simple formation of a cyclic diamide, 5-nitrophthal-hydrazide, by reaction of 3-nitrophthalic acid with hydrazine. Reduction of the nitro group with sodium dithionite affords luminol.

In neutral solution, luminol exists largely as a dipolar anion (zwitterion). This dipolar ion exhibits a weak blue fluorescence after being exposed to light. However, in alkaline solution, luminol is converted to its dianion, which may be oxidized by molecular oxygen to give an intermediate that is chemiluminescent. The reaction is thought to have the following sequence:

Luminol   Dianion

3-Aminophthalate
triplet dianion (T$_1$)

3-Aminophthalate
single dianion (S$_1$)

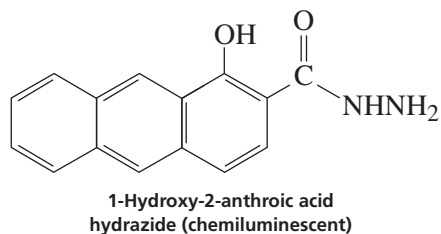3-Aminophthalate
ground-state dianion, S$_O$

The dianion of luminol undergoes a reaction with molecular oxygen to form a peroxide of unknown structure. This peroxide is unstable and decomposes with the evolution of nitrogen gas, producing the 3-aminophthalate dianion in an electronically excited state. The excited dianion emits a photon that is visible as light. One very attractive hypothesis for the structure of the peroxide postulates a cyclic endoperoxide that decomposes by the following mechanism:
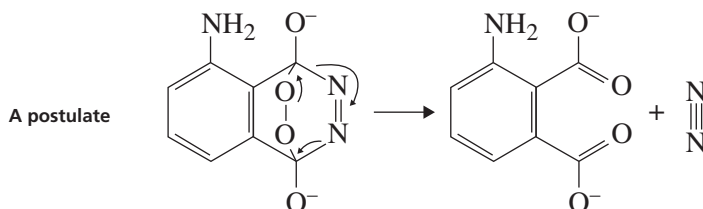

Certain experimental facts argue against this intermediate, however. For instance, certain acyclic hydrazides that cannot form a similar intermediate have also been found to be chemiluminescent.

1-Hydroxy-2-anthroic acid
hydrazide (chemiluminescent)

Although the nature of the peroxide is still debatable, the remainder of the reaction is well understood. The chemical products of the reaction have been shown to be 3-aminophthalate dianion and molecular nitrogen. The intermediate that emits light has been identified definitely as the *excited-state singlet* of the 3-aminophthalate dianion.[1] Thus, the fluorescence emission spectrum of the 3-aminophthalate dianion (produced by photon absorption) is identical to the spectrum of the light emitted from the chemiluminescent reaction. However, for numerous complicated reasons, it is believed that the 3-aminophthalate dianion is formed first as a vibrationally excited triplet state molecule, which makes the intersystem crossing to the singlet state before the emission of a photon.

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[1]The terms *singlet, triplet, intersystem crossing, energy transfer, and quenching* are explained in Experiment 51.

3-Aminophthalate dianion
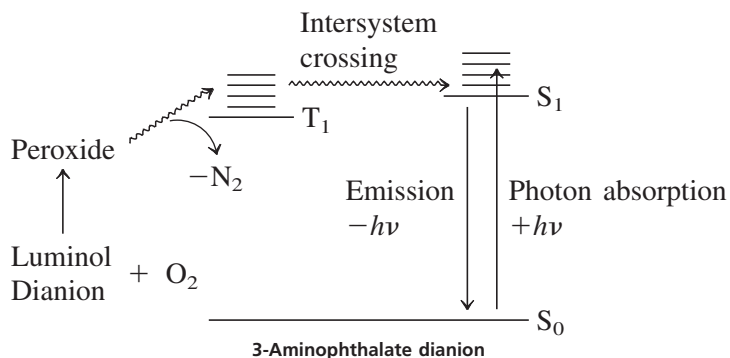
Fluorescence emission spectrum of the 3-aminophthalate dianion.

The excited state of the 3-aminophthalate dianion may be quenched by suitable acceptor molecules, or the energy (about 50–80 kcal/mol) may be transferred to give emission from the acceptor molecules. Several such experiments are described in the following procedure.

The system chosen for the chemiluminescence studies of luminol in this experiment uses dimethylsulfoxide [$(CH_3)_2SO$] as the solvent, potassium hydroxide as the base required for the formation of the dianion of luminol, and molecular oxygen. Several alternative systems have been used, substituting hydrogen peroxide and an oxidizing agent for molecular oxygen. An aqueous system using potassium ferricyanide and hydrogen peroxide is an alternative system used frequently.

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White, E. H.; Rosewell, D. F. The Chemiluminescence of Organic Hydrazides. *Acc. Chem. Res.* **1970,** *3*, 54.

REQUIRED READING

Review: Technique 7   Reaction Methods, Section 7.9

New: Essay   Fireflies and Photochemistry

SPECIAL INSTRUCTIONS

This entire experiment can be completed in about 1 hour. When you are working with hydrazine, you should remember that it is toxic and should not be spilled on the skin. It is also a suspected carcinogen. Dimethylsulfoxide may also be toxic; avoid breathing the vapors or spilling it on your skin.

A darkened room is required to observe adequately the chemiluminescence of luminol. A darkened hood that has had its window covered with butcher paper or aluminum foil also works well. Other fluorescent dyes, besides those mentioned (for instance, 9,10-diphenylanthracene), can also be used for the energy-transfer experiments. The dyes selected may depend on what is immediately available. The instructor may have each student use one dye for the energy-transfer experiments, with one student making a comparison experiment without a dye.

SUGGESTED WASTE DISPOSAL

Dispose of the filtrate from the vacuum filtration of 5-nitrophthalhydrazide in the container designated for nonhalogenated organic solvents. The filtrate from the vacuum filtration of 5-aminophthalhydrazide may be diluted with water and poured into the waste container designated for aqueous waste. The mixture containing potassium hydroxide, dimethylsulfoxide, and luminol should be placed in the special container designated for this material.

PROCEDURE

Part A. 3-Nitrophthalhydrazide

Place 0.60 g of 3-nitrophthalic acid and 0.8 mL of a 10% aqueous solution of hydrazine (use gloves) in a small (15-mm × 125-mm) sidearm test tube.[2] At the same time, heat 8 mL of water in a beaker on a hot plate to about 80°C. Heat the test tube over a microburner until the solid dissolves. Add 1.6 mL of triethylene glycol, and clamp the test tube in an upright position on a ring stand. Place a thermometer (do not seal the system) and a bolling stone in the test tube, and attach a piece of pressure tubing to the sidearm. Connect this tubing to an aspirator (use a trap). The thermometer bulb should be in the liquid as much as possible Heat the solution with a microburner until the liquid boils vigorously and the refluxing water vapor is drawn away by the aspirator vacuum (the temperature will rise to about 120°C). Continue heating and allow the temperature to increase rapidly until it rises just above 200°C. This heating requires 2–3 minutes, and you must watch the temperature closely to avoid heating the mixture well above 200°C. Remove the burner briefly when this temperature has been achieved, and then resume gentle heating to maintain a fairly constant temperature of 220–230°C for about 3 minutes. Allow the test tube to cool to about 100°C, add the 8 mL of hot water that was prepared previously, and cool the test tube to room temperature by allowing tap water to flow over the outside of the test tube. Collect the brown crystals of 5-nitrophthalhydrazide by vacuum filtration, using a small Hirsch funnel. It is not necessary to dry the product before you go on to the next reaction step.

Part B. Luminol (5-Aminoph-thalhydrazide)

Transfer the moist 5-nitrophthalhydrazide to a 20-mm × 150-mm test tube. Add 2.6 mL of a 10% sodium hydroxide solution, and agitate the mixture until the hydrazide dissolves. Add 1.6 g of sodium dithionite dihydrate (sodium hydrosulfite dihydrate, $Na_2S_2O_4 \cdot 2H_2O$). Using a pasteur pipet, add 2–4 mL of water to wash the solid from the walls of the test tube. Add a boiling stone to the test tube. Heat the test tube until the solution boils. Agitate the solution and maintain the boiling, continuing the agitation for at least 5 minutes. Add 1.0 mL of glacial acetic acid, and cool the test tube to room temperature by allowing tap water to flow over the outside of it. Agitate the mixture during the cooling step. Collect the light yellow or gold crystals of luminol by vacuum filtration, using a small Hirsch funnel. Save a small sample of this product, allow it to dry overnight, and determine its melting point (mp 319–320°C). The remainder of the luminol may be used without drying for the chemiluminescence experiments. When drying the luminol, it is best to use a vacuum desiccator charged with calcium sulfate drying agent.

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[2]A 10% aqueous solution of hydrazine can be prepared by diluting 15.6 g of a commercial 64% hydrazine solution to a volume of 100 mL using water.

Part C. Chemiluminescence Experiments

C A U T I O N

⚠

Be careful not to allow any of the mixture to touch your skin while shaking the flask. Hold the stopper securely.

Cover the bottom of a 10-mL Erlenmeyer flask with a layer of potassium hydroxide pellets. Add enough dimethylsulfoxide to cover the pellets. Add about 0.025 g of the moist luminol to the flask, stopper it, and shake it vigorously to mix air into the solution.[3] In a dark room, a faint glow of bluish white light will be visible. The intensity of the glow will increase with continued shaking of the flask and occasional removal of the stopper to admit more air.

To observe energy transfer to a fluorescent dye, dissolve 1 or 2 crystals of the indicator dye in about 0.25 mL of water. Add the dye solution to the dimethylsulfoxide solution of luminol, stopper the flask, and shake the mixture vigorously. Observe the intensity and the color of the light produced.

A table of some dyes and the colors produced when they are mixed with luminol is given below. Other dyes not included on this list may also be tested in this experiment.

Fluorescent Dye	Color
No dye	Faint bluish white
2,6-Dichloroindophenol	Blue
9-Aminoacridine	Blue green
Eosin	Salmon pink
Fluorescein	Yellow green
Dichlorofluorescein	Yellow orange
Rhodamine B	Green
Phenolphthalein	Purple

E S S A Y

The Chemistry of Sweeteners

Americans, as no other nationalities in the world do, possess a particularly demanding sweet tooth. Our craving for sugar, either added to food or included in candies and desserts, is astounding. Even when we are choosing a food that is not considered to be sweet, we ingest large quantities of sugar. A casual examination of the *Nutrition Facts* label and the list of ingredients of virtually any processed food will reveal that sugar is generally one of the principal ingredients.

Americans, paradoxically, are also obsessed by the need to diet. As a result, the search for noncaloric substitutes for natural sugar represents a multi-million-dollar

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[3]An alternative method for demonstrating chemiluminescence, using potassium ferricyanide and hydrogen peroxide as oxidizing agents, is described in E. H. Huntress, L. N. Stanley, and A. S. Parker, *Journal of Chemical Education, 11* (1934): 142.

business in this country. There is a ready market for foods that taste sweet but don't contain sugar.

For a molecule to taste sweet, it must fit into a taste bud site where a nerve impulse can carry the message of sweetness from the tongue to the brain. Not all natural sugars, however, trigger an equivalent neural response. Some sugars, such as glucose, have a relatively bland taste, and others, such as fructose, taste very sweet. Fructose, in fact, has a sweeter taste than common table sugar or sucrose. Furthermore, individuals vary in their ability to perceive sweet substances. The relationship between perceived sweetness and molecular structure is very complicated, and, to date, it is rather poorly understood.

The most common sweetener is, of course, common table sugar or **sucrose**. Sucrose is a disaccharide, consisting of a unit of glucose and a unit of fructose connected by a 1,2-glycosidic linkage. Sucrose is purified and crystallized from the syrups that are extracted from such plants as sugar cane and sugar beets.
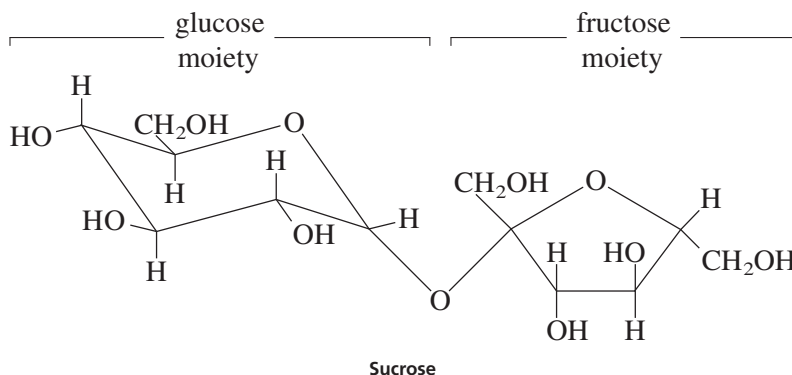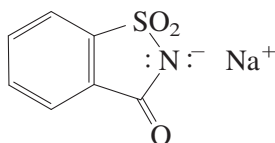

Sucrose

When sucrose is hydrolyzed, it yields one molecule of D-fructose and one molecule of D-glucose. This hydrolysis is catalyzed by an enzyme, **invertase**, and produces a mixture known as **invert sugar**. Invert sugar derives its name from the fact that the mixture is levorotatory, whereas sucrose is dextrorotatory. Thus, the sign of rotation has been "inverted" in the course of hydrolysis. Invert sugar is somewhat sweeter than sucrose, owing to the presence of free fructose. **Honey** is composed mostly of invert sugar, which is the reason it has such a sweet taste.

Persons who suffer from diabetes are urged to avoid sugar in their diets. Nevertheless, those individuals also have a craving for sweet foods. A substitute sweetener that is used for food items recommended for diabetics is **sorbitol**, which is an alcohol formed by the catalytic hydrogenation of glucose. Sorbitol has about 60% the sweetness of sucrose. It is a common ingredient in products such as sugarless chewing gum. Even though sorbitol is a different substance from sucrose, it still possesses about the same number of calories per gram. Therefore, sorbitol is not a suitable sweetener for diet foods or beverages.


Sorbitol
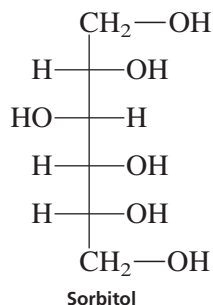
As sucrose and honey are implicated in problems of tooth decay, as well as being culprits in the continuing battle against obesity, an active field of study is the search for new, noncaloric, noncarbohydrate sweeteners. Even if such a nonnutritive sweetener possessed some calories, if it were very sweet, it would not be necessary to use as much of the sweetener; therefore, the impact on dental hygiene and on diet would be less.

The first artificial sweetener to be used extensively was **saccharin**, which is used commonly as its more soluble sodium salt. Saccharin is about 300 times sweeter than sucrose. The discovery of saccharin was hailed as a great benefit for diabetics, because it could be used as an alternative to sugar. As a pure substance, the sodium salt of saccharin has a very intense sweet taste, with a somewhat bitter aftertaste. Because it has such an intense taste, it can be used in very small amounts to achieve the desired effect. In some preparations, sorbitol is added to ameliorate the bitter aftertaste. Prolonged studies on laboratory animals have shown that saccharin is a possible carcinogen. In spite of this health risk, the government has permitted saccharin to be used in foods that are intended to be used by diabetics.


Saccharin (sodium salt)

Another artificial sweetener, which gained wide use in the 1960s and 1970s, is **sodium cyclamate**. Sodium cyclamate, which is 33 times as sweet as sucrose, belongs to the class of compounds known as the **sulfamates**. The sweet taste of many of the sulfamates has been known since 1937 when Sveda accidentally discovered that sodium cyclamate had a powerfully sweet taste. The availability of sodium cyclamate spurred the popularity of diet soft drinks. Unfortunately, in the 1970s, research showed that a metabolite of sodium cyclamate, cyclohexylamine, posed some potentially serious health risks, including a risk of cancer. This sweetener has thus been withdrawn from the market.
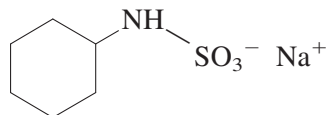
Sodium cyclamate

The most widely used artificial sweetener available today is a dipeptide, consisting of a unit of aspartic acid linked to a unit of phenylalanine. The carboxyl group of the phenylalanine moiety has been converted to the methyl ester. This substance is known commercially as **aspartame**, but it is also sold under the trade names **NutraSweet** and **Equal**. Aspartame is about 200 times sweeter than sucrose. It is found in diet soft drinks, puddings, juices, and many other foods. Unfortunately, aspartame is not stable when heated, so it is not suitable as an ingredient in cooking. Other dipeptides that have structures similar to that of aspartame are many thousands of times sweeter than sucrose.
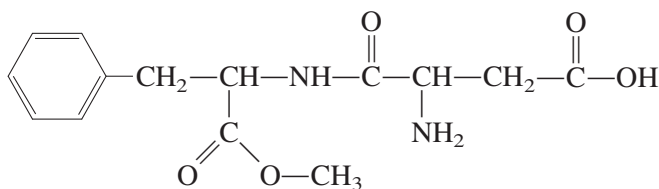
Aspartame

When aspartame was being developed as a commercial product, concern was raised over potential health hazards associated with its use. The potential cancer-causing effects of aspartame, along with other potential adverse side effects, were considered. Extensive testing of this product demonstrated that it met health-risk criteria established by the Food and Drug Administration, which granted approval for the sale of aspartame as a food additive in 1974.

The search for new substances that can serve as sweeteners continues. There is a great deal of interest in substances that are naturally occurring and that can be isolated from various plants. In addition, research, including studies on molecular modeling and spectroscopic investigations, is being conducted to clarify exactly what structural features are required for a sweet taste. Armed with that information, chemists will then be able to synthesize molecules that will be designed specifically for their sweet taste.

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Bragg, R. W.; Chow, Y.; Dennis, L.; Ferguson, L. N.; Howell, S.; Morga, G.; Ogino, C.; Pugh, H.; Winters, M. Sweet Organic Chemistry. *J. Chem. Educ.* **1978,** *55,* 281.

Crammer, B.; Ikan, R. Sweet Glycosides from the Stevia Plant. *Chem. Br.* **1986,** *22*, 915.

Sharon, N. Carbohydrates. *Sci. Am.* **1980,** *243*, 90.

53   EXPERIMENT 53

Carbohydrates

In this experiment, you will perform tests that distinguish among various carbohydrates. The carbohydrates included and the classes they represent are as follows:

Aldopentoses: xylose and arabinose

Aldohexoses: glucose and galactose

Ketohexoses: fructose

Disaccharides: lactose and sucrose

Polysaccharides: starch and glycogen

The structures of these carbohydrates can be found in your lecture textbook. The tests are classified in the following groups:

A. Tests based on the production of furfural or a furfural derivative: Molisch's test, Bial's test, and Seliwanoff's test

B. Tests based on the reducing property of a carbohydrate (sugar): Benedict's test and Barfoed's test

C. Osazone formation

D. Iodine test for starch

      E. Hydrolysis of sucrose

      F. Mucic acid test for galactose and lactose

      G. Tests on unknowns

REQUIRED READING

New: Read the sections in your lecture textbook that give the structures and describe the chemistry of aldopentoses, aldohexoses, ketohexoses, disaccharides, and polysaccharides.

SPECIAL INSTRUCTIONS

All of the procedures in this experiment involve simple test tube reactions. Most of the tests are short; however, Seliwanoff's test, osazone formation, and the mucic acid test take relatively longer to complete. You will need a minimum of 10 test tubes (15 mm × 125 mm) numbered in order. Clean them carefully each time they are used. The laboratory instructor will prepare the 1% solutions of carbohydrates and the reagents needed for the tests in advance. Be sure to shake the starch solution before using it.

Phenylhydrazine, which is used for the osazone formation procedure, is considered to be a potential carcinogen. It is important to wear protective gloves when using this reagent. Wash your hands thoroughly in case this substance accidentally comes in contact with your skin.

SUGGESTED WASTE DISPOSAL

The reagents used in this experiment are relatively harmless aqueous solutions. They can be discarded safely by diluting them and pouring them into the sink. Residues that contain copper should be placed in a designated waste container. Phenylhydrazine, which is used for the osazone formation procedure, must be dissolved in 6 M hydrochloric acid. The resulting solution may then be diluted with water and poured into a waste container marked specifically for the disposal of phenylhydrazine.
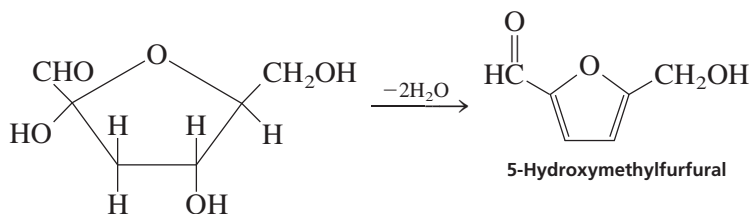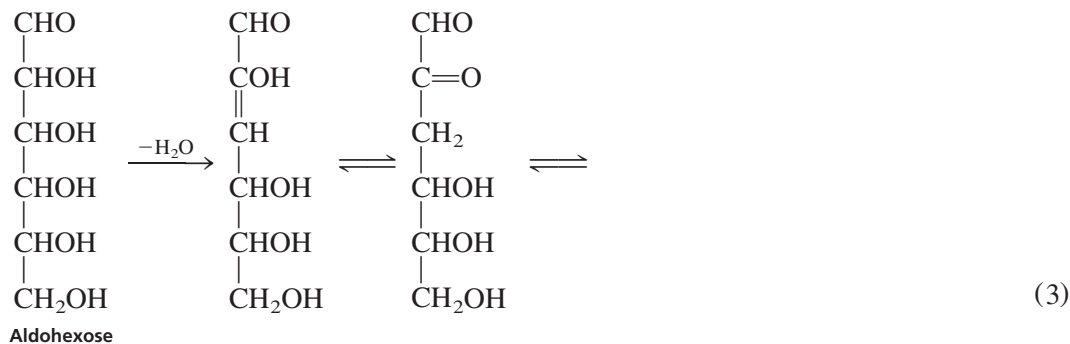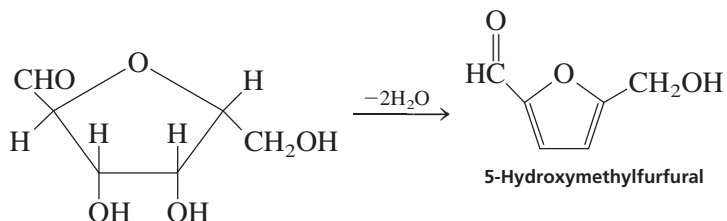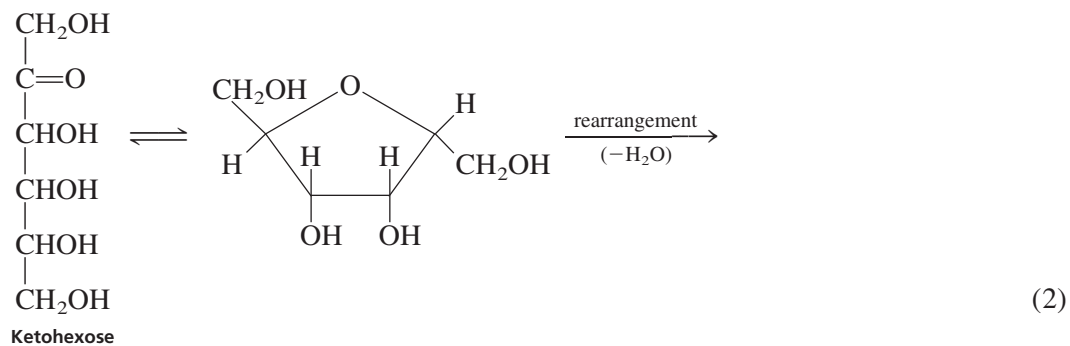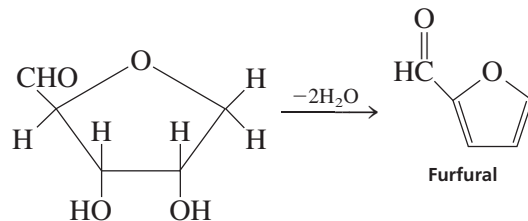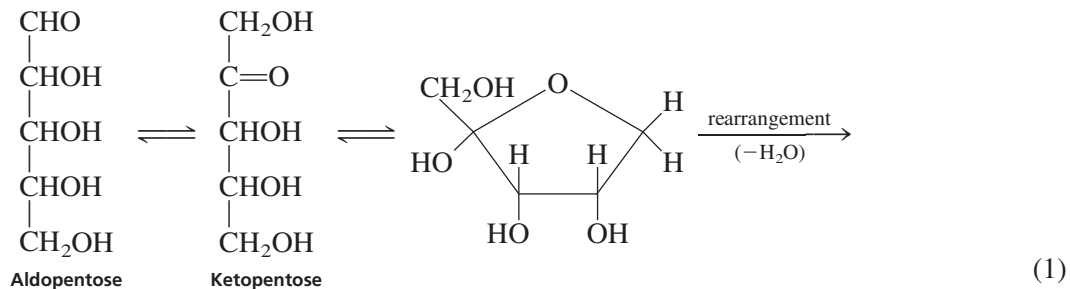
NOTES TO THE INSTRUCTOR

Phenylhydrazine is a suspected carcinogen. Students should wear gloves when handling this substance.
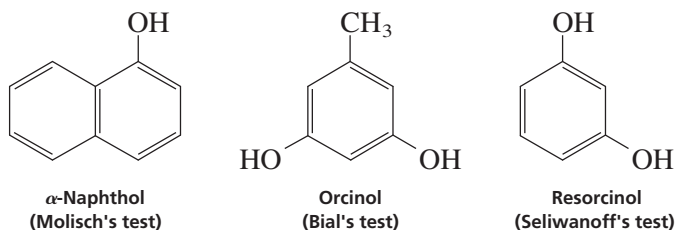
Part A. Tests Based on Production of Furfural or a Furfural Derivative

Under acidic conditions, aldopentoses and ketopentoses *rapidly* undergo dehydration to give furfural (see equation 1). Ketohexoses *rapidly* yield 5-hydroxymethylfurfural (see equation 2). Disaccharides and polysaccharides can first be hydrolyzed in an acid medium to produce monosaccharides, which then react to give furfural or 5-hydroxymethylfurfural.

Aldohexoses are *slowly* dehydrated to 5-hydroxymethylfurfural. One possible mechanism is shown in equation 3. The mechanism is different from that given in equations 1 and 2 in that dehydration occurs at an early step and the rearrangement step is absent.

Once furfural or 5-hydroxymethylfurfural is produced by equations 1, 2, or 3, either will then react with a phenol to produce a colored condensation product. The substance α-naphthol is used in Molisch's test, orcinol in Bial's test, and resorcinol in Seliwanoff's test.

CHO
CHOH
CHOH   ⇌
CHOH
CH₂OH
Aldopentose

CH₂OH
C=O
CHOH   ⇌
CHOH
CH₂OH
Ketopentose

CH₂OH   O
HO   H   H   H
HO   OH

$\xrightarrow[(-H_2O)]{\text{rearrangement}}$

(1)

CHO   O   H
H   H   H   H
HO   OH

$\xrightarrow{-2H_2O}$

O
HC   O
Furfural

CH₂OH
C=O
CHOH
CHOH   ⇌
CHOH
CH₂OH
Ketohexose

CH₂OH   O   H
H   H   H   CH₂OH
OH   OH

$\xrightarrow[(-H_2O)]{\text{rearrangement}}$

(2)

CHO   O   H
H   H   H   CH₂OH
OH   OH

$\xrightarrow{-2H_2O}$

O
HC   O   CH₂OH
5-Hydroxymethylfurfural

CHO
CHOH
CHOH
CHOH
CHOH
CH₂OH
Aldohexose

$\xrightarrow{-H_2O}$

CHO
COH
CH
CHOH
CHOH
CH₂OH

⇌

CHO
C=O
CH₂
CHOH
CHOH
CH₂OH

⇌

(3)

CHO   O   CH₂OH
HO   H   H   H
H   OH

$\xrightarrow{-2H_2O}$

O
HC   O   CH₂OH
5-Hydroxymethylfurfural

α-Naphthol
(Molisch's test)

Orcinol
(Bial's test)

Resorcinol
(Seliwanoff's test)

The colors and the rates of formation of these colors are used to differentiate between the carbohydrates. The various color tests are discussed in Sections 1, 2, and 3. A typical colored product formed from furfural and α-naphthol (Molisch's test) is the following (equation 4):

Purple
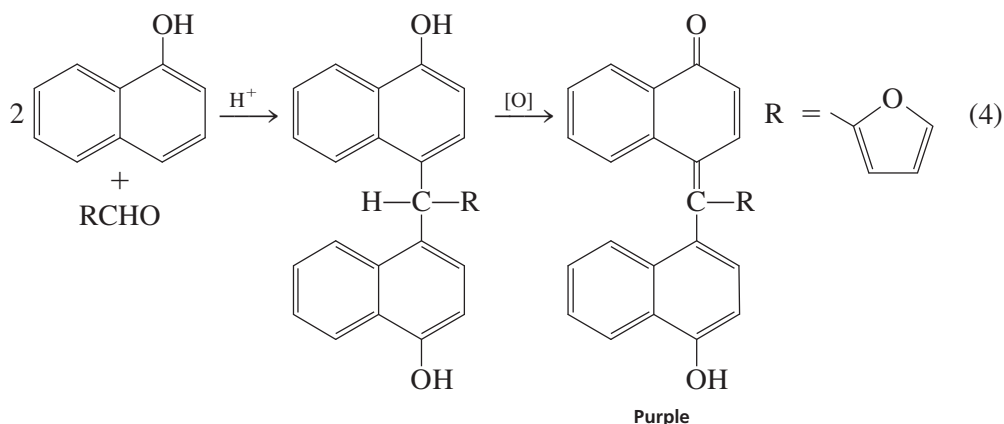
1. Molisch's Test for Carbohydrates

Molisch's test is a *general* test for carbohydrates. Most carbohydrates are dehydrated with concentrated sulfuric acid to form furfural or 5-hydroxymethyl-furfural. These furfurals react with the α-naphthol in the test reagent to give a purple product. Compounds other than carbohydrates may react with the reagent to give a positive test. A negative test usually indicates that there is no carbohydrate.

Procedure for Molisch's Test. Place 1 mL of each of the following 1% carbohydrate solutions in nine separate test tubes: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch (shake it), and glycogen. Also add 1 mL of distilled water to another tube to serve as a control.

Add two drops of Molisch's reagent to each test tube and thoroughly mix the contents of the tube.[1] Tilt each test tube slightly and cautiously add 1 mL of concentrated sulfuric acid down the sides of the tubes. An acid layer forms at the bottom of the tubes. Note and record the color at the interface between the two layers in each tube. A purple color constitutes a positive test.

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[1]For Molisch's reagent, dissolve 2.5 g of α-naphthol in 50 mL of 95% ethanol.

2. Bial's Test for Pentoses

Bial's test is used to differentiate pentose sugars from hexose sugars. Pentose sugars yield furfural on dehydration in acidic solution. Furfural reacts with orcinol and ferric chloride to give a blue-green condensation product. Hexose sugars give 5-hydroxy-methylfurfural, which reacts with the reagent to yield colors such as green, brown, and reddish-brown.

Procedure for Bial's Test. Place 1 mL of each of the following 1% carbohydrate solutions in separate test tubes: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch (shake it), and glycogen. Also add 1 mL of distilled water to another tube to serve as a control.

  Add 1 mL of Bial's reagent to each test tube.[2] Carefully heat each tube over a Bunsen burner flame until the mixture just begins to boil. Note and record the color produced in each test tube. If the color is not distinct, add 2.5 mL of water and 0.5 mL of 1-pentanol to the test tube. After shaking the test tubes, again observe and record the color. The colored condensation product will be concentrated in the 1-pentanol layer.

3. Seliwanoff's Test for Ketohexoses

Seliwanoff's test depends on the relative rates of dehydration of carbohydrates. A ketohexose reacts rapidly by equation 2 to give 5-hydroxymethylfurfural, whereas an aldohexose reacts more slowly by equation 3 to give the same product. Once 5-hydroxy-methylfurfural is produced, it reacts with resorcinol to give a dark red condensation product. If the reaction is followed for some time, you will observe that sucrose hydrolyzes to give fructose, which eventually reacts to produce a dark red color.

Procedure for Seliwanoff's Test. Prepare a boiling-water bath for this experiment. Place 0.5 mL of each of the following 1% carbohydrate solutions in separate test tubes: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch (shake it), and glycogen. Add 0.5 mL of distilled water to another tube to act as a control.

  Add 2 mL of Seliwanoff's reagent to each test tube.[3] Place all 10 tubes in a beaker of boiling-water for *60 seconds*. Remove them and note the results in a notebook.

  For the remainder of Seliwanoff's test, it is convenient to place a group of 3 or 4 tubes in the boiling-water bath and to complete the observations before going on to the next group of tubes. Place 3 or 4 tubes in the boiling-water bath. Observe the color in each of the tubes at 1-minute intervals for 5 minutes beyond the original minute. Record the results at each 1-minute interval. Leave the tubes in the boiling-water bath during the entire 5-minute period. After the first group has been observed, remove that set of test tubes and place the next
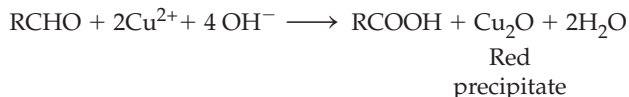
[2]Dissolve 3 g of orcinol in 1 L of concentrated hydrochloric acid, and add 3 mL of 10% aqueous ferric chloride.
[3]Dissolve 0.5 g of resorcinol in 1 L of dilute hydrochloric acid (one volume of concentrated hydrochloric acid and two volumes of distilled water).

group of 3 or 4 tubes in the bath. Follow the color changes as before. Finally, place the last group of tubes in the bath, and follow the color changes over the 5-minute period.

Part B. Tests Based on the Reducing Property of a Carbohydrate (Sugar)

Monosaccharides and those disaccharides that have a potential aldehyde group will reduce reagents such as Benedict's solution to produce a red precipitate of copper(I) oxide:
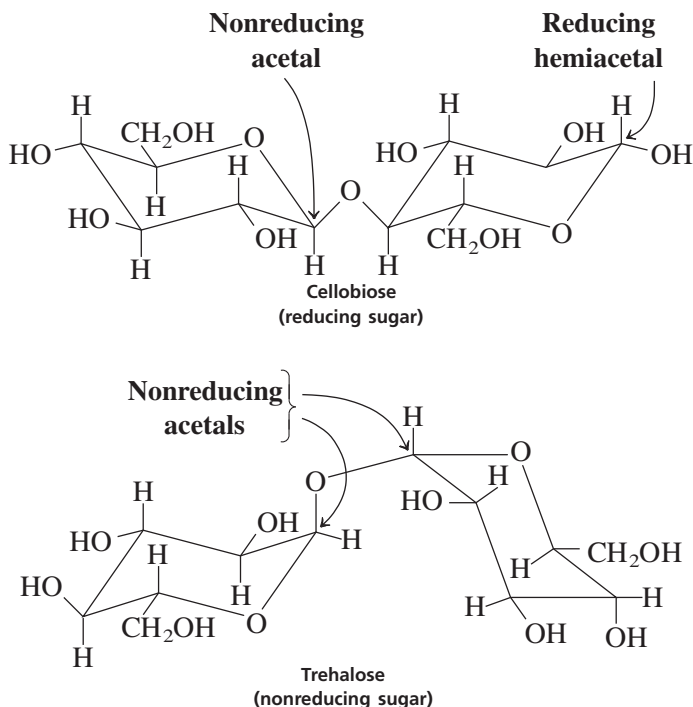
$$\text{RCHO} + 2\text{Cu}^{2+} + 4\,\text{OH}^- \longrightarrow \text{RCOOH} + \text{Cu}_2\text{O} + 2\text{H}_2\text{O}$$
$$\text{Red}$$
$$\text{precipitate}$$

Glucose, for example, is a typical aldohexose, showing reducing properties. The two diastereomic α- and β-D-glucoses are in equilibrium with each other in aqueous solution. The α-D-glucose opens at the anomeric carbon atom (hemiacetal) to produce the free aldehyde. This aldehyde rapidly closes to give β-D-glucose, and a new hemiacetal is produced. It is the presence of this free aldehyde that makes glucose a reducing carbohydrate (sugar). It reacts with Benedict's reagent to produce a red precipitate, the basis of the test. Carbohydrates that have the hemiacetal functional group show reducing properties.

If the hemiacetal is converted to an acetal by methylation, the carbohydrate (sugar) will no longer reduce Benedict's reagent.
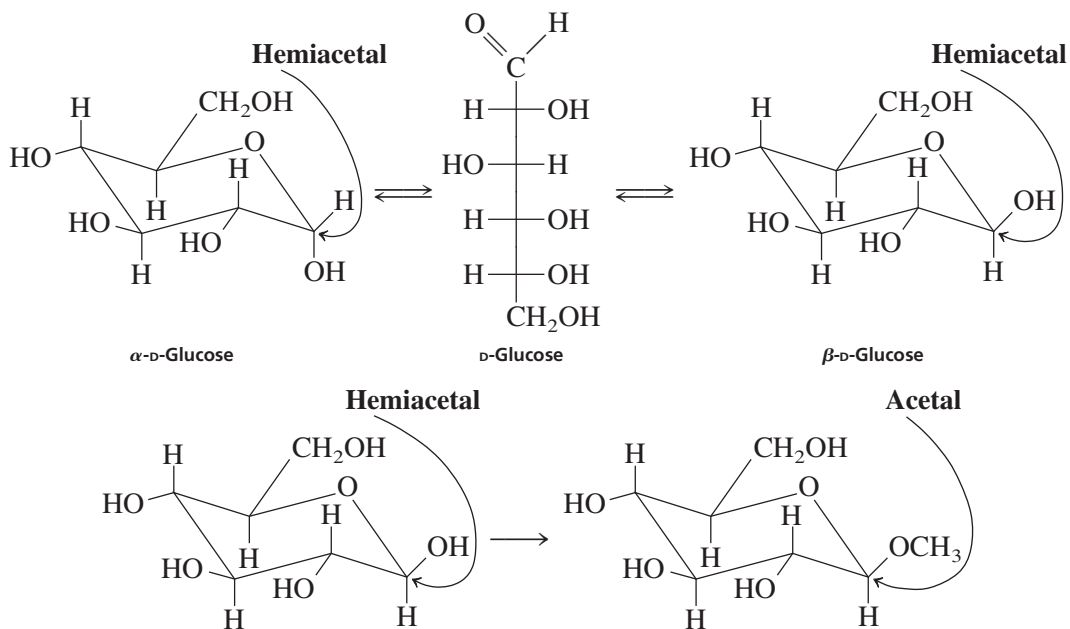
With disaccharides, two situations may arise. If the anomeric carbon atoms are bonded (head to head) to give an acetal, then the sugar will not reduce Benedict's reagent. If, however, the sugar molecules are joined head to tail, then one end will still be able to equilibrate through the free aldehyde form (hemiacetal). Examples of a reducing and a nonreducing disaccharide follow.

Nonreducing acetal

Reducing hemiacetal

Cellobiose (reducing sugar)

Nonreducing acetals

Trehalose (nonreducing sugar)

1. Benedict's Test For Reducing Sugars

Benedict's test is performed under mildly basic conditions. The reagent reacts with all reducing sugars to produce the red precipitate copper(I) oxide, as shown in the reaction below in Section 2. It also reacts with water-soluble aldehydes that are not sugars. Ketoses, such as fructose, also react with Benedict's reagent. Benedict's test is considered one of the classic tests for determining the presence of an aldehyde functional group.

Procedure for Benedict's Test. Prepare a boiling-water bath for this experiment. Place 0.5 mL of each of the following 1% carbohydrate solutions in separate test tubes: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch (shake it), and glycogen. Add 0.5 mL of distilled water to another tube to serve as a control.
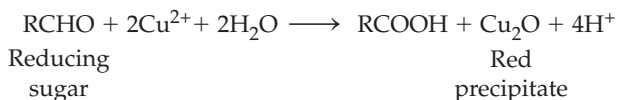
Add 2 mL of Benedict's reagent to each test tube.[4] Place the tests tubes in a boiling-water bath for 2–3 minutes. Remove the tubes and note the results in a notebook. A red, brown, or yellow precipitate indicates a positive test for a reducing sugar. Ignore a change in the color of the solution. A precipitate must form for the test to be positive.

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[4]Dissolve 173 g of hydrated sodium citrate and 100 g of anhydrous sodium carbonate in 800 mL of distilled water, while heating. Filter the solution. Add to it a solution of 17.3 g of copper(II) sulfate ($CuSO_4 \cdot 5H_2O$) dissolved in 100 mL of distilled water. Dilute the combined solutions to 1 L.

2. Barfoed's Test for Reducing Monosaccharides

Barfoed's test distinguishes reducing monosaccharides and reducing disaccharides by a difference in the rate of reaction. The reagent consists of copper(II) ions, like Benedict's reagent. In this test, however, Barfoed's reagent reacts with reducing monosaccharides to produce copper(II) oxide faster than with reducing disaccharides.

Reducing sugar

$$RCHO + 2Cu^{2+} + 2H_2O \longrightarrow RCOOH + Cu_2O + 4H^+$$

| Reducing sugar | Red precipitate |

Procedure for Barfoed's Test. Place 0.5 mL of each of the following 1% carbohydrate solutions in separate test tubes: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch (shake it), and glycogen. Add 0.5 mL of distilled water to another tube to function as a control.

Add 2 mL of Barfoed's reagent to each test tube.[5] Place the tubes in a boiling-water bath for 10 minutes. Remove the tubes and note the results in a notebook.

Part C. Osazone Formation

Carbohydrates react with phenylhydrazine to form crystalline derivatives called **ozazones**.
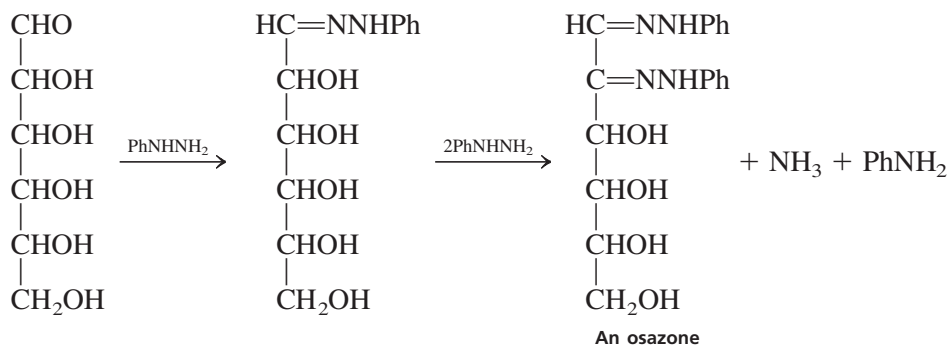
An osazone

An osazone can be isolated as a derivative and its melting point determined. However, some of the monosaccharides give **identical** osazones (glucose, fructose, and mannose). Also, the melting points of different osazones are often in the same range. This limits the usefulness of an isolation of the osazone derivative.

A good experimental use for the osazone is to observe its rate of formation. The rates of reaction vary greatly even though the *same* osazone may be produced from different sugars. For example, fructose forms a precipitate in about 2 minutes, whereas glucose forms a precipitate about 5 minutes later. The osazone is the same in each case. The crystal structure of the osazone is often distinctive. Arabinose, for example, produces a fine precipitate; glucose produces a coarse precipitate.

> **C A U T I O N**
>
> **Phenylhydrazine is a suspected carcinogen. Handle with gloves.**

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[5]Dissolve 66.6 g of copper(II) acetate in 1 L of distilled water. Filter the solution, if necessary, and add 9 mL of glacial acetic acid.

Procedure for Osazone Formation. A boiling-water bath is needed for this experiment. Place 0.5 mL of each of the following 10% carbohydrate solutions in separate test tubes: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch (shake it), and glycogen. Add 2 mL of phenylhydrazine reagent to each tube.[6] Place the tubes in a boiling-water bath simultaneously. Watch for a precipitate or, in some cases, cloudiness. Note the time at which the precipitate begins to form. After 30 minutes, cool the tubes and record the crystalline form of the precipitates. Reducing disaccharides will not precipitate until the tubes are cooled. Nonreducing disaccharides will hydrolyze first, and then the osazones will precipitate.

Part D. Iodine Test for Starch

Starch forms a typical blue color with iodine. This color is due to the absorption of iodine into the open spaces of the amylose molecules (helices) present in starch. Amylopectins, which are the other types of molecules present in starch, form a red to purple color with iodine.

Procedure for the Iodine Test. Place 1 mL of each of the following 1 % carbohydrate solutions in three separate test tubes: glucose, starch (shake it), and glycogen. Add 1 mL of distilled water to another tube to act as a control.

Add one drop of iodine solution to each test tube and observe the results.[7] Add a few drops of sodium thiosulfate to the solutions and note the results.[8]

Part E. Hydrolysis of Sucrose

Sucrose can be hydrolyzed in acid solution to its component parts, fructose and glucose. The component parts can then be tested with Benedict's reagent.

Procedure for the Hydrolysis of Sucrose. Place 1 mL of a 1 % solution of sucrose in a test tube. Add 2 drops of concentrated hydrochloric acid, and heat the tube in a boiling-water bath for 10 minutes. Cool the tube and neutralize the contents with 10% sodium hydroxide solution until the mixture is just basic to litmus (about 12 drops are needed). Test the mixture with Benedict's reagent (Part B). Note the results, and compare them with the results obtained for sucrose that has not been hydrolyzed.

Part F. Mucic Acid Test for Galactose and Lactose

A reaction of lactose and galactose is the oxidation of galactose by the mucic acid test. In this test, the acetal linkage between galactose and glucose units of lactose is cleaved by the acidic medium to give free galactose and glucose. Galactose is oxidized with nitric acid to form dicarboxylic acid and galactaric acid (mucic acid). Mucic acid is an insoluble, high-melting solid that precipitates from the reaction mixture. On the other hand, glucose is oxidized to a diacid (glucaric acid), which is more soluble in the oxidizing medium and does not precipitate.

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[6]Dissolve 50 g of phenylhydrazine hydrochloride and 75 g of sodium acetate trihydrate in 500 mL of distilled water. The reagent deteriorates over time and should be prepared fresh.

[7]The iodine solution is prepared as follows. Dissolve 1 g of potassium iodide in 25 mL of distilled water. Add 0.5 g of iodine, and shake the solution until the iodine dissolves. Dilute the solution to 50 mL.

[8]The sodium thiosulfate solution is prepared by dissolving 1.25 g of sodium thiosulfate in 50 mL of water.
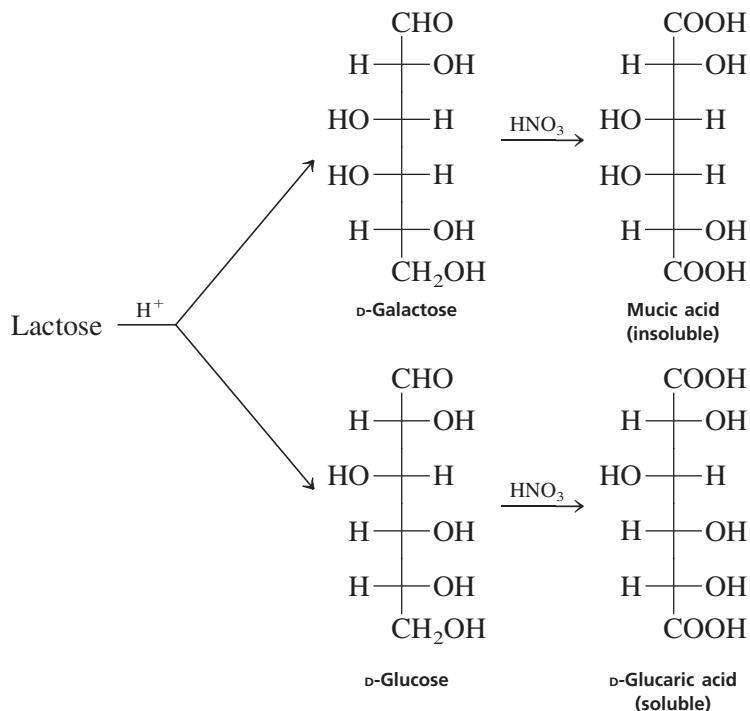
Procedure: Prepare a hot water bath (above 90°C) for this experiment, or use the one prepared for the Benedict's test. Place 0.1 g of the isolated lactose, 0.05 g of glucose (dextrose), and 0.05 g of galactose in 3 separate test tubes. Add 1 mL of water to each tube and dissolve the solids, with heating if necessary. The lactose solution may be somewhat cloudy but will clear when nitric acid is added. Add 1 mL of concentrated nitric acid to each tube. Heat the tubes in the hot-water bath for 1 hour in a hood (nitrogen oxide gases are evolved). Remove the tubes, and allow them to cool slowly after the heating period. Scratch the test tubes with clean stirring rods to induce crystallization. After the test tubes are cooled to room temperature, place them in an ice bath. A fine precipitate of mucic acid should begin to form in the galactose and lactose tubes about 30 minutes after the tubes are removed from the water bath. Allow the test tubes to stand until the next laboratory period to complete the crystallization. Confirm the insolubility of the solid formed by adding about 1 mL of water and then shaking the resulting mixture. If the solid remains, it is mucic acid.

Part G. Tests on Unknowns

Procedure. Obtain an unknown solid carbohydrate from the laboratory instructor or assistant. The unknown will be one of the following carbohydrates: xylose, arabinose, glucose, galactose, fructose, lactose, sucrose, starch, or glycogen. Carefully dissolve part of the unknown in distilled water to prepare a 1% solution (0.060 g carbohydrate in 6 mL water). Also prepare a 10% solution by dissolving 0.1 g of carbohydrate in 1 mL of water. Save the remainder of the solid for the mucic acid test. Apply whichever tests are necessary to identify the unknown.

At the instructor's option, the optical rotation can be determined as part of the experiment. Experimental details are given in Technique 23. Optical rotation data and decomposition points for carbohydrates and osazones are given in the standard reference works on the identification of organic compounds (Experiment 55).

QUESTIONS

1. Find the structures for the following carbohydrates (sugars) in a reference work or a textbook, and decide whether they are reducing or nonreducing carbohydrates (sugars): sorbose, mannose, ribose, maltose, raffinose, and cellulose.

2. Mannose gives the same osazone as glucose. Explain.

3. Predict the results of the following tests with the carbohydrates listed in question 1: Molisch, Bial, Seliwanoff (after 1 minute and 6 minutes), Barfoed, and mucic acid tests.

4. Give a mechanism for the hydrolysis of the acetal linkage in sucrose.

5. The rearrangement in equations 1 and 2 can be considered a type of pinacol rearrangement. Give a mechanism for that step.

6. Give a mechanism for the acid-catalyzed condensation of furfural with two moles of a-naphthol, shown in equation 4.

7. A student decided to determine the optical rotation of mucic acid. What should be expected as a value? Why?

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54   EXPERIMENT 54

Analysis of a Diet Soft Drink by HPLC

High-performance liquid chromatography

In this experiment, high-performance liquid chromatography (HPLC) will be used to identify the artificial additives present in a sample of commercial diet soft drink. The experiment uses HPLC as an analytical tool for the separation and identification of the additive substances. The method uses a reversed-phase column and eluent system, with isochratic elution. Detection is accomplished by measuring the absorbance of ultraviolet radiation at 254 nm by the solution as it is eluted from the column. The mobile phase that will be used is a mixture of 80% 1 M acetic acid and 20% acetonitrile, buffered to pH 4.2.

Diet soft drinks contain many chemical additives, including several substances that can be used as artificial sweeteners. Among these additives are the four substances that we will be detecting in this experiment: caffeine, saccharine, benzoic acid, and aspartame. The structure of these compounds are shown here.

Caffeine

Saccharine

Benzoic acid

Aspartame
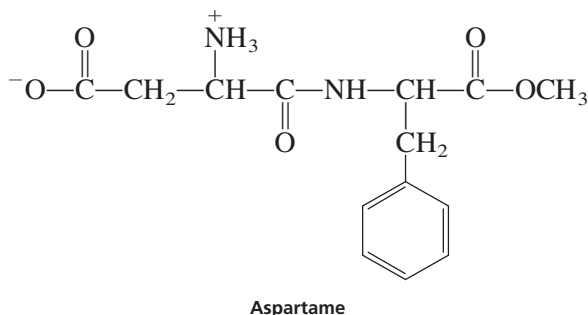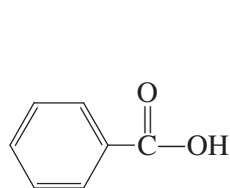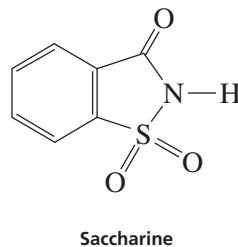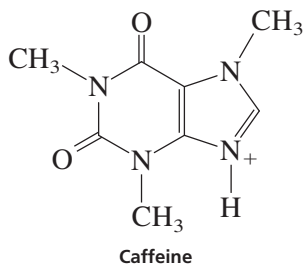
You will identify each compound in a sample of diet soft drink by its retention time on the HPLC column. You will be provided with data for a reference mixture of each substance in a test mixture in order to compare retention times in your test sample with a set of standards.

REQUIRED READING

New: Technique 21   High-Performance Liquid Chromatography (HPLC)

SPECIAL INSTRUCTIONS

The instructor will provide specific instruction in the operation of the particular HPLC instrument being used in your laboratory. The instructions that follow indicate the general procedure.

SUGGESTED WASTE DISPOSAL

Discard the excess acetic acid–methanol solvent in the organic waste container designated for the disposal of nonhalogenated organic wastes. The acetonitrile–acetic acid solvent mixture should be collected in a specially designated container so that it may be either safely discarded or reused.

PROCEDURE

Following your instructor's directions, form a small group of students to perform this experiment. Each small group will analyze a different diet soft drink, and the results obtained by each group will be shared among all students in the class.

The instructor will prepare a mixed standard of the four components, consisting of 200 mg of aspartame, 40 mg of benzoic acid, 40 mg of saccharine, and 20 mg of caffeine in 100 mL of solvent. The solvent for these standards is a mixture of 80% acetic acid and 20% methanol, buffered to pH 4.2 with 50% sodium hydroxide. The lab instructor will also run an HPLC of this standard mixture beforehand, and you should obtain a copy of the results. Some of the steps described in the next two paragraphs may be completed in advance by your instructor.

You may select from a variety of diet soft drinks with different chemical compositions.[1] Select a soft drink from the supply shelf, and dispense approximately 50 mL into a small flask.

Completely remove the carbon dioxide gas, which causes the bubbles in the soft drink, before examining the sample by HPLC. The bubbles will affect the retention times of the compounds and possibly cause damage to the expensive HPLC columns. Most of the gas can be eliminated by allowing the containers of soft drinks to remain open overnight. To remove the final traces of dissolved gases, set up a filtering flask with a Büchner funnel and connect it to a vacuum line. Place a 4-μm filter in the Büchner funnel. (*Note:* Be sure to use a piece of filter paper, not one of the colored spacers that are placed between the pieces of filter paper. The spacers are normally blue.) Filter the soda sample by vacuum filtration through the 4-μm filter, and place the filtered sample in a *clean* 4-dram snap-cap vial.

Before using the HPLC instrument, be certain that you have obtained specific instruction in the operation of the instrument in your laboratory. Alternatively, your instructor may have someone operate the instrument for you. Before your sample is analyzed on the HPLC instrument, it should be filtered one more time, this time through a 0.2-μm filter. The recommended sample size for analysis is 10μL. The solvent system used for this analysis is a mixture of 80% 1 M acetic acid and 20% acetonitrile, buffered to pH 4.2. The instrument will be operated in an isochratic mode.

When you examine the chart obtained from the analysis, you may find that the peak corresponding to aspartame appears to be rather small. The peak is small because aspartame absorbs ultraviolet radiation most efficiently at 220 nm, whereas the detector is set to measure the absorption of light at 254 nm. Nevertheless, the observed retention time of aspartame will not depend upon the setting of the detector, and therefore the interpretation of the results should not be affected. The expected order of elution is saccharine (first), caffeine, aspartame, and benzoic acid. Another interesting point is that although the caffeine peak appears to be quite large in this analysis, it is nevertheless quite small when compared with the peak that would be obtained if you injected coffee into the HPLC. For a caffeine peak from coffee to fit onto your graph, you would have to dilute the coffee *at least* 10-fold. Even decaffeinated coffee usually has more caffeine in it than most sodas (decaffeinated coffee is required to be only 95–96% decaffeinated).

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[1]Note to the instructor: The experiment will be more interesting if the diet soft drink TAB is included among the choices. TAB is one of the few readily available diet soft drinks that contains substantial amounts of saccharine.

When you have completed your experiment, report your results by preparing a table showing the retention times of each of the four standard substances. In your report, be sure to specify the diet soft drink that you used and to identify the substances that you found in that sample. Also report the substances that were found in each of the other soft-drink samples that were tested by other groups in your class.

REFERENCE

Bidlingmeyer, B. A.; Schmitz, S. The Analysis of Artificial Sweeteners and Additives in Beverages by HPLC. *J. Chem. Educ.* **1991,** *68* (A), 195.